Volume I

Neurology in Clinical Practice

Principles of Diagnosis and Management

Fourth Edition-

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S8G. Cancer and the Nervous System: Nervous System Metastases

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S7G. Vascular Diseases of the Nervous System: Central Nervous System Vasculitis

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52. *Principles of Neurosurgery*

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87. Neurological Problems of Pregnancy

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77. *Movement Disorders*

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28. Proximal, Distal, and Generalized Weakness

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S6B. Trauma of the Nervous System: Craniocerebral Trauma

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63. Deficiency Diseases of the Nervous System

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59D. Infections of the Nervous System: Parasitic Infections

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37A. Neuroimaging: Structural Neuroimaging

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82. Disorders of Peripheral Nerves

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61. Hypoxic/Anoxic and Ischemic Encephalopathies

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63. Deficiency Diseases of the Nervous System; 64B. Effects of Toxins and Physical Agents on the Nervous System: Effects of Drug Abuse on the Nervous System; 64C. Effects of Toxins and Physical Agents on the Nervous System: Neurotoxins of Animals and Plants; 64D. Effects of Toxins and Physical Agents on the Nervous System: Marine Toxins

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59A. Infections of the Nervous System: Bacterial Infections; 59B. Infections of the Nervous System: Viral Infections

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23. Ataxic Disorders; 78. Disorders of the Cerebellum, Including the Degenerative Ataxias

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14. Vision Loss; 40. Neuro-Ophthalmology: Afferent Visual System

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73. The Epilepsies

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Preface to the Fourth Edition

When preparing the preface to the first edition of *Neurology in Clinical Practice* in 1990, we highlighted the principles upon which the new textbook was based. We wrote that we had long felt the need for a practical textbook of neurology that covered all the clinical neuroscienccs and provided not only a description of neurological diseases and their pathophysiology but also a practical approach to their diagnosis and management. We emphasized that neurology is intellectually challenging because of the complexity of the nervous system, and fascinating because of the insight that neurological disease provides into the workings of the brain and mind. We recognized the major technological and research advances that were coming, and looked with excitement to the not-too-distant future when more of the neurological diseases would be completely understood, when many of the biochemical defects would be correctible, and when effective regeneration of the central and peripheral nervous systems might be possible. Nevertheless, we believed then, as we do now, that technology must remain the servant of the clinician and never become the master.

Now, thirteen years later, those words are yet more relevant, the hopes are nearer to achievement, and we believe that the book remains true to the original principles.

The first edition of *Neurology in Clinical Practice* won the Most Outstanding Book Award of the Association of American Publishers (Professional and Scholarly-Publication Division). At the time of publication of the third edition in 2000, we sadly lost David Marsden, a founder and co-editor of the first three editions. This fourth edition welcomes Joseph Jankovic as co-editor.

This fourth edition has been completely rewritten, and almost half of the chapters were prepared by new authors. In addition, new chaprers are provided on cndovascular surgery and mitochondrial and ion channel disorders.

This book is the amalgam of the scholarly contributions of all our colleagues who wrote the chapters and provided the illustrations and website material. We are deeply grateful to them for their selfless devotion to neurological education. A project of this magnitude would not have been possible without the encouragement and wisdom of Susan Pioli, Executive Publisher for Global Medicine at Elsevier. She was an active participant at every stage of the development of this book. Mary Beth Murphy, Senior Development Editor at Elsevier, was the key person drawing this, product together. Additionally, we thank Joan Sinclair, Production Manager, and Kelly Mabie, Production Editor, without whose energy and efficiency this book would not have seen the light of day. Finally, we acknowledge the contributions of our readers, whose feedback on the *NICP* family of books and website has been invaluable in assisting us to improve this scries of educational instruments,

Over these thirteen years, the *Neurology in Clinical Practice* family of publications has expanded to include the Pocket Companion, the Review Manual, several translations into other languages, and, most important, the website, www.nicp.com. Starting with the third edition of Neurology in Clinical Practice, we developed and launched this innovative and unique website. With this fourth edition, we will continue to expand this dynamic electronic edition of the book. The website publication provides what the print cannot: regularly posted updates on recent advances in clinical neurology; videos showing eye movements, movement disorders, EMG waveforms, and other material; expanded references to the literature; and additional depth of clinical material from other leading Elsevier neurology texts with e-commerce availability.

The *Pocket Companion to NICP*, which is a true synopsis of the two volumes, will be published shortly after the fourth edition of *Neurology in Clinical Practice.* It continues to be a rewritten, condensed, and accessible version ol the most clinically needed material derived from the "parent" two volumes. This companion is a portable quick reference that will lead the reader back to the two volumes for more in-depth coverage.

The *Review Manual for Neurology in Clinical Practice*, written by Karl Misulis and edited by the four Editors, will also be published shortly after the fourth edition of *Neurology in Cltntcal Practice.* This question-and-answer workbook is organized according to the chapters of the fourth edition of *Neurology in Clinical Practice.* The questions are useful in preparing for the Resident In-Service and Board examinations, and the answers provide explanations and referrals to the main two volumes for more complete consideration of the subject matter.

Walter G. *Bradley, DM., F.R.C.P.*
Robert B. Daroff, M.D.
Gerald M. Fenichel, M.D.
Joseph jankovic, M.D.

Parti

Approach to Common Neurological Problems

Parti

Approach to Common Neurological Problems

Chapter 1
Diagnosis of Neurological Disease

Walter G. Bradley, Robert B. Daroff, Gerald M. Fenichel, and Joseph Jankovic

The neurological diagnosis in a patient is sometimes easy, but at other times it may be quite challenging, requiring specialized skills. If a patient shuffles into the doctor's office and has a pill-rolling tremor of the hands and loss of facial expression, it is not difficult to come to a diagnosis of Parkinson's disease. However, it is important to remember that while it is very satisfying to make such a spot diagnosis, the patient may actually he coming for help with a totally different neurological problem, and therefore an evaluation of the whole problem is necessary.

In all branches of medicine, the history of the symptoms and the clinical examination of the patient are the keys to achieving a diagnosis. This is particularly true in neurology. The standard practice in neurology is to record the patient's chief complaint and take a history of the development of the symptoms, followed by the history of illnesses and surgeries, the family history, the personal and social history, and a review of any symptoms involving the main body systems. The neurologist then performs a neurological examination, and constructs a differential diagnosis of the possible causes of the patient's symptoms. Although this process is also used in making general medical and surgical diagnoses, whar is unique to neurology is the extreme attention to "localization." When a patient presents to an internist or surgeon with abdominal or chest symptoms, the localization is practically established by the symptoms, and the etiology then becomes the primary concern. However, a neurological patient with a weak hand may have a lesion localized to the muscles, the neuromuscular junction, nerve or nerves in the upper limb, brachial plexus, spinal cord, or brain. The neurological examination is essential in determining the site (localization) of the offending lesion. In general, the history provides the best clues fot etiology and the examination is essential for localization.

This diagnostic process consists of a series of steps (Figure 1.1). Although the standard teaching is that the patient should be allowed to provide the history in his or her own words, each step of the process involves active questioning of the patient by the neurologist. At each step, the neurologist should consider rhe possible anatomical localizations, and particularly the etiology of the symptoms (see Figure 1.1). From rhe patient's chief complaint and a detailed history, an astute neurologist can derive clues that lead first to a hypothesis about the location, and then to a hypothesis about the etiology of the neurological lesion. From these hypotheses, the experienced neurologist can predicr what abnormal neurological signs should he present and what should be absent, thereby allowing confirmation of the site of the dysfunction. Alternatively, analysis of the history may suggest two or more possible anatomical locations and diseases, each with a different predicted consrellation of abnormal neurological signs. The findings on neurological examination can be used to determine which of these various possibilities is the most likely. To achieve a diagnosis, the neurologist needs not only to have a good knowledge of the anatomy, physiology, and biochemistry of the nervous system, but also of the clinical features and pathology of the neurological diseases.

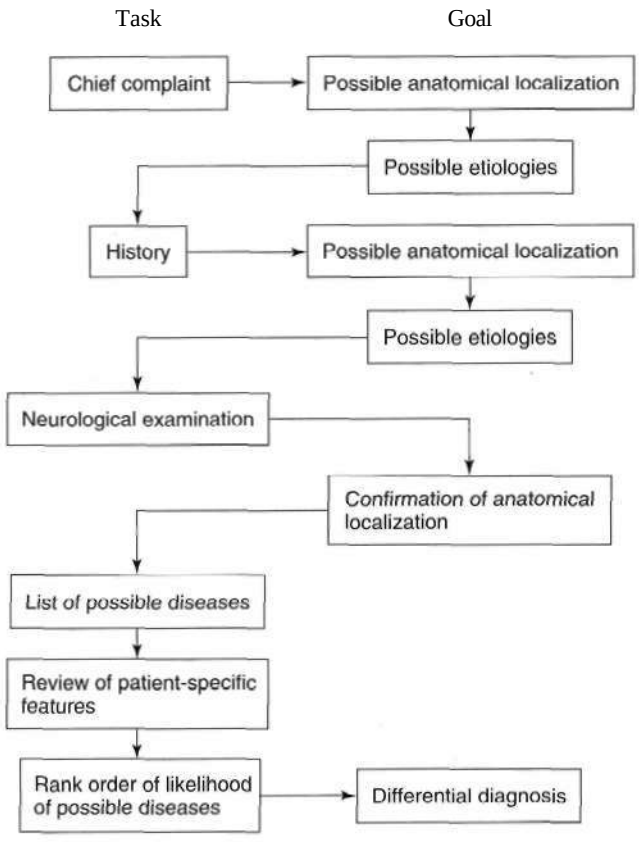

FIGURE 1.1 The diagnostic path is illustrated as a series of steps in which the neurologist collects data (the Task) with the object of providing information on the anatomical localization and nature of the disease process (the Goal).

THE NEUROLOGICAL INTERVIEW

The neurologist is often an intimidating figure for many patients. To add to the stress of the neurological interview and examination, the patient may already have a preconceived notion that the disease causing the symptoms is horrible and life threatening. Because of this background, the neurologist should do everything possible to put the patient at case, and to be empathetic. It is important to introduce oneself to the patient and exchange social pleasantries before leaping into the interview. A few opening questions can break the ice. "How old are you?" "What type of work have you done most of life?" "Who is your doctor, and who would you like me to write to?" "Are you right- or left-handed?" After this, it is easier to ask the first important question: "What brings you to see me? What is your main problem?"

Another technique is to begin by asking the patient, "How can I help you?" This establishes that the doctor is there to ptovide a service and allows patients to express their expectations for the consultation. It is important for the physician to get a sense of patient's expectations from the visit. Usually they want the doctor to find or confirm the diagnosis, and to cure the disease. Sometimes the patient comes hoping that something is *not* present ("Please tell me that my headaches are *not* caused by a brain tumor!"). Sometimes the patient says that other doctors "never told me anything" (which may be true, although in many cases the patient cither did not hear or did not like what was said).

CHIEF COMPLAINT

The chief complaint (or the several main complaints) is the usual starting point of the diagnostic process. An example might be a patient presenting with the triad of complaints of headache, clumsiness, and double vision. The complaints serve to focus attention on the questions to be addressed while taking the history and provide the first clue to the anatomy and etiology of the disease underlying the complaints. In this case, the neurologist would be concerned that the patient might have a tumor in the posterior fossa affecting the cerebellum and brainstem. The mode of onset is critically important in determining the etiology. For example, a sudden onset usually indicates a vascular etiology such as a cerebral infarction or hemorrhage. A course characterized by exacerbations and remissions may suggest multiple sclerosis, whereas a slowly progressive course indicates a neoplasm. Paroxysmal episodes suggest the possibility of seizures; migraines; or some paroxysmal dyskinesias, ataxias, or periodic paralyses.

HISTORY OF PRESENT ILLNESS

Often the patient will give a very clear history of the temporal development of the complaints, the location and severity of the symptoms, and the current level of disability. However, some patients, particularly the elderly, are tangential and insist on telling what other doctors did or said, rather than relating their own symptoms. Direct questioning is often needed to clarify the symptoms, but it is important not to lead the patient. Patients are all too ready to give a positive response to an authority figure, even if it is patently incorrect. It is important to consider whether the patient is reliable. Reliability depends on the patient's intelligence, memory, language function, educational and social status, and whether there are secondary gain issues, such as a disability claim or pending lawsuit.

One should suspect a somatofotm disorder in any patient who claims to have symptoms involving multiple organ systems. Getting information from an observer other than the patient is important for characterizing many neurological conditions, such as seizures and dementia. Taking a history from a child is complicated by shyness with strangers, a different sense of time, and a limited vocabulary. In children, the history is always the composite perceptions of the child and the parent.

Patients and physicians may use the same word to mean very different things. If the physician accepts the word at face value, without ensuring that the patient uses the word in the same way as the doctor, misinterpretation may lead to misdiagnosis. For instance, patients often describe a limb as being "numb" when it is actually paralyzed. Patients often use the term "dizziness" to refer to confusion or weakness and not vertigo. A patient may describe vision as being "blurred" when further questioning reveals diplopia. "Blackouts" may be loss of consciousness, loss of vision, or simply confusion. "Pounding" or "throbbing" headaches are not necessarily pulsating.

The neurologist must understand fully the nature, onset, duration, and progression of each symptom and the temporal relationship of one symptom to another. Are the symptoms getting better, staying the same, or getting worse? What relieves them and what makes them worse? In infants and young children, temporal sequence also includes the timing of developmental milestones; failure to achieve a milestone is as important as loss of achievement.

An example may clarify how the history leads to diagnosis. A 28-year-old woman presents with a 10-year history of recurrent headaches associated with her menses. The unilateral quality of pain in some attacks and the association of flashing lights, nausea, and vomiting points to the diagnosis of migraine. On the other hand, if the same patient has a progressively worsening headache upon wakening, has new onset seizures, and is developing a hemiparesis, this suggests an intracranial space-occupying lesion. Both the absence of expected features and the presence of unexpected features may assist in the diagnosis. A patient with numbness of the feet might have a peripheral neuropathy, but the presence of backache and loss of sphincter control suggests that a spinal cord or cauda equina lesion is more likely.

Patients may arrive for a neurological consultation with a folder of previous laboratory tests and neuroimaging studies. They often dwell on these tests and their interpretation by other physicians. Be wary of accepting the opinions of other doctors; they may have been wrong! The careful neurologist takes a new history and makes a new assessment of the prohlem.

The history of how the patient or the caregiver responded to the symptoms may be important. A pattern of overreaction may be of help in evaluating the significance of the complaints. However, a night visit to the emergency department for a new-onset headache should not be dismissed without investigation. Conversely, the child who was *not* brought to the hospital despite hours of seizures is likely to be the victim of child abuse, or at least of neglect.

REVIEW OF PATIENT SPECIFIC INFORMATION

Information about the patient's background often greatly helps the neurologist make a diagnosis of the cause of the symptoms. This information includes the history of medical and surgical illnesses; current medications and allergies; a review of symptoms in non-neurological systems of the body; the personal history in terms of occupation, marital status, and alcohol, tobacco, and illicit drug use; and the medical history of the parents, siblings, and children, looking for evidence of familial diseases. The order in which these items are considered is not important but consistency avoids something being forgotten.

In the outpatient office, the patient can be asked to complete a form with a series of questions on all of these matters before starting the consultation with the physician. This expedites the interview, although more details are often needed. What chemicals is the patient exposed to at home and at work? Did the patient *ever* use alcohol, tobacco, or prescription or illegal drugs? *h* thete excessive stress at home, in school, or in the workplace, such as divorce, death of a loved one, or loss of employment? Are there hints of abuse or neglect of children or spouse? Sexual preference is important information in this era of human immunodeficiency virus infection. The doctor should question children and adolescents away from their parents if there is a need to obtain mote accurate information about sexual activity and substance abuse.

Review of Systems

The review of systems should include the elements of nervous system function that did not surface in taking the history. The neurologist should have covered the following: cognition, personality and mood change; hallucinations; seizures and other impairments of consciousness; ortho static faintness; headaches; special senses; speech and language function; swallowing; limb coordination; slowness of movement; involuntary movements; strength and sensation; pain; gait and balance; and sphincter, bowel, and sexual function. A positive response m.iy help clarih a diagnosis. For instance, if a patient complaining of ataxia and hemiparesis admits to unilateral deafness, this may suggest an acoustic neuroma. Headaches in a patient with pataparesis suggest a parasagittal meningioma rather than a spinal cord lesion. The developmental history must be assessed in children and may also be of value in adults whose illness started during childhood. The review must include all the organ sysrems. Neurological function is adversely affected by dysfunction of many systems, including the liver, kidney, gastrointestinal tract, heart, and blood vessels. Several neurological diseases are characterized by multi-organ involvement, such as vasculitis, sarcoidosis, mitochondrial disorders, and storage diseases.

History of Previous Illnesses

Items in the patient's medical and surgical history may help explain the present complaint. For instance, seizures and

worsening headaches in a patient who previously had surgery for lung cancer suggest a brain metastasis. Chronic low-back pain in a patient complaining of numbness and weakness in the legs on walking half a mile suggests neurogenic claudication from lumbar canal stenosis. The record of the history should include dates and details of all surgical procedures; significant injuries, including head trauma and fractures; hospitalizations; and conditions requiring medical consultation and medications. For pediatric patients, information on the pregnancy and state of the infant at birth should be recorded.

Certain features in the patient's history should always alert the physician to the possibility that they may be responsible for the neurological complaints. Gastric surgery may lead to vitamin B12 deficiency. Sarcoidosis may cause Bell's palsy, diabetes insipidus, ophthalmoplegia, and peripheral neuropathy. Disorders of the liver, kidney, and small bowel can be associated with a wide variety of neurological disorders. Systemic malignancy can cause direct and indirect (paraneoplastic) neurological problems.

Do not be surprised if the patient fails to remember previous medical or surgical problems. It is common to find abdominal scars on a patient who described no surgical procedures until questioned about the scars.

Medications are often the cause of neurological disturbances, particularly chemotherapy drugs. Isoniazid may cause a peripheral neuropathy. Lithium carbonate may produce tremor and ataxia. Neuroleptic agents can produce a parkinsonian syndrome or dyskinesias. Most patients do not think of vitamins, oral contraceptives, non-prescription analgesics, and herbal compounds as medications, and specific questions about these agents are necessary.

Family History

Many neurological disorders are hereditary. Hence a history of similar disease in family members or of consanguinity may be of diagnostic importance. However, the expression of a gene mutation may be quite different from one family member to another with respect not only to the severity of neurological dysfunction but also to the organ systems involved. For instance, the mutations of the gene for Mach ado-Joseph disease (SCA 3) can cause several phenotypes. A patient with Charcot-Marie-Tooth disease (hereditary motor-sensory neuropathy) may have a severe peripheral neuropathy, whereas relatives may have only pes cavus.

Reported diagnoses may be inaccurate. In families with dominant muscular dystrophy, affected individuals in earlier generations are often said to have had "arthritis" that put them into a wheelchair. Some conditions, such as epilepsy, may be "family secrets." Therefore, one should be cautious in accepting a patient's assertion that there is no family history of a similar disorder. If there is a possibility that the disease is inherited it is helpful to obtain information from parents and grandparents and to examine relatives at risk. Minimum data for all first- and second-degree relatives should include age (currently or at death), cause of death, and any significant neurological or systemic diseases.

THE EXAMINATION

Neurological Examination

A description of the neurological examination may be found in several excellent textbooks (see References), Trainees must be able to perform and understand the complete neurological examination, in which every central nervous system region, peripheral nerve, muscle, sensory modality, and reflex is tested. However, the full neurological examination is too lengthy to perform in practice. Instead, the experienced neurologist uses the *focused neurological examination* to examine in detail the neurological functions that are relevant to the history, and performs a *screening neurological examination* to check the remaining parts of the nervous system. This approach should confirm, refute, or modify the initial hypotheses of disease location and causation derived from the history (see Figure 1.1). Both the presence and absence of abnormalities may be of diagnostic importance. For instance, if a patient's symptoms suggest a left hemiparesis, the neurologist searches carefully for a left homonymous hemianopia; evidence that the blink or smile is slowed on the left side of the face; that rapid, repetitive movements are impaired in the left limbs; that the tendon reflexes are more brisk on the left than the right; that the left abdominal reflexes are absent; and that the left plantar response is extensor. Along with testing the primary modalities of sensation on the left side, the neurologist may examine the higher integrative aspects of sensation, including graphesthesia, stereognosis, and sensory extinction with double simultaneous stimuli, The presence or absence of some of these features can separate a left hemiparesis arising from a lesion in the right cerebral cortex or from one in the left cervical spinal cord.

The screening neurological examination {Table 1.1) is designed for quick evaluation of the mental status, cranial nerves, motor system (strength, muscle tone, presence of involuntary movements and postures), coordination, gait and balance, tendon reflexes, and sensation. More complex functions are tested first; if these are performed well, then it may not be necessary to test the component functions. The patient who can walk hccl-to-toe (tandem gait) does not have a significant disturbance of the cerebellum or of joint position sensation. Similarly, the patient who can do a pushup, rise from the floor without using the hands, and walk on toes and heels will have normal limb strength when each muscle group is individually tested. Asking the patient to hold the arms extended in supination in front of the body with the eyes open allows evaluation of strength and posture. It may also reveal involuntary movements such as tremor, dystonia,

Table 1.1: Outline of the screening neurological examination

Mental status: Assess while recording the history.
Cranial nerves:
I: Not tested
II: Gross visual acuity each eye:
Visual fields by confrontation, including double simultaneous stimuli
Rmduscopy
III, IV, VI; Horizontal and vertical eye movements
Pupillary response to light
Presence of nystagmus
V: Pinprick and touch sensation on face, corneal reflex
VII: Close eyes, show teeth
VIII: Perception of whispered voice in each car or rubbing of fingers. If impaired, look in external auditory canals, and use tuning fork for lateralization and hone versus air sound conduction.
IX, X: Palate lifts in midline, gag reflex present
XI: Shrug shoulders
XI!: Protrude tongue
Limbs: Each limb tested separately:
Presence of involuntary movements
Muscle mass (atrophy, hypertrophy) and look for fascidilations
Muscle tone in response to passive flexion and extension
Power of main muscle groups
Coordination; finger-to-nose and hccl-to-shin testing, performance of rapid alternating movements
Tendon reflexes
Plantar responses
Pinprick and light touch on hands and feet
Double simultaneous stimuli on hands and feet
Joint position sense in hallux and index finger
Vibration sense at ankle and index finger
Gait and balance
Romberg test

myoclonus, or chorea. A downward or pronator drift of a weak arm is expected. Repeating the maneuver with the eyes closed allows assessment of joint position sensation.

The screening neurological examination may miss important neurological abnormalities. For instance, a bitemporal visual field defect may not be detected when the fields of both eyes are tested simultaneously. It is necessary to test each eye separately. Similarly, a parietal lobe syndrome may go undiscovered unless visuospatial function is assessed.

It is sometimes difficult to decide whether a physical finding is normal or abnormal, and only experience prevents the neurologist from misinterpreting as a sign of disease something that is the result of normal variation. Every person has some degree of asymmetry. Moreover, what is abnormal in young adults may be normal in the eldetly. Loss of the ankle reflex and loss of vibration sense at the big toes are common findings in patients older than 60 years. Conversely, children cannot detect the distal stimuli when the hand and face are simultaneously touched on the same side of the body until they are 7 years old.

The experienced neurologist understands the normal range of neurological variation, while the beginner frequently records mild impairment of a number of different functions. These include isolated deviation of the tongue or uvula to one side and minor asymmetries of reflexes or sensation. Such *soft signs* may be incorporated into the overall synthesis of the disorder if they are consistent with other parts of the history and examination; otherwise, they should be disregarded. If an abnormality is identified, all features that are usually associated should be sought. For instance, ataxia of a limb may result from a corticospinal tract lesion, sensory defect, or cerebellar lesion. If the limb incoordination is due to a cerebellar lesion, there will be ataxia on finger-to-nose and hccl-to-shin testing, abnormal rapid alternating movements of the hands (dysdiadochokinesia), and often nystagmus and ocular dysmetria. If some of these signs of cerebellar dysfunction are missing, examination of joint position sense, limb strength, and reflexes may demonstrate that this incoordination is due to something other than a cerebellar lesion.

At the end of the neurological examination, the abnormal physical signs should be classified as definitely abnormal *(bard signs)* or equivocally abnormal *(soft signs).* The hard signs, when combined with symptoms from the history, allow the neurologist to develop a hypothesis about the anatomical site of the lesion or at least about the neurological pathways involved. The soft signs can then be reviewed to determine if they conflict with or support the initial conclusion. Remember that the primary purpose of the neurological examination is to reveal functional disturbances that localize abnormalities. The standard neurological examination is less effective when used to monitor the course of a disease or its temporal response to treatment. Special quantitative functional tests and rating scales are needed to measure change in neurological function over time.

General Physical Examination

The nervous system is damaged in so many general medical diseases that a general physical examination is an integral pan ol the examination ol patients with neurological disorders. For instance, atrial fibrillation, valvular heart disease, or an atrial septal defect may cause embolic strokes in the central nervous system. Hypertension increases the risk for all types of stroke. Signs of malignancy raise the possibility of metastatic lesions of the nervous system or paraneoplastic neurological syndromes, such as a subacute cerebellar degeneration or progressive multifocal leukocnccphalopathy. In addition, some diseases such as vasculitis and sarcoidosis affect both the brain and other organs.

ASSESSMENT OF THE CAUSE OF THE PATIENT'S SYMPTOMS

Anatomical Localization

At the completion of the history, the experienced neurologist should attempt the first assessment of the anatomical

location of the lesion or the neurological systems involved, and of the pathophysiology of the disorder (see Figure 1.1). The experienced neurologist then uses the examination to localize the lesion before trying to determine its cause. The initial question is whether the disease is in the brain, spinal cord, peripheral nerves, neuromuscular junctions, or muscles. Then it must be established whether the disorder is focal, multifocal, or a system disorder. A system disorder is a disease that causes degeneration of one part of the nervous system, while it spares other adjacent ncutological systems. For instance, degeneration of the corticospinal tracts and spinal motor neurons with sparing of the sensory pathways of the central and peripheral nervous systems is the hallmark of the system degeneration termed *motor neuron disease* or *amyotrophic lateral sclerosis.* Another example of a system degeneration is multiple system atrophy, manifested by slowness of movement (parkinsonism), ataxia, and dysautonomia.

The first step in localization is to translate the patient's symptoms and signs into abnormalities of a nucleus, tract, ot system. For instance, loss of pain and temperature sensation on one-half of the body, excluding the face, indicates a lesion of the contralateral spinothalamic tract in the high cervical spinal cord. A left sixth nerve palsy, with weakness of left face and right limbs, points to a left pontine lesion, A left homonymous hemianopia indicates a lesion in the right optic tract, optic radiations, or occipital cortex. The neurological examination plays a crucial role in localizing the lesion. A patient complaining of tingling and numbness in the feet might initially be thought to have a peripheral neuropathy. If examination shows hyperreflcxia in the arms and legs, and no vibration sensation below the clavicles, the lesion is likely to be in the spinal cord, and the many causes of peripheral neuropathy can be dropped from consideration. A patient with a history of weakness of the left arm and leg who is found on examination to have a left homonymous hemianopia has a right cerebral lesion, not a cervical cord problem.

The neurologist must decide if the symptoms and signs could all arise from one focal lesion or whether several anatomical sites must be involved. The *principle of parsimony,* or *Occam's razor,* requires that we strive to hypothesize only one lesion. The differential diagnosis for a single focal lesion is significantly differenr from that for multiple lesions. Thus a patient complaining of loss of left-sided vision and left-sided weakness is likely to have a lesion in the right cerebral hemisphere, possibly caused by stroke or rumor. On the other hand, if the visual difficulty is due to a central scotoma in the left eye, and if the upper motor neuron weakness affects the left limbs but spates the lower cranial nerves, there must be two lesions: one in the left optic nerve and one in the left corticospinal tract below the medulla, as seen, for example, in multiple sclerosis. If a patient with symptoms of slowly progressive slurring of speech and difficulty walking is found to have ataxia of the arms and legs, bilateral extensor plantar responses, and optic atrophy, the lesions must either be multifocal (affecting brainstem and optic nerves, and hence probably multiple sclerosis) or a system disorder, such as a spinocerebellar degeneration. The complex vascular anatomy of the brain can sometimes cause multifocal neurological deficits to tesult from only one vascular abnormality. For instance, a patient with occlusion of one vertebral artery may suffer a srroke producing a midbrain lesion, a hemianopia, and an amnestic syndtome.

Synthesis of symptoms and signs into the anatomical localization of a lesion requires a good knowledge of neuroanatomy, including the location of all major pathways in the nervous system and their inter-relationships at different levels. In making this synthesis, the ttainee will find it helpful to refer to diagrams that show transverse sections of the spinal cord, medulla, pons, and midbrain; the brachial and lumbosacral plexuses; and the dermaromes and myotomes. Knowledge of the functional anatomy of the cerebral cortex and the blood supply of the brain and spinal cord is also essential.

Symptoms and signs may arise not only from disturbances caused at the focus of an abnormality *(focal localizing signs)* but also at a distance. One example is the damage that results from the shift of intracranial contents produced by an expanding supra tentorial tumor. This may cause a palsy of the third or sixth cranial nerve, even though the tumor is far from the cranial nerves. Clinical features caused by damage far from the primary site of abnormality are called *false localizing signs.* The term derives from the era before neuroimaging studies when clinical examination was the major means of lesion localization. In fact, these are not false signs but rarher rhe signs that the inttacranial shifts arc marked, alerting the clinician to the latge size of the tumor.

DIFFERENTIAL DIAGNOSIS

Once the likely site of the lesion is identified, the next step is to generate the differential diagnosis, that is, the list of diseases that may be responsible for a parienr's symptoms and signs (see Figure 1.1). The experienced neurologist automatically first considers the most likely cause of the symptoms, followed by less common causes. The beginner is happy to generate a list of the main causes of the symptoms in whatever order comes to mind. Experience indicates the most likely causes, based on the specific features of rhe patient, the parts of the nervous system affected, and the relative frequency of each disease. Remember that *rare presentations of common diseases are more common than common presentations of rare diseases.*

Sometimes only a single disease can be incriminated, but usually there are several candidate diseases. The list of possibilities should take into account both the temporal features of the patient's symptoms and the pathological

processes known to affect the relevant area of the nervous system. For example, in a patient with signs indicating a lesion of the internal capsule, the cause is likely to be stroke if the hemiplegia had a sudden onset. If there was progression over weeks or months, the cause is likely an expanding tumor. Another example is a patient with signs of multifocal lesions. If symptoms have relapsed and remitted over several years, the diagnosis is likely to be multiple sclerosis or multiple strokes (depending on the patient's age, sex, and risk factors). If symptoms appeared only recently and progressed, multiple metastases should be considered.

Again, the principle of parsimony or Occam's razor should be applied when constructing the differential diagnostic list. Consider a patient with a 3-week history of a progressive spinal cord lesion who suddenly experiences aphasia. Perhaps he or she had a tumor compressing the spinal cord and has incidentally developed a small stroke. However, parsimony would suggest a single disease, probably cancer with multiple metastases. Another example is a patient with progressive atrophy of the small muscles of the hands for 6 months before the appearance of a pseudobulbar palsy. She or he could have bilateral ulnar nerve lesions and recent bilateral strokes, but amyotrophic lateral sclerosis is more likely. However, remember that nature does not always obey the rules of parsimony.

The differential diagnosis generally starts with pathological processes, such as a stroke, a tumor, or an abscess. H;ich pathological process may result from several different diseases. Thus a clinical diagnosis of an intracranial neoplasm generates a list of the different types of tumors thar arc likely to be responsible for the clinical manifestations in this particular patient. Similarly, in a patient with a stroke the clinical history may help separate hemorrhage, embolism, thrombosis, vascular spasm, or vasculitis. The skilled diagnostician is justly proud of placing the correct diagnosis at the top of the list, but it is more important to ensure that all possible diseases are considered. If a disease is not considered, it is unlikely to be diagnosed. Treatable disorders should always be considered, even when there is a very low probability. This is especially true if they may mimic more common incurable neurological disorders, such as Alzheimer's disease or amyotrophic lateral sclerosis.

LABORATORY INVESTIGATIONS

Sometimes the neurological diagnosis can be made without any laboratory investigations. This is true for a clear-cut case of Parkinson's disease, myasthenia gravis, or multiple sclerosis. Nevertheless, even in these situations, appropriate laboratory documentation is important for other physicians who will see the patient in the future. In other cases the cause of the disease will only be elucidated by the use of laboratory tests. These tests may in individual cases include hematological and biochemical blood studies; neurophysiological testing (Chapter 36); neuroimaging (Chapter 37); organ biopsy; and bacteriological and virological studies. The use of laboratory tests in the diagnosis of neurological diseases is considered more fully in Chapter 35.

MANAGEMENT OF NEUROLOGICAL DISORDERS

Not all diseases arc curable. However, even if a disease is incurable the physician will be able to reduce the patient's discomfort and assist the patient and the family in managing the disease. The understanding of neurological diseases is a science. The diagnosis of neurological disease is a combination of science and experience. The management of neurological disease is an art, an introduction to which is provided in Chapter 48.

THE EXPERIENCED NEUROLOGIST'S APPROACH TO THE DIAGNOSIS OF COMMON NEUROLOGICAL PROBLEMS

The skills of a neurologist are learned. Seeing many cases of a disease teaches the neurologist which symptoms and signs *should he present,* and, just as important, which *should not be present.* Although there is no substitute for experience and pattern recognition, the trainee can learn the clues used by the seasoned practitioner to achieve a diagnosis. Part I of this book covers the main symptoms and signs of neurological disease. These chapters describe how an experienced neurologist approaches common presenting problems, such as a movement disorder, a speech disturbance, or diplopia, to arrive at the correct diagnosis. Part II of this book comprises rhe major fields of investigation and management of neurological disease. Part III provides a compendium of the neurological diseases themselves.

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Chapter 2
Episodic Impairment of Consciousness

Joseph Bruni

Temporary loss of consciousness may be caused by impaired cerebral perfusion (syncope, fainting), cerebral ischemia, migraine, epileptic seizures, metabolic disturbances, sudden increases in intracranial pressure, or sleep disorders. Anxiety attacks, psychogenic seizutes, panic disorder, and malingering may be difficult to distinguish from these conditions. At times, the diagnosis may not be clatified without detailed laboratory examinations and prolonged periods of observation.

Syncope may result from decreased cardiac output secondary to cardiac arrhythmias, outflow obstruction, hypovolemia, orthostatic hypotension, or decreased venous return. Cerebrovascular disturbances from transient ischemic attacks of the posterior or anterior cerebral circulations or cerebral vasospasm from migraine, subarachnoid hemorrhage, or hypertensive encephalopathy may tesult in temporary loss of consciousness. Metabolic disturbances caused by hypoxia, drugs, anemia, and hypoglycemia may result in frank syncope or, more frequently, may present with the sensation of an impending faint (ptesyncope).

Absence seizures, generalized tonic-clonic seizures, and complex partial seizures are associated with alterations of consciousness and, in most cases, can be easily distinguished from syncope. Epileptic seizutes may be difficult to distinguish from pseudoseizures (psychogenic seizures), panic attacks, and malingering. In children, breath-holding spells, a form of syncope that is discussed latet in the chapter, can cause a transitory alteration of consciousness that may mimic epileptic seizures.

Although sudden increases of intracranial pressure (which may result from intermittent hydrocephalus, severe head trauma, brain tumors, inttacerebral hemorrhage, or Reye's syndrome) may produce sudden loss of consciousness, these patients frequently have other neurological manifestations that lead to this diagnosis.

In patients with episodic impaitment of consciousness, a diagnosis relies heavily on the clinical history described by the patient and observers. Laboratory investigations, however, may provide useful information. In a small number of patients, a cause for the loss of consciousness may not be established, and these patients may require longer periods of observation. Tabic 2.1 compares the clinical features of syncope and seizures.

SYNCOPE

The pathophysiologic basis of syncope is the gradual failure of cerebral perfusion with a reduction in cerebral oxygen availability. *Syncope* is often preceded by a symptom complex (presyncopc) characterized by lightheadedness, generalized muscle weakness, giddiness, visual blurring, tinnitus, and gastrointestinal symptoms. The patient may appear pale and feel cold and sweaty. The onset of loss of consciousness is generally gradual but may be rapid, without prcsyncopal symptoms, if related to certain conditions, such as a cardiac arrhythmia. The gradual onset may allow patients to protect themselves from falling and injury. A simple faint is usually precipitated by emotional stress, unpleasant visual stimuli, prolonged standing, or pain. Although the duration of unconsciousness is brief, it may vary from seconds to minutes. During the faint, the patient may be motionless or display myoclonic jerks. Urinary incontinence is uncommon but not rare. The pulse is weak and often slow. Urea thing may be shallow and the blood pressure barely obtainable. As the fainting episode cotrects itself (e.g., by the patient becoming horizontal), the color returns, breathing becomes more regular, and the pulse and blood pressure return to normal. After the faint, there is some residual weakness, hut unlike

Table 2.1: Comparison of clinical features of syncope and seizures

Features	*Syncope*	*Seizure*
Relation to posture	Common	No
Time of day	Diurnal	Diurnal or nocturnal
Precipitating factors	Emotion, injury, pain, crowc s, heat	Sleep loss, drug/alcoliol withdrawal
Skin color	Pallor	Cyanosis or normal
Aura or premonitory symptoms	Long	Brief
Convulsion	Rare	Common
injury	Rare	Common (with convulsive seizures)
Urinary incontinence	Rare	Common
Postictal confusion	Rare	Common
Postictal headache	No	Common
Focal neurological signs	No	Occasional
Cardiovascular signs	Common (;ardiac syncope)	No
Abnormal electroencephalogram recording	Rare (may show generalized slowing during the event)	Common

Table 2.2: Classification of syncope

Cardiac arrhythmias
  Bradyarrhythmias
  Tachyarrhythmias
  Reflex arrhythmias
Decreased cardiac output
Cardiac outflow obstruction
Inflow obstruction
Cardiomyopathy
Hypovolemia
Hypotension
Drug use
Dysautonomia
Carotid sinus
Vertebrobasilar disease
Vasospasm
Takayasu's arteritis
Metabolic
Hypoglycemia
Anemia
Anoxia

Hyperventilation
Vasovagal (vasodepressor; neurocardiogenic; neural mediated)
Cardiac syncope
Cough, micturition
Multifactorial

with seizures, confusion, headaches, and drowsiness are uncommon sequelae. Nausea may be noted when the patient regains consciousness. The causes of syncope are generally classified according to the pathophysiological mechanism involved (Table 2.2), but the final common pathway is cerebral hypoperfusion.

History and Physical Examination

The history and physical examination are the most important parts of the initial evaluation of syncope. There are sitmificant age and sex differences in the frcq the various types of syncope. Syncope occurring in children and young adults is most commonly due to hyperventilation or vasovagal (vasodepressor) attacks and less commonly due to congenital heart disease (Lewis and Dhala 1999). Fainting associated with benign tachycardias without underlying organic heart disease may also appear in the younger age-groups. Syncope caused by basilar migraine is more common in young females. When repeated syncope begins in later life, organic disease of the cerebral circulation or cardiovascular system is usually responsible.

In establishing the cause of syncope, the most important step is a careful history. The diagnosis often can be made from the patient's description. The previously described presyncopal symptoms and certain clues in the history may help establish the cause. The neurologist should always obtain a full description of the first faint. The clinical features should be established, with emphasis on precipitating factors, posture, type of onset of the faint and whether it was abrupt or gradual, position of head and neck, the presence and duration of preceding and associated symptoms, duration of loss of consciousness, rate of recovery, and sequelae. If possible, an observer should be questioned about clonic movements, color changes, diaphoresis, pulse, respiration, urinary incontinence, and the nature of recovery.

Clues in the history that suggest cardiac syncope include a history of palpitations or a fluttering sensation in the chest before losing consciousness. These symptoms are common in arrhythmias. In vasodepressor syncope and orthostatic hypotension, preceding symptoms of lightheadedness may be common. Episodes of cardiac syncope are generally briefer than vasodepressor syncope, and the onset is usually rapid. Episodes caused by cardiac arrhythmias occur independent of position, whereas in vasodepressor syncope and syncope caused by orthostatic hypotension, the patient is usually standing.

Attacks of syncope precipitated by exertion suggest a cardiac etiology. Exercise may induce arrhythmic syncope or syncope caused by decreased cardiac output secondary to blood flow obstruction, such as may occur with aortic or subaortic stenosis. Exercise-induced syncope may also be caused by cerebrovascular disease, aortic arch disease, congenital heart disease, pulseless disease (Takayasu's disease), pulmonary hypertension, anemia, hypoxia, and hypoglycemia, but often no cardiac disease is uncovered (Colivicchi et al. 2002). A family history of sudden cardiac death, especially in females, might suggest the long QT syndrome. Because many drugs can induce orthostatic hypotension or produce cardiac arrhythmias, a careful and complete medical and medication history is mandatory (Goldschlager et al. 2003).

The neurologist should inquire about the frequency of attacks of loss of consciousness and the presence of cerebrovascular or cardiovascular symptoms between episodes. The patient should be questioned about whether all the episodes are similar, because some parienrs experience more than one type of attack.

With an accurate description of the attacks and familiarity with clinical features of various types of syncope, the physician should be able to correctly diagnose most patients. Some seizure types that have to be distinguished from syncope include orbitofronral complex partial seizures, which can be associated with autonomic changes, and complex partial seizures that are associated with sudden falls and altered awareness followed by confusion and gradual recovery (temporal lobe syncope). Features that distinguish syncope from seizures and other alterations of consciousness are discussed later in this chapter.

After a complete history, the physical examination is of next importance. Examination during the episode is very informative but frequently impossible unless presyncopal symptoms can be reproduced by a Valsalva maneuver or by recrearing the circumstances of the attack, such as by position change. In the patient with suspected cardiac syncope, particular attention should be paid to the vital signs and determination of supine and erect blood pressure. Normally, upon standing the systolic blood pressure *rises* and the pulse rate may *increase.* An orthostatic drop in blood pressure greater than 15 mm Hg may suggest autonomic dysfunction. Blood pressure should be assessed in both arms if cerebrovascular disease, subclavian steal, or Takayasu's arteritis is suspected.

During syncope caused by a cardiac arrhythmia, a heart rate faster than 140 beats per minute usually indicates an ectopic cardiac rhythm, whereas a bradycardia with a heart rate of less than 40 beats per minute suggests complete atrioventricular (AV) block. Supraventricular tachycardias can be terminated abruptly by carotid sinus massage, whereas a ventricular tachycardia shows no response. However, this technique is no longer advised because of the risk of cerebral embolism from atheroma in the carotid artery wall. Stokes-Adams attacks may be of longer duration and may be associated with audible atrial contraction and a variable first heart sound. Heart disease as a cause of syncope is more common in the elderly patient (Brady and Shen 2002).

The patient should undergo cardiac auscultation for the presence of cardiac murmurs and abnormalities of the heart sounds. There may be the murmur of aortic stenosis, subaortic stenosis, or mitral valve disease. An intermittent posture-related murmur may be heard with an atrial myxoma. A systolic click in a young person suggests mitral valve prolapse. A pericardial rub suggests pericarditis.

All patients should undergo observation of the carotid pulse and auscultation of the neck. The degree of aortic-stenosis may at times be reflected in a delayed carotid upstroke. Carotid, ophthalmical, and supraclavicular bruits suggest underlying cerebrovascular disease. Carotid sinus massage may be useful in older patients suspected of having carotid sinus syncope, but it is important to keep in mind that up to 25% of asymptomatic subjects may have some degree of carotid sinus hypersensitivity. Carotid sinus massage should be avoided in patients with suspected cerebrovascular disease, and when performed, it should be done in properly controlled conditions with electrocardiogram (ECG) and blood pressure monitoring.

Causes of Syncope

Cardiac Arrhythmias

Both bradyarrhythmias and tachyarrhythmias may result in syncope, and abnormalities of cardiac rhythm resulting from dysfunction from the sinoatrial (SA) node to the Purkinje network may be involved. Arrhythmias are a common cause of syncope and must be considered in all cases in which an obvious mechanism is not known. Syncope caused by cardiac arrhythmias generally occurs more quickly than syncope from other causes and may be more prolonged. Cardiac syncope may occur in any position, may occasionally be induced by exercise, and may occur in both congenital and acquired heart disease.

Although some patients experience palpitations during some arrhythmias, others are not aware of any cardiac-symptoms, The most common arrhythmias causing syncope are AV block, SA block, and paroxysmal supraventricular and ventricular tachyarrhythmias. *AV block* describes disturbances of conduction occurring in the AV conducting system, which include the AV node to the bundle of His and the Purkinje network. *SA block* describes a failure of consistent pacemaker function of the SA node. *Paroxysmal tachycardia* refers to a rapid heart rate secondary to an ectopic focus outside the SA node; this may be supraventricular or intraventricular,

Atrioventricular Block

AV block is probably the most common cause of arrhythmic cardiac syncope. The term *Stokes-Adams attack* describes disturbances of consciousness occurring in association with a complete AV block, which occurs primarily in elderly patients. The onset of a Stokes-Adams attack is generally sudden, although a number of visual, sensory, and perceptual premonitory symptoms may be experienced. During the syncopal attack, the pulse disappears and no heart sounds are audible. The patient is pale and, if standing, falls down, often with resultant injury. If the attack is sufficiently prolonged, respiration may be labored and urinary incontinence and clonic muscle jerks may occur. Prolonged confusion and neurological signs of cerebral ischemia may be present. Regain of consciousness is generally rapid.

The clinical features of complete AV block include a slow-collapsing pulse and elevation of the jugular venous pressure, sometimes with cannon waves. The firsr heart sound is of variable intensity, and heart sounds related to atrial contractions may be audible. The diagnosis is confirmed by ECG, which demonstrates the independence of atrial P waves and ventricular QRS complexes. During Stokes-Adams attacks, ECG recordings generally show ventricular standstill, but ventricular fibrillation or tachycardia may also occur.

Sinoatrial Block

SA block may result in dizziness, lightheadedness, and syncope. It is most frequent in rhe elderly. Palpitations are common, and the patient appears pale. Patients with SA node dysfunction frequently have other conduction disturbances, and certain drugs, such as verapamil, digoxin, and beta blockers, may further impair SA node function, On examination, the patient's pulse may be regular between attacks. During an attack, the pulse may be slow or irregular, and a number of rhythm disturbances may be present.

Paroxysmal Tachycardia

Supraventricular tachycardias include atrial fibrillation with a rapid ventricular response, atrial flutter, and Wo Iff-Park in son-White syndrome. These arrhythmias may suddenly reduce cardiac output enough to cause syncope.

Ventricular tachycardia or ventricular fibrillation may result in syncope if the heart rate is sufficiently fast and if the arrhythmia lasts longer than a few seconds. Patients are generally elderly and usually have evidence of underlying cardiac disease. Ventricular fibrillation may be part of long QT syndrome in association with congenital deafness in children. In most patients with long QT syndrome, episodes begin in the first decade of life, but onset may be much later. Exercise may precipitate an episode of cardiac syncope. Long QT syndrome may be acquired and may present in adults as epilepsy. Acquired causes include cardiac ischemia, mitral valve prolapse, myocarditis, and electrolyte disturbances (Ackerman 1998), as well as many drugs (Goldschlager et al. 2002). Brugada's syndrome may produce syncope as a result of ventricular tachycardia or ventricular fibrillation. The ECG demonstrates an incomplete right bundle branch block in leads V, and V_2 with ST-segment elevation in the right precordial leads (Goldschlager et al, 2003).

Reflex Cardiac Arrhythmias

A hypersensitive carotid sinus may be a cause of syncope in the elderly, mosr commonly in men. Syncope may result from a reflex sinus bradycardia, sinus arrest, or AV block; peripheral vasodilation with a decrease in arterial pressure; or from a combination of both. Although 10% of the population older than 60 years may have a hypersensitive carotid sinus, not all such patients experience syncope. Accordingly, this diagnosis should be considered only when the clinical history is compatible. Carotid sinus syncope may be initiated by a tight collar or by carotid sinus massage on clinical examination. When syncope occurs, the patient is usually upright and the duration of the loss of consciousness is generally a few minutes. When consciousness is regained, the patient is mentally clear. Unfortunately, there are no accepted diagnostic criteria for carotid sinus syncope, and the condition is overdiagnosed.

Syncope induced by unilateral carotid massage or compression may also be caused by partial occlusion, usually atherosclerotic, of the contralateral carotid or a vertebral artery, or it may be due to the release of atheromatous emboli. Because of these risks, carotid artery massage is no longer recommended. The rare syndrome of glossopharyngeal neuralgia is characterized by intense paroxysmal pain in the throat and neck and is accompanied by bradycardia or asystole, severe hypotension, and, if prolonged, seizures. Episodes of pain may be initiated by swallowing but also by chewing, speaking, laughing, coughing, shouting, sneezing, yawning, or talking. The episodes of pain always precede the loss of consciousness (see Chapter 75), Rarely, cardiac syncope may be due to bradyarrhythmias consequent to vagus nerve irritation caused by esophageal diverticula, tumors and aneurysms in the region of the carotid sinus, mediastinal masses, or gallbladder disease.

Decreased Cardiac Output

Syncope may occur as a result of a sudden and marked decrease in cardiac output. Both congenital and acquired conditions may be causal. Tetralogy of Fallot, the most common congenital malformation causing syncope, does so by producing hypoxia caused by right-to-left shunting.

Other congenital conditions associated with cyanotic heart disease may also cause syncope. Ischemic heart disease and myocardial infarction, aortic stenosis, idiopathic hypertrophic subaortic stenosis, pulmonary hypertension, and other causes of obstruction of pulmonary outflow, atrial myxoma, and cardiac tamponade may sufficiently impair cardiac output to cause syncope. Exercise-induced or effort syncope may occur in aortic or subaortic stenosis and other states in which there is reduced cardiac output and associated peripheral vasodilation induced by the exercise. Exercise-induced cardiac syncope may also be related to exercise-induced cardiac arrhythmias.

In patients with valvular heart disease, syncope may be related to arrhythmias. Syncope may also be due to reduced cardiac output secondary to myocardial failure, to mechanical prosthetic valve malfunction, or to thrombus formation. Mitral valve prolapse is generally a benign condition, but rarely cardiac arrhythmias can occur. The most significant arrhythmias are ventricular.

In atrial myxoma or with massive pulmonary embolism, a sudden decrease in left ventricular output may occur. In atrial myxoma, syncope is often positional and occurs when the tumor falls into the AV valve opening during a change in position of the patient, thereby causing obstruction of the left ventricular inflow.

Decreased cardiac output may also be secondary to conditions that result in inflow obstruction or reduced venous return. These include superior and inferior vena cava obstruction, tension pneumothorax, constrictive cardiomyopathies, constrictive pericarditis, and cardiac tamponade. Syncope associated with aottic dissection may he due to cardiac tamponade but may also be secondary to hypotension, obstruction of cerebral circulation, or a cardiac arrhythmia.

Hypovolemia

Acute blood loss, usually due to gastrointestinal tract bleeding, may cause weakness, faintness, and syncope if sufficient blood is lost. Blood volume depletion by dehydration may cause faintness and weakness, but true syncope is uncommon, unless the dehydration is combined with exercise.

Hypotension

A number of conditions cause syncope by producing a decrease in arterial pressure. The cardiac causes were already discussed. The common faint (designated variously as *vasovagal, vasodepressor, neurocardiogenic,* or *neuraliy mediated syncope)* is rhe most common cause of a transient decrease in blood pressure resulting in syncope (Grubb and Kanjwal 2003). It is often recurrent, tends to occur in relation to emotional stimuli, and may affect 20-25% of young people. Less commonly, it occurs in older patients with cardiovascular disease (Fenton et al. 2000).

The common faint may or may not be associated with bradycardia. The patient experiences impairment of consciousness, with loss of postural tone. Signs of autonomic hyperactivity are common, including pallor, diaphoresis, nausea, and dilated pupils. After recovery, patients may have persistent pallor, sweating, and nausea; if they get up too quickly, they may black out again. The common faint may he preceded by presyncopal symptoms of lethargy and fatigue, nausea, weakness, a sensation of an impending faint, and yawning. It is more likely to occur in certain circumstances, such as a hot crowded room, especially if the person is tired or hungry and upright or sitting. The episode of fainting may be brought on by venipuncture, the sight of blood, or a sudden painful or traumatic experience. When the patient regains consciousness, there usually is no confusion or headache, although weakness is commonly described. As in other causes of syncope, if the period of cerebral hypoperfusion is long enough, urinary incontinence and a few clonic movements may be observed (convulsive syncope).

Orthostatic syncope occurs when autonomic factors that compensate for the upright posture are inadequate. This can result from a variety of clinical disorders. Blood volume depletion or venous pooling may result in syncope when the individual assumes an upright posture. Orthostatic hypotension resulting in syncope may also occur with drugs that impair sympathetic nervous system function. Diuretics, antihypertensive medications, nitrates, arterial vasodilators, calcium-channel blockers, phenothiazincs, L-dopa, alcohol, and tricyclic antidepressants may all result in orthostatic hypotension.

Autonomic nervous sysrem dysfunction resulting in syncope caused by orthostatic hypotension may be a result of primary autonomic failute caused by Shy-Drager syndrome or Riley-Day syndrome. Neuropathies that affect the autonomic nervous system include those of diabetes mellitus, amyloidosis, Guillain-Barre syndrome, acquired immunodeficiency syndrome, chronic alcoholism, hepatic porphyria, and beriberi. Rarely, subacute combined degeneration, syringomyelia, and other spinal cord lesions may damage the descending sympathetic pathways, producing orthostatic hypotension.

Cerebrovascular Ischemia

Syncope may occasionally result from reduction of cerebral blood flow in either the carotid or the vertebrobasilar system. Most commonly, the underlying condition is atherosclerosis of the cerebral vessels, but reduction of cerebral blood flow resulting from cerebral embolism, mechanical factors in the neck (e.g., severe osteoarthritis), and arteritis (e.g., Takayasu's or cranial arteritis) may be responsible. In the subclavian steal syndrome, a very rare impairment of consciousness is associated with upper extremity exercise and resultant diversion of cerebral blood flow to the peripheral circulation. Occasionally,

cerebral vasospasm secondary to basilar migraine or subarachnoid hemorrhage may be responsible. Insufficiency of the cerebral circulation often causes other neurological symptoms, depending on the circulation involved.

Reduction in blood flow in the carotid circulation may lead to loss of consciousness, lightheadedness, giddiness, and a sensation of an impending faint. Reduction in blood flow in the vertebrobasilar system may also lead to loss of consciousness, but dizziness, lightheadedness, drop attacks without loss of consciousness, and bilateral motor and sensory symptoms are more common. Dizziness and lightheadedness alone, however, should not be considered symptoms of vertebrobasilar insufficiency. Syncope resulting from compression of the vertebral artery during certain head and neck movements may be associated with episodes of vertigo, disequilibrium, or drop attacks. Patients may describe blackouts when looking upward suddenly or when turning their heads quickly to one side. Generally, symptoms persist for several seconds after the movement stops.

In Takayasu's arteritis, there may be major occlusion of blood flow in the carotid and vertebrobasilar systems; in addition to fainting, other neurological symptoms are common. Pulsations in the neck and arm vessels are usually absent, and blood pressure in the arms is unobtainable. The syncopal episodes characteristically occur with mild or moderate exercise and with certain head movements.

Cerebtal vasospasm may result in syncope, particularly if the postetior circulation is involved. In basilar artery migraine, usually seen in young women and children, a variety of brainstem symptoms may also be experienced, and a pulsating headache is associated. The loss of consciousness is usually gradual, but a confusional state may last for hours (see Chapter 75).

Metabolic Disorders

A number of metabolic disturbances, including hypoglycemia, anoxia, and hyperventilation-induced alkalosis, may predispose to syncope, but usually only lightheadedness and dizziness ate experienced. The abruptness of onset of loss of consciousness depends on the acuteness and reversibility of the metabolic disturbances. Syncope caused by hypoglycemia generally develops gradually, The patient has a sensation of hunger; there may be a relationship to fasting, a history of diabetes mellitus, and a prompt response to ingestion of food. Symptoms are unrelated to posture but may be aggravated by exercise. During the syncopal attack, there is no significant change in blood pressure or pulse.

Anoxia may produce syncope because of the lack of oxygen or through the production of a vasodepressor type of syncope. Symptoms of lightheadedness are common, but true syncope is less common. Patients with underlying cardiac or pulmonary disease are susceptible. In patients with chronic anemia or certain hemoglobinopathies that impair oxygen transport, similar symptoms may occur. Syncopal symptoms may be more prominent with exercise or physical activity.

Hyperventilation-induced syncope usually has a psychogenic origin. During hyperventilation, the patient may experience paresthesia of the face, hands, and feet; a buzzing sensation in the head; lightheadedness; giddiness; blurring of vision; mouth dryness; and occasionally tetany. Patients often complain of tightness in the chest and a sense of panic. Symptoms can occur in the supine or erect positions and are gradual in onset. The symptoms of hyperventilation may be helped by having the patient rebreathc into a paper bag. During hyperventilation, a tachycardia may be present, but blood pressure generally remains normal.

Miscellaneous Causes of Syncope

In certain types of syncope, more than one mechanism may be responsible for the loss of consciousness. In the common faint, both vasodepressor and cardioinhibitory factors may be operational. In cardiac syncope, a reduction of cardiac output may be due to a single cause, such as obstruction to inflow or outflow or a cardiac arrhythmia, but multiple factors are common.

Cough or tussive syncope and micturition syncope are special cases of reflex syncope for which the mechanisms are poorly understood and probably multifactorial. In cough syncope, loss of consciousness occurs after a paroxysm of severe coughing. This is most likely to occur in obese men, usually smokers or patients with chronic bronchitis. The syncopal episodes occur suddenly, generally after repeated coughing but occasionally after a single cough. Before losing consciousness, the patient may feel lightheaded. The individual's face often becomes congested and then pale. Diaphoresis may be present, and there may be loss of muscle tone. Syncope is generally brief, lasting only seconds, and recovery is rapid. Several factors are probably operational in causing cough syncope. The most significant is blockage of venous return by raised intrathoracic pressure. In weight-lifting syncope, a similar mechanism is operational.

Micturition syncope most commonly occurs in men during or after micturition, usually after arising from bed to urinate in the erect position in the middle of the night. There may be a history of drinking alcohol before going to bed. The syncope may result from sudden reflex peripheral vasodilation caused by the release of intravesicular pressure and bradycardia. The relative peripheral vasodilation from recent alcohol use and a supine sleeping position arc contributory because blood pressure is lowest in the middle of the night. The syncopal propensity may increase with fever. Rarely, micturition syncope with headache may result from a pheochromocytoma in the bladder wall.

Defecation syncope is uncommon, hut it probably shares the underlying pathophysiological mechanisms responsible for micturition syncope. Convulsive syncope is an episode of syncope of any etiology, sufficiently prolonged to result in a few clonic jerks; the other features arc typically syncopal and should not be confused with epileptic seizures.

Investigations of Patients **with** Syncope

In the investigation of the patient with episodic impairment of consciousness, the diagnostic tests performed depend on the initial differential diagnosis (Kapoor 2002). Investigations should be individualized, but some, such as measurement of the hematocrit and blood glucose levels, as well as ECG recordings, are indicated in most patients. A resting ECG recording may reveal an abnormality of cardiac rhythm or the presence of underlying ischemic or congenital heart disease. In the patient suspected of cardiac syncope, a chest x-ray film may show evidence of cardiac hypertrophy, valvular heart disease, or pulmonary hypertension. Other noninvasive investigations include radionuclcotide catdiac scanning, echocardiography, and prolonged I lolrer monitoring for the detection of cardiac arrhythmias. Echocardiography is useful in the diagnosis of valvular heart disease, cardiomyopathy, atrial myxoma, prosthetic valve dysfunction, pericardial effusion, aortic dissection, and congenital heart disease. Holter monitoring detects twice as many ECG abnormalities as a routine ECG and may detect an arrhythmia at the time of a syncopal episode, 1 lolrer monimi'ing is commonly performed for 24 hours, although longer periods of recording may be required. Continuous loop recordings may be used in long-term monitoring and may be useful in a small number of patients (Krahn et al. 1999).

Exercise testing and electrophysiological studies are carried out in a select group of patients. Exercise testing may be useful in detecting coronary artery disease, and exercise-related syncopal recordings may help localize the site of conduction disturbances. Tilt testing may be useful in the evaluation of patients with syncope of unknown origin, although false-positive results occur. Tilt testing commonly employs pharmacological agents such as nitroglycerin or isoproterenol. The specificity of tilt-table testing is approximately 90%.

In patients suspected of syncope from cerebrovascular causes, noninvasive diagnostic studies, including Doppler flow studies of the cerebral vessels and magnetic resonance imaging (MRI) or magnetic resonance angiography, may provide useful information. Occasionally, cerebral angiography may be indicated. Electroencephalography (EEG) is useful in differentiating syncope from epileptic seizure disorders. An EEG should be obtained only when a seizure disorder is suspected.

Despite multiple investigations, in approximately 37% of patients, the cause is unknown (Soteriades ct al. 2002),

SEIZURES

Sudden, unexplained loss of consciousness in a child or adult may be caused by an epileptic seizure, which must be distinguished from syncope. An epileptic seizure is defined as a transient neurological dysfunction resulting from an excessive abnormal electrical discharge of cerebral neurons. The clinical manifestations are numerous, including disturbances of consciousness, changes in emotions, changes in sensation, abnormal movements, and changes in visceral functions or behavior. Epileptic seizures may be classified according to clinical manifestations and EEG findings (Chaptet 73). This section discusses only seizures associated with an alteration of consciousness. Both generalized seizures (absence and tonic-clonic) and complex partial seizures have alteration of consciousness as part of their clinical manifestations. Atonic seizures usually present as drop attacks and loss of consciousness is extremely brief. In most patients, a correct diagnosis can be made on the basis of the history, physical examination, and EEG findings.

History and Physical Examination

The most definitive way to diagnose epilepsy and the type of seizure is clinical observation of the seizure, although this is often not possible, except when seizures are frequent. The history of an episode, as obtained from the patient and an observer, is of paramount importance. The neurologist should obtain a family history and should inquire about birth complications, central nervous system infection, head trauma, and previous febrile seizures, because they may all have relevance.

The neurologist should obtain a complete description of the episode and should inquire about any warning before the event, possible precipitating factors, and other neurological symptoms that may suggest an underlying structutal cause. Important considerations are the age at onset, frequency, and diurnal variation of the events. Seizures are generally brief and have stereotyped patterns, as desctibed previously. With complex partial seizures and tonic-clonic seizures, a period of postictal confusion is highly characteristic. Unlike some types of syncope, seizures are unrelated to posture and generally last longer. In a tonic-clonic seizure, cyanosis is often present, pallor is uncommon, and breathing may be stertorous.

Absence seizures have onset between ages 5 and 15 years in most patients, and a family history of seizures is present in 20-40% of patients. Tonic-clonic and complex partial seizures may begin at any age from infancy to late adulthood, although infants may not demonstrate the typical features because of incomplete development of the nervous system.

The neurological examination may reveal an underlying structural disturbance responsible for the seizure disorder. Birth-related trauma may result in asymmetries of physical

development; cranial bruits may indicate an arteriovenous malformation; and space-occupying lesions may result in papilledema or in focal motor, sensory, or reflex signs. In the pediatric age-group, mental retardation may be found in association with birth injury or metabolic defects. The skin should be examined for abnormal pigment changes and other dysmorphic features characteristic of some of the neurodegenerative disorders.

If absence seizures are suspected, the diagnosis can often be made in the office by having the patient hyperventilate for *$-4* minutes, which often induces an absence seizure. If the patient is examined immediately after a suspected tonic-clonic seizure, the neurologist should search for abnormal signs, such as focal motor weakness and reflex asymmetry, and for pathological reflexes, such as Babinski's sign. These may help to confirm that the attack was a seizure and suggest a possible lateralization or location of the seizure focus.

Absence Seizures

The absence seizure is a well-defined clinical and EEG event. The essential feature is an abrupt, brief episode of decreased awareness without any warning, aura, or postictal symptoms. At the onset of the absence seizure, there is an interruption of activity. A simple absence seizure is characterized only by an alteration of consciousness. A complex absence seizure is characterized by an alteration of consciousness and other signs, such as minor motor automatisms. During a simple absence seizure, the patient remains immobile, breathing is normal, no color changes are observed, there is no loss of postural tone, and there are no motor manifestations. After the seizure, the patient immediately resumes the previous activities and may be unaware of the attack. An absence seizure generally lasts 10-15 seconds, but it may be shorter or as long as 40 seconds.

Complex absence seizures have additional manifestations, such as diminution of postural tone, which may cause the patient to fall; an increase in postural tone; minor clonic movements of the face or extremities; minor face or extremity automatisms; or autonomic phenomena, such as pallor, flushing, tachycardia, piloerection, mydriasis, or urinary incontinence.

Tonic-CIonic Seizures

The tonic-clonic seizure is the most dramatic manifestation of epilepsy and is characterized by motor activity and loss of consciousness. Tonic-clonic seizures may be the only manifestation of epilepsy or may be associated with other seizure types. In a primary generalized tonic-clonic seizure, the patient generally has no warning or aura, although some patients may experience a few myoclonic jerks. The seizure begins with a tonic phase, during which there is sustained muscle contraction lasting 10-20 seconds. This phase is followed by a clonic phase that lasts approximately 30 seconds and is characterized by recurrent muscle contractions. During a tonic-clonic seizure, a number of autonomic changes may be present, including an increase in blood pressure and heart rate, apnea, mydriasis, urinary or fecal incontinence, piloerection, cyanosis, and diaphoresis. Injury may result from a fall or tongue biting. In the postictal period, consciousness is regained slowly. The patient may remain lethargic and confused for a variable period. Pathological reflexes may be elicited.

Some generalized motor seizures with transient alteration of consciousness may have only tonic or only clonic components. Tonic seizures consist of an increase in muscle tone, and the alteration of consciousness is generally brief. Clonic seizures are characterized by a brief impairment of consciousness and bilateral clonic movements. Recovery may be rapid, but if the seizure is more prolonged, a postictal period of confusion may be noted.

Complex Partial Seizures

In a complex partial seizure, the first seizure manifestation may be an alteration of consciousness, but the patient commonly experiences an aura or warning. The seizure may have a simple partial onset, which may include motor, sensory, visceral, or psychic symptoms. The patient may initially experience hallucinations or illusions; affective symptoms, such as fear or depression; cognitive symptoms, such as a sense of depersonalization or unreality; or aphasia.

The complex partial seizure generally lasts 1-3 minutes but may be shorter or longer. A complex partial seizure may become generalized and evolve into a tonic-clonic convulsion. During a complex partial seizure, automatisms, generally more complex than those in absence seizures, may be noted. The automatisms could involve continuation of the patient's activity before the onset of the seizure, or they may be new motor acts. The automatisms are varied but frequently consist of chewing or swallowing movements, lip smacking, grimacing, or automatisms of the extremities, including fumbling with objects, walking, or trying to stand up. Rarely, patients with complex partial seizures have drop attacks and the term *temporal lobe syncope* is often used. The duration of the postictal period after a complex partial seizure is variable, with a gradual return to normal consciousness and normal response to external stimuli. Table 2,3 provides a comparison of absence seizures and complex partial seizures.

Investigations of Seizures

In the initial investigations of the patient with tonic-clonic seizures or complex partial seizures, a complete blood cell count, urinalysis, biochemical screening, blood glucose

Tabic 2.3: Comparison of absence and complex partial seizures

Feature	*Absence seizure*	*Complex partial seizure*
Age at onset	Childhood or adolescence	Any age
Aura or warning	No	Common
Onset	Abrupt	Gradual
Duration	Seconds	Up to minutes
Automatisms	Simple	Mure complex
Provocation by hyperventilation	Common	Uncommon
Termination	Abrupt	Gradual
Frequency	Possibly multiple seizures per day	Occasional
Postictal phase	No	Confusion, fatigue
KkvtrovncephalogtMm	Generalized spike and wave	Focal epileptic discharges or nonspecific lesions
Ncuroimaging	Usually normal	May demonstrate focal lesions

level, serum calcium concentration, and serological test fot syphilis should be obtained. Laboratory investigations generally are not helpful in establishing a diagnosis of absence seizures. In infants and children, biochemical screening for amino acid disorders should be considered.

MRI is the imaging modality of choice for the investigation of patients with suspected seizures. It is superior to computed tomographic scanning and increases the yield of focal structural disturbances. MRI can reveal tumors, cerebral atrophy, hydrocephalus, cerebral hemorrhage, infarction, subdural hematoma, cystic lesions, and vascular malformations. Although childten with absence seizures may have some abnormalities on MRI, this procedure is generally not required for diagnosis or management.

Cerebrospinal fluid (CSF) examination is not necessary in every patient with a seizure disotder and should be reserved for the patient whose recent seizure may be related to an acute central nervous system infection.

The role of the EFLG is to provide laboratory support for a clinical impression and to help classify the type of seizure. Epilepsy is a clinical diagnosis; therefore, EEG cannot produce a diagnosis with certainty unless the patient has a clinical event during the recording. A normal EEG does not exclude epilepsy, and minot nonspecific abnormalities do not confirm epilepsy. Some patients with clinically documented seizures show no abnormality even after serial EF.G recordings, sleep recordings, and special activation techniques. The EEG is most often helpful in the diagnosis of absence seizures. EEG evaluation can be supplemented with simultaneous video monitoring for the documentation of ictal events, allowing for a strict correlation between EEG changes and clinical manifestations. Simultaneous EEG and video monitoring is also useful in distinguishing epileptic seizures from noncpileptic phenomena.

Although an accurate diagnosis can be made in most patients on the basis of the clinical history and the foregoing investigations, some patients ptesent a diagnostic dilemma. A 24-hour ambulatory EEG recording can make more definite a diagnosis of an epileptic seizure rather than nonepileptic phenomena or a clearer classification of the specific type of seizure.

Psychogenic Seizures or Pseudoseizures (Noncpileptic Seizures)

Pscudoepileptic seizutes are paroxysmal episodes of altered behavior that superficially resemble epileptic seizures but lack the expected EEG epileptic changes (Ettinger et al. 1999). However, approximately 40% of patients with pscudoepileptic or nonepileptic seizures also experience true epileptic seizures.

A diagnosis is often difficult to establish based on initial history alone (Devinsky 1998). Often, a correct diagnosis can be made only after witnessing the patient's clinical episodes. Noncpileptic seizures occur in children and adults and are more common in females. Most commonly, they superficially resemble tonic-clonic seizures. They generally are abrupt in onset, occur in the presence of othct people, and do not occur during sleep. Motor activity is uncoordinated, but urinary incontinence is rare, and physical injury is uncommon. They tend to be more prolonged than true tonic-clonic seizures. Pelvic thrusting is often a manifestation of pseudoseizures. During and immediately after the seizure, the patient may not respond to verbal or painful stimuli. Cyanosis is not observed. Postictally, there are no focal neurological signs or pathological reflexes.

In the patient with known epilepsy, the diagnosis of nonepileptic seizures should be considered when previously controlled seizures become medically refractory. For the diagnosis of nonepileptic seizures, the patient should have a psychological assessment because the majority of such patients have other psychiatric disturbances. In this patient group, there is a high frequency of hysteria, depression, and personality disturbances. At times, a sccondaty gain can be identified. In some patients with psychogenic seizures, the clinical episodes can frequently be precipitated by suggestion and by certain clinical tests, such as hyperventilation, photic stimulation, intravenous saline infusion or tactile (vibration) stimulation, or pinching the nose to induce apnea. It is important to keep in mind that hyperventilation and photic stimulation may also induce true epileptic seizures, but their clinical features arc usually distinctive. Some physicians avoid the use of placebo

Table 2.4: Comparison of psychogenic and epileptic seizures

Feature	*Psychogenic seizure*	*Epileptic seizure*
Stereotypy of attack	May be variable	Usually stereotyped
Duration	May be prolonged	Brief
Diurnal variation	Daytime	Nocturnal or daytime
Injury	Rare	Can occur with tonic-clonic seizures
Tongue biting	Rare	Can occur with tonic-clonic seizures
Urinary incontinence	Rare	Common
Motor activity	Prolonged, uncoordinated; pelvic thrusting	Automatisms or coordinated tonic-clonic seizures
Postictal confusion	Rare	Common
Relation to medication changes	Unrelated	Usually related
Interictal KEG	Normal	Frequently abnormal
Ictal EEG	Normal	Abnormal
Presence of secondary gain	Common	Uncommon
Psychiatric disturbances	Common	Uncommon

EEG = electroencephalogram,

procedures because of the possibility that the patient may feel tricked and this could have an adverse effect on the doc tor-patient relationship (Parra et al. 1998).

The interictal EEG in patients with pseu do seizures is normal and remains normal during the clinical episode, demonstrating no evidence of a cerebral dysrhythmia. With the introduction of long-term ambulatory KEG monitoring, the episodic behavior of a patient can be correlated with EEG recordings; thus psychogenic seizures can be distinguished from true epileptic seizures. Table 2.4 compares the features of psychogenic seizures wirh those of epileptic seizures.

As an auxiliary investigation of suspected psychogenic seizures, plasma prolactin concentrations may provide additional supportive data. Plasma prolactin concentrations are commonly elevated after tonic-clonic seizures and less frequently after complex partial seizures. Serum prolactin levels are almost invatiably normal after psychogenic seizures, although such a finding does not exclude the diagnosis of true epileptic seizures. Elevated prolactin levels, however, may also be present after syncope and with the use of drugs such as antidepressants, estrogens, bromocriptine, ergots, phenothiazines, antiepileptic drugs, and others.

Miscellaneous Causes of Altered Consciousness

In children, alteration of consciousness may accompany breath-holding spells (see Chapter 55B) and metabolic disturbances (see Chapter 68), Breath-holding spells must be distinguished from epilepsy. Most spells start at 6-28 months of age, but they may occur as early as the first month of life; they usually disappear by 5 or 6 years of age. Breath-holding spells may occur several times per day and may manifest cither cyanosis or pallor. In cyanotic breath-holding spells, loss of consciousness is triggered by a sudden injury or fright, anger, or frustration. The child is initially provoked, cries vigorously for a few breaths, and then holds his or her breath in expiration, whereon cyanosis develops. Consciousness is lost because of hypoxia. Although stiffening, a few clonic movements, and urinary incontinence are occasionally observed, these episodes can be clearly distinguished from epileptic seizures on the basis of the history of provocation and by noting that the apnea and cyanosis occur before any alteration of consciousness. In these children, the neurological examination and EEG recordings are normal. Pallid breath-holding episodes are generally provoked by a mild painful injury or a startle. The infant cries initially, then becomes pale and loses consciousness. As in the cyanotic type, stiffening, clonic movements, and urinary incontinence may occur. In the pallid infant syndrome, loss of consciousness is secondary to excessive vagal tone, resulting in bradycardia and subsequent cerebral ischemia, similar to a vasovagal attack.

A number of pediatric metabolic disorders may have clinical manifestations of alterations of consciousness, lethargy, or seizures (see Chapter 68), These include disorders of amino acid metabolism, such as phenylketonuria, Hartnup disease, and maple syrup urine disease; the various disorders of the urea cycle; and miscellaneous metabolic disorders, such as hyperglycinemia and disorders of pyruvate metabolism. Neurological abnormalities in these patients may be seen at birth or later in infancy and childhood. Metabolic screening of urine and blood should be considered in an infant who presents with neurological disorders early in life; these include examination of the urine for the detection of aminoaciduria, excess urinary ketones, and urea excretion. Biochemical screening of the serum should also be considered for the infant or child who presents with transienr lethargy, apneic episodes, syncope, or seizures.

Increased intracranial pressure may result from a number of causes, including periodic obsttuction of the circulation of CSF, as in aqueductal stenosis or colloid cyst of the third ventricle. These patients are subject to paroxysmal increases of intracranial pressure rhat may last up to

20 minutes. These episodes may occur spontaneously or may be related to postural changes or Valsalva's maneuver. If sufficient to impair cerebral perfusion, the plateau waves of Lundberg may result in sudden, severe headaches, which may be followed by loss of consciousness. Occasionally, this is accompanied by opisthotonos and clonic movements. In intermittent obstruction of CSF circulation, leg buckling and atonic episodes may occur with changes in head position. Tinnitus is a common accompanying symptom.

Syringomyelia of the cervical spine, often associated with a Chiari malformation (see Chapter 79), is occasionally associated with repeated episodes of syncope in children and adults {Woelfle et al. 1998).

In the patient who presents with an apparent loss of consciousness, the neurologist must also consider the possibility of malingering or some other underlying psychogenic cause. However, it is always important to exclude organic causes first. The neurologist should also distinguish sleep disorders, such as cataplexy and other causes of drop attacks, from alterations of consciousness. These nonsyncopal spells include drop attacks of the elderly, narcolepsy, systemic mastocytosis, carcinoid syndrome, and pheochromocytoma. Systemic mastocytosis, carcinoid syndrome, and pheochromocytoma may also cause true syncope secondary to rapid changes in blood pressure.

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Chapter 3
Falls and Drop Attacks

Bernd F. Remler and Robert B. Daroff

Everyone occasionally loses balance and, infrequently, falls. When falls occur repeatedly or without a prior sense of imbalance, the patient may have a neurological problem. Various disease states and neurological impairments cause falls and drop attacks. Associated loss of consciousness implies syncope or seizures (see Chapter 2). Transient ischemic attacks (TIAs) in the posterior circulation or the anterior cerebral artery distribution can cause monosymptomatic drops. Third-ventricular or posterior fossa tumors may also be associated with abrupt drops. Patients with lower-extremity weakness, spasticity, rigidity, sensory loss, or ataxia frequently fall. Narcoleptics experience cataplexy, and patients with Meniere's disease occasionally fall as a result of otolithic dysfunction. Middle-aged women may fall with no discernible cause. Finally, the elderly, with their inevitable infirmities, fall frequently. These associations permit a classification of falls and drop attacks, as presented in Table 3.1, We use the words *falls* and *drops* interchangeably. The term *drop attacks,* on the other hand, describes sudden falls occurring without warning, that are primarily due to intracranial causes, such as midline tumors and transient ischemic attacks. Seizures and vestibular disorders arc much less common causes of drop attacks.

The medical history is essential in evaluating patients with falls and drop attacks. The situational and environmental circumstances of the event must be ascertained. On the basis of the causes listed in Table 3.1, basic questions must be asked of the patient or witnesses. Did the patient lose consciousness? If so, for how long? Did lightheadedness or palpitations precede the event? Is there a history of a seizure disorder? Were there previous symptoms suggestive of TIAs? Does the patient have headaches? Are there symptoms of distal sensory loss, limb weakness, or stiffness? Has the patient had excessive daytime sleepiness, and are the falls precipitated by strong emotions, such as elation or laughter? Is there a history of visual impairment, hearing loss, vertigo, or tinnitus? Given the tendency for middle-aged women and the elderly to fall, the patient's age and gender are imporranr to the evaluation.

The neurological examination is particularly relevant in ascertaining that falling might be related to disorders of the central or peripheral nervous system. Does the patient have motor or sensory deficits in the lower limbs; the rigidity and tremor of Parkinson's disease (PD); the ophthalmoparesis of progressive supranuclear palsy (PSP); ataxia, spasticity, or other signs compatible with multiple sclerosis? Patients with normal neurological examinations and no history of associated neurological or cardiac symptoms present a special challenge. If the falling is recurrent, magnetic resonance imaging (MRI) should be considered to rule out an otherwise silent midline cerebral neoplasm or malformation. Patients who frequently experience near-falls without injuries may have a psychogenic disorder of station and gait.

LOSS OF CONSCIOUSNESS

Syncope

The manifestations and causes of syncope are described in Chapter *2,* Severe ventricular arrhythmias and hypotension lead to cephalic ischemia, loss of consciousness, and falling. If there is a sudden third-degree heart block (Stokes-Adams attack), the patient loses consciousness and falls without warning. Less severe causes of decreased cardiac output, such as bradyarrhythmias or tachyarrhythmias, are associated with a prodromal sensation of faintness before the

Table 3.1: Causes and types of falls and drops

LIBS ot consciousness
Syncope
Seizures
Transient ischemic attacks (drop attacks)
Vertebrobasilar
Anteriot cerebral
Third ventricular and posterior fossa tumors (drop attacks)
Motor and sensory impairment of lower limbs
Basal ganglia disorders
Parkinson's disease
Progressive supranuclear palsy
Neuromuscular disorders (myopathy and neuropathy)
Myelopathy
Cerebral or cerebellar disorders
Cataplexy
Vestibular disorders
Cryptogenic falls in middle-aged women
Aged state

loss of consciousness. Elderly patients with cardioinhibitory ("sick") sinus syndrome, however, often describe dizziness and falling, rather than faintness (Kapoor 2000). Orthostatic hypotension conveys a markedly increased risk of falling in the elderly and confounds other factors contributing to falls. Hypotension is almost always associated with a presyncopal syndrome of progressive lightheadedness, faintness, dimming of vision, and rubbery legs before consciousness is lost. Orthostatic hypotension is particularly problematic in the frail elderly, who have many other risk factors for falling (Heitterachi et al. 2002) (see The Aged State, later in this chapter).

Seizures

Epileptic drop attacks are caused by asymmetrical tonic contractions of limb and axial muscles, loss of tone of postural muscles (Tinuper et al. 1998), and seizure-related cardiac arrhythmias. The arrhythmias mimic cardiogenic syncope and, like temporal lobe drop attacks, are typically associated with a period of altered consciousness after the drop. Video-EEG monitoring of epileptic patients with a history of falls permits the characterization of the various motor phenomena that cause loss of posture. For the clinician, however, the precise nature of these events is less important than establishing a diagnosis of seizures. This is often simple in patients with long-standing epilepsy, but falls in patients with poststroke hemiparesis may be falsely attributed to motor weakness rather than to new-onset seizures. Further confusion may result from the difficulties involved in differentiating the destabilizing extensor spasms of spasticity from focal seizures. Epileptic drop attacks in young patients with severe childhood epilepsies may respond favorably to callosotomy (Maehare and Shimizu 2001). Falling as a consequence of the tonic axial component of startle-induced seizures may be controllable with lamotriginc (Faught 1999). Paradoxically, some antiseizure drugs can precipitate drop attacks, such as carbamazepine in Rolandic epilepsy (Genton 2000).

Transient Ischemic Attacks

Drop attacks secondary to TIAs arc sudden falls occurring without warning or obvious explanation (e.g., tripping). There is no, or only momentary, loss of consciousness; the sensorium and lower-limb strength arc intact immediately or shortly after the patient hits the ground. The neurological examination should not reveal lower-limb motor or sensory dysfunction between episodes. If such abnormalities are present, it can be impossible to distinguish drop attacks from the falls associated with sensorimotor impairment of the lower limbs. The vascular distributions of drop attacks from TIAs are the posterior circulation and the anterior cerebral arteries.

Vertebrobasilar Insufficiency

Drop attacks caused by posterior circulation insufficiency result from transient ischemia to the corticospinal tracts or the paramedian reticular formation. They are rarely an isolated symptom of vertebrobasilar insufficiency because most patients have a history of TIAs, including the more common symptoms of vertigo, diplopia, ataxia, weakness, and hemisensory loss. Occasionally, a drop attack may herald progressive thrombosis of the basilar artery, hours before major and permanent neurological signs evolve.

Anterior Cerebral Artery Ischemia

Anterior cerebral artery ischemia causes drop attacks by impairing perfusion of the parasagittal prcmotor and motor cortex controlling the lower extremities. Derivation of both anterior cerebral arteries from the same internal carotid artery—a common vascular variant, with an approximate frequency of 20%—anatomically predisposes to this syndrome. In such patients, an embolus may lodge in the single anterior cerebral artery root and produce bilateral parasagittal ischemia with a consequent drop attack.

Third Ventricular and Posterior Fossa Tumors

Drop attacks can be manifestations of colloid cysts of the third ventricle or mass lesions within the posterior fossa. With colloid cysts, unprovoked falling is the second most common symptom, after position-induced headaches. This history may be the only clinical clue to the diagnosis because the neurological examination may be entirely normal. Abrupt neck flexion may precipitate drop attacks in

otherwise asymptomatic patients who are harboring posterior fossa tumors. Drop attacks occur in 2-3% of patients with Chiari malformations (Ziegler and Mallonce 1999). Drops induced by rapid head turning were considered pathognomonic of cysticercosis of the fourth ventricle in the early 20th century (Brun's sign). Other intracranial mass lesions, such as parasagittal meningiomas, foramen magnum tumors, or subdural hematomas, are usually associated with baseline abnormalities of gait and motor functions, and falling occurs consequent to these impairments (see Table 3.1) tather than to true drop attacks.

MOTOR AND SENSORY IMPAIRMENT OF THE LOWER LIMBS

A wide variety of neurological disorders impair motor functions, coordination, and balance. Such conditions are frequent causes of falls.

Disorders of the Basal Ganglia

Parkinson's Disease

Patients with PD frequently fall. Aggravating risk factors include previous falls, demenria, disease duration, benzodiazepine use, and poor performance on the Romberg test (Wood et al. 2002). Although many patients with PD have postural instability and often fall backward, the office testing of retropulsion is not reliable in predicting falls (Bloem et al. 2001), Patients with PD may also, without warning, drop directly to the ground. This is most commonly related to dopamine-induced motor fluctuations, particularly peak-dose dyskinesias and off periods (see Chapter 77). PD is also associated with a forward-flexed posture that diminishes the ability of patients to compensate for further shifts of the center of gravity. In particular, muscular rigidity and bradykinesia prevent rapid muscle activation and weight shifts when balance is offset,

Progressive Supranuclear Palsy

Patients with PSP (see Chapter 77) are characterized by parkinsonian features, axial rigidity, nuchal dystonia, spasticity, and ophthalmoparesis. They are more likely to fall backward than PD patients, even with equivalent functional impairment. Furthermore, loss of downgaze impairs their ability to avoid obstacles during ambulation. Idiopathic rapid eye movement sleep behavior disorder (sec Chapter 74) is a precursor of PSP as well as a cause of nocturnal falls in the elderly (Morfis er al. 1997). Clonazepam is usually effective in the treatment of this parasomnia and provides reliable prophylaxis for the associated falls.

Similar mechanisms to those described with PD and PSP contribute to falls in patients with related neurodegenerative disorders causing parkinsonism. Recurrent falls are a prominent feature of diffuse Lewy body disease (Imamura et al. 1999), multiple system atrophy, the pure akinesia syndrome, and cortical-basal ganglionic degeneration (sec Chapter 77).

NEUROMUSCULAR DISORDERS (MYOPATHY AND NEUROPATHY)

Myopathies characteristically involve proximal muscles and increase the tendency to fall. The multiple causes of myopathy and neuropathy (genetically determined or acquired) arc discussed in Chapters 82 and 85. Most neuropathies arc mixed (i.e., motor and sensory) in type, Regatdless of cause, neuropathies predispose the patient to falling because of lower-limb weakness and impaired afferent sensations from feet, joints, and muscles. Sensory neuropathies delay or reduce the relay of sensory signals from the lower limbs and promote falling when postural imbalance occurs. Falling may herald the onset of acute polyneuropathies, such as Guillain-Barre syndrome. Polio survivors, who are now reaching middle age and older, have a high annual frequency of falling that may exceed 60% (Silver and Aiello 2002!.

Myelopathy

Patients with spinal cord disease (see Chapter 27) are at *a* particularly high risk of falling because all descending motor and ascending sensory tracts traverse the cord. Aside from weakness, spasticity, and impaired sensory input from the lower limbs, there is disruption of vestibulospinal and cerebellar pathways. This precludes adequate corrections for sudden shifts in the center of gravity,

CEREBRAL OR CEREBELLAR DISORDERS

Motor, sensory, vestibular, and cerebellar dysfunction occur in isolation, or in any combination, in patients with central nervous system disease. Patients with acute basal ganglia lesions may show a slow, contralateral, tilting movement, causing falls. Strokes, as would be expected, increase the subsequent fall risk at least twofold. Right hemispheric stroke location, depression, and reduced arm function put these patients at particularly high risk (Jorgensen et al. 2002; Ugur et al. 2000). Metabolic encephalopathies cause characteristic transienr loss of the postural tone (asterixis). If this is extensive and involves the axial musculature, episodic loss of the uptight posture can mimic drop attacks in chronic uremic patients. Cerebellar disease causes gait ataxia, a prime cause of postural instability and falling. Moreover, patients with degenerative (see Chapter 78) or demyelinating (see Chapter 60)

cerebellar disease often have coexisting brainstem, spinal cord, or cerebral involvement.

Cataplexy

Cataplexy, the sudden loss of lower-limb tone, is a part of the tetrad of narcolepsy that also includes excessive daytime sleepiness, hypnagogic hallucinations, and sleep paralysis (see Chapter 74). Consciousness is preserved during a cataplectic attack, which varies from slight lower-limb weakness to complete flaccid paralysis and abrupt falling. Once on the ground, the patient is unable to move but continues breathing. The attacks usually last less than 1 minute and only rarely exceed several minutes. Cataplectic attacks are provoked by laughter, anger, surprise, and startle. Occasionally, they interrupt or follow sexual orgasm. During the attack, there is electromyographic silence in antigravity muscles, and deep tendon reflexes and the H-reflex (see Chapter 36B) cannot be elicited. Cataplexy occurs in the absence of narcolepsy when associated with cerebral disease (symptomatic cataplexy), as in Nicmann-Pick disease, Nome's disease, or brainstem lesions. It may occur rarely as an isolated problem in normal individuals, which may be familial (Aldrich 1998). A liquid formulation of gamma hydroxybutyrate (sodium oxybatc), an agent infamous for **its** use in date rape, is available for the treatment of cataplexy.

Vestibular Disorders (Otolithic Crisis)

During attacks of vertigo, patients often lose balance and fall. In contrast, Meniere's disease (see Chapter 18) may be complicated by drop attacks unassodated with preceding or accompanying vertigo (Tumarkm's otolithic crisis) (Kentala et al. 2001; Ishiyama et al. 2001). Presumably, stimulation of otolithic receptors in the saccule triggers inappropriate reflex postural adjustments, via vestibulospinal pathways, leading to the falls. The patients, without warning, feel as if they are being thrown to the ground. They may fall straight down or be propelled in any direction. Indeed, one of the authors (RBD) had a patient who suddenly saw and felt her legs moving forward in front of her as she did a spontaneous back-flip secondary to an otolithic crisis. This condition occurs only in patients with Meniere's disease.

CRYPTOGENIC FALLS IN MIDDLE-AGED WOMEN

Enigmatically, women older than 40 years of age have a tendency to fall. The fall is usually forward and occurs, without warning, while walking. There is no loss of consciousness, dizziness, or even a sense of imbalance. The patients are convinced that they have not tripped but that their legs suddenly gave way. As soon as they get to their feet, walking continues normally. It occurs in more than 3% of women; the disorder develops in 75% of these women after the age of 40. Twenty percent have at least one close relative (mother, aunt, or sister) with the condition. The falling frequency is quite variable. Most patients fall between 2 and 12 times per year. Only one fourth fall more than once per month or have clusters of frequent falls with prolonged asymptomatic intervals. Rarely, head trauma and significant intracranial injury results. Causal factors for this strictly female condition have been elusive. Footwear, specifically high heels, is not the cause. Occasional patients date the onset of the disorder to early in a pregnancy, before abdominal distention would be expected to **alter** postural stability. When falls begin during pregnancy, the women invariably continue falling even after delivery. The perimenstrual period makes some women with this condition more vulnerable. There is no relationship between falling and body weight. The most reasonable explanatory postulate is a prolonged long-loop (transcortical) reflex in women that delays the generation of sufficient quadriceps tension to decelerate a falling trunk.

The diagnosis is made in a middle-aged woman with inexplicable falls, a normal neurological examination, and no evidence of any other known cause of falling (see Table 3.1). There is no available pharmacological therapy. All that can be done is to reassure the patient and prevent injury by using protective knee and elbow padding. Some women, fearing falls, can become agoraphobic and should be treated with behavioral intervention,

THE AGED STATE

Most patients presenting to neurologists with a chief complaint of falling are elderly and chronically impaired. As the chance of falling increases with age, so does the severity of injury and the number of chronic disabilities predisposing to falls (Tideiksaar and **Fillit** 1997). Next to fractures, falls are the single most disabling condition leading to nursing home admission. As would be expected, elderly in sheltered accommodations have the highest frequency of falls; this may affect up to 50%. Many of these patients fall repeatedly, with elderly women bearing the highest risk. In the very old, falls constitute the leading source of injury-related deaths. This, and estimated annual health care expenditures of $20 billion for the consequences of falls, underscores their significance as a major health problem (KannuS et al. 1999).

The normal aging process is associated with a decline in multiple physiological functions that diminish the ability to compensate for external stressors that challenge the upright posture. Decreased proprioception, loss of muscle bulk (Pavol et al. 2002), arthritis of the knee and ankle joints, cardiovascular disturbances (Kario et al. 2001), deteriorating vision and ocular motor functions (Di **Fabio** et al,

2002), cognitive impairment, and failing postural reflexes (prcsbyastasis) summate and increase the risk of falling. Even the healthy elderly have a pronounced age-related decline in the ability to compensate for simulated forward falling. White matter abnormalities on brain MRIs correlate with postural instability and mobility impairment in the elderly (Kwa et al. 1998; Benson et al. 2002).

Some elderly individuals without a discernible neurological disorder lose their ability to restitute when their center of gravity is displaced backward. They retropulsc when gently pushed in the chest, and sometimes fall back when simply asked to stand up straight. They may adapt a compensatory tendency to stoop forward when upright, and walk cautiously, with a wide base and short steps.

Most of the falling elderly have one or, more commonly, several pathological predisposing conditions, and the chance of falling increases markedly with the number of identified risk factors (Tinctti 2003). In predisposed patients, a large proportion of these falls is accidental, reflecting an interaction between a debilitated patient and potential environmental hazards. This is in contrast to endogenous falls related to loss of consciousness, which are less frequent. Among tin[1] important conditions associated with tails arc dementia, metaholic and toxic encephalopathies, depression, arthritis (Tinetti 2003), cerebral infarcts, parkinsonism, neuropathy, and gait disorders (see Chapter 25).

Walking and postural recovery require more extensive attentional resources in the elderly (Brown et al. 1999). Accordingly, patients with Alzheimer's disease, when compared with healthy elderly, have slower walking speed, more difficulty clearing obstacles, and further deterioration of gait properties when asked to perform a simultaneous cognitive task, such as talking. Applying this paradigm to elderly patients in general, the observation of gait interruptions while speaking ("stops walking when talking," I.undin-Olsson et al. 1997) has a high predictive value for falling.

The clinical evaluation should aim at identifying predisposing medical conditions and differentiating accidental from endogenous falls. A detailed medication history is essential. Antidepressants, anticonvulsants, antihypertensives, antiarrhythmics, benzodiazepines and other tranquilizers, and neuroleptics increase the risk of falls (Tinetti 2003). Finally, a description of contributing environmental factors should be obtained, either from the patients or from others rami liar with their living circumstances.

Therapeutic ami risk reduction intervention for the falling elderly patient requires (1) treatment of correctable conditions, (2) provision of rehabilitative services and assistive devices, and (3) prevention by controlling environmental hazards. Pacemakers, supportive stockings, and medications may be helpful for patients experiencing autonomic dysfunction, cardiac dysrhythmias, and pharmacologically treatable movement disorders, but all unnecessary medications that increase the risk of falling (see the previous discussion) should be discontinued. Proper spectacle lenses and orthotic and other assistive devices, such as walkers, canes, and crutches, can return a progressively immobilized falling patient to a safer and more independent lifestyle. Women should be encouraged to wear sturdy low-heeled shoes. The risk of fall-related fractures may further be reduced by using specifically designed joint protectors (Kannus et al. 2000). A variety of exercise programs, particularly rhose stressing muscle strengthening and balance, reduce the risk of falls (Campbell et al. 1997; Gillespie et al. 2000). Rehabilitative efforts are indicated for those patients in whom, after a few falls, a postfall syndrome develops consisting of phobic avoidance and restrictive behavior (Friedman et al. 2002).

Controlling environmental hazards include lighting hallways, stairs, and entrances; anchoring rugs and using non-skid mats; and installing handrails in bathrooms, halls, and stairways. In addition, climbing ladders, or even stepladders, should be avoided.

SUMMARY

A careful history and physical examination should, in most cases, uncover the cause of falls and drop attacks. Unfortunately, with middle-aged women and the elderly, the cause may be merely a function of gender or age. Patients with fixed motor or sensory impairments must be advised honestly about their almost unavoidable tendency to fall. Nevertheless, environmental adjustments and use of protective devices can reduce the frequency of falls and related injuries.

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Chapter 4
Delirium

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Delirium is a ncurobehavioral disorder characterized by an acute mental status change, fluctuating course, and abnormal attention. Delirium is a common disorder among hospitalized patients, occurring in 10-30% of medically ill patients and among 14-56% of patients 65 years of age and older (Brown and Boyle 2002; Elie et al. 2000; Inouye et al. 1998). Delirium may be the most common presentation of disease in the elderly (Bucht, Gustafson, and Sandberg 1999). The consequences of delirium are serious: They include longer hospitalizations, increased mortality, high rates of discharge to institutions, and more than $4 billion of annual Medicare expenditures in the United States (Inouye et al. 1999).

Physicians have known about this disorder since antiquity. Hippocrates referred to it as *pbrenitis,* the origin of our word *frenzy.* In the first century AD, Celsus introduced the term *delirium* from the Latin for "out of furrow," meaning derailment of the mind, and Galen observed that delirium was often due to physical diseases that affected the mind "sympathetically." In the nineteenth century, Gowers recognized that these patients could he either lethargic or hyperactive. Bonhoeffer, in his classification of organic behavioral disorders, established that delirium is associated with clouding of consciousness. Finally, Kngel and Romano described alpha slowing and delta and thcta intrusions on electroencephalograms (LLCs) and correlated these changes with clinical severity. They noted that treating the medical cause resulted in reversal of both the clinical and the EEG changes of delirium.

Despite this long history, clinicians often fail to diagnose delirium. They often miss this syndrome more from lack of recognition than from misdiagnosis as something else. The elderly, in particular, may have a "quieter," more subtle presentation of delirium. Adding to the confusion about delirium are the many terms used to describe this disorder: acute brain failure, acute brain syndrome, acute cerebral insufficiency, acute confusional state, acute organic syndrome, delirium, exogenous psychosis, metabolic encephalopathy, organic psychosis, toxic encephalopathy, toxic psychosis, and others.

One of the problems in recognizing delirium is defining the disorder. Delirium often reflects a global failure of brain metabolism from a large variety of medical etiologies, yet it is difficult to judge the impact of medical conditions on the brain. Most delirium in the elderly is superimposed on dementia, yet several investigators question the reversibility of delirium and its distinction from dementia. In sum, the definition of delirium must emphasize an acute behavioral decompensation with fluctuating attention, regardless of etiology or the presence of baseline cognitive impairments. In addition, we must carefully define the terms used with these disorders. *Attention* is the ability to focus on specific stimuli to the exclusion of others. *Arousal,* a basic prerequisite for attention, indicates responsiveness or excitability into action. *Coma, stupor, wakefulness,* and *alertness* arc states of arousal. *Consciousness,* a product of arousal, means clarity of awareness of the environment.

CLINICAL CHARACTERISTICS

The essential elements of delirium are summarized in Tables 4.1 and 4.2. Among the American Psychiatric Association's criteria (American Psychiatric Association 2000) for these disorders are an acute onset **with** fluctuations over the course of a day, reduced ability to focus and sustain attention, disorganized thinking, and evidence of a neurological or medical cause. Furthermore,

Table 4,1: Clinical characteristics of delirium

Acute onset of mental status change with fluctuating course
Attentional deficits
Disorganized thinking
Altered level of consciousness
Perceptual disturbances
Disturbed sleep-wake cycle
Altered psychomotor activity
Disorientation and memory impairment
Other cognitive deficits
behavioral and emotional abnormalities

Table 4.2: *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition, Revised, criteria for delirium

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual dis turbance that is not better accounted for by pre-existing, established, or evolving demenria.
C. The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day.
D. There is evidence from the history, physical examination, or laboratory findings rhat the disturbance is caused by rhe direct physiological consequences of a general medical condition.

Source: Modified with permission from American Psychiatric Association. 2000, *Diagnostic and Statistical Manual of Me/ital Disorders,* 4th ed, revised text, American Psychiatric Associatioti, Washington, DC.

delirious patients have disorganized thinking and altered level of consciousness, perceptual disturbances, disturbance of the sleep-wake cycle, increased or decreased psychomotor activity, disorientation, and memoty impairment. Other cognitive, behavioral, and emotional disturbances may also occur as part of the spectrum of delirium.

Acute Onset with Fluctuating Course

Delirium develops rapidly over hours or days but tarely over more than a week, and fluctuations in the course occur throughout the day. There are lucid intervals interspersed with the daily fluctuations. Gross swings in attention, arousal, or both occur unpredictably and irregularly and become worse at night. Because of potential lucid intervals, medical personnel may be misled by patients who exhibit improved attention and awareness unless the patients are evaluated over time,

Attentional Deficits

A disturbance of attention is the cardinal symptom of delirium. Patients are distractible, and stimuli may gain attention indiscriminately, trivial ones often getting mote attention than important ones. All components of attention ate disturbed, including selectivity, sustainability, processing capacity, case of mobilization, monitoring of the environment, and the ability to shift attention when necessary. Although many of the same illnesses result in a spectrum of disturbances from mild inattention to coma, delirium is not the same as disturbance of arousal.

Disorganized Thinking

The stream of thought is disturbed in delirium. There are multiple intrusions of competing thoughts and sensations, and patients are unable to order symbols, carry out sequenced activity, and organize goal-directed behavior, *Confusion* refers to this inability to maintain the stream of thought with accustomed clarity, coherence, and speed.

The patient's speech reflects this jumbled thinking. Speech shifts from subject to subject and is rambling, tangential, and circumlocutory, with hesitations, repetitions, and perseverations. Decreased relevance of the speech content and decreased tcading comprehension are characteristic of delirium. Confused speech is further characterized by an abnormal rate, frequent dysarthria, and nonaphasic misnaming, particularly of words related to stress or illness, such as those referable to hospitalization.

Altered Level of Consciousness

Consciousness, or clarity of awareness, may be disturbed. Most patients have lethargy and decreased arousal. Others, such as [IIDM- with delirium tremens, arc hypcralerl and easily aroused. In hyperalert patients, the extreme arousal does not preclude attentional deficits because patients are indiscriminate in their alertness, are easily distracted by irrelevant stimuli, and cannot sustain attention. The two exttemes of consciousness may overlap or alternate in the same patient or may occur from the same causative factor.

Perceptual Disturbances

The most common perceptual disturbance is decreased perceptions pet unit of time; patients miss things that are going on around them. Illusions and other misperceptions result from abnormal sensory discrimination. Perceptions may be multiple, changing, or abnormal in size or location. Hallucinations also occur, particularly in younger patienrs and in those in the hyperactive subtype. They ate most common in the visual sphere and arc often vivid, three-dimensional, and in full color. Patients may see lilliputian animals or people that appear to move about. Hallucinations are generally unpleasant, and some patients attempt to fight them or run away with fear. Some

hallucinatory experiences may be release phenomena, with intrusions into wakefulness of dreams or of visual imagery. Psychotic auditory hallucinations, with voices commenting on the patient's behavior, are unusual.

Disturbed Sleep-Wake Cycle

Disruption of the day-night cycle causes excessive daytime drowsiness and reversal of the normal diurnal rhythm. "Sundowning"—with restlessness and confusion during the night—is common, and delirium may be manifest only at mght. Nocturnal peregrinations can result in a serious problem when the delirious patient, partially clothed in a hospital gown, has to be retrieved from the hospital lobby or from the street in the middle of the night. This is one of the least specific symptoms and also occurs in dementia, depression, and other behavioral conditions. In delirium, however, disruption of circadian sleep cycles may result in rapid eye movement or dream-state overflow into wakin».

Altered Psychomotor Activity

There are two subtypes of delirium, based on changes in psychomotor activity. The hypoactive-hypoalert subtype is characterized by psychomotor retardation. These are the patients with lethargy and decreased arousal. The hyperactive-hyperalert subtype is usually hyperalert and agitated and has prominent overactivity of the autonomic nervous system. Moreover, the hyperactive type is more likely to have delusions and perceptual disorders, such as ha 11 Lie illations. About half of patients with delirium manifest elements of both subtypes or fluctuate between the two. Only about 15% are strictly hyperactive. In addition to the patients being younger, the hyperactive subtype has more drug-related causes, a shorter hospital stay, and a better prognosis.

Disorientation and Memory Impairment

Disturbances in orientation and memory are related. Patients are disoriented first to time of day, followed by other aspects of time, and then to place. They may perceive abnormal juxtapositions of events or places. Disorientation to person—in the sense of loss of personal identity—is rare. Disorientation is one of the most common findings in delirium. Disorientation is not specific for delirium, however, and it occurs in dementia and amnesia as well. Among patients with delirium, recent memory is disrupted in large part by the decreased registration caused by attentional problems.

In delirium, reduplicative paramnesia, a specific memory-related disorder, results from decreased integration of recent observations with past memories. Persons or places are "replaced" in this condition. In general, delirious patients tend to mistake the unfamiliar for the familiar. For example, they tend to relocate the hospital closer to their homes. In a form of reduplicative paramnesia known as *Capgras' syndrome,* however, a familiar person is mistakenly thought to be an unfamiliar impostor.

Other Cognitive Deficits

Disturbances occur in visuospatial abilities and in writing. Higher visual-processing deficits include difficulties in visual object recognition, environmental orientation, and organization of drawings and other constructions.

Writing disturbance is the most sensitive language abnormality in delirium. The most salient characteristics are abnormalities in the mechanics of writing: The formation of letters and words is indistinct, and words and sentences sprawl in different directions (Figure 4.1). There is a reluctance to write, and there are motor impairments, such as tremors or micrographia, and spatial disorders (e.g., misalignment or leaving insufficient space for the writing sample). Sometimes the writing shows perseverations of loops or aspects of the writing. Spelling

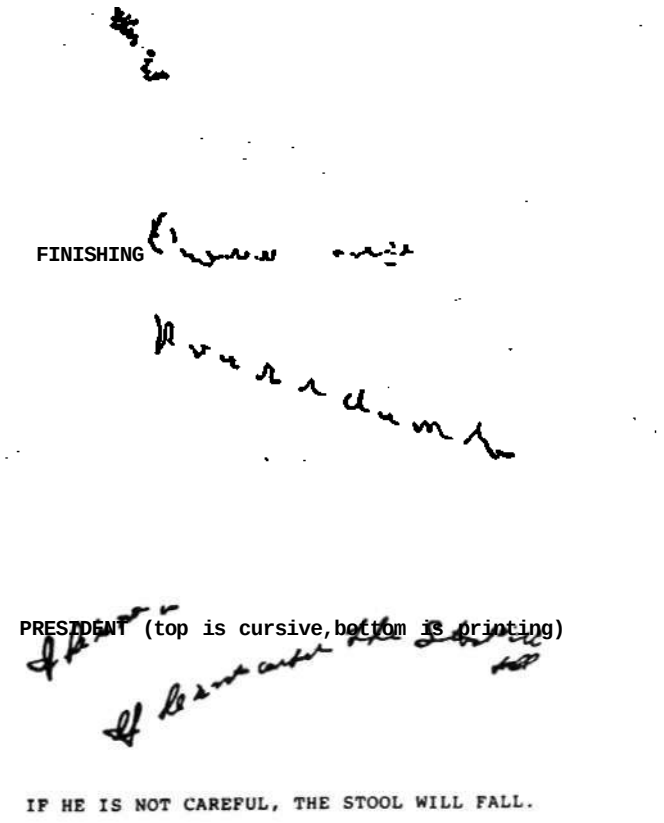

FIGURE 4.1 Writing disturbances in delirium. The patients were asked to write indicated words to dictation. (Reprinted with permission from Chédru, J. & Geschwind, N. 1972, "Writing disturbances in acute confusional states," *Neuropsychologia* vol. 10, pp. 343-353.)

and syntax are also disturbed, with spelling errors particularly involving consonants, small grammatical words (prepositions and conjunctions), and the last letters of words. Writing is easily disrupted in these disorders, possibly because it depends on multiple components and is the least-used language function.

Behavioral and Emotional Abnormalities

Behavioral changes include poorly systematized delusions, often with persecutory and other paranoid ideation and personality alterations. Delusions, like hallucinations, are probably release phenomena and are generally fleeting, changing, and readily affected by sensory input. These delusions are most often persecutory. Some patients exhibit facetious humor and playful behavior, lack of concern about their illness, poor insight, impaired judgment, and confabulation.

There can be marked emotional lability. Sometimes patients are agitated and fearful, or depressed, or quite apathetic. Dysphoric (unpleasant) emotional states arc the more common, and emotions are not sustained. Up to one half of elderly delirious patients display symptoms of depression with low mood, loss of interests, fatigue, decreased appetite and sleep, and other feelings related to depression, Thete may be mood-congruent delusions and hallucinations. The mood changes of delirium are probably due to direct effects of the confusional state on the limbic system and its regulation of emotions,

Finally, more elementary behavioral changes may be the principal symptoms of delirium. This is especially the case in the elderly, in whom decreased activities of daily living, urinary incontinence, and frequent falls are among the major manifestations of this disorder,

PATHOPHYSIOLOGY

The pathophysiology of delirium is not entirely understood, but it depends on a widely distributed neurological substrate. Normal attention requires both the ascending reticular activating system (ARAS) in the upper brainstem and polymodal association areas of the cortex. Stimulation of the ARAS elicits arousal, and lesions of the ARAS may result in sleep, coma, or akinetic mutism rather than attentional problems or delirium (see Chapters 5 and 74). The ARAS primes the cortex for stimulus reception, whereas the polymodal association cortex controls and focuses this arousal energy for attention.

Certain brain areas may be particularly involved in attention: bilateral or right prefrontal cortex in attcntional maintenance and executive control, the temporoparietal junction region in disengaging and shifting attention, the thalamus in engaging attention, and the upper brainstem structures in moving the focus of attention. Cortical blood flow studies suggest that the polymodal cortical areas and their limhic connections arc the "attentional gate" for sensory input through feedback to the reticular nucleus of the thalamus (Figure 4.2). The thalamic nuclei are uniquely positioned to further screen sensory information from the ARAS, and small lesions in the thalamus may cause delirium. As part of thalamofrontal circuits, the thalamic nuclei influence and regularc the activity of cerebral and limbic cortices. In addition, there is evidence that the right hemisphere is dominant for attention, although split-brain studies clearly point out the need for bihemispheric cooperation in maintaining attention.

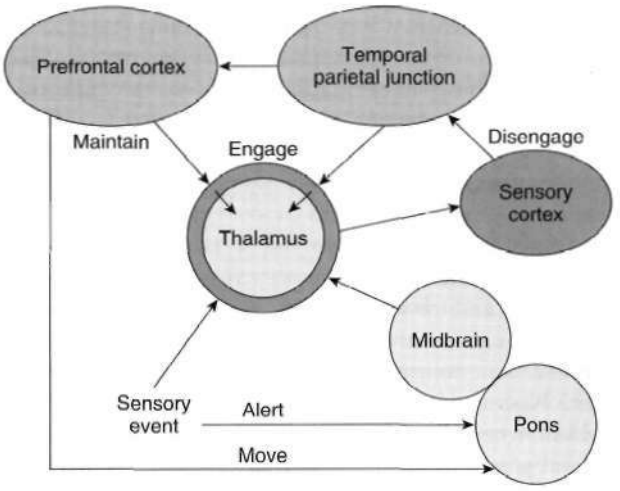

FIGURE 4.2 A proposed schema for the attention system. The important polymodal areas arc the prefrontal cortex and the temporal-parietal junction, particularly in the right hemisphere. A sensory signal leads to alerting and localization as it is relayed from the thalamus to the primary sensory cortex. Upon transmission to the temporal-parietal cortex, attention is disengaged from its current focus and moved to engage the sensory event. Environmental monitoring and the "'gate" function of attention may occur through feedback from the polymodal cortical areas to the nucleus reticularis of the thalamus (external thalamic ring), a modulator of sensory input.

A second explanation for delirium is alterations in neurotransmitters, particularly a cholinergic-dopaminergic imbalance. Anticholinergic agents can induce the clinical and EEC changes of delirium, which are reversible with the administration of cholinergic medications, such as physostigmine. The beneficial effects of tacrine and donepezil, acetylcholinesterase inhibitor medications used for Alzheimer's disease, may be partly due to an activating or attention-enhancing role, Moreover, cholinergic neurons project from the pons and the basal forebrain to the cortex and make cortical neurons more responsive to other inputs, A decrease in acetylcholine results in decreased perfusion in the frontal cortex. Hypoglycemia, hypoxia, and other metabolic-changes may differentially affect acetylcholinc-mediated functions. Other neurotransmitters may be involved in delirium, including dopamine, serotonin, norepinephrine, y-aminobutyric acid, glutamine, opiates, and histamine.

Dopamine appears to function in a reciprocal fashion to acetylcholine, hence the delirium-producing effects of i.-dopa and other antiparkinsonism medications. Opiates may induce the effects by increasing dopamine and glutamate activity. Future studies may show a role for inflammatory cytokines in the pathogenesis of delirium.

Any explanation of delirium must take into account not only specific structural lesions and neurotransmitter changes but also the diffuse metabolic causes that can result in the same disturbances of attention. The diffuse causes, the universal susceptibility to developing delirium, **and** the minimal or nonspecific pathologic changes suggest an impairment of some common metabolic pathways in nerve cells. Metabolic pathways involving the ARAS and i he poly modal cortex may he vulnerable because these lira areas have the most polysynaptic chains.

DIAGNOSIS OF DELIRIUM

Diagnosis is a two-step process. The first step is the recognition of delirium, which requires a thorough history, a bedside mental status examination focusing on attention, and a review of established diagnostic scales or criteria for delirium. The second step is to identify the cause from a large number of potential diagnoses. Because the clinical manifestations offer few clues to the cause, crucial to the differential diagnosis are the general history, the physical examination, and the laboratory assessment. In addition, the clinician should thoroughly review the patient's medication list.

History

An abrupt decline in mentation, particularly in the hospital, should be presumed to be delirium. Although patients may state that they cannot think straight or concentrate, family members or other good historians should be available to describe the patient's behavior and medical history. The observer may have noted early symptoms of delirium, such as inability to perform at a usual level, decreased awareness of complex details, insomnia, and frightening or vivid dreams. Furrhermore, it is crucial to obtain accurate information about systemic illnesses, drug use, recent trauma, occupational and environmental exposures, malnutrition, allergies, and any preceding symptoms leading to a confusional state.

The patient's risk factors for delirium should be carefully assessed (Table 4.3). Of the risk factors that predispose to incident delirium in the hospital, the most important are advanced age, pre-existing cognitive dysfunction or dementia, and chronic medical illnesses (Johnson 2001). Advanced age itself seems to be an independent risk factor, especially for those older than 80 years. Many of these elderly parients predisposed to delirium have cerebral atrophy or white matter and basal ganglia ischemic changes on neuroimaging. Among the elderly, those with dementia are five times more likely to develop delirium than those without dementia (Elie et al. 1998). As many as one half of hospitalized patients with delirium have an underlying dementia, and many of the remainder have mild cognitive impairment, A third factor is the severity of the illness and the degree of physical impairment. Additional risk factors include vision impairment (<20/70 binocular); hip and other bone fractures; dehydration, serum sodium changes, and azotemia; infections and fevers; and the use of multiple drugs, particularly those with narcotic, anticholinergic, or psychoactive properties. The risk factors are additive, each new factor increasing the risk considerably. Precipitating factors for incident delirium after hospitalization include the use of physical restraints, malnutrition defined as albumin levels less than 30 g/L, the addition of more than three new medications, the use of a bladder catheter, and any iatrogenic medical complications (lnouye and Charpentier 1996). Ultimately, delirium occurs in patients from a synergistic interaction of predisposing factors with precipitating factors.

Sensory overstimulation or undersrimulation facilitates confusional behavior, probably because optimal attention requires an optimal amount of sensory input. Novel situations and unfamiliar surroundings contribute to

Table 4.3: Risk factors for delirium

Elderly, especially SO years or older
Dementia, cognitive impairment, or other brain disorder
Fluid and electrolyte disturbances and dehydration
Other metabolic disturbance, especially elevated blood urea nitrogen level, or hepatic insufficiency
Number and severity of medical illnesses including cancer
Infections, especially urinary tract, pulmonary, and acquired immunodeficiency syndrome
Malnutrition, low serum albumin level
Cardiorespiratory failure or hypoxemia
Prior stroke or other nondementia brain disorder
Polypharmacy and use of analgesics, psychoactive drugs, or anticholinergics
Drug abuse, alcohol or sedative dependency
Sensory impairment, especially visual
Sensory overstimulation and "intensive care unit psychosis"
Sensory deprivation
Sleep disturbance
Functional impairment
Fever, hypothermia
Physical trauma or severe burns
Fractures
Male gendef
Depression
Specific operations
Cardiac, especially open heart surgery
Orthopedic, especially femoral neck and hip fractures, bilateral knee replacements
Ophthalmologics], especially cataract surgery
Noneardiac thoracic surgery and aortic aneurysmal repairs
Transurethral resection of the prostate

sensory overstimulation in the elderly, and sensory overload may be a factor in producing "intensive care unit (ICU) psychosis." Immobilization, with decreased kinesthetic inputs, contributes to sensory deprivation. Sleeplessness may cause confusion; however, it is not the decreased total amount of sleep that predisposes to delirium but the resulting disruption of circadian sleep cycles.

Mental Status Examination

Initial general behavioral observations are an important part of the neurological mental status examination. The most important arc observations of attentiveness and arousability. Attention may wander so much that it must constantly be brought back to the subject at hand. General behavior may range from falling asleep during the interview to agitation and combativeness. Slow and loosely connected thinking and speech may be present, with irrelevancies, perseverations, repetitions, and intrusions. Patients may propagate their errors in thinking and perception by elaboration and by bringing other observations into agreement with them. Finally, the examiner should evaluate the patient's general appearance and grooming; motor activity and spontaneity; mood and affect, propriety, and witticisms; and the presence of any special preoccupations or inaccurate perceptions.

Bedside tests of attention can be divided into serial recitation tasks, continuous performance tasks, and alternate response tasks. The digit span test is a serial recitation task in which a series of digits is presented, one digit per second, and the patient is asked to repeat the entire sequence immediately after presentation. Perceptual clumping is avoided by the use of random digits and a regular rhythm of presentation. Correct recitation of seven (plus or minus two) digits is considered normal. The serial reversal test is a form of recitation task in which the patient recites backward a digit span, the spelling of a word such as *world*, or the results of counting by ones, threes, or sevens from a predetermined number. Continuous performance tasks include the *A* vigilance test, in which the patient must indicate whenever she hears the letter *A* among random letters presented one per second. This can also be done visually by asking the patient to cross out every instance of a particular letter in a magazine or newspaper paragraph. Alternate response tasks are exemplified by the repetition of a three-step motor sequence (palm-side-fist), which is also a test of frontal functions. These attentional tests are not overly sensitive or specific, and they can be affected by the patient's educational background, the degree of effort, or the presence of other cognitive deficits. In sum, the best assessment of attention may be general behavioral observations and an appraisal of how "interviewablc" the patient is.

Attentional or arousal deficits may preclude the opportunity to pursue the mental status examination much further, but the examiner should attempt to assess orientation and other areas of cognition. Patients who are off 3 days on the date, 2 days on the day of the week, or 4 hours on the time of day may be significantly disoriented to time. The examiner should inquire whether the patient knows where he or she is, what kind of a place it is, and under what circumstances he or she is there. Disturbed recenr memory is demonstrated by asking the patient to retain the examiner's name or three words for 5 minutes. A language examination should distinguish between the language of confusion and that of a primary aphasia (sec Special Problems in Differential Diagnosis, later in this chapter). Attempts at simple constructions, such as copying a cube, may be unsuccessful. Hallucinations can somerimes be brought out by holding a white piece of paper or an imaginary string between the fingers and asking the patient to describe what he or she sees.

Diagnostic Scales and Criteria

The usual mental status scales and tests may not help in differentiating delirium from dementia and other cognitive disturbances. Specific criteria and scales are available for the diagnosis of delirium. Foremost among these are the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition *(DSM-1V)*, criteria for delirium (see Table 4,2). Investigators have criticized these criteria because of the required "disturbance of consciousness" and the broadness of "a change in cognition." The Confusion Assessment Method (CAM) is a widely used instrument for diagnosing delirium (Ely et al. 2001), It is a structured interview with nine ope rationalized questions from the *DSM-IV*. The CAM can be simplified to a diagnostic algorithm of four items: an acute onset with fluctuating course, inattention, and either disorganized thinking or an altered level of consciousness. A version of the CAM for ICU patients (CAMTCU) is a 2-minute assessment instrument that has been shown to be valid and reliable in detecting delirium in mechanically ventilated ICU patients (Ely et al. 2001). The Delirium Rating Scale-Revised-98 (DRS-R-98), a revision of the earlier Delirium Rating Scale (DRS), is a 16-item scale with 13 severity items and three diagnosric items that reliably distinguish delirium from dementia, depression, and schizophrenia (Trzepacz et al. 2001). The Memorial Delirium Assessment Scale (MDAS) is a 10-item scale designed to quantify the severity of delirium in medically ill patients that may also be useful as a diagnosric tool (Breirbart er al. 1997). The Delirium Symptom Interview is also a valuable instrument but may not distinguish delirium from dementia. The diagnosis of delirium is facilitated by the use of the CAM/CAM-ICU, DRS-R-98, MDAS, or the Delirium Symptom Interview along with the history from collareral sources, such as family and nursing notes; a mental status examination focusing on attention; and specific tests, such as a writing sample.

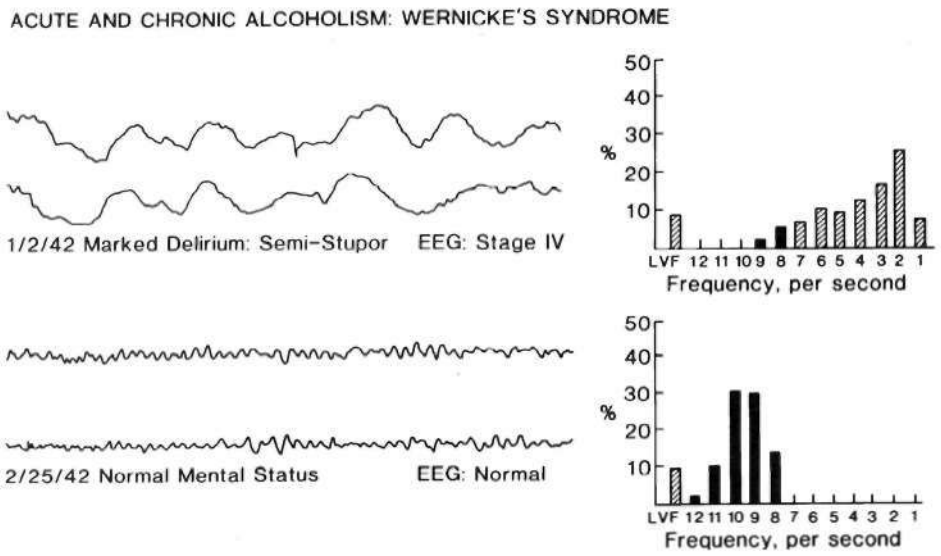

FIGURE 4.3 Electroencephalogram (EEG) showing changes caused by delirium. LVF = low-voltage filter. (Reprinted with permission from Romano, J. & Engel, G. L. 1944, "Delirium, 1: EEG data," *Arch Neurol Psychiatry*, vol. 51, p. 356.)

Physical Examination

The physical examination should elicit any signs of systemic illness, focal neurological abnormalities, meningism, increased intracranial pressure, extracranial cerebrovascular disease, or head trauma. In delirium, less specific findings include an action or postural tremor of high frequency (8-10 Hz), asterixis or brief lapses in tonic posture, especially at the wrist; multifocal myoclonus or shocklikc jerks from diverse sites; choreiform movements; dysarthria; and gait instability. Patients may manifest agitation or psychomotor retardation, apathy, waxy flexibility, catatonia, or carphologia ("lint-picking" behavior). The presence of hyperactivity of the autonomic nervous system may be life threatening because of possible dehydration, electrolyte disturbances, or tachyarrhythmias.

Laboratory Tests

EEG changes virtually always accompany delirium when the EEGs arc followed serially over time (see Chapter 36A). Disorganization of the usual cerebral rhythms and generalized slowing are the most common changes. The mean EEG trvqiiency or degree of slowing correlates with the degree of delirium. Both hypoactive and hyperactive subtypes of delirium have similar EEG slowing; however, predominant low-voltage fast activity is also present on withdrawal from sedative drugs or alcohol. Additional EEG patterns from intracranial causes of delirium include focal slowing, asymmetric delta activity, and paroxysmal discharges (spikes, sharp waves, and spike-wave complexes). Periodic complexes, such as triphasic waves, and periodic latcralizing epileptiform discharges may help in the differential diagnosis (see Chapter 36A). EEGs arc of value in deciding whether confusional behavior may be due to an intracranial cause, in making the diagnosis of delirium in patients with unclear behavior, in evaluating demented patients who might have a superimposed delirium, in differentiating delirium from schizophrenia and other primary psychiatric states, and in following the course of delirium over time. Romano and Engel (1944) demonstrated the presence of background slowing in all subtypes of delirium in their now classic paper (Figure 4.3).

Other essential laboratory tests include a complete blood cell count; measurements of glucose, electrolytes, blood urea nitrogen, creatinine, transaminase, and ammonia levels; thyroid function tests; arterial blood gas studies; chest x-ray films; electrocardiogram; urinalysis; and urine drug screening. Although they arc nonspecific, evoked potential studies often show prolonged latencies. The need for a lumbar puncture deserves special comment. This valuable test, which is often neglected in the evaluation of delirious patients, should be performed as part of the workup when the cause is uncertain. The lumbar puncture should be preceded by a computed tomographic or magnetic resonance imaging scan of the brain, especially if there are focal neurological findings or suspicions of increased intracranial pressure, a space-occupying lesion, or head trauma. The yield of functional imaging is variable, showing global increased metabolism in patients with delirium tremens and global decreased metabolism or focal frontal hypoactivity in many other delirious patients.

Differential Diagnosis

The following discussion is a selective commentary that illustrates some basic principles and helps organize the approach to working through the large differential diagnosis. Almost any sufficiently severe medical or surgical illness can cause delirium, and the best advice is to follow

Table 4.4: Major causes of delirium

Metabolic disorders	Hepatic encephalopathy, uremia, hypoglycemia, hypoxia, hyponatremia, hypocalcemia/ hypercalcemia, Hypomagnesemia/ hypermagnesemia, other electrolyte disturbances, acidosis, hyperosmolar coma, endocrinopathies (thyroid, parathyroid, pituitary), porphyria, vitamin deficiencies (thiamine, vitamin R|$_2$, nicotinic acid, folic acid), toxic and industrial exposures (carbon monoxide, organic solvent, lead, manganese, mercury, carbon disulfide, heavy metals)
Drug related	Withdrawal syndromes (alcohol, benzodiazepines, barbiturates, other), amphetamines, cocaine, coffee, phencyclidine, hallucinogens, inhalants, meperidine and other narcotics, antiparkinsonism drugs, sedative-hypnotics, corticosteroids, anticholinergic and antihistaminic drugs, cardiovascular agents (beta blockers, clonidinc, digoxin), psychotropics (phenothiazines, clozapine, lithium, tricyclic antidepressants, trazodone), 5-fluorouracil and cytotoxic antineoplastics, anticonvulsants (phenobarbital, phenytoin, valproate), cimetidine, disulfirarn, ergot alkaloids, salicylates, methyldopa, and selected anti-infectious agents (acyclovir, amphotericin B, cephalexin, chloroquine, isoniazid, rifampin)
Infections	Meningitis, encephalitis, brain abscess, neurosyphilis, Lyme neuroborreliosis, cerebritis, systemic infections with septicemia
Neurological	Strokes, epilepsy, head injury, hypertensive encephalopathy, brain tumors, migraine, other neurovascular disorders
Perioperative	Specific surgeries (cardiac, orthopedic, ophthalmologics!), anesthetic and drug effects, hypoxia and anemia, hyperventilation, fluid and electrolyte disturbances, hypotension, embolism, infection or sepsis, pain, fragmented sleep, sensory deprivation or overload
Miscellaneous	Cerebral vasculitidcs, paraneoplastic and limbic encephalitis, hyperviscosity syndromes, trauma, cardiovascular, dehydration, sensory deprivation

all available diagnostic leads (Table 4.4). (For further discussion of individual entities, the reader should refer to corresponding chapters in this book.) The confusion-inducing effects of these disturbances arc additive, and there may be more than one causal factor, the individual contribution of which cannot be elucidated. Nearly one half of elderly patients with delirium have mote than one cause of their disorder. Of the causes for delirium, the most common among the elderly are metabolic disturbances, infection, stroke, and drugs, particularly anticholinergic and narcotic medications. The most common causes among the young are drug abuse and alcohol withdrawal.

Metabolic Disturbances

Metabolic disturbances are the most common causes of delirium (see Chapters 55A and 5.SB, 61, 62, and *63).* Fortunately, the examination and routine laboratory tests screen for most acquired metabolic disturbances that might be encountered. Because of tlie potential lor life-threatening or permanent damage, some of these conditions—particularly hypoxia and hypoglycemia—must be considered immediately. Also consider dehydration, fluid and electrolyte disorders, and disturbances of calcium and magnesium. The rapidity of change in an electrolyte level may be as important a factor as its absolute value for the development of delirium. For example, some people tolerate chronic sodium levels of 115 mEq/L or less, but a rapid fall to this level can precipitate delirium, seizures, or even central pontine myelinolysis, particularly if the correction of hyponatremia is too rapid. Hypoxia from low cardiac output, rcspiratoty insufficiency, or other causes is another common source of delirium. Also consider other major organ failures, such as liver and kidney failure, including the possibility of unusual causes, such as undetected portocaval shunting or acute pancreatitis with the release of lipases. Delirium caused by endocrine dysfunction often has prominent affective symptoms, such as hyperthyroidism and Cushing's syndrome. Delirium occasionally results from roxins, including industrial agents, pollutants, and heavy metals, such as arsenic, bismuth, gold, lead, mercury, thallium, and zinc. Other considerations are inborn errors of metabolism, such as acute intermittent porphyria. Finally, it is particularly important to consider thiamine deficiency. In alcoholics and others at risk, thiamine must be given immediately to avoid precipitating Wernicke's encephalopathy with the administration of glucose.

Drugs

Drug intoxication and drug withdrawal are among the most common causes of delirium. In the elderly, medications contribute to delirium in up to 39% of patients (Inouye and Charpcnticr 1996). Drug effects are additive, and drugs that are especially likely to cause delirium arc those with anticholinergic properties, including many over-the-counter cold preparations, antihistamines, antidepressants, and neuroleptics. Patients with anticholinergic intoxication ptcscnt "hot as a hare, blind as a bat, dry as a bone, red as a beet, and mad as a hatter," reflecting fever, dilated pupils, dry mouth, flushing, and delirium. Other important groups of drugs associated with delirium, especially in the elderly, are sedative-hypnotics, narcotic analgesics, and I ^-receptor blockers. Antiparkinsonism drugs result in confusion, with prominent hallucinations and delusions in patients with Parkinson's disease, who are particularly susceptible. Corticosteroid psychosis may develop in patients taking the equivalent of 40 mg per day or more of prednisone. The behavioral effects of corticosteroids often begin with euphoria and hypomania and proceed to a hyperactive delirium. Any drug administered intra thee ally, such as metrizamide, is prone to induce confusional behavior. Drug withdrawal syndromes can be

caused by many agents, including barbiturates and other minor tranquilizers, sedative-hypnotics, amphetamines, cocaine or "crack," and alcohol. Delirium tremens begins 72-96 hours after alcohol withdrawal, with profound agitation, tremulousncss, diaphoresis, tachycardia, fever, and frightening visual hallucinations.

Infections

Infections and fevers often produce delirium. The main offenders are urinary tract infections, pneumonia, and sepricemia. In a sporadic encephalitis or meningoencephalitis, important causal considerations are herpes simplex virus, Lyme disease, and acquired immunodeficiency syndrome (AIDS) (see Chapter 59E). Patients with AIDS may be delirious because of the human immunodeficiency virus (HIV) itself or because of an opportunistic infection. Immunocompromised patients are at greater risk of infection, and any suspicion of infection should prompt culture of urine, sputum, blood, and cerebrospinal fluid.

Strokes

Delirium can be the nonspecific consequence of any acute stroke, but posrinfarct confusion usually resolves in 24-48 hours (see Chapter 57A). Sustained delirium can result from specific strokes, including right middle cerebral artery infarcts affecting prefrontal and posterior parietal areas, and posterior cerebral artery infarcts resulting in cither bilateral or left-sided occipitotemporal lesions (fusiform gyrus). The latter lesions usually involve the left hemisphere and can lead to agitation, visual field changes, and even Anton's syndrome (see Chapter 14), Delirium may also follow occlusion of the anterior cerebral artery or rupture of an anrerior communicating artery aneurysm with involvement of the anterior cingulate gyrus and septal region. Thalamic or posterior parietal cortex strokes may present with severe delirium, even with small lesions.

Other cerebrovascular conditions that can produce delirium include high-grade bilateral carotid stenosis, hypertensive encephalopathy, subarachnoid hemorrhage, and central nervous system (CNS) vasculitides, such as systemic lupus erythematosus, temporal arteritis, and Behcet's syndrome. Migraine can present with delirium, particularly in children. It must be emphasized that the frequency of delirium in transient ischemic attacks, even in vertebrobasilar insufficiency, is low. Transient ischemic attacks should not be consideted the cause of delirium unless there are other neurological signs and an appropriate time course.

Epilepsy

Abnormal brain electrical activity is associated with delirium in four conditions: (1) ictally, with absence status, complex partial srarus, tonic status without convulsions, or periodic lateralizing epileptiform discharges; (2) postictally, after complex partial or generalized tonic-clonic seizures; (3) interictally manifested as increasing irritability, agitation, and affective symptoms associated with the prodrome of impending seizures; and (4) from the cognitive effects of anticonvulsant medications.

Postoperative Causes

The cause of delirium in postoperative patients is often multifactorial (Winawer 2001). Predisposing factors to postoperative delirium include age older than 70 years, preexisting CNS disorders such as dementia and Parkinson's disease, severe underlying medical conditions, and a history of alcohol abuse. Precipitating factors include residual anesthetic and drug effects, especially after premedication with anticholinergic drugs; postoperative hypoxia; perioperative hypotension; electrolyte imbalances; infections; psychologic stress; and multiple awakenings with fragmented sleep. There is no clear correlation of delirium with specific anesthetic route. Postoperative delirium may start at any time but often becomes evident about the third day and abates by the seventh, although it may last considerably longer.

A number of surgeries are associated with a high rate of postoperative delirium. Between 30% and 40% of patients experience delirium after open heart or coronary artery bypass surgery. Patients older than 60 years are at special risk for postoperarive delirium after cardiac surgery. Additional factors are decreased postoperative cardiac output and length of time on cardiopulmonary bypass machine, with its added risk for microemboli. In addition to an alteady high rate of delirium following fractures, orthopedic surgeries, particularly femoral neck fractures and bilateral knee replacements, further increase the frequency of delirium by about 18%. Elective noncardiac thoracic surgery is also associated with a 9-14% frequency of delirium in the elderly. Cataract surgery is associated with a 7% frequency of delirium, possibly because of sensory deprivation. Patients who have undergone prostate surgery may develop water intoxication as a result of absorption of irrigation water from the bladder.

Other Neurological Causes

Other CNS disturbances predispose to delirium. In general, patients with dementia, Lewy body disease, Parkinson's disease, and atrophy or subcortical ischemic changes on neuroimaging are particularly susceptible. Electroconvulsive rherapy in these patients often produces a delirium of a week or more. Head trauma can result in delirium as a consequence of brain concussion, brain contusion, intracranial hematoma, or subarachnoid hemorrhage (see Chapter 56B). Moreover, subdural hematomas can occur in the elderly with little or no history of head injury. Rapidly growing tumors in the supratcntorial region are especially

likely to cause delirium with increased intracranial pressure. Paraneoplastic processes produce limbic encephalitis and multifocal leukoencephalitis. Delirium can result from acute demyelinating diseases and other diffuse multifocal lesions, and from communicating or noncommunicating hydrocephalus. In transient global amnesia, there is initial delirium, disproportionate anterograde amnesia, some retrograde amnesia for the preceding hours, and improvement within 24 hours. In Wernicke's encephalopathy, delirium accompanies oculomotor paresis, nystagmus, ataxia, and frequently residual amnesia (Korsakoff's psychosis).

Miscellaneous Causes

Various other disturbances can produce delirium. Bone fractures are associated with delirium in the elderly, and about 50% of those admitted with a hip fracture have delirium. In orthopedic cases, the possibility of fat emboli requires evaluation of urine, sputum, or cerebrospinal fluid for fat. ICU psychosis is associated with sleep deprivation, immobilization, unfamiliarity, fear, and frightening sensory overstimulation or sensory deprivation. Delirium results from blood dyscrasias, including anemia, thrombocytopenia, and disseminated intravascular coagulopathy. Finally, physical factors, such as heatstroke, electrocution, and hypothermia may be causal.

Special Problems in Differential Diagnosis

Delirium must be distinguished from dementia, Wernicke's aphasia, and psychiatric conditions (see Chapters 6, 8, 12, and 72). The main differentiating features of dementia are the longer time course and the absence of prominent fluctuating attentional and perceptual deficits. Chronic confusional states lasting 6 months or more are a form of dementia. Patients with delirium that becomes chronic tend to settle into a lethargic state without inattention or fluctuations throughout the day, and they have fewer perceptual problems and less disruption of the day-night cycle. In addition, delirium and dementia often overlap because demented patients have increased susceptibility for developing a superimposed delirium. Demented patients who suddenly get worse should always be evaluated for delirium. Moreover, distinguishing delirium from certain forms of dementia, such as vascular dementia and dementia with Lewy bodies, may be particularly difficult. Patients with vascular dementia may have an acute onset or sharp decline in cognition similar to delirium. Patients with dementia with Lewy bodies have fluctuations in attention and alertness and visual hallucinations that can look identical to delirium. Most of these patients, however, have parkinsonism, repeated falls, or other supportive features. Nevertheless, the differential diagnosis of delirium and dementia with Lewy bodies may not be possible until after a diagnostic workup is completed.

The language examination should distinguish Wernicke's aphasia from the language of delirium. Aphasics have prominent paraphasias of all types, including neologisms, and they have relatively preserved response to axial or whole-body commands. Their agraphia is also empty of content and is paragraphic compared with the mechanical and other writing disturbances previously described in patients with delirium.

Psychiatric conditions that may be mistaken for delirium include schizophrenia, depression, mania, attention-deficit disorder, autism, dissociative states, and Ganser's syndrome, which is characterized by ludicrous or approximate responses (see Chapter 8). In general, patients with psychiatric conditions lack the fluctuating attentional and related deficits associated with delirium. Schizophrenic patients may have a very disturbed verbal output, but their speech often has an underlying bizarre theme. Schizophrenic hallucinations are more often consistent persecutory voices rather than fleeting visual images, and their delusions arc more systematized and have personal reference. Conversely, delirious hallucinations are usually visual, and their delusions are more transitory and fragmented. Mood disorders may also be mistaken for delirium, particularly if there is an acute, agitated depression or a predominantly irritable mania. A general rule is that psychiatric behaviors may be due to delirium, especially if they occur in someone who is 40 years or older without a prior psychiatric history.

Table 4.5 outlines the special problems that must be considered in the differential diagnosis of acute confusional states.

MANAGEMENT

There are several steps in the management of delirium. First, attention is aimed at finding the cause and eliminating it. Second, the delirium is managed with symptomatic measures involving attention to fluid and electrolyte balance, nutritional status, and early treatment of infections. Third, management focuses on environmental interventions. Reduce unfamihanty by providing a calendar, a clock, family pictures, and personal objects. One should maintain a moderate sensory balance in the patient by avoiding sensory overstimulation or deprivation. Minimize staff changes, limit ambient noise and the number of visits from strangers, and provide a radio or a television set, a night light, and where necessary eyeglasses and hearing aids. Other environmental measures include providing soft music and warm baths and allowing the patient to take walks when possible. Fourth, proper communication and support are critical with these patients. As much as possible, everything should be explained. Delusions and

Table 4.5: Special problems in the differential diagnosis of delirium*

Clinical feature	*Delirium*	*Dementias*	*Stroke with Wernicke's aphasia*	*Schizophr*
Course	Acute onset; hours, days, or more	Insidious onset ; months or years; progressive	Sudden onset; chronic, stable deficit	Insidious more; acu
Attention	Markedly impaired attention and arousal	Normal early; impairment later	Normal	Normal t
Fluctuation	Prominent in attention arousal; disturbed day-night cycle	Prominent fluctuations absent; lesser disturbances in day-night cycle	Absent	Absent
Perception	Misperceptions; hallucinations, usually visual, fleeting; paramnesia	Perceptual abnormalities much less prominent*; paramnesia	Normal	Hallucin with pers
Speech and language	Abnormal clarity, speed, and coherence; disjointed and dysarthric; misnaming; characteristic dysgraphia	Early anornia; empty speech; abnormal comprehension	Prominent paraphasias and neologisms; empty speech; abnormal comprehension	Disorgan theme
Other cognition	Disorientation to time, place; recent memory and visuQspatial abnormalities	Disorientation to time, place; multiple other higher cognitive deficits	No other necessary deficits	
Behavior	Lethargy or delirium; nonsystematized delusions; emotional lability	Disinterested; disengaged; disinhibitcd; delusions and other psychiatric symptoms	Paranoia possibly ensuing	
Electroencephalogram	Diffuse slowing; low-voltage fast activity; specific patterns	Normal early; mild slowing later	Normal	

The characteristics listed are the relative and usual ones and arc not exclusive.
Vatients with vascular dementia may have an abrupt decline in cognition.
•Patients with dementia with diffuse cortical Lewy bodies often have a fluctuating mental status and hallucinations.

hallucinations should be neither endorsed nor challenged. Patients should receive emotional support including frequent family visits. They also benefit from frequent reorientation to place, time, and situation. Finally, the management of delirium includes attention to risk factors. A risk factor intervention strategy aimed at managing six key risk factors for delirium—cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration—can produce significant reductions in the number and duration of episodes of delirium in hospitalized older patients (Inouye et al. 1999}.

In general, it is best to avoid the use of drugs in confused patients because they further cloud the picture and may worsen the delirium. All the patient's medications should be reviewed, and any unnecessary drugs should be discontinued. When medication is needed, these patients should receive the lowest possible dose and should not get drugs such as phenobarbital, which can cause a paradoxical reaction. Many patients benefit from regulation of the sleep-wake cycle and from a good night's sleep, provided by hypnotics, such as chloral hydrate or temazepam. Medication may be necessary if the patient's behavior is potentially dangerous, interferes with medical care, or causes the patient profound distress. Drug rrcarment can be directed at anxiety, fear, paranoia, hallucinations, delusions, agitation, and aggression. Clinicians have used the older antipsychotic drugs, such as haloperidol (starting at 0.25 mg daily) for these symptoms; however, the arypical antipsychotics at low doses, such as risperidone (starting at 0.2.5-0.5 mg twice daily, which may be increased up to .3^ mg per day), olanzapine (2.5-5.0 mg at bedtime, increased if needed to up to 20 mg daily), and quetiapine (starting at 25-50 mg twice a day and increasing to 200 mg per day if necessary), may be better alternatives (Schwartz and Masand 2002). Ondansetron may be effective and safe in the treatment of delirium occurring after coronary artery surgery (Bayindir et al. 2001). Benzodiazepines and anticholinergic medications should be avoided, if possible. Whether these chemical restraints are better than physical restraint is controversial. One form of restraint may work better than another docs in individual patients; however, physical rcsrraints should be avoided if possible and a sirtcr used instead.

PROGNOSIS

If the causative factor is rapidly corrected, the prognosis is good in most cases. The average duration of delirium is a few days to 2 weeks, but it may extend to 12 weeks in the elderly. After hospital discharge, older patients who were delirious may not recover back to baseline (McCusker et a). 2001). A partial delirium, which meets some but not all criteria, occurs in about one third of postdelirium elderly, and less rhan 20% have returned to their baseline by *6* months. Moreover, after delirium, elderly patients often have a decline in activities of daily living and increased likelihood of nursing home placement. Delirium itself is an independent predictor of adverse outcomes in older hospitalized patients, including increased mortality (McCusker et al. 2002; O'Keeffe and Lavan 1997), and contributes to falls, pressure sores, and other adverse events. In general, an improved prognosis relates to an increased awareness of delirium, with more rapid diagnosis of the causative factor and better overall management One final reason for the vigorous management of delirium is that delirium itself is a stressor that may lead to depression or post-trail ma tic stress disorder.

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Chapter 5
Clinical Approach to Stupor and Coma

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DEFINITIONS

Consciousness may be defined as a state of awareness of self and surroundings. Alterations in consciousness are conceptualized into two types. One, which affects arousal, is the subject of this chapter. The other involves cognitive and affective mental function, sometimes referred to as the *content* of mental function. Examples of the latter type of alteration in consciousness include dementia (see Chapter 6), delusions, confusion, and inattention (see Chapter 8). These altered states of consciousness, with the exception of advanced dementia, do not affect the level of arousal. Sleep, the only normal form of altered consciousness, is discussed in Chapter 74.

The term *delirium* describes a clouding of consciousness with reduced ability to sustain attention to environmental stimuli (Taylor and Lewis 1993). Diagnostic criteria for delirium from the *DSM-SV-R* include at least two of the following: (1) perceptual disturbance (misinterpretations, illusions, ot hallucinations), (2) incoherent speech at times, (3) disturbance of sleep-wake cycle, and (4) increased or decreased psychomotor activity *(DSM-IV-R* 2000). Delirium is a good example of a confusional state in which a mild decline in arousal may be clinically difficult to separate from a change in cognitive or affective mental function. In clinical practice, the exact boundary between different forms of altered consciousness may be vague.

Alterations in arousal, although often referred to as levels of consciousness, do not actually form discrete levels but rather are made up of a continuum of subtly changing behavioral states that range from alert to comatose. It is clinically important to note that these states are dynamic and thus may change with time. Four points on the continuum of arousal are often used in describing the clinical state of a patient: alert, lethargic, stuporous, and comatose. *Alert* refers to a perfectly normal state of arousal. *Stupor* is defined as unresponsiveness from which the subject can be aroused only by vigorous and repeated stimuli. *"Coma* is unarousable unresponsiveness," in which the patient lies with the eyes closed (Plum and Posner 1980). *Lethargy* lies between alertness and stupor. The terms *lethargy* and *stupor* cover a broad area on the continuum of behavioral states and thus are subject to misinterpretation by subsequent observers of a patient when used without further qualification. In clinical

practice, where relatively slight changes in arousal may be significant, only the terms *alert* and *comatose* (the endpoints of the continuum) have enough precision to be used without further qualification.

BEHAVIORAL STATES CONFUSED WITH COMA

Several different behavioral states may appear similar to coma or may be confused with it (Table 5.1). Moreover, patients who survive initial coma may progress to certain of these syndromes after various lengths of time. Once sleep-wake cycles occur, true coma is no longer present. Differentiation of these states from true coma is important to administer appropriate therapy and to help determine prognosis.

In the *locked-in syndrome (de-efferented state),* patients are alert and aware of their environment but are quadriplegic, with lower cranial nerve palsies because of bilateral ventral pontine lesions that involve the corticospinal, corticopontine, and corticobulbar tracts. The patients are awake and alert but voluntarily able only to move their eyes vertically, to blink, or both. The locked-in syndrome is most often observed as a consequence of pontine infarction accompanying basilar attery thrombosis. Other causes include central pontine myelinolysis and brainstem mass lesions. A state similar to the locked-in syndrome may also be seen with severe polyneuropathy—in particular, acute inflammatory demyelinating polyradiculoneuropathy, myasthenia gravis, and neuromuscular blocking agents.

In the *persistent vegetative state,* patients have lost cognitive neurological function but retain vegetative or noncognitive neurological function such as cardiac action, respiration, and maintenance of blood pressure (ANA Committee on Ethical Affairs 1993). This state follows coma and is characterized by the absence of cognitive function or awareness of the environment, despite a preserved sleep-wake cycle. Spontaneous movements may occur and the eyes may open in response to external stimuli, but the patient does not speak or obey commands. A number of poorly defined syndromes have been used synonymously with persistent vegetative state, including *apallic syndrome* or *state, akinetic mutism, coma vigil, alpha coma, neocortical death,* and *permanent unconsciousness.* These terms, used variously by different authors, are probably best avoided because of their lack of precision (ANA Committee on Ethical Affairs 1993). The diagnosis of persistent vegetative state should be made cautiously and only after extended periods of observation (Childs et al. 1993).

The term *minimally conscious state* is distinguished from coma and persistent vegetative state by the preservation of discernible behavioral evidence of consciousness (Giancino et al. 2002). Patients in coma or persistent vegetative state may evolve into a minimally conscious state after acute brain injury. The diagnosis is established by the presence of one or more of the following behaviors: (1) ability to follow simple commands, (2) gestural or verbal yes/no responses, (3) intelligible verbalization, or (4) purposeful behaviors that are contingent upon and relevant to the external environment. It is important to differentiate this condition from coma and the persistent vegetative state for prognostic purposes.

Abulia is a severe apathy in which patients have blunting of feeling, drive, mentation, and behavior so that they neither speak nor move spontaneously (Mesulam 1986). Severe cast's resemble akinetic mutism, except that the patients remain alert and aware of their environment.

Catatonia may result in a state of muteness, with dramatically decreased motor activity. The maintenance of body posture, with preserved ability to sit or stand, distinguishes it from organic pathologic stupor. It is generally a psychiatric manifestation but may be mimicked by frontal lobe dysfunction or drug effect.

Pseudocoma is the term for patients who appear comatose (that is, unresponsive, unarousable, or both)

Tabic 5.1: Behavioral states confused with coma

Behavioral $tate	*Definition*	*Lesion*	*Comments*
Locked-in syndrome	Alert and aware, quadriplegic with lower cranial nerve palsy	Bilateral anterior pontine	A similar state may be seen with severe polyneuropathies, myasthenia gravis, and neuromuscular blocking agents
Persistent vegetative state	Absent cognitive function but retained "vegetative" components	Extensive cortical gray or subcortical white matter with relative preservation of brainstem	Synonyms include apallic syndrome, coma vigil, cerebral cortical death
Abuli;	Severe apathy, patient neither speaks nor moves spontaneously	Bilateral frontal medial	Severe cases resemble akinetic mutism, but patient is alert and aware
Catatonia	Mute, with marked decrease in motor activity	Usually psychiatric	May be mimicked by frontal lobe dysfunction or drugs
Pseudocoma	Feigned coma		

but have no structural, metabolic, toxic, or psychiatric disorder.

APPROACH TO COMA

The initial clinical approach to stupor and coma is based on the principle that *alt* alterations in arousal are acute, life-threatening emergencies until vital functions such as blood pressure and oxygenation are stabilized, potentially reversible causes of coma are treated, and the underlying cause of the alteration in arousal is understood. Urgent steps may be necessary to avoid or minimize permanent brain damage from reversible causes. In view of the urgency of this situation, every physician should develop a diagnostic and therapeutic routine to use with a patient with an altetation in consciousness. A basic understanding of the mechanisms that lead to impairment in arousal is necessary to develop this routine. The anatomic and physiologic bases for alterations in arousal are discussed in Chapter 74.

Although one should keep in mind the concept of a spectrum of arousal, for the sake of simplicity and brevity we use only the term *coma* in the rest of this chaptet. Table 5.2 lists many of the common causes of coma. More than half of all cases of coma are due to diffuse and metabolic brain dysfunction. In Plum and Posner's study (1995) of 500 patients initially diagnosed as having coma of unknown cause (in whom the diagnosis was ultimately established), "526 patients had diffuse and metabolic brain dysfunction. Almost half of these patients had dtug poisonings. Of the remaining patients, 101 had supra tentorial mass lesions, including 77 hemorrhagic lesions and nine infarctions; 65 had subtentorial lesions, mainly brainstem infarctions; and eight had psychiatric coma.

A logical decision tree often used in searching for the cause of coma divides the categories of diseases that cause coma into three groups: structural lesions, which may be above or below the tentorium; metabolic and toxic causes; and psychiatric causes. The history and physical examination determine the presence or absence of a structural lesion and quickly differentiate the general categories to decide what further diagnostic tests arc needed or to allow for immediate intervention if necessary.

Serial examinations are needed, with precise description of the behavioral state at different times, to determine if the patient is improving or, more ominously, worsening, and to decide if a change in therapy ot further diagnostic tests are necessary. Subtle declines in the intermediate states of arousal may herald precipitous changes in brainstem function, which may affect regulation of vital functions such as respiration or blood pressure. The dynamic quality of alterations of consciousness and the need for accurate documentation at different times cannot be overemphasized.

RAPID INITIAL EXAMINATION AND EMERGENCY THERAPY

A relatively quick initial assessment of the comatose patient is important to make sure the patient is medically and neurologically stable before a more detailed assessment is made. One must be sure that the patient is not in immediate need of medical or surgical intervention.

Urgent and sometimes empirical therapy is given to prevent further brain damage. Potential immediate metabolic needs of the brain are supplied by empirical use of supplemental oxygen, thiamine (at least 100 mg), and inttavenous 50% dextrose in water (25 g). A baseline serum glucose level should be obtained before glucose administration.

The use of intravenous glucose in patients with ischemic or anoxic brain damage is controversial. Fxtra glucose may augment local lactic acid production by anaerobic glycolysis and may worsen ischemic or anoxic damage. Clinically, however, we currently recommend empirical glucose administration when the cause of coma is unknown. There are two reasons for our approach: the frequent occurrence of alterations in arousal due to hypoglycemia, and the telativcly good prognosis for coma due to hypoglycemia when it is treated expeditiously and the potentially permanent consequences if it is not treated. In comparison, the prognosis for anoxic or ischemic coma is generally poor and probably will remain poor regardless of glucose supplementation.

Thiamine must always be given in conjunction with glucose to prevent precipitation of polioencephalitis hemorrhagica superioris (Wernicke's encephalopathy). Naloxone hydrochloride may be given parentcrally, preferably intravenously, in doses of 0.4 to 2.0 mg if opiate overdose is the suspected cause of coma. An abrupt and complete reversal of narcotic effect may precipitate an acute abstinence syndrome in individuals who are physically dependent on opiates.

An initial examination should include a check of general appearance, blood pressure, pulse, temperature, respiratory rate and breath sounds, best response ro stimulation, pupil size and responsiveness, and posturing or adventitious movements.

The neck should be stabilized in all instances of trauma until cervical spine fracture or subluxation can be ruled out. The airway is protected in all comatose patients and an intravenous line is placed.

Abdominal rigidity is a feature of peritonitis or perforated viscus. In coma, however, the classic signs of an acute condition in the abdomen may be subtle or nonexistent. In addition, the diagnosis of blunt abdominal trauma is difficult in patients with a change in mental status. Therefore, in unconscious patients with a history of trauma, peritoneal lavage by an experienced surgeon may be warranted.

Hypotension, marked hypertension, bradycardia, arrhythmias causing depression of blood pressure, marked

Table 5.2: Causes of coma

I. Symmetrical, Nonstructural

Toxins
- 1 tad
- Thallium
- Mushrooms
- Cyanide
- Methanol
- Ethylene glycol
- Carbon monoxide

Drills
- Sedatives
- Barbiturates*
- Other hypnotics
- Tranquilizers
- Bromides
- Alcohol
- Opiates
- Paraldehyde
- Salicylate
- Psychotropics
- Anticholinergics
- Amphetamines
- Lithium
- Phencyclidinc
- Monoamine oxidase inhibitors

Metabolic
- Hypoxia
- Hypercapnia
- Hypernatremia
- Hyponatremia *
- Hypoglycemia*
- Hyperglycemic nonketotic coma
- Diabetic ketoacidosis
- Lactic acidosis
- Hypercalcemia
- Hypocalcemia
- Hypermagnesemia
- Hyperthermia
- Hypothermia
- Reye's encephalopathy
- Aminoacidemia
- Wernicke's encephalopathy
- Porphyria
- Hepatic encephalopathy*
- Uremia
- Dialysis encephalopathy
- Addisonian crisis

Infections
- Bacterial meningitis
- Viral encephalitis
- Postinfectious encephalomyelitis
- Syphilis
- Sepsis
- Typhoid fever
- Malaria
- Waterhouse-Friderichsen syndrome

Psychiatric
- Catatonia

Other
- Postictal*
- Diffuse ischemia (myocardial infarction, congestive heart failure, arrhythmia)
- Hypotension
- Fat embolism*
- Hypertensive encephalopathy
- Hypothyroidism

II. Symmetrical, Structural

Supra tentorial
- Bilateral internal carotid occlusion
- Bilateral anterior cerebral artery occlusion
- Subarachnoid hemorrhage
- Thalamic hemorrhage*
- Trauma—contusion, concussion[1]
- Hydrocephalus

Infratentorial
- Basilar occlusion*
- Midline brainstem tumor
- Pontine hemorrhage*

III. Asymmetrical, Structural

Supra tentorial
- Thrombotic thrombocytopenic purpura!
- Disseminared intravascular coagulation
- Nonbacterial thrombotic endocarditis (marantic endocarditis)
- Subacute bacterial endocarditis
- Fat emboli
- Unilateral hemispheric mass (tumor, bleed) with herniation
- Subdural hemorrhage bilateral
- Intracerebral bleed
- Pituitary apoplexyf
- Massive or bilateral supratentorial infarction
- Multifocallcukoenccphalopathy
- Creutzfeldt-Jakob disease
- Adrenal leukodystrophy
- Cerebral vasculitis
- Cerebral abscess
- Subdural empyema
- Thrombophlebitis!
- Multiple sclerosis
- Leukoencenhalopathy associated with chemotherapy
- Acute disseminated encephalomyelitis
- Infratentorial
- Brainstem infarction
- Brainstem hemorrhage

* Relatively common asymmetrical presentation.
f Relatively symmetrical presentation.
Source: Data from Plum, F. 6t Posner, J. B. 1995, *The Diagnosis of Stupor and* Coma, 4th ed, FA Davis, Philadelphia; and Fisher, C. M. 19(59, "The neurological evaluation of the comatose patient," *Acta Neurol Stand,* vol. 45 [Suppl. 36].

hyperthermia, and signs of herniation mandate immediate therapeutic intervention.

Hyperthermia or meningismus leads to consideration of urgent lumbar puncture. *A computed tomography (CT) scan of the brain should he performed before lumbar puncture in any comatose patient.* Although the only absolute contraindication to lumbar puncture is the presence of an infection over the site of puncture, medicolegal considerations make a CT scan mandatory before lumbar puncture. To avoid a delay in therapy required to perform a CT scan, some authorities recommend initiating antibiotics immediately when acute bactetial meningitis is strongly suspected. If there is an inordinate delay in obtaining an emergency CT scan, lumbar puncture may have to be performed before the CT to allow the administration of antibiotics.

The risk of herniation from a lumbar puncture in patients with evidence of increased intracerebral pressure is difficult to ascertain from the literature; estimates range from 1% to 12%, depending on the series (Plum and Posner 1995). One must always keep in mind that both central and tonsillar herniation may increase neck tone.

Despite an elevated intracranial pressure, sufficient cerebrospinal fluid should always be obtained to perform the necessary studies. The performance of bacterial culture and cell count, essential in cases of suspected bacterial meningitis, requires but a few milliliters of fluid. Intravenous access and intravenous mannitol should be ready in case unexpected herniation begins after the lumbar puncture. When the cerebrospinal fluid pressure is greater rhan 500 mm H2O, some authorities recommend leaving the needle in place to monitor the pressure and administering intravenous mannitol to lower the pressure. If focal signs develop during or after the lumbar puncture, immediate intubation and hyperventilation may also be necessary to reduce intracerebral pressure urgently until more definitive therapy is available.

Ecchymosis, pctcchiae, or evidence of easy bleeding on general examination may indicate coagulation abnormality or thrombocytopenia. This increases the risk of epidural hematoma, which may cause devastating spinal cord compression. Measurements of prothrombin time, partial thromboplastin time, and platelet count should precede lumbar puncture in these cases, and the coagulation abnormality or thrombocytopenia should be corrected before lumbar puncture.

COMMON PRESENTATIONS

Coma usually presents in one of three ways. Most commonly, it occurs as an expected or predictable progression of an underlying illness. Examples of this are focal brainstem infarction with extension; the patient with chronic obstructive pulmonary disease who is given too high a concentration of oxygen, decreasing the patient's respiratory drive and resulting in carbon dioxide narcosis; and the patient with known barbiturate overdose when the ingested drug cannot be fully removed and begins to cause unresponsiveness. Second, coma occurs as an unpredictable event in a patient whose previous medical conditions are known to the physician. The coma may be a complication of an underlying medical illness, such as in a patient with arrhythmia who suffers anoxia after a cardiac arrest, or an unrelated event may occur, such as sepsis from an intravenous line in a cardiac patient or a stroke in a hypothyroid patient. Finally, coma can occur in a patient who is totally unknown to the physician. Sometimes this type of presentation is associated with a known probable cause, such as head trauma following a motor vehicle accident, but often the unknown comatose patient presents to the physician without an obvious associated cause. Although the patient without an obvious cause of coma may seem most challenging, thorough objective systematic assessment must be applied to every comatose patient. Special care must be taken not to be lulled or misled by an apparently predictable progression of an underlying illness or other obvious cause of coma.

HISTORY

Once the patient is relatively stable, clues to the cause of the coma should be sought by briefly interviewing relatives, friends, bystanders, or medical personnel who may have observed the patient before or during the decrease in consciousness. Telephone calls to family members may be helpful. The patient's wallet or purse should be examined for lists of medications, a physician's card, or other information.

Attempts should be made to ascertain the patient's social background and medical history and the circumstances in which the patient was found. The presence of drug paraphernalia or empty medicine bottles suggests a drug overdose. Newer recreational drugs, such as gamma hydroxybutyrate, must be considered in the differential diagnosis (Ryan and Stell 1997). Oral hypoglycemic agents or insulin in the medicine cabinet or refrigerator imply possible hypoglycemia. Antiarrhythmic agents such as procainamide or quinidine suggest existing coronary artery disease wirh possible myocardial infarction or warn that an unwitnessed arrhythmia may have caused cerebral hypoperfusion, with resulting anoxic encephalopathy. Warfarin is given to patients with deep venous thrombosis or pulmonary embolism, those at risk of cerebral emboli, and those with a history of brainstem or cerebral ischemia. Its use may be complicated by massive intracerebral bleeding. Patients found to be unresponsive at the scene of an accident, such as a motor vehicle accident, may be unresponsive because of trauma that occurred in the accident; alternatively, sudden loss of consciousness may have precipitated the accident.

The neurologist is often called when patients do not awaken following surgery or when coma supervenes following a surgical procedure. Postoperative causes of coma include many of those mentioned in Table 5.2. In addition, the physician must also have a high index of suspicion for certain neurological conditions that occur in this setting, including fat embolism, addisonian crisis, or hypothyroid coma (precipitated by acute illness or surgical stress); Wernicke's encephalopathy from carbohydrate loading without adequate thiamine stores; and iatrogenic overdose of a narcotic analgesic.

Attempts should be made to ascertain if the patient complained of symptoms before coma. Common symptoms include headache before subarachnoid hemorrhage, chest pain with aortic dissection or myocardial infarction, shortness of breath from hypoxia, stiff neck in meningoencephalitis, or vertigo in brainstem cerebrovascular accident. Nausea and vomiting are common in poisonings. Coma may also be due to increased intracranial pressure. Observers may have noted head trauma, drug abuse, seizures, or hemiparesis. Descriptions of falling to one side, dysarthria or aphasia, ptosis, pupillary dilation, or disconjugate gaze may help localize strucrural lesions. The time course of the disease as noted by family or friends may

help differentiate the often relatively slow, progressive course of toxic-metabolic or infectious causes from abrupt, catastrophic changes that are seen most commonly with vascular events.

Finally, family members or friends may be invaluable in identifying psychiatric causes of unresponsiveness. The family may describe a long history of psychiatric disease, previous similar episodes from which the patient recovered, current social stresses on the patient, or the patient's unusual, idiosyncratic response to stress. Special care must be taken with psychiatric patients because of the often biased approach to these patients, which may lead to incomplete evaluation. Psychiatric patients ate subject to all the causes of coma listed in Table 5.2.

GENERAL EXAMINATION

A systematic, detailed gcnctal examination is especially helpful in the approach to the comatose patient who is unable to describe his or her prior or current medical problems. This examination was begun in the initial rapid examination, with evaluation of blood pressure, pulse, respiratory rate, and temperature.

Blood Pressure Evaluation

Hypotension

Cerebral hypoperfusion secondary to hypotension may result in coma if the mean arterial pressure falls below the value for which the brain is able to autoregulate (normally 60 mm Hg). This value is substantially higher in chronically hypertensive individuals, as the cerebral blood flow-mean arterial pressure curve is shifted to the right. Among the causes of hypotension are hypovolemia, massive external or internal hemorrhage, myocardial infarction, cardiac tamponade, dissecting aottic aneurysm, intoxication with alcohol ot othet drugs (especially barbiturates), toxins, Wernicke's encephalopathy, Addison's disease, and sepsis. Although most patients with hypotension are cold because of peripheral vasoconstriction, patients with Addison's disease ot sepsis may have warm shock caused by peripheral vasodilation. Medullary damage may also result in hypotension because of damage to the pressor center.

Hypertension

Hypertension is the cause of alterations in arousal in hypertensive crisis and is seen secondarily as a response to cerebral infarction, in subarachnoid hemorrhage, with certain brainstem infarctions, and with increased intracerebral pressure. The Kocher-Cushing (or Claude Bernard) reflex is hypertension associated with bradycardia and respiratory irregularity caused by increased intracranial pressure- This response occurs more commonly in the setting of a posterior fossa lesion and in children. It results from compression or ischemia of the pressor area lying beneath the flour of the fourth ventricle. I lypertension is a common condition and thus may be present but unrelated to the cause of coma.

Heart Rate

In addition to the Kochet-Cushing reflex, bradycardia can result from myocardial conduction blocks, certain poison ings, and drugs, such as the beta blockers. Tachycardia is a result of hypovolemia, hyperthyroidism, fever, anemia, and certain toxins and drugs, including cocaine, atropine, and other anticholinergic medications.

Respiration

The most common causes of decreased respiratory rate are metabolic or toxic, such as carbon dioxide narcosis or drug overdose with central nervous system (CNS) depressants. Increased respiratory tate can result from hypoxia, hypercapnia, acidosis, hyperthermia, hepatic disease, toxins or drugs (especially those that produce a metabolic acidosis, such as methanol, ethylene glycol, paraldehyde, and salicylates), sepsis, pulmonary emboli (including fat emboli), and sometimes psychogenic unresponsiveness. Brainstem lesions causing hypopnea or hyperpnea are discussed below. Changes in respiratory rate or rhythm in a comatose patient may be deceiving, because a metabolic disorder may coexist with a CNS lesion.

Temperature

Core temperature must be measured with a rectal probe in a comatose patient, because oral or axillary temperatures are unreliable. Pyrexia is most often a sign of infection. Thus any evidence of fever in a comatose patient warrants strong consideration of lumbar puncture. Absence of an increased temperature does not rule out infection. Immunosuppresscd patients, elderly patients, and patients with metabolic or endocrine abnormalities such as uremia or hypothyroidism may not have increased temperature in response to overwhelming infection. Pure neurogenic hyperthermia is rare and is usually due to subarachnoid hemorrhage or diencephalic (hypothalamus) lesions. A clue to brainstem origin is shivering without sweating. Shivering in the absence of sweating, particularly when unilateral in nature, may also be observed with a deep intracerebral hemorrhage. Other causes of increased temperature associated with coma are heatstroke, thyrotoxic crisis, and drug toxicity. (Atropine and other anticholinergic agents elevate

core temperature but decrease diaphoresis, resulting in a warm, dry patient with dilated pupils and diminished bowel sounds.)

Except in heatstroke and malignant hyperthermia, fever does nor result in stupor or coma by itself. Conversely, hypothermia, regardless of cause, is anticipated to lead to altered consciousness. Hypothermia causes diminished cerebral merabolism and, if the temperature is sufficiently low, may result in an isoelectric electroencephalogram. Hypothermia is usually metabolic or environmental in cause; however, it is also seen with hypotension accompanied by vasoconstriction and may Occur with sepsis. Other causes of hypothermia associated with coma are hypothyroid coma, hypopituitarism, Wernicke's encephalopathy, cold exposure, drugs (barbiturates), and other poisonings. Central lesions causing hypothermia are found in the posterior hypothalamus. The absence of shivering or vasoconstriction or the presence of sweating is a clue to the central origin of these lesions.

General Appearance

The general appearance of the parient may provide further clues to the diagnosis. Torn or disheveled clothing may indicate prior assault. Vomitus may be a sign of increased intracranial pressure, drug overdose, or metabolic or other toxic cause. Urinary or fecal incontinence indicates an epileptic seizute or may result from a generalized autonomic discharge resulting from the same cause as the coma. Examination of body habitus may reveal a cushingoid patient at risk for an acute addisonian crisis with abrupt withdrawal of his or her medications or additional stress from intercurrent illness. Cachexia suggests cancer, chronic inflammatory disorders, Addison's disease, hypothyroid coma, or hyperthyroid crisis. The cachectic patient is also subject to Wernicke's encephalopathy in association with carbohydrate loading. Gynecomastia, spider nevi, testicular atrophy, and decreased axillary and pubic hair are common in the alcoholic with cirrhosis.

Head and Neck Examination

The head and neck must be carefully examined for signs of trauma. Palpation for depressed skull fractures and edema should be attempted, although it is not very sensitive. Laceration or edema of the scalp is indicative of head trauma. The term *raccoon eyes* refers to orbital ecchymosis resulting from anterior basal skull fracture. *Battle sign* is a hematoma overlying the mastoid, originating from basilar skull fracture extending into the mastoid portion of the temporal bone. The ecchymotic lesions are typically not apparent until 2 to 3 days after the traumatic event.

Meningismus

The slightest degree of neck stiffness may be a sign of infectious or carcinomarous meningitis, subarachnoid hemorrhage, or central or tonsillar herniation. Neck stiffness is absent in coma from any cause but may be present in less severe alterations in arousal. Scars on the neck may be from endarterectomy, implying vascular disease, or from thyroidectomy or parathyroidectomy, suggesting concomitant hypothyroidism, hypoparathyroidism, or both. Goiter may be found with hypothyroidism or hyperthyroidism.

Eye Examination

Examination of the eyes includes observation of the cornea, conjunctiva, sclera, iris, lens, and eyelids. Edema of the conjunctiva and eyelids may occur in congestive heart failure and nephrotic syndrome. Congestion and inflammation of the conjunctiva often occur in the comatose patient as a result of exposure. Enophthalmos indicates dehydration. Scleralicterus is seen with liver disease, and yellowish discoloration of the skin without scleral involvement may be due to drugs such as rifampin. Band keratopathy is caused by hypercalcemia, whereas hypocalcemia is associated with cataracts. Kayser-Fleischer rings are seen in progressive lenticular degeneration (Wilson's disease). Arcus senilis is seen in normal aging but also in hyperlipidemia. Fat embolism may cause petechiae in conjunctiva and eye grounds.

Funduscoptc Examination

Funduscopic examination demonstrates evidence of hypertension or diabetes. Grayish deposits surrounding the disc have been reported in lead poisoning. The retina is congested and edematous in methyl alcohol poisoning, and the disc margin may be blurred. Subhyloid hemorrhage appears occasionally as a consequence of a rapid increase in intracranial pressure resulting from subarachnoid hemorrhage. Papilledema results from increased intracranial pressure and may be indicative of an intracranial mass lesion or hypertensive encephalopathy.

Otoscopic Examination

Otoscopic examination should rule out hemotympanum or otorrhea from a basilar skull fracture involving the petrous ridge as well as infection of the middle ear. Infections of the middle ear, mastoid, and paranasal sinuses are the most common sources of underlying infection in brain abscess (Osenbach and Loftus 1992). Rhinorrhea, which appears as clear fluid from the nose, may depend on head position. The presence of glucose in this watery discharge is virtually diagnostic, though false-positive results may be observed.

Oral Examination

Alcohol intoxication, diabetic ketoacidosis (acetone odor), uremia, and hepatic encephalopathy (musty odor of cholemia or fetor hepatis) may be suspected from the odor of the breath. Arsenic poisoning produces the odor of garlic. Poor oral hygiene or oral abscesses may be a source of sepsis or severe pulmonary infection with associated hypoxemia. Pustules on the nose or upper lip may seed the cavernous sinus with bacteria by way of the angular vein. Lacerations on the tongue, whether old or new, suggest seizure disorder. Thin, blue-black pigmentation along the gingival margin may be seen in certain heavy-metal poisonings (bismuth, mercury, and lead).

Integument Examination

Systematic examination of the integument includes inspection of the skin, nails, and mucous membranes. A great deal of information can be gained by a brief examination of the skin (Table *53).* Hot, dry skin is a feature of heatstroke. Sweaty skin is seen with hypotension or hypoglycemia, Drugs may cause macular-papular, vesicular, or petechial-purpuric rashes or bullous skin lesions. Bullous skin lesions are most often a result of barbirurates but also may be caused by imipramine, meprobamate, glutcthimide, phcnothiazine, and carbon monoxide. Kaposi's sarcoma, anogenital herpetic lesions, or oral candidiasis should suggest the acquired immunodeficiency syndrome (AIDS), with its plethora of CNS abnormalities.

Examination of Lymph Nodes

Generalized lymphadenoparhy is nonspecific; it may be seen with neoplasm, infection (including AIDS), collagen vascular disease, sarcoid, hyperthyroidism, Addison's disease, and drug reaction (especially due to phenytoin). Local lymph node enlargement or inflammation, however, may provide clues to a primary tumor site or source of infection.

Cardiac Examination

Cardiac auscultation will confirm the presence of arrhythmias such as atrial fibrillation, with its inherent increased risk of emboli. Changing mitral murmurs are heard wirh atrial myxomas and papillary muscle ischemia, which is seen with current or impending myocardial infarction. Constant murmurs indicate valvular heart disease and may be heard with the valvular vegetation of bacterial endocarditis.

Abdominal Examination

Possibly helpful findings on abdominal examination include abnormal bowel sounds, organomegaly, masses, or ascites. Bowel sounds are absent in an acute abdominal condition as well as with anticholinergic poisoning. Hyperactive bowel sounds may be a consequence of increased gastrointestinal motility from exposure to acetylcholinesterase inhibitor (a common pesticide ingredient). The liver may be enlarged as a result of right heart failure or tumor infiltration. Nodules or a rock-hard liver may be caused by hepatoma or metastatic disease. The liver may be small and hard in cirrhosis.

Splenomegaly is caused by porral hypertension, hematologic malignancies, infection, and collagen vascular diseases. Intra-abdominal masses may indicate carcinoma. Ascites occurs with liver disease, right heart failure, neoplasms with metastasis to liver, or ovarian cancer.

Miscellaneous Examinations

Examination of the breasts in the female and the testicles in the male and rectal examination may reveal common primary tumors. Stool from a rectal examination that tests positive for blood is consistent with gastrointestinal bleeding and, possibly, bowel carcinoma. Blood in the gastrointestinal tract may be sufficient to incite hepatic encephalopathy in the patient with cirrhosis.

NEUROLOGICAL EXAMINATION

Neurological signs may show every degree of change along a continuum, and they may be partial or incomplete. For example, the patient may have a partial third nerve palsy with pupillary dilation rather than a complete absence of all third nerve funcrion, or muscle rone may be decreased but not absent. This concept is especially important in the examination of the stuporous or comatose patient because the level of arousal may also influence the expression of neurological signs. In the stuporous or comatose patient, findings that are not completely normal should not be dismissed as unimportant. These findings should be carefully considered until their pattern or meaning is understood.

The neurological examination of a comatose patient serves three purposes: (1) to aid in determining the cause of coma, (2) to provide a baseline, and (3) to help determine the prognosis of coma. For prognosis and localization of a structural lesion, certain parts of the examination have been found to be most helpful: (I) state of consciousness, (2) respiratory pattern, (3) pupillary size and response to light, (4) spontaneous and reflex eye movements, and (5) skeletal muscle motor response.

Tabic '5..1: Skin lesions and rashes in coma

Lesion or rash	*Possible cause*
Antecubital needle marks	Opiate drug abuse
Pale skin	Anemia or hemorrhage
Sallow, puffy appearance	Hypopituitarism
Hype melanosis (increased pigment)	Porphyria, Addison's disease, chronic nutritional deficiency, disseminated malignant melanoma, chemotherapy
Generalized cyanosis	Hypoxemia or carbon dioxide poisoning
Grayish-blue cyanosis	Methemoglobin (aniline or nitrobenzene) intoxication
Localized cyanosis	Arterial emboli or vasculitis
Cherry-red skirl	Carbon monoxide poisoning
Icterus	Hepatic dysfunction or hemolytic anemia
Perec hi ae	Disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, drugs
Ecchymosis	Trauma, corticosteroid use, abnormal coagulation from liver disease or anticoagulants
Telangiectasia	Chronic alcoholism, occasionally vascular malformations of the brain
Vesicular rash	Herpes simplex Varicella Behcet's disease Drugs
Petechial-purpuric rash	Meningococcemia Other bacterial sepsis (rarely) Gonococcemia Staphylococcemia *Pseudomonas* Subacute bacterial endocarditis Allergic vasculitis Purpura fulminans Rocky Mountain spotted fever Typhus Fat emboli
Macular-papular rash	Typhus *Candida* *Cryptococcus* Toxoplasmosis Subacute bacterial endocarditis Staphylococcal toxic shock Typhoid Leptospirosis *Pseudomonas* sepsis Immunological disorders Systemic lupus erythematosus Dcrmatomyositis Scrum sickness
Other skin lesions	
Ecthyma gangrenosum	Necrotic eschar often seen in the anogenital or axillary area in *Pseudomonas* sepsis
Splinter hemorrhages	Linear hemorrhages under the nail, seen in subacute bacterial endocarditis, anemia, leukemia, and sepsis
Osier's nodes	Purplish or erythematous painful, tender nodules on palms and soles, seen in subacute bacterial endocarditis
Gangrene of digits' extremities	Emboli to larger peripheral ur arteries

Source: Data from Corey, L. & Kirby, P. 1987, "Rash and fever," in *Harrison's Principles of Internal Medicine,* 11th ed, eds K. Braunwald, K. J. isselbacher, & R. G. Petersdorf, McGraw-Hill, New York.

State of Consciousness

The importance of a detailed description of the state of consciousness has been stressed previously. It is imperative that the exact stimulus and the patient's specific response be recorded. Several modes of stimulation should be used, including auditory, visual, and noxious. Stimuli of progressively increasing intensity should be applied to the patient, with the maximal state of arousal noted and the stimuli, site of stimulation, and patient's exact response described. One should start with verbal stimuli, softly and then more loudly calling the patient's name or giving simple instructions to open his or her eyes. If there is no significant response, more threatening stimuli, such as taking the patient's hand and advancing it toward the patient's face, are applied. Finally, painful stimuli may be needed

to arouse the patient. All patients in apparent coma should be asked to open their eyes and look up and down, thus avoiding the possibility of mistaking the locked-in syndrome, in which these voluntary movements are preserved, for coma.

Supraorbital pressure evokes a response in patients who may have lost afferent pain pathways as a result of peripheral neuropathy or spinal cord or some brainstem lesions. Pinching the chest or extremities may help localize a lesion. Care must be taken to avoid soft-tissue damage. Purposeful movements indicate a milder alteration in consciousness. Vocalization to pain in the early hours of a coma, even if only a grunt, indicates relatively light alteration in consciousness. Later, primitive vocalization may be a feature of the vegetative state. Asymmetry in response from either side of the face or body may localize structural lesions.

The Glasgow Coma Scale (Table 5.4) is used widely ro assess rhe initial sevcriry of traumatic brain injury. This battery assesses three separate aspects of a patient's behavior: the stimulus required to induce eye opening, rhe best motor response, and the host verbal response. Degrees of increasing dysfunction are scored. Its reproducibility and simplicity make the Glasgow Coma Scale an ideal method of assessment for non-neurologists involved in the care of comatose patients, such as neurological inrensive care nurses. However, its failure to assess other essential neurological parameters limits its utility. Additionally, in patients who arc intubated or who have suffered facial trauma, it may be difficult to assess certain components of the Glasgow Coma Scale, such as eye opening and speech. Wijdicks and colleagues (1998) have suggested two new tools that may serve as substitutes for the Glasgow Coma Scale in these patients as well as those with fluctuating levels of consciousness. One test referred to as the "continuous performance test" monitors level of alertness and requires the patient to raise his hand every time he hears a certain letter in a standardized sentence. Another, the "hand position test,[11] is a test of praxis in which the patient must mimic three different hand positions that are demonstrated to him.

Table S.4: The Glasgow Coma Scale

Best motor response	
Obeys	M6
Localizes	5
Withdraws	4
Abnormal flexion	3
Extensor response	2
Nil	1
;rbal response	
Oriented	V5
Confused conversation	4
Inappropriate words	3
Incomprehensible sounds	2
Nil	1
e opening	
Spontaneous	E4
To speech	3
To pain	2
Nil	1

Respiration

Normal breathing is quiet and unlabored. The presence of any respiratory noise implies airway obstruction, which must be dealt with immediately to prevent hypoxia. Normal respiration depends on two components: a brainstem mechanism, located between the mid pons and cervical medullary junction, that regulates metabolic needs, and forebrain influences that subserve behavioral needs such as speech production. The organization and function of brainstem mechanisms responsible for respiratory rhyrhm generation as well as forebrain influences are complex and beyond the scope of this chapter. For an excellent review of this subject, the reader is referred to Long and Duffin (J986). Neuropathologies correlates of respiration are presented in Figure 5.1

Respiratory patterns that arc helpful in localizing level of involvement include Cheyne-Stokes respiration, central neurogenic hyperventilation, apneustic breathing, cluster brearbing, and ataxic respiration. *Cheyne-Stokes respiration* is a respiratory pattern that slowly oscillates between hyperventilation and hypoventilation. In 1818 Cheyne described his patient in rhe following manner: "For several days his breathing was irregular; it would entirely cease for a quarter of a minute, then it would become perceptible, though very low, then by degrees it became heaving and quick and then it would gradually cease again. This revolution in the state of his breathing occupied about a minute during which there were about 30 acts of respiration," Cheyne-Stokes respiration is associated with bilateral hemispheric or diencephalic insults, but it may occur as a result of bilateral damage anywhere along rhe descending pathway between the forebrain and upper pons. It also is seen with cardiac disorders that prolong circulation time. Alertness, pupillary size, and heart rhythm may vary during Cheyne-Stokes respiration (Plum and Posner 1995). Patients are more alert during the waxing portion of breathing.

A stable pattern of Cheyne-Stokes respiration is a relatively good prognostic sign, usually implying that pcrmanenr brainstem damage has not occurred. However, the emergence of Cheyne-Stokes respiration in a patient with a unilateral mass lesion may be an early sign of herniarion. A change in pattern from Cheyne-Stokes respiration to the respiratory patterns described in the following is ominous.

Two breathing patterns similar to Cheyne-Stokes respiration should not be confused with it. *Short-cycle periodic breathing* is a respiratory pattern with a shorter cycle {faster rhythm) than Cheyne-Stokes respiration, with one

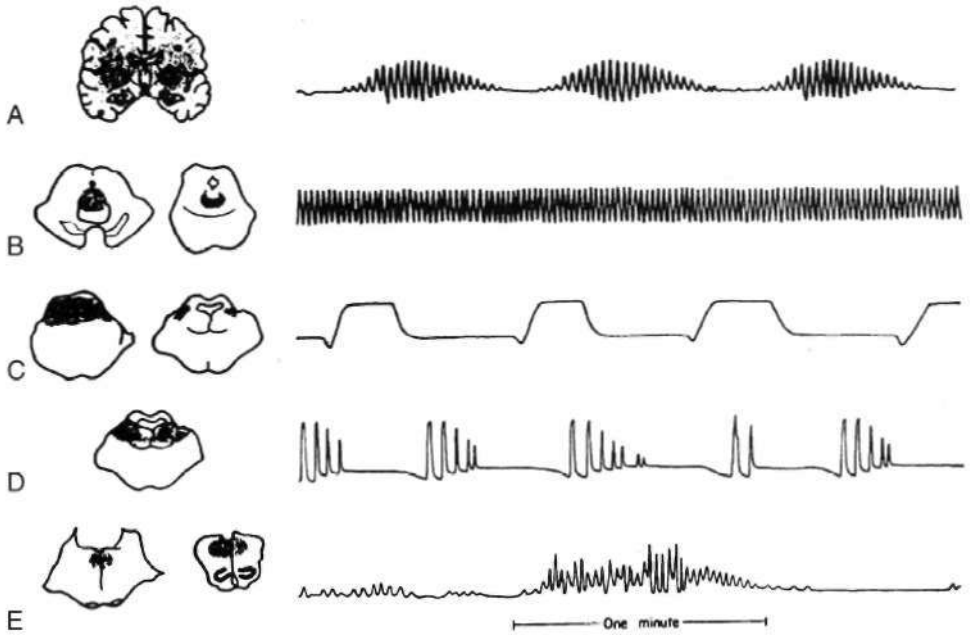

FIGURE 5.1 Abnormal respiratory patterns associated with pathologic lesions (shaded areas) at various levels of the brain. Tracings by chest-abdomen pneumograph; inspiration reads up. (A) Chcync-Stokes respiration—diffuse forebrain damage. (B) Central neurogenic hyperventilation—lesions of low midbrain ventral to aqueduct of Sylvius and of upper pons ventral to the fourth ventricle. (Q Apneusis—dorsolateral tegmental lesion of middle and caudal pons. (D) Cluster breathing—lower pontine tegmental lesion. (E) Ataxic breathing—lesion of the reticular formation of the dorsomedial part of the medulla. (Reprinted from Plum, K, &; Posner, J. B. 1995, *The Diagnosis of Stupor and Coma,* 3rd ed, Oxford University Press, New York. Copyright 1966, 1972, 1980, 1996, Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.)

or two waxing breaths, followed by two to four rapid breaths, then one or two waning breaths. It is seen with increased intracranial pressure, lower pontine lesions, or expanding lesions in the posterior fossa (Plum and Posner 1995). A similar type of respiration, in which there are short bursts of seven to ten rapid breaths, then apnea without a waning and waxing prodrome, has been erroneously referred to as *Biot's breathing.* Biot, in fact, described an ataxic respiratory pattern.

Central neurogenic respiration refers to rapid breathing, from 40 to 70 breaths per minute, usually caused by central tegmental pontine lesions just ventral to the aqueduct or fourth ventricle (Plum and Posner 1995). This type of breathing is rare and must be differentiated from reactive hyperventilation resulting from metabolic abnormalities of hypoxemia secondary to pulmonary involvement. Large CNS lesions may cause neurogenic pulmonary edema, with associated hypoxemia and increased respiratory rate. Increased intracerebral pressure causes spontaneous hyperpnea. Hyperpnea cannot be ascribed to a CNS lesion when arterial oxygen pressure is less than 70 to 80 mm Hg or carbon dioxide pressure is greater than 40 mm Hg.

Kussmaui breathing is a deep, regular respiration observed with metabolic acidosis. *Apneustic breathing* is a prolonged inspiratory gasp with a pause at full inspiration. It is caused by lesions of the dorsolateral lower half of the pons (Plum and Posner 1995). *Cluster breathing,* which results from high medullary damage, involves periodic respirations that are irregular in frequency and amplitude, with variable pauses between clusters of breaths.

Ataxic breathing is irregular in rate and rhythm and is usually due to medullary lesions. Ataxic respiration and bilateral sixth nerve palsy may be a warning sign of brainstem compression from an expanding lesion in the posterior fossa. This is an important sign, because brainstem compression resulting from tonsillar herniation (or other causes) may result in abrupt loss of respiration or blood pressure. Ataxic and gasping respiration are signs of lower brainstem damage and are often preterminal respiratory patterns.

Pupil Size and Reactivity

Normal pupil size in the comatose patient depends on the level of illumination and the state of autonomic innervation. The sympathetic efferent innervation consists of a three-neuron arc. The first-order neuron arises in the hypothalamus and travels ipsilaterally through the posterolateral tegmentum to the ciliospinal center of Budge at the level of Tl spinal cord. The second-order neuron leaves this center and synapses in the superior cervical sympathetic ganglion. The third-order neuron travels along the internal carotid artery and then through the ciliary ganglion to the puptllodtlator muscles. The parasympathetic efferent

innervation of the pupil arises in the Edinger-Westphal nucleus and travels in the oculomotor nerve to the ciliary ganglion, from which it innervates the pupillosphinctcr muscle (Figure 5.2).

Afferent input depends on the integrity of the optic nerve, optic chiasm, optic tract, and projections into the midbrain tectum and efferent fibers through the Edinger-Westphal nucleus and oculomotor nerve. Abnormalities in pupil size and reactivity help delineate structural damage between the thalamus and pons (Figure 5.3), act as a warning sign heralding brainstem herniation, and help differentiate structural causes of coma from metabolic causes.

Thalamic lesions cause small, reactive pupils, which are often referred to as *diencephalic pupils.* Similar pupillary findings arc noted in many toxic-metaholic conditions resulting in coma. Hypothalamic lesions or lesions elsewhere along the sympathetic pathway result in *Horner's syndrome.* Midbrain lesions produce three types of pupillary abnormality, depending on where the lesion occurs. Dorsal tcctal lesions interrupt the pupillary light reflex, resulting in *midposition eyes,* which arc fixed to light but react to accommodation, though the reaction is impossible to test in the comatose patient. Spontaneous fluctuations in size occur, and the ciliospinal reflex is preserved. Nuclear midbrain lesions usually affect both sympathetic and parasympathetic pathways, resulting in *fixed, irregular midposition pupils,* which may be unequal. Lesions of the third nerve in the brainstem or after the nerve has left the brainstem parenchyma cause *wide pupillary dilation,* unresponsive to light. Pontine lesions interrupt sympathetic pathways only to cause small, so-called *pinpoint pupils,* which remain reactive, although magnification may be needed to observe this. Lesions above the thalamus and below the pons should leave pupillary function intact, except for Horner's syndrome in medullary or cervical spinal cord lesions. The pathophysiology of pupillary response is discussed further in Chapter 17.

Asymmetry in pupillary size or reactivity, even of minor degree, is important. Asymmetry of pupil size may be due to dilation (mydriasis) of one pupil, such as with third nerve palsy, or contraction (miosis) of the other, as in Horner's syndrome. These may be differentiated by associated neurological deficits. A dilated pupil caused by a partial third nerve palsy is less reactive and may also be associated with extraocular muscle involvement. The pupil in Horner's syndrome is reactive and, if it results from a lesion in the CNS, may be associated with anhidrosis of the entire ipsilateral body. Cervical sympathetic lesions produce anhidrosis only of face, neck, and arm. A partial or complete third nerve palsy causing a dilated pupil may result from an intramedullary lesion, most commonly in the midbrain, such as an intramedullary glioma or infarction; uncal herniation compressing the third nerve; or a posterior communicating artery aneurysm. A sluggishly reactive pupil may be one of the first signs of uncal herniation, soon to be followed by dilation of that pupil and, later, complete third nerve paralysis.

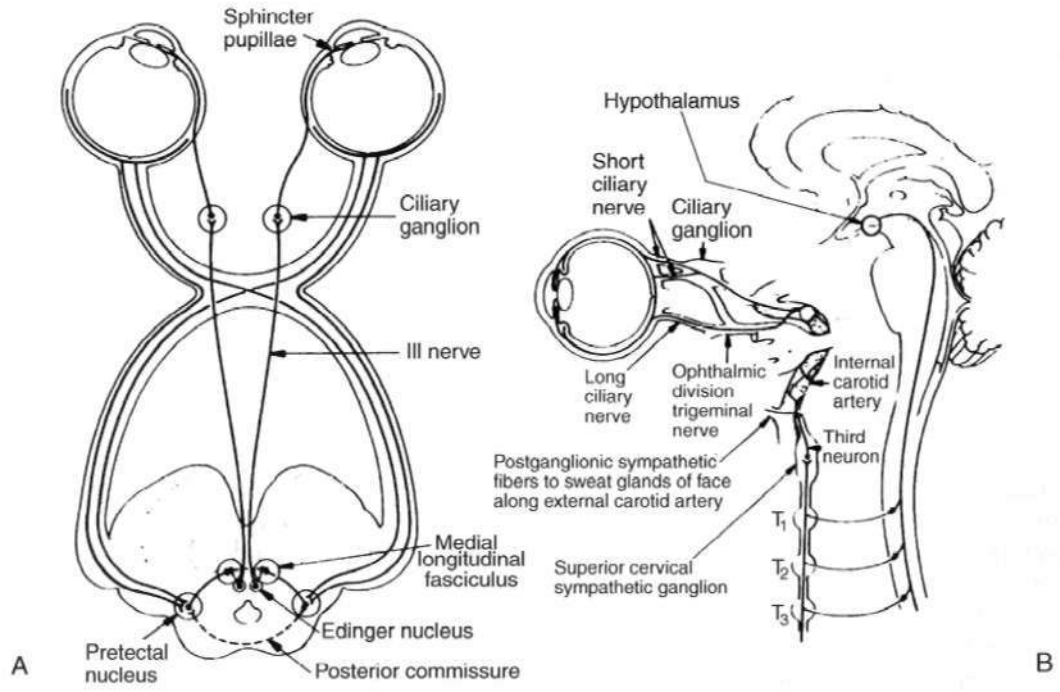

FIGURE 5.2 (A) The parasympathetic pupilloconstrictor pathway. (B) The sympathetic pupillodilator pathway. (Reprinted from Plum, F. & Posner, J. B. 1995, *The Diagnosis of Stupor and Coma*, 3rd ed. Oxford University Press, New York. Copyright 1966, 1972, 1980, 1996, Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.)

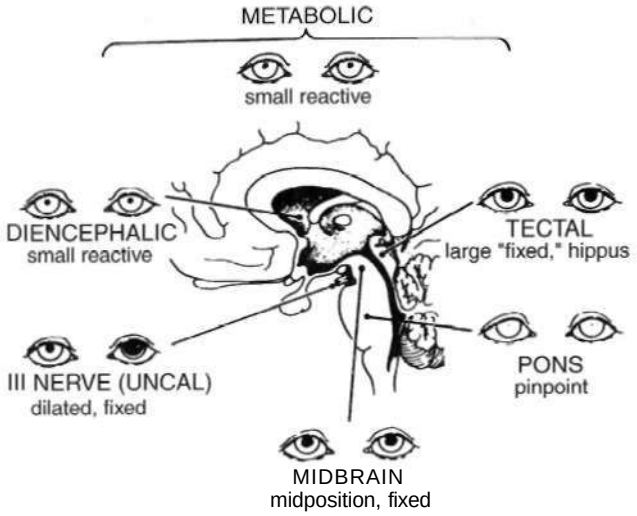

FIGURE 5.3 Pupils in comatose patients. (Reprinted from Plum, F. & Posner, J. B. 1995, *The Diagnosis of Stupor and Coma*, 3rd ed. Oxford University Press, New York. Copyright 1966, 1972, 1980, 1996, Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.)

Several caveats are important when examining the pupil or pupillary reflexes. A common mistake is the use of insufficient illumination. The otoscope may be useful in this regard because it provides both adequate illumination and magnification. Rarely, pre-existing ocular or neurological injury may fix the pupils or result in pupillary asymmetry. Seizures may cause transient anisocoria. Local and systemic medications may affect pupillary function. Topical ophthalmologic preparations containing acetylcholinesterase inhibitor, used in the treatment of glaucoma, result in miosis. The effect of a mydriatic agent placed by the patient or a prior observer may wear off unevenly, resulting in pupillary asymmetry. Some common misleading causes of a unilateral dilated pupil include prior mydriatic administration, old ocular trauma or ophthalmic surgery, and, more rarely, carotid insufficiency.

Ocular Motility

Normal ocular motility depends on the integrity of a large portion of the cerebrum, cerebellum, and brainstem. Preservation of normal ocular motility implies that a large portion of the brainstem from the vestibular nuclei at the pontomedullary junction to the oculomotor nucleus in the midbrain is intact. Voluntary ocular motility cannot be judged in the comatose patient, so one must rely on reflex eye movements that allow for assessment of the oculomotor system. The eyes normally are conjugate and in the midposition in the alert person. Sleep or obtundation alone may unmask a latent vertical or horizontal strabismus, resulting in disc on jugate gaze; therefore, patients must be examined when maximally aroused. The eyes return to the midposition when patients are brain dead.

Evaluation of ocular motility consists of three main elements: (1) observation of the restmi; position of the eyes, including eye deviation; (2) notation of spontaneous eye movements; and (3) testing of reflex ocular movements.

Abnormalities in Resting Position

Careful attention must be paid to the resting position of the eyes. Even a small discrepancy in eye position may represent a partial extraocular nerve palsy. Partial nerve palsies or combined nerve palsies predictably result in a more complex picture on examination. Unilateral third nerve palsy from either an intramedullary midbrain lesion or extra medullary compression causes the affected eye to be displaced downward and laterally. A sixth nerve palsy produces inward deviation. Isolated sixth nerve palsy, however, is a poor localizer because of its extensive course and because nonspecific increases in intracranial pressure may cause a sixth nerve palsy, presumably from stretching of the extramedullary portion of the nerve. A fourth netve palsy is difficult to assess in the comatose patient because of the subtle nature of the deficit in ocular motility. Extraocular nerve palsies often become more apparent with the doll's eye maneuver or cold caloric testing in the comatose patient.

Eye Deviation

Spontaneous eye deviation may be conjugate or dysconjugate. Conjugate lateral eye deviation is usually caused by an ipsilateral lesion in the frontal eye fields but may be due to a lesion anywhere in the pathway from the ipsilateral eye fields to the contralateral parapontine reticular formation (lateral gaze center). Dysconjugate lateral eye movement may result from a sixth nerve palsy in the abducting eye, a third nerve palsy in the adducting eye, or an internuclear ophthalmoplegia. An internuclear ophthalmoplegia may be differentiated from a third nerve palsy by the preservation of vertical eye movements.

Downward deviation of the eyes below the horizontal meridian is usually caused by brainstem lesions (most often from tectal compression); however, it may also be seen in metabolic disorders such as hepatic coma. Thalamic and subthalamic lesions produce downward and inward deviation of the eyes. Patients with these lesions appear to be looking at the tips of their noses. Sleep, seizure, syncope, apnea of Cheync-Stokes respiration, hemorrhage into the vermis, and brainstem ischemia or encephalitis cause upward eye deviation, making it a poor localizing sign. Skew deviation is a maintained deviation of one eye above the other (hypertropia) that is not due to a peripheral neuromuscular lesion or a local extracranial problem in the orbit. It usually indicates a posterior fossa lesion (brainstem or cerebellar) (Leigh and Zee 1991). Dysconjugate vertical

eye position may sometimes occur in the absence of a brainstem lesion in the obtunded patient.

Spontaneous Eye Movements

Spontaneous eye movements are of many types. Purposeful-appearing eye movements in a patient who otherwise **seems unresponsive** lead **to** consideration **ot the locked-in** syndrome, catatonia, pseudocoma, or the persistent vegetative state. *Roving eye movements* are slow, conjugate, lateral to-and-fro movements. For roving eye movements to be present, the oculomotor nuclei and their connections must be intact. Generally, when roving eye movements are present, the brainstem is relatively intact and coma is the result of a metabolic or toxic cause or bilateral lesions above the brainstem. Roving eye movements may be complicated by ocular palsies or internuclear ophthalmoplegia. These superimposed lesions produce relatively predictable patterns but often obscure the essential roving nature of the movement for the inexperienced observer,

Nystagmus occurring in comatose patients suggests an irritative or epileptogenic supratentorial focus. An epileptogenic focus in one frontal eye field causes contralateral conjugate eye deviation. Nystagmus due to an irritative focus may rarely occur alone, without other motor manifestations of seizures. In addition, inconspicuous movements of the eye, eyelid, face, jaw, or tongue may be associated with electroencephalographic status epilepticus. An electroencephalogram may be required to ascertain this condition.

Spontaneous conjugate vertical eye movements are separated into different types according to the relative velocities of their downward and upward phases. In *ocular bobbing,* there are rapid downward jerks of both eyes, followed by a slow return to the midposition (Leigh and Zee 1991). In the typical form, there is associated paralysis of both reflex and spontaneous horizontal eye movements. *Monocular* or *paretic bobbing* occurs when a coexisting ocular motor palsy alters the appearance of typical bobbing. The term *atypical bobbing* refers to all other variations of bobbing that cannot be explained by an ocular palsy superimposed on typical bobbing. Most commonly, the term is used to describe ocular bobbing when lateral eye movemenrs are preserved. *Typical ocular bobbing* is specific but not pathognomonic for acute pontine lesions. Atypical ocular bobbing occurs with anoxia and is nonlocaiizing. *Ocular dipping,* also known as *inverse ocular bobbing,* refers to spontaneous eye movements in which an initial slow downward phase is followed by a relatively rapid return. Reflex horizontal eye movements are preserved. It is usually associated with diffuse cerebral damage. In *reverse ocular bobbing* there is a slow initial downward phase, followed by a rapid return that carries the eyes past the midposition into full upward gaze. Then the eyes slowly return to the midposition. It is n on localizing.

Vertical nystagmus, caused by an abnormal pursuit or vestibular system, is slow deviation of the eyes from the primary position, with a rapid, immediate return to the primary position. It is differentiated from bobbing because there is no latency between the corrective saccade and the next slow deviation. *Ocular-palatal myoclonus* occurs after damage to the lower brainstem involving the Guillain-Mollaret triangle, which extends between the cerebellar dentate nucleus, red nucleus, and inferior olive, Ocular movements, which may be rotatory or circular, move with the same beat as palatal movements. Ocular flutter is back-to-back saccades in the horizontal plane and may be a feature of cerebellar disease.

Reflex Ocular Movements

Examination of ocular movement is not complete in the comatose patient without assessment of reflex ocular movements, including the oculocephalic reflex (doll's eye phenomenon) and, if necessary, the vestibulo-oculogyric reflex, by caloric (thermal) testing. In practice, the terms *doll's eye phenomenon* and *doll's eye maneuver* are used synonymously to refer to the oculocephalic reflex, but rhese terms are often confusing to the non-neurologist. It is better to use the term *oculocephalic reflex,* followed by a description of the response. This reflex is tested by sudden passive rotation of the head in both directions laterally and flexion and extension of the neck wink- observing the motion of the eyes. When supranuclear influences on the oculomotor nerve are removed, the eyes appear to retain their fixation on a point in the distance when the head is turned. *This maneuver should not be performed on any patient until the stability of the neck has been adequately assessed.* If there is any question of neck stability, a neck brace should be applied and caloric testing substituted. In the normal oculocephalic reflex (normal or positive doll's eye phenomenon), the eyes move conjugately in a direction opposite to the direction of movement of the head. Cranial nerve palsies predictably alter the response to this maneuver (Table *5.5).*

Clinical caloric testing (as distinct from quantitative calorics, used to assess vestibular end organ disorders} is commonly done by applying cold water to the tympanic membrane. It is done with the head tilted backward 60 degrees from the horizontal to allow maximal stimulation of the lateral semicircular canal, which is most responsible for reflex lateral eye movements. After carefully checking to make sure that the ear canal is patent and the tympanic membrane is free of defect, 10 mL of ice-cold water are slowly injected into one ear canal. For purposes of the neurological examination, irrigation of each ear with 10 mL of ice water is generally sufficient.

Cold water applied to the tympanic membrane causes currents to be set up in the cndolymph of the semicircular canal. This results in a change in the baseline firing of the vestibular nerve and slow (tonic) conjugate deviation of

Table 5.5: Oculocephalic reflex (to be performed only after neck stability has been ascertained)

Method	*Response*	*Interpretation*
Lateral: rotation of the head	Eyes remain conjugate, move in direction opposite to head movement (appear to maintain fixation)	Notmal
	No movement in either eye on rotating head to left or rijiln	Brainstem lesion
	Eyes move appropriately when head is rotated in one direction but do not move when head is rotated in opposite direction	Bilateral labyrinth dysfunction
	One eye abducts, the other eye docs not adduct	Drugs
	One eye abducts, the othet does not adduct	Anesthesia Unilateral lesion in lateral ga/.c center (PPRF) Third nerve palsy Intranuclear ophthalmoplegia Fourth nerve palsy
Vertical: flexion and extension of the head	Eyes remain conjugate, move in direction opposite ro head movement	Normal
	No movement in either eye	Same as above with no movement on lateral head rotation
	Only one eye moves	Third nerve palsy
	Bilateral symmetrical limitation of upg;ue	Aging

the eyes toward the stimulated ear. In an awake person, the eye deviation is corrected with a resulting nystagmoid jerking of the eye toward the midline (fast phase). Warm-water irrigation produces reversal of flow of the endolymph, which causes conjugate eye deviation with a slow phase away from the stimulated ear and a normal corrective phase toward the ear. By tradition, the nystagmus is named by the direction of the fast phase. The mnemonic COWS (raid opposite, warm same) refers to the fast phases. Simultaneous bilateral cold water application results in slow downward deviation, whereas simultaneous bilateral warm water application causes upward deviation.

Oculocephalic or caloric testing may elicit subtle or unsuspected ocular palsies. Abnormal dysconjugate responses occur with cranial nerve palsies, intranuclear ophthalmoplegia, or restrictive eye disease. Movements may be hyperactive, sluggish, or absent. Sometimes reinforcement of cold caloric testing with superimposed passive head turning after injection of cold water into the ear may reveal eye movement when either test alone shows none.

False-negative or misleading responses on caloric testing occur with pre-existing inner ear disease, vestibulopathy like that caused by ototoxic drugs such as streptomycin, vestibular paresis caused by illnesses such as Wernicke's encephalopathy, and drug effects. There is no response when the labyrinth is destroyed; however, partial lesions of the labyrinth may increase or decrease the response. Lesions of the vestibular nerve cause a decreased or absent response. Drugs that suppress eirher vestibular or oculomotor function, or both, include sedatives, anticholinergics, anticonvulsants, tricyclic antidepressants, and neuromuscular blocking agents. If the response from one ear is indeterminate, both cold- and warm-water stimuli should be applied to the other ear. If the test remains equivocal, superimposition of the doll's eye maneuver is recommended. The interpretation of abnormal cold caloric responses is summarized in Table 5.6.

An unusual ocular reflex that has been observed in the setting of the persistent vegetative state is reflex opening of both eyes triggered by flexion of an arm at the elbow. This reflex is distinct from reflex eye opening in the comatose patient induced by raising the head or turning it from side to side.

MOTOR SYSTEM

Examination of the motor system of a stuporous or comatose patient begins with a description of the resting posture and adventitious movements. Purposeful and nonpurposeful movements are noted and the two sides of the body compared. Head and eye deviation to one side, with contralateral hemiparesis, suggests a supratentorial lesion, whereas ipsilatcral paralysis indicates a probable brainstem lesion. External rotation of the lower limb is a sign of hemiplegia or hip fracture.

Decerebrate posturing is bilateral extensor posture, with extension of the lower extremities and adduction and internal rotation of the shoulders and extension at the elbows and wrist. Bilateral midbrain or pontine lesions are usually responsible for decerebrate posturing. Less commonly, deep metabolic encephalopathies or bilateral supratentorial lesions involving the motor pathways may produce a similar pattern.

Tabic 5.6: Caloric testing

Method	*Response*	*interpretation*
Cold water instilled in right ear	Slow phase to right, fast (corrective) phase to the left	Normal
	No response (make sure canal is patent, apply warm-water stimulus to opposite ear)	Obstructed ear canal, "dead" labyrinth, eighth nerve or nuclear dysfunction, false negative (see text)
	Slow phase to right, no fast phase	Toxic-metabolic disorder, drugs, structural lesion above brainstem
	Down beating nystagmus	1 lori/ontal gaze palsy
Cold water instilled in left ear		Responses should be opposite to above
Warm water instilled in left car after no response from cold water in right ear	Slow phase to right, fast phase to left	Peripheral eighth nerve or labyrinth disorder on right (assuming right canal is patent)

Decorticate posturing is bilateral flexion at **the** elbows and wrists, with shoulder adduction and extension of the lower extremities. It is a much poorer localizing posture, as it may result from lesions in many locations, although usually above the brainstem. Decorticate posture is not as ominous a sign as decetebrate posture because the former occurs with many relatively reversible lesions.

Unilateral decerebrate or decorticate postures are also less ominous. Lesions causing unilateral posturing may be anywhere in the motor system from cortex to brainstem. Unilateral extensor posturing is common immediately after a cerebrovascular accident, followed in time by a flexor response.

Posturing may occur spontaneously or in response to external stimuli such as pain, or may even be set off by minimal events, such as the patient's breathing. These postures, although common, may also be variable in their expression because of other associated brainstem or more rostral brain damage. Special attention should be given to posturing because it often signals a brainstem herniation syndrome. Emergency room personnel and inexperienced physicians may mistake these abnormal postures for convulsions (seizures) and institute anticonvulsant therapy, resulting in an unfortunate delay of apptoptiate thetapy for these patients.

Adventitious movements in the comatose patient may be helpful in sepatating metabolic from structural lesions. Tonic-clonic ot othet steteotyped movements signal seizure as the probable cause of decreased alertness. *Myoclonic jerking,* nonrhythmic jerking movements in single or multiple muscle gtoups, is seen with anoxic encephalopathy ot othet metabolic comas, such as hepatic encephalopathy, *Rhythmic myoclonus,* which must be differentiated from epileptic movements, is usually a sign of brainstem injury, Tetany occurs with hypocalcemia. *Cerebellar fits* result from intermittent tonsillar herniation. They are characterized by a deterioration of level of arousal, opisthotonos, respiratory rate slowing and irregularity, and pupillary dilation.

The motor response to painful stimuli should be tested, although it should be noted that the pattern of tesponse may vary depending on the site stimulated. Purposeful responses may be difficult to discern from more primitive reflexes. Flexion, extension, and adduction may be eithet voluntary or reflex in nature. In general, abduction is most reliably voluntary, with shoulder abduction stated to be the only definite nonreflex reaction. This is tested by pinching the medial aspect of the upper arm.

Reflex flexor response to pain in the upper extremity consists of adduction of the shoulder, flexion of the elbow, and pronation of the arm. The *triple flexion response* in the lower extremities refers to reflex withdrawal, with flexion at the hip and knee and dorsiflcxion at the ankle, in response to painful stimulation on the foot or lower extremity. Such reflexes are seldom helpful in localizing a lesion.

Spinal reflexes are reflexes mediated at the level of the spinal cotd and do not depend on the functional integrity of the brain or brainstem. Most patients with absent cortical or brainstem function have some fotm of spinal reflex.

The *plantar reflex* may be extensor in coma from any cause, including drug overdoses and postictal states. It becomes flexor on recovery of consciousness if there is no underlying structural damage,

Muscle tone and asymmetry in muscle tone are helpful in localizing a focal structural lesion and may help differentiate metabolic from structural coma. Acute structural damage above the btainstem usually results in decreased or flaccid tone. In oldct lesions, tone is usually increased. Metabolic insults generally cause a symmetric decrease in tone. Finally, one must remember **that** generalized flaccidity is ultimately seen after brain death.

BRAIN HERNIATION

Clinical Signs of Herniation

Herniation syndromes are explained in Chapter 56B. However, a knowledge of some of the clinical signs of herniation is especially important in the clinical approach

to coma. Traditional signs of herniation due to supratcntorial masses are usually variations of either an uncal or central pattern. Classically, in the former, there are early signs of third nerve and midbrain compression. The pupil initially dilates as a result of third nerve compression but later returns to the midposition with midbrain compression that involves the sympathetic as well as the parasympathetic tracts. In the central pattern, the earliest signs are mild impairment of consciousness, with poor concentration, drowsiness, or unexpected agitation; small but reactive pupils; loss of the fast component of cold caloric testing; poor or absent reflex vertical gaze; and bilateral corticospinal tract signs, including increased tone of the body ipsilateral to the hemispheric mass lesion responsible for herniation (Plum and Posner 1995}.

Signs of herniation tend to progress generally in a rostrocaudal manner. An exception occurs when intraventricular bleeding extends to the fourth ventricle and produces a pressure wave compressing the area around the fourth ventricle. Also, when a lumbar puncture reduces cerebrospinal fluid pressure suddenly in the face of a mass lesion that produced increased intracranial pressure, sudden herniation of the cerebellar tonsils through the foramen magnum may result (Plum and Posner 1995). In both cases there may be sudden, unexpected failure of medullary functions that support respiration or blood pressure. The clinical examination of patients with herniation syndromes may be confusing because of changing signs or the expression of scattered, isolated signs of dysfunction in separate parts of the brain. In addition, certain signs may be more prominent than others.

Increased intracranial pressure invariably accompanies brainstem herniation and may be associated with increased systolic blood pressure, bradycardia, and sixth nerve palsies. These signs, however, as well as many of the traditional signs of herniation described previously, actually occur relatively late. Earlier signs of potential herniation are decreasing level of arousal, slight change in depth or rate of respiration, or the appearance of a Babinski sign. It is important to suspect herniation early, because once midbrain signs develop, structural injury is likely to have occurred; subsequently there is less chance of reversal.

DIFFERENTIAL DIAGNOSIS

Differentiating Toxic-Metabolic Coma from Structural Coma

Many features of the history and physical examination help differentiate structural from metabolic and toxic causes of coma. Some have already been mentioned above. When the history is available, a patient's underlying illnesses and medications or the setting in which he or she is found often guide the physician to the appropriate cause. The time course of the illness resulting in coma can be helpful. Generally, structural lesions have a more abrupt onset, whereas metabolic or toxic causes are more slowly progressive. Multifocal structural diseases such as vasculitis or leukoencephalopathy arc an exception to this rule, as they may exhibit slow progression, usually in a stepwise manner. Supratentorial or infratentorial tumors characterized by slow growth and surrounding edema may also mimic metabolic processes.

The response to initial emergency therapy may help differentiate metabolic or toxic causes of coma. The hypoglycemic patient usually awakens following administration of glucose, the hypoxic patient responds to oxygen, and the patient experiencing an opiate drug overdose responds to naloxone.

In general, structural lesions have focal features or at least notable asymmetry on neurological examination. Toxic, metabolic, and psychiatric diseases are characterized by their symmetry. Bilateral and often multilevel involvement is frequently seen with metabolic causes. Asymmetries may be observed but are generally of small degree and tend to fluctuate over time.

Many features of the neurological examination differentiate metabolic or toxic causes from structural lesions:

1. *State of consciousness.* Patients with metabolic problems often have milder alterations in arousal and tend to have waxing and waning of the behavioral state. Patients with acute structural lesions tend to stay at the same level of arousal or progressively deteriorate. Toxins may also cause progressive decline in level of arousal.
2. *Respiration.* Deep, frequent respiration is most commonly due to metabolic abnormalities, although rarely it is caused by pontine lesions or by neurogenic pulmonary edema secondary to acute structural lesions.
3. *Funduscopic examination.* Subhyaloid hemorrhage or papilledema are almost pathognomonic of structural lesions. Papilledema caused by increased intracranial pressure may be indicative of an intracranial mass lesion or hypertensive encephalopathy. Papilledema does not occur in metabolic diseases except hypoparathyroidism, lead intoxication, and malignant hypertension.
4. *Pupil size-* The pupils are usually symmetric in coma from toxic-metabolic causes. Patients with metabolic or toxic encephalopathies often have small pupils with preserved reactivity. Exceptions occur with methyl alcohol poisoning, which may produce dilated and unreactive pupils, or late in the course of toxic or metabolic coma if hypoxia or other permanent brain damage has occurred. In terminal asphyxia the pupils dilate initially and then become fixed at midposition within 30 minutes. The initial dilation is attributed to massive sympathetic discharge.
5. *Pupil reactivity.* Assessment of the pupillary reflex is one of the most useful means of differentiating

metabolic from structural causes of coma. Pupillary reactivity is relatively resistant to metabolic insult and is usually spared in coma from drug intoxication or metabolic causes, even when other brainstem reflexes are absent. Hypothermia may fix pupils, as does severe barbiturate intoxication; neuromuscular blocking agents produce midposition or small pupils, and glutethimide and atropine dilate them.

6. *Ocular motility.* Asymmetry in oculomotor function is typically a feature of structural lesions.
7. *Spontaneous eye movements,* Roving eye movements with full excursion most often suggest metabolic or toxic abnormalities.
8. *Reflex eye movements.* Reflex eye movements are normally intact in toxic-metabolic coma, except rarely in phenobarbital or phenytoin intoxication or deep metabolic coma from other causes.
9. *Adventitious movement.* Coma punctuated by periods of motor restlessness, tremors, or spasm is often due to drugs or toxins such as chlorpromazine or lirhium. Brainstem herniation or intermittent CNS ischemia may also produce unusual posturing movements. Myoclonic jerking is generally metabolic and often anoxic in origin.
10. *Muscle tone.* Muscle tone is usually symmetric and normal or decreased in metabolic coma. Structural lesions cause asymmetric muscle tone. Tone may be increased, normal, or decreased by structural lesions.

The examiner should be aware of common structural lesions that mimic toxic-metabolic causes and, conversely, toxic or metabolic causes of coma that may have focal findings on examination. Structural lesions that may mimic toxic-metabolic causes include subarachnoid hemorrhage, sinus vein thrombosis, chronic or bilateral subdural hemorrhage, and other diffuse or multifocal disorders, such as vasculitis, demyelinating diseases, or meningitis. Any toxic-metabolic cause of coma may be associated with focal findings; however, focal features are most often observed with barbiturate or lead poisoning, hypoglycemia, hepatic encephalopathy, and hyponatremia. Old structural lesions such as stroke may leave residual findings on neurological examination in a patient who is comatose from toxic or metabolic causes. Moreover, metabolic abnormalities such as hypoglycemia may unmask relatively silent structural abnormalities. Detailed descriptions of the toxic and metabolic encephalopathies arc provided in Chapter 62,

Differentiating Psychiatric Coma and Pseudocoma from Metabolic or Structural Coma

The patient who appears unarousable as a result of psychiatric disease and the patient who is feigning unconsciousness for other reasons may be difficult to differentiate from a patient with true coma or stupor. In these cases, the history, when available, and the physical examination may seem suspect to the physician, hinting that a nonphysiologic mechanism is at work. Multiple inconsistencies are present on examination, and abnormalities that are found do not fit the pattern of usual neurological syndromes. Examinations of the eyelid, pupil, adventitious eye movements, and vestibulo-oculogyric reflex by cold caloric testing are especially useful to confirm the suspicion of pseudocoma.

Eyelid tone is difficult to alter voluntarily. In the patient with true stupor or coma, passive eyelid opening is easily performed and is followed by slow, gradual eyelid closure. The malingering or hysterical patient often gives active resistance to passive eye opening and may even hold his or her eyes tightly closed. It is nearly impossible for the psychiatric or malingering patient to mimic the slow, gradual eyelid closure. Blinking also increases in hysterical patients but decreases in true stupor.

The pupils normally consrrict in sleep or (eyes-closed) coma but dilate with the eyes closed in the awake state. Passive eye opening in a sleeping person or a truly comatose patient (if pupillary reflexes are spared) results in pupillary dilation. Opening the eyes of an awake person produces constriction. This principle may help to differentiate a comatose patient from a patient with pseudocoma.

Roving eye movements cannot be mimicked and thus arc also a good sign of true coma. Finally, if the fast phase of ocular movement is preserved on cold caloric testing, the diagnosis of coma is suspect. Cold caloric testing often serves as a sufficient stimulus to awaken the patient.

Laboratory Studies

Laboratory tests that are extremely helpful in evaluating the comatose patient are listed in Table 5.7. Arterial blood gas determinations rule out hypoxemia and carbon dioxide narcosis and help differentiate primary CNS problems from secondary respiratory problems. Liver disease, myopathy, or rhabdomyolysis increase alanine aminotransferase and aspartate aminotransferase levels. Liver function tests may be misleading in end-stage liver disease because they may be normal or only mildly elevated with markedly abnormal liver function. Although the blood ammonia level does not correlate well with the level of hepatic encephalopathy, it often may be markedly elevated and thus helpful in cases of suspected liver disease with relatively normal liver function studies. Hepatic encephalopathy may continue for up to 3 weeks after liver function studies return to normal.

Thyroid function studies are necessary to document hypothyroidism or hyperthyroidism. When addisonian crisis is suspected, a serum Cortisol level should be obtained. A low or normal level in the stressful state of coma or illness strongly suggests adrenal insufficiency. Further

testing of adrenal function should be performed as appropriate.

When the cause of coma is not absolutely certain, or in possible medicolegal cases, a blood alcohol level and a drug and toxin screen are mandatory. The results of these tests are not usually available immediately but may be invaluable later. Serum osmolality can usually be measured rapidly by the laboratory and may be used to estimate alcohol level because alcohol is an osmotically active particle and increases the osmolar gap in proportion to its blood level. Serum osmolality can be calculated by the following;

- Serum osmolality = 2 Na^+(mEq/liter)
- + BUN (mg/dI.)/2.8
- + glucose (mg/dL)/18

The osmolar gap, which is the difference between the measured serum osmolality and the calculated serum osmolality, represents unmeasured osmotically active particles.

Creatine kinase levels should routinely be measured in comatose patients initially and then at least daily for the first several days because of the great risk of rhabdomyolysis and subsequent preventable acute tubular necrosis in these patients. Measuring creatine kinase MB isoenzyme levels every 8 hours for the first 24 hours helps rule out a myocardial infarction.

Other Studies

Electroca rdiogtaphy

The electrocardiogram is useful to show myocardial infarction, arrhythmia, conduction blocks, bradycardia, or evidence of underlying hypertension or atherosclerotic coronary vascular disease. Hypocalcemia causes QT prolongation. Hypercalcemia shortens the QT interval. The heart rate is slow in hypothyroid patients with low-voltage QR.S, flat or inverted T waves, and flattened ST segments. Hyperthyroid patients are generally tachycardic.

Neuroradioiogical Imaging

Once the patient is treated and stabilized, the initial examination is complete, and necessary laboratory studies

Table 5.7: Laboratory tests helpful in cuma

Laboratory study	*Result*	*Associated disorders*
Electrolytes (Na, K, CI, $C0_2$)		See Chapters 55A and 62 for discussion of disorders associated with abnormalities of electrolytes, glucose, blood urea nitrogen, calcium, and magnesium
Glucose		
Blood urea nitrogen		
Creatinine		
Calcium		
Magnesium		
Complete blood tell count with differential	Hematocrit:	
	Increased	Volume depletion, underlying lung disorder, myeloproliferative disorder, cerebellar hemangioblastoma; may be associated with vascular sludging (hypoperfusion)
	Decreased	Anemia, hemorrhage
	White blood cell count:	
	Increased	Infection, acute stress reaction, steroid therapy, afrer epileptic fit, myeloproliferative disorder
	Decreased	Chemotherapy, immunotherapy, viral infection, sepsis
	Lymphocyte count:	
	Decreased	Viral infection, malnutrition, acquired immune deficiency syndrome
Platelet count	Decreased	Sepsis, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, drugs; may be associated with intracranial hemorrhage
Prothrombin time	Increased	Coagulation factor deficiency, liver disease, anticoagulants, disseminated intravascular coagulation
Partial thromboplastin time	Increased	Heparin therapy, lupus anticoagulant
Arterial blood gases		See text
Creatine phosphokinasc		See text
Liver function studies		See text
Thyroid function studies		See text
Plasma Cortisol level		See text
Drug and toxin screen		See text
Scrum osmolality		See text

are ordered, the next test of choice is a CT scan of the brain, without contrast enhancement, but with 5-mm cuts of the posterior fossa. Alternatively, magnetic resonance imaging (MRI) may be performed, depending on the clinical setting and the stability of the patient's condition. MRI provides superb visualization of the posterior fossa and its contents, an extremely useful feature when structural disease of the brainstem is suspected. However, MRI is not specific for visualizing early intracranial hemorrhage, as the CT scan is, and ii is limited at present by the time required to perform the imaging, image degradation by even a slight movement of the patient, and the relative inaccessibility of the patient during the imaging process. The CT scan, when performed as described, is currently the most expedient imaging technique, giving the physician the most information aboui possible structural lesions with the least risk to the patient. Intravenous dye may later be necessary to better define lesions seen on the initial CT scan.

The value of the CT scan in demonstrating mass lesions and hemorrhage is undeniable. Furthermore, it may demonstrate features of brain herniation. Uncal herniation is characterized on CT scan by (1) displacement of the brainstem toward the contralateral side, with increase in width of subarachnoid space between the mass and ipsilateral free edge; (2) medial stretching of the posterior cerebral and posterior communicating arteries; (3) obliteration of the interpeduncular cistern; (4) occipital lobe infarction; and (5) distortion and elongation of the 1.1-shaped tentorial hid sura. The clinician should be aware that the CT scan may miss early infarction, encephalitis, and isodense subdural hemorrhage. Special caution must be taken in evaluating CT scans in comatose patients, especially before lumbar puncture, to rule out isodense subdural or bilateral subdural hemorrhage. Interpretation of CT scans is discussed in Chapter 37B.

In severe head injury, studies of cerebral metabolism with use of single-photon emission computed tomography (SPECT) may be of prognostic value (Delia Corte et al. 1997). Although cerebral blood flow in the first 48 hours after trauma does not appear to correlate with severity or prognosis, cerebral metabolic rate of oxygen (CMRO2), like the Glasgow Coma Scale, may be useful in predicting prognosis.

Electroencephalography

The electroencephalogram (EEG) is hcipfu! in many situations, including confirming underlying cortical structural damage in patients too unstable to travel to a CT scan; postictal states in patients slow to wake after a presumed seizure; partial complex seizures; electroencephalographic or nonconvulsive status epilepticus, such as that seen in comatose patients following anoxic ischemic damage; and toxic-metabolic disorders. With metabolic disorders, the earliest LEG changes are typically a decrease in the frequency of background rhythms and the appearance of diffuse theta activity that progresses to more advanced slowing in association with a decrease in the level of consciousness. In hepatic encephalopathy, bilaterally synchronous and symmetric, medium- to high-amplitude, broad triphasic waves, often with a frontal predominance, may be observed. Herpes simplex encephalitis may be suggested by the presence of unilateral or bilateral periodic sharp waves with a temporal preponderance. The EEG also helps confirm the clinical impression of catatonia, pseudocoma, the locked-in syndrome, the persistent vegetative state, and brain death. Electroencephalograms arc discussed further in Chapter 36A.

Evoked Potentials

Evoked potentials may help in evaluating brainstem integrity and in assessing prognosis for comatose patients. Brunko and Zegers de Beyl (1987) studied 50 hemodynamically stable patients remaining in coma 4 hours after resuscitation from cardiopulmonary arrest with short latency somatosensory-evoked potentials within 8 hours after arrest. They found that none of the 30 patients without cortical potentials recovered cognition. Five of the 20 patients with cortical potentials recovered. Forty percent of their patients who did not recover had preserved brainstem reflexes, allowing some evaluation of prognosis in a group of patients in whom prognosis is difficult to assess by other means. Event-related potentials may prove particularly useful as an objective assessment of cognitive function in patients with the locked-in syndrome (Onofrj ctal. 1997).

Intracranial Pressure Monitoring

Intracranial pressure (ICP) measurements provide an index of the degree of brain swelling and are particularly useful in the treatment of patients who have suffered severe head injury. Postmortem studies of fatal head injuries demonstrate a direct correlation between very elevated ICP and death due to tentorial herniation. In the absence of intracranial hematomas, however, comatose patients with normal brain imaging studies have a low incidence of increased ICP and almost never develop uncontrolled intracranial hypertension.

CLINICAL APPROACH TO PROGNOSIS

Given our current state of knowledge, one cannot reliably predict outcome in any comatose patient with 100% certainty unless that patient meets the criteria for brain death, as described below. Available studies do not allow us to say definitely that any single non-brain-dead patient will not recover from coma, nor do they allow us to prognosticate on how much recovery may occur in specific

cases. However, general statistics on the outcome of coma based on serial exams at various times after the onset of coma have been compiled (Levy etal. 1981;Torner 1992) and give the examiner a general idea of expected prognosis.

The natural history of coma can be considered in terms of three subcategories: drug-induced, nontraumatic, and traumatic coma. Drug-induced coma is usually reversible unless the patient has nor had appropriate systemic support while comatose and has sustained secondary injury from hypoperfusion, hypoxia, or lack of other necessary metabolic substrates.

Nontraumatic Coma

Only approximately 15% of patients in nontraumatic coma make a satisfactory recovery. Functional recovery is related to the cause of coma. Diseases causing structural damage, such as cerebrovascular disease including subarachnoid hemorrhage, have the worst prognosis; coma from hypoxia-ischemia due to causes such as cardiac arrest has an intermediate prognosis; coma due to hepatic encephalopathy and other metabolic causes has the best ultimate outcome. Age does not appear to be predictive of recovery. The longer a coma lasts, the less likely the patient is to regain independent functioning (Levy et al. 1981).

In the early days after the onset of nontraumatic coma, it is not possible to predict with certainty which patients will ultimately enter or remain in a persistent vegetative state. Although rare cases have been reported of patients awakening after prolonged vegetative states, patients with nontraumatic coma who have not regained awareness by the end of 1 month are unlikely to regain consciousness. Even if they do regain consciousness, they have practically no chance of achieving an independent existence. A large multi-institutional study determined that within 3 days of cardiac arrest, evaluation in the intensive care unit is sufficiently predictive of neurological outcome to allow for informed decisions regarding life support (Edgren et al. 1994), The absence of pupillary light response, motor response to pain, and low Glasgow Coma scores (<5) were predictive of poor neurological outcome.

Clinical experience must be combined with data from studies such as this one to aid the individual physician in prognosticating about each individual patient who is comatose from nontraumatic causes but not clinically btain dead.

Traumatic Coma

The prognosis for traumatic coma differs from that for nontraumatic coma in many ways. First, many patients with head trauma are young. Second, prolonged coma of up to several months does not preclude a satisfactory outcome in traumatic coma. Third, in relationship to their initial degree of neurological abnormality, traumatic coma patients do better than nontraumatic coma patients (Levy et al. 1981).

The prognosis for coma from head trauma may be considered in terms of survival; however, because many more patients survive traumatic coma than nontraumatic coma, it is equally important to consider the ultimate disabilities of the survivors because many who survive are left with profound disabilities.

The Glasgow Outcome Scale is a practical system for describing outcome in traumatic coma. As originally proposed, there arc five categories in this scale: (1) death; (2) persistent vegetative state; (3) severe disability (conscious but disabled and dependent on others for activities of daily living); (4) moderate disability (disabled but independent); and (5) good recovery (resumption of normal life even though there may be minor neurological and psychiatric deficits).

Jennettet al, (1979) studied 1000 patients in coma longer than 6 hours from severe head trauma: 49% of these patients died, 3% remained vegetative, 10% survived with severe disability, 17% survived with moderate disability, and 22% had good recovery. Depth of coma, as evaluated by the Glasgow Coma Scale; pupil reaction; eye movements; and motor response in the first week after injury and the patient's age were found to be the most reliable predictors of outcome 6 months later.

In summary, early predictors of the outcome of posttraumatic coma include the patient's age, motor response, pupillary reactivity, eye movements, and depth and duration of coma. The prognosis worsens with increasing age. The cause of injury, skull fracture, lateralization of damage to one hemisphere, and extracranial injury appear to have little influence on the outcome.

CLINICAL APPROACH TO BRAIN DEATH

A thorough knowledge of the criteria for brain death is essential for the physician whose responsibilities include evaluation of comatose patients. Despite differences in state laws, the criteria for the establishment of brain death are fairly standard within the medical community. These criteria include the following:

1. *Coma.* The patient should exhibit an unarousable unresponsiveness. There should be no meaningful response to noxious, externally applied stimuli. The patient should not obey commands or demonstrate any verbal response, either reflcxivcly or spontaneously. Spinal reflexes, however, may be retained.
2. Wo *spontaneous respirations.* The patient should be removed from ventilatory assistance and carbon dioxide should be allowed to build up because of the respiratory drive that hypercapnia produces. The diagnosis of absolute apnea requires the absence of spontaneous tespiration at a carbon dioxide tension of

at least 60 mm Hg, A safe means of obtaining this degree of carbon dioxide retention involves the technique of apneic oxygenation, in which 100% oxygen is delivered endotracheal!}' through a thin sterile catheter for 10 minutes. Arterial blood gas levels should be obtained to confirm the arterial carbon dioxide pressure.

3. *Absence of brainstem reflexes.* Pupillary, oculocephalic, vestibulo-oeulogyric on cold calorics, corneal, and gag reflexes must all be absent.
4. *Extracerebral silence.* An isoelectric EEG should denote the absence of cerebrocortical function. Some authorities do not regard rhe performance of an EEG as mandatory in assessing brain death, and instances of preserved cortical function, despite irreversible and complete brainstem disruption, have been reported.
5. *Absence of cerebral blood flow.* Cerebral contrast angiography or radionuclide angiography can substantiate the absence of cerebral blood flow, which is expected in brain death. These tests are considered confirmatory rather than mandatory. On rare occasions in the presence of supratentorial lesions with preserved blood flow to the brainstem and cerebellum, cerebral angioscintigraphy may be misleading.
6. *Absence of any potentially reversible causes of marked CNS depression.* This includes hypothermia (temperarure 32°C or less), drug intoxication {particularly barbiturate overdose), and severe metabolic disturbance,

Brain Death Survival

Despite aggressive therapeutic measures, survival of longer than 1 week in "brain-dead" individuals is uncommon. Shewmon found in a meta-analysis of 56 of 175 cases surviving longer than 1 week after diagnosis of "brain death" (Shewmon, 1998) that one half survived longer than 1 month, one third longer than 2 months, and only four longer than 1 year. Survival correlated inversely with age; the longest survivors (2.7, 5.1, and 14.5 years) were all children (Shewmon 1998). Longer survival was more common with primary brain pathology than other etiologies. The tendency to cardiovascular collapse in brain death may be transient and more likely attributable to systemic than brain pathology.

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Chapter 6
Approaches to Intellectual and Memory Impairments

Howard S. Kirshner

The term *intellect* designates the totality of the mental or cognitive operations that comprise human thought, the higher cortical functions that make up the human mind. The intellect and its faculties, the subject matter of human psychology, are the qualities that most separate human beings from other animals. Memory is a specific cognitive function: the storage and retrieval of information. As such, it is the prerequisite for learning, the building block of all human knowledge. Other "higher" functions, such as language, calculations, spatial topography and reasoning, music, and creativity, all represent the functions of specific brain systems. The relationship of the mind and brain has long been of philosophical interest. Recent advances in cognitive neuroscicncc have made mind-brain questions the subject of practical scientific and clinical study. It is now possible to study how the metabolic activation of brain regions and firing patterns of neurons give rise to the phenomenon of consciousness, the sense of self, the ability to process information, and develop decisions and attitudes. The pattern of an individual's habitual decisions and attitudes amount to one's personality. Francis Crick (1994), who with James Watson discovered the structure of deoxyribonucleic acid (DNA), expressed the "astonishing hypothesis" that "you, your joys, and your sorrows, your sense of personal identity, and free will, are in fact no more than the behavior of a vast assembly of nerve cells and their associated molecules." This chapter considers our knowledge of intellect and memory, mind and brain, from the perspective of the clinical neurologist who must assess disorders of the higher functions.

This chapter is dedicated to the memory of Dr. D. Frank Benson, author of the chapter in the first and second editions of this book and a friend and mentor to all who study the higher functions in humans.

NEURAL BASIS OF COGNITION

Cerebral Cortex

The cognitive operations discussed in this chapter take place among a large network of cortical cells and connections, the neural switchboard that gives rise to conscious thinking. The cortical mantle of the human brain is very large compared with animal brains, containing more than 14 billion neurons, The information stored in the human cerebral cortex rivals that of large libraries. Within the cortical mantle, the areas that have expanded the most from animal to human are the "association cortices," cortical zones that do not carry out a primary motor or sensory function but inter-relate the functions of the primary motor and sensory areas. According to Nauta and Feirtag's 1986 text, 70% of neurons in the human central nervous system are in the cerebral cortex, and 75% of those are in the association cortex. Higher conical functions, with few exceptions, take place in the association cortex.

The neuroanatomy of the cerebral cortex has been known in considerable detail since the 1800s. Primary cortical sensory areas include the visual cortex in the occipital lobe, the auditory cortex in the temporal lobe, the somatosensory cortex in the parietal lobe, and probably gustatory and olfactory cortices in the fronral and temporal lobes. Each of these primary cortices receives signals in only one modality (vision, hearing, or sensation) and has cortical-cortical connections only to adjacent portions of the association cortex also dedicated to this modality, called *unimodal association cortex.* Sensory information is sequentially processed in increasingly complex fashion, leading from raw sensory data to a unified percept. Within each cortical area are columns of cells with similar function, called *modules.*

The organization of the primary sensory and unimodal association cortex has been especially well worked out in the visual system through the Nobel prize-winning research of Hubcl and Wiesel and others. Retinal ganglion cells are

activated by light within a bright center, with inhibition in the surround. These cells project through the optic nerve to the lateral geniculate body of the thalamus, then via the optic radiations to the primary visual cortex in the occipital lobes. In the primary visual cortex, a vertical band of neurons may be dedicated to the detection of a specific bright area, but in the cortex, this is usually a bar or edge of light rather than a spot. These "simple" cells of the visual cortex respond to bright central bars with dark surrounds. Several such cells project to complex cells, which may detect an edge or line with a specific orientation or a specific direction of movement but with less specificity about the exact location within the visual field. By the operation of these cells, visual shapes are perceived. Complex cells, in turn, project to cells in the visual unimodal association cortex (Brodmann's areas 18 and 19), where cells may detect movement or patterns. Complex cells also respond to movement anywhere in the visual field, an important characteristic because of the organism's need to maintain visual attention for possible hazards in the environment. In the visual association cortex, columns may respond to specific shapes, colors, or qualities, such as novelty. In this fashion, the functions of cell columns or modules become more sophisticated from the primary cortex to the association cortex. In Fodor's model, the modules of primary visual perception project to central systems. Cognitive science has yet to develop a clear understanding of higher perceptual functions, such as the concept of beauty in a starry sky or in a painting, or the cross-modality processes that underlie, for example, the adaptation ot a ballet to a specific musical accompaniment.

Unimodal association cortices communicate with each other via still more complex connections to the hetero-modal association cortex, of which there are two principal sites. The posterior heteromodal association cottex involves the posterior inferior parietal lobe, especially the angular gyrus. The posterior heteromodal cortex makes it possible to perceive an analogy between an association in one modality (e.g., a picture of a boat and the printed word *boat* in the visual modality) with a percept in a different modality (e.g., the sound of the spoken word *boat).* These intermodality associations are difficult for animals, even chimpanzees, but easy for human beings. Cross-sensory associations involve the functioning of *cortical networks* of multitudes of neurons; the analogy drawn by neuroscien-tists is to the vast arrays of circuits active in computer networks. The product of such associations is a concept.

The second heteromodal association cortex involves the lateral prefrontal region (G-oldman-Rakic 1996). This region is thought to be involved with attention or "working memory" and with sequential processes, such as storage of temporally ordered stimuli and the planning of motor activities. This temporal sequencing of information and of motor planning is referred to by neuropsychologists as the *executive function* of the brain: the decisions we make every instant regarding which of the myriad sensory stimuli reaching the sensory cortices merit attention, which require a motor response, and in what sequence and timing these motor responses will occur.

Another frontal cortical area, the orbitofrontal pottion of the prefrontal cortex, is thought to be involved in emotional states, appetites, and drives, or in integration of internal bodily states with sensations with the external world. The orbirofrontal cortex is known as the *supramodal cortex* (Benson 1996) because it relates the functions of the heteromodal cortex, regarding attention and sequencing of responses, with interoceptive inputs from the internal milieu of the body. The orbitofrontal area has close connections with the limbic system and autonomic, visceral, and emotional processes. In studying brain evolution from primitive reptiles to humans, Paul Mac-Lean hypothesized that the internal and emotional parts of the brain, the limbic system, must be tied into the newer neocortical areas responsible for intellectual function and that the linking of these two systems must underlie the phenomenon of consciousness. Benson and Ardila (1996), in reviewing clinical data from individuals with frontal lobe damage, state that the supramodal cortex is the brain system that "anticipates, conjectures, ruminates, plans for the future, and fantasizes." In other words, it is rhis part of the brain that brings specific cognitive processes to conscious awareness and may be responsible for the phenomena of consciousness and self-awareness.

Consciousness

All human beings have a subjective understanding of what it means to be conscious and have a concept of self, yet the neural basis for conscious awareness and the sense of self remain poorly understood. Until recently, many neuro-scientists left consciousness to the realm of religion and philosophy. Even Hippocrates, however, knew that con-sciousness emanated from the brain: "to consciousness the brain is messenger." For Crick (1994), the best model for the study of consciousness is visual awareness, because the anatomy and physiology of the visual system are well understood. Crick argues that neurons in the primary visual cortex likely do nor have access to conscious awareness. Stated another way, we do not pay attention to much of what our eyes see and our visual cortex analyzes. A perceived object, however, excites neurons in several areas of rhe visual association cortex, each with associations that enter consciousness or are stored in short-term memory.

Crick and Koch (1995) argue that activation of the frontal cortex is necessary for visual percepts to enter consciousness, although subconscious awareness in rhe form of "blindsight" may exist at the level of the occipital cortex. Conscious visual perception involves interactions between the visual parts of the brain and the prefrontal systems for attention and working memory (Ungerleider, Courtney, and Haxby 1998). The orbitofrontal cortex

contains neurons that integrate interoceptive stimuli related to changes in the internal milieu with exteroceptive sensory inputs, such as vision. As stated earlier, this interaction between attention to external stimuli and internal stimuli underlies conscious awareness.

There are many clinical examples of "unconscious" mental processing, and a number of these involve vision. Patients with cortical blindness sometimes show knowledge of items they cannot See, a phenomenon called "blindsight." Patients with right hemisphere lesions who extinguish objects in the left visual field when presented with bilateral stimuli nonetheless show activation of the right visual cortex by functional magnetic resonance imaging (fMRI), indicating that the objects are perceived, though not consciously (Rees et al. 2000). Libet (1999) demonstrated experimentally that visual and other sensory stimuli have to persist at least 500 ins to reach conscious awareness, yet stimuli of shorter duration can elicit reactions. An experimental example of unconscious visual processing comes from Gur and Snodderly (1997), who tested color vision in monkeys. When two colors were projected at a frequency of more than 10 Hz, the monkey perceived a fused color, yet cellular recordings clearly demonstrated coding of information about the two separate colors in the monkey's visual cortex. Motor responses to sensory stimuli can occut before conscious awareness, as in the ability to pull one's hand away ftom a hot stove before feeling the heat. Racers begin running before they are aware of having heard the staffing gun (Crick and Koch 1998), A familiar example of unconscious visual processing is the drive home from work; most individuals can remember very little that they saw on the trip, yet they drove without accidents. Crick and Koch (1998) refer to the unconscious visual processing as an "online visual system," They suggest that the "dorsal visual stream," an occipitoparietal system for perception of location and movement direction of objects, is largely conscious, whereas the "ventral visual stream," an occipitotemporal system for identification of objects, is largely unconscious. We shall discuss unconscious or "implicit" memories later in this chapter (see Othet Types of Memory [Nondeclarative or Implicit Memory]). In language syndromes, patients can match spoken to written words without knowledge of their meaning, suggesting that there are unconscious rules of language. Brust (2000) has called all of these unconscious mental processes the "non-freudian unconscious."

Recent research has linked the right frontal cortex to the sense of self. Keenan et al. (2001) studied patients undergoing Wada tests, in which a barbiturate is injected into the carotid artery to determine cortical language dominance, They presented subjects with a self-photograph and a photograph of a famous person, followed by a "morphed" photograph of a famous person and the patient. When the left hemisphere was anesthetized, the subjects said that the morphed photograph represented themselves, whereas with right hemisphere anesthesia, the subjects selected the famous face. Patients with frontotemporal dementia also indicate a relationship between the right frontal lobe and self-concept. In the series of Miller et al. (2001), six of the seven patients who developed a major change in self-concepr during their illness had predominant atrophy in the nondominant frontal lobe.

The frontal lobes, as the executive center of the brain and the determining agent for attention and motor planning, are the origin of several critical networks for cognition and action. Cummings (1993) described five frontal networks for consciousness and behavior. The frontal cortex projects to the basal ganglia, then to thalamic nuclei, and back to the cortex.

Clinical neurology provides important information about how lesions in the brain impair consciousness. The functioning of the awake mind requires the ascending inputs referred ro as the *reticular activating system,* with its way stations in the brainstem and thalamus, as well as an intact cerebral cortex. Bilateral lesions of the brainstem or thalamus produce coma. Very diffuse lesions of the hemisphetes produce an "awake" patient who shows no responsiveness to the environment, a state sometimes called *coma vigil.* Less severe, diffuse abnormalities of the association cortex produce encephalopathy, delirium, or dementia; stupor and coma are discussed in Chapter 5, and encephalopathy, or delirium, is covered in Chapter 4.

Focal lesions of the cerebral cortex generally produce deficits in specific cognitive systems. A detailed listing of such disorders would include the whole subject matter of behavioral neurology. Examples include Broca's aphasia from a left frontal lesion, Wernicke's aphasia from a left temporal lesion, and Gerstmann's syndrome (acalculia, left-right confusion, finger agnosia, and agraphia) from a left parietal lesion, visual agnosia or failure to recognize visual objects (usually from bilateral posterior lesions), apraxia from a left parietal lesion, and constructional impairment from a right parietal lesion. Multiple focal lesions can affect cognitive function in more global fashion, as in the dementias {Chapter 72). Some authorities separate "cortical" dementias, such as Alzheimer's disease, in which combinations of cortical deficits are common, from "subcortical" dementias, in which mental slowing is the most prominent feature.

The frontal lobes are heavily involved in integration of the functions provided by other areas of the cortex, and lesions there may affect personality and behavior in the absence of easily discernible deficits of specific cognitive, language, or memory function. In severe form, extensive lesions of the orbirofrontal cortex may leave the individual awake but staring, unable to respond to the environment, a state called *akinetic mutism.* With lesser lesions, patients with frontal lobe lesions may lose their ability to form mature judgments, reacting impulsively to incoming stimuli in a manner reminiscent of animal behavior. Such patients may be inappropriately ftank or disinhibited. A familiar example is the famous case of Phineas Gage, a worker who

FIGURE 6.1 Luna's test of alternating sequences. (Adapted with permission from Luria, A. R. 1969, "Frontal lohe syndromes," in *Handbook of Clinical Neurology,* vol. 2, eds P. J. Vynken, G. W. Bruyn, Elsevier, New York; and reprinted wirh permission from Kirshner, H. S. 2002, *Behavioral Neurology: Practical Science of Mint! and Brain.* Bntterworth-Heinemann, New York.)

sustained a severe injury to the frontal lobes. Gage became irritable, impulsive, and so changed in personality that co-workers said he was "no longer Gage." Bedside neurological testing and even standard neuropsychological tests of patients with frontal lobe damage may reveal normal intelligence, except for concrete or idiosyncratic interpretation of proverbs and similarities. Experimentally, subjects with frontal lobe lesions can be shown to have difficulty with sequential processes or shifting of cognitive sets, as tested by the Wisconsin Card Sorting Test or the categories rest of the Halstead-Reitan battery. I.uria introduced a simple bedside test of sequential shapes (Figure 6.1). In contrast to the subtlety of these deficits to the examiner, the patient's family may state that there is a dramatic change in the patient's personality.

Another clinical window into the phenomena of consciousness comes from surgery to separate the hemispheres by cutting the corpus callosum. In split-brain or eommissurotomized patients, each hemisphere seems to have a separate consciousness. The left hemisphere, which has the capacity for speech and language, can express this consciousness in words. For example, a split-brain patient can report words or pictures that appear in the right visual field. The right hemisphere cannot produce verbal accounts of items seen in the left visual field, **but** the patient can choose the correct item by pointing with the left hand, at the same time the patient claims to have no conscious knowledge of the item. In terms of the speaking left hemisphere, the right hemisphere has "unconscious" visual knowledge, or Hindsight. At times, the left hand of the patient may seem to operate under a different agenda from the right hand: A split-brain patient may select a dress from a rack with the right hand while the left hand puts it back or selects a more daring fashion. This rivalry of the left hand with the right is called the *alien band syndrome,* a striking example of the separate consciousnesses of the two divided hemispheres (Gazzaniga 1998). Callosal syndromes, including the alien hand syndrome, have also been described in patients with strokes involving the corpus callosum (Chan and Ross 1997).

MEMORY

Memory Stages

Memory refers to the ability of the brain to store and retrieve information. Some memories are so vivid that they seem like a reliving of a prior experience, as in Marcel Proust's sudden recollections of his youth on biting into a madeleine. Other memories are more vague or bring up a scries of facrs rather than a perceptual experience. Memory has been divided into several types and several stages, leading to a confusing set of terms and concepts. Clinical neurologists divide memory into three temporal stages. The first stage, called *immediate memory span,* corresponds to Baddelcy's concept of *working memory. Immediate memory* refers to the amount of information a subject can keep in conscious awareness without active memorization. The normal human being can retain seven digits in active memory span. Perhaps by coincidence, seven digits comprise a local telephone number. Most normal people can hear a telephone number, walk across the room, and dial the number without active memorization. Numbers of more than seven digits, called *supraspan numbers,* do require active memory processing, as do unnatural tasks, such as reverse digit span. Disorders of attention affect digit span, and very focal lesions of the superior frontal neocortex, affecting Brodmanu's areas 8 and 9, may have profound effects on immediate memory (Goldman-Rakic 1996). Many patients with aphasia secondary to left frontal lesions have impaired immediate memory. The items in immediate memory are normally forgotten as soon as the subject's attention switches to another topic (telephone numbers that we look up and call once tend to be completely forgotten quickly unless we actively try to "memorize" them).

The second stage of memory, referred to by clinicians as *short-term* or *recent* memory, involves the ability to register and recall specific items, such as words or events, after a delay of minutes or hours. Some memory researchers refer to immediate memory span as *short term* and recent memory as *long term.* This second stage of memory, which has also been called *declarative* or *episodic* memory (Squire and Zola 1996), requires the function of the hippocampus and parahippocampal areas of the medial temporal lobe for both storage and retrieval. The amygdala, an adjacent structure of the medial temporal cortex, is not essential for episodic memory but seems crucial for recall of emotional contexts of specific events and the reactions of fear or pleasure associated with these events. The familiar bedside test of recalling three unrelated memory items at 5 minutes demonstrates short-term memory, as do questions about this morning's breakfast.

Long-term memory, also called *remote memory,* refers to long-known information, such as where one grew up, who was one's first-grade teacher, or the names of grandparents. Recall of famous figures, such as presidents, is also used as a test of remote memory, but these questions really probe the subject's fund of information, which can be continuously replenished by reading and conversation. Remote memory, as we shall see later, resists the effects of medial temporal damage; once memory is well stored, probably in the neocortex, it can be retrieved without use of the hippocampal system.

Amnestic Syndrome

The *amnestic syndrome* (Table 6.1) refers to profound loss of the second Stage of recent or short-term memory. These patients, most of whom have bilateral hippocampal damage, have normal immediate memory span and largely normal ability to recall remote memories, such as their childhood upbringing and education. Other cognitive or higher cortical functions may be completely intact, which distinguishes these patients from those with dementias, such as Alzheimer's disease. Motor memories (see Other Types of Memory [Nondeclarative or Implicit Memory], later in this chapter) tend to be preserved in patients with amnestic-syndrome. Other more variable features of the amnestic syndrome are disorientation to time and sometimes place and "confabulation," or making up information that the memory system does not supply. Amnestic patients live in an eternal present tense, in which they can interact, speak intelligently, and reason appropriately, but they do not remember anything about the interaction a few minutes after it ends. An amnestic patient may complete an intelligence quotient (IQ) test with high scores but not recall taking the examination minutes later. These patients are condemned to repeat the same experiences without learning from them.

The registration of short-term memory involves a consolidation period, during which a blow to the head, as in a football injury, can prevent memories from being stored or recalled. The recognition or recall of items appears to require the hippocampus. The site of storage of memories is not known but probably involves large areas of the neocortex, specialized for specific cognitive functions, such as auditory or visual analysis. Once processed in the neocortex and stored for a long period, items can be recalled even in the presence of hippocampal damage, as in the case of remote memories. After an injury producing hippocampal damage, a retrograde period of memory loss may extend back from minutes to years, and the subject cannot form new antegrade memories. As the ability to form new memories returns, the period of retrograde amnesia shortens, or shrinks. After a minor head injury, the permanent amnestic period may involve a few minutes of retrograde amnesia and a few hours or days of anterograde amnesia. In experimental studies in which amnestic subjects are shown famous people from past decades, a temporal gradient has been found in which subjects have excellent memory for remote personages but recall progressively less from periods dating up to the recent past.

Tabic 6.1: Amnestic syndrome features

Impaired recent memory (anterograde, retrograde)
Global amnesia
Spared procedural memory
Preserved immediate memory
Preserved remote memory
Intact general cognitive function
Disorientation to time or place
Confabulation

The neuroanatomy of the amnestic syndrome is one of rhe best-studied areas of cognitive neuropsychology. In animal models, bilateral lesions of the hippocampus, parahippocampal gyrus, and entorhinal cortex produce profound amnesia (Squire and Zola 1996). Human patients undergoing temporal lobectomy for epilepsy have shown very similar syndromes. In the early period of this surgery, a few parients were deliberately subjected to bilateral medial temporal ablations, with disastrous results for memory, as seen in the famous patient H, M. (Corkin 2002). In other cases, unilateral temporal lobectomy caused severe amnesia. In one such case, an autopsy many years later showed preexisting damage to the contralateral hippocampus. Patients currently receive extensive evaluation, such as the Wada test of intracarotid barbiturate infusion, to ensure that ablation of one hippocampus will not result in the amnestic syndrome, although partial memory deficits still occur. Other common causes of the amnestic syndrome involving bilateral medial temporal lesions include bilateral strokes in the posterior cerebral artery territory, involving the hippocampus, and herpes simplex encephalitis, which has a predilection for the orbital frontal and medial temporal cortices.

The anatomy of memory storage and retrieval has been known for many years, with numerous recent refinements. Figure 6.2 shows a simplified diagram of the memory system in the human brain. The hippocampus on each side projects via the fornix to the septal areas, then to the mamillary bodies, which project to the anterior nucleus of the thalamus and on to the cingulatc gyrus of the frontal lobe, which projects back to the hippocampus. This circuit (the Papez circuit) is critical for short-term memory registration and retrieval. Disease processes that affect extrahippocampal parrs of this circuit also cause amnesia. One well-studied example is Wernicke-Korsakoff syndrome induced by thiamine deficiency, usually in the setting of alcoholism, with damage to the mamillary bodies and dorsomedial thalamic nuclei. A second clinical example is that of patients with ruptured aneurysms of the anterior communicating artery, which is associated with damage to the deep medial frontal areas, such as the septal nuclei. These two amnestic syndromes arc commonly associared with confabulation. Traumatic brain injuries commonly produce memory loss, probably because the most common sites of damage are in the frontal and temporal lobes, but other deficits in addition to memory frequently occur. Of course, memory loss can be seen in several other neurological conditions, including brain tumors of the thalamus or temporal lobes; white matter diseases, such as multiple sclerosis; and dementing diseases, such as Alzheimer's disease, which has a predilection for the hippocampus, basal frontal nuclei, and neocortex. In these other disorders, memory loss is usually not as isolated a deficit as in the amnestic syndrome.

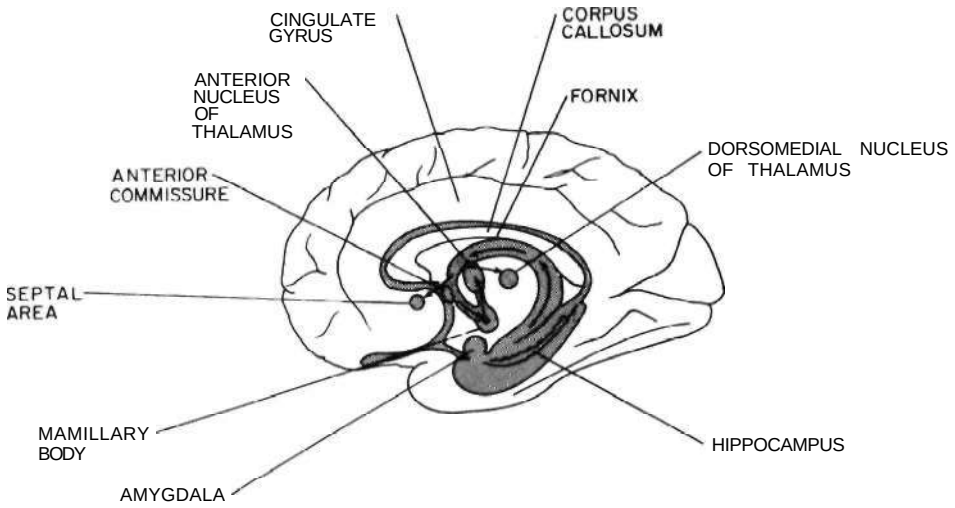

FIGURE 6.2 The Papez circuit and the neuroanatomy of memory. The hippocampus projects, via the fornix, to the septal area and mamillary hodies. The mamillary hodies project to the anterior nucleus of the Thalamus and then to the cingulate gyrus to the frontal lohe. Recurrent pathways (not shown) lead back from the cingulate and frontal cortex to the hippocampus. (Reprinted with permission from Kirshner, H. S. 2002, *Behavioral Neurology: Practical Science of Mind and Brain,* 2nd cd, Butterworth-Hcincmann, Boston.)

Recently, functional brain imaging in awake patients has contributed to knowledge of the anatomy of memory function. According to one positron emission tomography (IT. 1 i study, six brain regions show consistent activation in normal subjects during memory testing. These brain regions are (1) the prefrontal cortex, especially on the right; (2) the hippocampal and adjacent medial temporal regions; (3) the anterior cingulate cortex; (4) the posterior midline regions of the cingulate, prccuneatc, and cuneate gyri; (5) the inferior parietal cortex, especially on the right; and (6) the cerebellum, particularly on the left (Cabeza et al. *1997).* Preliminary analyses of the functions of these areas in memory are as follows: The prefrontal cortex appears to relate to retrieval activation and to attention. The hippocampi relate to conscious recollection, the cingulate cortex to the activation of memory and selection of a specific response, the posterior midline regions to visual imagery, the parietal cortex to spatial awareness, and the cerebellum to voluntary, self-initiated retrieval. In subjects asked to recognize previously presented pairs of associated words, the right prefrontal cortex, anterior cingulate cortex, and inferior parietal region were the most activated. When the subject had to recall the words, the basal ganglia and left cerebellum also became active. In similar studies using functional MRI, Wagner et al. (1998) found that the left prefrontal region was predominantly involved when words were semantically encoded in memory; the right frontal activations seen in the previous study reflected nonverbal memory stimuli. In studies of the recognition of visual designs, Petersson, Elfgren, and Ingvar (1997) found that the medial temporal cortex activates more during new learning tasks than during previously trained and practiced memory tasks. Other areas activated during the new learning task included the prefrontal and anterior cingulate areas, more on the right side, and the parieto-occipital lobes bilaterally. Trained tasks activated the hippocampi much less but did activate the right inferior occipitotemporal region. This finding correlates with human studies indicating that ovcrlcarned memories gradually become less dependent on the hippocampus. Rugg et al. (1997) also found greater activation of the left medial temporal cortex in tasks in which the subject remembered words by "deep encoding" their meaning compared with simpler "shallow" encoding of the specific word. Other studies have shown that the deeper the encoding of a word's meaning, the better the subject remembers it (Schacter 1996). Finally, the amygdala appears necessary for affective aspects of memory items such as recall of fear associated with a specific stimulus.

Basic research on animals has begun to unravel the fundamental biochemical processes involved in memory, Bailey, Bartsch, and Kandel (1996) have studied memory formation in the giant snail, *aplysia.* Development of long-term facilitation, a primitive form of memory, requires activation of a gene called *CREB* (cyclic adenosine monophosphate response element binding protein) in sensory neurons. In this system and in similar studies on the fruit **fly** *Drosophila,* gene activation and protein synthesis are necessary for memory formation. Injection of protein synthesis inhibitors into the hippocampus can prevent the consolidation of memories (McGaugh 2000). Although similar studies have not been performed in humans, it is likely that similar gene activation and protein synthesis, perhaps beginning in the hippocampi bur proceeding through irs ncocortical connections, are necessary for the transition from immediate working memory to longer term storage of memory (Bear 1997). This field of research may hold promise for the development of drugs to enhance memory storage.

Syndromes of Partial Memory Loss

In contrast to the global amnesia seen in amnestic syndrome, patients have been described who have memory loss for selected classes of items. For example, patients with left temporal lobectomy for intractable epilepsy usually have detectable impairment of short-term verbal memory,

whereas those undergoing right temporal lobe resection have impairment only of nonverbal memory. Isolated sensory-specific memory loss syndromes have also been described, such as pure visual or tactile memory loss. Ross (1980) described two patients with bilateral occipital lesions, which disconnected the visual correx from the memory structures. These patients could draw a diagram of their homes but could not learn new spatial layouts. Ross postulated thai diagnosis oi a selective visual recenl memory deficit requires documentation of normal visual perception, absence of aphasia sufficient to impair testing, intact immediate visual memory, intact remote visual memory, and normal recenr memory in other modalities. A similar syndrome of isolated tactile memory loss has also been described.

Transient Amnesia

Transient amnesia is a temporary version of amnestic syndrome. The most striking example of transient amnesia is the syndrome of transient global amnesia (TGA), lasting from several hours to 24 hours. In this syndrome, an otherwise cognitively intact individual suddenly loses memory of recent events, asks repetitive questions about his or her environment, and sometimes confabulates. During the episode, the patient has both anterograde and retrograde amnesia, as in the pcrmanenr amnestic syndrome. As recovery occurs, however, the retrograde portion "shrinks" to a short period, leaving a permanent gap in memory of the brief retrograde amnesia before the episode and the period of no learning during the episode. The syndrome is of unknown cause but can be closely imitated by known disorders, such as complex partial seizures, migraine, and possibly transient ischemia of the hippocampus on one or both sides. Srrupp et al. (1998) reported that 7 of 10 patients imaged during TGA episodes showed an abnormal diffusion-weighted MRI signal in the left hippocampus, 3 of whom had bilateral hippocampal abnormalities. Permanent infarctions were not found. Other investigators have found frontal lobe abnormalities by diffusion-weighted MRI or PET imaging. These studies do not prove an ischemic etiology for TGA; rather, they indicate transient dysfunction in the hippocampus or its connections. The last six patients with TGA observed at our hospital have had normal diffusion-weighted MRI studies. Drug intoxication, alcoholic "blackouts," and minor head injuries can also produce transient amnesia.

OTHER TYPES OF MEMORY (NONDECLARAT1VE OR IMPLICIT MEMORY)

The three-stage model of immediate, short-term, and long-rerm memory has proved inadequate to describe the complexity of human memory. A confusing array of memory classifications and terminology has arisen, as shown in Table 6.2. Several aspects of memory do not involve the conscious recall involved in the three memory stages. A simple example is motor memory, such as the ability to ride a bicycle, which is remarkably resistant to hippocampal damage. Such motor memories probably reside in the basal ganglia and cerebellum. In the classification by Squire and Zola (1996), motor memories of this type are called *procedural* or *nondeclarative* memories.

Table 6.2: Types of memory and their localization

Types of recent memory	*Localization*
Declarative (explicit): facts, events	Medial temporal lobe
Nondeclarative (implicit)	
Procedural skills	Basal ganglia, frontal lobes
Classical conditioning	Cerebellum (plus amygdala)
Probabilistic classification learning	Basal ganglia
Priming	Neocortex

Another term for the whole class of memories for which subjects have no conscious awareness is *implicit* memory (in contrast to the explicit memory of episodic events). Implicit memories have in common storage and retrieval mechanisms that do not involve the hippocampal system; perhaps for this reason, the subject has no conscious knowledge of them. These procedural memories involve "knowing how" rather than "knowing that." Amnestic patients can learn new moror memories, such as mirror drawing, which they can perform once started, although they have no recollection of knowing the task. Motor learning likely involves the motor cortex and basal ganglia. Another type of memory, localized to the cerebellum, is classical conditioning, in which an unconditioned stimulus hecomes associated with a reward or punishment given when the conditioned stimulus is presented (Thompson and Kim 1996). The conditioning itself clearly involves the cerebellum, but the emotional aspect of the reward or punishment stimulus may reside in the amygdala. Classical conditioning can continue to function after bilateral hippocampal damage. Squire and Zola (1996) outlined other types of nondeclarative memory that take place independent of the hippocampal system. Probabilistic classification learning, such as predicting the weather from a combination of cues that are regularly associated with sunny or rainy weather, is unaffected by hippocampal damage but is impaired in diseases of the basal ganglia, such as Huntington's and Parkinson's diseases. Learning artificial grammar can also take place in the presence of amnestic syndrome. In all of these memory experiments, the patient has no awareness of how he or she is able to answer the questions. The last form of nondeclarative memory is called *priming,* the presentation of a stimulus associated with the word or idea to be remembered, which then aids in the retrieval of the item (e.g., recalling the word "doctor"

when "nurse" appears on a priming list). Priming appears to involve the neocortex (Thompson and Kim 1996). Schacter and Buckner (1998) have shown that deliberate use of priming can help amnestic patients compensate for their memory loss in everyday life.

BEDSIDE TESTS OF MEMORY AND COGNITIVE FUNCTION

The most important point to be made about bedside evaluations of cognition and memory is that they are an integral part of the neurological examination and a tool by which the neurologist localizes lesions affecting the higher cortical functions, just as the motor or cerebellar examinations localize neurological deficits. The most common error made by neurologists is to omit a systematic evaluation of mental function in patients who seem "alert and oriented." Deficits of memory, fund of knowledge, or focal deficits, such as apraxia, agnosia, acalculia, or constructional impairment, can be missed. Some patients have a "cocktail party" speech pattern that belies such deficits, whereas others become expert at deferring questions to a spouse or family member. Every neurologist has the task of deciding which patients need formal cognitive testing and whether to make up an individual test routine or to rely on one of the standard tests. Again, it is more important to make the assessment than ro follow a specific format.

Several versions of bedside mental status testing have been published. Perhaps the most widely used is Folstein's Mini-Mental State examination (MMSE). The MMSE consists of 30 points:

- 5 for orientation to time (year, season, month, date, and day)
- 5 for orientation to place (state, county, town, hospital, and floor)
- 5 for attention (either serial 7s with one point for each of the first five subtractions or "spell *world* backward")
- 3 for registration of three items
- 3 for recall of three items after 5 minutes
- 2 for naming a pencil and a watch
- 1 for repeating "no ifs, ands, or buts"
- 3 for following a three-stage command
- 1 for following a printed command "close your eyes"
- 1 for writing a sentence
- 1 for copying a diagram of two intersecting pentagons

The advantages of the MMSE are short time of administration and quantitation, which is useful in documentation for insurance benefits, such as rehabilitative therapies or drug therapy, and for disability assessment.

Several disadvantages of the MMSF have been identified. First, the normal range of scores depends on education. The low-normal curoff is estimated by Crum et al. (1993) to be 19 for uneducated people, 23 for graduates of elementary or junior high school, 27 for high school graduates, and 29 for college graduates. Age is aiso a factor. In addition, the test is weighted toward orientation and language, and it can be normal in patients with right hemisphere or frontal lobe damage. Finally, even an abnormal score does not distinguish a focal lesion from a more diffuse disorder, such as an encephalopathy or dementia.

One answer to the dilemma of mental status testing is to use the MMSE as a screening test and then supplement it with more focused tests. Teng and Chui (1987) suggested adding four items to the test and making it more quantitative, but this test has not gained wide acceptance. Table 6.3 lists the key elements of a mental status examination, whether the examiner chooses to adopt the MMSE or to create an individual test battery. Several texts provide further detail on such a battery. Although the mental status examination is the most neglected area of the neurological examination, it generally requires only a few minutes, and its cost-effectiveness compares well with brain imaging studies, such as MRI or PET.

An experienced examiner can learn much about the subject's mental status by careful observation during the history. Considerable insight can be gained into the subject's recent memory, orientation, language function, affect or mood, insight, and judgment. Affect and mood are best assessed in this fashion; if there is doubt, the examiner should consider how the patient makes the examiner feel: A depressed patient often makes the examiner feel depressed, whereas a manic patient makes the examiner feel happy and amused.

The formal mental status examination should always include explicit testing of orientation, including the date, place, and situation. Memory testing should include an immediate attention test, of which the most popular are forward digit span, serial-7 subtractions from 100, or the MMSE test "spell *world* backward." Short-term memory should include recall of three unrelated words at 5 minutes. The subject should always be asked to say them back after presentation, to make sure that the three items have registered. At times, nonverbal short-term memory, such as recalling the locations of three hidden coins or reproducing drawings, can be useful to test. Remote memory can be tested by having the subject name children or siblings. Fund of information can be tested with recent

Table 6.3: Bedside mental status examination

Orientation (time, place, person, situation)
Memory (immediate, short term, long term)
Fund of information
Speech and language
Praxis
Calculations
Visuaa I-construction a I abilities
Abstract reasoning, sequential processes

presidents or other political figures. For patients who do not pay attention to politics, use of athletic stars or television celebrities may be more appropriate. Language testing should include spontaneous speech, naming, repetition, auditory comprehension, reading, and writing (the bedside language test is described in more detail in Chapter 12). Praxis testing should include the use of both imaginary and real objects, such as a saw, hammer, and pencil. Both hands should be tested separately. Calculation tasks include the serial-7 subtraction test and simple change-making problems. Visual-spatial-constructional tasks can include line bisection, copying a cube or other design, and drawing a clock or a house (Figure 6.3). The MMSE contains only one constructional task, the copying of intersecting pentagons. Insight and judgment are probably best tested by assessing the patient's understanding of his or her own illness. Artificial tests include interpretation of proverbs, such as "Those who live in glass houses should not throw stones," or stating why an apple and an orange are similar. An artificial test sometimes used to test frontal lobe processing is the copying and continuation of Luria's test of sequential squares and triangles (see Figure 6.1). With these tests, preliminary localization can be made in the deep memory structures of the medial temporal lobes, the frontal lobes (insight and judgment, proverbs, similarities, Luria's sequence test), the left hemisphere language cortex in the frontal and temporal lobes, the left parietal region (calculations), and the right parietal lobe (visual-constructional tasks).

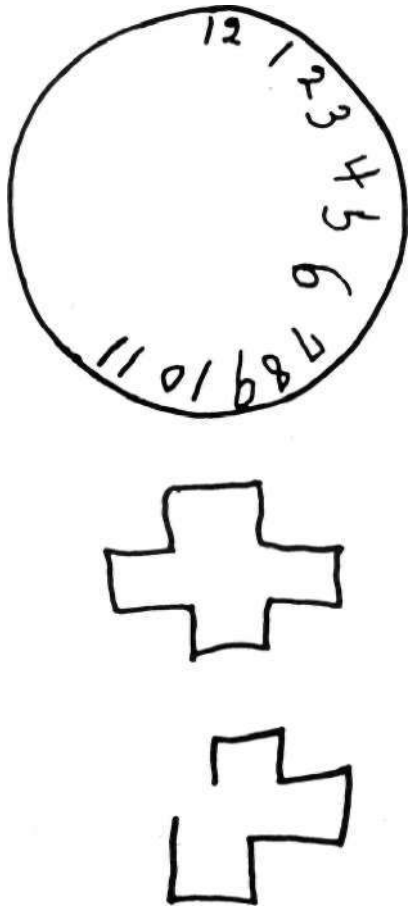

FIGURE 6.3 Luna's test of alternating sequences. Spontaneous clock drawing and copying of a cross by a patient with a right parietal infarction. The patient had only mild hemiparesis but dense left hemianopia and neglect of the left side of the body. The neglect of the left side of space is evident in both drawings. (Reprinted with permission from Kirshner, H. S. 2002, *Behavioral Neurology; Practical Science of Mind and Brain,* 2nd ed, Butter worth -Heinemann, Boston.)

CONCLUSION

This chapter considers the areas of neurology that most physicians find the most abstruse, namely, the higher cortical functions, intellect, and memory. As stated at the outset, this area of neurology can be treated as a series of specific functions to be analyzed at the bedside and localized, just like other functions of the nervous system. In fact, the rapidly increasing knowledge of cognitive neuroscience and our vastly improved ability to image the brain, both at rest and during functional activities, promises a new era of practical diagnosis of higher cognitive disorders.

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Chapter 7
Global Developmental Delay and Developmental Regression

David J. Michelson and Stephen Ashwal

Early measurement of a child's intellectual potential is made more difficult by the innate variability of normal maturation, Developmental disability, estimated to affect 5-10% of children, is defined as a disturbance in the acquisition of cognitive, motor, language, or social skills with a significant and continuing impact on developmental progress.

The term *global developmental delay* refers to *significant* delay seen across multiple domains of function and adaptation, whete *significant* is defined as performance that is two standard deviations below the mean for chronological peers. The diagnosis of *mental retardation* is reserved for children older than 5 years, in whom standardized intelligence quotient (1Q) testing can be reliably performed.

A slowed pace of development and a diminished intellectual potential can result from any of several adverse early influences, causing nonprogressive or *static encephalopathy,* or from diseases causing slow neurological deterioration. Most progressive neurological disorders eventually cause *developmental regression,* with loss of previously acquired motor or cognitive skills, as well as signs of nervous and organ system dysfunction. Children demonstrating neurological deterioration, especially when the deterioration is acute, require urgent evaluation.

The many goals of the physician managing a child with suspected developmental disability include (1) evaluating prior and current levels of function to confirm the presence of delay or regression, (2) undertaking a reasonable search for an underlying cause, (3) assessing and managing associated medical, behavioral, and psychosocial needs, and (4) providing appropriate referrals for ongoing rehabilitation and support services.

GLOBAL DEVELOPMENTAL DELAY

Evaluation

Primary care physicians have been encouraged to become familiar with the range of normal age-appropriate development and to monitor their pediatric patients during routine clinical encounters. Children with biological or social risk factors for later developmental disability are often targeted for additional periodic screening.

The Denver Developmental Screening Test II **(DDST-II)** is the tool most often used or referred to for esrimating a child's personal/social, fine motor/adaptive, language, and gross motor skills. Although the DDST-II is insensitive on its own, it remains useful when combined with parental concern to identify children who need further evaluation,

Observant caregivers provide valuable descriptions of a child's past development and possible loss of milestones but may have difficulty reliably recollecting the details of language acquisition. The expected milestones of infants arc shown in Table 7.1.

Once a problem is suspected, a child's motor, cognitive, behavioral, social, and functional abilities should undergo formal assessment. This requires the assistance of other members of a multidisciplinary ream, including psychologists and physiotherapists, who are trained to administer standardized testing. The tests most often used to provide both full-scale and categorical **IQs** are the Bay ley Scales of Infant Development, the Stanford-Binet Intelligence Scale, and the Wcchslcr scales {Wechslcr Preschool and Primary Scale of Intelligence-Revised, Wechslcr Intelligence Scale for Children III, and Wechsler Adult Intelligence Scale}. Test results should be confirmed by repetition and should not be unduly influenced by sensory, language, or attention deficits.

Etiology

The perception among primary care providers and third-party payers of a low diagnostic yield when evaluating global developmental delay or mental retardation is unfortunate and incorrect. The diagnostic yield is now estimated at 60-80% because of improved understanding

Table 7.1: Normal developmental milestones by age (50th to 75th percentile)

Age	*Language*	*Social*	*Motor*
1 111)	Cooing (ooh, ah)	Smiles with social contact	Holds head up 45 degrees
4 nni	Laughs and squeals	Sustained social contact	Grasps objects, hears weight on legs
6 mo	imitates speech sounds, single syllables	Prefers mother, enjoys mirror	Transfers objects between hands, uses a raking grasp, sits with support
8 mo	Jabbering (dadada, bababa)	Plays peekaboo or patty-cake, waves bye-bye	Sits without support, creeps or crawls
12 mo	"Da da/ma ma" specific	Plays simple ball games, adjusts body to dressing	Stands alone, uses a thumb-finger pineer grasp
14 mo	l-2-word vocabulary	Indicates desires by pointing, hugs parents	Walks alone, stoops and recovers
IS mo	6-word vocabulary	Feeds self	Walks up steps with hand held, imitates scribbling
24 mo	Combines words, 250-word vocabulary	Helps to undress, listens to stories with pictures	Runs well, makes circular scribbles, copies a horizontal line
50 mo	Refers to self as "I," knows full name	Pretends in play, helps put things away	Climbs stairs with alternate feet, copies a vertical line
16 mi>	Counts three objects correctly, knows age and sex	Helps in dressing	Rides a tricycle, stands on one foot briefly, copies a circle
4S mo	Tells a story, counts four objects	Plays with other children, uses toilet alone	Hops on one foot, uses scissors to cut out pictures, copies a square and a cross
60 mo	Names 4 colors, counts 10 objects	Asks about word meanings, domestic role playing	Skips, copies a triangle

of developmental pathophysiology, increased imaging resolution, and availability of genetic testing {Shevell ct al. 2000). Establishing the cause of a retardation syndrome may not always alter medical management but does ptovide a family with important information regarding prognosis and recurrence risk for future pregnancies, and it also limits the need for further testing. A child's development depends on the complex interplay of biological, social, and environmental influences. Table 7.2 summarizes the biological conditions associated with developmental disability and organizes examples by presumed time of onset and disease category. (The interested reader is referred to the appropriate chapters of this textbook for detailed descriptions of these conditions.)

History

The caregiver's report of a child's past developmental history is the first step in estimating the degree and scope of developmental delay. Questions should address the child's current level of function and possible associated medical problems, seizures, or difficulties with feeding, sleeping, or behavior. Prior medical records, past and current classroom placements, and reports from teachers provide corroboration.

A family history of similar illness suggests a genetic syndrome and should be pursued in detail, including consanguinity, ethnicity, relatives with neurological impairments, and early postnatal deaths. Although family history is becoming increasingly difficult as families spread geographically, information should be sought from both parents and from both sets of grandparents. An equally detailed prenatal, birth, and postnatal history may reveal those risk factors that arc associated with neurological injury (Table 7.3).

Physical Examination

Observing a child's interactions with parents and with age-appropriate toys allows an initial assessment of motor skill and dexterity; curiosity, impulsivity, and artcntion span; and social skills, eye contact, and communicative intent. The hands-on physical examination should be as complete as a child will allow, focusing on possible etiological clues such as growth parameters; abnormalities of the eyes, skin, and hair; dysmorphic features; abnormal tone, posture, movements, and reflexes; signs of cerebellar or peripheral nerve dysfunction; and organomegaly. Findings that suggest specific syndromes are listed in Tables 7.4 and 7.5.

Diagnostic Testing

An evidence-based and stepwise search for an underlying cause is preferable to the use of a large panel of screening tests. One stepwise approach is presented in Figure 7.1.

Table 7.2: Etiology of developmental delay by time of onset

Prenatal/perinatal	*Examples.*
Congenital malformations of the CNS	Lissencephaly, Chiari malformation
Ch romos om a 1 a bn orma 1 ities	Down syndrome, Turner's syndrome
Endogenous toxins from maternal organs	Maternal hepatic or renal failure
Exogenous toxins from maternal use	Alcohol, anticonvulsants, anticoagulants, drugs of abuse
Fetal infection	Congenital infections (toxoplasmosis, rubella, cytomegalovirus, HIV, and syphilis)
Prematurity and/or fetal malnutrition	Periventricular leukomalacia, intraventricular hemorrhage
Perinatal trauma	Intracranial hemorrhage, spinal cord injury
Perinatal asphyxia	H y pox ic-i sch e mic en c e ph a lo pa thy
Postnatal	*Examples*
Inborn errors of metabolism	Aminoacidopathies, mitochondrial diseases, urea cycle defects
Abnormal storage of metabolites	Lysosomal storage diseases, glycogen storage diseases
Abnormal postnatal nutrition	Vitamin or calorie deficiency
Endogenous toxins from organ failure	1 k-paiic or renal failure, kern icterus
Exogenous toxins	Prescription drugs, illicir substances, lead
Endocrine organ failure	Neonatal or acquired hypothyroidism, hypoadrenocorticism (Addison's disease)
CNS infection	Meningitis, cerebral abscess, viral meningoencephalitis, HIV encephalopathy, subacute sclerosing panencephalitis
CNS trauma	Nonaccidental trauma, traumatic brain injury
Neoplasia	Infiltration, edema, hydrocephalus, radiarion
Neurocutaneous syndromes	Neurofibromatosis, tuberous sclerosis, incontinentia pigmenti, Sturgc-Weber syndrome
Neuromuscular disorders with CNS involvement	Congenital muscular dystrophy, congenital myotonic dystrophy, congenital myopathies
Vascular conditions	Systemic lupus erythematosus, moyamoya disease, stroke, venous sinus thrombosis
Other	Autism, uncontrolled epilepsy, severe mood disorder, schizophrenia

CNS = central nervous system; HIV = human immunodeficiency virus.
Source: Adapted with permission from Shevell, M. I. & Swaiman, K. F. 1999, "Global developmental delay and mental retardation," in *Pediatric Neurology, Principles and Practice,* eds K. F. Swaiman & S. Ashwal, Mosby, St. Louis.

Metabolic Testing

Universal newborn screening in the United States, particularly the use of tandem mass spectroscopy, identifies many of the more common metabolic disorders. Metabolic screening of children with unexplained global developmental delay has a less than 1% yield. The yield remains less than 5% even when a metabolic etiology is suggested by history or examination. Screening these children with basic metabolic tests before ordering specific metabolic tests may increase the yield to 14% (Papavasiliou et al. 2000). Thyroid studies are not indicated in children with global developmental delay who have already been screened as newborns unless clinical features are also present.

Table 7.3: Perinatal risk factots for neurological injury

Material Up renatal	*Natal*	*Postnatal*
Age less than 16 or more than 40 yr	Cesarean section after a trial of labor	Abnormal sucking or feeding
Cervical or pelvic abnormalities	Firstborn male	Abnormal crying
Infection	Premature twins	Asymmetrical face or extremities
Diabetes mellitus	Cyanosis	Dysmorphic features
Drug addiction	Need for resuscitation	Hyperbilirubinemia
Malnutrition	Low Apgar score	Hypotonia
I [ypertension or toxemia	Gestational age less than 30 wk	Birth injuries
Thyroid disease	Hypoxic-ischemic encephalopathy	Seizures
Hemorrhagic shock	Midforceps delivery	Fever
Polyhydramnios or oligohydramnios	Breech presentation	Need for an incubator or oxygen
Low socioeconomic status	Placental abruption	Poor weight gain
Prior miscarriages or stillbirths	Umbilical prolapse	Malnutrition
Vaginal bleeding after first trimester		
Prior placental abnormalities		

Source: Adapted with permission from Shevell, M. I. &: Swaiman, K. F, 1999, "Global developmental delay and mental retardation," in *Pediatric Neurology, Principles and Practice,* eds K. F. Swaiman & S. Ashwal, Mosby, St. Louis.

Table 7.4: Ocular findings associated with selected syndromic developmental disorders

Finding	*Examples*
Cataracts	CerebrotendinouS xanthomatosis, galactosemia, Lowe's, LSD, Wilson's
Chorioretinitis	Congenital infections
Corneal opacity	Cockayne's, Lowe's, LSD, xeroderma pigmentosa, Zellweger's
Glaucoma	Lowe's, mucopolysaccharidoses, Sturge-Weber, Zellweger's
Lens dislocation	Homocystinuria, sulfite oxidase deficiency
Macular cherry-red spot	LSD, multiple sulfatase deficiency
Nystagmus	Aminoacidopathies, AT, CDG, Chediak-Higashi, Friedrich's ataxia, Leigh's, Marinesco-Sjogren, metachromatic leukodystrophy, neuroaxonal dystrophy, Pelizaeus-Merzbacher, SCD
Ophthalmoplegia	AT, Basscn-Kornzwcig, LSD, mitochondrial diseases
Optic atrophy	Alpers', Leber's optic atrophy, leukodystrophies, LSD, neuroaxonal dystrophy, Pelizaeus-Merzbacher, SCD
Photophobia	Cockayne's, Hartnup's, homocystinuria
Retinitis pigmentosa or macular degeneration	AT, Bassen-Kornzweig, Cockayne, CDG, Hallervorden-Spatz, Laurence-Moon-Beidl, LSD, mitochondrial diseases, Refsum's, Sjogren-La rsscn, SCD

AT = ataxia-telangiectasia; CDG = congenital disorders of glycosylation; LSD = lysosomal storage diseases; SCD = spino-cerehellar degeneration.

Source: Adapted with permission from Shevell, M. 1. & Swaiman, K. F. 1999, "Global developmental delay and mental retardation," in *Pediatric Neurology, Principles and Practice,* eds K. F. Swaiman & S. Ashwa!, Moshy, St. I.ouis.

Metabolic testing should he considered when the history or physical examination is suggestive of a metabolic disorder or when newborn screening results are not available. Tests to consider include a capillary blood gas, scrum lactate and pyruvate (energy metabolism), serum ammonia (aminoacidopathies and urea cycle defects), serum amino acids (aminoacidopathies), urine organic acids (organic acidopathies), serum creatine kinase (myopathies), serum very-long-chain fatty acids (peroxisomal disorders), urine mucopolysaccharides and oligosaccharides (mucopolysaccharidoses), and thyroid function tests,

Genetic Testing

Cytogenetic study of children with global developmental delay, using karyotyping at the 500-band level of resolution, has a yield of about 3.5%. For children with multiple minor dysmorphic features of the face and limbs, the yield is up to 20% (Graham and Selikowitz 1993). Down syndrome, recognizable by its characteristic dysmorphic features and hypotonia, is the most common chromosomal abnormality found, accounting for 25-50% of severe retardation. The fragile X mutation (FMR-1) is the most common inherited cause of mental retardation. Its prevalence among developmental!;- delayed children is 2.5-5,0%. The yield of FMR-1 testing in postpuhertal males increases to 7.6% when common clinical features are used for selection (DeVries et al. 1999) (Table *7.6).* The X-1inked Rett's syndrome mutation (McCP2) is the most common cause of mental retardation in females after Down syndrome. The features at presentation arc listed in Table 7,7. In one study, the Rett's mutation was found in 2.5% of institutionalized female children (Vorsanova ct al. 2001). The prevalence of the mutation in males and in more mildly affected females is unknown. Using fluorescence in situ hybridization (FISH) and microsatellitc markers to screen for the more subtle subtelomeric chromosomal rearrangements may have a yield as high as 8.5% in moderately to severely affected children (Baker et al. 2002).

Routine cytogenetic testing should be performed on all developmentally delayed children. Testing for the fragile X mutation should also be considered, although clinical preselection can be used to exclude some postpuhertal males. Rett's syndrome testing should be considered for all moderately to severely delayed females, especially those demonstrating typical clinical features. Subtelomeric testing should be considered in children whose moderate to severe delay remains unexplained. FISH testing for other less common single gene mutations and contiguous gene deletions are warranted when clinical features of those syndromes are present (Table 7.8).

Imaging Studies

Routine imaging with computed tomography (CT) yields the etiology in 33% of unselccted populations of children with global developmental delay. This yield increases to 65% when magnetic resonance imaging (MRI) is used because MRI is more sensitive for cerebral dysgenesis and white matter abnormalities, the most common radiological findings (Dcmaerel, Kingsley, and Kendall 1993). Yields are higher still in patients with cerebral palsy, focal neurological deficits, or microcephaly.

Brain imaging with MRI should be routine in children with developmental disability. CT still has a place in the evaluation of children with suspected calcifications (as from congenital infections or tuberous sclerosis) or craniosynostosis.

Table 7.5: Other findings associated with selected syndromic developmental disorders

binding	*Examples*
Cerebellar dysfunction	Aminoacidopathics, AT, Bassen-Kornzwcig, CDG, cercbrotendinous xanthomatosis, Chediak-Higashi, Cockayne's, Friedreich's ataxia, Lafora's disease, LSD, Marim-sco Sjogren's, mitochondrial disease, neuroaxonal dystrophy, Pelizaeus-Merzbacher, Ramsay Hunt syndrome, SCD, Wilson's
Hair abnormalities	
Synophrys	Cornelia de Lange's
Fine hair	Homocysrinuria, hypothyroidism
Kinky hair	Argininosuccinic aciduria, Menkc's
Hirsutism	LSD
Balding	Leigh's, progeria
Gray hair	AT, Chediak-Higashi, Cockayne's, progeria
Hearing abnormalities	
Hyperacusis	LSD, Subacute sclerosing panencephalitis, sulfite oxidase deficiency
Conductive loss	Mucopolysaccharidoses
Sensorineural loss	Adn.'r1t>l::i.ikudvMr<iph\ . (JIAfUIL, (nck.r. -ic's, inirodn uulri.il diseases, M i l Relsurn's
Infantile hypotonia	Caiisi van's, myopathica. LSI). Leigh's, Menkes", ncuroaMinal *d*\ sii oph\. spina! musc.ibr ainiphy. Zellweger's
Limb abnormalities	
Mkromelia	Cornelia de Lange's
Broad thumbs	Rubinstein-Taybi
Macroccphaly	Alexander's, Canavan's, histiocytosis X, LSD
Microcephaly	Alpers', CDG, Cockayne's, incontinentia pigmenti, neuronal ceroid lipofuscinosis, Krabbe's, neuroaxonal dystrophy, Rett's
Movement disorders	AT, LSD, dystonia musculorum deformans, Hallervorden-Spatz, juvenile Huntington's, juvenile Parkinson's, Lcsch-Nyhan, phenylketonuria, Wilson's, xeroderma pigmentosa
Odors	
Cat urine	p-merhyl-crotonyl-CoA-carboxylase deficiency
Maple	Maple syrup urine disease
Musty	Phenylketonuria
Rancid butter	Methionine malabsorption syndrome
Sweaty feet	Isovaleric acidemia
Organomegaly	Aminoacidopathies, CDG, galactosemia, glycogen storage diseases, LSD, Zellweger's
Peripheral neuropathy-	AT, Bassen-Kornzweig, cerebrotendinous xanthomatosis, Cockayne's, LSD, Refsum's
Short stature	Cockayne's, Cornelia dc Lange's, hypothyroidism, leprechaunism, LSD, Prader-Willi, Rubinstein-Taybi, Seckel's bird-headed dwarfism
Seizures	Aminoacidopathies, CDG, glycogen synthetase deficiency, HIE, LSD, Menkes', mitochondrial diseases, neuroaxonal dystrophy
Skin abnormalities	
Hyperpigmentation	Adrenoleukodystrophy, AT, Farber's, neurofibromatosis, Niemann-Pick, tuberous sclerosis, xeroderma pigmentosa
Hypopigmentation	Chediak-Higashi, incontinentia pigmenti, Menkes' tuberous sclerosis
Nodules	Cerebrorendinous xanthomatosis, Farber's, neurofibromatosis
Thick skin	LSD, Refsum's, Sjogren-Larsson
Thin skin	AT, Cockayne's, progeria, xeroderma pigmentosa

AT = ataxia-telangiectasia; CHARGE = (colohoma, heart disease, choanal atresia, retardation, genital anomalies, ear anomalies); CI Hi • congenital disorders ot glycosylation; HIE ▬ h\ poxic ischemii. euu'phalopa-.liy; 1 MJ \\ sosouiai sUir.:s;e diseases: SIT) spinocerebellar degeneration.

Source: Adapted with permission from Shcvell, M. I. &. Swaiman, K. F. 1999, "Global developmental delay and mental retardation," in *Pediatric Neurology, Principles and Practice,* eds K. F. Swaiman & S. Ashwal, Mosby, St. Louis.

Other Tests

Lead exposure is unlikely to cause a significant degree of developmental delay but does correlate with lower IQ scores. Testing in developmentalIy delayed children should be reserved for those who have risk factors for excessive exposure, as established by consensus guidelines. In this group, the yield is about 10% (Lewendon et al. 2001).

Electroencephalography (EEG) is useful in classifying epileptic syndromes in children with clinically apparent seizures but rarely contributes an etiological diagnosis. There is not sufficient evidence to support routinely performing 11 d testing on dcvcloptncnrally delayed children without clinically evident seizures. However, pseudo-retardation can very rarely result from an unrecognized but treatable epileptic syndrome such as electrical

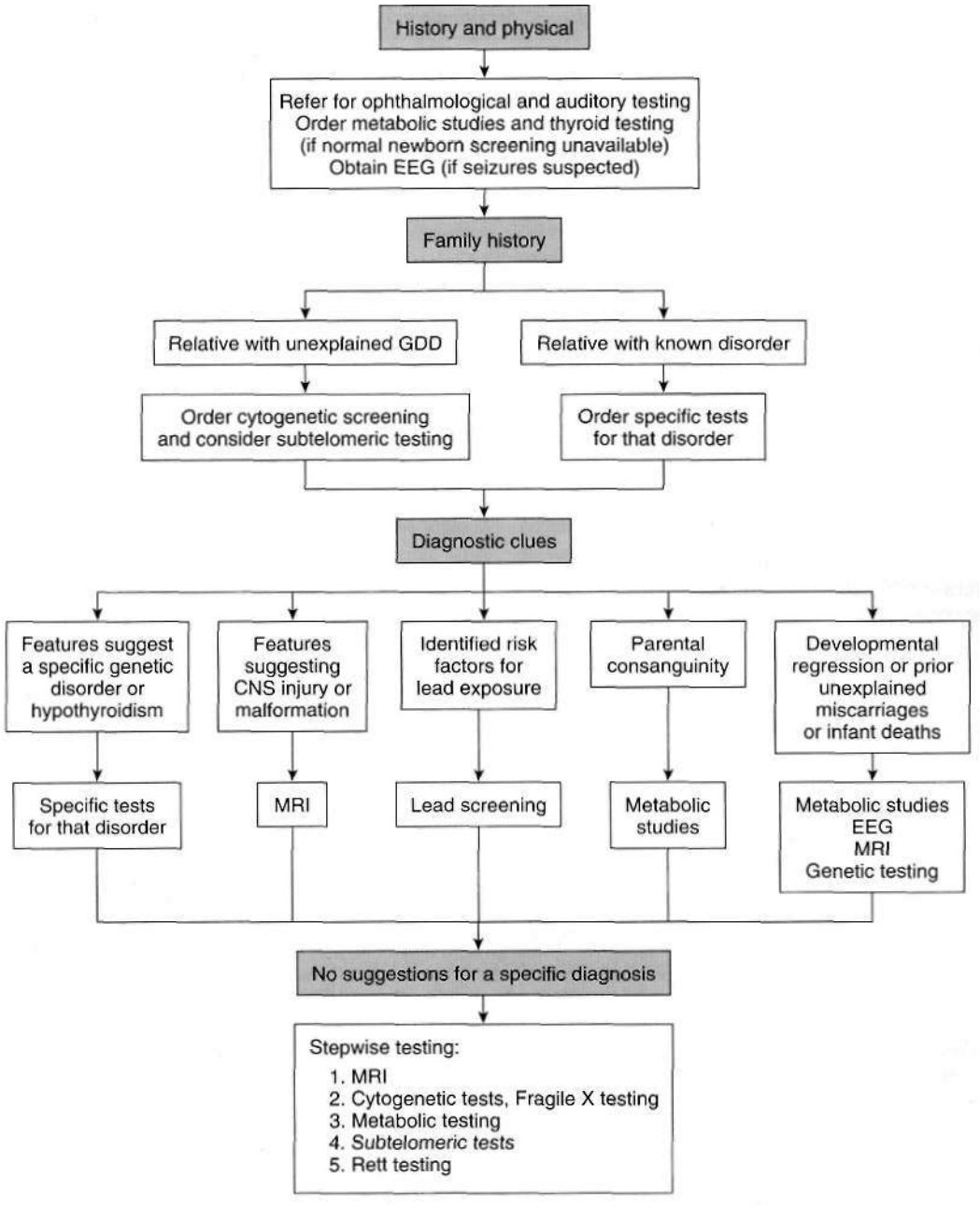

FIGURE 7.1 Stepwise evaluation of unexplained global developmental delay. CXS = central nervous system; EEG = electroencephalogram; GDD = global development delay; MRI = magnetic resonance imaging. (Adapted with permission from Shevell, M., Ashwal, S., et al. 2003, "Practice parameter: Evaluation of the child with global developmental delay," *Neurology,* vol. 60, no. 3, pp. 367-380.)

table 7.6: Clinical features of fragile X syndrome

1. Family history of mental retardation
2. Long jaw or high forehead
3. Large and/or protuberant ears
4. I I\ |viY\:ciisiKi- Mini-.
5. Soft and velvet)' palmar skin with redundancy on the dorsum of the hand
6. Large testes *(>9S%* percentile)
7. Initial shyness and lack of eye contact followed by friendliness and verbosity

Tabic 7.7: Clinical features of Rett's syndrome

1. Normal development up ro age 6-18 mo
2. Loss of purposeful hand use
3. Autistic features and loss of speech
4. Seizures
5. Acquired microcephaly
6. Trunk and limb ataxia
7. Eventual loss of ambulation

Table 7.8: Selected syndromes with available fluorescence in situ hybridization probes

Syndrome	*Genetics*	*Clinical features*
Angelman's	Deletion 15qll-ql3 or paternal disomy of chromosome 15	Microcephaly, puppet-like ataxic and apracfic movements, inappropriate laughter, absent speech
Di George's	Deletion 22q 11	Thymic hypoplasia, conotruncal cardiac defects, low-set ears, micrognathia, hypertelorism, antimongoloid palpebral slant, palatal clefts
Gri du chat	Deletion 5p	High-pitched cry, hypertelorism, epicanthal folds, brachyecphaly, moon face, antimongoloid palpebral slant, micrognathia, hypotonia, strabismus
Langer-Giedion	Deletion 8q24.1	Microcephaly, large ears, bulbous nose, broad nasal bridge, elongated philtrum, sparse scalp hair, multiple nevi, skeletal anomalies
Miller Dicker	Deletion 17p13.3	Lissencephaly, hypotonia, seizures
Prader-Willi	Deletion Uqll-ql3 or maternal disomy of chromosome 15	Almond-shaped eyes, thin upper lip, down-turned mouth, infantile hypotonia and failure to thrive followed by hyperphagia and obesity in childhood, hypogonadism
Smith-Magenis	Deletion 17pll.2	Short stature, brachydactyly, organ malformations, self-injurious behaviors
Williams	Deletion 7q I I	Cardiac valvular stenosis, hypotonia, hyperacusis, "elfin fades," short stature
Wol f - H i rsch h or n	Deletion 4pl6.3	Microcephaly, "greek helmet" facies, midline fusion defects

status epilepticus during slow-wave sleep, Landau-Kleffner syndrome, or severe absence epilepsy.

Complete visual and auditory testing, including a full ophthalmological examination, vision screening, and behavioral audiometry or brainstem auditory evoked response testing, is indicated for all children with developmental disability. The prevalence of visual and auditory impairments, including refractive errors, ranges from 25-50%.

More invasive tests, such as cerebrospinal fluid analysis, nerve conduction velocities, nerve or muscle biopsies, or cell cultures for enzyme analyses have utility in specific clinical situations, after screening tests have been done.

DEVELOPMENTAL REGRESSION

A progressive neurological disorder should be suspected when a child loses function or fails to progress beyond a prolonged plateau after a period of relatively normal development. Repeated medical evaluations, prior photographs, and home movies can help support the diagnosis of regression and establish the timing of its onset. Children with a static encephalopathy can experience neurological deterioration with the onset or worsening of a seizure or movement disorder, worsening of spasticity, progression of hydrocephalus, or the influence of sedating medications, or intervening medical illness.

Other elements from the history and examination that should raise suspicion of genetic-metabolic disease are (1) parental consanguinity or close relatives with similar or related neurological disorders, (2) new or worsening neurological deficits including blindness and deafness, (3) recurrent, episodic weakness, hypotonia or spasticity, ataxia, lethargy, or vomiting, and (4) dysfunction of other organ systems, including organomegaly and ocular, hair, or skin abnormalities.

The possible causes of progressive neurological decline include genetic, metabolic, degenerative, infectious, inflammatory, neoplastic, and vascular diseases. Most metabolic disorders are rare and are transmitted in an autosomal or X-linked recessive manner.

It is useful to conceptualize neurological decline as, at least initially, predominantly affecting gray matter or alternatively white matter within the central nervous system. Features suggestive of gray matter involvement include seizures or EEG changes, movement disorders, blindness with retinal changes, personality changes, and dementia. An MRI scan of the brain may not show significant change early on, but generalized atrophy and vcntriculomegaly are seen later. Features of white matter involvement include spasticity, rigidity, visual impairment with optic atrophy but no retinal changes, and demyelination on MRI.

Diagnostic clues from a detailed physical and ophthalmological examination, listed in Tables 7.4 and 7.5, are helpful in suggesting specific syndromes. Table 7.9 lists the usual age at onset of neurological decline for some of the more common diseases.

A stepwise approach to the evaluation of a child with developmental regression is shown in Figure 7.2. If suspicion of a metabolic disease is high despite normal results, tests may need to be repeated during an exacerbation or after a high-protein or high-carbohydrate meal. Determining a definitive diagnosis at times requires more invasive testing, including biopsies of brain, skin, conjunctiva, muscle, nerve, or bone marrow.

Tabic 7.9: Age at onset of selected degenerative and metabolic disorders

Age	*Examples*
Neonatal	Alport's, aminoacidopathies, urea cycle disorders, galactosemia, incontinentia pigmenti, leukodystrophies, Menkes', Pclizaeus Met/bacher, progressive spinal muscular atrophy, sphingolipidoses, Zellweger's
Infancy	leukodystrophies, lysosomal storage diseases, mitochondrial diseases, neuroaxonal dystrophy, Pelizaeus-Merzbacher, Sjdgren-Larsson
Early childhood	Aminoacidopathies, ataxia-telangiectasia, Cheduik-Higashi, Cockayne's, leukodystrophies, lysosomal storage diseases, Marinesco-Sjogren, mitochondrial diseases, neuroaxonal dystrophy, xeroderma pigmentosa
Late childhood to adolescence	Adrenolcukodystrophy, Bassen-Komzweig, cerebrotendinous xanthomatosis, dystonia musculorum deformans, Friedreich's ataxia, Hallervorden-Spatz, homocystinuria, juvenile Huntington's, juvenile Parkinson's, Lafora body, Lesch-Nyhan, lysosomal storage diseases, Ramsay Hunt, spinocerebellar degeneration, subacute sclerosing panencephalitis, Wilson's

Children with Rett's syndrome experience an initial 6-18 months of normal development before undergoing regression, but the MeCP2 gene defect is thought to directly influence postnatal brain development, and thus it was considered in the previous section with global developmental delay. Most children with infantile autism also appear normal during their first year but later show regression and impairment of verbal and nonverbal communication, poor socialization, and the onset of testricted and repetitive patterns of behavior. Although many children with retardation of definable etiology have autistic features, few cases of isolated autism have been associated with a definite genetic disorder or neurological insult. The screening and diagnosis of autism have recently been reviewed (Filipek et al. 2000).

Management

Counseling

Stating the problem as clearly as possible is important in communicating the diagnosis of developmental delay or retardation. Clinicians should be prepared to address a range of emotional reactions, from guilt and sorrow to denial and anger. Once the diagnosis is accepted, families often wish to know the functional level and degree of

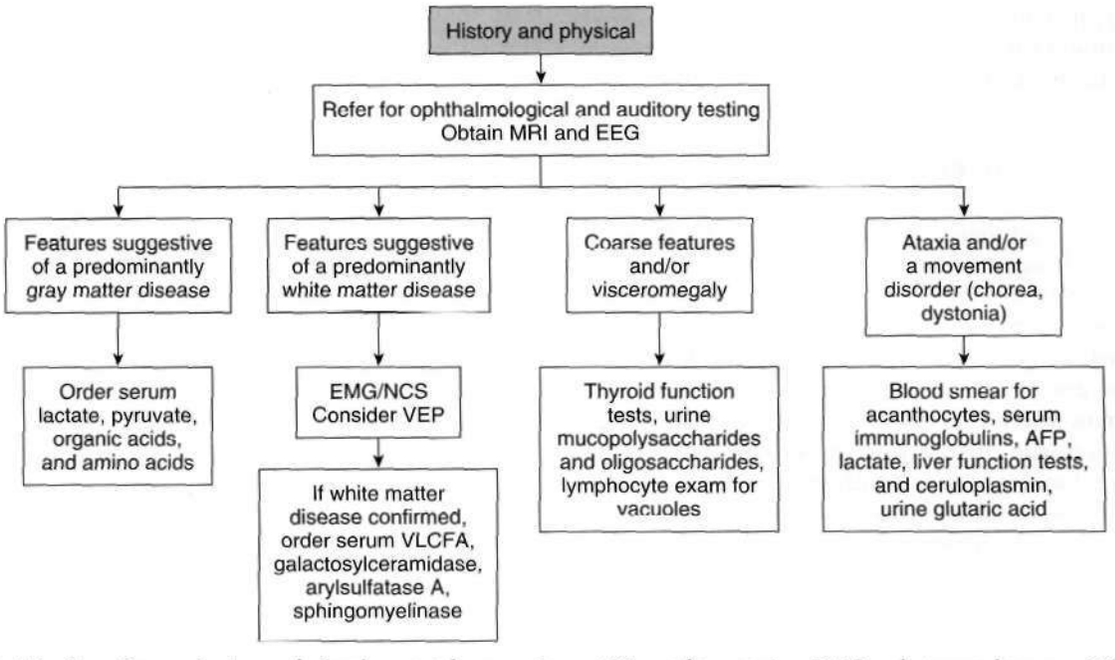

FIGURE 7.2 Stepwise evaluation of developmental regression. AFP = α-fetoprotein; EMG = electromyelogram; NCS = nerve conduction studies; VEP = visual evoked potentials; VLCFA = very-long-chain fatty acids.

independence the child will eventually attain. Because this cannot always be predicted with certainty, a balance should be sought between preparing parents for the worst and allowing room for reasonable hope,

Prognosis

In the absence of cardiorespiratory disease, mildly retarded children have a normal life expectancy. Mortality in more severely affected children is not directly related to the underlying etiology of the retardation but is secondary to immobility, aspiration, and seizures. Many of the progressive neurological diseases have no specific therapy and lead to death relatively soon after diagnosis.

Children with mild to moderate mental tetardation can continue to develop cognitivcly and functionally with appropriate education and should be encouraged to undergo vocational training if possible. Issues of sexuality, living arrangements, employment, and financial support become significant challenges during the transition to adulthood,

Children identified as having developmental delay are not all destined to be mentally retarded adults. Children whose development is affected by significant environmental deprivation or medical illness have the potential for recovery if their circumstances improve. Early development is predominantly that of sensorimotor function and many infants with cerebral palsy or neuromuscular disorders who are identified as delayed eventually demonstrate normal cognition,

Treatment

Psychologists, physical therapists, occupational therapists, and language therapists can provide families with more formal assessments of their child's function, as well as with structured interventions toward rehabilitation. Many of these resources are made available on referral through county-specific programs and schools. In the United States, federal law mandates the provision of early intervention programs for at-risk children aged 3 to 5, and appropriate public school education for children up to age 21.

As there are no specific treatments for most developmental disorders. Treatments focus on the medical, emotional, and behavioral problems that affect up to 30% of children with mental retardation. Feeding difficulties may require supplemental nutrition through a gastrostomy tube. Mood disorders, schizophrenia, aggressive behaviors, hyperactivity, and disrupted sleep may require pharmacological therapy. Seizures affect up to 20% of children with mental retardation and may be difficult to control.

Children in whom the cause of developmental delay remains unclear after the initial evaluation should be followed on a regular basis for possible regression and the need for more extensive testing. Institutionalized care is a consideration for some severely and profoundly retarded

Tabic 7.10: Selected Internet resources related to developmental delay

Site name	*Internet address*	*Features*
Community		
Exceptional Parent Magazine	www.epa renr.com	Monthly print and Internet publication with features of general interest to families with disabled children.
Family Village	www.familyvillage.wisc.edu	Disease-specific listings of organizations, support groups, Web pages, and chat rooms. General information regarding disability and adaptive equipment.
Kids Move	www.wi'mow.org/kidsmove	A comprehensive resource for movement disorders affecting children, providing information, discussion forums, links to organizations, and a calendar of educational meetings.
NORD	ww. penet .com/orp h a n	Catalog of rare diseases offering brief descriptions and listings of support groups, organizations, published research, and ongoing clinical trials.
Genetics		
(ie ne-Tests	www.genetests.org	Searchable catalog of genetic disorders with summary descriptions, reviews of the appropriate genetic tests, and directories of genetic labs and prenatal testing clinics.
OMIM	www3, ne b i. nlm.nih.gov/omim	Catalog of genetic disorders searchable by clinical features with links to academic publications.
Child neurology		
Child Neurology Foundation	www.childneurologyfoundation.org	Provides news and links to resources for families and clinicians.
Child Neurology Society	www.childneurologysociety.org	A resource for professionals treating children with neurological disorders.

OMIM = Online Mcndelian Inheritance in Man; NORD = National Office of Rare Disorders.

children whose needs are greater than what their families can provide. Families who continue to care for their affected children should be referred to community setviccs providing social support and respite cate. Physicians and families alike can benefit from the growing availability of support and practical information available through Internet sites. Several examples are listed in Table 7,10.

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Chapter 8
Behavior and Personality Disturbances

Jane S. Paulsen and Carissa Nehl

Behavioral and personality disturbances are quite common in individuals with neurological disease, traumatic brain injury (TBI), and stroke (Table 8.1). Identification and treatment of behavioral disturbances are critical as they are associated with reduced functional capacity, decreased quality of life, greater economic cost, larger caregiver burden, and increased morbidity.

Historically clear divisions between the fields of psychiatry and neurology have existed. Psychiatry has primarily focused on disruptions of behavior and personality resulting from "nonorganic" or psychological causes, whereas neurology has historically focused on disease and injury with "organic" causes. As research continues to detect neuroanatomical and biochemical correlates of behavior and personality disturbances, the division between psychiatry and neurology becomes less clear. Within the last two decades, increased collaboration and partnership between these two fields have begun. An example of this collaboration is the creation of the American Neuropsychiatric Association (ANPA) established in 1988. ANPA's mission statement notes that it is dedicated to the advancement of clinical, educational, and research activities in the field of clinical neutoscience and that it supports collaboration between professionals in psychiatry, neuropsychiatry, behavioral neurology, neuroradiology, neuropathology, neurosurgery, and researchers in the basic sciences. In addition, journals such as the *Journal of Neuropsychiatry and Clinical Neurosciences*, the official journal of ANPA, present research conducted at the crosstoads of neurology and psychiatry.

The aim of this chapter is twofold. First, theoretical information linking frontal-subcortical circuitry and behavior and personality disturbances is described. Second, information regarding the prevalence, phenomenology, and treatment of behavior and personality disturbances in dementia, movement disorders, epilepsy, stroke, and TBI is presented.

FRONTAL-SUBCORTICAL CIRCUITRY

The frontal-subcortical circuits provide a unifying framework for understanding the behavioral changes that accompany cortical and subcortical brain dysfunction. In the past three decades, a number of significant advances have been made in our understanding of the neuroanatomy, neurophysiology, and ehemoarchitecture of the frontal-subcortical circuits. An increasingly broad spectrum of neuropsychiatric phenomenology is now being interpreted in the context of frontal-subcortical circuit dysfunction. A brief overview of the frontal-subcortical circuits and their signature behavioral syndromes is offered as a strategy to better understand the behavior and personality changes that accompany neurological conditions. Alexander and colleagues (1986) described five discrete parallel circuits linking regions of the frontal cortex to the striatum, the globus pallidus and substantia nigra, and the thalamus. These circuits consist of "direct" and "indirect" pathways. In general, the direct pathway facilitates the flow of information, and the indirect pathway inhibits it. The overall model for the frontal-subcortical circuits can be observed in Figure 8.1.

Five frontal-subcortical circuits were initially described: motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate. Disruption of the final three of these circuits is associated with behavioral and personality disruptions. Each of these circuits is associated with distinct neurological correlates. See Table 8.2 for descriptions of specific neuroanatomical pathways for these circuits.

Efforts to link functional domains to this brain circuitry have been developed and revised over the past few decades. It has been proposed that the basal ganglia be divided into a neurologist's, psychologist's, and psychiatrist's portion responsible for motor, cognitive, and emotional disorders, respectively. In this schema, the neurologist's circuit is the

Table 8.1: Prevalence of behavioral and psychiatric disturbances in neurological disorders

	Depression	*Apathy*	*Anxiety*	*Euphoria*	*Psychosis*	*Aggression*
AD	0-86%	Up to 92%			10-73%	33-67%
FTD	—	95%	—	33%	20% delusions 7% hallucinations	—
VaD	32%	—	19-70%	—	33% delusions 13-25% hallucinations	—
HIV	43-55%	—	17-36%	—	—	—
I'D	40-50%	16.5^(0.0%	—	—	16% delusions 30% hallucinations	—
HD	Up to 63%	59%	—	—	3-12%	19-59%
TS	73%	—	—	—	—	—
MS	43-65%	—	9.2-25.0%	10-25%	—	—
Epilepsy	8-63%	—	5-32%	—	0,6-7.0%	4.8-50.0%
Stroke	30^0%	—	27%	—	—	32%
TBI	6-77%	10-60%	—	—	2-20%	11-98%

AD = Alzheimer's disease; FTD = frontotemporal dementia; HD = Huntington's disease; HlV = human immunodeficiency virus and HIV dementia; MS = multiple sclerosis; PD = Parkinson's disease; TS = Tourette's syndrome; TBI = traumatic brain injury; VaD = vascular dementia.

putamen-based motor circuits (i.e., motor and oculomotor circuits), the psychologist's emphasis is on the caudate-dorsolateral prefrontal circuit, and the psychiatrist's pathway is the anterior cingulate circuit. More recently, specific behavioral syndromes have been attributed to dysfunction in these circuits (Table 8.3). Disruptions at any point in the circuit (e.g., the frontal cortex, striatum, pallidum) may result in behavioral changes.

Disruption of the dorsolateral circuit {Figute 8.2) is associated with executive dysfunction and motor programming abnormalities. Mote specifically, a disruption of this circuit is associated with poor organization skills, memory retrieval deficits, and poor set shifting. See Table 8,4 for examples of neurological disotders associated with disruption of the dorsolateral circuit. The orbitofrontal circuit (see Figure 8.2) is associated with increased irritability', impulsivity, mood lability, tactlessness, and socially inappropriate behavior, whereas disruptions of the latter part of the orbitofrontal circuit may also result in mood disorder and/or obsessive-compulsive disorder (OCD), Table 8.5 provides examples of disorders associated with disruption of the orbitofrontal citcuit. Finally, the anterior cingulate circuit is associated with decreased motivation, apathy, decreased speech, and akinesia. (See Table 8.6 for a list of disorders associated with disruption of the anterior cingulate circuit.) Although these models may be heuristic in developing function-structure hypotheses, it is unlikely that any current model is sufficient to explain the complex interface of behavior and brain circuitry.

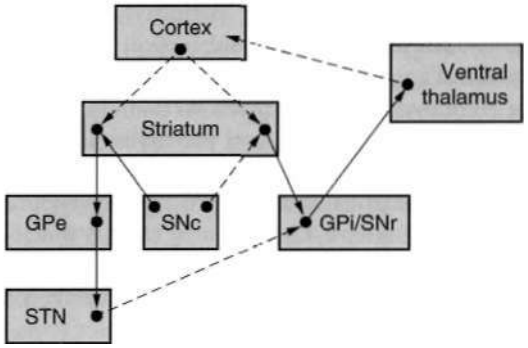


FIGURE 8.1 Fronta(-subcortical circuit general model. Note: Solid line represents inhibitory neurons while dotted lines represent excitatory neurons, GPe = external segment of the globus pallidas; GPi = internal segment of the globus pallidus; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus.

BEHAVIOR AND PERSONALITY DISTURBANCES ASSOCIATED WITH CEREBRAL DYSFUNCTION

Dementia

Alzheimer's Disease

Patients with Alzheimet's disease (AD) experience a wide range of behavioral disturbances, including affective symptoms, agitation, aggression, and psychosis. Behavioral disturbances in AD are associated with increased caregiver burden, patient and caregiver abuse, greater use of psychotropic medications, more tapid cognitive decline, and earlier institutionalization. Longitudinal research suggests that once psychiattic symptoms are present in patients with AD, they frequently recur. Early identification and intervention may help alleviate the chronicity of psychiattic disturbance in AD and may contribute to improved outcomes fur patients with AD and caregivers. In general, social comportment is relatively spated in AD. Subtle personality changes occur in nearly every person with AD, although profound changes in judgment or behavior are unusual. Often, patients show decreased

Table 8.2: Frontal-subcortical circuitry

Circuit	*Frontal lobe*	*Striatum*	*GPi and SNr*	*Thalamus*
Dorsolateral	Dorsolateral PFC	Dorsolateral CN	Lateral Mediodorsal GPi Rostrolateral SNr	VA nucleus
Orbitofronral	Orbitofrontal PFC	Ventromedial CN	Mediodorsal GPi Rostromedial SNr	VA nucleus
Anterior cingulate	Supracallosal Anterior cingulate	Ventral Striatum	Rostromedial GPi Ventral pallidum Rostrodorsal SNr	Mediodorsal nucleus

CN = caudate nucleus; GPi: internal segment of the globus pallidus; PFC = prefrontal cortex; SNr = substantia nigra pars reticulata; VA = vcntral anterior; ventral striatum = ventromedial caudate nucleus, ventral putamen, nucleus accumbens, and olfactory tubercle.

energy, indifference, egocentncity, impulsivity, or irritability. Social withdrawal and selfishness are seen in some individuals with AD. In contrast to patients with frontotemporal demenria (FTD), many patients with AD show normal social skills.

Depression. The true prevalence of depression in AD is controversial, with estimates ranging from 0-86%. One reason for the mixed findings lies in the inherent difficulty of detecting depression in AD. Some studies use family intetviews, and others emphasize patient evaluation. Recent research has suggested that concordance between patient and caregivers on endorsement of depression is less than 13%. Patients with AD tend to endorse more neurovegetative symptoms, whereas cognitive and mood symptoms are more readily endorsed by caregivers. Some symptoms of depression are confounded with other components of AD (e.g., concentration, energy, and interest), making the detection of depression difficult. The probability of depression in AD appears to be greater if there is a history of depression either in the patient or in the family. Table 8.7 suggests differences between the signs of depression and possibly confounding signs from the AD itself.

Selective serotonin reuptake inhibitors (SSRIs) are the preferred mode of treatment for depression in AD. Tricyclic antidepressants (TCAs) are avoided because of their anticholinergic effects on cognitive performance. Although clinical trials are relatively few, sertraline and citalopram have been shown to be effective (Lyketsos et al. 2000).

Apathy. Apathy, defined as diminished motivation not attributable to decreased level of consciousness, cognitive impairment, or emotional distress, is the most common behavioral change noted in AD and may occur in up to

Table 8.3: Behavioral syndromes associated with dysfunction of the motor circuits

Symptoms associated with disruption of the dorsolateral circuit
Poor organizational strategies
Poor memory search strategies
Stimulus-bound behavior
Environmental dependency
Impaired set-shifting and maintenance
Symptoms associated with disruption of the orbitofrontal circuit
Emotional incontinence
Tactlessness
Irritability
Undue familiarity
Antisocial behavior
Environmental dependency
Mood disorders (depression, lability, mania)
O bsessi ve-co mpu I s ive disorder
Symptoms associated with disruption of the anterior cingulate circuit
Impaired motivation
Akinetic mutism
Apathy
Poverty of speech
Psychic emptiness
Poor response inhibition

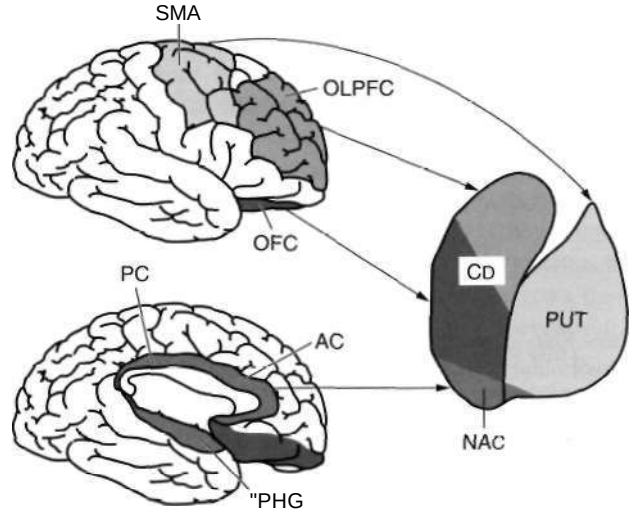


FIGURE 8.2 Frontal-striatal projections. AC = anterior cingulate gyrus; CD = caudate nucleus; DI.PFC = dorsal lateral pre frontal cortex; NAC = nucleus accumbens; OFC = orbital frontal cortex; PC = posterior cingulate gyrus; PHG = parahippocampal gyrus; PUT = putamen; SMA = supplementary motor area. [Reprinted with permission from Brody, A. L. &: Saxena, S. 1996, "Brain imaging in obsessive-compulsive disorder: Evidence for the involvement of frontal-subcortical circuitry in the mediation of symptomatology," CMS *Spectrums*, vol. 1, pp. 27-41.)

Table 8.4: Disorders associated with disruptions of the dorsolateral frontal-subcorticaI circuit

Corticobasal degeneration	Neuroacanthocyrosis
Dementia syndrome of depression	Parkinson's disease
Frontoremporal dementia	Progressive supranuclear palsy
Human immunodeficiency virus dementia	Schizophrenia
Huntington's disease	Stroke
Lacunar state/Binswanger's disease	Subcortical dementia
Multiple system atrophy	Sydenham's chorea
	Tumor
	Vascular dementia

Source: Reprinted with permission from Chow, T. W. & Cummings, J. L. *1999,* "Fronta l-subcortical circuits, in *The Human Frontal Lobes: Functions and Disorders,* eds R. L. Miller &*c* J. L. Cummings, The Guilford Press.

92% of patients. The assessment of apathy in AD may be difficult because it may be unclear whether decreased activity is due to apathy or inability to perform activities. In addition, apathy is often confused with depression, although recent research has demonstrated their independence (Figure 8.3). Apathy typically occuts early in AD and is present throughout the course of the disease, although apathy has been associated with seventy of dementia.

Aggression. Aggressive verbalizations and acts are common in AD. Reported prevalence rates range from 25-67%. Studies have indicated that verbal aggression is more common in men and in individuals with delusions or agitation. Verbal aggression and aggressive behavior do not appear to be associated with depression, although sertraline was assoeiared with a 38% response rate for the treatment of aggression and irritability in AD.

Psychosis. Ptcvalcncc rates of psychotic symptoms in AD range from 10-73%, with tates in clinical populations exceeding community-based samples. In a recent study of 329 patients with AD, the cumulative 4-year incidence of new-onset psychosis of AD was computed to be 51%. Once present, delusions tecur or persist for several years in

Table 8.5: Disorders associated with disruptions of the orbito fronta I-s n bco rti ca I circuit

Carbon monoxide toxicity	Multiple sclerosis
Creutzfeldt-Jakob disease	Neuroacanthocyrosis
Frontal temporal dementia	Obsessive compulsive disorder
Gilles de la Tourette's syndrome	Postcncephalic Parkinson's disease
	Ruptured anterior communicating artery aneurysm
Herpes simplex viral encephalitis	Stroke
Huntington's disease	I iimor
\1;1IH',;1I1CM' Intoxication	

Source: Reprinted with permission from Chow & Cummings. *1999,* "Frontal-subcortkal circuits, in *The Human Frontal Lobes: Functions and Disorders,* eds Miller &: Cummings, The Guilford Press.

Tabic 8.6: Disorders associated with disruptions of the anterior dngulatc fro nra l-subcortica I circuit

Alzheimer's disease	Parkinson's disease
Creutzfeldt-Jakob disease	Postencephalitic Parkinson's disease
Epilepsy	Progressive supranuclear palsy
Frontoremporal dementia	Stroke
Huntington's disease	Trauma
Multiple sclerosis	Tumor

Source: Reprinted with permission from Chow 6c Cummings. 1999, "Fronral-subcortical circuits, in *The Human Frontal Lobes: Functions and Disorders,* eds Miller & Cummings, The Guilford Press.

most patients with AD (Figure 8.4). Psychotic symptoms have implications for the management, treatment, course, prognosis, and pathophysiology of AD. Specifically, psychotic symptoms are chronic and are associated with longer duration of illness, more rapid progression of clinical course, and earlier institutionalization. Predictors of psychosis in AD have included parkinsonian gait, bradyphrenia, exaggerated general cognitive decline, and exaggerated semantic memory decline (Paulsen et al. 2000). Personality and behavioral changes including increased aggression, asocial behavior, and functional impairment are associated with psychotic symptoms in AD. These findings have contributed to diagnostic subtyping of AD based on the presence of delusions,

The most common psychotic symptoms reported in patients with AD are delusions and hallucinations. The delusions are typically paranoid type, nonbizzare, and simple. Complex or bizarre delusions seen in patients with schizophrenia are conspicuously absent in **the** patients with AD. Misidentification phenomena however are common in AD. Whereas hallucinations in AD are more often visual than auditory, the reverse is true for schizophrenia (Table 8,Si, I'syehonc symptoms tend to disappear in advanced stages of dementia; this could reflect an apparent remission, rather than real remission, because the patient with severe dementia may be unable to articulate his or her delusions and hallucinations.

Evidence from neuropsychological investigations suggests relatively mote executive dysfunction, and findings from clinicoanatomic studies implicate increased frontal dysfunction in AD with psychotic symptoms than AD

Table 8.7: Clinical aspects differentiating dementia from depression

Major depression	*Dementia*
Acute, nonprogressive	Insidious and progressive
Affective before cognitive	Cognitive before affective
Attention impaired	Memory impaired
Orientation iniaa	Orientation impaired
Complains of memory	Minimizes/normalizes memory
Gives up on testing	(>lividiis ft Ion i>ri testins:
Language intact	Aphasic errors
Better at night	Sundown ing
Self-refer red	**Referred** by others

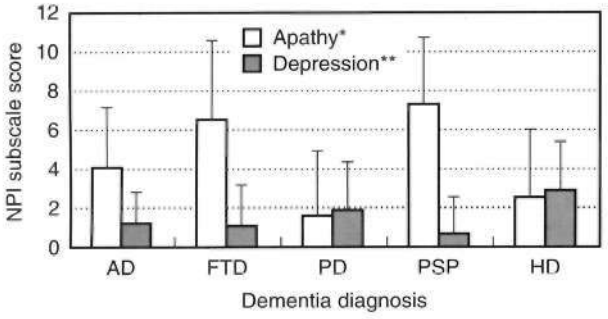


FIGURE R.3 Neuropsychiatric inventory subseale scores for apathy and depression. AD = Alzheimer's disease; FTD = frontotemporai dementia; PD = Parkinson's disease; PSP = pr og re ss i vc supranuclear palsy; HD = Huntington's disease. (Reprinted with permission from Levy, M. L., Gummings, J. L., Fairbanks, L. A., et al. *1998,* "Apathy is not depression,"/ *Neuropsychiatry Clin Neurosci,* vol. 10, pp. 314-319.)

without these symptoms (Rao and Lyketsos 1998). For example, compared with patients with AD without psychotic symptoms, neuropsychological studies indicated that patients with AD with delusions were more impaired on an abstraction task and were more perseverative. Using survival analyses, wc recently found that lower scores on measures of fluency, grooved pegboard, trail making, and digit span wete predictors ($p < .05$) of future psychosis in AD. In addition, greater worsening on the Dementia Rating Scale (DRS), attention and construction subscales, total DRS, and fluency scores were associated with a twofold to threefold increase in the risk of developing psychosis. For instance, for every one z-score change in fluency, the risk of psychosis increased threefold.

Atypical antipsychotics are the preferred method of treatment for psychosis in AD because of the lowered anticholinergic and hypotensive effects. Although few treatment studies have been performed, the National Institutes of Health is currently supporting a multisite study of atypical antipsychotics (e.g., quetiapine, olanzapine, risperidone, and citalopram) in AD.

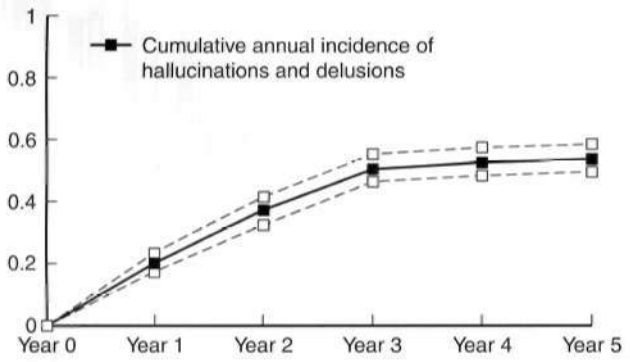


FIGURE 8.4 Incidence of psychosis in patients with Alzheimer's disease. (Reprinted with permission from Paulsen, J. S., Salmon, D. P., et al. 2000, "Incidence of and risk factors for hallucinations and delusions in patients with probable AD," *Neurology*, vol. 54, no. 10, pp. 1965-1971.)

Frontotemporal Dementia

FTD, previously called Pick's disease, is composed of at least three syndromes: semantic dementia, progressive nonfluent aphasia, and frontal lobe degeneration of non-Alzheimer type (FLD). The term FTD therefore describes a heterogeneous group of disorders. Clinical presentation of FTD may vary significantly. A distinct neuropsychological profile of FTD has not yet emerged; as a result, some have described FTD as a ncurobehavioral disorder rather than ;i neuropsychological disorder. Recent consensus criteria for diagnosis of FTD have been reported and primary criteria relate to the presence of behavioral change (Table 8.9).

Behavioral Disruption. As the name suggests, FTD syndromes are marked by progressive atrophy of the frontal and temporal lobes. Atrophy within the frontal lobes leads to disruption of the frontal-subcortical circuits and the associated behavioral syndromes described earlier, Individuals with FTD exhibit symptoms of orbitofrontal syndrome, such as disinhibition, poor impulse control, tactlessness, and poor judgment. In addition, loss of empathy, mental inflexibility, and stereotyped behaviors are common. Individuals with FLD frequently have impaired social relationships and inappropriate social interactions. Symptoms associated with Kliiver-Bucy syndrome, such as byperorality and hypersexuality, may occur in late stages of FTD. Patients may develop a propensity for sweets.

Disruption of the anterior cingulate circuit may also occur, resulting in symptoms of apathy and lack of motivation, which may be the earliest signs of FTD. In addition, these individuals may show little concern for personal hygiene, appearing unkempt. Finally, disruption of the dorsolateral circuit in FTD is associated with impaired planning and organization.

The inability to demonstrate basic and social emotions is also common. Often, the family members and caregivers are the ones who report these behavioral disturbances because many patients with FTD experience a lack of insight into their current difficulties. Although no large-scale clinical trials have been conducted, evidence suggests that behavioral disturbances, such as disinhibition, overeating, and compulsions, may respond to treatment with SSRIs,

Studies have attempted to distinguish FTD from AD based on behavioral symptoms. Disinhibition, apathy, aberrant motor behavior, and euphoria are more common in FTD than AD, as illustrated in Figure 8.5. Others have noted that lack of insight and emotion, food cramming, indifference, and impulsivity are more common in FTD than vascular dementia (VaD).

Psychiatric Disturbances. Although the more classic psychiatric syndromes, such as depression, anxiety, and psychosis, are observed in FTD, symptoms are rarely severe enough to meet criteria for diagnosis. Depression in FTD is associated with irritability, increased appetite with weight

Table 8.8: Psychotic symptoms in Alzheimer's disease vs. schizophrenia in elderly patients

	Psychosis in AD	*Schizophrenia in the elderly*
Incidence	30-50%	<1%
Bizarre or complex delusions	Rare	Common
Misidentification of caregivers	Common	Rare
Common form of hallucinations	Visual	Auditory
Schneiderian first-rank symptoms	Rare	Common
Active suicidal ideation	Rare	Common
History of psychosis	Rare	Very common
Eventual remission of psychosis	Common	Uncommon
Need for many years of maintenance on antipsychotics	Uncommon	Very common
Average optimal daily dose of an antipsychotic	15-25% of that in young adult with schizophrenia	40-60% of that in a young adult with schizophrenia

Source: Reprinted with permission from jeste, D. V. & Finkel, S. I. 2000, "Psychosis of Alzheimer's disease and related dementias," *Am j Geriatr Psychiatry,* vol. 8, pp. 29-34.

gain, anhedonia, withdrawal, and alexithymia. In contrast, apathy is reported in nearly all (95%) patients with FTD.

Approximately 20% of patients with FTD exhibit delusions, hut hallucinations are less common (7%). Euphoric symptoms such as elevated mood and exaggerated self-esteem arc reported in up to one third of individuals with FTD. Finally, disinhibition is observed in a high proportion (68%) of individuals with FTD.

Table 8.9: Consensus criteria for the diagnosis of fro n tote in poral dementia

I. Core diagnostic features:
  A. Insidious onset and gradual progression
  li. I'.iiilv decline in social interpersonal conduct
  (.'.. Karly impairment in regulation *at* personal conduct
  D. Early emotional blunting
  E. F.arly loss of insight
II. Supportive diagnostic features
  A. Behavioral disorder
    1. Decline in personal hygiene and grooming
    2. Mental rigidity and inflexibility
    3. Distractibility and impersistence
    4. Hyperorality and dietary changes
    5. Perseveration and stereotyped behavior
    6. Utilization behavior
  B. Speech and language
    I. Altered speech output (aspontaneity and economy of speech, press of speech), stereotypy of speech, echolalia, perseveration, mutism
  C. Physical signs
    1. Primitive reflex, incontinence, akinesia, rigidity, tremor, low/labile blood pressure
  D. Investigations
    1. Neuropsychology: impaired frontal lobe test results; no amnesia or perceptual deficits
    2. Electroencephalogram (EEG): normal on most conventional EEGs despite clinically evident dementia
    3. Brain imaging: predominant frontal and/or anterior temporal abnormality

Source: Modified with permission from Neary, D,, Snowden, J. S., et al. 1998, "Fron totem poral lobar degeneration: A consensus on clinical diagnostic criteria," *Neurology,* vol. 15, pp. 1546-1554.

Relationship to Primary Pathology. Underlying pathology varies widely in individuals with FTD; asymmetrical brain involvement has been linked to distinct behavioral profiles (Mychack etal. 2001). Individuals with primary left frontal involvement typically present with nonfluent aphasia, intact social abilities, depression, and social withdrawal. Left temporal involvement is associated with a diagnosis of semantic dementia, or loss of semantic knowledge. Primary right frontal involvement is usually associated with social dysfunction and presentation. Patients with primary right temporal dysfunction also exhibit significant behavioral dysfunction. In addition, irritability, impulsiviry, lack of

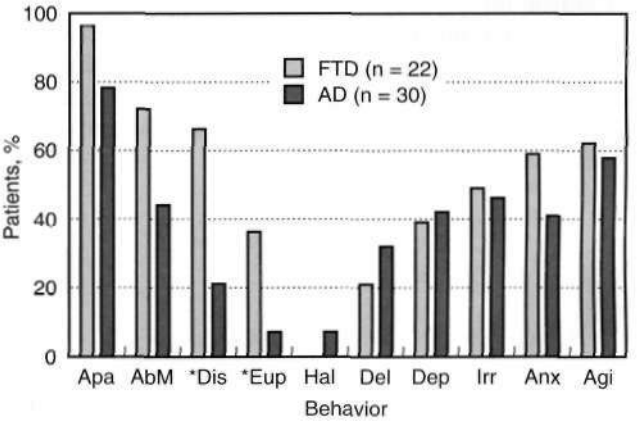


FIGURE 8.5 Psychiatric disturbance in frontotemporal dementia and Alzheimer's disease. Note: The percentage of patients with FTD and AD with non-0 scores on the neuropsychiatric inventory. Apa = apathy; AbM = aberrant motor behavior; Dis = disinhibition; Eup = euphoria; Hal = hallucinations; Del = delusions; Dep = depression; Irr = irritability; Anx = anxiety; Agi = agitation; * = χ^2, $p \leq .01$. (Reprinted with permission from Levy, M. L., Miller, B. L., Fairbanks, L. A., & Craig, A. H. 1996, "Alzheimer disease and frontotemporal dementias. Behavior distinctions," *Arch Neurol,* vol. 53, pp. 687-690.)

empathy, and changes in self-concept (i.e., patients may drastically alter their religious or political beliefs) are common. Involvement of the right hemisphere is associated with changes in expression of affect; spouses may report that the patient seems like a different person with a blunted affect.

Vascular Dementia

VaD primarily affects subcortical structures; therefore fronral-subcortical circuits are disrupted and behavioral disturbances are common. These disturbances often result in increased challenges to health care providers and caregivers. Apathy, depression, and behavioral changes are common in VaD; however, a clear relationship between these behavioral changes and dementia severity has not been well established.

Depression. The mean reported prevalence of depression in VaD is 32%, although rates vary widely between studies (Ballard and O'Brien 2002). Sample source likely influences the reported prevalence rates, with community samples exhibiting lower rates of depression than clinic samples. Depression in VaD is qualitatively different from typical major depression. Individuals with VaD and depression are less likely to have had a stroke and are more likely to have a history of depression and impairments in memory or attention than patients with VaD without depression. The relationship between age and depression in VaD is unclear; some have noted that depression is more common in younger patients and others have noted increased rates in older patients.

Distinct differences exist in the comparison of depression in VaD and AD. First, depression is both more common and more severe in patients with VaD than AD. Patients with VaD experience more behavioral symptoms of depression, accounting for the increased severity. Few studies have assessed depression through the progression of VaD; however, initial studies indicate depression is more likely to enter remission in VaD than AD. Depression phenomenology differs in VaD and AD patients such that VaD patients report more low affect, withdrawal, and psychomotor slowing than AD patients (Figure 8.6).

Apathy. Apathy in VaD is associated with increased impairment in both basic and instrumental activities oi daily living. This relationship is particularly apparent in patients with VaD who have also experienced a stroke.

Psychosis. Rates of psychotic symptoms are similar in AD and VaD. Delusions (33%) and visual hallucinations (13-25%) are reported in VaD and are associated with impaired cognitive functioning (Ballard and O'Brien 2002). Care must be taken in the assessment of delusions in VaD and in dementia in general. It is important to differentiate delusions from confabulation or thought processes based on impaired cognitive functioning.

Anxiety. Anxiery symptoms are reported in 19% of the population and up to 70% of inpatient samples. Generalized anxiety disorder (GAD) is more common than panic disorder. Anxiety is not associated with severity of cognitive impairment or changes in functional abilities. However, it has been noted that anxiety is more common in individuals with Mini-Mental State examination (MMSE) scores of less than 10.

Dementia with Letvy Bodies

Dementia with Lewy bodies (DUB) has recently received significant attention. Difficulty remains in attaining an accurate diagnosis of DLB before performing a neuropathologic examination. There is significant clinical presentation overlap between the presentation of DLB and both AD and Parkinson's disease (PD).

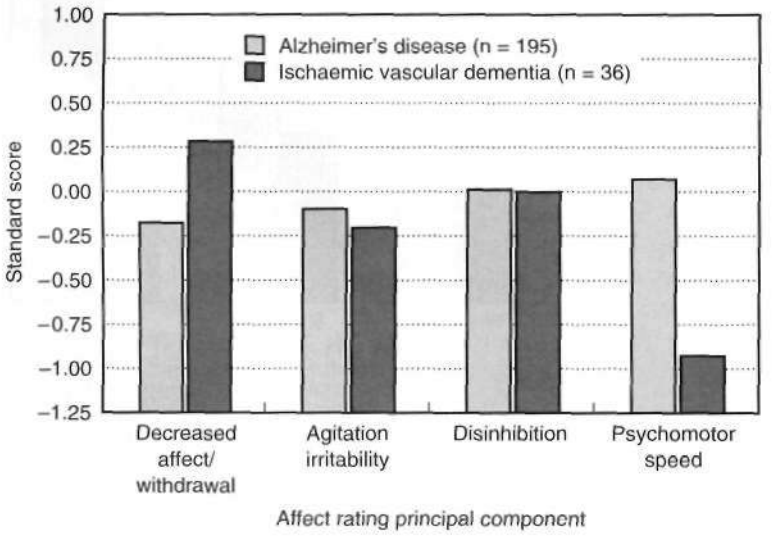


FIGURE 8.6 Depressive symptoms in vascular dementia versus Alzheimer's disease. Note: Values are expressed in standard score units with a mean of 0 and a standard deviation of 1 based on the overall subject sample. (Reprinted with permission from Hargrave, R., Geek, L. C, Reed, B., & Mungas, D. 2000, "Affective behavioral disturbances in Alzheimer's disease and ischaemic vascular disease," / *Neurol Neurosurg Psychiatry*, vol, 68, pp. 41-46.)

Psychotic symptoms, particularly hallucinations, are a hallmark symptom of DLB, with between 48% and 100% of individuals with DLB experiencing visual hallucinations, Insight is usually poor. It has been suggested that psychotic symptoms observed in DLB are similar to symptoms seen in L-dopa-induced psychosis. Disruptions of the nigro-amygdaloid connection and the resultant hypersensitivity of the dopamine receptors in the amygdala is a potential explanation for the cause of hallucinations in DLB. Mania in DLB has been noted in at least one case study.

Management of psychosis in DLB is critical because it is associated with distress in the patient, increased caregiver burden, early entrance in institutional care, and earlier morbidity. Typical neuroleptics are typically avoided in DLB because patients exhibit high sensitivity to these drugs and may experience severe parkinsonian symptoms and other side effects. In contrast, atypical neuroleptics, such as clozapine and quetiapinc, as well as cholinesterasc inhibitors are associated with improved cognition and decreased psychotic symptoms (McKeith 2002).

Human Immunodeficiency Virus and Human Immunodeficiency Virus Dementia

Depression. Psychiatric and behavioral disturbances have been noted in individuals with human immunodeficiency virus (HP/) and with HiV dementia. Depression is common in individuals with HIV and is associated with number of years living with HIV diagnosis, coping style, and low levels of social support. The World Health Organization Neuropsvchiatric AIDS study noted that 3.0-10.9% of individuals with asymptomatic HIV and 4.0-18.4% of individuals with symptomatic HIV meet criteria for major depressive disorder (MDD). Lifetime rates of major depression are particularly high, with 43-55% of individuals meeting criteria for MDD during at least one period in their lifetime. A recent path analysis assessed the relationship between cognition, social support, life events, disability, stress, and depression in men with HIV, They noted that life events and disability were directly related to depression in individuals with HIV. Higher intelligence quotient (IQ) was associated with increased social support, which is associated with lower rates of depression.

Much of the research assessing psychiatric symptoms in HIV has been conducted with homosexual male populations, Reported rates of depression in women with HIV vary from 1.9-35.0% in clinical and 30-60% in community samples. Current diagnosis of major depressive disorder was four times more common in HIV-positive women (19.4% vs. 4,8%). Depression severity was associated with older age, white race, and lower education.

Anxiety. Approximately 17-36% of individuals with HIV meet criteria for an anxiety disorder (Martin ct al. 2002). Although individuals with HIV report more severe anxiety symptoms, diagnoses of anxiety disorders are not any more common in women with HIV than in women without HIV.

Movement Disorders

Parkinson's Disease

Depression. Depression is the most common psychiattic disturbance in persons with PD, with the overall frequency as high as 70%, depending on threshold for diagnosis. Cross-sectional studies have demonstrated that approximately 20% of patients with PD have major depression and another 20% have minor depression. Longitudinal studies show that more than 50% of patients with PD will develop depression at some point in the disease. Nearly 20% of patients with PD without depression will develop depression within a year and depression onset predates the onset of motor symptoms in 12-37% of cases. Risk factors for depression in PD have included greater cognitive impairment, earlier disease onset, and family history of depression.

The typical duration of depression in PD is more than 1 year; however, patients with PD with minor depression experience a briefer duration. Patients with PD with majot depression, but not those with minor depression, exhibit impaired cognitive functioning and more rapid disease progression (Figure 8.7). Given the association between depression severity and course, effective treatment of depression in PD may result in slowed progression of disease.

Some have proposed rhat the degeneration of dopaminergic neurons likely causes dysfunction of orbitofrontal cortex, which secondarily affects serotonergic connections

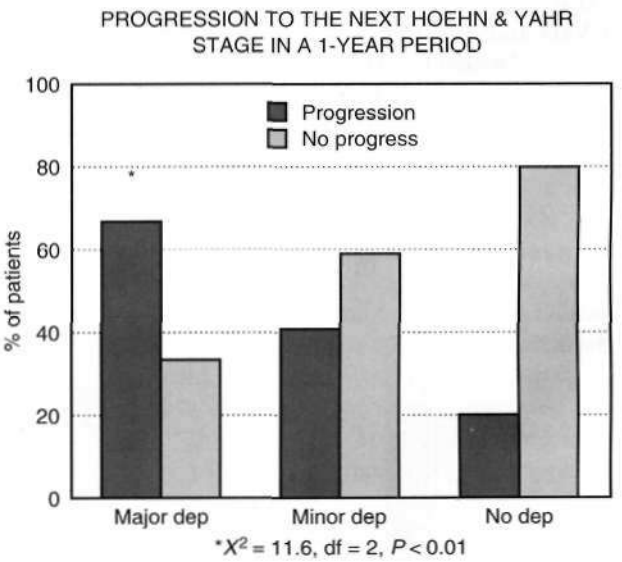


FIGURE 8.7 Faster progression of Parkinson's disease in patients with major depression. (Reprinted with permission from Starkstein, S. E. & Mayberg, H. S. 1993, "Depression in Parkinson disease," in *Depression in Neurologic Disease*, eds S. E. Starkstein & R. G. Robinson, Johns Hopkins University Press, Baltimore.)

of the dorsal raphe nucleus. This dysfunction in the dorsal raphe nucleus affects the serotonergic cell bodies.

There are only four controlled clinical trials of antidepressant therapy in PD. SSRIs are considered first-line therapy for depression in patients with PD, although SSRIs can worsen motor symptoms. In such cases, TCAs may be an effective alternative. A survey of the Parkinson Study Group documented that 26% of patients with PD are prescribed an antidepressant. Double-blind prospective studies are needed to evaluate the safety and efficacy of antidepressants in PD. The largest prospective study of SSRIs in PD suggests that paroxetine is well tolerated over 3 months and effective in decreasing depressive symptoms in PD (Tesei et al. 2000).

Psychosis. Hallucinations occur in up to 40% of patients with PD, and 16% report delusions. Psychotic symptoms are more common in patients with PD with greater cognitive impairment, longer duration of illness, greater daytime somnolence, and older age and in those who are institution;ili/L'd.

Researchers have long suggested a relationship between L-dopa treatment and psychosis in PD (in part because psychosis in untreated PD is rare). Although L-dopa may be responsible for psychosis in a portion (20%) of patients with PD, no relationship between i.-dopa dosage and psychosis is observed in these patients. There are a number of possible explanations for this lack of relationship. It is possible that clinicians regularly reduce L-dopa dosage in individuals who experience hallucinations or delusions in an attempt to reduce these symptoms. It is plausible that individuals diagnosed with PD who experience psychotic symptoms are actually suffering from DI.B. Newer theories regarding psychotic symptoms in PD suggest that cholinergic deficits may be the cause of these symptoms. Cholinergic therapy may reduce psychotic symptoms in PD.

Psychosis is among the most difficult complications of L-dopa treatment. Hallucinations that are nonthreatening often remain untreated. However, paranoid delusions and threatening hallucinations require treatment. Most practitioners recommend a simplification of antiparkinsonian drugs followed by a discontinuation of anticholinergics, selegiline, and amantadine before reducing i.-dopa. Atypical antipsychotics are added only when a reduction of other medications has not resulted in improvement.

Apathy. Individuals with PD often experience increased rates of apathy. Hstimates of apathy in PD have ranged from 16.5^10.0%. Apathy may occur with or without the presence of depression. Apathy is associated with increased dementia and lower rates of disability.

Progressive Supranuclear Palsy

Psychiatric and behavioral symptoms are common in progressive supranuclear palsy (PSP). Nearly all (>90%) patients with PSP show high levels of apathy, whereas about half of patients with PSP exhibit a change in personality and less than half suffer from depression. Disinhibition, or loss of control for emotions, is noted in 30-36% of patients with PSP.

Huntington's Disease

Psychiatric and behavioral symptoms are common in Huntington's disease (HD) and have been reported as the presenting disease manifestations in up to 79% of patients. Research on the incidence of psychiatric symptoms in HD is variable though, encumbered by limitations within and across studies. Some limitations of the available research are as follows: (1) affected people are often medicated to minimize abnormal involuntary movements; such treatment may mask psychiatric and behavioral symptoms; (2) most available tieuropsychiatrie assessment tools use conventional psychiatric terminology based on idiopathic psychiatric illness, which fails to distinctly reflect the symptoms associated with striatal deterioration; and (3) most research has emphasized the motor and cognitive impairments associated with HD, despite family reports that psychiatric disturbances are most strongly associated with stress, disability, and placement decisions. Data from 1857 Huntington Study Group (HSG) subjects with a diagnosis of symptomatic HD arc presented in Table 8.10. Subjects are grouped into disease stages according to ratings obtained on the Total Functional Capacity Scale.

Depression. Depression is one of the most common concerns for individuals and families with HD, occurring in up to €*3>%* of patients. It has been suggested that depression can precede the onset of neurological symptoms in HD by 2 to 20 years, although large-scale empirical research has been minimal. Recent data from the HSG indicate that depression is most common immediately before diagnosis, when neurological soft signs and other subtle abnormalities become evident. Following a definite diagnosis of HD, however, depression is most prevalent in the middle stages of the disease (i.e., Shoulson-Fahn stages 2 and 3) and may diminish in the later stages. Positron emission tomography (PET) studies indicate that patients

Table 8.10: Percentage of patients with Huntington's disease endorsing psychiatric symptoms by TFC stage

Symptom	*(n = 4.U)*	*(n = 660)*	*(n = 520)*	*(n = 221)*	*(n = 84)*
Depression	57.5%	62.9%	59.3%	ill'!-,,	42.2%
Suicide	6.0%	9.7%	10.3%	9.9%	5.5%
Aggression	39.5%	47.7%	51.8%	54.1%	54.4%
Obsessions	13.3%	16.9%	25.5%	28.9%	13.3%
Delusions	2.4%	3.5%	6.1%	9.9%	2.2%
Hallucinations	2.3%	4.2%	<-..:'•.	11.2%	3.3%

Source: Data provided by the Huntington Study Group.

with HD with depression have hypermetabolism in the inferior frontal cortex and thalamus relative to nondepressed patients with HD or normal age-matched controls. Though less well studied, mania episodes occur in 2-12% of patients with HD.

Suicide. Suicide is more common in HD than in other neurological disorders with high rates of depression, such as stroke and I'D. Most studies have found a fourfold to sixfold increase of suicide in HD, and some studies have reported it to be 8-20 times higher than the general population. Suicidal ideation, as measured by the Behavioral Rating Scale on the Unified Huntington's Disease Rating Scale (UHDR.S), is highly prevalent throughout the disease, with 8% of all individuals diagnosed with HD having active ideation. Suicidal ideation was recently examined in 4342 individuals in the HSG database. Two primary "critical periods" were evident, during which suicidal ideation in HD increased dramatically. First, frequency of suicidal ideation doubled from 10.4% in at-risk persons with a normal neurological examination to 20.5% in at-risk persons with soft neurological signs. Second, in persons with a diagnosis of HD, 16% had suicidal ideation in stage 1, whereas nearly 21% had suicidal ideation in stage 2 (Figure 8.8). Although the underlying mechanisms for suicidal risk in HD are poorly understood, it may be beneficial for health care providers to be aware of periods during which patients may be at an increased risk of suicide.

Psychosis. Psychosis occurs with increased frequency in HD, with estimates ranging from 3-12%. Although the majority of the research has been conducted using the Johns Hopkins sample, data are consistent with others' clinical experience, suggesting that psychosis in HD is broad and similar to that seen in other psychiatric disorders. Psychosis is more common among early adulthood-onset cases than among those whose disease begins in middle or late adulthood. Psychosis associated with HD is more resistant to treatment than psychosis in schizophrenia. HSG data suggest that psychosis may increase somewhat as the disease progresses (see Table 8.10), although psychosis can become difficult to measure in the later stages of disease.

Obsessive-Compulsive Traits. Although true OCD is not often reported in HD, obsessive and compulsive behaviors are prevalent (13-30%). Obsessional thinking often increases with pruximin in disease onset and then remains somewhat stable throughout the illness. Obsessional thinking associated with HD is reminiscent of perseveration, such that individuals get "stuck" on a previous occurrence or need and are unable to shift,

Aggression. A spectrum of behaviors ranging from irritability to intermittent explosive disorders occur in 19-59% of patients with HD. Although aggressive outbursts are often the principal reason for admission to a psychiatric facility, research on the prevalence and incidence of irritability and aggressive outbursts in HD is spatse. The primary limitation in summarizing these symptoms in HD is the varied terminology used to describe this continuum of behaviors. A recent survey of several clinicians and HD family members suggested that difficulty with placement, because of aggression, was among the principal obstacles to providing an effective continuum of care for people with HD. Table 8.11 shows that skilled nursing facilities surveyed rated behaviors such as agitation, irritability, disinhibition, and depression as the most common behavior problems in institutionalized patients with HD,

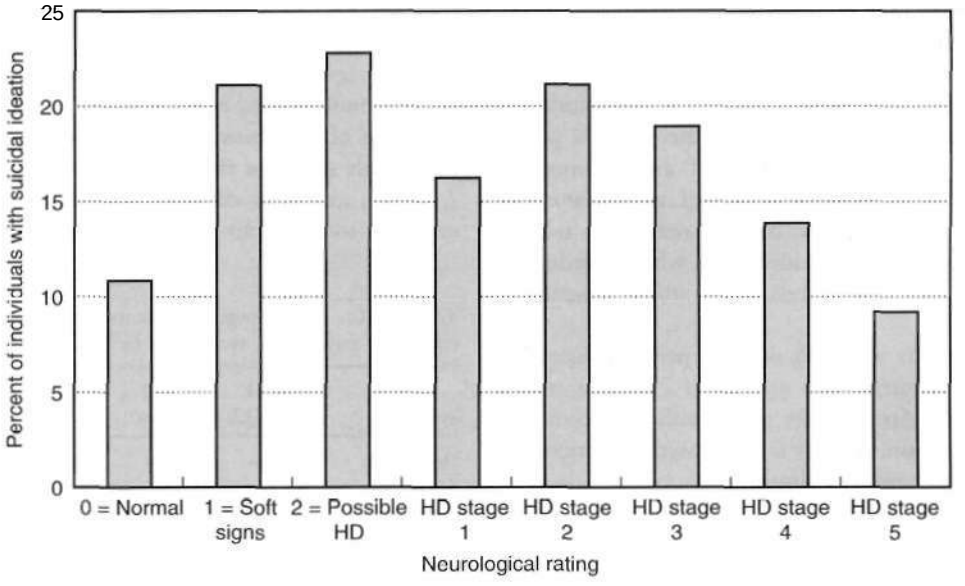


FIGURE 8.8 Suicidal ideation by Huntington's disease stage. (Reprinted with permission from Ferneyhough, K. C., Stierman, L. M., Turner, B. M., et al. 2002, "Critical periods of suicide risk in Huntington's disease," *J Neuropsychiatry Clin Neurosci*, vol. 14, p. 104.)

Table 8.11: Ratings by nursing home staff of problematic behaviors in patients with Huntington's disease

Behavior problem	*Percentage*	*Rank*
Agitation	76	2.0
Irritability	72	2.9
Disinhibition	59	3.3
Depression	51	4.2
Anxiety	50	4.4
Appetite	54	5.1
Delusions	43	5.5
Sleep disorders	50	5.5
Apathy	51	6.8
Euphoria	40	6.9

Source: From Paulsen & Hamilton.

Apathy. Early signs of HD may include withdrawal from activities and friends, decline in personal appearance, lack of behavioral initiation, decreased spontaneous speech, and constriction of emotional expression. However, these symptoms are considered merely reflective of depression, and more conclusive evaluations are precluded. Though difficult to distinguish, apathy is defined as diminished motivation not attributable to cognitive impairment, emotional distress, or decreased level of consciousness. Depression involves considerable emotional distress, evidenced by tearfulness, sadness, anxiety, agitation, insomnia, anorexia, feelings of worthlessness and hopelessness, and recurrent thoughts of death. Both apathy (59%) and depression (70%) are common in HD. However, 5.3% of individuals experienced only one of these symptoms rather than the two combined. Furthermore, depression and apathy were not correlated. Apathy was correlated with lower cognitive function, replicating previous research indicating telationships between apathy and dementia. Although the frequency of complaints from patients and family members about apathy may be low, the prevalence of this behavior is not. The consequences of apathy are rarely problematic (in contrast to temper outbursts, which are less common but highly distressing), but patients and family members typically appreciate effective treatment of apathy.

Tourette's Syndrome

Psychiatric comorbidity is common in individuals with Tourette's syndrome (TS) (Jankovic 2001). Rates of psychiatric disorders vary widely; significantly higher rates of psychiatric disorders are reported when samples are drawn from psychiatric clinics than from movement disorder clinics. Traditionally, clinicians focused on the high rates of attention-deficir/hypcractivity disorder (ADHD), OCD, and oppositional defiant disorder (ODD) in children and adults with TS.

ADHD is estimated to co-occur in 40-70% of individuals with TS. ADHD symptoms may precede the onset of TS by 2-3 years. Approximately 30% of individuals with TS meet criteria for OCD, The rares of oppositional behaviors are somewhat mixed; although earlier reports suggested that children with TS exhibited higher rates of oppositional behavior, some studies suggest that the rate of conduct difficulties is lower than in the general child psychiattic clinic population.

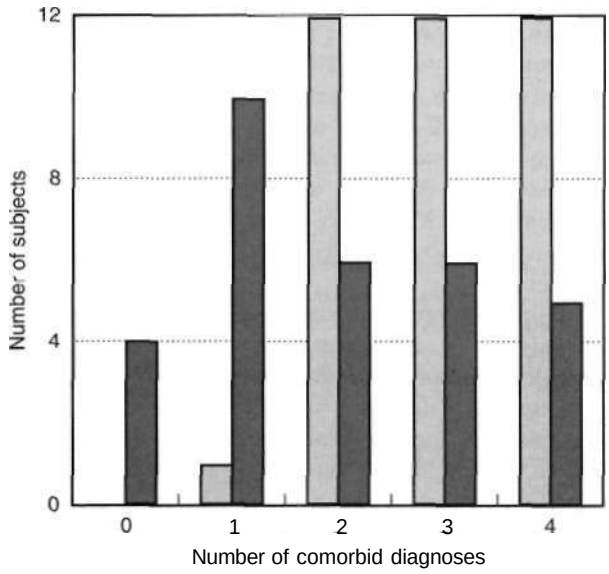


FIGURE 8.9 Comorbid diagnoses in individuals with Tourette's syndrome (TS), Light bars = TS with explosive outbursts; dark bars = TS without explosive outbursts. (Reprinted with permission from Budman, C. L., Bruun, R. D., Park, K. S., et al. 2000, "Explosive outbursts in children with Tourette's disorder,"/ *Am Acad Child Adoiesc Psychiatry,* vol. 39, no. 10, pp. 1270-1276.)

Other behavioral and personality disturbances occur in TS. Individuals with TS are also more likely to meet criteria for a personality disorder. Approximately 64% of individuals with TS meet criteria for one or more personality disorders. Borderline, depressive, obsessive-compulsive, paranoid, and passive-aggressive personality disorders were among the most common diagnoses. In addition, approximately 25% of patients with TS experience explosive outbursts. These outbursts arc more common in children (35%) than in adults (8%) with TS (Budman et al. 2000). Explosive outbursts are associated with increased psychiatric comorbidity in TS (Figure 8.9).

Finally, mood and anxiety symptoms are common in TS. Reports suggest that up to 73% of children with TS experience clinically significant difficulties with depression.

Multiple Sclerosis

The assessment of behavioral symptoms in multiple sclerosis (MS) is particularly difficult because one of the hallmark symptoms of MS is the variability within patients across time. In addition, there is significant variation between patients with MS, Charcot (1877) and Surridge (1969) noted that many patients with MS show dissociation between subjective mood state and outward affect.

Deptession. Depression is the most common behavioral symptom in MS, with rates of 37-54%. Up to one half of patients with MS with depression experienced periods of depression before disease onset. Patients with MS may report symptoms of depression even with outward signs of euphotia. In addition, a large proportion (73%) of individuals with MS report difficulty in controlling their emotions and incteased irritability (57%) (Fcinstein and Feinstein 2001),

Although tesearch has suggested that a family history of deptession of alcoholism is mote common in patients with MS with depression, more recent studies suggest that this relationship does not hold. Depression in MS is *not* associated with increased rates of stressful events, disease duration, type of MS, age, gender, or socioeconomic status.

A psychological cause of deptession in MS has been proposed, which suggests that depression is a result of ftustration with progressive disability and uncertainty regarding the future. Although some studies have noted a relationship between depression and increased disability in MS, others have failed to replicate these findings. Depression in MS is more common in patients experiencing an exacerbation of MS symptoms and increased feelings of uncertainty regarding the future, lending support to the psychosocial models of depression etiology.

Furthermore, patients with MS report highct rates of depression than patients with othet chronic disabling disorders. Imaging studies in MS, howevet, have failed to show clear neuropathological correlates of depression. Results have shown that depression in MS is associated with right parietal, right temporal, or right frontal involvement, implying disruption of ftontal-subcortical circuitry. In addition, diffetences have been noted in regional blood flow asymmetries in the limbic cortex among individuals with both MS and deptession. It is likely that depression in MS results ftom a combination of psychosocial and biological factors.

Some pharmacological interventions used in the treatment of MS may be associated with increased rates of depression. Although research results have been mixed, studies suggest that depression is a side effect for some individuals being treated with interferon-/!-1 b (IFN-/S-lb) (Feinstein 2000). Thus a consensus statement was put forth suggesting that patients with severe depression should be closely monitored while receiving IFN-^-lb, and SSRIs were suggested as the treatment of choice fot depression in MS.

The relationship between depression and other treatments of MS has received less attention. The association between depression and IFN-j8-la and interferon-a is equivocal, as conflicting results have been reported; glatiramer acetate has not been associated with increased depressive symptoms. Research has shown that the increased tates of depression apparent following tteatment with IFN-^-la may represent a return of pretreatment levels of depression. Thus physicians should take care to thoroughly assess patients' history of depression before beginning IFN interventions because patients with recent histotics of depression may be more likely to rc-cxperience symptoms of deptession after IFN treatment.

Anxiety. Anxiety often occurs in individuals with MS. Unfortunately, this symptom is often ovetlookcd because anxiety symptoms may be viewed as being solely associated with poor coping skills. Some strategies to minimize anxiety in individuals with MS ate described in Table 8.12. Clinically significant anxiety has been reported in 25% of individuals with MS recruited ftom a clinic; 9.2% of these individuals were also experiencing clinically significant symptoms of depression. Anxiety symptoms are more common in women with MS than in men with MS. The combination of anxiety and depressive symptoms was more strongly associated with somatic complaints, social difficulties, and suicidal ideation than either anxiety or depression alone.

Euphoria and Pathological Laughing and Crying. In contrast to other neurological disorders, increased rates of cheerfulness, optimism, denial of disability, and pathologic laughing are noted in MS. Early studies suggested that more than 70% of individuals with MS experienced periods of euphoria. However, more recent studies suggest that

Tabic 8.12: Strategies to minimize anxiety in patients with multiple sclerosis

Respect adaptive denial as a useful coping mechanism.
Provide referrals to the National Multiple Sclerosis Society (1-800-Fight-MS) early in disease.
Help patients to live "one day at a time," and restrict predictions regarding the future.
Help patients manage stress with relaxation techniques.
Involve occupational therapists for energy conservation techniques.
Focus on the patient's abilities, not disabilities.
Consider patient's educational and financial background when giving explanations and referrals.
Realize that patients have access to the Internet, self-help groups, and medical journals and may ask "difficult" questions.
Expect grief reactions to losses.
Deal with losses one at a time.
Attend to the mental health needs of the patients' families and caregivers.
Respect the patient's symptoms as real.
Avoid overmedicating.
Focus supportive psychotherapy on concrete, reality-based cognitive and educational issues related to multiple sclerosis.
Provide targeted pharmacotherapy.
Refer appropriate patients for cognitive remediation training.
Ask about sexual problems, as well as bowel and bladder dysfunction.
Keep an open dialogue with the patient about suicidal thoughts.

Source: Modified with permission from Riether. 1999, "Anxiety in patients with multiple sclerosis," *Seniin neuropsychiatry*, vol. 4, pp. 103-113.

prevalence rates for symptoms of euphoria are likely closer to 25%, although those for individuals with sustained petiods of elevated mood are closer to 10%. Individuals with euphoria are more likely to have cerebral involvement, enlarged ventricles, poorer cognitive and neurological function, and increased social disability.

A small (9.9%) but significant proportion of individuals with MS exhibit periods of pathological laughing and crying (PLC), the inability to control outbursts of laughter or crying. PLC is more common in patients with MS who have entered the chronic-progressive disease course and who have high levels of disability and cognitive dysfunction.

Amyotrophic Lateral Sclerosis

Little empirical research has assessed psychiatric or behavioral disturbances in individuals with amyotrophic lateral sclerosis (ALS). Some observations have noted that individuals with ALS exhibit unexpected cheerfulness and stoicism. One study employed a clinical interview to assess the prevalence of psychiatric disorders in individuals with ALS. This study showed that 11% of individuals with ALS met criteria for MDD (Ganzini et al, 1998). In a study assessing 56 patients with ALS, only 2% of their sample met criteria for MDD; however, 28% of their sample endorsed significant depressive symptoms (>13 on the Beck Depression Inventory). Depression in ALS is associated with increased physical impairment, although these results are not always replicated. Individuals with low psychologic well-being were at increased risk of mortality {Figure 8.10). Mortality risk was more strongly associated with psychological distress than age and similar to the association of risk associated with severity of illness.

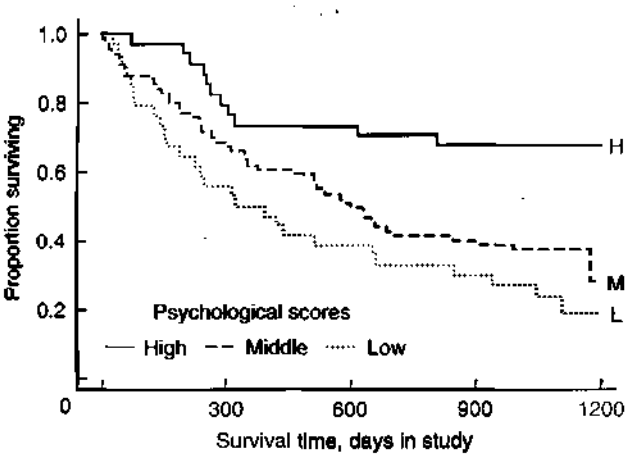


FIGURE 8.10 Psychological well-being and morbidity in amyotrophic lateral sclerosis. Note: High psychological well-being is associated with decreased morbidity. (Reprinted with permission from McDonald, E. R., Wiedenfeld, S., Hillel, A., et al. 1994, "Survival in amyotrophic lateral sclerosis: The role of psychological factors," *Arch Neurol*, vol. 51, pp. 17-23.)

Epilepsy

Behavioral and personality disturbances occur in up to 50% of individuals with epilepsy (Lambert and Robertson 1999; Torta and Keller 1999). Few adequate population-based studies have fully assessed the comorbidity of psychological disorders in individuals with epilepsy, so the prevalence estimates remain relatively crude. One of the largest population-based studies suggests that adults with childhood-onset epilepsy have a fourfold increased risk of having a psychiatric disorder when compared with controls.

Factors related to risk of psychiatric disturbance in patients with epilepsy may he separated into clinical, biological, and social factors. Some specific risk factors have been identified: additional brain injury, type and severity of epilepsy syndrome, and medication effects. Historically, behavioral disturbances were thought to be more severe in patients with temporal lobe epilepsy. Research suggests, however, that patients with any focal epilepsy tend to exhibit increased rates of psychiatric disturbances. In epilepsy, psychiatric disturbances may be associated with ictal, postictal, and/or interictal states (Table 8.13).

To facilitate understanding of the patient and for accurate treatment of symptoms, we must recognize that behavioral and personality disturbances can occur during the ictal state. Individuals in the ictal period may experience episodes of anxiety, depression, psychosis, and aggression. Similarly, patients with epilepsy may report mood disturbances

Table 8.13: Psychiatric disturbances in ictal, postictal, and interictal states

ictal	*Postictal*	*Interictal*
A n \ ion-	Confusion	Major depression
Intense feelings of horror	Depression	Adjustment disorders
Panic attacks	Agitation	Dysthymic disorder
Depressed mood	Paranoia	Atypical depressive syndromes
Tearfulness	Hallucinations	Med ica ti o n - i n d u c ed mood changes
Sexual excitement	Mania	Panic disorder
Paranoia	Aggression/ violence	Generalized anxiety disorder
Hallucinations		Obsessive-compulsive disorder
Illusions		l'hobias
Laughter		Conversion disorder
Forced thoughts resembling obsessions		Medication-induced conditions
Obsessions		Psychotic syndromes
Deja vu and other memory experiences		Aggress ion/violence
Confusion		
Aggression/violence		

Source: Reprinted with permission from Marsh, L. & Rao, V. 2002, "Psychiattic complications in patients with epilepsy: A review," *Epilepsy Res,* vol. 49, pp. 11-33.

immediately before or after an ictal period. Much of the discussion regarding psychiatric disturbances in epilepsy focused on interictal behavioral and personality disturbances; thus these disturbances arc the focus of this section.

Depression

Depression is the most common psychiatric disorder in epilepsy. Prevalence rates are widely varying with reports of 8-63% of individuals with epilepsy experiencing depression. Rates of depression vary as a function of the sample assessed (clinical samples report higher rates of depression than population samples) and measures used to diagnosis depression.

Deptcssion often goes undiagnosed in patients with epilepsy because symptoms of depression may be viewed as a normal reaction to illness. However, accurate diagnosis of depression is critical because depression is associated with decreased quality of life. Depression in patients with epilepsy typically presents differently than in individuals with MDD alone. Depression in epilepsy is associated with fewer "neurotic" traits such as anxiety, rumination, low self-esteem, and somatization than typically observed in MDD. In conttast, depression in epilepsy is associated with more "psychotic" traits, such as paranoia, delusions, and hallucinations, than in MDD. Depression in epilepsy typically runs a chronic course, with periods of major depression separated by periods of dysthymic mood.

Attempted and completed suicides are common in epilepsy. The suicide rate in epilepsy is four times that of the general population. Rates of suicide are even higher in temporal lobe epilepsy (25 times that of the general population). Risk factors include history of self-harm, family history of suicide, stressful life situations, poot morale, stigma, and psychiatric disorders.

The cause of depression in epilepsy is unclear. Psychosocial stressors, genetic disposition, and neuropathology all likely play a contributing role. Although psychosocial stressors have been suggested as important in the cause of depression in epilepsy, observed rates of depression in epilepsy are higher than those in other chronically ill patient populations, lending support to theories of biologic etiology. Although few studies have assessed the relationship between depression and gender, most of these studies suggest that men with epilepsy ate at a higher risk of developing depression than women with epilepsy. Though results are somewhat mixed, there appears to be no relationship between age at onset or duration of epilepsy and depression. Depression appears to be more common in individuals with focal epilepsy than in those with primarily generalized epilepsy. Lateralization of seizure foci may be related to depression, with left-sided foci more commonly associated with depression.

Pharmacological treatment of epilepsy may contribute to depression and psychiatric symptoms in general. Table 8.14 notes commonly used antiepileptic drugs and their psychotropic effects. Medications associated with sedation (e.g., barbiturates and benzodiazepines) may lead to depression, fatigue, and mental slowing. Approximately 8-10% of patients with epilepsy experience an episode of depression following epilepsy surgery. These episodes tend to remit within 18 months of surgery. Increased mood lability and irritation are also common occurrences in the month following epilepsy surgery.

Tabic 8.14: Psychotropic effects of antiepileptic drugs

	Pmitine effects	*Negative effects*	*Complications*
Barbiturates, primidone	—	Aggression, depression, Withdrawal syndromes	ADHD in children
Benzodiazepines	Anxiolytic, sedative	Withdrawal syndromes	Disinhibition
I'tliDsuximide		Insomnia	Alternative psychoses
Phenytoin	—		Toxic schizophreniform psychoses, encephalopathy
Carbamazepine	Mood stabilizing, impulse control	Rarely mania and depression,	
Valproate	Mood stabilizing, anr/imamc		Acute and chronic encephalopathy
Vigabatrin		Aggression, depression, psychosis, withdrawal syndromes	ADHD, encephalopathy, alternative psychoses
Lamuirigini	Mood stabilizing, a nti depressive	Insomnia	Rarely psychoses
Felbamate	Stimulating?	Agitation	Psychoses possible
Gabapenrin	Anxiolytic, antidepressive?	Rarely aggression in children	
Tiagabine		Depression	Nonconvulsive status epilepticus
Top ira mate	Mood stabilizing?	Depression	Psychoses
Levetiraceram			

?=minimal data; — = not applicable; ADHD = anention-deficitmyperactiviry disorder.

Source: Reprinted with permission from Schmitz, B. 2002, "Effects of antiepileptic drugs on behavior," in *The Neuropsychiatry of Epilepsy*, eds M. Trimble *ik*, B. Schmitz, Cambridge University Press.

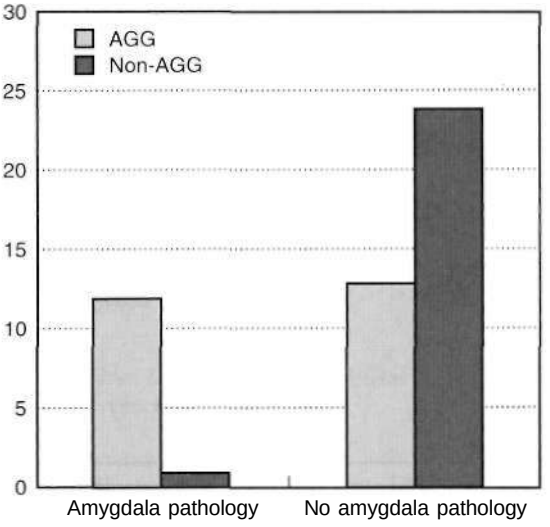
Although the phenomenology of depression in epilepsy may prove dissimilar from that in general patients with depression, similar treatments are efficacious in the treatment of depression. Supportive psychotherapy may prove beneficial, particularly after initial diagnosis as patients begin to adapl to rheii illness. 'Xiiiideprcssani medications are largely effective in the treatment of depression in the general population. However, few clinical trials have assessed the efficacy of antidepressant medications in patients with epilepsy. Older antidepressants and the antidepressant bupropion have been associated with increased seizures and thus should be avoided. SSRLs were reportedly also associated with increased seizures in early reports; however, newer research suggests that these antidepressants are less strongly associated with seizures than previously believed.

Psychosis

The association between epilepsy and psychosis has been debated throughout the past century. In 1931, Kracpelin noted an increased incidence of seizures in individuals with dementia praecox. More recent studies have suggested that 0.6-7,0% of individuals with epilepsy also exhibit psychotic symptoms (Torta and Keller 1999). individuals with epilepsy onset before age 20 years, duration of illness of greater than 10 years, history of complex partial seizures, and temporal lobe epilepsy are at increased risk of psychotic disturbances (Torta and Keller 1999). Epileptic patients with psychosis may experience exacerbations of their psychoses following epilepsy surgery, and it is unlikely that successful epilepsy surgery will result in complete cessation of psychoses. In addition, new psychotic disturbances appear after approximately 3.8-35.7% of temporal lobectomies. These new episodes occur more often with resections of the nondominant hemisphere and in patients with pre-existing personality disorders.

Aggression

The relationship between epilepsy and aggression remains controversial. Early research suggested that the prevalence of aggression in epilepsy ranged from 4.8-50.0%. Though controversial, rates of aggression are believed to be higher in individuals with temporal lobe epilepsy. Results vary because of definition of aggression and method of group selection. Interictal aggression may be described as episodic dyscontrol or, as in *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition *(DSM-IV),* nosology, intermittent explosive disorder (IED), which is characterized by periods of largely unprovoked anger, rage, severe aggression, and violent behavior. Hippocampal sclerosis is less common in individuals with epilepsy and aggression. Aggression in epilepsy is associated with increased temporal lobe pathology. A subgroup of individuals with epilepsy and aggression had significant amygdala atrophy (Figure 8.11).



FIGURF, 8.11 Amygdala pathology in patients with temporal lobe epilepsy with and without aggression, Agg = aggrcssion. (Reprinted with permission from van Elsr, L. Tebartz, 2002, "A)',!',ivssiii]i and epilepsy," in *The Neuropsychiatry of Epilepsy,* eds M. Trimble *St* B. Schmitz, Cambridge University Press, Cambridge, U.K.)

Stroke

Defyression

Within the first year following a stroke, 30^40% of patients experience depression, with most developing depression within the first month post-stroke (Ballard and O'Brien 2002). Approximately 20% of patients will be diagnosed with major depression and another 20% will be diagnosed with minor depression. Depression following stroke is associated with age, time since stroke, cognitive impairment, social support, neuroticism, and history of depression.

Depression is associated with longer hospital stays, suggesting that it affects rehabilitation efforts. Depression is associated with poorer recovery of activities of daily living and increased morbidity (Figure 8.12). Studies assessing the relationship between disability and depression in stroke patients have been equivocal. Depression is associated with poorer quality of life in individuals who have had a stroke, even when neurological symptoms and disability ate held constant.

The relationship between depression and lesion location has been the focus of significant research and controversy. In 1982, Robinson and Price followed 103 individuals for 2 years following stroke and noted that left anterior lesions were associated with increased rates and severity of depression. Lesions nearer the left frontal pole or left caudate nucleus were associated with increased rates of depression. Some have replicated these findings, but others have failed to do so. A meta-analysis by Carson et al. (2000) assessed the relationship between lesion location and depression in post-stroke patients. This review noted that there is significant heterogeneity m previous studies,

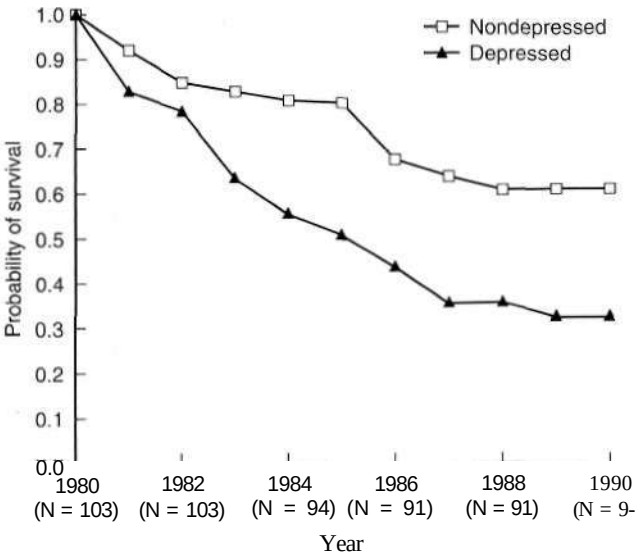


FIGURE 8.(2 Probability of survival following stroke for depressed and nondepressed patients. (Reprinred with permission from Morris, P. L. P., Robinson, R. G., Androzejewski, P., et al. 1993, "Association of depression with 10-year postsrroke mortality," *Am j Psychiatry,* vol. 49, pp. 11-33.)

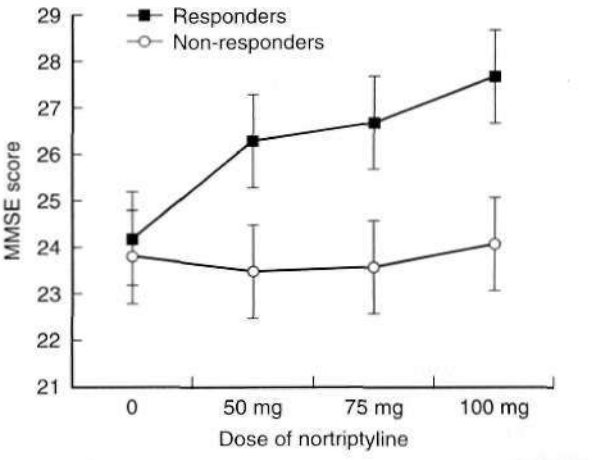


FIGURE 8.13 Mini-Mental Stare examination score with response to nortriptyline in stroke patients. Note: Treatment responders (n—13) show significantly greater improvement in cognitive function than n on responders (n=!8) (/? = .087). F.rmr bars represent standard errors of the mean. (Reprinted with permission from Kimura, M., Robinson, R. G., & Kosier, F. T. 2000, "Treatment of cognitive impairment after poststroke depression; A double-blind treatment trial," *Stroke,* vol. 31, pp. 1482-1486.)

particularly between different sample sources. Results of this meta-analysis did not support an overall relationship between left frontal lesions and depression following stroke.

The relationship between lesion location and depression in 60 patients followed for approximately 2 years post-stroke has been studied (Shimoda and Robinson 1999). Shimoda and Robinson (1999) noted that left-sided lesions closer to the frontal pole were associated with depression in hospitalized patients immediately following stroke. Depression was correlated with nearness of lesion to the frontal pole in either the right or rhe left hemisphere at approximately 4 months post-stroke. At 1-2 years post-stroke, depression was associated with nearness of lesion to the frontal pole in the right hemisphere. In addition, the authors noted that depression in short-term and long-term follow-up was associated with lesion volume and functional impairment. This heterogeneity in relationship between lesion location and depression may explain some of the divergent tesults reported in the literature.

Few studies have assessed the effectiveness of various treatments for depression in these patients. One study suggests that nortriptyline was more effective in the treatment of depression than cither placebo or fluoxetine (Robinson and Schultz 2000). Response to treatment of depression with nortriptyline is associated with improvement in cognitive and functional abilities. The relationship between MMSE score and response to nortriptyline is displayed in Figure 8.13,

Emotional Incontinence

A portion of individuals who are post-stroke experience emotional incontinence, that is, pathological laughing or crying (PLC) not under their control. Between 11% and 35% of individuals experience emotional incontinence after stroke. Emotional incontinence is associated with lesions of the frontal lobe, pons, and medulla, as well as cognitive dysfunction. Although no clinical trials have assessed treatments for pathological laughing or crying, case studies described patients effectively treated for pathological crying with paroxetine.

Aggression

Reports have suggested that individuals have difficulty controlling aggression and anger following a stroke. Approximately 32% of stroke patients experience inability to control anger or aggression (Kim et al. 2002). Many of those individuals (23%) exhibited anger or aggression without provocation. Inability to control anger or aggression was associated with increased motor dysfunction and dysarthria. Although sample six.c in the Kim et al. (2002) study was small, results suggest that lesions in the area supplied by the subcortical middle cerebral artery arc associated with inability to control anger or aggression.

Anxiety

Though less studied, anxiety disorders arc also common after stroke. Approximately 27% of individuals met criteria for GAD following stroke, which does not decrease in frequency within 3 years following stroke. In addition, a twofold increase in panic disorder post-srroke has been noted. Anxiety is associated with increased disability.

Traumatic Brain Injury

Significant behavioral and psychiatric disturbances are noted in individuals following TBI (Table 8.15). Rao and Lyketsos (2002) provide a comprehensive summary of recent literature regarding psychiatric symptoms following brain injury. Physical disabilities associated with TBI typically stabilize with time; however, mood and behavioral changes tend to become more disabling in years following TBI. Psychiatric disturbances remain elevated for decades following injury (Koponen ct ah 2002). Behavioral or mood disturbances are associated with decreased quality of life, increased caregiver burden, and more challenges to the treating physician. Overall, psychiatric disturbances following TBI are more common in individuals with a history of psychiatric illness, poor social functioning, alcoholism, arteriosclerosis, lower MMSE score, and fewer years of education.

Depression

Between 6% and 77% of individuals with TBI meet criteria for MDD following injury {Rao and Lyketsos 2002). Within the first year following TBI, approximately 26% of individuals meet criteria for MDD. Diagnosis of depression in TBI is complicated, because symptoms of depression (e.g., fatigue and sleep disturbances) are common symptoms following TBI. In addition, rates of depression in TBI vary as a function of severity of TBI assessed, method of depression diagnosis, and sample source. Early onset symptoms of depression are believed to be associated with distuption of brain circuitry, whereas persistent depression in TBI is theorized to he associated with psychological reaction to injury. Early onset depression is associated with left dorsolateral frontal or left basal ganglia lesions (1-3 months post-TBI), but late-onset depression is not. Although no large-scale clinical trials have been conducted, case studies suggest SSRIs, psychostimulants, and electroconvulsive therapy are effective treatments for depression in TBI.

Suicidal ideation (65%) and attempts (8.1%) are common following TBI. In contrast to sex differences reported in the general population, women with a TBI are more likely to commit suicide than men with a TBI. Furthermore, suicide was more common in individuals with more severe injury and those younger than 21 years or older than 60 years at the time of injury.

Anxiety

Less research has assessed the prevalence of anxiety disorders in TBI; however, studies suggest that 11-70% of individuals meet criteria for anxiety. A meta-analysis suggested that the mean prevalence of anxiety disorders following TBI is 29%. Panic disorder occurs in 3.2-9.0% of individuals with a TBI. Case studies suggest that SSRIs, naltrexone, and buspirone are effective in the treatment of anxiety in TBI.

Psychosis

Between 2% and 20% of patients post-TBI report psychotic symptoms (Rao and Lyketsos 2002), Psychosis following TBI is associated with severe closed-head injury, temporal lobe epilepsy, and head injury before adolescence.

Behavioral Dyscontrol Disorder

Behavioral dyscontrol disorder is characterized by disturbance in mood, behavior, and cognition (Rao and Lyketsos 2002). Some have considered this disorder consisting of two variants, major and minor. The major variant, which is present in 11-98% of individuals with TBI, is associated with agitation, impulsive behavior, and aggressive outbursts. Individuals with this syndrome often have very little insight into these difficulties. This syndrome is associated with lesions to the frontotcmporal regions.

An area of controversy in the behavioral disturbances following TBI is the existence of the minor variant of behavioral dyscontrol disorder, also called *postcancussian syndrome.* This syndrome is characterized by mood, cognitive, and somatic symptoms typically following mild TBI. Between 80% and 100% of individuals who experience a mild closed-head injury report some or all of the described symptoms of postconcussion syndrome. These symptoms typically resolve within *2-6* months after TBI; however, a small portion (15%) of individuals report symptoms 1 year following TBI.

Table 8.15: Lifetime prevalence of major psychiatric disorders by head injury status from the New Haven Epidemiologic Catchment Area Study (n = 5034)

	Head injury (%)	No *head injury* ***(%)***
Major depression (n = 242)	11.1	*S.I*
Dysthymia (n = 172)	5.5	*13*
Bipolar disorder (n = 45)	*1.6*	1.1
Panic disorder (n = 60)	3.2	1.3
OCD(n=102)	4.7	2.3
Phobic disorder *(n — 36l)*	11.2	7.4
Alcohol abuse/dependence (n = 412)	24.5	10.1
Drug abuse/dependence (n = 175)	10.9	5.2
Schizophrenia (n = 73)	3.4	*1.9*

.Wire- Adjusted tor *ajx,* sex, marital status, SHS, alcohol abuse, and quality of life.

Source: Reprinted with permission from Silver, J. M., Kramer, R., Greenwald, S., *&c* Francis Ltd. 2001, "The association between head injuries and psychiatric disorders: Findings from the New Haven NIMH epidemiologic catchment area study," *Brain Injury,* vol. 15, pp. *925-945.*

Apathy

Symptoms of apathy are reported in 10-60% of individuals with a TBI. Apathy in TBI is associated with depressive symptoms, although a significant number of individuals (28%) report experiencing apathy, but not depression. Lesions effecting the right hemisphere and subcortical regions are more strongly associated with apathy than lesions affecting the left hemisphere.

Personality Change

The classic case of Phineas Gage is used to exemplify the frank behavioral changes that can follow TBI, particularly when lesions affect the orbito fronts I cortices. This behavioral syndrome has been called the *pseudopsychopathic syndrome.* Facctiousness, irritability, distractibility, impulsivity, sexual disinhibition, inappropriate social and personal behavior, and little concern for others characrerize this syndrome.

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Chapter 9
Depression and Psychosis in Neurological Practice

John A. Bertelson and Bruce H. Price

Conditions primarily characterized by behavioral disturbances have traditionally been considered to be poorly understood and of little interest or relevance to most neurologists. However, the recent explosion of knowledge in basic and clinical neuroscience has led to an increased understanding of the underlying biology of behavior, These disturbances are now recognized as integral features, if not presenting symptoms, of many neurological disorders. The development of fields such as cognitive/behavioral neurology and neuropsychiatry has emphasized the existence of a shared body of knowledge and has encouraged collaboration and complementary approaches.

PRINCIPLES AND COMPLEXITIES OF DIFFERENTIAL DIAGNOSIS

The neurological investigation of psychiatric symptoms requires a paradigmatic shift from traditional neurological thinking. It presents challenges not ordinarily encountered in other neurological consultations. Guiding principles include the following:

1. Depression, mania, delusions, hallucinations, obsessions and compulsions, dissociation, and personality alterations are etiologically nonspecific symptoms. They are common in both primary neurological and psychiatric disease.
2. Persistent behavioral sequelae are often more disabling to the patient's personal and professional lives than elemental or cognitive neurological deficits.
3. Atypical presentations of neuropsychiatric syndromes are common. No single feature is present in all forms of neurological disease with behavioral disorders.
4. Disturbances of frontal, temporal, limbic, and striatal regions are most likely to produce psychiatric manifestations.

Considerable complexities must be taken into account as well.

1. A comprehensive assessment of mental status and elemental neurological examination may be impossible in the setting of agitation or psychosis.
2. A patient's decompensated behavior may be concordant with the past psychiatric profile. However, this concordance does not necessarily imply that decompensation is psychiatric in nature.
3. Normal findings on elemental examination, routine laboratory testing, brain imaging, electroencephalography, and cerebral spinal fluid analysis do not necessarily exclude diseases of neurological origin.
4. Psychopharmacologic medications often complicate the neurological picture.
5. Beneficial responses to neuroleptics, antidepressants, or even electroconvulsive therapy do not necessarily point to a specific disease or narrow the differential diagnosis.

DEFINITIONS OF PSYCHIATRIC TERMS

The increasing collaboration between neurology and psychiatry necessitates a shared vocabulary. Specific

Table 9.1: Key psychiatric terms of relevance to neurologists

Abulia is the state of reduced impulse to act and think associated with indifference about consequences of action.

Anxiety is the feeling of apprehension caused by anticipation of danger that may be internal or external,

Apathy is dulled emotional tone associated with detachment Of indifference.

Comportment refers to complex mental processes that include insight, judgment, self-awareness, empathy, and social adaptation.

Compulsion is the pathologic need to act on an impulse that, if resisted, produces anxiety. The action has no true end in itself other than to prevent something from occurring in rhe future.

Confusion is the inability to maintain a coherent stream of thought due to impaired attention and vigilance. Secondary deficits in
language, memory, and visual spatial skills are common.

Delusion is a false, unshakable conviction or judgment that is out of keeping with reality and with socially shared beliefs of the individual's background and culture.

Dementia is the insidious onset of progressive mental decline that gradually interferes with activities of daily living appropriate for age and background.

Depression is a sustained psycho pathologic feeling of sadness often accompanied by a variety of associated symptoms, particularly anxiety, agitation, feelings of worth lessn ess, suicidal ideas, abulia, psychomotor retardation, and various somatic symptoms and physiologic dysfunctions and complaints that cause significant distress and impairment in social functioning.

Hallucination is a sensory misperceprion in any modality occurring in the absence of the appropriate external stimulus.

Mania is a disorder in which mood is elevated out of keeping with the individual's circumstances. It may vary from irritability to carefree joviality to almost uncontrollable excitement. Elation is accompanied by increased energy, difficulties sustaining attention, marked distractibility, and impaired judgment. Self-esteem is often inflated with grandiose ideas.

Obsession is the pathologic persistence of an irresistible thought or feeling that cannot be eliminated from consciousness by logical effort despite the individual's knowledge that it is not true. It is associated with anxiety and rumination.

Paranoia is a descriptive term designating either morbid dominant ideas or delusions of self-reference concerning one or more of several themes, most commonly persecution, love, hate, envy, jealousy, honor, litigation, grandeur, or the supernatural.

Psychosis is a gross disorder of perception and thought. It is the misapprehension of the nature of reality.

Schizophrenia is a disorder characterized by fundamental and characteristic distortions of thinking and perception accompanied by an affect that is inappropriate or blunted, while clear consciousness and intellectual capacity are usually maintained. Although no strictly pathognomonic symptoms can be identified, the most important positive psychopathologic phenomena include thought echo, insertion, withdrawal, or broadcasting; delusions of control, influence, or passivity; perceptions of hallucinatory voices commenting on or discussing the patient in the third person; and disorders in the train of thought. Negative symptoms include poverty in quantity or con rent of speech; impairment of attention; psychomotor slowing; affective blunting; apathy; social withdrawal; and poor nonverbal communi carion, self-care, and social performance.

psychiatric terms which should be incorporated into a neurologist's practice are presented in Table 9.1 {See *DSM 1V-TR* 2000, for further details).

NEUROANATOMY OF AFFECTIVE **AND** PSYCHOTIC DISORDERS

The specific anatomic substrates of neuropsychiatric symptoms are less well understood than the more elemental aspects of neurology. The clinical heterogeneity of neuropsychiatric symptoms arising from similar focal lesions, the difficulty of measuring neuropsychiatric symptoms, and the bilateral otigin of many of these symptoms are complicating factots. However, given that the nature of the symptoms genetatcd is often more dependent upon the location of a lesion than the actual pathology, a brief review of the anatomy of behavior is useful.

The human cortex can be divided into five functional levels: primary sensory-motor, unimodal association, heteromodal association, paralimbic, and limbic cortices. The general cytoarchitectural trend is one of less organization (limbic cortex) to greater organization (primary cortex). Primary sensory-motor cortex is involved in the processing of direct interactions with extrapersonal space and is not believed to significantly contribute to complex emotional Of cognitive states. Unimodal association cortices provide modality specific, higher-order processing and relay of information between their adjacent primary sensory-mo tor cortices. Lesions at this level can produce selective perceptual deficits such as "pure word deafness," prosopagnosia, and achromatopsia. Heteromodal cortex, which includes prefrontal, lateral temporal, posterior parietal, and portions of parahippocampal cortices, has a widespread pattern of connectivity throughout the brain. Tasks mediated by heteromodal correx are extremely diverse, but include complex cognitive functions and behaviors such as motivation, attention, and problem-solving. Paralimbic cortex, consisting of the orbitofrontal cortex, insula, tempotal pole, patahippocampal cortex, and cingulate complex, is a key transition between limbic cortex and isocortcx. Anatomically, it forms a belt of tissue between limbic and heteromodal regions. Functionally, it serves a transitional role, merging cognitive, emotional, and visceral states. Limbic cortex consists of poorly laminated corticoid structures such as the amygdala and

Table 9,2: Cortical and subcortical structures implicated in selected psychiatric symptoms

Depression	*Hallucinations*	*Delusions*
Orbitofrontal cortex	Unimodal association cortex	Orbitofrontal cortex
Dorsolateral prefrontal cortex	Orbitofrontal cortex	Amygdala
Anterior cingulacc gyrus	Paralimbic cortex	Striatum
Striatum	Limbic cortex	Thalamus
	Striatum	
	Thalamus	

substantia innominata, as well as allocortical structures such as the hippocampus. In addition to the significant connections to the hypothalamus and the "internal milieu" it subserves, limbic structures play a key role in memory, emotion, and drive.

The generation of aberrant behavior can occur in structures ranging from the brainstem to the prefrontal cortex. Table 9.2 presents a partial listing of structures that have been associated with specific psychiatric symptoms. Although attempts to detetmine absolute rules regarding behavior and lesion localization have proven difficult, observations have led to a number of widely accepted generalizations. The majority of studies suggest a greater incidence of post-stroke depression (PSD) with left prefrontal infarcts, whereas right prefrontal strokes are more likely to he associated with mania. There is an association between selective right hemisphere dysfunction and delusions, hallucinations, and impaired emotional communication. Disorders with predominant subcortical pathology can disrupt the connections of hehaviorally relevant frontal networks and are commonly associated with a variety of mood disorders and psychotic symptoms. Subcortical nuclei with particular behavioral relevance include the caudate nucleus, nucleus accumbens, and the ventral anterior and dorsomedial thalamic nuclei. Huntington's disease is a prototypical subcortical disease, where depression and psychosis are not only very common late in the disease, but may precede the onset of chorea and other abnormal movements by years. The disproportionate incidence of depression and psychosis in multiple sclerosis demonstrates the contribution of white matter to the pathogenesis of neuropsychiatry symptoms. **Finally,** there is evidence that midline cerebellar lesions are associated with abnormalities in the modulation of affect and cognition.

CLINICAL SYMPTOMS AND SIGNS SUGGESTING NEUROLOGICAL DISEASE

It is clear that ;s variety of neurological disorders can produce psychiatric symptoms. It is also clear that not every patient who carries a psychiatric diagnosis requires a neurological evaluation. However, both neurologists and psychiatrists should be aware of components of **the** history or physical examination that raise suspicion for the presence of an underlying neurological disease. Table 9.3 presents features from the medical history that suggest potential neurological etiologies of psychiatric symptoms. Table 9.4 reviews abnormalities in the elemental neurological examination associated with diseases that can manifest significant neuropsychiarric features.

Table 9.3: Historical features suggesting neurological disease in patients with psychiatric symptoms

- Patient has atypical psychiatric features:
  - Late age of onset with no prior psychiatric history
  - Acute or subacute onset
  - Lack of significant psychosocial stressors
  - Catatonia
  - Diminished comportment
  - Cognitive decline
  - Intractability despite adequate therapy
  - Progressive symptoms
- History of present illness includes:
  - New or worsening headache
  - Inattention
  - Somnolence
  - Incontinence
  - Anorexia
  - Neuroendocrine changes
- Patient has a history of:
  - Risk factors for cerebrovascular disease
  - Malignancy
  - Immune-compromised state
  - Significant head trauma
  - Seizures
  - Movement disorder
  - Hepatobiliary disorders
  - Abdominal crises (without known cause) and surgeries
  - Multiple first-degree relatives with similar diseases
- Patient has unexplained diagnostic abnormalities, including:
  - Screening laboratory studies
  - Electroencephalogram
  - Magnetic resonance imaging
  - Cerebrospinal fluid

PSYCHIATRIC MANIFESTATIONS OF NEUROLOGICAL DISEASES

Depression, the most common major psychiatric complication of neurological disease, and psychosis arc hut two of a myriad of psychiatric symptoms encountered in neurological practice. Virtually any abnormal process affecting the neuroanatomy substrates cited previously may have associated psychiatric symptoms at some point in its natural history. A sampling of specific diseases is presented in Table *9.5.* Psychiatric manifestations may be the initial and most salient symptoms of these disorders, preceding the

Table 9,4: Selected neurological abnormalities suggesting diseases associated with psychiatric symptoms

Examination abnormalities	*Selected disease(s) or underlying etiology*
Vital signs	
Fever	1 Icrpcs simplex or other CNS infection
Tachypnea	Delirium secondary to systemic infection
Hypoventilation	Hypoxia, alcohol withdrawal Sedative intoxication
Cranial nerve	
Visual field deficit	Stroke, mass, multiple sclerosis, lupus
Pupils	
Argyll Robertson	Neurosyphilis
Unilateral dilation	Mass, acute intermittent porphyria
Ophthalmoplegia	
Vertical gaze palsy	Progressive supranuclear palsy
Mixed	Wernicke-Korsakoff syndrome, lupus Chronic basilar meningitis
Cornea	
Kayser-Fleischer rings	Wilson's disease
Fundi	
Papilledema	Mass, lupus, multiple sclerosis
Optic pallor	Multiple sclerosis, Tay-Sachs disease, acute intermittent porphyria
Deafness	Superficial siderosis
Extrapyramidal	Parkinson's disease, Lewy body disease Huntington's disease, Wilson's disease Lupus, neurosyphilis
Cerebellar	MS, lupus, AIP, Tay-Sachs disease
Motor Neuron	Motor neuron disease with frontotemporal dementia
Peripheral Nerve	Vitamin B^ deficiency, acute intermittent porphyria, metachromatic leukodystrophy
Gait	
Apraxia	Normal pressure hydrocephalus
Spasticity	Stroke, multiple sclerosis
Bradykinesia	Multi-infarct dementia Parkinson's disease, progressive supranuclear palsy, Lewy body disease

neurological symptoms by years or even decades in some degenerative diseases. A discussion of selected neurological diseases and their psychiatric manifestations follows. Disease-specific diagnostic investigations and therapeutic interventions are beyond the scope of this chapter and are covered elsewhere in this text.

Vascular

Stroke

Because it is the leading cause of neurological disability in the United States, the public health impact of cerebrovascular disease is profound. Unfortunately, the relatively frequent cognitive and behavioral manifestations of stroke are often under-appreciated. PSD occurs in .30-50% of stroke survivors, but is estimated to be under-diagnosed by nonpsychiatrists in more than 50% of cases. It is a misconception that depression is merely a normal psychological reaction to a devastating physical impairment; there appears to be a higher incidence of depression in stroke survivors than other patients with equally debilitating diseases. Middle cerebral artery, anterior cerebral artery, and subcortical lacunar strokes appear particularly prone In producing PSD. The greatest incidence of depression occurs in the first few months following infarction, Esta Wishing a diagnosis of PSD can be especially challenging. Patients with strokes, particularly those affecting the frontal lobe of the dominant hemisphere, may become depressed but (due to aphasia) lack the ability to verbally express their symptoms. In contrast, nondominant hemisphere infarctions can result in speech devoid of emotional expression (affective aprosody) but the patients may remain euthymic. These scenarios highlight the importance of observing for depressive behaviors, including abnormal sleep and eating patterns, anhedonia, fatigue, tearfulness, and social withdrawal. Features of obsessive compulsive disorder have also been associated with strokes, particularly stroke involving the caudate nucleus {Kwak and Jankovic 2002). Currently, the standard therapy of PSD remains pharmacology and supportive psychotherapy. Improvement in symptoms is usually observed 2-6 weeks following initiation of treatment with antidepressants.

Although much less common than PSD, mania and psychosis are known sequelae of stroke. Infarcrs in the right hemisphere, particularly the frontal, temporal, and parietal lobes, more often result in psychosis than left hemisphere strokes. Peduncular hallucinations are vivid visual hallucinations that can occur in ventral midbrain infarctions. Psychotic episodes can be the manifestations of complex partial seizures secondary to strokes; patients with poststroke psychosis are observed to be more prone to have comorbid epilepsy than are stroke survivors without psychosis. The psychosis may partially respond to anticonvulsants, whether or not overt seizures have been identified.

Multi-infarct Dementia

In addition to occurring secondary to a single stroke, neuropsychiatric symptoms often occur in the setting of multi-infarct dementia. Such patients generally have suffered multiple strokes in a variety of cortical or subcortical locations, resulting in impaired cognition. Generally, elemental neurological deficits arc seen, including visual field deficits, hemiparesis, or hemi-neglect. The presence of depression and psychosis is likely dependent upon the locations of infarcts. Bilateral fronto-temporal lobes, subcortical nuclei such as the caudate and puramen, and the interconnecting white matter are associated with an increased risk of psychotic and depressive symptoms.

Tabic 9.5: Selected neurological etiologies of depression and psychosis

Category	*Disorders*
Vascular	Stroke
	Multi-infarct dementia
	Central nervous system vasculitis
	CADASIl.
Infectious	Lyme disease
	Prion diseases
	Neurosyphilis
	HIV encephalopathy
	Whipple's disease
	Cerebral malaria
	Encephalitis
	(herpes simplex, Epstcin-Barr, etc.)
	Systemic infection (urinary tract
	infection, pneumonia, etc)
	Congenirally acquired infections
	(toxoplasmosis, cytomegalovirus, etc.)
Metabolic,	Hepatic encephalopathy
acquired	Uremia
	I !\ pn/hypiTihyroktiMii
	Hy po/hy pe rp a ra t h y roi d i sm
	Addison's disease/tbushing's syndrome
	Vitamin B12 deficiency
	Folic acid deficiency
	Niacin deficiency
	Hypoglycemia
Inflammatory	Lupus (SLE)
	Sjogren's syndrome
	Hashimoto's encephalitis
	Sydenham's chorea
Toxic	Medications:
	Analgesics
	Antiarrhythmics
	Anticholinergics
	Antiepileptics
	Antimicrobials
	Dopamine agonists
	^-Blockers
	Sedatives
	Other (steroids, digitalis)
	Drugs of abuse and toxins:
	Amphetamines
	Carbon monoxide poisoning
	Cocaine

Category	*Disorders*
Toxic	Drugs of abuse and toxins *(Continued):*
	ETOH
	Hallucinogens
	Heavy metals
	Inhalants
	Marijuana
	3,4-methy I enedi o xy metha m p h e ta m i ne
	(MDMA, "Ecstasy")
	Phencyclidinc
Neoplastic	Mass lesion
	Paraneoplasia
	Limbic encephalitis
	Treatment effects
	(. IIIHT (pancreatic adenocarcinoma '•
Demyelinating/	Acute disseminated encephalomyelitis
D ysm yc I i nating	Multiple sclerosis
	Metachromatic leukodystrophy
	Adrcnolcukodystrophy
Degenerative	Alzheimer's disease
	FrontO-temporal dementia
	Diffuse Lewy body disease
	Parkinson's disease
	Progressive supranuclear palsy
	Corticobasal degeneration
	Idiopathic basal ganglia calcifications
	Huntington's disease
Metabolic, inherited	Wilson's disease
	Tay-Sachs disease
	Adult neuronal ceroid lipofuscinosis
	Niemann-Pick, type C
	Acute intermittent porphyria
	Mitochondrial encephalopathy.
	lactic acidosis, and strokclikc episodes
Trauma	Traumatic brain injury
	Subdural hematoma
Epilepsy	Ictal
	Interim]
	Postictal
Other	Migraine
	Narcolepsy
	Normal pressure hydrocephalus
	Sensory deprivation

Infectious

Acquired Immunodeficiency Syndrome

In addition to the effects of opportunistic infections and malignancies on behavior in patients with acquired immunodeficiency syndrome (AIDS), there are direct neurotoxic effects of the human immunodeficiency virus (HIV) itself. HIV-associatcd dementia (HAD, also known as the AIDS dementia complex and subacute encephalitis) is the AlDS-defimng illness in up to 10% of patients with HIV. Relevant pathologic changes may be present at autopsy in more than 50% of patients. The usual clinical presentation is that of a subcortical dementia, with bradyphrenia, apathy, memory decline, and impaired concentration. Autopsy studies demonstrate a concentration of viral load in the basal ganglia and hypothalamus. Elevated HIV ribonucleic acid (RNA) levels and reduced C1D4 counts are associated with a progressive!) increasing risk of developing HAD, with significantly increased risks with HIV RNA levels > 3000 copics/cc and CD4 <500 cells/mm . The development of HAD is a poor prognostic sign, with a median time to death of & months after onset.

Psychiatric manifestations are common in HAD, Delusions, hallucinations, anxiety, depression, apathy, emotional lability, and mania arc frequently encountered.

These symptoms tend to become more severe as the dementia progresses. Observational studies of the specific clinical presentations are complicated by frequent comorbidities of substance abuse and/or prior psychiatric diagnoses. In addition to therapy with antidepressants and antipsychotics, psychostimulants such as merhylphcnidare have demonstrated efficacy in treating various symptoms of depression.

Creutzfeldt-Jakob Disease

Sporadic Creutzfcldt-Jakob disease (sCJD) is the prototypical prion disease. It is a rare, rapidly progressive disorder of behavior, cognition, and motor function. Cognitive (especially short-term memory) and cerebellar difficulties are common initial symptoms. However, there are case reports of psychiatric manifestations, including hallucinations and delusions, preceding the typical motor signs. Depression, anxiety, and othet psychiatric symptoms generally become more prominent as the dementia progresses. New variant CJD (nvCJD) is a distinct entity from sCJD and was first reported in 1996. Since then, more than 100 cases have been documented. Unlike sCJD, nvCJD typically presents in much younger patients and with more prominent psychiatric manifestations. Spencer et al. reported that 63% demonstrated purely psychiatric symptoms at onset (i.e., dysphoria, anxiety, anhedonia), 15% had purely neurological symptoms, and 22% had features of both. Median duration of illness was 13 months, and by time of death, prominent neurological and psychiatric manifestations were universal. Delusions, hallucinations, and depressive symptoms occurred in a significant percentage of patients, as presented in Tabic 9.6.

Neurosyphilis

With the recent AIDS epidemic, there has been a resurgence of neurosyphilis, which had become rare in the industrialized world following the advent of antibiotics. Neurosyphilis can occur at both early and late stages of infection. Early neurosyphilis, seen in the first weeks to years of infection, is primarily a meningitic process in which the parenchyma is not typically involved. Complications of chronic, granulomatous meningitis may include cranial neuropathies, hydrocephalus, and arteritis, which can lead to infarction. Cognitive and behavior changes can occur with early neurosyphilis; however, they are typically secondary to the complications of stroke or hydrocephalus. Late neurosyphilis occurs as tabes dorsal is, general paresis, or commonly a combination of the two. General paresis typically occurs with a latency of 10-20 years or more following primary infection. This form presents as a slowly progressive dementia, which may be accompanied by Argyll Robertson pupils, tremor, seizures, and dysarthria. Psychiatric manifestations, including mania, depression, and psychosis, rarely present before significant cognitive decline.

Tabic 9.6: Psychiatric symptoms associated with new variant Creutzfcldt-Jakob disease, according to frequency and latency following initial presentation of disease

Vrcqwiic-y	*Early onset* *{< 4 mo)*	*Later onset* *(4-6 mo)*	*Late onset* *(•> 6 mo)*
>50%	Dysphoria Withdrawal Anxiety Irritability Insomnia Loss of interest	Poor memory Impaired concentration Aggression	Disorientation Agitation
25%-50%	Behavioral changes Anergia Poor performance	Tearfulness Weight loss Appetite change 1 Jypersonmu Con fusion	Hallucinations Impaired self-care Paranoid delusions Inappropriate affect
<25%	Obsessive features Losing things Suicidal ideation Panic attacks	Psychomotor retardation Diurnal mood variation Loss of confidence	Bizarre behavior Paranoid ideation Recognition impairment Confabulation Lack of emotion Perseveration Impaired comprehension Change in food preferences Impaired use of devices Acalculia

Adapted from Spencer, M. D., Knight, R. S. G., 8c Will, R. G. 2002, "First hundred cases of variant Crcutzfeldt-Jakob disease: Retrospective case note review of early psychiatric and neurological features," BM/, vol. 324, pp. 1479-1482.

Metabolic

Essentially any metabolic derangement, if severe enough, can adversely affect behavior and cognition. In general, the systemic and neurological signs and symptoms arise before significant psychopathology develops. Metabolic disorders should remain within the differential diagnosis when confronted by patients with psychiatric symptoms.

Thyroid Disease

Hypothyroidism results from a deficiency in circulating thyroxine (T4). It can result from impaired function at the level of the hypothalamus (tertiary hypothyroidism), the anterior pituitary (secondary hypothyroidism), or the thyroid gland (primary hypothyroidism, the most common cause of hypothyroidism). Elemental neurological symptoms include ataxia, seizures, and cranial neuropathies. Cognitive and behavioral symptoms, which typically progress over weeks, are manifested by cognitive slowing, apathy, depression, psychosis, and dementia, Psychosis with hypothyroidism, commonly referred to as myxedema madness, typically presents with paranoid delusions and auditory hallucinations. It can be fatal if untreated. The dementia associated with hypothyroidism may not fully remit despite the return to a euthyroid state,

Hyperthyroidism may be due to a number of etiologies that produce increased serum T4. With mild hyperthyroidism, patients typically arc anxious, irritable, emotionally labile, rachycardic, and tremulous. When apathy and depression are present, the term *apathetic hyperthyroidism* is often used. Thyroid storm results from an abrupt elevation in T4, often provoked by a significant stress such as a surgery. It can be associated with fever, tachycardia, seizures, and coma; untreated, it is often fatal. Psychosis and paranoia frequently occur during thyroid storm; they are rare with milder hyperthyroidism, as is mania.

Hashimoto's encephalopathy is a rare disorder involving autoimmunity to thyroid peroxisomes. It is associated with the subacute onset of confusion, delirium, seizures, myoclonus, and tremulousness. Psychosis can be prominent. It is characterized by elevated antithyroid peroxisomal antibodies, an encephalopathy electroencephalogram (EEG), and elevated CSF protein. Importantly, levels of thyroid-stimulating hormone (TSH) can be normal in Hashimoto's encephalopathy. The psychiatric manifestations tend to resolve with treatment, which generally involves high-dose steroids.

Vitamin B12 and Folic Acid Deficiency

Vitamin B12 (cyanocobalamin) is present in substantial amounts in products such as meat, fish, eggs, and cheese. The daily dietary requirement is low and the accumulated storage in the liver is so high that a deficiency state due to inadequate dietary intake or absorption generally takes years to develop. The most common sign of vitamin B12 deficiency is macrocytic anemia. However, signs and symptoms attributed to the central nervous system (CNS) are diverse and can occur in the absence of anemia or macroeytosis. Furthermore, a normal serum cobalamin level does not exclude the possibility of a clinical deficiency. Serum homocysteine, which is elevated in more than 90% of vitamin B12 deficiency states, can verify clinical disease in the appropriate settings.

Subacute combined degeneration (SCD) refers to the combination of spinal cord and peripheral nerve pathology associated with vitamin Bi_2 deficiency. Patients often complain of unsteady gait and distal paresthesias; the examination may demonstrate evidence of posterior column, pyramidal tract, and peripheral nerve involvement. Cognitive, behavioral, and psychiatric manifestations can occur in isolation or together with rhe elemental signs and symptoms. Personality change, cognitive dysfunction, mania, depression, and psychosis have been reported. Prominent psychotic features include paranoid or religious delusions and auditory and visual hallucinations. Dementia is often comorbid with cobalamin deficiency; however, the causative association is unclear.

Folate deficiency can produce a clinical picture similar to cobalamin deficiency, although some report that folate deficiency tends to produce more depression whereas vitamin B12 deficiency rends to produce more psychosis. Elevated serum homocysteine is also seen with a functional folate deticieno slate. Repletion of folate, it comorbid vitamin B12 deficiency is not first corrected, can result in an acute exacerbation of the neuropsychiatry symptoms.

Acute Intermittent Porphyria

The porphyrias are caused by enzymatic defects in the heme biosynthetic pathway. Acute intermittent porphyria (AIP) is the most common type of porphyria reported in the United States. AIP follows an autosomal dominant pattern of inheritance and is due to a mutation in the gene for porphobilinogen (PBG) deaminase. The disease is characterized by artacks lasting days to weeks, with relatively normal function between attacks. The attacks may be spontaneous, but are typically precipitated by a variety of factors, such as medications (including anticonvulsants, tricyclic antidepressants, and oral contraceptives), infection, alcohol, pregnancy, and anesthesia.

Porphyric attacks are characterized by the clinical triad of abdominal pain, peripheral neuropathy, and neuropsychiatric manifestations. Abdominal pain is the most common symptom, may be associated with ileus, constipation, and diarrhea, and can result in surgical exploration if the diagnosis of AIP is unknown. The peripheral neuropathy is primarily axonal and preferentially affects motor nerves. Seizures may also be seen. A variety of cognitive and behavioral changes can occur, including depression,

hallucinations, delusions, anxiety, and confusion. However, it is rare for the neuropsychiatry symptoms to occur in the absence of peripheral nerve or abdominal complaints.

The diagnosis of AIP should be suspected in the context of a young adult with severe abdominal pain, psychosis, and weakness or paresthesias. During attacks, there is increased urinary excretion of porphyrin precursors, which may result in urine that is deep red or brown. The urine can appear normal between attacks; in these situations diagnosis can be confirmed by examining cultured erythrocytes or fibroblasts. There is no cure; patients require supportive measures during attacks, and at all times care must be taken to avoid precipitating further attacks.

Inflammatory

Systemic Lupus Erythematosus

Systemic lupus erythematosus (lupus, SEE) is a multisystem inflammatory disorder that affects all ages, although young females are at significantly elevated risk. CNS involvement is common, with clinical manifestations seen at some point during their disease course in up to 90% of patients. The criteria for neuropsychiatric lupus (CNS-SEE) require seizures or psychosis in the setting of lupus and the absence of other contributing factors. However, neurological involvement can be much more extensive, including headache, strokes, seizures, peripheral neuropathy, and chorea. Small infarctions are more common than large vessel strokes; infarcts often are subclinical and can occur secondary to local vasculitis, antiphospholipid antibody-mediated thrombosis, and cardiogenic embolization.

Neuropsychiatric symptoms are common and often episodic. Depression and anxiety each occur in approximately 25% of patients; psychosis is more rare and tends to occur in the context of acute confusional states. Many of the neuropsychiatric symptoms in lupus can also occur secondary to corticosteroid therapy, which may lead to significant dilemmas in management. Cognitive manifestations eventually occur in many patients, ranging from mild attcntional difficulties to dementia. Relevant laboratory investigations include antinuclear antibody titers (which arc positive in 95% of patients with SLE), double-stranded deoxyribonucleic acid (DNA) antibodies (anti-dsDNA), and antibodies to Smith nuclear antigen (anti-Sm). A false-positive RPR may occur. Advances in immunosuppression have resulted in improved morbidity and mortality.

Demyelinating

Multiple Sclerosis

Multiple sclerosis (MS) likely represents a heterogeneous group of disorders that produce focal areas of CNS demyelination. In general, there is relative preservation of axons, although significant neuronal loss can occur. It primarily affects the young, with a peak age of onset in the mid-twenties, and affects females more than males at a 2:1 ratio. It is characterized cither by attacks of neurological deficits with variable remittance or by a steady, progressive course of neurological decline. There is no known cure, although there arc several immuuomodulating agents that reduce the frequency of attacks and can slow the radiographic progression of disease.

Ncuropsychiarric manifestations of MS are common, likely occurring in at least 60% of patients at some point in their disease. More severe symptoms arc correlated with greater lesion burden. Depression arises in about 50%, whereas mania is rare. Suicide risk is reported to be 7.5 times that of an age-matched general population. Psychosis occurs in 5-10%, with manifestations including delusions and hallucinations. The presence of psychiatric symptomatology does not preclude the use of corticosteroids to abbreviate clinical attacks of MS. Otherwise, pharmacological and behavioral treatment mirrors the management of depressed and psychotic patients without MS.

Toxic

Drug Abuse

Psychoactive chemicals have been a part of human society for thousands of years. The abuse of such substances represents a substantial public health concern. Up to 20% of Americans will suffer from a substance abuse disorder at some point in their lives. Common neurological manifestations are broad and include the direct effects of intoxication (i.e., tcspiratory depression from sedatives), side effects (i.e., stroke or vasculitis with stimulant abuse), and indirect effects (i.e., traumatic brain injury sustained as a result of an intoxicated state). However, neuropsychiatric manifestations are much more prevalent, occur with abuse of all classes of drugs, and are summarized in Table 9.7. There is growing evidence that drug use may promote the development of chronic neuropsychiatric states such as depression and impaired cognition due to changes in structural and functional neuroanatomy. Routine urine and serum toxicology assays may not screen for some of the less common or newer substances of abuse, such as barbiturates and 3,4-methylenedioxymethamphetamiue (MDMA, "ecstasy").

Neoplastic

There arc a variety of neoplasm-related causes of cognitive and behavioral disorders. Of particular relevance are mass lesions and paraneoplastic syndromes. Mass lesions can be single or multiple and can be primary to the CNS or

Table 9.7; Potential behavioral and cognitive manifestations of substance abuse

Depression	Cognitive deficits
Panic attacks	Attention
Anxiety	Calculation
Hallucinations	Executive tasks
Delusions	Memory
Mania	Fatigue
Depersonalization	Impulsivity
Disinhibition	Sedation

metastatic. Sources of common metastatic tumors include primary lung, breast, renal, and skin (melanoma) malignancies. The number of patients presenting with a primary psychiatric diagnosis secondary to an unidentified brain tumor is likely to be less than 5%. However, 15-20% of patients with intracranial tumors may present with neuropsychiatric manifestations before primary neurological problems, such as motor or sensory deficits, develop. The behavioral manifestations of mass lesions are diverse and are related to a number of factors, including direct disruption of local structures or circuits, seizures, and increased intracranial pressure. Meningiomas are classic examples of tumors that can present solely with behavioral manifestations. Common locations include the olfactory groove and sphenoid wings, which can disrupt adjacent limbic structures such as the orbital frontal gyri and medial temporal lobes.

Depression, mania, psychosis, personality disorder, and cognitive abnormalities have all been reported secondary to CNS mass lesions. Certain generalizations can be made about the behavioral manifestations of brain tumors. Supratentorial masses are more likely to produce neuropsychiatric symptoms than infratentorial lesions. Aggressive tumors are more likely to produce delirium, agitation, and psychosis, whereas indolent tumors are more likely to produce affective disorders and alterations in personality. Older patients are more likely to develop significant cognitive changes than young patients.

Paraneoplastic syndromes represent remote, nonmctastatic manifestations of malignancy. Neurological paraneoplastic syndromes are primarily immune-mediated disorders that may develop as a result of antigens shared between the nervous system and tumor cells.

The most common primary malignancies that promote neurological paraneoplastic syndromes are ovarian and small-cell lung carcinomas (SCLC). These syndromes generally develop subacutely, often before the primary malignancy is identified, and may preferentially involve selected regions of the CNS. Typical sites of involvement include muscle, neuromuscular junction, peripheral nerve, cerebellum, and limbic structures. When involvement is widespread, the term *encephalomyelitis* is used. Limbic encephalitis produces a significant amnestic syndrome and may be associated with complex partial and generalized seizures. Common neuropsychiatric accompaniments of limbic encephalitis include delirium, psychosis, apathy, personality change, and depression. Magnetic resonance imaging (MRI) may document increased T2 signal abnormalities in the medial temporal structures and cingulare gyri. Relevant paraneoplastic markers include anti-Hu antibodies, associated with SCLC, and anti-Ta (Ma2) antibodies, associated with testicular neoplasms. If a paraneoplastic syndrome is suspected before diagnosis of a malignancy, aggressive investigation to identify the suspected tumor should occur. Paraneoplastic disorders are often progressive and refractory to therapy, although in some cases there is significant improvement following complete tumor resection.

Degenerative

Neuropsychiatric symptoms are common in most degenerative disorders that produce significant dementia. The individual presentations of such symptoms are related to a number of factors specific to the disease, including location of lesion burden, rate of progression of disease, and factors specific to the individual such as premorbid personality, education level, psychiatric history, and coping skills. This section reviews the salient neuropsychiatric manifestations of selected degenerative disorders.

Alzheimer's Disease

Alzheimer's disease (AD) is the leading etiology of dementia in the elderly, with an estimated prevalence in the United States of more than 2 million patients. The natural history, pathology, and clinical features of AD are described elsewhere in this text.

Most patients with AD experience significant neuropsychiatric manifestations. Depressive symptoms occur in approximately 50% and there may be an increased risk of suicide. In addition, there is evidence that the onset of depression in the elderly is associated with an increased risk of developing AD, Psychosis is rarely the presenting symptom of AD. However, as the illness progresses, psychotic symptoms such as hallucinations and delusions become prevalent. Psychosis been noted to occur in 30-40% of patients with AD over the course of their disease, with a recurrence rate of more than 90%. Delusions tend to be paranoid in nature, and a variety of delusional themes have been reported. Hallucinations occur almost as frequently as delusions. Hallucinations are generally visual; less often they are auditory, and rarely do they involve other sensory systems. Data supporting a relationship between the degree of dementia and depression or psychosis are equivocal. Mania is rare, occurring in <5% of patients.

Personality and behavior changes are perhaps the most common neuropsychiatric manifestations of AD. Apathy is the most commonly reported behavioral change, but

irritability, aggression, and disinhibition are also often noted. Behavioral abnormalities, rather than depression or psychosis, appear to be the leading neuropsychiatrie-symptom resulting in admission to inpatient services. There is evidence char personality and behavior problems correlate with degree of severity of the dementia. In mild to moderate cases of AD, patients typically retain social skills and interpersonal relationships.

Frontotemporal Dementia

Frontotcmporal dementia (FTD), the most common progressive focal cortical syndrome, is characterized by atrophy of the frontal and anterior temporal lobes. The age of presentation is typically between 45 and 65 years; the onset of FTD is rare after 75 years. It occurs equally in males and females; a significant minority have a positive family history of the disorder. There are two main manifestations of FTD: a behavioral presentation and a language presentation.

The behavioral form of FTD occurs when frontal atrophy predominates and is primarily characterized by deterioration in behavior. Apathy and disinhibition are the most prevalent features. As the disease progresses, a variety of behaviors may develop, including obsessive tendencies, impulsivity, and inappropriate sexual behavior. The patient generally has little insight or concern about his or her condition. In contrast, the language variant occurs when atrophy of the perisylvian regions of the dominant hemisphere predominates. Anomia is the prominent language deficit and deterioration is often to the point of muteness; fluency is variable but the most common presentation is a nonfluent aphasia. Behavioral and other cognitive domains are relatively spared early in this variant and can remain so for decades in some patients. Depressive symptoms are common in both forms of FTD, occurring in 30-40% of patients. However, the presence of significant apathy can make the diagnosis of depression difficult. Active suicidal behavior is rare.

Idiopathic Parkinson's Disease

In addition to the motor manifestations for which Parkinson's disease (PD) is well recognized, there is a significant neuropsychia trie component to this disorder. Depression is the most common psychiatric symptom, with a reported prevalence of approximately 40%. Establishing the diagnosis of depression in patients with PD is complicated by the common presence of comorbid symptoms including dementia, apathy, facial masking, hypophonia, and psychomotor retardation. Despite the high prevalence of depressive symptoms, the rate of completed suicide is no different than that of the general population.

Psychosis is also particularly prevalent. Hallucinations are typically visual and occur in 30% of treated patients, while auditory and olfactory hallucinations are rare. Visual hallucinations are associated with an impaired cognitive state, the use of anticholinergic medications, and impaired vision. However, a dose-dependent relationship between hallucinations and dopamine agonists is unclear. In contrast to the hallucinations associated with Lcwy body disease, patients with PD generally have at least partial insight into the nature of their hallucinations. Delusions are less common, occur in about 10% of patients, and arc often persecutory in nature.

Cognitive changes associated with PD occur to some degree in most patients. Approximately 40% will eventually develop frank dementia, the majority of whom will show comorbid AD pathology. Initial deficits can include cognitive slowing, diminished attention, visual spatial difficulties, and mild executive impairments. Memory problems early in the disease typically represent limitations in retrieval, but in advanced disease memory encoding and storage can become impaired. Primary language abilities are not typically involved until the disease has significantly progressed.

Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB, Lewy body disease) is now estimated to account for 10-20% of cases of dementia in the elderly. It is characterized as a progressive dementing disorder that is strongly associated with cognitive fluctuations, visual hallucinations, delusions, parkinsonian features, and unprovoked falls. Although memory abilities arc impaired, they tend to be less affected than in AD. Visual spatial and executive functions may be worse in DLB patients when compared to patients with AD. The parkinsonian features associated with DLB are relatively mild and less functionally relevant than the cognitive or behavioral problems.

Psychotic symptoms are very common in patients with DLB. Visual hallucinations are present in 50-80% of patients at some point in their disease; they are often described as being well formed and quite distressing to the patient. Auditory hallucinations are less common, occurring in approximately 30% of patients. Olfactory hallucinations have been reported to occur in 5-10%. Delusions are present in up to 50% of patients over the course of their disease, with common themes of misidentification, paranoia, and phantom boarders. Treatment of the psychoses can be challenging secondary to the hypersensitivity to the adverse effects on the motor system from antidopaminergic neuroleptic agents. Depression occurs in patients with DLB at a greater incidence than that of the general population, and is probably at least as common as depression in AD.

Huntington's Disease

Huntington's disease (HD) is a degenerative disorder of autosomal dominant inheritance resulting from an

expanded trinucleotide (CAG) repeat on chromosome 4. Symptoms typically develop during the fourth or fifth decade, initially presenting with neurological ti/ntures, psychiatric features, or both,

Neurologically, patients often demonstrate generalized chorea, motor impersistence, and oculomotor dysfunction. In the juvenile form, the Westphal variant, early parkinsonian features are prominent, as are seizures, ataxia, and myoclonus. Significant cognitive impairment is inevitable and is often present early in the disease. There are features of a subcortical dementia, with significant cognitive slowing and memory disturbance secondary to retrieval rather than encoding deficits. The dementia that gradually ensues is profound and is responsible for the majority of the morbidity associated with this disease.

Psychiatric features are prominent in HD. Personality changes are uniform, most notably apathy, irritability, and aggression. Depression occurs in approximately 40% and can happen at any stage of the disease. The suicide rate is estimated to be greater than 10%, which is higher than in patients with depression and stroke or PD. Psychosis may occur in up to 25% and can manifest as hallucinations, delusions, or both. Psychosis tends to remit as the dementia progresses. Anxiety and obsessive tendencies may also occur.

Wilson's Disease

Wilson's disease (WD), also known as *hepatolenticular degeneration,* is an autosomal recessive disorder that localizes to chromosome 13 and is caused by widespread copper accumulation. Median age of onset is 16-17 years. The rule of thirds applies to irs presentation, with one third of patients each presenting with hepatic, neurological, or psychiatric symptoms. Neurological manifestations are largely extrapyramidal, including tremor, rigidity, dystonia, and chorea. Other symptoms include ataxia, dysarthria, dysphagia, and a fixed smile. Seizures occur in a minority. Dementia may occur but remains relatively mild.

Potential psychiatric symptoms are numerous but most notable are depression and personality changes. Depression occurs in about 30% of patients, whereas suicidal ideation is recognized in about 5-15%. Personality changes are reported in approximately 30-50% of patients, with irritability and aggression being most commonly noted, Psychosis is less common, occurring in approximately 5-10% of cases. Not surprisingly, these psychiatric manifestations tend to occur more commonly in association with primarily neurological WD rather than with primarily hepatic forms.

Diagnosis is suggested by identification of Kayser-Flcischer rings in patients with a clinical picture consistent with WD and confirmed by demonstrating reduced scrum ceruloplasmin and elevated urine copper. MRI studies show abnormal T2 signal in the putamen, pons, thalami, and other structures. Atrophy is commonly present. Treatment consists of copper chelating or depleting agents. Early treatment results in partial improvement of the MRI changes as well as most of the neurological and psychiatric symptoms. However, recovery is usually incomplete when treatment is delayed. Therapy is lifelong.

Tourette Syndrome

Another neurological disorder often associated with psychiatric and behavioral symptoms, including attention deficit, obsessive-compulsive behavior, impulsivity, and mood changes includes Tourette syndrome. Although most cases of Tourette syndrome exhibit no neurologic abnormalities except for motor and phonic tics, in many cases "tourettism" may be associated with structural cortical and subcortical brain lesions (Kwak and Jankovic 2002).

Other

Epilepsy

Approximately 0.5% of the U.S. population carries the diagnosis of epilepsy; approximately 5% of all Americans will have a seizure at some point in their lifetimes. The incidence of epilepsy tends to follow a bimodal distribution. The highest rate is in the first decade, it is low during most of adulthood, and it begins to increase during the seventh decade. Partial seizures are the most common, followed by generalized tonic-clonic seizures.

Seizure disorders are commonly associated with ncuropsychiatric manifestations. It is estimated that more than 60% of patients with epilepsy meet diagnostic criteria for at least one psychiatric disorder during their lifetime. Depression is the most common, with a lifetime risk of 30%. It generally occurs as a chronic, interictal phenomenon, However, in some patients depression is only significant during the preictal or postictal periods; in a minority of patients depression can be the sole manifestation of the ictus itself. Foci in the frontal or temporal lobes appear most likely to he associated with depression; the data suggesting laterality are equivocal. Other prominent psychiatric symptoms associated with epilepsy include panic disorders, anxiety, aggression, and personality disorders.

Psychosis in association with epilepsy is less well described. Interictal psychotic symptoms are more common in patients with temporolimbic foci; these patients primarily display the positive psychopathological phenomena of schizophrenia. In addition, psychosis can be a prominent postictal phenomenon and generally occurs after severe secondary generalized events or runs of complex partial scizutes. The psychosis generally does not develop

until after recovery from the seizures and may take several days to reach maximal severity. Finally, psychosis is rarely the primary manifestation of the seizure ictus. In patients with psychosis secondary to epilepsy, anticonvulsant medications are more efficacious in managing the psychosis than conventional neuroleptics, although a combination of medications from each class may be required.

Traumatic Brain Injury

Traumatic brain injury (TBI) is a leading cause of death and disability in the United States, with an estimated one to two million cases per year. The leading causes of TBI are motor vehicle accidents, falls, assaults, and recreational accidents. The pathologic correlates of moderate and severe traumatic brain injury are numerous, and include penetrating wounds, depressed skull fractures, diffuse axonal injury (DAI), petechial hemorrhages, contusions, hematomas, increased intracranial pressure, edema, and ischemia. The pathology associated with mild TBI is less well understood. Lesions such as subdural hematomas and contusions can be associated with relatively mild clinical deficits. However, other processes likely play a role, including the formation of axonal edema and the release of cytotoxic substances such as cytokines, free radicals, and excitatory amino acids.

There is a lack of consensus as to what clinical findings constitute mild TBI. The occurrence of loss of consciousness is believed by many to not be an absolute requirement. Rather, any traumatic process associated with a generalized alteration in cerebral function, including amnesia (retrograde or anterograde) or alteration in consciousness at the time of the accident, may be associated with a clinical brain injury. In contrast, postconcussive syndrome refers to the constellation of signs and symptoms that persist for weeks to years after the injury.

There is a body of evidence that reports the development of a variety of psychiatric disorders following traumatic brain injury. Depression occurs in up to 50% of patients. Both right and left hemisphere lesions have been implicated. Premorbid psychiatric history, family psychiatric history, level of education, occupational status, and history of abuse of alcohol or drugs may contribute to the development of depression following TBI. Psychosis is less commonly reported in TBI, with a reported incidence between 0,7% and 20%. A recent review suggests a profile typical for patients with TBI-rclated psychosis (Fujii and Ahmed 2002). There is a median latency to onset of 1 year, delusions arc present in more than 75% of patients, and hallucinations occur in almost 50%. Patients with TBI were differentiated from patients with schizophrenia by their relative lack of negative symptoms. Approximately 70% of patients were noted to have abnormal EEGs. When neuropsychological testing was done, almost 90% demonstrated abnormalities. The psychosis in the majority of patients eventually improved, and neuroleptics, followed by anticonvulsants, appeared to be the most efficacious medications.

SPECIAL CONSIDERATIONS

Three conditions—delirium, depression-related cognitive impairment (DRCI}, and catatonia—fall within the border between neurology and psychiatry and thus merit special consideration.

Delirium

Delirium represents one of the most common causes of acute neuropsychiatric disturbances in the hospital setting. It is characterized by impaired attention, fluctuation in mental status, and impaired sleep-wake cycles. Visual hallucinations are particularly common. Delirium is often multifactorial in origin. Advanced age is an independent risk factor for its development, as are a number of other factors including pre-existing CNS disease, metabolic derangements, infections, major surgeries, medications, sleep disruption, and sensory deprivation (especially impaired eyesight). In the elderly, a common comorbidity is an underlying dementia, which may not have been diagnosed previously. In these patients, return to their pre-delirium cognitive state may be prolonged or incomplete despite elimination of the offending agcnt(s). Compared to EEGs of mild to moderate cases of dementia, the EEC of delirium is almost always abnormal, often demonstrating a slow, disorganized background, triphasic waves, or ictal rhythmic patterns suggestive of elcctrographic seizures.

Depression-Related Cognitive Impairment

DRCI refers ro the complex pattern of cognitive impairment secondary to affective disorders such as major depression. Several factors distinguish DRCI from dementia. Patients with DRCI tend to complain of memory and concentration problems, whereas demented patients often deny that problems exist despite impairment that is obvious to their family members. DRCI patients may have a relatively normal bedside mental status examination. There are attention-mediated deficits in memory encoding and spontaneous retrieval, but recognition is generally intact. In AD, attention may be normal although spontaneous retrieval and recognition of memory is impaired. Language is generally well preserved in patients with DRCI, whereas aphasia often occurs with progressive dementias. Unfortunately, the distinction between dementia and DRCI is often difficult to achieve, in part because of the common comorbid nature of these two disorders in elderly patients, If depression appears to be comorbid with a degenerative

disorder, cognition may improve if the depression is adequately treated.

Catatonia

Catatonia is an uncommon but potentially lethal disorder that may be encountered in a general neurological practice. The specific manifestations of catatonia are variable and may include diminished motor function (including waxy flexibility), increased motor function that is characterized by purposeless and spontaneous movements, and mutism. Although the majority of catatonic patients have an underlying affective disorder, approximately 10-20% have significant medical or neurological conditions that contribute to their catatonic state. Stroke, demyelinating disease, encephalitis, trauma, medication, and CNS malignancy are individually associated with an increased risk of catatonia. Medical disorders that can result in catatonia include hyperthyroidism, diabetic ketoacidosis, and Cushing's disease. Treatment with intravenous benzodiazepines or electroconvulsive therapy (ECT) can result in dramatic improvement. The increased risk of mortality in patients with catatonia is secondary to the underlying medical or neurological disotder, poor nutrition and hydration, and infection.

TREATMENT PRINCIPLES

A comprehensive discussion of psychopharmacological interventions in neuropsychiatric disorders is beyond the scope of this chapter. However, there are several general principles that merit discussion. In many ways, the pharmacology of psychiatric symptoms is similar whether the underlying disease is primarily neurological or psychiatric. However, patients with underlying neurological disorders tend to be more susceptible to the adverse reactions of psychotropic medications, particularly to extrapyramidal and cognitive effects. These adverse reactions tend to be minimized, but not always eliminated, with use of the newer generation medications, for example the selective serotonin reuptake inhibitor class of antidepressants and atypical neuroleptics. Advetse reactions are also minimized when low doses are initiated and the rate of increase is slow. However, the minimum dose necessary for therapeutic benefit is often the same in neurological and psychiatric populations, so care must be taken not to discontinue the medication before a therapeutic dose has been attained. Finally, given the large number of medications many neuropsychiatric patients receive for their medical, neurological, and psychiatric disorders, a careful review of potential toxicities and drug interactions should be undertaken before prescribing new drugs. Fortunately, symptoms of both depression and psychosis often respond to pharmaceutical intervention when used appropriately.

ECT is staging a resurgence and, when patients are appropriately screened, may be the most efficacious antidepressant treatment available. Its adverse effects on cognition and memory are well known and thought to be only transient There are few absolute medical or neurological contraindications to ECT. Relative contraindications include increased intracranial pressure associated with mass lesions and recent stroke. Risk associated with cerebral aneurysms is unknown. However, given that the estimated prevalence of unruptured, intracranial aneurysms is up to 5% and that thousands of ECT procedures arc performed annually without evidence of rupture, the risk of aneurysmal rupture secondary to ECT is likely small.

CONCLUSIONS

We are just beginning to understand complex human behaviors in a coherent and verifiable manner. Progress in neuroscience, neurology, and psychiatry is inevitably drawing our specialties closer together, rendering the traditional boundaries increasingly indistinct. Fundamental changes in our practice paradigms are required. Clearly, multiple disciplines working in close collaboration are necessary to diagnose and treat complex behavioral and cognitive disorders.

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Chapter 10
Intentional Motor Disorders and the Apraxias

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In humans the corticospinal motor system together with the motor units can mediate an almost infinite number of movements. Because the purpose of motor systems is to allow people to interact with their environment, the pyramidal motor neurons need to be guided by instructions or programs. For the motor system to deal effectively with the environment, it needs at least two major types of programs: *praxic* and *intentional.* The praxic programs provide the corticospinal system with the knowledge of *how* to make learned skilled movements. The intentional programs provide the corticospinal system with information about *when* to move. In this chapter, we first discuss disorders of the intentional, or "when," system and then we discuss praxic, or "how," system disorders.

INTENTIONAL (WHEN) DISORDERS

Unlike the praxic systems that program the temporospatial aspects of a movement, the intentional systems provide instructions about goals. There are four types of intentional instructions: (1) when to start a movement; (2) when not to start a movement; (3) when to continue or sustain a movement or posture; and (4) when to stop or complete a movement.

The inability to initiate a movement in the absence of a corticospinal or motor unit lesion is termed *akinesia. Hypokinesia* is a delay in initiating a response. The inability to withhold a response to a sensory stimulus is called *defective response inhibition.* The inability to sustain a movement or posture is called *motor impersistence,* and the inability to stop a movement or an action program is termed *motor perseveration.*

In the next section, we describe each of these intentional disorders, including subtypes of each category, and we discuss bow to examine patients for these disorders. We also discuss the pathophysiological and neuropsychological mechanisms that may be associated with these disorders.

Akinesia

An organism might fail to initiate a movement for many reasons, but comprehension, attentional, perceptual, and sensory disorders that lead to a failure of movement initiation should not be termed *akinesia.* Dysfunction of the motor system, including the motor unit (lower motor neuron, myoneural junction, and muscle) and the upper motor neuron (pyramidal or corticospinal system) may also be associated with a failure to initiate a movement. Disorders of these systems, however, cause weakness rather than akinesia, and akinesia is defined by an initiation failure that cannot be attributed to dysfunction in the corticospinal system or the motor units. Akinesia is caused by a failure of the systems that activate these corticospinal motor neurons.

There are three major methods by which a clinician can distinguish an akinesia from extreme weakness caused by dysfunction of the motor systems. One is behaviotal, the second depends on the pathological locus of a lesion, and the third uses stimulation of the corticospinal system and recording of motor evoked potentials. Regarding the behavioral method, certain types of akinesia are present under certain sets of circumstances and absent in others. If one can demonstrate that a patient makes movements in one set of circumstances and not in the other, then one

cannot attribute this failure to move purely to dysfunction in the motor system. However, if the akinesia is not limited to a set of circumstances but is global, then one may have to depend on brain imaging (e.g., computed tomography or magnetic resonance imaging), pathology, or physiological techniques such as magnetic stimulation to demonstrate that the brain lesion did not involve the motor system.

Types of Akinesia

There arc several forms of akinesia. For ease of discussion, we have divided them into three major categories: (1) body part, (2) action space, and (3) stimulus-response conditions. These three categories may be interactive.

1. Body part: Akinesia may involve the eyes, the head, a limb, or the total body.
2. Action space: Akinesia of the limbs, eyes, or head may depend on where in space the body part is moved or in what direction it is moved. There may also be a hemispatial or directional component to the akinesia. In *directional akinesia,* there is a reluctance to move in a specific spatial direction usually contralateral to a hemispheric lesion. For example, horizontal gaze palsy is a form of directional akinesia. Similarly, there may be directional akinesias of both head and arms that results in a reluctance to move these in a contralesional direction. *Spatial akinesia* has been described for the arm where independent of direction, an arm that fails to move or has decreased movements in contralesional hemispacc, as defined by the mid-sagittal plane of the body, can move in ipsilesional hemispace. Whether hemispatial akinesia that is totally independent of direction has been described for the eyes or head is not known.
3. Stimulus-response conditions: Movements can be produced in response to an external stimulus or they can occur in the absence of an external stimulus. We term movements that arc in response to a stimulus *exogenously evoked motor activation (exo-evoked),* and those that appear to be spontaneous *endogenously evoked activation (endo-evoked).* A patient may have both exo-cvoked and endo-evoked akinesia, which we term *mixed akinesia.*

Testing for Akinesia

When testing for akinesia, one may want to assess the various body parts discussed earlier. To determine whether a patient has endo-evoked akinesia, one has to observe spontaneous behavior or the lack of it. Patients with endo-evoked akinesia often have symptoms of *abulia,* an uncommon lack of spontaneous, goal-directed behavior that is seen predominantly with lesions of the basal ganglia and the frontal lobes. Patients with endo-evoked akinesia, despite having reduced spontaneous activity, may respond normally to external stimuli. For example, endo-evoked akinesia is usually associated with Parkinson's disease. The patient with severe Parkinson's disease will often fail to move spontaneously; however, when stimulated, such a patient may show almost normal movements (paradoxical kinesia).

When a patient has good strength and spontaneously moves but fails to move to a specific stimulus, the failure to move in response to a stimulus is often attributed either to an elemental sensory defect or to sensory inattention and neglect. Although sensory defects and sensory neglect may be responsible for a failure to respond, exo-cvoked akinesia is often confused with sensory defects and sensory neglect. The basic testing method used for dissociating sensory defects and sensory neglect from exo-evoked akinesia (motor neglect) is the *crossed response task.* This was first tested in monkeys by training a monkey to respond with its right arm to a left-sided stimulus and to respond with its left arm to a right-sided stimulus. If the animal failed to respond to a contralesional stimulus using the ipsilesional arm, it was considered to have sensory neglect. However, if the animal demonstrated no weakness of the contralesional extremity bur failed to move the contralesional extremity in response to ipsilesional stimuli, it was considered to have exo-evoked akinesia, or motor neglect. The crossed response task can be used not only to test the limbs but also to test the eyes, the head, or the whole body.

When assessing for akinesia, as a function of action space, one should test both directional and hemispatial movements of the eyes, the head, and the limbs. One may want to determine whether the directional or hemispatial movements are endogenously or exogenously evoked. When attempting to determine whether there is an endo-evoked directional akinesia of the eyes, one can observe the spontaneous eye movements and see whether there is ipsilesional deviation of the eyes or a failure of the patient to spontaneously look into contralesional space. To determine whether a patient has an exo-evoked directional akinesia of the eyes, one can use a modification of the crossed response paradigm in which the patient must look cither toward (ipsilesional direction) or away (contralesional direction) from ipsilesional and contralesional stimuli. For example, the examiner stands directly in front of a patient and asks the patient to fixate on the examiner's nose. The examiner raises both hands to eye level and keeps one hand in the patient's right visual field and the other in the left visual field. The patient is instructed to look away from the moving hand if the hand moves downward and toward the hand if it moves upward. When the contralesional hand is moved upward, a failure to look at the contralesional hand (moving in a contralesional direction) may be related to either a hemianopia, sensory neglect, or a directional akinesia. However, when the ipsilesional hand moves downward, a failure to look toward the contralesional hand suggests an exo-evoked directional akinesia of the eyes (Butter et al. 1988).

To test for directional and hemispatial akinesia of the head or an arm, one can use similar tests. To test fot a directional bias of an arm (similar to eye deviation), one can ask the patient to close his or her eyes and point to his or her sternum. The subject is then asked to point with his or her index finger to a point in space perpendicular to the sternum (e.g., the midsagittal plane). Patients with a motor (intentional) bias will point toward their lesioned hemisphere.

A task was developed that can be used to test for endo-evoked directional limb akinesia. In our modification, a patient is blindfolded and small objects such as pennies are randomly placed in wells that are scattered on a board in both body hemispatial fields within arm's reach. The patient is asked to retrieve as many pennies as possible. The task is considered endogenously evoked because the patient cannot see the pennies and must initiate exploratory behavior in the absence of an external stimulus. Patients with an endo-evoked directional akinesia of the arm may fail to move their arm fully into contralateral hemispace and explore for pennies.

To test for directional and hemispatial akinesia, one can also use one of the several video camera paradigms that allows one to dissociate deficits of perception and attention from those of intention and action (Coslett et al. 1990). In these paradigms, patients can see only their hand bisecting a line through a TV monitor. In this technique, the line (where the action takes place) can be positioned in contralesional or ipsilesional hemispace and the TV monitor can be independently placed in either hemispace or the image can be reversed. If, as demonstrated by Coslett et al., abnormal performance on the line bisection is not affected by the spatial position of the monitor or the reversal of the image on the monitor, it suggests that the patient has a hemispatial or directional akinesia of the arm.

Hypokinesia

Many patients with milder defects in their intentional ("when") systems may not demonstrate a total inability to initiate a response (e.g., akinesia); rather their intentional disorder may be primarily a delay in initiating a response. We have termed this delay *hypokinesia.* This hypokinesia may be defined in a manner similar to akinesia. Because a teaction time paradigm is required to detect hypokinesia, it cannot be divided into exo-evoked and endo-evoked subtypes.

Hypokinesia can be seen both in the limbs and in the eyes and may be either independent of direction or directionally specific such that when making directional movements, there is a greater delay initiating movements in a contralesional direction than there is initiating movements in an ipsilesional direction. Hypokinesia can also be hemispatial such that movements with the same limb may be slower in one hemispace than they are in the other hemispace.

Testing

The same patadigms that are used to test for akinesia of the eyes and limbs can be used to test for hypokinesia. Although some patients with hypokinesia have such markedly slowed initiation times that hypokinesia can easily be detected, others have more subtle defects and reaction time paradigms may be needed to observe their defects. Reaction times can be slowed for various reasons including impaired attention, bradyphrcnia, or hypokinesia. To detect hypokinesia, one should use simple reaction times that do not require cognition and therefore cannot be impaited by bradyphrcnia. Similarly, to test for hypokinesia, one has to use stimulus parameters that ensure that inattention cannot masquerade as hypokinesia.

Hypometria

Movements of a decreased amplitude are called *hypometria.* Hypometria may be directional or hemispatial or it may involve specific body parts such as a limb or the eyes. For example, as mentioned earlier, a patient with a right hemisphere lesion may at first be unable to saccade to the left. However, as the patient recovers, he or she may be delayed at initiating a leftward saccade or may make multiple small (hypometric) saccades. Hypometria may be related to akinesia or impersistence.

Motor Extinction

Patients with sensory extinction may be able to detect a single stimulus on the contralesional side of thcit body, but when presented with a simultaneous distracting stimulus, they may then be unaware of the contralesional stimulus. To test for milder forms of intentional deficits including akinesia and hypokinesia, one can use a similar extinction principle. For example, one patient made unilateral movements well and did not have sensory extinction. However, when he had to make bilateral simultaneous movements, he either did not move his contralesional arm or moved it after a prolonged delay.

Motor Impersistence

Motor impersistence is the inability to sustain a motor act. *Persistence* is the intentional equivalent of attentional vigilance, and impersistence may be analogous to increased attentional distractibility. Like akinesia, impersistence can be associated with various body parts including the limbs and eyes. However, impersistence may also include other body parts such as the eyelids, jaw, and tongue. Like akinesia, it may also be directional or hemispatial.

Testing

When testing for impersistence of midline structures, one can ask patients to keep their eyes closed for 20 seconds or to keep their mouth open or protrude their tongue for 20 seconds. Patients who can successfully persist at these acts may be further taxed by asking them to persist at two movements simultaneously. For example, they may be asked to both keep theit eyes closed and keep theit mouth open for 20 seconds.

Limb impersistence can be tested by asking a patient to maintain a posture such as keeping an atm extended for 20 seconds. Because limb impersistence can be hemispatial, one may want to test each limb in its own and in its opposite hemispace. i leinispatial impersisrence, in the absence of directional impersistence, has not been tepotted tor the bead or eyes, perhaps because it has never been tested. One could ask a patient to sustain upgaze (or downgaze) for 20 seconds while the eyes are directed either toward the right or toward the left. If the patient can maintain gaze in one hemispace (e.g., the right), but cannot do so in the other (e.g., left), it would suggest that the patient has hemispatial impersistence of the eyes. If a patient has a directional impersistence of the eyes, he or she may be unable to maintain his ot het eyes directed to either the right or the left hemispace, and therefote one may not be able to test for hemispatial impersistence. To test for directional impersistence of the eyes, one tequests the patient to look either to the left or to the right for 20 seconds. A similar procedure can also be used to test the head for directional impersistence.

Defective Response Inhibition

Defective response inhibition is defined as responding when no response of that body part is required. Defective response inhibition can be seen in the eyes, head, ot limbs. Directional defective tesponse inhibition has been reported for the eyes, but not for the limbs or head. However, it may never have been tested. Similarly, hemispatial defective response inhibition has not been reported; however, attain ll may never have been lusted.

Testing

There are several forms of defective response inhibition. **In** one **form,** when using the crossed response task, the ipsilesional limb moves when the correct response was a movement of the contralesional limb, or the eyes or head move in an ipsilesional direction when the correct response was a movement in the contralesional direction. This type of defective response inhibition may be termed *motor {limb* or *directional) allochiria* or *ipsilesional response disinhibition.* However, before one terms such a condition *motor allochiria* or ipsilateral disinhibition, one must be certain a perceptual problem has not induced the abnormal behavior, in which case it is not defective tesponse inhibition but true *allochiria* or *allesthesia.* In the second form of defective response inhibition, when performing the crossed response task, the patient's contralesional limb moves when it should not move or movement is in a contralesional direction when there should be either no movement or movements should have been in an ipsilesional direction. We call this *contralesional response disinhibition.* Contralesional response disinhibition can also be exogenously ot endogenously evoked. If a patient is able to understand complex instructions, the best way to test for both ipsilesional and contralesional exo-evoked response disinhibition of the limbs is to insttuct the patient to move or lift the opposite hand (off a table) when a hand is sttoked downward and to move the same hand as touched when it is sttoked upward. Before testing for the different forms of defective response inhibition, it is important to establish that the patient does not have a perceptual disorder and can correctly detect stimuli and recall instrucrions. If, when the contralesional hand is brushed up, the patient moves the ipsilesional atm rather than the contralesional, the patient has ipsilesional disinhibition ot motor allochiria. If, when the contralesional arm is brushed downward (which is a signal to move the ipsilesional arm), the contralesional arm is moved instead of the ipsilesional arm, the patient has a contralesional exo-evoked limb disinhibition. If this happens with both arms, the patient has bilateral exo-evoked disinhibition.

Patients with exo-evoked limb disinhibition may also fail on the types of go-no-go tasks described by Lufia. Fot example, the patient may be instructed to put up two fingers when the examiner puts up one finger and to put up no fingers if the examiner puts up two fingers. If the patient mimics the examiner such that when the examiner puts up one fingct, the patient puts up one finger and when the examiner puts up two fingers, the patient puts up two fingers, the patient has *echopraxia* (a third form of defective response inhibition).

A paradigm similar to that used for directional akinesia of the eyes can be used to determine wherher there is an ipsilesional, or a contralesional disinhibition of the eyes or head. The patient is told to fix the eyes on the examinet's nose. If either hand moves down, the patient is to direct the eyes to the opposite hand, and if the hand moves up, the patient is to direct the eyes to the hand that moved. If, when the hand in the patient's contralesional visual field moves up and instead of looking at that hand, the patient looks at the opposite hand, an ipsilatetal directional disinhibition is present. If, when the contralesional hand moves down, the patient looks at this hand ratber than looking in the opposite direction, a contralesional directional disinhibition (ot *visual grasp)* is present. This directional disinhibition or visual grasp may also be bilateral.

Motor Perseveration

Perseveration is when a patient incorrectly repeats a prior response. Although there are many types of perseveration and several classification systems, there seems to be a spectrum between cognitive and motor perseveration. Cognitive perseveration is when one uses a previously used cognitive strategy inappropriately for a new or different task. Sandson and Albert (1987) call this "stuck in set" perseveration. Luria discussed two types of motor perseveration, In one type of motor perseveration, the patient is unable to switch to a different motor program and repeats the prior program even though the task requirements have changed. Luria (1965) calls this *inertia of program action* and Sandson and Albert (1987) call this *recurrent perseveration.* In rhe second type, the patient continues to perform a movement even though the task is completed, but when instructed, the patient can switch to other movements. Luria (1965) called this *efferent perseveration,* This is similar to Sandson and Albert's (1987) *continuous perseveration.*

Both continuous and recurrent perseveration are forms of motor perseveration and may represent defects in the when or intentional system. This is a defect of when to stop a motor program. Patients may show motor (efferent) perseveration on drawing and copying tasks. For example, a patient can be asked to draw or copy a cube. Patients with motor perseveration will repeatedly draw over lines. When performing a cancellation task, patients with motor perseveration will perform multiple cancellations of the same target. When asked to draw or copy a double loop, patients with motor (efferent) perseverarion will draw more than two loops.

Pathophysiology of Intentional or When Disorders

Right-Left Asymmetries

In our introductory discussion, we advanced the hypothesis that there are generally two major types of programs that control the motor system, the how or praxis system and the when or intentional system. As we discuss in the next section, in right handers disorders of the praxis production system, as evidenced hy ideomotor apraxia (IMA), are almost always associated with left hemisphere dysfunction (Heilman and Rothi 1985). Although intentional disorders are often associated with bilateral hemispheric lesions, when the lesions that induce intentional disorders are unilateral, they arc more commonly associated with right hemisphere lesions. For example, limb akinesia is more often associated with right hemisphere lesions than left hemisphere lesions. The intentional defects associated with right hemisphere dysfunction, however, are often nor limited to the left limb. Using a reaction time paradigm, right hemisphere infarctions are associated with a greater slowing of reacrion times than left hemisphere infarctions even when rhe ipsilcsional arm is used and lesions arc matched for size. These patients may have hypokinesia.

Rehabilitation specialists have noted that it is more difficult to rehabilitate patients with left hemiplegia than those with right hemiplegia. In addition, patients with left hemiplegia are more likely to develop decubiti and pulmonary emboli. Both of these conditions may be related to a global akinesia associated with right hemisphere dysfunction. Directional kinesia of the limbs as determined by tasks such as those used by Heilman and Rothi (1985) were also more often reported with right hemisphere lesions. The case of hemispatial limb akinesia also had a right hemisphere lesion. Alrhough impersistence is often associated with bilateral hemispheric dysfunction, when it is associated with unilateral hemispheric disease, it most commonly occurs with right hemisphere lesions. Defective response inhibition of the eyes or arms may be seen with bilateral hemispheric dysfunction, but when it is seen with unilateral hemispheric disease, it has been associated with right hemispheric dysfunction. Lasdy, motor (or continuous) perseveration has also been reported to be associated with right hemisphere dysfunction.

The term *dominance* implies that one hemisphere contains specialised processing systems or representations (programs) cither that the other hemisphere does not contain or that are less developed. The nondominant hemisphere therefore by itself is not fully competent to mediate a specific activity. Although our discussion has provided evidence that the right hemisphere may be dominant for inrentional control of the motor systems, this evidence is indirect. However, several studies in normal subjects provide further evidence for right hemisphere intentional dominance.

Although the anatomic and physiologic basis for the right hemisphere's special role in intentional activity is unknown, the limbic system, which plays a critical role in motivation, has two major outputs to the cortex: one from the hippocampus and the other via the cingulate gyrus. Although bilateral medial temporal lobe lesions are associated with profound amnesia, severe motivational or intentional disorders have not been associated with these lesions. However, bilateral medial hemispheric lesions that involve the cingulate gyrus are associated with a profound intentional disorder termed *akinetic mutism,* suggesting that the cingulate gyrus provides motivational information to ncocortical areas. The right cingulate gyrus has more input into the neocortex than the left.

Intrabemispheric Networks

The intrahemisphcric networks that are important in mediating intention have also not been fully elucidated. However, studies of patients with focal lesions and studies of monkeys suggest that the frontal lobes may play a critical role in intentional activity. For example, motor neglect of

the limbs has been reported in monkeys from dorsolateral frontal lesions and although the ipsilesional limbs are not as akinetic as the contralcsional limbs, there is a hypokinesia of the ipsilesional limbs as measured by reaction times. Medial frontal lesions are also associated with limb akinesia. An ocular directional akinesia can also be seen with dorsolateral frontal lesions, and a directional limb hypokinesia may be seen with frontoparietal lesions (Heilman and Rothi 1985). In addition, motor impersistence is most frequently seen with dorsolateral frontal lesions defective response inhibition of the eyes is seen with dorsolateral frontal lesions, and defective response inhibition of the limbs is associated with medial frontal lesions. Lastly, motor perseveration may also be associated with frontal lesions.

The frontal cortex has strong projections to the striatum. The dorsolateral frontal lobe projects to the caudate, the supplementary motor area (SMA) projects to the putamen, and the cingulate gyrus projects to the ventral striatum. The striatum projects to the internal portion of the globus pallidus and the pars reticularis of the substantia nigra, which in turn projects to thalamic nuclei (e.g., VA, VL, and Ml)). These thalamic nuclei project back the same area of the frontal cortex where this frontal, basal ganglia, and thalamic loop was initiated including the dorsolateral frontal lobe, SMA, and cingulate gyrus.

Based on the previous discussion, it should not be surprising that intentional disorders may be associated with diseases that affect both the basal ganglia and the thalamus. The most common disorder that induces akinesia is Parkinson's disease. The akinesia associated with Parkinson's appears to be induced by a loss of the dopaminergic neurons that project to the striatum. Dopamine antagonists may also produce akinesia and dopamine agonists may reverse this akinesia. Thalamic lesions of VA/VL or the medial nuclei such as centromedian parafascicularis can also induce akinesia.

Not only do diseases that affect frontal lobe cortex, basal ganglia, and thalamus induce intentional disorders, but these disorders, especially akinesia, are also associated with diseases that affect the white matter that connects the frontal lobes with these subcortical structures. Therefore akinesia is often associated with white matter diseases such as arteriosclerotic encephalopathy (Binswanger's disease or multiple lacunar infarcts), advanced multiple sclerosis, and hydrocephalus.

Lastly, akinesia has also been reported with temporoparietal lesions, in both monkeys and humans. Although the akinesia associated with basal ganglia diseases such as Parkinson's disease appears to be endogenously evoked, the akinesias associated with frontal and parietal cortical dysfunction appear to be exogenously evoked.

Based on the pathological evidence cited, one can postulate that the frontal lobes play a central role in human's intentional network. The dorsolateral frontal lobes receive projections from both the parietal lobe, which is a polymodal association cortex, and the multimodal primary association cortices. The frontal lobes also have strong reciprocal connections to the cingulate gyrus, the medial thalamic nuclei, and nonreciprocal connections with the striatum, which project to the globus pallidus and substantia nigra and from there to the thalamus and hack to the cortex, as previously described.

The frontal lobe's connections with the inferior parietal lobe may provide the frontal lobe with stored knowledge (e.g., semantic and spatial information) and the limbic connections may provide the frontal lobe with motivational information. Unimodal sensory and polymodal sensory association areas may provide the frontal lobe with information about external stimuli that may call the organism to action. Afferents from the mesencephalic and thalamic reticular system may be important for modulating arousal and activation.

Physiological studies have provided support for the role of the frontal lobes in intention-motor activation. Neurons in the dorsolateral frontal lobe of monkeys who were trained to make a rapid movement to a stimulus were recorded. When the animal was prepared to make a movement, the cells were active. When the animal was **not** prepared to initiate a response, as determined by a delay in response time, these cells were less active. Stimulus parameters did not affect these cells' activity, suggesting that these cells were intentional neurons. The dorsolateral frontal lobes contained neurons that discharge before purposeful saccades. Lesions of the frontal lobe destroy these intentional cells, and in their absence, there is defective activation of the motor neurons.

The manner in which these frontal lobe intentional neurons influence the motor neurons has not been definitely established. However, as discussed, the dorsolateral frontal lobe and the thalamic areas such as the ventrolateral, dorsomedial, and intralaminar nuclei share anatomic connections with each other and form a network with the basal ganglia, premotor, and motor cortices. Because lesions in these structures (dorsolateral frontal lobe, basal ganglia, ventrolateral thalamus, medial thalamus) and premotor areas (i.e., SMAs) induce akinesia, Watson, Valenstein, and Heilman (1981) posited that this network mediates intentional activity.

We do not know whether the different forms of intentional activity we have discussed arc mediated by the same network or whether different systems or subsystems mediate different forms of intentional activity. Some of the intentional disorders we discussed may be related to the "release" of phylogenctically more primitive systems. For example, neurons in the dorsolateral frontal lobes have a role in the preparation of saccadic eye movements. One would predict that unilateral frontal lobe lesion would induce a directional akinesia of the eyes. However, patients with frontal lobe lesions have been reported unable to saccade away from a stimulus before they made a saccade toward the stimulus (defective response inhibition or

visual grasp). Directional akinesia and defective response inhibition would appear to be mutually incompatible behaviors, but a patient with a unilateral frontal lobe lesion was assessed using a crossed response task. Initially the patient showed both contra lesional sensory neglect and a directional contralcsional akinesia. Subsequently, the patient was able to detect contralcsional stimuli and move his eyes in a contralesional direction. However, in the crossed response task, when presented a contra-lesional stimulus that was a signal to move the eyes in an ip si lesional direction, the patient often incorrectly responded by first making a contralesional saccade before making an ipsilesional saccade. **Although** it has been demonstrated that neurons in the dorsolateral frontal lobe have a role in preparing for a saccade, collicular neurons can perform a similar function. Perhaps after frontal lobe damage, which initially was associated with a directional akinesia, recovery was mediated by the colliculus. Activity of the colliculus, however, unlike the frontal lobes, cannot be altered by task instructions. Perhaps normally the dorsolateral frontal lobes exert an inhibitory influence on the colliculus, which is absent aftct ftontal lesions. This inhibitory effect cannot be direct because no frontal lobe eye field cells have been reported that arc tonically active except during saccades. However, the pars reticulata of the substantia nigta projects to the colliculus and has tonic activity. The frontal lobe may influence the substantia nigra through its connections to the caudate. A similar release of inhibition may also be responsible for other nonocular defects whereby the brain-damaged patients cannot either withhold or terminate responses.

Clinical Pathology

Intentional disotders can be caused by any neurological disease that impairs the systems we have discussed. Neoplasms of the frontal lobes, the cingulatc corpus callosum region and colloid cysts of the third ventricle may all be associated with intentional disorders. However, vascular diseases including multiple lacunae and Binswanger's disease may be the most common cause of intentional disotders. Infarctions of the thalamus and ventral tegmental areas may also cause intentional disorders. Hydrocephalus and drugs that block dopamine receptors such as neuroleptics may also cause intentional disorders. Head trauma and central nervous system infections are other common causes of intentional disorders. Some infections and inflammatory diseases that must be considered include acquired immunodeficiency syndrome, syphilis, Lyme, prion diseases such as Creut/ieldt-Jakob disease, chronic meningitis (e.g., fungal, sarcoid), Whipple's, and progressive multifocal leukoencephalopathy. There are many degenerative diseases that also may present with intentional disorders. These include Pick's disease, and Pick's disease without Pick's bodies (frontotcmporal dementia), olivopontocerebellar atrophy, progressive supra-nuclear palsy, corticobasal degeneration, striatonigral degeneration, Shy-Drager syndrome, Parkinson's disease, Huntington's disease, Behcet's disease, and ftontal lobe dementia associated with motor neuron disease. De-myelinating diseases such as multiple sclerosis and the leukodystrophies may also have intentional components. Lastly, there are several toxic/metabolic diseases that may he associated with intentional disorders. These include chronic alcoholism with alcohol dementia and Marchiafava-Bignami disease, vitamin Bj2 deficiency, hypothyroidism, anoxia, hypoparathyroidism with basal ganglia calcification, Wilson's disease, and status dysmyelinatus (iton deposition in the basal ganglia with rigidity, athetosis, and mental degeneration).

PRAXIC (HOW) **DISORDERS**

The praxic programs provide several types of instructions:

1. How to position one's limb when petfotming **skilled** movements, including working with tools and objects.
2. How to move the limb in space or the spatial trajectory of the skilled movement. This program may contain both alloccmric (in relation to the object upon which the organism is acting) and egocentric (in relation to the organism's own body) information.
3. How to orient the limb toward the target of the limb's action,
4. How tapidly to move in space, or the timing of a skilled movement.
5. How to imitate a movement.
6. How to solve mechanical ptoblems.
7. How to order components of an act to achieve a goal.

Disorders of this how ot praxic system are called apraxias (Table 10.1). A loss of the ability to make precise and independent movement (i.e., a loss of deftness) is called *limb-kinetic apraxia.* Failure to correctly position a limb, move the limb correctly in space, and properly orient the limb is called *IMA.* Patients with IMA also make temporal errors. There are patients, however, who perform imitation worse than they gesture to command. **These** patients have what is called *conduction apraxia.* Patients with ***disassociation*** *apraxia* may be impaired when attempting to perform skilled movements in response to stimuli in one modality (e.g., verbal command) but be able to cotrectly perform movements in response to stimuli of a different modality (e.g., seeing a tool). The inability to solve mechanical problems is termed *conceptual apraxia.* Lastly, the inability to cotrectly order a series of movements is termed *ideational apraxia.* In the following sections, we discuss each of these disorders.

Although limb apraxia is defined as an inability to correctly perform skilled movements with a limb, when

Table 10.1: Error types associated with each of the apraxii: syndromes

Apraxia type	*Postural*	*l'.<i»t»iaitd orientation*	*Movement*	*Discrimination comprehension*	*Imitation*	*Series*	*Mechanical knowledge*
Ideomotor							
Anterior	-H-+	+++	+++	—	++		—
Posterior	+++	+++	+++	+++	++		
Conduction	+	+	-I-	—	+++	—	—
Dissociation	+++-	+++	+++	—	—	—	—
Ideation	—	—	—	—	—	Mr	—
Conceptual	—	—	—	—	—	—	

Note: This tahle lists the error types that define each apraxia syndrome. However, often patients may have more than one apraxic disorder. +++ = severe; ++ = moderate; + = less severe.

this inability to perform skilled movements is not caused by sensory loss or by more elemental motor disorders such as weakness, tremors, dystonia, chorea, ballismus, athetosis, myoclonus, ataxia, and seizures. Patients with severe cognitive, memory, motivational, and attentional disorders may also have difficulty performing skilled acts. Whereas the presence of these disorders does not preclude that the patient also has apraxia, before diagnosing apraxia, the clinician should be certain that these behavioral disorders do not fully account for the patient's inability to perform skilled acts.

Apraxia often goes unrecognized and there are several possible reasons for poor recognition. The apraxia associated with hemispheric injury such as strokes and trauma is often associated with an injury to the dominant hemisphere. Thus these patients often have a hemiparesis of theit preferred arm and hand. When these patients attempt to perform skilled acts with their nonpreferred arm and find that they are impaired, they may attribute their difficulty to premorbid clumsiness of the nonpreferred arm. However, even when these patients are able to use their preferred arm, apraxic patients may be anoSOgnosic for their deficits. Unfortunately, many health professionals also do not test for limb apraxia, and they are not fully aware of the nature of errors associated with apraxia.

Limb apraxia has been noted to be a heterogeneous group of disorders with both different clinical pictures and anatomic substrates. In the following sections, we discuss several forms of limb apraxia. These types are defined by both the nature of errors made by the patient and the means by which these errors are elicited. Liepmann {1920) was the first to systematically study limb apraxia. He discussed three types of limb apraxia: melokinetic (or limb kinetic), ideomotor, and ideational. In addition to describing these forms of apraxia, we also discuss three other forms of apraxia which we have called *disassociation apraxia, conduction apraxia,* and *conceptual apraxia.* Although dressing and constructional apraxia are disorders of learned skills that do involve limb use, these disorders are often associated with neglect and visual perceptual disorders, so we do not discuss these here.

Limb-Kinetic Apraxia

Patients with limb-kinetic apraxia demonstrate a loss of deftness or the ability to make finely graded, precise, independent finger movements.

Testing

There are several means by which deftness can be tested. In most patients, both hands should be tested, A small flat object such as a dime may be placed on a table and the patient is asked to pick up the dime. Patients with limb-kinetic apraxia will not be able to use a pincher grasp, which requires independent movements of the thumb and index finger, to pick up the dime. Another aspect of deftness can be tested by measuring rapid finger tapping and by tests that use a pegboard (e.g., Purdue). We have found that one of the most sensitive bedside tests is asking patients to rotate a coin between their thumb, index finger, and middle finger as rapidly as they can. Patients with limb-kinetic apraxia have trouble rotating the coin.

Pathophysiology

Limb-kinetic apraxia most often occurs in the limb contralateral to a hemispheric lesion. Monkeys with lesions confined to the corticospinal system do not show severe weakness but have difficulty making independent finger movements including the pincher grasp. In the clinic, however, patients with limb-kinetic apraxia often have injured their premotor cortex. Recent studies have revealed that when limb-kinetic apraxia is induced by injury to the hemisphere opposite the preferred hand, limb-kinetic apraxia may also be present in the nonpreferred hand, suggesting that the dominant hemisphere may in part have ipsilateral projections.

Ideomotor Apraxia (IMA)

IMA is probably the most common type of apraxia. As discussed in a later section, when patients with

IMA perform learned skilled movements including the performance of pantomimes, imitations, and using actual objects, they make spatial and temporal errors.

Testing

When possible, both the right and the left arm and hand should be tested. When one arm is weak or has another motor disorder that would preclude testing, the nonparctic limb should be tested. Testing of praxis involves selectively varying input as well as varying task demands, When possible, the same items should be used for all subtests. First, patients should be requested to pantomime to verbal command (e.g., "Show me how you would use a bread knife to cut a slice of bread"). Both transitive (i.e., using tools and instruments) and intransitive gestures (i.e., communicative gestures such as waving good-bye) should be tested. Independent of the results of the gesture to command tests, patients should be asked to imitate the examiner performing both meaningful and meaningless gestures. The patient should also be allowed to hold actual tools or objects and to demonstrate how to use the tool or object. In addition to having a patient pantomime to a verbal command, the examiner may want to show the patient pictures of tools or objects and have the patient pantomime in response to these stimuli. The examiner may also want to show the patient real tools or the objects that tools work on (e.g., nail) and without having the patient hold the tool or object request that the patient pantomime the action associated with the tool or object. It may be valuable to see whether the patient can name or recognize transitive and intransitive pantomimes made by the examiner and discriminate between well and poorly performed pantomimes.

When performing skilled acts, patients with IMA make ptimarily spatial and temporal production errors. Spatial errors can be divided into several subtypes including postural (or internal configuration), spatial movement, and spatial orientation. Regarding postural errors, Goodglass and Kaplan (1963) noted that when apraxic patients are asked to pantomime, they often used a body part as the tool. For example, when patients with IMA are asked to pantomime using a pair of scissors, they may use their fingers as if they were the blades. Many normal subjects make similar errors and it is important that the patient be instructed not to use a body part as a tool. Unlike normal subjects who imptove with these instructions, patients with IMA may continue using their body patts as tools (Raymer et al. 1997). When not using their body parts as tools, patients with IMA will often fail to cortectly position their hands as if they were holding the tool or object.

When norma] subjects are asked to use a tool, they will orient that tool to an imaginary target of that tool's action. Patients with IMA often fail to correctly orient their foreiimbs to an imaginary target. For example, when asked to pantomime cutting a piece of paper in half with scissors, rather than keeping the scissors oriented in the sagittal plane, cither the scissors may be oriented laterally (Rothi et al. 1988) or the scissors may not maintain any consistent plane of movement.

When patients with IMA attempt to make a learned skilled movement, they will often make the correct core movement {e.g., twisting, pounding, cutting), but the trajectory of their limb through space is often incorrect (Rothi et al. 1988; Poizner et al. 1990). These spatial trajectory errors are caused by incorrect joint movements. Apraxic patients will often stabilize a joint that they should be moving and move joints they should not be moving, For example, when pantomiming the use of a screwdriver, patients with IMA may rotate their arm at the shoulder and fix their elbow. Shoulder rotation moves the hand in arcs when the hand should be rotating on a fixed axis. When multiple joint movements must be coordinated, patients with apraxia may be unable to coordinate multiple joint movements to get the desired spatial trajectory. For example, when asked to pantomime slicing bread with a knife, the shouldet and elbow joints must be alternately flexed and extended. When the joint movements are not well coordinared, these patients may make primarily chopping or stabbing movements.

Poizner et al. (1990) have noted that patients with IMA may also make timing errors including a long delay before initiating a movement and brief multiple stops (stutteting movements). When normal subjects make a curved movement, they reduce the speed of their movement, and when they move in a straight line, they increase the speed of their movement. Patients with IMA, howevet, do not demonstrate a smooth sinusoidal hand speed when performing cyclic movements such as cutting with a knife.

Path op bysiology

In right-handed individuals IMA is almost always associated with left hemisphere lesions, but in left-handed people, IMA is usually associated with right hemisphere lesions. IMA is associated with lesions in a variety of structures including the corpus callosum, the inferior parietal lobe, and the premotor areas. IMA has also been reported with subcortical lesions that involve the basal ganglia and white matter. We discuss each of these anatomic areas and also attempt to develop a model of how the brain mediates learned purposive movements.

Lesions of the Corpus Callosum. A male patient was described by I.iepmann and Mass (1907) with a right hemiparesis from a lesion of the pons. The patient also had a lesion of his corpus callosum. This patient was unable to correctly pantomime to command with his left atm. Because this patient had a right hemiparesis, his right hand could not be tested. Since the work of Broca, it has been known that the left hemisphere of right-handed people is dominant for language. The patient's inability to

p.um>mime could lie associated with a disconnection between language and motor areas such that the left hemisphere that mediates comprehension of the verbal command could not influence the right hemisphere's motor areas that are responsible for controlling the left hand. This patient, however, could also nor imitate gestures or correctly use actual tools or objects. Therefore a lan-^iLi^-inmiii' disconnection could 1101 account tor these findings. Thus Liepmann and Mass posited that the left hemisphere of right handers contains movement formulas and that the callosal lesion in this patient disconnected these movement formulas from the right hemisphere's motor areas.

Gazzaniga et al. (1967) also found that their patients with callosal disconnection could not correctly pantomime to command with their left hand, but unlike the patient described by Liepmann and Mass, their patients could imitate and correctly use actual tools and objects with their left hand. The preserved ability to imitate and use actual tools and objects suggests that the inability to gesture to command in these patients with callosal lesions was induced by a language-motor disconnection, rather than a movement formula-motor disconnection. In addition, a disconnection between movement formula and motor areas should produce spatial and temporal errors, but many of the errors made by the patient discussed by Liepmann and Mass appeared to be content errors. Watson and Heilman (1983), however, described a patient with an infarction limited to the body of the corpus callosum, Watson and Heilman's patient had no weakness in her right hand and performed all tasks flawlessly with her right hand. In contrast, with her left hand, she could not correctly pantomime to command, imitate, or use actual tools. Immediately after her cerebral infarction, she made some content errors, but subsequently she made primarily spatial and temporal errors. Her performance indicated that not only language but also movement representations were stored in her left hemisphere and her callosal lesion disconnected these movement formulas from the right hemisphere's motor areas.

Lesions of the Inferior Parietal Lobe. It has been proposed by Heilman et al. (1982) that the movement re presentations or movement formulas are stored in the left parietal lobe of right handers and that destruction of the left parietal lobe should induce not only a production deficit (apraxia) but also a gesture comprehension-discrimination disorder. Apraxia induced by (1) premotor lesions, (2) lesions of the pathways that connect premotor areas to motor areas, and (3) lesions of the pathways that lead to the premotor areas from the parietal lobe may also cause production deficits. In contrast to parietal lesions, however, these premotor lesions should not induce gesture comprehension and discrimination disorders. Patients with anterior and posterior lesions have been tested (Heilman et al. 1982); although both groups of patients were apraxic, the patients with a damaged parietal lobe had comprehension and discrimination disturbances, but those without parietal lesions did not.

Liepmann and Mass (1907) proposed that handedness was related to the hemispheric laterality of the movement representations. However, it is not unusual to see right-handed patients with left hemisphere lesions who are not apraxic. Although it is possible that such patients' lesions did not destroy one of the left hemispheric areas important for praxis, many of these patients' lesions arc large and do involve the parietal lobe and other critical left hemisphere areas. As we discussed, not all callosal lesions cause an IMA of the left hand. These results suggest that not all right handers have movement formulas entirely represented in their left hemisphere. Some people may have cither bilateral movement representations or even right hemisphere representations. Apraxia from a right hemisphere lesion in a right hander is rare but has been reported, suggesting that hand preference is not entirely determined by the laterality of the movement representations and may he multifactorial. Whereas the laterality of the movement formula may be the most important factor, there are other factors including deftness (i.e., speed, precision), strength, and even environmental factors.

Supplementary Motor Area Lesions. Muscles move joints, and motor nerves from the spinal cord activate these muscles. The spinal motor nerves are acrivated by corticospinal neurons and the corticospinal neurons are activated by the premotor areas. The premotor areas must instruct the motor area on which neurons to fire and in what order these should he tired.

For each specific skilled movement there is a set of spatial loci that must be traversed in a specific temporal pattern. We proposed that movement formulas represented in the inferior parietal lobe are stored in a three-dimensional supramodal code (Heilman and Rothi 2003). For the corticospinal neurons to properly activate the motor nerves, the stored spatial temporal knowledge has to be transformed into a motor program.

The medial premotor cortex or SMA appears to play an important role in mediating skilled movements. Whereas electrical stimulation of the primary motor cortex induces simple movements, SMA stimulation induces complex movements that may include the entire forelimb. The SMA receives projections from parietal neurons and projects to motor neurons. SMA neurons discharge before neurons in the primary motor cortex. Studies of cctebtal blood flow, an indicator of cerebral metabolism and synaptic activity, have revealed that single repetitive movement increases activation of the contralateral primary motor cortex, but complex movements increase flow in contralateral motor cortex and bilaterally in the SMA. When subjects remain still and think about making complex movements, blood flow is increased to the SMA but not rhe primary motor cortex. Watson et al. (1986)

reported several patients with left-sided medial frontal lesions that included the SMA who demonstrated an IMA when tested with cither arm. Unlike patients with parietal lesions, these patients could both comprehend questions or pantomimes and discriminate between correctly and incorrectly performed pantomimes.

Apraxia has also been reported to be associated with lesions of the convexity premotor cortex. The convexity premotor cortex may be important in coordinating the synchronous actions of multiple joints. Figure 10.1 provides a model for the action processing system we have described thus far. In this figure the label "praxicon" is the theoretical store of the temporospatial representations of learned skilled movements. When performing a skilled act, these representations are transformed into innervatory patterns by SMA and convexity premotor cortex. By the term *innervatory patterns* we mean the program that activates the motor neurons such that the extremity moves in the correct spatial trajectory with the correct timing of each movement.

Conduction Apraxia

A patient was reported who, unlike patients with IMA was more impaired when imitating than when pantomiming to command (Ochipa et al. 1994). Because this patient was similar to the conduction aphasic who repeats poorly, the researchers termed this disorder *conduction apraxia.*

Testing

Testing for conduction apraxia is the same as testing for IMA. Whereas most patients with IMA will improve with imitation, patients with conduction apraxia appear to perform worse with imitation than they do to command.

Patbnphysio logy

The patient with conduction apraxia in the study by Ochipa et al. (1994) could comprehend the examiner's pantomimes and gestures. Wc therefore believe that the patient's visual system could access the movement representations or what we have termed *praxicons,* and these movement representations could activate semantics. It is possible that decoding a seen gesture requires accessing different movement representations than programming an action. Therefore there may be two different stores of movement representations, an input praxicon and an output praxicon. In the verbal domain a disconnection of the hypothetical input and output lexicons induces conduction aphasia, and in the praxis domain a disconnection between the input and output praxicons could induce conduction apraxia.

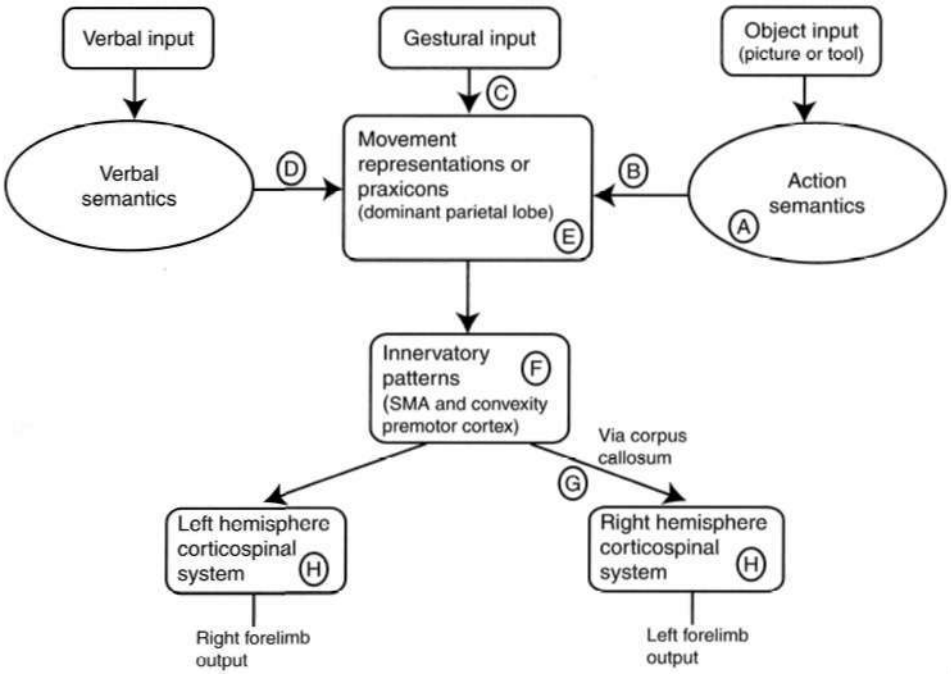

FIGURE 10.1 Diagrammatical model of the praxis system. Degradation of action semantics *(A)* produces conceptual apraxia. Lesions that prevent afferent stimuli from activating movement representations (B, C, D) induce dissociation apraxia. Degradation of the movement representations *(F.)* causes ideomotor apraxia with impaired gesture discrimination and comprehension. Dysfunction of the premotor cortex (F) where the movement representations are converted to motor programs or innervatory patterns induces an ideomotor apraxia with preserved discrimination and comprehension of transitive gestures. Injury to the corpus eallosum (G) produces an ideomotor apraxia of the nonpreferred limb, and injury to the motor cortex *(H)* induces a loss of independent finger movement and precision called *limb-kinetic apraxia.* SMA = supplementary motor area.

Wheteas the lesions that induce conduction aphasia are usually in the supramarginal gyrus, the arcuate fasciculus, ot Wernicke's atea, the lesions that induce conduction apraxia arc unknown.

Dissociation Apraxia

Heilman (1973) described three patients who, when asked to pantomime to command, looked at their hand but would not perform any recognizable actions. Unlike patients with ideomotot or conduction apraxias described earlier, these patients' imitation and use of objects were flawless. Other researchers not only reported patients similar to those reported by Heilman (1973) but also other patients who had a similat defect in other modalities. For example, when asked to pantomime in response to visual or tactile stimuli, they may have been unable to do so but could correctly pantomime to vetbal command.

Testing

The testing that is performed to assess for this disorder is the same as that used for IMA.

Pathopb ysiology

Callosai lesions may not only be associated with an IMA, but callosai disconnection may also cause dissociation apraxia. The subjects of Gazzaniga, Bogcn, and Sperry (1967) and others had dissociation apraxia of theit left hand. With their left hand they could not gesture normally to command but perfotmed well with imitation and actual tools. Whereas language in these patients was mediated by the left hemisphere, movement representations may have been bilaterally represented. Thetefore their callosai lesion induced a dissociation apraxia only of the left hand because the verbal command could not get access to the movement representations stored in the right hemisphere. Whereas the patient with callosai dissociation apraxia will not be able to correctly perform skilled purposive movements of the left arm to command, these patients can imitate normally and use actual tools with their left hand. They perform normally because these tasks do not need vetbal mediation and the movement representations stored in their right hemisphere can be activated by tactile or visual input.

Right-handed patients who have both language and movement formulas represented in their left hemisphere may show a combination of dissociation and IMA with callosai lesions (Watson and Heilman 1983). When asked to pantomime with their left hand, they perform no recognizable movement (disassociation apraxia), but when imitating or using actual rools, they may demonstrate the spatial and temporal errors seen with IMA.

Left banders may demonstrate an IMA without aphasia from a right hemisphere lesion. These left handers are apraxic because their movement tepresentations are stored in their right hemisphere and their lesions destroyed these representations (Heilman 1973; Valenstein and Heilman 1979). These left handers were not aphasic because language was mediated by their left hemispheres (as is the case in most left handers). If these left banders had a callosai lesion, they may have demonstrated a dissociation apraxia of theit left arm and an IMA of their right arm.

These patients reported by Heilman (1973) and those of othct studies probably have an intrahemispheric language-movement formula, visual-movement formula, or somesrhetic-movement formula dissociation. The locations of the lesions that cause these intrahemispheric dissociation apraxias are not known.

Ideational Apraxia

Unfortunately, use of the term *ideational apraxia* has been confusing, with the term erroneously used to label a variety of disorders. For example, Heilman (197,3) used this term when he first desctibed dissociation apraxia. Patients with IMA usually improved when using actual tools and objects, but other researches have reported patients who made errors with the use of actual tools and objects, Heilman (1973) also termed this disturbance *ideational apraxia.* Although the inability to use actual tools and objects may be associated with a conceptual disorder, a severe production disotder may also impair object use. Lastly, the term has also been used to desctibe patients who make conceptual errors. These patients are discussed in the next section. The inability to catry out a series of acts or sequence of actions, an ideational plan that leads to a goal, has also been called *ideational apraxia.* In this chapter, we also define *ideational apraxia* as an inability to correctly sequence a scries of acts that lead to a goal.

Testing

Unfortunately there are no standatdized tests that assess fot ideational apraxia. To test for ideational apraxia, the patients should be tested for their ability to perform multistep sequential tasks, bor example, the examiner may place two slices of bread, mustard, a knife (not too sharp), several slices of ham, and a sandwich bag in front of the patient and ask the patient to prepare a sandwich for work. If the subject fails to perform each step in the correct order that subject may have ideational apraxia.

Path ophysioiogy

Ideational apraxia is most often associated with degenerative dementia but may also be associated with focal lesions of the left hemisphere.

Conceptual Apraxia

To perform a skilled act, we require two types of knowledge: conceptual knowledge and production knowledge. Whereas dysfunction of the praxis production system induces IMA, defects in the knowledge needed to successfully select and use the tools and objects we term *conceptual apraxia.* Therefore patients with IMA make production errors (e.g., spatial and temporal errors), and patients with conceptual apraxia make content and tool-selection errors. The patients with conceptual apraxia may not recall the type of actions associated with specific tools, utensils, or objects (tool-object action knowledge) and therefore make content errors (DcRenzi and Luccelli 1988; Ochipa, Rothi, and Heilman 1989). For example, when asked to demonstrate the use of a screwdriver either by pantomiming or using the tool, the patient with the loss of tool-object action knowledge may pantomime a hammering movement or use the screwdriver as if it were a hammer.

Content errors (i.e., using a tool as if it were another tool) can also be induced by an object agnosia. However, Ochipa et al. (1989) reported a patient who could name tools (and therefore was not agnosic) that he used inappropriately.

Patients with conceptual apraxia may be unable to recall which specific tool is associated with a specific object (tool-object association knowledge). For example, when shown a partially driven nail, they may select a screwdriver rather than a hammer from an array of tools. This conceptual defect may also be in the verbal domain such that when an actual tool is shown to a patient, the patient may be able to name it (e.g., hammer), but when this patient with conceptual apraxia is asked to name or point to a tool when its function is described, he or she cannot. The patient may also be unable to describe the functions of tools.

Patients with conceptual apraxia may also have impaired mechanical knowledge. For example, if they are attempting to drive a nail into a piece of wood and there is no hammer available, they may select a screwdriver rather than a wrench or pliers (which are hard, heavy, and good for pounding) (Ochipa et al. 1992). Mechanical knowledge is also important for tool development and patients with conceptual apraxia may also be unable to correctly develop tools (Ochipa et al. 1992).

Testing

In one test of associative knowledge (tool or object-action), patients may be shown tools such as a screwdriver or objects that tools work on, such as nails, and asked to demonstrate the action that is associated with this tool or object. Patients with conceptual apraxia may make content errors such that they demonstrate the actions of tools other than the one they wetc asked to pantomime. In another test of associative knowledge (tool-object), the patients may be shown an object such as a screw and then are asked to select the proper tool from a group of five tools.

To test mechanical knowledge in patients with normal associative knowledge, one can show them an object such as a partially driven in nail and have them select from five tools the one that would work best for completing the task. The tools from which they may select could include a wrench, a knife, a hand saw, a screwdriver, and scissors. Unfortunately, tests of tool fabrication require special equipment.

Pathophysiology

Licpmann (1920) thought that conceptual knowledge was located in the caudal parietal lobe and DeRenzi and Luccelli (1988) placed it in the temporoparietal junction. The patient reported by Ochipa et al. (1989) was left handed and rendered conceptually apraxic by a lesion in the right hemisphere, suggesting that both production and conceptual knowledge have lateralized representations and that such representations are contralateral to the preferred hand. Further evidence that these conceptual representations are lateralized contralateral to the preferred hand comes from the observation of a patient who had a callosal disconnection and demonstrated conceptual apraxia of the nonpreferred (left) hand (Watson and Heilman 1983). More recently, it has been demonstrated that conceptual apraxia in people who prefer their right hand is most often associated with left hemisphere lesions (Heilman et al. 1997). Conceptual apraxia is perhaps most commonly seen m degenerative dementia of the Alzheimer type (Ochipa et al. 1992). Although both IMA and conceptual apraxia co-occur, Ochipa et al. also noted that the severity nl conceptual and IMA did not always correlate. The observation that patients with IMA may not demonstrate conceptual apraxia and patients with conceptual apraxia may not demonstrate IMA provides support for the postulate that the praxis production and praxis conceptual systems are independent. Although Heilman et al. (1997) demonstrated that lesions located in the hemisphere opposite the preferred hand induce conceptual apraxia, these investigators did not find a specific anatomic area that appeared critical, suggesting that conceptual representations might be widely distributed.

Clinical Pathology

The different forms of limb apraxia discussed in this chapter are most commonly associated with strokes and degenerative dementia of the Alzheimer's and Pick's types. Aptaxia may be seen with many other diseases of the central nervous system including tumors and trauma. Certain forms of apraxia (i.e., limb kinetic and ideomotor)

may be the presenting symptom of basal ganglia disorders such as corticobasal degeneration.

CONCLUSION

Although cognitive-motor disorders are a common, disabling, and enduring sequelae of brain damage, these may be the least recognized neuropsychological disorders associated with cerebral disease. The proper evaluation and diagnosis of these cognitive-motor disorders may not only aid in the diagnosis of the underlying neurological disease but knowledge of these disabilities may help the physician provide the patient and caregiver with information that may help optimize residual resources and thereby improve the patient's quality of life. When possible, the underlying disease should he treated. Although there are no proven specific pharmacologic treatments, cognitive rehabilitation may be of help to some of these patients.

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Chapter 11
The Agnosias

Todd E. Feinberg and Martha J. Farah

The word *agnosia* is Greek for "not knowing" and refers to a class of neu to psycho logical disorders in which patients fail to recognize familiar objects despite seemingly adequate perception, memory, language, and general intellectual ability. The very idea that a patient could "not know" an object or face by sight, for example, yet retain other prerequisite abilities seems paradoxical to some and was once fiercely contested in the neurological literature. As recently as the 1950s, it was suggested that pure visual agnosia does not exist but is merely an effect of the combination of subtle perceptual problems and genctal intellectual impairment. As we have come to understand more about perception, however, the appearance of paradox has receded. We now know that perception involves many levels of internal representation, ranging from lower level sensory images to more abstract representations of object shapes, sounds, feels, and so on. When perception is viewed in this way, it can be seen how various interruptions in processing along this cascade of representations could interfere with recognition while preserving at least some perceptual abilities, as well as language, memory, and intellect. From this perspective, it also follows that there should be a range of agnosic disturbances, depending on the perceptual modality affected and the level of processing at which it is affected. In this chapter, we focus on the three best known types of agnosia: visual, auditory, and tactile agnosia. Within visual agnosia, we delineate subtypes of clinical and theoretical interest. We review the clinical features of each disorder, along with their anatomy and their theoretical implications for basic neuroscience.

VISUAL AGNOSIA

Perhaps because the **human** brain has devoted more tissue to vision than to any of the other senses, visual agnosias appear to be the most common form of agnosia, with the largest number of distinct subtypes. In any case, more is known about the visual agnosias than agnosias in other senses, and our review accordingly treats visual agnosia in greatest detail.

Appcrceptive-Associative Distinction

Understanding of visual agnosia began in 1890, when Lissauer first suggested that disorders of visual recognition could be divided into two types: apperceptive agnosia and associative agnosia. According to Lissauer, apperceptive agnosics have a disorder of complex visual perceptual processes. They arc not blind because they can describe their visual experience; however, they do not have sufficient higher level visual perception to enable object recognition.

In contrast to apperceptive agnosia, Lissauer suggested that perception could be normal in associative agnosia, and the problem could lie downstream in the process of associating a perceptual representation with more general knowledge. Associative visual agnosics set' ":i normal percept stripped of its meaning." The apperceptivc-associative dichotomy is useful insofar as it distinguishes between two broad but fairly distinct classes of patients: those with frank perceptual impairments and those without. However, the underlying theoretical assumption that perception is at fault only in agnosics in the apperceptive group is no longer held; many cases of so-called *associative agnosia* are believed to result from the loss of highct level visual processes.

Within the broad classes of apperceptive and associative agnosia, many finer distinctions can be made. For example, disruption of different types of perceptual processes can result in different agnosias with pronounced perceptual impairment. Among the associative agnosias, recognition

of different types of visual stimuli may be disproportionately impaired. Each major subtype of apperceptive and associative visual agnosia is reviewed here.

Apperceptive Visual Agnosia

Apperceptive visual agnosia is sandwiched, clinically and theoretically, between cortical blindness and associative visual agnosia. These patients arc not cortically blind; they have conscious visual experience, yet their visual perceptual processes are grossly abnormal and are clearly the cause of the object-recognition impairment. It could be argued that given the definition offered—of agnosia as a disorder of object recognition not resulting from a more basic perceptual impairment—these patients should not even be considered agnosic at all. The difference between apperceptive visual agnosia and patients who fall outside the exclusionary criteria is the relatively preserved primary visual capacities of the apperceptive visual agnosic, including acuity, brightness discrimination, color vision, motion perception, and other elementary visual capacities (Farah and Feinberg 1997), It is in contrast to these capacities that their shape perception and hence object recognition seem disproportionately impaired.

The dramatic impairment of shape perception is suggested by the performance of one typical apperceptive agnosic (whose agnosia was secondary to carbon monoxide poisoning) in a shape-matching task, shown in Figure 11.1A. The patient's attempts at copying simple geometric figures are shown in Figure 11.IB, Recognition of real objects may be somewhat better than recognition of geometric shapes, although performance is still very poor and depends on nonshapc cues, such as size, color, texture, and specularity. In several cases of apperceptive agnosia, motion facilitates shape perception. This is true whether the motion is of the whole object or whether a simple shape, such as a letter or geometric figure, is "drawn" in the air with a finger. In most cases of apperceptive agnosia, the brain damage is diffuse and posterior, with carbon monoxide poisoning a common cause.

One way of interpreting apperceptive agnosia is in terms of a disorder of grouping processes that normally operate over the array of local features representing contour, color, depth, and so on at each point in the visual field. Outside of their field detects, apperceptive agnosics have surprisingly good perception of local visual properties. They fail when they must exttact more global structure from the image. Motion is helpful because it provides another cue to global structure in the form of correlated local motions. The perception of structure from motion may also have different neural substrates from the perception of structure from static contour (Marcar and Cowey 1992), and this may conttibutc to its sparing in apperceptive agnosia.

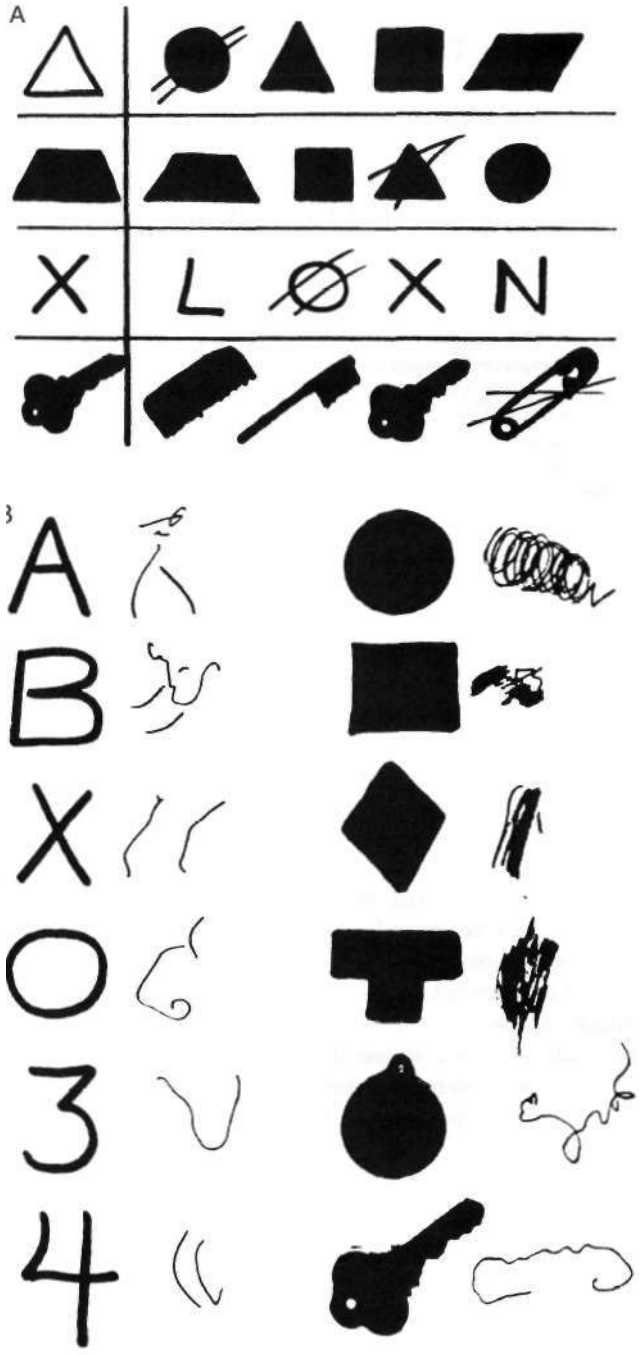

FIGURE 11.1 Evidence of impaired shape matching (A) and copying ability (B) in a patient with apperceptive agnosia. (Reprinted with permission from Benson, R. & Greenberg, J, P. 1969, "Visual form agnosia. A specific defect in visual discrimination," *Arch Neurol*, vol. 20, pp. 82-89.)

Related Syndromes

Some authors have grouped other types of visually impaited patients with the ones cited here as cases of apperceptive agnosia. A description of these disorders follows.

SiniitltiiHtiguosiii is a term used to describe impaired perception of multi element or multipart visual displays. When shown a complex picture with multiple objects or people, simultanagnosics typically describe them in a piecemeal manner, sometimes omitting much of the material entirely and therefore failing to interpret the overall nature of the scene being depicted.

In dorsal simultanagnosia, patients have an attentional limitation that prevents them from seeing more than one object at a time. Occasionally, their attention may be captured by just one part of an object, leading to misidentification of the object and the appearance of petception confined to relatively local image features. The similarity to apperceptive agnosia is limited, however. Once they can attend to an object, dotsal simultanagnosics recognize it quickly and accurately, and even their "local" errors encompass much more global shape information than that available to apperceptive agnosics. Their lesions are typically in the posterior parietal cortex bilaterally.

In ventral simultanagnosia, patients can recognize whole objects but are limited in how many objects can be recognized in a given period. Their descriptions of complex scenes are slow and piecemeal, but unlike apperceptive agnosics, their perception of single shapes is not obviously impaired. This impairment is most apparent when reading because the individual letters of words are recognized in an abnormally slow and generally serial manner. Unlike dorsal simultanagnosics, their detection of multiple stimuli appears normal; the bottleneck is in recognition *per se.* Unlike apperceptive agnosics, they perceive individual shapes reasonably well. In fact, the perceptual disorder of these patients is mild compared with both dorsal simultanagnosics and apperceptive agnosics, and for this reason it may be more sensible to consider them to have a form of associative agnosia. Indeed, they are discussed later in this chapter in rhe context of associative agnosia, ["heir lesions are typically in rhe left inferior tcmporo-occipital cortex.

A final category of impairment whose relation to apperceptive agnosia should be made clear is perceptual categorization deficit. It is equivalent to the impairment that Warrington termed *apperceptive agnosia* but is quite distinct from what we and most other writers mean by the term. The hallmark of perceptual categorization deficit is poor performance at recognizing or matching objects seen from unusual views or illuminated in unusual ways so as to produce confusing shadows, such as the pictures shown in Figure 11,2. This impairment has been interpreted as a breakdown in the mechanisms of object shape constancy, that is, the visual mechanisms that allow us to appreciate the equivalence of an object's three-dimensional shape across different views and under different lighting conditions. Two considerations suggest that we should be cautious before accepting this interpretation. First, the impairment has been demonstrated only with unusual views, in which major axes arc foreshortened or salient features occluded, whereas a rrue loss of shape constancy affects the matching of any views that differ from each other, whether or not they are unusual. Second, the impairmenr is often seen in patients who have no problems with everyday object recognition. Thus perceptual categorization deficit may represent a loss of a certain type of visual problem-solving ability, rather than loss of an essential component of object recognition.

Associative Visual Agnosia

Associative visual agnosia refers to a visual object-recognition impairment due neither to a more basic perceptual deficit, as seen in apperceptive visual agnosia, nor to a

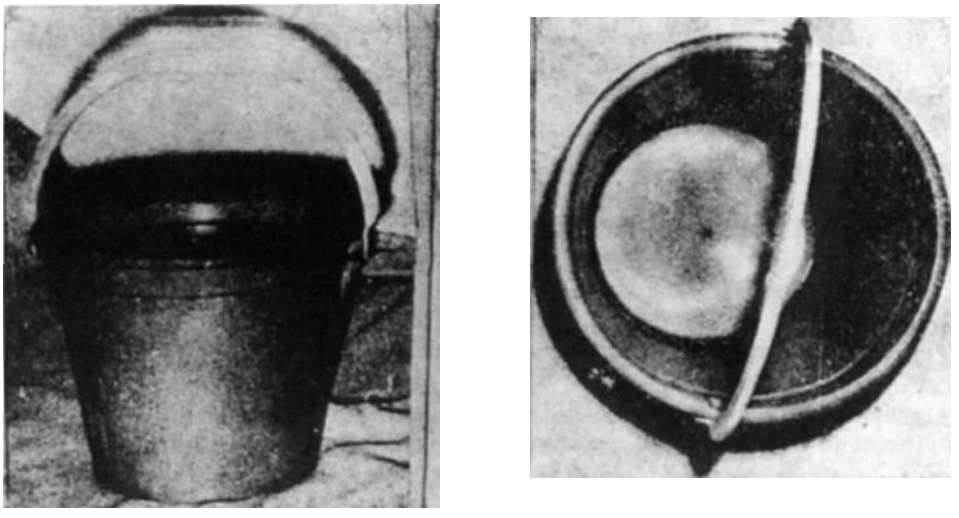

FIGURE 11.2 Unusual views of common objects pose particular problems for patients with "perceptual categorization deficit.

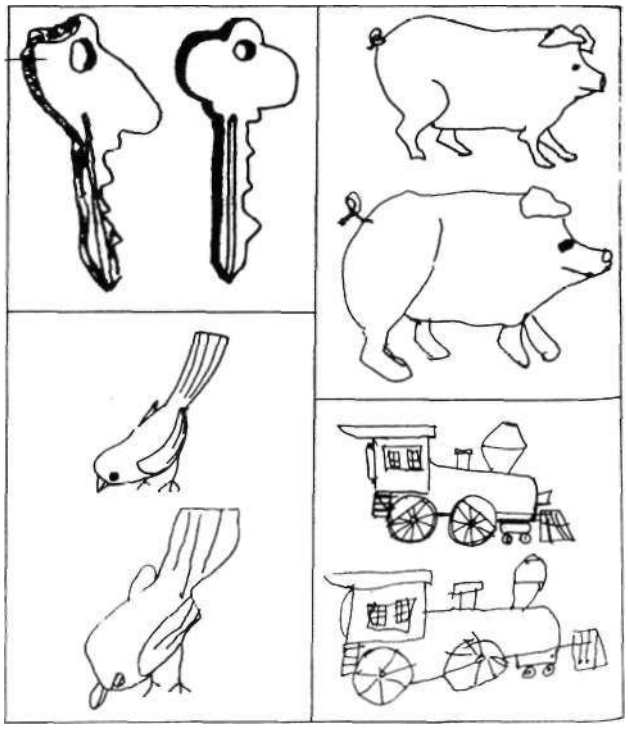

FIGURE 11.3 Example of the preserved copying ability of associative agnosic patients.

higher order disorder of language, communication, intellectual impairment, or other deficits (Weinberg et al. 1994). Unlike the patient with apperceptive agnosia, associative visual agnosics are able to make good copies of objects they cannot recognize. Figure 11.3 shows examples of such copies. The preservation of copying seems to demonstrate that perception is not at fault in associative agnosia, but this conclusion is probably not correct. By its very nature, copying requires piecemeal processing because lines can he drawn only one at a time, whereas normal object recognition requires seeing the whole object simultaneously. When tested directly, the ability of associative visual agnosics to apprehend the whole of an object is impaired. The errors of agnosics often reflect their reliance on local features (e.g., calling a fork "a comb" on the basis of the tines) or an impoverished overall view of the object (e.g., calling a salt shaker "a barrel"). The functional locus of damage in associative visual agnosia is therefore presumed to be high-level visual perceptual representations of object shape.

Dissociations within Associative Visual Agnosia

Associative visual agnosics vary in the scope of their recognition impairment, with some encountering difficulty primarily with faces, others with printed words, and others showing sparing of these categories of stimuli. The dissociations among visual stimulus categories are of interest, theoretically, for what they tell us about the organization of normal visual recognition processes.

Prosopagnosia

Prosopagnosics cannot recognize familiar people by their faces alone and must rely on other cues for recognition, such as voice, distinctive clothing, or hairstyle. The disorder can be so severe that even close friends and family members are not recognized. Although many prosopagnosics have some degree of difficulty recognizing objects other than faces, in some cases the deficit appears strikingly selective for faces. Some writers have suggested that prosopagnosia is simply a mild agnosia and that faces are simply the most difficult type of object to recognize. Evidence is accumulating against this position. Prosopagnosics have been found to be *disproportionately* impaired with faces, when the recognition difficulty for normal subjects has been taken into account relative to a variety of comparison stimuli, including sheep faces {McNeil and Warrington 1993), eyeglass frames (Farah, Klein, and Levinson 1995), and inverted faces {Farah et al. 1995). Further evidence that prosopagnosia represents damage to a distinct system for face recognition comes from agnosic patients who show relative preservation of face recognition (Feinberg er al. 1994).

Pure Alexia

The impairment of visual word recognition, in the context of intact auditory word recognition and writing ability, is known as *pure alexia* and may be found alone or in association with visual object agnosia. Although visual-verbal disconnection plays a role in some cases, impairment of visual letter and word representations is invariably found. As with prosopagnosia, the opposite dissociation also exists, namely, spared word recognition with impaired object and face recognition.

Neuropathology of Associative Visual Agnosia

A variety of lesion locations have been reported to be responsible for cases of associative visual agnosia. Almost invariably, the lesions are posrerior and inferior, affecting ventral temporal and occipital regions. Damage is frequently bilateral, although in some cases only the left or right hemisphere is affected. The precise location of damage appears to correlate with the scope of the agnosic impairment. In patients who are agnosic for objects, faces, and printed words, damage is bilateral. If the impairment mainly affects faces, damage may be bilateral or confined to the right hemisphere (De Renzi et al. 1994), as in Figure 11.4. When face recognition is spared, the damage is generally confined to the left hemisphere, with medial structures, including the parahippocampal, fusiform, and lingual gyri, generally involved, as shown in

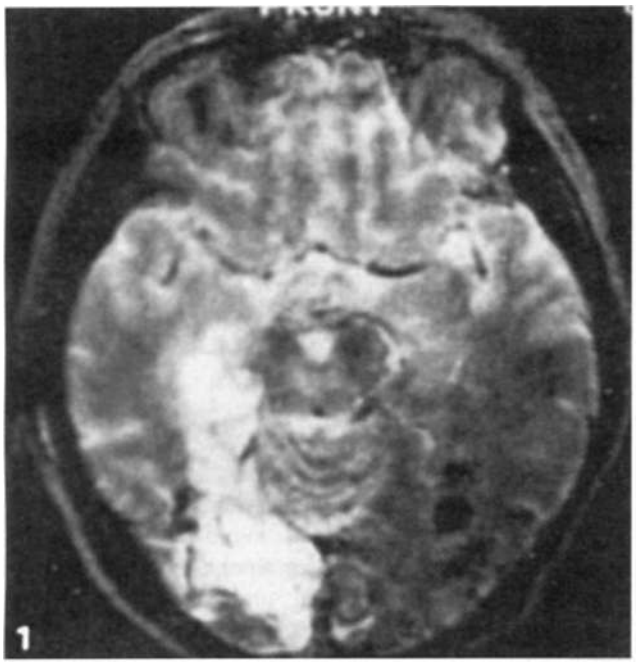

FIGURE 11,4 Typical partem of brain damage in a case of associative agnosia with prosopagnosia. (Reprinted with permission from De Renzi, E., Perani, D., Carlesimo, G. A., et a). 1994, "Prosopagnosia can be associated with damage confined to the right hemisphere: An MRI and PET study and a review of the literature," *Neuropsychologic,* vol. 32, pp. 893-902.)

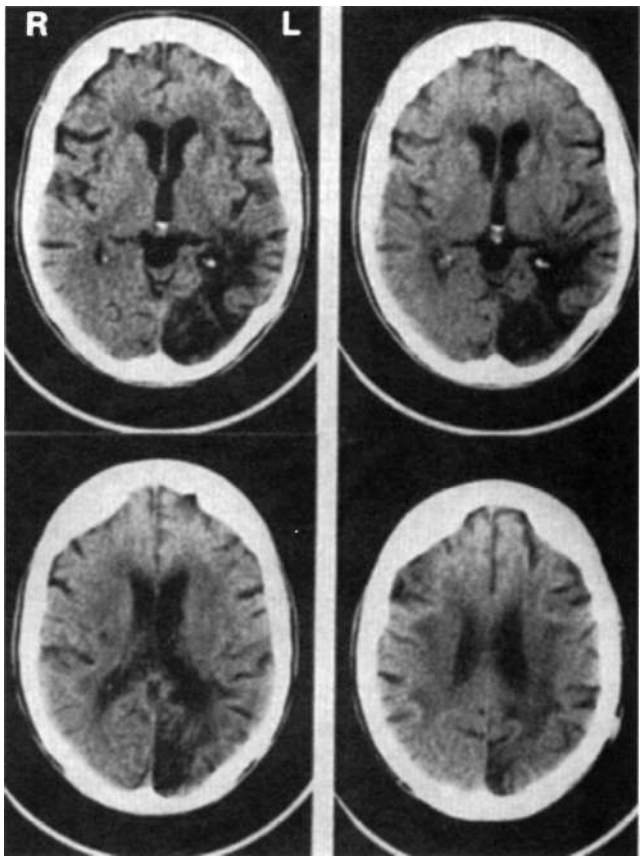

FIGURE 11.5 Typical pattern of brain damage in a case of associative agnosia sparing face recognition. (Reprinted with permission from Feinberg, T. E., Schindler, R. J., Ochoa, E., et al. 1994, "Associative visual agnosia and alexia without prosopagnosia," *Cortex,* vol. 30, pp. 395-412.)

Figure 11.5 (Feinberg et al, 1994). When face recognition alone is impaired, or when face and object recognition are impaired but reading is spared, the lesions are generally cither in the right occipitotemporal region or bilateral. When reading alone is impaired, or when reading and object recognition are impaired but face recognition is spared, the lesions are generally on the left.

Recently, several investigations have studied object recognition using functional magnetic resonance imaging (fMRI). Kanwisher et al. (1996) compared regional brain activity as measured by fMRI while subjects viewed photographs of either objects or faces. These investigators initially found an inferolateral area located at the occipitotemporal junction that was activated during the extraction of processing of an object's shape. Further investigations (Kourrzi and Kanwisher 2000} suggested that an area known as the lateral occipital complex (LOC), a region composed of the lateral and ventral occipital cortex that extends into the posterior temporal lobe, is activated during the processing of an object's shape. The activation of this territory during shape discrimination was independent of the image cues that defined the shape (lines, shading, texture, etc.). Similar fMRI results regarding the role of the LOC in object shape processing were reported by Mazer and Gallant (2000).

Ear et al. (2001) investigated fMRI activation during a task that required subjects to recognize briefly presented photographs of masked objects. They found ventral temporal activation eatly in the process of object identification. Furthermore, the degree of activation in this region correlated with the degree of object identification. Finally, awareness of an object's identity correlated with more anterior activation, and full awareness of an object's identity was associated with activation as far anterior as anterior fusiform gyrus. The authors argue that these findings suggest there is a gradient t>t object identification that spreads from posterior to more anterior visual areas as explicit object identification unfolds.

Related Syndromes

As with apperceptive agnosia, the term *associative agnosia* has been applied to a number of distinct but related syndromes. Two that merit discussion here are semantic memory impairments and optic aphasia. In the fonnct, patients lose general knowledge about the world (termed *semantic memory* by cognitive psychologists), resulting in an inability to name, or otherwise indicate recognition of, visually presented objects {Farah and Grossman 1997).

The impairment may affect all types of stimuli, as when it occurs in Alzheimer's disease or in the selective loss of semantic memory known as *semantic dementia,* or it may disproportionately affect knowledge from specific categories, such as living things. Because the functional locus of damage is postperccptual, in semantic memory, these patients also perform poorly in entirely nonvisual tasks, such as answering verbal questions about objects. Optic aphasics encounter difficult)' when naming visually presented objects. They can convey their recognition of a visual stimulus by pantomime (e.g., a drinking motion when shown a cup) or sorting semantically related stimuli together and can name stimuli in modalities other than vision. Most authors currently distinguish between associative agnosia and optic aphasia, although patients with the latter have sometimes been called *associative agnosics.* The underlying impairment in optic aphasia is unclear. To the extent that optic aphasics are able to derive semantic understanding of visual stimuli, it seems strange that they should be unable to name them.

Assessment of Visual Agnosia

The first step in the assessment of visual agnosia is to establish the preservation of adequate elementary visual abilities, including tests of visual acuity and visual fields. If these are not sufficiently preserved to allow successful object recognition, the patient fails to meet a key exclusionary criterion for agnosia. Computed tomographic (CT) or magnetic resonance imaging (MRI) scans should be obtained and compared with the known patterns of neuropathology for associative visual agnosia and, although they are often less clear, for apperceptive visual agnosia. Difficulty with naming (anomia) can be distinguished from difficulty with visual recognition by comparing visual and tactile naming, naming of verbally described objects, and sorting of objects or pictures by semantic category (e.g., putting kitchen items together, separate from sports equipment). Patients with semantic memory impairment also, like anomics, fail to produce a name for touched or described objects and fail to sort. A purely anomic patient may be able to indicate the identity of a visually presented object by circumlocution and pantomime, even if the name escapes him or her. Patients with optic aphasia can be identified by assessing naming of objects through techniques other than vision and by assessing visual recognition nonverbally. These patients are generally able to name objects by touch or description (in contrast to patients with anomia and semantic memory impairment), as well as to circumlocute and pantomime an identification response to visually presented objects and sort semantically related objects (all in contrast to visual agnosics). Error types are also useful diagnostically. Visual agnosics generally misidentify an object as one that is visually similar (e.g., snake for hose, a "visual error"), whereas patients with semantic memory impairment or optic aphasia make more "semantic errors" (e.g., lettuce for cucumber). Perseverative errors often predominate in optic aphasia.

The distinction between the apperceptive and associative agnosias can be made by gauging the patient's perception of relatively simple shapes with tasks such as matching and copying. Associative agnosics perform these tasks accurately, whereas apperceptive agnosics do poorly on them.

AUDITORY AGNOSIA

Like visual agnosia, auditory agnosia is not one disorder but a group of disorders, characterized by a failure to recognize verbal or nonverbal sounds. In this section, we focus on a few specific conditions that may exist in relatively pure form, with the understanding that most clinical cases have a unique profile of deficits representing a mixture of these characteristics.

The auditory agnosias can be thought of as a spectrum of disorders, bounded by cortical deafness on one end and disorders of language and thought at the other. A patient who is cortically deaf fails to meet one of the primary exclusionary criteria for auditory agnosia, namely, elementary perceptual processes that are adequate for sound recognition. Such patients commonly demonstrate a host of auditory perceptual deficits, including abnormal pure-tone audiology, sound localization, and temporal auditory analysis. Cortical deafness has generally been described in patients with cerebrovascular disease resulting in bilateral infarcts of the temporal lobes destroying Heschl's gyri. The classic clinical presentation is of a patient with a pre-existing unilateral lesion of one temporal lobe who suddenly develops deafness because of a second lesion in the opposite hemisphere. In the process of recovery from cortical deafness, the patient may pass through one or another of the auditory agnosic disorders described here.

Nonverbal Auditory Agnosia

The auditory agnosia that seems most analogous to visual associative agnosia is nonverbal auditory agnosia, also known as *auditory sound agnosia* or *environmental sound agnosia.* The patient with this condition fails to recognize common objects and events by their sounds, such as a dog barking, keys jingling, or a door slamming. Although the patients are not cortically deaf, most reported cases initially present with the clinical picture of cortical deafness. They then recover to the point that standard audiometry is near normal or normal, but auditory recognition remains impaired. Just as visual agnosics' errors tend to be visual, auditory agnosics are often acoustically based. For instance, one patient misidentified a telephone ring as

"sound of railroad crossing," a car honk as "hoot," and thunder as "fireworks."

Just as visual agnosias may affect the recognition of some classes of visual stimuli more than others (e.g., words and faces), so auditory agnosia may affect recognition of certain classes of sounds more than others. The impairment of environmental sound recognition described here is usually found in conjunction with impaired recognition of speech sounds, although selective nonverbal auditory agnosias have been reported. "When the recognition deficit is largely restricted to nonverbal sounds, there is a tendency for right hemisphere lesions to predominate (Bauer and Zawacki 1997).

Engelien et al. (1995} and Engclien, Stern, and Silbersweig (2001) performed a positron emission tomography (PET) study of a patient with bilateral perisylvian strokes and auditory agnosia. During one stage in recovery, the patient remained word deaf but made a partial recovery in his ability to make semantic judgments on meaningful nonverbal auditory stimuli. During this period, the investigators compared this subject's PET activation during passive listening of environmental sounds to PET activation during active semantic categorization of meaningful nonverbal sounds. The authors found that the patient's recovery of auditory nonverbal recognition was associated with "bilateral activation of a distributed network comprising prefrontal, middle temporal, and inferior parietal cortices." The authors suggest that in normal subjects during this auditory recognition task, this pattern of activation occurs exclusively in the left hemisphere.

Auditory agnosias also exist for spoken words (analogous to pure alexia), for voices (analogous to prosopagnosia), and for music. It is to these more domain-specific forms of agnosia that we now turn.

Pure Word Deafness

Pure word deafness (also known as *auditory agnosia for speech* or *verbal auditory agnosia)* is characterized by a disturbance in comprehension of spoken language not explainable by the more generalized auditory processing defects seen in cortical deafness or the broader linguistic impairments typical of Wernicke's aphasia or transcortical sensory aphasia. Pure word deafness is distinguished from cortical deafness by the patient's relative preservation of prrmary sensory processing, as judged by pure-tone audiometry and other psycho acoustic measures. The patient's relatively preserved recognition of nonverbal environmental sounds, such as the ringing of a telephone or the whistling of a bird, separates the disorder from generalized auditory agnosia. It is further distinguished from Wernicke's aphasia by the relative preservation of reading, writing, and normal spontaneous speech. Unlike the patient with transcortical sensory aphasia, the patient with pure word deafness has impaired word repetition.

A variety of auditory perceptual processing deficits may be found in pure word deafness. For example, a generalized disturbance in the temporal resolution of the auditory stimuli, abnormal click-fusion thresholds, difficulties with phonemic discrimination, and abnormalities on dichotic listening tasks showing prominent right ear suppression have been reported (Bauer and Zawacki 1997). In reality, all cases of so-called "pure word deafness" that were adequately studied show other perceptual or agnosic disturbances. In spite of this, the term is still useful because cases do occur in which the primary deficit in word agnosia is the outstanding impairment and occurs out of proportion to whatever other cortical auditory defects may be present,

As is the case with cortical deafness, pure word deafness most commonly occurs as a result of bilateral temporal cortical-subcortical infarcts. It may occur as a stage of recovery in a new onset Wernicke's aphasia or in a patient with a recovered Wernicke's aphasia with a new right temporal lobe infarction. It follows therefore that the lesions reported in pure word deafness are of two varieties. One circumstance is that of bilateral lesions located in the anterior or middle portions of the first temporal gyri, often with some sparing of Hcschl's gyri (area 41). A second localization is a single lesion involving Heschl's gyrus of the dominant hemisphere, as well as the subjacent white matter. In the latter case, the white matter lesion is presumed to destroy the auditory projection from the ipsilatcral medial geniculate nucleus, as well as the callosal fibers from the opposite superior temporal region. In both cases, the lesions arc presumed to isolate the Wernicke's areas from auditory input, resulting in a patient who is neither deaf nor aphasic but in whom auditory input cannot reach language areas necessary for auditory comprehension.

Other Auditory Agnosias

Auditory amusia and *sensory amusia* are terms used to describe the condition in which a patient has lost the ability to recognize a range of features of heard music, such as distinguishing a particular singing voice or recognizing previously learned melodies. Due to the multifactorial nature of music appreciation and the effect of premorbid musical ability and training, it is difficult to make clear-cut clinicopathological correlations. It appears that both hemispheres normally contribute to music cognition. On the basis of two cases of auditory amusia, Peretz et al. (1994) suggested that bilateral lesions of auditory association cortices that spare Heschl's gyri are the critical lesions sufficient to impair melody, voice, and speech prosody discrimination or recognition.

Pbonagnosia refers to a condition comparable to prosopagnosia, in which patients lose the ability to recognize familiar voices. This specific disorder in recognition of familiar voices has been linked to pathology to the right parieral lobe.

Assessment of Auditory Agnosia

The first step in the detection and diagnosis of auditory agnosia is to assess primary auditory perception. This can range from the simple detection of softly spoken words or finger snaps at the bedside through a complete audiologic evaluation, including pure-tone audiometry and speech detection thresholds. Brainstem auditory evoked responses should also be obtained. The examiner must also rule out aphasia as the cause of the patient's auditory recognition disturbance. Thus in addition to assessment of verbal repetition and comprehension, a full assessment should be made of reading silently for comprehension, the ability to follow written commands, and visual naming, as well as a close observation of spontaneous speech for the presence of aphasia. Finally, the subtype of auditory agnosia can be distinguished by the relative disturbance in verbal versus nonverbal material, spoken speech, and melody appreciation. Melody appreciation can be assessed using various subtests of the Seashore Test of Musical Talent. CT scan or MRI should be helpful in distinguishing focal brain pathology as a cause of an agnosic disturbance from impairment resulting from more generalized dementias.

TACTILE AGNOSIA

Tactile agnosia refers to a disorder of object recognition via the tactile modality that cannot be attributed to a more basic somatosensory impairment, language dysfunction, hemispatial neglect, or generalized intellectual impairment. The existence of a pure tactile agnosia has been disputed {Caselli 1997). One likely reason is that tactile agnosia is often subtle and escapes clinical detection. The lack of precise quantitative testing of somatosensory function for most clinical cases has also added to the difficulty of documenting a dissociation between tactile agnosia and more basic somatosensory disorders. Another complicating factor is that we normally recognize objects through vision and occasionally through sound, only rarely using purely tactual information (e.g., searching for keys or lipstick at the bottom of a handbag), and therefore it is not obvious what normal performance is.

As with vision and hearing, tactile perception can break down at a number of stages. Caselli (1997) divides somesthetic functions into basic, intermediate, and complex types. Basic somesthetic functions include light touch, vibration, position sense, superficial pain and temperature, and two-point discrimination. Intermediate somesthetic functions include weight and texture discrimination and the type of simple form discrimination that would generally fall under the category of astereognosis. Complex somesthetic functions are those that are disturbed in the pure forms of tactile agnosia. In detailed somesthetic and psychologic testing of a tactile agnosic, Reed and colleagues (Reed and Caselli 1994; Reed, Caselli, and Farah 1996) found that the simple and intermediate functions mentioned earlier were intact. They also found that tactual memories were intact (assessed by questions such as "Which is smoother, an orange skin or a golf ball?") but that the integration of complex tactile form information was impaired. Figure 11.6 shows a parienr's drawing of an object that she was unable to recognize. The two holes of the cassette were repeatedly touched in the course of her attempt to identify the object, and she was apparently unable to integrate the informarion from the separate touches into an accurate representation of the overall shape of the object. It is important to note that her spatial integration ability for separately encoded features of a visual stimulus was normal. Tactile agnosia is typically a unilateral disorder, which enables the examiner to use the normal hand as a control.

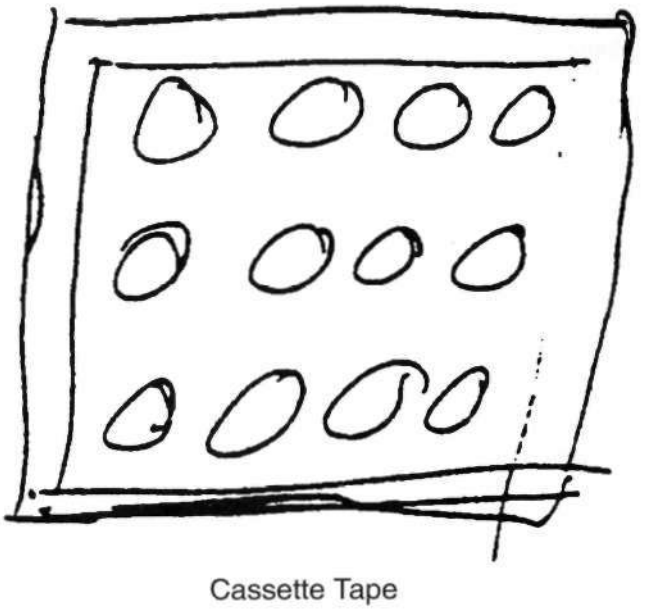

FIGURE 11.6 The attempt of a tactile agnosic to draw a cassette tape that she felt but could not recognize.

Anatomical Considerations

Figure 11.7 shows the anatomy of somatosensory cortex in the human brain. The first somatosensory area (SI) receives the primary thalamic projections for cortical

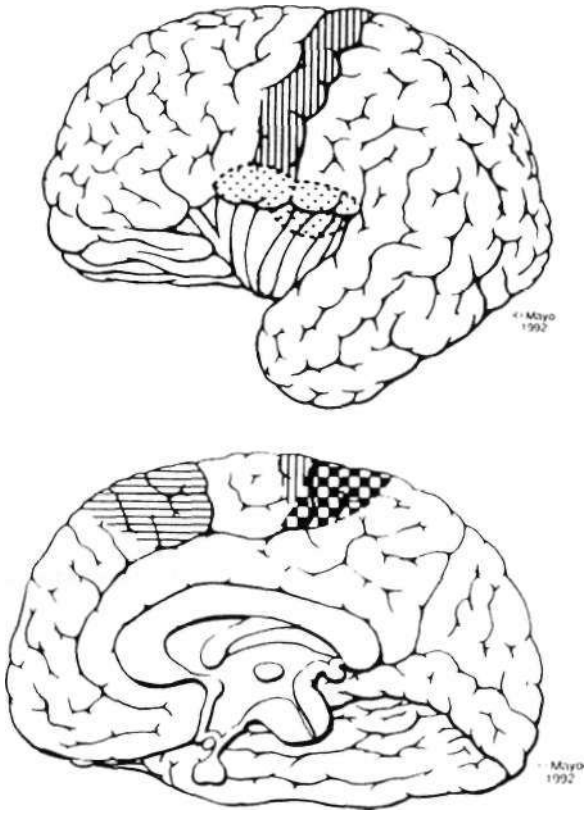

FIGURE 11.7 Areas of the human brain involved in somatosensory perception and recognition, (Reprinted with permission from Caselli, R. J. 1993, "Ventrolateral and dorsomedial somatosensory association cortex infarction produce distinct sonicsthetic syndromes," *Neurology,* vol. 43, pp. 762-771.)

somatosensory functioning. It includes Brodmann's areas 3a, 3b, 1, and 2. Neurons in these regions are responsible for initial cortical sensory processing. Lesions in the region of SI produce impairment in basic and intermediate sense modalities, Caselli (1997) suggested that pure tactile agnosia results from lesions located in ventrolateral association cortices, in a region corresponding to the second somatosensory area (SII), located largely within the parietal operculum. He felt that the posterior insula may play a role in higher order tactile object identification. He also found that lesions in dorsomedial association cortex (the supplementary sensory area) produced a profound disturbance in basic somatosensory processing resembling that of patients with SI lesions, and these patients were additionally found to have severe contralateral limb apraxia. Furthermore, with time, these patients improved considerably and a chronic tactile agnosia occurred only in patients with ventrolateral damage. The role of the SII in higher order tactile rccogntion has found additional support from the fMRI study of Reed et al. (1999) who found selective activation of SII during tactile identification of common real objects.

Assessment of Tactile Agnosia

As with visual or auditory agnosia, basic perceptual functions must be assessed and found adequate for object recognition. These include light touch, vibration, position sense, superficial pain and temperature, and two-point discrimination, as well as weight and texture discrimination and simple form discrimination, such as distinguishing flat from curved surfaces and edges. Language and other cognitive functions required for object identification through any modality must also be examined. Because the ipsilesional hand is available as a control, norma! naming of palpated objects with that hand provides good evidence that higher order linguistic and cognitive factors are not the cause of the tactile agnosia. MRI or CT scans should be evaluated relative to the known anatomy of this disorder.

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Chapter 12
Language and Speech Disorders

A. APHASIA

Howard S. Kirshner

The study of language disorders involves the analysis of the most human of attributes, the ability to communicate through common symbols. Language has provided the foundation of human civilization and learning, and **its** study has been the province of philosophers and physicians. When language is disturbed by neurological disorders, analysis of the patterns of abnormality has practical usefulness in neurological diagnosis. Historically, language was the first higher cortical function to be correlated with specific sites of brain damage. It continues to serve as a model for the practical use of a cognitive function in the localization of brain lesions and for the understanding of human cortical processes in general.

Aphasia is defined as a disorder of language that is acquired secondary to brain damage. This definition, adapted from Alexander and Benson (19.97), separates aphasia from several related disorders. First, aphasia is distinguished from congenital or developmental language disorders, called *dysphasias.* {Contrary to British usage, in the United States, the term *dysphasia* applies to developmental language disorders rather than partial or incomplete aphasia.}

Second, aphasia is a disorder of language rather than speech. Speech is the articulation and phonation of language sounds; language is a complex system of communication symbols and rules for their use. Aphasia is distinguished from motor speech disorders, which include dysarthria, dysphonia (voice disorders), stuttering, and speech apraxia. Dysarthrias arc disorders of articulation of single sounds. Dysarthria may result from mechanical disturbance of the tongue or larynx or from neurological disorders, including dysfunction of the muscles, neuromuscular junction, cranial nerves, bulbar anterior horn cells, corticobulbar rracts, cerebellar connections, or basal ganglia. Apraxia of speech is a syndrome of misarticulation of phonemes, especially consonant sounds. Unlike dysarthria, in which certain phonemes are consistently distorted, apraxia of speech contains inconsistent distortions and substitutions of phonemes. The disorder is called an apraxia because there is no primary motor deficit in articulation of individual phonemes. Clinically, speech-a praxic patients produce inconsistent articulatory errors, usually worse on the initial phonemes of a word and with polysyllabic utterances. Apraxia of speech, so defined, is commonly involved in speech production difficulty in the aphasias.

Third, aphasia is distinguished from disorders of thought. Thought involves the mental processing of images, memories, and perceptions, usually but not necessarily involving language symbols. Psychiatric disorders derange thought and alter the content of speech without affecting its linguistic structure. Schizophrenic patients, for example, may manifest bizarre and individualistic word choices, with loose associations and a loss of organization in discourse, together with vague or unclear references and communication failures (Docherty, DeRosa, and Andreasen 1996). Lk'int'iirary language and articulation, however, are intact. Abnormal language content in psychiatric disorders is therefore not considered aphasia. Language disorders associated with diffuse brain diseases, such as encephalopathies and dementias, do qualify as aphasias, but the involvement of other cognitive functions distinguishes them from aphasia secondary to focal brain lesions.

An understanding of language disorders requires an elementary review of linguistic components. *Phonemes* are the smallest meaning-carrying sounds; *morphology* is the use of appropriate word endings and connector words for tenses, possessives, and singular versus plural; *semantics* refers to word meanings; the *lexicon* is the internal dictionary; and *syntax* is the grammatical construction of phrases and sentences. *Discourse* refers to the use of these elements to create organized and logical expression of thoughts. Specific language disorders affect one or more of these elements.

Language processes have a clear neuroanatomic basis. In simplest terms, the reception and processing of spoken language takes place in the auditory system, heginning with the cochlea and proceeding through a series of way stations to the auditory cortex, Heschl's gyrus, in each superior temporal gyrus. The decoding of sounds into linguistic information involves the posterior part of the left superior temporal gyrus, Wernicke's area or Brodmann's area 22, which gives access to a network of cortical associations to assign word meanings. For both repetition and spontaneous speech, auditory information is transmitted to Broca's area in the posterior inferior frontal gyrus. This area of cortex "programs" the neurons in the adjacent motor cortex, subserving the mouth and larynx, from which descending axons travel to the brainstem cranial nerve nuclei. The inferior parietal lobule, especially the supramarginal gyrus, may also be involved in phoneme processing in language comprehension and in phoneme production for repetition and speech (Hickok and Poeppel 2000). These anatomic relationships are shown in Figures 12A.1 and 12A.2. Reading requires the perception of visual language stimuli by the occipital cortex, followed by correlation with auditory language information, via the intermodal association cortex of the angular gyrus. Writing involves the activation of motor neurons projecting to the arm and hand.

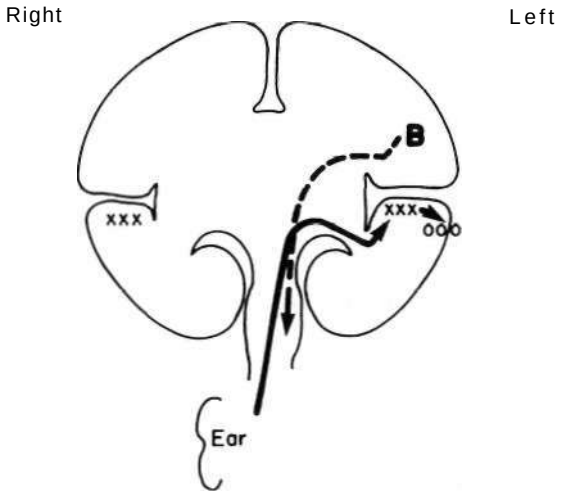
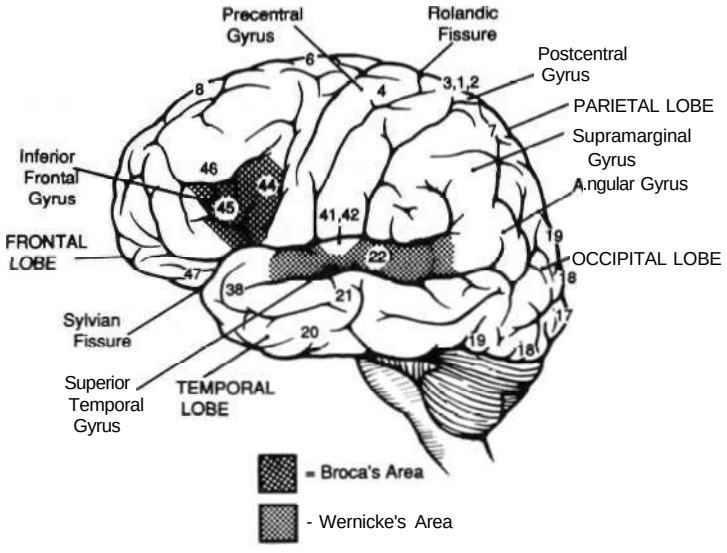


FIGURE 12A.2 Coronal plane diagram of the brain, indicating the inflow of auditory information from the cars to the primary auditory cortex in both superior temporal regions *(xxx),* and then to Wernicke's area *[poo)* in the left superior temporal gyrus. The motor outflow of speech descends from Broca's area *[&)* to the cranial nerve nuclei of the brainstem via the corticobulbar tract *[dashed arrow).* In actuality, Broca's area is anterior to Wernicke's area, and the two areas would not appear in the same coronal section.

These pathways, and doubtless others, constitute the cortical circuitry for language comprehension and expression. In addition, other cortical centers involved in cognitive processes project into the primary language cortex, influencing the content of language. Finally, subcortical structures play increasingly recognized roles in language functions. The thalamus, a relay for the reticular activating system, appears to alert the language cortex, and lesions of the dominant thalamus often produce fluent aphasia. Nuclei of the basal ganglia involved in motor functions, especially the caudate nucleus and putamen, participate in expressive speech. It is no wonder, then, that



HGURK I 2A. I The lateral surface of the left hemisphere, showing a simplified gyral anatomy and the relationships between Wernicke's area and Broca's area. Not shown is the arcuate fasciculus, which connects the two cortical speech centers via the deep subcortical white matter.

language disotdcrs are seen in a wide variety of brain lesions and are important in practical neurological diagnosis and localization.

In right-handed people, and in most left-handers, clinical syndromes of aphasia result from left hemisphere lesions. Rarely, aphasia may result from a right hemisphere lesion in a right-handed patient, a phenomenon called *crossed aphasia* (Bakar, Kirshncr, and Wert?. 1996). In left-handed persons, language disorders are usually similar to those of right-handed persons with similar lesions, but occasional cases present with atypical syndromes that suggest a right hemisphere capability for at least some language functions. For example, a patient with a large left frontal temporo-parietal lesion may have preserved comprehension, suggesting right hemisphere language comprehension. For the same reason, recovery from aphasia may be better in some left-handed than right-handed patients with left hemisphere strokes.

SYMPTOMS AND DIFFERENTIAL DIAGNOSIS OF DISORDERED LANGUAGE

Muteness, a total loss of speech, may represent severe aphasia (see Aphemia, later in this chapter). Muteness can also be a sign of dysarthria; frontal lobe dysfunction with akinetic mutism; severe extrapyramidal system dysfunction, as in Parkinson's disease; non-neurological disorders of the larynx and pharynx; or even psychogenic syndromes, such as catatonia. Caution must therefore he taken in diagnosing the mute patient as aphasic. A good rule of thumb is that if the patient can write or type and the language form and content are normal, the disorder is probably not aphasic in origin. If the patient cannot speak or write but makes apparent effort to vocalize, and if there is also evidence of deficient comprehension, aphasic muteness is likely. Associated signs of a left hemisphere injury, such as right hemiparesis, also aid in diagnosis. Finally, if the patient gradually begins to make sounds containing paraphasic errors, aphasia can be identified with confidence.

Hesitant speech is a symptom not only of aphasia, but also of motor speech disorders, such as dysarthria or stuttering, and may be a manifestation of a psychogenic disorder. A second rule of thumb is that if one can transcribe the utterances of a hesitant speaker into normal language, the patient is not aphasic. Hesitancy occurs in many aphasia syndromes for varying reasons, including difficulty in speech initiation, imprecise articulation of phonemes, deficient syntax, or word-finding difficulty.

Anomia, or the inability to produce a specific name, is generally a reliable indicator of a language disorder, although it may also reflect memory loss. Anomia is manifest in aphasic speech by word-finding pauses and circumlocutions or use of a phrase when a single word would suffice.

Paraphasic speech refers to the presence of errors in the patient's speech output. Paraphasic errors arc divided into literal or phonemic errors, involving substitution of an incorrect sound (e.g., shoon for spoon), and verbal or semantic errors, involving substitution of an incorrect word (e.g., fork for spoon). A related language symptom is perseveration, the inappropriate repetition of a previous response. Occasionally, aphasic utterances involve nonexistent word forms called *neologisms.* A pattern of paraphasic errors and neologisms that so contaminate speech that the meaning cannot be discerned is called *jargon speech.*

Another cardinal symptom of aphasia is the failure to comprehend the speech of others. Most aphasic patients also have difficulty with comprehension and production of written language (reading and writing).

Fluent, paraphasic speech usually makes an aphasic disorder obvious. The chief differential diagnosis here involves aphasia, psychosis, acute encephalopathy or delirium, and dementia. Aphasic patients are usually not confused or inappropriate in behavior; they do not appear agitated or misuse objects, with occasional exceptions in acute syndromes of Wernicke's or global aphasia. By contrast, most psychotic patients speak in an easily undet-**stood,** grammatically appropriate manner, but their behavior and speech content are abnormal. Only rarely do schizophrenics speak in "clang association" or "word salad" speech. Sudden onset of fluent, paraphasic speech in a middle-aged or elderly patient should always be suspected of representing a left hemisphere lesion with aphasia.

Patients with acute encephalopathy or delirium may manifest paraphasic speech and "higher" language disorders, such as inability to write, but the grammatical expression of language is less disturbed than is its content. These language symptoms, moreover, are less prominent than accompanying behavioral disturbances, such as agitation, hallucinations, drowsiness, or excitement, and cognitive difficulties, such as disorientation, memory loss, and delusional thinking.

Chronic encephalopathies, or dementias, pose a more difficult diagnostic problem because involvement of the language cortex produces readily detectable language deficits, especially involving naming, reading, and writing. **These** language disorders (see Language in Dementing Diseases, later in this chapter) differ from aphasia secondary to focal lesions mainly by the involvement of other cognitive functions, such as memory and visuospatial processes.

BEDSIDE LANGUAGE EXAMINATION

The first part of any bedside examination of language is the observation of the patient's speech and comprehension during the clinical interview. A wealth of information about language function can be obtained if the examiner pays deliberate attention to the patient's speech patterns and responses to questions. In particular, minor word-finding

difficulty, occasional paraphasic errors, and higher-level deficits in discourse planning and in the pragmatics of communication, such as the use of humor and irony, can he detected principally during the informal interview.

D. Frank Benson and Norman Gcschwind popularized a bedside language examination of six parts, and it has been updated by Alexander and Benson (1997) (Table 12A.1). This examination provides useful localizing information about lira in dysfunction and is well worth the few minutes it takes.

The first part of the examination is a description of spontaneous speech. A speech sample may be elicited by asking the patient to describe the weather or the reason for coming to the doctor. If speech is sparse or absent, recitation of lists, such as counting or listing days of the week, may be helpful. The most important variable in spontaneous speech is fluency: Fluent speech flows rapidly and effortlessly; nonfluent speech is uttered in single words or short phrases, with frequent pauses and hesitations. Attention should first be paid to such elementary characteristics as initiation difficulty, articulation, phonation or voice volume, rate of speech, prosody or melodic intonation of speech, and phrase length. Second, the content of speech utterances should be analyzed in terms of the presence of word-finding pauses, circumlocutions, and errors such as literal and verbal paraphasias and neologisms.

Naming, the second part of the bedside examination, is tested by asking the patient to name objects, object parrs, pictures, colors, or body parts to confrontation. A few items from each category should be tested because anomia can be specific to word classes. Proper names of persons are often affected severely. The examiner should ask questions to be sure that the patient recognizes the items or people that he or she cannot name.

Auditory comprehension is tested first by asking the patient to follow a series of commands of one, two, and three steps. An example of a one-step command is "stick out your tongue"; a two-step command is "hold up your left thumb and close your eyes." Successful following of commands ensures adequate comprehension, at least at this simple level, but failure to follow commands does not automatically establish a loss of comprehension. The patient must hear rhc command, understand the language the examiner speaks, and possess the motor ability to execute it, including absence of apraxia. *Apraxia* (sec Chapter 10 for full discussion) is defined operationally as the inability to carry out a motor command despite normal comprehension and normal ability to carry out the motor act in another context, such as by imitation or with use of a real object. Because apraxia is difficult to exclude with confidence, it is advisable to test comprehension by tasks that do not require a motor act, such as yes-no questions, or by commands that require only a pointing response. The responses to nonsense questions (e.g., "Do you vomit every day?") quickly establish whether the patient comprehends. Nonsense questions often produce surprising results, given the tendency of some aphasics to cover up comprehension difficulty with social chatter.

Tabic 12A.1: Bedside language examination

1. Spontaneous speech
   a. Informal interview
   b. Structured task
   c. Automatic sequences
2. Naming
3. Auditory comprehension
4. Repetition
5. Reading
   a. Reading aloud
   h. Ri-iiJnii; comprehension
6. Writing
   a. Spontaneous sentences
   b. Writing to dictation
   c. Copying

Repetition of words and phrases should be deliberately tested. Dysarthric patients have difficulty with rapid sequences of consonants, such as "Methodist Episcopal," whereas aphasics have special difficulty with grammatically complex sentences. The phrase "no ifs, ands, or huts" is especially challenging for aphasics. Often, aphasics can repeat familiar or "high-probability" phrases much better than unfamiliar ones.

Reading should be tested both aloud and for comprehension. The examiner should carry a few printed commands to facilitate a rapid comparison of auditory to reading comprehension. Of course, the examiner must have some idea of the patient's premorbid reading ability.

Writing, the element of the bedside examination most often omitted, not only provides a further sample of expressive language but also allows an analysis of spelling, which is not possible with spoken language. A writing specimen may be the most sensitive indicator of mild aphasia, and it provides a permanent record for future comparison. Spontaneous writing, such as a sentence describing why the patient has come for examination, is especially sensitive for the detection of language difficulty. When this fails, writing to dictation and copying should be tested as well.

Finally, the neurologist combines the results of the bedside language examination with those of the rest of the mental status examination and of the neurological examination in general. These "associated signs" help classify the type of aphasia and localize the responsible brain lesion.

DIFFERENTIAL DIAGNOSIS OF APHASIC SYNDROMES

Broca's Aphasia

In 1861, the French physician Paul Broca described two patients, establishing the aphasic syndrome that now bears

his name. The speech pattern is nonfluent; on hedsidc examination, the patient speaks hesitantly, often producing the principal, meaning-containing nouns and verbs but omitting small grammatical words and morphemes. This pattern is called *agrammatism* or *telegraphic speech.* An example is "wife come hospital." Patients with acute Broca's aphasia may be mute or may produce only single words, often with dysarthria and apraxia of speech. They make many phonemic errors, inconsistent from utterance to utterance, with substitution of phonemes usually differing only slightly from the correct target (e.g., *p* for *b).* Naming is deficient, but the patient ofren manifests a "tip of the tongue" phenomenon, getting out the first letter or phoneme of the correct name. Paraphasic errors in naming arc more often of the literal type than the verbal type. Auditory comprehension seems intact, but detailed testing usually reveals some deficiency, particularly in the comprehension of complex syntax. For example, sentences with embedded clauses involving prepositional relationships cause difficulty for Broca's aphasics in comprehension and in expression. A recent positron emission tomography (PET) study in normal subjects (Caplan, Alpert, and Waters 1998) showed activation of the Broca area in the frontal cortex during tests of syntactic comprehension. Repetition is hesitant in these patients, resembling their spontaneous speech. Reading is often impaired despite relatively preserved auditory comprehension. Benson termed this reading difficulty of Broca's aphasics the "third alexia," in distinction to the two classic types of alexia (see Aphasic Alexia, later in this chapter). Patients with Broca's aphasia may have difficulty with syntax in reading, jusr as in auditory comprehension and speech. Writing is virtually always deficient in Broca's aphasics. Most patients have a right hemiparesis, necessitating use of the nondominant, left hand for writing, but this left-handed writing is far more abnormal than the awkward renditions of a normal, right-handed patient. Many patients can scrawl only a few letters.

Associated neurological deficits of Broca's aphasia include right hemiparesis, hemisensory loss, and apraxia of the oral apparatus and the nonparalyzed left limbs. Apraxia in response to motor commands is important to recognize because it may be mistaken fot comprehension disturbance. Comprehension should be tested by responses to yes-no questions or commands to point to an object. The common features of Broca's aphasia arc listed in Table 12A.2.

An important clinical feature of Broca's aphasia is its frequent association with depression (Robinson 1997). Patients with Broca's aphasia are typically aware of and frustrated by their deficits. At times they become withdrawn and refuse help or therapy. Usually, the depression lifts as the deficit recovers, although it may be a limiting factor in rehabilitation.

The lesions responsible for Broca's aphasia usually include the traditional Broca's area in the posterior part of the inferior frontal gyrus, along with damage to the adjacent cortex and subcortical white matter. Most patients with

Tabic 12A.2: Bedside features of Broca's aphasia

feature	*Syndrome*
Spontaneous speech	Nonfluent, mute or telegraphic, usually dysarthria
Naming	Impaired
Comprehension	Intact (mild difficulty with complex grammatical phrases)
Repetition	Impaired
Reading	Often impaired ("third alexia")
Writing	Impaired (dysmorphic, dysgrammatical)
Associated signs	Right hemiparesis Right hemisensory loss iApraxia of left limbs

lasting Broca's aphasia, including Broca's original cases, have much larger left frontoparietal lesions, including most of the territory of the upper division of the left middle cerebral artery. Such patients typically evolve from global to Broca's aphasia over weeks to months. Patients who manifest Broca's aphasia immediately after their strokes, by-contrast, have smaller lesions of the inferior frontal region, and their deficits generally resolve quickly. In computed tomography (CT) scan analyses at the Boston Veterans Administration Medical Center, lesions restricted to the lower precentral gyrus produced only dysarthria and mild expressive disturbance. Lesions involving the traditional Broca's area (Brodmann's areas 44 and 45) resulted in difficulty initiating speech, and lesions combining Broca's area, the lower precentral gyrus, and subcortical white matter yielded the full syndrome of Broca's aphasia. In studies by the same group, damage to two subcortical white matter sites—-the rostral subcallosal fasciculus deep to Broca's area and the periventricular white matter adjacent to the body of the left lateral ventricle—was required to cause permanent nonfluency. Figute 12A.3 shows a magnetic resonance imaging (MR1) scan from a case of Broca's aphasia.

Aphcmia

A rare variant of Broca's aphasia is aphemia, a nonfluent syndrome in which the patient is initially mute and then able to speak with phoneme substitutions and pauses. All other language functions are intact, including writing. This rare and usually transitory syndrome results from small lesions either of Broca's area or its subcortical white matter or of the inferior precentral gyrus. Because written expression and auditory comprehension are normal, aphemia is not a true language disorder; aphemia may be equivalent to pure apraxia of speech.

Wernicke's Aphasia

Wernicke's aphasia may be considered a syndrome opposite to Broca's aphasia, in that expressive speech is

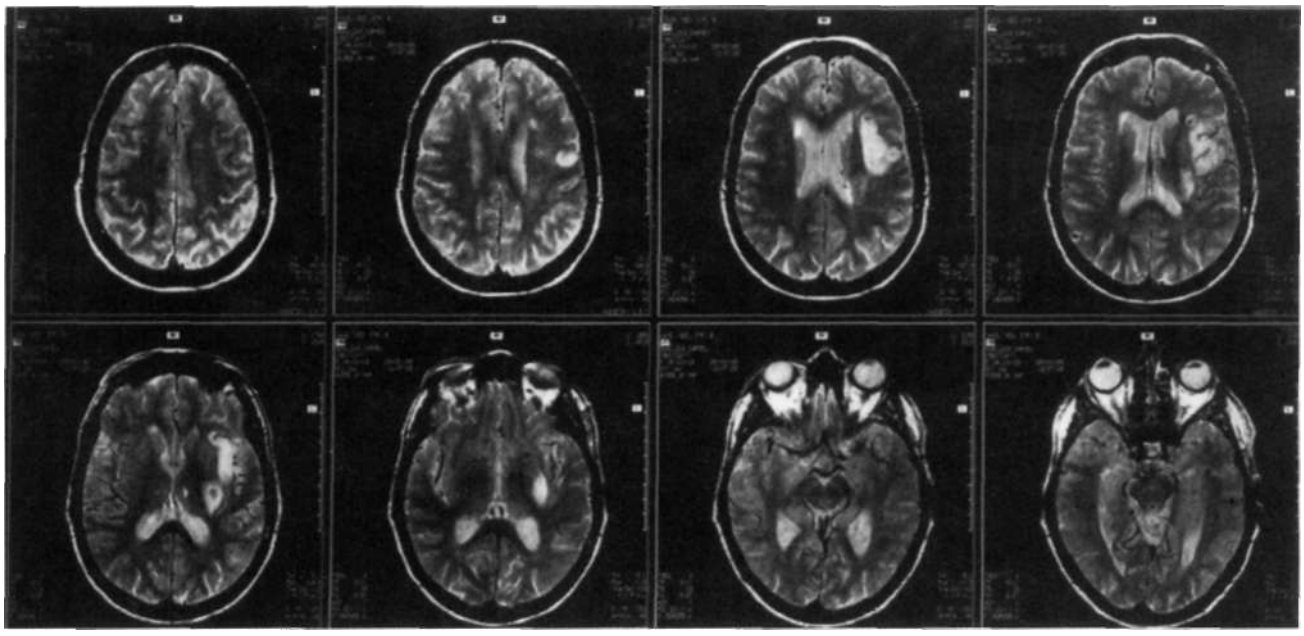


FIGURE 12A.3 Magnetic resonance imaging scan from a patient with Broca's aphasia. In this patient, the cortical Broca's area, subcortical white matter, and the insula were all involved in the infarction. The patient made a good recovery.

fluent but comprehension is impaired. The speech pattern is effortless and sometimes even excessively fluent (lognrrhea). A speaker of a foreign language would notice nothing amiss, but a listenet who shares the patient's language detects speech empty of meaning, containing verbal paraphasias, neologisms, and jargon productions. Neurolinguists refer to this pattern as *paragrammatism.* In milder cases, the intended meaning of an utterance may be discerned, but the sentence goes awry with paraphasic substitutions. Naming in Wernicke's aphasia is deficient, often with bizarre, paraphasic substitutions for the correct name. Auditory comprehension is impaired, sometimes even for simple nonsense questions. Auditory perception of phonemes is deficient in Wernicke's aphasia, but deficient semantics is the major cause of the comprehension disturbance; disturbed access both to semantics and to the internal lexicon is central to the deficit of Wernicke's aphasia. Repetition is impaired; whispering a phrase in the patient's ear, as in a hearing test, may help cue the patient to attempt repetition. Reading comprehension is usually affected similarly to auditory comprehension, but some patients show greater deficit in one modality. The discovery of spared reading ability in Wernicke's aphasics is important in allowing these patients to communicate. In addition, neurolinguistic theories of reading must include access of visual language images to semantic interpretation, even in the absence of auditory comprehension. Writing is also impaired, but in a manner quite different from that of Broca's aphasia. The patient usually has no hemiparesis and can grasp the pen and write easily. Written productions are even more abnormal than oral ones, however, in that spelling errors are also evident. Writing samples are especially useful in the detection of mild Wernicke's aphasia.

Associated signs are limited in Wernicke's aphasia; most patients have no elementary motor or sensory deficits, although a partial or complete right homonymous hemianopia may be present. The characteristic bedside examination findings in Wernicke's aphasia are summarized in Table 12A.3.

The psychiatric manifestations of Wernicke's aphasia are quite different from those of Broca's aphasia. Depression is less common; many Wernicke's aphasics seem unaware of or unconcerned about their communicative deficits. With time, some patients become angry or paranoid about the inability of family members and medical staff to understand them. This behavior, like depression, may hinder rehabilitative efforts.

The lesions of patients with Wernicke's aphasia are usually in the posterior portion of the superior temporal

Table 12A.3: Bedside features of Wernicke's aphasia

Feature	*Syndrome*
Spontaneous speech	Fluent, with paraphasic errors Usually not dysarthric Sometimes logorrhcic
Naming	Impaired (often bi/.arre paraphasic misnaming)
Comprehension	Impaired
Repetition	Impaired
Reading	Impaired for comprehension, reading aloud
Wntinn	Well-formed, paragraphic
Associated signs	±Right hemianopia Motor, sensory signs usually absent

gyrus, sometimes extending into the inferior parietal lobule. Figure 12A.4 shows a typical example. The exact confines of Wernicke's area have been much debated. Damage to Wernicke's area (Brodmann's area 22) has been reported to correlate most closely with persistenr loss of comprehension of single words, although others (Kertesz, Lau, and Polk 1993) have found only larger temporoparietal lesions in patients with lasting Wernicke's aphasia. In the acute phase, the ability to match a spoken word to a picture is quantitatively related to decreased perfusion of Wernicke's area on perfusion-weighted MR1 scans, indicating less variability during the acute phase than after recovery has taken place (Hillis et al. 2001). Electrical stimulation of Wernicke's area produces consistent interruption of auditory comprehension, supporting the importance of this region for decoding of auditory language. A receptive speech area in the left inferior temporal gyrus has also been suggested by electrical stimulation studies and by a few descriptions of patients with seizures involving this area (Kirshner et al. 1995), but aphasia has not been recognized with destructive lesions of this area. Extension of the lesion into the inferior parietal region may predict greater

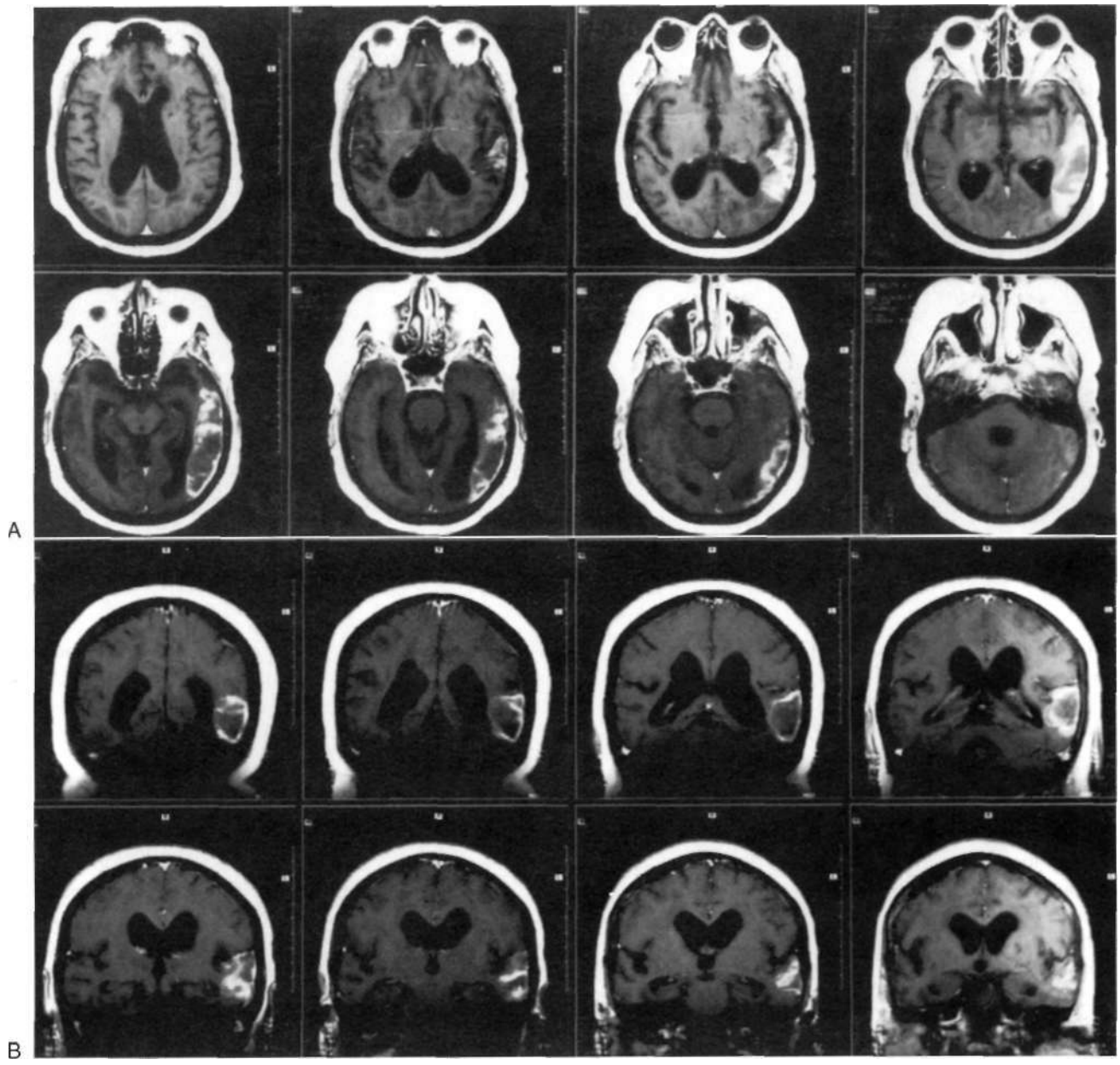


FIGURE 12A.4 Axial and coronal magnetic resonance imaging slices (A and B), and an axial positron emission tomographic (PET) scan view (C) of an elderly woman with Wernicke's aphasia. There is a large left superior temporal lobe lesion. The onset of the deficit was not clear, and the PET scan was useful in showing that the lesion had reduced metabolism, favoring a stroke over a tumor.

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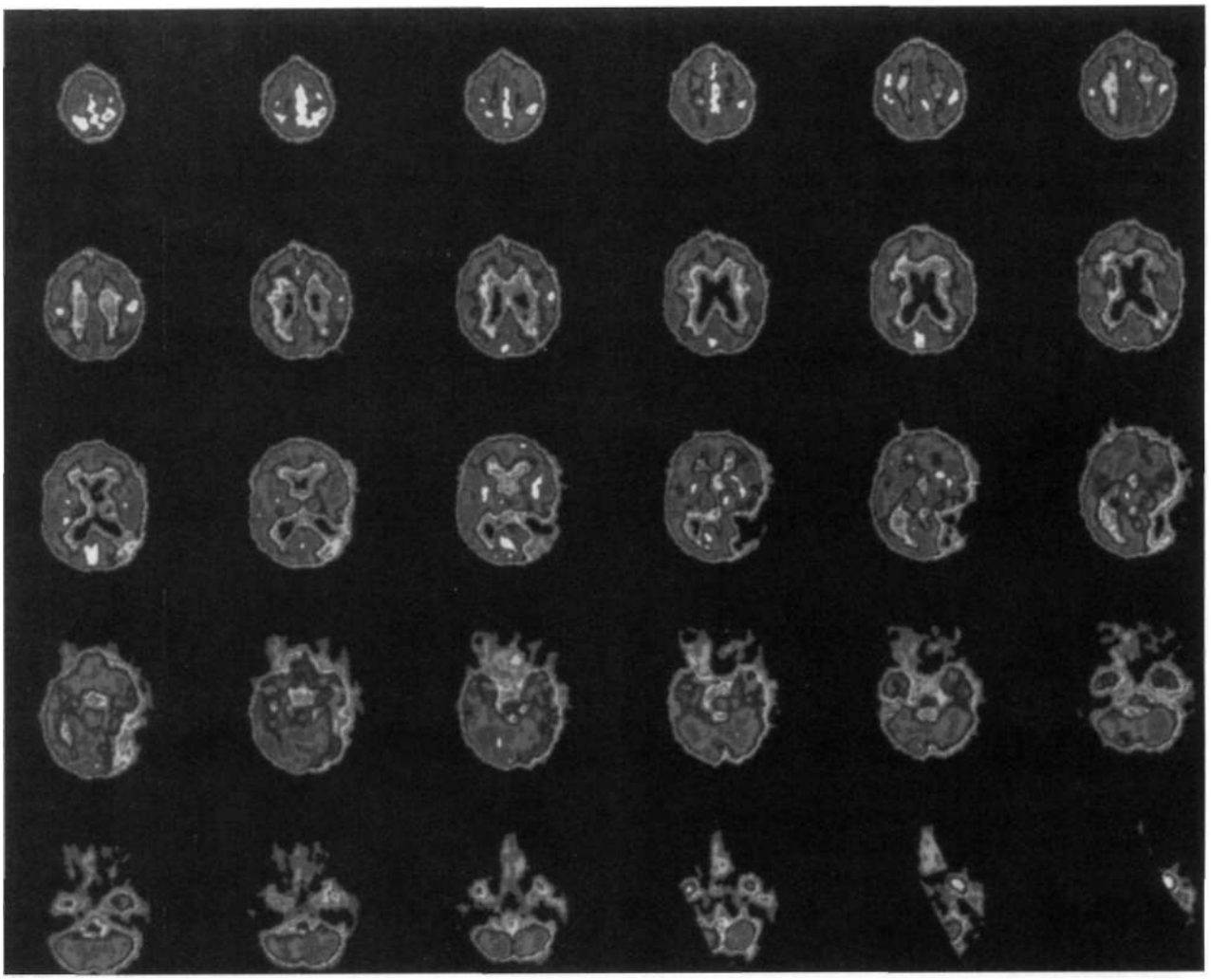

FIGURE 12A.4, cont'd.

involvement of reading comprehension. In terms of vascular anatomy, Wernicke's area lies within the territory of the inferior division of the left middle cerebral artery.

Pure Word Deafness

Pure word deafness is a rare but striking syndrome of isolated loss of auditory comprehension and repetition, without any abnormality of speech, naming, reading, or writing. Hearing for pure tones and for nonverbal noises, such as animal cries, is intact. Most cases have mild aphasic deficits, especially paraphasia speech. Classically, the anatomic substrate is a bilateral lesion, isolating Wernicke's area from input from both Heschl's gyri. Pure word deafness is thus an example of a "disconnection syndrome," in which the deficit results from loss of white matter connections rather than of gray matter language centers. Some cases of pure word deafness, however, have unilateral left temporal lesions. These cases closely resemble Wernicke's aphasia with greater impairment of auditory comprehension than of reading.

Global Aphasia

Global aphasia may be thought of as a summation of the deficits of Broca's aphasia and Wernicke's aphasia. Speech is nonfluent or mute, but comprehension is also poor, as are naming, repetition, reading, and writing. Most patients have dense right hemiparesis, hemisensory loss, and often hemianopia, although few patients have little hemiparesis. Milder aphasic syndromes in which all modalities of language are affected are often called *mixed aphasias.* The lesions of patients with global aphasia are usually latge, involving both the inferior frontal and superior temporal regions, and often much of the parietal lobe in between. This lesion represents most of the territory of the left middle cerebral artery. Patients in whom the superior temporal gyrus is spared tend to recover their auditory

Table 12A.4: Bedside features of global aphasia

henture	*Syndrome*
Spontaneous speech	Mute or n on fluent
Naming	Impaired
Comprehension	Impaired
Repetition	Impaired
Reading	Impaired
Writing	Impaired
Associated signs	Right hemiparesis Right hemisensory Right hemianopia

comprehension and to evolve toward the syndrome of Broca's aphasia. Recovery in global aphasia may be prolonged; global aphasics may recover more during the second month than in the first *6* months after a stroke. Characteristics of global aphasia are presented in Table 12A.4.

Conduction Aphasia

Conduction aphasia is an uncommon but theoretically important syndrome that can be remembered by its striking deficit of repetition. Most patients have relatively normal spontaneous speech, although some make literal paraphasic errors and hesitate frequently for self-correction. Naming may be impaired, but auditory comprehension is preserved. Repetition may be disturbed to seemingly ridiculous extremes, such that a patient who can express himself or herself at a sentence level and comprehend conversation may be unable to repeat even single words. One such patient could not repeat the word "boy" but said "I like girls better," Reading and writing are somewhat variable, but reading aloud may share some of the same difficulty as repeating. Associated deficits include hemianopia in some patients; right-sided sensory loss may be present, but right-sided hemiparesis is usually mild or absent. Some patients have limb apraxia, creating a misiinpressioti that comprehension is impaired. Bedside examination findings in conduction aphasia are summarized in Table 12A.5.

The lesions of conduction aphasia are usually in either the superior temporal or inferior parietal regions. Benson et al. suggested that patients with limb apraxia have parietal lesions, whereas those without apraxia have temporal lesions. Conduction aphasia may represent a stage of recovery in patients with Wernicke's aphasia in whom the damage to the superior temporal gyrus is not complete.

Conduction aphasia has been advanced as a classic disconnection syndrome. Wernicke originally postulated that a lesion disconnecting Wernicke's and Broca's areas would produce this syndrome; Geschwind later pointed to the arcuate fasciculus, a white matter tract traveling from the deep temporal lobe, around the sylvian fissure to the frontal lobe, as the site of disconnection. Anatomic involvement of the arcuate fasciculus is present in most, if not all, cases of conduction aphasia, but there is usually also cortical involvement of the supramarginal gyrus or temporal lobe. The supramarginal gyrus appears to be involved in auditory immediate memory and in phoneme perception related to word meaning, as well as phoneme generation (Hickok and Poeppel, 2000). Lesions in this area are associated with conduction aphasia and phonemic paraphasic errors. Others have pointed out that lesions of the arcuate fasciculus do not always produce conduction aphasia. Another theory of conduction aphasia has involved a defect in auditory verbal short-term memory.

Anomic Aphasia

Anomic aphasia refers to aphasic syndromes in which naming, or access to the internal lexicon, is the principal deficit. Spontaneous speech is normal except for the pauses and circumlocutions produced by the inability to name. Comprehension, repetition, reading, and writing are intact, except for the same word-finding difficulty in written productions. Anomic aphasia is common but less specific in localization than other aphasic syndromes. Isolated, severe anomia may indicate focal left hemisphere pathology. Alexander and Benson (1997) refer to the angular gyrus as the site of lesions producing anomic aphasia, but lesions there usually produce other deficits as well, including alexia and the four elements of Gerstmann's syndrome: agraphia, right-left disorientation, acalculia, and finger agnosia, or inability to identify fingers. Isolated lesions of the temporal lobe can produce pure anomia, and PET studies of naming in normal subjects have also shown consistent activation of the superior temporal lobe. Inability to produce nouns is characteristic of temporal lobe lesions, whereas inability to produce verbs occurs more with frontal lesions (Damasio 1992). Even specific classes of nouns may be selectively affected in some cases of anomic aphasia. Anomia is also seen with mass lesions elsewhere in the brain and in diffuse

Table 12A.5: Bedside features of conduction aphasia

Feature	*Syndrome*
Spontaneous speech	Fluent, some hesitancy, literal paraphasic errors
Naming	May be moderately impaired
Comprehension	Intact
Repetition	Severely impaired
Reading	ilnability to read aloud; some reading eomprehension
Writing	Variable deficits
Associated signs	±Apraxia of left limbs ± Right hemiparesis, usually mild ± Right hemisensory loss ± Right hemianopia

Tabic 12A.6: Bedside features of amimic aphasia

i'dititri-	*Syndrome*
Spontaneous speech	Fluent, some word-finding pauses, circumlocution
Naming	Impaired
Comprehension	Intact
Repetition	Intact
Reading	Intact
Writing	Intact, except for anomia
Associated signs	Variable or none

degenerative disorders, such as Alzheimer's disease (AD), Anomic aphasia is also a common stage in the recovery of many aphasic syndromes. Anomic aphasia thus serves as an indicator of left hemisphere or diffuse brain disease, but it has only limited localizing value. The typical features of anomic aphasia are presented in Table 12A.6.

Transcortical Aphasias

The transcortical aphasias arc syndromes in which repetition is normal, presumably because the causative lesions do not disrupt the perisylvian language circuit from Wernicke's area through the arcuate fasciculus to Broca's area. Instead, these lesions disrupt connections from other cortical centers into the language circuit (hence the name *transcortical).* The transcortical syndromes are easiest to think of as analogues of the syndromes of global, Broca's, and Wernicke's aphasias, with intact repetition. Thus mixed transcortical aphasia, or the syndrome of the isolation of the speech area, is a global aphasia in which the patient repeats, often echolalically, but has no prepositional speech or comprehension. This syndrome is rare, occurring predominantly in large, watershed infarctions of the left hemisphere or both hemispheres that spare the perisylvian cortex or in advanced dementias. Transcortical motor aphasia is an analogue of Broca's aphasia in which speech is hesitant or telegraphic, comprehension is relatively spared, bur repetition is fluent. This syndrome occurs with lesions in the frontal lobe, anterior to Broca's area, and hence within the territory of the anterior cerebral artery. Disruption of the supplementary motor area or disconnection of this area from Broca's area by subcortical frontal white matter lesions may produce the syndrome. The occurrence of transcortical motor aphasia in an arterial territory other than the middle cerebral artery separates this syndrome from the many middle cerebral artery syndromes discussed previously. The third transcortical syndrome, transcortical sensory aphasia, is an analogue of Wernicke's aphasia in which fluent paraphasic speech, paraphasic naming, impaired auditory and reading comprehension, and abnormal writing coexist with normal repetition. This syndrome is relatively uncommon, occurring in strokes of the left temporo-occipital area and in dementias. Bedside examination findings in the transcortical aphasias are summarized in Table 12A.7.

Subcortical Aphasias

A current area of interest in aphasia research involves the "subcortical" aphasias. Although all the syndromes discussed so far are defined by behavioral characteristics that can be diagnosed on the bedside examination, the subcortical aphasias are defined by lesion localization in the basal ganglia or deep cerebral white matter. As knowledge about subcortical aphasia has accumulated, two major groups of aphasic symptomatology have been described: aphasia with thalamic lesions and aphasia with lesions of the subcortical white matter and basal ganglia.

Left thalamic hemorrhages often produce a Wernickc-like fluent aphasia, with better comprehension than cortical Wernicke's aphasia. A fluctuating or "dichotomous" state has been described, alternating between an alert state with nearly normal language and a drowsy state in which the patient mumbles paraphasically and comprehends poorly. Luria has called this a *quasi-aphasic abnormality of vigilance,* in that the thalamus plays a role in alerting the language cortex. Thalamic aphasia can occur even with a right thalamic lesion in a left-handed patient, indicating that hemispheric language dominance extends to the thalamic level. Whereas some skeptics have attributed thalamic aphasia to pressure on adjacent structures and secondary effects on the cortex, cases of thalamic aphasia have been described with small ischemic lesions, especially those involving the paramedian or anterior nuclei of the thalamus, in the territory of the tuberothalamic artery. Because these lesions produce little or no mass effect, such cases indicate that the thalamus and its connections play a definite role in language function.

Lesions of the left basal ganglia and deep white matter also cause aphasia. As in thalamic aphasia, the first syndromes described were in basal ganglia hemorrhages, especially those involving the putamen, the most common site of hypertensive intracerebral hemorrhage. Here the aphasic syndromes are more variable but most commonly involve global or Wcrnickc-Iikc aphasia. As in thalamic lesions, ischemic strokes have provided better localizing information. The most common lesion is an infarct involving the anterior putamen, caudate nucleus, and anterior limb of the internal capsule. Patients with this lesion have an "anterior subcortical aphasia syndrome" involving dysarthria, decreased fluency, mildly impaired repetition, and mild comprehension disturbance (Mega and Alexander 1994). This syndrome most closely resembles Broca's aphasia, but with greater dysarthria and less language dysfunction. Figure 12A.5 shows an example of this syndrome. More restricted lesions of the anterior putamen, head of caudate, and periventricular white matter produce hesitancy or slow initiation of speech but little true

Table 12A.7: Bedside features of transcortical aphasias

Feature	*Isolation syndrome*	*Transcortical motor*	*Transcortical sensory*
Speech	Nonfluent, echolalic	Nonfluent	Fluent, echolalic
Naming	Impaired	Impaired	Impaired
Comprehension	Impaired	Intact	Impaired
Repetition	Intact	Intact	Intact
Reading	Impaired	±Intact	Impaired
Writing	Impaired	±Intact	Impaired

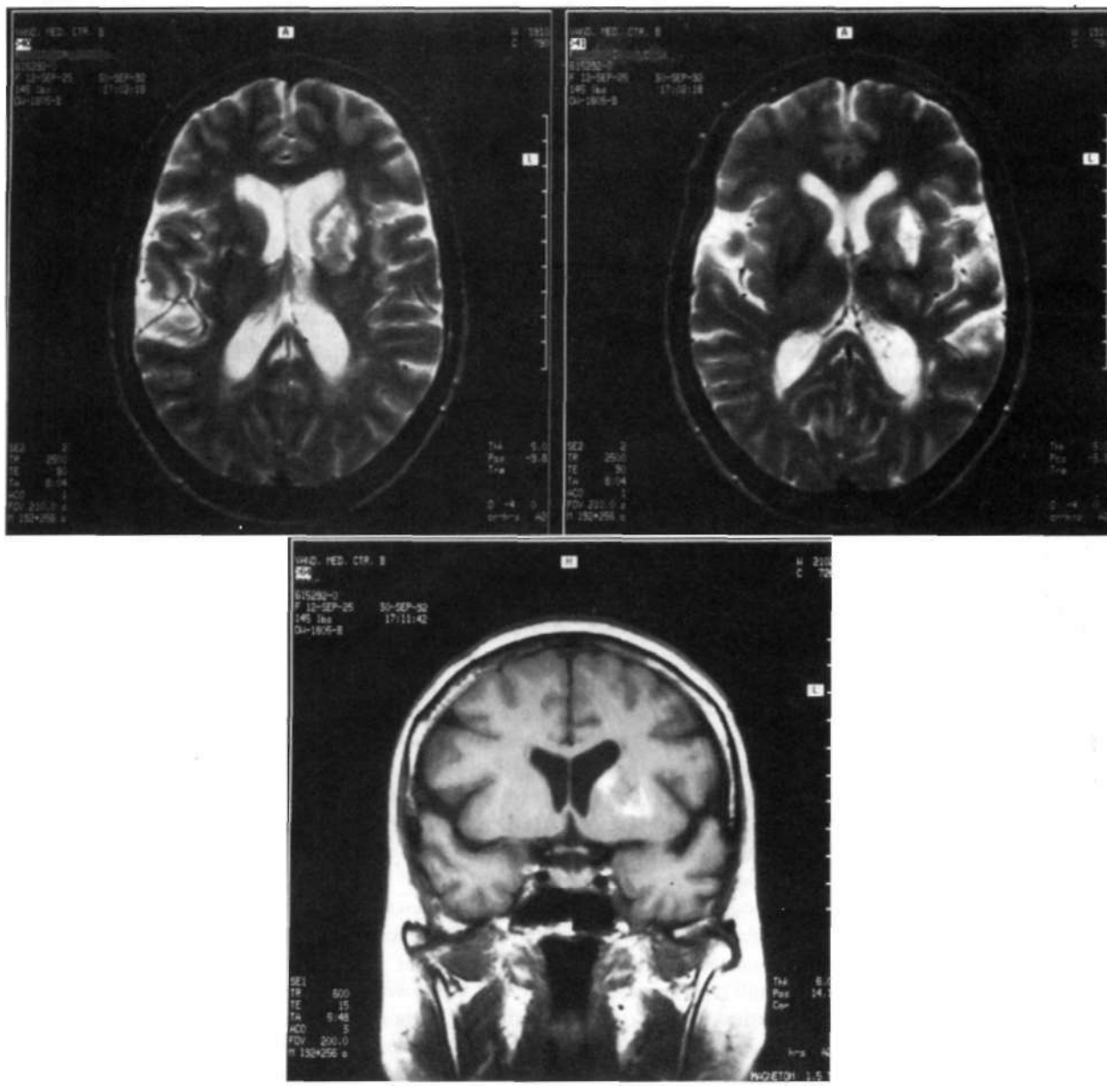

FIGURE 12A.S Magnetic resonance imaging (MRI) scan slices in the axial, coronal, and sagittal planes from a patient with subcortical aphasia. The lesion is an infarction involving the anterior caudate, putamen, and anterior limb of the left internal capsule. The patient presented with dysarthria and mild, nonfluent aphasia with anomia, with good comprehension. The advantage of MRI in permitting visualization of the lesion in all three planes is apparent. *Continued*

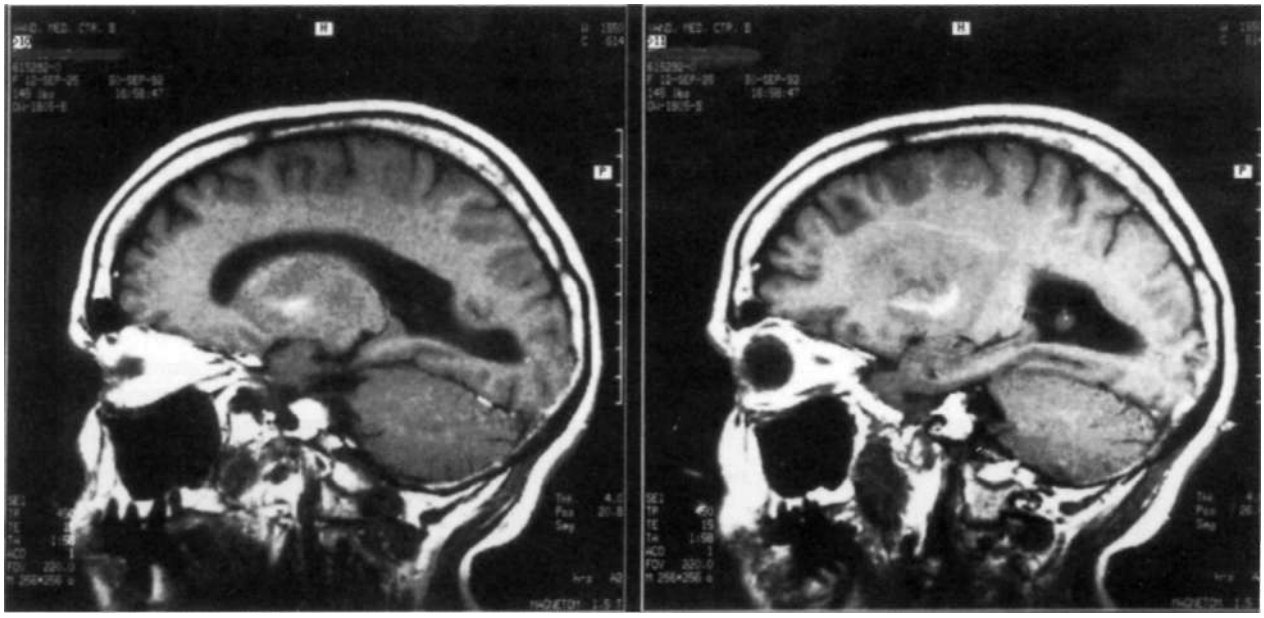

FIGURE 12A.5, cont'd.

language disturbance. More posterior lesions involving the putamen and deep temporal white matter, referred to as the *temporal isthmus,* are associated with fluent paraphasic speech and impaired comprehension resembling Wernicke's aphasia. Small lesions in the posterior limb of the internal capsule and adjacent putamen cause mainly dysarthria, but mild aphasic deficits may occasionally occur. Finally, larger subcortical lesions involving both the anterior and posterior lesion sites produce global aphasia. A wide variety of aphasia syndromes can thus be seen with subcortical lesion sites. Nadeau and Crosson (1997) discussed the anatomic model of the basal ganglia involvement in speech and language based on the known motot functions and fiber connections of these structures. Evidence from PET studies indicates that basal ganglia lesions affect language, both directly and indirectly, via decreased activation of cortical language areas.

The "insula," a cortical structure that shares a deep location with the subcortical structures, may also be important to speech and language function. Dronkers (1996) reported that involvement of this area is closely associated with the presence of apraxia of speech in aphasic patients.

In clinical terms, subcortical lesions do produce aphasia, although less commonly than cortical lesions, and the language characteristics of subcortical aphasias are often atypical. The presentation of a difficult-to-classify aphasic syndrome, in the presence of dysarthria and right hemiparesis, should lead to suspicion of a subcortical lesion.

Pure Alexia without Agraphia

"Alexia," or the acquired inability to read, is a form of aphasia by the definition given at the beginning of this chapter. The classic syndrome of alexia, pure alexia without agraphia, was described by the French neurologist Dejerine in 1892. This syndrome may be thought of as a linguistic blindfolding: Patients can write but cannot read their own writing. On bedside examination, speech, auditory comprehension, and repetition arc normal. Naming may be deficient, especially for colors. Patients initially cannot read at all; as they recover, they learn to read letter by letter, spelling out words laboriously. They cannot read words at a glance, as normal readers do. By contrast, they quickly understand words spelled orally to them, and they can spell normally. Some patients can match words to pictures, indicating that some subconscious awareness of the word is present, perhaps in the right hemisphere. Associated deficits include a right hemianopia or right upper quadrant defect in nearly all patients and, frequently, a deficit of short-term memory. There is usually no hemiparesis or sensory loss.

The causative lesion in pure alexia is nearly always a stroke in the territory of the left posterior cerebral artery, with infarction of the medial occipital lobe, often the splenium of the corpus callosum, and often the medial temporal lobe. Dejerine postulated a disconnection between the intact right visual cortex and the left hemisphere language centers, particularly the angular gyrus. (Figure 12A.6 is an adaptation of Dejerine's original diagram.) Gcschwind later rediscovered this disconnection hypothesis. Although Damasio and Damasio found splenial involvement in only 2 of 16 cases, they postulated a disconnection within the deep white matter of the left occipital lobe. As in the disconnection hypothesis for conduction aphasia, the theory fails to explain all the behavioral phenomena, such as the sparing of single letters. A deficit in short-term memory for visual language elements

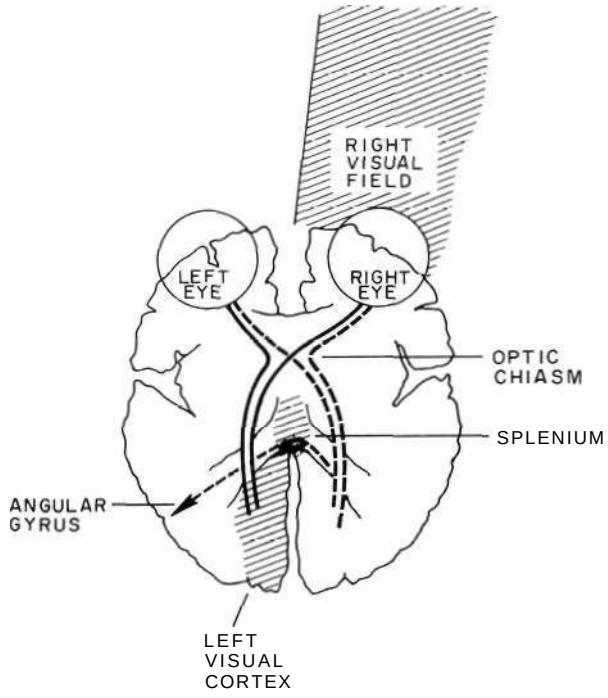

FIGURE 12A.6 Horizontal brain diagram of pure alexia without agraphia, adapted from that of Dejerine, in 1892. Visual information from the left visual field reaches the right occipital cortex but 15 "disconnected" from the left hemisphere language centers by the lesion in the splenium of the corpus callosum.

or an inability to perceive multiple letters at once (simultanagnosia) can also explain many features of the syndrome. Typical findings of pure alexia without agraphia are presented in Table 12A.8.

Alexia with Agraphia

The second classic alexia syndrome, alexia with agraphia, described by Dejerine in 1891, may be thought of as an acquired illiteracy, in which a previously educated patient is rendered unable to read or write. The oral language modalities ol speech, naming, auditory comprehension, and repetition are largely intact, but many cases manifest a fluent paraphasic speech pattern with impaired naming.

Table 12A.8: Bedside features of pure alexia without agraphia

Feature	*Syndrome*
Spontaneous speech	Intact
Wunmt;	±Impaired, especially colors
Comprehension	Intact
Repetition	Intact
Reading	Impaited (some sparing of single letters)
Writing	Intact
Associated signs	Right hemianopia or superior quadrantanopia
	Short-term memory loss
	Motor, sensorx signs usually absent

Table 12A.9: Bedside features of alexia with agraphia

I Ciiturc	*Syndrome*
Spontaneous speech	Fluent, often some paraphasia
Naming	ilmpaired
Comprehension	Intact, or less impaired than reading
Repetition	Intact
Reading	Severely impaired
Writing	Severely impaired
Associated signs	Right hemianopia
	Motor, sensory signs often absent

This syndrome thus overlaps Wernicke's aphasia, especially in cases in which reading is more impaired than auditory comprehension. Associated deficits include right hemianopia and elements of Gerstmann's syndrome: agraphia, acalculia, right-left disorientation, and finger agnosia. The lesions are typically in the inferior parietal lobule, especially the angular gyrus. Etiologies include strokes in the territory of the angular branch of the left middle cerebral artery or mass lesions in the same region. Characteristic features of the syndrome of alexia with agraphia are summarized in Table 12A.9.

Aphasic Alexia

In addition to the two classic alexia syndromes, many patients with aphasia have associated reading disturbance. Examples already cited are the "third alexia" syndrome of Broca's aphasia and the reading deficit of Wernicke's aphasia. Neurolinguists and cognitive psychologists have divided alexias according to breakdowns in specific stages of the reading process. The linguistic concepts of surface structure versus the deep meanings of words have been instrumental in these new classifications. Four patterns of alexia (or dyslexia, in British usage) have been recognized: letter-by-letter, deep, phonological, and surface dyslexia. Figure 12A.7 diagrams the steps in the reading process and the points of breakdown in the four syndromes. Letter-by-letter dyslexia is equivalent to pure alexia without agraphia. Deep dyslexia is a severe reading disorder in which patients recognize and read aloud only familiar words, especially concrete imageable nouns and verbs. They make semantic or visual errors in reading and fail completely in reading nonsense syllables or nonwords. Word reading is not affected by word length or by regularity of spelling; one patient, for example, could read ambulance but not am. Most patients have severe aphasia, with extensive left frontoparietal damage.

Phonologic dyslexia is similar to deep dyslexia, with poor reading of nonwords, but single nouns and verbs are read in a nearly normal fashion, and semantic errors are rare. Patients appear to read words without understanding. The fourth type, surface dyslexia, involves spared ability to read laboriously by grapheme-phoneme conversion **but** inability to recognize words at a glance. These patients can

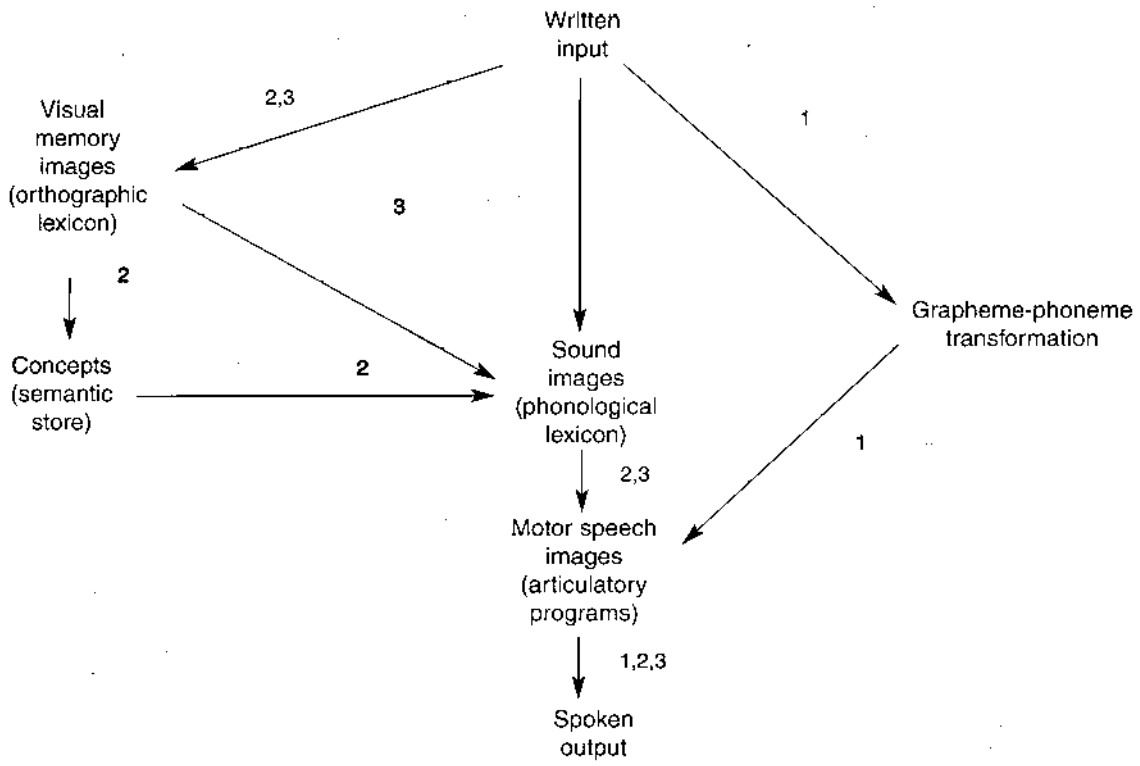

FIGURE 12A.7 Neurolinguistic model of the reading process. According to evidence from the alexias, there are three separate routes to reading: Route 1 is the phonologic (or grapheme-phoneme conversion) route; route 2 is the semantic (or lexical-semantic-phonologic) route; and route 3 is the nonlexical phonologic route. In deep dyslexia, only route 2 can operate; in phonological dyslexia, route 3 is the principal pathway; in surface dyslexia, only route 1 is functional. (Adapted with permission from Margolin, D. I. 1991, "Cognitive neuropsychology. Resolving enigmas about Wernicke's aphasia and other higher cortical disorders," *Arch Neurol,* vol. 48, pp. 751–765.)

read nonsense syllables but not words of irregular spelling, such as colonel or yacht. Their errors tend to be phonologic rather than semantic or visual (e.g., pronouncing *rough* and *though* alike).

Agraphia

Like reading, writing may be affected either in isolation (pure agraphia) or in association with aphasia (aphasic agraphia). In addition, writing can be impaired by motor disorders, by apraxia, and by visuospatial deficits. Isolated agraphia has been described with left frontal or parietal lesions.

Agraphias can be analyzed the same way as the alexias (Figure I2A.S). Thus phonologic agraphia involves the inability to convert phonemes into graphemes or write pronounceable nonsense syllables, in the presence of ability to write familiar words. Deep dysgraphia is similar to phonologic agraphia, but the patient can read nouns and verbs better than articles, prepositions, adjectives, and adverbs. In lexical or surface dysgraphia, patients can write regularly spelled words and pronounceable nonsense words but not irregularly spelled words. These patients have intact phoneme-graph erne conversion but cannot write by a whole-word or "lexical" strategy.

LANGUAGE IN RIGHT HEMISPHERE DISORDERS

Language and communication disorders are important even in parienrs with right hemisphere disease. First, left-handed patients may have right hemisphere language dominance and may develop aphasic syndromes from right hemisphere lesions. Second, right-handed patients occasionally become aphasic after right hemisphere strokes, a phenomenon called *crossed aphasia* (Bakar, Kirshner, and Wertz 1996), These patients presumably have crossed or mixed dominance. Third, even right-handed persons with typical left hemisphere dominance for language have subtly altered language function after right hemisphere damage. Such patients are not aphasic, in that the fundamental mechanisms of speech production, repetition, and comprehension are undisturbed. Affective aspects of language arc impaired, however, so the speech sounds flat and unemotional; the normal prosody, or emotional intonation, of speech is lost. Syndromes of loss of emotional aspecrs of speech are termed *aprosodias* Motor aprosodia involves loss of expressive emotion with preservation of emotional comprehension; sensory aprosodia involves loss of comprehension of affective language, also called *affective agnosia.* More than just emotion, stress and emphasis within a sentence are also affected by right hemisphere

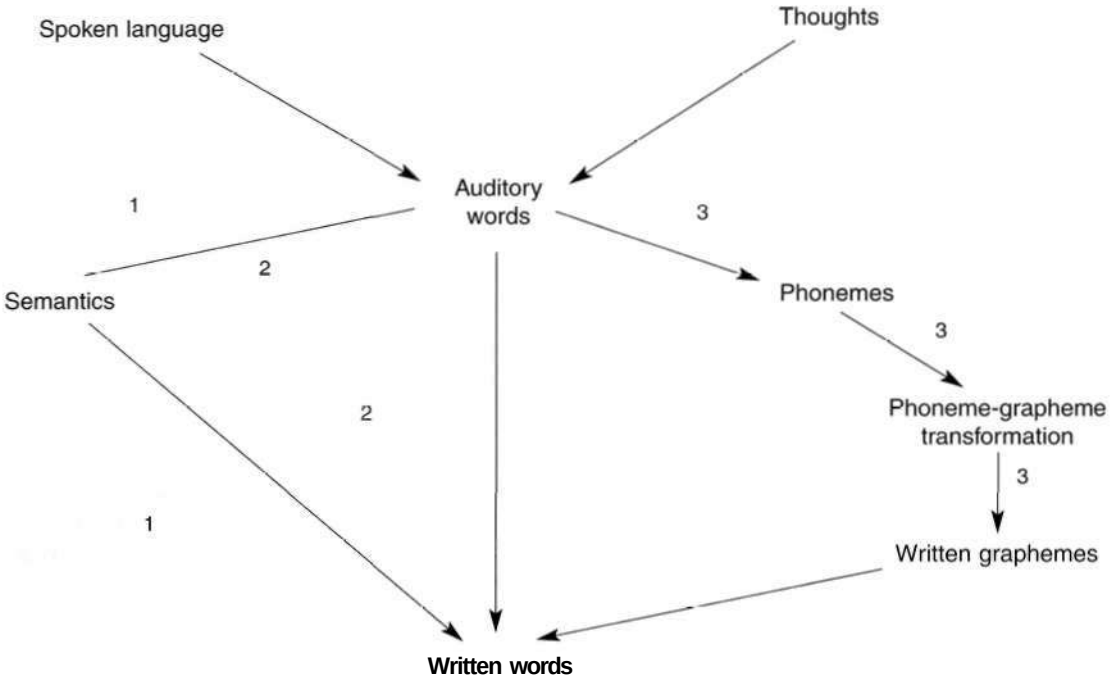

FIGURE 12A.8 Neurolinguistic model of writing and the agraphias. In deep agraphia, only the semantic (phonological-scmantic-lexkal) route (route 1) is operative; in phonologic agraphia, route 2, the nonlexical phonologic route produces written words directly from spoken words; in surface agraphia, only route 3, the phone me-grapheme pathway, can be used to generate writing.

dysfunction. More importantly, such vital aspects of human communication as metaphor, humor, sarcasm, irony, and related constituents of language that transcend the literal meaning of words are especially sensitive to right hemisphere disease. These deficits significantly impair patients in the pragmatics of communication. In other words, patients with right hemisphere damage understand what is said, but not how it is said. They may have difficulty following a complex story. Such higher level language deficits are related to the right hemisphere disorders of inattention and neglect, discussed in Chapters 4 and 38.

LANGUAGE IN DEMENTING DISEASES

Language impairment is commonly seen in patients with dementia. Despite considerable variability from patient to patient, two patterns of language dissolution can be described. The first, the common presentation of AD, involves early loss of memory and general cognitive deterioration. In these patients, mental status examination results are most remarkable for deficits in short-term memory, insight, and judgment, but language impairments can be found in naming and in discourse, with impoverished language content and loss of abstraction and metaphor. The mechanics of language—grammatical construction of sentences, receptive vocabulary, auditory comprehension, repetition, and oral reading—tend to remain preserved until later stages. By aphasia testing, patients with early AD have anomic aphasia. In later stages, language functions become more obviously impaired. In terms of the components of language mentioned earlier in this chapter, the semantic aspects of language tend to deteriorate first, then syntax, and finally phonology. Reading and writing—the last-learned language functions—are among the first to decline. Auditory comprehension later becomes deficient, whereas repetition and articulation remain normal. The language profile may then resemble that of transcortical sensory or Wernicke's aphasia. In terminal stages, speech is reduced to the expression of simple biological want--; eventually, even muteness can develop. By this time, most patients are institutionalized or bedridden.

The second pattern of language dissolution in dementia, considerably less common than the first, involves the gradual onset of a progressive aphasia, often without other cognitive deterioration. Auditory comprehension is involved early in the illness, and specific aphasic symptoms are evident, such as paraphasic or nonfluent speech, misnaming, and errors of repetition. These deficits worsen gradually, mimicking the course of a brain tumor or mass lesion rather than a typical dementia (Grossman et al. 1996; Mesulam 2001), The syndrome is generally referred to as *primary progressive aphasia.* CT scans may show focal atrophy in the left perisylvian region, whereas electroencephalographic (EEG) studies may show focal slowing. **PET** has shown prominent areas of decreased metabolism in the left temporal region and adjacent cortical areas. The pathology underlying primary progressive

aphasia varies (Kertesz et al. 2000). Some cases show the frontotemporal lobar atrophy of Pick's disease and localized spongiform degeneration. In Fnglnnd, this pattern of clinical syndrome and neuropathology is referred to as *frontotemporal dementia,* a term gaining popularity in the United States. In one study of 10 patients with primary progressive aphasia followed prospectively until they became nonfluent or mute, Kertesz and Munoz (2003) found that at autopsy all had evidence of frontotemporal dementia: corticobasal degeneration in 4, Pick body dementia in 3, and tau- and synuclein-negativc ubiquinated inclusions of the motor neuron disease in 3. Imaging studies have shown that primary progressive aphasia is often associated with atrophy in the left frontotemporal region, and other areas such as the fusiform and precentral gyri and intraparietal sulcus are activated, possibly as a compensatory neuronal strategy (Neary and Snowden 1996; Sonty et al. 2003). Familial cases of frontotemporal dementia have recently been linked to chromosome 17 (Heutink et al. 1997). Cases of isolated aphasia secondary to Creutzfeldt-Jakob disease and corticobasal degeneration have also been reported. Finally, a few patients with pathologically proven AD have presented with focal involvement of the language cortex, always with fluent aphasia.

INVESTIGATION OF THE APHASIC PATIENT

Clinical Tests

The bedside language examination is useful in forming a preliminary impression of the type of aphasia and the localization of the causative lesion. Follow-up examinations are also helpful; as in all neurological diagnoses, the evolution of a neurological deficit over time is the most important clue to the specific disease process. For example, an embolic stroke and a brain tumor might both produce Wernicke's aphasia, but strokes occur suddenly, with improvement thereafter, whereas tumors produce gradually worsening aphasia.

In addition to the bedside examination, a large number of standardized aphasia test batteries have been published. The physician should think of these tests as more detailed extensions of the bedside examination. They have the advantage of quantitation and standardization, permitting comparison over time and, in some cases, even a diagnosis of the specific aphasia syndrome. Research on aphasia depends on these standardized tests. For neurologists, the most helpful battery is the Boston Diagnostic Aphasia Examination, or its Canadian adaptation, the Western Aphasia Battery. Both tests provide subtest information analogous to the bedside examination, and therefore meaningful to neurologists, as well as aphasia syndrome classification. The Porch Index of Communicative Ability quantitates performance in many specific functions, allowing comparison over time. Other aphasia tests arc designed to evaluate specific language areas. For example, the Boston Naming Test evaluates a wide variety of naming stimuli, whereas the Token Test evaluates higher level comprehension deficits. Further information on neuropsychologic tests can be found in Chapter 38.

Further diagnosis of the aphasic patient rests on the confirmation of a brain lesion by neuroimaging (Figure 12A.9). The CT brain scan (discussed in Chapter 37B) revolutionized the localization of aphasia by permitting "real-time" delineation of a focal lesion in a living patient; previously, the physician had to outlive the patient to obtain a clinicopathologic correlation at autopsy. MRI scanning provides better resolution of areas difficult to see on CT, such as the temporal cortex adjacent to the petrous bones, and more sensitive detection of tissue pathology, such as early changes of infarction. The anatomic distinction of cortical from subcortical aphasia is best made by MRI. Acute strokes are visualized early on diffusion-weighted MRI.

The EEG is helpful in aphasia in localizing seizure discharges, interictal spikes, and slowing seen after destructive lesions, such as traumatic contusions and infarctions. The EEG can provide evidence that aphasia is an ictal or postictal phenomenon and can furnish early clues to aphasia secondary to mass lesions or to herpes simplex encephalitis. In research applications, electrophysiologic resting via subdural grid and depth electrodus. or stimulation mapping of epileptic foci in preparation for epilepsy surgery, have aided in the identification of cortical areas involved in language.

Cerebral arteriography is useful in the diagnosis of aneurysms, arteriovenous malformations (AVMs), arterial occlusions, vasculitis, and venous outflow obstructions. In preparation for epilepsy surgery, the Wada test, or infusion of amobarbital through an arterial catheter, is useful in the determination of language dominance. Other related studies by language activation with functional MRI (fMRI) or PET are beginning to rival the Wada test for the study of language dominance (Ahou-Khalil and Schlaggar 2002).

Single-photon emission CT (SPECT), PET, and fMRI (see Chapter 38} arc contributing greatly to the study of language. Patterns of brain activation in response to language stimuli have been recorded, mainly in normal persons, and these studies have largely confirmed the localizations based on pathology such as stroke over the past 140 years. In addition, these techniques can be used to map areas of the brain that activate during language functions after insults such as strokes, and the pattern of recovery can be studied. Some such studies have indicated right hemisphere activation in patients recovering from aphasia (Cappa et al. 1997}, hut others have found that only left hemisphere activation is associated with full recovery (Hciss et al. 1999}. Subcortical contributions to aphasia and language in degenerative conditions have been studied

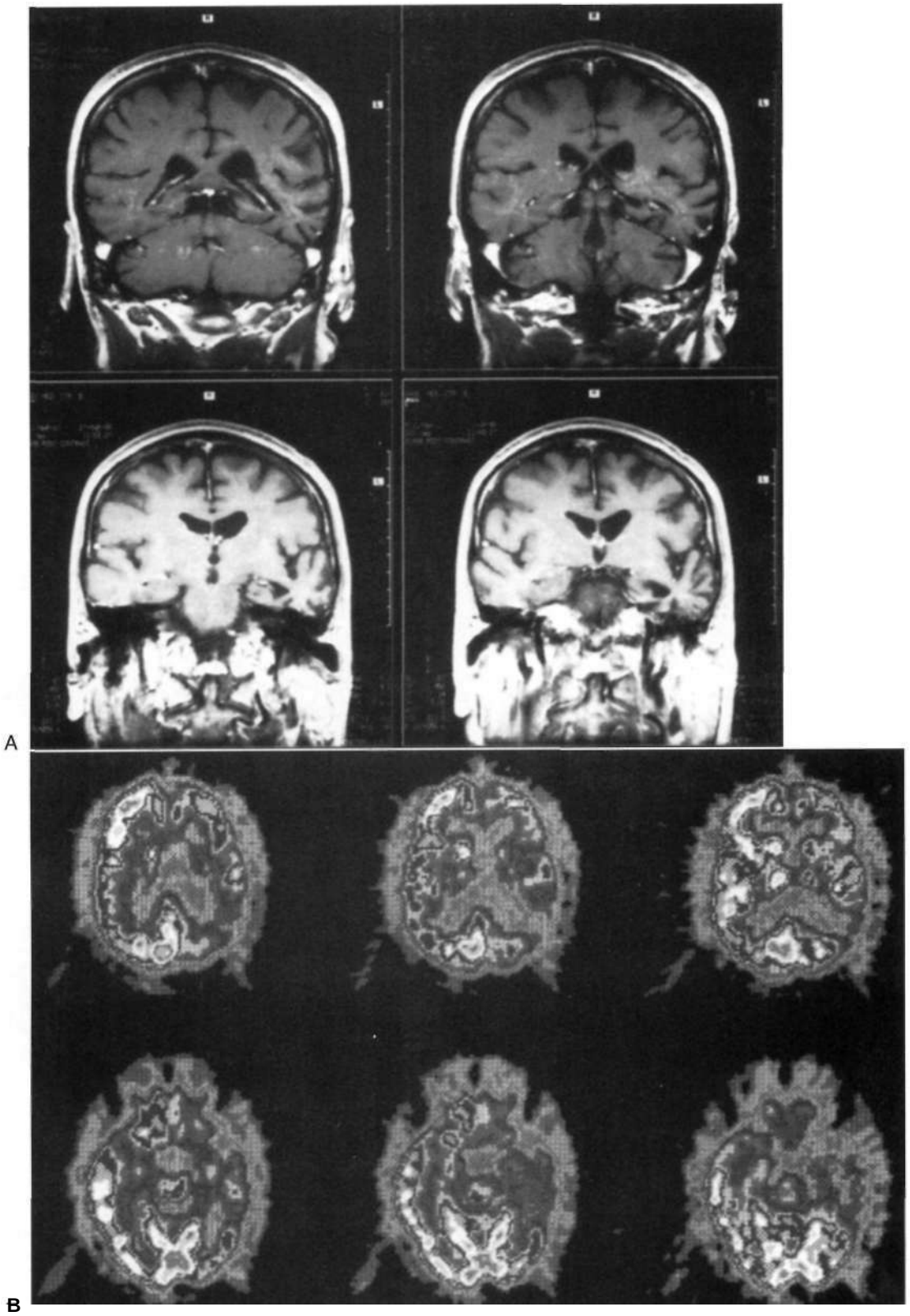

FIGURE 12A.9 (A) Coronal Tl-weighted magnetic resonance imaging scan of a patient with primary progressive aphasia. Note the marked atrophy of the left temporal lobe. (B) Axial fluorine-2-deoxyglucose positron emission tomographic scan showing extensive hypometabolisin in the left cerebral hemisphere, especially marked in the left temporal lobe.

with PET. These techniques provide the best correlation between brain structure and function currently available and should help advance our understanding of language disorders and their recovery.

DIFFERENTIAL DIAGNOSIS

Vascular lesions, especially ischemic strokes, are the most common causes of aphasia. Historically, most research studies in aphasia have used patients who have had a stroke because stroke is an "experiment" of nature in which one area of the brain is damaged while the rest remains theoretically intact. Strokes are characterized by the abrupt onset of a neurological deficit in a patient with vascular risk factors. The precise temporal profile is important: Most embolic strokes are sudden and maximal at onset, whereas thrombotic strokes typically wax and wane or increase in steps. The bedside aphasia examination is helpful in delineating the vascular territory affected. For example, the sudden onset of Wernicke's aphasia nearly always indicates an embolus to the inferior division of the left middle cerebral artery. Global aphasia may be caused by an embolus to the middle cerebral artery stem, thrombosis of the internal carotid artery, or even a hemorrhage into the deep basal ganglia. Whereas most aphasic syndromes involve the territory of the left middle cerebral artery, transcortical motor aphasia is specific to the anterior cerebral territory, and pure alexia without agraphia is specific to the posterior cerebral artery territory. The clinical features of the aphasia are thus of crucial importance to the vascular diagnosis.

Hemorrhagic strokes are also an important cause of aphasia, most commonly the basal ganglionic hemorrhages associated with hypertension. The deficits tend to worsen gradually over minutes to hours, in contrast to the sudden ot stepwise onset of ischemic strokes. Headache, vomiting, and obtundation are more common with hemorrhages. Because hemorrhages compress cerebral tissue without necessarily destroying it, the ultimate recovery from aphasia is often better in hemorrhages than in ischemic strokes, although hemorrhages are more often fatal. Other etiologies of intracerebral hemorrhage include anticoagulant use, head injury, blood dyscrasias, thrombocytopenia, and bleeding into structural lesions, such as infarctions, tumors, AVMs, and aneurysms. Hemorrhages from AVMs mimic strokes, with abrupt onset of focal neurological deficit. Patients with ruptured aneurysms, on the other hand, present with severe headache and stiff neck or with coma; most patients have no focal deficits, but delayed deficits (e.g., aphasia) may develop secondary to vasospasm. Lobar hemorrhages may occur in elderly patients without hypertension. These hemorrhages occur near the cortical surface, sometimes extending into the subarachnoid space, and they may be recurrent. Pathological studies have shown amyloid deposition in small arterioles, or amyloid angiopathy. A final vascular cause of aphasia is cerebral vasculitis (see Chapter 57G).

Traumatic brain injury is a common cause of aphasia. Cerebral contusions, depressed skull fractures, and hematomas of the intracerebral, subdural, and epidural spaces all cause aphasia when they disrupt or compress left hemisphere language structures. Trauma tends to be less localized than ischemic stroke, and thus aphasia is often admixed with the general effects of the head injury, such as depressed consciousness, encephalopathy or delirium, amnesia, and other deficits. Head injuries in young people may be associated with severe deficits but excellent long-term recovery. Language deficits, especially those involving discourse organization, can be found in most cases of significant closed-head injury. Gunshot wounds produce focal aphasic syndromes, which rival stroke as a source of clinicoanatomic correlation. Subdural hematomas are infamous for mimicking other neurological syndromes. Aphasia is occasionally associated with subdural hematomas overlying the left hemisphere, but it may be mild and may be overlooked because of the patient's more severe complaints of headache, memory loss, and drowsiness.

Tumors of the left hemisphere frequently present with aphasia. The onset of the aphasia is gradual, and other cognitive deficits may be associated because of edema and mass effect. Aphasia secondary to an enlarging tumor may thus be difficult to distinguish from a diffuse encephalopathy or early dementia. Any syndrome of abnormal language function should therefore be investigated for a focal dominant-hemisphere lesion.

Infections of the nervous system may cause aphasia. Brain abscesses can mimic tumors in every respect, and those in the left hemisphere can present with progressive aphasia. Chronic infections, such as tuberculosis or syphilis, can result in focal abnormalities that run the entire gamut of central nervous system symptoms and signs. Herpes simplex encephalitis has a predilection for the temporal lobe and orbital frontal cortex, and aphasia can be an early symptom, along with headache, confusion, fever, and seizures. Aphasia is often a permanent sequela in survivors of herpes encephalitis. Acquired immunodeficiency syndrome (AIDS) is rapidly becoming a common cause of language disorders. Opportunistic infections can cause focal lesions anywhere in the brain, and the neurotropic human immunodeficiency virus agent itself produces a dementia (AIDS-dementia complex), in which language deficits play a part.

Aphasia is frequently caused by the degenerative central nervous system diseases. Reference has already been made to the focal, progressive aphasia in patients with Pick's disease and spongiform degenerations as compared with the more diffuse cognitive deterioration characteristic of AD. Language dysfunction in AD may be more common in familial cases and may predict poor prognosis. Cognitive deterioration in patients with Parkinson's disease may also include language deterioration similar to that of AD,

although Parkinson's disease tends to involve more fluctuation in orientation and greater tendency to active hallucinations and delusions, A striking abnormality of speech (i.e., initial stuttering followed by ttue aphasia and dementia) has been described in the dialysis dementia syndrome. This disorder may be associated with spongiform degeneration of the frontotcmporal cortex, similar to Creutzfeldt-Jakob disease. Paraphasic substitutions and nonsense speech are also occasionally encountered in acute encephalopathies, such as hyponatremia or lithium toxicity.

A final cause of aphasia is seizures. Seizures can be associated with aphasia in children as part of the Landau-Kleffner syndrome or in adults as either an ictal or a postictal Todd's phenomenon. Epileptic aphasia is important to recognize, in that anticonvulsant drug therapy can prevent the episodes, and unnecessary investigation or treatment for a new lesion, such as a stroke, can be avoided. As mentioned earlier, localization of language areas in epileptic patients has contributed greatly to the knowledge of language organization in the brain. The work of Ojemann (1991) has shown that more than 15% of young epileptic patients have no Broca's or no Wernicke's area. In addition, a new language area, the basal temporal language area, has been discovered through epilepsy stimulation studies and only later confirmed in patients with spontaneous seizures (Kirshner et al. 1995).

RECOVERY AND REHABILITATION OF APHASIA

Patients with aphasia from acute disorders, such as stroke, generally show spontaneous improvement over days, weeks, and months. In general, the greatest recovery occurs during the first 3 months, but improvement may continue over a prolonged period, especially in young patients and in global aphasics. The aphasia type often changes during recovery: Global aphasia evolves into Broca's aphasia, and Wernicke's aphasia into conduction or anomic aphasia. Language recovery may be mediated by shifting of functions to the right hemisphere or to adjacent left hemisphere regions. As mentioned earlier, studies of language activation PET and SPECT scanning techniques are advancing our understanding of the neuroanatomy of language recovery (Heiss et al. 1999). In addition, study of patients in the very acute phase of aphasia, with techniques of diffusion- and perfusion-weighted MRI, has suggested less variability in the correlation of comprehension impairment with left temporal ischemia than has been suggested from testing of chronic aphasia, after recovery and compensation have commenced (Hillis et al. 2001).

Speech therapy, provided by speech-language pathologists, attempts to facilitate language recovery by a variety of techniques and to help the patient compensate for lost functions (see Chapter 54), Repeated practice in articulation and comprehension tasks has traditionally been used to stimulate improvement. Other techniques include melodic intonation therapy, which uses melody to involve the right hemisphere in speech production; visual action therapy, which uses gestural expression; and treatment of aphasic perseveration, which aims to reduce repetitive utterances. Two other therapeutic techniques are functional communication therapy, which takes advantage of extralinguistic communication, and cVIC or Lingraphica, a computer program originally developed for primate communication. Patients who cannot speak can learn to produce simple sentences via computer. Augmentative devices make language expression possible through use of printers or voice simulators. Speech therapy has remained controversial: Some studies have suggested that briefly trained volunteers can induce as much improvement as speech-language pathologists, but large randomized trials have clearly indicated that patients who undergo formal speech therapy recover better than untreated patients (Robey 1998).

A new approach to language rehabilitation is the use of pharmacological agents to improve speech. Albert and colleagues first reported that the dopaminergic drug bromocriptine promotes spontaneous speech output in transcortical motor aphasia. Several other studies have supported the drug in nonfluenr aphasias, although one controlled study showed no benefit. Stimulant drugs are also heing tested in aphasia rehabilitation. As new information accumulates on the neurochemistry of cognitive functions, other pharmacologic therapies may he forthcoming.

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Chapter 12
Language and Speech Disorders

B. DYSARTHRIA AND APRAXIA OF SPEECH

Howard S. Kirshner

MOTOR SPEECH DISORDERS

Motor speech disorders are syndromes of abnormal articulation, the motor production of speech, without abnormalities of language. A patient with a motor speech disorder should be able to produce normal expressive language in writing and to comprehend both spoken and written language. If a listener transcribes into print or type the speech of a patient with a motot speech disorder, the text should read as normal language. Motor speech disorders include dysarthrias, disorders of speech articulation, apraxia of speech, a motor programming disorder for speech, and five rarer syndromes: aphcmia, foreign accent syndrome, acquited stuttering, primary progressive anarthria, and the opercular syndrome. In an analysis of speech and language disorders at the Mayo Clinic, Duffy (1995) reported that 46.3% of the patients had dysarthria, 27.1% had aphasia, 4.6% had apraxia of speech, 9% had other speech disorders (such as stuttcting), and 13% had other cognitive or linguistic disorders.

DYSARTHRIAS

Dysarthrias involve the abnormal atticulation of sounds or phonemes because of abnormal activation of the otomandibular pharyngeal muscles, affecting the speed, strength, timing, range, or accuracy of speech (Duffy 1995). Dysarthria is generally neurogenic, related to dysfunction of the central nervous system, nerves, neuromusculat junction, and muscle, with a contribution of sensoty deficits in some cases, but local structural problems of the palate, tongue, ot larynx may also cause speech abnormalities. Dysarthria can affect not only articulation, but also phonation, breathing, or prosody (emotional tone) of speech. Total loss of ability to articulate is called *anarthria,* wheteas dysarthria usually involves the distortion of consonant sounds.

Like the aphasias, dysatthtias can be analyzed in terms of the specific brain lesion sites associated with specific-patterns of speech impairment. Analysis of dysarthria at the bedside is useful for the localization of neurological lesions and the diagnosis of neurological disorders. An experienced examiner should be able to tecognize and categorize the majoi types of dysarthria, rather than referring to "dysarthria" as a single disorder.

The examination of speech at the bedside should include repeating syllables, words, and sentences. Repeating consonant sounds (such as /p/, /p/, /p/) or shifting consonant sounds (/p/, /t/, *Ik!)* can help identify which consonants consistently cause trouble.

The Mayo Clinic classification of dysarthria (Duffy 1995), widely used in the United States, includes six categories: (1) flaccid, (2) spastic and "unilateral upper motor neuron" (UMN), (3) ataxic, (4) hypokinetic, (5) hyperkinetic, and (6) mixed dysarthria. These types of dysarthria are summarized in Table 12B.1.

Flaccid dysarthria is associated with disorders involving lower moror neuron weakness of the bulbar muscles, such as polymyositis, myasthenia gtavis, and bulbar poliomyeliris. The speech pattern is breathy and nasal, with indistinctly pronounced consonants. In the case of myasthenia gtavis, the patient may begin reading a paragraph with normal enunciation, but by the end of the paragraph, the atticulation is soft, breathy, and frequently interrupted by labored respirations.

Spastic dysarthria occurs in patients with bilateral lesions of the motor cortex or corticobulbat tracts, such as bilateral strokes. The speech is harsh or "strain strangle" in vocal

Table 12B.1: Bedside features of transcortical aphasias

Type	*Localization*	*Auditory signs*	*Diseases*
Flaccid	Lower motor nei	Breathy, nasal voice, imprecise consonants	Stroke, myasthenia gravis
Spastic	Bilateral upper motor neuron	Strain strangle, harsh voice; slow rate; imprecise consonants	Bilateral strokes, tumors, primary lateral sclerosis
Unilateral upper motor neuron	Unilateral upper motor neuron	Consonant imprecision, slow rate, harsh voice quality	Stroke, tumor
Ataxic	(.i.Tcbi'llum	Irregular articulatory breakdowns, excessive and equal stress	Sttoke, degenerative disease
Hypokinetic	Extrapyramidal	Rapid rate, reduced loudness, monopitch and monoloudness	Parkinson's disease
] ty perk im-tic	Extrapyramidal	Prolonged phonemes, variable rate, inappropriate silences, voice stoppages	Dystonic, Huntington's disease
Spastic flaccid	Upper and lower motor neuron	Hypernasality; strain strangle, hatsh voice, slow rate, imprecise consonants	Amyotrophic lateral sclerosis, multiple strokes

Adapted with permission from Duffy, J, R. 1995, *Motor Speech Disorders: Substrates, Differential Diagnosis, and Management,* Mosby, St. Louis; and Kirshner, H. S. 2002, *Behavioral Neurology: Practical Science of Mind and Brain* , Butterworth-Hcinemann, Boston,

quality, with reduced rate, low pitch, and consonant errors. Patients often have the features of "pseudobulbar palsy," including dysphagia, exaggerated jaw jerk and gag reflexes, and easy laughter and crying (emotional incontinence or pathological laughter and crying). Another variant is the "opercular syndrome" (see Opercular Syndrome, later in this chapter).

A milder variant of spastic dysarthria, *"unilateral UMN"* dysarthria, is associated with unilateral UMN lesions (Duffy 1995). This type of dysarthria has similar features to spastic dysarthria, only in a less severe form. Unilateral UMN dysarthria is one of the most common types of dysarthria, occurring in patients with unilateral strokes.

Ataxic dysarthria or "scanning speech," associated with cerebellar disorders, is characterized by one of two patterns: irregular breakdowns of speech with explosions of syllables interrupted by pauses or a slow cadence of speech with excessively equal stress on every syllable. The second pattern of ataxic dysarthria is referred to as *scanning speech.* A patient with ataxic dysarthria, attempting to repeat the phoneme /p/ as rapidly as possible, produces either an irregular rhythm, resembling popcorn popping, or a very slow rhythm. Causes of ataxic dysarthria include cerebellar strokes, tumors, multiple sclerosis, and cerebellar degenerations.

Hypokinetic dysarthria, the typical speech pattern in Parkinson's disease, is notable for decreased and monotonous loudness and pitch, rapid rate, and occasional consonant errors. In a recent stud) of brain activation by positron emission tomography (PET) methodology (Liotti et al. 2003), premotor and supplementary motor area activation was seen in untreated patients with Parkinson's disease and hypokinetic dysarthria, but not in normal subjects. Following a voice treatment protocol, these premotor and motor activations diminished, whereas right-sided basal ganglia activations increased. Hypokinetic dysarthria responds both to behavioral therapies and to pharmacologic treatment of Parkinson's disease.

Hyperkinetic dysarthria, a pattern in some ways opposite to hypokinetic dysarthria, is characterized by marked variation in tate, loudness, and timing, with distortion of vowels, harsh voice quality, and occasional sudden stoppages of speech. This speech pattern is seen in hyperkinetic movement disorders such as Huntington's disease. The final category, *mixed* dysarthria, involves combinations of the other five types. One common mixed dysarthria is a spastic-flaccid dysarthria seen in amyotrophic lateral sclerosis (ALS). The patient with ALS has the harsh strain-strangle voice quality of spastic dysarthria, combined with the breathy and hypernasal quality of flaccid dysarthria. Multiple sclerosis may feature a spastic - flaccid-ataxic or spastic-ataxic mixed dysarthria, in which slow rate or irregular breakdowns arc added to the other characteristics seen in spastic and flaccid dysarthria. Wilson's disease can involve hypokinetic, spastic, and ataxic features,

The management of dysarthria includes speech therapy techniques to strengthen muscles, train more precise articulations, slow the rate of speech to increase intelligibility, or teach the patient to stress specific phonemes. Devices such as pacing boards to slow articulation, palatal lifts to reduce hypernasality, amplifiers to increase voice volume, communication boards for subjects to point to pictures, and augmentative communication devices and computer techniques can be used when the patient is unable to communicate in speech. Injections of collagen into the vocal folds and surgical procedures such as a pharyngeal

flap to reduce hypcrnasality or vocal fold transposition surgery to increase loudness may help the patient speak more intelligibly.

APRAXIA OF SPEECH

Apraxia of speech is a disorder of the programming of articulation of sequences of phonemes, especially consonants. The motor speech system makes errors in selection of consonant phonemes, in the absence of any "weakness, slowness, or incoordination" of the muscles of speech articulation (Wert/., LaPointe, and Roscnbek 1991). The phrase "apraxia of speech" implies that the disorder is one of a skilled, sequential motor activity (as in other apraxias), rather than a primary motor disorder. Consonants are often substituted rather than distorted, as in dysarthria. Patients have special difficulty with polysyllabic words and consonant shifts, as well as in initiating articulation of a word. Errors arc inconsistent from one attempt to the next, in contrast to the consistent distortion of phonemes in dysarthria.

The four cardinal features of apraxia of speech are (1) effortful, groping, or rrial-and-error" attempts at speech, with efforts at self-correction; (2) dysprosody; (3) inconsistencies in articulation errors; and (4) difficulty initiating utterances. Usually the patient has the most difficulty with the first phoneme of a polysyllabic utterance. The patient may make an error in attempting to produce a word on one trial, a different error the next time, and a normal utterance the third time.

Apraxia of speech is rare in isolated form, but it frequently contributes to the speech and language deficit of Broca's aphasia. A patient with apraxia of speech, in addition to aphasia, will often write better than he or she can speak, and comprehension is relatively preserved. Dronkers (1996) presented evidence from computed tomographic (CT) and magnetic resonance imaging (MRI) scans indicating that although the anatomic lesions vary, patients with apraxia of speech virtually always have damage in the left hemisphere insula, whereas patients without apraxia of speech do not.

Testing of patients for speech apraxia includes the repetition of sequences of phonemes (pa/ta/ka), as discussed previously (see Dysarthria). Repetition of a polysyllabic word (e.g., "catastrophe" or "television") is especially likely to elicit apraxic errors.

Oral or Buccolingual Apraxia

Apraxia of speech is not the same as oral-buccolingual apraxia, or ideomotor apraxia for learned movements of the tongue, lips, and larynx. Oral apraxia can be elicited by asking a subject to lick his or her upper lip, smile, or stick out the tongue. Oral apraxia is discussed in Chapter 13. Both oral apraxia and apraxia of speech can coexist with Broca's aphasia.

APHEMIA

Another differential diagnosis with both apraxia ol speech and dysarthria is the syndrome of *aphemia,* Broca first used the term *aphemie* to designate the syndrome later called "Broca's aphasia," but recently, the term has been reserved for a syndrome of near muteness, with normal comprehension, reading, and writing. Aphemia is clearly a motor speech disorder, rather than an aphasia, it written language and comprehension are indeed intact. Patients are often anarthric, with no speech whatever, and then effortful nonfluent speech emerges. Some patients have persisting dysarthria, with dysphonia and sometimes distortions of articulation that sound similar to foreign accents (see The "Foreign Accent Syndrome," later in this chapter). Alexander, Nacscr, and Palumbo (1990) associated pure anarthria with lesions of the face area of motor cortex. Functional imaging studies also suggest that articulation is mediated at the level of the primary motor face area (Riecker et al. 2000), and disruption of speech articulation can be produced by transcranial magnetic stimulation over the motor face area (Epstein et al. 1999). Controversy remains over whether aphemia is equivalent to apraxia of speech, as suggested by Alexander, Benson, and Stuss (1989). In general, aphemia is likely to involve lesions in the vicinity of the primary motor cortex and perhaps Broca's area, whereas apraxia of speech may be localized to the insula.

THE "FOREIGN ACCENT SYNDROME"

The "foreign accent syndrome" is an acquired form of motor speech disorder, related to the dysarthrias, in which the patient acquires a dysflucncy resembling a foreign accent, usually after a unilateral stroke (Kurowski, Blumstcin, and Alexander 1996; Takayama et al. 1993). Lesions may involve the motor cortex of the left hemisphere. The disorder can also be mixed with aphasia.

ACQUIRED STUTTERING

Another uncommon motor speech disorder following acquired brain lesions is a pattern resembling developmental stuttering, referred to as *acquired* or *cortical stuttering.* Acquired stuttering involves hesitancy in producing initial phonemes, with an associated dysrhythmia of speech. Acquired stuttering clearly overlaps with apraxia of speech but may lack the other features of apraxia of speech discussed earlier in this chapter. Acquired stuttering has been described most often in patients with left

hemisphere cortical strokes {Franco et al. 2000; Turgut, Utku, and Balci 2002), but the syndrome has also been reported with subcortical lesions including infarctions of the pons, basal ganglia, and subcortical white matter (Ciabarra ct al. 2000). Recurrence of childhood stuttering has been reported in patients with Parkinson's disease, suggesting involvement of the dopaminergic system (Shahcd and Jankovic2001).

PRIMARY PROGRESSIVE ANARTHRIA

A few cases have been described of progressive motor speech difficulty, usually leading to complete muteness. These cases are closely related to the syndrome of primary progressive aphasia (sec Chapter 12A). Most such patients have a progressive language disorder, but a few have had either dysarthria or apraxia of speech (Tyrrell ct al. 1991; Kertesz et al. 1994; Chapman ct al. 1997), These cases have all had lobar degeneration of the frontal cortex, some with involvement also of the temporal and parietal lobes. The clinical diagnoses of these patients have included fronto-temporal dementia or cortical basal ganglionic degeneration. We studied a patient whose final pathology was most consistent with multiple system atrophy.

OPERCULAR SYNDROME

The opercular syndrome, also called Foix-Chavany-Marie syndrome, Worster-Drought syndrome, or cheiro-oral syndrome (sensory disturbance in one hand and the ipsilateral otal corner) (Bakar, Kirshner, and Nia?. 1998), is a severe form of pseudobulbar palsy in which patients with bilateral lesions of the pcrisylvian cortex or subcortical connections become completely mute. These patients can follow commands involving the extremities but not of the cranial nerves; for example, they may be unable to open or close their eyes or mouth or smile voluntarily, yet they smile when amused, yawn spontaneously, and even utter cries in response to emotional stimuli. **The ability to follow** limb commands shows that the disorder is not an aphasic disorder of comprehension. The discrepancy between automatic activation of the cranial musculature and inability to perform the same actions voluntarily has been called an *automatic-voluntary dissociation.* The syndrome is usually seen in patients with multiple strokes, but rare cases of progressive disease, as in the syndrome of primary progressive anarthria, may occur.

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Chapter 13
Neurogenic Dysphagia

Ronald F. Pfeiffer

Swallowing is like a wristwarcb. It appears, at first glance, to be a simple, even mundane, mechanism but under the unassuming face is a process that is both tremendously complex and fascinating. When operating properly, it functions unobtrusively and is afforded scant attention. Malfunction can go completely unnoticed for a time, but when it finally becomes manifest, serious, and sometimes catastrophic, consequences can ensue.

Impaired swallowing, or dysphagia, can originate from disturbances in the mouth, pharynx, or esophagus and can involve mechanical, musculoskeletal, or neurogenic mechanisms. Although mechanical dysphagia is an important topic, this chapter primarily focuses on neuromuscular and neurogenic causes of dysphagia because processes in these categories are what the neurologist is most likely to encounter.

Dysphagia is actually a quite common problem in neurological patients and can occur in a broad array of neurological or neuromuscular conditions. It has been estimated that neurogenic dysphagia develops in approximately 400,000-800,000 people per year (Robbins 1999) and that dysphagia is present in roughly 50% of inhabitants of long-term care units (Lin et al. 2002). Moreover, dysphagia can lead to superimposed problems such as inadequate nutrition, dehydration, recurrent upper respiratory tract infections, and frank aspiration with consequent pneumonia and even asphyxia. It thus constitutes a formidable and common problem confronting the neurologist in everyday practice.

NORMAL SWALLOWING

Swallowing is a surprisingly complicated and intricate phenomenon, comprising a mixture of voluntary and reflex or automatic actions that arc engineered and carried out by a combination of 26 pairs of pharyngeal and laryngeal muscles (not counting muscles used for chewing) and 5 cranial nerves that in turn receive directions from centers within the central nervous system (Wuttge-Hanning and Hannig 1995). Reflex swallowing is coordinated and carried out at the brainstem level, where centers act directly on information received from sensory structures within the oropharynx and esophagus. Volitional swallowing is not surprisingly accompanied by additional activity that originates not only in motor and sensory cortices, but also in other cerebral structures (Hamdy et al. 1999; Zald and Pardo 1999).

The process of swallowing can conveniently be broken down into three distinct stages or phases: oral, pharyngeal, and esophageal. These components have also been distilled into what have been termed the *horizontal* and *vertical subsystems,* reflecting the direction of bolus flow in each component (when the individual is upright when swallowing). The oral phase of swallowing comprises the horizontal subsystem and is largely volitional in character, whereas the pharyngeal and esophageal phases comprise the vertical subsystem and are primarily under reflex control.

In the oral, or swallow preparatory, phase food is taken into the mouth and if needed is chewed; saliva is secreted to provide both lubrication and the initial "dose" of digestive enxymes, and the food bolus is formed and shaped by die tongue. The tongue then propels the bolus backward to the pharyngeal inlet where, in a piston-like action, it delivers the bolus into the pharynx. This in turn initiates the pharyngeal phase in which a cascade of intricate, extremely rapid, and exquisitely coordinated movements seal off the nasal passages and protect the trachea while the cricopharyngeal muscle, which functions as the upper esophageal sphincter (UES), relaxes and allows the bolus to enter the

pharynx. As an example of the intricacy of movements during this phase of swallowing, the UES, prompted in part by traction produced by elevation of the larynx, actually relaxes just before arrival of the food bolus, creating suction that assists in guiding the bolus into the pharynx. The bolus then enters the esophagus where peristaltic contractions usher it distally and, upon relaxation of the lower esophageal sphincter, into the stomach.

NEUROPHYSIOLOGY OF SWALLOWING

Central control of swallowing has traditionally been ascribed to brainstem structures, with cortical supervision and modulation emanating from the inferior precentral gyrus. However, recent positron emission tomography (PET) (Zald and Pardo 1999) and transcranial magnetic stimulation (TMS) (Hamdy et al. 1996) studies of volitional swallowing reveal a considerably more complex picture in which a broad network of brain regions are active in the control and execution of swallowing.

It is, perhaps, not surprising that the strongest activation in PET studies of volitional swallowing docs occur in the lateral motor cortex within the inferior precentral gyrus, wherein lie the cortical representations of tongue and face (Hamdy et al. 1999; Zald and Pardo 1999), There is disagreement among investigators, however, in that some have noted bilaterally symmetrical activation of the lateral motor cortex (Zald and Pardo 1999), whereas others have noted a distinctly asymmetrical activation, at least in a portion of subjects tested (Hamdy et al. 1999).

Some additional, and perhaps somewhat surprising, brain areas arc also activated during volitional swallowing (Hamdy et al. 1999; Zald and Pardo 1999). The supplementary motor area may play a role in preparation for volitional swallowing and the anterior cingulate cortex may be involved with monitoring autonomic and vegetative functions. Another area of activation during volitional swallowing is the anterior insula, particularly on the right. It has been suggested that this activation may provide the substrate that allows gustatory and other intraoral sensations to modulate swallowing. PET studies also consistently demonstrate distinctly asymmetrical, left-sided activation of the cerebellum during swallowing. This activation may reflect cerebellar input concerning coordination, timing, and sequencing of swallowing. Activation of putamen has also been noted during volitional swallowing, but it has not been possible to differentiate this activation from that seen with tongue movement alone.

Within the brainstem, swallowing appears to be regulated by central pattern generators that contain the programs directing the sequential movements of the various muscles involved with swallowing. These pattern generators reside in the medial reticular formation of the rostral medulla and the reticulum adjacent to the nucleus tractus soiitarius (Hunter et al. 1997). These centers then project to the nucleus ambiguus and the dorsal motor nucleus of the vagus, which directly control motor output to the pharyngeal musculature and proximal esophagus.

It has thus become evident that a large network of structures participates in the act of swallowing, especially volitional swallowing. The presence of this network presumably accounts for the broad array of neurological disease processes that can produce dysphagia as a part of their clinical picture.

MECHANICAL DYSPHAGIA

Structural abnormalities, both within and adjacent to the **mouth,** pharynx, and esophagus, can interfere with swallowing on a strictly mechanical basis, despite fully intact and functioning nervous and musculoskeletal systems (Table 13.1). Within the mouth macroglossia., temporomandibular joint dislocation, certain congenital anomalies, and intraoral tumors can impede effective swallowing and produce mechanical dysphagia. Pharyngeal function can be compromised by processes such as retropharyngeal tumor or abscess, cervical anterior osteophyte formation, Zenker's diverticulum, or thyroid gland enlargement. An even broader array of structural lesions can interfere with esophageal function, including malignant or benign esophageal tumors, metastatic carcinoma, esophageal stricture from numerous causes, vascular abnormalities such as aortic aneurysm or aberrant origin of the subclavian artery, or even primary gastric abnormalities such as hiatal hernia. Gastroesophageal reflux can also produce dysphagia. Individuals with these problems, however, are more likely to wind up in the hands of a gastrocntcrologist rather than a neurologist.

NEUROMUSCULAR DYSPHAGIA

A variety of neuromuscular disease processes of diverse etiology can involve the oropharyngeal and esophageal musculature and produce dysphagia as part of their broader neuromuscular clinical picture (Table 13.2). Certain muscular dystrophies, inflammatory myopathies, and mitochondrial myopathies all can display dysphagia, as can disease processes affecting the myoneural junction, such as myasthenia gravis.

Oculopharyngeal Muscular Dystrophy

Oculopharyngeal muscular dystrophy (OPMD) is a rare autosomal dominant disorder that is most frequently encountered in individuals with a French Canadian ethnic background. It is the consequence of a GCG trinucleotide repeat expansion in the poly{A)-binding protein nuclear 1 gene (also called poly|A]-binding protein 2, or PABP2,

Table 13.1: Mechanical dysphagia

- Oral
  - Amyloidosis
- Congenital abnormalities
  - Intraoral tumors
  - Lip injuries
    - Burns
    - Trauma
  - Macroglossia
  - Scleroderma
  - Temporomandibular joint dysfunction
  - Xerostomia
    - Sjogren's syndrome
- Pharyngeal
  - Cervical anterior osteophytes
  - Infection
    - Diphtheria
  - Thyromegaly
  - Retropharyngeal abscess
  - Rctrophatyngeal tumor
  - Zenker's diverticulum
- Esophageal
  - Aberrant origin of right subclavian artery
  - Caustic injury
  - Esophageal carcinoma
  - Esophageal diverticulum
  - Esophageal infection
    - *Candida albicans*
    - Herpes simplex virus
    - Cytomegalovirus
    - Varicella-zoster virus
  - Esophageal intramural pseudodiverticula
  - Esophageal stricture
  - Esophageal ulceration
  - Esophageal webs or rings
  - Gasttoesophageal reflux disease
  - Hiatal hernia
  - Metastatic carcinoma
  - Posterior mediastinal mass
  - Thoracic aortic aneurysm

Table 13.2: Neuromuscular dysphagia

- Oropharyngeal
  - Inflammatory myopathies
    - Detmatomyositis
    - Inclusion body myositis
    - Polymyositis
  - Mitochondrial myopathics
    - K earns- Say re syndrome
    - Mitochonilriiil lk'nro^istrointi-stinal eiicephalomyopnthy
  - Muscular dystrophies
    - Due hen tie's
    - Facioscapulohumeral
    - Limb-girdle
    - Myotonic
    - Oculopharyngeal
  - Neuromuscular junction disorders
    - Botulism
    - Lambert-Eaton syndrome
    - Myasthenia gravis
    - Tetanus
  - Scleroderma
  - Stiff-man syndrome
- Esophageal
  - Amyloidosis
  - Inrl.imiii.itory myopathics
    - Derma tomy os itis
    - Polymyositis
  - Scleroderma

gene) on chromosome 14 (Hill et al. 2001). OPMD is unique among the muscular dystrophies because of its appearance in older individuals, with symptoms typically first appearing between ages 40 and 60 years (Brais et al. 1999). It is characterized by slowly progressive ptosis, dysphagia, and proximal limb weakness. Because of the ptosis, patients with OPMD may assume an unusual posture characterized by raised eyebrows and extended neck.

Dysphagia in OPMD is due to impaired function of the oropharyngeal musculature. Although ir evolves slowly over many years, OPMD can eventually result not only in difficulty or discomfort with swallowing, but also in weight loss, malnutrition, and aspiration (Christopher et al. 2001). No specific treatment for the muscular dystrophy itself is available, but cricopharyngeal myotomy affords dysphagia relief in more than 80% of treated individuals (Fradet et al. 1997). More recently, botulinum toxin injections have been successfully used to treat dysphagia in OPMD (Restivo et al. 2000).

Myotonic Dystrophy

Myotonic dystrophy is an autosomal dominant disorder whose phenotypic picture includes not only skeletal muscle, but also cardiac, ophthalmologic^!, and endocrinological involvement. Mutations at two distinct locations have now been associated with the clinical picture of myotonic dystrophy. Type 1 myotonic dystrophy is due to a CTG expansion in the DMPK gene on chromosome 19, whereas type 2 is the consequence of a CCTG repeat expansion in the ZNF9 gene on chromosome 3 (Ranum and Day 2002).

Gastrointestinal (GI) symptoms develop in more than 50% of individuals with the clinical phenotype of myotonic dystrophy and may be the most disabling component of the disorder in 25%. GI symptoms may actually antedate the appearance of other neuromuscular features. Subjective dysphagia is one of the most prevalent GI features and has been repotted to be present in 37-56% of patients (Fate-kin et al. 2001). Coughing when eating, suggestive of aspiration, may occur in 33%. Objective measures paint a picture of even more pervasive impairment, demonstrating disturbances in swallowing in 70-80% of persons with myotonic dystrophy (Errekin et al. 2001). In one study,

75% of patients asymptomatic for dysphagia were still noted to have abnormalities on objective testing.

A variety of abnormalities in objective measures of swallowing have been documented in myotonic dystrophy. Abnormal cricopharyngeal muscle activity is present in 40% of patients during electromyographic (EMG) testing (Ertekin ct al. 2001). Impaired esophageal peristalsis has also been noted in affected individuals studied with esophageal manometry. In vidcofluoroscopic testing, incomplete relaxation of the UES and esophageal hypotonia are the most frequently noted abnormalities. Both muscle weakness and myotonia are felt to play a role in the development of dysphagia in persons with myotonic dystrophy, and in at least one study, a correlation was noted between the size of the CTG repeat expansion and the number of radiologic abnormalities in myotonic patients.

Other Muscular Dystrophies

Although less well characterised, dysphagia also occurs in other types of muscular dystrophy. Difficulty swallowing and choking while eating occur with increased frequency in children with Duchenne's muscular dystrophy. Dysphagia has also been documented in patients with limb-girdle dystrophy and facioscapulohumeral muscular dystrophy (Williget al. 1994).

Inflammatory Myopathies

Dermatomyositis and polymyositis arc the most commonly occurring of the inflammatory myopathic disorders. Both are characterized by progressive, usually symmetrical, weakness affecting proximal muscles more prominently than distal. Fatigue and myalgia may also occur. Malignant disease is associated with the disorder in 10-15% of patients with dermatomyositis and 5-10% of those with polymyositis. In individuals older than *65* years, more than 50% are found to have cancer.

Although dysphagia can develop in both conditions, it more frequently is ptesent, and when present more severe, in dermatomyositis. Dysphagia is present in 20-55% of individuals with dermatomyositis, but in only 18% with polymyositis (Parodi et al. 2002). It is the consequence of involvement of striated muscle in the pharynx and proximal esophagus. Involvement of pharyngeal and esophageal musculature in polymyositis and dermatomyositis is an indicator of poor prognosis and can be the source of significant morbidity (Marie et al. 1999). The resulting dysphagia can be severe enough to require enteral feeding. Acute total obstruction by the cricopharyngeal muscle has been reported in dermatomyositis, necessitating cricopharyngeal myotomy. Dysphagia in both conditions may respond to corticosteroids, and intravenous immune globulin (IVIG) therapy has produced dramatic improvement in dysphagia in individuals who were unresponsive to steroids (Marie et al. 1999).

Although dysphagia develops less often in inclusion body myositis, it can occur. In fact, in a group of individuals in whom inclusion body myositis mimicked and was confused with motor neuron disease, dysphagia was present in 44%. A focal inflammatory myopathy involving the pharyngeal muscles and producing isolated pharyngeal dysphagia has also been described in elderly individuals older than 69 years. It has been suggested that this is a distinct clinical entity characterized by cricopharyngeal hypertrophy, although polymyositis localized to the pharyngeal musculature has also been reported.

Mitochondrial Disorders

The mitochondrial disorders are a family of diseases that develop as a consequence of dysfunction in the mitochondrial respiratory chain. Most are the result of mutations in mitochondrial deoxyribonucleic acid (DNA) genes, but nuclear DNA mutations may be responsible in some. Mitochondrial disorders are by nature multisystemic, but myopathic and neurological features often predominate and symptoms may vaty widely, even between individuals within the same family.

In addition to the classic constellation of symptoms that include progressive external ophthalmoplegia, retinitis pigmentosa, cardiac conduction defects, and ataxia, individuals with Kcarns-Sayre syndrome may also develop dysphagia (Katsanos et al. 2001, 2002; Kornblum et al. 2001). Severe abnormalities of pharyngeal and upper esophageal peristalsis have been documented in this disorder. Cricopharyngeal dysfunction is common, but impaired deglutitive coordination may also develop (Kornblum et al. 2001). Dysphagia has also been described in other mitochondrial disorders, but descriptions are only anecdotal and formal study has not been undertaken.

Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disorder characterized by the production of autoantibodies directed against the postsynaptic i/| muscle nicotinic acetylcholine receptors at the neuromuscular junction, with destruction of the receptors and reduction in their number. The clinical consequence of this process is the development of fatigable muscle weakness that progressively increases with repetitive muscle action and improves with rest. MG occurs more often in women than men, and although symptoms can develop at any age, the reported mean age at onset in women is 28-35 years and in men 42—49 years (Kalb et al. 2002). Although myasthenic symptoms tcmain confined to the extraocular muscles in about 20% of

patients, in most individuals more widespread muscle weakness becomes evident (Kalb et al. 2002; Wirtz et al. 2002).

Involvement of bulbar musculature, with resultant dysphagia, is relatively common in MG. In approximately 6-30% of patients, bulbar involvement is evident from the beginning (Wirtz et al. 2002), but most patients eventually develop bulbar symptoms such as dysphagia and dysarthria as the disease progresses. Dysphagia in MG can be due to dysfunction at oral, pharyngeal, or even esophageal levels. Oral phase involvement can be due to fatigue and weakness of the tongue or masticatory muscles. In patients with MG who have bulbar symptoms, repetitive nerve stimulation studies of the hypoglossal nerve have demonstrated abnormalities (Lo et al. 2002), whereas studies using EMG of the masticatory muscles recorded while chewing have also revealed impaired performance (Weijnen et al. 2002). Pharyngeal dysfunction is also common in patients with MG who have dysphagia, as demonstrated with videofluoroscopy. Aspiration, often silent, may be present in 35% or more of these individuals (Colron-Hudson ct al. 2002); in elderly patients, the frequency of aspiration may be considerably higher. Motor dysfunction involving the striated muscle of the proximal esophagus has also been documented in MG. In one study, 96% of patients with MG demonstrated abnormalities, such as decreased amplitude and prolongation of the peristaltic wave, in this region on testing with esophageal manometry. Cricopharyngeal sphincter pressure was also noted to be reduced.

NEUROGENIC DYSPHAGIA

A variety of disease processes originating in the central and peripheral nervous systems can also disrupt swallowing mechanisms and produce dysphagia. Processes affecting cerebral cortex, subcortical white matter, subcortical gray matter, brainstem, spinal cord, and peripheral nerves can elicit dysphagia as a component of their clinical picture (Table 13.3).

Table 13.3: Neurogenic dysphagia

- Oropharyngeal
  - Arnold-Chiari malformation
  - Basal ganglia disease
    - Biotin responsive
    - Corticobasal degeneration
    - Dementia with Lewy bodies
    - Huntington's disease
    - Multiple system atrophy
    - Ne u ro aca n t h oc y to s is
    - P.)rkiiiM>n\ J:v;uc
    - Progressive supranuclear palsy
    - Wilson's disease
  - Central pontine myelinolysis
  - Cerebral palsy
  - Drug related
    - Cyclosporin
    - Tardive dyskinesia
    - Vincristine
  - Infectious
    - Brainstem encephalitis
      - *listeria*
      - Epstein-Barr virus
    - Diphtheria
    - Poliomyelitis
    - Progressive multifocal leu^encephalopathy
    - Rabies
  - Mass lesions
    - Abscess
    - Hemorrhage
    - Metastatic tumor
    - Primary tumor
  - Motor neuron diseases
    - Amyotrophic lateral sclerosis
  - Multiple sclerosis
  - Peripheral neuropathic processes
    - Chareot-Marie-Tooth disease
    - Guillain-Barre syndrome (Miller Fisher's variant)
  - Spinocerebellar ataxias
  - Stroke
  - Syringobulbia
- Esophageal
  - Achalasia
  - Autonomic neuropathies
    - Diabetes mellitus
    - Familial dysautonomia
    - Paraneoplastic syndromes
  - Basal ganglia disorders
    - Parkinson's disease
  - Chagas' disease
  - Esophageal motility disorders
  - Scleroderma

Stroke

Cerebrovascular disease is an extremely common neurological problem and stroke is the third leading cause of death in the United States, It has been estimated that 500,000-750,000 strokes occur in the United States each year and that approximately 150,000 persons die following stroke annually. The mechanism of stroke is ischemic in 80-85% of cases, and in the remaining 15-20%, it is hemorrhagic (Shah and Biller 1998). Approximately 25% of ischemic strokes are due to small-vessel disease, 50% to large-vessel disease, and 25% to a cardioembolic source. Although stroke can occur at all ages, 75% of strokes occur in individuals older than 75 years.

Dysphagia develops in 45-51% of individuals following stroke and its presence is associated with increased likelihood of severe disability or death (Lawrence et al. 2001; Mann, Hankey, and Cameron 2000). Aspiration is the most widely recognized complication of dysphagia following stroke, but undernourishment and even malnutrition occur with surprising frequency (Ullman and

Reding 1996). Reported frequencies of nutritional deficits in patients with dysphagia following stroke range from 48-65%. The presence of dysphagia following stroke has been noted as an independent risk factor for severe disability and death (Sharma et al. 2001).

Although it is commonly perceived that the presence of dysphagia following stroke indicates a brainstem localization for the stroke, this is not necessarily so. Impaired swallowing has been documented in a significant proportion of strokes involving cortical and subcortical structures. The pharyngeal phase of swallowing is primarily impaired in brainstem infarction, whereas in hemispheric strokes, the most striking abnormality often is a delay in initiation of voluntary swallowing (Aydogdu et al. 2001). Dysphagia has been reported as the sole manifestation of infarction in both the medulla and the cerebrum (Celifarco er al. 1990).

Approximately 50-55% of patients with lesions in the posteroinferior cerebellar artery distribution, with consequent lateral medullary infarction (Wallenberg's syndrome:, develop dysphagia (Tcasell et al, 2002). The fact that unilateral medullary infarction can produce bilateral disruption of the brainstem swallowing centers suggests that they function as one integrated center (Vigderman et al. 1998). Infarction in the distribution of the anteroinferior cerebellar artery can also result in dysphagia.

Following stroke within the cerebral hemispheres, dysphagia can develop by virtue of damage to either cortical or subcortical structures involved with volitional swallowing. Bilateral hemispheric damage is more likely to produce dysphagia, hut it can also occur in the setting of unilateral damage. Infarction of the frontoparietal operculum bilaterally may result in the anterior operculum (Maric-Foix-Chavany) syndrome, which is characterized by inability to perform voluntary movements of the face, jaw, tongue, and pharynx with fully preserved involuntary movements of the same muscles (Billith, Jorgler, and Baumhackl 2000). Impairment of volitional swallowing may be a component of this syndrome. Individuals with subcortical strokes have a higher incidence of dysphagia and aspiration than those with cortical damage. In one study, more than 85% of individuals with unilateral subcortical strokes demonstrated videofluoroscopic evidence of delayed initiation of the pharyngeal stage of swallowing, and in 75%, some radiographic aspiration was noted. Although tongue deviation is classically associated with medullary lesions damaging the hypoglossal nucleus, it has also been documented in almost 30% of persons with hemispheric infarctions (Umapathi et al. 2000). When present in hemispheric stroke, tongue deviation is always associated with facial weakness and dysphagia is present in 43% of affected patients.

Aspiration is a potentially life-threatening complication of stroke. Studies have documented its occurrence in 30-55% of stroke patients (Teasell et al. 2002). In one study, videofluoroscopic evidence of aspiration was observed in 36% of patients with unilateral cerebral stroke, 46% with bilateral cerebral stroke, 60% with unilateral brainstem stroke, and SO",, with bilateral brainstem lesions. Other studies have suggested that the incidence of aspiration in brainstem strokes may be considerably higher—more than 80%—and that subcortical strokes may result in aspiration in 75% of cases (Horner et al. 1991). The risk of developing pneumonia is almost seven times greater in persons experiencing aspiration post-stroke compared with those who do not (Holas, Del'ippo, and Reding 1994). Individuals in whom aspiration occurs post-stroke do not always experience clinical symptoms such as coughing or choking during food or liquid ingestion. Furthermore, an absent gag reflex does not help differentiate those aspirating from those who are not. Therefore the employment of objective testing measures to detect the presence and predict the risk of aspiration has been advocated. Modified barium swallow (MBS) testing using vidcofluoroscopy is the gold standard to do this, but simple bedside techniques, such as a water swallowing test, have also been advocated as practical, though somewhat less sensitive, alternatives (Marietal. 1997),

Swallowing often improves spontaneously in the days and weeks following stroke. Tube feeding can temporarily provide adequate nutrition and buy time until swallowing improves sufficiently to allow oral feeding but does entail some risks itself, such as increasing the possibility of reflux wirh consequent aspiration. Various methods of behavioral swallow therapy can be useful in managing persistent post-stroke dysphagia, but in a small percentage of individuals, placement of a percutaneous endoscopic gastrostomy (PEG) will be necessary.

Dysphagia can also develop in the setting of various other cerebrovascular processes. Within the anterior circulation, dysphagia has been reported with carotid artery aneurysms, and within the posterior circulation, processes such as elongation and dilatation of the basilar artery, posterior inferior cerebellar artery aneurysm, intracranial vertebral artery dissections, and cavernous malformations within the medulla may produce dysphagia in addition to other symptoms.

Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system that primarily, though not exclusively, affects young adults. The mean age at onset is approximately 30 years. In its most common guise, MS is characterized by exacerbations and remissions, although some individuals may follow a chronic progressive course right from the start. The etiology of MS is uncertain, but an autoimmune process is suspected.

Dysphagia is a common, but often overlooked, problem in MS (Wiesncr et al. 2002). Survey studies have indicated the presence of dysphagia in 24-34% of individuals with

MS (Hartelius and Svcnsson 1994; Calcagno et al. 2002). The prevalence of dysphagia in MS rises with increasing disability, reaching *65%* in the most severely affected (De Pauw et al. 2002). Individuals with scvcte brainstem involvement as parr of their MS are especially likely to experience dysphagia (Thomas and Wiles 1999).

Objective studies demonstrate a somewhat higher frequency of dysphagia than their survey study counterparts. In fact, in such studies, approximately 50% of individuals with ob]ective abnormalities were not aware of any difficulty swallowing (Thomas and Wiles 1999), Abnormalities in oral, pharyngeal, and even esophageal phases of swallowing have been documented. Rare instances of the anterior operculum syndrome, with buccolingual facial apraxia, have been reported in MS. Abnotmalities in the oral phase of swallowing are common in patients with MS who have mild disability, but additional pharyngeal phase abnormalities develop in those with more severe disability. Disturbances in both the sequencing of laryngeal events and the functioning of the pharyngeal constrictor muscles are typically present in persons experiencing dysphagia. Pharyngeal sensory impairment may also play a role in the development of dysphagia in some patients (Groher 1996).

Parkinson's Disease

Parkinson's disease (I'D) is a neurodegenerative disorder m which symptoms typically emerge between the ages of *55* and 65 years. Although the most prominent neuropathology in PD involves the pigmented dopaminergic neurons in the substantia nigra, neuronal loss in other areas of the nervous system, including wirhin the enteric nervous system, has also been documented.

Dysphagia was first documented in PD by James Patkinson himself in his original description of the illness in 1817 (Parkinson 1817). Recent survey studies have confirmed that dysphagia is indeed a common phenomenon in PD. Reported frequencies of dysphagia in these studies range from 30-82% (Edwards et al. 1991; Clarke et al. 1998), with the broad range probably reflecting differences in the detail within the questionnaires. Objective testing indicates an even higher frequency of dysphagia in PD and has allowed its separation into two categories, oropharyngeal and esophageal (Pfeiffer 2003).

Studies using MBS testing have demonstrated some abnormality in the oropharyngeal phase of swallowing in 75-97% of persons with PD (Fuh et al. 1997; Leopold and Kagel 1997). Even individuals asymptomatic for dysphagia frequently display abnormalities on MBS testing. Within the oral phase, difficulty with bolus formation, delayed initiation of swallowing, repeated tongue pumping, and other abnormalities have been described (Nagaya et al. 1998), although pharyngeal dysmotility and impaired relaxation of the cricopharyngeal muscle constitute examples of abnormalities noted in the pharyngeal phase (Byrne, Pfeiffer, and Quigley 1994; Ali et al. 1996; Pfeiffer 2003).

Esophageal dysfunction can also trigger dysphagia in PD. Studies using esophageal manometry have demonstrated abnormalities in 61-73% of patients with PD (Bassotti et al. 1998), and videofluoroscopic studies show a broader range with some abnormality reported in 5-86% of individuals (Stroudley and Walsh 1991; Edwards et al. 1994; Leopold and Kagel 1997). A wide variety of abnormalities of esophageal function have been described, including slowed esophageal transit, both segmental and diffuse esophageal spasm, ineffective or tertiary contractions, and even aperistalsis. Lower esophageal sphincter dysfunction may also be present in PD and can produce symptoms of reflux and dysphagia.

Aspirarion has been noted to be present in 15-56% of patients with PD (Robbins, Logemann, and Kirshner 1986; Stroudley and Walsh 1991; Ali et al. 1996; Nagaya et al. 1998), and completely silent aspiration in 15-33% {Robbins, Logemann, and Kirshner 1986). Even more striking is a study in which vallecular residue, believed to indicate an incteased risk of aspiration, was found to be present in 88% of patients with PD who do not have clinical dysphagia.

Dysphagia demonstrates an inconsistent response to L-dopa or dopamine agonist therapy (Pfeiffer 2003). Objective improvement in swallowing, documented by MBS testing, has been observed in 33-50% of patients in some, but not all, studies (Fuh et al. 1997; Hunter et al. 1997). In patients with cricopharyngeal muscle dysfunction, both cricopharyngeal myotomy (Born et al. 1996) and botulinum toxin injections (Restivo, Palmcri, and Marchese-Ragona 2002} have been used successfully. Behavioral swallowing therapy approaches are of benefit to some individuals. On rare occasions, PEG placement may be necessary.

Other Basal Ganglia Disorders

In the parkinsonism-plus syndromes, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB), dysphagia is a common problem and, in contrast to PD, often develops relatively early in the course of the illness (Litvan, Sastry, and Sonies 1997; Muller et al. 2001). Although the median latency to the development of dysphagia in PD is more than 130 months, it is 67 months in MSA, 64 months in CBD, 43 months in DLB, and 42 months in PSP (Muller et al. 2001). In fact, the appearance of dysphagia within 1 year of symptom onset virtually eliminates PD as a diagnostic possibility, although it does not help distinguish between the various parkinsonism-plus syndromes (Muller et al. 2001).

Dysphagia can be a prominent problem in patients with Wilson's disease and is frequently a component of the

clinical picture in neuroacanthocytosis (Rampoldi, Danek, and Monaco 2002). A unique basal ganglia process characterized by the presence of subacute encephalopathy, dysarthria, dysphagia, rigidity, dystonia, and eventual quadriparesis has been shown to improve promptly and dramatically to biotin administration (Ozand et al. 1998),

Dysphagia is also a well-documented complication of botulinum toxin injections for cervical dystonia, presumably as a consequence of diffusion of the toxin {Cornelia et al. 1992). It should be noted, however, that 11% of patients with cervical dystonia experience dysphagia as parr of the disease process itself and 22% may display abnormalities on objective testing (Cornelia et al. 1992).

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease. It is characterized by progressive loss of motor neurons in the cortex, brainstem, and spinal cord, which results in a clinical picture of progressive weakness that combines features of both upper motor neuron dysfunction, with spasticity and hyper-reflexia, and lower moror neuron dysfunction, with atrophy, fasciculations, and hyporeflexia (Borasio and Miller 2001). The mean age at symptom onset is 54-58 years (Borasio and Miller 2001).

Although dysphagia eventually develops in most individuals with ALS, bulbar symptoms can be the presenting feature in approximately 25% of patients. A sensation of solid food sticking in the esophagus may provide the initial clue to emerging dysphagia, but abnormalities in the oral phase of swallowing are most often evident in patients with early ALS (Kawai et al. 2003). Impaired function of lips and tongue, particularly its posterior portion, due to evolving muscle weakness typically appears first, followed next by involvement of jaw and suprahyoid musculature and finally by weakness of pharyngeal and laryngeal muscles (Hillel and Miller 1989). Lip weakness can result in spillage of food from the mouth, whereas tongue weakness leads to impaired food bolus formation and transfer (Groher 1996). Inadequate mastication due to the jaw muscle weakness adds to the difficulty with bolus formation, and the eventual development of pharyngeal and laryngeal weakness opens the door for aspiration. Neurophysiologic testing in patients with ALS who have dysphagia demonstrates delay in and eventual abolishment of triggering of the swallowing reflex for voluntarily initiated swallows, with relative preservation of spontaneous reflexive swallows until the terminal stages of the disease (Ertekin et al. 2000).

Spasm of the UES, with hyper-reflexia and hypertonicity of the cricopharyngeal muscle, has been reported in patients with ALS who have bulbar dysfunction, presumably as a consequence of upper motor neuron involvement, and has been considered an important cause of aspiration (Ertekin et al. 2000). This has prompted the employment of cricopharyngeal myotomy as a treatment measure in such patients, but this approach should be limited to those with objectively demonstrated UES spasm.

Control of oral secretions can be a difficult problem for patients with ALS. Because ^-adrenergic stimulation increases production of protein and mucus-rich secretions, which may thicken saliva and make it especially difficult for patients to handle, administration of beta blockers has been proposed to reduce thickness of oral, nasal, and pulmonary secretions. Surgical procedures to reduce salivary production, such as tympanic neurectomy and submandibular gland resection, have also been employed but not extensively studied.

Behavioral therapy approaches can be useful in treating mild to moderate dysphagia in ALS. Alterations in food consistency (such as thickening liquids), swallowing compensation techniques and voluntary airway protection maneuvers all provide benefit and can be taught by speech/swallowing therapists (Groher 1996). Eventually, however, enteral feeding becomes necessary in many individuals with advanced ALS. Placement of a PEG can stabilize weight loss, relieve nutritional deficiency, and improve quality of life for individuals with advanced ALS and severe dysphagia (Borasio, Voltz, and Miller 2001; Chio et al. 1999; Kasarskis et al. 1999).

Brainstem Processes

Any process damaging the brainstem swallowing centers or lower cranial nerve nuclei can lead to dysphagia. Therefore in addition to stroke and MS, a number of other processes affecting brainstem function may display dysphagia as part of their clinical picture. Brainstem tumors, both primary and metastatic, may be responsible for dysphagia, as can central pontine myelinolysis, progressive multifocal leukocncephalopathy, and leukoencephalopathy due to cyclosporin toxicity. Brainstem encephalitis, produced by organisms such as *Listeria* and Epstein-Barr virus (Follet-Bouhamed er al. 1999) may also result in dysphagia.

Cranial Neuropathies

Pathological processes involving the lower cranial nerves can produce dysphagia, usually as a part of a broader clinical picture. Dysphagia can be prominent in the Miller Fisher variant of acute inflammatory demye I mating polyneuropathy (Guillain-Barre syndrome). Response to plasmapheresis is expected in this situation. Dysphagia may also be present in herpes-zoster infection, where it has been attributed to cranial ganglionic involvement. Examples of other processes from which cranial nerve involvement can result in dysphagia include Charcot-Marie-Tooth disease and primary or metastatic tumors involving the skull base. Severe, but reversible, dysphagia with significantly

prolonged esophageal transit time has been attributed to vincristine therapy (Wang et al. 2000).

EVALUATION OF DYSPHAGIA

Various diagnostic tests, ranging from simple bedside analysis to sophisticated tadiologic and neurophysiology procedures, have been developed to evaluate dysphagia (Logemann 1996). Although most are actually performed by specialists other than neurologists, it is important for neurologists to have an awareness of them so they can be employed when clinical citcumstanccs arc appropriate (Table 13.4).

Clinical examination is somewhat limited because of the inaccessibility of some structures involved with swallowing, but both history and examination results can provide useful clues to localization and diagnosis (Table 13.5). Difficulty initiating swallowing or the need for repeated attempts to succeed at swallowing suggests an oropharyngeal source for the dysphagia, whereas a sensation of food "hanging up" in a retrosternal location implicates esophageal dysfunction. Individuals who report dysphagia for solid food hut not liquids are more likely to have a mechanical obstruction, whereas dysphagia for both solids and liquids equally is more typical for an esophageal motility disorder. Lip and rongue function can be easily assessed during routine neurological examination, and both palatal and gag reflexes can be evaluated.

Cervical auscultation is not widely used to evaluate swallowing but may be useful to assess coordination between respiration and swallowing (Table 13.6 and Figure 13.1) (Logemann 1996). In the normal situation, swallowing occurs during exhalation, which reduces the risk of aspiration. Dys-coordinatcd swallowing in the midst of inhalation, conversely, increases the possibility that food might be drawn into the tespiratory tract.

Timed swallowing tests, which require repetitive swallowing of specific amounts of water, have also been employed in the evaluation of dysphagia. Individuals with swallowing impairment may display a number of abnormalities, including slower swallowing speed (<1() nil. pet second) and coughing, which may indicate the presence of dysphagia or aspiration (Logemann 1996). Some concern has been voiced, however, that the relatively large amounts of fluid used in these timed tests could present a significant risk for pulmonary complications as a consequence of aspiration, even if it is water that is used (Logemann 1996),

A standardized 3-ounce water swallow test has been advocated as a simple bedside evaluation of oropharyngeal dysphagia. The presence of cough on swallowing during this test has been reported to provide a positive predictive value with regard to the presence of aspiration of 84% and a negative predictive value of 78% (Mari et al. 1997). The test, however, does not provide any information regarding the specific mechanism of dysphagia in the patient.

Table 13.4: Diagnostic tests

- Oropharyngeal
  - Clinical examination
  - Cervical auscultation
  - Timed swallowing tests
  - 3-ounce water swallow test
  - Modified barium swallow test
  - Pharyngeal videoendoscopy
  - Pharyngeal manometry
  - Videomanofluorometry
  - Electromyographic recording
- Esophageal
  - Endoscopy
  - Esophageal manometry
  - Videofluoroscopy

Table 13.5: Dysphagia clues

l)it(ii:iill\ iniliatini; swallowing	Oropharyngeal dysfunction
Repetitive swallowing	Oropharyngeal dysfunction
Retrosternal "hanging up" sensation	l'.snplia,nfLil dysfunction
Difficulty with solids, hut not liquids	Mechanical obstruction
Difficulty with both solids and liquids	Esophageal dysmotility
Regurgitation of undigested food	Zenker's diverticulum
Halitosis	Zenker's diverticulum

Table 13.6: Dysphagia testing

- If oral phase dysfunction suspected:
  - Screening tests:
    - Clinical examination
    - Cervical auscultation
    - 3-ounce water swallow
  - Primary test:
    - Modified barium swallow
  - If pharyngeal phase dysfunction suspected:
    - Screening tests:
      - Clinical examination
      - 3-ounce water swallow
      - Timed swallowing
    - Primary test:
      - Modified barium swallow
    - Complementary tests:
      - Pharyngeal videoendoscopy
      - Pharyngeal manometry
      - Electromyography
      - Videomanofluorometry
- If esophageal dysfunction suspected:
  - Primary test:
    - Videofluoroscopy
    - Endoscopy
  - Complementary test:
    - Esophageal manometry

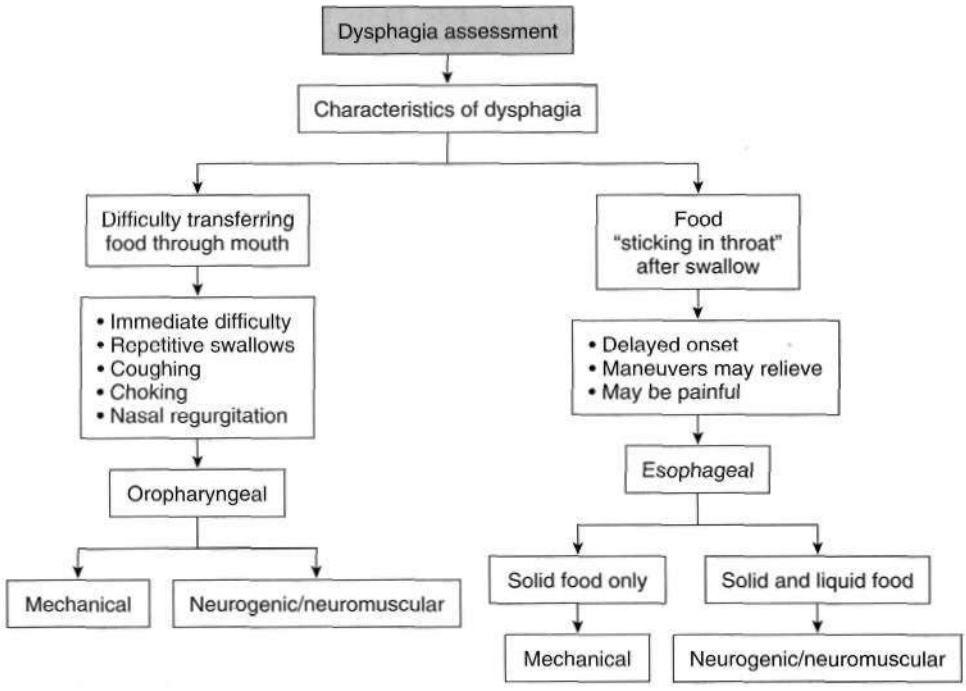

FIGURE **13.1** Dysphagia assessment.

The MBS test has become a standard method for assessing oropharyngeal dysphagia (Logemann 1396). Patients are observed via videofluoroscopy swallowing barium-impregnated **food of** differing consistencies (thin liquid, pudding, cookie). Both oral and pharyngeal function can be characterized, the presence of aspiration can be accurately documented, and the response to corrective measures, such as positioning techniques, can also he evaluated.

Video endoscopy of the pharynx, via the nasal passageway, allows direct visualization of the pharyngeal component of swallowing before and after passage of the food bolus. Its primary value is to demonstrate the presence of residual material in the pharynx after a swallow, indicative of increased risk of aspiration,

Pharyngeal manometry provides physiologic information regarding function of both the pharynx and the UES (Hila, Castell, and Castell 2001). The information derived is complementary to that obtained by videofluoroscopy and a combined procedure, termed *videomanofluorometry,* in which both videofluoroscopy and manometry are performed simultaneously, can also be used (Higo ct al. 2002). Though very useful, this procedure is not always readily available,

Evaluation of esophageal function can be assessed by endoscopy, esophageal manometry, and videofluoroscopy. Scintigraphic procedures can also be employed to evaluate oral, pharyngeal, and esophageal function but are not widely used (Galli et al. 2000),

More sophisticated electrodiagnostic procedures have also been developed to study dysphagia. EMG recording of cricopharyngeal function and integrated submental activity has been useful in a research setting to characterize aspects of swallowing, but this procedure has not yet come into general use.

CONCLUSION

Because of the broad nerwork of structures involved with the control and execution of swallowing, dysphagia can be an important component of the clinical picture in patients with a wide variety of neurological diseases. Determination of the specific mechanism responsible for dysphagia in individual patients can be of great value in both diagnosis and treatment of this disorder.

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Chapter 14
Vision Loss

Robert L. Tomsak

Vision loss commonly accompanies neurological illness and is one of the most disturbing symptoms a patient may experience. Loss of vision is often due to a benign or treatable process, but it may be the first sign of a blinding or life-threatening disease. Common causes of impaired vision include uncorrected refractive errors, corneal problems, cataracts, glaucoma, retinal and choroidal diseases, strabismus, and amblyopia. Ocular causes of loss of vision often are not apparent to the nonophthalmologist. Conversely, neurological causes of visual deterioration often confuse ophthalmologists. Thus the approach to evaluating vision loss must be systematic and methodical so that important causes are not missed and simple causes ate not evaluated to the extreme. This chapter deals primarily with the symptoms of visual loss; examination techniques are discussed in Chapter 40, and the appearance of specific funduscopic abnormalities is covered in Chapter 15.

TYPE AND SEVERITY OF VISION LOSS

Central Visual Field Loss

Any defect in the field of vision is called a *scotoma,* from the Greek word meaning "darkness." Loss of central vision, resulting in a central or centrocecal scotoma, is usually quickly noticed and reported. Peripheral visual field defects, such as homonymous hemianopia, may be asymptomatic, or they may be referred to the eye with the larger homonymous hemifield (Figure 14.1), Central and centrocecal scotomas arc usually due to disease involving the central retina or optic nerve anywhere along its intraocular, intraorbital, intracanalicular, or intracranial course. In the case of predominantly one-sided involvement of the optic chiasm, a central scotoma may be associated with a contralateral silent temporal hemianopia (Figure 14,2). Therefore visual function of each eye should be assessed separately in history-taking and during the examination.

In general, scotomas caused by macular disease are positive, meaning that they are perceived as a black or gray spot in the visual field. Patients with macular vision loss may also complain of distortion of images, so that straight edges or geometric figures appear crooked or distorted. This symptom, called *metamorphopsia,* is almost always caused by a retinal problem; only rarely docs metamorphopsia represent a disorder of the visual correx.

Optic nerve lesions characteristically produce negative scotomas, or areas of absent vision not otherwise perceptible, often in conjunction with decreased appreciation of color and light brightness. On occasion, paradoxical photophobia, especially to fluorescent lighting, is a prominent symptom of optic nerve damage. Photopsias (light flashes) may be perceived with vitreoretinal traction, retinal disease (e.g., cancer-associated retinopathy), drugs (e.g., digitalis), or optic nerve disease (e.g., during the healing phase of optic neuropathies), Photopsias may also be part of migraine visual aura,

Aside from ocular diseases, bilateral central visual loss can be produced by optic nerve or chiasmal lesions or by bilateral lesions in the macular portion of the visual cortex. The possibility of psychogenic vision loss must also be considered (see Chapter **40),**

PATTERNS OF VISUAL FIELD LOSS

For simplicity, visual field defects can be classified in one of three groups: prechiasmal, chiasmal, or retrochiasmal. Unilateral prechiasmal lesions affect the visual field in one eye only; chiasmal lesions affect the fields of both eyes in a nonhomonymous fashion; and retrochiasmal lesions

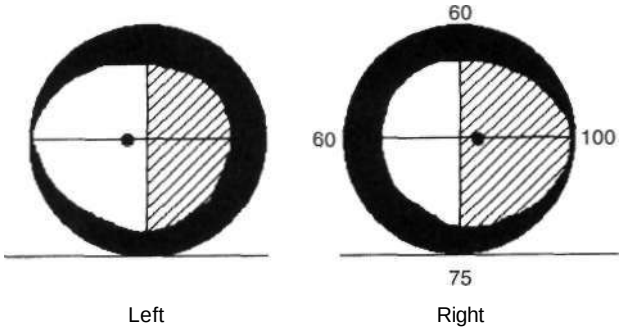


FIGURE 14.1 Right homonymous hemianopia. Vision loss may be referred to the right eye because the temporal visual field is larger than the nasal visual field. Numbers refer to normal extent of visual field in degrees.

cause homonymous field defects with variable degrees of congruiry, depending on their location (Figure 14.3) (Glaser 1999). See Chapter 40 for additional discussion of patterns of visual field loss.

TEMPORAL PROFILE OF VISION LOSS

Vision Loss of Sudden Onset

Vision loss of sudden onset can be divided into three temporal patterns: transient (Table 14.1), nonprogressive, or progressive.

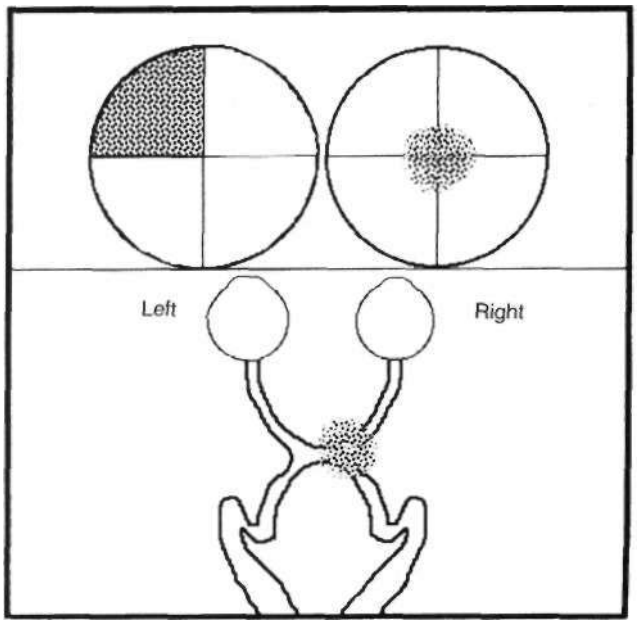


FIGURE 14.2 Junction scotoma with chiasmal lesion. The right optic nerve is primarily involved, leading to centroeecal scotoma. Crossing fibers are also affected, resulting in an upper temporal visual field defect; this is often asymptomatic and must be documented by visual field testing (see Chapter 40).

Unilateral Transient Vision Loss

Amaurosis Fugax. The term *amaurosis fugax* is commonly reserved for transient monocular blindness (TMB) caused by emboli to the retinal circulation from carotid vessels or from the heart. Typically, these attacks are sudden in onset, last 5-15 minutes, and are accompanied by scotomas that often arc described as a shade or curtain being pulled in front of the eye (usually downward) {Donders 2001). The vision loss may also be quadrantic or total. Ipsilateral hemispheric symptoms may or may not be present.

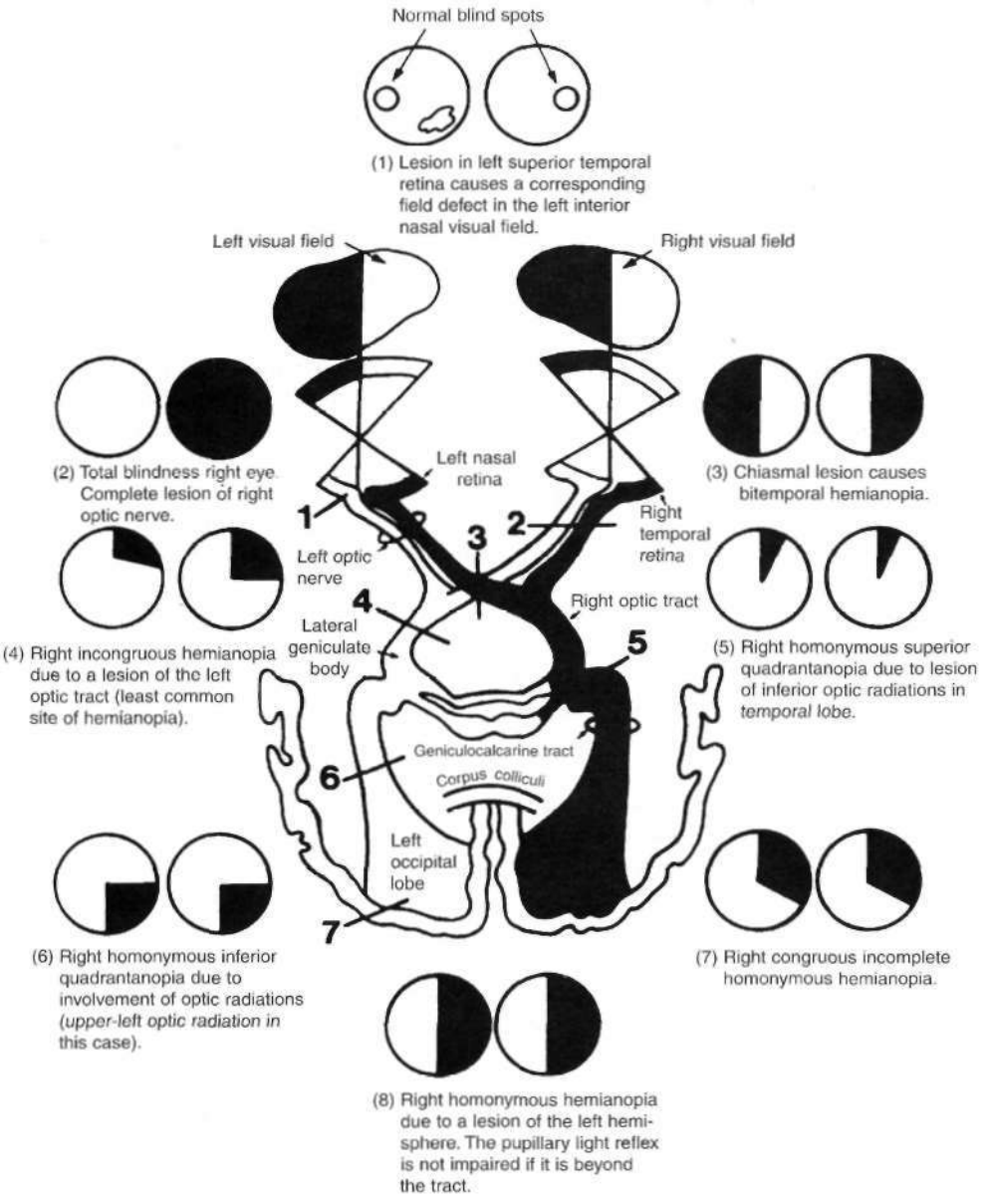
Retinal Artery Vasospasm. TMB can be caused by retinal artery vasospasm and is called "retinal migraine" only if accompanied by migraine headache. Vasospastic TMB is usually benign and often responds to calcium-channel blockers (Winterkorn et al. 1993).

Angle-Closure Glaucoma. Subacute attacks of angle-closure glaucoma should also be considered in the differential diagnosis of intermittent monocular vision loss, especially if the patient complains of halos around lights. This latter symptom results from corneal edema related to rapid elevarions of intraocular pressure that may not be associated with eye pain or redness.

Vision Loss in Bright Light. Some patients with severe impairment of blood flow to the eye lose vision in bright light, presumably as a result of impaired regeneration of photopigments secondary to ocular ischemia. This symptom can be thought of as a pathologic variant of the macular photo-stress phenomenon (see Chapter 40) and most often indicates complete internal carotid artery occlusion or high grade stenosis (Kaiboriboon et al. 2001). A variety of ocular abnormalities, most commonly retinal hemorrhages, are seen in this setting and collectively are termed the "ocular ischemic syndrome" (Ishikawa et al. 2002), Other retinal diseases, such as cone dystrophy and age-related macular degeneration, cause evanescent visual worsening in bright light, otherwise known as hemeralopia or day blindness.

Uhthoff's Phenomenon. Temporary loss of vision with elevation of body temperature (Uhthoff's phenomenon) most often occurs in optic neuritis associated with demyelinating disease but can be experienced with other optic neuropathies.

Transient Visual Obscurations. Vision loss (unilateral or bilateral) lasting seconds in patients with chronic swelling of the optic discs is called a transient visual obscuration. The visual disturbance may be described as a gray-out, is often brought on by postural change or straining, and probably represents transient hypoperfusion of the swollen nerve or nerves. Transient visual obscurations that are



FIGURF. 14.3 Topographical diagnosis of visual field defects. (Reprinted with permission from Vaughn, C., Asbury, T., & Tabbara, K. F. 1989, *Genera! ophthalmology,* 12th ed, Appleton & Lange, Norwalk, Conn, p. 244.)

Tabic 14.1: Causes of transient monocular blindness

1. F.mbolic cerebrovascular disease
2. Migraine (vasospasm)
3. Hypoperfusion (hypotension, hyperviscosity, hypercoagulability)
4. Ocular (intermittent angle-closure glaucoma, hyphema, optic disc edema, partial retinal vein occlusion)
5. Vasculitis (e.g., giant cell arteritis)
6. Other (Uhthoff's phenomenon/ idiopathic, psychogenic)

^Temporary decrease in acuity consequent to exercise or other causes of increased body temperature in patients with demyelinating opric neuropathy.

gaze-evoked are a hallmark of orbital tumors but may also occur with systemic hypotension, temporal arteritis, or retinal venous stasis.

Other Remitting Vision Loss. Recurrent remitting vision loss may be secondary to cystic lesions, such as sphenoid sinus mucocele, craniopharyngioma, and pituitary tumor (Wray 1995).

Bilateral Transient Vision Loss

Other than transient visual obscurations in patients with bilateral optic disc swelling, simultaneous complete

Tabic 14.2: Causes of bilateral transient vision loss

1. Migraine
2. Cerebral hypoperfusion
   a. Thromboembolism
   b. Systemic hypotension
   c. Hyperviscosity
   d. Vascular compression
3. Epilepsy
4. Papilledema (transient visual obscurations)

or incomplete loss of vision in both eyes is virtually always evidence of transient visual cortex dysfunction. This symptom is usually due to decreased cerebral perfusion resulting from vasospasm, thromboembolism, systemic hypotension, hyperviscosity, or vascular compression (Table 14,2) (Glaser 1999). Transient post-traumatic blindness may occur, especially in children, and may represent a variant of migraine. Hysteria or malingering may also be causes (see Chapter 40), Epileptic visual hallucinations can be elementary or complex in character depending on the location of the seizure focus (Bien et al. 2000), Cortical blindness as an epileptic phenomenon occurs mainly as part of the syndrome of benign occipital epilepsy in childhood (see Chapter 73).

In most neuro-ophthalmological practices, visual migraine auras are the most common cause of bilateral transient visual disturbances, especially when they occur in patit'nrs younger than 40 years (see Chapter 75).

Nonprogressive Unilateral Sudden Vision Loss

Ischemic events affecting the optic nerve or retina are characteristically of sudden onset and are usually nonprogressive, although rarely a stuttering decline in vision may occur,

Anterior ischemic optic neuropathy presents mostly as infarction of the optic disc that is readily observable with the direct ophthalmoscope. In patients younger than 60 years, it is caused by as yet undefined abnormalities affecting the microcirculation to the optic nerve head (Table 14.3) and may be the result of nocturnal hypotension (Hayreh 2000). Congenital structural features of optic-disc anatomy may also play a role. In patients older than 60 years, cranial (temporal or giant cell) arteritis must be considered. Retrobulbar optic nerve infarction, also termed *posterior ischemic optic neuropathy*, is far less common but may occur in the setting of severe perioperative hypotension and other causes of hemodynamic shock. Optic nerve infarction of embolic cause, or related to migraine, is exceptionally rare.

Table 14.3: Causes of unilateral sudden vision loss—nonprogressive

1. Branch or central retinal artery occlusion
2. Anterior ischemic optic neuropathy—arteritic or nonarteritic
3. Branch or central retinal vein occlusion
4. Traumatic optic neuropathy
5. Central serous choroidopathy
6. Retinal detachment
7. Vitreous hemorrhage
8. Functional (psychogenic) vision loss

By contrast, branch or central retinal artery occlusions are mostly caused by embolic or thrombotic events; opacification of the retinal nerve fiber layer with a cherry-red spot at the macula is the classic ophthalmoscopic presentation of central retinal artery occlusion (see Chapter 15). Altitudinal, quadrantic, or complete unilateral visual field loss may occur wirh retinal arterial occlusions.

Occlusion of the central retinal vein presents as sudden vision loss with a characteristic hemorrhagic retinopathy. It usually occurs in adults with systemic hypertension or diabetes and results from venous thrombosis at the level of the lamina cribrosa of the sclera. A dense central scotoma with spared peripheral visual field is characteristic.

Idiopathic central serous chorioretinopathy can present as the sudden onset of a positive scotoma, often with symptoms of metamorphopsia or micropsia and a positive photo-stress test result (see Chapter 40). This condition results from leakage of fluid into the subretinal space and occurs most often in men 20-45 years old. The diagnosis may be difficult to make without the aid of fluorescein angiography. Spontaneous recovery usually occurs within a period of weeks to months, but occasionally laser photocoagulation is needed to seal leaking vessels.

Seemingly mild periocular contusion injuries can result in permanent optic nerve dysfunction. The mechanisms for traumatic optic neuropathy include contusion or laceration of the optic nerve in its canal or shearing of nutrient vessels with subsequent ischemia.

Nonprogressive Bilateral Sudden Vision Loss

Sudden, permanent vision loss affecting bilateral vision, if not caused by trauma, is usually the result of an infarct in the visual radiations causing a homonymous hemianopia (Table 14.4) (Glaser 1999). In patients who are otherwise neurologically asymptomatic, the site of the insult is commonly the occipital lobe. Bilateral occipital lobe infarcts can result in tubular visual fields, checkerboard visual fields (see Figure 14.3), or total cortical blindness. Cortical blindness from bilateral occipitoparietal lobe infarcts may be accompanied by denial of the visual defect and confabulation, also known as *Anton's syndrome.*

Sudden, bilateral loss of vision may also accompany pituitary apoplexy. This condition is usually associated with severe headache, diplopia, and alteration of mental status (Glaser 1999).

Table 14,4: Causes of bilateral sudden vision loss—nonprogressive

1. Occipital lobe infarctions
2. Pituitary apoplexy
3. Functional (psychogenic) vision loss
4. Head trauma

Vision Loss of Sudden Onset with Progression

Unilateral vision loss that appears suddenly and progressively worsens is often due to optic nerve demyelination (optic neuritis). The usual period for worsening is hours to days but almost never longer than 2 weeks. An unusual presentation of bilateral optic neuritis combined with transverse myelitis is called *Devic's disease* (neuromyelitis optica). Less often, long-standing vision loss may be suddenly discovered and misinterpreted as being of sudden onset; in these cases, the examiner should consider a compressive problem (Table 14.5),

Leber's hereditary optic neuropathy is a maternally transmitted disease associated with mitochondrial deoxyribonucleic acid (DNA) mutations in the genes encoding subunits of respiratory chain complex I. Primary mutations have been identified at positions 11,778; 3460; 15,257; and 14,484 (Miller and Newman 1999) (see Chapter 69). This condition presents as acute or subacute, often permanent, loss of central vision, usually in men during early adulthood. Most often, both eyes are affected within 1 year, but rarely simultaneously. Visual recovery is variable and somewhat dependent on the mitochondrial DNA mutation with the 11,778 mutation having the worst prognosis and the 14,484 mutation the best. In the acute phase, the classic triad of findings includes circumpapillary telangiectatic microangiopathy, nonedematous elevation of the optic disc (pseudoedema), and absence of fluorescein leakage during angiography. Arteriolar narrowing can be marked, and vascular tortuosity is often a clue early in the disease. Although Leber's hereditary optic neuropathy may cause loss of vision in women, it tends to be less severe than in men.

Table 14.5; Causes of progressive vision loss

1. Anterior visual pathway inflammation
   a. Optic neuritis
   b. Sarcoidosis
   c. Meningitis
2. Anterior visual pathway compression
   a. Tumors
   b. Aneurysms
   c. Dysthyroid optic neuropathy
3. Hereditary optic neuropathies
   a. Leber's hereditary optic neuropathy
4. Optic nerve drusen
5. Low-tension glaucoma
6. Chronic papilledema
7. Toxic and nutritional optic neuropathies
8. Drugs (e.g., cthambutol)
9. Radiation damage to anterior visual pathways
10. Paraneoplastic retinopathy or optic neuropathy

Vision Loss of Gradual Onset

Gradual onset is the hallmark of a compressive lesion affecting the prcchiasmal or chiasmal visual pathways. Common causes include pituitary tumors, aneurysms, craniopharyngiomas, meningiomas, and gliomas (see Table 14.5) (Glaser 1999; Miller and Newman 1999). Granulomatous involvement of the optic nerve from sarcoidosis or tuberculosis can cause chronic progressive vision loss. Compression of the optic nerve at the orbital apex from ocular dysthyroidism may occur with minimal periocular signs of ocular motility disturbance. As noted previously, the vision loss may be so insidious as to go unnoticed until it is fortuitously discovered by the patient or during a routine examination.

Heredirary or degenerative diseases of the optic nerve or retina also must be included in the differential diagnosis. The familial optic atrophies are bilateral and are usually discovered in the first two decades of life (Miller and Newman 1999). Vision loss may range from mild to severe and can be asymmetrical. Central and centrocecal scotomas with sparing of the peripheral fields are generally found. Temporal pallor of the discs sometimes occurs in association with a focal area of cupping. Color vision is usually abnormal, with red-green and blue-yellow defects predominating. Nystagmus, as well as other neurological and endocrine abnormalities, may be present.

Drusen of the optic nerve, a common form of pseudopapilledema, are often associated with visual field defects (see Chapter 15). Approximately 75% of patients have some form of visual field loss, which may include arcuate defects, sectorial scotomas, enlargement of the blind spot, and generalized visual field constriction. Loss of central visual acuity is unusual and is most commonly the result of a subretinal neovascular membrane forming with subsequent hemorrhage into the macula or from anterior ischemic optic neuropathy (Kamath et al, 2000). If loss of central visual acuity occurs with optic disc drusen without obvious retinal pathology, a search for a retrobulbar compressive lesion should be undertaken. Drusen represent extracellular deposition of plasma proteins and a variety of inorganic materials that compress optic nerve axons near the surface of the nerve head. They are often imaged by computed tomography and appear as calcifications (Kurz-Levin and Landau 1999).

Normal-tension glaucoma (NTG) is often a diagnostic and therapeutic conundrum because it can masquerade

as other conditions causing progressive visual loss and because other diseases can mimic it {Tomsak 1997). True NTG is a condition in which glaucomatous disc and field changes develop in the presence of normal levels of intraocular pressure. It is bilateral in 70% of patients and the average age at diagnosis is *66* years. Women are affected approximately twice as frequently as are men. Small disc hemorrhages are seen in approximately 10% of patients. A history of cardiovascular shock is acknowledged by approximately 5% of patients. The disease may be either progressive or static (Anderson etal. 2001).

Chronic papilledema from pseudotumor cerebri can become a bilateral progressive optic neuropathy. It is characterized by the development of a milky gray color to the discs. Sheathing of peripapillary retinal vessels occurs commonly. Visual fields tend to become constricted, with nasal defects progressing to involve fixation. Opticociliary shunt vessels can develop, as can sudden vision loss from ischemic optic neuropathy in rare cases. On occasion, optic atrophy progresses despite the relief of elevated intracranial pressure, possibly from an apoptotic mechanism.

Toxic and nutritional amblyopias also are bilateral and usually progressive (Tomsak 1997; Miller and Newman 1999). This subject is controversial, and the disease is difficult to define. The nutritional variety is characterized by a history of a poor diet, gradual painless onset of visual impairment over weeks to months, impairment of color vision early, centrocecal scotomas, and development of optic atrophy late in the disease. Most cases of tobacco-alcohol amblyopia are probably related to vitamin B deficiencies. Other conditions that lead to nutritional deficiency states, such as jejunoileal bypass and ketogenic diet, may cause bilateral optic neuropathy as well.

Medications that may be toxic to the optic nerve in certain situations include ethambutol, amiodarone, isoniazid, chloramphenicol, and diiodohydroxyquin. Retinal toxins include vigabatrin (Nicolson et al. 2002), digitalis, chloroquine, hydroxychloroquine, and phenothiazines.

Slowly progressive vision loss from radiation damage to the anterior visual pathways, especially the retina, may result from direct radiation therapy to the eye for primary ocular tumors or metastases or may occur after periocular irradiation for basal cell carcinoma, sinus carcinoma, and related malignancies {Guy and Schatz 1995). It may also occur after whole-brain irradiation for metastases of gliomas or after parasellar radiation therapy for pituitary tumors or other neoplasms in this region. Radiation retinopathy becomes clinically apparent after a variable latent period of 3 months to a few years after radiation therapy and is usually irreversible. It is directly related to fraction size, total dose of radiation, and the use of concomitant chemotherapy (Guy and Schatz 1995). Radiation-induced retinal capillary endothelial cell damage is the initial event that triggers a retinopathy usually indistinguishable from diabetic retinopathy.

A rapidly progressive paraneoplastic retinopathy (cancer-associated retinopathy syndrome) causes bilateral vision loss in some patients with cancer over weeks to months. Small cell carcinoma of the lung is the most often associated malignancy, but gynecologic, endocrine, breast, and other tumors have also been described. The vision loss, usually associated with photopsias, often precedes the diagnosis of cancer and is associated with circulating antibodies directed at the tumor and retinal and optic nerve antigens (see Chapter 58H). Retinitis pigmentosa-likc signs and symptoms arc present, including night blindness, constricted visual fields, and a subnormal to extinguished electroretinogram. No effective treatment is available. Melanoma-associated retinopathy is also well described. Autoimmune-related retinopathy and optic neuropathy occurs in patients who do not have cancer (Keltner et al. 2001).

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Chapter 15
Abnormalities of the Optic Nerve and Retina

Roy W. Beck and Laura J. Balcer

Disorders of the optic nerve and retina are common causes of afferent visual loss in clinical neurology. The diagnosis of optic neuropathy should be considered when the following clinical features arc present: (1) visual loss in association with a swollen, pale, or anomalous optic disc; or (2) a normal disc appearance in the setting of vision loss (visual acuity, color vision, or visual field) combined with an afferent pupillary defect (APD) (see Chapter 17). The specific etiology for optic neuropathy in a given patient often can be established without the need for neuro-imaging on the **basis of clinical** history (i.e., character/ progression of vision loss), whether one or both eyes are involved, the pattern of visual field loss, and the optic disc appearance. Chapter 14 describes the various patterns of visual field loss and clinical history typically elicited in patients with specific optic nerve disorders. This chapter presents the differential diagnosis for optic neuropathies based on the optic disc appearance. Many of the entities described in this chapter are discussed in more detail in Chapter 40.

Acquired optic neuropathies can be classified according to whether the optic disc appears normal, swollen, or pale. Table 15.1 provides a differential diagnosis based on the appearance of the optic disc.

SWOLLEN OPTIC **DISC**

In assessing an elevated optic disc, the examiner must first determine whether acquired disc edema (true disc swelling) is present, or if the disc appearance is that of pscudo-papilledema.

Pseudopapilledema

In patients with pseudopapilledema, visible optic disc druscn (hyaline bodies) may be present (Plate 15.1 and Plate **15.11).** Even when disc drusen (hyaline bodies) are not apparent, the distinction between true disc swelling and pseudopapilledema can almost always be made on the basis of ophthalmoscopic findings (Table 15.2). The most important distinguishing feature is the clarity of the peripapillary nerve fiber layer. In patients with true disc edema, the nerve fiber layer is hazy, obscuring the underlying retinal vessels. Because pseudopapilledematous discs usually do not show spontaneous venous pulsations (SVP), evaluation for SVP is not helpful in these patients. Hemorrhages may be present in patients with pseudo-papilledema (particularly in the setting of optic disc drusen) and therefore do not exclude this possibility in the setting of optic disc elevation.

Optic disc druscn arc a common cause of pseudopapille-dema, and may be inherited in an autosomal dominant pattern. The prevalence is approximately 2% within the general population. Optic disc druscn are much more common in patients of white descent than in African Americans. The pathogenesis of optic disc drusen has been postulated to be related to axonal degeneration ftom altered axoplasmic flow. In children, disc drusen tend to be buried, whereas in adults, they often are visible on the

Tabic 15.1: Causes of unilateral and bilateral optic neuropathy catcgoriwd by optic disc appearance

Edematous		*Normal-appearing*		*Atrophic*	
Unilateral	*Bilateral*	*Unilateral*	*Bilateral*	*Cupped*	*Not cupped*
Optic neuritis	Papilledema (increased intracranial pressure)	Retrobulbar neuritis	**Tobacco-alcohol**	**Glaucoma**	Any optic neuropathy
Ischemic optic neuropathy					
Orbital tumor	Malignant hypertension	Compressive lesion	**Nutritional**	**Giant** cell arteritis	
Other: papillophlebitis, central retinal vein occlusion, infiltrative disorders	Diabetic papillopathy	Infiltration: granulomatous. carcinomatous, lymphomatous	Drugs		
	Any of the unilateral causes	Any of the unilateral causes	Toxins		
			Hereditary*		

"Optic disc may appear swollen acutely in Leber's optic neuropathy.
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disc surface. The progression from buried to surface drusen in individual patients has been well documented.

Optic disc drusen generally do not produce visual symptoms, although rarely a patient may experience transient visual obscurations similar to those described by patients with papilledema (optic disc swelling caused by increased intracranial pressure). Visual field defects are common, however, occurring in approximately 70% of eyes with visible disc drusen and in *3>5%* of those with pseudopapillcdcma but no visible drusen. These visual field defects generally follow a nerve fiber bundle distribution, with inferior nasal visual field loss being the most common. Enlargement of the blind spot and generalized field constriction may also occur. Progression of visual field defects is well documented, but visual acuity loss is rare. If decreased visual acuity is present in a patient with optic disc drusen, evaluation for alternative causes should be performed. Visual field loss in the setting of optic disc drusen may also occur secondary to hemorrhage, or to an associated retinal degeneration. Approximately 2% of patients with retinitis pigmentosa also have optic disc drusen; the potential combination of these two entities should be considered in patients with otherwise unexplained bilateral disc elevation and visual field loss.

Unilateral Optic Disc Edema

If true optic disc edema is determined to be present, it is useful to distinguish patients with bilateral disc swelling from those with unilateral swelling. Whether optic nerve function is normal or abnormal is likewise an important diagnostic feature.

The most common causes of unilateral optic disc edema are optic neuritis (termed *papillitis* when disc swelling is present), anterior ischemic optic neuropathy (AION), and orbital compressive lesions. As a rule, optic nerve function is abnormal in each of these entities. Although characteristics of the optic disc appearance may overlap between optic neuritis, AION, and compressive optic

I able 1>,2: Differentiation oi early papilledema and pseudopapillcdcma

Feature	*Papilledema*	*Pseudopapiltedema*
Disc color	Hyperemic	Pink, yellowish pink
Disc margins	Indistinct early at superior and inferior poles, later entire margin	Irregularly blurred, may be lumpy
Disc elevation	Minimal	Minimal to marked; center of disc most elevated
Vessels	Normal distribution, slight fullness; spontaneous venous pulsations absent	Emanate from center, frequent anomalous pattern, ± spontaneous venous pulsations
Nerve fiber layer	Dull as a result of edema, which may obscure blood vessels	No edema: may glisten with circumpapillary halo of feathery light reflections
Hemorrhages	Splinter	Subretinal, retinal, vitreous

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neuropathies, certain features may be more suggestive of a specific diagnosis. Disc hemorrhages, for example, are much more common in AION than in optic neuritis or compressive lesions (Plate 15.111). A cellular reaction in the vitreous overlying the optic disc, and the presence of retinal exudates, are both highly suggestive of optic neuritis (Plate 15.IV). In patients with acute demyelinating optic neuritis (the most common form of optic neuritis, associated with multiple sclerosis [MS]), optic disc swelling is present in about 33% of patients. Disc hemorrhages arc uncommon in these patients, however, and their presence should suggest an alternative diagnosis,

Both optociliary shunt vessels and glistening white bodies on the disc surface (pscudodrusen) can be seen with chronic disc edema due to compressive lesions (Plate 15.V), but would not be expected in patients with acute optic neuritis or AION. Optociliary shunt vessels represent communications between the ciliary and retinal venous circulations. In addition to occurring with orhu.il tumors, such as optic nerve sheath meningiomas, shunt vessels can be seen in retina) vein occlusions, glaucoma, malignant hypertension, chronic papilledema, and as a congenital variant.

Although it is often not possible to distinguish optic neuritis, AION, and compressive optic neuropathies on the basis of disc appearance alone, the diagnosis can usually be made based on the clinical history (acute presentation vs. progression of vision loss) and the pattern of the visual field deficit. Vision loss is generally slowly progressive in patients with compressive lesions, is sudden with subsequent improvement in those with optic neuritis, and is sudden with no or incomplete improvement in patients with AION, Both optic neuritis and compressive lesions generally produce some form of central visual loss (central scotoma), while AION typically produces a nerve fiber bundle type field defect (originating from, and involving, the physiologic blind spot). However, there is considerable overlap in the patterns of visual field loss for optic neuropathies. Chapter 14 describes these features in further detail.

Consecutive involvement of the fellow eye is also an important clinical feature that may distinguish optic neuropathies with respect to etiology. For example, AION affects the two eyes consecutively in up to 25% of cases. When the second eye is affected in AION, the presence of optic atrophy in one eye and disc edema in the fellow eye occurs (pseudo-Foster Kennedy syndrome) (Figure 15.1). A true Foster Kennedy syndrome is produced by a tumor that causes optic atrophy in one eye caused by compression and papilledema in the fellow eye secondary to increased intracranial pressure.

Compressive lesions producing disc edema almost always involve the intraorbital portion of the optic nerve. Meningiomas of the optic nerve sheath or sphenoid wing are common causes of compressive unilateral disc edema (see Plate 15.V). Intracranial compressive lesions only rarely produce disc edema, unless they arc large enough to raise intracranial pressure, A nontumor cause of compressive disc edema is Graves' ophthalmopathy (thyroid eye disease).

When optic neuritis, with associated disc swelling, is associated with macular exudates (often in a star pattern), the condition is termed *ncuroretinitis.* Recognition of retina! exudates in patients with unilateral optic disc swelling is important for distinguishing neuroretinitis from acute demyelinating optic neuritis or AION.

Uncommon Causes of Unilateral Disc Edema

Less common causes of unilateral optic disc edema include central retinal vein occlusion/obstruction and infiltrative disorders, such as leukemia and lymphoma. Retinal vein obstruction occasionally manifests primarily as optic-disc edema with minimal or no retinal hemorrhages. Papillophlebitis is a syndrome of presumed retinal vein inflammation producing optic disc edema in young adults (Plate 15.VI). The disc elevation is often marked, and the retinal veins are generally dilated. Other than enlargement of the blind spot, the visual field is usually normal. This condition tends to resolve wirhout residual vision loss. In older patients, retinal vein obstruction may be caused by compression of the vein by an atherosclerotic artery. The disc typically appears extremely hyperemia, but edema is usually mild (Plate 15.VII). Optociliary shunt vessels may also be present. As with papillophlebitis, visual function is usually not affected, but the disc edema tends to persist chronically.

Infiltration of the optic nerve can occur secondary to carcinomatous, lymphoreticular, and granulomatous processes. One or both optic nerves may be affected, Optic discs may appear swollen or normal, the latter indicating a retrobulbar involvement. Occasionally, optic-nerve infiltration produces optic disc edema without affecting visual function, but more often there is a decrease in visual acuity and visual field loss. Almost any form of carcinoma can metastasize to the optic nerve; breast and lung carcinomas are the most common. Carcinomatous meningitis is often associated. Lymphomas and leukemias also can involve rhe optic nerve. Sarcoidosis often presents with a characteristic disc appearance, including disc edema and whitish nodules on the disc surface (Plate 15.VIII).

Optic neuropathy as a delayed effect of radiation therapy can occur with or without disc edema. When this rare complication occurs, it usually follows the radiation by 6 to 24 months. There are a number of other causes of unilateral optic disc edema. Some of the entities described under the section Bilateral Optic Disc Edema, including diabetic papillopathy, occasionally produce only unilateral edema.

Leber's hereditary optic neuropathy (LHON) is an uncommon optic nerve disorder that occurs predominantly in males. Although not a cause of true disc edema, the

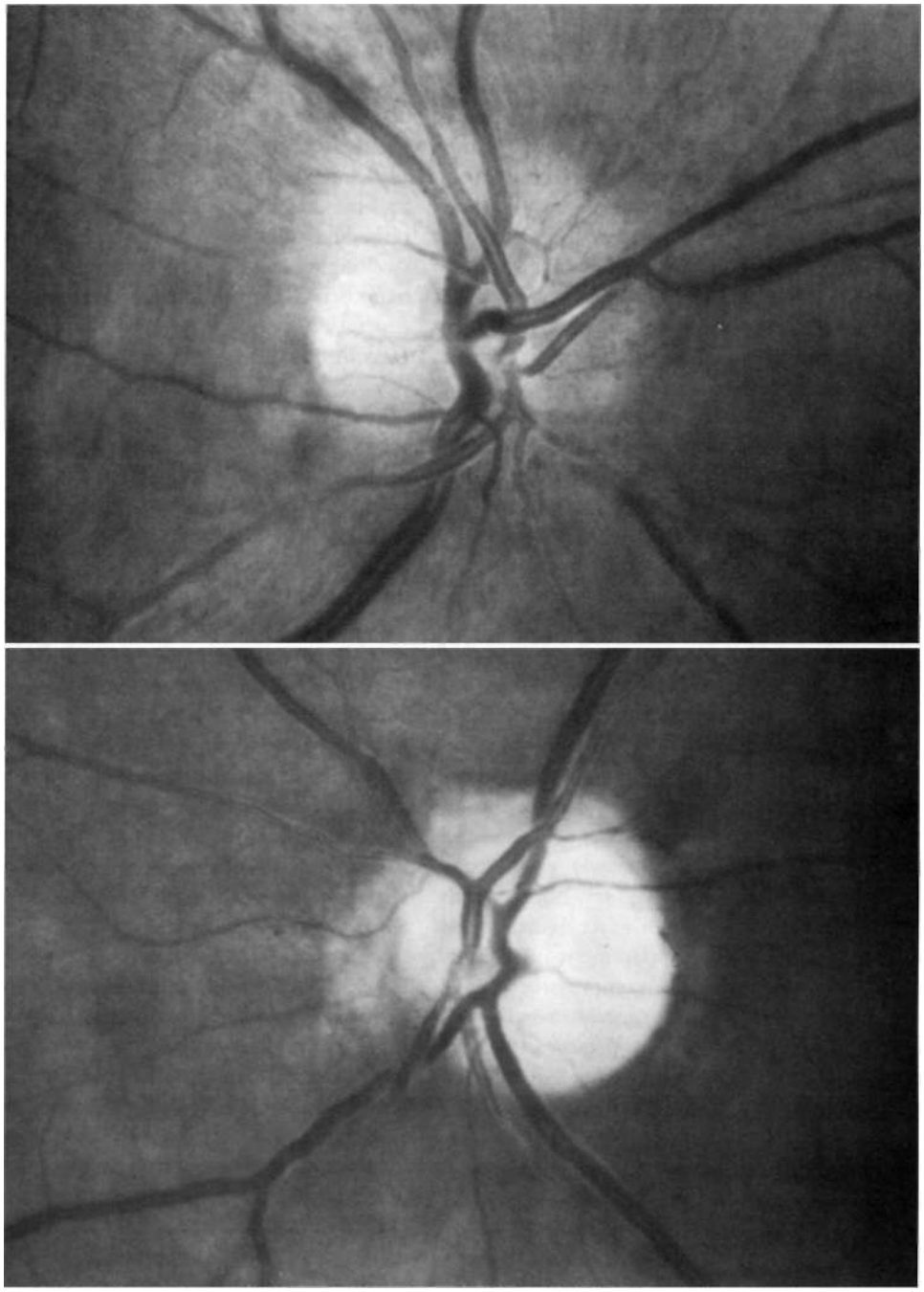

FIGURE 15.1 Pseudo-Foster Kennedy syndrome from (A) acute ischemic optic neuropathy in the right eye (disc edema) and from (B) previous ischemic optic neuropathy in the left eye (optic atrophy} in a 53-ycar-old man. (Reprinted with permission from Beck, R. W. Se Smith, C. H. 1988, *Neuro-Ophthabnology: A Problem-Oriented Approach,* Little, Brown, Boston.)

optic disc may appear hyperemic and mildly swollen in the acute phase (Plate 15.IX). If fluorescein angiography is performed, however, there is no leakage from the disc, as would be present in true disc edema. Telangiectatic vessels, frequently present in the peripapillary nerve fiber layer, are an important clue to the diagnosis. These funduscopic changes may also be noted in pre symptom a tic eyes. Thus a patient may present with symptoms of involvement of only one eye, hut be suspected of having LHON clinically based on characteristic disc changes in both eyes. Genetic diagnosis of LHON is based upon the identification of related mitochondrial DNA mutations (see Chapter 69).

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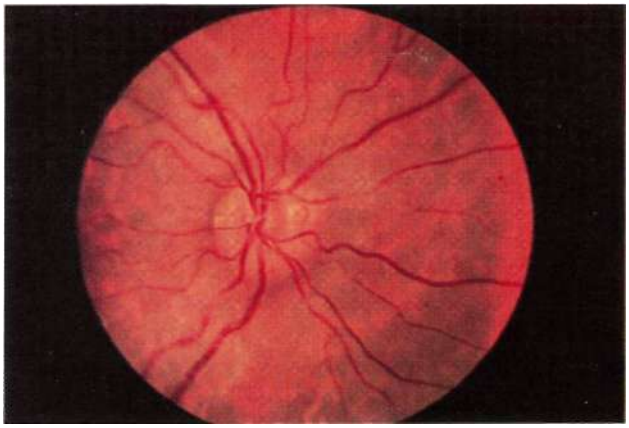

PLATE J5.1 Pseudopapilledema in a 14-year-old boy. Note that the disc margins are blurred but the nerve fiber layer appears clear. No drusen are evident on the surface. The fellow eye appeared similar. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Ophthalmology: A Problem-Oriented Approach,* Little, Brown, Boston.)

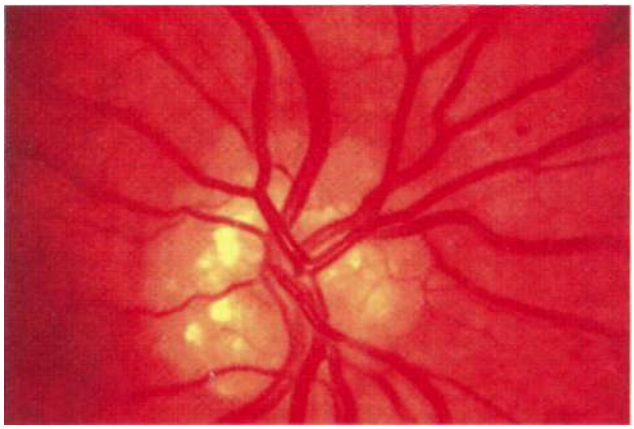

PLATE 15.II Optic disc drusen in a 50-year-old man. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Ophthalmology: A Problem-Oriented Approach,* Little, Brown, Boston.)

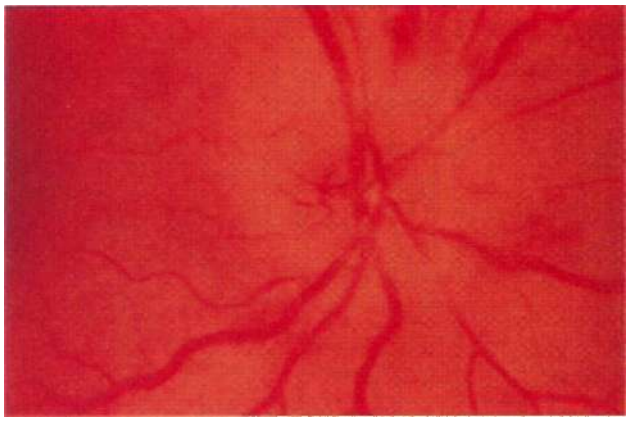

PLATE 15.ni Anterior ischemic optic neuropathy in a 52-year-old woman.

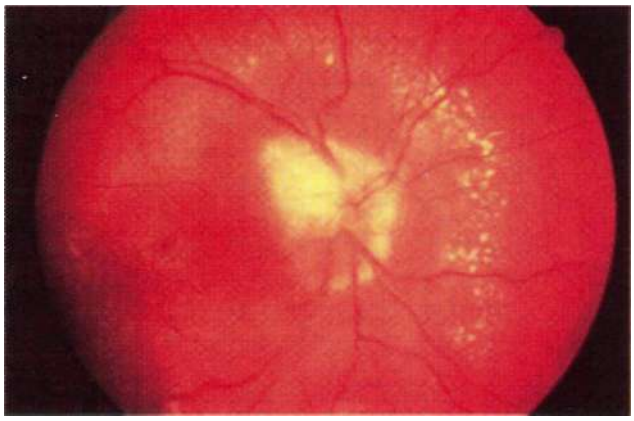

PLATE 15.IV Neurorerinitis in a 6-year-old boy. Although exudates of this type are usually not present in optic neuritis, when present, they indicate an inflammatory cause for the disc edema. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Ophthalmology: A Problem-Oriented Approach,* Little, Brown, Boston.)

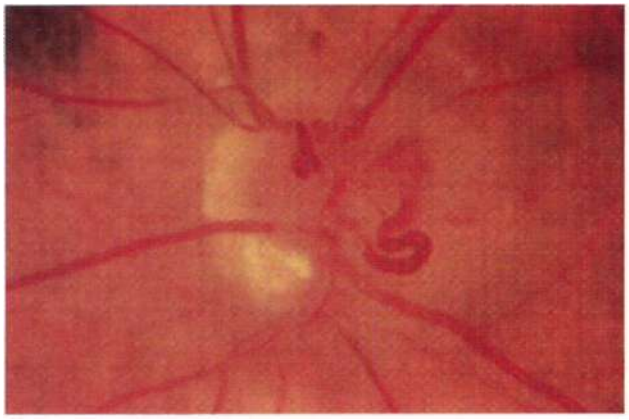

PLATE 15.V Optic disc swelling and optociliary shunt vessels in a 44-year-old woman with a sphenoid meningioma. (Reprinted with permission from Beck, R. W. &c Smith, C. H. 1988, *Neuro-Ophthalmology: A Problem-Oriented Approach,* Little, Brown, Boston.)

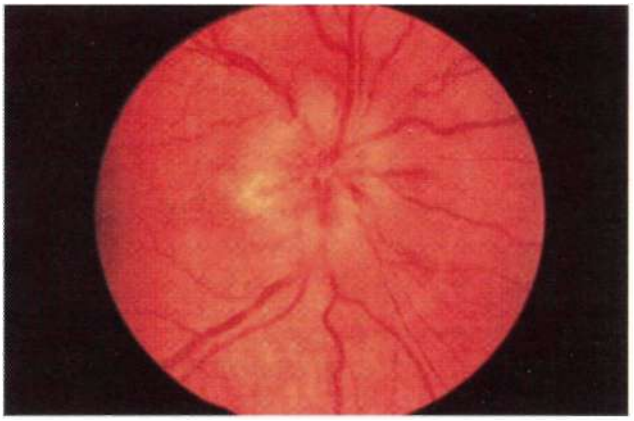

PLATE 15.VI Papillophlebitis in a 23-year-old woman. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Ophthalmology: A Problem-Oriented Approach,* Little, Brown, Boston.)

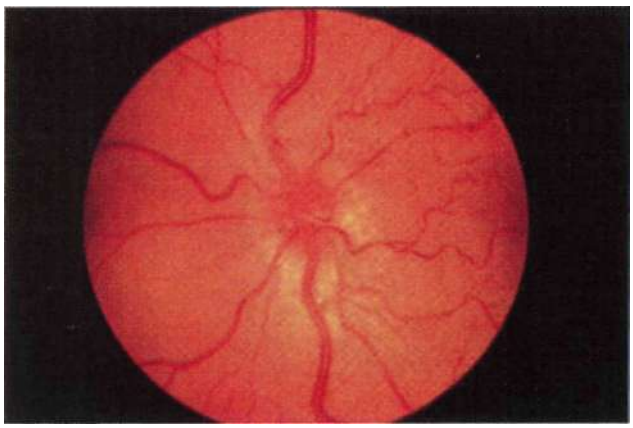

PLATE 15.**VII** Optic disc edema and hyperemia from central retinal vein occlusion in a 55-year-old asymptomatic woman. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Opbthalmology: A Problem-Oriented Approach,* Little, Brown, Boston.)

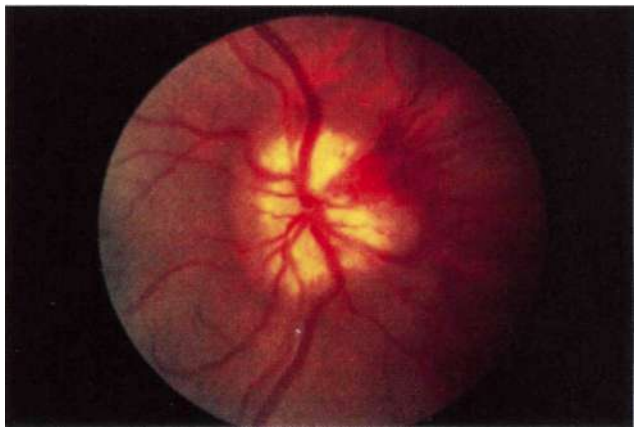

PLATE **15.VIII** Optic disc swelling, hemorrhage, and infiltration in sarcoidosis in a 30- year-old man. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Ophthalmology: A Problem-Oriented Approach,* Little, Brown. Boston.)

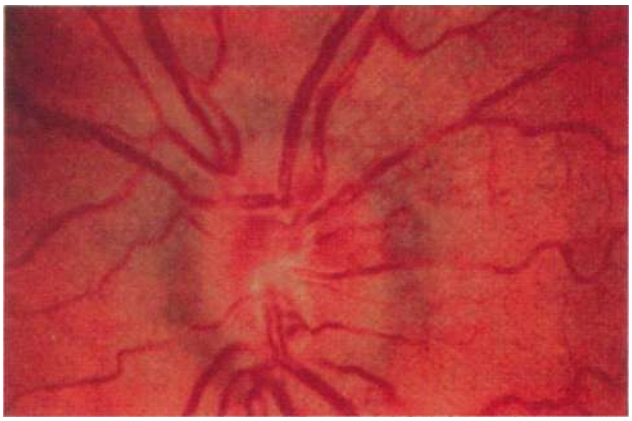

PLATE 15.**IX** Hypcremic disc with telangiectatic vessels in the peripapillary nerve fiber layer in a 26-year-old man with Leber's optic neuropathy. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Ophthalmology: A Problem-Oriented Approach,* Little, Brown, Boston.)

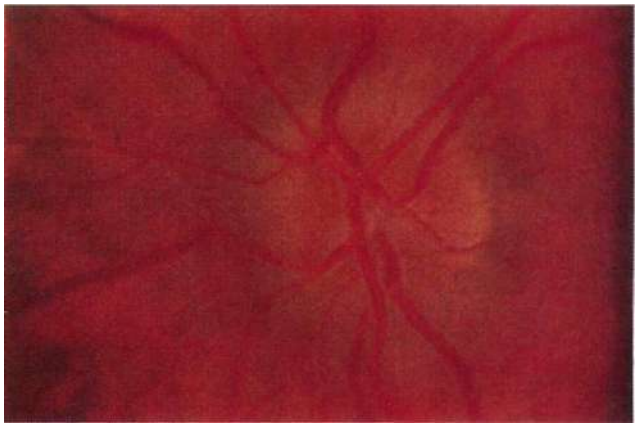

PLATE 15.X Swollen optic disc in early papilledema. Note that the swelling is more prominent superiorly and inferiorlv than it is temporally. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Opbthalmology: A Problem-Oriented Approach,* Little, Brown, Boston.)

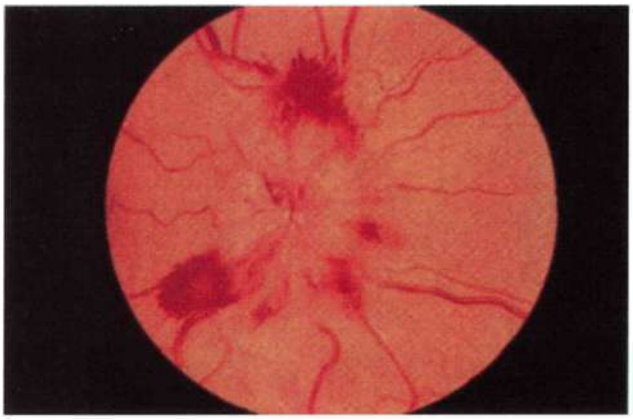

PLATE 15.XI Disc edema and hemorrhages in acute (fully developed) papilledema. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Ophthalmology- A Problem-Oriented Approach,* Little, Brown, Boston.)

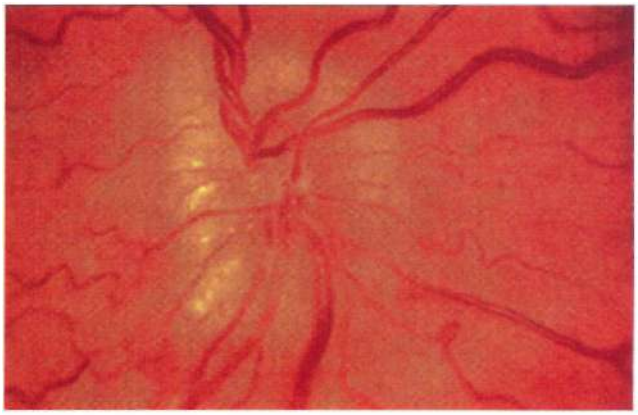

PLATE 15.**XII** Chronic papilledema with glistening white bodies called pseudodrusen. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Ophthalmology: A Problem-Oriented Approach,* Little, Brown, Boston.)

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PLATE 15.Xm Chronic papilledema with marked disc elevation and gliotic appearance to the disc surface. Note that hemorrhages are not present.

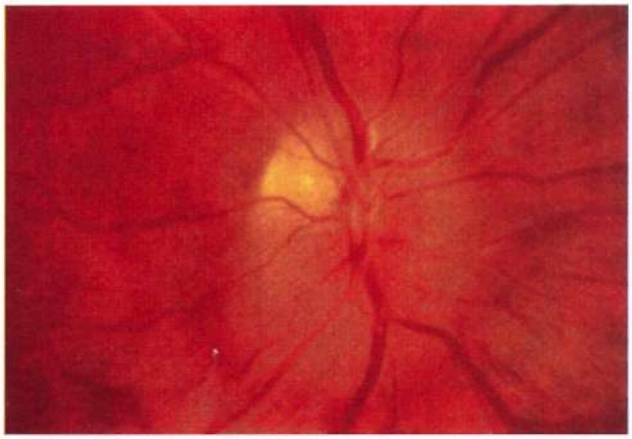

PLATE 15.XIV Chronic papilledema with optic atrophy. Note that the superior portion of the optic disc is pale and not swollen, a result of damaged axons. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Opbthalmology: A Problem-Oriented Approach,* Little, Brown, Boston.)

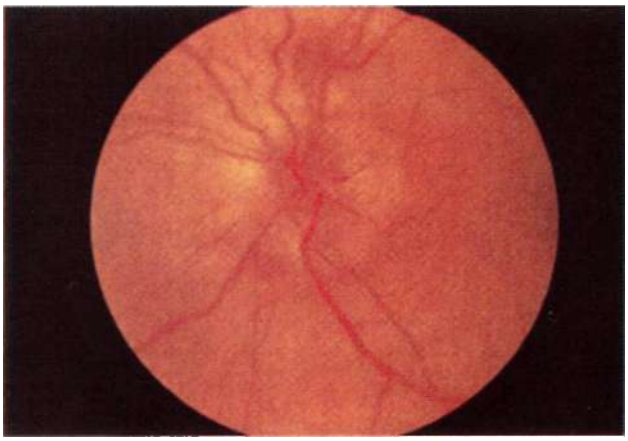

PLATE 15.XV Swollen optic disc in a patient with malignant hypertension. The fellow-eye disc had a similar appearance. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Opbthalmology: A Problem-Oriented Approach,* Little, Brown, Boston.)

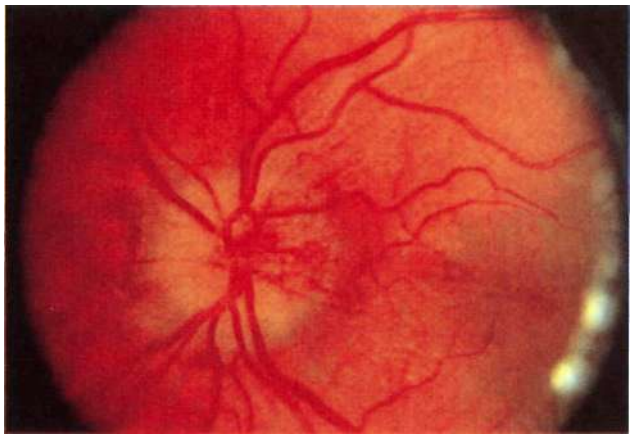

PLATE 15.XVI Diabetic papillopathy in a 17-year-old girl. Note the telangiectatic vessels on the disc surface. (Reprinted with permission from Beck, R. W. &c Smith, C. H. 1988, *Neuro-Ophthalmology: A Problem-Oriented Approach,* Little, Brown, Boston.)

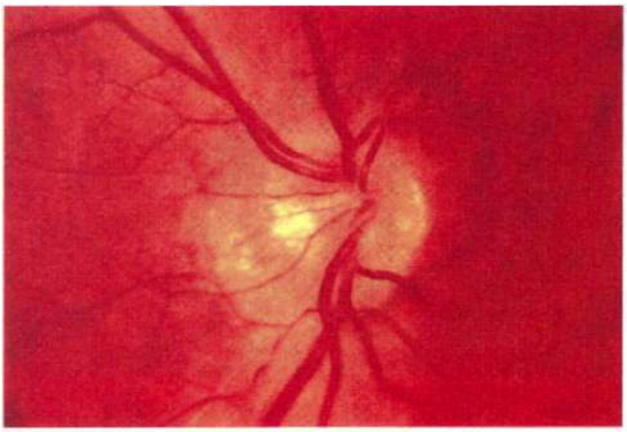

PLATE 15.XVII Tilted optic disc. The fellow eye disc has a similar appearance.

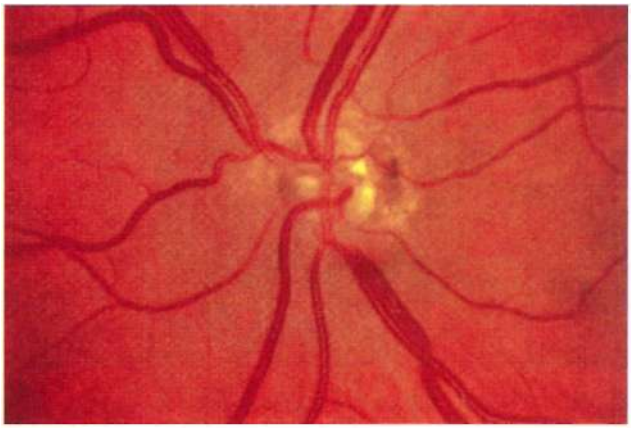

PLATE 15.XVHI Optic nerve hypoplasia. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Ophthalmology: A Problem-Oriented Approach,* Little, Brown, Boston.)

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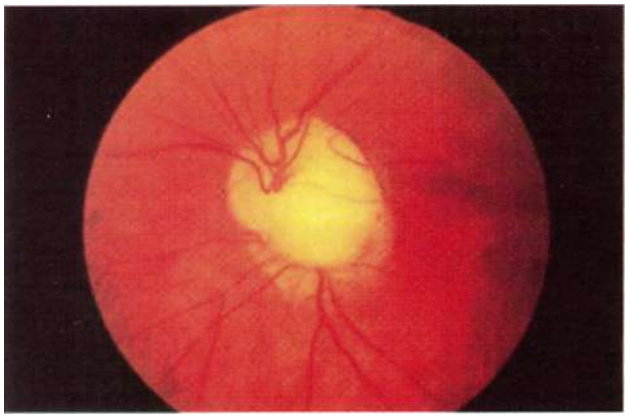

PLATE 15.XIX Optic disc coloboma. (Reprinted with permission from Beck, R. W. & Smith, C. H. 1988, *Neuro-Opbthalmology; A Problem-Oriented Approach,* Little, Brown, Boston.)

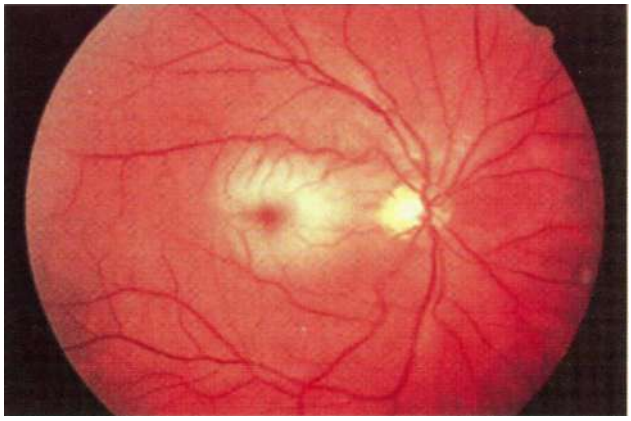

PLATE 15.XX Central retinal artery occlusion. Note the cherry-red spot in the center of the macula, with surrounding whitening of the retina.

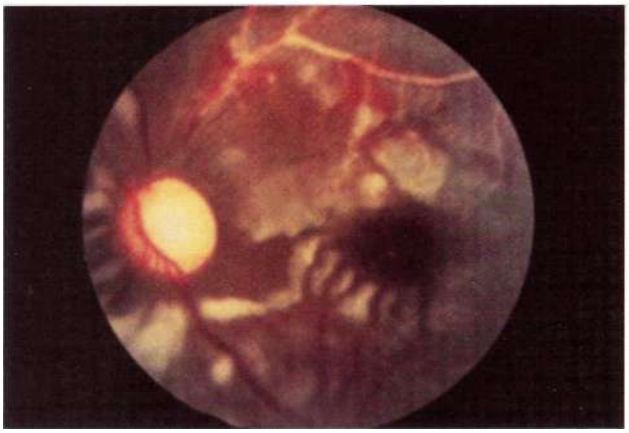

PLATE 15.XXI Multiple cotton-wool spots in a patient with systemic lupus erythematosus.

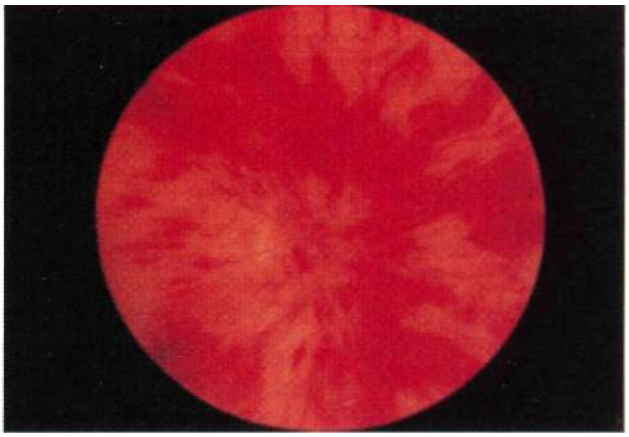

PLATE 15.XXII Central retinal vein occlt

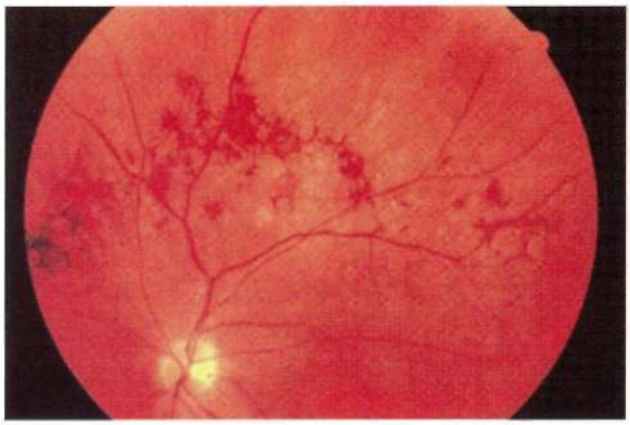

PLATE 15.XXHI Retinal findings in retinitis pigmentosa.

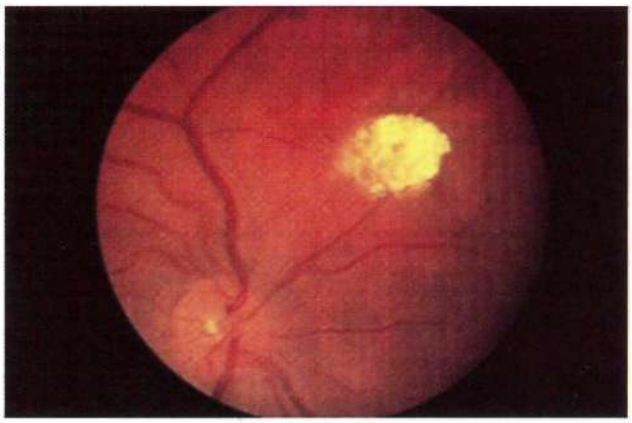

PLATE 15.XXIV Astrocytic hamartoma in a patient with tuberous sclerosis.

Us/c

Bilateral Optic Disc Edema

Papilledema

The term *papilledema* refers specifically to optic disc swelling that occurs secondary to increased intracranial pressure. In the acute phase of papilledema, optic nerve function, particularly central visual acuity, is generally normal. The most common visual field defects encountered in patients with early or acute papilledema are enlargement of the physiologic blind spot, concentric constriction, and inferior nasal field loss.

Disc swelling in papilledema results from blockage of axoplasmic flow in nerve fibers, with a consequent increase in the volume of axoplasm in the optic disc. Based on the chronicity and funduscopic appearance, papilledema can be divided into four stages: early, fully developed (acute), chronic, and atrophic.

In early papilledema, swelling is most prominent at the superior and inferior poles of the optic disc (Plate 15.X). The retinal veins may he slightly distended, and the disc may appear mildly hyperemic. Spontaneous venous pulsations are usually absent.

With further development of papilledema, swelling encompasses the disc surface more uniformly, and the degree of disc elevation increases. The physiological cup becomes increasingly obscured, and retinal venous distension becomes more prominent. Splinter hemorrhages develop on the disc and at its margin in acute (fully developed) papilledema (Plate 15.XI), As papilledema becomes chronic, usually after weeks to months, the disc appearance changes. The nerve fiber layer may take on a gliotic appearance. Hemorrhages are less prominent (or may have resolved completely), and small glistening white bodies (pseudodrusen) are noted (Plate 15.XII). With further chronicity, a characteristic champagne-cork disc appearance develops (Plate 15.XIII).

With prolonged increased intracranial pressure and papilledema, optic nerve axons are damaged, and visual field loss develops. At this stage, optic disc swelling lessens, and disc pallor develops (atrophic papilledema) (Plate 15.XIV).

Patients with end-stage papilledema therefore manifest optic nerve atrophy (disc pallor), without evidence of swelling. Chronic and atrophic papilledema, unlike the early and acute phases, are often characterized by visual acuity as well as visual field loss (i.e., ccnttal acuity is generally spared until late in the course of papilledema).

Malignant Hypertension

A marked elevation in blood ptcssure may produce bilateral optic disc swelling rh.it is indistinguishable from papilledema (Plate 15.XV). Encephalopathy signs are usually but not always present. Disc edema tends to develop at a lower blood pressure in patients with renal failure than in those without renal disease. Peripapillary cotton-wool spots arc also a prominent funduscopic feature in patients with malignant hypertension.

Diabetic Papillopatby

Diabetic papillopathy is a rare cause of bilateral (or sometimes unilateral) disc swelling in patients with Type I diabetes. This entity is distinct from AION in that there is often bilateral, simultaneous optic nerve involvement; often there is no visual field loss with the exception of an enlarged physiologic blind spot. Disc edi'inn is accompanied by marked capillary telangiectasias overlying the disc surface (Plate 15.XVI). Measurement of cerebrospinal fluid pressure (after neuroimaging ro rule out intracranial mass lesions or venous sinus thrombosis) may be necessary to distinguish this condition from papilledema. In many cases, the optic disc edema resolves without residual visual deficit.

Other Causes of Bilateral Disc Edema

Anemia, hyperviscosity syndromes, pickwickian syndrome, hypotension, and severe blood loss are less common causes of bilateral optic disc swelling. The clinical setting generally provides clues to diagnosis. Any of the entities described under unilateral optic disc edema (see Table 15.1) can cause bilateral disc swelling, particularly infiltrative disorders. In children, for example, optic neuritis is commonly bilateral and is often associated with papillitis (disc swelling). Bilateral AION should prompt immediate suspicion and treatment for giant cell (temporal) arteritis in individuals older than 55 years. Although most toxic optic neuropathies present with normal-appearing optic discs, disc edema is characteristic of methanol poisoning and may also occur in patients with ethambutol toxicity.

OPTIC NEUROPATHIES WITH NORMAL-APPEARING OPTIC DISCS

Many optic neuropathies present initially with a completely normal disc appearance; these are classified as retrobulbar optic neuropathies. The differentia! diagnosis depends upon whether unilateral or bilateral optic nerve involvement is present.

Unilateral Cases

The most common causes of unilateral retrobulbar optic neuropathy are optic neuritis (most commonly acute demyelinating optic neuritis) and compressive lesions. The time course of vision loss is usually helpful in distinguishing these two entities. There is no definite way to distinguish these disorders on examination, but the detection of a superior temporal field defect in the fellow eye is highly suggestive of a compressive lesion affecting the anterior

optic chiasm as well as the posterior optic nerve. Retrobulbar ischemic optic neuropathy is a rare condition in patients with giant cell arteritis, other vascuhtides, and after shock or severe blood loss. For practical purposes, there is no retrobulbar correlate to nonarteritic AlON.

Bilateral Cases

Bilateral optic neuropathies in which the optic discs appear normal include nutritional optic neuropathy (including tobacco-alcohol amblyopia), vitamin B, > or folate deficiencies, toxic optic neuropathy (heavy metals), drug-related optic neuropathy (chloramphenicol, isoniazid, ethambutol, cthchlorvynol, chlorpropamide, and others), and inherited optic neuropathies. When these conditions are chronic, optic atrophy may ensue. Other diagnostic considerations in this category include bilateral compressive lesions and bilateral retrobulbar optic neuritis.

OPTIC NEUROPATHIES WITH OPTIC ATROPHY

Any optic neuropathy that produces damage to the optic nerve may result in optic atrophy. At this stage, the optic disc appearance is rarely helpful in determining the underlying cause. The presence of gliotic changes suggests that the disc was previously swollen. Deep disc cupping is, of course, typical of glaucoma, but it is also common after AION as a result of giant cell arteritis, Dominantly inherited optic atrophy often has a characteristic disc appearance, with pallor and excavation of the temporal portion of the disc. Rarely, disc cupping is acquired in the setting of intracranial lesions that cause nerve compression.

Optic atrophy also occurs as consequence of disorders of the retina, optic chiasm, and optic tract. A specific pattern of disc pallor is noted in patients with optic-tract lesions; this pattern, termed bow-tie atrophy, is characterized hy temporal pallor of the ipsilateral disc and both nasal and temporal pallor of disc contralateral to the lesion. Acquired geniculocalcarine lesions (posterior to the optic tract) do not produce disc pallor, although congenital lesions in this area may do so.

CONGENITAL OPTIC DISC ANOMALIES

Optic disc drusen were discussed earlier in this chapter. Other congenital optic nerve anomalies include a tilted optic disc and optic nerve dysplasia.

Tilted Optic Disc

A tilted optic disc is usually easily recognized on ophthalmoscopy. The disc may appear foreshortened on one side, and one portion may appear elevated with the opposite end depressed (Plate 15.XVII). Often, the retinal vessels run in an oblique direction. Tilted optic discs are of neurological importance in that they ate usually bilateral and may be associated with temporal field loss, thus mimicking a chiasmal syndrome. Differentiation from chiasmal disease is virtually always possible based on the pattern of visual field loss. Unlike chiasmal field loss, visual field defects in patients with tilted discs generally do not respect the vertical meridian.

Optic Nerve Dysplasia

There are several types of optic nerve dysplasia. Optic nerve hypoplasia is the most common and is often associated with midline craniofacial anomalies that are of interest to the neurologist. In this condition, the optic disc appears small, and the nerve substance is surrounded by choroid and retinal pigment changes that resemble a double ring (Plate 15.XVIII). The abnormality may be unilateral or bilateral. In most cases, a specific cause cannot be identified. The frequency of optic nerve hypoplasia appears to be increased in children of mothers with diabetes mcllitus or mothers who ingested antiepileptic drugs, quinine, or lysergic acid diethylamide during pregnancy. Endocrine abnormalities and midline craniofacial anomalies may he associated, particularly in bilateral cases. De Morsier's syndrome (septo-optic dysplasia) is characterized by bilateral optic nerve hypoplasia, absent septum peilucidum, and pituitary gland dysfunction (classic growth hormone deficiency) (see Chapter 66). Nystagmus is commonly present when visual loss is severe. Optic nerve aplasia, or complete absence of the optic discs, is extremely rare.

Optic nerve coloboma is more common than optic nerve hypoplasia and results from incomplete closure of the fetal fissure (Plate 15.XIX). It may occur as an isolated finding or as part of a congenital disorder, such as Aicardi's syndrome, trisomy 13, or Goldenhar's syndrome. Another type of congenital anomaly, the optic pit, is manifested as a small grayish area, usually located in the inferior temporal portion of the optic disc.

In some optic nerve dysplasias, the disc appears enlarged. This is true of the so-called "morning glory disc," in which a large whitish concavity is surrounded by pigmentation that resembles a morning glory flower. This condition may be associated with other developmental anomalies, such as basal encephalocele.

RETINAL, DISORDERS IN NEUROLOGICAL DISEASE

Several retinal disorders are of interest to neurologists. The reader is referred to ophthalmology texts for more detailed descriptions of common and less common retinal diseases.

Retinal Arterial Disease

Retinal arterial disease can present as a central retinal artery occlusion or branch retinal artery occlusion (CRAO/BRAO), or as amaurosis fugax (transient monocular visual loss). Carotid artery atherosclerotic disease is the most common cause; cardiac valvular disease must also be considered. The evaluation and treatment of retinal arterial disease are similar to that of stroke and cerebrovascular disease in general (see Chapter 57a). Acute retinal artery occlusion (CRAO/BRAO) is characterized by retinal whitening (edema) secondary to infarction. In CRAO, these findings are usually more prominent in the posterior pole than they are in the periphery (Plan." I 5,XX). A marked narrowing of the retinal arterioles is often noted. Because there are no retinal ganglion cells in the fovea (the center of the macula), this area retains its normal reddish-orange color, producing the characteristic cherry-red spot. The retinal edema usually recovers fairly rapidly over days to weeks. After resolution, the retinal appearance typically returns to normal, although the prognosis for visual recovery is generally poor,

When present, retinal emboli are most often located at arteriolar bifurcations (Figure 15.2). Retinal emboli take on a glistening or whitish/yellowish appearance, and may be located on or near the optic disc or in the retinal periphery. There are three major types of retinal emboli: (1) cholesterol (Hollenhorst plaques; most common source carotid artery); (2) platelet-fibrin (cardiac valves most common source); and (3) calcific (carotid or cardiac source). With impaired blood flow after a CRAO, a portion of a retinal arteriole may take on a whitish appearance. This does not represent an embolus but, rather, stagnant lipid in the blood or changes in the arteriole wall.

Vasculitis

In vasculitis, focal areas of retinal infarction develop. These areas, known as *cotton-wool spots,* are usually bilateral and may be extensive (Plate 15.XXI).

Branch Retinal Artery Occlusions and Encephalopathy (Susac's Syndrome)

Branch retinal artery occlusions and encephalopathy (Susac's syndrome) is a rare disorder of unknown etiology characterized by multiple branch retinal artery occlusions and neurological dysfunction, Susac's syndrome most commonly affects women between the ages of 20 and 40 years. A viral syndrome may precede the development of ocular and neurological signs. The most prominent neurological manifestations are impaired mentation and sensorineural hearing loss. Cerebrospinal fluid in patients with Susac's syndrome shows a mild lymphocytic pleocytosis and elevated protein. Antinuclear antibody (ANA) testing and cerebral arteriography are generally normal, but brain magnetic resonance imaging (MRI) most often demonstrates multiple areas of high signal on T2-weighted images that resemble demyelinating plaques.

Ocular Ischemic Syndrome

Generalized ocular ischemia indicates involvement of both retinal and ciliary circulations in the eye. Signs of optic nerve and retinal ischemia may be present as well as evidence of anterior segment ischemia (iris atrophy, loss of pupil reactivity, cataract formation, rubeosis iridis). Carotid

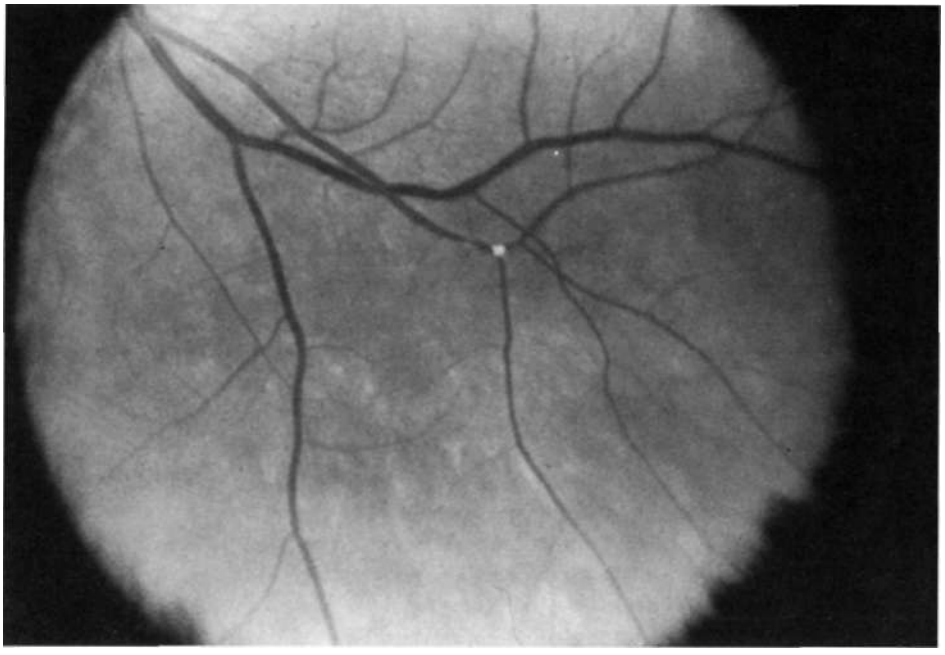

FIGURE 15.2 Hollenhorst plaque at a retinal arteriole bifurcation, (Reprinted with permission from Beck, R. W. Be Smith, C. H. 1988, *Neuro-Ophtbaimology: A Problem-Oriented Approach,* Little, Brown, Boston.)

attcry occlusion/dissection and giant cell arteritis arc the primary considerations in patients with ocular ischemia.

RETINAL VEIN OCCLUSION

Central or branch retinal vein occlusions rarely occur in patients younger than 50 years. The diagnosis is established clinically by the presence of diffuse (central retinal vein occlusion) or focal (branch retinal vein occlusion) retinal hemorrhages (Plate 15.XXII). Disc edema is often present and, in some cases, is the predominant funduscopic feature (see earlier discussion in Uncommon Causes of Unilateral Disc Edema). There are no direct associations between retinal vein occlusion and carotid artery atherosclerotic disease. Patients should be evaluated for vascular risk factors, but carotid imaging/ultrasound is generally not indicated. Bilateral cases of retinal vein occlusion should be evaluated for hyperviscosity syndromes or hypercoagulable states.

NEUROLOGICAL DISEASES WITH RETINAL FINDINGS

Retinal Degenerations

There are a multitude of retinal degenerations, many of which may be associated with neurological disease. Retinitis pigmentosa (RP) is caused by degeneration of the retinal rods and cones. Early in the course of RP, rods are predominantly affected, thus impairing night vision. Visual field loss occurs first in the midperiphery and progresses to severe field constriction.

Pigmentary changes in the retina look like bony spicules and are the hallmark of RP (Plate 15.XXIII). In some cases, however, pigment changes are not prominent, and the visual field loss may mistakenly be thought to have a neurological basis. Even without bone spicule-type changes, the diagnosis of RP is usually obvious to the astute observer because of the retinal thinning, narrowing of retina! arterioles, and waxy optic disc pallor. Regardless of the degree of pigment change, electroretinography is the test of choice for diagnosing RP.

RP usually appears without systemic findings. However, a retinal degeneration of this type may be seen in Kearns-Sayre syndrome, Laurence-Moon-Bardct-Biedl syndrome, Marie's ataxia, Cockayne's syndrome, Refsum's syndrome, Batten's disease, inherited vitamin E deficiency, and spinocerebellar ataxia type 7.

Retinal photoreceptor degenerations can also occur as a remote effect of cancer (cancer-associated tetinopathies [CAR]). This entity has been best characterized in association with small-cell lung carcinoma and with melanoma. Arteriolar narrowing is a consistent finding, but pigmentary changes in the retina arc variable. Elcctrorctinogtaphy is markedly abnormal (showing reduced to extinguished rod and cone components), and antiphotoreceptor antibodies can often be identified in the serum.

Progressive cone dystrophies are retinal degenerations occurring most commonly through autosomal dominant inheritance. Typically, vision loss develops in both eyes beginning in the teens and worsens over several years. Early in the course of cone dystrophy, the fundus may appear normal; with time, however, pigmentary changes develop in the macula, and electroretinography demonstrates characteristic losses of the photopic response.

Uveoretinal Meningoencephalitis Syndromes

Uveoretinal meningoencephalitis syndromes produce inflammatory changes in both the eye and the central nervous system, Vogt-Koyanagi-Harada syndrome, the most common uvcomeningoencephalitis syndrome, is marked by exudative retinal detachments. Table 15.3 lists causes of ocular and central nervous system inflammation.

Phakomatoses

Retinal findings arc common in phakomatoses that affect the nervous system, particularly tuberous sclerosis and

Table 15.3: Causes of uveoretinal meningoencephalitis syndromes

Infectious	*Inflammatory*	*Malignant*
Syphilis	Vogt-Koyanagi-Harada syndrome	Reticulum cell sarcoma
Lyme disease	Sarcoidosis	Lymphoma
Tuberculosis	Multiple sclerosis	leukemia
Cytomegalovirus	Behcet's disease	Metastatic carcinoma
Herpes simplex	Systemic lupus erythematosus	
Herpes zoster	Inflammatory bowel disease	
Subacute sclerosing panencephalitis	Acute posterior multifocal placoid pigment epitheliopathy	
Miscellaneous infections		
Toxoplasmosis		
Whipple's disease		
Acquired immunodeficiency syndrome		

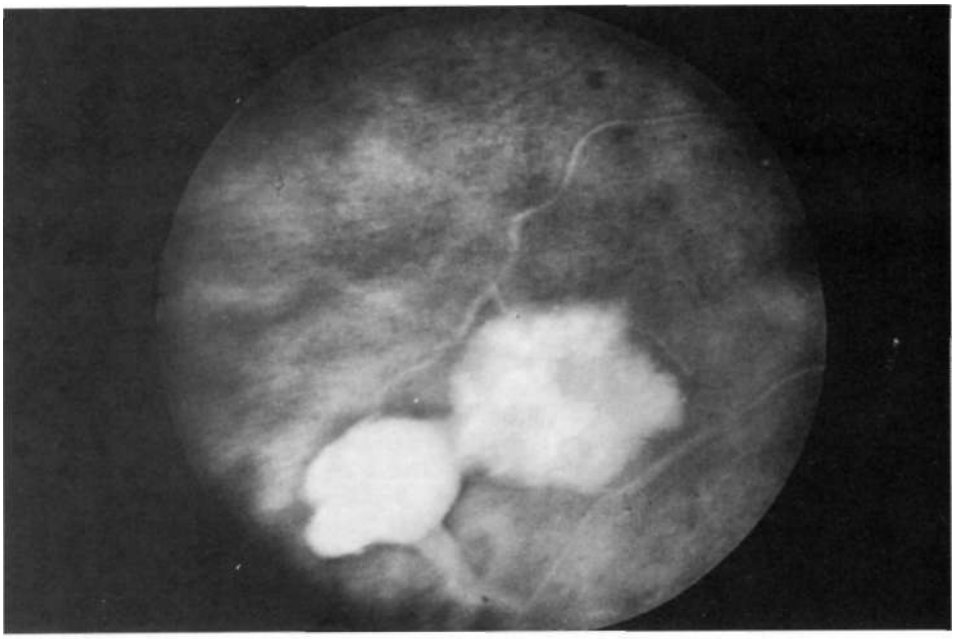

FIGURE 15.3 Retinal angioma in a patient with von Hippel-Lindau disease.

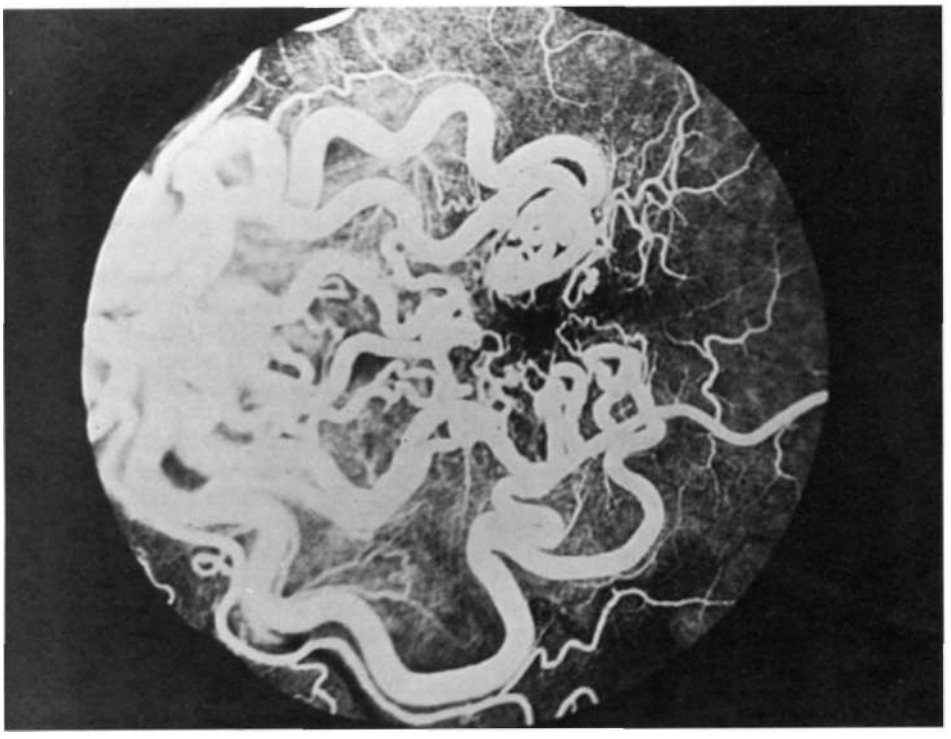

FIGURE 15.4 Fluorescein angiogram of a racemose arteriovenous malformation in the retina in a patient with Wy bum-Ma son disease.

von Hippel-Lindau disease. Neurological features of phakomatoses are described in Chapter 71. In tuberous sclerosis, retinal astrocytic hamartomas are characteristic (Plate 15.XXIV). These are usually multiple and may appear cither as a fullness in the retinal nerve fiber layer or as a nodular refractile lesion (mulberry type}. Von Hippel-Lindau disease is characterized by one or more retinal angiomas that appear as reddish masses with a feeding artety and a draining vein (Figure 15.3). Wybum-Mason disease is characterized by racemose arteriovenous malformations in the retina (Figure 15.4),

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Chapter 16
Eye Movement Disorders: Diplopia, Nystagmus, and Other Ocular Oscillations

Patrick J. M. Lavin

This chapter discusses disorders of extraocular muscle function that cause diplopia, strabismus, nystagmus, ocular flutter, opsoclonus, and other ocular oscillations. A brief outline of the anatomy, physiology, and innervation of the extraocular muscles is followed by a discussion of the mechanisms and types of nystagmus. The reader is guided through the clinical assessment of a patient with an ocular motility disorder, from analysis of symptoms to specialized clinical tests used in evaluating eye movement abnormalities. Therapeutic strategies are discussed at appropriate points throughout the chapter. The development and suptanuclear control of the ocular motor system, supranuclear gaze disorders, and oculographic recording techniques are discussed in Chapter 39.

The human fovea is a highly sensitive part of the retina capable of resolving angles of less than 20 arc seconds. The ocular motor system places images of objects of regard on the fovea and maintains foveation if the object, ot head, moves. Each eye has six extraocular muscles (Table 16.1), yoked in pairs (Table 16.2), that move the eyes **conjugately** (versions) to maintain alignment of the visual axes (Figure 16.1). The actions of the medial and lateral recti are essentially confined to the horizontal plane. The actions of the superior and inferior recti are solely vertical when the eye is abducted 23 degrees; the oblique muscles, the main cyclotortors, also act as pure vertical movers when the eye is adductcd 51 degrees (Figure 16.2). For practical purposes, the vertical actions may be tested at 30 degrees of adduction and abduction. According to HeHng's law of dual innervation, yoked muscles receive equal and simultaneous innervation while their antagonists are inhibited (Sherrington's law of reciprocal inhibition), thereby allowing the eyes to move conjugately and with great precision. The pulling actions of the extraocular muscles evolved to move the eyes in the planes of the semicircular canals, which are not strictly horizontal or vertical. These pulling actions are influenced by both the conventional insertions of the global layer of each extraocular muscle directly into the eyeball, as well as by the insertion of the orbital layer into the fibtomuscular connective tissue sheath that envelopes each rectus muscle (Figure 16.3). This arrangement forms a pulley system that is actively innervated (Demer 2002), stabilizes rotation of the globes in three dimensional space during complex eye movements (for example when a horizontal muscle contracts during upgaze), and prevents excessive **retraction of** the globe within the orbit during extraocular muscle contraction.

Images of the same object must fall on corresponding points of each retina to maintain binocular single vision (fusion) and stereopsis (Figure 16.4). If the visual axes are not aligned, the object is seen by noncortesponding (disparate) points of each retina, and diplopia results (Figure 16.5). In patients with paralytic strabismus, the image from the nonfixating paretic^ eye is the false image and is displaced in the direction of action of the weak

'^In nonparalytic (comitant) strabismus, the image is projected in the direction opposite the deviation.

Table 16.1: Actions of extraocular muscles

Muscle	*Primary*	*Secondary*	*Tertiary*
Medial rectus	Adduction		
Lateral rectus	Abduction		
Superior rectus	Elevation	Intorsion	Adduction
Inferior rectus	I (epression	Excursion	Adduction
Superior oblique	intorsion	I Vjirvssioii	Abduction
Inferior oblique	Extorsion	Elevation	Abduction

muscle. Thus a patient with esotropia has uncrossed diplopia (sec Figure 16.5A), and one with exotropia has crossed diplopia (sec Figure 16.5B). After a variable period, the patient learns to ignore or suppress the false image. If suppression occurs before visual maturity (approximately 6 years of age) and persists, central connections in the afferent visual system will fail to develop fully and lead to permanent visual impairment in that eye (developmental amblyopia). Amblyopia is mote likely to develop in esotropic than in exotropic patients because exotropia is commonly intermittent. After visual maturity, suppression and amblyopia do not occur; instead the patient learns to avoid diplopia by ignoring the false image.

HETEROPHORIAS AND HETEROTROPIAS

When the degree of misalignment—that is, the angle of deviation—of the visual axes is constant, the patient has a comitant strabismus {heterotopia). When it varies with gaze direction, the patient has a noncomitant (paralytic or restrictive) strabismus. In general, comitant strabismus is ophthaltnological in origin, whereas noncomitant strabismus is neurological. Some form of ocular misalignment is present m .3-4% of preschool children.

Most people have a latent tendency for ocular misalignment, *beteropboria,* which may become manifest (a *heterotopia)* under conditions of stress, such as fatigue; bright sunlight; or ingestion of alcohol, anticonvulsants, or sedative medications. Divergent eyes are designated exotropic and convergent eyes are esotropic. Vertical misalignment of the visual axes, which is less common, is termed *hypertropia* (determined by the higher eye, irrespective of which eye is paretic; for example, when the right eye is higher, a right hypertropia exists}. When stress unmasks such a latent tendency for the visual axes to deviate, the diplopia is usually present in most directions of gaze (relatively comitant). Asymptomatic hypertropia on lateral gaze is often a congenital or "physiologic hyperdeviation."

Table 16.2: Yoked muscle pairs

Ipsihteral	*Contralateral*
Medial rectus	Lateral rectus
Superior rectus	Inferior oblique
Inferior rectus	Superior oblique

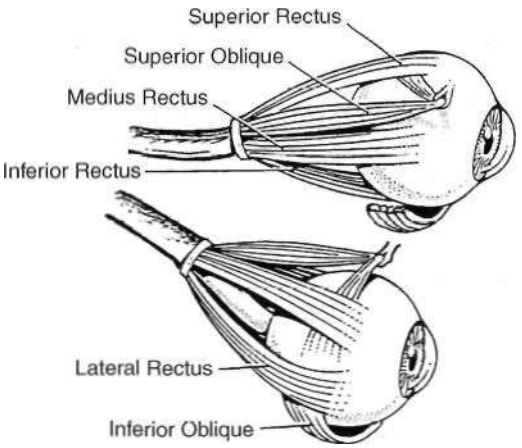

FIGURE 16.1 Each eye has six extraocular muscles.

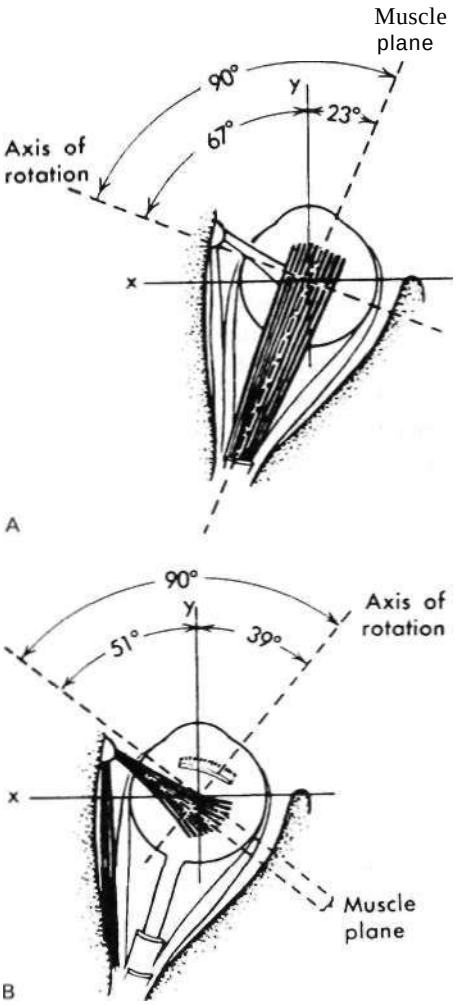

FIGURE 16.2 (A) Relationship of muscle plane of vertical rectus muscles to X- and Y-axes. (B) Relationship of muscle plane of oblique muscles to X- and Y-axes. (Reprinted with permission from Von Noorden, G. K. 1985, *Burian-Von Noorden's Binocular Vision and Ocular Motility*, 3rd ed, Mosby, St. Louis.)

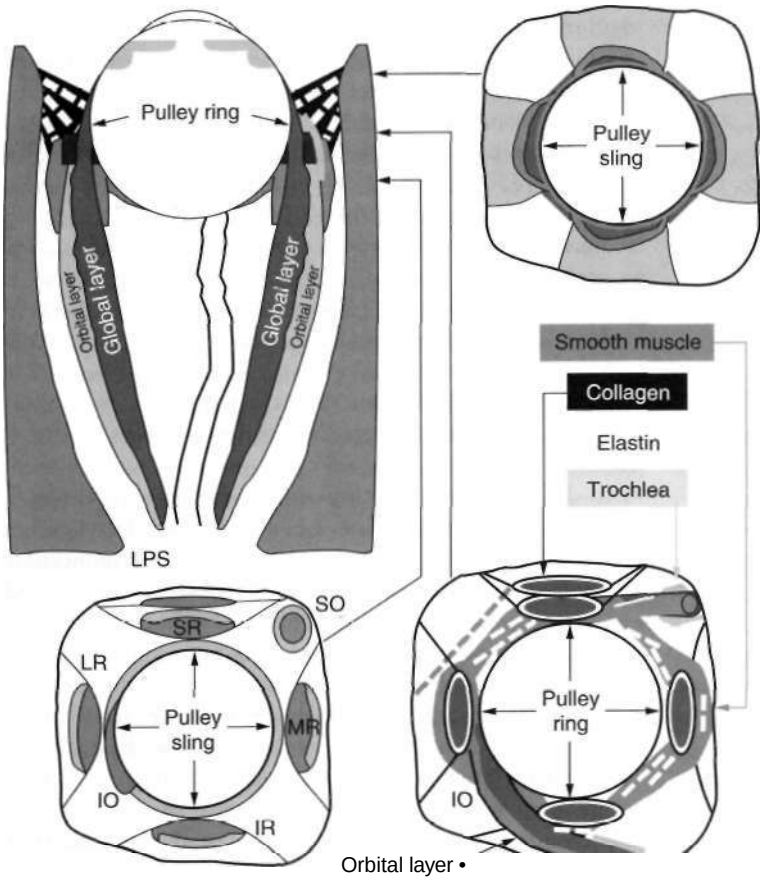

FIGURE 16.3 Diagrammatic representation of the structure of orbital connective tissues and their relationship to the fiber layers of the rectus extraocular muscles. Coronal views are represented at levels indicated by the arrows in horizontal section. (1R = inferior rectus; LLA = lateral levator aponeurosis; LP = levator palpebrae; LR = lateral rectus; MR = medial rectus; SO = superior oblique; SR = superior rectus.) (Redrawn from Demer, J. L. 2002, "The orbital pulley system: A revolution in concepts of orbital anatomy," *Ann NY Acad Sci,* vol. 956, pp. 17-32.)

Comitant Strabismus

Comitant strabismus occurs early in life; the degree of misalignment (deviation) is constant in all directions of gaze, and each eye has a full range of movement (ductions). It probably occurs because of failure of the central synchronizing mechanism in the brain to keep the eyes aligned. Infantile (congenital) esotropia may be associated with maldevelopment of the afferent visual system, including the visual cortex. Cases of comitant esotropia that present between the third and fifth year of life are caused by hyperopia resulting in *accommodative esotropia.*

Occasionally, children with Chiari malformations or posterior fossa tumors present with isolated esotropia before developing other symptoms or signs. Features that suggest a structural cause for the esotropia include: presentation after 6 years of age; complaints such as diplopia or headache; incomitance in horizontal gaze; esotropia greater at distance than near; and neurological findings such as abduction deficits, ataxia, optic disc edema, pathological nystagmus (see section on nystagmus below), and saccadic pursuit (see Chapter 39). Adults who develop isolated esotropia, particularly when they become presbyopic in their early forties, should have a cycloplegic refraction to detect *latent hyperopia.* Other causes of adult-onset esotropia include Chiari malformations and acute thalamic hemorrhage (see Table 39.6).

Noncotnitant (Incomitant) Strabismus

Noncomitam strabismus occurs when the degree of misalignment of the visual axes varies with the direction of gaze as a result of weakness or restriction of one or more extraocular muscles. When a patient with a noncomitant strabismus fixates on an object with the nonparctic eye, the angle of misalignment is referred to as the *primary deviation;* if the patient fixates with the paretic eye, the angle of misalignment is referred to as the *secondary deviation.* Secondary deviation is always greater than primary deviation in noncomitant strabismus because of Hering's law ol dual innervation and may mislead die examiner to believe that the eye with the greater deviation is the weak one (Figure \6.6).

Diplopia

Theoretically, the onset of double vision should be abrupt. However, in practice the history of the onset may be vague. This occurs because the patient may interpret subtle diplopia as blurring unless one eye is covered, either inadvertently or intentionally; or, the onset may be uncertain because the diplopia is intermittent initially, of small amplitude, or compensated for by head position, as may be the case in disorders such as congenital

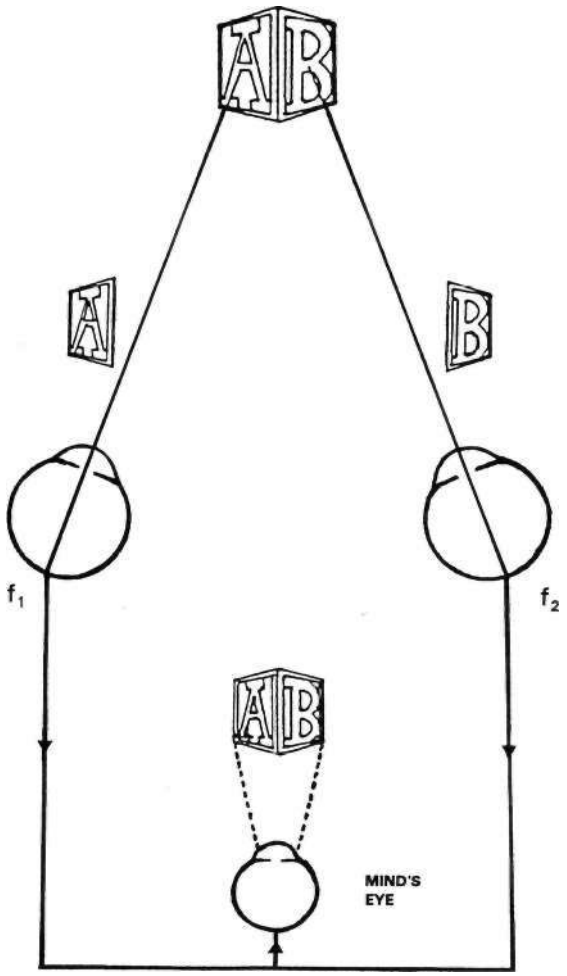

FIGURE 16.4 Each eye views the target AB from a different angle. The fovea of the left eye *(f\)* views the "A" side of the target; the fovea of the right eye *if2)* views the "B" side of the target. The occipital cortex—the cyclopcan (mind's) eye—integrates the disparate images so that a three-dimensional image *{AB)* of the target is perceived. This phenomenon is called *sensory fusion.*

superior oblique palsy, ocular myasthenia, and thyroid orbitopathy. Guidelines for evaluation of diplopia are presented in Table 16.3.

Most adult patients with acquired heterotopia complain of frank double vision. If the images are close together, however, the patient may not be aware of frank diplopia but merely perceive blurring or strain. Others may be aware of overlapping images (ghosting). Occasionally, visual confusion occurs because each fovea fixates a different object, causing the perception of two objects in the same place at the same time (Figure 16.7).

Anxious or histrionic subjects may misinterpret physiologic diplopia, a normal phenomenon, as a pathologic symptom. Physiologic diplopia occurs when *a* subject fixates an object in the foreground and then becomes aware of another object farther away but in the direction of gaze; the nonfixated object is seen by noncorresponding parts of each retina and is perceived by the mind's cyclopean eye as double (Figure 16.R). Alternatively, when the subject fixates a far object, a near object may appear double.

Isolated vertical diplopia (Table 16.4) is most commonly caused by superior oblique muscle palsy (90%). If the palsy is acquired, one image is virtually always tilted, an infrequent finding when the palsy is congenital. If recently acquired diplopia is worse in downgaze, the weak muscle is a depressor; if worse in upgaze, it is an elevator. If one image is tilted, then the weak muscle is more likely an oblique than a vertically acting rectus.

Spread of comitance—that is, the tendency for the ocular deviation to "spread" to all fields of gaze—occurs in long-standing cases; the diplopia then no longer obeys the usual rules.

If double vision persists when one eye is covered, the patient has monocular diplopia; monocular diplopia may be bilateral. The most common cause of monocular diplopia is optical aberration (refractive error) and a need for appropriate spectacles (Table 16.5). Less commonly, monocular diplopia is psychogenic; occasionally, it can he attributed to dysfunction of the retina or the cerebral cortex. The pinhole test quickly settles the matter. The patient is asked to look through a pinhole. If the cause is refractive, the diplopia abates because optical distortion is eliminated as the light rays entering the eye through the pinhole are aligned along the visual axis and thus not deflected. Oscillopsia may be misinterpreted as diplopia.

Occasionally, disorders that displace the fovea, such as a subretinal neovascular membrane, can cause binocular diplopia by disrupting the alignment of tin- photoreceptors (foveal displacement syndrome). The diplopia probably results from rivalry between central and peripheral fusional mechanisms (Brazis and Lee 1998).

Clinical Assessment

History

Table 16,6 shows the procedure for assessing patients with diplopia. The following points should be clarified, if the patient has not volunteered the information: Is the diplopia telieved by covering either eye? (If not, it is monocular diplopia; see Table 16.5). Is it worse in the morning or in the evening? Is it affected by fatigue? Are the images separated horizontally, vertically, or obliquely? If obliquely, is the horizontal or vertical component more obvious? Is the distance between images constant despite the direction of gaze, or does it vary? Is the diplopia worse for near vision or for distance? Is one image tilted? Do the eyelids droop? Is the diplopia influenced by head posture? Has this condition remained stable, improved, or deteriorated? Are there any general health problems? Are thetc associated symptoms, such as headache, dizziness, vertigo,

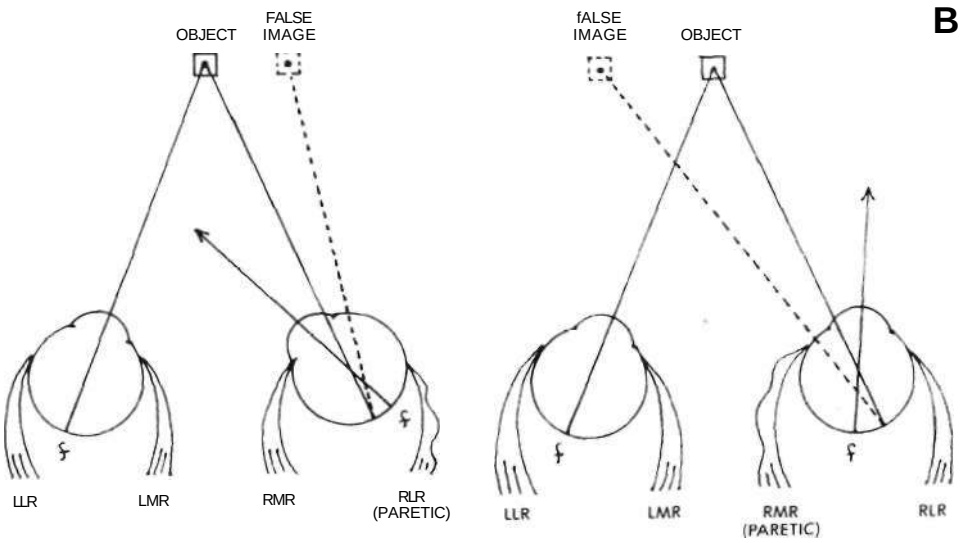

FIGURE 16.5 Misalignment of the visual axes. (A) Esotropia caused by a right lateral rectus (RI.R) palsy results in the right eye turning inward so that the image falls on the retina, nasal to the fovea (f), and is projected, by the mind's eye, ro the temporal field. That is, the false image is projected in the direction of action of the paretic muscle, causing uncrossed (homonymous) diplopia. (B) Fxorropia caused by a paretic right medial rectus muscle (RMR) results in the image falling on the retina temporal to the fovea with projection to the nasal field, in the direction of the action of the paretic RMR, causing crossed (heteronymous) diplopia LLR = left lateral rectus; LMR = left medial rectus,

or weakness? What medications are taken? Is there a family history of ocular, neurological, autoimmune, or endocrine disease? Has the patient had a "lazy" eye, worn a patch, or had strabismus surgery?

For example, latetal rectus muscle weakness causes diplopia that is worse at distance and worse on looking to the side of the weak muscle. Acutely, superior oblique weakness causes diplopia that is worse on looking downward to the side opposite the weak muscle and causes difficulty with tasks such as reading, watching television in bed, going down a staircase, and walking on uneven ground. Medial rectus muscle weakness causes diplopia that is worse for near than for distance vision and is worse to the contralateral side.

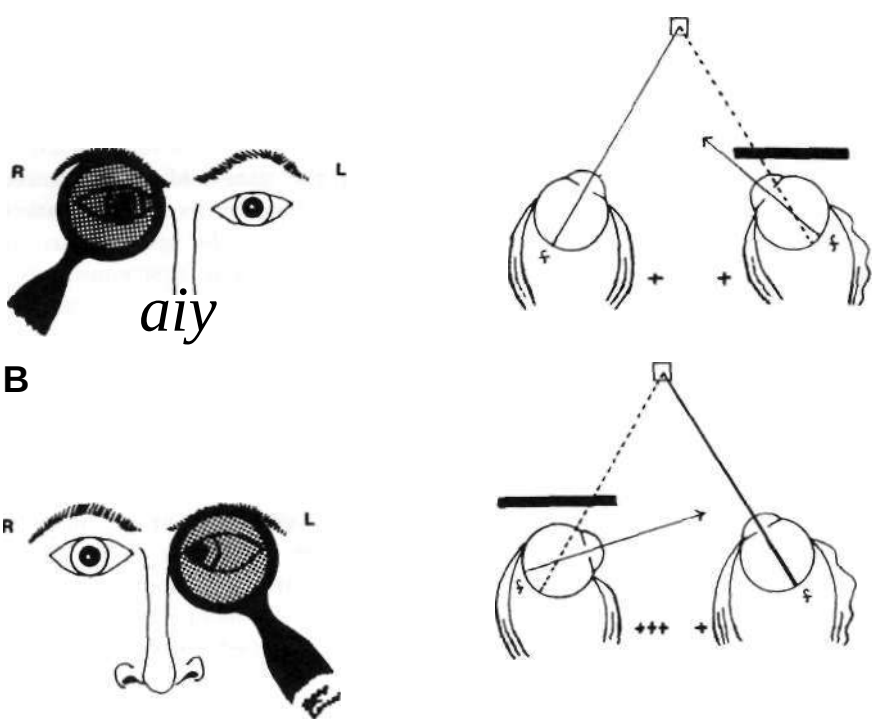

FIGURE 16.6 Primary and secondary deviation with palsy of the right lateral rectus muscle. (A) The right eye is covered with an occluder while the left eye fixates on the target. A small right esotropia (primary deviation) is demonstrated. (The opaque occludet is shown here to be partly transparent so the reader can observe the position of the covered eye.) (B) The left eye is covered while the paretic right eye fixates on the target. The right eye can fixate on the target despite the weak right lateral rectus muscle because that muscle is overdriven by the central nervous system. The normal left medial rectus muscle is also overdriven (Hcring's law of dual innervation), resulting in a large esotropia (secondary deviation). *f*= fovea.

Tabic 16.3: Rules for evaluating diplopia

1. *}\t'ad tilt:* When the weak extraocular muscle is unable to move the eye, the head moves the eye. Therefore the head tilts and turns in the direction of action of the weak muscle (sec Figure 16.9).
2. *The image from the nonfixing eye is the false image* and is displaced in the direction opposite the deviation; thus when the patient fixes with the nonparetic eye, the false image is displaced in the direction of action of the paretic muscle (sec Figure 16.5).
3. *The false image is the most peripheral image* and is displaced in the direction of action of the weak muscle, except when the patient fixes with the paretic eye. When the lateral rectus is paralyzed, the eyes are *esotropic* (crossed), but the images are uncrossed (see Figure 16.5A). The diplopia is worse at a distance and on looking to the side of the weak muscle. When I lie medial reel us is paralyzed, the eves are *exotropic* (wall-eyed), but the images are crossed (see Figure 16.5B). The diplopia is worse at near and on looking to the opposite side.
4. *The images are most widely separated when an attempt is made to look in the direction of the paretic muscle.*
5. *Secondary deviation* (the angle of ocular misalignment when the paretic eye is fixating) is always greater than primary deviation (when the good eye is fixating) (see Figure 16.6). Patients who fixate with the paretic eye may appear to have intracranial disease.
6. *Comitance:* With a comitant strabismus, the angle of ocular misalignment is relatively constant in all directions of gaze. With a *noncomitant (paralytic) strabismus,* the angle of misalignment varies with the direction of gaze.

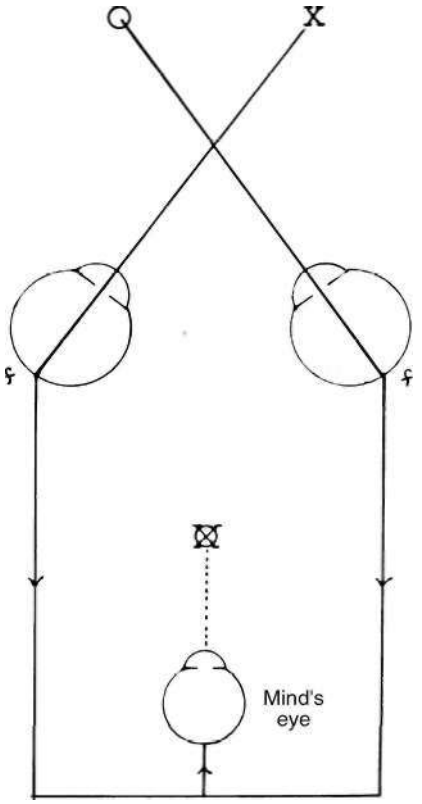

FIGURE 16.7 Visual confusion. Each fovea *(f)* views a different object, which is projected to the visual cortex by the cyclopean (mind's) eye and perceived in the same place at the same time, causing visual confusion (rare).

General Inspection

Ptosis that fatigues suggests myasthenia gravis. Ptosis associated with a dilated pupil suggests an oculomotor nerve palsy. Lid lag suggests thyroid orbitopathy or myotonia. Lid retraction suggests thyroid orbitopathy, aberrant rcinnervation after a third nerve palsy, a cyclic third nerve palsy (see Chapter 39), a dorsal midbrain lesion, hypokalemic periodic paralysis, or chronic corticosteroid use. Proptosis suggests an orbital lesion and, if associated with conjunctival injection and petiotbital swelling, an inflammatory disorder, such as orbital pseudotumor or lymphoma, dura! shunt fistula, or infection. Facial asymmetry suggests a superior oblique palsy **that** is congenita), contralatetal to the hemiatrophic side.

Head Posture

Because the weak extraocular muscle cannot move the eye fully, patients compensate by tilting or turning the head in the direction of action of the weak muscle. For example, with right lateral rectus palsy, the head is slightly turned to the right; then on attempted right gaze, the patient turns the head further to the right (Figure 16.9A). With a right superior oblique palsy, the head lilts forward and to the left (Figure 16.9B). The rule is as follows: The head turns or tilts in the direction of action of the weak muscle.

Sensory Visual Function

Visual acuity, color vision, and confrontation visual fields should be carefully checked in each eye, separately.

Stability of Fixation

Fixation and stability of the gaze-holding mechanism should be checked. This is done by having the patient look at a target and then observing for spontaneous eye movements, such as drift, microtremor, nystagmus, opsoclonus, ocular myokymia, ocular myoclonus, or saccadic intrusions.

Versions (Pursuit, Saccades, and Ocular Muscle Overaction)

Pursuit movements are tested by asking the patient to fixate on and follow (track) a moving tatget in all directions (see Figure 16.9A). This test determines the range of eye movement and provides an opportunity to observe for gaze-evoked nystagmus. If spontaneous primary-position nystagmus is present, the effects of the direction of gaze and convergence on the nystagmus may be determined. Pursuit movements should be smooth and

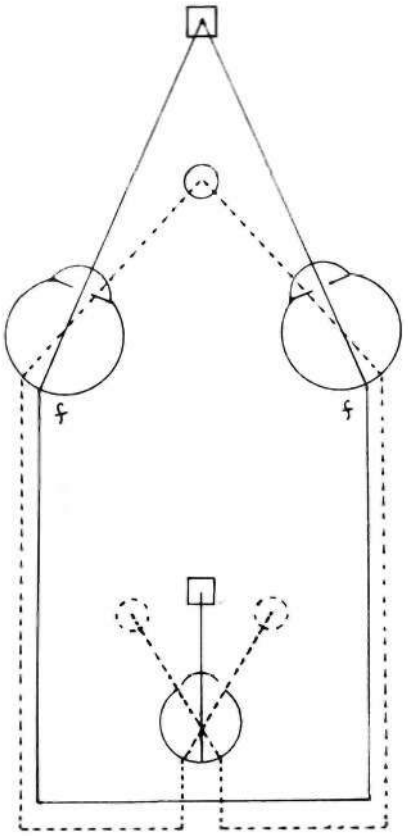

FIGURE 16.8 Physiological diplopia. The cyclopean eye views the target *(the square)* as a single object because each fovea *(f)* fixates it. The images of a nonfixated target *(the circle)* fall on n on corresponding points of each retina and so appears as double.

full. Cogwheel (saccadic) pursuit is a nonspecific finding and is normal in infants; when present in only one direction, however, it suggests a defect of the ipsilateral pursuit system (see Chapter 39).

Saccades (fast eye movements) are tested by asking the patient to look rapidly from one target to another (e.g., from the examiner's nose to a pen) while observing for a delay in initiating the movement (latency) as well as the movement's speed, accuracy, and conjugacy. An internuclear ophthalmoplegia is best detected by this method (see Chapter 39). If a specific muscle, particularly an oblique, is underacting or overacting, this can be observed in eccentric gaze before testing ductions in each eye separately, as shown in Figure 16.1OB. Assessment of disorders of conjugate (supranuclear) gaze is discussed in more detail in Chapter 39.

Convergence

Convergence is tested by asking patients to fixate on a target moving toward their nasion while observing the alignment of the eyes and for constriction of the pupils. Miosis confirms an appropriate effort, while its absence suggests less than optimal effort (see Chapter 39).

Tabic 16.4: Causes of vertical diplopia

Common causes
- Superior oblique palsy
- Dysthyroid orhitopathy (muscle infiltration)
- Myasthenia
- Skew deviation (brainstem, cerebellar, hydrocephalus)

Less common causes
- Orbital inflammation (myositis, pseudotumor)
- Orbital infiltration (lymphoma, metastases, amyloid)
- Primary orbital tumor
- Entrapment of the inferior rectus (blowout fracture}
- Third nerve palsy
- Superior division third nerve palsy
- Atypical third nerve (partial nuclear lesion)
- Aberrant third nerve rcinncrvation
- Brown's syndrome (congenital, acquired)
- Congenital exttaocular muscle fibrosis, or muscle absence
- Double elevator palsy (monocular elevator deficiency) is controversial in origin

Other causes
- Chronic progressive external ophthalmoplegia
- Fisher's syndrome
- Botulism
- Monocular supranuclear gaze palsy
- Verrical nystagmus (oscillopsia)
- Superior oblique myokymia
- Dissociated vertical deviation (divergence)
- Wernicke's encephalopathy
- Vertical one-and-a-half syndrome
- Monocular vertical diplopia (see Table 16.5)

Ductions

Ductions are tested monocularly by having the patient cover one eye and checking the range of movements of the other eye (see Figure I6.I0B). If ductions arc not full, the physician should check for restrictive limitation by moving the eye forcibly (see Forced Ductions, later in this chapter).

Ocular Alignment and Muscle Balance

Before determining ocular alignment, the examiner must first neutralize a head tilt or turn by placing the patient in

Table 16.5: Causes of monocular diplopia

- After surgery for long-standing tropia (eccentric fixation)
- Corneal disease, such as astigmatism, dry eye, or keratoconus
- Corrected long-standing tropia (eccentric fixation)
- Equipment failure (defective conract lens, ill-fitting bifocals in patient with dementia)
- Foteign body in aqueous or vitreous media
- Iris abnormalities (polycoria, trauma)
- I.ens: mulri-refractile (combined cortical and nuclear) cataracts, subluxation
- Monocular oscillopsia (nystagmus, superior oblique myokymia, eyelid twitching)
- Occipital cortex: migtaine, epilepsy, sttoke, tumor, trauma (palinopsia, polyopia)
- Psychogenic
- Retinal disease (rarely)

Tabic 16.6: Assessment of a patient with diplopia

History
- Define symptoms
- Effect of covering either eye?
- Horizontal or vertical separation of the images?
- Monocular?
- Effect of distance of target (worse at near or far}?
- Effect of gaze direction?
- Tilting ▷i oiii: image:

Observation
- Head tilt or turn? ("FAT scan")
- Ptosis (fatigue)?
- Pupil size?
- Proptosis?
- Spontaneous eye movements?

Examination
- Visual acuity (each eye separately)
- Versions (pursuit, saccades, and muscle overaction)
- Convergence (does miosis occur?)
- Ductions
- Ocular alignment (muscle balance) in the "forced primary position"
- Pupils
- Lids (examine palpebral fissures, levator function, fatigue)
- Vestibulo-ocular reflexes (doll's eyes)
- Bell's phenomenon
- I'I'KIII measurements
- Stereopsis ('Litmus stereo rest)
- Optokinetic nystagmus

General neurological examination
- Bruits
- Forced ductions
- Edrophonium (Tensilon) test

FAT= family album tomography—that is, review of old photographs for head tilt, pupil size, lids, ocular alignment, etc. For magnification, use ophthalmoscope or magnifying glass.

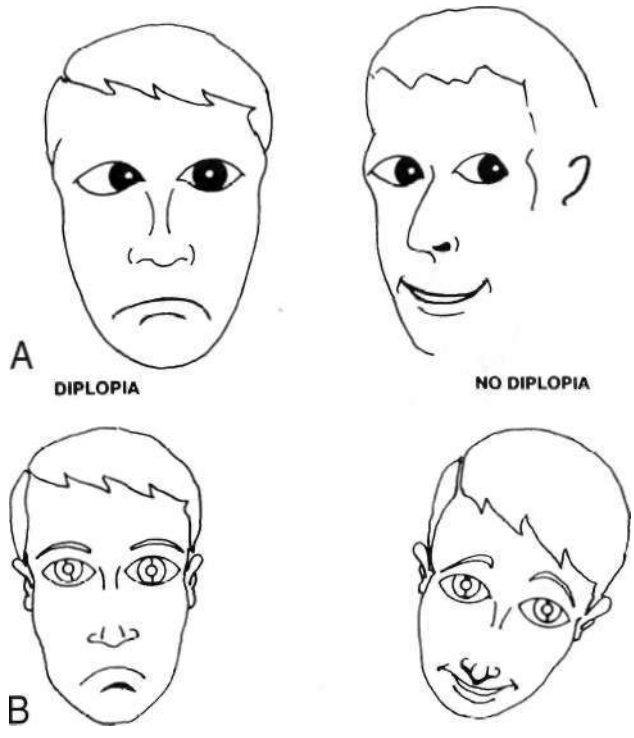

FIGURE 16.9 (A) Right lateral rectus palsy. A right esotropia is present in primary gaze; however, by turning the head to the right (in the direction of action of the weak right lateral rectus muscle), the patient can maintain both eyes on target (orthotropia), and thus have binocular single vision. (B) Acute right superior oblique muscle palsy. The right eye extorts (excycloduction) because of the unopposed action of the right inferior oblique muscle. By tilting the head to the left and forward (in the direction of action of the weak muscle), the right eye is passively intortcd while the left eye actively intorts to compensate and maintain binocular single vision. The head also tilts forward to compensate for the depressor action of the weak right superior oblique.

the "forced (or controlled) primary position"; otherwise, the misalignment may go undetected because of the compensating head posture. Subjective tests of ocular alignment include the red glass, Maddox rod, Lancaster red-green, and Hess screen.

In the red glass test, the patient views a penlight while a red filter or glass is placed, by convention, over the right eye. This allows easier identification of each image; the right eye views a red light and the left a white light. The addition of a green filter over the left eye, using red-green glasses, further simplifies the rest for younger or less cooperative patients. The target light is shown to the patient in the nine diagnostic positions of gaze (see Figure 16.10A). As the light moves into the field of action of a paretic muscle, the images separate. The patient is asked to signify where the images are most widely separated and to describe their relative positions. Interpretation of the results is summarized in Figure 16.11.

The Maddox rod uses the same principle as the red glass test but completely dissociates the images by changing the point of light seen through the rod, which is a scries of half cylinders, to a straight line perpendicular to the cylinders (Figure 16.12). This dissociation of images (a point of light and a line) breaks fusion, allowing detection of heterophorias as well as heterotropias. Cyclotorsion may be detected by asking if the image of the line is tilted (see Figure 16.15B). The Maddox rod can be positioned to produce a horizontal, vertical, or oblique line.

A further extension of these tests includes the Lancaster red-green and Hess screen tests, which use similar principles. Each eye views a different target (a red light through the red filter and a green light through the green filter). The relative positions of the targets are plotted on a grid screen and analyzed to determine the paretic muscle. These haploscopic tests are used mainly by ophthalmologists when quantitatively following patients with motility disorders.

The Hirschberg test, an objective method of determining ocular deviation in young or uncooperative patients, is performed by observing the point of reflection of a penlight held approximately 30 cm from the patient (Figure 16.13);

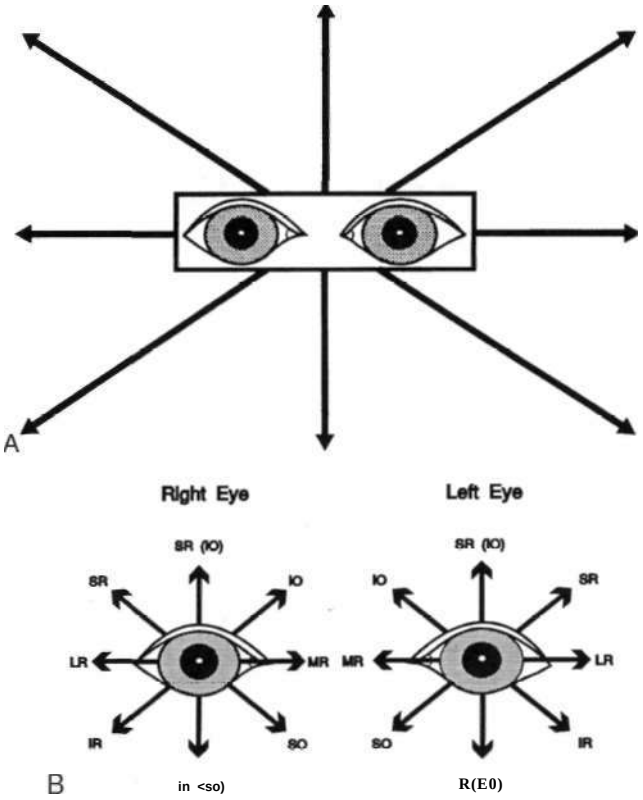

FIGURE 16.10 (A) The nine diagnostic positions of gaze, used for testing versions (saccades and pursuit). (B) Ductions, used to test the isolated action of each of the six muscles of each eye (assuming the other five muscles are functioning normally). Pure elevation (supraduction) and depression (iufraduction) of the eyes are predominantly functions of the superior (SR) and inferior (IR) rectus muscles, respectively, with some help from the oblique muscles. That is, the eyes are rotated directly upward primarily by the superior rectus, with some help from the inferior ohlique (IO). The eyes are rotated directly downward primarily by the inferior rectus, with some help from the superior oblique (SO). LR = lateral rectus; MR = medial rectus,

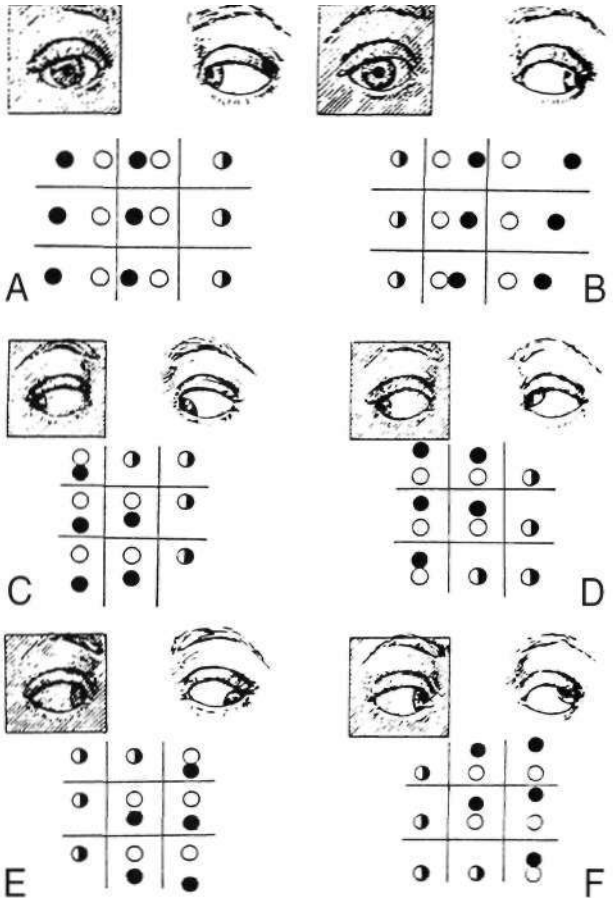

FIGURE 16,11 The red glass test. Diplopia fields for each muscle paralysis are shown. By convention, the red glass is placed over the right eye. The charts below each case are displayed as the subject, facing the examiner, indicates the position of the red (dark circle) and the white (white circle) images in the nine diagnostic positions of gaze. (A) Right lateral rectus palsy. (B) Right medial rectus palsy. (C) Right inferior rectus palsy. (D) Right superior rectus palsy. (E) Right superior oblique palsy. (F) Right inferior ohlique palsy. (Reprinted with permission from Cogan, D. G. 1956, *Neurology of the Ocular Muscles*, 2nd cd, Thomas, Springfield, 111. Courtesy of Charles C Thomas, Publisher.)

1 mm of decentration is equal to 7 degrees of ocular deviation. One degree is equal to approximately two prism diopters. One prism diopter is the power required to deviate (diffract) a ray of light by 1 cm at a distance of 1 m (Figure 16.14).

The cover-uncover test is determined for both distance (6-m) and near (33-cm) vision. The patient is asked to fixate an object held at the appropriate distance. The left eye is covered while the patient maintains fixation on the target, If the right eye was fixating, it remains on target, but if the left eye was fixating, the right eye moves onto the target. If the uncovered right eye moves in (ad ducts), the pan cut has a right cxotropia; if it moves out, the deviation is an esotropia; if it moves down, a right hypertropia; if it moves up, .i left hypertropia. *The physician should always observe the uncovered eye.* The cover should be removed and the test repeated by covering the other eye. If the patient has a tropia, the physician must determine whether it is comitant or noncomitant by checking the degree of deviation in the nine diagnostic positions of gaze (see Figure 16,10A), With lateral rectus palsy, the esotropia increases on looking to the side ɨ>t the weak muscle and disappears on looking to the opposite side (see Figure 16.11A). Similarly, with a medial rectus weakness, the patient has an cxotropia that increases on looking in the direction of action of that muscle (see Figure 16.1 IB). Prisms are used, mainly by ophthalmologists, to measure the degree of ocular deviation (see Figure 16.14). If diplopia is due to breakdown of a long-standing (congenital) deviation, prism measurement can detect supranormal fusional amplitudes (large fusional reserve). If no manifest deviation of the visual axes is found using the cover-uncover rest, the patient is orthotropic. The physician should then perform the cross-cover test.

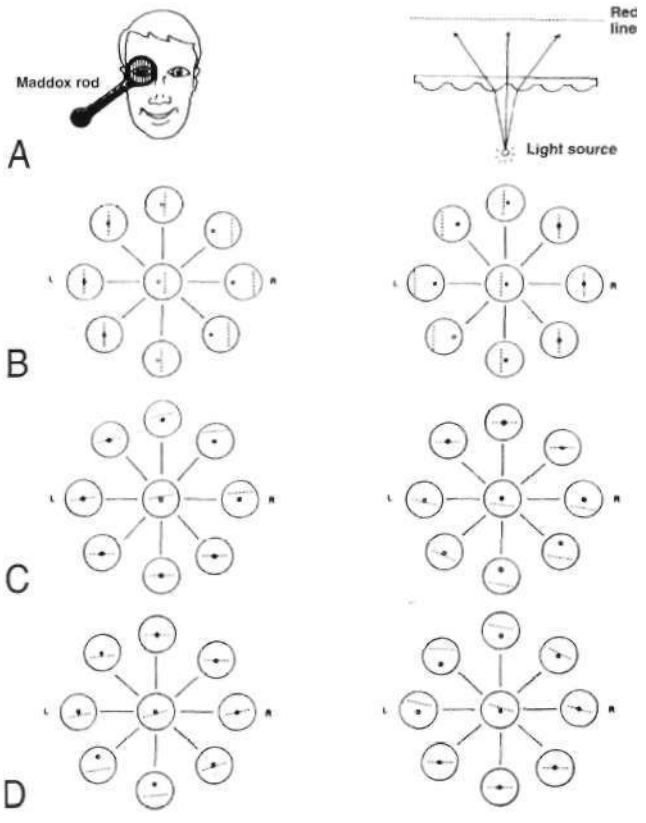

FIGURE 16.12 The Maddox rod test. (Unlike in Figure 16.11, the images are displayed as rhe patient perceives them.) (A) By convention, the right eye is covered by the Maddox rod, which may be adjusted so the patient sees a red line, at right angles to the cylinders, in the horizontal or vertical plane, as desired (red image seen by the right eye; light source seen by the left eye). (B) The Maddox rod is composed of a series of cylinders that diffract a point of light to form a line. (C) Right lateral rectus palsy. (D) Right medial rectus palsy.

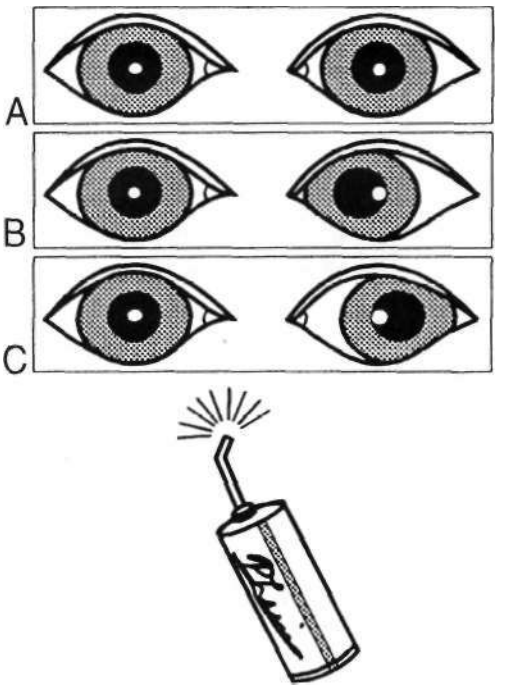

FIGURE 16.13 Hirschberg's method to estimate the amount of ocular deviation. The displacement of the corneal light reflex of the deviating eye varies with the amount of ocular misalignment. One millimeter is equivalent to approximately 7 degrees of ocular deviation, and 1 degree equals approximately 2 prism diopters. (A) No deviation (orthotropic). (B) Left esotropia. (C) Left exorropia.

During the cross-cover (alternate-cover) test, the patient is asked to fixate on a target, then one eye is covered for at least 4 seconds. The examiner should observe the uncovered eye. If the patient is orthotropic, the uncovered eye does not move, but the covered eye loses fixation and assumes its position of rest—latent deviation (heterophoria or phoria). In that case, when the covered eye is uncovered, it refixates by moving back; the uncovered eye is immediately covered and loses fixation. The cross-cover test prevents binocular viewing, and thus fovcal fusion, by always keeping one eye covered. Unlike the cover-uncover test, the cross-cover test detects heterophoria; most normal subjects are exophoric because of the alignment ot the orbits.

Fixation switch diplopia occurs in **patients with** long-standing strabismus who partially lose visual acuity in the fixating eye, usually as a result of a cataract or refractive-error. Such patients normally avoid double vision by ignoring the false image from the nonfixating eye, but a significant fall in acuity in the "good" eye forces them to fixate with the weak eye; this causes misalignment of the previously good eye and results in diplopia. Fixation switch **diplopia** can usually be treated successfully with appropriate optical management.

Dissociated vertical deviation (divergence) is an asymptomatic congenital anomaly that is usually discovered during the cover test. While the patient fixates **a** target, one eye is covered. The covered eye loses fixation and rises; the uncovered eye maintains fixation but may turn inward. This congenital ocular motility phenomenon is usually bilateral but frequently asymmetric; it is often associated with amblyopia, esotropia, and latent nystagmus (LN). Whether there ate an excessive number of axons decussating in the chiasm, as suggested by evoked potential studies, remains controversial. Dissociated vertical deviation has no other clinical significance.

Three-Step Test for Vertical Diplopia

Fight muscles arc involved in vertical eye movements: Four muscles arc elevarors and four arc depressors. The three-step test endeavors to determine if one particular paretic muscle is responsible for vertical diplopia (Figure 16.15). Using the cover-uncover test, which is objective, or one of the subjective tests, such as the red glass test, the physician can apply the three-step test. It is important to remember that the hypertrophic eye views the lower image.

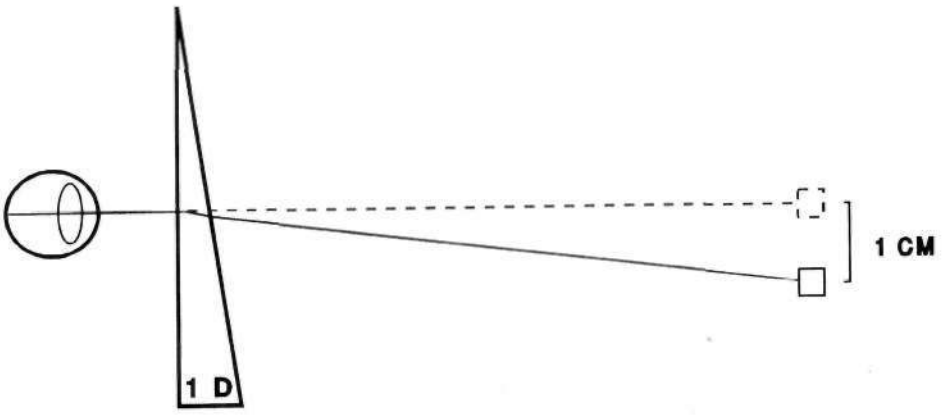

FIGURE 16.14 A prism with rhe power of I prism diopter (D) can defract a ray of light 1 cm at I meter.

Step 1 determines which eye is higher (hypertrophic) in primary position. The patient's head may have to he repositioned (forced primary position) because of a compensatory tilt. If the right eye is higher, the weak muscle is either one of the two depressors of the right eye (inferior rectus or superior oblique) or one of the two elevators of the left eye (superior rectus or inferior oblique).

Step 2 determines whether the hypertropia increases on left or right gaze. If it increases on left gaze, the weak muscle is cither rhe depressor in the right eye that acts best in adduction (i.e., the superior oblique) or the elevator in the left eye that acts best in abduction (i.e., the superior rectus), and vice versa.

Step 3 determines whethet the hypertropia changes when the head tilts to the left or right. If it increases on head tilt left, the weak muscle must be an intortor of the left eye (superior rectus); if it increases on head tilt right, the weak muscle must be an intortor of the right eye (superior oblique).

Two more optional steps can be introduced:

Step 4 (optional), using one of a number of techniques (such as the double Maddox rod, visual field blind spots, indirect ophthalmoscopy, or fundus photography), determines if ocular torsion is present. Establishing the degree and direction of ocular torsion, if any, can differentiate a skew deviation (see Chapter 39) from a true superior oblique palsy. Because the primary action of the superior oblique muscle is intorsion (sec Table 16.1), an acute palsy typically results in approximately 5 degrees of extorsion of the affected eye because of unopposed action of the ipsilateral inferior oblique muscle. If cither eye is intorted, a superior oblique palsy is not responsible, and the patient may have a skew deviation (Donahue et al. 1999).

Step 5 (optional) is helpful in the acute phase. If the deviation is greater on downgaze, the weak muscle is a depressor; if it is worse on upgaze, the weak muscle is likely to be an elevator. This fifth step is helpful only in the acute stage hecause, with time, the deviation becomes more comitant and may he misleading in a patient with a long-standing palsy, especially if the third step is omitted.

The examiner should he aware of the pitfalls of the three-step test, namely, where the rules break down. These include restrictive ocular myopathics (Table 16.7), long-standing strabismus, skew deviation (see Chapter *39),* and disorders involving more than one muscle.

The four fundamental features of the fourth cranial nerve are (1) it has the longest intracranial course, and is the thinnest of all the cranial nerves, and thus very susceptible to injury; (2) it is the only cranial nerve that exits the neuraxis dorsally; (3) its nucleus of origin is on the contralateral side of the neuraxis (the oculomotor subnucleus for the superior rectus is also on the opposite side); (4) the most common cause of isolated vertical diplopia is a fourth nerve (superior oblique) palsy. Lee et al. (1998) and Jaeohson (2002) comprehensively reviewed causes of superior oblique palsies.

Fatigability

Once the weak muscle is identified, the physician should determine whether it fatigues by testing its rapid (saccadic) action repetitively and its ability to sustain eccentric eye position without drift.

Forced Duct ions

If the weak muscle does not fatigue, the physician should determine whether it is restricted by performing forced ductions. The use of phenylephrine hydrochloride

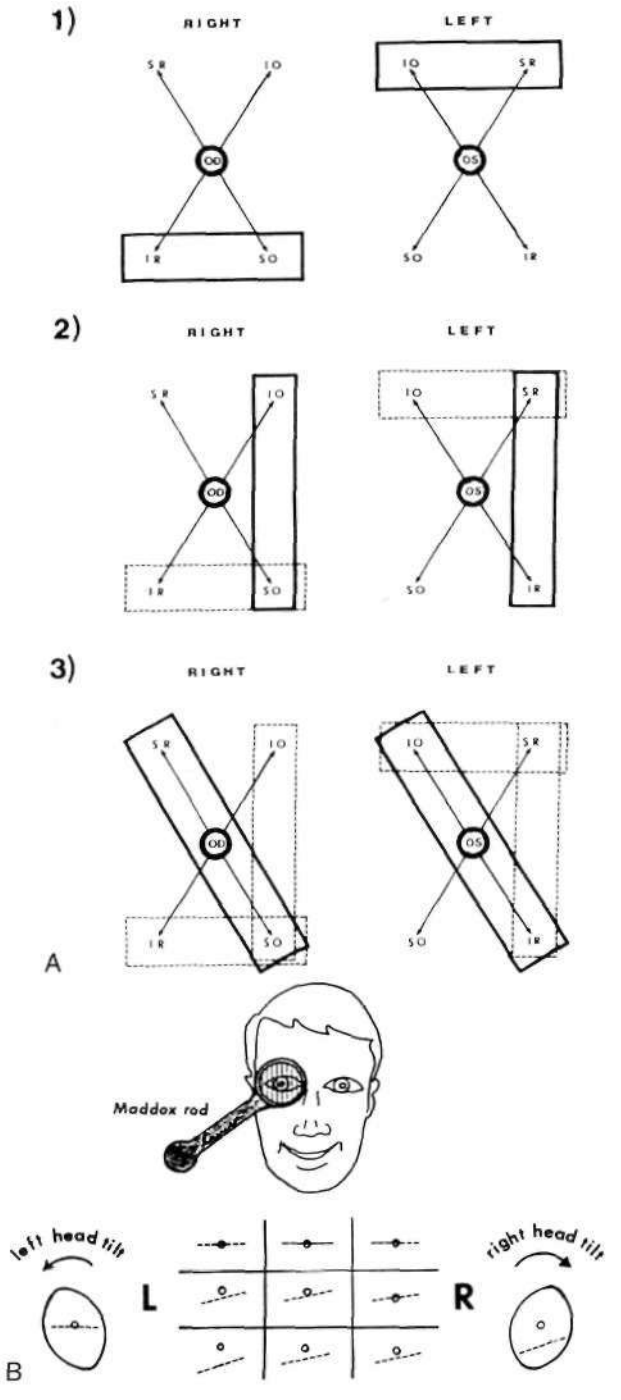

Table 16.7: Positive forced ductions (restrictive)

Acquired: superior oblique tendinitis, myositis, or injury
Brown's syndrome
Carotid-cavernous or dural shunt fistula
Congenital: superior oblique tendon sheath syndrome
Duane's syndrome
Entrapment (blowout fracture)
Extraocular muscle fibrosis (congenital, postoperative)
Long-standing muscle weakness
Orbital infiltration: myositis, lymphoma, metastasis, amyloidosis, cysticcrcosis, trichinosis
Thyroid ophthalmopathy

eye drops beforehand reduces the risk of subconjunctival hemorrhage. Although this test is in the realm of the ophthalmologist, it may be performed in the office using topical anesthesia and a cotton-tipped applicator, but great care must be taken to avoid injuring the cornea. The causes of restrictive myopathy are listed in Table 16.7; however, any cause of prolonged extraocular muscle paresis can result in contracture of its antagonist.

Signs Associated with Diplopia

Extraocular muscle or lid fatigue suggests myasthenia gravis, as does Cogan's lid twitch sign. Weakness of other muscles, such as the orbicularis oculi, othet facial muscles, neck flexors, or bulbar muscles, may he found in oculopharyngeal dystrophy and myasthenia gravis (see Chapters 28, 84, and 88). Narrowing of the palpebral fissure and retraction of the globe on adduction, associated with an abduction deficit, suggest Duane's retraction syndrome (Gutowski 2000).

Paradoxical elevation of the upper lid on attempted adduction or downgaze occurs with aberrant reinnervation of the third cranial nerve, which is virtually always a result of trauma or compression caused by tumor or aneurysm (see Chapter 77); the pupil may also constrict on attempted adduction or downgaze. Miosis accompanying apparent bilateral sixth nerve palsy occurs with spasm of the near reflex (see Chapter *S9).* Horner's syndrome, ophthalmoplegia, and impaired sensation in the distribution of the first division of the trigeminal nerve occur

FIGURE 16.15 Example of the three-step test in a patient with an acute right superior oblique palsy. (A) In a patient with hypcrtropia, one of eight muscles may be responsible for vertical ocular deviation. Identifying the higher eye eliminates four muscles. *(1)* With a right hypcrtropia, the weak muscle i-. either one of the two depressors of the right eye (IR or SO) or one of the two elevators of the left eye (IO or .SR) (enclosed by the solid line). (2) If the deviation (or displacement of images) is greater on left saw, one of the muscles acting in left gaze (enclosed by the solid line) must be responsible, in this case cither the depressor in the right eye (SO) or the elevator in the left eye (SR). (.?) If the deviation is greater on right head tilt, the incyclotortors of the right eye (SR and SO) or the exeyclotortors of the left eye (IR and 10) (enclosed) must be responsible, in this case, the right SO—that is, the muscle enclosed thtee times. If the deviation is greater on left head tilt, the left SR would be responsible. IO = inferior oblique; IR = inferior rectus; SO = superior oblique; SR = superior rectus. lii I he Maddux rod tci ul^pl.nvd ,is in Figure 1(S. I 2, as [he subject perceives the images) in a paiienl with a right superior oblique palsy shows vertical separation of the images that is worse in the direction of action of the weak muscle and demonstrates subjective tilting of the image from the right eye. When the head is tilted toward the left shoulder, the separation disappears, bur when the head is tilted to the right shoulder, to the side of the weak muscle, the separation is exacerbated (Biclschowsky's third step).

with superior orbital fissure and anterior cavernous sinus lesions. A third nerve palsy with pupillary involvement is most often caused by a compressive lesion; when this occurs acutely, a posterior communicating aneurysm is usually responsible.

Proptosis suggests an orbital lesion, such as thyroid disease (bilateral), inflammatory or infiltrative orbital disease (tumor, pseudotumor, or amyloidosis), or carotid-cavernous fistula, in which case it may be pulsatile. Ocular bruits, often heard by both patient and doctor, occur with carotid-cavernous or dural shunt fistulas. Other findings include entrapment (blowout fracture), which is a sign of periorbital and ocular injury, and nystagmus (see Chapter 39) seen with intcrnuclear ophthalmoplegia. Other cranial nerve deficits and various miscellaneous signs may be present. Ophthalmoplegia, ataxia, nystagmus, and confusion suggest Wernicke's encephalopathy. Pyramidal and spinothalamic signs with crossed hemiparcsis suggest brainstem syndromes (see Chapter 22). Facial pain, hearing loss, and ipsilateral lateral rectus weakness indicate Gradenigo's syndrome. Myotonia and retinitis pigmentosa suggest more widespread disorders.

Edrophonium (Tensilon) Test

The edrophonium test is discussed in detail in Chapter 84, but a few points are stressed here. The test must have an objective endpoint, such as ptosis, a tropia, or limited ductions; the physician must observe an objective change. The edrophonium test is negative when forced ductions are positive (restrictive myopathy) and is difficult to interpret when the patient has no objective signs of extraocular muscle weakness or ptosis,

Optokinetic Nystagmus

True optokinetic nystagmus (OKN) is a rhythmic involuntary conjugate ocular oscillation in response to a compelling full visual field stimulus, such as that produced by rotating an image of the environment around the patient or by turning the patient in a revolving chair. The oscillation is biphasic and consists of an initial slow phase provoked by, and in the direction of, the stimulus; this is followed by a fast, corrective, phase (see Chaprer 39). OKN in response to a pocket tape is a useful bedside test, but it evaluates only foveal pursuit and refixation saccades, which arc helpful in several circumstances. These circumstances are (1) detecting a subtle internuclear ophthalmoplegia; (2) provoking convergence-retract ion nysragmus, where the tape is moved downward in an attempt to induce upward saccades; (3) congenital nystagmus (CN), where the direction of the fast phase may be paradoxical—that is, in the direction of the slowly moving tape or drum; (4) patients feigning complete blindness or ophthalmoplegia; (5) homonymous hemianopia caused by a large, **deep**-seated parietotemporo-occipital lesion, where the OKN response is depressed or absent as the tape moves toward the side of the lesion.

A large mirror may be used to induce true optokinetic movements in patients with psychogenic ophthalmoplegia or psychogenic blindness. The examiner holds the mirror in front of rbi' patient, whose eyes *.ax* open, The minor is gently rocked so that the reflected environment (full visual field) moves. This compelling optokinetic stimulus forces reflex slow eye movements. The patient may close the eyes, look away, or converge in an attempt to avoid the reflex response. Care must be taken in diagnosing psychogenic disorders with this test in patients with supranuclear gaze palsies, ocular motor apraxia, or poor vision; those with "count-fingers" vision may still have an OKN response.

Vergence Disorders

Vergence disorders may cause diplopia (see Chapter 39).

Central Fusion Disruption

Central fusion disruption causes diplopia and is described in Chapter 39.

Acute Bilateral Ophthalmoplegia

The causes of acute bilateral ophthalmoplegia are outlined in Table 16.8.

Chronic Bilateral Ophthalmoplegia

The causes of chronic bilateral ophthalmoplegia are outlined in Table 16.9.

Treatment

Patching (occlusive) therapy is used mainly to eliminate one image during the acute phase. In children under age 6, each eye should be patched alternately to prevent developmental amblyopia. Such young patients should be followed by an experienced ophthalmologist. Adult patients may wear the patch over whichever eye is more comfortable, although some clinicians feel that alternating the patch reduces the incidence of contractures.

Prisms are helpful in eliminating double vision if the deviation is not too great. A reasonable range of binocular single vision may be achieved with prisms, provided the patient's expectations arc not too high and there is no significant cyclodeviation.

Botulinum toxin is used in patients with both comitant and noncomitant strabismus, with mixed success. It may be helpful in patients with acute abducens palsies, particularly if bilateral and traumatic in origin.

Extraocular muscle surgery can correct long-standing strabismus (comitant or noncomitant). Finally, orthoptic

Tabic 16.8: Causes of acute bilateral ophthalmoplegia*

Acquired immunodeficiency syndrome encephalopathy
Basilar meningitis, hypertrophic cranial pachymeningitis, or neoplastic infiltration
Botulism
Brainstem encephalitis
Brainstem stroke*
Carotid-cavernous or dural shunt fistula
Cavernous sinus thrombosis (febrile, ill)*
Centra] herniation syndrome
Ciguatera poisoning
Diphtheria
Fisher's syndrome
HMG-CoA reductase inhibitors* (may he transient, may he associated with anti-AchR antibodies) (Negvesky et al. 2000, personal observation 2002)
Intoxication (sedatives, tricyclics, organophosphates, anticonvulsants—consciousness impaired)
Leigh's disease (subacute necrotizing encephalomyelitis)
Multiple sclerosis
Myasthenia
Neuroleptic malignant syndrome (personal observation)
Orbital pseudotumor*
Paraneoplastic encephalomyelitis
Pituitary apoplexy*
Polyradiculopathy (associated with)
Psychogenic
Thallium poisoning
Tick paralysis
Tolosa-Hunt syndrome[1]
Trauma (impaired consciousness, signs of injury)*
Wernicke's encephalopathy

'"All may be unilateral.
Pain may be present. Painful ophthalmoplegia is discussed in Chapter 76.

exercises are of use in patients with convetgence insufficiency (see Chapter 39).

Related Disorders

Asthenopia (the visual concomitant of neurasthenia) is characterized by symptoms such as episodic blutring; watering; itching; diplopia; eyestrain; tiredness of the eyes or lids, especially after reading; sleepiness; and photophobia. Patients with this condition often exaggerate normal phenomena, such as physiologic diplopia, floaters, persistence of afterimages, and difficulty reading fine print. Their symptoms may he associated with accommodative insufficiency, headache, and other asthenic complaints. Care must be taken to exclude true refractive etrots, defective accommodation, convergence insufficiency, medication, dry eye syndrome, and diabetes mellitus (Waltz and Lavin 1993). Although asthenopia is usually psychogenic, a cause for isolated accommodative insufficiency, such as paneto-occipital stroke, may be found. Management includes a thorough examination, recognition of real abnormalities, and confident and authoritative reassurance.

Tabic 16.9: Causes of chronic ophthalmoplegia

Brainstem neoplasm
Chronic basal meningitis (infection, sarcoid, or carcinoma)
Congenita] extraocular muscle fibrosis
Dysthyroidism
Leigh disease
Multiple sclerosis
Myasthenia gravis
Myopathies (e.g., mitochondrial, fiber-type disproportion [see Table 39,2])
Nuclear, paranuclear, and supranuclear gaze palsies (see Chapter 39)
Vitamin t" deficiency

Occasionally, after extremely prolonged monotonous visual and vestibular stimulation, as in interstate or highway driving, interstate illusions (highway hallucinosis) may occur: The environment may appear to be sloping downward when in fact it is flat. This perception is somewhat similar to the prolonged sensation of movement after a long sea voyage (mal de debarquenient).

Micropsia, defined as the reduction in apparent size of an object of a given retinal angle, is the illusion of objects appearing smaller than normal. It can occur with optical aberrations, such as overcorrection of myopia with minus spherical lenses, retinal disorders (e.g., macular edema), and disorders of parietal region, such as stroke or, more commonly, migraine (the "Alice in Wonderland" syndrome). Convergence and accommodation are associated with micropsia to avoid a sense of enlargement as an object gets closer to the eye. Occasionally, a disturbance of convergence or accommodation, or both, can induce micropsia.

Monocular elevator deficiency (double elevator palsy) is discussed in Chapter 39.

Oscillopsia, an illusion of movement or oscillation of the environment, occurs with acquired nystagmus, superior oblique myokymia, other ocular oscillations, and disorders of the vestibulo-ocular reflex.

Polyopia, the perception of multiple images, is frequently optical and can be determined by the pinhole test, discussed under Diplopia, earlier in this chapter. Polyopia may also be caused by cortical lesions (see Table 16.5).

Palinopsia (or paliopia), the pathologic persistence or recurrence of visual images after the stimulus has been removed, may cause cerebral diplopia or polyopia. The images become more apparent and numerous when the target moves relative to the retina because it provokes multiple persistent afterimages (Figure 16.16). Sometimes patients describe the visual disturbance as trailing, vibrating, echoing, smearing, or ghosting of images. This visual perseveration occurs more frequently in patients with mild left homonymous visual field defects caused by right parieto-occipital lesions; it may he ictal and respond to anticonvulsant medication. It can also occur with metabolic

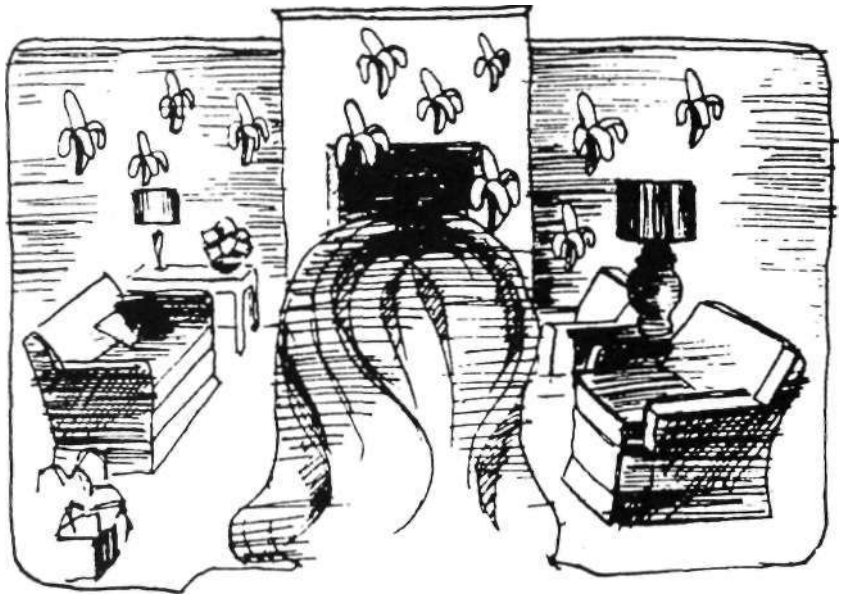

FIGURE 16.16 Palinopsia (cerebral poly opia). Visual images experienced by a patient moments after peeling a banana. (Reprinted with permission from Michel, E, N. & Troost, B. N. 1980, "Palinopsia: Cerebral local!'/.ation with computed tomography," *Neurology,* vol. 30, pp. 887-889.)

disorders, carbon monoxide poisoning, and a variety of drugs including domiphenc, interleukin-2, lysergic acid diethylamide, mescaline, nefazodonc, trazodone, and 3,4-methylenedioxymcthamphetamine (Ecstasy). Palinopsia can occur in patients with ocular or optic nerve disease and in apparently healthy people; occasionally, it may be associated with auditory perseveration (palinacusis) (Pomeranz and l.essell 2000).

Superior oblique myokymia is a small, rapid, monocular torsional-vertical oscillation (discussed under Superior Oblique Myokymia, later in this chapter).

Tortopia, the illusion of tilting or even inversion of the visual environment for a period of seconds to minutes, may occur in patients with posterior fossa disease, most commonly vertebrobasilar ischemia. Tortopia may be associated with headache, dizziness, vertigo, and double vision and is presumed to be due to dysfunction of the vestibulo-otohthic system or its central connections.

NYSTAGMUS

Nystagmus is an involuiitan hiphasic rhythmic ocular oscillation in which one or both phases are slow (Figure 16.17). The slow phase of jerk nystagmus is responsible for the initiation and generation of the nystagmus, whereas the fast (saccadic) phase is a corrective movement bringing the fovea back on target,

For clinical purposes, nystagmus may be divided into pendular and jerk forms. Either form may be horizontal or, less commonly, vertical. Jerk nystagmus is labeled conventionally by the direction of the fast phase and is divided into three types on the basis of the shape of the slow phase, detected by oculographic recordings (see Figure 16.17).

Mechanisms of Nystagmus

Nystagmus may result from dysfunction of the vestibular end organ, vestibular nerve, brainstem, cerebellum, or cerebral centers for ocular pursuit {see Chapter 39), Pendular nystagmus (see Figure 16.17A) is central (brainstem or cerebellum) in origin (Averbuch-Heller et al. 1995b), whereas jerk nystagmus may be either central or peripheral. Jerk nystagmus with a linear (constant-velocity) slow phase (see Figure 16.17B) is caused by peripheral vestibular dysfunction resulting in an imbalance in vestibular input to the brainstem gaze centers. When the slow phase has a decreasing velocity exponential (see Figure 16.17Q, the brainstem neural integrator (see Chapter 39) is at fault and is said to be leaky. The integrator is unable to

FIGURE 16.17 Oculographic diagrams of nystagmus waveforms. (A) Pendular (sinusoidal nystagmus). (B) Left-beating jerk nystagmus with a constant-velocity (linear) slow phase. (C) Left-beating jerk nystagmus with a decreasing (exponential) velocity slow phase. (D) Left-beating jerk nystagmus with an increasing (exponential) velocity slow phase.

maintain a constant output to the gaze center to hold the eyes in an eccentric position, resulting in gaze-paretic nystagmus. An increasing-velocity exponential slow phase (see Figure 16.17D) in the horizontal plane is central in origin and is the usual form of CN.

Clinical Evaluation

The physician should determine whether the nystagmus was present since birth or is acquired and whether there is a family history. CN is usually asymptomatic and rarely bothers the patient or causes oscillopsia (see Congenital Nystagmus below). Symptoms such as headache, diplopia, impaired vision, oscillopsia, vertigo, or other neurological abnormalities must be taken into account. Examination should include visual acuity, confrontation visual fields, pupil reflexes, observation for ocular albinism, and ophthalmoscopy. The latter may be used to detect subtle nystagmus not apparent to the naked eye. Ocular motility must also be assessed. The following features must be determined:

- Is the nystagmus present in primary position or only with eccentric gaze (gaze-evoked}?
- Is the nystagmus binocular and conjugate or is it dissociated?
- Is the waveform pendular or jerk? If jerk, whar is the direction of the fast phase?
- Is there a latent component (i.e., an increase in nystagmus intensity when one eye is covered)?
- Is there a torsional componenr?
- Is there spontaneous alteration of direction, as with periodic alternating nystagmus, which must be distinguished from rebound nystagmus (discussed later in the chapter) and which requires observation for some period?
- Is there a null zone (a direction of gaze where the nystagmus is minimal or absent)?
- Does convergence damp the nystagmus or change its direction?
- Is the nystagmus altered (accentuated or suppressed) by head positioning or posture or by head shaking (as in spasmus nutans)?
- What is the effect of optokinetic stimulation? In CN, the response is paradoxical, that is, the fast phase is in the direction of the slow-moving target.
- Are there associated rhythmic movements of other muscle groups, such as the face, tongue, ears, neck, palate (as in oculopalaral myoclonus), or limbs?

Nystagmus Syndromes

Table 16.10 summarizes the localizing value of nystagmus syndromes and non-nystagmus ocuiar oscillations.

Congenital Nystagmus

CN is usually present from birth but may not be noticed for the first few weeks, or occasionally even years, of life. It may be accompanied by severe visual impairment but is not the result of poor vision. Disorders, through genetic association, that are responsible for poor vision in patients with CN include achiasma (Jansionus et al. 2001), achromatopsia, albinism, amaurotic idiocy of Leber (Leber's congenital amaurosis), aniridia, congenital stationary night blindness, congenital cataracts, retinopathy of prematurity, optic nerve hypoplasia, and fovea! hypoplasia. Paradoxical pupil constriction in darkness, particularly in patients with poor vision, suggests an associated retinal or optic nerve disorder. Myopia, uncommon early in life, in infants with CN suggests a retinal disorder, such as congenital stationary night blindness, and high myopia suggests Leber's congenital amaurosis; such retinal disorders can be confirmed by electroretinography. CN is sometimes associated with head tirubation. CN may be familial and is inherited in an autosomal recessive, X-linked dominant or recessive pattern. Genetic defects identified in some families include a dominant form of CN linked to chromosome 6p12 (Kerrison etal. 1998), an X linked form ot CN with incomplete penetrance among female carriers associated with a defect on the long arm of the X chromosome (Kerrison et al. 2001), and a deletion in the OA1 gene (ocular albinism) in a family with X-linked CN associated with macular hypoplasia and ocular albinism (I'reising et al. 2001).

CN usually appears horizontal in most patients and may be either pendular or jerk in primary position. Pendular nystagmus often becomes jerk on lateral gaze. The horizontal oscillation may be accentuated during vertical tracking. However, oculography with 3-D scleral search coils demonstrates that many patients with CN have a torsional component, phase-locked with the horizontal component {Averbuch-Heller et al. 2002).

Patients with CN often have good vision unless there is an associated afferent defect (above). CN damps with convergence; latent super imposition *[Afi* increase in nys tagmus amplitude when one eye is covered) may be present. A null zone, where the nystagmus intensity is minimal, may be found; if this is to one side, the subject turns his head to improve vision. The head often oscillates as well. Both features—damping of nystagmus with convergence and a null zone—can be used in therapy by changing the direction of gaze with prisms or extraocular muscle surgery to improve head posture and visual acuity. Oculographic recordings (see Chapter 39) usually demonstrate cither a sinusoidal (see Figure 16.17A) or slow phase with an increasing exponential waveform (see Figure 16.17D). However, in the first few months of life the waveform of CN may be more variable, evolving into the more classic pattern as the child gets older.

Patients with CN do not experience oscillopsia (an illusory oscillation of the environment), unless a head

Table 16.10: Localizing value of nystagmus syndromes and n on -nystagmus ocular oscillations

Nystagmus syndromes	*Localization*
Downbeat nystagmus	Bilateral cervicomcdullary junction (flocculus) Floor of the fourth ventricle
Periodic alternating nystagmus	Cervicomedullary junction (nodulus)
Upbeat nystagmus	Bilateral pontomesencephalic junction Bilateral pontomcdullary junction Cerebellar vermis
Pendular nystagmus	Deep cerebellar (fastigial) nuclei
Seesaw nystagmus (SSN)	Mesodiencephalic junction, chiasm, disorders that disrupt central vision
Hemi-jerk SSN	Unilateral mesodiencephalic {upper poles of the eyes jerk toward side of lesion) or Lateral medullary lesions (upper poles of the eyes jerk away from side of lesion)
Alternating bemi-SSN with vertical ga/.e	Middle cerebellar peduncle
Rebound	Cerebellum
Brun's nystagmus	Cerebellopontine angle, AICA territory stroke
Torsional nystagmus, jerk	Centra] vesribular system
Torsional nystagmus, pendular	Medulla
Non-nystagmus syndromes	*Localization*
C on vergenee- re t rac ri o n "uysta gm us"	Dorsal midbrain
Opsoclonus	Cerebellum or brainstem
Ocular flutter	(eivbclUim or hraniMem
Ocular dysmetria	Cerebellum (dorsal vermis and fastigial nuclei)
Ocular myoclonus (oculopalateal)	Guillain-Mollarct's triangle (central tegmental tracr in the pons}
Ocular bobbing	See Table 16.15
Square wave jerks (Chapter 39)	See Table 39.4
Square wave pulses (Chapter 39)	Cerebellar outflow tracts (may be associated with rubral rremor)

injury, decompensated strabismus, or retinal degeneration causes a decline in vision, ocular motor function, or both; then, pnsms or strabismus surgery may correct such Lire-onset oscillopsia (Hertle et al. 2001a).

Rarely, CN may be pendular in the vertical plane or circumductory, in which the eyes move conjugately in a circular or cycloid pattern. Occasionally CN may be unilateral, occur later in the teens or adult life, or become symptomatic if changes in the internal or external environment alter fovcation stability and duration, causing oscillopsia. Less common patterns of CN, such as periodic alternating, upbeat, downbeat, and seesaw nystagmus (SSN), are discussed under those sections later in this chapter.

Because of considerable controversy classifying and defining nystagmus syndromes, particularly in infancy, the National Eye Institute sponsored a workshop to resolve such issues (CKMAS Working Group 2001).

Latent Nystagmus and Manifest Latent Nystagmus

LN and manifest LN (MLN) are both congenital forms of nysragmus.

LN occurs with monocular fixation, that is, when one eye is covered. The slow phase is directed toward the covered eye. The amplitude of the oscillations increases on abduction of the fixating eye. With MLN, the oscillation is present with both eyes open. However, only one eye is seeing; vision in the other is ignored or suppressed as a result of strabismus or amblyopia. The nystagmus waveform has a decreasing-velociry slow phase (sec Figure 16.16C), which differs from true CN. Some patients with LN can suppress it at will.

The pathogenesis of LN may be related to impaired development of binocular vision mechanisms. Under monocular viewing conditions, rhesus monkeys, deprived of binocular vision early in life, have poor nasal-to-temporal optokinetic responses. The pretectal nucleus of the optic tract (NOT) is necessary for generation of slow-phase eye movements in response to horizontal full-field visual motion. In normal monkeys, the NOT on each side is driven binocularly and responds well to visual stimuli presented to either eye. In monkeys with LN, each NOT is driven mainly by the conrralateral eye. Thus in the altered monkeys, when only one eye is viewing, one optic tract nucleus is stimulated, causing an imbalance between each NOT; this imbalance is believed to be responsible for LN (Kaminski and Leigh 1997). Interestingly, under monocular viewing conditions, patients with congenital esotropia have poor temporal-ro-nasal pursuit, and some have LN or MLN. Indeed, LN may be unmasked in dim light or by shining a bright light at the dominant eye, as when testing pupil reflexes, in esotropic patients.

Spasmus Nutans

Spasmus nutans is a transient, high-frequency, low-amplitude pendular nystagmus that occurs between the ages of 6 and 12 months and lasts approximately 2 years but

occasionally as long as 5 years. The direction of the oscillation may he horizontal, vertical, or torsional and is often dysconjugate, asymmetrical, even monocular, and variable. It may he associated with torticollis and tituhation (spasmus nutans triad}. The titubation (head nodding) has a lower frequency than the nystagmus and is thus not compensatory. Patients can improve vision by vigorously shaking the head, presumably to stimulate the vestibulo-ocular reflex and suppress or override the ocular oscillation. Some patients may have esotropia. Although spasmus nutans is a benign and transient disorder, it must be distinguished from acquired nystagmus caused by structural lesions involving the anterior visual pathways in approximately 2% of patients. In the latter situation, a careful ophthalmological examination reveals clinical evidence, such as impaired vision, a relative afferent pupillary defect, or optic atrophy. Retinal disorders may also masquerade as spasmus nutans; paradoxical pupil constriction in darkness is suggestive, but an electroretinogram is confirmatory.

Pendular Nystagmus

Pendular nystagmus (see Figure 16.17A) has a sinusoidal waveform and is usually horizontal. It may be either congenital or acquired. Large amplitude ("searching") pendular nystagmus is usually associated with poor vision as a result of afferent disorders such as optic atrophy. The most common cause of acquired pendular nystagmus is multiple sclerosis, followed by brainstem vascular disease involving the deep cerebellar nuclei or their efferent connections. Other disorders of myelin, including Cockayne's syndrome, Pelizaeus Mcrzbachcr disease, and toluene abuse can cause pendular nystagmus.

Barton and Cox (1993) found on magnetic resonance imaging (MR1) changes in the dorsal pontine tegmentum in their patients with pendular nystagmus, implicating the central tegmental tract, which is also affected in oeulopalatal myoclonus (discussed later in this section). Lopez et al. (1995) confirmed this by demonstrating a predominance of pontine lesions on MRI in patients with horizontal pendular nystagmus and a predominance of medullary lesions in those with torsional pendular nystagmus. The extent of involvement of the central tegmental tracts, the medial vestibular nuclei, the paramedian tracts, and the inferior olives led them to hypothesize that deafferentation of the inferior olive, by injury to the tracts projecting to it, is partly responsible for the rhythmic pendular oscillations. Disruption of preuuclear ocular motor pathways necessary for orthotropia (and conjugacy) must also be affected.

Convergent-divergent nystagmus, a rare variant of acquired pendular nystagmus, is dysconjugate and occurs in patients with demyelinating disease, brainstem stroke, Chiari malformations, cerebral Whipple's disease (see Oculomasticatory Myorhythmia, later in this chapter), and progressive ataxia (Averbuch-Hcllcr ct al. 1995a, 1995b). The eyes oscillate, mainly horizontally, in opposite directions simultaneously, although they sometimes form circular, elliptical, or oblique trajectories, depending on the phase relationship of the horizontal, vertical, and torsional vectors responsible for the oscillations,

Cyclovergcnt nystagmus (i.e., dysconjugate torsional nystagmus in which the upper poles of the eyes oscillate in opposite directions) was detected, by scleral search coil oculography, in a patient with progressive ataxia and palatal myoclonus (Averbuch-Hellei et al. 1995a). On rare occasions, cyclovergcnt nystagmus may be observed clinically.

Vertical pendular nystagmus closely resembles the vertical ocular oscillation associated with palatal myoclonus (the oculopalatal syndrome) (Dell'Osso and Daroff 1999a) and may be a form of the same disorder, which also results from lesions of the deep cerebellar nuclei and their connections.

Elliptical pendular nystagmus, with a larger vertical component and superimposed or interposed upbeat nystagmus, is characteristic of Pelizaeus-Merzbacher disease. This nystagmus can be difficult to discern with the naked eye. It is seen more easily with an ophthalmoscope, but oculography using scleral search coils may be necessary to detect it (Dell'Osso and Daroff 1999b).

Oculomasticatory Myorhythmia

Oculomasticatory myorhythmia, described in patients with Whipple's disease and, to date, pathognomonic of that disorder, consists of continuous rhythmic jaw contractions synchronous with dissociated pendular vergence oscillations. It may be associated with supranuclear vertical gaze palsy, altered mentation, somnolence, mild uveitis, or retinopathy (Knox et al. 1995). Myorhythmia of the face and arms is described in Hashimoto's encephalopathy (Erickson et al. 2002),

Pendular Pseudonystagmus

Patients with vestibular end organ damage and "essential" head tremor may develop pendular pseudonystagmus to compensate for an absent or defective vestibulo-ocular reflex (see Chapter 39). In the absence of a normal vestibulo-ocular reflex, head movements take the fovea off the target, causing blurred vision or oscillopsia. Eye movements, with longer latencies than normal vestibulo-ocular reflexes, are generated by alternative mechanisms (pursuit, cervico-ocular, and optokinetic movements) to maintain the fovea on target. This ocular oscillation, which is compensatory and not a sign of central nervous system disease, disappears when the patient's head is held still.

Gaze-Paretic Nystagmus

Gaze-paretic nystagmus, the most common type of nystagmus, is usually symmetrical and evoked by eccentric gaze to either side, but it is absent in the primary position,

It is also commonly present on vertical gaze with upward - beating nystagmus on upgaze and downward-heating nystagmus on downgaze. It may be asymmetrical with asymmetrical central nervous system disease or disorders such as myasthenia. It has a jerk waveform with the fast phase in the direction of gaze. Oculographic recordings show a decreasing exponential slow phase (see Figure 16.17C). Gaze-paretic nystagmus results from dysfunction of the neural integrator (see Chapter 39) and is commonly caused by alcohol or drug intoxication (anticonvulsants and tranquilizers). When it is caused by structural disease, it tends to be asymmetrical.

Vestibular Nystagmus

Vestibular nystagmus results from damage to the labyrinth, the vestibular nerve, the vestibular nuclei, or their connections in the brainstem or cerebellum. Vestibular nystagmus may be divided into central and peripheral forms on the basis of the associated features outlined in Chapter 18. Peripheral vestibular nystagmus, caused by dysfunction ot the vestibular end organ or nerve, has a linear slow phase (see Figure 16.17B), whereas with central lesions, the slow phase may be variable. Peripheral vestibular nystagmus is usually associated with severe vegetative symptoms, including nausea, vomiting, perspiration, and diarrhea; it may also be associated with hearing loss and tinnitus. On the other hand, with central vestibular nystagmus, vegetative symptoms are less severe, but other neurological features may be present, such as headache, dysconjugate gaze, and pyramidal tract signs (see Chapter 22).

Caloric-Induced Nystagmus

Caloric-induced nystagmus is discussed in Chapter 41.

Physiologic Nystagmus

Physiologic (endpoint) nystagmus is a jerk nystagmus observed on extreme lateral or upward gaze. If the bridge of the nose obstructs the view of the adducting eye, physiologic nystagmus may be dysconjugate because the amplitude is greater in the abducting eye. A torsional component is sometimes seen. Physiological nystagmus is distinguished from pathological nystagmus by its sym- • metry on right and left gaze and by the absence of other neurological features; it is not present when the angle of gaze is less than 30 degrees from primary position, Oculographic recordings primarily demonstrate a linear slow phase (see Figure 16.17B) and may detect transient small-amplitude rebound nystagmus.

Dysconjugate Nystagmus

Dysconjugate (dissociated) nystagmus occurs when the ocular oscillations are out of phase (different directions).

Tabic 16.11: Causes of monocular nysraj>mus

Acquired monocular blindness (nystagmus in blind eye)
Amblyopia
Brainstem infarction (thalamus and upper midbrain)
lctal nystagmus
Internuclear and pseudointernudear ophthalmoplegia
Multiple sclerosis
Nystagmus with monocular ophthalmoplegia
Nystagmus with one eye absent
Pseudonystagmus (lid fasciculations)
Spasmus nutans
Superior oblique myokymia

It is seen with internuclear ophthalmoplegia (see Chapter *3>9),* other brainstem lesions (see convergent-divergent nystagmus under Pendular Nystagmus, earlier in the chapter), and spasmus nutans. Monocular nystagmus is also dysconjugate and may be associated with amblyopia and other forms of vision loss (Table 16.11).

Monocular Nystagmus

Monocular nystagmus may be pendular or jerk and may also be horizontal, vertical, or oblique. Oculographic recordings may reveal small-amplitude oscillations in the fellow eye. Monocular nystagmus may occur in patients with amblyopia, strabismus, monocular blindness, spasmus nutans, internuclear ophthalmoplegia, multiple sclerosis, rarely with seizures, and of course when the other eye is completely ophthalmoplegic or absent.

The Heimann-fSielschowsky phenomenon is a rare form of monocular vertical pendular oscillation, with a frequency of 1-5 *Hz,* that occurs in an amblyopic eye or after acquired monocular vision loss, such as cataract. In the latter situation, it may be reversible after successful treatment of the underlying condition.

Superior oblique myokymia may be mistaken for a monocular torsional or vertical nystagmus (see Tabic 16.11).

Upbeat Nystagmus

Upbeat nystagmus is a spontaneous jerk nystagmus with the fast phase upward while the eyes are in primary position (Hirose et al. 1998). It is attributed to interruption of the anterior semicircular canal projections, which are responsible for the upward vestibulo-oculat teflex, causing downward drift of the eyes with corrective upward saccades. The amplitude and intensity of the nystagmus usually increase on upgaze. This finding strongly suggests bilateral paramedian lesions of the brainstem, usually at the pontomedullary or pontomesencephalic junctions, the paramedian tract neurons in the lower medulla, or midline cerebellum (vermis). Rarely, upbeat nystagmus may be congenital, or result from Wernicke's encephalopathy or intoxication with anticonvulsants, organophosphates,

lithium, nicotine, or thallium (personal observation). In infants, upbeat nystagmus may be a sign of anterior visual pathway disease, such as Leber's congenital amaurosis {see Chapter 40), optic nerve hypoplasia, aniridia, or cataracts, Small-amplitude upbear nystagmus may be seen in carriers of blue-cone monoehromatism, whereas affected patients may have intermittent pendular oblique nystagmus. If the intensity of upbeat nystagmus diminishes in downgaze, base-up prisms over both eyes may improve the oscillopsia; gabapentin may also be helpful.

Downbeat Nystagmus

Downbeat nystagmus is a spontaneous downward-beating jerk nystagmus present in primary position and is attributed to either (1) interruption of the posterior semicircular canal projections, which are responsible for the downward vcstibulo-oeular reflex, causing upward drift of the eyes with corrective downward saccades, or (2) impaired cerebellar inhibition of the vestibular circuits for upward eye movements, resulting in uninhibited upward drifts of the eyes with corrective downward saccades. The amplitude of the oscillation increases when the eyes arc deviated laterally, and slightly downward (Daroff sign). Downbeat nystagmus may he apparent only with changes in posture (positional downbeat nystagmus), particularly the head-hanging position. Downbeat nystagmus results from damage to either the commissural fibers between the vestibular nuclei in the floor of the fourth ventricle or bilateral damage to the flocculus that disinhibits the VOR in pitch and occurs frequently with structural lesions at the craniocervical junction (Table 16.12). A thorough investigation for such should be made; MRI of the foramen magnum region, in the sagittal plane, is the investigation of choice. Olson and Jacobson suggested that some cases of unexplained downbeat nystagmus are caused by radiographically occult infarctions {2001), The lesions that cause downbeat nystagmus are bilateral {Brandt and Dietrich 1995).

Causes of downbeat nystagmus are listed in Table 16.12.

The treatment of downbeat nystagmus involves correction of the underlying cause, when possible. When downbeat nystagmus damps on convergence, it may be treated successfully with base-out prisms, reducing the oscillopsia and improving the visual acuity; baclofen or clonazepam may also help.

Both upbeat and downbeat nystagmus may be altered in amplitude and direction by a variety of maneuvers, such as convergence, head tilting, and changes in posture.

Periodic Alternating Nystagmus

Periodic alternating nystagmus (PAN) is a horizontal jerk nystagmus in which the fast phase beats in one direction and then damps or stops for a few seconds before changing direction to the opposite side. During the short transition period, the nystagmus may beat vertically, A complete cycle takes approximately 3 minutes. PAN has the same clinical significance as downbeat nystagmus and may sometimes coexist. Attention should be focused at the craniocervical junction. PAN may also occur in Crcutzfeldt-Jakob disease.

When PAN is congenital, it may be associated with albinism. In one series of patients with congenital PAN, none had pure vertical oscillations, even during the transition period (Gradstcin ct al. 1997). Although not all patients with acquired PAN have vertical nystagmus during the transition period, its presence may distinguish acquired from congenital PAN {author's personal observation); this finding does not obviate further evaluation, when appropriate. Transient episodes of PAN were provoked by attacks of Meniere's disease in a patient with a hypoplastic cerebellum and an enlarged cistcrna magna (Chiu and Hain 2002). Episodic PAN may be a manifestation of a seizure {see ictal nystagmus below). An atypical form of paroxysmal alternating skew deviation and nystagmus has followed partial destruction of the inferior uvula and

Tabic 16.12: Causes of downbeat nystagmus

- Congenital (rare)
- Transiently in normal neonates
- Craniocervical junction abnormalities
  - Basilar invagination (Pager's disease, etc.)
  - Chiari malformations
  - Dohchoectasia of the vertebrobasilar arterial system
  - Foramen magnum tumors
  - Syringobulbia
- Cerebellar disorders
  - Alcoholic cerebellar degeneration (chronic usage)
  - Anoxic cerebellar degeneration
  - Familial spinocerebellar degeneration, particularly SCA-6 (Gomez et al. 1997)
  - l.pisnJk' ataxia
  - Cerebellar degeneration following Human T-lymphocyte virus types I and II (Castillo er al. 2000)
  - Paraneoplastic cerebellar degeneration
  - Heat stroke-induced cerebellar degeneration
- Metabolic disorders (drugs, toxins, and deficiencies)
  - Alcohol intoxication
  - A mi o da rone
  - Anticonvulsants
  - Lithium
  - Meperidine (personal observation)
  - Toluene abuse
  - Magnesium depletion
  - Wernicke's encephalopathy
  - B12 deficiency
- Other
  - Brainstem eiiccpluiiitis
  - Carriers of blue-cone monoehromatism may have small-amplitude downbeat nystagmus
  - Cephalic tetanus (Orwitz et al. 1997)
  - Hydrocephalus
  - Leukodystrophy
  - Multiple sclerosis
  - Vertebrobasilar ischemia

adjacent pyramis during biopsy of a suspected brainstem glioma (Radtke et al. 2001).

Although the pathogenesis of PAN is speculative, lesions of the cerebellar nodulus in monkeys and humans have produced this unusual oscillation. Furthermore, instability in the velocity storage mechanism (see Chapter 39), hyperactive vestibular responses, and poor vestibular fixation suppression, also found in patients with PAN, are attributed to involvement of the nodulus and uvula. Instability in the velocity storage and cyclical firing between reciprocally connected inhibitory neurons may be responsible for generating PAN.

Treatment of PAN should be directed at correcting the cause, such as a Chiari malformation, when possible. Baclofen is usually effective in the acquired form of the disease; Dextroamphetamine has improved PAN in a patient who also had rod-cone dystrophy and strabismus (Hertleetal. 2001b).

Rebound Nystagmus

Rebound nystagmus is a horizontal gaze-evoked nystagmus in which the direction of the fast phase reverses with sustained lateral gaze or beats transiently in the opposite direction when the eyes return to primary position; the latter is occasionally a physiological finding. It is caused by dysfunction of the cerebellum or the perihypoglossal nuclei in the medulla. Occasionally, rebound nystagmus may be torsional.

Centripetal Nystagmus

Cerebellar dysfunction can cause a form of gaze-evoked nystagmus in which rhe fast phase beats toward primary position (i.e., centripetally), and the slow phase drifts peripherally toward an eccentric target. Centripetal nystagmus is similar to rebound nystagmus and may result from overcompensation by the cerebellar nodulus and uvula to adjust for a directional bias by temporarily moving the null zone during eccentric gaze. Centripetal nystagmus, in both the horizontal and vertical plane, may be associated with Creutzfeldt-Jakob disease.

Convergence-Evoked Nystagmus

Convergence-evoked nystagmus is an unusual ocular oscillation, usually pendular, induced by voluntary convergence (see convergent-divergent nystagmus under Pendular Nystagmus, earlier in the chapter). The movements may be conjugate or dissociated. This condition may be congenital or acquired, such as in patients with multiple sclerosis (Barton et al. 1999). A jerk form has been associated with a Chiari I malformation. Convergence-evoked vertical nystagmus (upbeat more common than downbeat) also occurs. Convergence-evoked nystagmus should be distinguished from voluntary nystagmus and from convergence retraction nystagmus (sec Non-Nystagmus Ocular Oscillations, later in this chapter).

Seesaw Nystagmus

SSN is a spectacular ocular oscillation in which one eye rises and intorts as the other eye falls and extorts. The waveform appears pendular. The oscillations usually become faster and smaller on upgaze but slower and larger on downgaze; they may cease in darkness. Disordered control of the normal ocular counter-rolling reflex (see Chapter 40) may be responsible. Bitemporal hemianopia, as a result of acquired chiasmal defects, or impaired central vision plays a significant role in generating SSN. Disruption of retinal error signals, necessary for vestibulo-ocular reflex adaptation, which are normally conveyed to the inferior olive by the chiasmal crossing fibers, results in an unstable visuovestibular environment. Fixation and pursuit feedback accentuate this instability, causing synchronous oscillations of floccular Purkinje's cells, which relay to the nodulus, and result in SSN. This mechanism may also be the basis for the ocular oscillations of oculopalatal myoclonus. The observations of SSN and CN in achiasmatic humans and achiasmatic Belgian sheepdogs support this hypothesis (Dell'Osso and Daroff 1998). Significantly, the onset of both SSN and oculopalatal myoclonus may be delayed after central nervous system lesions.

SSN occurs with lesions in the region of the mesodiencephalic junction, particularly the zona incerta and the interstitial nucleus of Cajal. Congenital SSN may be associated with a superimposed horizontal pendular nystagmus; some patients with congenital SSN may be achiasmatic or have septo-optic dysplasia. Acquired SSN may be associated with suprasellar tumors, Joubert's syndrome, and Leigh's disease, particularly the jerk form described below. Acquired SSN may be accompanied by a bitemporal hemianopia as a result of trauma, an expanding lesion in the third ventricular region, or severe loss of centra] vision caused by disorders such as choroiditis, cone-rod dystrophy, and vitreous hemorrhage (Dell'Osso and Daroff 1998).

Transient (latent) SSN may occur for a few seconds after a blink, perhaps because of loss of fixation, in patients with chiasmal region lesions,

If SSN damps with convergence, base-out prisms may be helpful. Baclofen may also improve SSN.

A jerk-waveform hcmi-SSN occurs with unilateral mesodiencephalic lesions, presumably due to selective unilateral inactivation of the torsional eye-velocity integraror in the interstitial nucleus of Cajal (see Chapter 39). During the fast (jerk) phases, the upper poles of the eyes rotate toward the side of the lesion. In hemi-jerk SSN caused by lateral medullary lesions, the fast phases jerk away from the side of the lesion. In both situations, the torsional component is always conjugate. With mesodiencephalic lesions, the

vertical component is always disjunctive {the eyes oscillate in opposite directions with the intorting eye rising and the extorting eye falling), but with medullary lesions it may be either conjugate {usually upward) or disjunctive. Other features of brainstem dysfunction may be necessary to localize the lesion.

Torsional (Rotary} Nystagmus

In torsional nystagmus (TN), the eye oscillates in a pure rotary or plane. TN may be present in primary position or with either head positioning or gaze deviation. It is usually the result of lesions in the central vestibular pathways. Pure TN occurs only with central vestibular dysfunction, whereas mixed torsional-linear nystagmus may occur with peripheral vestibular disease. When the waveform of torsional nystagmus is pendular (i.e., torsional pendular nystagmus), the lesion is usually in the medulla (Lopez et at. 1995). Skew deviation frequently coexists with torsional nystagmus (see Chapter *39).*

Torsional nystagmus with a jerk waveform, similar to jerk SSN, may be evoked by vertical pursuit eye movement and during fixation suppression of the vertical vestibulo-ocular reflex in patients with lesions of the middle cerebellar peduncle. The direction of the fast phase changes with direction- it is usually toward the side of the lesion on downward pursuit and away from the side of the lesion on upward pursuit (FitzGibbon et al. 1996).

Ictal Nystagmus

lctal nystagmus often accompanies adversive seizures and beats to the side opposite the focus, lctal nystagmus may be associated with transient pupillary dilation of either the abducting or adducting eye (Masjuan et al. 1997). Pupillary oscillations synchronous with the nystagmus may rarely occur. Nystagmus as the only motor manifestation of a seizure is rare; there are reports, however, of isolated ictal nystagmus, such as occurs in patients with vivid ictal visual hallucinations. Monocular nystagmus, associated with ipsilateral hemianopic visual hallucinations, in a binocular patient can occur as the only manifestation of a partial seizure caused by a focal discharge in the contralateral medial occipital lobe (Grant et al. 2002). It is difficult to draw any conclusion, clinically, regarding the location of the seizure discharge in these patients because seizure foci have been in occipital, parietal, temporal, and frontal areas. The nystagmus is usually horizontal, but there are occasional reports of vertical nystagmus, mainly in comatose patients. Periodic eye movements in comatose patients should alert the physician to the possibility of status cpilepticus; indeed, PAN associated with periodic alternating gaze deviation and periodic alternating head rotation may be a manifestation of a seizure (Moster and Schnayder 1998).

Brun's Nystagmus

Brun's nystagmus occurs in patients with large cerebellopontine angle tumors. The nystagmus is bilateral but asymmetrical with a jerk waveform. It is characterized by large-amplitude, low frequency oscillations on gaze toward the side of the lesion but small-amplitude, high-frequency oscillations on gaze to the other side. The ipsilateral large-amplitude (coarse) nystagmus has an exponentially decreasing-velocity slow phase attributed to compression of the brainstem neural integrator, which includes the ipsilateral medial vestibular nucleus (see Chapter 39). The contralateral small-amplitude, high-frequency nystagmus has a linear slow phase attributed to ipsilateral vestibular dysfunction (see Figure 16.17). Occasionally, an anterior inferior cerebellar artery territory stroke can cause Brun's nystagmus (author's personal observation).

Episodic Nystagmus

Episodic nystagmus is associated with a disorder in which the patient has paroxysmal episodes of vertigo, ataxia, and nystagmus lasting up to 24 hours. The nystagmus may be torsional, vertical, or dissociated. The frequency of attacks varies from once a day to only a few times per year. Such periodic ataxia occurs in patients with hereditary inborn errors of metabolism, in an autosomal dominant form without any detectable metabolic defect (channelopathy), and in patients with basilar migraine or multiple sclerosis. Accta/olaniiile may alleviate or prevent attacks in the familial form (see Chapter 78).

],id Nystagmus

I,id nystagmus, characterized by rhythmic jerking movements of the upper eyelids, occurs in the following situations: (1) synchronous with vertical ocular nystagmus; (2) synchronous with the fast phase of gaze-evoked horizontal nystagmus in some patients with the lateral medullary syndrome; (3) evoked by horizontal gaze in some patients with midbrain tumors; and (4) during voluntary convergence in some patients with brainstem or cerebellar disease (Dell'Osso and Daroff 1997a).

Nystagmus Treatment

Visual acuity should be corrected where necessary (Table 16.13), With the exception of CN, in which prisms, surgery, and contact lenses are helpful, the treatment of other forms of nystagmus is discouraging. Prisms are occasionally helpful in acquired nystagmus. Various pharmacological agents, including benzodiazepines, baclofen, isoniazid, trihexyphenidyl, tetrabennzine, prochlorper azine, carbamazepine, L-dopa, alcohol, and carisoprodol, have been tried. There has been some success treating

Tabic 16.13: Treatment of nystagmus and non-nystagmus oscillations (treat underlying cause where possible)

Nystagmus syndrome	*Treatment*
Congenital nystagmus	Prisms Contact lenses Extra ocular muscle surgery Kestenbaum-Anderson procedure Tenotomy (experimental)
Acquired pendular nystagmus	Trihexyphenidyl, benztropine, gabapentin, memantine, valproate, diethylpropion hydrochloride
Convergence-evoked horizontal nystagmus	Base-in prisms
Downbeat nystagmus	Base-out prisms (if nystagmus damps with convergence) Base-down prisms over both eyes if intensity of nystagmus diminishes in upgaze Baclofen, clonazepam, gabapentin, scopolamine, 3,4-diaminopyridine
PAN	
Congenital	Dextroamphetamine, Baclofen (?), 5-HT
Acquired	Baclofen, Dilantin
Upbeat nystagmus	Base-up prisms over both eyes if intensity of nystagmus diminishes in downgazc Gabapentin
Ocular myoclonus	Chronically patch one eye Baclofen, carbamazepine, cerulein, clonazepam, gabapentin, scopolamine, trihexyphenidyl, valproate,
Seesaw nystagmus	Baclofen, clonazepam, base-out prisms
Ictal nystagmus	Anti-epileptic drugs
Episodic nystagmus	
Episodic ataxia!	Acetazol amide
Episodic ataxia-2	Acetazolamide
Oculomasticatory myorhythmia	Antibiotics for Whipple's disease
Non-nystagmus ocular oscillations	*Treatment*
Opsoclonus	Steroids, clonazepam, ondansetron, if paraneoplastic protein A immunoabsorption
Superior oblique myokymia	Gabapentin, oxcarbazepine, other AEDs, topical beta-blockers, sumatriptan—transient effect (Quisling and Donahue, in press), base-down prism over the affected eye, muscle/tendon surgery, microvascular decompression
Ocular neuromyotonia (see Chapter 39)	Carbamazepine
Microflutter	Propranolol, verapamil
Square wave jerks (see Chapter 39)	Valproate (Traccis et al. 1997)
Square wave oscillations (see Chapter 39)	Valproate (Traccis ct al. 1997)

acquired pendular and downbeat nystagmus with the central muscarinic antagonists benztropine and scopolamine. Gabapentin, memantine, and valproate may be effective in acquired pendular nystagmus; clonazepam, baclofen, 3,4-diaminopyridine, and gabapentin may be helpful in downbeat nystagmus (Averbuch-I Idler et al. 1997; Strupp et al. 2003), as is gabapentin in upbeat nystagmus. Otherwise, with the exceptions of clonazepam and baclofen for acquired PAN and upbeat and downbeat nystagmus, and trihexyphenidyl for the pendular nystagmus of multiple sclerosis, there has been little success. For an extensive review, see Leigh et al. (1994) and Stahl et al. (2002).

NON-NYSTAGMUS OCULAR OSCILLATIONS

Voluntary Nystagmus

Voluntary nystagmus is not true nystagmus but, rather, ocular flutter under voluntary control. It consists of a series of fast (saccadic) back-to-back eye movements, without any interval or slow phase (Figure 16.18A). The oscillation is usually horizontal but may be vertical, torsional, or, rarely, cycloid (author's personal observation). The ability to induce flutter voluntarily tends to be familial. Subjects usually converge to initiate the oscillation but are unable to sustain it for longer than 30 seconds. Occasionally, patients use this ability to feign acquired illness, but the phenomenon should be easily recognized.

Ocular Flutter

Ocular flutter (see Figure 16.18A) occurs with brainstem or cerebellar disease and consists of horizontal conjugate back-to-back saccades that occur spontaneously, in intermittent bursts. It is aggravated by attempts at fixation. Occasionally, it is triggered by a change in posture. Ocular flutter results from loss of pause cell inhibition of the burst neurons in the paramedian pontine reticular formation (PPRF) (see Chapter 39) caused by cither injury to die I'PRl (Schon et al. 2001) or to the cerebellar neurons that

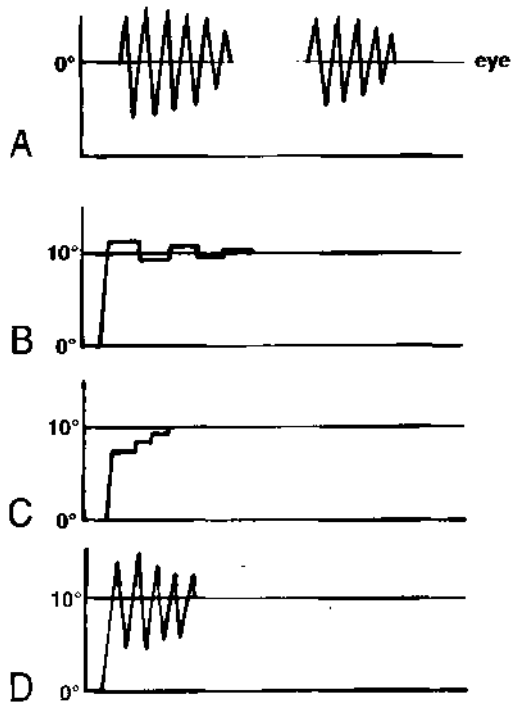

FIGURE 16.18 (A) Spontaneous ocular flutter in primary position. (B) Overshoot dysmetria (hypermetria). (C) Undershoot dysmetria (hypomctria). (D) Flutter dysmetria exacerbated by refixation of 1-10 degrees.

influence the pause cells, or both. Flutter is often associated with ocular dysmetria and may progress to opsoclonus.

Microsaccadic Ocular Flutter

Microsaccadic ocular flutter, or microflutter, is a rare symptomatic ocular oscillation requiring magnification for detection (Dell'Osso and Daroff 1999b). Patients complain of episodes of "shimmering" vision. It has been associated with cerebellar degeneration and multiple sclerosis bur in some patients may be a variant of voluntary nystagmus. Microflutter may respond to propranolol or verapamil in individual patients (Leigh and Zee 1999).

Opsoclonus

Opsoclonus is a spontaneous, chaotic, multivector saccadic eye movement disotder that is virtually always conjugate. Opsoclonus is aggravated by attempts at fixation and may be associated with myoclonic jerks of the limbs and cerebellar ataxia (dancing eyes-dancing feet syndrome). It is caused by dysfunction of the pause cells in the pons (see Chapter 39) as a result of cerebellar or brainstem disease. The most common causes (Table 16,14) include viral or postviral encephalitis and toxic, metabolic, and

Table 16.14A: Causes of opsoclonus

Acquired immunodeficiency syndrome-related brainstem encephalitis or lymphoma
Adults: carcinoma (thiamine-responsive)
Biotin-responsivc multiple carboxylase deficiency
Children: neuroblastoma (corticotropin-responsive)
Drugs (amitriptyline, chlordecone, cocaine, dichlorodiphcnyltriehloroethane, haloperidol, phencyclidine, phenytoin, diazepam, thallium, toluene, vidarabine)
Encephalitis (viral, pyogenic)
Hashimoto's encephalopathy
Hydrocephalus
Hyperosmolar coma
Lipidoses
Multiple sclerosis
Paraneoplastic
Pontine hemorrhage
Postencephalitic
Thalamic glioma
Thalamic hemorrhage
Transient phenomenon in healthy neonates

paraneoplastic disorders. The paraneoplastic opsoclonus-myoclonus-cerebellar syndrome that is a manifestation of neuroblastoma (7%), found in children, may be responsive to adrenocorticotropic hormone. In adults, opsoclonus may accompany paraneoplastic parenchymal cerebellar degeneration as a result of a remote carcinoma or lymphoma. Opsoclonus may also occur in hyperosmolar states and with many drugs at toxic levels. The efficacy of immunotherapy in adults with paraneoplastic syndromes is difficult to assess because of spontaneous fluctuations and remissions. However, in addition to treatment of the underlying neoplasm, early and aggressive immunotherapy, including the use of immunoadsorption therapy with plasma exchange through a protein A column (Cher et al. 1995), may be effective in opsoclonus. Responsiveness probably depends on the degree of the inflammatory component rather than the neuronal loss. Opsoclonus may occasionally respond to thiamine or clonazepam.

Tabic 16.14B: Age-related likely causes and features of opsoclonus

Neonates	Parainfectious Paraneoplastic (neuroblastoma in chest or abdomen)
Fight months to three years	Neural crest tumor or regressed neural crest tumor
Greater than three years	Regressed neural crest tumor
Children with opsoclonus	Good prognosis for tumor Poor prognosis for ocular movements (Respond to ACTH)
Adults	Paraneoplastic (breast, ovary) (May respond to protein A immunoa bso rption)

Ocular Dysmetria

Ocular dysmetria occurs with rcfixation saccades that overshoot (see Figure 16.18B) the target and often oscillate before coming to rest (see Figure 16.18C). It results from cerebellar dysfunction (dorsal vermis and fastigial nuclei). There is an intersaccadic latency of approximately 200 milliseconds (Leigh and Zee 1999).

Flutter Dysmetria

Flutter dysmetria occurs immediately after the patient rcfixates on a target; the eye then briefly oscillates without intersaccadic intervals across the line of the target for a few cycles (see Figure 16.18D). Both flutter and opsoclonus result from dysfunction of the pause cells in the paramedian pontine reticular formation, which tonically suppresses the burst cells (see Chapter 39). The pause cells have input from the cerebellum; thus cerebellar or brainstem dysfunction may result in flutter or opsoclonus.

Convergence Retraction Nystagmus

Convergence retraction nystagmus is not a true nystagmus but a rapid dysmetric horizontal eye movement induced by attempted upward saccades. It occurs as part of the dorsal midbrain (Parinaud's) syndrome. Clinically, rapid convergence with synchronous retraction of both globes caused by simultaneous co-contraction of the extraocular muscles is followed by a slow divergent movement. Less commonly, if lateral rectus innervation is dominant, a rapid divergent movement occurs initially.

Ocular Bobbing

Ocular bobbmg is a rapid downward movement of both eyes followed by a slow drift back to primary position. The oscillation recurs between 2 and 15 times per minute and is found in patients, usually comatose, with severe central pontine destruction and horizontal gaze palsies (Table 16.15). In atypical bobbing, horizontal eye movements arc spared.

With *reverse bobbmg.*, the initial fast phase is upward, followed by a slow downward drift, whereas with *inverse bobbing (dipping),* the initial deviation is a slow downward movement followed by a rapid return to primary position. The latter two phenomena occur in patients with severe metabolic disorders or structural damage involving the inesodiencephalic region. Reverse dipping, a slow upward movement followed by a fast downward movement, was described in an obtunded patient with a seizure disorder and chronic meningitis. Bobbing may also be dysconjugatc (see Table 16.15).

V-parte in pretectal pseu do bobbing, a higher-frequency, more rapid downward convergent movement with a slower-than-normal return toward primary position, occurs with acute obstructive hydrocephalus and is an indication of urgent decompression.

Some patients may have more than one type of bobbing.

Ocular Myoclonus (Oculopalatal Tremor)

Ocular myoclonus is a vertical pendular oscillation, with a frequency of approximately 160 Hz, usually associated with similar oscillations of the soft palate (palatal tremor) and, sometimes, other muscles of the branchial origin (Leigh and Zee 1999). The latter condition, referred to as the oculopalatal syndrome, occurs after brainstem

Tabic 16.15: Ocular bobbing

7 ype	*Movement*	*Cause*
Ocular bobbing (atypical bobbing, horizontal eye movements preserved)	hast down; slow upward return to primary position	Severe central pontine destruction, central pontine myelinolysis, encephalitis, extra-axial pontine compression (usually a cerebellar hematoma), organophosphate poisoning
Reverse bobbing	Fast up; slow downward return to primary position	Usually nonlocali/ing encephalopathy: anoxia, metabolic encephalopathy, head injury, poststatus cpilcpticus
Dipping (inverse bobbing)	Slow down; fast upward return to primary position	Anoxic, metabolic, and toxic encephalopathies, poststatus cpilcpticus
Reverse dipping	Slow up; fast downward return to primary position	Cryptococcal meningitis or obtundation (in an acquired immunodeficiency syndrome patient), pontine stroke
V-pattern pretectal pseudobobbing	Fast downward convergent movements at higher frequency than typical bobbing; slower than normal return to primary position	Acute obstructive hydrocephalus

infarction, particularly of the pons, involving the central tegmental tract. Following a latency of months, hypertrophy of the inferior olives develops and the myoclonus begins. The association of a facial nerve palsy and the one-and-a-half syndrome (see Chapter 39} may predict the development of oculopalatal myoclonus, probably because of the proximity of the central tegmental tract to the facial nerve (Wolin et al. 1996). Oculopalatal myoclonus also is reported to occur spontaneously in association with progressive ataxia, with a fourth ventricular tumor, and hydrocephalus following subarachnoid hemorrhage (Eggenberger et al. 2001). Dysfunction of the cerebellar nuclei or their connections (Guillain-Mollaret's triangle) and disruption of retinal error signals relayed to the inferior olive may be responsible for oculopalatal myoclonus, which is confined to the muscles of branchial origin. Patients may get some relief from anticonvulsants such as carbamazepine, clonazepam, and valproic acid and agents such as trihexyphenidyl HCl and cerulein, or by chronically patching one eye.

Superior Oblique Myokymia

Superior oblique myokymia is a paroxysmal, rapid, small-amplitude monocular torsional-vertical oscillation caused by contraction of the superior oblique muscle predominantly on the right side (Yousry et al. 2002). Patients may complain of monocular blurring, torsional or vertical oseillopsi.t, torsional or vertical diplopia, or twitching ot the eye. Oculography using magnetic search coils (see Chapter 39) has demonstrated both phasic and tonic contractions of in torsi on, depression, and to a much lesser extent, abduction of the superior oblique muscle (Leigh and Zee 1999). MRI demonstrated that the affected superior oblique muscle was smaller in some patients, suggesting antecedent injury to the fourth nerve (Mehta and Demer 1994); this hypothesis is supported by an MRI finding of neurovascular compression of the fourth nerve at its root exit zone (Hashimoto et al. 2001; Yousry et al. 2002).

Superior oblique myokymia may be difficult to detect with the unaided eye and is more easily detected with a direct ophthalmoscope. It may be precipitated by activating the superior oblique muscle when the patient looks down in the direction of action of that muscle or tilts the head toward the affected eye. Superior oblique myokymia has a relapsing-remitting course in otherwise normal, healthy adults. It has been reported with adrenoleukodystrophy, lead poisoning, cerebellar astrocytoma, a dural arteriovenous fistula, and microvascular compression (Samii et al. 1995; Hashimoto et al. 2001; Yousry et al. 2002).

Superior oblique myokymia may respond dramatically to carbamazepine or gabapentin (Tomsak et al 2002). Propranolol in low dosage, amitriptyline, baclofen, phenytoin, benzodiazepines, and topical beta blockers (used for glaucoma) may also be helpful. A base-down prism in front of the affected eye may alleviate the patient's symptoms, avoid potential side effects of long-term medication, and avoid superior oblique muscle or tendon surgery, which some advocate when the disorder is prolonged. Disabling superior oblique myokymia may respond to microvascular decompression of the trochlear nerve at is root exit (Samii et al. 1995; Scharwey et al. 2000) and one patient artained transient relief with repeated use of sumatriptan, (Quisling and Donahue in press); the researchers suggesred the vasospastic effects of sumatriptan were responsible.

Table 16.16; Saccadic oscillations (see Chapter *39)*

Flutter (voluntary, involuntary)
Flutter dysmetria
Microsaceadic flutter (variant of voluntary flutter?)
Opsoclonus
Macro square wave jerks (now designated square wave pulses)
Ocular bobbing, reverse and inverse bobbing, dipping, and reverse dipping
Superior oblique myokymia
Convergence-re traction nystagmus
Abduction nystagmus with internuclear ophthalmoplegia
Tic-like ocular myoclonic jerks (eye tics)

Saccadic Lateropulsion

See Chapter *39* for a discussion of saccadic lateropulsion.

Saccadic Intrusions and Oscillations

Saccadic intrusions, such as square wave jerks (see Chapter 39), are brief, unwanted, nonrepetitive saccadic interruptions of fixation (Table 16.16). Other intrusions are saccadic pulses (stepless saccades), which interrupt fixation and arc followed by a slow drift back on target (glissade); double saccadic pulses (fragment of flutter); and dynamic overshoots. Macrosaccadic oscillations, macro square wave jerks (Dell'Osso and Daroff 1999b), are saccadic oscillations that are discussed in Chapter 39.

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Chapter 17
Pupillary and Eyelid Abnormalities

Terry A. Cox and Robert B. Daroff

ABNORMALITIES OF **THE** PUPILS

Clinical Presentation

The medical history of a patient rarely begins with the statement "I have unequal pupils." In fact, most patients with anisocoria {unequal pupils) first hear of it from a doctor, friend, or relative. Those who notice anisocoria themselves may confuse the diagnostician by giving a misleading account of the duration of the condition. Occasionally, a patient has visual dysfunction caused solely by abnormal pupillary size. Photophobia and slow dark adaptation occur when a fixed, dilated pupil fails to protect the retina from increased illumination. Less often, a complaint of poot night vision (or dim daytime vision) may atise in patients with small, poorly reactive pupils; this symptom is caused by pupils not dilating normally, which decreases the light-gathering power of the eye in conditions of dim illumination.

Because pupillaty disorders usually present as an abnotmality on physical examination father than a visual complaint, the following discussion is based on the various ways that abnormal pupils can be described by the clinician. Terms used include *anisocoria, poorly reactive pupils, light-near dissociation, pupillary irregularity,* and *hippus* (pupillary unrest); many pupillary disorders can be included in several of these categories. In her two-volume text, Loewcnfeld *(1999)* provides detailed discussions of all aspects of every pupillary abnormality. Thompson and Miller (1998) give a more succinct presentation.

Anisocoria

Many unilateral and bilatctal disorders affecting the iris or its innervation present as anisocotia, but there are only a few categories to consider in evaluating this sign: local disease of the eye, parasympathetic defects (affecting the third nerve or pupillary sphincter), sympathetic defects (affecting the ins dilator muscle or its innervation), and simple anisocoria.

A number of local conditions affecting the iris can cause unequal pupils. Blunt trauma to the eye can damage the pupillary sphincter, causing mydriasis with poor pupillary constriction to both light and near stimuli. Immediately after injury, the pupil may be smaller than normal, but after a few minutes, the pupil becomes dilated and poorly reactive. This course of events may simulate uncal herniation,

Acute inflammatory disease of the eye (iritis) can cause mild pupillary constriction. If inflammation petsists, adhesions between the iris and the anterior lens capsule may lead to pupillary irregularity and immobility. Usually, the inflamed eye is red and the patient has a great deal of photophobia. However, some chronic forms of iritis, such as sarcoid, can cause iris adhesions without these manifestations.

Ischemia of the iris can cause mydriasis and poor pupillary reactivity. Two situations in which ischemia occurs are acute angle-closure glaucoma and ocular ischemic syndrome; in both disorders, associated symptoms include poor vision and pain.

Syphilis causes a number of pupillary disorders, the best known being Argyll-Robertson pupils (see later discussion). A more common pupillary finding in syphilis, however, is anisocoria associated with degeneration of iris stroma.

Some rare forms of iris degeneration, such as essential iris atrophy and Fuchs' hetetochromic iridocyclitis, cause pupillary dilation, often with irregularity of the pupillary outline.

Causes of patasympathctic defects include oculomotor (third) nerve palsy, tonic pupils, and phatmacological mydriasis. Third cranial nerve palsies are discussed in Chapter 76. Usually, pupillary involvement in third ctanial nerve palsies is accompanied by paresis of other extraocular muscles; isolated pupillary dilation occurs most commonly in the setting of early uncal herniation.

Tonic pupils are characterized by light-near dissociation with slow redilation of the pupil after prolonged near effort. This condition is caused most often by Holmcs-Adic

(or Adie's) syndrome (Thompson and Miller 1998), a henign condition that usually affects only one eye. Holmes-Adie syndrome affects younger adults most often, and women are more commonly affected than men. Loss of one or more deep tendon reflexes occurs in 90% of cases. The site of ocular pathology is the ciliary ganglion, and the associated loss of accommodation often causes difficulties with reading. Tonicity of accommodation can cause periocular pain and headaches in some patients. The affected pupil tends to become smaller as time passes, and it may even be the smaller pupil when the patient first presents. Other causes of tonic pupil include orbital trauma, herpes zoster ophthalmicus, syphilis, temporal arteritis, and various peripheral neuropathies.

Pharmacological mydriasis usually occurs after accidental or intentional instillation of atropinic agents. Accidental mydriasis usually occurs by hand-eye contact in individuals who have contact with the agents; examples include use of a scopolamine skin patch for motion sickness and administration of eyedrops to a family member with eye disease. Pharmacologically dilated pupils tend to be larger than the dilated pupil of third cranial nerve palsy. Sympathomimetic agents, such as phenylephrine, cause mydriasis that is less extensive and prolonged than that caused by parasympathomimetic agents.

Sympathetic denervation causes pupillary miosis and ipsilateral ptosis (Horner's syndrome). Acutely, conjunctival vessels may he dilated, mimicking "pink eye."

Simple (physiologic, essential) anisocori.i occurs in approximately 20% of the normal population. Usually, the difference in pupil size is small—rarely more than 0.6 millimeters. The amount of anisocoria may differ in a given individual at different times. Pharmacological testing (Digre 1998) or pupillography may be necessary to confirm the diagnosis.

Episodic Anisocoria

Anisocoria may be intermittent. Simple anisocoria can vary from week to week and occasionally from hour to hour. A rare condition known as *tadpole pupils* results from intermittent spasms of segments of the pupillary dilator muscle; often, these patients have an underlying Horner's syndrome. A related phenomenon is oculosympathetic spasm associated with lesions of the cervical spinal cord.

In benign episodic unilateral mydriasis, episodes of pupillary dilation last from minutes to a few days (Jacobson 1995). Some patients have typical migraine headaches during the episodes, but most patients have only monocular visual blurring or no symptoms at all. The frequency of episodes varies from a few per week to one every few years. Some patients appear to have parasympathetic insufficiency and others sympathetic hyperactivity of the pupil, but no other neurological problems develop.

Cyclic oculomotor palsy is a rare condition in which periodic oculomotor spasms occur in a patient with third cranial nerve palsy. During the spasms, the eyelid rises, the exotropic eye moves to the midline, and the pupil constricts. In some cases, the spasms are limited to the pupil. Intermittent spasm of portions of the pupillary sphincter may occur in traumatic third cranial nerve paralysis and with aberrant oculomotor regeneration. Unilateral pupillary dilation and other pupillary signs can occur during seizures.

Poorly Reactive Puprfs without Anisocoria

Large pupils that arc poorly reactive but roughly equal in diameter can occur with hypothalamic and midbrain lesions, syphilis, botulism, the Miller Fisher variant of the Guillain-Barre syndrome, and autonomic neuropathy, Toxic and pharmacological causes should also be considered. Occasionally, bilateral mydriasis can be congenital. Anxious teenagers and young adults often have latge, poorly reactive pupils.

Small, poorly reactive pupils, often combined with simple anisocoria, are common in the aging individual (sometimes prematurely so). Other acquired causes of this finding include syphilis, diabetes, and long-standing Holmes-Adic pupils. Patients with glaucoma using drops containing pilocarpine have small pupils that do not react to light or near stimuli. Congenital miosis can be caused by Marfan syndrome or congenital rubella infection, but this may also be an isolated finding.

Light-Near Dissociation

The term *tight-near dissociation* refers to pupils that have marked diminution of constriction to light, with a much better constriction to near stimuli. When the pupils are large, the differential diagnosis includes syphilis, tonic pupils, pretectal lesions (Wilhelm et al. 2002), and bilateral afferent pupillary defects (e.g., from bilateral optic atrophy). Small pupils with light-near dissociation can occur in patients with syphilis (Argyll-Robertson pupils), long-standing Holmes-Adie pupils, and diabetic neuropathy. In some patients with aberrant regeneration of the oculomotor nerve, the pupil constricts poorly to light and much better with eye movements such as adduction; this disorder could be mistaken for true light-near dissociation.

Irregular Pupils

Irregular pupils are usually caused by local iris disease. Conditions mentioned earlier that cause pupillary irregularity include syphilis, ischemia, posterior synechiae (adhesions of iris to lens), traumatic iridoplegia, degenerative disease of the iris, and Holmes-Adie syndrome. Infiltration of the iris by tumor or amyloid can also cause irregular pupils. Oval or eccentric pupils (corectopia) may occur with midbrain disease and increased intracranial pressure.

Hippus (Pupillary Unrest)

In most individuals with reactive pupils, shining a lighr in the eyes elicits spontaneous conjugate oscillations in pupillary diameter. These movements are probably a result of changes in retinal illumination induced by pupillary movements (the pupil constricts, causing the light to appear dimmer; then it dilates, causing the lighr to appear brighter; then ir constricts, and so on), but oscillation in midbrain activity may play a role. Changes in the level of central nervous system alertness also cause the pupil to change size; somnolent individuals have large-amplitude, low-frequency oscillations in pupillary diameter just before they fall asleep.

Afferent Pupillary Defects

Pupillary defects caused by diseases of the afferent visual system arc discussed in Chapter 40.

Examination

Figure 17.1 provides a systematic approach to the evaluation of the patient with anisocoria. first, the pupillary response to light should he checked. Isolated Horner's syndrome affects pupil dilation only, sparing the light response, and anisocoria is less apparent in bright light. Simple anisocoria also tends to be less apparent in bright

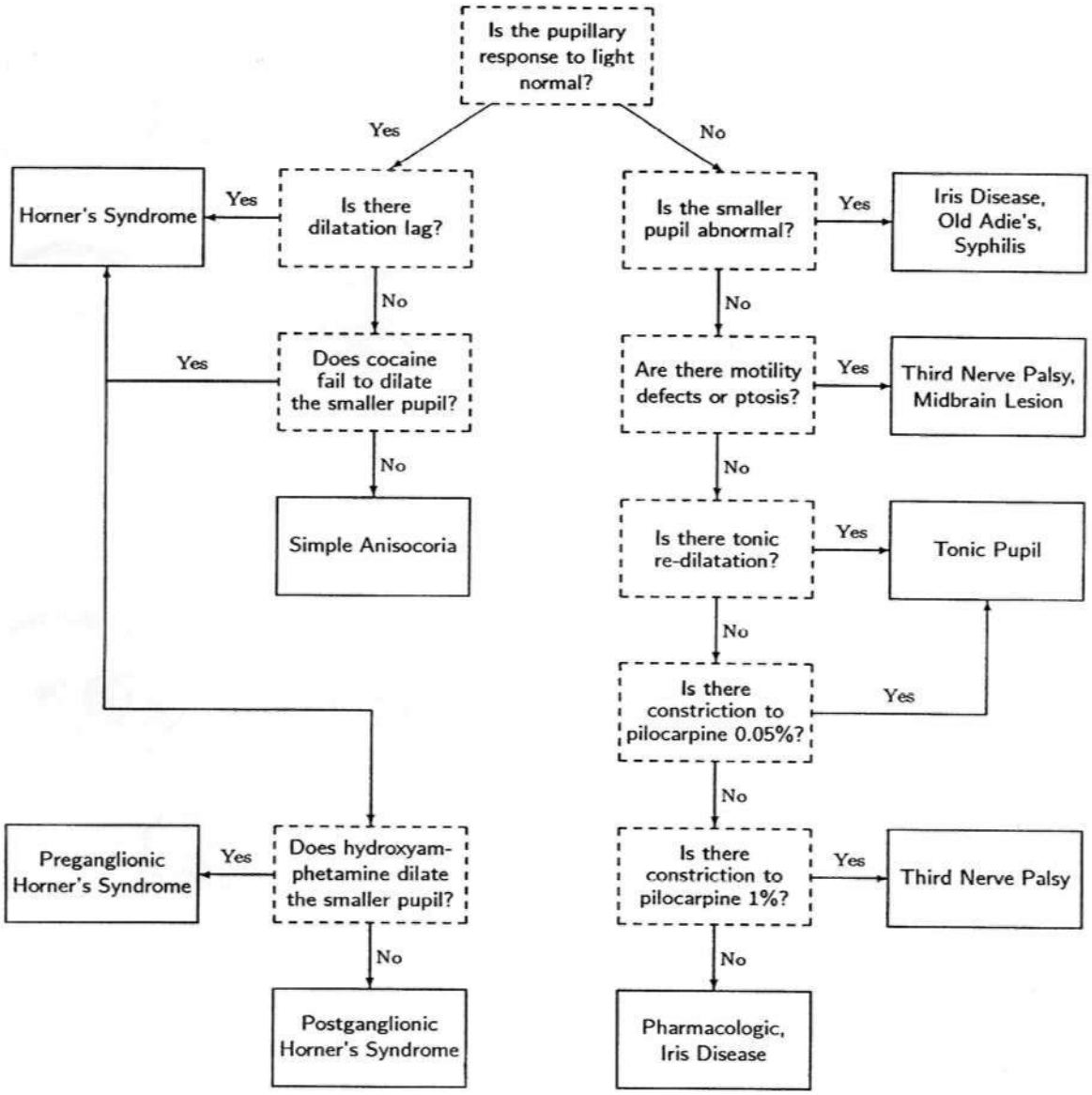

FIGURE 17.1 Flowchart for evaluation of anisocoria.

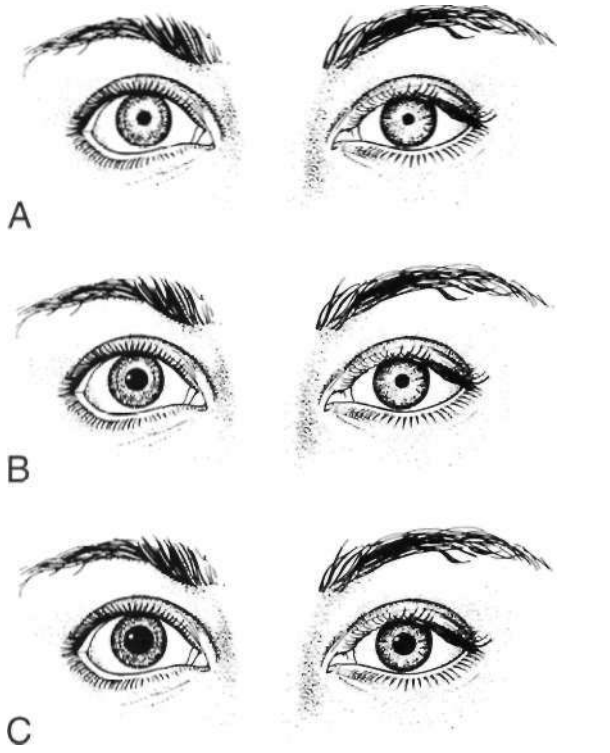

FIGURE 17,2 Homer's syndrome, left eye. (A) Room light. Mild upper lid ptosis and lower lid elevation, simulating enophthalmos. (B) Five seconds after lights off. Anisoeoria increases. (C) Fifteen seconds after lij-hts off. I)ilation las; manifested by more .nmocorui in middle than in bottom.

light. When the light response is abnormal, the iris sphincter on rhat side is defective. In this case, the differential diagnosis includes third cranial nerve palsy, traumatic iridoplegia, and pharmacological mydriasis. Table 41.1 provides a simple method for recording the examination.

If Horner's syndrome is a consideration, the pupils should be examined for dilation lag. The small pupil of Horner's syndrome dilates more slowly in darkness than the normal pupil. Therefore anisoeoria is maximal in these patients 3-5 seconds after the **lights** are turned off, compared to anisoeoria 15 seconds later (Figure 17.2). This sign is often difficult to elicit, particularly in brown-eyed individuals, because a certain amount of illumination of the pupils is necessary for the examiner to see. If there is any question about this finding, pharmacological testing should be done (Digre 1998).

If the pupillary response to light is poor, the reactivity to near should be assessed. If there is a near response, look for tonic redilation, a sign rhat establishes the diagnosis of tonic pupil. If a patient with a large unilateral tonic pupil has tonic redilation, the defective pupil can actually be transiently smaller than normal afrer near effort (Figure 17.3). Poor constriction to both light and near usually implies a local iris problem, parasympathetic defects, or midbrain disease; however, borh aging and anxiety may be causal.

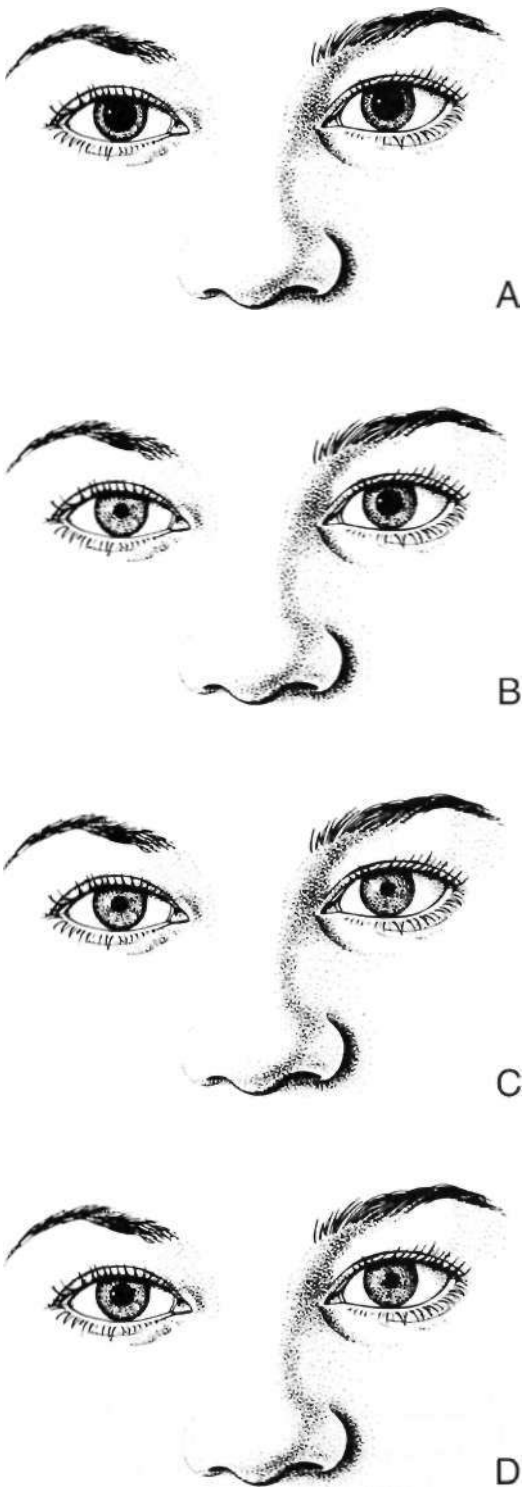

FIGURE 17,3 Tonic pupil, left eye. (A) Darkness. Anisoeoria is minimal. (B) Bright light. (C) Near, showing light-near dissociation. (D) A few seconds after return of gaze to a distant target, Tonicity of redilation on the affected side has caused transient reversal of anisoeoria.

After initial categorization of the pupil defect, the examination proceeds with evaluation of visual function, eyelid position, ocular motility, and the ocular fundus.

Light-near dissociation that is caused by visual sensory deficits can be diagnosed by testing visual acuity and visual fields (confrontation techniques are adequate) and looking for optic atrophy or other fundus abnormalities.

Both acute glaucoma and the ocular ischemic syndrome cause poor vision. Signs of acute glaucoma include corneal edema, ocular injection, and a pupil that is mid-dilated and unrcactive. The ocular ischemia syndrome arises in patients with marked stenosis of an internal carotid artery or narrowing of both internal and external carotid arteries on one side; associated eye findings include retinal neovascularization, rubeosis iridis, mild iritis, ocular hypotony, and corneal edema. Rubeosis iridis, a fine vascular network on the surface of the iris, is caused by diabetes, retinal vein occlusion, and other conditions associated with prolonged ocular ischemia.

Unilateral loss of accommodation often occurs in patients with parasympathetic denervation or pharmacological mydriasis; an eye with poor accommodation has greatly reduced near vision compared with distance vision.

Patients with Horner's syndrome have ipsilatcral ptosis, but this finding is not completely reliable. The combined prevalence of simple anisocoria and mechanical ptosis (congenital or senile) is such that a small pupil and ptosis do not always imply sympathetic denervation.

Generally, a third cranial nerve palsy can be diagnosed by associated findings of ptosis and limited ocular motility. Pretectal and other midbrain diseases that affect pupillary pathways cause abnormalities of ocular motility, such as upgazc palsy and convergence-retraction nystagmus. Irregular pupils caused by midbrain disease can be diagnosed by the associated neurological findings.

Assessment of deep tendon reflexes helps to establish the diagnosis of Holmes-Adie syndrome, and examination of the neck, brachial plexus function, and facial sweating pattern helps to localize the lesion in Horner's syndrome.

Investigations

Further evaluation of pupillary abnormalities begins with examination using the slit-lamp biomicroscopc or the ophthalmoscope with high plus lens. The Holmes-Adie pupil usually has segmental constriction to light, characterized by asymmetric contraction of the pupillary circumference. Similar segmental constrictions can be seen with eye movements in some patients with aberrant oculomotor regeneration. Eyes with traumatic iridoplcgia often have tears at the pupillary margin. Iris transillumination defects are usually seen in eyes with the small pupils of congenital rubella or Marfan syndrome, as well as in eyes affected by syphilis. Posterior synechiac can be seen only with **the slit** lamp. Ischemic eyes usually have rubeosis of the iris. Neurologists without access to a slit lamp can diagnose tonic pupils by using dilute pilocarpine as described later in this section.

Instillation of various drugs is often necessary to establish the cause of anisocoria (Loewenfeld 1999; Thompson and Miller 1998). Cocaine acts by blocking reuptake of notcpinephrinc; in a 44-10% solution, cocaine dilates the normal pupil of simple anisocoria but not the sympathetically denervated pupil of Horner's syndrome. Hydroxyamphetamine 1% acts by releasing norepinephrine from the presynaptic terminal and can be used for pharmacological localization of Horner's syndrome. When the lesion causing sympathetic denervation affects the postsynaptic pathway originating in the superior cervical ganglion, the nerve terminal degenerates, and norepinephrine is not available for release. More proximal lesions leave this neuron intact. Therefore hydroxyampheramine dilates normal pupils and those with preganglionic sympathetic lesions but not those with postganglionic sympathetic lesions. However, hydroxyamphetamine may dilate pupils with acute postganglionic lesions for the first week after onset. Hydroxyamphetamine eyedrops are no longer marketed in the United States but are obtainable from Leiter's Park Avenue Pharmacy, 1756 Park Avenue, San Jose, CA 95126 (www.lcitenx.com; phone SO0-2M2-6773).

Pilocarpine in a 0.05% solution is roo dilute to cause pupillary constriction, except in eyes with tonic pupils, where there is denervation suprasensitivity. Pilocarpine 0.05% is not commercially available and must be prepared from stronger solutions, diluted with normal saline without preservative. Pilocarpine in a 1% solution causes marked pupillary constriction in normal individuals and in those with third cranial nerve palsies but not in pharmacologic mydriasis. Eyes with local iris disease may or may not constrict in response to pilocarpine in a 1% solution, depending on the severity of involvement of the pupillary sphincter.

Examining old photographs of the patient (with a magnifying glass or ophthalmoscope) can help to establish the length of time that a pupillary abnormality has been present. Horner's syndrome that has been present for years has a better prognosis (less likely to be secondary to a serious condition) than Horner's syndrome that began in the past month, regardless of the localization. Old photographs may also help in establishing the diagnosis of episodic anisocoria.

Laboratory studies for tertiary syphilis (the fluorescent treponemal antibody absorption test or the microhemagglutination assay for *Treponema pallidum)* should be performed for any patient with bilateral tonic pupils, poorly reactive or irregular pupils, or pupils with light-near dissociation, if the cause is uncertain. Because of the high frequency of false-negative results, the serum Venereal Disease Research Laboratory test should not be used for detecting tertiary disease in these cases.

Almost all stable pupillary conditions will have been diagnosed by this point in the investigation. Further workup depends on the specific diagnosis. Preganglionic Horner's syndrome may require a chest radiograph, computed tomography of the brachial plexus, or magnetic resonance imaging of the head and cervical spine (Nagy et al. 1997), depending on associated findings. Postganglionic Horner's syndrome of recent onset may require investigation for carotid dissection. Episodic conditions may not be well characterized after the initial examination. In these cases, either performing follow-up office evaluations or having the patient take pupil photographs at home is necessary.

ABNORMALITIES OF THE EYELIDS

Clinical Presentation

Lid abnormalities present as ptosis, lid retraction, insufficient eyelid closure, or excessive lid closure. Ptosis causes symptoms when the lid or lashes intrude on the visual axis; more often, the drooping lid is perceived as a cosmetic defect. Lid retraction usually causes no symptoms. Insufficient lid closure may result in exposure keratitis, causing the patient to complain of eye pain and blurred vision. Blepharospasm or inappropriate levator inhibition {apraxia of lid opening) may cause a functional disability equivalent to severe bilateral vision loss. Sibony and Evinger (1998) provide an excellent, comprehensive review of the conditions discussed here.

Ptosis

Congenital ptosis can be caused by abnormalities of the levator muscle or its innervation and can be either unilateral or bilateral. Muscular abnormalities include congenital maldevelopment and neonatal myasthenia. Congenital abnormalities of innervation include trigeminal-levator synkinesis (the Marcus Gunn's jaw-winking phenomenon), Duanc's syndrome, third cranial nerve palsies, and Horner's syndrome. Trigeminal-levator synkinesis causes unilateral ptosis that varies in degree with movements of the jaw. This congenital condition can usually be diagnosed soon after birth: The affected infant has a drooping upper eyelid that twitches upward during bottle feeding or nursing. In older people, lid movements occur with opening the mouth, moving the jaw from side to side, or clenching the teeth. Duanc's syndrome consists of paresis of abduction, adduction, or both, associated with ptosis and globe retraction on attempted adduction, In this congenital condition, the third cranial nerve innervates the lateral rectus muscle, and the abducens nerve is absent.

One common cause of acquired ptosis is dehiscence of the levator aponeurosis. This condition occurs most often as an aging change (senile ptosis), but trauma can also be responsible, as in lid manipulation associated with contact lens wear. Ptosis can also occur when a contact lens becomes embedded in the conjunctiva of the upper lid. Other local lid diseases causing ptosis include inflammatory conditions, such as chalazion or giant papillary conjunctivitis, and infiltrative conditions, such as amyloidosis or lymphoma.

Myopathic causes of acquired ptosis include myasthenia, botulism, myotonic dystrophy, and chronic progressive external ophthalmoplegia (CPEO). In these cases, the associated systemic and ocular findings usually help the physician make the diagnosis. Myasthenia is the most common cause of acquired, isolated, painless, monocular ptosis.

Neuropathic causes of ptosis include Horner's syndrome, oculomotor paresis, Guillain-Barrc syndrome, midbrain lesions, and facial paresis. Ptosis and a number of other eyelid abnormalities can be caused by diseases affecting the cerebral hemispheres (Averbuch-Heller et al. 2002) (Table 17.1).

Pseudoptosis can be caused by blepharospasm, apraxia of lid opening, dcrmatochalasis, or contralateral lid retraction. The term *dcrmatochalasis* refers to redundancy of the skin of the eyelids, often associated with prolapse of orbital fat; treatment is surgical (blcpharoplasty).

Table 17,1: Lid abnormalities associated with cerebral hemisphere lesions

Lid abnormality	*Pathological findings*
Unilateral ptosis	Contralateral hemisphere lesions; contralateral and ipsilateral hemisphere lesions
Bilateral ptosis	Bilateral frontal lobe lesions; unilateral and bilateral hemisphere lesions
Impairment of voluntary lid opening and closure	Dominant hemisphere or bilateral hemisphere lesions or basal ganglia disease
Impairment of voluntary and reflex lid opening (apraxia of lid opening)	Basal ganglia disease; bilateral hemisphere lesions; nondominant cerebral lesion
Difficulty maintaining lid closure (motor impersistenee)	Nondominant hemisphere or bilateral hemisphere lesions
Difficulty maintaining lid opening (reflex blepharospasm)	Nondominant hemisphere or bilateral hemisphere lesions

Source: Modified with permission from Nutt, J. G. 1977, "Lid abnormalities secondary to cerebral hemisphere lesions," *Annals of Neurology,* vol. 1, pp. 149-151; and Johnston, J. G, Roscnbaum, D. M., Picone, C. M., et al. "Apraxia of eyelid opening secondary to right hemisphere infarction," *Ann Neurol,* vol. 25, pp. 622-624.

Lower lid elevation may accompany upper lid ptosis. Elevation of the lower lid occurs in enophthalmos (e.g., from orbital blowout fractures). The lower lid contains sympathetically innervated smooth (Midler's) muscle, and in Horner's syndrome, this muscle is paretic, causing lid elevation that mimics enophthalmos. Other causes of lower lid elevation are local edema, excessive lid closure (see Excessive Lid Closure, later in this chapter), and factitious ptosis.

Voluntary mimicking of ptosis by contraction of the orbicularis oculi causes lowering of the eyebrows and elevation and wrinkling of the lower lids.

Lid Retraction

Although elevated upper eyelids may be a normal variant, lid retraction is most commonly caused by hyperthyroidism or Graves* ophthalmopathy. It also occurs with increased adrenergic tone, as in very anxious patients.

In patients with thyroid disease, upper (and often lower) lid retraction may be present when the patient looks either straight ahead or down, and lid lag can be elicited by having the eyes pursue a target moving down (von Graefe's sign). Normally, the upper lid stays at the upper corneal limbus as the eyes move down; any visible sclera between lid and limbus during this movement is evidence of lid lag.

Patients with unilateral ptosis (e.g., from myasthenia) may have lid retraction on the opposite side. When the ptotic lid is raised manually, the retracted lid falls. Generally, these patients have contraction of forehead muscles as well. Patients with aberrant regeneration of the third cranial nerve often have retraction of the eyelid with depression or adduction of the eye (pseudo-von Graefe's sign). In patients with trigeminal-levator synkinesis, the affected lid may elevate with jaw movements so that the palpebral fissure is transiently wider than normal. Upper lid retraction occasionally occurs as part of Parinaud's dorsal midbrain syndrome (Collier's sign). Usually, there are also difficulties with conjugate upgaze, slow saccades upward, and vertical diplopia (see Chapter 22). Upper lid retraction may also occur in hepatic disease (Summerskill's sign) and Guillain-Barre syndrome. In Horner's syndrome, the smooth muscle of the upper lid often develops denervation supersensitivity. In stressful situations, circulating catecholamines can cause transient lid retraction on the affected side. Failure of levator inhibition (spastic eyelids) may occur with brainstem disease; in these patients, the eyes may remain open during sleep.

Lower lid retraction may be congenital, but more often it is a sign of proptosis. Lower lid retraction can also be caused by conditions that contract or displace the lid, including lower lid tumor or chalazion, trauma with scarring, and aging (senile ectropion). The lower lid may appear to be spuriously retracted in three situations: (1) when the contralateral lower lid is elevated (as in Horner's syndrome), (2) when the globe is elevated in conditions that cause hypertropia, such as fourth cranial nerve palsy, and (3) when the lower lid is weak from myasthenia or seventh cranial nerve palsy.

Insufficient Lid Closure

Poor eyelid closure does not usually pose a diagnostic dilemma but can cause serious ocular damage. Failure of the lids to cover the cornea during sleep, blinks, or forced eyelid closure results in exposure keratitis-—corneal epithelial defects, eye pain, and conjunctival injection—with the risk of corneal ulceration or scarring.

Insufficient closure of the eye can result from marked proptosis, but the more usual cause is weakness of the orbicularis oculi muscle. Such weakness can result from myasthenia, CPEO, myotonic dystrophy, or seventh cranial nerve palsy.

Another cause of insufficient lid closure with the threat of corneal damage is a reduced rate of blinking. This sign occurs frequently in patients with Parkinson's disease or progressive supranuclear palsy. In these disorders, blinks tend to be incomplete as well. Most normal blinks result in complete coverage of the cornea by the upper lid; incomplete or partial blinks cover only the superior cornea. Some normal individuals tend to have incomplete blinks, which are generally asymptomatic unless they try to wear contact lenses.

Excessive Lid Closure

The most common causes of excessive lid closure are blepharospasm, apraxia of lid opening, hemifacial spasm, myokymia, and myotonia. Blepharospasm consists of uncontrolled bilateral contraction of the orbicularis oculi causing eyelid closure (Figure 17.4). Ocular causes of photophobia and secondary blepharospasm include conjunctival disorders (dry eyes), cornea) disease (abrasion, keratitis), uveitis, and pupillary dilation (e.g., after an eye examination). When the condition is bilateral, with no associated ocular or neurological abnormalities, the diagnosis is benign essential blepharospasm, which is a focal dystonia. When there arc dystonic movements of the lower

FIGURE 17,4 Blepharospasm. Bilateral contraction of the orbicularis oculi.

face, jaw, tongue, or neck, the designation is otomandibular dystonia with blepharospasm (Meige's syndrome), a segmental dystonia. In Parkinson's disease and other disorders of the basal ganglia, the condition is called *central blepharospasm.* When orbicularis contraction occurs only with lid manipulation or other stimulation, the term *reflex blepharospasm* is sometimes used; this finding has been reported in patients with lesions of the cerebral hemispheres and in one family with no other neurological disorder. Most patients with parkinsonism have reflex blepharospasm, and all types of blepharospasm are made worse by lid manipulation or conditions causing photophobia. Factitious (voluntary) blepharospasm is rare.

The term *apraxia of lid opening* (Boghcn 1997) is used to describe inappropriate inhibition of the levator palpcbrac muscle that occurs in some patients with central nervous system disorders or bilateral or noudominant cerebral lesions or in association with benign essential blepharospasm. Rare patients have an isolated i.-dopa-responsive syndrome.

Hemifacial spasm is characterized by paroxysmal, involuntary, synchronous contraction of all muscles innervated by the facial nerve on one side (Figure 17.5) (see Chapters 76 and 77). Occasionally, the condition is bilateral; in these cases, the paroxysms on each side are asynchronous.

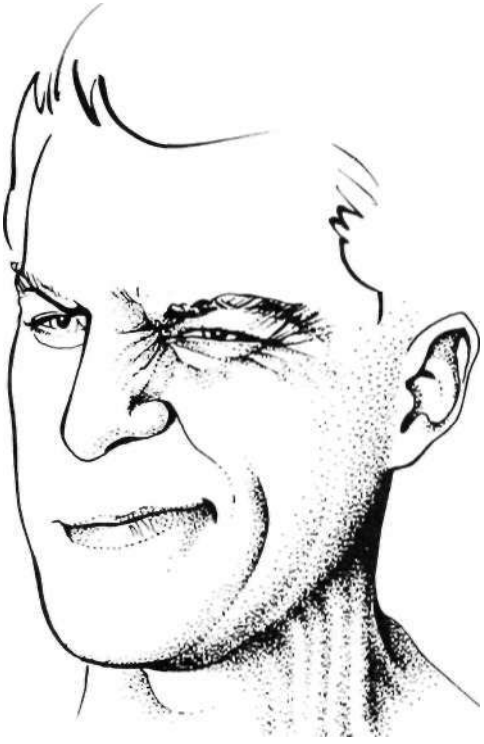

FIGURE 17.5 Hemifacial spasm. Synchronous contraction of muscles innervated by the left facial nerve, including platysma. Ohm, tilt- nrbimhns omii musdi's .ire involved ;is illuMr.ned. but with less obvious contraction of other facial muscles.

Involuntary twitches of portions of the orbicularis muscle (orbicularis myokymia, "live flesh") are common in normal individuals. These generally affect the lower eyelid; some patients describe oscillopsia when the twitches arc strong enough to move the globe. In facial myokymia, these muscular contractions involve other facial muscles. Occasionally, facial myokymia is associated with spastic paretic hemifacial contracture, a condition characterized by tonic contraction of facial muscles on one side with associated weakness of the same muscles. Facial myokymia may be unilateral or bilateral. This sign indicates brainstem disease; the most common causes are multiple sclerosis and brainstem neoplasm (usually gliomas), but Guillain-Barrc syndrome and extra-axial neoplasms may be causal.

Myotonia of lid closure may occur in myotonic dystrophy, hypothyroidism, and hyperkaiemic (and more rarely, hypokalemic) familial periodic paralysis.

Examination

Steps in the examination of the eyelids are summarized in Table 17.2. First, the eyelids and face should be observed and inspected and the blink rate measured. At rest, the upper eyelid normally covers the upper 1-2 mm of the cornea (Figure 17.6) and the upper border of the lower lid normally just touches the lower border of the cornea. In an eye with mild upper lid retraction (Figure 17.7), the lid just touches the upper limbus of the cornea, or sclera is visible between the cornea and the upper lid margin (superior scleral show). With lower lid retraction, sclera is visible between the cornea and the lower lid margin (inferior scleral show). Patients with factitious (voluntary) ptosis have some contraction of both upper and lower lid orbicularis; the contraction of the lower orbicularis raises the eyelid and wrinkles the skin near the lid margin. Patients with bilateral ptosis often have associated frontalis

Tabic 17.2: Clinical examination of the eyelids

Observe for at least 1 minute
Look for proptosis and enophthalmos
Assess lid position in different gaze directions
Observe gentle and forceful lid closure
Examine for pupillary and ocular motor abnormalities

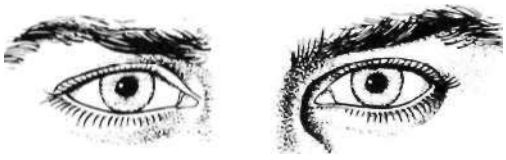

FIGURE 17.6 Normal eyelid position. The upper lid covers the upper 1-2 mm of the cornea. The lower lid just touches the lower limbus.

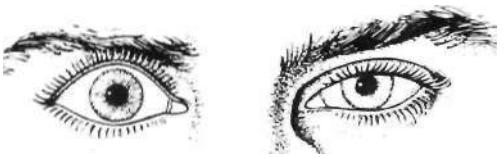

FIGURE 17.7 Lid retraction of the right eye and ptosis of the left upper iid.

contraction that elevates the eyebrows. Inspection of the lids is important to detect scarring or swelling caused by trauma, tumor, or inflammation; lid changes from these causes are usually not difficult to detect. Normally, the blink rate during conversation is at least 18 per minute. Patients with parkinsonism and related disotders often have a greatly reduced rate of normal blinks. Subtle seventh cranial nerve weakness may be manifested by incomplete spontaneous blinks on the affected side. In patients with excessive lid closure, the clinician should determine whether other facial muscles are involved, whether the contractions are synchronous in several facial muscle groups, and whether the problem is unilateral or bilateral. In hemifacial spasm, the facial muscle contractions are synchronous. In blepharospasm, the orbicularis contractions are bilateral and synchronous. Myokymic contractions involve smaller muscle groups and are not synchronous. Facial synkinesis after seventh cranial nerve paralysis can be evaluated by inspecting the lower face during spontaneous blinks; synkinetic mentalis, orbicularis oris, or platysma contractions are most common.

Proptosis (exophthalmos) can be evaluated by inspecting globe position with respect to the orbital rim by looking tangentially across the orbital margin from above, from below, or laterally.

The next step in the evaluation is to assess lid position in different gaze directions. Lid retraction on downgaze suggests lid lag or aberrant regeneration of the third cranial nerve. The latter condition also causes lid retraction on adduction. Ptosis on adduction occurs in Duane's syndrome. There are a variety of lid findings in myasthenia. Ptosis often worsens with sustained upgaze; after looking down, the patient's ptosis often improves. When the eyes return to the primary position after looking down for several seconds, the eyelids often demonstrate transient elevation before settling down to the previous ptotic position (Cogan's lid-twitch sign). Occasionally, several twitches occur before the lids stabilize. Transient elevation alone is not specific for myasthenia, but the twitches are virtually diagnostic of disease of the neuromuscular junction, such as myasthenia or botulism.

The next step is to observe both gentle and forceful lid closure. Fatigue of gentle lid closure occurs in myasthenia and can be demonstrated by asking the patient to close the eyes gently, as in sleep; after a few seconds, the lids may open slightly. Poor lid closure is the rule in facial weakness from disorders such as facial nerve paralysis and CPFO.

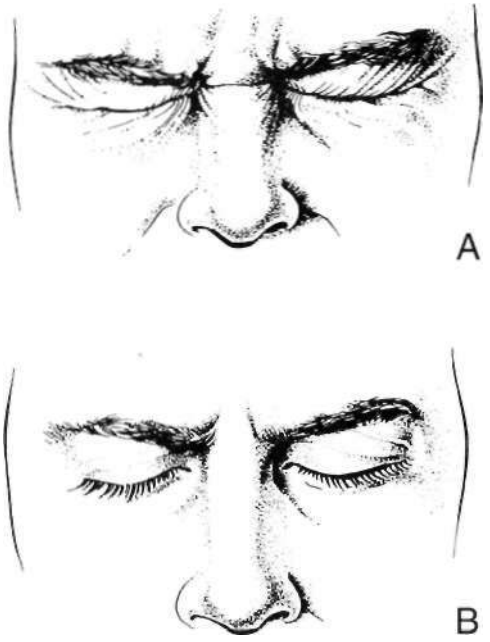

FIGURE 17.8 Forceful eyelid closure. (A) Normal forced eyelid closure. (B) Weak eyelid closure. The lashes remain visible.

Weak orbicularis function can also be assessed by asking patients to close their eyes forcefully (Figure 17.8). With forced eyelid closure, the eyelashes are normally buried by folds of skin; with even mild facial paresis, the lashes are more exposed. Forced lid closure with rapid reopening is an excellent technique for evaluating myokymia, hemifacial spasm, apraxia of lid opening, and blepharospasm, conditions that are often worsened by this maneuver.

Patients with apraxia of lid opening contract their forehead and elevate their brows when asked to open their eyes after forced lid closure, but their eyes remain closed (Figure 17.9). Patients with blepharospasm have persistent orbicularis contraction after being asked to open their eyes.

The next step is to look for abnormalities of the pupil and ocular motility, suggesting Horner's syndrome, third

FIGURE 17.9 Apraxia of lid opening. F.levated eyebrows and forehead contraction with persistent eyelid closure.

crania! nerve palsy, muscle disease, or congenital anomalies of innervation. Trigeminal-levator synkinesis can involve either external or internal pterygoid muscles. When the external pterygoid is involved, the eyelid rises with mouth opening or movement ot the jaw to the opposite side. With internal pterygoid involvement, the lid elevates with clenching of the teeth. Babies with this congenital condition have movements of the involved eyelid when they suck.

In patients with eyelid disturbances associated with more generalized disease, the neurological examination provides essential diagnostic information.

Investigations

Ophthalmologics! examination should be done in most patients with lid abnormalities. It should include exophthalmometry and tonometry in primary position and upgaze {an increase in intraocular pressure by 5 millimeters or more in upgaze suggests dysthyroid orbitopathy; low pressures occur in myotonic dystrophy). Slit-lamp examination for the lens opacities of myotonic dystrophy should also be performed, along with ophthalmoscopy to detect the pigmentary degeneration of the retina seen in some cases of CPEO and myotonic dystrophy. Cardiac evaluation of patients with CPEO is important because of associated heart block. Quantitative orbital echography is a sensitive test for detecting dysthyroid orbitopathy. Computed tomographic scanning of the orbit is the most useful test for evaluation of proptosis and enophthalmos. Magnetic resonance imaging of the head should be done in patients with blepharospasm, hemifacial spasm, and facial myokymia. Laboratory tests to consider include acetylcholine receptor antibodies and thyroid function studies.

The edrophonium test is essential in the diagnosis of myasthenia, but two other noninvasive procedures may be useful (Kubis ct al. 2000). The ice test consists of assessing changes in lid position before and after applying ice to the closed eye for 2 minutes. The sleep test consists of having the patient rest (or sleep) with closed eyes in a quiet room for 30 minutes and then assessing ocular motility and lid position immediately after the eyes are opened. Myasrhcnic ptosis is usually improved after cither of these tests.

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Chapter 18
Dizziness and Vertigo

B. Todd Troost

Dizziness, vertigo, and disequilibration are common complainrs in patients referred for neurological evaluation. Because the entire physical examination and all diagnostic test results may be normal, the diagnosis depends primarily on the history. Vestibular tests (described in Chapter 41) rarely provide an exact diagnosis; they should be used as confirmatory measures in an attempt to document abnormality in the peripheral or central vestibular system.

SYMPTOMS AND SIGNS

Vertigo, strictly defined, refers to a hallucination of movement. Although some patients do experience a definite sense of environmental spin or self-rotation, the majority do not present solely with true vertigo as defined. The most common complaint is of *dizziness,* a term that represents a wide tange of symptoms (Table **18.1).** The first attempt should be to elicit an exact description of what the patient is experiencing. Is it a spinning sensation that could be characterized as vertigo, pointing to the peripheral vestibular apparatus? Is it a sensation of falling without rotation? Is it a sensation of unsteadiness or imbalance? Is there a particular direction in which the patient tends to fall? When the patient's complaint is actually of incoordination or clumsiness, the possibility of cerebellar dysfunction or peripheral neuropathy is raised. When the description is of lightheadedness or a swimming head, one thinks of pre syncope or syncope and would, perhaps, favor a consideration of systemic factors, including vasodepressor syncope, postural hypotension, or cardiac dysrhythmia (see Chapter 2).

After trying to define the true qualitative nature of the symptom complex, the neurologist must proceed to a consideration of temporal factors. Is the patient's experience continuous? Are there episodes of severe symptomatology with symptom-free intervals? If the symptoms ,irc episodic, do they occur only when the patient is upright?

Patients often have a great deal of difficulty describing their symptoms. Initially, it is paramount that patients provide their own description before the physician biases the outcome by suggesting desctiptive phrases. Often, patients who are asked to describe their symptoms without using the word *dizziness* cannot further characterize the symptoms but revert to descriptions such as "I'm just dizzy all the time."

The signs that accompany vertigo and dizziness depend primarily on the cause. When the cause is an acute peripheral vestibulopathy, the patient probably has a nystagmus with a fast phase beating away from the side of the involved car. The patient may tend to fall toward the side of the involved ear during a Romberg test and to past-point (i.e., overshoot when attempting to point at an object with the eyes closed) in a similar direction. If the symptom is really lightheadedness and the cause is postural hypotension, the drop in blood pressure should be documented on examination. Central neurological causes of dizziness are almost always accompanied by other signs of central nervous system (CNS) dysfunction, such as gaze-evoked nystagmus, facial weakness, other cranial nerve abnormalities, ataxia, hemisensory loss, or even paralysis.

If the cause is anxiety, the examiner may observe other signs of nervousness, such as tremulousness or hyperventilation.

ELUCIDATING THE HISTORY

In addition to determining whether the symptom complex is episodic, the history must define factors such as duration, length of symptoms, and any associated symptoms, such as

Tabic 18.1: Symptoms encompassed by the term *dizziness*

Blurring vision	Listing	Staggering
Bouncing	Moving	Swaying
Disorientation	Oscillating	Swimming
falling	Passing out	Tilting
Fainting	Poor equilibrium	Twisting
Floating	Rocking	Unsteadiness
Imbalance	Rolling	Vertigo
Lightheadedness	Spinning	Weaving

tinnitus, hearing loss, double vision, slurred speech, numbness, or weakness. A history of episodic discquilibration accompanied by diplopia, slurred speech, perioral numbness, dimming of vision, and occasional drop attacks suggests transient vertebrobasilar episodes. Are there associated symptoms, such as headache, and have they occurred before? If the patient has experienced severe episodes of imbalance in early life, followed by pulsating occipital or generalized headaches, the history is very suggestive of a basilar type of migraine. Did the dizziness follow head trauma, a systemic illness accompanied by aminoglycoside antibiotic therapy, or a mild upper respiratory tract infection? Episodic positional vertigo after head trauma is suggestive of cupulolithiasis {see Post-Traumatic Vertigo, later in this chapter). Did the symptom complex occur after ear surgery or infection, deep-sea diving, or a concussive blow to the ear? Such a history, with or without hearing loss, suggests a perilymph fistula.

In many large clinics dealing with balance disorders, a significant number of patients experience anxiety. If the symptom of disequilibrationor dizziness is of long duration, it is often difficult to tell whether the symptom complex is the result of anxiety or depression or the anxiety or depression is secondary to the dizziness. I believe that very few (<207o) patients with a clear movement sensation (vertigo) have a symptom complex caused solely by anxiety. One should be able to make a positive diagnosis of chronic-anxiety disorder based on other symptomatology and historical information. There usually is a history of previous episodes of serious depression or anxiety attacks (Baloh 1995).

Migrainous vertigo was reviewed by Neuhauser et al. (2001), who proposed new criteria for the definition of both probable and definite migrainous vertigo, finding that migraine is more common in dizziness clinic patients than in orthopedic controls and that patients who carry the diagnosis did not fill International Headache Society (1HS) criteria for migraine with aura- or basilar-type migraine (see Chapter 25). Physicians should ask for migrainous symptoms in patients with vertigo to determine whether they have migrainous vertigo and might be treated with antimigraine medication. Neurologists and neuro-otologists follow a large number of patients with chronic vertiginous sensations who remain undiagnosed. Such patients complain of constant or intermittent discquilibration, often aggravated by position change, as well as by visual stimuli, such as moving traffic, patterned wallpaper, striped rugs or curtains, or passing food displays in supermarkets. Many of these patients have become agoraphobic; they hesitate to leave their homes and particularly fear driving a car because of passing other automobiles. Some of these people have had a single attack of acute peripheral vestibulopathy but have never made appropriate central compensation or adapted to their peripheral abnormality. Although mechanisms for compensation remain unclear, most patients, particularly those younger than 30 years, rapidly recover from an acute peripheral vestibulopathy. Elderly patients or patients with a previously existing brainstem or cerebellar abnormality rarely make adequate compensation for an acute peripheral vestibulopathy. Such patients continue to complain of severe disequilibration. Symptoms may be exacerbated by various visual inputs. These dizzy patients have chronic symptoms and often consult more than one physician. They often have completely normal examination and vestibular test results.

Figures 18.1 and 18.2 illustrate what might happen after an acute peripheral vestibular abnormality. Figure 18.1 shows a different afferent input to the two peripheral end organs during the act of normal head turning. The stylized drawing is not meant to represent true anatomy but the concept of asymmetrical afferent input. The right panel of Figure 18.1 suggests that when there is a unilateral injury to one peripheral vestibular end organ, the result may be asymmetrical input to the CNS. This could be interpreted centrally as a sensation of turning or vertigo. In Figure 18.2, there has been, as a result of CNS plasticity, some attempt to compensate for an injured peripheral vestibular system. In this situation, there may still be a difference in afferent input, but adjustments have been made so that the patient no longer experiences a sensation of vertigo and no nystagmus is present. In some individuals, as shown in the right panel of Figure 18.2, there is either lessened or no ability to compensate for peripheral abnormality. One possible explanation for this is a congenital inability to make CNS compensation. Other explanations include (1) an acquired central inability to compensate because of a CNS lesion, as from multiple sclerosis or previous posterior circulation stroke; (2) *a* fluctuating peripheral vestibular problem, such as might occur in Meniere's disease; (3) relative physical inactivity without much afferent input; and (4) a peripheral vestibular apparatus providing inaccurate, though nonfluctuating, afferent information. Careful history taking may reveal childhood meningitis, a remote head injury, or particular susceptibility to motion sickness in childhood. An explicit search during the history should be made to define these possibilities.

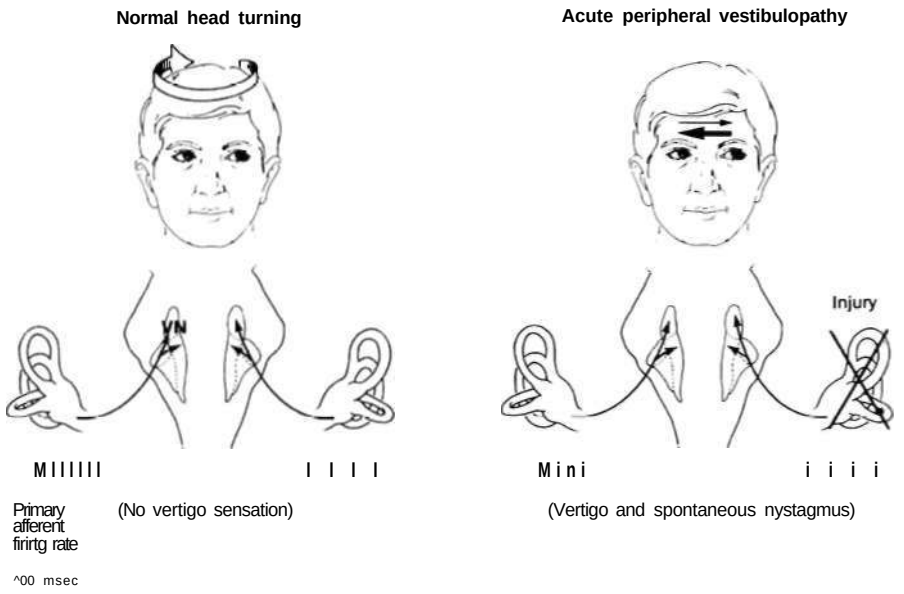

FIGURE 18.1 (A) Vestibular afferent input during normal horizontal head rotation to the right. Increased firing rate from right peripheral vestibular apparatus. Ocular deviation shows slow-phase deviation to the left. (VN = vestibular nuclei.) (B) Acute left peripheral vestibulopathy with resultant acute vertiginous sensation simulating head rotation to the right. Slow-phase ocular deviation to the left *{small arrow)* and fast phase of nystagmus to the right *[bold arrow)* and away from the side of the peripheral vestibular injury.

DIFFERENTIAL. DIAGNOSIS

Because ongoing or episodic conditions accompanied by vertigo, unsteadiness, or presyncope are produced by multiple and often subtle causes, a significant number of patients cannot be readily diagnosed. A major differential diagnostic classification includes broad categories, such as (1) peripheral vestibulopathy, (2) central neurological disorders, and (3) systemic conditions. There is some ambiguity in the term *central,* which otolaryngologists may use to include causes that are central, or proximal, to the vestibular end organ and therefore include the vestibular portion ot the eighth nerve. Neurologists, however, consider conditions that affect the vestibular nerve (e.g., tumors) peripheral in location because they are extra-axial. Because masses or neoplasms can enlarge to involve other structures in the cerebellopontine angle, particularly the brainstem, conditions that affect the eighth nerve are discussed in the central category.

Peripheral Causes of Vertigo

Peripheral causes of vertigo result from dysfunction of vestibular end organs (semicircular canals, utricle, and saccule) (Table 18.2).

Peripheral Vestibulopathy

Peripheral vestibulopathy has been described as *vestibular neuronitis, labyrinthitis,* or *viral neurolabyrinthitis.* Such terms imply an inflammatory mechanism, which is unproved. *Vestibular neuronitis,* strictly speaking, is characterized by single or recurrent sudden episodes of

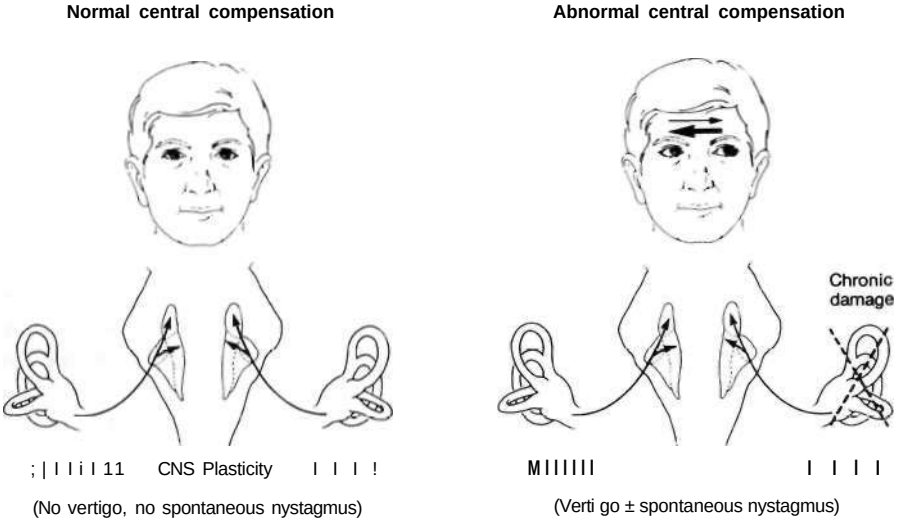

FIGURE 18.2 (A) Normal adaptation for prior left peripheral vestibulopathy. Despite a reduced firing rate from the left side, the central nervous system has compensated for the disparity and there is no nystagmus or vertigo. (B) Abnormal compensation for prior left peripheral vestibulopathy. The patient continues ro experience vertiginous sensations and may have nystagmus with a fast phase to the right *(bold arrow).*

Tabic 18.2: Peripheral causes of vertigo*

1. Peripheral vestibulopathy (includes labyrinthitis, vestibular neuronitis, and acute and recurrent peripheral vestibulopathy)
2. Benign positional vertigo (includes benign positional nystagmus, benign paroxysmal vertigo)
3. Post-traumatic vertigo
4. Vcstibulotoxic, drug-induced verrigo
5. Meniere's disease
6. Other focal peripheral diseases (includes local bacterial infection, degeneration of hair cells, genetic anomalies of labyrinth, cupulolithiasis, rumor of eighth nerve, otosclerosis, fistula of labyrinth, and, rarely, focal ischemia)

"Hearing loss is often present.

true vertigo lasting from hours to days and often associated initially with vomiting. When the condition is associated with hearing loss, the entire labyrinth is assumed to be involved, and the term *labyrinthitis* is used. Despite this technical distinction, many neuro-otologists, otologists, and neurologists use the terms *vestibular neuronitis* and *labyrinthitis* interchangeably, whether or not auditory symptoms are present. In such patients, the vertiginous sensation may be provoked by head movement but not necessarily by a particular head position.

Whether isolated viral involvemenr of the vestibular nerves is a cause of acute or episodic vertigo is controversial. Many prefer the term *acute* or *recurrent peripheral vestibulopathy.* In the acute phase, most patients presenr with sudden severe vertigo, nausea, and vomiting without any hearing disturbance or facial weakness. The acute symptoms usually resolve in a few days to a week but may recur in weeks or months. If true vertigo is part of the symptom complex, the condition is most likely to be associated with some disorder of the peripheral end organ. However, patienrs with either acute peripheral vestibulopathy or more commonly recurrent attacks may experience only a sensation of lightheadedness or floating or a feeling of "walking on tennis balls." Even if the patient has had hundreds of episodes, it is important to try to determine whether any of them were associated with spinning vertigo. With time, the nature of the patient's symptom complex may change, even with peripheral vestibulopathy, from vertiginous sensations to those of pure unsteadiness or disequilibration.

Epidemic and seasonal outbreaks of acute vertigo have suggested an infectious origin caused by viral disease, but this remains largely unproved. Viral labyrinthitis can also be part of a systemic viral infection, such as mumps, measles, infectious mononucleosis, or upper respiratory tract viral infections. Isolated viral infections of the labyrinth are also believed to cause the sudden onset of hearing loss, vertigo, or both, m children and adults. Otitic herpes zoster is an infection characterized by pain in the ear, followed in 1-10 days by a vesicular eruption in the external ear. When the seventh and eighth nerves are affected, there is a combination of facial weakness, heating loss, and vertigo known as the *Ramsay Hunt syndrome.* Whenever vertigo is associated with severe ear pain or facial pain, one must consider this possibility. A dyscsthetic area of skin may precede, by many days, the appearance of the skin eruption (see Chapter 76).

Benign Paroxysmal Positional Vertigo

Benign paroxysmal positional (or "positioning") verrigo (BPPV) is a symptom complex suggesting benign peripheral (end-organ) disease (Furman and Cass 1999). It is a major cause of vertigo. Historical factors that should lead to the consideration of BPPV include the following: (1) symptoms associated with certain head positions, (2) episodic rotational vertigo of brief duration, (3) antecedent episode of severe rotary vertigo with or without nausea and vomiting, associated with an upper respiratory tract infection that suggests prior viral neurolabyrinthitis, (4) history of head trauma before attacks of vertigo, (5) most severe symptomarology early in the day, with lessening symptoms as the day progresses, and (6) relative absence of spontaneous symptoms without head movement or position change. These symptoms, differentiated from central neurological symptoms, arc outlined in Table 18.3. The signs and symptoms of benign positional vertigo are transient and rarely last longer than 40 seconds. They usually occur when a certain position is assumed, such as lying down or turning in bed. Depending on whether the symptom (vertigo) or sign (nysragmus) is being emphasized, this condition can be called *benign paroxysmal positional nystagmus* or *BPPV.* Physical examination findings include (1) vertical rotary benign positional paroxysmal nystagmus produced by provocative maneuvers (Figure 18.3), (2) latency to onset of symptoms once precipitating head position is achieved, (3) short-duration nystagmus (3-30 seconds), and (4) adaptation of nystagmus and symptoms (i.e., disappearance with repeated maneuvers). The finding of rhe typical nystagmus on assumption of certain head positions is considered the most important physical finding in making the diagnosis of BPPV (Figure 18.4).

Post-Traumatic Vertigo

Post-traumatic vertigo immediately follows head trauma in most cases. It implies end-organ damage in the absence of other CNS signs and may be related to fracture of the temporal bone. The interval between injury and onset of symptoms can, however, be days or even weeks. The mechanism for the delay of symptoms is uncertain but may be hemorrhage into the labyrinth, with later development of serous labyrinthitis. Another mechanism for delayed post-traumatic positional vertigo is cupulolithiasis, in which the calcateous deposits (otoconia) of a damaged organ of the labyrinth are displaced to a sensitive region of the posterior canal, making it more susceptible to stimulation in certain head positions. Another possible mechanism

Table 18.3: Characteristics of peripheral versus central positional vertigo

Symjitinii iir s/yj;	*Peripheral*	*Central*
Latency (time to onset of vertigo or nystagmus)	0-40 sec (mean 7.8*)	No latency; begins immediately
Duration	<1 min	Symptoms may persist (signs and symptoms of single episode)
Fatigability (habituation) (lessening signs and symptoms with repetition of provocative maneuver)	Yes	No
Nystagmus direction	Direction fixed, torsional, up, upper pole of eyes toward ground	Direction changing, variable
intensity of signs and symptoms	Severe vertigo, marked nystagmus, nausea	Usually mild vertigo, less intense nystagmus, rare nausea
Reproducibility	inconsistent	More consistent

* According to Baloh, R. W,, Honrubia, V., & Jacobson, K. 1987, "Benign positional vertigo: Clinical and oculographic features in 240 cases," *Neurology,* vol. 37, pp. 371-378.

is the presence of freely moving pathological densities in the endolymph of the semicircular canal. This is known as the *canalitb theory* (Brandt, Steddcn, and Daroff 1994). In post-traumatic vertigo, the symptoms may be those of general peripheral vestibulopathy or benign positional vertigo. The prognosis is usually good, with symptoms gradually resolving within weeks to months. Disabling persistent positional vertigo that is untesponsive to medical therapy does occur, however. Most patients respond to exercise therapy, as described in Chapter 41 (Figure 18.5).

Drug Toxicity

Patients with dizziness produced by vestibulotoxic drugs are presumed or documented to have petsistent injury to the peripheral end organ. Among the agents causing such end-organ injury are the aminoglycosides. Streptomycin and gentamicin have their greatest effect on the vestibular end organ; kanamycin, tobramycin, and neomycin cause more damage to the auditory end organ (Minor 1998; Troost and Waller 1998). Patients usually report

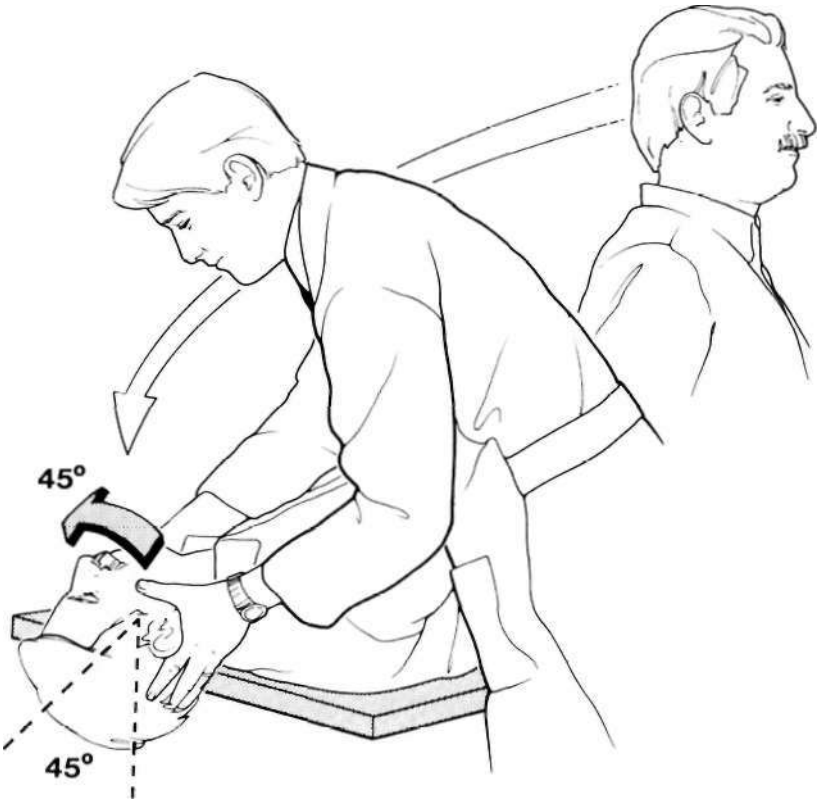

FIGURE 18.3 Provocative maneuvers for positional vertigo and nystagmus. The patient is abruptly moved from a seated position to one with the head hanging 45 degrees below the horizontal plane and rotated 45 degrees to one side. The patient is then observed for positional nystagmus. The maneuvers are repeated with the head straight back and turned to the other side.

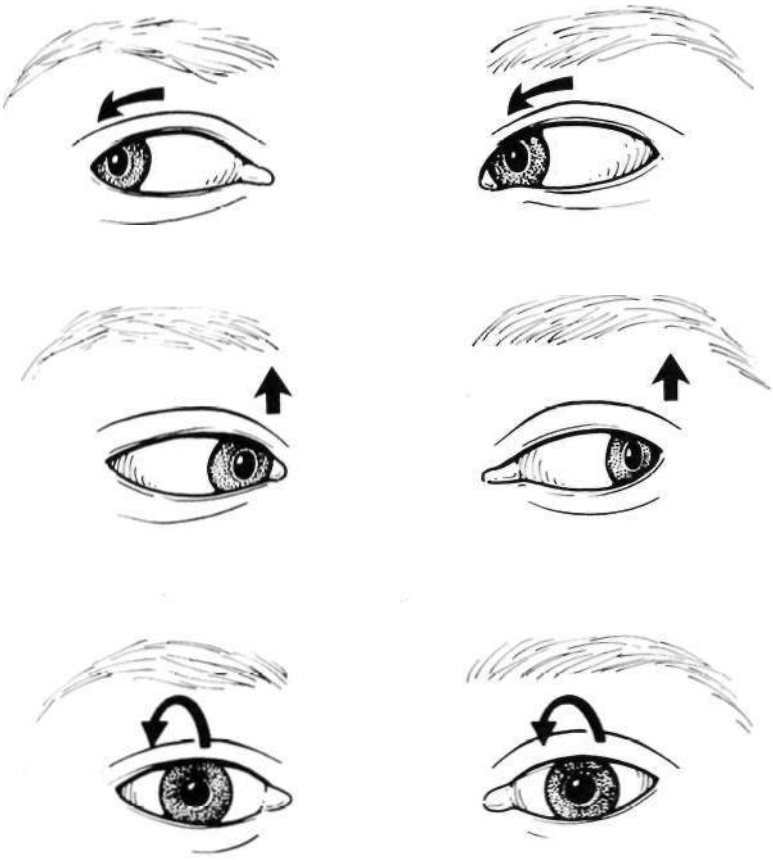

FIGURE 18.4 In benign paroxysmal positional vertigo, the nystagmus fast phase is horizontal-rotary directed toward the lower ear (A). The nystagmus fast phase is upward toward the tore-head when gaze is directed to the upper car (B). With the eyes in the central orbital position, the nystagmus fast phase is vertical upward and rotary toward the lower ear (C).

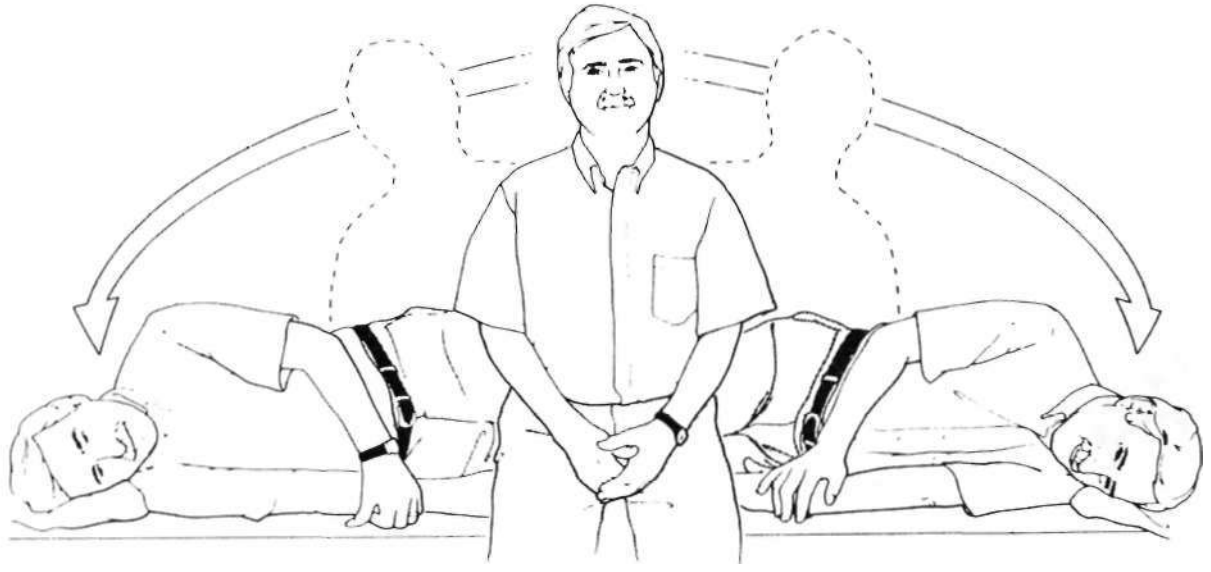

FIGURE 18.5 Exercise therapy. The patient begins in the seated position and then leans rapidly to the side, placing the head on the bed or table. The patient remains there until the vertigo subsides and then returns to the seated upright position, remaining there until all symptoms subside. The maneuver is repeated toward the opposite side, completing one full repetition. Ten to twenty repetitions should be performed three times a day.

Tabic 18.4: Systemic causes of vertigo and dizziness

t. Drugs (including anticonvulsants, hypnotics, antihypertensives, alcohol, analgesics, tranquilizers)
2. Hypotension, presyncopc (including primary cardiac causes and postural hypotension from a wide variety of causes)
3. infectious diseases (including syphilis, viral and other bacterial meningitides, and systemic infection)
4. Endocrine diseases (including diabetes and hypothyroidism)
5. Vasculitis (including collagen vascular disease, giant ceil arteritis, and drug-induced vasculitis)
6. Other systemic conditions [including hematological disorders [polycythemia, anemia, and dysproteinemia], sarcoidosis, granulomatous disease, and systemic toxins)

progressive unsteadiness, particularly when visual input is diminished, as happens at night or in a darkened room. Vestibular testing documents a progressive bilateral loss of vestibular function. The aminoglycosides are concentrated in the endolymph and petilymph, so the hair cells are exposed to high concentrations of the drugs. Extreme caution should be used in patients with even mild renal disease because most of these agents are primarily eliminated by the kidney. This type of end-organ toxicity should be contrasted with that produced by the large group of drugs with widespread reversible CNS and peripheral nervous system effects (Table 18.4); these drugs cause transient disequilibration, which subsides with cessation of the medication.

Meniere's Disease

Meniere's disease is characterized by attacks of severe vertigo and vomiting, tinnitus, fluctuating hearing loss, ill-described aural sensations of fullness and pressure, and spontaneous recovery in hours to days. Usually, the patient develops a sensation of fullness and pressure associated with decreased hearing and tinnitus in a single ear. This is followed by severe vertigo, which reaches peak intensity within minutes and slowly subsides over hours, with a persistent sense of disequilibration for days after an acute episode. Occasionally, severe attacks cause sudden falls to the ground. Consciousness is not lost in such episodes, although awareness of surroundings may be altered by the intensity of the accompanying vertigo nausea. The most consistent pathological finding in Meniere's disease is an increase in the volume of the endolymphatic fluid and distention of the canals, hence the term *endolymphatic hydrops* (Saced 1998). Although some specific causes, such as bacterial, viral, and syphilitic infections, may lead to the same pathological changes and symptoms, most cases are idiopathic.

Other Peripheral Vestibular Conditions

Many other disorders affect the peripheral labyrinth, including acute and chronic otitis media, hereditary degenerative disorders of the end organ, and local tumors. Conditions such as a vertebrobasilar transient ischemic attack (TIA) or focal ischemic stroke of the end organ, particularly in an elderly patient, are often cited as a cause of vertigo. Such isolated involvement is difficult to document, and vertebrobasilar insufficiency is unusual without associated brainstem symptoms and signs,

Central Causes of Vertigo

Central pathological causes of vertigo result from dysfunction of the vestibular portion of the eighth nerve, the vestibular nuclei within the brainstem, and their central connections (Table 18.5}. Neural connections with the central vestibular nuclei include the vestibular portions of the cerebellum (primarily the cerebellar flocculus, nodulus, and uvula).

Normal people experience physiological vertiginous sensations when visual and vestibular inputs are in conflict (such as in motion sickness or watching motion pictute automobile chase scenes), or when they are exposed to heights while standing on a ledge.

Central pathological causes of vertigo are less common than either peripheral or systemic causes, the vertiginous symptoms are usually less prominent, and additional neurological signs are usually present on examination (Froehling et al. 1994).

Brainstem Ischemia and Infarction

Vertigo, including brief episodes of isolated vertigo, can be caused by posterior circulatory disturbances (Baloh 2002), The posterior circulation supplies blood to the brainstem, cerebellum, and peripheral vestibular apparatus, in addition to other structures. In general, brainstem TIAs should be accompanied by neurological symptoms or signs, in addition to vertigo or dizziness, for a clear diagnosis to be entertained, but isolated episodes of vertigo lasting many minutes may be due to posterior circulation dysfunction.

Table 18.5; Central neurological causes of vertigo*

1. Brainstem ischemia and infarction
2. Demyelinatmg disease: multiple sclerosis, postinfectious demyelination, remote effect of carcinoma
3. Cerebellopontine angle tumor: acoustic neuroma, meningioma, cholesteatoma, metastatic tumor, etc.
4. Cranial neuropathy: focal involvement of eighth nerve or in association with systemic disorders
5. Intrinsic brainstem lesions (tumor, arteriovenous malformation)
6. Other posterior fossa lesions (primarily other intrinsic or extra-axial masses of the posterior fossa, such as hematoma, metastatic tumor, and cerebellar infarction)
7. Seizure disorders (rare)
8. Heredofamilial disorders (such as spinocerebellar degeneration) (Ohetal. 2001)

"Hearing loss is rare except in the condition listed in no, 3.

The usual TIA symptoms include transient clumsiness, weakness, loss of vision, diplopia, perioral numbness, ataxia, drop attack, and dysarthria (Chapter 57a). Common signs include disorders of motor function, such as weakness, clumsiness, or paralysis. A crossed detect (i.e., a motor or sensory deficit on one side of the face and the opposite side of the body) is good evidence of brainstem dysfunction. If the occipital lobes are the site of ischemia, transient vision loss in the form of complete blindness or partial homonymous hemianopia occurs. Ataxia, imbalance, unsteadiness, or disequilibrium, not necessarily associated with spinning vertigo, may occur because of labyrinthine or cerebellar ischemia.

Sudden hearing loss with dizziness may be due to infarction in the distribution of the internal auditory artery. In isolation, this symptom complex is uncommon in elderly patients with atherosclerotic vertebrobasilar disease and is more suggestive of diseases affecting small- and intermediate-diameter arteries, such as syphilis, systemic lupus erythematosus, or periarteritis nodosa. In the atherosclerotic patient, such symptoms usually accompany other signs of brainstem or cerebellar dysfunction, which allow a more certain diagnosis. If actual brainstem infarction occurs, neurological signs are often present on examination. Such signs include nystagmus of the central type, hyperreflexia, internuclear ophthalmoplegia, homonymous visual field defects, dysarthria, and ataxia.

Severe vcttigo, mimicking labyrinthine disease, may be an early symptom of acute cerebellar infarction. To differentiate this condition from labyrinthine disease, particular attention is directed to the type of nystagmus that is present. Acute peripheral vestibulopathy usually causes unidirectional nystagmus, with the fast phase in the opposite direction. This is similar to the mnemonic COWS (cold, opposite—warm, same) for the direction of the nystagmus fast phase during thermal irrigation of the ear. The fast phase is away from the side of the cold water irrigation. Cold water mimics a peripheral destructive lesion of the labyrinth, and almost all lesions are destructive. Therefore with a peripheral labyrinthine disturbance, the nystagmus fast phase is in the opposite direction or away from the involved ear. The nystagmus increases during gaze in the direction of the fast phase (Alexander's law) or contralateral to the peripheral vestibulopathy. Swaying or falling occurs toward the side of the lesion (opposite the nystagmus fast phase). The nystagmus is unidirectional and remains horizontal on upward gaze.

By contrast, with incipient cerebellar infarction, the sway or fall is ipsilateral to the lesion, and the nystagmus may be variable in direction but is most prominent ipsilateral to the lesion. In other words, with central lesions the fast phase of the nystagmus is in the direction of gaze (direction-changing nystagmus) but becomes more prominent when gaze is directed ipsilateral to the lesion (Oas and Baloh 1992). Other ocular motor findings are often present in brainstem disease; such conditions as limitation of vertical gaze, upbeat or downbeat nystagmus, or dysconjugate nystagmus are often present (see Chapter 16). However, in certain syndromes of the posterior circulation, the initial presentation can mimic acute vestibulopathy, particularly the syndrome of the anterior cerebellar artery {Oas and li.iluh 1992) and the syndrome of the distal posterior interior cerebellar artery.

Cerebellopontine Angle Tumors

Tumors of the cerebellopontine angle rarely present solely with episodic vertigo. The most common tumor in this location results from a proliferation of the Schwann cells (schwannoma). Most of these tumors arise on the vestibular portion of the eighth nerve within the internal auditory-canal. They progressively enlarge, deforming the internal auditory meatus and compressing adjacent neural structures, such as the acoustic portion of the eighth nerve, facial nerve, trigeminal nerve, brainstem, and cerebellum.

The most common symptoms associated with eighth nerve tumors are progressive hearing loss and tinnitus. Vertigo occurs in approximately 20%, but a symptom of imbalance or disequilibration is more common, approaching 50%.

Cranial Neuropathy

Multiple or isolated cranial neuropathies occur in focal or systemic disease, including vasculitis, granulomatous disease, and meningeal carcinomatosis. Often, however, the cause is elusive. Evidence of systemic involvement is elicited by history, physical examination, and laboratory evaluation. Cogan's syndrome may be considered with cranial neuropathies and is characterized by nonsyphilitic keratitis associated with vertigo, tinnitus, ataxia, nystagmus, rapidly progressive deafness, and systemic involvement,

Posterior Fossa Lesions

Posterior fossa lesions in various locations are unusual causes of isolated vertigo. The symptoms are usually positional vertigo of the central type (see Table 18.3).

Brainstem and cerebellar disease cause a variety of types of nystagmus that sometimes present as a complaint of oscillopsia—an illusion of environmental movement characterized by bouncing or jiggling of objects. Although oscillopsia is a common complaint with significant bilateral labyrinthine abnormality, the presence of vertical oscillopsia indicates upbeat or downbeat nystagmus (see Chapter 16). These nystagmus types are reliable indicators of CNS abnormality (Troost and Waller 1997).

Seizure Disorders

Seizure disorders, especially temporal lobe epilepsy, are rare causes of dizziness or vertigo. The history almost always

re VIM Is additional symptoms, such as loss of awareness, automatic behavior, or generalized seizure activity after an aura of vertigo. I lowever, some epileptics with psychomotor seizures have isolated auras of the symptoms listed in Table 18.1.

Systemic Causes of Vertigo

Systemic causes are discussed as a separate category to include more widespread conditions that secondarily affeci peripheral or central vestibular structures, or both, to produce vertigo (see Table 18.4).

Drugs

Side effects of drug ingestion often cause dizziness in the broadest definition of the term. Vestibulotoxic drugs, as previously described, can produce true vertigo. The dizziness produced by other drugs is more a sense of weakness, disequilibration, or "fuzzy hcadedness." The agents listed in Table 18.4 are among the most common offenders. Every attempt should be made to determine the type and quantity of medication being taken by the dizzy patient. Frequently, the elimination or reduction of medication, such as a mild tranquilizer, produces a clear improvement. However, the dizzy patient with a systemic condition will have been treated with a variety of medications that may add to disequilibration or dizziness.

Hypotension

The multiple causes of presyncope or postural hypotension are often responsible for complaints of vertigo or dizziness (see Chapter 2). Presyncope is often described as lightheadedness and is actually a common mechanism for dizziness or even vertiginous sensations. Postural hypotension is a common side effect of antihypertensive agents, diuretics, and dopaminergic agents.

Endocrine Disorders

Among the endocrinopathies that cause disorders of equilibration are diabetes and hypothyroidism. The mechanism in diabetes is probably an accompanying autonomic neuropathy and orthostatic hypotension. Though much less common as a specific cause, hypothyroidism should be considered when the symptoms of vertigo remain undiagnosed. The remaining systemic conditions (listed in Table 18.4) rarely present with isolated vertigo.

Multiple Afferent Sensory Loss

The vestibular system functions to provide (1) spatial orientation at rest or during acceleration, (2) visual fixation during head or body movement (the vestibulo-ocular reflex fVOR|), and (3) feedback control of muscle tone to maintain posture. These functions and their control mechanisms arc interconnected in a complex fashion. Thus the symptoms of episodic vertigo may reflect disturbances in more than one system. The combination of multiple sensory deficits can produce disorientation or disequilibration that is interpreted as dizziness or vertigo. This often occurs in the elderly, in whom vision (cataracts), hearing (presbycusis), and proprioception (peripheral neuropathy) may all be impaired. Presbylibrium, or imbalance resulting from aging, may be due to a selective progressive deterioration of the peripheral vestibular apparatus or a combination of sensory deficits.

Even a young, healthy person is easily confused by afferent sensory information, as exemplified by the sensation of spinning or true vertigo experienced during full-field optokinetic stimulation. Almost every individual, while quietly seated, experiences a compelling illusion of rotation while viewing a moving environment of optokinetic stripes (the circular vection illusion). Thus patients with abnormalities of peripheral or central vestibular mechanisms experience periods of disorientation while viewing a moving patterned environment or experience vertigo during vehicular travel.

An age-related degeneration of vestibular receptors, analogous to presbycusis, contributes to vertigo. Although most younger patients readily compensate for unilateral peripheral vestibular damage, older patients usually cannot because of bilateral peripheral vestibular dysfunction or a separate central abnormality that decreases their ability to compensate.

Dizziness in Childhood

The most common causes of vertigo and dizziness in childhood and infancy are similar to those in the adult: acute peripheral vestibulopathy, trauma, and infection. Vertigo after air travel is more common in children than in adults because of the frequency of accompanying middle ear infection and effusion. Migtaine is a significant cause of episodic dizziness or vertigo in childhood and should be considered even when the symptoms of headache are absent.

Benign paroxysmal vertigo in childhood is thought by some to be a variety of vestibular neuronitis and by others to be a migraine variant. Although an attack may be unaccompanied by loss of consciousness, children may fall during its course and often indicate a sensation of spinning. The episodes may last minutes to hours or recur for many weeks or even months, gradually decreasing in severity. The preservation of consciousness during an attack distinguishes the condition from temporal lobe seizures with a vestibular component and from vcstibulogenic epilepsy, in which an attack is triggered by labyrinthine stimulation. Congenital anomalies of the inner ear and brainstem, vascular disease, and tumor are rare causes in childhood.

EXAMINATION OF **THE** DIZZY PATIENT

General Examination

Every patient with a disorder of equilibration or true vertigo should have a screening general physical examination. In particular, patients who exhibit symptoms suggesting presyncope or actual syncope must have particular attention paid to theit cardiovascular system and blood pressure on standing (see Chapter 2). One should also evaluate the musculoskeletal system because abnormalities adversely affect balance. Attention should also focus on systemic conditions that could give rise to a general feeling of malaise or weakness, which the patient may intetpret as a disorder of balance.

Neurological Examination

The neurological examination should be specifically determined by the patient's history (see Chapter 1). In patients with cleat episodic vertigo, the neurological examination usually shows no abnormalities, with the exception of the ocular motor findings to be described. However, when the patient's symptom complex is more vaguely defined and includes disequilibration or unsteadiness, examination of the motor system, reflexes, sensation, and cerebellar function may uncovet abnormalities.

All patients with undiagnosed disorders of equilibration, however described, should have a complete neurological examination. The vatious parts of the neurological examination are described here only briefly, with each part followed by a suggestion of which entities might be discovered.

Mental Status Examination

Signs of diffuse alterations in consciousness may suggest overmedieation, metabolic encephalopathy, or an acquired dementing process. Focal disturbances in intellectual function, such as a subtle aphasia, may lead to the consideration of either a mu hi-infarction state (multi-infarct dementia) with accompanying brainstem infarctions or an intracranial mass lesion,

Cranial Nerve Examination

Alterations in visual sensory function may be a primary or exacerbating cause of disequilibration. Even the recent addi[ion of a new refractive correction, particularly lenses for presbyopia, may be an added or primary cause of imbalance. Visual field defects, such as unsuspected bitemporal or homonymous field defects from tumors or infarcts, may cause patients to tun into objects or feel disoriented in space. The presence of papilledema or absent venous pulsations on funduscopy should be an immediate clue to raised intracranial pressure. Altctcd corneal sensation may be the clue to a previously unsuspected cerebellopontine angle mass. Tuning fotk tests (see Chaptet 19) may confirm the patient's complaint of hearing loss and should lead to audiologic assessment. Abnormalities on examination of cranial nerves IX-XII raise the differenrial diagnosis of multiple cranial neuropathies, such as collagen vascular disease, tumors of the base of the skull, and nasopharyngeal carcinoma.

Ocular Motor Examination

The presence of spontaneous or induced nystagmus is of crucial importance in making a diagnosis of peripheral, central, or systemic causes of imbalance. The patient should be evaluated for the ptesence of strabismus because this may be a relatively nonspecific cause of dizziness and intermittent diplopia. Some types of nystagmus that are of particular importance are described (sec Directed Neuro-Otological Examination, latet in this chapter). Failute of vertical gaze, particularly in a downward direction, may be the first sign of disequilibration caused by progressive supranuclear palsy. The presence of asymmetrical slowing of the adducting eye may be a subtle but important clue to the presence of brainstem multiple sclerosis, brainstem infarction, or mass lesion of the posterior fossa.

Motor System Examination

Motor sysrem examination may reveal focal or diffuse weakness indicative of CNS or neuromuscular disorders. A subtle hemiparesis may be the true cause of the patient's balance complaint. Diffuse hyper-rcflexia may reflect cerebral or spinal cord dysfunction and, in combination with cerebellar abnormality, may lead to the diagnosis of a spinocctcbellar degeneration (sec Chapter 78).

Sensory Examination

Sensory examination may reveal a significant peripheral neuropathy, leading to a diagnosis of diabetes or toxic neuropathy. Selective loss of proprioception and vibration may indicate that the patient has vitamin B deficiency ot early tabes dorsalis. Such patients may be relatively steady during the Romberg test with eyes open but rapidly lose balance and fall in any direction when visual compensation is eliminated by eye closure. Patients with symptomatic petiphetal vestibulopathy tend to fall towatd the side of the abnormality during eye closure with the head directed straight ahead.

Cerebellar System Examination

Clear limb or body ataxia should be an immediate clue to a CNS abnormality as the cause of the patient's imbalance. Unsteadiness during Romberg testing with eyes open and only slight exaggeration on eye closure indicates a cerebellar abnormality. It is usually accompanied by a definite

abnormality during gait testing or even difficulty maintaining balance while seated. Unilateral limb ataxia is almost always an indicator of focal posterior fossa abnormality, such as infarct, dcmyelination, abscess, or tumor.

Directed Neuro-Otohgical Examination

A directed neuro-otological examination should be performed, particularly when there are abnormalities of the auditory, ocular motor, and vestibular systems. Audiometric testing is discussed in Chapter 19. During the neurological examination, there may be subtle signs of peripheral vestibular dysfunction indicated by nystagmus. During the funduscopic examination, particular attention should be paid to the movement of the optic disc. A rhythmic, subtle, horizontal slow and fast component is commonly present in patients with new peripheral vestibular dysfunction. For example, with the patient staring at a dimly lit target in the distance, the presence of a slow ocular drift to the left and a fast phase to the right of the optic disc should indicate to the examiner that the patient has a subtle left-beating nystagmus in the primary position. This indicates a right peripheral vestibular abnormality. Vertical drifts of the optic disc seen during funduscopy may signify the presence of vertical nystagmus, thus directing the examiner to search for the presence of nystagmus during upward, downward, and oblique gaze.

The need to determine the presence of any type of nystagmus during the directed neuro-otological examination cannot be overemphasized; all too often thete is unnecessary dependence on the results of clectrony stag mographic testing. The directed neuro-otological examination should include an otoscopic examination of the external auditory canal and the tympanic membrane. The presence of a retracted or scarred eardrum may be the clue to prior middle ear infection. The presence of a blue mass behind the tympanic membrane points to a glomus jugulare tumor.

The patient should be tested for balance during standing, walking, and turning and for the presence of past-pointing—that is, a tendency for the repetitively elevated and lowered outstretched fingers to drifr in one direction. Past-pointing is a clear indication of tonic imbalance in the vestibular system.

The physician **may also** clinically test for the presence of an intact VOR and may observe whether the patient is able to maintain steady ocular fixation during funduscopic examination as the head is gently rotated from side to side (Sharpe and Barber 1993). The patient with an intact VOR can still maintain fixation on distant objects during head turning. The absence of this ability produces an apparent nystagmus, most easily observed during funduscopic examination, which is good evidence for a defective VOR. A different test of vestibulo-ocular control is for the patient to fixate on his or her own moving rhumb while rotating his or her head in the same direction. During this maneuver, the patient must suppress the VOR to permit combined head and eye tracking. The loss of this ability may be a subtle clue to cerebellar system dysfunction. The patient may also be examined for the presence of nystagmus when visual fixation is reduced by the wearing of Frenzel glasses, which blur the patient's vision and magnify the eyes, thereby allowing the examiner to observe previously undetected nystagmus.

INVESTIGATIONS

Screening Tests

Patients with undiagnosed vertigo should have metabolic screening tests, including blood cell count, electrolytes, glucose, erythrocyte sedimentation rate, thyroid function testing, and possibly a rheumatologic battery. Many physicians involved in the evaluation of dizzy patients also perform lipid screens for the presence of hypercholesterolemia or increased triglycerides. The laboratory investigation, like the physical examination, is directed particularly by the patient's history. If **there** is a history of presyncope or syncope, the patient must have a cardiac evaluation, to include at least an electrocardiogram and rhythm strip. A more suggestive history would lead to use of 24-hour Holter monitoring or an event monitor, during which the patient wears a battery-powered apparatus that can be activated when symptoms occur. This device then records the cardiac rhythm. The presence of auditory symptoms requires audiometric tests, as described in Chapter 19. Multiple or recurrent cranial neuropathy leads to a variety of screening tests for collagen vascular disease or basal skull or meningitic processes.

Vestibular Tests

Vestibular testing may be divided into categoties such as standard electronystagmographic testing, specific ocular motor testing, rotational tests, and posturography. Each test is reviewed briefly in Chapter 41.

DIAGNOSTIC FORMULATIONS

Symptoms, findings, and the results of investigations that would lead to a tentative diagnosis in each of the **major** categories of vestibular disorders are briefly discussed here.

Peripheral Vestibulopathy

A patient who complains of episodic spinning vertigo, with or without auditory symptoms, whose neurological examination shows no abnormalities, and who has evidence of reduced vestibular function in one ear on caloric testing

Table 18.6: Differential diagnosis of dizziness attacks

Hiiii-le	*Recurrent*	*Chronic disequilibration*
Acute peripheral vestibulopathy	Peripheral vestibulopathy	Uncompensated peripheral vestibulopathy
Trauma	Benign positional paroxysmal vertigo	Cerebellopontine tumor
Perilymph fistula	Meniere's disease	Multiple sclerosis
Air travel	Vertebrobasilar ischemia	Brainstem infarct
Ramsay Hunt syndrome	Migraine	Drugs
Syncope and presyncope	Complex partial seizure	Ototoxicity
	Familial periodic ataxia	Chronic otomastoiditis
		Autonomic neuropathy
		Multiple sensory deficits
		Arteritis
		Cogan's syndrome

should initially be placed in this diagnostic category. Such patients often respond to vestibular suppressant medication early in the course and, thereafter, to vestibular exercises. Peripheral vestibulopathy of idiopathic, infectious, or post-traumatic origin is one of the most common causes of a single attack of vertigo (Table 18.6).

Central Vestibular Disorders

Patients with central vestibular disorders usually have vague descriptions of their symptomatology; they rarely describe true spinning vertigo or symptoms evoked by position change (but see Table 18.3), and they have abnormalities, such as nystagmus or hyperreflexia, on physical examination. These patients are candidates for additional neurological diagnostic investigations. If a history of alteration of consciousness is present, the neurologist may consider a rare presentation of temporal lobe seizures and perform an electroencephalogram and magnetic resonance imaging. The presence of progressive hearing loss or central auditory findings during audiometric testing leads to suspicion of a cerebellopontine angle tumor and the appropriate neuroradiology investigations. When faced with a patient with chronic vestibular symptoms (even including episodic imbalance) and failure to respond to medical therapy, however, one should carry out a neuroradiologic investigation, even in the presence of a completely normal neurological examination. Such patients may have unsuspected multiple cerebral and brainstem infarctions or may be experiencing the late-life onset of multiple sclerosis. Central vestibular disorders, including uncompensated peripheral vestibulopathy, are among the most common causes of chronic dizziness. There is considerable overlap in the conditions causing single recurrent or chronic attacks of dizziness (see Table f 8.6).

Systemic Conditions

Alteration in vestibular function may be suspected in patients who are taking multiple drugs to lessen their vertiginous symptoms. In fact, the drugs often initially used to treat such patients, such as benzodiazepines, may later give rise to systemic effects, including imbalance. The patient's symptoms are usually vague but often present as symptoms of disequilibration or imbalance rather than dizziness. The description of lightheadedness particularly suggests this category of disease and may prompt a more detailed search for postural hypotension occurring minutes after rising or a search for cardiac arrhythmia. Such patients deserve a complete metabolic workup and often consultation with other specialists. Syncope and presyncope are listed as a cause of a single attack of dizziness, but recurrent episodes are common.

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Chapter 19
Hearing Loss and Tinnitus without Dizziness or Vertigo

B$_t$ Todd Troost and Lisa C. Arguello

The diagnosis and management of patients with hearing disorders are the responsibility of a variety of specialists, including the audiologist, the otolaryngologist, and, occasionally, the neurologist. Each may view the problem from a different perspective, but all should work in concert to provide the best possible care. Most neurologists' knowledge of hearing disorders is fragmentary. This chapter provides basic information for understanding the approach to a patient with hearing loss or tinnitus.

HEARING LOSS

In the assessment of hearing impairment, one must remember that dysfunction of the auditory system may be a manifestation of a systemic and possibly life-threatening disorder. Therefore, the examiner must elicit a history of complaints referable to other systems. The examination of the patient, the complaints, and the preliminary audiologic findings determine how inclusive the examination must be and what subsequent tests must be ordered. Be aware that audiologic tests do not always provide an exact diagnosis, Audiologic test data should be used with the neurological, otoneurological, and radiological information for the maximum diagnostic accuracy.

Types of Hearing Loss

Hearing loss can result from a lesion anywhere in the auditory system (Nadol 1993). An abnormality in the outer or middle ear creates a conductive loss of hearing because of inefficient transmission of sound to the inner car system. When the loss of hearing is due to pathology in the cochlea or is along the eighth cranial nerve from the inner ear to the brainstem, the loss is referred to as a *sensorineural* hearing loss. Patients may exhibit both conductive and sensorineural loss, which is known as *mixed* hearing loss. Central hearing loss (or central auditory dysfunction) is present when a lesion exists in the central auditory pathway beyond the eighth cranial nerve, such as the cochlear nucleus in the pons or the primary or association auditory cortex of the temporal lobe.

In addition to these organic types of hearing loss, one should consider functional hearing loss when a patient claims to have a loss but discrepancies in objective test measures or behavior suggest that the loss does not exist, at least to the degree claimed.

Auditory Neuropathy

Individuals with auditory neuropathy (AN), also known as *auditory dyssyncbrotty,* is increasingly recognized (Sininger and Starr 2001). Identification of AN is now readily available by the use of otoacoustic emissions (OAEs) in the test battery. A typical presentation of a patient with AN is that of a variable bilateral hearing loss with test findings as follows:

1. Presence of OAEs that indicate normal outer hair cell function.
2. Presence of cochlear microphonics on auditory brainstem responses. These findings would be consistent with functioning outer hair cells. The cochlear microphonic is differentiated from a neural response by performing one test run with what is termed a *condensation click* and then performing a second test run with what is termed a *rarefaction click* (Sininger and Starr 2001). Hair cell response will reverse with the change in click polarity, whereas the standard neural response is not affected by the change.
3. Absent or elevated acoustic reflexes. Most often children with AN will have speech/language delays and require remediation by a speech pathologist. The patient's own speech will sometimes sound distorted but will not have the typical distortions seen with sensorineural impairment. Noisy backgrounds are particularly difficult with AN because speech is already

Tabic 19.1; Diagnoses of 70 patients with auditory neuropathy

Hereditary (total = 30}	
With peripheral neuropathy	18
Hereditary sensory motor neuropathy	(9)
Olivopontocerebellar	(1)
Friedreich's ataxia	(3)
Spinocerebellar defeneration	(2)
Leukodystrophy	(1)
Unknown	(2)
Without peripheral neuropathy	12
Others (total = 15)	
Immune	1
Postinfectious	2
Hyperbilirubinemia	5
Premature	7
Idiopathic (total = 25)	
Associated diagnoses	
F.hlcrs-Danlos syndrome	I
Gonad dysgenesis	I
Seizures	4
Stevens-Johnson syndrome	I

Source: Modified from Sininger, Y. *&C* Starr, A. 2001, "The neurology of auditory neuropathy," in *Auditory Neuropathy: A New Perspective on Hearing Disorders,* Singular, Toronto, Canada.

distorted. Treatment varies with some functional improvement over time, but those with progressive hearing loss are candidates for cochlear implantation or the use of frequency modulation (FM) systems. **"The** mechanisms underlying AN could be sensory, dendritic, or axonic in nature. Possible sites could include the inner hair cells, the synaptic juncture between the inner hait cells and the auditory nerve, or the auditory nerve itself" (Hood 2002).

AN is an important consideration for neurologists because 25-30% occur in association with hereditary sensory motor neuropathies or spinocerebellar degenerations (Table 19.1).

Examination. A number of audiologic tests provide differential information on the function of the auditory system, and various tests arc grouped to form test battcties. One such grouping can be used to differentiate conductive from sensorineural impairments and may futther help in localizing a sensorineural loss to either the cochlea or the eighth cranial nerve. Other tests ate used to examine auditory deficits of the central auditory sysrem. Still anothct set of tests is designed to detect functional or nonorganic hearing disorders. Although the results from these batteries may be helpful in establishing a diagnosis, differential auditoty measures cannot be used to establish the disease process. The findings from any audiologic study must be integtatcd with the histoty, physical examination, and laboratory tests.

Basic Office Examination of Hearing. Whether or not **the** patient's complaint is one of hearing loss, a basic assessment of auditory function should be part of the neurological examination. The external ear should be inspected with an otoscope to determine the patency of the external ear canal and the integtity of the tympanic membrane. If the external canal is occluded by cerumen, simple tests of heating may be invalidated. Assuming thete is no cerumen in rhe external ear canal, the tympanic membrane should be inspected. The neurologist shouid be able to tecognize an inflamed, bulging, or scarred drum and should note whether there is perforation of rhe tympanic membrane; blood behind the eardrum; or a pulsating blue mass, which may indicate a glomus jugulare tumor. An excellent desctiption of tympanic membrane findings may be found in modern texts of otology {Hughes and Pensak 1997).

The office examination of hearing loss may include tuning fork rests of air and bone conduction. Tuning forks at a frequency of 256 Hz or 128 Hz should not be used because the vibrations they produce by bone conduction may be mistaken for sound; the 512-Hz fork is the lowest useful ftequency. Two standard timing fork tests ate the Weber and the Rinne tests.

Weber Test. The Weber test is based on the principle that signal transmitted by bone conduction is localized to the ear with the greatest conductive deficit or the ear opposite to the one with a M::IMH nn.uial loss, 1 lie test can determine the type of hearing impairment when the two cars arc affected to different degrees. The stem of a vibrating tuning fork is placed on the skull in the midline, and the patient is asked to indicate in which ear the sound is heard. The usual location described is for placement on the forehead, but better locations are the nasal bones or teeth when a stronger bone conduction stimulus is tequircd. In unilateral hearing losses, lateralization to the poorer hearing car indicates an clement of conductive impairment in that ear. lateralization to the better hearing ear suggests a sensorineural problem in the opposite ear.

Rinne Test. The Rinne test is probably the most commonly used tuning fork test, but the name is usually mispronounced; the originatot was Gentian, not French, and the accent is on the first syllable. The Rinne test compares a patient's hearing sensitivity by bone conduction versus air conduction. A person with normal hearing or sensorineural impairment perceives the air-conducted sound as loudet than or the same volume as bone-conducted sound. Proper placement of the tuning fork in each situation is important. When testing by bone conduction, the stem of the fork should be placed firmly on the mastoid, as near to the posterosuperior edge of the ear canal as possible. The stem should not touch the auricle of the external canal, which should be held to the side by the examiner's fingers. Touching the external ear itself could give false results because of vibration of the auricle. When testing by air conduction, the fork is held approximately 2.5 cm lateral to the ttagus. In the Rinne test, when the conduction mechanism is normal in an ear (i.e., in

individuals with normal hearing and with sensorineural hearing impairment), air conduction is heard better than bone conduction because it is a more efficient means of sound transmission. This finding is termed a *positive Rinrte.* Bone conduction is heard better than air conduction when there is a deficit in the conduction mechanism (a *negative Rinne).* When tested by bone conduction, patients should remove their eyeglasses because the earpieces can interfere with proper placement of the tuning fork or give inappropriate conduction or vibratory information. Although tuning fork tests allow the examiner to screen for a conductive versus a sensorineural loss, they do not evaluate the degree of impairment or the effects of that impairment on speech understanding.

Audio logic Assessment. An a ud io I og ic a ss ess m en t com - priscs pure-tone air and bone conduction testing, speech reception threshold, and word recognition measures. The threshold is defined as the lowest intensity, measured in decibels, at which an individual can detect a pure-tone or speech signal. Pure-tone air thresholds arc established for frequencies of 250-8000 Hz. Bone conduction thresholds are measured from 250-4000 Hz. This frequency range is important to the detection and understanding of the speech signal. Hearing is considered normal when threshold sensitivity is 0-25 dB for frequencies of 250-8000 Hz (Figure 19.1). Responses greater than 25 dB are classified by degree as mild, moderate, moderately severe, severe, and profound (Figure 19.2). Responses at 500 Hz, 1000 Hz, and 2000 Hz are averaged to compute the pure-tone average.

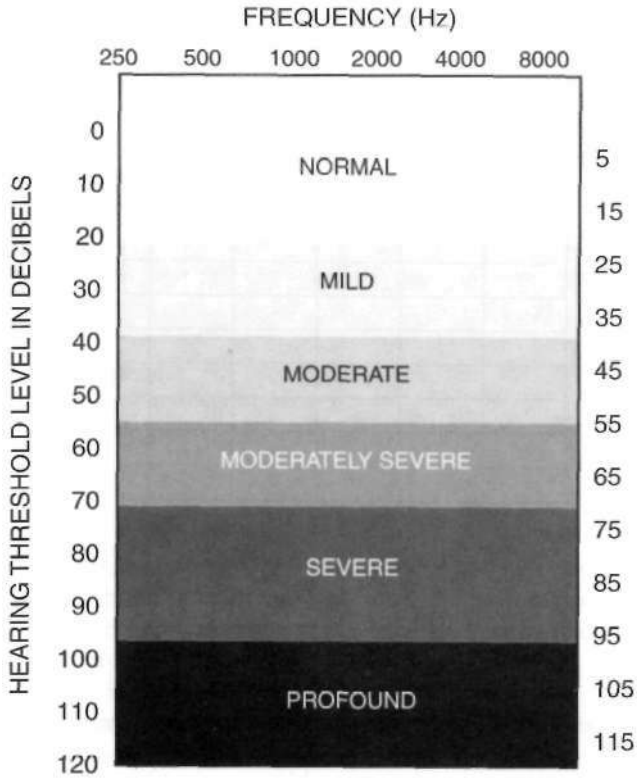


FIGURE 19.2 Classification of degree of hearing loss. (Reprinted with permission from American Spin-li I alienage I tearing Association. 1990, "Guidelines For audiometric symbols," *ASHA* vol. 32, suppl. 2, pp. 25-30.)

In the measurement of bone conduction thresholds, pure-tone signals are transmitted via a bone oscillator, usually placed on the mastoid. This signal directly stimulates the cochlea, bypassing the external and middle ear. The presence of decreased air conduction threshold and normal sensitivity of bone conduction suggests abnormality in the external ear or middle car system (conductive hearing loss) (Figure 19.3),

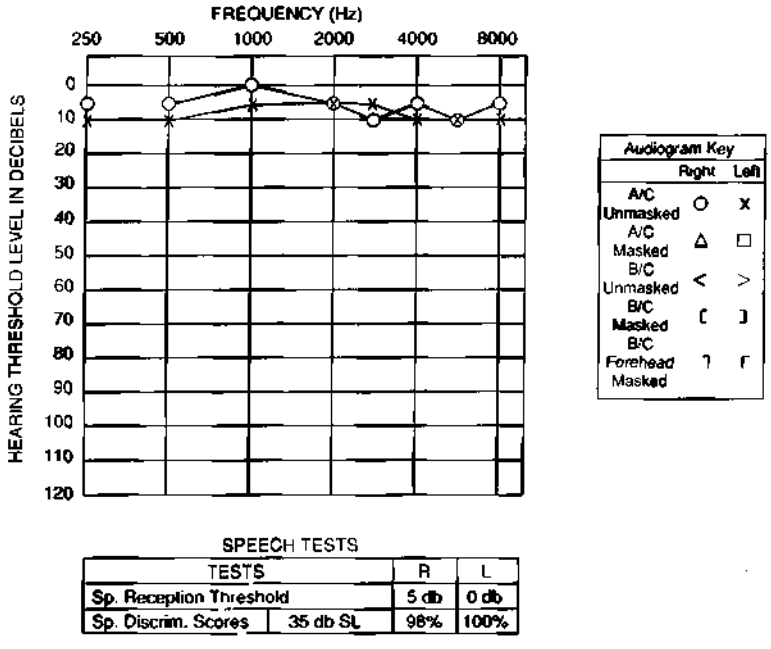
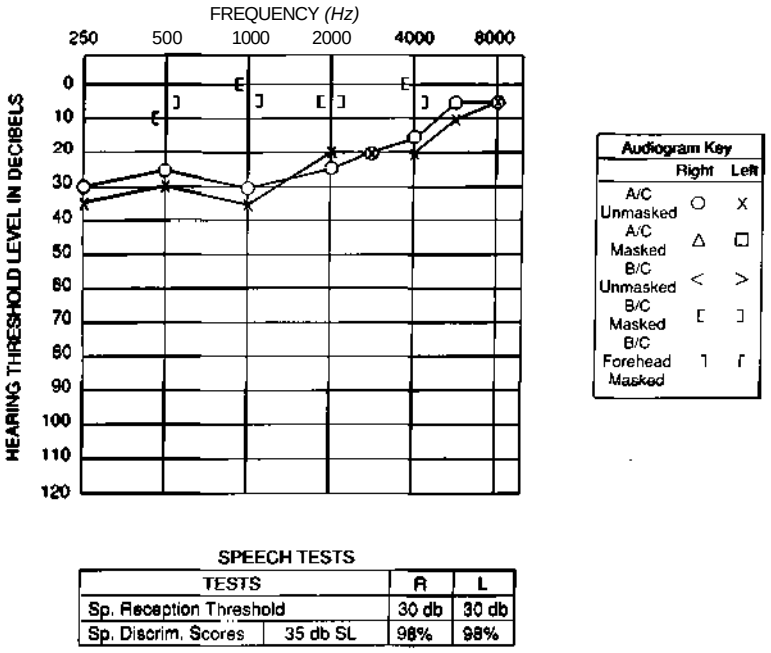


FIGURE 19.1 Normal hearing sensitivity.



SPEECH TESTS

TESTS		R	L
Sp. Reception Threshold		30 db	30 db
Sp. Discrim. Scores	35 db SL	96%	98%

FIGURE 19.3 Pure-tone air and bone conduction (B/C) findings for a conductive hearing loss. (A/C = air conduction; SL = sound level.)

The speech reception threshold is the lowest intensity at which an equally weighted, two-syllable word is understood approximately 50% of the time. The pure-tone average and speech reception threshold should be within 7 dB of each other. Comparing the speech reception threshold and the pure-tone average serves as a check on the validity of the pure-tone thresholds. Large discrepancies between these measures may suggest a functional or nonorganic hearing loss.

Word recognition is used to assess an individual's ability to understand a speech signal. Most commonly, a phonetically balanced word list of 50 one-syllable words is presented to the patient at a sup rath res ho Id level. The patient's score is represented as the number of words correct. Generally, word recognition ability decreases proportionately with an increase of hearing impairment. However, there is an exception in conductive hearing loss in which word recognition ability remains relatively good because the inner ear system is normal. Poor word recognition ability in the presence of relatively good hearing sensitivity may suggest retrocochlear pathology, such as acoustic neuroma, and should be aggressively pursued by the clinician. A more detailed discussion of audiologic tests is provided in Chapter 41.

Immittance Test Battery. Tympanometry, static acoustic immittance, and acoustic reflex threshold measures make up the acoustic immittance test battery. Static acoustic immittance measures the contribution of the middle ear to the immittance of the auditory system. This measure is most useful for the detection of even small perforations of the tympanic membrane. It may also assess the patency of tympanostomy tubes. Tympanometry is a measure of middle ear mobility when air pressure in the external canal is varied. Results are graphically represented with pressure along the X-axis and compliance along the Y-axis. Normal tympanograni measurements have a pressure peak point of ±100 mm H_20.

Static compliance refers to the ease of flow of acoustic energy through the middle ear. Compliance measures are obtained at +200 mm H_20 {first point of compliance, or CI) and again at the point the tympanic membrane is most compliant (second point of compliance, or C2). The point at which the tympanic membrane is most compliant allows maximal transmission of energy through the middle ear cavity. Compliance of the tympanic membrane is derived by subtracting CI from C2. Values less than 0.25 cm^3 of equivalent volume indicate a stiff or noncompliant middle ear system. Values greater than 2.0 cm^3 suggest an overly compliant system. Abnormalities associated with reduced mobility of the tympanic membrane in middle ear structures include otitis media, otosclerosis, and large cholesteatomas. Ossicular chain discontinuity is the most common cause of excessive tympanic membrane mobility. Examples of tympanometry are shown in Figure 19,4, Extremely high equivalent middle ear volume and low static compliance suggest a nonintact tympanic membrane from a perforation or previously placed tympanostomy tube.

The acoustic reflex threshold is the lowest intensity of a pure-tone stimulus needed to elicit a contraction of the stapedius and tensor tympani muscles (sec Chapter 41). The introduction of an intense sound into the ear canal results in a temporary increase in middle ear impedance. This phenomenon occurs bilaterally, but it is typically measured in one ear at a time. Contralateral reflexes are measured by stimulating one ear and measuring the reflex from the other. Ipsilatcral reflexes are measured by stimulating and recording from rhe same ear. Reflexes occur between 70- and 100-dB sound pressure level in normal ears.

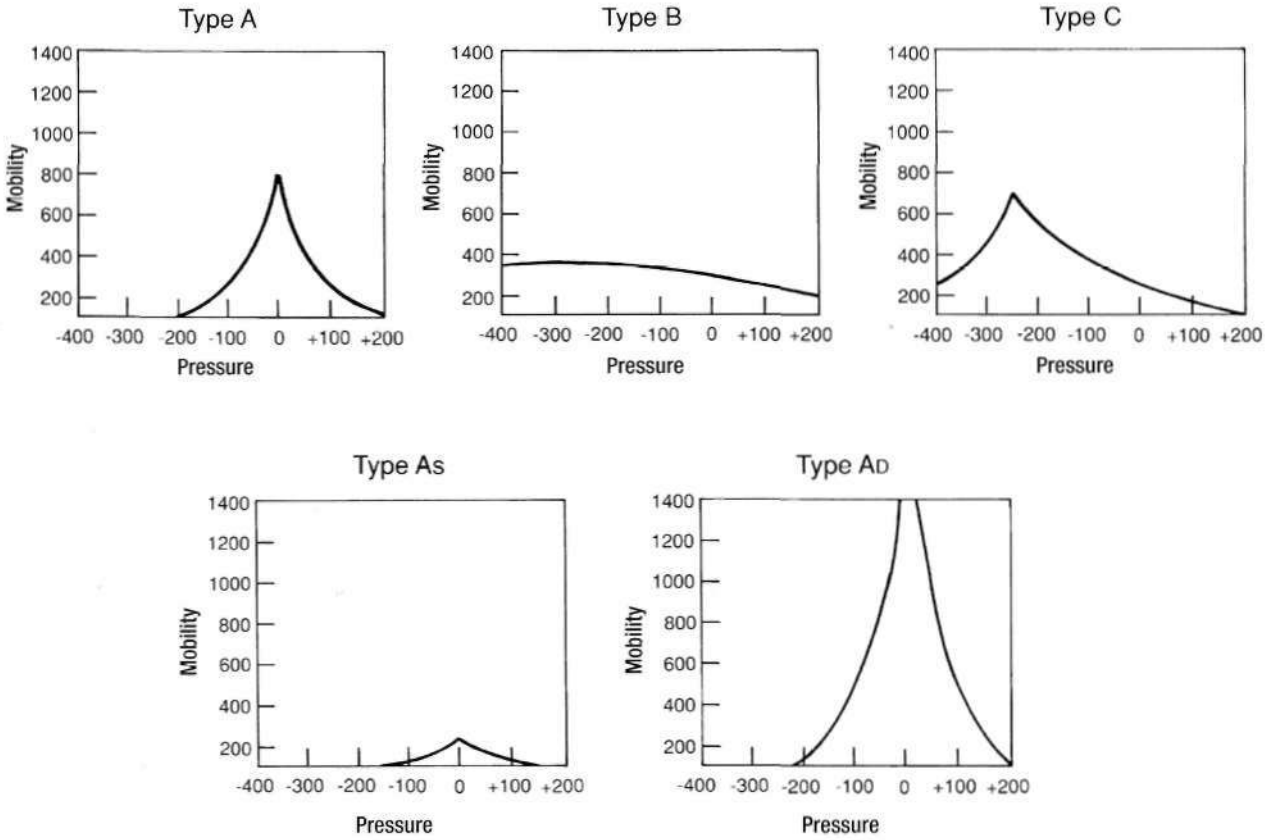


FIGURE 19.4 Tympanometry classifications: Type A represents normal middle ear function. Type A curves have normal mobility and pressures and are typically seen with normal hearing and sensorineural hearing loss with normally functioning middle car systems. Type B represents restricted tympanic membrane mobility. Type B curves have little or no point of maximum mobility and reduced compliance. This curve is typical of a stiff middle ear system, as seen in otitis media and sometimes with cholcstoma. Type C represents significant negative pressure in the middle ear cavity. Type C curves have normal mobility and negative pressure at the point of maximum mobility (negative pressure is considered significant for treatment with greater than -200 mm H^O). Type As represents normal middle ear pressure hut reduced mobility, suggesting limited mobility of the tympanic membrane and middle ear structure. commonly seen in fixation of the ossicular chain. Type An represents normal middle car pressure bur hypermobility. This pattern indicates a flaccid tympanic membrane due to disarticulation of the ossicular chain or scarring of the eardrum.

Middle ear abnormalities or significant sensorineural hearing losses may elevate or obliterate the acoustic reflexes. Retrocochlcar pathology and facial nerve disorders may also affect contralateral and ipsilatcral acoustic reflexes (see Table 41.1).

Ear Reflexes. Because the seventh cranial nerve innervates the stapedial muscle, the acoustic reflex is sometimes helpful in detecting the location of a seventh cranial nerve lesion. If the abnormality of the facial nerve is proximal to the stapedial branch of the facial nerve, facial paralysis results and the acoustic reflex is elevated or absent with ipsilateral and contralateral stimulation by probe on the affected side. If the facial nerve abnormality is distal to the stapedial branch of the facial nerve, facial palsy results, but the acoustic reflexes are normal.

Some neurologists and otolaryngologists monitor acoustic reflexes in patients with Bell's palsy. The reflex is absent at the onset of Bell's palsy and gradually returns as the Bell's palsy improves. There is usually a return of acoustic reflexes several days before the return of any facial nerve function.

Otoacoustic Emissions. OAEs are sounds produced by the outer hair cells of the cochlea in response to an acoustic stimulus. The outer hair cells in the cochlea are not just passive receptors, they actively respond to enhance or amplify incoming sound vibrations from the middle car. A sensitive microphone in the external canal can pick up **the** outer hair cell response. The two most clinically useful types of OAEs are transient evoked OAEs (TEOAEs) and distortion-product OAEs (DPOAEs) (Lonsbury-Martin ct al. 1995).

TEOAEs are almost always present in cars when hearing is better than 30 dB and the middle ear is normal. Significant negative middle ear pressure, wax, fluid, or other middle ear pathology can adversely affect or even eliminate the OAE response. A sensory hearing loss worse than 35 dB does not have a TEOAE because the outer hair cells in the cochlea are damaged. A loss greater than 45-55 dB docs not have a

DPOAE for the same reason. OAEs are most useful as an objective screening tool for infants or children who cannot be tested by traditional audiometry.

Conductive Hearing Loss

Conductive hearing losses occur with pathology in the outer or middle car. Bone conduction thresholds arc normal, but air conduction results suggest a decrease in hearing sensitivity. The patient with a conductive hearing loss tends to have approximately the same loss of sensitivity for sounds of all frequencies. Sometimes hearing is better for the higher frequencies than it is for the lower ones, and occasionally the reverse may be true, but the loss pattern is usually relatively flat across the frequencies (see Figure 19.3). Another symptom of conductive loss is that speech discrimination is relatively unimpaired.

Conductive pathologies affect the tympanogram in various ways (see Figure 19.4). With conductive hearing loss, acoustic reflexes are almost always elevated or absent, and OAEs are usually absent. Frequently, the patient with a conductive loss of hearing complains of tinnitus, which may be localized in one ear, in both ears, or unlegalized in the head. The tinnitus tends to be of relatively low pitch.

Sensorineural Loss

Sensorineural loss occurs with pathology in the inner ear or along the nerve pathway from the inner ear to the brainstem. Hearing loss from cochlear disorders alone is rermed *sensory loss.* There is some disagreement among audiologists, neurologists, and otologists over what is a *retrococblear* problem and what is a *central* problem. For the purposes of this discussion, we define *retrococblear* as an abnormality between the cochlea and the brainstem.

The term *sensorineural* includes both cochlear and retrocochlcar disorders. A pure sensorineural impairment exists when the sound-conducting mechanism (outer and middle ear) is normal in every respect but a disorder is present in the cochlea or auditory nerve. Sensorineural impairment can be congenital or acquired. Congenital sensorineural hearing loss may result from hereditary factors that cause underdevelopment or early degeneration in the auditory nerve, from viral infections in utero, or from birth trauma. Acquired sensorineural hearing loss may be caused by noise exposure, acoustic tumor, head injury, infection, toxic drug effects, vascular disease, autoimmune inner ear disease, or presbycusis.

The patient with a sensorineural impairment may speak with excessive loudness of voice in situations in which a loud voice is inappropriate. The configuration of the audiogram demonstrating a sensorineural hearing loss may vary significantly and in some instances may suggest the cause of the loss. Many people with sensorineural losses experience a hearing loss only in the high frequencies. These individuals have no difficulty understanding speech at normal intensities in a quiet environment because their low-frequency hearing is unimpaired. They do experience difficulty in understanding speech in a noisy environment. Generally, the low frequencies are defined as rhe range of 250-750 llz, middle frequencies as 1000-2000 Hz, and high frequencies as 300O-K0O0 Hz on rhe standard audiogram.

Loudness recruitment is usually associated with sensory loss of cochlear origin, which constitutes the majority of sensorineural losses. Recruitment is an abnormally rapid growth of loudness with an increase in intensity. The recruiting patient with sensory loss cannot hear low-intensity sounds and may just barely hear sounds of moderate intensity, but recruitment may cause louder sounds to be perceived as uncomfortably loud. There is a narrow range between the point of detection of sound and that where sound is uncomfortable.

The patient with sensorineural hearing loss is subject to tinnitus (usually a constant ringing or buzzing), which may be localized in either ear or both ears. In general, the pitch of tinnitus tends to be higher in sensorineural impairment than in conductive impairment.

In sensorineural loss, the audiometric Weber test is expected to lateralize to the better ear. Audiometrically, sensorineural loss is characrerized by overlapping air and hone conduction Thresholds. The tympanogram is typically normal, and acoustic reflexes may be present, elevated, or absent (Chapter 41), With cochlear hearing losses, the degree of hearing loss and recruitment plays a large role in the ability to elicit a reflux. If the patient's hearing loss is less than 60 dB, a reflex can be seen. As the hearing loss increases above this level, a measurable reflex response becomes less and less likely. *Reflex decay* refers to the ability of the facial nerve to sustain a contraction of the stapedial muscles for 10 seconds. Reflex decay is negative with cochlear pathology. TEOAEs are typically present in cochlear pathology if the hearing thresholds are between 0 and 20 dB of hearing loss (dBHL) and are sometimes present when the thresholds range from 20 to 30 dBHL. DPOAEs arc usually present if the hearing threshold is between 0 and *iS* dBHL and are sometimes present when the thresholds are 30-50 dBHL. The audiometric findings for a typical sensorineural hearing loss are displayed in Figure 19.5.

Contrary to a commonly held misconception, individuals with sensorineural hearing loss may be helped by the use of hearing aids. An array of technologies are available for persons with different degrees and configurations of hearing loss. Digital hearing aid technology provides a broader, clearer auditory signal than traditional hearing aids, which merely amplify the sound. Many digital and some programmable hearing aids use multimicrophone Technology. Hearing aid users are now often able to use different computerized programs in their hearing aid, depending on the nature of the acoustic environment.

Other technology includes implantable hearing aids for individuals with severe sensorineural hearing loss. There

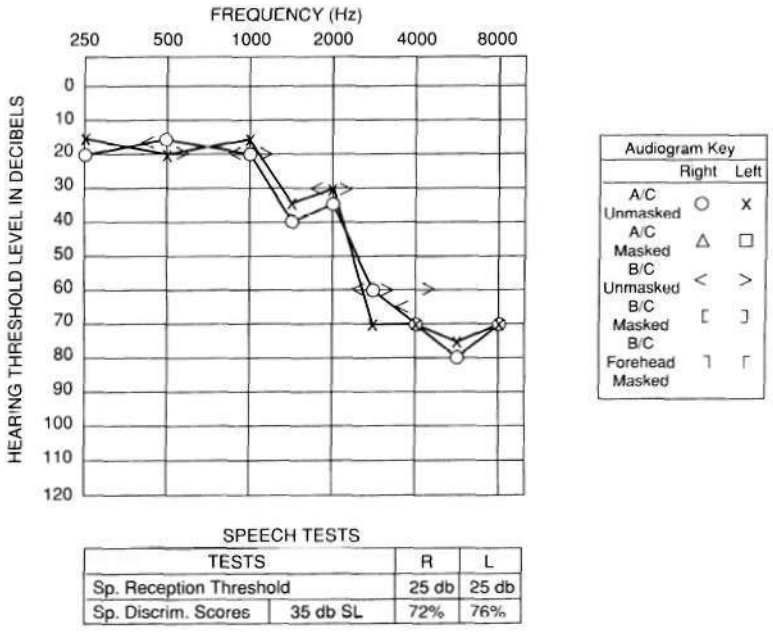


FIGURE 19.5 Pure-tone air and bone conduction (B/C) findings for a sensorineural hearing loss. (A/C = air conduction; SL = sound level.)

are bone-anchored hearing aids for individuals with conductive hearing loss. Frequency-transposition hearing aids are used for those with little or no mid- to high-frequency hearing. Cochlear implants are available for those with severe to profound bilateral hearing loss with extremely poor word recognition.

Mixed Loss

A mixed hearing loss consists of a conductive and a sensorineural component in the same ear. The patient's behavior has attributes of both conductive and sensorineural disorders. Causes of mixed hearing loss may be any combination of the conditions described earlier for conductive and sensorineural hearing loss. The conductive component of the mixed hearing loss may be corrected by successful treatment, but the sensorineural component is not reversible. Examples of successful treatment include tympanostomy tubes for fluid accumulation or stapedectomy for otosclerosis. The pure-tone audiometric pattern for a mixed hearing loss is displayed in Figure 19.6. With a mixed loss, both air and bone conduction thresholds are elevated, but bone conduction thresholds are better than air conduction thresholds. The difference between the two thresholds is referred to as the *air-bone gap* and represents the amount of conductive loss.

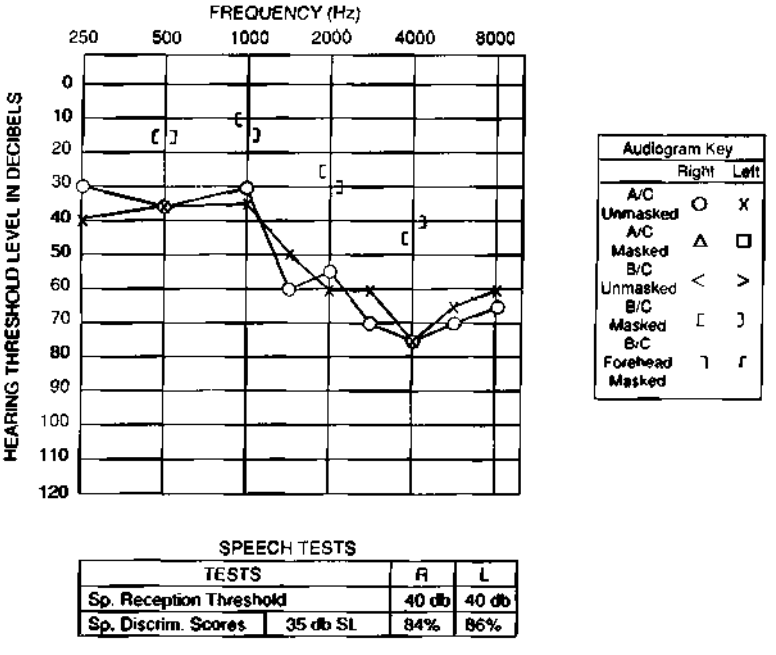


FIGURE 19.6 Pure-tone air and bone conduction (B/C) findings for mixed hearing loss. (A/C = air conduction; SL = sound level.)

Sensory Vctsus Neural Lesions

The problems of differentiating cochlear dysfunction from eighth cranial nerve lesions have received major emphasis. The neurologist's interest in sensorineural hearing loss pertains to the possibility of a cerebellopontine angle tumor. Although many referrals for audiometric evaluation are made for this reason, even the more sophisticated special auditory tests cannot determine the specific pathology underlying the disorder. Similarly, magnetic resonance imaging may locate the presence of an abnormality (Fitzgerald and Mark 1998), hut it does not necessarily define the nature of the pathology. Audiometric tests, however, highlight patterns of auditory behavior that are generally associated with cochlear or neural involvement.

Routine pure-tone and speech testing can yield valuable information on the site of lesion during the initial phase of the differential audiologic study. For example, a pure-tone configuration that often occurs in patients with a presumptive diagnosis of Meniere's disease (a cochlear disorder) is a unilateral hearing loss most pronounced in the low frequencies. In sharp contrast, patients with eighth cranial nerve lesions often have a unilateral hearing impairment most evident in the high frequencies and with poor speech discrimination. Although such generalizations may describe a substantial number of cases falling into these two categories, numerous exceptions are encountered.

OAEs may prove helpful in differentiating sensory from neural lesions, OAEs test the prcncural function of the auditory system. The presence of a TEOAE with hearing loss greater than 30-35 dB suggests an intact cochlea and therefore a retrocochlear cause. Caution must be used in interptetation, however, when a tumor reaches such a size that it impinges on the cochlear blood supply, thereby affecting the emission response. Thus absence of OAEs does not necessarily signify that the loss is purely cochlear. Acoustic reflexes are usually elevated or absent with pathology of the eighth cranial nerve if the hearing loss is 30 dB or worse. In contrast, a cochlear hearing loss of 60 dB or less usually has a reflex. Reflex decay is usually present with eighth cranial nerve involvement. If there is an intra-axial brainstem tumor or lesion, the ipsilateral reflexes are usually present and the contralateral reflexes absent. If a brainstem tumor or lesion above the level of the pons is present, the reflexes are usually normal.

Central Auditory Disorders

Lesions within the central auditory system are difficult to detect or localize. Indeed, many central auditory dysfunctions cannot be demonstrated by conventional audiologic measurements. Total removal of one hemisphere of the brain in humans docs not result in any major change of auditory sensitivity in either ear. Measures such as acoustic reflex testing, acoustic reflex decay, and speech discrimination at high intensity levels must be used to distinguish between eighth cranial nerve, extra-axial, and intra-axial brainstem dysfunction. The auditory evoked response and, particularly, magnetic resonance imaging (sec Chapter 41) are very useful in making such a differentiation.

TINNITUS

Ear noise and head noise are the most common complaints presented to audiologists and otolaryngologists, and often to the neurologist. As much as .32% of the adult population has tinnitus, with 20% rating their condition as severe. Tinnitus may be considered a significant symptom when its intensity so overrides normal environmental sounds that it invades consciousness. The patient experiencing tinnitus may describe the sound as ringing, roaring, hissing, whistling, chirping, rustling, clicking, or buzzing. Although most patients report the presence of tinnitus as constant, others report it as intermittent, fluctuating, or pulsating. Tinnitus may be perceived as a high- or a low-pitched tone, a band of muse, or some combination of such sounds,

The perceived loudness of tinnitus in any patient may be sufficiently intense to be disquieting. Most patients with sensorineural hearing loss report tinnitus as a high-frequency tone, but tinnitus associated with conductive hearing loss tends to be low in frequency. In sensorineural loss, the pitch of the tinnitus is usually located in the region of maximal hearing loss. However, knowledge of the pitch of the tinnitus is of little diagnostic benefit other than allowing for the gross distinction between conductive versus neural pathology.

Most patients with tinnitus have concomitant hearing loss, which may be either conductive or sensorineural. No more than 8% of patients with tinnitus have audiometrically normal hearing sensitivity. Tinnitus may precede or follow the onset of a loss in hearing, or the two may occur simultaneously.

Tinnitus is a symptom of an underlying disease or specific lesion when it is perceived above the intensity levels of environmental sounds. Tinnitus may be an early symptom of a tumor in the internal auditory meatus or in the cerebellopontine angle, a glomus tumor, or a vascular abnormality in the temporal hone or skull. Because tinnitus may be a characteristic symptom of a number of disorders, a complete medical and audiological evaluation of the patient with tinnitus is an important initial step in the management process.

Classification

Subjective tinnitus is an auditory sensation heard only by the patient. It may he present in one or both ears or localized within the head. For most patients, tinnitus is a subjective sensation. Although this type of tinnitus can

result from a lesion involving the external ear canal, tympanic membrane, ossicles, cochlea, auditory nerve, brainstem, or cortex, the most common cause is cochlear disease. Tinnitus associated with Meniere's disease is often low pitched and continuous and is described as a hollow seashell sound or very loud roaring. Tinnitus with otosclerosis is also low pitched, is described as a buzzing or roaring sound, and may be continuous or intermittent. Continuous bilateral high-pitched tinnitus often accompanies chronic noise-induced hearing loss, presbycusis, and hearing loss due to ototoxic drugs. A number of drugs, such as aminoglycosides, quinidinc, salicylates, indomethacin, catbamazepine, propranolol, i.-dopa, aminophyllinc, and caffeine, may produce tinnitus with or without associated hearing loss.

Objective tinnitus is less common than subjective tinnitus. It is perceived by the examiner and the patient. Objective tinnitus may be vascular (an arteriovenous malformation or fistula) or mechanical in origin. Objective mechanical tinnitus is due to abnormal muscular contraction of the nasopharynx or middle ear, as may occur in palatal myoclonus. Objective tinnitus of vascular origin may also be a referred bruit from stenosis in the carotid or vertebrobasilar system.

Tinnitus may be classified as mild, moderate, or severe. Mild tinnitus is usually noticed only in quiet environments or at bedtime. It is usually not very disturbing, and the patient can easily be distracted from the tinnitus by other stimuli. Moderate tinnitus is more intense and is constantly present; the patient is conscious of the tinnitus when attempting to concentrate or when trying to sleep. Severe tinnitus may disable individuals to the extent ih.it thov cannot concentrate on anything other than the tinnitus itself,

Evaluation and Management

The complete evaluation of the patient with tinnitus should be approached from a multidisciplinary perspective (Ruth and Hamill-Ruth 2001). The patient with tinnitus, regardless of location, type, or severity, must first have a thorough otological and audiological examination. If there arc accompanying symptoms, a complete neurological examination may be appropriate. The patient with an isolated symptom of a persistent, unexplained tinnitus should receive follow-up examinations at definite intervals when initial medical, otologic, and neurological studies reveal no evidence of disease.

Otologic management is indicated when a specific otologic cause for the tinnitus is identified. When a specific lesion or disease process is not identifiable, there is no effective surgery or medical therapy for tinnitus.

Research on the effectiveness of pharmacologic therapy for tinnitus involves medications, such as carbamazepine, and intravenous lidocaine or barbiturates. There are potentially serious side effects that limit their usefulness. AntianMctv drugs such as diazepam and alprazolam, in low doses, or antidepressants such as amitriptyline may prove effective in tinnitus management.

Masking

The use of masking as a management tool in the treatment of the patient with tinnitus has met with mixed success over the years. Tinnitus maskers are designed to provide relief to the patient with tinnitus by introducing an external masking sound into the affected ear or ears, thereby minimizing or eliminating the perception of the tinnitus. The actual efficacy of tinnitus maskers is probably less than 30%. A hearing aid may be beneficial by addressing the primary bearing problem and providing relief to some individuals with tinnitus by masking the tinnitus itself.

Biofeedback

Many patients with tinnitus have high levels of anxiety, tension, or other symptoms of chronic stress. There is a significant correlation between tinnitus and tension. Biofeedback may be effective in the relief of tinnitus or the associated annoyance produced by it.

Counseling

The need for effective counseling is an important aspect of tinnitus management. Many patients are frightened by the presence of tinnitus and need a clear explanation of the disorder, coupled with firm reassurance from both the neurologist and the audiologist.

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Chapter 20
Disturbances of Taste and Smell

Pasquale F. Finelli and Robert G. Mair

Taste and smell rely on chemical stimuli to excite their receptors—hence the designation *chcmosensory system.* The two senses arc closely relared: Their combination produces the sensation of flavor, and dysfunction in one is often perceived as an abnormality in the other. Disorders of the chemosensory system, though common, may he ignored by the patient as insignificant or downplayed by the physician who views testing as imprecise, time consuming, and cumbersome. Nevertheless, accurate diagnosis is essential because these disorders may herald a serious illness or affect the patient's life in areas of nutrition, satisfaction in eating, personal hygiene, and livelihood {as in the case of chefs, food handlers, and perfumers). They also pose the dangers inherent in the inability to recognize spoiled food or the presence of natutal gas and smoke.

SMELL (OLFACTION)

Pathophysiology

In humans, there are two well-characterized nasal chemosensory systems: the free nerve endings of the trigeminal nerve and the sensory receptors of the olfactory system. A vomeronasal organ is located along the anterior portion of the nasal septum about 1 mm above the nasal floor (Meredith 2001), but little is known about the organ's function in humans. The free nerve endings of the trigeminal system innervate the walls of the nasal passages and respond nonselectively to a large variety of volatile chemical substances. Human psychophysical studies indicate that stimulation of the trigeminal nerve contributes the sensation of general nasal irritability that is provoked by high concentrations of most odorants. Olfactory receptors respond to chemical stimuli at lower concentrations and with greater selectivity than the trigeminal endings do and are responsible for distinguishing among odorous substances. In cases of total anosmia, the capacity to distinguish odors is lost, but the response to nasal irritation is generally preserved. Thus cases of malingering occasionally can be exposed by comparing responses to odorants that differ in their propensity to stimulate trigeminal nerve endings.

The olfactory receptor cell is a bipolar sensory neuron having a dendritic knob extending into the mucous lining of the nasal cavity and a thin unmyelinated axon that travels in bundles through the cribriform plate into the olfactory bulb (Figure 20.1). The dendritic knobs bear cilia, wherein odorant transduction occurs. The receptor neurons have a limited life span, averaging 30 days, and are replaced by newly formed cells that differentiate as they migrate from the basement membrane toward the surface of the sensory epithelium. The plasticity of the receptor neuron is clinically important fot two reasons: (1) Treatments that affect cell division (radiation, antiproliferative agents) can disrupt olfactory receptor function by interfering with the replacement of degenerate neurons, and (2) under some circumstances, receptor function can be restored by tissue regeneration. Ciliary regrowth occurs within days, but months are required for neural regeneration.

The axons of the first cranial (olfactory) nerve terminate within the glomeruli of the olfactory bulb, where they form synaptic contacts with inter neurons that have processes restricted to the bulb and with output neurons (mitral and internal tufted cells) that contribute axons to the lateral olfactory tract. The olfactory nerve is potentially important as a pathway for environmental toxins or viruses to enter the brain. The olfactory bulb provides a direct pathway from the periphery to important cholinergic and adrenergic systems implicated in the etiology of dementing diseases.

Axons of the olfactory tract terminate in primitive cortical areas, including piriform cortex and adjacent areas of uncus, hippocampal gyrus, amygdaloid complex, and entorhinal cortex. These and other areas of the frontal cortex and cingulate gyrus, not previously associated with processing olfactory information, are activated by olfactory stimuli on functional magnetic resonance imaging (fMRI) (Levy et al. 1997). Patients with hypos mi a who are exposed

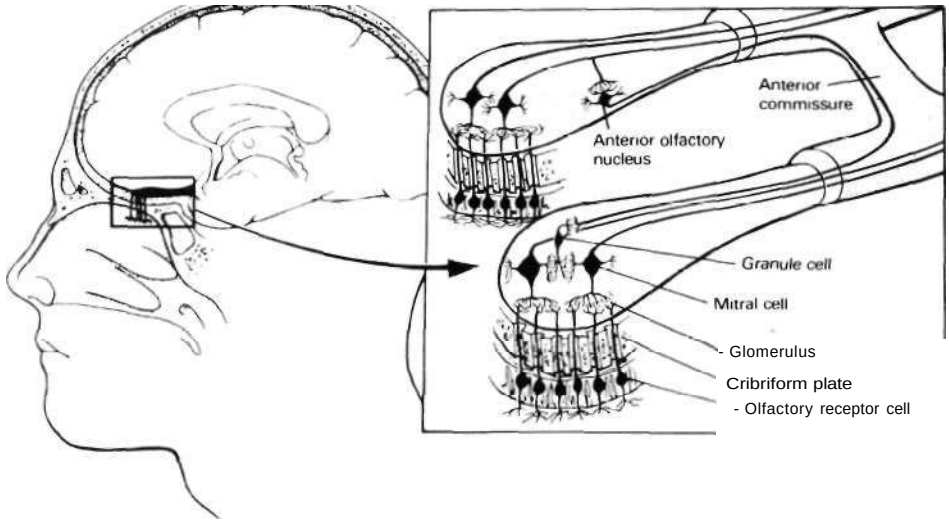

FIGURE 20.1 Olfactory nerve and bulb connections. Within the glomerulus, the olfactory receptor neuron terminals make synaptic contacts onto the dendritic branches of the mitral cells. Deep within these layers are the granule cells, whose main dendrites make synaptic contact with the secondary dendrites of the mitral cells. The mitral cells project axonal branches to the anterior olfactory nucleus, which is made up of cells in the posterior olfactory bulb. The pyramidal cells of the anterior olfactory nucleus project their main axons, after passing through the anterior commissure, to synapse with the granule cells in the contralateral olfactory bulb. The output of the bulb is earned by the axons of the mitral cells via the olfactory tract and the olfactory striae to the primary olfactory cortex. (Adapted with permission from Otroson, D. 1983, *Physiology of the Nervous System,* Oxford University Press, Oxford, England.)

to olfactory stimuli exhibit significantly less brain activation on fMRI than individuals with normal smell acuity. After theophylline treatment in patients with hyposmia, there is increased brain activation on fMRI in response to odors (Levy et al. 1998). Also, olfactory stimulation increases cerebral blood flow in the region of the piriform cortex. Temporal lobectomies affecting the piriform cortex disrupt odor identification, as measured by the University of Pennsylvania Smell Identification Test (UPS1T), and impair odor recognition memory while sparing the ability to detect odorants (Jones-Gotman et al. 1997). In humans, olfactory auras may represent activation of the uncus or amygdala by seizures.

Clinical Evaluation of Smell

Olfactory discrimination can be disrupted by (1) nasal obstructions that prevent volatile substances from reaching the receptor epithelium (transport olfactory loss), (2) impairment of receptor or olfactory nerve function (sensory olfactory loss}, and (3) pathologic processes affecting central pathways from the bulb to the primary olfactory cortex, medial dorsal thalamic nucleus, and orbitofrontal neocortex (neural olfactory loss). The second and third processes are designated *neurogenic.*

A primary objective in assessing impaired sense of smell is to distinguish an intranasal from a neurogenic cause. Transport olfactory loss can be produced by viral upper respiratory tract infection, rhinitis, sinusitis, polyps, neoplasms, and abnormalities in mucus secretion. There is loss of or decreased ability to detect odors (anosmia or hyposmia), distortions of normal smells (parosmia or dysosmia), increased sensitivity to some or all odorants (hyperosmia), or impaired ability to discriminate among different odors. Sensory olfactory loss produces similar symptoms and is caused by direct olfactory nerve damage (closed-head injury, viral infection, toxic substances) or impairment of normal receptor cell turnover (radiation or antiproliferative drug therapy). Neural olfactory loss can impair discrimination without producing anosmia,

Unilateral loss of smell is not recognized by the patient and, when found on examination, can be a useful sign of a focal neurogenic lesion. Such patients, or those complaining of loss of smell, should be asked about a history of head trauma, recent upper respiratory tract infection, drug use (both prescribed and abused), systemic illness, occupational exposure to toxins, dental procedures and prostheses, smoking and alcohol history, seizure disorder, radiation therapy, and pending litigation (loss of smell is a compensable disorder). System review should include headache, vision changes, nosebleeds, nasal obstruction, menstrual history, decline in intellectual capacity, and psychiatric disturbances, including mood changes, such as depression. Physical examination, in addition to taste and smell testing, should evaluate the ears, nose, mouth, oronasopharynx, and cranial nerves (specifically, decreased visual acuity, impaired color vision, papilledema, optic atrophy, and ocular motility abnormality). Mental status evaluation for evidence of dementia and depression is important.

In clinical practice, examination of odor discrimination or identification is sufficient to screen for deficits in

transport, sensory, and neural olfactory functions. Traditionally, the sense of smell is tested by having the patient sniff a familiar odoriferous substance (small bottle of coffee, oil of cloves, oil of peppermint) held in turn beneath each nostril while the other is occluded by a finger. Suggestion is minimized by having the patient keep the eyes closed and indicating that the bottle may or may not have something in it. If the patient detects an odor, he or she is then asked to identify the smell. Appreciation of an odor, despite the inability to name it, excludes anosmia. Hysterical patients may demonstrate unilateral anosmia on the side of an alleged neurological deficit. A malingerer can be detected by testing with ammonia, which stimulates the trigeminal nerve; if the patient denies noticing the stimulus, it is likely that the anosmia is false.

The UPSIT, which uses microencapsulated odorants (the so-called *scratch-and-snifftest),* consists of 40 odorants with a forced choice of one of four alternative responses for each item. The UPSIT is practical, easily administered, and reliable and is able to identify patients with a wide variety of olfactory disorders, including total and partial anosmia and malingering.

The extent of the laboratory investigation depends on the history and physical examination. If no obvious cause can be identified, appropriate studies for an underlying systemic illness should include complete blood cell count, routine blood chemistries, serum vitamin B_{125} thyroid function tests, glucose, syphilis serology, imaging examination of the skull and sinuses, and an electroencephalogram. A formal otorhinolaryngologic evaluation is essential to exclude local nasal disorders. If a cause is still not evident and the condition persists, magnetic resonance imaging (MRI) of the head and paranasal sinuses is needed.

Disease Entities

The causes of smell disturbances are diverse (Table 20.1), but nasal and paranasal sinus disease disorders that follow upper respiratory tract infections, head trauma, and idiopathic conditions account for more than 85% of the total (Table 20.2). The high frequency of nasal and parasinus disease causing anosmia and hyposmia underscores the need for thorough otorhinolaryngologic evaluation. Although intracranial causes (excluding head trauma and intracranial surgery) are rarely responsible for loss of smell, they result in the greatest morbidity if not diagnosed.

Olfactory Groove Meningioma

Anosmia may be the first symptom of an olfactory groove meningioma. In one scries of *19* patients with an olfactory groove meningioma in whom smell could be tested, anosmia was bilateral in 26 and unilateral in 3, Although most such patients mentioned this complaint to a physician, anosmia alone was never the cause of subsequent diagnosis in this series. The most egregious error in dealing with a chemosensory disturbance is the failure to capitalize on the symptom of anosmia as the sole or principal feature of an olfactory groove meningioma. This diagnosable and treatable condition, if not detected, frequently enlarges and causes seizures, vision loss, and dementia. Headache is present in most patients. The importance of imaging studies in this condition cannot be overemphasized. MRI should he performed in all patients in whom loss of sense of smell cannot be explained by head injury, other disease, or surgical procedure of the olfactory region. Viral infection should he a diagnosis of exclusion for patients with permanent anosmia.

Head Trauma

Loss of smell from head trauma may result from damage to the olfactory nerve as it enters **the** skull at the cribriform plate of the ethmoid bone, damage to the olfactory bulb, and possibly cerebral cortical injury. Shearing forces, fracture of the anterior fossa, and direct contusion are the mechanisms most commonly responsible. Most such injuries are to the occipital or frontal areas and are associated with motor vehicle accidents. The frequency of smell dysfunction after head trauma is 10% to 20% and is proportional to the severity of the injury. Anosmia and hyposmia after head injury may be unilateral or bilateral, transient or permanent, and with or without fracture at the base of the skull in the anterior fossa. MRI changes are present in 88% of patients, predominantly in the olfactory bulbs and tracts of the inferior frontal lobes (Yousem et al. 1996b). Recovery of smell occurs in up to 30-40% of patients after the head injury but is unlikely if the loss of smell persists for more than 1 year after injury.

Aging

Olfactory changes due to aging include reduced sensitivity, intensity, identification, and discrimination. These may relate to problems at the receptor or neuronal level, to associated disease states, to pharmacologic agents, and to changes in hormonal and neurotransmitter levels. Age-related deficits can alter food choices and subsequently exacerbate disease states and impair nutritional status and immunity. Use of flavor-enhanced food can help to maintain appetite and food enjoyment (Schiffman 1997).

Other Causes

Impaired odor detection and discrimination occur in Parkinson's disease (PD) and Alzheimer's disease. Patients with Korsakoff's psychosis retain a normal capacity to detect odors presented at threshold concentrations and yet exhibit a consistent inability to discriminate between odorants or to perform the UPSIT. Similarly, surgical

Table 20.1: Smell and taste dysfunction

- Tumors
  - Intracranial
  - Meningioma, olfactory groove S
  - Glioma
    - frontal lobe S
    - Temporal lobe S
    - Cerebellum Ti
    - Pituitary S
    - Metastatic S
  - Intranasal
    - Papilloma S
    - Adenoma S
    - Squamous cell carcinoma S
    - Esthesioneuroepithelioma S
  - Systemic cancer T
  - Cholesteatoma T
  - Jugular foramen T
- Vascular
  - Aneurysm, anterior cerebral S
  - Aneurysm, anterior communicating S
  - Subarachnoid hemorrhage S
  - Hemorrhage, pontine T
  - Carotid artery dissection Td
- Infections, inflammation, granulomatous
  - Creutzfeldt-Jakob disease S, T, Ds
  - Encephalitis, viral S, T
  - Idiopathic midline granuloma S, T
  - Syphilis S
  - Meningitis S
  - Coryza S
  - Rhinitis, allergic/bacterial S
  - Sinusitis S
  - Bronchial asthma S
  - Ozena S, P
  - Hepatitis, acute viral S
  - Influenza S,T
  - Sjogren's syndrome S, T
  - I eprosy S
  - Sarcoid S
  - Dengue fever S
  - Gingivitis T
  - lVriodotiritis T
  - Sialadenitis T
  - Clowns, lvk'Ti'rijl/limg.il I
  - Middle car infection T
  - Guillain-Barrc syndrome
- Systemic illness
  - Diabetes mellitus S, T
  - Refsum's disease S
  - Pager's disease S
  - Pseudohypoparathyroidism S, T
  - Cystic fibrosis S, T
  - Adrenal insufficiency T
  - Cirrhosis S, T
  - Thermal burns T
  - Renal failure S, T
  - Familial dysautonomia T
  - Congenital adrenal hyperplasia T
  - Panhypopituitarism T
  - Hypertension T
  - Cushing's syndrome S, T
  - Hypothyroidism S, T
  - Gonadal dysgenesis (Turner's syndrome) S, T
  - Primary amenorrhea S
  - Korsakoff's psychosis Ds
  - Alcohol withdrawal OH
  - Cretinism T
  - Temporal arteritis S, T
  - Granulomatous angiitis S
- Traumatic
  - Olfactory nerve, olfactory bulb S, T, P
  - Chorda tympani nerve T
  - Lingual nerve T
  - Glossopharyngeal nerve T
  - Cerebral cortex S, T, Ds
- Epileptic
  - Uncinate seizures OH, GH
- Psychiatric
  - Depression P, OH, T
  - Schizophrenia GH, OH, T
  - Hysteria S
  - Malingering S
- Drugs
  - See Table 20.3
- Surgical intervention or iatrogenic
  - Thalamotomy, bilateral T
  - Rhinoplasty S
  - Laryngectomy T
  - Intracranial surgery S
  - Radiation therapy S, T
  - Middle car surgery T
  - Orotracheal intubation T
  - Chorda tympani section T
  - I IUIHHILIUM'. [k
- Deficiency states
  - Niacin (vitamin Bj) T
  - Vitamin A T
  - Vitamin B^ S
  - Zinc S, T
- Degenerative
  - Lewy body disease S
  - Parkinson's disease S, Ds
  - Alzheimer's disease S, OH
  - Multiple sclerosis S, T
  - Huntington's chorea Ds
  - Motor neuron disease S
  - Wolfram's syndrome S
- (>!igiTiii,il or hired irarv
  - Kallmann's syndrome S
  - Albinism S
  - I'iimiluil S
- Developmental
  - Facial hypoplasia T
- Other
  - Idiopathic S
  - Bell's palsy T
  - Raeder's paratrigeminal neuralgia T
  - Smoking S, T
  - Dentures T
  - Pregnancy S, T
  - Inhaled toxic chemicals S
  - Hydrocephalus, obstructive S
  - Aging S, T, Ds
  - High-altitude sickness T
  - Ciguatera fish poisoning Td

*Also asymptomatic relatives.
Ds = discrimination decreased for smells; GH = gustatory hallucination; OH = olfactory hallucination; P = parosmia; S = smell decreased or absent; T = taste decreased or absent; Td = taste distorted; Ti = taste increased,

removal of the parts of the orbitofrontal cortex that receive projections from medial dorsal thalamic nucleus produces a comparable deficit. In patients with PD, there is no correlation between degree of olfactory impairment and age, duration of disease, disease severity, cognitive impairment, and dopaminergic or cholinergic treatment. Hyposmia in asymptomatic relatives of patients with PD suggests subclinical dopamine dysfunction (Bcrendse et al. 2001). Normal olfactory function in progressive supranuclear palsy and benign essential tremor supports the distinctness of these disorders from PD, Other studies in PD demonstrate abnormal olfactory evoked potentials and Lewy bodies on pathologic examination of the olfactory bulb, particularly in the anterior olfactory nucleus. As with idiopathic PD, familial PD is also associated with olfactory impairment, and [his heritable detect occurs independent of the parkinsonian phenotype (Markopoulou et al. 1997). Significant neurofibrillary tangle formation and cell loss in the anterior olfactory nuclei occur in Alzheimer's disease, along with reduced choline acety[transferase activity in the olfactory tubercle. Olfactory impairment is also present in other neurodegenerative conditions, such as motor neuron disease, Lewy body disease, Huntington's chorea, granulomatous angiitis of the central nervous system, idiopathic midline granuloma, Wolfram's syndrome, and hypogonadotropic hypogonadism {Kallmann's syndrome).

Table 20.2; Causes of smell disturbance

Cause	*Patients affected (%)*
Nasal or paranasal sinus disease	15
Idiopathic	22
Post-upper respiratory tract infection	26
Head trauma	I 8
Miscellaneous	I 5
Postexposure (environmental toxins, noxious vapors, metals)	2
Dental	2
MfdiLiilion induced	2

Source: Adapted with permission from Deems, D. A., Doty, R. L., Settle, R. G., et al. 1991, "Smell and taste disorders: A study of 750 patients from the University of Pennsylvania Smell and Taste Center," *Arch Otolaryngol Head Neck Surg,* vol. 117, pp. 519-528.

In patients with reduced or no sense of smell since birth, there is absence or hypoplasia of olfactory bulbs and tracts on MRI; thus congenital anosmia or hypoplasia may be an olfactory bulb-olfactory tract phenomenon rather than a cerebral process (Yousem et al. 1996a).

Olfactory dysfunction, reported in almost 40% of patients with multiple sclerosis, correlated with the number of demyelinating plaques on MRI involving areas of olfaction in the inferior frontal and temporal lobe regions (Doty et al. 1997), An increased sense of smell, *hyperosmia,* is uncommon and may occur with depression and exposure to toxic vapors.

Parosmia, the distortion of normal smell, may reflect an intracranial disease, such as a temporal lobe seizure or a tumor, olfactory bulb injury from rrauma, depression, or a local nasopharyngeal condition, such as sinusitis. Approximately 75% of patients with parosmia have associated hyposmia or anosmia.

Olfactory hallucinations occur in association with Alzheimer's disease, depression, schizophrenia, alcohol withdrawal, and uncinare seizures. In seizures, the olfactory auras are characteristically unpleasant or foul and rarely, if ever, appear as isolated epileptic events. One study, however, showed the olfactory sensation was unpleasant in only 7 of 13 patients; tumor was the most common etiology (10/13 patients), most likely involving the amygdala, with mesial temporal sclerosis a rare cause (Acharya V, Acharya J, and I.udcrs 1998). Cigarette smoking, a variety of drugs (both prescribed and recreational), radiation therapy, and hemodialysis, as well as environmental and industrial toxins, cause disturbances of smell (sec Table 20,2). Abnormalities of taste and smell may be an early manifestation of temporal arteritis.

TASTE

In humans, the gustatory system is responsible for the perception of sweet, salty, bitter, and sour. Disturbances of taste arc far less common than disturbances of smell. Although patients with chemosensory disorders often have complaints that food no longer has any taste, most such patients have olfactory dysfunction with normal taste. Disorders of taste are characterized as absence of taste (ageusia), diminished sensitivity (hypogeusia), increased sensitivity to some or all taste qualities (hypcrgeusia), distortion of normal taste (dysgeusia or parageusia), and gustatory hallucinations.

Pathophysiology

Gustatory receptor cells are clustered in taste buds, which are located in the papillae on the surface of the tongue and, to a lesser extent, at the back of the mouth and pharynx. Taste buds are innervated by sensory fibers of the chorda tympani and greater superficial petrosal bundles of the facial nerve, the glossopharyngeal nerve, and the superior laryngeal branch of the vagus nerve. Receptor cells have a limited life span and undergo constant replacement. Unlike the olfactory system, taste receptor cells lack axons; thus their replacement does not involve regenerative processes within the nervous system.

Taste afferent fibers from the anterior two thirds of the tongue course through the lingual nerve, a branch of the trigeminal nerve, which they leave via the chorda tympani to join the facial nerve as the nervus intermedius with cell bodies in the geniculare ganglion. The posterior one third of the tongue, pharynx, and soft palate are subserved by taste fibers in the glossopharyngeal nerve; the cell bodies lie in the nodose ganglion. Gustatory nerve fibers from the facial, glossopharyngeal, and vagus nerves terminate in the brainstem in the ipsilareral nucleus of the solitary tract. The central pathway from this nucleus projects via the parvocellular division of the ventral posterior medial nucleus and then via the posterior limb of the internal capsule to the frontal operculum and the anterior insular cortex. Studies of cerebral blood flow in humans (Small et al. 1997) and single-unit activity in monkeys indicate a secondary gustatory area in caudal orbitofrontal cortex. Damage to these central pathways may explain why temporal lobectomies affect the ability to recognize tastes without affecting taste detection. There may be an alternative or accessory taste pathway through the trigeminal nerve. This is supported by abnormal electrogustometric detection thresholds in patients with trigeminal neuralgia and trigeminal sensory neuropathy, with a further moderate but significant threshold increase after surgical treatment.

Gustatory responses depend on the adaptive state of the tongue. For example, if the tongue is exposed (i.e., adapted) to a variety of substances, water itself becomes capable of evoking tastes (the so-called *water taste).* This phenomenon has important clinical implications in conditions associated with changes in the rate of flow or composition of saliva.

These can be affected by food or drug consumption; diseases affecting salivary secretions, such as cystic fibrosis, Sjogren's syndrome, Cushing's disease, or Addison's disease; destruction of salivary tissue by irradiation; or periodontal conditions that add gustatory stimulants to the fluid bathing the tongue. In all cases of dysgeusia or parageusia, it is important to rule our conditions affecting salivary fluids before considering less common causes ot altered taste perception.

Clinical Evaluation of Taste

Patients presenting with a disturbance of taste should be asked about any associated disorder of smell; any pre-existing medical conditions and their treatment, such as ear infection, ear surgery, Bell's palsy, significant head injury, or tracheal intubation; recent upper respiratory tract illness; dental procedures or prostheses; and a detailed drug history.

In addition to a physical examination and testing of taste and smell, special attention should be paid to the oral cavity for evidence of infection, inflammation, degeneration, and masses, as well as atrophy and dryness of tongue, gums, dentition, and surrounding mucous membranes. Specific investigations are ordered to identify suspected causative considerations suggested by the clinical features. If no local cause is suggested, patients with taste abnormalities, particularly unilateral, should have audiologic evaluation and imaging studies to include the middle ear.

The sense of taste can be tested with natural stimuli, such as aqueous solutions of sugar, sodium chloride, acetic acid, and quinine, or with electrical stimulation of the tongue (clectrogustometry). A cotton applicator is used to rub the aqueous solution gently on one quadrant of the protruded tongue. The patient should not talk but should identify the perceived taste by pointing to cards printed with the words *sweet, salt, sour,* and *bitter.* The mouth is rinsed with water between tests. Elecrrogtistometry is the evaluation of taste by applying graded electrical currents to the tongue to produce a sensation described as sour or metallic. In normal subjects, the two sides of the tongue have similar thresholds for electrical stimulation, rarely differing by more than 25%. The technique has the advantages of simplicity, speed, and case of quantification and is capable of providing a reliable objective recording of the gustatory detection threshold.

Disease Entities

Although the cause of most cases of hypogeusia is unknown, the two most common are nasal disorders and a prior respiratory tract infection. Disturbances of taste may result from local disorders involving the tongue, taste buds, or both and from damage to neural pathways in the peripheral or central nervous system.

Drugs, Physical Agents, and Aging

Heavy smoking, particularly of pipe tobacco, and pharmaceutical agents, especially antirheumatic drugs, antiproliferative drugs, and drugs with sulfhydryl groups, such as penicillamine and captopril, are frequent causes of taste dysfunction (Table 20.3). Calcium-channel blockers, such as nifedipine and diltiazem, as well as antifungal agents, smokeless tobacco, anticonvulsants, and sumatriptan nasal spray may cause abnormalities of taste. Other local causes, in part related to drying of the mouth (xerostomia), include Sjogren's syndrome, radiation therapy, and pandysautonomia; these illustrate the important role saliva plays in taste perception. In the elderly, the taste threshold is more than twice as high as that of the general population, and drugs and disease states may further decrease taste (Schiffman 1997). Loss of taste may be the initial symptom of primary amyloidosis and is reported with variant Creutzfeldt-Jakob disease and ciguatera fish poisoning.

Belt's Palsy (See Chapter 76)

Although Bell's palsy is frequently associated with ipsllateral loss of taste over the anterior two thirds of the tongue, the patient usually does not recognize the loss. Loss of taste with facial palsy indicates involvement of the nervus intermedins portion of the facial nerve and localizes the lesion to the region between the pons and the point where the chorda tympani joins the facial nerve in the facial canal, distal to the geniculate ganglion. Recovery of taste within the first 14 days of onset of Bell's palsy is usually associated with complete recovery from paralysis. Impairment of taste for more than 2 weeks suggests a poor prognosis for the rapid return ol facial movement.

Trauma

The chorda tympani is particularly vulnerable to injury in its course through the middle ear on the medial superior surface of the tympanic membrane between the malleus and the incus. Isolated involvement of the chorda rympani is rare but can occur with middle ear lesions, such as cholesteatoma, otitis media, ear surgery (including tympanoplasty, stapedectomy, and mastoidectomy), and head trauma. Injury to preganglionic parasympathetic fibers within the chorda tympani, with loss of salivary secretion, may contribute to long-term impairment of taste even if taste fibers regenerate.

Injury to the lingual nerve (a branch of the mandibular division of the trigeminal nerve) causes loss of both general somatic sensation, resulting in numbness, and special visceral sensation, with taste loss over the anterior two

Tabic 20.3: Drugs affecting taste and smell

Classification	*Drug*
Amebic ides and anthelmintics	Metronidazole, niridazole
Anesthetics, local	Ben^ocaine, procaine hydrochloride (Novocain), and others, cocaine hydrochloride, tetracaine hydrochloride
Antilipemic	Clofibrate
Anti coagulants	Phenindione
Anticonvulsants	Lamotrigine
Antihistamines	Chlorpheniramine maleate
Antimicrobial agents	Amphotericin B, ampicillin, cefamandole, griseofulvin, ethambutol hydrochloride, lincomycin, protease inhibitors, sulfasalazine, sulfortes, streptomycin, terbinafine, tetracyclines, tyrothricin
Antiproliferative, including immunosuppressive agents	Doxorubicin and methotrexate, azathioprine, earmustine, vincristine sulfate
Antirheumatic, analgesic-antipyretic, anti-inflammatory agents	Allopurinol, colchicine, gold, levamisole, o-penicillamine, phenylbutazone, 5-thiopyriodoxine
Antiseptics	Hexetidinc
Antithyroid agents	Catbimazole, methimazole, methylthiouracil, propylthiouracil, thiouraeil
Agents for dental hygiene	Sodium lauryl sulfate (toothpaste)
Calcium-channel blockers	Nifedipine, diltiazem
Diuretics and antihypertensive agents	Captopril, diazoxide, ethacrynic acid
Hypoglycemic drugs	Glipizide, phenformin, and derivatives
Muscle relaxants and drugs for treatment of Parkinson's disease	Baclofen, chlormezanone, L-dopn
Opiates	Codeine, hydromorphone hydrochloride, morphine
Psycho pharmacologic, including antiepileptic, dtugs	Carbamazepine, lithium carbonate, phenytom, psilocyhin, trifluoperazine
Sympathomimetic drugs	Amphetamines, phenmetrazinc thcoclatc and fenhutrazate hydrochloride (combined)
Vasodilators	Oxyfedrine, bamifylline hydrochloride
Others	Germine monoacctatc, hydroquinone, idoxuridinc, ironsorbitex, vitamin D, industrial chemicals (including insecticides), smokeless tobacco, sumatriptan nasal spray

Source: Modified with permission from Schiffman, S. S. 1983, "Taste and smell in disease," *N Engl J Med*, vol. 308, p. 1275.

thirds of the tongue. This nerve may be injured as a result of jaw trauma and wounds, but most cases are iatrogenic due to laryngoscopy, difficult orotracheal intubation, and removal of wisdom teeth.

Head Injury

Taste disorders after head injury are rare and, when present, arc almost always due to disturbance of smell. They may be central or peripheral in origin. The frequency of ageusia after head injury is approximately 0.5%, with approximately 6% of all patients with post-traumatic anosmia also having ageusia. Recovery from ageusia is much more likely than from anosmia and usually occurs in most over a period of a few weeks to a few months.

Areas of brainstem damage that can cause taste disturbance include the tractus solitarius and its nucleus (ipsilateral ageusia) and the pontine tegmentum, involving both gustatory lemnisci (bilateral ageusia). Ipsilateral hypogeusia may follow pontine hemorrhage or infarcts involving the tegmentum. Ageusia may occur after bilateral thalamotomy. Unilateral thalamic or parietal lobe lesions may cause contralateral impairment of taste sensation. Gustatory hallucinations occur much less frequently than olfactory hallucinations hut may occur with similar structural lesions and with psychosis.

Dysgeusia is commonly experienced in association with dental problems, presence of dental prosthesis, poor oral hygiene, recent upper respiratory tracr infection, aging, depression, and psychotic conditions. Dysgeusia with facial numbness may occur with dissecting aneurysms of the carotid artery, possibly related to an alteration in blood supply to the seventh cranial nerve or branches of the chorda tympani,

Other Causes

Impaired raste may follow a focal disturbance of anatomic structures subserving taste, including jugular foramen tumors and more diffuse processes, such as idiopathic midline granuloma, high-altitude sickness, and diabetes mellitus. Hcmiagcusia can accompany vascular and demyelinating processes of the brainstem. Increased sensitivity to taste (hypergeusia) is uncommon and is reported in

association with cerebellar glioma, the mechanism of which is unclear.

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Chapter 21
Cranial and Facial Pain

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Headache is a common symptom with a high prevalence in most epidemiological studies of Western populations (Rasmussen and Lipton 2000). Headache is one of the 10 most common reasons for outpatient physician visits in the United States. Patients typically present with head and facial pain because the discomfort is severe, intetferes with work or other activities, or raises concerns about a serious underlying cause.

The diagnosis of a painful cephalic condition depends on three elements: the history, neurological and general examinations, and appropriate investigations.

HISTORY

The diagnostic advice offcted by the late Dr. A. L, Sahs is useful also for rhe patient with headache: "If you have 30 minutes to see a patient, spend 29 on history, one on the examination."

The method of taking a histoty for headache or facial pain is usually straightforward. Nevertheless, several specific aspects need to be addressed. The scheme of questions listed in Table 21.1 can be useful tor nhnnning a pertinent history. The discussion that follows illustrates some responses and theit implications.

It is usually helpful to begin by asking the patient to describe the pain or, alternatively, simply by asking what kind of help the patient seeks. This approach allows patients to relax and to say what they had planned to say previously. Usually, the patient continues to speak fot only a few minutes if not interrupted (Langcwitz et al. 2002). Once the patient has had an opportunity to speak, directed but open-ended questions (see Table 21.1) can be asked. The questions typically contain the word *headache,* although *facial pain* could easily be substituted, if appropriate.

Types of Headaches

Many individuals, especially those with a long-standing problem, have more than one rype of headache. It is valuable to establish this information at the beginning of the interview so each type of pain can be carefully delineated. For instance, some patients have frequent or persistent headaches that are punctuated occasionally by migraine headaches. Other patienrs have clearly separated migraine and tension-type headaches (formerly called *muscle contraction* or *tension headaches).* A patient with a chronic headache disorder may also develop a new headache that is a manifestation of a new different condition.

Onset of Headaches

A headache disorder of many years' duration, with little change, is almost always of benign origin. Migraine headaches often begin in childhood or early adulthood. A headache of recent onset obviously has many possible causes, including the new onset of either a benign or a more serious condirion. An increasingly severe headache raises rhe possibility of an expanding intracranial lesion. A new headache in an older patient suggests an intracranial lesion

Tabic 21.1: Questions for obtaining the history of headache

How many types of headaches occur?
When and how did the headaches begin?
If the headaches are episodic, what is their frequency and periodicity?
How long does it take for the headaches to reach maximal intensity, and how long do they last?
When do the headaches tend to occur, and what factors precipitate a headache?
Where does the pain start, and how does it evolve?
What is the quality and the severity of the pain?
Is the pain pulsatile (throbbing)?
Are there symptoms dun herald the onset or that accompany the headaches?
Does anything aggravate the pain?
What measures tend to reduce the pain?
Is then- ;i family history of headaches?
What prior evaluation has the patient undergone?
What medications have been used to treat the headaches?
What ideas does the patient have about the headaches?
How disabling are the headaches?
Why is the patient seeking help now?
Are there other medical or neurological problems?

(e.g., subdural hematoma) or giant cell (temporal or cranial) arteritis. Headaches of instantaneous onset suggest an intracranial hemorrhage, usually in the subarachnoid space, but also may be caused by cerebral venous sinus thrombosis, spontaneous cerebrospinal fluid (CSF) leaks, pituitary apoplexy, and severe hypertension (Dodick 2002). Occasionally, mass lesions, such as third ventricular tumors and posterior fossa or cervicomedullary tumors, can produce intermittent acute headaches if there is interference with CSF circulation.

Frequency and Periodicity of Episodic Headaches

Migraine may be episodic or chronic. Chronic migraine (formerly referred to as *transformed migraine)* usually occurs in individuals with a history of episodic migraine headaches. Episodic migraine may become chronic with or without medication overuse.

Episodic cluster headaches typically occur daily for several weeks or months and are followed by a long, headache-free interval, although chronic cluster headaches may occur daily for years. A related disorder, chronic paroxysmal hemicrania, occurs multiple times per day, often for years. A chronic daily headache without migrainous or autonomic features is likely to be a chronic tension-type headache. If there is no regular periodicity, it is useful to inquire about the longest and shortest periods of freedom between headaches. Asking the patient to monitor headache frequency, intensity, and medication use on a "headache calendar" often provides very helpful information.

Peak and Duration of Headaches

Migraine usually peaks within 1-2 hours of onset and usually lasts 6 to 36 hours. Cluster headache is typically maximal immediately if the patient awakens with the headache in progress or peaks within a few minutes if it begins during wakefulness. Cluster headaches characteristically last 45-120 minutes but occasionally last a few hours. Headaches similar to cluster headaches but lasting only about 15 minutes several times a day are typical of chronic or episodic paroxysmal hemicrania. "Ice-pick" head pains (idiopathic stabbing pain) are momentary, lasting only seconds. Tension-type headaches commonly build up over hours and may last days to years. These headaches may include some migraine features and were formerly called a *mixed* or *tension-vascular* headache but more appropriately fall under the rubric of chronic migraine. A new sudden, severe headache that is maximal at onset suggests intracranial hemorrhage, cerebral venous sinus thrombosis, or pituitary apoplexy. A chronic, continuous, unilateral headache of moderate severity with superimposed attacks of more intense pains that are associated with autonomic features suggests the diagnosis of hemicrania continua, an indomethacin-rcsponsive syndrome (Goadsby and Lipton 1997). Occipital neuralgia and trigeminal neuralgia manifest as brief shocklike pains, sometimes occurring in a crescendo pattern over a period of seconds to minutes. Occasionally, a duller pain in the same nerve distribution persists longer. Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) is a rare syndrome manifested by paroxysms of retro-orbital pain lasting seconds but with 3-100 episodes per day and the associated autonomic symptoms for which it is named.

Time and Occurrence and Precipitating Factors

Cluster headaches often awaken patients from a sound sleep and have a tendency to occur at the same time each day in a given person. Hypnic headaches typically affect elderly patients, regularly awakening the patient at a particular time of night. Unlike cluster headaches, they are typically diffuse and not associated with autonomic phenomena (Raskin 1997). Migraine can occur at any time during the day or night but usually begins in the morning, A headache of recent onset that disturbs sleep or is worse on waking may be caused by increased intracranial pressure. Tension-type headaches are typically present during much of the day and are often more severe late in the day. Obstructive sleep apnea may be accompanied by the chronic occurrence of headaches on awakening.

Patients with chronic, recurrent headaches often can recognize factors that trigger an attack. Migraine headaches may be precipitated by bright light, menstruation,

weather changes, caffeine withdrawal, sleeping longer or less than usual, and ingested substances, such as alcohol. Trauma, emotional or physical, may be an important causative factor in the pathogenesis of headache.

If bending, lifting, coughing, or Valsalva's maneuver produces a headache, an intracranial lesion, especially involving the posterior fossa, must be considered; however, most exertional and cough headaches are benign. Intermittent headaches that are precipitated by assuming the upright position and promptly relieved by lying down are characteristic ot a CST leak. If no Iiisrorv exists of a lumbar puncture, head trauma, or neurosurgical procedure, a spontaneous leak may be the cause. Alcohol is often a potent precipitant of cluster headaches.

Headache occurring during sexual activity, especially during or shortly after orgasm, may be of benign origin, especially if a headache has occurred on multiple occasions previously. A single headache in this circumstance, however, may be caused by a subarachnoid hemorrhage.

Lancinating face pain triggered by facial or intraoral stimuli occurs with trigeminal neuralgia. Glossopharyngeal neuralgia is most commonly triggered by chewing, swallowing, and talking, although cutaneous trigger zones in and about the ear are occasionally present.

Location and Evolution

Asking the patient to delineate the location of the pain with a finger is often helpful. Trigeminal neuralgia is confined to one or more branches of the trigeminal nerve. The patient may be able to localize one or more trigger points over the face or in the mouth and then outline the spread of the pain. Pain in the throat may be related to a local process or glossopharyngeal neuralgia. Pain in the lower portion of the face and neck can be produced sometimes by either a cluster or a migraine variant—a so-called *lower half headache.* Carotid dissection commonly presents with neck, face, and head pain ipsilateral to the dissection; this should be considered in any patient with pain of recent onset in these locations.

Migraine is most often unilateral, commonly in the frontotemporal region, but it may be generalized or may evolve from a unilateral location to become generalized. Cluster headaches are virtually always unilateral during an attack and are typically centered in, behind, or about the eye. At different times (different clusters), some patients do experience cluster headaches that have switched sides from a prior cluster.

A typical tension-type headache is generalized, although it may originate across the nuchal muscles only to spread and perhaps predominate in the frontal or occipital regions. When pain is localized to an eye, the intraoral region, or the ear, local processes involving these structures must be considered. Otalgia may be caused by a process involving the tonsillar fossa and the posterior tongue. Unilateral facial pain when chronic often does not have an underlying lesion. Occasionally, though, facial pain may be a symptom of nonmetastatic lung cancer (Eross et al. 2003).

Quality and Severity

Although it is often difficult for the patient to describe the quality of the pain, this information may be useful. It may be helpful to ask the patient to grade the severity of pain on a scale of 1 to 10. Migraine often has a pulsating quality that may be superimposed on a more continuous pain. Cluster headache is characteristically severe, boring, and steady and is often described as similar to a "hot poker." SUNCT produces moderately severe pain in the orbital or temporal region and may be described as stabbing or pulsatile. Tension-type headaches are usually described as a feeling of fullness, tightness, or pressure, or as being like a cap, band, or vise. Headaches caused by meningeal irritation, whether related to infectious meningitis or to a hemorrhage, are typically severe. Trigeminal neuralgia is severe, brief, and stabbing, occurring up to several times per minute; a milder ache may occur between paroxysms of pain. Pain caused by glossopharyngeal neuralgia is similar in character to that of trigeminal neuralgia.

Premonitory Symptoms, Aura, and Accompanying Symptoms

Leading questions may be necessary. Some patients have premonitory symptoms that precede a headache attack by hours. These can include psychological changes, such as depression, euphoria, and irritability, or more somatic symptoms, such as constipation, diarrhea, abnormal hunger, fluid retention, or increased urination. The term *aura* refers to focal cerebral symptoms associated with a migraine attack. These symptoms most commonly last 20-30 minutes and precede the headache. At other times, the aura may continue into the headache phase or arise during the headache phase. Visual symptoms are the most common kind of cerebral dysfunction and may consist of either positive or negative phenomena or a mixture of both. Other hemispheric symptoms, such as weakness, somatosensory disturbances (usually paresthesias), or language dysfunction, may precede the headache. Aura symptoms usually have a gradual onset and spread over minutes. If more than one symptom occurs (e.g., visual and somatosensory), the onsets are usually staggered and not simultaneous. The slow spread is a helpful feature to differentiate these from focal neurological symptoms caused by cerebral ischemia. Symptoms of brainstem origin, such as vertigo, dysarthria, ataxia, quadriparesis, diplopia, and loss of

consciousness, accompany basilar migraine. Nausea, vomiting, photophobia, phonophobia, and osmophobia characteristically accompany migraine attacks. In addition, lacrimation, rhinorrhea, and nasal congestion accompany migraine headache in many patients and should not be confused with a headache of sinus origin (Cady and Schreiher 2002).

Ipsilateral miosis and ptosis (oculosympathetic paresis or Horner's syndrome), lacrimation, conjunctival injection, and nasal stuffiness commonly accompany cluster headache. Sweating and facial flushing on the side of the pain have been described but are uncommon. Facial swelling, usually periorbital in location, may develop with repeated attacks. Shorter lived attacks occurring multiple times per day with similar autonomic features suggest a diagnosis of episodic or chronic paroxysmal hemicrania, an indomethacin-responsive syndrome (Goadsby and Lipton 1997). An oculosympathetic paresis is also a common feature associated with ipsilateral interna! carotid artery dissection. In the setting of acute transient or persistent monocular blindness, giant cell arteritis and carotid dissection should be considered.

Temporomandibular joint dysfunction often is characterized by jaw pain precipitated by movement of the jaw, clenching of the teeth, reduction in the range of jaw movement, joint clicking, and tenderness over the joint.

Headache accompanied by fever suggests an infectious cause. Persistent or progressive diffuse or focal central nervous system symptoms, including seizures, suggest a structural cause for a headache. Purulent or bloody nasal discharge suggests an acute sinus cause for the headaches. Likewise, a red eye raises the possibility of an ocular process, such as infection or acute glaucoma. A history of polymyalgia rheumatica, jaw claudication, or tenderness of the scalp and superficial arteries in an elderly person suggests the possibility of giant cell arteritis. Transient visual obscurations, tinnitus, diplopia, and the finding of papilledema may be associated with increased intracranial pressure from any cause, particularly idiopathic intracranial hypertension {pseudotumor cerebri).

An important principle is that symptoms that accompany a headache can be key in accurate diagnosis.

Aggravating Factors

The worsening of headache as a result of a cough or jolt suggests an intracranial element to the pain, whereas aggravation by torsion of the neck may indicate a musculoskeletal component. Sufferers of cluster headaches tend to endure their pain in an agitated state, pacing and moving about, whereas patients with migraines prefer to lie still. Precipitation or marked aggravation of headache in the upright position suggests intracranial hypotension.

Mitigating Factors

Rest, especially sleep and avoidance of light and noise tends to provide relief to the migraineur. Massage or heat may ameliorate the pain associated with a tension-type headache. Local application of pressure over the affected eye or ipsilateral temporal artery, and local application of heat or cold, or rarely short-lasting intense physical activity may alleviate the pain of cluster headache. Headache caused by intracranial hypotension typically is relieved or markedly benefited by recumbency.

Family History of Headaches

Migraine is often an inherited disorder, and a family history of migraine or "sick headaches" should he sought. Tension-type headaches are also frequently familial. Cluster headache is familial in a minority of cases (approximately 7%). Familial hemiplegic migraine is a rare, autosomal dominant variant of migraine with aura, wherein the migraine attack includes hemiparesis lasting minutes to weeks.

Prior Evaluation

The patient should be asked about prior consultations and testing for the headaches. If appropriate, the records and imaging study films can be obtained for review.

Prior Medications

Response to medications should be sought, including those used to treat individual headache attacks and those used prophylactically. The dose, route of delivery, dosage schedule, and duration of treatment should be established. This information also provides an opportunity to determine whether medications such as ergot preparations and analgesics have been overused. It also establishes whether prophylactic medications were optimized. A history of the use of caffeine-containing substances also should be elicited, because they may cause or aggravate headaches.

Disability

The assessment of head ache-re I a ted disability is important. A baseline determination with follow-up assessments is useful when judging the effects of treatment and can be useful in guiding headache therapy. In addition, disability can be useful in guiding the headache therapy (Upton et al. 2000). The Migraine Disability Assessment Scale (MIDAS) is an example of a useful, validated clinical tool (Stewart et al. 2001).

Patient Concerns

Headache pain can produce significant fear and anxiety regarding serious disease. The patient should be allowed to articulate any concerns so each aspect can be appropriately addressed by the physician.

Reason for Seeking Help

The question of why the patient is seeking help may be irrelevant if the problem is of recent onset. If the problem is chronic, however, it can be useful to inquire why the patient has come for aid at this point.

Other Medical or Neurological Problems

A history of past or current medical and neurological conditions and history of trauma, operations, and medication allergies should be obtained. Additionally, a history of the use of other medications and dietary supplements unrelated to the headaches should be obtained.

EXAMINATION

In the patient with headache, the physical examination often shows no abnormalities. However, findings on examination may yield important clues about the underlying cause. Even when the results of the examination are normal, both the physician and the patient gain confidence that nothing has been overlooked.

Although, strictly speaking, the history and the examination are separate parts of the evaluation, in practice the examination begins the moment the physician encounters the patient. Careful observation helps determine whether the patient has physical illness, appears anxious or depressed, and whether the patient's history is reliable. For instance, with respect to reliability, a patient who is unable to give a reasonably coherent history is suspected of having an abnormal mental status.

It is important to perform a neurological examination, including examination of the mental status, gait, cranial nerves, motor system, and sensory system, as discussed in Chapter 1. A neurovascular examination also should be performed.

The skull and cervical spine should be examined. The skull should be palpated for lumps and local tenderness. There may be tenderness over inflamed sinuses. Thickened, tender, irregular temporal arteries with an associated reduction in pulse suggest giant cell arteritis. Occasionally, other scalp lesions may be present that point to a cause for head pain. In tension-type headaches, the scalp muscles may be tender.

A short neck or low hairline suggests basilar invagination or an Arnold-Chiari malformation. In an infant, separation of the sutures suggests increased intracranial pressure, most commonly caused by hydrocephalus. Measuring the head circumference is always worthwhile in a child.

The cervical spine also should be tested for tenderness and mobility. Nuchal rigidity on passive neck flexion and Kernig's sign are evidence of meningeal irritation.

Vital signs, especially blood pressure and pulse, always should be assessed. If there is a question of fever, temperature should be measured. The body habitus should be noted. This observation may be relevant especially in young women with headache possibly related to pseudotumor cerebri, who are almost always obese. The general examination also includes auscultation of the heart and lungs, palpation of the abdomen, and examination of the skin.

Differential Diagnosis

In most cases, the history and examination are all that are needed to make a diagnosis, especially in the patient with a chronic headache. Migraine, tension-type headaches, and cluster headaches usually can be diagnosed with a high degree of certainty, particularly if the headaches have been recurrent over a long period and the examination is normal. In this case, it may be possible to proceed directly to management.

In some situations, however, the diagnosis is uncertain. These situations specifically raise concerns of a serious organic cause for rhe headaches. Headaches that are progressive are a worrisome indication of a possible intracranial process. A new headache of abrupt onset always raises concern about an intracranial process, especially hemorrhage and sometimes a mass lesion. Headaches that interfere with sleep, though sometimes benign, must be considered to have a potential serious cause. Headaches precipitated by exertion, change of position, cough, sneeze, or strain may be benign, although again they raise the possibility of an intracranial lesion, especially in the posterior fossa. Systemic symptoms, such as weight loss, fever, or those associated with another known systemic disease, such as malignancy or human immunodeficiency virus infection, should be investigated with care. Headaches that are associated with neurological symptoms, except those that are typical for migraine, should raise concern. Unexplained findings on neurological examination and a history of seizures should prompt additional evaluation.

The investigations used to evaluate a patient with headaches can include almost all of the tests used in neurology and neurosurgery, as well as various medical tests. Selection of the appropriate studies depends on the formulation after the history and examination. Indiscriminate use of batteries of tests is unwarranted.

Neuroimaging Tests

Computed Tomographics! Scanning and Magnetic Resonance Imaging

Computed tomographic (CT) scanning and magnetic resonance imaging (MRI) are extremely useful tests in the evaluation of patients with headache. Tumors, hematomas, cerebral infarctions, abscesses, hydrocephalus, and many meningeal processes can be identified with CT scanning and MRI. Abnormalities of the skull base, pituitary gland craniocervical junction, and white matter are better seen with MRI. The cost of an MRI study is severalfold that of a CT scan, but MRI is safer because x-rays are not used to generate the image and the enhancing agent used with MRI {gadolinium) is safer than the iodinated contrast used with CT. CT can detect acute subarachnoid hemorrhage if sufficient bleeding has occurred. If the CT scan is normal and the history is suggestive of recent subarachnoid hemorrhage, a lumbar puncture should be performed. CT scanning can be helpful for evaluating abnormalities of the skull, orbit, sinuses, facial bones, and the cervical spine. Changes associated with intracranial hypotension are best shown with MRI (Mokri 2001). The cervical spinal cord and exiting nerve roots and the craniocervical junction are much better shown with MRI.

Magnetic resonance angiography (MRA) is a noninvasive method that can demonstrate intracranial and extracranial vascular occlusive disease including large vessel dissection, intracranial arteriovenous malformations, and aneurysms. Intracranial venous sinus thrombosis is best diagnosed with magnetic resonance venography.

Evidence-based guidelines for neuroimaging of patients with nonacute headache {Frishberg et al. 2000) found MRI to be more sensitive in finding white matter lesions and developmental venous anomalies than CT.

For the acute onset of headache, CT is the optimal imaging study; in patients with subacute and chtonic headache, MRI is likely to reveal more, but many of rhe abnormalities will be incidental.

Plain X-ray Films of the Skull, Sinuses, and Cervical Spine

Plain x-ray films of the skull arc unnecessary in the routine evaluation of patients with headache but can he obtained if there has been acute head trauma or if there is an unusual bony abnormality on physical examination. Although plain x-ray films of the sinuses can show infection, hemorrhage, or tumor, CT scanning and MRI provide greatet definition. The role of the cervical spine in the cause of headaches remains uncertain, but occipitonuchal pain may result from degenerative disc and joint disease of the mid- and upper cervical spine. Rheumatoid arthritis can lead to craniocervical junction instability and pain. Tomographic films may be needed to show bony changes in the upper cervical spine and craniocervical junction. Flexion and extension, odontoid, and pillar views of the cervical spine can help to exclude ligamentous damage and fractures in patients with a history of head and neck injury. Congenital abnormalities of the cervical spine, such as the Klippel-Feil syndrome, may be associated with other disorders such as an Arnold-Chiari malformation.

Other Imaging Studies

Panoramic x-ray examination, MRI, or CT of the temporomandibular joints may be helpful in selected patients. The presence of temporomandibular joint disease should not be taken as proof that a patient's headaches arc related. Dental x-ray films are useful if dental-origin pain is suspected.

Cerebral Angiography

Cerebral angiography is rarely needed in the initial investigation of headache. It can be helpful in confirming vascular disease including arterial dissections, arteriovenous malformations, intracranial aneurysms, and the presence of central nervous system vasculitis.

Radioisotope and Computed Tomographic Studies for Cerebrospinal Fluid Leaks

Isotope cisternography can be helpful in determining the presence and location of a spontaneous, post-trail ma tic, or postoperative CSF leak. Alternatively, CT scanning ol the spine after instillation of contrast into the lumbar spinal fluid can be used to identify the location of CSF leaks.

Cerebrospinal Fluid Tests

CSF examination is used to diagnose or exclude meningitis, encephalitis, subarachnoid hemorrhage, and leptomeningeal cancer and lymphoma and is required to confirm increased or decreased intracranial pressure. Measurement of the opening CSF pressure should be performed in all cases,

Electroencephalography

Electroencephalography is not useful in the investigation of headache unless the patient also has a history of seizures, syncope, or episodes of altered awareness (Quality Standards Subcommittee of the American Academy of Neurology 1995).

General Medical Tests

A few blood tests are important in the investigation of headache. Detetmining the erythrocyte sedimentation rate

is essential in the evaluation of giant cell arteritis. Although a normal value does not exclude this condition, it greatly reduces the likelihood (see Chapter 75), Episodic headaches associated with unusual behavior ot impairment of consciousness may suggest an insulinoma. A diagnosis of insulinoma is supported by elevated insulin and C-peptide levels in the face of a low or relatively low fasting glucose level. Levels of carboxyhemoglobin can be measured in patients complaining of early morning headaches during the winter when home heating is used, especially when several members of the same household are affected. Estimation of blood alcohol levels and drug screening may be helpful in certain patients. Sensitive thyroid-stimulating hormone and serum thyroxine levels should be measured in patients with chronic headache because hypothyroidism may present with headaches. Urine concentrations of mctancphtines and free catecholamines should be measured if a pheochromocytoma is suspected.

Special Examinations and Consultations

Perimetry is helpful in the delineation of visual field defects. Tonometry is necessary to document elevated intraocular pressure in glaucoma, hut unless the eye is red or the cornea is cloudy, glaucoma is an unlikely cause of head or even eye pain. These tests are routinely done by ophthalmologists, who also have the equipment and expertise to perform slit-lamp examinations and other specialized examinations.

If pain of dental or temporomandibular joint origin is suspected, a dentist or oral surgeon skilled in the detection and trearment of these disorders should be consulted.

Diagnosis of tumors of the sinuses, nasopharynx, and neck, as well as inflammation of the sinuses, is aided by the expertise of an otorhinolaryngologist.

Temporal artery biopsy is performed to confirm or exclude giant cell arteritis (see Chapters 55A and 75).

In some selected cases (e.g., headaches as a manifestation of a chronic pain disorder with or without a history of drug abuse), psychiatric consultation may be helpful for diagnosis and management.

Further Observation

Sometimes, a definitive diagnosis cannot be reached after history taking, examination, and investigation. In such cases, further observation, perhaps coupled with a trial of therapy, usually reveals the diagnosis.

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Chapter 22
Brainstem Syndromes

Michael Wall

Other chapters in this hook that deal with symptoms emphasize history as the starting point for generating a differential diagnosis. The differential diagnosis is then tefined during the examination. This chaptet calls for a different approach. When the neurologist evaluates a patient with a brainstem disorder, often the most effective method of diagnosis is to organize the differential diagnosis around the objective physical findings, particularly in patients with an altered mental status, such as coma. The symptoms are still integrated in the approach, but the physical findings take centct stage.

Organization around physical findings is efficient because very specific neurological localization, which limits the diagnostic alternatives, is often possible. The long tracts of the nervous system traverse the entire brainstem in the longitudinal (rostrocaudal) plane. Cranial nerve nuclei and their respective cranial nerves originate and exit at distinct levels of the brainstem. This allows for exquisite localization of function based on the findings of the neurological examination,

The chapter begins with a discussion of the brainstem ocular motor syndromes followed by miscellaneous brainstem, brainstem stroke, diencephalic, and thalamic syndromes.

OCULAR MOTOR SYNDROMES

Combined Vertical Gaze Ophthalmoplegia

Combined vertical gaze ophthalmoplegia is defined as paresis of both upward and downward gaze. Vertical gaze ophthalmoplegia is an example of a brainstem syndrome in which the objective physical findings dictate the diagnostic approach to the problem. Symptoms of vertical gaze ophthalmoplegia, when ptesent, are relatively nonspecific and usually occur in patients who have difficulty looking down, as when reading, eating from a table, and walking down a flight of stairs. In addition, symptoms may be unobtainable because of mental status changes caused by dysfunction of the reticular formation that lies adjacent to the vettical gaze generator in the rostral midbrain (see Chapter 39),

The neutological examination discloses associated signs of the disorders listed in the differential diagnosis (Table 22.1). Coma may be associated with reticular system involvement. Long-ttact signs and loss of pupillary reflexes are commonly associated. The syndrome of combined vertical gaze ophthalmoplegia is diagnosed when the ocular findings occur in isolation from long-tract signs.

With combined vertical gaze ophthalmoplegia, there is loss of vertical saccades and pursuit. This gaze limitation may be overcome by the oculocephalic (doll's head or doll's eye) maneuver, which tests the vestibulo-oculat reflex (VOR; see Chapter 39). It is demonstrated by having the patient focus on an object, rotating the patient's head, and looking for a conjugate eye movement in the opposite direction. Bell's phenomenon (reflex movement of the eyes up and out in response to forced eye closure) is often absent. Skew deviation (vertical malalignment of the eyes) may occur. Absence of convergence and loss of pupillary reactions to light are common.

The location of the lesion of combined vertical gaze ophthalmoplegia is the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) for loss of vertical pursuit and saccades (Leigh and Zee 1999).

Table 22.1: Differential diagnosis of combined vertical gaze ophthalmoplegia

- Stroke
  - Ischemic
  - Hemorrhagic
- Progressive supranuclear palsy
- Corticobasal ganglionic degeneration
- Arteriovenous malformation
- Multiple sclerosis
- Thalamic and mesencephalic tumors
- Whipple's disease
- Syphilis
- Vasculitis (e.g., systemic lupus erythematosus)
- Metabolic disorders
  - Lipid storage diseases
  - Wilson's disease
  - Kern icterus
  - Wernicke's encephalopathy

Table 22.1 lists the disorders involving the rostral mesodiencephalic region (differential diagnosis) that cause combined vertical gaze ophthalmoplegia (see Chapter 39). The most common causes of isolated combined vertical gaze ophthalmoplegia are stroke and progressive supranuclear palsy (PSP). Cortical-basal ganglionic degeneration has similar ocular motility findings to PSP, but they are less severe. Whereas the supranuclear vertical gaze ophthalmoplegia may be prominent early in the course of PSP, obvious vertical and horizontal gaze restriction is usually a late finding in cortical-basal ganglionic degeneration (Rottach et ah 1996).

The diagnostic formulation varies with the age of the patient. Isolated combined vertical gaze ophthalmoplegia is usually due to infarction of the rostral dorsal midbrain (Bogousslavsky et al, 1994). When onset is gradual instead of abrupt or the patient is young, other disorders should be considered (see Table 22.1). In the elderly, PSP (see Chapter 77) is likely if the onset is gradual. PSP can be mimicked by the treatable Whipple's disease (Averbuch-Heller et ah 1999).

For Whipple's disease, the movement disorder oculomasticatory myorhythmia is pathognomonic. Laboratory investigations used to evaluate combined vertical gaze ophthalmoplegia include computed tomographic (CT) scan or, preferably, magnetic resonance imaging (MRI). Care should be taken not to overlook lesions inferior to the floor of the third ventricle. Lumbar puncture, syphilis serology, erythrocyte sedimentation rate, and an antinuclear antibody test complete the evaluation when the cause is not obvious. One should consider small bowel biopsy if Whipple's disease is a possible diagnosis. A polymerase chain reaction (PCR) assay of small bowel biopsy, cerebrospinal fluid (CSF), or other tissues for the 16S ribosomal ribonucleic acid (RNA) gene of *Tropberyma whippleii* appears to have both sensitivity and specificity for the diagnosis of Whipple's disease (Lee 2002).

Upgaze Paresis (Dorsal Midbrain or Parinaud's Syndrome)

Another brainstem syndrome that often occurs without symptoms is the dorsal midbrain syndrome. When symptoms do occur, the patient has difficulty looking up and may have blurry distant vision caused by accommodative spasm.

Tin- trtnid of findings in the dorsal midbrain syndrome are (1) loss of upgaze, which is usually supranuclear (loss of pursuit and saccades with preservation of the VOR); (2) normal-to-large pupils with light-near dissociation (loss of the light reaction with preservation of pupilloconstriction in response to a near target) or pupillary areflexia; (3) convergence-retraction nystagmus, in which the eyes make convergent and retracting oscillations after an upward saccade; and (4) lid retraction,

The location of the lesion causing the upgaze paresis of the dorsal midbrain syndrome is the posterior commissure and its inrersririal nucleus (Leigh and Zee 1999). The presence of the full syndrome implies a lesion of the dorsal midbrain (including the posterior commissure), a bilateral lesion of the pretectal region, or a large unilateral tegmental lesion.

The differential diagnosis is listed in Table 22,2. Other than the mild upgaze limitation that occurs with age, the most common cause of loss of upgaze is a tumor of the pineal region. The next most common causes are stroke and trauma. The upgaze palsy portion of the syndrome can be mimicked by (1) double elevator palsy; (2) PSP; (3) orbital causes, such as thyroid ophthalmopathy and bilateral Brown's superior oblique tendon sheath syndrome; (4) pseudo-dorsal midbrain syndrome, secondary to myasthenia gravis, or the Cuillain-Barre syndrome; and (5) congenital upgaze limitation. Forced ductions

Table 22.2: Differential diagnosis of dorsal midbrain syndrome

- Pineal tumors
- Stroke
  - Ischemic cerebrovascular disease
  - Thalamic hemorrhage
- I r;nini:I
- Hydrocephalus
- Multiple sclerosis
- Transtentorial herniation
- Congenital aqueductal stenosis
- Metastatic tumors
- Infections
  - Encephalitis
  - Cysticercosis
- Midbrain arteriovenous malformation
- Stereotactic midbrain surgery
- Metabolic disorders
  - Lipid storage disease
  - Wilson's disease
  - Kern icterus
  - Wernicke's encephalopathy

(see Chapter 16) may be performed by grasping anesthetized sclera with forceps and moving the globe through its range of motion. The presence of restriction of movement with forced ductions implies a lesion within the orbit, as distinct from a midbrain lesion.

The diagnostic formulation of the dorsal midbrain syndrome varies with age. In children and adolescents, pineal region tumors are usually the cause. In young and middle-aged adults, the disorder is uncommon, and the cause may be trauma, multiple sclerosis, or arteriovenous malformation. In the elderly, stroke and PSP are rhc most common causes.

The laboratory investigation needed to evaluate dorsal midbrain syndrome is MRi. If no tumor is present and an infectious or inflammatory cause is suspected, a lumbar punctute should be performed.

Downgaze Paresis

Isolated downgaze paresis is uncommon. Symptoms, when they occur, are difficulty in reading, eating, and walking down staits.

Neurological examination reveals loss of downward pursuit and saccades, although occasionally pursuit may be spared. The vertical oculocephalic maneuver may be normal or may disclose gaze limitation. Convergence may be lost, and gaze-evoked upbeat nystagmus may be present on upwatd gaze. In young patients, one should evaluate forced ductions for evidence of congenital downgaze limitation.

The site of the lesion for isolated downgaze paresis is bilateral involvement of the lateral portions of the riMLF. The differential diagnosis is ischemic stroke, PSP, and Whipple's disease. Laboratory investigations to support the clinical diagnosis include CT or preferably MRI. Lesions may be detected in the rostral mesodiencephalic junction inferior to the floor of the third ventricle.

The diagnostic formulation of isolated downgaze limitation is uncomplicated. When acute in onset, it is usually due to ischemic cerebrovascular disease. In an elderly patient with a progressive course, PSP should be considered.

In ternu clear Ophthalmoplegia

Internuclear ophthalmoplegia (INO) is characterized by paresis of adduction of one eye, with horizontal nystagmus in the contralateral eye when it is abducted. It is due to a lesion of the MLF ipsilateral to the side of the adduction weakness.

Surprisingly, most patients with INO have no symptoms. The symptoms that may be associated with INO are diplopia, oscillopsia of one of the two images, and blurred vision. When diplopia is present, it is due to medial rectus paresis (horizontal diplopia) ot skew deviation (vertical diplopia).

The MLF carries information for vertical pursuit and the vertical VOR. Consequently, other associated findings with MLF lesions are abnormal vertical smooth pursuit and impaired reflex vertical eye movements (doll's eye maneuver, Bell's phenomenon). Voluntary vertical eye movements (pursuit and saccades) are unaffected, daze-evoked vertical nystagmus, usually on upgaze, and skew deviation may be present. Skew deviation is a pure vertical ocular deviation that is not due to a cranial nerve palsy, orbital lesion, or strabismus but to disturbed suptanuclcar input to the third and fourth cranial nerve nuclei. It is thought to be due to unilateral damage to the otolith-oculat pathways or the pathways mediating the VOR. The topic is discussed further in Chapter 39.

INO may occur as a false localizing sign. Cases of brainstem compression due to subdural hematoma with transtentorial herniation and cerebellar masses may cause INO. Myasthenia gravis and the Guillain-Barre syndrome may also simulate INO.

The differential diagnosis is varied. Kxamination can differentiate a lesion of the MLF from a partial third cranial nerve palsy, myasthenia gravis, strabismus, or thyroid ophthalmopathy. The common causes of INO are stroke (including vertebral artery dissection) in older age-groups (Eggenberger et al. 2002) and multiple sclerosis in the young.

Laboratory investigations are performed to elucidate the cause including MRI. An edrophonium (Tensilon) test should be performed to evaluate for myasthenia gravis unless there are associated signs of obligatory brainstem dysfunction.

The diagnostic formulation for INO first necessitates accurate localization of the lesion. Limitation of adduction is initially formulated simply as an adduction deficit. It may be due to (1) a lesion of the midbrain or third cranial nerve disrupting innervation, (2) a disorder of the neuromuscular junction (myasthenia gravis), or (3) a lesion directly involving the medial rectus muscle.

Horizontal Gaze Paresis

Although there are no common symptoms of horizontal gaze paresis, this condition seldom occurs in isolation. Patients may complain of inability to see or to look to the side. Because supranuclear gaze pareses are conjugate by definition, diplopia does not occur.

On examination, with unilateral isolated involvement of the paramedian pontine reticular formation (PPRF), there is loss of ipsilateral saccades and pursuit. However, full horizontal eye movements are demonstrated with the oculocephalic maneuver.

Lesions of the sixth cranial nerve nucleus cause horizontal gaze paresis with inability of the oculocephalic maneuver to overcome the gaze limitation. Although there is usually an associated ipsilateral peripheral facial palsy

from involvement of the fascicle of the seventh cranial nerve coursing over the sixth cranial nerve nucleus, cases of isolated horizontal gaze paresis caused by sixth nerve nuclear lesions have been reported (Miller et al. 2002). With bilateral lesions, there is loss or limitation of horizontal saccades and (usually) pursuit in both directions. Gaze-paretic nystagmus may be present. In the acute phase, transient vertical gaze paresis and vertical nystagmus or upgaze paresis can occur. In the chronic phase, vertical eye movements are full, although there may be nystagmus on upgaze.

The location of the lesion for horizontal gaze paresis is the frontopontine tract, mesencephalic reticular formation, PPRF, and sixth cranial nerve nucleus. The explanation of gaze palsy occurring with a nuclear lesion is given in Syndromes Involving Ocular Motor Nuclei, later in this chapter.

The differentia] diagnosis is varied. As with other ocular motility disorders, myasthenia gravis may cause gaze limitation that simulates a central nervous system (CNS) lesion. The diagnostic formulation varies with age, rapidity of onset, and associated clinical findings. For patients with an acute onset whose age is older than 50 years, cerebrovascular disease, ischemic or hemorrhagic, is a likely cause. With a subacute onset before age 50 years, one should consider multiple sclerosis. Congenital cases are usually due to Mobius' syndrome. Systemic lupus erythematosus, syphilis, and Wernicke's encephalopathy should be considered for any acquired cases.

Laboratory investigations for horizontal gaze paresis include MRI. If there are no obligatory signs of CNS dysfunction, myasthenia gravis needs to be considered.

Global Paralysis of Gaze

The common symptoms of the global paralysis of gaze arc inability to look voluntarily (saccades and pursuit) in any direction. Global paralysis of gaze rarely occurs in isolation, however, and signs and symptoms of involvement of other local structures are usually present.

The location of the lesion is the frontopontine tract for saccades, and the parieto-occipito-pontinc tract for pursuit, where they converge at the subthalamic and upper midbrain level.

The differential diagnosis for total ophthalmoplegia is given in Table 22.3. The common causes for this presentation arc diseases outside the CNS, such as Guillain-Barre syndrome, myasthenia gravis, and chronic progressive external ophthalmoplegia (CPEO); for intra-axial lesions, consider stroke, Wernicke's encephalopathy, and PSP.

The diagnostic formulation is usually concerned with extra-axial (cranial nerve, neuromuscular junction, or muscle) pathology, because isolated complete ophthalmoplegia is rarely caused by a brainstem lesion. Myasthenia gravis (sometimes in combination with thyroid ophthalmopathy) and Guillain-Barre syndrome are much more likely possibilities if the onset is subacute. If the presentation is long-standing, slowly progressive, and accompanied by eyelid ptosis, the CPF.O syndromes, such as Kearns-Sayre syndrome, should be considered. In these extra-axial disorders, oculocephalic reflexes do not overcome the gaze limitations. PSP is a diagnostic possibility in the elderly, whereas Wernicke's encephalopathy should be considered in alcoholics and nutritionally deprived patients, Whipple's disease can also cause this rare clinical presentation.

Table 22,3: Differential diagnosis of total ophthalmoplegia

Oculomotor a praxis
Guillain-Barre syndrome
Myasthenia gravis
Thyroid ophthalmopathy (especially in combination with myasthenia gravis)
Chronic progressive external ophthalmoplegia syndromes
Wilson's disease
Pituitary apoplexy
Botulism
Tetanus
Progressive supranuclear palsy
Anticonvulsant intoxication
Wernicke's encephalopathy
Acute bilateral pontine or mesodieneephalic lesions

Laboratory investigations for patients with global paralysis of gaze should include MRI. An edrophonium test is performed when myasthenia gravis is suspected. When botulism is suspected, elecrtomyography with repetitive stimulation and serum assay for botulinum toxin should be performed.

One-and-a-Half **Syndrome**

The one-and-a-half syndrome is characterized by a gaze palsy when looking toward the side of the lesion, together with INO on looking away from the lesion. The common symptoms are diplopia, oscillopsia (the illusion that objects or scenes are oscillating), and blurred vision. Associated findings arc skew deviation and gaze-evoked nystagmus on upgaze or lateral gaze, and less commonly on downgaze. Acutely, in the primary position there may be exotropia (one eye deviated outward). There may also be limitation of upgaze, saccadic vertical pursuit, and loss of convergence.

The location of the lesion is the PPRF or sixth cranial nerve nucleus with extension to involve the intemuclear fibers crossing from the contralateral sixth cranial nerve nucleus, which causes the INO.

The differential diagnosis is multiple sclerosis, stroke (Kataoka et al. 1997), arteriovenous malformation, or tumor of the lower pons. A pseudo-one-and-a-half syndrome may occur with myasthenia gravis or the Giiill.lm-l'.urc syndrome. The diagnostic formulation tor

the one-and-a-half syndrome is similar to that for INO. Before age 50 years, the wusc is usually multiple sclerosis; after age 50 years, it is usually cerebrovascular disease.

Laboratory investigations for the one-and-a-half syndrome are MRI and if indicated lumbar puncture.

SYNDROMES INVOLVING OCULAR MOTOR NUCLEI

Patients with lesions of the third or sixth cranial nerve nucleus not only present with accompanying long-tract signs but also show different ocular motility disturbances than with lesions of the third or sixth cranial nerve.

Third Cranial Nerve Nucleus

The common symptoms of nuclear third cranial nerve palsies are diplopia and eyelid ptosis.

The signs present on the side of the lesion are weakness of the inferior and medial recti and the inferior oblique muscles. Upgaze limitation is present in both eyes because the superior rectus subnucleus is conttalateral, and the axons cross within the nuclear complex. In addition, eyelid ptosis and dilated, unreactive pupils may be present on both sides because the levator subnucleus and Edinger-Westphal nuclei arc bilaterally represented.

To localize a lesion to the third cranial nerve nucleus, both eyes must have some involvement because of the bilateral representation. The superior rectus and levator of the eyelid, however, are bilaterally represented and thus cannot demonstrate single muscle involvement. In addition, because the medial rectus subnucleus is in the most ventral portion of the nucleus, and all the dorsal subnuclei send axons through it, single muscle involvement of the medial rectus may not be possible. The eyelid levator subnucleus may be spared, because it is located at the dorsocaudal periphery of the nuclear complex.

The differential diagnosis is stroke (either ischemic or hemorrhagic), metastatic tumor, and multiple sclerosis. Of these diagnoses, only ischemic stroke is common. Disorders that simulate nuclear third cranial nerve palsy are myasthenia gravis, CPEO, thyroid ophthalmopathy, and the Guillain-Barre syndrome.

The laboratory investigation for this syndrome is MRI, which usually demonstrates the ischemic cerebrovascular lesion. Once the proper localization has been made, the diagnostic formulation is straightforward.

Sixth Cranial Nerve Nucleus

The sixth cranial nerve nucleus has two populations of neurons. The abducens motor neurons terminate on the ipsilatetal lateral rectus muscle. Internuclear neurons cross at the level of the sixth cranial nerve nucleus, join the MLF, and terminate on the medial rectus subnucleus of the third cranial nerve. Therefore a lesion of the sixth cranial nerve nucleus causes ipsilateral gaze palsy.

Patients with isolated horizontal gaze paresis are usually asymptomatic. If they do have symptoms, they complain of difficulty looking to one side. On examination, there is conjugate horizontal gaze paresis not overcome by an oculocephalic maneuver or caloric stimulation. This occurs because the fibers mediating this response, the VOR, synapse in the sixth cranial nerve nucleus. A peripheral seventh cranial nerve palsy invariably accompanies a lesion of the sixth cranial nerve nucleus. The differential diagnosis is stroke (Miller et al. 2002), Wernicke's encephalopathy, multiple sclerosis, and a tumor of the pontomcdullary junction.

Laboratory investigations for evaluating a lesion of the sixth cranial nerve nucleus are MRI, possibly lumbar puncture, and an edrophonium test to evaluate for myasthenia gravis if there are none of the long-tract signs obligatory for intra-axial disease.

OTHER BRAINSTEM AND ASSOCIATED SYNDROMES

Diencephalic Syndrome (Russell's Syndrome)

The common symptoms of diencephalic syndrome are emaciation with increased appetite, euphoria, vomiting, and excessive sweating (Pcrilongo et al. 1997). Patients may also have an alert appearance with motor hyperactivity. Most cases occur in children younger than 3 years.

The differential diagnosis at this stage is hyperthyroidism, diabetes mellitus, a tumor in the region of fourth ventricle, vein of Galen malformation, and a hypothalamic tumor. Most patients appear pale despite lack of anemia. Ophthalmological findings include optic atrophy and less commonly nystagmus.

Laboratory investigations for diencephalic syndrome may show an elevated serum growth hormone level that is incompletely suppressed by hyperglycemia. MRI usually demonstrates a hypothalamic mass lesion. Malignant cells may be present in the CSF, which are diagnostic. The CSF may also contain human chorionic gonadotropin in cases of germinomas. A lumbar puncture should not be performed if neuroimaging studies demonstrate a mass effect.

Thalamic Syndrome

Thalamic syndrome was first described by Dejerine and Roussy in 1906. The common symptoms of this syndrome are pain (thalamic pain), numbness, and hemisi'nsory loss. The pain may be spontaneous or evoked by any form of stimulation. It often has a disagreeable and lasting quality.

Patients may also complain of a distorted sense of taste. Right thalamic lesions appear to predominate.

On examination, there is marked hemianesthesia, which may be dissociated; that is, pain and temperature or light touch and vibration sense may be separately lost. There is usually proprioceptive loss, often with astereognosis. A transitory hemiparesis sometimes occurs.

The location of the lesion for this type of pain is usually the ventroposterolateral nucleus of the thalamus. In addition to the thalamus, thalamic-type pain can occur with lesions of the parietal lobe, medial lemniscus, and dorsolateral medulla (MacGowan et a I. 1997),

The differential diagnosis is stroke or tumor. The diagnostic formulation depends on the rate of onset of symptoms, associated signs, and neuroimaging studies. The apoplectic onset of symptoms implicates cerebrovascular disease. Gradual onset with progressive worsening of symptoms and signs is characteristic of brain tumor, Neuroimaging studies should confirm the clinical impression. The imaging modality of choice is MRI.

Tectal Deafness

The symptoms associated with tectal deafness are bilateral deafness associated with other related CNS symptoms, such as poor coordination, weakness, or vertigo. The differential diagnosis of the deafness is conduction-type hearing loss, cochlear disorders, bilateral eighth cranial nerve lesions, tectal deafness, and pure word deafness (sec Chapter 19).

On examination, there is deafness that usually spares pure tones. Pure word deafness with lesions of the inferior eolliculi has been reported (Vitte et a I. 2002). Other brainstem signs, including the dorsal midbrain syndrome, are often associated. The location of the lesion is the inferior eolliculi, with the most common causes being a tumor of the brainstem, cerebellum, or pineal region, trauma, and stroke.

The diagnostic formulation for hearing loss caused by lesions rostral to the cochlear nuclei is the presence of hearing loss characterized by sparing of pure tone, with marked deterioration when background noise distortion or competing messages are added. In addition, signs of damage to adjacent nervous system structures are present. Neuroimaging studies may confirm the diagnosis.

The pertinent laboratory investigations include MRI and an audiogram. Tests that reveal CNS auditory loss are distorted speech audiometry, dichotic auditory testing, and auditory brainstem-cvoked responses, although the latter may be normal (Vitte et al. 2002).

Foramen Magnum Syndrome

Foramen magnum syndrome is characterized by upper motor neuron-type weakness and sensory loss in any modality below rhe head. Detecting this syndrome is important, because it is often caused by benign tumors, such as meningiomas or fibromas, which may be removed completely when detected early in their course. Its only manifestations may be those of a high spinal cord syndrome {see Chapter 27).

The common, initial symptoms are typically neck stiffness and pain, which may radiate into the shoulder. Occipital headache also may be an early symptom. Other common symptoms are weakness of the upper or lower extremities, numbness (most commonly of hands or arms}, clumsiness, and a gait disturbance.

The differential diagnosis at this stage is cervical spondylosis, syringomyelia, multiple sclerosis, transverse myelitis, atlantoaxial subluxation, Chiari malformation, and foramen magnum or upper cervical cord tumor.

On examination, hemiparesis or quadriparesis and sensory loss are common. The loss of sensation may involve all modalities. It may be dissociated and capelike or occurring in a C2 distribution. Some patients have a hemisensory pattern below the cranium or involvement of only the lower extremities. Pseudoathctosis resulting from loss of joint position sense may be an early sign. Atrophy of muscles of the upper extremities may occur at levels well below the lesion (e.g., intrinsic muscles of the hands). Electric shock-like sensations radiating down the spine, which may be transmitted into the extremities, may occur with neck flexion (Lhermitte's sign). This finding occurs with lesions of the posterior columns, most commonly multiple sclerosis. Lower cranial nerve patsies are less common. The presence of downbeat nystagmus in primary position or lateral gaze strongly suggests a lesion of the cranioccrvical junction. This sign may be missed unless the eyelids are manually elevated and the nystagmus is sought when the patient gazes laterally and slightly downward.

The differential diagnosis at this stage is a foramen magnum or upper cervical cord tumor. The tumor type is usually meningioma, neurofibroma, glioma, or metastasis. Cervical spondylosis, multiple sclerosis, syringobulbia, and the Chiari malformation (often accompanied by a syrinx) are other diagnostic considerations. The definitive laboratory investigation for evaluation of the foramen magnum syndrome is MRI.

Patients with foramen magnum tumors may have a relapsing-remitting course that simulates multiple sclerosis. Because many of these tumors are meningiomas, one slit HI Id lv alert for patients at. risk. Meningiomas occur with increased frequency in women in their childbcaring years and increase in size during pregnancy. Cervical spondylosis is usually associated with a related radiculopathy and is not accompanied by downbeat nystagmus or lower crania] nerve abnormalities. Diagnosis requires a high index of suspicion early in the patient's course. Foramen magnum tumors are known to present difficult diagnostic problems because signs may be minimal despite a large tumor.

Syringobulbia

Syringobulbia is a disorder of the lower brainstem caused by progressive enlargement of a fluid-filled cavity that involves the medulla and almost invariably the spinal cord (syringomyelia). The symptoms and signs are primarily those of a disorder of the central spinal cord region (see Syringomyelia in Chapter 79; also sec Chaprct *66).*

The common symptoms of syringobulbia and syringomyelia arc painless burns, hand numbness, neck and arm pain, leg stiffness, and headache together with oscillopsia, diplopia, or vertigo. On examination, there are signs of lower brainstem dysfunction. Lower motor neuron signs of the ninth through twelfth cranial nerves may be present. Nystagmus, if present, is hotizontal, vertical, or rotatory. Signs of a spinal cord lesion characteristically coexist. In the upper extremities, there may be dissociated anesthesia of an upper limb or forequartet (i.e., loss of pain and temperature sensation with sparing of other modalities). The sensory loss may also be in a hemisensory distribution. Absent or decreased deep tendon reflexes in the upper extremities are the rule.

Spastic patapatesis, usually asymmettic, may occur. Loss of facial sensation can occur in an onionskin pattern emanating from the corner of the mouth. Charcot's (neuropathic) joints and trophic skin disorders can appear in long-standing cases. Horner's syndrome and bowel and bladder disturbances are other occasional findings.

The lesion is located in a rostrocaudal longitudinal cavity from the medulla into the spinal cord. The cavity is usually located near the fourth ventricle or central canal of the spinal cotd. The definitive laboratoty investigation fot syringobulbia is MRl, the most reliable and sensitive test to demonsttate a syrinx.

The differential diagnosis is intrinsic central cord and lowet brainstem lesion (syrinx, tumor, or trauma) and compressive foramen magnum syndrome caused by a tumor. Less likely causes are multiple sclerosis and spinal arachnoiditis.

The diagnostic formulation for syringobulbia involves history, examination, and laboratory evaluation. It is usually a disease of young adults, with a peak incidence in the third and fourth decades. Painless burns and dissociated segmental anesthesia of the upper extremities are of major diagnostic significance. Multiple sclerosis requires the presence of other noncontiguous lesions, oligoclonal bands in the CSF, and characteristic MRl findings. Tumors usually produce a more rapid course. Williams (1993) reviewed the treatment.

BRAINSTEM ISCHEMIC STROKE. SYNDROMES

Caplan, Pesin, and Mohr (1992) found that vcrtcbtobasilar ischemic lesions often have a rostrocaudal or patchy localization (Figure 22.1}, rather than the simplified transverse localization that is usually schematized. In addition, all the patient's symptoms and signs may not be explainable in anatomical terms; thai is, clinicopathological correlation may not be precise.

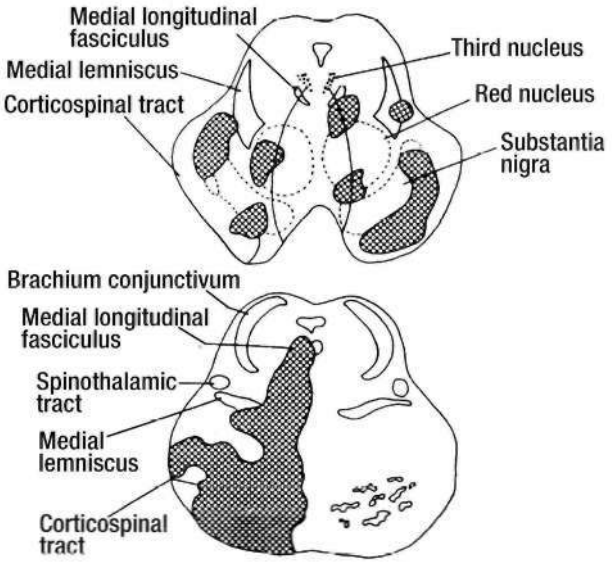

FIGURE 22.1 A postmortem examination of a patient of Kubik and Adams with embolism of the basilar artery. Note the rostrocaudal extension of the infarction along with its patchy nature. (Reprinted with permission from Kubik, C. S. *&c* Adams, 11. D. 1946, "Occlusion of the basilar artery: A clinical and pathological study," *P>rain,* vol. *69,* pp. 73-121.)

The cardinal manifestations of brainstem stroke are involvement of the long tracrs of the brainstem in combination with cranial nerve deficits. Crossed cranial nerve and motor or sensory long-tract deficits are characteristic. The cranial nerve palsy is ipsilatetal to the lesion and the long-tract signs are contralateral, hence the term *crossed.* Coma, ataxia, and vertigo, which ate common with vcrtcbtobasilar stroke, ate uncommon with internal carotid artery circulation stroke. INO, unreactive pupils, lower motor neuron cranial nerve impairment, and ocular skew deviation, when caused by stroke, occur only with posterior circulation lesions. The same is usually true fot nystagmus and most other ocular oscillations.

Another characteristic of vertebrobasilar ischemia is bilateral involvement of the long tracts. This can result in locked-in syndrome. This syndrome, usually caused by a lesion of the basis pontis, is characterized by quadriplegia with corticobulbar tract involvement and loss of the ability to produce speech. The reticular activating system is spared, and thus consciousness is preserved. Lye movements or blinking may be all that is left under voluntary control.

Anothet manifestation of bilateral lesions of the long tracrs is pseudobulbar palsy. The symptoms resemble those that occut with lesions of the medulla (bulb). However, cranial nerve nuclei have been disconnected from cortical input. This causes dysarthria, dysphagia, bilateral facial weakness, extremity weakness, and emotional lability.

A more descriptive term for this syndrome is *supranuclear bulbar palsy.*

Blindness occurs with bilateral posterior cerebral artery occlusion and concomitant occipital lobe infarction.

Ischemic stroke syndromes arc outlined in the following sections. These syndromes occur in isolation, as presented here, and in combination. The combinations can be medial, with lateral or often rostrocaudal extension.

Thalamic Stroke Syndromes

The blood supply of the thalamus is from the posterior cerebral, posterior communicating, basilar communicating (Figure 22,2), and anterior and posterior choroidal arteries. Thalamic stroke syndromes are listed in Table 22.4. They have been reviewed by Kumral et al. 2001,

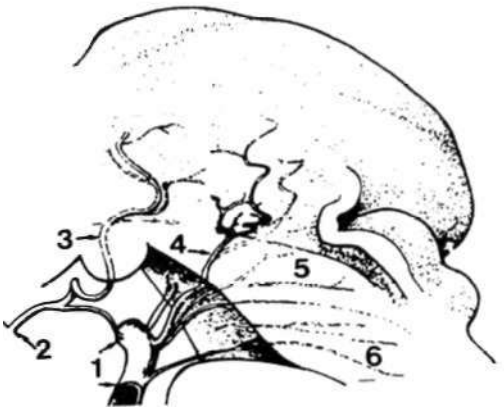

FIGURE 22.2 Branches of the basilar communicating artery as seen in a sagittal section of the brainstem. (1) Thalamic polar, (2) posterior communicating, (3) posterior th alamo subthalamic paramedian, (4) superior paramedian, (5) inferior paramedian, and (6) mesencephalic paramedian. (Reprinted with permission from Percheron, G. 1976, "Les arteres et territoires du thalamus humain: II. Arteres et territoires thalamiques paramedians de 1'artere basilare communicante," *Rev Neurol,* vol. 132, pp. 309-324.)

Midbrain Stroke Syndromes

Ischemia of the midbrain is characterized by long-tract signs combined with involvement of the third and fourth

Tabic 22.4: Ischemic stroke syndromes of the diencephalon

- Anterolateral
  - Common symptoms
    - Contralateral weakness, vision loss
    - Confusion
    - Disorientation
    - Language disturbance
  - Signs
    - Contralateral
      - I Icimparesis
      - Hemiataxia
      - Hemisensory loss
      - Homonymous hemianopia
    - Right-sided lesion: visuospatial abnormalities, hemincglect, nonverbal intellect affected
    - Left-sided lesion: disorientation, aphasia
  - Arterial territory involved: thalamic polar (tuberothalamie) artery (see Figures 22.2 and 22.3)
- Medial
  - Common symptoms
    - Disorientation and confusion
    - Coma with occlusion of mainstem variant
    - Visual blurring
  - Signs
    - Vertical gaze ophthalmoplegia
    - Loss of pupillary reflexes
    - Loss of convergence
    - Disorientation and confusion, stupor, coma, and various neuropsychiatry disturbances
  - Arterial territory involved: posterior tliaUunosLtbthahimic paramedian artery (thalamic paramedian or deep interpeduncular profundus artery [see Figures 22.2 and 22.3])
- Lateral and posterior internal capsule
  - Common symptoms
    - Contralateral
      - Hemiparesis
      - Numbness
      - Confusion
  - Signs
    - Contralateral
      - Hemiparesis
      - Diminished pain and temperature
      - Dysarthria
      - Homonymous hemianopia; characteristically with a tongue of visual field spared along the horizontal meridian (Figure 22.4]
    - Memory impairmenr
    - With right-sided lesions: visuoperceptual abnormalities
  - Arterial territory involved: anterior choroidal artery (see Figure 22.3)
- Posterolateral
  - Common symptoms
    - Contralateral
      - Weakness
      - Numbness
      - Vision loss
      - Neglect
      - Confusion
  - Signs
    - Contralateral
    - Loss of touch, pain, temperature, and vibration sense (common)
    - Hemiparesis in some
    - Hemiataxia
    - Homonymous hemianopia
    - Left hemispatial neglect
    - Poor attention span
  - Arterial territory involved: gcniculothalamic artery (see Figure 22.3)

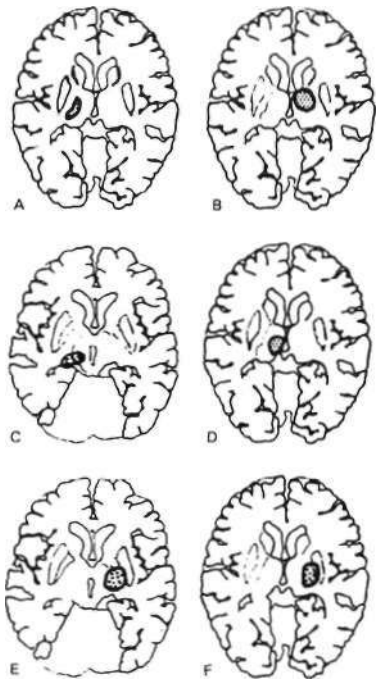

FIGURE 22.3 Schematic computed tomography sections showing the five arterial territories of the thalamus: (A) geniculothalamic (inferolateral) artery territory; (B) anterior thalamosubthalamic paramedian (tuberorhalamic} territory; (C) posterior choroidal territory; (D) posterior thalnmosubrhalamic paramedian territory; (E, F) anterior choroidal territory. (Modified with permission from Bogousslavsky, J,, Regti, F., & Uske, A. 1988, "Thalamic infarcts: Clinical syndromes, etiology and prognosis," *Neurology,* vol. 38, pp. 837-848.)

cranial nerves (Kumral et al. 2002b). Supratentorial (anterior circulation) stroke syndromes may present with midbrain signs when rostrocaudal deterioration occurs, causing transtentorial herniation. There are numerous classifications of the blood supply to the brainstem, and this is nowhere more apparent than in the midbrain.

Blood flows to the upper mesencephalon via perforating btanches of the basilar communicating artery. The basilar communicating artery (PI segment of the posterior cerebral artery or mesencephalic artery) connects the basilar artery with the posterior communicating artery. A simplified scheme used here divides the vasculat tctritories into median and lateral transverse regions.

The medial midbrain syndromes are characterized by an ipsilateral thitd cranial nerve palsy associated with a contralateral hemi paresis. Loss of the discriminative sensations (proprioception, vibration, and stereognosis) with involvement of the medial lemniscus may occur. The lateral syndromes are composed of contralateral loss of pain and temperature sensation and ipsilateral Horner's syndrome and loss of facial sensation. Ataxia may occur on either side. Ischemic stroke syndromes of the mesencephalon are outlined in Table 22.5, and the eponymic designations are given in Table 76.1.

Pontine Stroke Syndromes

The pons is supplied by numerous penetrating branches of the basilar artery. These arteries have little collateral supply; consequently, lacunar syndromes (see Chapter 57A) commonly occur (Table 22.6). These syndromes may be clinically indistinguishable from lacunar syndromes due to lesions of the interna! capsule. The medial syndromes are characterized by contralateral hemiparcsis and ipsilateral ataxia, 1NO, and conjugate horizontal gaze paresis.

The lateral syndromes arc distinguished by contralateral hemianesthesia and loss of discriminative sensation with ipsilateral Horner's syndrome, facial hemianesthesia, and ataxia. Ipsilatetal lower motor neuron-type facial paresis, sixth cranial nerve paresis, deafness, and vertigo occur with inferior pontine lesions.

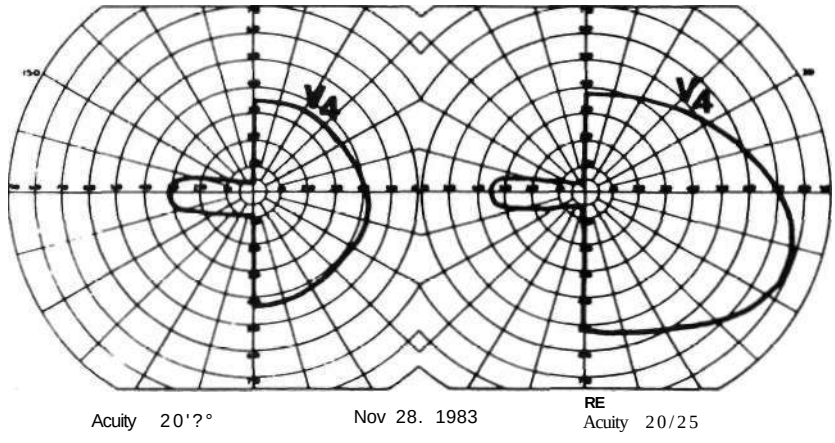

FIGURE 22.4 Typical homonymous hemianopia associated with anterior choroidal artery infarction. Notice the tongue of preserved vision along the horizontal meridian. This pattern is highly localizing to the lateral geniculate nucleus. (LE = left eye; RE = right eye.) (Reprinted with permission from Hclgason, C, Caplan, L., Goodwin, J., et al. 1986, "Anterior choroidal artery territory infarction: Report of cases and review," *Arch Neurol,* vol. 43, pp. 681686.)

Table 22.5: Ischemic sttoke syndromes of the mesencephalon

- Middle median midbrain syndrome
  - Common symptoms
    - Contralateral
      - Weakness
      - Ataxia
      - Numbness
    - Ipsi lateral
      - Eyelid ptosis
      - Ataxia
    - Diplopia
  - Signs
    - Contralateral
      - Weakness
      - Ataxia
      - Supranuclear horizontal gaze paresis
    - lpsilateral
      - Third cranial nerve palsy
      - Nuclear
      - Fascicular
    - [nternuclear ophthalmoplegia
  - Arterial territory involved: median and paramedian perforating branches of the hasilar or mesencephalic arteries
- Middle lateral midbrain syndrome (Figure 22.5)
  - (.ominoii symptoms
    - Numbness: contralateral
    - Clumsiness: ipsilateral
  - Signs
    - Contralateral
      - Hemianesthesia
      - Ataxia
    - Ipsilateral
      - Facial hemianesthesia (or contralateral)
      - Horner's syndrome
      - Ataxia (if lesion is ventral to brachium conjunctivum)
  - Atterial territory involved: superior cerebellar artery
- Inferior medial midbrain syndrome (Figure 22.6)
  - Common symptoms
    - Diplopia
    - Contralateral weakness
    - (Itiiusiuess
  - Signs
    - Contralateral
      - Fourth cranial nerve palsy
      - Ataxia (may he ipsilateral, depending on whether the lesion is before or after the crossing of the brachium conjunctivum)
      - Hcmiparesis
      - Supranuclear horizontal gaze paresis (ipsilateral if below decussation in lower midbrain)
    - Ipsilateral
      - Internuclear ophthalmoplegia
  - Arterial territory involved: median branches of the hasilar artery
- Inferior lateral midbrain syndrome (sec Figure 22.6)
  - Common symptoms
    - Contralateral numbness
  - Signs
    - Contralateral
      - Hemianesthesia
    - Ipsilateral
      - Hemianesthesia of face
      - Horner's syndrome
  - Arterial territory involved: superior cerebellar artery

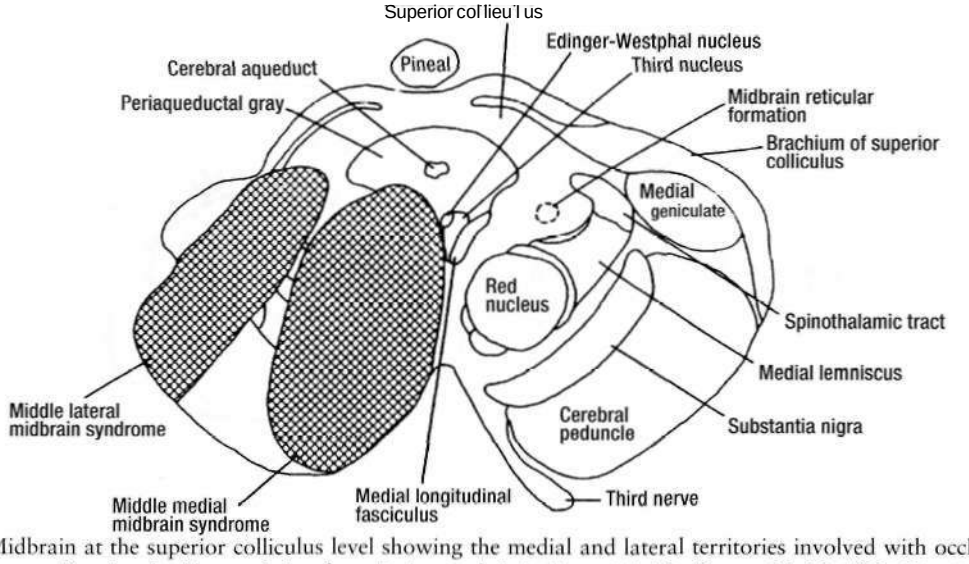

FIGURE 22.5 Midbrain at the superior colliculus level showing the medial and lateral territories involved with occlusive stroke syndromes in this area. (Reprinted with permission from DeArmond, S. J., Fusco, M. M., Dewey, M. M. 1976, *Structure of the Human Brain*, 2nd ed, Oxford University Press, New York.)

Tabic 22.6: I sell emit stroke syndromes of the pons

- Superior medial pontine syndrome (Figure 22.7)
  - Common symptoms
    - Contralateral weakness
    - Clumsiness
  - Signs
    - On side of lesion
      - Ataxia
      - Internuclear ophthalmoplegia
      - Myoclonus of palate, pharynx, vocal cords
    - On side opposite lesion
      - Paralysis of face, arm, and leg
  - Arterial territory involved: median branches of the basilar artery
- Superior lateral pontine syndrome (see Figure 22.7)
  - Common symptoms
    - Clumsiness; ipsilateral
    - Contralateral numbness
    - Dizziness, nausea, vomiting
  - Signs
    - On side of lesion
      - Ataxia of limbs and gait, falling to side of lesion
      - Horner's syndrome
      - Facial hemianesthesia
      - Paresis of muscles of mastication
    - On side opposite lesion
      - Hemianesthesia (trigeminothalamic tract) impaired touch, vibration, and position sense
  - Arterial territory involved: superior cerebellar artery
- .Middle medial pontine syndrome (Figure 22.8)
  - Common symptoms
    - Contralateral hemiparesis
    - Ipsilateral clumsiness
  - Signs
    - On side of lesion
      - Ataxia of limbs
      - Conjugate gaze paresis toward the side of the lesion
      - Internuclear ophthalmoplegia
    - On side opposite lesion
      - Paresis of face, arm, and leg
    - With bilateral lesions, locked-in syndrome may occur
  - Arterial territory involved: median branches of the basilar artery
- Middle lateral pontine syndrome (sec Figure 22.8)
  - Common symptoms
    - Numbness
    - Clumsiness
    - Chewing difficulty
  - Signs
    - Contralateral
      - Hemisensory loss
    - Ipsilateral
      - Ataxia of limbs
      - Paralysis of muscles of mastication
      - Impaired pain sensation over side of face
      - Horner's syndrome
  - Arterial territory involved: long lateral branches of basilar artery
- Inferior medial pontine syndrome (Foville's syndrome) (Figure 22.9)
  - Common symptoms
    - Contralateral weakness and numbness
    - Facial weaknesses: ipsilateral
    - Diplopia
  - Signs
    - Contralateral
      - Paralysis of arm and leg
      - Impaired tactile and proprioceptive sense over half the body
      - Internuclear ophthalmoplegia
    - Ipsilateral
  - Paresis of conjugate gaze to side of lesion; to oeulocephalic maneuver also if the sixth cranial nerve nucleus is involved
    - One-and-a-half syndrome
    - Nystagmus
    - Diplopia on lateral gaze
    - Lower motor neuron—type facial palsy
  - Arterial territory involved: median branches of the basilar artery
- Inferior lateral pontine syndrome (anterior inferior cerebellar artery syndrome) (see Figure 22.9)
  - Common symptoms
    - Vertigo, nausea, vomiting
    - Oscillopsia
    - Deafness, tinnitus
    - Facial numbness
    - Dyscoordination
  - Signs
    - Contralateral
      - Impaired pain and thermal sense over half the body (may include the face)
    - Ipsilateral
      - Deafness
      - Facial paralysis
      - Ataxia
      - Impaired sensation over face
  - Arterial territory involved: anterior inferior cerebellar artery

Medullary Stroke Syndromes

Medial medullary ischemia can cause crossed hypoglossal hemiparesis syndrome (Table 22."). In addition, patients may have loss of discriminative-type sensation (position sense, graphesthesia, and stereognosis) when there is associated medial lemniscus involvement. Kumral et al. (2002a) have described four patterns of medial medullary stroke: (1) the most frequent classic crossed hypoglossal hemiparesis syndrome, (2) sensorimotor stroke without lingual palsy, (3) pure hemiparesis, and (4) bilateral medial medullary stroke.

Lateral medullary syndrome (Wallenberg's syndrome) is one of the most dramatic clinical presentations in neurology (see Table 22.7). Long-tract signs (i.e., contralateral loss of pain and temperature sensation over half the body, ipsilateral ataxia, and Horner's syndrome) are accompanied by involvement of the nuclei and fasciculi of cranial nerves V, VIII, IX, and X, Nystagmus is often present. The critical sign that distinguishes this from a lateral

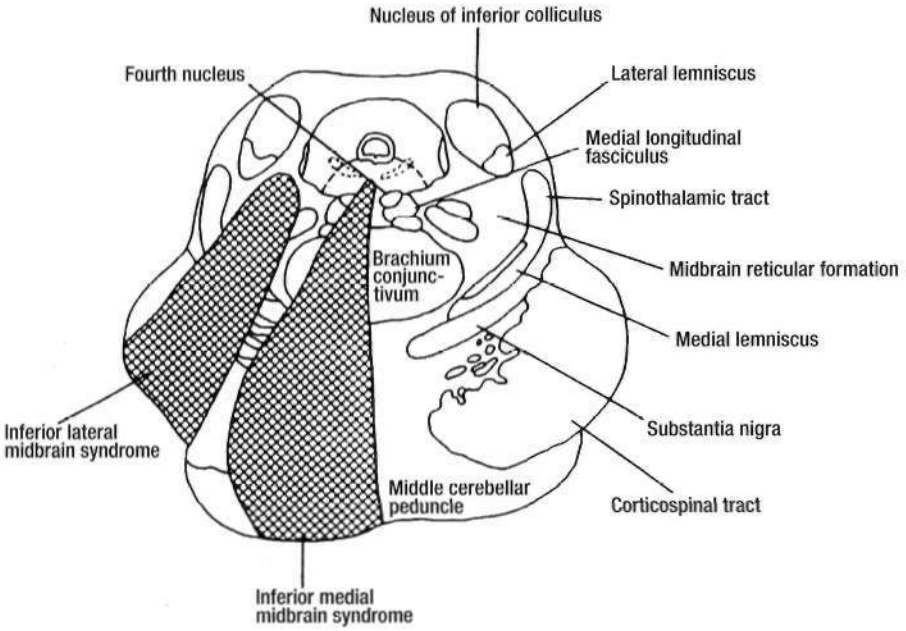

FIGURE 22.6 Midbrain at the inferior colliculus level showing the medial and lateral territories involved with ischemic stroke syndromes in this area. (Reprinted with permission from DeArmond, S. J., Fusco, M. M., & Dewey, M. M. 1976, *Structure of the Human Brain*, 2nd ed, Oxford University Press, New York.)

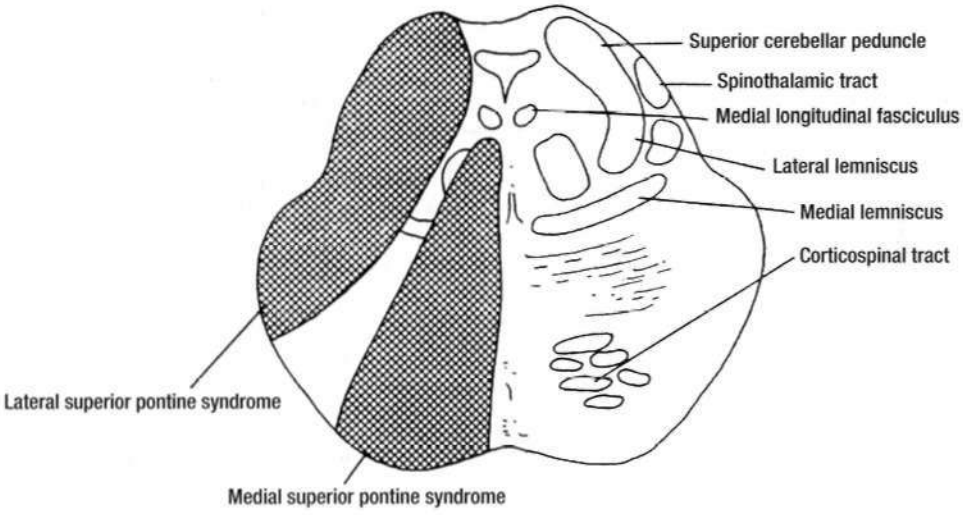

FIGURE 22.7 Superior pontine level showing the medial and lateral territories involved with occlusive stroke in this region. (Reprinted with permission from Adams, R. D. & Victor, M. 1993, *Principles of Neurology*, 5th ed, McGraw-Hill, New York.)

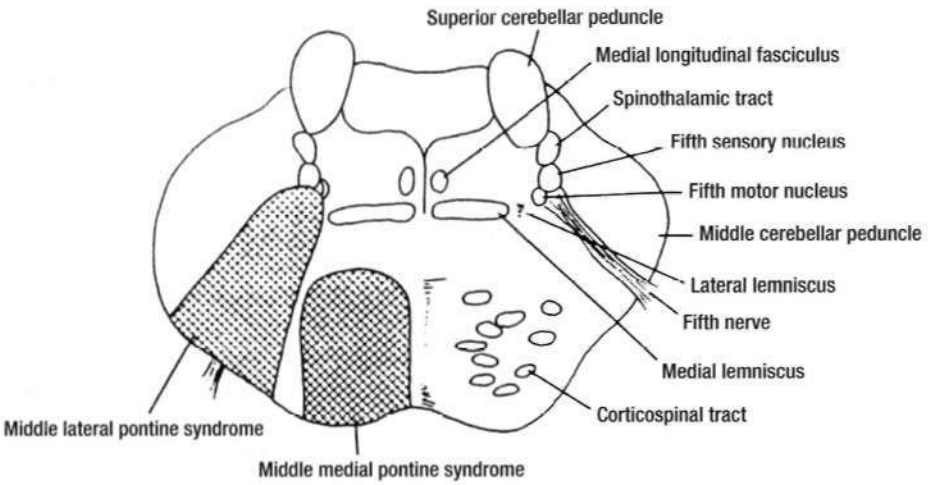

FIGURE 22.8 Middle pontine level, showing the medial and lateral territories involved with ischemic stroke syndromes in this locality. (Reprinted with permission from Adams, R. D. & Victor, M. 1993, *Principles of Neurology*, 5th ed, McGraw-Hill, New York.)

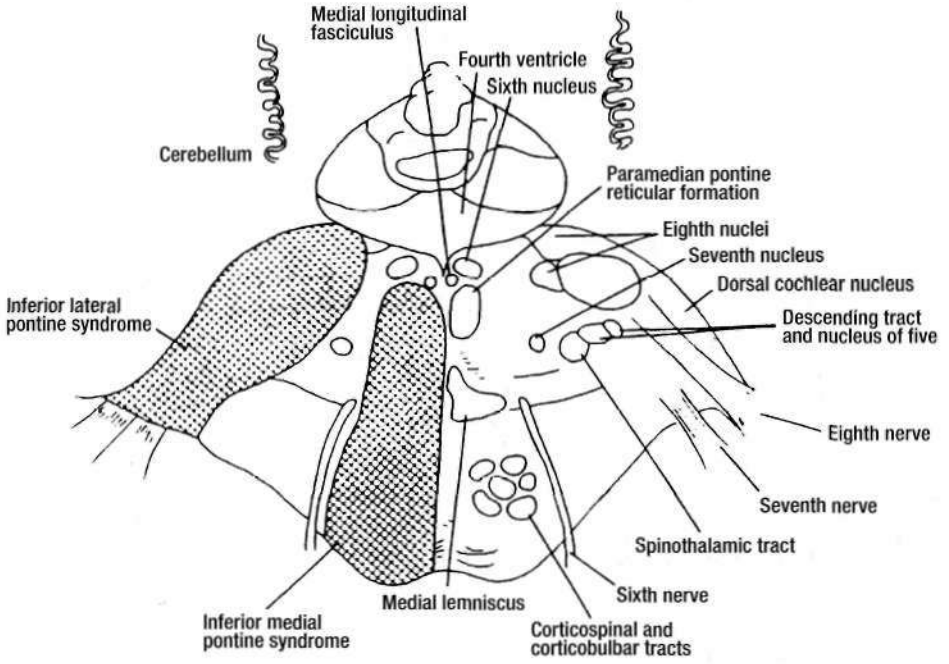

FIGURE 22.9 Inferior pons at the level of the sixth cranial nerve nucleus showing the medial and lateral territories involved with occlusive stroke in this area. (Reprinted with permission from Adams, R. D. & Victor, M. 1993, *Principles of Neurology*, 5th ed, McGraw-Hill, New York.)

Table 22.7: Ischemic stroke syndromes of the medulla

Medial medullary syndrome (Figure 22.10)
- Common symptoms
  - Contralateral weakness
  - Dysarthria
- Signs
  - Contralateral
    - Paralysis of arm and leg, sparing face
    - Impaired tactile, vibratory, and proprioceptive sense over half the body
  - Ipsilateral
    - Paralysis with atrophy (late) of hall the Longue
  - Primary-position upbeat nystagmus
- Arterial territory involved: occlusion of vertebral artery or branch of vertebral or lower basilar artery or anterior spinal artery

Lateral medullary syndrome (Wallenberg's syndrome) (see Figure 22.10)
- Common symptoms
  - Ipsilateral facial pain and numbness
  - Vertigo, nausea, and vomiting
  - Ipsilateral clumsiness
  - Diplopia, oscillopsia
  - Numbness ipsilateral or contralateral to lesion
  - Dysphagia, hoarseness
- Signs
  - Contralateral
    - Impaired pain sensation over half the body, sometimes including the face
  - Ipsilateral
    - Impaired sensation over half the face
    - Ataxia of limbs, falling to side of lesion
    - Horner's syndrome
    - Dysphagia, hoarseness, paralysis of vocal cords
    - Diminished gag reflex
    - Loss of taste
  - Other
    - Nystagmus
    - Primary-position rotatory
    - Gaze-evoked horizontal
    - Downbeating on lateral gaze
    - Ocular skew deviation
    - Hiccup
- Arterial territory involved: occlusion of any of five vessels may be responsible: vertebral; posterior inferior cerebellar; or superior, middle, or inferior lateral medullary arteries

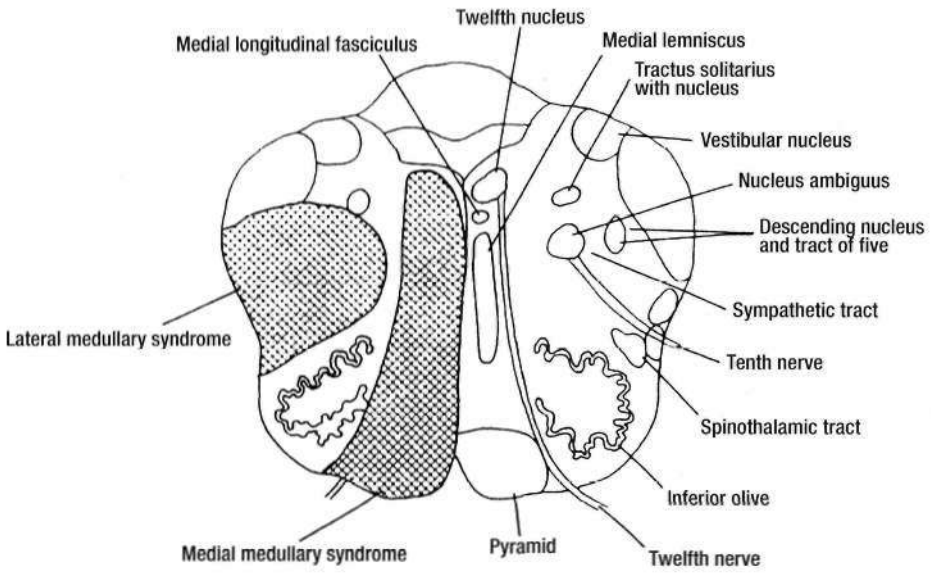

FIGURE 22.10 Cross section of medulla at the level of the inferior olivary complex showing the medial and the more common lateral territory involved with ischemic stroke in this brainstem site. (Reprinted with permission from Adams, R. D. & Victor, M. 1993, *Principles of Neurology*, 5th ed, McGraw-Hill, New York.)

pontine syndrome is involvement of the nucleus ambiguus or its fasciculus and consequent weakness of the ipsilatcral palate and vocal cord. (A more detailed discussion of stroke is found in Chapter 57A.)

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Chapter 23
Ataxic Disorders

S. H. Subramony

The term *ataxia* is used by clinicians to denote a syndrome of imbalance and incoordination involving gait and limbs, as well as speech; it usually connotes a disorder involving the cerebellum or its connections (Middleton and Strick 1998). Ataxia can also result from disturbances of sensory input to the cerebellum, especially proprioceptive input. The clinical approach to patients with ataxia involves differentiating ataxia from other sources of imbalance and incoordination, distinguishing cerebellar from sensory ataxia, and designing an evaluation based on knowledge regarding various causes of ataxia and cerebellar disorders (Massaquoi and Hallett 2002). This chapter describes the clinical features of ataxia and outlines a basic approach to patients presenting with ataxia.

SYMPTOMS AND SIGNS OF ATAXIC DISORDERS

In the case of cerebellar diseases, a few general statements can be made. In lateralized lesions of the cerebellum, signs and symptoms occur ipsilateral to the lesion. Generalized cerebellar lesions give rise to symmetrical symptomatology. Acute cerebellar lesions often produce severe abnormalities early but may show remarkable recovery with time. Chronic progressive diseases of the cerebellum tend to cause a gradually declining balance with longer lasting effects. To some extent, signs and symptoms have a relation to the location of the lesions in the cerebellum (Fine, Ionita, and Lohr 2002). Thus vestibulocerebellar lesions cause disequilibrium and an ataxic gait. Lesions of the vermis, which is primarily a "spinocerebellar organ," cause truncal and gait ataxia with relative sparing of the limbs. Neocerebellar lesions (cerebellar hemispheres) produce more severe appendicular ataxia.

Symptoms in Patients with Ataxia

1. *Gait disturbances:* Patients with cerebellar and sensory ataxia often present with abnormalities of gait. The initial symptom may be a sense of insecurity while walking, especially when doing acts that require a bit more skill such as turning or balancing on a narrow ledge. Even before gait becomes abnormal, patients may note problems with specialized skills they have previously learned, such as skiing, bicycling, or climbing. Patients may report the sense of imbalance as dizziness, but the sensation is more like being on a boat rather than vertigo. Patients and family notice that the patient feels more secure with feet progressively apart. An increase in imbalance when visual cues are removed suggests a sensory component to the ataxia.
2. *Limb ataxia:* Ataxic diseases cause a variety of symptoms in the upper limbs, resulting from incoordination and tremor. Patients report clumsiness with activities such as writing, picking up small objects, and buttoning. Patients become slow in their movements in an attempt to be more accurate. These symptoms are one sided with lateralized lesions of the cerebellum.
3. *Truncal ataxia:* Midline cerebellar lesions cause truncal ataxia. Patients may experience head tremor and a truncal instability leading to oscillatory movement of the head and trunk while sitting or standing {tituhation). Because of associated hypotonia, they may need back support while sitting.
4. *Dysarthria and bulbar symptoms:* Ataxic diseases of cerebellar origin result in slurred speech and abnormalities of pitch and volume control. Dysphagia may result from incoordination of swallowing muscles.
5. *Visual symptoms:* Patients may experience blurriness or a sense of environmental movements as a result of ocular oscillations associated with cerebellar disease.
6. *Symptoms in sensory ataxia:* Patients with a sensory basis for ataxia usually do not experience dysarthria or visual symptoms. They may report other symptoms of peripheral nerve disease such as paresthesias and numbness.

Neurological Signs in Patients with Cerebellar Ataxia

Gordon Holmes (1922; 19.39) is often credited with the initial descriptions of cerebellar deficits, although certainly earlier works had reported on the effects of cerebellar lesions. Lesions of the cerebellum can cause deficits involving gait and stance, limb incoordination, muscle tone, speech, and oculomotor system. There is also recent interest in the possibility that the cerebellum may have some role in cognitive function.

1. *Stance and gait:* Patients with cerebellar disease experience an increase in body sway, initially when the feet are placed together. The trunk moves excessively in the sideways direction (latcropulsion). With more severe disease, patients experience the increased sway with even normal stance and learn that balance is better with feet apart. Healthy persons have a spread of feet during normal stance of usually less than 12 cm; patients with cerebellar disease tend to have a much larger spread of feet during quiet stance (Manto 2002). In the clinic, one can detect problems with balance even earlier by asking the patient to do a tandem stance or stand on one foot; normal adults can do these maneuvers for at least 30 seconds. The Romberg test is usually positive in patients with cerebellar ataxia, although this tends to be more prominent in patients with proprioceptive or vestibular lesions. Lastly, many patients experience rhythmic oscillations of the trunk and head known as titubation. Severe truncal ataxia can also result in inability to sit without back support. Gait can be tested by asking the palienl lo walk naturally down a straiglil path. Ataxic gait is characterized by a widened base and an irregular staggering appearance resembling alcoholic intoxication. Overall, the speed of movements is not severely impaired, although patients may deliberately slow down to keep their balance. The steps are irregular and the patient may lurch in unpredictable ways. Ataxic gait disturbance can be detected even earlier by testing tandem gait; patients with cerebellar lesions lose their ability to do heel-to-toe walking in a straight line.
2. *Limb incoordination:* A number of clinical tests have been designed to test limb incoordination and the presence of tremor usually associated with cerebellar lesions. The finger-to-nose test involves touching the tip of the nose with the tip of the index finger repeatedly after extending the arm. The finger-to-finger test is done by asking the patient to touch the examinct's finget repeatedly and rapidly as the examiner moves his or her finger to a different location. Action tremor can be examined by placing the arms in the outstretched position and asking the patient to point the index fingers at each other at about chest level separated by about 1 cm. Rapid alternating movements are examined by asking the patient to supinatc and pronatc the forearm in the unsupported position. This can also be done by having the patient clap one hand on the other (stationary) hand alternately with the palm and dorsum of the clapping **hand.** Rebound is examined by allowing the patient to flex the elbow against the examiner's hand and then abruptly removing the resistance and assessing the ability of the patient to arrest the sudden flexion movement. In the lower limbs, the heel-to-shin maneuver is done by having the patient bring the heel of the leg being tested to the opposite knee and then sliding it in a straight line down the anterior aspect of the tibia to the ankle. The foot should be nearly vertical while doing this. Having the patient rest the heel on the opposite knee for a period can elicit tremor in the leg. The toc-to-finger test is done by asking the patient to touch the examiner's finger repeatedly as the examiner moves the finget to a new position. Lower limb testing is best done in the supine position. These tests detect the following abnormalities in patients with ataxia:

   a. *Dysmetria:* This term refers to an error in the path of movement so that the desired target is either under-reached (hypometria) or over-reached (hypermetria). Dysmetria is evident in the finger-to-finger and toe-to-finger tests. Holmes thought of dysmetria as a disturbance of the rate, range, and force of movement. Dysmetria is often increased by adding a mass to the hand.
   b. *Intention (kinetic) tremor:* Oscillations of the limbs that show a characteristic increase in amplitude at the end of a voluntary movement intended to reach a target are typically seen with cerebellar lesions. The oscillations appeat to result from instability at the proximal, rather than the distal, portions of the limbs and are typically perpendicular to the axis of motion. In contrast, patients with essential tremor who do not have any other cerebellar signs may exhibit an cxaggctation of their tremor at the termination of a purposeful movement that is primarily in the distal portions of their limbs. The finger-to-nose and heel-to-shin maneuvers detect the kinetic tremor. Kinetic tremor is better evaluated when mass is added to the hand.
   c. *Action tremor:* Cerebellar lesions can give rise to a postural tremor initiated by keeping the arms outstretched or pointing the fingers steadily at each other. In the legs, maintaining one heel on the opposite knee can bring out such a tremor.
   d. *Other types of tremor:* Ataxic patients can exhibit an axial tremor involving the head and shoulders. Also, a severe tremor in the upper limbs that has both an intention and a postural component can appear in cerebellar outflow tract disease. This has been also

called a "rubral" tremor or "wing-beating" tremor. This cerebellar outflow tremor is often seen in multiple sclerosis, Wilson's disease, and midbrain strokes.

e. *Dysdiadochokinesis:* This term refers to irregularity of the rhythm and amplitude of rapid alternating movements. Simple tapping movements such as the index finger on the thumb crease or the feet on the floor can also detect the disturbance in rhythm (dysrhyth mokincsis).

f. *Decomposition of movements;* The characteristic jerkiness and the appearance that the movements are composed of their elemental components rather than a smooth finished product are referred to as *decomposition of movements.* This overall feature of ataxic movements can be conceptualized as being secondary to a combination of dysdiadochokinesis, dysmetria, and kinetic tremor,

3. *Abnormalities of muscle tone and strength;* Although hypotonia can occur with acute cerebellar lesions, this is not a major feature of most cerebellar diseases. The inability of patients to check forearm movement in the rebound test is often quoted to result from hypotonia but may have other explanations. Similarly, cerebellar lesions do not cause a loss of strength in the traditional sense, but many patients experience problems with sustaining a steady force during sustained hand use (isometrataxia) (Manto 2002).

4. *Oculomotor disturbances* (Martin and Corbett 2000): Routine eye movement examination can detect most of the signs of cerebellar disease. Fixation abnormalities are examined by asking the patient to maintain sustained gaze at the examiner's finger held about 2 feet in front. Then the patient is asked to follow the finger as it is moved slowly in all directions of gaze (pursuit). Eccentric gaze is maintained (at about 30-degree deviation) to check for nystagmus. Saccades are tested by having the patient shift gaze quickly between an eccentrically held finger and the examiner's nose in the middle. More sophistication can be brought to clinical examination by looking at the vestibulo-ocular reflex (VOR), with the patient in a rotary chair and looking at an object that moves with the chair. Rotating striped drum is used to examine for optokinetic nystagmus (OKN) and Frenzel goggles can be used to remove fixation.

   a. *Disorders of pursuit:* Pursuit movements include fixation (pursuit at 0 degree velocity). Small, 0.1-0.3-degrce square wave movements of the eyes are often seen even in normal persons during fixation. Square wave jerks exceeding 10 per minute are indicative of central nervous system (CNS) disease but arc not as specific for cerebellar ataxia as are large-amplitude square wave jerks. Square wave jerks larger than 10 degrees in amplitude are called *macrosquare wave jerks.* The square wave jerks are so called because in eye movement recordings they appear as 2 saccades in opposite directions separated by a short period of no movement, giving a "square" appearance to the waveform. Cerebellar disease also slows down pursuit movements, requiring catch-up saccades to keep up with a moving target. Such saccadic intrusions and intrusions of square wave jerks give a "ratchety" appearance to pursuit movement.

   b. *Disorders of saccades:* Saccade velocity is normal in cerebellar disease, but its accuracy is impaired so that both hypermetric and hypomctric saccades are seen. Such saccades are followed by a corrective saccade in the appropriate direction (Munoz 2002).

   c. *Other saccadic intrusions:* Ocular flutter differs from square wave jerks in that the back and forth horizontal saccades are not separated by an intcr-saccade interval. Opsoclonus is characterized by continuous saccades in all directions in a chaotic fashion. Both ocular flutter and opsoclonus are associated with cerebellar disease, especially paraneoplastic or postinfectious syndromes.

   d. *Nystagmus:* Gaze-evoked nystagmus is elicited when eccentric gaze is maintained at about 30 degrees from the midline. There arc repetitive drifts of the eyes toward midline followed by saccades to the eccentric position. The fast phase of the nystagmus is always to the side of the eccentric gaze. This nystagmus is usually seen in cerebellar disease. When typical gaze-evoked nystagmus fatigues and reverses direction after a few seconds, this is called *rebound nystagmus.* Rebound nystagmus may also appear as a transient nystagmus in the opposite direction when the eye is first returned to the midline. Rebound nystagmus is also seen in cerebellar disease. Downbeat nystagmus is characterized by a rapid phase in the down direction in primary position of the eyes. Such downbeat nystagmus becomes more prominent with downgaze or gaze to the side. Downbeat nystagmus is typically seen in abnormalities of cranio vertebral junction such as A mold-Chiari malformation but can also occur in some degenerative ataxias such as spinocerebellar ataxia type 6. Finally, upbeat primary position nystagmus can be seen in lesions ot the anterior vermis.

   e. VOR; In a rotary chair, normal individuals can suppress the VOR and keep their eyes on an object moving slowly with the chair. Patients with cerebellar disease cannot inhibit the VOR, so the eyes tend to drift away from the object and make catch-up saccades as the chair is rotated,

5. *Speech and bulbar function:* Speech is evaluated by listening to the spoken words and asking the patient

to speak a standard phrase. Speech in cerebellar disease is characterized by some slowness, slurring of the words, and a general inability to control process of articulation, leading to unnecessary hesitations and stops, omission of pauses when needed, and an accentuation of syllables when not needed Also, there is a moment to-moment variability in the volume and pitch conttol and inappropriate control of the breathing needed for speech, causing a scanning dysarthria. Mild dysphagia is not uncommon in cerebellar disease. In children, a form of "cerebellar mutism" has been described after posterior fossa surgery. This is transient and followed by more typical cerebellar dysarthria.

Cognitive function (Scmahmann 2002): A cerebellar cognitive affective syndrome has been described and includes defective executive function, visuospatial difficulties, mild language disturbances such as agrammatism, and behavioral changes including inappropriate behavior and attention deficits. Such cognitive deficits arc modest compared with the motor difficulties in these patients.

Neurological Signs in Patients with Sensory Ataxia

In this situation, the major basis of ataxia is defective proprioception. Patients can be shown to have impaired position and vibration sense and the deep tendon reflexes are often lost because of the afferent fiber pathology. The Romberg test is positive. Many "degenerative" ataxic syndromes combine features of cerebellar and proprioceptive deficits in a variable combination. This led Greenfield to classify ataxic disorders as spinal, cerebellar, or spinocerebellar in nature.

APPROACH TO PATIENTS WITH ATAXIA

The recognition of an ataxic basis to the gait and coordination problems a patient may have is usually easy (see Chapter *7H:* Disorders of the Cerebellum, including the Degenerative Ataxies). Other neural disorders that can give

Table 23.1: Acquired and genetic causes of ataxias

Acquired disorders causing ataxia	
Congenital	Ataxic cerebral palsy; other early insults
Vascular:	Ischemic strokes, hemorrhagic stroke, AV malformations
Infectious:	Acute cet'cbellins; postinfectious encephalomyelitis; cerebellar abscess; HIV; CJD
Toxic:	Alcohol; anticonvulsants; mercury; 5-FU; cytosine arabinoside
Neoplastic:	Gliomas, ependymomas, meningiomas; basal meningeal carcinomatosis
Immune:	Multiple sclerosis; paraneoplastic syndromes; anti-GAD, gluten ataxia
Deficiency:	Hypothyroidism, vitamin B^, vitamin Bi
Genetic disorders causing ataxia	
Recessive:	Friedreich's ataxia, AT, other DNA repair defects; metabolic errors
Dominant:	SCA type 1 through SCA type 23; episodic ataxias
linked	
Mitochondrial	NARP; MERRF; others including Kearns-Sayre syndrome and MELAS

AT = ata x la -te I a ng icctasi a; A V = atri o ven tri c u la r; CJ D = G reutz-Creut/feldr-Jakob disease; DNA = deoxyribonucleic acid; 5-FU = 5-fluorouracil; GAD = glutamate decarboxylase; HIV = human immunodeficiency virus; MELAS = mitochondrial, encephalopathy, lactic acidosis, and strokelike episodes; MF.RRF = myoclonus epilepsy and ragged red fibers; NARP = neuropathy, ataxia, and retinitis pigmentosa; SCA = spinocerebellar ataxia.

Tabic 23.2: Causes of ataxia related to age at onset

Age at onset	*Acquired*	*Genetic*
Infancy	Ataxic cerebral palsy, other intrauterine insults	Inherited congential ataxias such as Joubert's syndrome, Gillespie's syndrome
Childhood	Infections like acute cerebellitis, abscess; posterior fossa tumors like cerebellar gliomas, ependymomas, pontine glioma; vascular malformations; congential anomalies like Arnold-Chiari malformation; toxic such as anticonvulsants; immune related to neoplasms, especially opsoclonus-myoclonus	Ataxias related to "inborn errors of metabolism" such as the aminoacidurias, organic acidurias, Wilson's disease, etc.; Friedreich's ataxia; AT; ataxia with oculomotor apraxia; vitamin *E* deficiency syndromes; some dominant SCAs like SCA-7, SCA-13, and DRPLA, as well as episodic ataxia syndromes
Young adults	Infections such as abscesses, HIV; posterior fossa mass lesions such as meningiomas, gliomas; congenital anomalies including vascular malformations, Arnold-Chiari malformation; hypothyroidism; toxic such as anticonvulsants and alcohol; immune causes such as MS	Friedreich's ataxia; dominantly inherited SCAs such as SCA-1, SCA-2, MJD, SCA-7; inherited tumor syndromes such as von Hippel-I.andau syndrome
Older adults	Same as above plus idiopathic ("sporadic") ataxias; immune lesions such as paraneoplastic ataxias; anti-GAD and anti-gliadin antibodies	More benign SCAs such as SGA-6

AT = ataxia-telangiectasia; DRPLA = dentatorubral-pallidoluysian atrophy; HIV = human immunodeficiency virus; GAD = glutamate decarboxylase; MJD = Machado-Joseph disease; MS = multiple sclerosis; SCA = spinocerebellar ataxia.

Table 23.3: Causes of ataxia based on mode of onset and subsequent course

'ii-ui/iu	*Acquired diseases*	*Genetic diseases*
Episodic		Many "metabolic ataxias" of childhood; autosomal dominant episodic ataxia syndromes
Acute (hours to days)	Strokes, ischemic and hemorrhagic; MS; infections and parainfectious causes such as acute ccrcbcllitis and abscesses; toxic disorders	
Subacute (weeks to months)	Mass lesions such as gliomas, ependymomas, meningeal infiltrates; infections such as HIV and CJD; deficiency syndromes such as B_{12} and *B,;* hypothyroidism; immune causes such as paraneoplastic and anti-GAD/anri-gliadin; alcohol	
Chronic (years)	Some mass lesions such as meningiomas, cranio vertebra I junction anomalies; alcoholic; idiopathic cerebellar and "olivopontocerebellar" atrophies; MSA	Most genetic disorders such as FA, AT, and other recessive ataxias; all progressive SCA (dominant inheritance)

AT = ataxia-telangiectasia; CJD = Creutzfeldt-Jakob disease; FA = Friedreich's ataxia; CAD = glutamate decarboxylase; HIV : human immunodeficiency virus; MS = multiple sclerosis; MSA = multiple system atrophy; SCA — spinocerebellar ataxia.

rise to such problems with gait and dexterity, including nerve and muscle diseases, spinal cord diseases, and basal ganglia disorders, can usually be distinguished on the basis of physical signs alone.

Some patients with bilateral frontal lobe lesions may have a gait disorder superficially resembling ataxia (Bruns' ataxia or frontal ataxia}. However, limb and eye movement signs of cerebellar disease are absent and the gait is narrower based. Other gait disorders such as those associated with dystonia or chorea may also be occasionally mistaken for cerebellar ataxia.

The next task is to determine whether the ataxia is primarily cerebellar, primarily proprioceptive, ot a combination of both. Further diagnostic considerations and avenues for investigations and therapy arc dependent on arriving at a specific diagnosis (Table 23.1). This can be a daunting task, especially when the disease appears to be "degenerative" in naIlire (i.e., associated with cerebellar atrophy). As an example, the Online Mendelian Inheritance in Man Web site lists more than 400 genetic disorders alone in which ataxia can occur. In a patient with ataxia, many additional pieces of information may be useful in arriving at a diagnosis. These include the age at onset (Table 23.2); the tempo of disease (Table 23.3); whether the ataxia is predominantly spinal, spinocerebellar, cerebellar, or associated with spasticity (Tabic 23.4); the presence or absence of nonccrebellar neurological signs (Table 23.5); the occurrence of any distinctive systemic features (Table 23.6); and the nature of imaging abnormalities (Table 23.7).

Table 23.4; Ataxias that are primarily cerebellar, proprioceptive, and cerebellar, primarily proprioceptive and associated with spasticity

t <• rubellar araxias	
	Most of the acquired lesions in Table 23.1; dominant ataxias characterized by pure cerebellar ataxia
Proprioceptive-cerebellar ataxias	
	AT; SCA-2, MJD, SCA-4
Proprioceptive ataxias	
	FA; vitamin F. deficiency; acquired sensory ataxias such as those associated with paraneoplastic sensory ncuronopathy, Sjogren's syndrome, and diabetes
Spastic ataxias	
	SCA-1, MJD, SCA-7, some cases of FA

AT = ataxia-telangiectasia; FA = Friedreich's ataxia; MJD = Machado-Joseph disease; SCA — spinocerebellar ataxia.

Table 23,5: Systemic signs that may be useful in the differential diagnosis of ataxia

Systemic feature	*Possible diagnosis*
Short stature	Mitochondrial disease; early CNS insults
Hair loss	Hypothyroidism
Conjunctival telangiectasia	AT
(annuls	Marinesco-Sjogren syndrome
KF rings	Wilson's disease
Cervical lipoma	Mitochondrial disease
Abnormal ECG, echocardiogram	FA, mitochondrial disease
Organomegaly	Niemann-Pick disease, Gaucher's disease
Hypogonadism	Ataxia with hypogonadism (Holmes's ataxia)
Diabetes	FA
Spine and foot deformity	FA, AT
Hematological malignancy	AT
Sinopulmonary infections	AT
Tendon xanthomas	Cerebrotendinous xanthomatosis
High CK	AR ataxia with high CK and neuroparhy; mitochondrial
High uric acid	Partial HGPRT deficiency

AR = autosomal recessive; AT = ataxia-telangiectasia; CK = creatine kinase; CNS = central nervous system; ECG = electrocardiogram; FA = Friedreich's ataxia; HGPRT = hypoxanthine guanine phosphorihosyl transferase.

Table 23.6: Noncerebellar neurological signs or symptoms that may help in the differential diagnosis of ataxia

Neurological signs or symptoms	*Possible diagnosis*
Focal and laterali/ed brainstem deficits such as facial palsy, hemiparesis	Posterior circulation strokes, posterior fossa tumors, MS
Visual loss from optic atrophy or retinopathy	MS, FA, mitochondrial diseases, SCA-7
Papilledema, headache	Posterior fossa tumors or ataxia as a "false localizing" sign
Internuclear ophthalmoplegia	Posterior circulation strokes, MS, some SCAs
Gaze palsies	MS, strokes, SCAs 1, 2, 7, and MJD
Ptosis and ophthalmoplegia	Strokes, mitochondrial disease
Slow saccades and ocular apraxia	SCA-2, AT, SCA-7, recessive ataxia with oculomotor apraxia
Downbeat nystagmus	Aniokl-Clnari malformation, basilar invagination. SCA-<S and LA-2, lithium toxicity
Spasticity, UMN signs	Posterior circulation strokes, tumors/malformations compressing brainstem, MS, many SCAs, FA
Basal ganglia deficits	Many SCAs like MJD, SCA-2, SCA-1, and DRPLA; ataxic form of MSA; Wilson's disease, Fahr's disease, mitochondrial disease
Autonomic failure	Ataxic form of MSA
Proprioceptive loss	Bi2 deficiency, other sensory ataxias, FA
Epilepsy	Ataxia associated with anticonvulsants, some idiopathic ataxias, SCA-IO, DRPLA
Myoclonus	Mitochondrial disease, Unverricht-Lundbotg disease, DRPLA, and SCA-7 of childhood onset, sialidosis, ceroid lipofuscinosis, "idiopathic" ("Ramsay Hunt syndrome")
Cognitive decline	Alcohol related, MS, CJD, HIV, DRPLA, SCAs at endstage

CJD = Creutzfeldt-Jakob disease; DRPLA = dentatorubral-pallidoluysian atrophy; F,A = episodic ataxia; FA = Friedreich's ataxia; HIV = human immunodeficiency virus; MJD — Machado-Joseph disease; MS = multiple sclerosis; MSA = multiple system atrophy; SCA = spinocerebellar atrophy; UMN = upper motor neuron.

Table 23.7: Brain imaging abnormalities that can serve to differentiate the ataxias

MRl abnormality	*Possible diagnostic considerations*
Mass in cerebellum/posterior fossa	Tumors such as gliomas, posterior fossa meningiomas, abscess
Abnormal cranio vertebral junction	Arnold-Chiari malformation, basilar invagination
Infarcts, vascular malformations	Ischemic lesions; vascular malformations
Signal density changes in the cerebellum	MS, acute cerehellitis
Pure cerebellar atrophy	Inherited ataxias such as SCA-6, SCA-5, and others; idiopathic cortical cerebellar atrophy; other acquired atrophic cerebellar diseases such as hypothyroidism, toxic diseases, autoimmune ataxias
Pontocerebellar atrophy	Common inherited ataxias such as SCA-1, SCA-2, MJD; sporadic olivopontocerebellar atrophy; "ataxic" form of MSA
Cervical cord atrophy	"Spinal" forms of ataxia such as FA and vitamin E deficiency
White matter changes	Leukodystrophies presenting with ataxia, MS

FA = Friedreich's ataxia; MJD = Machado-Joseph disease; MR] = magnetic resonance imaging; MS = multiple sclerosis; MSA = multiple system atrophy; SCA = spinocerebellar atrophy

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Chapter 24
Movement Disorders: Diagnosis and Assessment

Joseph Jankovic and Anthony E. Lang

The term *movement disorders* often is used synonymously with *basal ganglia* or *extrapyramidal diseases,* but neither of those terms adequately encompasses all the disorders included under the broad umbrella of movement disorders. Movement disorders are neurological motor disorders manifested by slowness or poverty of movement {bradykinesia or hypokinesia, such as that seen in parkinsonian disorders} at one end of the spectrum and abnormal involuntary movements (hyperkinesias) such as tremor, dystonia, athetosis, chorea, ballism, tics, myoclonus, restless legs syndrome, stereotypies, akathisias, and other dyskinesias at the other. Although motor dysfunctions resulting from upper and lower motor neuron, spinal cord, peripheral nerve, and muscle diseases usually are not classified as movement disorders, abnormalities in muscle tone {e.g., rigidity, spasticity, and stiff man syndrome), incoordination (cerebellar ataxia; Chapters 23 and 78), and complex disorders of execution of movement denoted by the term *apraxia* (Chapter 10) arc now included among movement disorders.

Abnormal movements are a clinical sign for which there are many possible causes. In most fields of neurology, the recommended clinical approach to movement disorders is to determine where in the nervous system the disease process is located and what that process could be. When dealing with movement disorders, however, the first step is to define the most appropriate broad movement disorder class, based on knowledge and recognition of phenomenology. Some abnormal movements may appear to be bizarre and therefore difficult to categorize. Despite attempts at uniformity in definition, classification errors are common. Inaccurate categorization occasionally has resulted in clinical, generic, and epidemiological misinformation becoming embedded in the literature. Video documentation is very useful in clarifying the phenomenology, thereby minimizing the risk of misdiagnosis.

Many movement disorders have no known or established cause. These disorders, sometimes called essential or idiopathic, are now best classified as primary and should be distinguished from those that arc secondary to identifiable diseases. In the following sections, historical and clinical features are emphasized that help the clinician make this distinction. Family history, including the ethnic origin (e.g., Ashkenazi Jewish} and parental consanguinity, often is helpful in arriving at a diagnosis. It is crucial to recognize-that the symptoms in other family members may be different from those in the patient because of variability of gene expression and penetrance. For example, some family members of patients with primary dystonia may have dystonic features, whereas others may have predominantly tremor. Additional problems that may hamper the acquisition of an adequate family history include adoption, uncertain paternity, and even the deliberate withholding of important family information. Denial of positive family history is particularly common in patients with Fluntington's disease and the genetic ataxias. An adult-onset disorder may not have been evident in a family member who died at an early age. It is particularly important to exclude Wilson's disease because of the specific therapy available and its universally fatal outcome if left untreated (Svetel etal, 2001}.

A history of birth and early developmental abnormalities also must be obtained, especially emphasizing the possibility of anoxia or kernictcrus. A history of encephalitis must be sought. Certain drugs and toxins have a strong potential for causing movement disorders, particularly drugs that block dopamine receptors. These include antipsychotic drugs; certain antiemetic drugs and other drugs used for various gastrointestinal disorders such as metoclopramide, prochlorperazine, and promethazine; calcium channel blockers such as cinnarizine and flunarizine; central nervous system (CNS) stimulants such as methylphenidate and cocaine; and dopaminergic drugs such as levodopa.

Besides documenting the movement disorder, neurological examination should search for additional findings that would help indicate the secondary nature of the problem. General physical examination must be thorough. An extremely important component of the examination is a corneal evaluation, including slit-lamp examination, to exclude the presence of a Kayser-Fleischer ring, characteristic of Wilson's disease (Plate 24.1). The nature and extent of laboratory investigations depend on the clinical suspicions. Without clues from the history and physical examination, however, very few specific or special investigations assist in diagnosing these patients.

PARKINSONISM

The initial feature of many basa! ganglia diseases is slowness of movement (bradykincsia) and paucity or absence of movement (akinesias), often associated with rigidity and ttemor (Jankovic 2003). Some authors have used the term *hypokinesia* to describe a reduction in amplitude of movement. Many parkinsonian symptoms are explained by the combination of slowness and poverty of movement and increase in muscle tone. The term *parkinsonism* is used to describe a syndrome manifested by a combination of the following six cardinal features: (1) tremor at rest, (2) rigidity, (3) bradykincsia, (4) loss of postural reflexes, (5) flexed posture, and (6) freezing (motor blocks). A combination of these signs is used to clinically define definite, probable, and possible parkinsonism. Diagnosis of definite parkinsonism requires **that at** least two of these features must be present, with one of them being resting tremor or rigidity; probable parkinsonism consists of resting tremor or rigidity alone; and possible parkinsonism includes at least two of the remaining four features. The four major characteristics of parkinsonism—tremor, rigidity, akinesia, and postural disturbances {forming the acronym TRAP)—account for most of the clinical abnormalities described here.

The most common cause of idiopathic parkinsonism (akinetic-rigid syndrome) is Parkinson's disease (PD). As a resulr of advances in genetics, many forms of idiopathic parkinsonism have been found to result from mutations in specific genes, such as those coding fot cc-synuclein or the Parkin protein. Whereas some of the gene mutations (e.g., *a-synuclein* gene) are very rare causes of parkinsonism, *Parkin* gene mutations account for up to 50% of all patients with early-onset parkinsonism. Because PD is defined as idiopathic parkinsonism, the notion of multiple Parkinson's diseases should be considered to draw attention to the different genetic causes of idiopathic parkinsonism, Besides genetic causes, there are many other causes of pure parkinsonism and of parkinsonism combined with other neurological deficits (parkinsonism-plus syndromes) (Table 24.1).

Motor Abnormalities

Early in the course of the disease, many patients with parkinsonism are unaware of any motor deficit. Often, the patient's spouse comments on a reduction in facial expression (often misinterpreted as depression), a reduction in arm swing while walking, and a slowing of activities of daily living, most notably dressing, feeding, and walking. The patient may then become aware of a reduction in manual dexterity, with slowness and clumsiness interfering with activities. PD often is asymmetrical, especially early in **the** course. A painful shoulder is one of the most common early symptoms of incipient unilateral rigidity and bradykinesia. This symptom, probably related to decreased arm swing and secondary joint changes or shoulder muscle rigidity, often is misdiagnosed as bursitis, arthritis, or rotator cuff disorders. All recreational and work tasks, household chores, and self-care functions eventually become impaired. Handwriting often becomes slower and smaller (micrographia), with speed and size decreasing as the task continues. Eventually, the writing may become illegible. Use of eating utensils becomes difficult, chewing is laborious, and choking while swallowing may occur. If the latter is an early and prominent complaint, one must consider bulbar involvement in one of the parkinsonism-plus syndromes, such as progressive supranuclear palsy (PSP) and multiple system atrophy (MSA; Thomas and Jankovic 2003b; Table 24.2). Dressing tasks, such as fastening small buttons or getting arms into sleeves, often are difficult. Hygiene becomes impaired. As with most other tasks, disability is greater if the dominant arm is more affected (e.g., shaving, brushing teeth, and other repetitive movements usually arc affected the most).

Speech becomes slurred and loses its volume (hypophonia), as a result of which patients are often asked to repeat themselves. A large number of additional speech disturbances may occur, including stuttering and palilalia (involuntary repetition of a phrase with increasing rapidity). Early pronounced voice changes often indicate a diagnosis other than PD (e.g., palilalia is more commonly a feature of PSP and MSA). Another problem related to impairment of bulbar function is excessive salivation and drooling. Initially, this may occur only at night, but later it

Tabic 24.1: Classification of parkinsonism

1. Primary (idiopathic) parkinsonism
   - Parkinson's disease
   - Juvenile parkinsonism

II. Multisystem degenerations ("parkinsonism plus")
   - Progressive supranuclear palsy
   - Multiple system atrophy
     - Striatonigral degeneration
     - Olivopontocerebellar atrophy
     - Shy-Drager syndrome
   - Lytico-Bodig or parkinsonism-dementia-ALS complex of Guam
   - Corticobasal degeneration
   - Progressive pallidal atrophy
   - Parkinsonism-demcnria complex
   - Pallidopyramidal disease

III. Heredodegencrative parkinsonism
   - Hcreditaty juvenile dystonia-parkinsonism (autosomal recessive *Parkin* mutation)
   - Do pa-responsive dystonia
   - Autosomal dominant Lewy body disease
   - Huntington's disease
   - Wilson's disease
   - Hereditary ceruloplasmin deficiency
   - Pantothenate kinase associated neurodegencration, also known as ncurodegeneration with brain iron accumulation, and Hallervotden-Spatz disease
   - Olivopontocerebellar and spinocerebellar atrophies including Macliado-Joseph disease
   - Familial amyotrophy-dementia-parkinsonism
   - Disinhibition-dementia-parkinsonism-amyotrophy complex
   - Gerstmann-Straussler-Scheinker disease
   - Familial progressive subcortical gliosis
   - I.ubag (X-linked dystonia-parkinsonism)
   - Familial basal ganglia calcification
   - Mitochondrial cytopathies with striatal necrosis
   - Ceroid lipofuscinosis
   - Familial parkinsonism with peripheral neuropathy
   - Parkinsonian-pyramidal syndrome
   - Neuroacanthocytosis
   - Hereditary hemochromatosis

IV. Secondary (acquired, symptomatic) patkinsonism
   - Infectious: postencephalitic, acquired immunodeficiency syndrome, subacute sclerosing panencephalitis, Crcutzfeldt-Jakob disease, prion diseases
   - Drugs: dopamine receptor blocking drugs (antipsychotic, antiemetic drugs), rcscrpine, tetrabenazine, a-mcthyldopa, lithium, fhtnarizine, cinnarizine
   - Toxins: MPTP, carbon monoxide, manganese, mercury, carbon disulfide, cyanide, methanol, ethanol
   - Vascular: multi-infarct, Binswangcr's disease
   - Trauma: pugilistic encephalopathy
   - Other: parathyroid abnormalities, hypothyroidism, hepatocerebral degeneration, brain tumor, paraneoplastic, normal-pressure hydrocephalus, nonco m mu n ica ti ng h y d rocephaluSj sy ri ngomescneep ha I i a, hemiatrophy - h em i p a rk i nso nism, peripherally induced tremor and parkinsonism, and psychogenic

Table 24.2: Park in son ism-pi us syndromes: differential diagnosis

	PD	*rsr*	*SDS*	*SND*	*OPCA*	*CBD*	*DLB*	*PDACG*
Brady kinesia	+	+	+	+	±	-	±	+
Rigidity	+	+	+	+	+	+	*1.*	1
Gait disturbance	+	+	+	+	+	-	±	+
Tremor	+	-	-	-	±	±	-	+
Ataxia	-	-	±	-	F	-	-	+
Dysautonomia	±	±	+	±	±	-	-:	±
Dementia	±	+	±	-	-	±	-	+
Dysarthria or dysphagia	±	i	_L	+	4-	+	±	-
Dystonia	+	±	-	±	-	+	-	-
Eyelid apraxia	-	+	±	±	-	±	-	-
Limb apraxia	-	-	-	-	-	-	±	-
Motor neuron disease	-	-	±	±	-	-	-	+
Myoclonus	±	-	-	±	±	+	±	-
Neuropathy	-	-	±	-	±	-	-	-
Oculomotor deficit	-	+	±	-	t-	+	±	+
Sleep impairment	±	±	+	±	±	-	±	-
Asymmetrical findings	+	-	-	±	-	+	-	-
l.-dopa response	+	±	±	±	±	-	-	-
i.-dopa dyskinesia	+	-	-	±	-	-	-	-
Family history	±	-	-	-	-	-	-	-
Putaminal T2 hypo in tensity	-	±	+	+	+	-	-	-
Lewy bodies	+	-	±	±	±	±	+	-

CBD = corticobasal degeneration; DLB = dementia with Lewy bodies; OPCA = olivopontocerebellar atrophy (the cerebellar form of sporadic multiple system atrophy); I'D = Parkinson's disease; PDACG = parkinsonism-dementia-amyottophic lateral sclerosis complex of Guam; PSP = progressive supranuclear palsy; SDS = Shy-Drager syndrome; SND = sttiatonigral degeneration.

Source: Modified from Jankovic, J. 1995b, "Treatment of parkinsonian syndromes," in *Treatment of Movement Disorders,* ed R. Kurlan, J.B. Lippincorr, Philadelphia, 95-114.

can be present throughout the day, at times necessitating the constant use of a tissue or handkerchief.

Getting in and out of a chair or car and climbing in and out of the bathtub cause problems; patients often switch to showering. Many patients interpret these difficulties as resulting from "weakness." Generalized loss of energy and easy fatigability arc also common complaints. "Walking becomes slowed and shuffling, with flexion of the knees and narrow base. When involvement is asymmetrical, one leg may drag behind the other. Stride then becomes shortened, and turns include multiple steps (turning en bloc). Later, patients may note a tendency to advance more and more rapidly with shorter and shorter steps (festination), at times seemingly propelled forward with a secondary inadequate attempt to maintain the center of gravity over the legs. When this occurs, a nearby wall or an unobstructed fall may be the only method of stopping. Alternatively, the feet may seem to become glued to the floor, the so-called freezing phenomenon or motor block. Early on, this is appreciated when the patient initiates walking (start hesitation), is turning (especially in an enclosed space), or attempts to walk through an enclosed area, such as a doorway (an elevator door is a common precipitant). When combined with poor postural stability, prominent freezing results in the tendency to fall forward or to the side while turning. Later, impaired postural reflexes may cause falls without a propulsive or freezing precipitant. The early occurrence of falls suggests a diagnosis of PSP or other parkinsonian disorder besides PD. Turning over in bed and adjusting the bedclothes often become difficult. Patients may have to sit up first and then turn, and later the spouse may have to help roll the person over or adjust position for comfort.

Cognitive, Autonomic, and Sensory Abnormalities

The complaints of patients with parkinsonism are not limited to the motor system (see Table 24.2). Dementia may be seen in a variety of parkinsonism syndromes (see Chapters 72 and 77), Depression also is a common problem, and patients often lose their assertiveness and become withdrawn, more passive, and less motivated to socialize. The term *bradyphrenia* has been used to describe the slowness of thought processes and inattentiveness that are often seen.

Complaints related to autonomic dysfunction arc also common. In all parkinsonian syndromes, constipation is a common complaint and may become severe. However, fecal incontinence is not seen in PD unless the motor disability is such that the patient cannot maneuver to the bathroom or dementia is superimposed. Bladder complaints, such as frequency, nocturia, and the sensation of incomplete bladder emptying, may occur. A mild to moderate degree of orthostatic hypotension is common in parkinsonian disorders, and antiparkinsonian drugs often aggravate the problem (see Chapter 77). If the autonomic features, particularly erectile dysfunction, sphincter problems, and orthostatic lightheadedness, occur early or become the dominant feature, one must consider the possibility of MSA (see Chapter 77). Besides impotence with early loss of nocturnal or morning erections and inability to maintain erection during intercourse, the other symptom that may precede the onset of motor problems associated with MSA is a sleep disorder, such as sleep apnea or REM sleep behavior disorder,

Visual complaints usually are not a prominent feature, with the following specific exceptions. In PD, diplopia may occur during reading secondary to impaired convergence. Other parkinsonian disorders, particularly PSP and the olivopontocerebellar atrophies, sometimes have visual complaints (see Chapter 78). Oculogyric crises, which are sudden episodes of involuntary ocular deviation (most often up and to the side) in the absence of neuroleptic drug exposure, arc virtually pathognomonic of parkinsonism after encephalitis lethargica, although they may be seen in rare neuromctabolic disorders as well. Sensory loss is not part of parkinsonism, although patients with PD may have poorly explained positive sensory complaints, such as numbness and tingling, aching, and painful sensations, which are sometimes quite disabling.

Although a variety of neurophysiology] and computer-based methods have been proposed to quantitate the severity of the various parkinsonian symptoms and signs, most studies rely on clinical rating scales, particularly the Unified PD Rating Scale (UPDRS), Hoehn-Yahr Stages, and Schwab-England Scale of activities of daily living (Table 24,3). The historical section of the UPDRS can be self-administered and reliably completed by nondemented patients. In some clinical research studies the UPDRS is supplemented by a more objective timed test such as the Purdue pegboard test and movement and reaction times. Many scales, such as the PD questionnaire 39 (PDQ-39) and the PD quality of life questionnaire (PDQL), attempt to assrss the overall qualm <t lite.

Onset and Course

As in other movement disorders, the age of onset of a parkinsonian syndrome is clearly important in considering a differential diagnosis. Although the majority of patients arc adults, parkinsonism can be seen in childhood (see fable 24.1 j. I'D usually lias a slow onset and very gradual progression. Generally, patients with early-onset PD and those with tremor-dominant form tend to progress at a slower rate and arc less likely to have an associated cognitive decline than those with postural instability and the gait difficulty form of PD. Other disorders (such as those caused by toxins, cerebral anoxia, or infarction) may present abruptly or progress more rapidly (resulting in so-called malignant parkinsonism) and may even improve spontaneously (as in those caused by drugs, multiple infarcts, and certain forms of encephalitis).

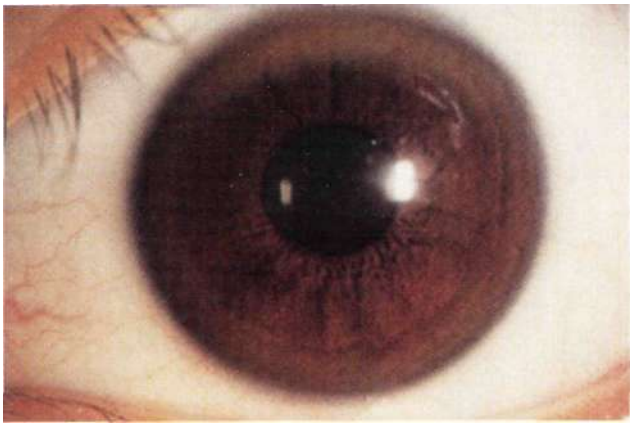

PLATE 24,1 Kayser-Fleischer ring. Note the golden-brown full-circumference ring thickest and most readily seen between the 11 o'clock and 1 o'clock positions of the cornea.

Tabic 24.3: Unified PD Rating Scale (UPDRS) definitions of 0-4

Mentation, behavior, and mood

1. Mentation
   0 = None.
   1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
   2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
   3 = Severe memory loss with disorientation to time and often place. Severe impairment in handling problems.
   4 — Severe memory loss with orientation preserved to person only. Unable to make judgments or solve problems. Needs much help with personal care. Cannot be left alone at all.
2. Thought disorder (caused by dementia or drug intoxication)
   0 = None.
   1 = Vivid dreaming.
   2 = "Bemgn" hallucinations with insight retained.
   3 — Occasional to frequent hallucinations or delusions, without insight, could interfere with daily activities.
   4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.
3. Depression
   0 = Not present.
   1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
   2 = Sustaincd depression (1 week or more).
   3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
   4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.
4. Motivation and initiative
   0 = Normal.
   1 = Less assertive than usual; more passive.
   2 = Loss of initiative or disinterest in elective (nonroutine) activities.
   3 = Loss of initiative ot disinterest in day-to-day (routine) activities.
   4 = Withdrawn, complete loss of motivation.

Activities of daily living

5. Speech
   0 = Normal.
   1 = Mildly affected. No difficulty being understood.
   2 = Moderately affected. Sometimes asked to repeat statements.
   3 = Severely affected. Frequently asked to repeat statements.
   4 = Unintelligible most of the time.
6. Salivation
   0 = Normal.
   1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
   2 — Moderately excessive saliva with some drooling.
   3 = Marked excess of saliva with some drooling.
   4 = Markcd drooling, needs constant tissue or handkerchief.
7. Swallowing
   0 = Normal.
   1 = Rare choking.
   2 = Occasional choking.
   3 = Needs soft food.
   4 — Needs nasogastric tube or gastrotomy feeding.
8. *H.* Handwriting
   0 = Normal.
   1 = Slightly slow or small.
   2 — Moderately slow or small; all words are legible.
   3 = Severely affected; not all words are legible.
   4 = The majority of words are not legible.
9. Cutting food
   0 = Norma I.
   1 = Somewhat slow and clumsy, but no help needed.
   2 = Can cut most food, although clumsy and slow, some help needed.
   3 = Food must be cut by someone but can still feed slowly.
   4 = Needs to be fed.
10. Dressing
   0 = Normal.
   1 = Somewhat slow but no help needed.
   2 = Occasional assistance with buttoning, getting arms in sleeves.
   3 = Considerable help needed bur can do some things alone.
   4 = Helpless.
11. Hygiene
   0 = Normal.
   1 = Somewhat slow but no help needed.
   2 = Needs help to shower or bathe; or very slow in hygienic care.
   3 = Needs assistance for washing, brushing teeth, combing hair, going to bathroom.
   4 = Foley catheter or other mechanical aids.
12. Turning in bed
   0 = Normal.
   1 = Somewhat slow and clumsy but no help needed.
   2 = Can turn alone or adjust sheets, but with great difficulty.
   3 = Can initiate but not turn or adjust sheets alone.
   4 = Helpless.
13. Falling
   0 = Normal.
   1 = Rare falling.
   2 — Occasionally falls, less than once per day.
   3 = Falls an average of once daily.
   4 = Falls more than once daily.
14. Freezing
   0 = None.
   1 = Rare freezing when walking; may have start hesitation.
   2 = Occasional freezing when walking.
   3 = Frequent freezing. Occasionally falls from freezing.
   4 = Frequent falls from freezing.
15. Walking
   0 = Normal.
   1 = Mild difficulty. May not swing arms ot may tend to drag leg.
   2 = Moderate difficulty but needs little or no assistance,
   3 = Severe disturbance of walking, needs assistance.
   4 = Cannot walk at all, even with assistance.
16. Tremor
   0 = Absent.
   1 = Slight and infrequently present.
   2 = Moderate, bothersome to patient.
   i — Severe, interferes with many activities.
   4 = Marked, interferes with most activities.

Continued

Table 24.3: Unified PD Rating Scale (UPDRS) definitions of *0-4* scale—cnnr'd

17. Sensory symptoms
    I) • - \(HH'.
    1 = Occasionally has numbness, tingling, or mild aching.
    2 — Frequently has numbness, tingling, or aching, not distressing.
    3 = Frequent painful sensations.
    4 = Excruciating pain.

Motor examination

18. Speech
    0 = Normal.
    1 = Slight loss of expression, diction, or volume.
    2 — Monotone, slurred but understandable; moderately impaired.
    3 = Marked impairment, difficult to understand,
    4 — Unintelligible,
19. Facial expression
    0 = Normal.
    1 = Minimal hypomimia, could be normal ("poker face").
    2 = Slight but definitely abnormal diminution of facial expression.
    3 = Moderate hypomimia, lips parted some of the time.
    4 = Masked or fixed facies with severe or complete loss of facial expression, lips parted 1/4 inch or more.
20. Tremor at rest
    0 = Absent.
    1= Slight and infrequently present.
    2 = Mild in amplitude and persistent. Or moderate in amplitude but only intermittently present.
    3 = Moderate in amplitude and present most of the time.
    4 = Marked in amplitude and present most of the time.
21. Action tremor
    0 = Absent.
    1 -• Slight; present with action.
    2 = Moderate in amplitude; present with action.
    3 = Moderate in amplitude, with posture holdings as well as action,
    4 = Marked in amplitude, interferes with feeding.
22. Rigidity (judged on passive movement of major points with patient telaxed in sitting position; cogwheeling to be ignored)
    0 = Absent.
    1 = Slight or detectable only when activated by mirror or other movements.
    1 — Mild to moderate.
    3 = Marked, but full range of motion easily achieved.
    4 = Severe, range of motion achieved with difficulty.
23. Finger taps (patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately)
    0 = Normal.
    1 = Mild slowing or reduction in amplitude.
    2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
    3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
    4 = Can barely perform the task.
24. Hand movements (patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately)
    0 = Normal.
    1 = Mild slowing or reduction in amplitude.
    2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
    3 —Severely **impaired. Ireijiienr hesitation** in **niiu.mrii;** movements or arrests in ongoing movement.
    4 = Can barely perform the task.
25. Hand pronation-supination (pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously)
    0 = Normal.
    1 = Mild slowing or reduction in amplitude.
    2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
    3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
    4 = Can barely perform the task.
26. Leg agility (patient taps heel on ground in rapid succession, picking up entire lei',; amplitude should be about 3 inches)
    0 = Normal,
    1 = Mild slowing or reduction in amplitude.
    2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
    3 = Severely lmpaited. Frequent hesitation in initiating movements or arrests in ongoing movement.
    4 = Can barely perform the task.
27. Arising from chair (patient attempts to arise from a straight-back wood or metal chair with arms folded across chest)
    0 = Normal.
    1 = Slow, or may need more than one attempt.
    2 = Pushes self up from arms of seat.
    i Tends to fall **hack and may have** to **try more than one** time but can get up without help.
    4 = Unahle to arise without help.
28. Posture
    0 = Norma I.
    1 = Not quite erect, slightly stooped posture; could he normal for older person.
    2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
    3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
    4 = Marked flexion with extreme abnormality of posture.
29. Gait
    0 = Norma I.
    1 = Walks slowly, may shuffle with short steps, but no festination or propulsion.
    2 = Walks with difficulty but needs little or no assistance; may have some fcstination, short steps, or propulsion.
    3 = Severe gait disturbance necessitating assistance.
    4 = Cannot walk at all, even with assistance.
30. Postural stability (response to sudden posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
    0 = Normal.
    1 = Retropulsion, but recovers unaided.
    2 — Absence of postural response, would fall if not caught by examiner.
    3 = Very unstable, tends to lose balance spontaneously.
    4 = Unable to stand without assistance.
31. Body bradykinesia (combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general)
    0 = None.
    1 = Minimal slowness, giving movement a deliberate character; could be normal for some people. Possibly reduced amplitude.

Continued

Table 24.3: Unified PD Rating Scale (UPDRS) definitions of 0-4 scale—cont'd

2 — Mild degree of slowness, giving and poverty of movement that is definitely abnormal. Alternatively, some reduced amplitude.
,i — Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

Complications of Therapy

Score these items to represent the status of the patient in the week before the examination.

Dyskinesias

32. Duration

What proportion of the waking day are dyskinesias present? (historical information)

0 = None
1 = 1-25% of day
2 = 26-50% of day
3 = 51-75% of day
4 = 76-100% of day

33. Disability

How disabling are the dyskinesias? (historical information; may be modified by office examination!

0 = Not disabling
1 = Mildly disabling
2 = Moderately disabling
3 = Severely disabling
4 = Completely disabling

34. Pain

How painful are the dyskinesias?

0 = No painful dyskinesia
1= Slight
2 = Moderate
3 =Severe
4 = Marked

i5. Presence of early morning dystonia (historical information)

0 = No
1 = Yes

Clinical Fluctuations

36. "Offs" duration

What proportion of the waking day is the patient "off on average?

0 = None
1 = 1-25% of day
2 = 26-50% of day
3 = 51-75% of day
4 = 76-100% of day

37. "Offs" predictable

Arc any "off" periods predictable as to timing after a dose of medication?

0 = No
l=Yes

38. "Offs" unpredictable

Are any "off" periods unpredictable as to timing after a dose of medication?

0 = No
I=Yes

39. "Offs" sudden

Do any of the "off periods come on suddenly (e.g., over a few seconds)?

0 = No
1 = Yes

()ther complications

40. Anorexia, nausea, vomiting

Docs the patient have anorexia, nausea, or vomiting?

0 = No
1 = Yes

41. Sleep disturbances

Does the patient have any sleep disturbances (e.g., insomnia or hypersomnolence)?

0 = No
1=Yes

42. Symptomatic orthostasis

Does the patient have symptomatic orthostasis?

0 = No
l=Yes

Modified Hoehn and Yahr Staging

Stage 0 = No signs of disease
Stage I = Unilateral disease
Stage 1.5 = Unilateral disease plus axial involvement
Stage II = Bilateral disease, without impairment of balance
Stage 11,5 = Mild bilateral disease, with recovery on pull test
Stage IH = Mild to moderate bilateral disease; some postural instability; physically independent
Stage IV = Severe disability; still able to walk or stand unassisted
Stage V = Wheelchair bound or bedridden unless aided

Modified Schwab and England Activities of daily living scales

100%: Completely independent. Able to do all chores without slowness, difficulty, or impairment. Essentially normal. Unaware of any difficulty.
90%: Completely independent. Able to do all chores with some degree of slowness, difficulty, and impairment. Might take twice as long. Beginning to be aware of difficulty.
80%: Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70%: Not completely independent. More difficulty some chores. Three to four times as long in some. Must spend a large part of the day with chores.
60%: Some dependency. Can do most chores, hut exceedingly slowly **and** with much effort. Errors; some impossible.
50%: More dependent. Help with half, slower, etc. Difficulty with everything.
40%: Very dependent. Can assist with all chores, but few alone.
30%: With effort, now and then does a few chores alone or begins alone. Much help needed.
20%: Nothing alone. Can be a slight help with some chores. Severe invalid.
10%: Totally dependent, helpless. Complete invalid.
0%: Vegetative functions such as swallowing; bladder and bowel are not functioning. Bedridden.

Examination and Clinical Signs

The diagnosis of parkinsonism often is immediately apparent on first contact with the patient. The facial expression, vocal characteristics, tremor, poverty of movement, and flexed posture give an immediate and irrevocable first impression. However, the physician must remember the need for detailed assessment in attempting to

distinguish between the various causes of this clinical syndrome.

Loss of facial expression (hypomimia) often is an early sign. Occasional patients have a wide-eyed, anxious expression, with deep facial folds, and this can be pronounced in cases of PSP. Blink frequency usually is reduced, although blepharoclonus (repetitive spasms of the lids on gentle eye closute) and reflex blepharospasm (e.g., precipitated by shining a light into the eyes or manipulating the lids) also may be seen. Spontaneous blepharospasm and apraxia of lid opening occur less often. Patients with apraxia of lid opening often open their eyes using their hands, and once the eyes are fixed on an object the eyelids remain open. In addition to the facial characteristics, patients with parkinsonian disorders develop excessive greasiness of the skin and seborrheic dermatitis, characteristically seen over the forehead, eyebrows, and malar area,

The voice of a patient with PD typically is hypophonic, monotonous, often hesitant, stuttering, and more rapid than normal. The speech, like the gait, may be festinating, that is, it gets faster and faster. One must attempt to discern additional pseudobulbar or cerebellar features that suggest alternative diagnoses. Palilalia and echolalia (involuntary repetition of wotds and phrases spoken by others) occur in several parkinsonian disorders. Careful observation of facial and vocal characteristics may be immediately rewarding. One example is the combination of poor eye contact caused by the disturbance of refixation eye movements, furrowing of the brow, and deepening of the nasolabial folds secondary to facial rigidity in patients with PSP. A harsher, higher-pitched nasal quality of the voice, which is quite distinctive from the hypophonic monotone of PD, also suggests the diagnosis of PSP.

Various types of tremor, most notably resting and postural varieties, often accompany parkinsonian disorders. Patients should be observed with hands resting on their laps or thighs, and they should be instructed to hold their arms in an outstretched position or in a horizontal position with shoulders abducted, elbows flexed, and hands palms-down in front of their faces, in the so-called wing-beating position. A true kinetic (intention) tremor, elicited by the finger-to-nose maneuver, is much less common in patients with PD and other parkinsonian disorders and usually indicates involvement of cerebellar connections. Head tremor (titubation) suggests a diagnosis other than PD, such as essential tremor, dystonic neck tremor, or a cerebellar tremor associated with multiple sclerosis.

Rigidity is an increase in muscle tone, usually equal in flexors and extensors and present throughout the passive range of movement. This contrasts with the distribution and velocity-dependent nature of spasticity. Paratonia (or gcgenhalten), on the other hand, increases with repetitive passive movement and with attempts to get the patient to relax. It may be difficult to distinguish between milder forms of paratonia and rigidity, especially in the legs. Characteristically, rigidity is brought out or aggravated by the performance of voluntary movements in the opposite limb (such as opening and closing the fist or abduction-adduction of the shoulder), a phenomenon known as activated rigidity (Froment's sign). Superimposed on the rigidity may be a tremor or cogwheel phenomenon. This, like the milder forms of rigidity, is better appreciated by placing one hand over the muscles being tested (e.g., the left thumb over the biceps and the remaining fingers over the triceps while flexing and extending the elbow with the right hand). The distribution of the rigidity sometimes is helpful in differential diagnosis. For example, pronounced nuchal rigidity with much less hypertonicity in the limbs suggests the diagnosis of PSP, whereas an extreme degree of unilateral arm rigidity might suggest corticobasal degeneration.

Akinesia and bradykincsia may be appreciated on examination in several ways. Automatic movements normally expressed in conversation, such as gesturing with hands while speaking, crossing and uncrossing the legs, and repositioning the body in the chair, are reduced or absent. Rapid, repetitive, and alternating movements, such as finget tapping, opening and closing of the fist, pronation-supination of the forearm, and foot tapping, arc performed slowly, with a gradual reduction in amplitude and eventual cessation of movement (freezing). In addition to fatiguing, there may be hesitation in initiating movement and arrests in ongoing movement. The severely afflicted patient may be barely able to perform the task. There is a tendency for rapid, repetitive movements to take on the frequency of an accompanying tremor. In such cases, the patient should be instructed to slow the movement and attempt to complete it voluntarily.

Watching the patient write is an important part of the examination. Observation may reveal great slowness and effort, even in someone with minimal change in the size of the script. In addition to micrographia, writing and drawing show a tendency to fatigue, with a further reduction in size as the task proceeds and a concomitant action tremor.

Postural disturbances are common in akinetic-rigid syndromes. The head usually tilts forward and the body becomes stooped, often with pronounced kyphosis and varying degrees of scoliosis. The arms become flexed at the elbows and wrists, with varying postural deformities in the hands, the most common being flexion at the metacarpophalangeal joints and extension at the interphalangeal joints, with adduction of all the fingers and opposition of the thumb to the index finger ("striatal hand"). Flexion also occurs in the joints of the legs. Variable foot deformities occur, the most common being hammet toe-like disturbances in most of the toes, occasionally with extension of the great toe ("striatal foot"), which may be misinterpreted as an extensor plantar response. Initially, abnormal foot posturing may be induced by action, occurring only during walking or weight bearing. The flexed or simian posture sometimes is extreme, with sevete flexion at the waist and maintenance of the hands above the beltline because

of flexion of the elbows. Occasional patients remain upright or even demonstrate a hyperextended posture. Hyperextension of the neck is particularly suggestive of PSP, whereas extreme flexion of the neck suggests MSA.

Postural instability is characteristic of parkinsonian disorders, particularly the postural instability and gait difficulty form of PD, PSP, and MSA. As patients rise from a sitting position, poor postural stability, slowness, narrow base, and not repositioning the feet often combine to cause patients to fall back into the chair "in a lump." The patient may need to make several attempts, push off the arms of the chair, or be pulled by an assistant. Gait disturbances in typical parkinsonism include lack of arm swing, shortened and later shuffling stride, freezing in the course of walking (especially at a door frame or when approaching a potential obstruction or a chair), and, in more severe cases, propulsion and spontaneous falls (J.inkovic, Nun, and Sudarsky 2001). In addition, walking often brings out or exacerbates a resting tremor. To assess postural instability, the physician performs the pull test. Standing behind the patient, the examiner pulls the patient backward by the shoulders (or by a hand on the sternum), carefully remaining close behind to prevent a fall. Once postural reflexes are impaired, there may be retropulsion or multiple backward steps in response to the postural perturbation, Later, there is a tendency to fall en bloc without retropulsion or even normal attempts to recover or to cushion the fall.

The base of the gait usually is narrow, and tandem gait is performed well. When the gait is wide based, a superimposed ataxia must be considered, as is seen in MSA with prominent cerebellar involvement, although some of the spinocerebellar atrophies may present with parkinsonism and ataxia (Abele et al. 2002). Toe walking (cock-walk) is seen in some parkinsonian disorders (e.g., those caused by manganese poisoning), and a peculiar loping gait may indicate the rare patient with akinesia in the absence of rigidity. The so-called magnetic foot or marche a petits pas of senility (also seen in multiple infarctions, Binswanger's disease, and normal pressure hydrocephalus) more commonly results in a lower-body parkinsonism, typically associated with cerebrovascular disorders such as lacunar strokes. A striking discrepancy of involvement between the lower body and the upper limbs, with normal or even excessive arm swing, is an important clue to this disorder (sec Chapter 25).

Differential Diagnosis

Although dementia occurs in some patients with PD, this feature must alert the physician to other possible diagnoses (see Chapter 72), including the coincidental association of unrelated causes of cognitive decline. Prominent eye movement disturbances are found in a number of conditions, including olivopontocerebellar atrophy form of MSA, postencephalitic parkinsonism, and PSP. It is important to assess optokinetic nystagmus in order to note whether vertical saccadic eye movements are impaired, as in PSP. The oculocephalic (doll's eye) maneuver must be performed where ocular excursions are limited, seeking supportive evidence of supranuclear gaze palsy (see Chapter 39). Although obvious pyramidal tract dysfunction nsu.ilk suggests another diagnosis or additional disorder, mild rigidity can accentuate the reflexes. When the parkinsonism is asymmetrical, this may cause confusing reflex changes. Primitive reflexes, including the inability to inhibit blinking in response to tapping over the glabella (Myerson's sign), are nonspecific and commonly present in many parkinsonian disorders. However, a pathologically brisk jaw jerk suggests an additional corticobulbar tract disorder. Palmomental reflex and exaggerated grasp response indicate disturbance of the frontal lobes and the possibility of a concomitant dementing process. Occasionally, a pronounced flexed posture in the hand may be confused with a grasp reflex, and the examiner must be convinced that there is active contraction in response to stroking of the palm. The abnormalities of rapid, repetitive, and alternating movements described earlier must not be confused with the disruption of rate, rhythm, and force typical of the dysdiadochokinesia of cerebellar disease. A helpful maneuver in testing for the presence of associated cerebellar dysfunction is to have the patient tap with the index finger on a hard surface. Watching and, in particular, listening to the tapping often allow a distinction between the slowness and decrementing response of parkinsonism and the irregular rate and force of cerebellar ataxia. Testing for apraxia as seen in corticobasal degeneration should also be performed by asking the patient to mimic certain hand gestures such as the "victory sign" or the "University of Texas hook 'em horns sign" (extension of the second and fifth finger and flexion of the third and fourth finger) or to simulate certain activities such as brushing teeth and combing hair. However, in the later stages of many parkinsonian disorders, rigidity and other motor disturbances may make these tests difficult to interpret.

The presence of other abnormal movements in an untreated patient may indicate a diagnosis other than PD. Stimulus-sensitive myoclonus should be sought by using light touch or pinprick in the digits and the proximal palm or the sole of the foot. Easily elicited and nonfatiguing myoclonic jerks in response to these stimuli may be seen in corticobasal degeneration and MSA.

Despite a variety of sensory complaints, patients with PD do not show prominent abnormalities on the sensory examination, aside from the normal increase in vibration threshold that occurs with age. Wasting and muscle weakness are also not characteristic of PD, although later in the course, severely disabled patients show disuse atrophy and severe problems in initiating and maintaining muscle activation that are often difficult to separate from true weakness. Combinations of upper and lower motor

neuron weakness may be seen in several other parkinsonian disorders (sec Table 24.1).

Autonomic function must be assessed. At the bedside this includes an evaluation of orthostatic changes in blood pressure and pulse and, in appropriate circumstances, their response to the Valsalva maneuver, mental arithmetic, and the cold pressor test, among others.

Finally, sequential examinations are needed over time, carefully searching for the development of additional findings that may provide a clue to the diagnosis. Several of the parkinsonian syndromes present initially as pure parkinsonism, and only later as the disease progresses do other signs develop,

TREMOR

Tremor is a rhythmic oscillation of a body part, produced by either alternating or synchronous contractions of reciprocally innervated antagonistic muscles. Tremors usually have a fixed periodicity, although the rate may appear irregular. The waveform and amplitude of the tremor can vary widely, depending on both physiological and psychological factors. Tremor usually is further categorized on the basis of the position, posture, or motor performance necessary to elicit it. Tremor terminology is confusing and is being redefined. A rest tremor is seen with the body part in complete repose, although when a patient is totally relaxed or asleep this tremor usually disappears. Maintenance of a posture, such as extending the arms parallel to the floor, reveals a postural tremor; moving the body part to and from a target brings out an intention tremor. The use of other descriptive categories has caused some confusion in tremor terminology. *Static tremor* has been used to describe both resr and postural tremors. *Action tremor* has been used for both postural and intention tremors. One source of confusion here is that many postural tremors appear as one approaches a target. The term *terminal tremor* probably avoids this confusion most successfully. In contrast, an intention tremor is present throughout goal-directed movement but is also exaggerated as the target is neared. The term *kinetic tremor* may be more accurate and is gradually replacing the traditional term *intention tremor. Ataxic tremor* has been used to refer to a combination of this type of tremor plus limb ataxia. Table 24.4 provides a list of differential diagnoses for the three major categories of tremor and other rhythmic movements that occasionally are confused with tremor.

Common Symptoms

Symptoms are described under the various categories of tremor. All people have a normal or physiological tremor that can be demonstrated with sensitive recording devices. Two common pathological tremor disorders that are often confused arc parkinsonian rest tremor and essential tremor.

Table 24,4: Classification and differential diagnosis of tremor

- Resting tremors
  - Parkinson's disease
  - Other parkinsonian syndromes (less common)
  - Midbrain (rubral) tremor: rest < postural < intention
  - Wilson's disease (also acquired hepatocerebral degeneration)
  - Essential tremor
- Postural tremors
  - Physiological tremor
  - Exaggerated physiological tremor; these factors can also aggravate other forms of tremor
    - Stress, fatigue, anxiety, emotion
    - Endocrine: hypoglycemia, thyrotoxicosis, pheochromocytoma, Cushing's disease
    - Drugs and toxins: adrcnocorticosteroids, beta agonists, dopamine agonists, amphetamines, lithium, tricyclic antidepressants, neuroleptics, theophylline, caffeine, valproic acid, alcohol withdrawal, mercury ("hatter's shakes"), lead, arsenic, others
  - Essential tremor (familial or sporadic)
  - Primary writing tremor and other task-specific tremors
  - Orthostatic tremor
  - With other CNS disorders
    - Parkinson's disease (postural tremor, rc-cmergent tremor, associated essential tremor)
    - Other akinetic-rigid syndromes
    - Idiopathic dystonia, including focal dystonias
  - With peripheral neuropathy
    - Charcot-Marie-Tooth disease (called the Roussy-Levy syndrome)
    - Other peripheral neuropathies
  - Cerebellar tremor
    - Intention tremors
  - Disease of cerebellar outflow (dentate nuclei, intcrpositus nuclei, or both, and superior cerebellar peduncle); multiple sclerosis, trauma, tumor, vascular disease, Wilson's disease, acquired hepatocerebral degeneration, drugs, toxins (such as mercury), others
- Miscellaneous rhythmic movement disorders
  - Psychogenic tremor
  - Rhythmic movements in dystonia (dystonic tremor, myorhythmia)
  - Rhythmic myoclonus (segmental myoclonus, e.g., palatal or branchial myoclonus, spinal myoclonus), myorhythmia
  - Oscillatory myoclonus
  - Asterixis
  - Clonus
  - Epilepsia partialis continua
  - Hereditary chin quivering
  - Spasmus nutans
  - Head bobbing with third ventricular cysts
  - Nystagmus

Although both conditions are discussed in detail in Chapter 77, we discuss helpful distinguishing points next, in view of the frequency of misdiagnosis.

Rest Tremor

A rest tremor occurs with the body part in complete repose and often dampens or subsides entirely with action. For this reason, patients with pure resting tremor experience greater social embarrassment than functional disability. Indeed, in some cases it is a family member or friend who first observes the tremor, which is noticeable to the patient only later. Alternatively, some patients complain of the sensation of trembling inside long before a rest tremor becomes overt. Early on, rest tremor may be intermittent and often is precipitated only by anxiety or stress. Most types of tremor are experienced first in the arms, often beginning asymmetrically. In the face, resting tremor usually affects the lips and jaw, and the patient may note a rhythmic clicking of the teeth. In the limbs, the tremor usually is most pronounced distally in the fingers {pill rolling} or may be manifested by a supination-pronation oscillatory movement of the wrist and forearm and flexion-extension movement of the ankle. In severe forms, it may be present more proximally, causing the entire body to shake. The complaint of prominent head tremor (titubation) should raise the possibility of essential tremor or of dystonic tremor associated with cervical dystonia or cerebellar outflow tremor, as is seen in patients with multiple sclerosis or posterior fossa disorders. Tremor in the legs, and especially in the feet while sitting, usually is caused by parkinsonian resting tremor. A history of progression from unilateral arm tremor ro additional involvement of the ipsilateral leg suggests parkinsonism rather than essential tremor. Once the tremor has become noticeable to the patient, a variety of methods are used to conceal the movement, such as holding one hand with the other, sitting on the affected hand, or crossing the legs to dampen a tremulous lower limb. Many patients find that they can aborr the tremor transiently at will.

Postural Tremor

In contrast to a pure resting tremor, postural rremors, especially with pronounced terminal accentuation, can result in significant disability. Many such patients are mistakenly thought to have "bad nerves." People who perform delicate work with their hands (e.g., jewelers and surgeons) become aware of this form of tremor earlier than most. The average person usually first appreciates tremor in the acts of feeding and writing. Carrying a cup of liquid, pouring, or eating with a spoon often brings out the tremor. Writing is tremulous and sloppy, and the patient's signature on a check may be questioned. The voice may be involved in essential tremor. Again, anxiety and stress worsen the tremor, and patients often notice that their symptoms are especially bad in public. The most common cause of postural tremor seen in movement disorders clinics is essential tremor (Jankovic 2002).

Patients often adopt compensatory mechanisms to lessen the disability caused by tremor. Many give up certain tasks, such as serving drinks and eating specific foods (e.g., soup), especially in public. When rhe tremor is very asymmetrical, patients often switch to using the less affected hand for many tasks, including wriring. Two hands may be used to bring a cup to the mouth; later, a straw may be needed. When writing, patients may use the other hand to steady the paper or the writing hand itself. Patients often switch to printing, and heavier or thicker writing instruments sometimes make the script more legible. In some patients with parkinsonian disorders and severe rest tremor, the tremor may also be presenr while the patient holds an outstretched or wing-beating posture. This tremor usually occurs afrer a latency of several seconds, hence the term "re-emergent tremor."

Other Types of Tremor

Various types of writing disturbances may be combined with tremor. Primary writing tremor is one form of task-specific tremor that affects the writing act in isolation, with little or no associated postural or terminal tremor interfering with other acts. Dystonic writer's cramp can involve additional tremulousness on wriring. This must be distinguished from the voluntary excessive squeezing of the pen or pressing onto the page often seen in patients with essential tremor or primary writing tremor, which is attributable to their attempts to lessen the effect of tremor on wtiting. In addition, patients with postural rremor may consciously slow their writing down to improve accuracy, but this is a voluntary compensatory mechanism not associated with the micrographia and fatigue that accompany parkinsonism.

Tremor in the head and neck, or titubation, can occur in isolation or can be combined with a postural tremor elsewhere, especially in the arms, as is seen in patients with essential tremor. When the head tremor is irregular and is associated with abnormal head posture and uneven contractions or hypertrophy of the neck muscles, the possibility of cervical dystonia should be considered (dystonic tremor). Head tremor is rarely a source of physical disability but may create social embarrassment. Patients occasionally complain of a similar tremor of the voice. This is particularly noticeable to others who are listening to the patient on the telephone, and many patients are asked whether they are sad or have been crying.

Less often, patients with postural tremors note a similar tremor in the legs and trunk. The awareness of this form of tremor clearly depends on rhe activity being performed. One unusual form of postural tremor has been called *orthostatic tremor.* Here, patients often do not note any tremor but complain of difficulty standing (associated with a 14- to 16-Hz tremor in the legs and trunk),

Characteristically, the tremor subsides if the patient can walk about, lean against something, or sit down.

Other Clites in the History

Although patients with several different types of tremor may indicate that alcohol transiently reduces their shaking, a striking response to small amounts of alcohol is particularly characteristic of essential tremor. Clues to the possible ptesence of factors aggravating the notmal physiological tremor (see Table 24.4} must also be sought by further inquiry.

Examination

In addition to clinical examination, tremor can be assessed by various physiological, aceelerometric, and other computer-hased techniques, but a clinical rating scale usually is most practical, particularly in clinical trials. The Tremor Research Group (TRG) has developed a rating scale that can be used to quantitatively assess all types of tremor, particularly essential ttemor, the most common type of tremor encountered in clinical practice (Table 24.5). The TRG scale also provides instructions on how to examine for tremor. Besides rest, postural, and kinetic limb tremot, patients should be examined for ttemor of the head. With the patient seated or standing, head tremor may be evident as vertical ("yes-yes") nodding *{tremblement affirmatif)* or side-to-side ("no-no") horizontal shaking *{tremblement negatif).* There may be combinations of the two, with rotatory movements. Head tremors usually range from 1.5 to 5.0 Hz and are most commonly associated with essential ttemor or cervical dystonia and with diseases of the cerebellum and its outflow pathways. A parkinsonian resting ttemor may involve the jaw and lips. A similar tremor of the perioral and nasal muscles, the rabbit syndtome, has been associated with antipsychotic dtug therapy but also occurs in PD. In many disorders, voluntary contraction of the facial muscles induces an action ttemor. In addition, a postural ttemor of the tongue often is present on tongue protrusion. In the case of tremors of head and neck structures, it is important to observe the palate at rest for the slowet rhythmic movements of palatal myoclonus (also called palatal ttemor). Occasionally, the palate is spared, with similar movements affecting othet branchial structures. A voice tremor is best demonstrated by asking the patient to hold a note as long as possible. Superimposed on the vocal trcmulousness may be a harsh, stfaincd quality or abrupt cessation of air flow during the course of maintaining the note, which suggests a superimposed dystonia of the latynx (spasmodic dysphonia).

A parkinsonian rest ttemor is chatactctistically in the 4- to 6-Hz range. The frequency of postural arm tremots varies depending on cause and severity. Essential tremot usually is in the range of 5-10 Hz, with the greater-amplitude tremors tending to be slower. Exaggerated physiological tremor has a frequency of 8-12 Hz. Many patients with parkinsonism demonstrate a combination of slower resting and faster postutal tremors. Some patients with slower, larger-amplitude forms of essential tremor have a definite testing component.

A rest tremor in the limbs is seen with the muscles in complete repose. Even a small amount of muscle activity, as may occur if the patient is somewhat anxious or the limb is not completely at rest, may bring out a higher-frequency action postural tremor. It is sometimes impossible to abate this postural tremor during a stressful office interview. An occult resting tremor also may be brought out by stress or concentration, such as the performance of serial sevens. Although a resting tremor characteristically subsides when the patient maintains a posture (e.g., holding the arms outstretched patallel to the floor), it may recur after a few seconds. Carrying out goal-directed movements, such as finger-to-nose testing, usually causes the tremor to dampen further or subside completely. On the other hand, a typical postural tremor usually is seen without significant latency after the initiation of a posture and may worsen further at the endpoints of goal-directed movement (terminal tremor), The slower intention tremor of cerebellar disease is seen throughout the movement but also worsens as the target is reached. Occasionally, pronounced bursts of muscle activity in a patient with terminal ttemot cause individual separate jerks, which give the impression of superimposed myoclonus.

Having the patient point the index fingers at each other under the nose (without touching the fingers together or touching the face) with the arms abducted at the sides and the elbows flexed can demonstrate both distal tremor in the hands and proximal tremors. An example of proximal tremor is the slower wing-beating tremor of cerebellar outflow pathway disease, as may be seen in Wilson's disease. Tremor during the course of slowly pronating and supinating the forearms with the arms outstretched or with forceful abduction of the fingers may be seen in patients with primary writing tremor. Holding a full cup of water with the arm outstretched often amplifies a postural tremor, and picking up the full cup, bringing it to the mouth, and tipping it to drink enhances the terminal tremor, often causing spillage. In addition to writing, one should have the patient draw with both hands separately. Useful drawing tasks include an Archimedes spiral, a wavy line from one side of the page to the other (Figure 24.1), and an attempt to draw carefully a line or spiral between two well-defined, closely opposed borders.

In the legs, in addition to the standard heel-to-shin testing, which brings out terminal and intention tremors, it may be possible to demonstrate a postural tremor by having the patient hold the leg off the bed and attempt to touch the examiner's finger with the great toe. With the legs flexed at the knees and abducted at the hips and the feet held flat on the bed, synchronous rhythmic 3-Hz abductions of the

Table 24,5: Tremor Research Group Rating Scale

Instructions for completing the observed tremor portion

1. Head tremor: Subject is seated upright. The head is observed for 10 seconds in midposirion and for 5 seconds each during several provocative maneuvers. First the subject is asked to rotate his or her head to the maximum lateral positions slowly in each direction. The subject is then asked to deviate his or her eyes to the maximum lateral positions while the examiner touches the subject's chin gently.
   0 = No tremor.
   1 = Tremor seen or felt during provocative maneuvers.
   2 — Mild tremor seen at midposirion or moderate tremor seen with provocative maneuvers.
   3 = Moderate tremor at midposition or severe tremor seen with provocative maneuvers.
   4 — Severe tremor seen at midposition.

2a. Face tremor: Subject is seated upright and asked to smile and pucker his or her lips, each for 5 seconds. Tremor is specifically assessed for the lower facial muscles (excluding jaw and tongue and upper face [eye closure]).
   0 = No tremor.
   1 = Mild tremor seen only with active muscle contraction.
   2 = Mild tremor seen at rest or moderate tremor seen with active muscle contraction.
   3 = Moderate tremor seen at rest or severe tremor seen with muscle contraction.
   4 = Severe tremor seen at rest.

2b. Tongue tremor: Subject is seated upright. The subject is asked to open his or her mouth for *5* seconds and then stick out his or her tongue for 5 seconds.
   0 = No tremor.
   1 = Mild tremor seen only with active muscle contraction.
   2 = Mild tremor seen at rest or moderate tremor seen with active muscle contraction.
   3 = Moderate tremor seen at rest or severe tremor seen with active muscle contraction.
   4 = Severe tremor seen at rest.

2c. Jaw tremor: Subject is seated upright. The subject is asked to maximally open his or her mouth and clench ihe j;iw I'or 5 seconds.
   0 = No tremor.
   1 =Mild tremor seen only with active muscle contraction.
   2 = Mild tremor seen at rest or moderate tremor seen with active muscle contraction.
   3 = Moderate tremor seen at rest or severe tremor seen with active muscle contraction.
   4 = Severe tremor seen at rest.

3. Voice tremor: First assess speech during normal conversation then ask subject to produce an extended "aaa" sound and "eee" sound for 5 seconds each.
   0 = No tremor.
   1= Barely perceptible tremor only during provocative maneuver ("aaa," "eee").
   1 — Mild but clear tremor present with speaking.
   3 = Moderate tremor (no voice breaks).
   4 = Severe tremor (with voice breaks or unintelligible speech).

4. Arm tremor: Subject is seated upright. Tremor is assessed during four arm maneuvers (rest, forward horizontal reach posture, lateral "wing beating" posture, and kinesis). Each arm is assessed for *5* seconds in each posture. Left and right arms may be assessed simultaneously. Amplitude assessment should be estimated using the maximally displaced point of the hand at the point of greatest displacement along any single plane. For example, the amplitude of a pure supination-pronation tremor, pivoting around the wrist, would be assessed at either the thumb or fifth digit.

   a. Rest tremor: The subject should have his or her elbows on the arm rests. (If this is the subject's natural posture after the previous assessment, no specific instructions should be given. If the subject did not naturally assume an acceptable arm position for "rest" evaluation, ask him or her to rest elbows on the arm rests with hands resting freely.) Begin the 10-second assessment only after the subject appears relaxed in the new position.
   b. Forward outstretched postural tremor: Subject should bring his or her arms forward, slightly lateral to midline and parallel to the ground. The wrists should also be straight and the fingers slightly and comfortably abducted so that they do not touch each other.
   c. Lateral "wing beating" postural tremor: Subject abducts his or her arms parallel to the ground and flexes the elbows so that the two hands do not quite touch each other, The fingers are slightly and comfortably abducted so that they do not touch each other, with the pointer finger at shoulder height.
   d. Kinetic tremor: Subject extends only his or her pointer finger. The subject then touches a set object or the examiner's finger located to the full extent of the subject's reach, which is at the same height (parallel to the ground) and slightly lateral to the midline. The subject then touches his or her own nose or chin and repeats this back-and-forth motion five times. Only the position along the trajectory of greatest tremor amplitude is assessed. This will typically be cither at the nose or chin or at the point of full finger.
   e. Tremor while walking: Have the patient walk a minimum *<it 6* m at a normal pace to and from the examiner and observe his or her hands.

   Rest tremor
      0 = No tremor.
      1 = Tremor is barely visible or present only with mental provocation or reinforcement.
      1.5 = Tremor is visible but less than 1 cm.
      2 — Tremor is 1-3 cm amplitude.
      2.5 = Tremor is 3-5 cm amplitude.
      3 = Tremor is 5-10 cm amplitude.
      3.5 = Trcmor is 10-20 cm amplitude.
      4 = Tremor is >20 cm amplitude.

   Postural tremor
      0 = No tremor.
      1 ^Tremor is barely visible.
      1.5 = Tremor is visible but less than I cm.
      2=Tremor is 1-3 cm amplitude.
      2.5 = Tremor is 3-5 cm amplitude.
      3 = Tremor is 5-10 cm amplitude.
      3.5 = Tremor is 10-20 cm amplitude.
      4 = Tremor is >20 cm amplitude.

   Kinetic tremor
      0 = No tremor.
      1 = Tremor is barely visible,
      1.5s= Tremor is visible but less than 1 cm.
      1 — Tremor is 1-3 cm amplitude.
      2,5 = Tremor is 3-5 cm amplitude.
      3 = Tremor is 5-10 cm amplitude.
      3.5 = Tremor is 10-20 cm amplitude.
      4 = Trcmor is >20 cm amplitude.

   Tremor while walking
      0 = No tremor.
      1 = Tremor is barely visible.
      1.5 = Tremor is visible but less than 1 cm.
      2 = Tremor is 1-3 cm amplitude.
      2.5 = Tremor is 3-5 cm amplitude.
      3 = Tremor is 5-10 cm amplitude.

Continued

Table 24.5: Tremor Research Group Raring Scale—cont'd

3.5 = Tremor is 10-20 cm amplitude.
4 — Tremor is >20 cm amplitude.

5. Trunk tremor: Subject is comfortably seated in a chair. The subject flexes both legs at rhe hips 30 degrees above parallel to the ground for 5 seconds. The knees are passively bent so that the lower leg is perpendicular to the ground. The legs are not allowed to touch. Tremor is evaluated around the hip joints and the abdominal muscles.
   0 = No tremor,
   1 = Present only with hip flexion.
   2 — Obvious but mild tremor.
   3 = Moderate tremor.
   4 = Severe tremor.
6. Leg tremor action: Subject is comfortably seated. The subject is asked to raise his or her legs parallel to the ground with knees extended for 5 seconds. The legs are slightly abducted so that they do nor touch. The tremor .miplinide is assessed at the end of the feet.
   0 = No tremor.
   1 = Barely perceptible.
   1 — Obvious but mild tremor.
   3 = Moderate tremor is <5 cm at any point.
   4 = Severe tremor is >5 cm.
7. Leg tremor rest: Subject is comfortably seated with knees flexed and feet resting on the ground. The tremor amplitude is assessed at the point of maximal displacement.
   0 = No tremor.
   1 = Barely perceptible.
   1 — Obvious but mild tremor.
   3 = Moderate tremor is <5 cm at any point.
   4 = Severe tremor is >*S* cm.
8. Standing tremor: Subject is standing, unaided if possible. The internal malleoli are 5 cm apart. Arms are down at the subject's side. Tremor is assessed at any point on the legs or trunk.
   0 No rreiiior.
   1 = Barely perceptible tremor,
   2 = Obvious but mild tremor.
   3 = Moderate tremor.
   4 = Severe tremor.
9. Spiral drawings: Ask rhe subject to draw rhe requested figures. Test each hand without leaving the hand or arm on the table. Use only a ballpoint pen.
   0 = Normal.
   1 = Slightly tremulous. May cross lines occasionally.
   2 = Moderately tremulous or crosses lines frequently.
   3 = Accomplishes the task with great difficulty. Figure still recognizable.
   4 = Unable to complete drawing. Figure not recognizable,
10. Handwriting: Have patient write "Today is a nice day."
   0 = Normal.
   1 = Mildly abnormal. Slightly untidy, tremulous.
   2 = Moderately abnormal. Legible, but with considerable **tremor.**
   3 = Markedly abnormal. Illegible.
   4 = Severely abnormal. Unable to keep pencil or pen on paper without holding down with the orher hand.
11. Hold pencil approximately 1 mm above a point on a piece of paper for 10 seconds.
   0 = No tremor.
   1 = Tremor is barely visible,
   1.5 = Tremor is visible but less than 1 cm.
   2 = Tremor is 1-3 cm amplitude.
   2.5 = Tremor is *i-S* cm amplitude.
   3 = Tremor is 5-10 cm amplitude.
   3.5 = Tremor is 10-20 cm amplitude.
   4 = Tremor is >20 cm amplitude.
12. Pour water from one glass inro another, using Styrofoam coffee cups filled 1 cm from rop. Rated separately for right and left hands.
   0 = Absolutely no visible tremor.
   1 = More careful than a person without tremor. No water is spilled.
   2 = Spills a small amount (<I0%).
   3 = Spills large amount (10-50%).
   4 = Unable to pour without spilling most.

thighs may be seen in patients with atrophy of the anterior vermis, as seen in alcoholic cerebellar degeneration,

On standing unsupported, patients with orthostatic tremor develop rapid, rhythmic contractions of leg muscles, causing the kneecaps to bob up and down. This dampens or subsides on walking. In contrast, cerebellar disease results in slower titubation of axial sttuctutcs and head seen in the upright position. Observing the gait often helps differentiate between uppet limb testing tremor and postural tremor that persists at rest as a result of stress. The former usually is clearly evident during walking, whereas the latter usually subsides. Obviously, observing additional featutes of the **gait is helpful in** making these distinctions as well.

Certain tremors persist in all positions. Disease in the midbrain involving the superior cerebellar peduncle near the ted nucleus (possibly also involving the nigrostriatal fibers) results in the so-called midbrain or rubral tremor (Holmes's tremor). Characteristically, this form of tremor combines features of the three tremor classes. It is often present at rest, increases with postural maintenance, and increases still further, sometimes to extreme degrees, with goal-directed movement. Tremor also may be a feature of psychiatric disease, representing a conversion reaction ot even malingering. Usually, certain features arc atypical ot incongruous. This psychogenic tremor differs from most organic tremors in that the ftequency often is quite vatiablc, and concentration and distraction often abate the tremor instead of incteasing it.

CHOREA

The tetm *chorea* is derived from the Greek *chore ia,* meaning "a dance." This hyperkinetic movement disorder consists of irregular, unpredictable, brief, jerky movements that flit randomly from one part of the body to another. The movements are brisk and abrupt in some conditions, such as Sydenham's chorea, whereas in others they are

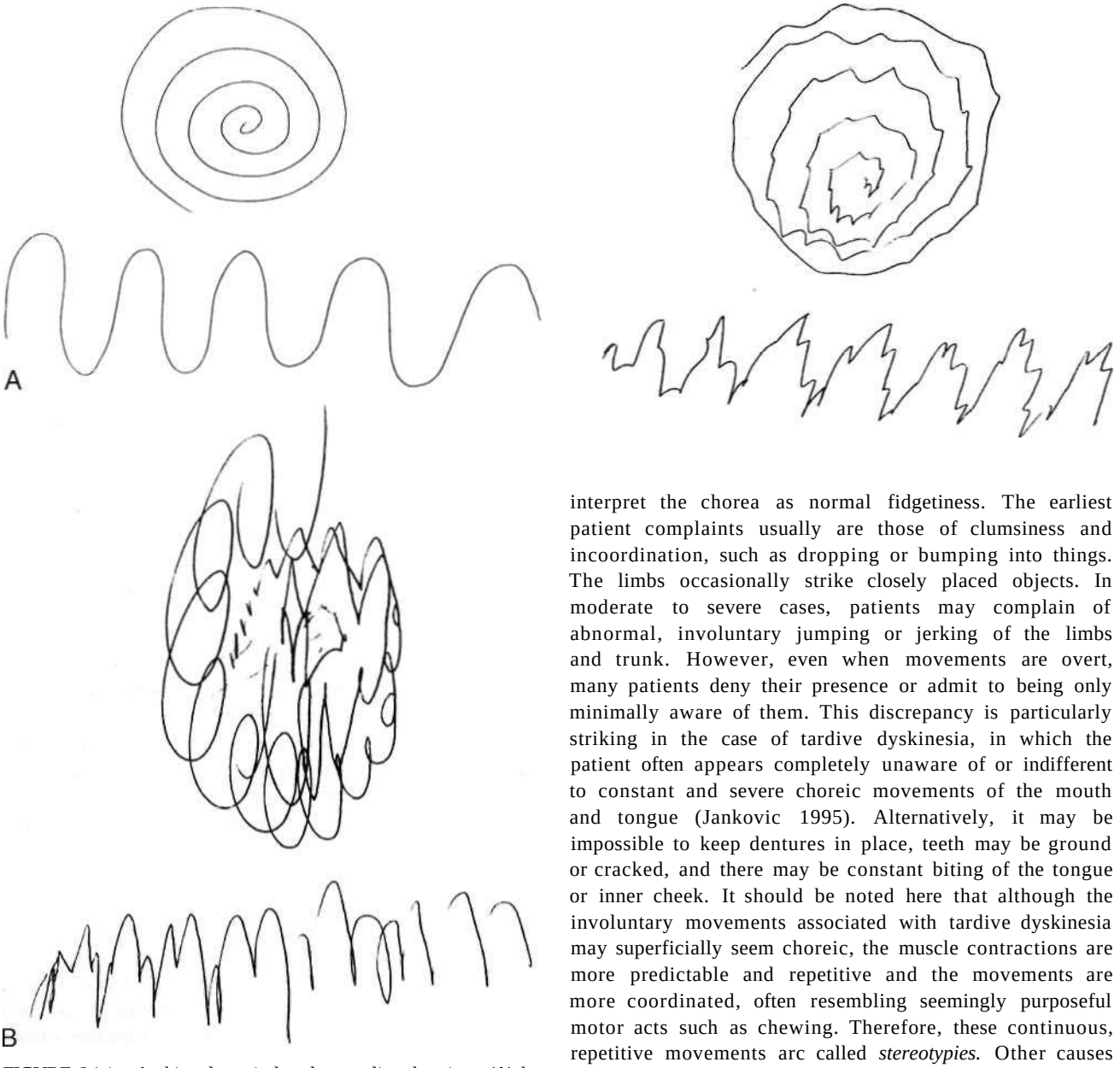

FIGURE 24,1 Archimedes spiral and wavy line drawings (A) by the examiner and a paticm with essential tremor in whom the tremor is asymmetrical and more evident (B) in the right hand than (C) in the left hand.

somewhat slower and more flowing, as in Huntington's disease. The term *choreoathetosis* has been used to describe slow chorea, typically seen in patients with cerebral palsy. There are numerous causes of chorea, most of which are listed in Table 24.6.

Common Symptoms

Initially, patients often are unaware of the presence of involuntary movements, and the family may simply interpret the chorea as normal fidgetiness. The earliest patient complaints usually are those of clumsiness and incoordination, such as dropping or bumping into things. The limbs occasionally strike closely placed objects. In moderate to severe cases, patients may complain of abnormal, involuntary jumping or jerking of the limbs and trunk. However, even when movements are overt, many patients deny their presence or admit to being only minimally aware of them. This discrepancy is particularly striking in the case of tardive dyskinesia, in which the patient often appears completely unaware of or indifferent to constant and severe choreic movements of the mouth and tongue (Jankovic 1995). Alternatively, it may be impossible to keep dentures in place, teeth may be ground or cracked, and there may be constant biting of the tongue or inner cheek. It should be noted here that although the involuntary movements associated with tardive dyskinesia may superficially seem choreic, the muscle contractions are more predictable and repetitive and the movements are more coordinated, often resembling seemingly purposeful motor acts such as chewing. Therefore, these continuous, repetitive movements arc called *stereotypies.* Other causes of stereotypies, besides tardive dyskinesia, include autistic disorders and schizophrenia.

Other features often associated with chorea, particularly Huntington's disease, include motor impersistence manifested by inability to maintain tongue protrusion (trombone tongue) and pendular reflexes, probably caused by motor hypotonia. Speech may be slurred, halting, and periodically interrupted, especially in Huntington's disease, in which speech disturbances arc severe and often do not correlate with the severity of chorea. Here, in addition to dysarthria, there is usually a reduction in the spontaneity and quantity iit speech output. Problems with feeding result from a combination of limb chorea, which causes sloppiness, and swallowing difficulties, which can result in choking and aspiration. Fating is particularly difficult for patients with neuroacanthocytosis (chorea-acanthocytosis), in which

Tahlc 24.6: Etiological classification of chorea

- Developmental and aging choreas
  - Physiological chorea of infancy
  - Cerebral palsy (anoxic), kernicterus
  - Buctal-ural-lingual dyskinesia and edentulous orodyskinesia
  - In older adults, senile chorea (probably several causes)
- Hereditary choreas
  - Huntington's disease
  - Benign hereditary chorea
  - Neuroacanthocytosis
  - Other central nervous system degenerations: olivopontocerebellar atrophy, Machado-Joseph disease and other spinocerebellar atrophies, ataxia telangiectasia, tuberous sclerosis, Friedreich's ataxia, familial calcification of basal ganglia, pantothenate kinase associated neurodegeneration, neurodegeneration with brain iron accumulation (Hallervorden-Spati disease)
- Neurometabolic disorders: Wilson's disease, Lesch-Nyhan syndrome, lysosomal storage disorders, amino acid disorders, Leigh's disease, porphyria
- Drugs: neuroleptics (tardive dyskinesia), antiparkinsonian drugs, amphetamines, cocaine, tricyclics, oral contraceptives
- Toxins: alcohol intoxication and withdrawal, anoxia, carbon monoxide, manganese, mercury, thallium, toluene
- Metabolic
  - Hyperthyroidism
  - Hypoparathyroidism (various types)
  - Pregnancy (chorea gravidarum)
  - Hypernatremia and hyponatremia, hypomagnesemia, hypocalcemia
  - Hypoglycemia and hyperglycemia (the latter may cause hemichorea, hemiballism)
  - Acquired hepatocerebral degeneration
  - Nutritional (e.g., beriberi, pellagra, vitamin B|i deficiency in infants)
- Infectious and postinfectious
  - Sydenham's chorea
  - Encephalitis lethargica
  - Various other infectious and postinfectious encephalitis, Creutzfeldt-Jakob disease
- Immunological
  - Systemic lupus erythematosus
  - Henoeh-Schonlein purpura
  - Others (rarely): sarcoidosis, multiple sclerosis, Behcet's disease, polyarteritis nodosa
- Vascular {often hemichorea)
  - Infarction or hemorrhage
  - Arteriovenous malformation, moyamoya disease
  - Polycythemia rubra vera
  - Migraine
- Tumors
  - Trauma, including subdural and epidural hematoma
  - Miscellaneous, including paroxysmal choreoathctosis

severe orolingual dystonia can cause the tongue to push the food out of the mouth almost as quickly as the patient puts it in. Here, patients often place food at the back of the tongue and throw the head back to initiate swallowing.

Disturbances of stance and gait can be an early complaint in patients with chotea. The patient may note a tendency to sway and jerk while standing and an unsteady, uneven gait often likened to a drunken stagger. Later still, added postural instability in Huntington's disease can tesult in falls. Respiratory dyskinesias may cause the patient to feel short of breath or unable to obtain enough air. Patients with involvement of the pelvic region may complain bitterly of thrusting and rocking movements in the lower trunk and pelvis. Respiratory and pelvic-involvement are sources of complaint more often in tardive dyskinesia than in other choreic movement disorders (Jankovic 1995a).

Other Clues in the History

It is obvious from a review of Table 24.6 that it is impractical to discuss additional historical clues for every cause of chorea. We therefore limit discussion here to a few practical and important points.

Age of onset and manner of progression vary depending on the cause. A helpful distinction can be made here between benign hereditary chorea and Huntington's disease. In the former, chorea typically begins in childhood with a slow progression and little cognitive change, whereas Huntington's disease presenting in childhood is more often of the akinetic-rigid variety, with severe mental changes and rapid progression.

In most cases, the onset of chorea is slow and insidious. An abrupt or subacute onset is more typical of many of the symptomatic causes of chorea, such as neuroleptic drug withdrawal (withdrawal emergent syndrome), Sydenham's chorea, hyperthyroidism, systemic lupus etythematosus (SLE), or multiple infarcts. A pattern of remissions and exacerbations suggests the possibility of drugs, SLE, and rheumatic fever, whereas brief (minutes to hours) bouts of involuntary movement indicate a paroxysmal dyskinesia.

A recent history of streptococcal throat infection and of musculoskeletal or cardiovascular problems in a child suggests a diagnosis of Sydenham's chorea. One may obtain a previous history of rheumatic fever, particularly in women who develop chorea during pregnancy or while taking the birth control pill. In women, chorea during pregnancy or a history of previous fetal loss suggests the possibility of SLE, even in the absence of other features of collagen vascular disease. Symptoms isolated to one side of the body suggest a structural lesion in the contralateral basal ganglia. However, many patients who complain of unilateral involvement have abnormalities of both sides on examination.

A careful family history is crucial. The most common cause of inherited chorea is Huntington's disease, which has fully penetrant autosomal dominant transmission (Jankovic and Ashizawa 2003). The family history can be misleading, however, because the clinical features of the disease in other family members may have been mainly behavioral and psychiatric disturbances and the chotea hardly noticed.

Examination

The range of choreiform movements is quite broad, including eyebrow lifting or depression, lid winking, lip pouting or pursing, cheek puffing, lateral or forward jaw movements, tongue rolling or protruding, head jerking in any plane (a common pattern is a sudden, backward jerk followed by a rotatory sweep forward), shoulder shrugging, trunk jerking or arching, pelvic rocking, and flitting movements of the fingers, wrists, toes, and ankles. Patients can be seen to incorporate choreic jerks into voluntary movement, perhaps in part to mask the presence of the dyskinesia (so-called parakinesis).

Performance of various tasks, such as finger-to-nose testing and rapid alternating movements, often is altered by the chorea, which can cause a jerky, interrupted performance. Standing and walking often aggravate the chorea. Particularly in Huntington's disease, the gait is irregular and lurching and has bizarre characteristics that may not simply be explained by increased chorea. The gait usually is wide based despite the absence of typical ataxia. Patients may deviate from side to side in a zigzag fashion, with lateral swaying and additional spontaneous flexion. In addition, the stride usually is shortened and the speed slowed, with some features similar to those of a parkinsonian gait, such as loss of arm swing, festination, propulsion, and retropulsion.

Respiratory irregularities are common, especially in tardive dyskinesia. Periodic grunting, respiratory gulps, humming, and sniffing may be present in this and other choreic disorders, including Huntington's disease. Other movement disorders often are combined with chorea. Dystonic features probably are the most common and are seen in many conditions. Less common but well recognized are parkinsonism (e.g., with juvenile Huntington's disease, neuroacanthocytosis, and Wilson's disease), tics (e.g., in neuroacanthocytosis), myoclonus (e.g., in juvenile Huntington's disease and others), tremor (e.g., in Wilson's and Huntington's diseases}, and ataxia (e.g., in juvenile Huntington's disease and some spinocerebellar ataxias). Tone usually is normal to low. Muscle bulk typically is preserved, although weight loss and generalized wasting are common in Huntington's disease. When distal weakness and amyotrophy are present, one must consider accompanying anterior horn cell or peripheral nerve disease, as in neuroacanthocytosis, ataxia telangiectasia, Machado-Joseph disease, and spinocerebellar ataxias (see Chapter 78; Abele et al, 2002). Here the reflexes may be reduced. On the other hand, chorea often results in a so-called hung-up reflex, probably caused by the occurrence of a choreic jerk after the usual reflex muscle contraction.

Depending on the cause (see Table 24.6), several other neurological disturbances may be associated with chorea. in 1 luntington's disease, for example, cognitive changes, motor impersistence (e.g., difficulty maintaining eyelid closure, tongue protrusion, or constant hand grip), apraxias {especially orolingual), and oculomotor dysfunction arc all quite common (see Chapter 77), "Milkmaid grip," appreciated as an alternating squeeze and release when the patient is asked to maintain a constant, firm grip of the examiner's fingers, probably is caused by a combination of chorea and motor impersistence.

TARDIVE DYSKINESIA

The usual movements seen in tardive dyskinesia should be distinguished from those of chorea. In contrast to the random and unpredictable flowing nature of chorea, tardive dyskinesia usually demonstrates repetitive stereotypical movements, which are most pronounced in the orolingual region (Jankovic 199.Sa). These include chewing and smacking of the mouth and lips, rolling of the tongue in the mouth or pushing against the inside of the cheek ("bon-bon sign"), and periodic protrusion or flycatcher movements of the tongue. The speed and amplitude of these movements can increase markedly when the patient is concentrating on performing rapid alternating movements in the hands. Patients often have a striking degree of voluntary control over the movements and may be able to suppress them for a prolonged period when asked to do so. On distraction, however, the movements return immediately. Despite severe facial movements, voluntary protrusion of the tongue is rarely limited, and this act often dampens or completely inhibits the ongoing facial movements. This contrasts with the pronounced impersistence of tongue protrusion seen in Huntington's disease, which is far out of proportion to the degree of choreic involvement of the tongue. Besides stereotypies, many other movement disorders arc associated with the use of dopamine receptor blockers (Table 24.7).

Besides impersistence typically seen in Huntington's disease, several other clinical factors help distinguish between Huntington's disease and tardive dyskinesia. Involuntary movements in tardive dyskinesia typically are localized to the lower face, whereas in Huntington's disease irregular contractions of the frontalis muscles and

Table 24.7: Neuroleptic-induced movement disorders

Acute, transient	*Chronic, persistent*
Dystonic; reaction	Tardive stereotypy
Parkinsonism	Tardive chorea
Akathisia	Tardive dystonia
Neuroleptic malignant syndrome	Tardive akathisia
	Tardive tics
	Tardive myoclonus
	Tardive tremor
	Persistent parkinsonism
	Tardive sensory syndrome

Source: Modified from Jankovic, J. 1995a, "Tardive syndromes and other drug-induced movement disorders," *Clin Neuropbarmacol,* vol. 18, pp. 197-214,

associated elevation of the eyebrows is very common. Despite the rocking movements of the pelvis, tapping of the feet, and shifting of the weight from side to side while standing (some of which may be caused by akathisia), the gait often is normal in patients with tardive dyskinesia, although a bizarre ducklike gait can be seen. This contrasts with the strikingly abnormal gait in many other choreic disorders, especially in Huntington's disease.

Tardive dyskinesia caused by chronic neuroleptic drugs is not the only cause of stereotypical oro-bucco-linguo-masticatory movements. Other drugs, particularly dopamine agonists in PD, anticholinergics, and antihistamines, cause a similar form of dyskinesia. Multiple infarctions in the basal ganglia and possibly lesions in the cerebellar vermis result in similar movements. Older adults, especially the edentulous, often have a milder form of orofacial movement, usually with minimal lingual involvement. Here, as in tardive dyskinesia, inserting dentures in the mouth may dampen the movements; and placing a finger to the lips can also suppress them. Another important diagnostic consideration and source of clinical confusion is idiopathic oromandibular dystonia.

BALLISM

Ballism or ballismus is the least common of the well-defined dyskinesias. The name is derived from the Greek word meaning "to throw," and the movements of ballism are high in amplitude, violent, and flinging or flailing in nature. As in chorea, they are rapid and nonpatterned. The prominent involvement of more proximal muscles of the limbs usually accounts for the throwing or flinging nature. Lower-amplitude distal movements also may be seen, and occasionally there is even intermittent prolonged dystonic posturing. Some authors emphasize the greater proximal involvement and the persistent or ceaseless nature of ballism in contrast to chorea. However, it is more likely that ballism and chorea represent a continuum rather than distinct entities. The coexistence of distal choreic movements, the discontinuous nature in less severe cases, and the common evolution of ballism to typical chorea during the natural course of the disorder or with treatment all support tins theory. Ballism is most often confined to one side of the body, when it is called *hemiballismus.* Occasionally, only one limb is involved (monoballism), and, rarely, both sides (biballism) or both legs {paraballism) may be affected.

Table 24.8 lists the various causes of hemiballism. These flinging movements often are extremely disabling to patients, who drop things from their hands or damage closely placed objects. Self-injury is common, and examination often reveals multiple bruises and abrasions. Additional signs and symptoms depend on the cause, location, and extent of the lesion, which is usually in the contralateral subthalamic nucleus or striatum (see Chapter 77).

Table 24.8: Causes of ballism

Infarction or ischemia, including transient ischemic attacks; usually lacunar disease, hypertension, diabetes, atherosclerosis, vasculitis, polycythemia, thrombocytosis, other causes
Hemorrhage
Tumor
Metastatic
Primary
Other focal lesions (e.g., abscess, arteriovenous malformation, tuberculoma, toxoplasmosis, multiple sclerosis plaque, encephalitis, subdural hematoma)
Hyperglycemia (nonketotic hyperosmolar state)
Drugs (phenytoin, dopamine agonists in Parkinson's disease)

DYSTONIA

Dystonia can be defined as a disorder dominated by sustained muscle contractions, which often cause twisting and repetitive movements or abnormal postures (Jankovic and Fahn 2002). The term *dystonia* has been used in three major contexts. It may be used to describe the specific form of involuntary movements just described (i.e., a physical sign). It also may be used to refer to a syndrome caused by a large number of different disease states (Table 24.9).

Dystonic movements may be slow and twisting. In addition, however, dystonic movements may be quite rapid, resembling the shocklike jerks of myoclonus. There may be additional rhythmic movements, especially when the patient attempts to resist the involuntary movement actively. Here, if the patient is asked to relax and allow the limb to move as it pleases, the abnormal dystonic posturing usually becomes evident, and the rhythmic dystonic tremor lessens. A faster distal postural tremor also may occur. It is the varied nature of these movements that often causes the misdiagnosis of dystonia as some other type of movement disorder.

Another common error in diagnosis is the mislabeling of dystonia as hysteria. The movements typically are aggravated by stress and anxiety and are improved by rest and even hypnosis. Patients often discover a variety of peculiar maneuvers ("sensory tricks") that they can use to lessen or even completely abate the dystonic movements and postures (discussed later in this chapter and in Chapter 77). The abnormal movements and postures may occur only during [he performance of certain acts and not others that use the same muscles. An example of this action, task-specific dystonia, is involvement of the hand only in writing (writer's cramp or graphospasm) or playing a musical instrument but not with other manual tasks, such as using utensils. Dystonia of the oromandibular region only on speaking or eating is another example of task-specific dystonia, as is dystonia in legs and trunk occurring only on walking forward but not on walking backward, climbing stairs, or running. A final source of possible confusion with hysteria is the occurrence of dystonia after injury to the affected limb or after prolonged immobilization

Table 24.9: Etiologic classification of dystonia

- [. Primary dystonia
  - A. Sporadic
  - R. Inherited (all autosomal dominant)
    - Classic (Oppenheim's) dysronia (common in Ashkena/i Jews, DYT1, 9q34)
    - Childhood- and adult-onset cranial-cervical-limb dystonia (DYT6, 8p21-22)
    - Adult-onset cervical and other focal dystonia (DYT7, 18p>
- II. Secondary dystonia (dystonia-pius syndromes)
  - A. Sporadic
    - Parkinson's disease
    - Progressive supranuclear palsy
    - Multiple system atrophy

Corticobasal degeneration

- B. Inherited
  - 1. Autosomal dominant
    - Dopa-responsive dystonia (DYT5, GTP cyclohydrolase I 14q22.1)
    - Myoclonus-dystonia (llq23)
    - Alternating hemiplegia of childhood
    - Mach ado-Joseph disease (SCA3)
    - Dystonia-ataxia (SCA6)
  - 2. Autosomal recessive
    - Dopa-responsive dystonia (11 p 11,5)
    - Tytosine hydroxylase deficiency (chromosome 21)
    - Bioptenn deficient diseases
    - Aromatic amino acid decarboxylase deficiency (dopamine agonist-responsive dystonia)
- III. Hcredodegc iterative diseases (typically not pure dystonia)
  - A. X-linked recessive
    - [.tiling (X-linka! dystonia-parkinsonism, DYT3, Xql2-Xq21)
    - Pelizaeus-Merzbacher disease
    - Lesch-Nyhan syndrome
    - Dystonia-dcafness (Xq22)
    - Deafness, dystonia, retardation, blindness
  - B. Autosomal dominant
    - Rapid-onset dystonia-parkinsonism
    - Juvenile parkinsonism-dystonia
    - Huntington's disease (IT15, 4pl6.3)
    - Spinocerebellar degenerations (SCA1-SCA8)
    - Dentato-rubral-pallidoluysian atrophy
    - Hereditary spastic paraplegia with dystonia
    - Thalamo-olivary degeneration with Wernicke's encephalopathy
  - C. Autosomal recessive
    - Wilson's disease (Cu-ATPase, 13ql4.3)
    - Ncurodegeneration with brain iron accumulation type 1 (Hallervorden-Spatz disease, 20pl2.3-pl3)
    - Hypoprcbetahpoptoteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degenetation
    - Ataxia telangiectasia
  - *Associated with metabolic disorders*
    - I, Amino acid disorders
      - Glutaric acidemia
      - Methylmalonic acidemia
      - Homocystinuria
      - Harm up disease
      - Tyrosinosis
    - 2. Lipid disorders
      - Metachromatic leukodystrophy
      - Ceroid lipofuscinosis
      - Niemann-Pick type C (dystonic lipidosis, "sea blue" histiocytosis); defect in cholesterol esterification; caused by mutation in NPC1 gene (18qll) and HE1 gene(14q24.3)
      - Gangliosidoses GM1, GM2 variants
      - Hexosaminidase A and B deficiency
    - 3. Other metabolic disorders
      - Biopterin deficient diseases
      - Triosephosphate isomerase deficiency
      - Aromatic amino acid decatboxylase deficiency (dopamine agonist-responsive dystonia)
      - Biotin-responsive basal ganglia disease
  - D. Mitochondrial
    - Leigh disease
    - Leber's disease
  - E. Unknown inheritance
    - Neuroacanrhocytosis
    - Rett's syndrome
    - Intraneuronal inclusion disease
    - Infantile bilateral striatal necrosis
    - Familial basal ganglia calcifications
    - Hereditary spastic paraplegia with dystonia
    - Deletion of 18q
  - *Of a known specific cause*
    - Perinatal cerebral injury and kernicterus: athetoid cerebral palsy, delayed-onset dystonia
    - Infection: Viral encephalitis, encephalitis lethargica, Rcyc's syndrome, subacute sclerosing panencephalitis, Creutzfeldt-Jakob disease, human immunodeficiency virus infection
    - Other: tuberculosis, syphilis, acute infectious torticollis
    - Drugs: i,-dopa and dopamine agonists, dopamine receptor-blocking drugs, fenfluramine, anticonvulsants, flecaiuide, ergots, certain calcium channel blockers
    - Toxins: magnesium, carbon monoxide, carbon disulfide, cyanide, methanol, disulfiram, 3-nitroproprionic acid, wasp sting
    - Metabolic: hypoparathyroidism
    - Pataneoplastic brainstem encephalitis
    - Vitamin E deficiency
    - Primary antiphospholipid syndrome
    - Cerebral vascular or ischemic injury, Sjogren's syndrome
    - Multiple sclerosis
    - Central pontine myelinolysis
    - Brainstem lesions
    - Spinal cord lesions
    - Syringomyelia
    - Brain tumor
    - Arteriovenous malformation
    - Head trauma and brain surgery (thalamotomy)
    - Lumbar stenosis
    - Peripheral trauma (with causalgia)
    - Electrical injury
- IV. Other hyperkinetic syndromes associated with dystonia
  - A. Tic disorders with dystonic tics
  - B. Paroxysmal dyskinesias
    - 1. Paroxysmal kinesigenic dyskinesia (16pll.2-ql2.1)
    - 2. Paroxysmal nonkinesigenic dyskinesia (2q33-35)
    - 3. Paroxysmal exertion-induced dyskinesia (16pl2-ql2)
    - 4. Paroxysmal hypnogenic dyskinesia (20ql3.2-13.3)

Continued

Tabic 24.9: Etiologic classification of dystonia—cont'd

V. Psychogenic
VI. Pseudodystonia
- Atlanto-axial subluxation
- Syringomyelia
- Arnold-Chiari malformation
- Trochlear nerve palsy
- Vestibular torticollis
- Posterior fossa mass
- Soft tissue neck mass
- Congenital postural torticollis
- Congenital Klippel-Feil syndrome
- Isaac's syndrome
- Sandiffer's syndrome
- Satoyoshi syndrome
- Stiff man syndrome
- Dupuytren's contractures
- Trigger digits
- Ventral hernia

Source: Modified from Jankovic, J. *&c* Halm, S. 2002, "Dysronic disorders," in *Parkinson's Disease and Movement Disorders,* 4th ed, eds J. Jankovic & *E.* Tolosa, Lippincott Williams 5c Wilkins, Philadelphia, pp. 331-357.

such as casting. Such peripherally induced dystonia may be associated with a complex regional pain syndrome, depression, and personality changes and may occur on a background oi secondary gain or litigation.

Common Symptoms

Dystonia can affect almost all striated muscle groups. Common symptoms include forced eyelid closure (blepharospasm); jaw clenching, forced jaw opening, or involuntary tongue protrusion (otomandibular or lingual dystonia); a harsh, sttaincd, or breathy voice (laryngeal dystonia or spasmodic dysphonia); and involuntary deviation of the neck in any plane or combination of planes (cetvical dystonia or spasmodic torticollis). Other symptoms are spasms of the trunk in any direction, which vatiably interfere with lying, sitting, standing, or walking (axial dystonia); interference with manual tasks (often only specific tasks in isolation: the occupational cramps); and involvement of the leg, usually with inversion and plantar flexion of the foot causing the patient to walk on the toes. All these disorders may slowly progress to the point of complete loss of voluntary function of the affected part. On the othet hand, only certain actions may be impaired, and the disorder may remain focal in distribution. Chapter 77 deals with each of these forms of dystonia in mote detail.

"I lie age at onset and distribution of dystonia often are helpful in determining the possible cause. The many causes of secondary dystonia ate detailed in Table 24,9. Whereas some patients with dystonia have "pure dystonia" without any other neurological deficit (primary dystonia), others have additional clinical features (dystonia-plus syndrome), such as parkinsonism, spasticity, weakness, myoclonus, dementia, seizures, and ataxia. Typically, childhood-onset primary dystonia (e.g., classic, Oppenheim's DYT1 dystonia) begins in distal parts of the body (e.g., graphospasm or foot inversion) and spreads to a generalized dystonia. On the other hand, dystonia beginning in adult life usually is limited to one or a small number of contiguous regions, such as the face and neck, and it remains focal or segmental and rarely becomes generalized. Ceneralized involvement or onset in the legs in an adult nearly always implies the possibility of a secondary cause, such as PD or some other parkinsonian disorder. Involvement of one side of the body (hemidystonia) is strong evidence of a lesion in the contralateral basal ganglia, particularly the putamen.

Most ptimary dystonias start as action dystonia occurring during some activity such as writing and walking or running, but when the dystonia occurs at rest and consists of a fixed postutc, secondary causes, such as peripheral or central trauma, should be considered. A fixed posture maintained during sleep implies superimposed contractures or a musculoskeletal distutbance mimicking the postutes of dystonia. Although many patients find that dystonia is lessened by test and sleep, some note a striking diurnal variation. The diurnal variation manifests with little ot no dystonia on rising in the morning, followed by the progressive development of problems as the day goes on, sometimes to the point of becoming unable to walk late in the day. This diurnal variability strongly suggests a diagnosis of dopa-responsive dystonia. The natute of the onset of the symptoms (sudden versus slow) and their course, whether rapid progression, slow changes, or episodes of spontaneous remission, all provide important clues to the possible cause.

The family history must be reviewed in detail, with the awareness that affected relatives may have limited or distinctly different involvement from that of the patient. A birth and developmental history must be obtained in view of the frequency of dystonia after birth trauma, birth anoxia, and kernicterus. As with the other dyskinesias, a history of such features as previous encephalitis, drug use, and head trauma must be sought. Thete is also increasing support for the ability of peripheral trauma to precipitate various forms of dystonia, and occasionally this is combined with the syndrome of complex regional pain, also called reflex sympathetic dystrophy.

Examination

Action dystonia is commonly the earliest manifestation of primary (idiopathic) dystonia. It is important to observe patients performing the acts that ate most affected. Later, other tasks precipitate similar problems, the use of other

parts of the body causes the dystonia to become evident in the originally affected site, and the dystonia may overflow to other sites. Still later, dystonia is evident periodically at rest, and even later the posturing may be persistent and difficult to correct passively, especially when secondary joint contractures develop. A significant deviation from this progression, particularly with the early appearance of dystonia at rest, should encourage the physician to search carefully for a secondary cause (see Table 24.9).

It is important to recognize the natural variability of dystonia, especially the effects of stress and anxiety, which may be somewhat paradoxical. This is especially the case with blepharospasm, in which the increased concentration or anxiety associated with a visit to the doctor often mil lies the severity lit" the problem. It reliance is placed only on the degree of disability seen in the office, the physician may underestimate the severity of the blepharospasm and may misdiagnose the problem as hysterical.

Depending on the cause of the dystonia, several other neurological abnormalities may be associated. Wilson's disease should be considered in any patient with onset of dystonia before age 60 (Svctcl ct al. 2001). Many secondary dystonic disorders (listed in Table 24.9) result in additional psychiatric or cognitive disturbances, seizures, or pyramidal ttaet or cerebellar dysfunction. Ocular motor abnormalities suggest a diagnosis of I.eigh disease, dystonic lipidosis, ataxia telangiectasia, Huntington's disease, Machado-Joscph disease, or other spinocerebellar atrophies. Optic nerve or retinal disease raises the possibility of Leigh disease, other mitochondrial cytopathics, GM_2 gangliosidosis, ceroid lipofuscinosis, and neurodegeneration with brain iron accumulation or pantothenate kinase-associated neurodegeneration, previously called *Hallervorden-Spatz disease* (Hayflick ct al. 2003). Lower motor neuron and peripheral nerve dysfunction may be seen with neuroacanthocytosis, ataxia telangiectasia, metachromatic leukodystrophy, Machado-Joseph disease, and other multisystem degenerations. The dystonia itself may cause additional neurological problems, such as spinal cord or cervical root compression from long-standing torticollis and peripheral nerve entrapment from limb dystonia. Also independent of the cause, long-standing dystonic muscle spasms often result in hypertrophy of affected muscles {e.g., the sternocleidomastoid in cervical dystonia).

Although the general medical examination must be thorough, it is usually unrevealing. As always, the ophthalmological and systemic signs of Wilson's disease must be carefully sought. Abdominal organomegaly also may indicate a storage disease. Severe self-mutilation is typical of Lesch-Nyhan syndrome. Minor tongue and lip mutilation is seen in neuroacanthocytosis, in which orolingual action dystonia may be prominent. Oculocutaneous telangiectasia and evidence of recurrent sinopulmonary infections suggest ataxia telangiectasia. Musculoskeletal abnormalities may simulate dystonia and, rarely, dysmorphic features may serve as a clue to a mucopolysaccharidosis.

TICS

Tics are the most varied of all movement disorders. Patients with Tourcttc's syndrome, the most common cause of tics, manifest both motor, vocal, or phonic tics and a wide variety of associated symptoms (Jankovic 2001). Tics are brief and intermittent movements (motor tics) or sounds (phonic tics). Motor tics typically consist of sudden, abrupt, transient, often repetitive and coordinated (stereotypical) movements that may resemble gestutes and mimic fragments of normal behavior, vary in intensity, and are repeated at irregular intervals. The movements are most often brief and jerky (clonic); however, slower, more prolonged movements (tonic ot dystonic tics) also occur, Several other characteristic features arc helpful in distinguishing this movement disorder from other dyskinesias. Patients usually cxpcticncc an inner urge to make the movement or a local premonitory sensation, which is temporarily relieved by its performance. Tics are voluntarily suppressible for variable periods, but this occurs at the expense of mounting inner tension and the need to allow the tic to occur. Indeed, a large proportion of these patients, when questioned carefully, admit that the movements or sounds that make up their tics are produced intentionally (in contrast to most other dyskinesias) in response to the uncontrollable inner urge or a premonitory sensation, Table 24.10 provides examples of the various types of tics.

Motor and phonic tics can be further subdivided as simple or complex. Simple motor tics are random, brief, irregular muscle twitches of isolated body segments, particularly the eyelids and other facial muscles, the neck, and the shoulders. In contrast, complex motor tics are coordinated, patterned movements involving a number of muscles in their normal synergistic telationships. A wide variety of other motor disturbances may be

Table 24.10: Phenomenological classification of tics

Simple motor tics: eye blinking; eyebrow raising; nose flaring; grimacing; mouth opening; tongue protrusion; platysma contractions; head jerking; shoulder shrugging, abduction, or rotation; neck stretching; arm jerks; fist clenching; abdominal tensing; pelvic thrusting; buttock or sphincter lightening; hip flexion or abduction; kicking; knee and foot extension; toe curling

Simple phonic tics: sniffing, grunting, throat clearing, shrieking, yelping, barking, growling, squealing, snorting, coughing, clicking., hissing, humming, moaning

Complex motor tics: head shaking, teeth gnashing, hand shaking, finger cracking, touching, hitting, jumping, skipping, stamping, squatting, kicking, smelling hands or objects, rubbing, finger twiddling, echopraxia, copropraxia, spitting, exaggerated startle

Complex phonic tics: coprolalia (wide variety, including shortened words), uninrelligible words, whistling, panting, belching, hiccoughing, stuttering, stammering, eeholalia, palilalia (also mental coprolalia and palilalia)

associated with tic disorders, and it is sometimes difficult to separate complex tics from some of these. These motor disturbances include obsessive-compulsive behavior, copropraxia (obscene gestures), echopraxia (mimicked gesnires), hyperucriviry with aitcnrional deficits ;uul impulsive behavior, and externally directed and self-destructive behavior, including self mutilation. Some Tourette's patients also manifest sudden and transient cessation ot all motor activity (blocking tics), including speech, without alteration of consciousness. These "blocking" tics are caused by either prolonged tonic or dystonic tics that interrupt ongoing motor activity such as speech ("intrusions") or a sudden inhibition of ongoing motor activity ("negative tic").

Simple and complex phonic ties comprise a wide variety of sounds, noises, ot formed words (see Table 24.10). Possibly the best known (although not the most common) example of complex vocal tics is coprolalia, the utterance of obscenities or profanities. These are often slurred or shortened or may intrude into the patient's thoughts but not become verbalized (mental coprolalia).

Like most dyskinesias, tics usually increase with stress. In contrast to other dyskinesias, however, relaxation (e.g., watching television at home) often results in an increase in the tics, probably because the patient docs not feel the need to suppress them voluntarily. Distraction or concentration usually diminishes tics, which also differs from most other types of dyskinesia. Many patients with idiopathic tics note spontaneous waxing and waning in their nature and severity over weeks to months, and periods of complete remission are possible. Many people with tics are only mildly affected, and many are even unaware that they demonstrate clinical features. This must be kept in mind when reviewing the family history and planning treatment. Finally, tics are one of the few movement disorders that can persist during all stages of sleep.

Table 24.11: Etiological classification of tics

1. Physiological tics
   A. Mannerisms
II. Pathological tics
   A. Primary
   Sporadic
      1. Transient motor or phonic tics (<1 year)
      2. Chronic motor or phonic tics (>1 year)
      3. Adult-onset (recurrent) tics
      4. Tourette's syndrome
   Inherited
      1. Tourette's syndrome
      2. Huntington's disease
      3. Primary dystonia
      4. Neuroacanthocyrosis
   B. Secondary ("tourettism")
      1. Infections: encephalitis, Creutzfeldt-jakob disease, Sydenham's chorea
      2. Drugs: stimulants, i.-dopa, carbamazepine, phenytoin, phenobarbital, antipsychotics
      3. Toxins: carbon monoxide
      4. Developmental: static encephalopathy, mental retardation, chromosomal abnormalities
      5. Other: head trauma, stroke, neurocutaneous syndromes, chromosomal abnormalities, schizophrenia, neuroacanthocytosis degenerative disorders
HI. Related disorders
   1. Stereotypies
   2. Self-injurious behaviors
   3. Hyperactivity syndrome
   4. Compulsions
   5. Excessive srartle
   6. Jumping disease, latah, myriachit

Source: Modified from [ankovic, j. 2001, "Tourette's syndrome," *N Engl J Med,* vol. 345, pp. 1184-1192.

Common Symptoms

The causes of tic disorders are listed in Table 24.11. Most are primary or idiopathic, and within this group the onset is almost always iu childhood or adolescence (Tourette's syndrome). Men are affected more often than women. Idiopathic tics occur on a spectrum from a mild, transient, single, simple motor tic to chronic, multiple, simple, and complex motor and phonic tics.

Patients and their families complain of a wide variety of symptoms (see Table 24.10). They may have seen numerous other specialists (e.g., allergists for repetitive sniffing, otolaryngologists for throat clearing, ophthalmologists for excessive eye blinking or eye rolling, and psychologists and psychiatrists for various neurobehavioral abnormalities). The true diagnosis of Tourette's syndrome often is first suggested after someone close to the patient has learned about it in the media. Children may verbalize few complaints or feel reluctant to speak of the problem, especially if they have been subject to ridicule by others. Even young children, when questioned carefully, can provide the history of urge to perform the movement that gradually culminates in the release of a tic and the ability to control the tic voluntarily at the expense of mounting inner tension. Children may be able to control the tics for prolonged periods but often complain of difficulty concentrating on other tasks while doing so. Some give the history of tequesting to leave the schoolroom and then releasing the tics in private (e.g., in the washroom). Peers and siblings often chastise or ridicule the patient, and parents or teachers, not recognizing the nature of the disorder, may scold or punish the child for what are thought to be voluntary bad habits (indeed, an older term for tics is *habit spasms).*

The hisrory may include an exposure to stimulants for hyperactivity. The family history must be reviewed for rhe wide range of potential manifestations (especially obsessive-compulsive behavior). Additional neurological complaints, including other dyskinesias, suggest the possibility of a secondary cause of the tics.

Examination

In most patients with tics, the neurological examination is entirely normal. In patients with primary tic disorders, the presence of other neurological, cognitive, behavioral, and neuropsychological disturbances may simply relate to extension of the underlying cerebral dysfunction beyond the core that accounts for pure tic phenomena. Patients with secondary forms of tics (e.g., neuroacanthocytosis, tardive tics) may demonstrate other involuntary movements, such as chorea, dystonia, and other neurological deficits (see Table 24.11). Careful interview stressing the subjective features that precede or accompany tics usually allows the distinction between true dystonia or myoclonus, and dystonic or clonic tics.

Despite bitter complaints by the family, it is common for patients to show no evidence of a movement disorder during an office appointment. Aware of this, the physician must attempt to observe the patient at a time when he or she is less likely to be exerting voluntary control, such as in the waiting room. If no movements have been witnessed during the interview, the physician should seemingly direct attention elsewhere (e.g., to the parents) while observing the patient out of the corner of the eye. The patient often releases the tics while changing in the examining room, particularly if they have been held back during the interview. The physician should attempt to view the patient at this time or at least listen for the occurrence of phonic tics. Despite these maneuvers, one may have to ask the patient to voluntarily mimic the movements. This, in combination with associated symptoms, such as urge, voluntary release and control, and the often varied and complex nature of the movements, usually is enough to provide the diagnosis, even if the spontaneous tics are not witnessed in the office. Finally, the parents should be asked to provide home videos of the patient.

MYOCLONUS

Myoclonus can be defined as sudden, brief, shocklikc involuntary movements that may be caused by active muscle contraction (positive myoclonus) or inhibition of ongoing muscle activity (negative myoclonus). The differential diagnosis of myoclonus is broader than that of any other movement disorder (Table 24.12). To exclude muscle twitches, such as fasciculations caused by lower motor neuron lesions, some authors have insisted that an origin in the CNS be a component of the definition. Although the majority of causes of myoclonus originare in the CNS, occasional cases of brief shocklike movements, clinically indistinguishable from CNS myoclonus, occur with peripheral nerve disease.

A wide range of clinical patterns of myoclonus exist. The frequency varies from single, rare jerks to constant, repetitive contractions. The amplitude may range from a small contraction that cannot move a joint to a very large jerk that moves the entire body. The distribution ranges from focal involvement of one body part, to segmental (involving two or more contiguous regions), to multifocal, to generalized. When the jerks occur bilaterally, they may be symmetrical or asymmetrical. When they occur in more than one region, they may be synchronous in two body parts (within milliseconds) or asynchronous. Myoclonus usually is arrhythmic and irregular, but in some patients it is very regular (rhythmic), and in others there may be jerky oscillations that last for a few seconds and then fade away (oscillatory). Myoclonic jerks may occur spontaneously, without a clear precipitant, or in response to a wide variety of stimuli, including sudden noise, light, visual threat, pinprick, touch, or muscle stretch. Attempted movement (or even the intention to move) may initiate the muscle jerks (action or intention myoclonus). Palatal myoclonus is a form of segmental myoclonus manifested by rhythmic contractions of the soft palate. Symptomatic palatal myoclonus, usually manifested by contractions of the levator palatini, may persist during sleep; this form of palatal myoclonus usually is associated with some brainstem disorder. In contrast, essential palatal myoclonus consists of rhythmic contractions of the tensor palatini, often associated with a clicking sound in the ear, and disappears with sleep. When the tensor muscle contracts, as in essential palatal myoclonus, the entire soft palate moves, whereas only the edges of the soft palate move when the levator muscle contracts. Symptomatic but not essential palatal myoclonus often is associated with hypertrophy of the inferior olive.

Common Symptoms

As may be seen from the foregoing description and the long list of possible causes of myoclonus, the symptoms in these patients are quite varied. For simplification, we briefly review the possible symptoms with respect to four major etiological subcategories in Table 24.12.

Physiological forms of myoclonus occurring in normal subjects vary depending on the precipitant. Probably the most common form is the jerking most of us have experienced on falling asleep (hypnagogic jactitation). This very familiar phenomenon is rarely a source of concern. Occasionally, patients do become concerned by anxiety- or exercise-induced myoclonus. The history usually is clear, and there is little to find (including abnormal movements) when the patient is seen.

In the essential myoclonus group, patients usually complain of isolated muscle jerking in the absence of other neurological deficits (with the possible exception of tremor and dystonia). The movements may begin at any time from early childhood to late adult life and may remain static or progress slowly over many years. The family history may be positive, and some patients note a striking

Table 24.12: Etiological classification of myoclonus

- Physiological myoclonus (normal subjects}
  - Sleep jerks (hypnic jerks)
  - Anxiety-induced
  - Exercise-induced
  - Hiccough (singultus)
  - Benign infantile myoclonus with feeding
- Essential myoclonus (no known cause and no other gross neurological deficit)
  - Hereditary
  - Sporadic
- Epileptic myoclonus (seizures dominate and no encephalopathy, at least initially)
  - Fragments of epilepsy
    - Isolated epileptic myoclonic jerks
    - Epilepsia partialis continua
    - Idiopathic stimulus-sensitive myoclonus
    - Photosensitive myoclonus
    - Myoclonic absences in petit mal
  - Childhood myoclonic epilepsies
    - Infantile spasms
    - Myoclonic astatic epilepsy (Lennox-Castaut)
    - Cryptogenic myoclonus epilepsy (Aicardi's)
    - Awakening myoclonus epilepsy of Janz
  - Benign familial myoclonic epilepsy (Rabot's)
  - Progressive myoclonus epilepsy: Baltic myoclonus (Unvcrricht-Lundborg)
- Symptomatic myoclonus (progressive or static encephalopathy dominates)
  - Storage disease
    - I.afora body disease
    - Lipidoses, such as GM2 gangliosidosis, Tay-Sachs, Krabbe's
    - Ceroid lipofuscinosis (Batten's, Kufs's)
    - Sialidosis (cherry-red spot)
  - Spinocerebellar degeneration
    - Ramsay Hunt syndrome (many causes)
    - Friedreich's ataxia
    - Ataxia telangiectasia
  - Basal ganglia degenerations
    - Wilson's disease
    - Torsion dystonia
    - Hallervorden-Spatz disease
    - Progressive supranuclear palsy
    - Huntington's disease
    - Parkinson's disease
    - Cortical basal degeneration
    - Pallidal degenerations
    - Multiple system atrophy
  - Mitochondrial encephalopathies, including myoclonic epilepsy and ragged-red fibers
  - Dementias
    - Creutzfeldt-Jakob disease
    - Alzheimer's disease
  - Viral encephalopathies
    - Subacute sclerosing panencephalitis
    - Encephalitis lethargica
    - Arbovirus encephalitis
    - Herpes simplex encephalitis
    - Postinfectious encephalitis
  - Metabolic
    - [lepacic failure
    - Renal failure
    - Dialysis syndrome
    - Hyponatremia
    - Hypoglycemia
    - Infantile myoclonic encephaloparhy (polymyoclonus, wirh or without neuroblastoma)
    - Nonketotic hyperglycemia
    - Multiple carboxylase deficiency
  - Toxic encephalopathies
    - Bismuth
    - Heavy metal poisons
    - Methyl bromide, dichlorodiphenyltrichloroethane
    - Drugs, including 1-dopa, tricyclics
  - Physical encephalopathies
    - Posthypoxia (Lance-Adams syndrome)
    - Post-trau marie
    - Heat stroke
    - I.livtnc ^lidL'k
    - Decompression injury
  - Focal central nervous system damage
    - Posts troke
    - Post-th a la m otomy
    - Tumor
    - Trauma
  - Olivodenrare lesions (palatal myoclonus)
  - Spinal cord lesions (segmental or spinal myoclonus)

Source: Modified from Fahn, S., Marsden, C. D., & van Woert, M. H. 1986, "Definition ;ind classification of myoclonus," *Adv Neurol,* vol. 43, pp. 1-5.

beneficial effect of alcohol. Associated dystonia, present in some patients, also may respond to ethanol.

Myoclonus occurring as one component of a wide range of seizure types is called *epileptic myoclonus.* Many of these patients give a clear history of seizures as the dominant feature. Myoclonic jerks may be infrequent and barely noticeable to the patient or may occur frequently and cause pronounced disability. Myoclonus on waking in the morning or an increasing frequency of the myoclonic jerks may forewarn of a seizure soon to come. The clinical pattern of myoclonus in this instance also varies widely. Sensitivity to photic stimuli and other sensory input may be prominent. Occasional patients demonstrate isolated myoclonic jerks in the absence of additional seizure activity. In these cases, the family history may be positive for seizures, and the electroencephalogram often demonstrates a typical centrencephalic seizure pattern that is otherwise asymptomatic (such as a 3-Hz spike and wave pattern). In others, myoclonus and seizures are equally prominent (the myoclonic epilepsies). These may or may not be associated with an apparent progressive encephalopathy (most often with cognitive dysfunction and ataxia} in the absence of a definable, underlying, symptomatic cause.

In the disorders classified as causing symptomatic myoclonus, seizures may occur, but the encephalop-athy (either static or progressive) is the feature that

predominates. All sorts of myoclonic patterns are seen in this broad category. As can be appreciated from review of Table 24.12, a plethora of other neurological and systemic symptoms may accompany the encephalopathy. Two clinical subcategories of this larger grouping have been distinguished to assist in differential diagnosis. In progressive myoclonic epilepsy, myoclonus, seizures, and encephalopathy predominate, whereas in progressive myoclonic ataxia (often called *Ramsay Hunt syndrome),* myoclonus and ataxia dominate the clinical picture, with less frequent or severe seizures and mental changes. Myoclonus may also originate in the brainstem and spinal cord. Spinal segmental myoclonus often is rhythmic and limited to muscles innervated by one or a few contiguous spinal segments. Propriospinal myoclonus is another type of spinal myoclonus that usually results in flexion jerks of the trunk.

Examination

Considering the varied causes, a wide range of neurological findings are possible. Alternatively, despite the complaint of abnormal movements, some patients with myoclonus (like those with tics and certain paroxysmal dyskinesias) have little to reveal on examination. This is particularly the case for the physiological forms of myoclonus and for those associated with epilepsy and some symptomatic causes. When myoclonus is clearly present on examination, the physician should try to characterize the movement, as outlined earlier in the chapter. When the jerks are single or repetitive but arrhythmic, one must differentiate these movements from tics. Myoclonus usually is briefer and less coordinated or patterned. Furthermore, myoclonus is not associated with a premonitory urge or sensation. Rhythmic forms of myoclonus may be confused with tremors. Here, the pattern of movement is more one of repetitive, abrupt-onset, square wave movements caused by contractions of the agonists, in contrast to the smoother sinusoidal activity of tremor produced by alternating or synchronous contractions of antagonist muscles. Rhythmic myoclonus usually is in the 1- to 4-Hz range, in contrast to the faster frequencies seen in most types of tremor. The oscillations of so-called oscillatory myoclonus may be faster. These are distinguished by their bursting or shuddering nature, usually precipitated by sudden stimulus or movement, lasting for a few seconds and then fading away.

The distribution of the myoclonus is helpful. Focal myoclonus may be more common in disturbances of an isolated region of the cerebral cortex. Segmental involvement, particularly when rhythmic, may occur with brainstem lesions (such as branchial or palatal myoclonus) or spinal lesions (spinal myoclonus). Multifocal or generalized myoclonus suggests a more diffuse disorder, particularly involving the reticular substance of the brainstem. When multiple regions of the body arc involved, it is helpful to attempt to estimate whether movements are occurring in synchrony. It is sometimes difficult to do this clinically, and multichannel electromyographic (EMG) monitoring may be needed.

Throughout the examination, it is important to define whether the movements occur spontaneously or with various precipitants, such as sudden loud noise, visual threat, perturbation, or a pinprick. A number of special sense and somesthctic sensory inputs should be tested. In addition, it is important to evaluate the effects of passive and active movement. In the case of action or intention myoclonus, jerking occurs during voluntary motor activity, especially when the patient attempts to perform a fine motor task, such as reaching for a target. This disturbance is often confused with severe ataxia. Action myoclonus may be evident in such activities as voluntary eyelid closutc, pursing of lips or speaking, holding the arms out, finger-to-nose testing, writing, bringing a cup to the mouth, holding the legs out against gravity, heel-to-shin testing, and walking. In addition to the positive myoclonus that results from a brief active muscle contraction, negative myoclonus also may occur. Although clinically these, too, appear as brief jerks, they are caused by periodic inhibition of ongoing muscle activity and sudden loss of muscle tone. The most common example of negative myoclonus is asterixis, which may be seen in liver failure ("liver flap") and, to a lesser extent, in other metabolic encephalopathies, and occasionally with focal brain lesions. The best-recognized location of asterixis is the forearm muscles, where it causes a flapping, irregular tremor-like movement when the wrists are held extended. When mild and of low amplitude, this may be confused with 5- to 6-Hz postural tremor. A similar form of negative myoclonus accounts for the periodic loss of postural tone in axial and leg muscles in some patients with action myoclonus syndromes, such as postanoxic action myoclonus. This results in a bobbing movement of the trunk while standing and may culminate in falls.

MISCELLANEOUS MOVEMENT DISORDERS

Hemifacial spasm is a common disorder in which irregular tonic and clonic movements involve the muscles of one side of the face innervated by the ipsilateral seventh cranial nerve. Unilateral eyelid twitching usually is the first symptom, followed at variable intervals by lower facial muscle involvement. Rarely, both sides of the face are affected, in which case the spasms are asynchronous on the two sides, in contrast to other pure facial dyskinesias, such as cranial dystonia.

The term *akatbisia* refers to a sense of restlessness and the feeling of a need to move. This was first used to describe what was thought to be a hysterical condition, and later the term was applied to the restlessness with inability to sit or stand still (motor impatience) seen in patients with idiopathic and postencephalitic parkinsonism. The syndrome is

now most commonly seen as a side effect of major tranquilizing or antiemetic drugs (neuroleptics) that act by blocking dopamine receptors. Akathisic movements occur in response to the subjective inner feeling of restlessness and need to move, although some authors believe that the subjective component is not necessary. The movements of akathisia are varied and complex. They include repetitive rubbing; crossing and uncrossing the arms; stroking the head and face; repeatedly picking at clothing; abducting and adducting, crossing and uncrossing, swinging, or up-and-down pumping of the legs; and shifting weight, rocking, marching in place, or pacing while sitting and standing. Occasionally, patients demonstrate a variety of vocalizations, such as moans, grunts, and shouts. Akathisia can be an acute ot delayed complication of antipsychotic drug therapy (acute akathisia and tardive akathisia, respectively). It also occurs in PD, secondary to selective serotonin reuptake inhibitors, and in cerrain confusional states or dementing processes.

Anothet disotder in which movements occur secondary to the subjective need to move is the restless legs syndrome (Ondo, Vuong, and Jankovic 2002). Here, unlike in akathisia, the patient typically complains of a variety of sensory disturbances in the legs, including pins and needles, creeping or crawling, aching, itching, stabbing, heaviness, tension, burning, or coldness. Occasionally, similar symptoms are appreciated in the upper limbs. These complaints usually are experienced during recumbency in the evening and often are associated with insomnia. This condition commonly is associated with another movement disorder, periodic leg movements of sleep, sometimes inappropriately called *nocturnal myoclonus.* These periodic, slow, sustained (1- to 2-second) movements range from synchronous or asynchronous dorsiflexion of the big toes and feet to triple flexion of one or both legs. More rapid myoclonic movements or slower, prolonged dystonic-like movements of the feet and legs also may be present in these patients while awake, and these too may have a natutal periodicity. Leg myoclonus or foot dystonia may be the presenting feature of the stiff man syndrome.

Another uncommon but well-defined movement disorder of the lower limbs has been called *painful legs and moving toes.* Here, the patient typically complains of a deep pulling or searing pain in the lower limb and foot associated with continuous wriggling or writhing of the toes, occasionally the ankle, and less commonly more proximal muscles of the leg. Rarely, a similar problem is seen in the upper limb as well. In some cases, there is a history of root or nerve injury, and the examination may demonstrate evidence of peripheral nerve dysfunction.

Some dyskinesias occur intermittently rather than persistently. This is typical of tics and certain forms of myoclonus. Dystonia often occurs only with specific actions, but this is usually a consistent response to the action rather than a periodic and unpredictable occurrence. Some patients with dystonia have a diurnal variation (dopa-responsive dystonia) characterized by essentially normal motor function in the morning with emergence or worsening of dystonia as the day progresses so that by the end of the day the patients are unable to ambulate because of severe generalized dystonia. A small group of patients with chorea or dystonia have bouts of sudden-onset, short-lived, involuntary movements known as *paroxysmal cboreoathetosis* or, more appropriately, *paroxysmal dyskinesia* (Table 24.13). Certain features characterize these disorders and sometimes help to separate them into diagnostic categories (such as precipitants, duration, frequency, age of onset, and family history} (sec Chapter 77). Thus, paroxysmal dyskinesias may be categorized as kinesigenic (precipitated by voluntary movement such as arising from a chair or starting to tun), nonkinesigenic, exertional, or nocturnal. In many cases, the movements are so infrequent that the physician never sees them, and so a careful history is needed to determine the nature of the disorder (Jankovic and Demirkiran 2002). There may be a family history of seizures or migraines. Periodic ataxias often are included in the group of paroxysmal movement disorders.

There are also disorders in which an abnormal or excessive response to startle occurs. In some patients, one simply finds an exaggerated startle response, which habituates poorly after repeated stimuli. In others, there is an abnormal response to the stimuli that normally evoke startle. Hyperekplexia, also known as *startle disease,* may be more akin to certain forms of myoclonus than to a normal startle response. A variety of other unusual disorders, first described in the nineteenth century together with Tourette's syndrome, manifest excessive startle. Jumping disease, latah, and myriacbit also involve sudden striking out, echo phenomena, automatic obedience, and several other less common features. It is believed that these disorders arc quite distinct from Tourette's syndrome and possibly represent culturally related operant-conditioned behavior rather than true neurological disease, although this point remains conrroversial.

Tahle 24.13: Classification of paroxysmal dyskinesias

Paroxysmal kinesigenic dyskinesia
Paroxysmal nonkinesigenic dyskinesia
Paroxysmal exertion-induced dyskinesia
Paroxysmal nocturnal dyskinesia
Paroxysmal psychogenic dyskinesia
  Each category includes the following:
    Short-lasting (<5 minutes)
      Idiopathic (familial fir sporadic)
      Secondary
    Long-lasting (>5 minutes)
      Idiopathic (familial or sporadic)
      Secondary

Source: Modified from Jankovic, J. 8c Demirkiran, M. 2002, "Classification of paroxysmal dyskinesias and ataxias," in *Myoclonus and Paroxysmal Dyskinesias, Advances in Neurology,* eds S. Fruchr & S. Fahn, Lippineott Williams *&c* Wilkins, Philadelphia, pp. 387-400.

Finally, psychogenic movement disorders, characterized by abnormal slowness or excessive movements or postures that cannot be directly attributed to a lesion or an organic dysfunction in the nervous system, are emerging as one of the most common groups of disorders encountered in movement disorder clinics (Miyasaki et al, 2003). Derived primarily from psychiatric or psychological disorders, because of their rich spectrum of phenomenology and variable severity, psychogenic movement disorders present a major diagnostic and therapeutic challenge. Diagnosis of psychogenic movement disorders is facilitated by various clues that include somatic and psychiatric complaints and movement disorders whose phenomenology is incongruous with typical movement disorders. These include sudden onset often related to some emotional trauma, secondary gain, variable frequency of tremor, distractibility, exaggeration of symptoms, or lack of concern, called "la belle indifference" (Table 24.14).

Tabic 24.14: Clues to the presence of a psychogenic movement disorder

- Physical Factors
  - Movement disorder
    - Abrupt onset
    - Incongruous movements
    - Inconsistent movements
    - Response to placebo or suggestion
    - Selective disability
    - Dramatic resolution
    - Maximum early disability
    - Deliberate slowing
    - Rhythmic shaking
    - Bizarre gait
  - Other neurological findings
    - Transient weakness
    - Sensory symptoms
    - Dizziness and fainting
    - Seizures
    - Convergence spasm
    - Bursts of verbal gibberish
    - Visual disturbances
    - Headache
    - Pain
    - Amnesia
    - Insomnia
    - Exhaustion
  - Multiple somatizations
    - Self-inflicted injuries
    - Unwitnessed paroxysmal disorders
- Psychiatric Problems
  - Depression
  - Anxiety disorder
  - Somatization disorder
  - Malingering
  - factitious disorder
- Predisposing Event
  - Trauma
  - Surgery
  - Major life event
- Social Factors
  - Work-related injuries
  - Litigation
  - Relationship problems (spouse or children)
  - Physical abuse
  - Sexual abuse
  - Substance abuse
  - Secondary gain

INVESTIGATION OF MOVEMENT DISORDERS

The nature and extent of the investigation of a patient presenting with a movement disorder vary depending on the clinical circumstances. When the historical and clinical features are typical of certain primary (idiopathic) disorders, further investigations may be unnecessary. Examples of these include normal physiological tremor and myoclonus, essential tremor {especially if familial), adult-onset focal dystonias, childhood tic disorders, and even PD. However, one must always he mindful of the possibility of additional occult aggravating factors superimposed on a known pre-existing movement disorder. The reverse is also possible, in which the presumed cause is actually an aggravating factor or simply a coincidental association, particularly in the case of patients thought to have drug-induced disturbances. For example, chorea apparently caused by the birth control pill (or chorea gravidarum) may be a manifestation of underlying SLE. When dealing with presumed neuroleptic-induced movement disorders, it is important to consider the possibility that the antipsychotic drug was given for initial psychiatric manifestations of a disease that is now causing the movement disorder in question. Huntington's disease and Wilson's disease are two disorders in which this may occur,

The importance of excluding Wilson's disease cannot be overemphasised. This includes slit-lamp examination, measurement of serum ceruloplasmin and copper, liver function tests, and, if necessary, measurement of 24-hour urinary copper excretion and liver biopsy. Children, adolescents, and young adults presenting with parkinsonism, chorea, or a dystonic or myoclonic syndrome need additional careful hematological and biochemical assessment, as indicated in Table 24.15.

Although in the majority of movement disorders the diagnosis depends on the recognition of typical clinical phenomenology, diagnosis of certain movement disorders can be aided by blood tests. Ncuroacanthocytosis, usually presenting in adolescence or early adulthood with chorea, dystonia, tics, and progressive weakness, may be diagnosed by demonstrating blood acanthocytes, elevated serum creatine kinase, and altered nerve conduction studies (Thomas and Jankovic 2003a). Biochemical screening may also reveal evidence of hypoparathyroidism, which can cause calcification of the basal ganglia, resulting in several movement disorders. Hyperthyroidism, polycythemia rubra vera, and SLE are common enough causes of

Table 24.15: Investigation of movement disorders

Movement disorder investigation	*A*	*C*	*B*	*D*	*T*	*M*
Routine hematology (including sedimentation rate)		+	-	-	-	+
Routine biochemistry (including Ca , uric acid, liver function tests)	+	+	1	+	1	+
Scrum copper, ceruloplasmin (with or without 24-hour urine Cu, liver biopsy, radiolabeled Cu studies)	++	++	-	++	1	-
Slit-lamp examination	11	++	-	++	+	1
Thyroid function	+	++	-	+	-	+
Antistreptolysin O test, anti-DNase B, antihyaluronidase	-	+	-	+	+	-
Antinuclear factor, LE cells, other immunological studies, anticardiolipin antibodies, Venereal Disease Research Laboratories test	+	++	+	+	-	+
Blood acanthocytes	+	+	-	+	+	+
Lysosomal enzymes	+	+	-	+	+	+
Urine organic and amino acids	-	+	-	+	-	+
Urine oligosaccharides and mucopolysaccharides	+	+	-	+	-	+
Scrum lactate and pyruvate	-	1	-	+	-	+
DNA tests for gene mutations	+	+	-	-	-	+
Bone marrow for storage cells (including electron microscopy)	+	+	-	+	-	+
Electron microscopy of leukocytes; biopsy ot liver, skin, and conjunctiva	+	+	-	+	-	+
Nerve or muscle biopsy	+	+	-	-	-	h
Oligoclonal bands	1	1	1	+	-	t
Computed tomography or magnetic resonance imaging	++	++	++	+4-	+	4
Electroencephalography	1	+	-	+	+	++
Electromyography and nerve conduction studies	\	+	-	+	+	1
Evoked potentials	+	+	-	-	-	•f+
Elec t ro re ti nogra m	+	+	-	+	-	+
Neuropsychological testing	+	+	-	-	+	-

Note: The extent of investigation depends on factors such as age of onset, nature of progression, and presence of historical or clinical atypical features suggesting a secondary cause of the movement disorder in question.
A = akinetic rigid syndrome; B = hemiballism; C = chorea; l) = dystonia; M = myoclonus; T = tics.
++ = very important or often useful; + = sometimes helpful; + = questionably helpful; - tarely or never helpful.

undiagnosed chorea in an adult to necessitate exclusion in all cases. Early clues are a history of recurrent fetal loss, an elevated partial thromboplastin time, a false positive Venereal Disease Research Laboratories test, and thrombocytopenia, which indicates the presence of amiphospholipid immunoglobulins, such as the lupus anticoagulant and anticardiolipin ami bodies. Sydenham's chorea must be considered in a child presenting with chorea of unknown origin; antistreptolysin O titer, antihyaluronidase, and electrocardiogram should be obtained, In a patient with hemiballism, one should search for potential risk factors for vascular disease by measuring levels of blood sugar, hemoglobin, platelets, erythrocyte sedimentation rale, cholesterol, and triglycerides. Adults with generalized dystonia or dystonia beginning in the legs must be suspected of having a symptomatic cause and investigated accordingly. A test for DYT'l dystonia is available commercially, and some research laboratories perform tests for *e-sarcoglycan (SGCE)* gene responsible for the myoclonus-dystonia syndrome. Other DNA tests that may be helpful in the diagnosis of movement disorders include tests for Huntington's disease; spinocerebellar atrophies; Friedreich's ataxia; dentatorubral-pallidoluysian atrophy; pantothenate kinase-associatcd neurodegeneration (PKAN), formerly known as Ilallervorden-Spatz disease; Unverricht-Lundborg disease (EPM1), celiac disease (antigliadin antibodies), anti-GAD antibodies (stiff man syndrome}, and antibodies for various paraneoplastic syndromes.

Imaging studies, such as computed tomography (CT) and, particularly, magnetic resonance imaging (MRI), are useful in certain disorders. Most patients with heimdystoiua have a definable lesion in the contralateral basal ganglia (most often the putamen). Hemiballism or hemichorea usually is caused by a structural lesion in the contralateral subthalamic nucleus or striatum. The cause is commonly a small lacunar infarction, so MRI typically is more successful than CT in localizing the lesion. In patients with parkinsonism, imaging must assess the possibility of hydrocephalus (either obstructive or communicating), midbrain atrophy (as in PSP), and cerebellar and brainstem atrophy (as in olivopontocerebellar atrophy). MRI clearly is much more effective in demonstrating these posterior fossa abnormaiities than is CT. Atrophy of the bead of the caudate nucleus is found in Huntington's disease, but it is not specific for this disorder and does not correlate with the presence or severity of chorea. Multiple infarctions, intracerebral calcification (better seen on CT), mass lesions (such as tumors and arteriovenous malformations), and basal ganglia lucencies (as seen in various disorders) may be found in patients with

several movement disorders, such as parkinsonism, chorea, and dystonia. In patients with striatonigral degeneration (one subcategory of MSA with prominent parkinsonism), T2-weighted and proton density MRf scans often demonstrate a combination of striatal atrophy and hypointensity, with linear hypcrintensity in the posterolateral putamen. Striatal Tl hyperintensity is seen in hyperglycemia, manganese toxicity, hepatocerebral disease, Wilson's disease, abnormal calcium metabolism, neurofibromatosis, hypoxia, and hemorrhage; striatal T1 hypointensity and T2 hyperintensity suggest mitochondria] disorders; striatal T2 hypointensity with hyperintensity of the mesencephalon sparing the red nucleus and the lateral aspect of the substantia nigra gives the appearance of "face of the giant panda sign," the typical MRI appearance of Wilson's disease; and striatal T2 hypointensity is typically seen in MSA, PSP, and pantothenate kinase-associated neurodegeneration. In the latter disorder, a T2-weighted MRI brain scan typically shows hypointensity in the globus pallidus surrounding an area of hyperintensity, the "eye of the tiger" sign. The "hot cross bun" sign in the pons also suggests MSA, as does T2-weighted gradient echo MRI, which often demonstrates hypointense putaminal changes. Further developments in MRI promise to improve our ability to differentiate between various degenerative disorders, especially if they are associated with characteristic pathological features, such as deposition of pigments or heavy metals.

Magnetic resonance spectroscopy also holds promise for differentiating disorders with various neurodegenerative patterns or ncurometabolic disturbances. Positron emission tomography using fluorodeoxyglucosc, fluorodopa, and other radiolabeled compounds (e.g., demonstrating labeling of dopamine receptors) has shown reproducible changes in such conditions as Huntington's disease and parkinsonian disorders. For example, F-dopa positron emission tomography scans show reduced uptake in both the putamen and caudate in patients with atypical parkinsonism, such as PSP and MSA, whereas the caudate usually is preserved in patients with PD. The patterns of abnormalities seen may predict the underlying pathological changes and thus may be useful in differential diagnosis. Developments in single photon emission CT suggest that this will probably become a useful diagnostic tool in evaluating and diagnosing certain movement disorders.

Routine electrophysiological testing, including electroencephalography, somatosensory evoked potentials, EMG, and nerve conduction studies, may provide supportive evidence of disease involving structures outside the basal ganglia. EMG analysis of the activity in various muscle groups has been used extensively to study most movement disorders, and tremor can be further documented by accelerometric recordings. Although these and other electrophysiological procedures have contributed to the understanding of the pathophysiology of movement disorders, they have been most crucial to the study of myoclonus. Here, a variety of disturbances may be found on routine electroencephalography, such as spikes, spike-and-wave patterns, and periodic discharges. Occasionally, spikes are seen ro precede EMG myoclonic discharges, particularly if the myoclonus is associated with epilepsy. In the majority of cases, however, it is impossible to determine a correlation between spike discharges and myoclonic jerks by simple visual inspection. Special electrophysiological techniques averaging cortical activity that occurs before a myoclonic jerk (triggered back-averaging) may show focal contralateral central negativity lasting 15-40 milliseconds, preceding the muscle jerk by 10-25 milliseconds in the upper limbs or 30-35 milliseconds in the legs. This is evidence of so-called cortical myoclonus, indicating that cortical activity results in the muscle jerks. In other forms of myoclonus that originate in subcortical areas, cortical discharges may be seen but arc not time-locked in the same fashion to the jerks. In these cases, there may be generalized 25- to 40-millisecond negativity before, during, or after the muscle jerking.

The muscle bursts as seen on EMG typically are synchronous in antagonistic muscles and usually are less than 50 milliseconds in duration. In one form of essential myoclonus, ballistic reflex myoclonus, the EMG bursts show alternating activity in antagonists that lasts 50-150 milliseconds. With multichannel EMG recording, it may be possible to demonstrate the activation order of muscles. In cortical myoclonus, muscles are activated in a rostrocaudal direction, with cranial nerve muscles firing in descending order before the limbs. In myoclonus originating from subcortical or reticular sources, it may be possible to show that the myoclonus propagates in both directions from a point source, up the brainstem, usually starting in muscles innervated by the eleventh cranial nerve, and down the spinal cord. In propriospinal myoclonus, the spread up and down the spinal cord occurs at a speed that suggests the involvement of a slowly conducting polysynaptic pathway,

Somatosensory evoked potentials and late EMG responses (C reflexes) often are enhanced in patients with myoclonus. Giant sensory evoked potentials can be seen in the hemisphere contralateral to the jerking limb in patients with cortical myoclonus. This is especially true in patients with focal myoclonus that is sensitive to a variety of sensoty stimuli applied to the affected part (cortical reflex myoclonus). The cortical components of the sensory evoked potentials usually are not enhanced in subcortical or spinal myoclonus, but the latencies may be prolonged, depending on the location of the disease process.

In caring for a patient with a movement disorder, the clinician must always keep an open mind to the possibility of finding a secondary cause. This should be the case even when the onset, progression, and clinical features of the movement disorder in question ate typical of an idiopathic condition and the pteliminary laboratory testing has not revealed another cause. Thorough neurological examination should be repeated periodically in a search for clues

that might indicate the need to pursue the investigation further,

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Chapter 25
Gait Disorders

Philip D. Thompson

The maintenance of an upright posture and the act of walking are among the first and the most complex motor skills humans acquire. From an early age, these skills are modified and refined. In later years, the interplay between voluntary and automatic control of posture and walking provides a rich and complex repertoire of movement. The pattern of walking may be so distinctive that an individual can be recognized by the "motor fingerprint" of his or her gait. Many diseases of the motor system produce characteristic disturbances of gait and posture that permit the identification of an underlying disease by the manner in which gait is altered.

PHYSIOLOGICAL AND BIOMECHANICAL ASPECTS OF GAIT

Humans assume a stable upright posture before beginning to walk. Mechanical stability when standing is based on musculoskeletal linkages between the trunk and legs. Dynamic equilibrium in the upright posture is maintained by a hierarchy of postural reflexes. These postural responses are generated by the integration of visual, vestibular, and proprioceptive inputs in the context of voluntary intent and any ongoing changes in the environment in which the subject is moving. Postural responses consist of coordinated synergistic axial and limb muscle contractions, correcting for and controlling body sway and maintaining an upright posture of the trunk. These range from automatic righting reflexes keeping the head upright on the trunk, supporting reactions controlling antigravity muscle tone, anticipatory postural reflexes occurring before limb movement (feed forward) or in response to perturbation during movement (feedback), and reactive postural responses counteracting body perturbations, to actions that are modified by voluntary control in accordance with the circumstances, such as rescue reactions to preserve the upright posture (a step or windmill arm movements), and protective reactions to prevent injury (an outstretched arm to break a fall).

Once the trunk is upright and stable, locomotion may begin. The initiation of gait is heralded by a complex shift in the center of pressure beneath each foot, first posteriorly, then laterally toward the stepping foot, and finally away toward the stance foot to allow the stepping foot to swing forward {Elble et al. 1994). This sequence is then **followed** by the stetcoryped stance, swing, and step phases of the gait cycle.

ANATOMICAL ASPECTS OF GAIT

The ncuroanatomical structures responsible for these components of normal walking are poorly understood in humans. Studies in lower species suggest two basic-anatomical components. Supraspinal centers signal when to

start walking, when to stop, the speed of locomotion, and the size and direction of stepping. These signals descend to the spinal level where spinal locomotor centers elaborate walking patterns of muscle activity.

In quadripedal animals, spinal locomotor centers are capable of maintaining and coordinating rhythmic stepping movements after spinal transection. This spinal stepping is generated by assemblies of interneurons, referred to as *central pattern generators*, which activate limb muscles in a locomotor synergy. They exist for the hind limb, forelimb, and trunk and are interlinked by propriospinal networks to facilitate interlimb coordination. In monkeys, spinal stepping requires preservation of the ventrolateral tracts of the spinal cord containing descending reticulospinal and vestibulospinal pathways. The isolated spinal cord in humans can produce spontaneous movements, but cannot genetate rhythmic stepping or maintain truncal balance. Higher brainstem and cortical connections are therefore necessary for bipedal walking. Brainstem locomotor centers arc present in lower species and probably exist in humans, High-frequency stimulation in the region of the mesencephalic locomotor region in the posterior midbrain elicits locomotor activity in the thalamic monkey. This region overlaps with the peduneulopontinc nucleus, which is thought to be important in rhythm generation. The basal ganglia are involved in the initiation of walking and the quality of stepping, mediated through the cerebral cortex and brainstem structures such as the pedunculopontine nucleus. The cerebellum is important in modulating the rate, thythm, amplitude, and force of voluntary movement and accordingly regulates these aspects of stepping. The cerebral cortex is required for precision movements of the legs when walking. Corticospinal activation modifies spinal locomotor activity to start and stop walking, conveying the voluntary commands. Sensory feedback during the walking cycle in turn modifies motor cortical activity.

Brainstem structures arc important in maintaining postural righting reflexes that control axial extensor tone. Lesions of the medial brainstem interrupt descending reticulospinal, vestibulospinal, and tectospinal systems rh.it innervate proximal and axial muscles, resulting in dysequilibrium. In humans, postural reflexes controlling truncal equilibrium are organized by a poorly understood network involving the flocculonodular and anterior lobes of the cerebellum, the brainstem, central vestibular pathways, basal ganglia, thalamus, and frontal lobes. Lesions of each of these areas interfere with postural control, particularly when standing.

HISTORY AND COMMON SYMPTOMS OF GAIT DISTURBANCE

A detailed account of the walking difficulty and its evolution provides the first clues to the underlying diagnosis. When evaluating the history, we find it helpful to note the particular circumstances in which the walking difficulty occurs, the leg movements most affected, and any associated symptoms. Because disorders at many levels of the peripheral and central nervous systems give rise to difficulty walking, it is necessary to consider whether the problem is primarily motor, caused by muscle weakness, a defect of higher motor control, or imbalance, due to cerebellar disease or proprioceptive sensory loss.

Walking on uneven ground exacerbates most walking difficulties and leads to tripping, stumbling, and falls. A ligamentous ankle strain or even a bony fracture may result from tripping and falling in this situation and may be the presenting symptom of a gait disorder. Fear of falling may lead to various voluntary protective measures to minimize the risk of injury. In some patients, particularly the elderly, a fear of falling and a "cautious" gait may dominate the clinical picture and be a presenting feature.

Weakness

Weakness of the legs may be described several ways. Complaints of stiffness, heaviness, or "legs that do not do what they arc told" may be the presenting symptoms of a spastic paraparesis or hemiparesis. Patients with spastic paraparesis often report that they drag their legs to walk or their legs may suddenly give way, causing them to stumble and fall.

Weakness of certain muscle groups also may be described in terms of difficulties in performing particular movemenrs. A tendency to trip because of catching or scraping the toe on the ground may be the presenting symptom of hemiplegia {causing a spastic cquinovarus foot posture) or footdrop caused by weakness of ankle dorsiflexion. Similarly, weakness of certain movements may first become apparent in particular situations; for example, difficulty in climbing stairs or rising from a seated position is suggestive of proximal muscle weakness, which is most commonly caused by a myopathy. Rarely, these complaints may be the presenting symptoms of an acute inflammatory polyneuropathy (Guillain-Barre syndrome). Weakness of knee extension (caused by a femoral neuropathy or quadriceps myopathy) may impose difficulty walking down stairs.

Slowness

Slowness of walking and limb stiffness are common in extrapyramidal disease. These symptoms are produced by difficulty engaging the legs in brisk motion and increased muscle tone (rigidity). This slowness of movement may be accompanied by shuffling with small shallow steps. Difficulty initiating the first few steps when starting to walk (start hesitation), pronounced shuffling for a few steps, and freezing at the slightest obstacle, a doorway, or

other distraction are common. Some patients, particularly those with Parkinson's disease, overcome the shuffling and facilitate stepping and walking by carefully watching and treading over lines on the floor or other objects such as the handle of an upturned walking stick. It is useful to inquire about axial mobility. Difficulty rising from a chair or getting out of bed may be due to a loss of truncal mobility and axial rigidity in diffuse cerebrovascular disease, hydrocephalus, and extrapyramidal diseases. Axial muscle weakness resulting from peripheral neuromuscular diseases may also interfere with truncal mobility. Fatigue during walking occurs in muscular weakness of any cause and is often a symptom of the extra effort required to walk in upper motor neuron (UMN) syndromes and extrapyramidal disease.

The circumstances in which leg stiffness occurs when walking may be revealing. For example, the presenting symptom of idiopathic torsion dystonia in childhood may be stiffness and abnormal posturing of one leg, with inversion and plantar flexion of the foot and a tendency to walk on the toes, because of an action dystonia of the leg and foot. This may be evident only when walking or running. Patients with dopa-rcsponsive dystonia and prominent diurnal fluctuation develop their symptoms only in the afternoon.

Loss of Balance

Symptoms of poor balance and unsteadiness are cardinal features of the ataxic syndromes caused by cerebellar disease or proprioceptive sensory loss. The patient with a cerebellar gait ataxia complains of unsteadiness and an inability to walk in a straight line or turn and change direction suddenly without veering to one side or staggering as if intoxicated. A sensory ataxia may first give rise ro symptoms of unsteadiness when walking in the dark because visual compensation for the proprioceptive loss is not possible. Patients with impaired proprioception and sensory ataxia complain of being uncertain of the exact position of their feet when walking. They may be unable to appreciate the texture of the ground beneath their feet and describe abnormal sensations in the feet that give the impression of walking on a spongy surface or cotton wool. Acute disturbances of balance and equilibrium suggest a vascular insult to the cerebellum, thalamus, or basal ganglia. Acute severe vertigo caused by a peripheral vestibulopathy may also lead to a sensation of imbalance and a tendency to veer toward one side.

Falls

When taking a history of falls, wc must establish the circumstances in which they occur and whether there are any clear precipitants. Tripping may be due to footdrop or shallow steps, the effect of which may be exaggerated when walking on uneven ground. Proximal muscle weakness may result in the legs giving way. Unsteadiness and poor balance in an ataxic syndrome may lead to falls. Spontaneous falls or falls following postural adjustments, either forward or backward, suggest an impairment of postural reflexes. Falls when looking upward are common in the elderly. In the extreme form of loss of postural reflexes, patients may fall backward "like a board". In the setting of the early stages of an akinetic-rigid syndrome, spontaneous falls are an important clue to diagnoses such as multiple system atrophy or progressive supranuclear palsy {Steele-Richardson-Olszewski syndrome) rather than Parkinson's disease.

Sensory Symptoms and Pain

The distribution of any accompanying sensory complaints provides further information about the site of the lesion producing walking difficulties. A common example is cervical spondylosis and myelopathy presenting with cervical radicular pain or paresthesias and a spastic paraparesis. Paresthesias in a radicular distribution (caused by radiculopathy) and sensations of tight bands around the trunk {caused by spinal sensory tract compression), or a combination of truncal and limb sensory symptoms and a spastic paraparesis, are suggestive of a myelopathy. Distal symmetrical paresthesias affecting the limbs point toward a peripheral neuropathy.

It is important to determine whether complaints of leg pain and weakness in patients with difficulty walking share a common cause or whether the pain is of musculoskeletal origin and exacerbated by walking. An example of the former is cxcrcisc-induccd pain and weakness of the legs caused by neurogenic intermittent claudication of the cauda equina. These symptoms are often accompanied by transient paresthesias or radicular sensory loss in the legs, which is relieved after a few minutes by sitting and leaning forward. This should be distinguished from vascular intermittent claudication in which ischemic muscle pain, usually of the calves, interrupts walking but is relieved after a few seconds of rest. Skeletal pain caused by degenerative joint disease is common in elderly patients. It is often present at rest and aggravated by leg movements. The normal pattern of walking is often modified in these situations. The patient may voluntarily engage various strategies to minimize pain by avoiding bearing the full weight on the affected limb and by limiting its range of movement (antalgic gait).

Incontinence

Loss of the voluntary control of sphincter function in a patient with a spastic gait suggests a spinal cord lesion.

Parasagittal cere bra I lesions Mich as frontal lobe rumors (parasagittal meningioma), frontal lobe infarction caused by anterior cerebral artery disease, and hydrocephalus should also be considered, in addition to spinal cord disease. Impairment of higher mental function may be an important clue to a cerebral cause of paraparesis.

EXAMINATION OF POSTURE AND WALKING

The examination of posture and walking is summarized in Table 25.1. A convenient starting point is to observe the overall pattern of whole-body movement during walking. Normal walking progresses in a smooth and effortless manner, with an upright posture of rhe trunk. The legs swing in a free and fluid motion with regular strides of appropriate length accompanied by flowing associated synergistic head, trunk, and upper limb movement. Careful observation of the overall pattern of body movement during walking often enables rhe experienced observer to decide whether the gait problem is caused by a focal leg abnormality, muscle weakness, or a more generalized disorder ol movement, and whether it is unilateral or bilateral. After observing the overall walking pattern, the clinician should examine a number of specific aspects of gait, as outlined in rhe checklist for clinical examination of posture and gait (see Table 25.1).

Table 25.1: Checklist for the clinie.il examination of posture and gait

- Posture
  - Trunk posture (upright or stooped)
  - Postural reflexes (displace the paiii-m's center of gravity forward and backward)
  - Stance (narrow or wide based)
- Walking
  - Initiation (start hesitation, shuffling, magnetic feet)
  - Stepping
  - Rhythm (regular, irregular)
  - Length (normal, short)
  - Trajectory (shallow, high stepping)
  - Speed
  - Festi nation
  - Freezing
- Associared trunk movement and arm swing
- Special maneuvers
  -] led to roe walking
  - Romberg test
  - Walking backward or running
- Formal motor and sensory examination (supine)
  - Leg size and length
  - Range of joint movement
  - Muscle bulk
  - Muscle tone
  - Muscle strength
  - Voluntary movement
  - Trunk movement (rolling over)
  - Leg movement when not standing
  - Tendon reflexes
  - Sensation: proprioception
  - I kel-shin test

Posture

Trunk Posture

The trunk is normally upright during standing and walking. Flexion of the trunk is a prominent feature of Parkinson's disease but also may be seen in cautious gait syndromes in which the center of gravity is lowered to minimize body sway and the risk of falling. Neck and trunk extension is characteristic of progressive supranuclear palsy. Tilt of the trunk to one side may be a sign of dystonia but can also be seen in acute thalamic, basal ganglia, and vestibular lesions. An exaggerated lumbar lordosis, caused by hip-girdle weakness, is typical of proximal myopathies. Paraspinal muscle spasm and rigidity also produce an exaggerated lumbar lordosis and are striking features of the stiff person syndrome. A variety of axial muscle spasms are seen in torsion dystonia, with the most common being exaggerated flexion of rhe trunk and hip when walking. Abnormal thoracolumbar postures also may result from spinal ankylosis and spondylitis. Paraspinal myopathies may lead to severe rruncal weakness and a posture of marked truncal flexion (bent spine or eamptocormia). A restricted range of spinal movement and persistence of an abnormal spinal posture when supine or during sleep are useful pointers toward a bony spinal deformity as the cause of an abnormal trunk posture. Altered truncal postures, particularly in the lumbar region, may occur either to compensate for a shortening of one lower limb or disease of the hip, knee, or ankle or in response to leg pain.

Postural Reflexes

Postural teflcxes arc examined with patients standing and gently pulling the upper trunk backward or forward. The examiner should sr.md in front of or behmd patients and be prepared to catch or support them to prevent them from falling. An impairment of postural righting reactions is evident after each displacement by a few short shuffling steps backward (retropulsion) or forward (propulsion). Severe loss of postural reflexes abolishes reflex stepping or compensatory arm movements to adjust posture and restore balance and may render a patient susceptible to falls after minor perturbations or postural changes. A tendency to fall backward spontaneously is a sign of impaired postural reflexes in progressive supranuclear palsy. A pronounced rruncal rilr is observed in some thalamic and basal ganglia hemorrhages with rhe rrunk leaning away from the side of the lesion, leading to a fall to that side or backward (Masdeu and Gorelick 1988; Labadie et al. 1989). In the lateral medullary syndrome, the trunk may sway or tilt

Tabic 25.2: Summary of the major clinical features distinguishing different types of gait ataxia

Vi-atum	*Cerebellar ataxia*	*Sensory ataxia*	*Frontal lobe ataxia*
Trunk posture	Stooped, leans forward	Stooped, upright	Upright
Stance	Wide based	Wide based	Wide based
Postural reflexes	Variable	**Intact**	Impaired or absent
Initiation of gait	Normal	Normal	Start hesitation
Steps	Staggering, lurching	f ligh stepping	Short, shuffling
Speed	Normal, slow	Normal, slow	Very slow
Heel-toe test	Unable	Variable	Unable
Turning corners	Veers away	Minimal effect	Freezing, shuffling
Romberg test	Variable	Increased unsteadiness	Variable
Heel-shin test	Usually abnormal	Variable	Normal
Falls	Uncommon	Yes	Very common

toward the side of the lesion as a result of the acute imbalance in vestibulat postural control (lateropulsion). The presence of injuries to the knees, shins, face, or back of the head sustained during falls provides a clue to the loss of postural reactions, including impairment of the rescue reaction of an outstretched arm to break a fall.

Stance

Stance base (the distance between the feet during quiet standing) and walking give some indication of balance. Wide-based gaits are typical of cerebellar or sensory ataxia but may be seen in diffuse cetebtal vascular disease and frontal lobe lesions {Table 25.2). People whose balance is insecure for any reason tend to adopt a wider stance, adopt a posture of mild generalized flexion, and take shorter steps. Widening the stance base is an efficient method of reducing body sway in the lateral and anteroposterior planes. Those who have attempted to walk on ice ot other slippery surfaces will recognize this phenomenon.

Walking

Initiation of Gait

Difficulty initiating the first step (start hesitation) is a featutc of Parkinson's disease and frontal lobe disease and is occasionally seen in relative isolation in the syndrome of gait-ignition failure (Atchison et al. 1993). Start hesitation ranges in severity from a few shuffling steps, to small shallow steps on the spot without forward progress ("slipping clutch'"), to complete immobility with the feet seemingly glued to the floor ("magnetic feet"). Patients may make exaggerated upper body movements in an effort to engage their legs in motion.

Stepping

Once walking is undetway, the rhythm of stepping and the length and trajectory of each step should be noted. Short, regular, and shallow steps or shuffling is characteristic of the akinetic-rigid syndromes. Shuffling is usually most evident when starting to walk, stopping, ot turning corners. Repeatedly observing these maneuvers may highlight a subtle tendency to shuffle. Once underway, freezing may interrupt walking with further shuffling and start hesitation.

Jerky steps of irregular rhythm and variable length and trajectory suggest an ataxic syndtome. Abnormal leg and foot trajectories occur in sensory ataxia, footdrop, spasticity, and dystonia. Each is associated with a distinctive leg posture during stepping.

The speed of walking is revealing. Slowness is charactetistic of the akinetic-rigid syndromes but is also seen in ataxic and spastic syndromes. Festination (increasingly rapid, small steps) is common in Parkinson's disease but is rare in other a kinetic-rigid syndromes, which usually are associated with poor balance and falls rather than festination.

A reduction in associated trunk movement and arm swing is most evident in unilateral UMN, extrapyramidal, and acute cerebellar syndromes. Bilateral loss of synergistic arm movement when walking is a valuable sign of Parkinson's disease in the early stages, when most symptoms are unilateral.

Subtle degrees of cerebellar ataxia may be unmasked by asking the patient to walk in a straight line heel to toe (tandem gait), to stand on one leg, or to walk and turn quickly. If vision is important in helping maintain balance, as in sensory ataxia caused by proprioceptive loss, the removal of vision greatly exaggerates the ataxia. This is the basis of **the** Romberg test in which eye closure leads to a dramatic increase in unsteadiness and even falls in the patient with sensory ataxia. When pctforming the Romberg test, the patient must be standing comfortably before eye closure and **the** observer must remember that normal subjects and patients with cerebellar ataxia also show a modest increase in body sway with eye closure.

It may be necessary to examine the patient running to identify an action dystonia of the legs in the early stages of primary torsion dystonia.

MOTOR AND SENSORY EXAMINATION

After observing the patient walking, the clinician examines motor and sensory function in the limbs with the patient supine in the conventional examination position. The size and length of the limbs should be measured in any child presenting with a limp. An asymmetry in leg si/e is suggestive of a congenital malformation of the spinal cord, brain, or (rarely) local overgrowth of tissue. The spinal column should be inspected for scoliosis and the lumbar region for skin defects or hairy patches, which are indicative of spin a 1 dysraphism.

Changes in muscle tone such as spasticity, lead-pipe or cogwheel rigidity, or paratonic rigidity (gegenhalten) point toward diseases of the UMN, basal ganglia, and frontal lobes, respectively. In the patient who complains of symptoms in only one leg, a detailed examination of the other leg is important. If signs of a UMN syndrome are presenr in both legs, a disorder of the spinal cord or parasagittal region is likely.

Muscle bulk and strength are examined, and evidence of muscle wasting and the presence and distribution of muscle weakness are documented. Examination reveals whether the abnormal posture of the leg in a patient with a footdrop (Table 25.3) is caused by spasticity or weakness of ankle dorsiflexors, which in turn may be due to anterior horn cell disease, a peripheral neuropathy, a peroneal compression neuropathy, or an L5 root lesion. Subtle degrees of ankle dorsiflexion weakness may be detected by observing the patient walking on his or her heels. Joint position sense should he examined for defects of proprioception in the ataxic patient.

Discrepancies on Examination of Gait

Several conditions are notable for producing minimal abnormal signs on physical examination of the recumbent patient, in striking contrast to the observed difficulty when walking.

Tabic 25.3: Causes of footdrop and an cquinovarus foot posture when walking

Peripheral nerve
- L5 radiculopathy
- Lumbar plexopathy
- Sciatic nerve palsy
- Peroneal neuropathy (compression)
- Peripheral neuropathy (bilateral)
- Anterior horn cell disease (motor neuron disease)

Myopathy
Sc a p uIo peronea 1 syndromes
Spastieity
Dystonia
Sensory ;It;l\i;l

Patients with a cerebellar gait ataxia caused by a vermis lesion may perform the heel shin test normally when supine but when standing are unable to walk heel to toe. The finding of normal muscle strength, muscle tone, and tendon reflexes is common in dystonic syndromes in which an action dystonia causes abnormal posturing of the feet only when walking. A dystonic gait may exhibit a striking discrepancy between the difficulty walking forward, which may not be evident when walking backward. Gegenhalten, with or without brisk tendon reflexes, may be the only abnormal signs in the legs of the recumbent patient with a frontal lobe lesion, hydrocephalus, or diffuse cerebrovascular disease who is totally unable to walk. Moreover, such patients may be able to perform the heel-shin test and make bicycling movements of their legs when lying on a bed. A similar discrepancy can be seen in spastic paraplegia caused by hereditary spastic paraplegia, cerebral palsy (Little's disease), or cervical spondylotic myelopathy, in which only minor changes in muscle tone, strength, and tendon reflexes are evident during the supine examination in contrast to the profound leg spasticity apparent when walking.

Multiple Sensory Deficits

Elderly patients with walking difficulties and falls often have signs of multiple deficits. The most common are cervical spondylotic myelopathy with a mild spastic paraparesis and a degree of proprioceptive loss, as well as a peripheral neuropathy with absent ankle reflexes and mild proprioceptive loss. Additional sensory deficits such as visual, hearing, and vestibular impairment also contribute to imbalance, falls, and gait difficulties. Musculoskeletal factors and postural hypotension also interfere with mobility in this age-group.

The Cautious Gait

Finally, due account must be taken of the fear of falling that often accompanies gait difficulties. This may lead to a marked loss of confidence when walking and a cautious or protected gait (Nutt, Marsden, and Thompson 1993). Such patients may be unable to walk without support. They hold on to furniture, lean on walls, and avoid crowded or open spaces because of a fear of falling. Their gait may improve dramatically when support is provided.

PHYSICAL SIGNS AND INVESTIGATIONS

Spastic Gait

Spasticity of the arm and leg on one side produces the characteristic clinical picture of a spastic hemlparesis. The arm is held adducted, internally rotated at the shoulder,

and flexed at the elbow, with pronation of the forearm and flexion of the wrist and fingers. The leg is slightly flexed at the hip and extended at the knee, with plantar flexion and inversion of the foot. The swing phase of each step is accomplished by slight lateral flexion of the trunk toward the unaffected side, and hyperextension of the hip on that side to allow the slow circumduction of the stiffly extended paretic leg, as it is swung forward from the hip, dragging the toe or catching it on the ground beneath. A minimum of associated arm swing occurs on the affected side. The stance may be slightly widened, and the speed of walking is slow. Balance may he poor because the hemiparesis interferes with corrective postural adjustments on the affected side. Muscle tone in the affected limbs is increased, clonus may be present, and the tendon reflexes are abnormally brisk with an extensor plantar response. Examination of the sole of the shoe may reveal wear of the toe and outer borders of the shoe, suggesting that the spastic gait is long standing.

After identifying a spastic hemiparesis, the next step is to determine the level of the lesion that is responsible. Attention should be paid to the face, because UMN facial weakness on the same side indicates that the level probably lies above the pons, the most common cause of which is cerebral infarction, suggested by a history of acute onset. A UMN type of facial weakness on the side opposite the hemiparesis (crossed hemiparesis) suggests a pontine lesion. When the face is not involved, ciues to the site of the lesion must he sought by examining the motor function of the lower cranial nerves. Weakness of shoulder shrugging on the same side points to a lesion above the foramen magnum. A cervical spinal cord lesion involves the arms unci legs only, whereas a lesion ot the thoracic cord affects only the legs. When lesions of the spinal cord are suspected, magnetic resonance imaging (MRI) of the cord is indicated.

Spasticity of both legs gives rise to a spastic paraparesis. The legs are stiffly extended at the knees, plantar flexed at the ankles, and slightly flexed at the hips. The gait is slow and labored. The legs are dragged forward with each step, both legs circumduct, and there is a tendency of adduction of the legs, particularly when the disorder begins in childhood. This appearance gave rise to the term *scissor gait.* The causes of a spastic paraparesis include hereditary spastic paraplegia, in which the arms and sphincters are unaffected and there may be little or no leg weakness, and other myelopathies. An indication of the extent and level of the spinal cord lesion can be obtained from the presence or absence of weakness or sensory loss in the arm, a spinothalamic sensory level or posterior column sensory loss, and alterations in sphincter function. Most patients with paraparesis of recent onset should be investigated with MRI of the spinal cord or myelography, to exclude potentially treatable causes, such as spinal cord compression.

Occasionally, bilateral leg dystonia (dystonic paraparesis) may mimic a spastic paraparesis. This typically occurs in dopa-responsive dystonia in childhood, which may be misdiagnosed as hereditary spastic paraplegia or cerebral diplegia. Differentiation between these conditions can be difficult. Brisk tendon reflexes may occur in both, and spontaneous extension of a great toe in patients with striatal disorders may be interpreted as a Babinski response. Fanning of the toes and knee flexion suggest the latter. Other distinguishing features include changes in muscle tone, such as spasticity in hereditary spastic paraparesis and rigidity in dystonic paraparesis. In young children, the distinction is important, because a proportion of such patients can be treated successfully with L-dopa {discussed in the following sections).

Cerebellar Ataxia

The gait disorder that accompanies disease of the vermis and anterior lobe of the cerebellum consists of a loss of normal truncal balance resulting in increased body sway and dyseqiulibrium. The patient adopts a wide-based stance and may flex the hips slightly to crouch forward and minimize body sway. Patients with anterior lobe atrophy develop a 3-Hz anteroposterior sway of the trunk, which may be accompanied by a rhythmic truncal and head tremor (titubation). Patients with lesions of the flocculo-nodular lobe of the cerebellum (the vestibulocerebellum) exhibit multidirectional body sway and dysequilibrium and may fall. Limb ataxia resulting from involvement of the cerebellar hemispheres is characterized by a decomposition of normal leg movement with steps that are irregular and variable in timing (dyssynergia), length, and direction (dysmetria). Steps are taken slowly and carefully to reduce the tendency to lurch and stagger. These defects are exacerbated when attempting to walk heel to toe in a straight line. Ataxia is also made worse by the rapid postural adjustments needed when changing direction to turn a corner, avoid obstacles, and when stopping or starting to walk. Cerebellar ataxia may be improved by minor support, such as holding the patient's hand during walking. Visual compensation helps the patient with a cerebellar ataxia reduce body sway or plot a secure path ahead while walking. Eye closure may increase anxiety about falling but does not produce the dramatic deterioration in balance seen in a sensory ataxia,

With lesions confined to one cerebellar hemisphere, ataxia is limited to the affected (ipsilateral) limb and affects coordination of limb movement more than balance, if the vermis is not involved. Conversely, a purely truncal ataxia may be the sole feature of a midline (anterior lobe and vermis) cerebellar syndrome. As discussed earlier, this may escape notice if the patient is not examined when standing because leg coordination during the heel-shin test may be relatively normal when the patient with a vermis lesion is examined in the supine position.

An isolated cerebellar gait ataxia may be caused by malnutrition in alcoholism, producing a relatively selective vermis and anterior lobe syndrome. Midline cerebellar masses and paraneoplastic, hereditary, or sporadic cerebellar degenerations may also produce a predominantly truncal cerebellar ataxia.

Spastic Ataxia

A combination of spasticity and ataxia produces a characteristic springing or bouncing gait. Such gaits may be seen in multiple sclerosis, the Amold-Chiari malformation, and hydrocephalus in young people. The gait is wide based, and clonus is readily elicited by stretching the leg muscles when examining muscle tone or tapping the tendon reflexes. Even voluntary leg movements may precipitate clonus, which throws the ataxic patient off balance. Compensatory reflex and voluntary movements, made in an effort to regain balance, set up a vicious cycle of ataxic movements, clonus, and increasing unsteadiness, so such patients may be totally unable to stand and walk. Bouncing gaits must be distinguished from action myoclonus of the legs and from leg and truncal tremors seen in cerebellar disease (see Action Myoclonus and Tremor of the Legs, later in this chapter).

Sensory Ataxia

The loss of proprioceptive input from the legs deprives patients of knowledge of their position in space, the progress of ongoing movement, the state of muscle contraction, and finer details of the texture of the surface of the ground on which they are walking. Patients without such information tend to adopt a wide base and take slow steps, advancing cautiously with the aid of visual guidance. The feet are thrust out with each step, and the sole of the foot strikes the floor forcibly, giving rise to a slapping noise (slapping gait). Patients with sensory ataxia find it difficult to walk on uneven surfaces or at night. Lesions at any point in the sensory pathways that interrupt large-diameter proprioceptive afferent fibers may produce this clinical picture. Peripheral neuropathies, posterior root or dorsal root ganglion lesions such as tabes dorsalis, and dorsal column lesions, for example, in vitamin B_{12} deficiency, are some of the diseases responsible for a sensory ataxia of gait.

Akinetic-Rigid Gait

The most common akinetic-rigid gait disturbance is that seen in Parkinson's disease. The patient adopts a stooped posture with flexion of the shoulders, neck, and trunk. Tremor of the upper limbs may be evident when walking (but parkinsonian tremor of the legs rarely affects walking). The gait is typically slow and shuffling, with small shallow steps on a narrow stance base. These signs may be dramatically reversed by L-dopa treatment. There is little associated body movement. Arm swing is reduced or absent and the arms are held immobile at the sides or slightly forward of the trunk. A characteristic feature is the tendency to begin walking with a few rapid, short shuffling steps {start hesitation) before breaking into a more normal walking rhythm. Walking, once underway, may be interrupted by further shuffling or even complete cessation of movement (freezing) if a doorway or other obstacle is encountered. Freezing becomes increasingly troublesome in the later stages of Parkinson's disease when it is helped more by sensory cues to trigger a step than L-dopa medication.

The posture of generalized flexion of the patient with Parkinson's disease exaggerates the normal tendency to lean forward when walking. To maintain balance when walking and avoid falling forward, the patient may advance with a series of rapid small steps (festination). Rctropulsion and propulsion are similar manifestations of a flurry of small-si/.ed parkinsonian steps made in an effort to preserve equilibrium in response to external perturbations. Instead of a single large step, a series of small steps are taken to restore balance. If these compensatory festinating steps are too small to maintain or restore balance, the patient may fall forward. Other causes of falls in Parkinson's disease include tripping or stumbling over rough surfaces, because each step is too small or shallow to clear obstacles, as well as profound start hesitation or freezing. In each of these examples, falling stems from locomotor hypokinesia and a lack of normal-sized, rapid, compensatory voluntary movements, Late in the illness, falls may occur either spontaneously or after minor perturbations resulting from loss of postural and righting reflexes. These deficits do not respond to L-dopa medication, unlike the hypokinetic steps and flexed truncal posture early in the disease,

A similar slowness of leg movement and shuffling when walking may occur in various other akinetic-rigid syndromes (Table 25.4). These include multiple system atrophy, cerebrovascular disease, and progressive supranuclear palsy. A number of clinical signs help distinguish between these conditions (Table 25.5). In progressive supranuclear palsy, the typical neck posture is one of extension rather than flexion, as in Parkinson's disease. A stooped posture with exaggerated neck flexion is sometimes a feature of multiple system atrophy. A distinguishing feature of progressive supranuclear palsy and multiple system atrophy is the early loss of postural and righting reflexes in comparison ro the preservation of these reflexes in Parkinson's disease until the late stages of the illness. There also may be an element of ataxia in these akinetic-rigid syndromes, which is not evident in Parkinson's disease. Accordingly, the patient who presents with falls and an akinetic-rigid syndrome is more likely to

Tabic 25.4: Differential diagnosis in the patient presenting with an a kinetic-rigid syndrome and a gait disturbance

Parkinson's disease
Drug-induced parkinsonism
Multiple system atrophy
  Stria ton igral degeneration
  Shy-Drager syndrome (idiopathic orthostatic hypotension)
  Olivopontocerebellar atrophy
Progressive supranuclear palsy (Steele-Riehardson-Olszcwski syndrome)
Pick's disease (frontotemporal dementia)
Corticobasal degeneration
Creutzfeldt-Jakoh disease
Cerebrovascular disease (Binswanger's disease)
Hydrocephalus
Frontal lobe tumor
juvenile Huntington's disease
Wilson's disease
Cerebral anoxia
Neurosyphilis

have symptomatic parkinsonism, rathet than Parkinson's disease.

The gait of patients with hydrocephalus and Binswanger's disease caused by periventricular white mattet ischemia is characterized by short shuffling steps, often of variable length, with a wide-based stance (and stride width) and a degree of imbalance. The truncal posture is upright with exaggetated arm swing during walking, giving the **gait a** military appearance. Examination also teveals preservation of upper body movement in contrast to Parkinson's disease. These stance and stepping chatactctisties have also been demonstrated by kinematic studies of gait in hydrocephalus and Binswanger's disease (Ebcrsbach et al. 1999; Stolze et al. 2001). Finally, the dramatic response to L-dopa that is typical of idiopathic Patkinson's disease does not occur in symptomatic parkinsonism, although sonic patients with multiple system atrophy respond partially for a short period.

Dystonic Gait

Of all gait disturbances, dystonic syndromes may produce the most bizarre and often the most difficult diagnostic problcms. The classic presentation of childhood-onset primary torsion dystonia (dystonia musculorum deformans) is an action dystonia of a leg with a sustained abnormal posture of the foot (typically, plantat flexion and inversion) on attempting to run. In contrast, walking forward or backward or even running backward may be entirely normal at an early stage. An easily ovctlooked sign in the early stages is tonic extension of the great toe (the striatal toe) when walking. This may be a subtle finding but occasionally is so pronounced that a hole is worn in che roe of the shoe. With time, dystonia may progress to involve the whole leg and then become generalized.

More difficult to identify are those dystonic syndromes that ptesent with bizarre, seemingly inexplicable postures of the legs and trunk when walking. A characteristic featute common to all these dystonic postures is excessive flexion of the hip when walking. These patients may hop or walk sideways in a crablike fashion with hypcrflexion of the hips, producing an attitude of general body flexion in a simian posture, or with a birdlikc (peacock) gait with excessive flexion of the hip and knee and plantar flexion of the foot during the swing phase of each step. Many of these patients have been thought to be hysterical because of the bizarre nature of their gait disturbance and because formal neurological examination shows no abnormalities if the patient is examined when lying supine. Each of these gait patterns has been described in association with identifiable secondary dystonic syndromes, including postencephalitic movement disorders, manganese poisoning, and Wilson's

Table 25.5; Summary of the clinical features that help differentiate between Parkinson's disease and symptomatic or secondary parkinsonism in patients with an akinetic-rigid gait syndrome

Feature	*Parkinson's disease*	*Symptomatic parkinsonism*
Posture	Stooped (trunk flexion)	Stooped or upright (trunk flexion or extension)
Stance	Narrow	Often wide based
Initiation of walking	Start hesitation	Start hesitation, magnetic feet
Steps	Small, shuffling	Small, shuffling
Stride length	Short	Short
Freezing	Common	Common
Leg movement	Stiff, rigid	Stiff, rigid
Spi-cd	Slow	Slow
Festi nation	Common	Rare
Arm swing	Minimal or absent	Reduced or excessive
Heel-to-toe walking	Normal	Poor (truncal ataxia)
Postural reflexes	Preserved in early stages	Absent at early stage
Falls	Late (forward, tripping)	Early and severe (backward, tripping or without apparent reason)

disease. Finally, tardive dystonia after the ingestion of neuroleptic drugs also may produce similar bizarre abnormalities of gait,

It is always important to look for asymmetry in the assessment of childhood-onset dystonia, because a hemidystonic syndrome should be investigated to exclude symptomatic causes. Similarly, an isolated dystonic leg also should point toward symptomatic causes in an adult, though not in childhood, Should there be an early loss of postural responses and righting reflexes in association with a dystonic gait disturbance, attention also should be directed toward excluding underlying secondary causes.

Dystonia with diurnal fluctuation (dopa-rcsponsive dystonia) characteristically presents with walking difficulties in childhood. Typically, the child walks normally in the early morning but develops increasing rigidity and dystonic posturing of the legs with difficulty walking as the day progresses. These dystonic leg postures usually become evident or worsen after exercise. Examination reveals a dystonic foot posture of plantar flexion and inversion, with the additional feature of brisk tendon reflexes. Some of these patients respond dramatically to L-dopa-containing preparations, and early recognition is important. Indeed, all children presenting with a dystonic foot or leg should have a therapeutic trial of L-dopa before other therapies, such as anticholinergic drugs, are commenced.

Paroxysmal dyskinesias also may present with difficulty walking. Paroxysmal kincsigenic choreoathetosis may present with the sudden onset of difficulty walking as a result of dystonic postures and involuntary movements of the legs that often appear after standing from a seated position. Similarly, dystonia of the legs, cither paroxysmal or exercise induced, may interfere with walking.

Choreic Gait

The random movements of chorea are accentuated and often most noticeable during walking. The gait is often described as having a dancing quality because of the supcrimposition of chorea on the trunk and leg movements of the walking cycle. Chorea may be incorporated into the stepping and truncal movements of the walking cycle, resulting in exaggerated motion of the legs when stepping and excessive associated arm swing. Chorea may interrupt the normal movements of walking, leading to a hesitant gait, and there may be additional voluntary compensatory movements in response to perturbations from the chorea. Choreic movements in Sydenham's chorea or chorea gravidarum may be sufficiently violent to throw patients off their feet or be unable to walk at **all.** Chorea of this severity is uncommon in Huntington's disease and usually causes a lurching or occasionally stumbling gait with frequent additional steps cither forward, backward, or to one side. In Huntington's disease, walking is slow, the stance is wide based, the trunk sways excessively, and steps are variable in length and timing. Spontaneous knee flexion and leg raising are also common. Haloperidol reduces the chorea but does not improve gait in Huntington's disease. Balance and equilibrium usually are maintained until the terminal stages of Huntington's disease, when an akinetic rigid syndrome may supervene.

Mixed Movement Disorders and Gait

Many conditions, notably athetoid cerebral palsy, produce :i range of motor signs that refleci abnormalities at many levels of the nervous system. All interfere with and disrupt normal patterns of walking. These include spasticity of the legs, truncal and gait ataxia, and dystonic spasms and postures affecting the trunk and limbs. Difficulties may arise in distinguishing such patients from those with primary torsion dystonia, which may begin at a similar age in childhood. The patient with cerebral palsy usually has a history of hypotonia and delayed achievement of developmental motor milestones. Often, there is a history of perinatal injury or birth asphyxia, but in a substantial proportion of patients, such an event cannot be identified. A major distinguishing feature is poor balance at an early age, which may be a contributing factor to the delay in sitting and later walking. As the child begins to walk, the first signs of dystonia and athetosis appear. The presence of spasticity and ataxia also helps distinguish **this** condition from primary dystonia.

Childhood neurodegenerative diseases also may first manifest as a disorder of walking with a combination of motor syndromes. A progressive course should raise the possibility that the syndrome is symptomatic and secondary to an underlying cause.

ACTION MYOCLONUS AND TREMOR OF THE LEGS

Some causes of involuntary movements of the legs when standing or walking are listed in Table 25.6.

Action Myoclonus

Action myoclonus and reflex myoclonus affecting the legs are rare but striking disorders. Postanoxic action myoclonus of the legs is often accompanied by negative myoclonus (or astcrixis) and severely disrupts normal postural control and any attempts to use the legs to stand or walk. Repetitive action myoclonus produces jerky movements of the legs, throwing the patient off balance, and lapses of muscle activity between the jerks (negative myoclonus) cause the patient to sag toward the ground. This sequence of events gives rise to an exaggerated bouncing appearance, which the patient is able to sustain for only a few seconds

Table 25.6: Differential diagnosis of involuntary movements of the legs when standing

Action myoclonus of legs (as in postanoxic myoclonus)
Benign essential tremor
Orthostatic tremor
Cerebellar truncal tremor
Clonus in spasticity
Spastic ataxia

before falling or seeking relief by sitting down. Difficulty walking is one of the major residual disabilities of postanoxic myoclonus, and many patients remain wheelchair bound. The stance is wide based, and there is often an element of cerebellar ataxia, although this may be difficult to distinguish from the severe action myoclonus. Stimulus-sensitive cortical reflex myoclonus also may produce a similar disorder of stance and gait, with reflex myoclonic jerking of leg muscles, particularly the quadriceps, resulting in a bouncing posture.

Tremor of the Trunk and Legs

An action tremor of the legs may produce a similar though less severe bouncing standing posture and gait. Leg tremor in benign essential tremor is occasionally symptomatic. Trunk and leg tremor may be a cause of unsteadiness in cerebellar disease. Orthostatic tremor has a unique frequency of 16 Hz and distribution, affecting trunk and leg muscles while standing. It produces an intense sensation of unsteadiness, rather than shaking, which is relieved by walking or sitting down. Patients avoid standing still, for example, in a queue, and may shuffle on the spot or pace about in an effort to avoid the unsteadiness experienced when standing still. Falls are rare. Examination may reveal only a rippling of the quadriceps muscles during standing, and the rapid tremor is often only appreciated by palpation of leg muscles. The differentiation among leg tremors and the diagnosis of orthostatic tremor is best made by recording the clectromyographical activity of leg muscles during standing and measuring tremor frequency.

GAIT IN THE ELDERLY

Healthy, neurologically normal elderly people tend to walk at slower speeds than their younger counterparts (Murray, Kory, and Clarkson 1*969).* The slower speed of walking is related to shorter and shallower steps with reduced excursion at lower limb joints. In addition, stance width may be slightly wider than usual, and synergistic arm and trunk movements are less vigorous. The rhythmiciry of stepping is preserved. These changes give the normal elderly gait a cautious or guarded appearance. Factors contributing to this general decline in mobility of the elderly include degenerative joint disease, reduced range of limb movement, and dcctcascd cardiovascular fitness, limiting exercise capacity. The reduced speed of walking and associated changes in gait pattern in the elderly also may represent one method of providing a more secure base to compensate for a subtle age-rein red deterioration in balance. In imsclccicd elderly populations, a more pronounced deterioration in gait is evident (Imms and F.dholm 1981). Steps are shorter, stride length is reduced, and the stance phase of walking is increased, leading to a reduction in walking speed, particularly in those who fall.

Neurological causes of walking difficulty in the elderly, such as myelopathy, parkinsonism, cerebellar disease, and imbalance caused by sensory loss, are common etiologies, as are frontal gait disorders and gait apraxias (Sudarsky and Ronthal 1983). The etiology of imbalance and an insecure gait in the elderly is often multifactorial. The cumulative effects of lesions at many sites can interfere with walking without any one lesion being severe enough to explain the difficulty. Multiple sensory deficits affecting vision, vestibular, and proprioceptive function cause imbalance and an insecure gait. Multiple mild sensory deficits of peripheral nerve or posterior column origin, combined with modest leg weakness of peripheral nerve or corticospinal tract origin, as in cervical and lumbar spondylosis, are also common causes of this clinical picture. Loss of confidence, especially after falls, adds to the multifactorial age-related gait disturbance. A formal program of gait retraining may correct this loss of confidence and improve the ability to walk.

In some patients, difficulty walking and even standing is related to dysequilibrium because of impaired postural reflexes and a tendency to fall, often with injury. Acute vascular lesions of the thalamus (thalamic astasia) or basal ganglia produce this clinical picture with falls away from the side of the lesion without corrective postural adjustments. Similar dysequilibrium with impaired postural reflexes occurs in progressive supranuclear palsy and multiple system atrophy, with falls forward or backward. Impaired central vestibular function may also account for isolated dysequilibrium in some elderly patients and correlate with increased body sway (Fife and Baloh 1993).

The mechanisms responsible for the disturbances of gait that accompany lesions of the frontal lobes are poorly understood {Thompson 2001). Frontal lobe tumors (glioma or meningioma), anterior cerebral artery infarction, obstructive or communicating hydrocephalus (especially normal pressure hydrocephalus), and diffuse cerebrovascular disease (multiple lacunar infarcts and Binswanger's disease) all produce a similar disturbance of gait. The clinical appearance of the gait of patients with such lesions vanes from a predominantly wide-based ataxic gait to an akinetic-rigid gait with slow short steps and a tendency to shuffle. It is common for a patient to present with a combination of these features. In the early stages, the stance

base is wide with an upright posture of the trunk and short shuffling steps. This may be most noticeable on starting to walk or turning corners. There may be episodes of freezing. Arm swing is often normal or even exaggerated when walking, but the normal fluidity of trunk and limb motion is lost, giving the appearance of a "military two-step" gait. Examination often reveals normal voluntary upper limb and hand movements and a lively facial expression. This lower half parkinsonism is commonly seen in diffuse cerebrovascular disease. The marchc a petits pas of Dejerine and Critchley's atherosclerotic parkinsonism refers to a similar clinical picture. Patients with this clinical syndrome commonly are often misdiagnosed as having Patkinson's disease. The normal motor function of the upper limbs, the upright truncal posture, UMN signs, including a pseudobulbar palsy, and the absence ot a resting tremor distinguish this syndrome from Parkinson's disease. In addition, the lower half parkinsonism of diffuse cerebrovascular disease does not respond to i.-dopa treatment, further distinguishing it from Parkinson's disease (see Table 25.4). The slowness of movement and the lack of heel-shin ataxia distinguish the wide-stance base of this syndrome from cerebellar gait ataxia.

As the underlying condition progresses, the elements of ataxia and parkinsonism become more pronounced. There may be great difficulty initiating a step, as if the feet were glued to the floor (the magnetic foot response). Attempts to take a step require assistance with the patient clutching for the support of neatby objects or persons. There may be excessive upper body movement as the patient tries to ftee the feet to initiate walking, and when undetway, shuffling becomes even more pronounced. Such patients rarely exhibit the festination of Parkinson's disease, but a few steps of propulsion or retropulsion may be taken. Postural and righting reactions are impaired and eventually lost, and falls are common at the slightest perturbation. By contrast, these patients often can move their legs with greater facility when seated or lying supine. They may be able to make stepping, walking, or bicycling leg movements when lying but be quite unable to do so when standing.

A severe loss of truncal mobility and truncal balance may develop in the advanced stages of a frontal gait disorder, so patients are unable to stand or turn over when lying in bed. Walking then becomes impossible, and even simple leg movements ate slow and clumsy when lying down. Paratonic rigidity (gegcnhalten) of the arms and legs is common. Tendon reflexes may be brisk with extensor plantar responses. Gtasp reflexes in the hands and feet may be elicited and urinary incontinence and dementia commonly occut. Investigation by MRI or computed tomography of the brain reveal the majority of conditions causing this syndrome.

Some patients display fragments of this clinical picture. Those with gait-ignition failure exhibit profound start hesitation without disturbance of stepping once walking is underway. Balance while standing or walking is normal. Initiation of the first step is hampered by shuffling, and walking may be interrupted by freezing (Atchison ct al. 1993). Sensory cues may facilitate stepping. These findings are similar to walking in Parkinson's disease, but speech and upper limb function are normal and there is no response to i.-dopa. Results of imaging of the brain are normal. The cause of this syndrome is not known, but the slowly progressive evolution of symptoms suggests a degenerative condition.

Occasionally, isolated episodic festination with truncal flexion is encountered. Others complain of a loss of the normal fluency of stepping when walking and a conscious effort is required to maintain a normal stepping rhythm and step size. These symptoms may be associated with subtle dysequilibrium manifesting as a few brief staggering steps to one side or a few steps of retropulsion after standing up, turning quickly, or other rapid changes in body position. Finally, there remain elderly patients with severe walking difficulties that resemble those described in frontal lobe disease. The history in these syndromes is one of gradual onset, without strokclike episodes or identifiable structural or vascular lesions of the frontal lobes or cerebral white matter on imaging. The cause of these syndromes is not known. The criteria fot normal pressure hydrocephalus are not fulfilled, there are no signs of parkinsonism, L-dopa is ineffective, and thcte is no evidence of more generalized cerebral dysfunction, as occurs in Alzheimer's disease. Indeed, it is rare for patients with Alzheimer's disease to develop difficulty walking until the later stages of the disease.

Nomenclature of Gait in the Elderly

Early descriptions of frontal gait syndromes emphasized the imbalance and ataxic components. The term *frontal ataxia* was used to reflect the perceived involvement of the frontopontocerebellar pathway as the most likely mechanism. Indeed, the gait ataxia of many midline cerebellar lesions associated with obstructive hydrocephalus can be out of ptoportion to the degree of lower limb heel-shin ataxia and may be largely relieved by the insertion of a ventricular drain or shunt. This observation confirms the importance ot hydrocephalus in the gait ataxia associated with these lesions. Others were impressed by the slowness of movement and the discrepancy between the pronounced disability when attempting to walk and the preservation of leg movements when lying or sitting. This combination of signs was considered a form of limb-kinetic apraxia and referred to as *frontal apraxia* and later *gait apraxia.* Gait apraxia is defined as an inability to properly use the lower limbs in the act of walking that cannot be accounted for by demonstrable sensory impairment or motor weakness (Meyer and Barron 1960). Meyer and Barron (1960) emphasized that gait apraxia included ataxia plus

hypokinesia, rigidity (gegenhalten), and brisk reflexes, the latter signs distinguishing apraxia of gait from cerebellar ataxia. The combination of bradykinesia and ataxia in frontal lobe or diffuse cerebral white matter disease is explained by interruption of the connections between motor, premoror, and supplementary motor cortex and other subcortical motor areas, such as the cerebellum and basal ganglia. Use of the term *apraxia* in this context remains controversial because these gaits probably encompass a spectrum of higher motor syndromes (Nutt, Marsden, and Thompson 1993). Discussions concerning the classification of higher gait syndromes have variously emphasized the presumed anatomical or physiological basis of the problem (Nutt, Marsden, and Thompson 1993; Jankovic, Nutt, and Sudarsky 2001). For example, a frontal gait disorder refers to a combination of elements of dyseciuilibrium, marche a petits pas, and gait-ignition failure. Subcortical dysequilibrium refers to a predominant disorder of equilibrium with a loss of postural reflexes and severe falls as seen in thalamic and basal ganglia astasia and progressive supranuclear palsy.

MYOPATHIC WEAKNESS AND GAIT

Weakness of proximal leg and hip-girdle muscles interferes with the stabilization of the pelvis and legs on the trunk during all phases of the gait cycle. Failure to stabilize the pelvis produces exaggerated rotation of the pelvis with each step (waddling or Trendelenburg gait), the hips are slightly flexed as a result of weakness of hip extension, and an exaggerated lumbar lordosis occurs. Weakness of hip extension interferes with the ability to stand from a squatting or lying position and patients may use their arms to push themselves up from a squatting position (Gowers' sign). The classic descriptions of this gait were of patients with Duchenne's muscular dystrophy, but any myopathy affecting these muscles results in such a picture. Similarly, neurogenic weakness of proximal muscles, for example, spinal muscular atrophy and, occasionally the Guillain-Barre syndrome, may mimic this waddling gait.

NEUROGENIC WEAKNESS AND GAIT

Muscle weakness of peripheral nerve origin, as in a peripheral neuropathy, typically affects distal muscles of the legs and results in a steppage gait. The patient lifts the leg and foot high above the ground with each step because of weakness or paralysis of ankle dorsiflexion and a foordrop (steppage gait). When this clinical picture is confined to only one leg (unilateral footdrop), a common peroneal or sciatic nerve palsy or an L5 radiculopathy is the usual cause. Less common is footdrop caused by myopathic weakness, for instance, in the scapuloperoneal syndromes.

A femoral neuropathy, such as in diabetes mellitus, is another example of a strategic mononeuropathy that may disable walking. Weakness of knee extension allows the knee to buckle when walking or standing. This may first be evident when walking down stairs. Such focal weakness also may be the presenting feature of the progressive muscular atrophy in motor neuron disease or be an early feature of quadriceps myopathy, for instance, caused by inclusion body myositis.

HYSTERICAL AND PSYCHOGENIC GAIT DISORDERS

The wide range of abnormalities of gait seen in lesions of different parts of the nervous system make hysterical and psychogenic gaits among the most difficult to diagnose. In a hysterical paralysis, there may be complete inability to use a leg when walking, but normal synergistic movements of the affected leg may be observed when the patient is examined while lying down or when changing position. This discrepancy is further illustrated by Hoover's sign. The patient with an apparently paralyzed leg or legs is examined when supine. As the patient lifts the normal leg, the examiner places his or her hand under the "paralyzed" leg and feels the presence (and strength) of synergistic hip extension. The apparent severe weakness of hysterical paresis often presents little disability or inconvenience. In contrast, other patients with hysterical paraplegia may he totally confined to bed and may even develop contractures from lack of leg movements.

A gait disorder is one of the more common manifestations of a psychogenic or hysterical movement disorder and various gait patterns are encountered. These include transient fluctuations in posture while walking, knee buckling without falls, excessive slowness and hesitancy, a crouched, stooped, or other abnormal posture of the trunk, complex postural adjustments with each step, exaggerated body sway or excessive body motion, and trembling weak legs. Suggestibility and improvement with distraction are common features, as is the case with other psychogenic movement disorders.

The more acrobatic hysterical disorders of gait indicate the extent to which the nervous system is functioning normally. These patients are able to take advantage of high-level motor skills and coordination to perform various complex maneuvers. This is an important observation in the assessment of suspected hysterical gait disorders, as is a rapid, dramatic, and complete recovery. One must be cautious in accepting a diagnosis of hysteria though, because a bizarre gait may be a presenting feature of primary torsion dystonia and unusual truncal and leg postures may be encountered in truncal and leg tremors.

MISCELLANEOUS GAIT DISORDERS

Space Phobia and Gait

A syndrome of space phobia is described in which middle-aged people develop an inability to walk and a fear of falling in open spaces. These patients seek the support of nearby fences or walls and may even crawl about on all fours. Falls may occur in the course of the illness. Other neurological symptoms and cardiovascular disease are common accompaniments. Some patients may experience symptoms while driving or simply standing, suggesting the condition is related to the perception of visuospatial information and is distinct from simple agoraphobia.

Painful (Antalgic) Gaits

At one time or another, most people experience a limp caused by a painful or injured leg. Limps and gait difficulties that are caused by joint disease or by local bony or soft tissue injury are not usually accompanied by muscle weakness or by reflex or sensory change. Limitation of the range of movement at the hip, knee, or ankle joinrs may lead ro short steps with a fixed leg posture.

Pain in the leg caused by intermittent claudication of the cauda equina is most commonly caused by spinal stenosis with lumbar spondylosis and, rarely, by a spinal tumor. Diagnosis is confirmed by spinal imaging. Occasionally, it may be difficult to distinguish this syndrome from claudication of the calf muscles caused by peripheral vascular disease, although the duration of the pain after rest (see earlier discussion) is usually characteristically different in the two syndromes. Examination of the patient after inducing the symptoms by exercise may resolve rhe issue by revealing a depressed ankle jerk or radicular sensory loss, with preservation of arterial pulses in the leg.

Skeletal Deformity and Joint Disease

Degenerative osteoarthritis of the hip may produce leg shortening, in addition to mechanical limitation of leg movement at the hip, giving rise to a waddling gait or a limp.

Leg shortening with limping in childhood may be the presenting feature of hemiatrophy caused by a cerebral or spinal lesion. Such walking difficulties between the ages of 1 and 5 years are the most common mode of presentation of spinal dysraphism. On examination, various additional abnormalities may be detected, including lower motor neuron signs in the legs and sensory loss with trophic ulcers of the feet. Occasionally, UMN signs, such as a brisk knee reflex, are present in the same limb. Lumbosacral vertebra] abnormalities (spina bifida), bony foot deformities, and a cutaneous hairy patch over the lumbosacral region are clues to the diagnosis. In adult life, spinal dysraphism (diastcmatomyelia with a tethered cord) may first become symptomatic after a back injury, with the development of walking difficulties, leg and lower back pain, neurogenic bladder disturbances, and sensory loss in a leg. Imaging of the spinal canal reveals the abnormality.

Epileptic Falls in Childhood

Seizure disorders of the myoclonic or akinetic-atonic type typically produce falls but may present as an unsteady or uncoordinated gait in childhood. Tonic seizures or flexor spasms also may produce this clinical picture. Simultaneous video, electroencephalographical, and electromyographic recordings arc helpful in diagnosing and identifying these various seimre patterns.

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Chapter 26
Hemiplegia and Monoplegia

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ANATOMY

Accurate neurological diagnosis begins with anatomical localization. Many disorders have diffuse localizations, but hemiplegia and monoplegia arc more likely to be due to focal structural lesions and are therefore easier to localize. Imaging studies are often confirmatory of the structural lesion, but clinical localization must precede imaging studies.

Hemiplegia and monoplegia are motor symptoms and signs, but associated sensory abnormalities are discussed along with the motor findings because they are commonly-present and helpful for accurate localization. Sensory deficit syndromes are discussed in more depth in Chapter 31.

Motor power begins with initiative or volition, lack of which does not produce weakness, but akinesia. Projections from the premotor regions of the frontal lobes to the motor strip result in activation of corticospinal tract (CST) neurons. The descending fibers pass through the internal capsule and the cerebral peduncles, and then remain in the ventral brainstem before crossing in the medulla at the pyramidal decussation. Most of the CST crosses at this point. Descending CST axons project to the spinal cord segments where the fibers exit the CST and enter the spinal gray. Here, motoneurons are activated, which then conduct action potentials in the motor axons to the muscle. Transmission at the neuromuscular junction provides for one action potential in the muscle fiber for each action potential in the motor axon. Depolarization of the muscle fiber results in release of calcium, which then promotes the repeated cross-linking and release of actin and myosin filaments, which results in contraction. The contraction is terminated when the calcium is sequestered and prepared for reuse.

Localization begins with identification of weakness. Differentiation is made between the following distributions:

- Generalized weakness
- Monoplegia
- Hemiplegia
- Paraplegia

Only hemiplegia and monoplegia are discussed here.

HEMIPLEGIA

Cerebral Lesions

Cerebral lesions arc the most common causes of hemiplegia with lesions in either conical or subcortical structures (Table 26.1).

Cortical Lesions

Cortical lesions produce weakness, which is more focal than the weakness seen with subcortical lesions. Figure 26.1 shows a diagrammatic representation of the surface of the brain, showing how the body is mapped on the surface of the motor sensory cortex. This is the *homunculus.* In this representation, the face and arm are laterally represented on the hemisphere, whereas the leg is draped over the top of the hemisphere and into the interhemispheric fissure. Small lesions of the cortex can produce prominent focal weakness of one area, such as the leg or the face and hand, but hemiplegia—prominent involvement of both the leg and arm—is not expected unless there is a stroke involving the whole territory of the internal carotid artery.

Table 26.1; Cerebral lesions

Lesion	*Symptoms*	*Signs*
.Motor cortex	Weakness and poor control of the affected extremity, which may involve face, arm, and leg to different degrees	Incoordination and weakness that depends on the location of the lesion within the cortical homunculus; often associated with neglect, apraxia, aphasia, or other signs of cortical dysfunction
Internal capsule	Weakness rhar usually affects the face, arm, and leg almost equally	Often associated with sensory impairment in same distribution
Basal ganglia	Weakness and incoordination on the contralateral side	Weakness, often without sensory loss; no neglect or aphasia
Thalamus	Sensory loss	Sensory loss with tittle or no weakness

Infarction. Cortical infarctions are more likely to be associated with sensory abnormalities than subcortical infarctions. Also, cortical infarctions are associated with a so-called *cortical sign*—neglect with non-dominant hemisphere lesions and aphasia with dominant hemisphere lesions. Unfortunately, this distinction is not absolute, because rarely subcortical lesions can produce these signs.

Diagnosis of infarction is usually made on clinical grounds, especially early in the course. The abrupt onset of the deficit is typical. Weakness that progresses over several days is unlikely to be caused by infarction, although some infarcts can show worsening for a few days after onset. Progression over days suggests demyelinating disease. Progression over weeks suggests a mass lesion, such as a tumor or an abscess. Progression over seconds to minutes in a marching fashion suggests cither epilepsy (which usually produces convulsions and not weakness) or migraine; remember that not all migraine-associated deficits are associated with subsequent headache.

Computed tomography (CT) scans often do not show infarction for up to 3 days after the event, and magnetic resonance imaging (MRI) is not available on an urgent basis in most hospitals. Confirmation of the ischemia can be made by MRI or follow-up CT scan 2-3 days after the onset of symptoms. Infarcts show particularly well on flair images of the MRI. Recent infarction can be distinguished from remore infarction on diffusion-weighted imaging.

Middle Cerebral Artery. The middle cerebral artery (MCA) supplies rhe lateral aspect of the motor sensory cortex, which controls the face and arm. In addition, on the

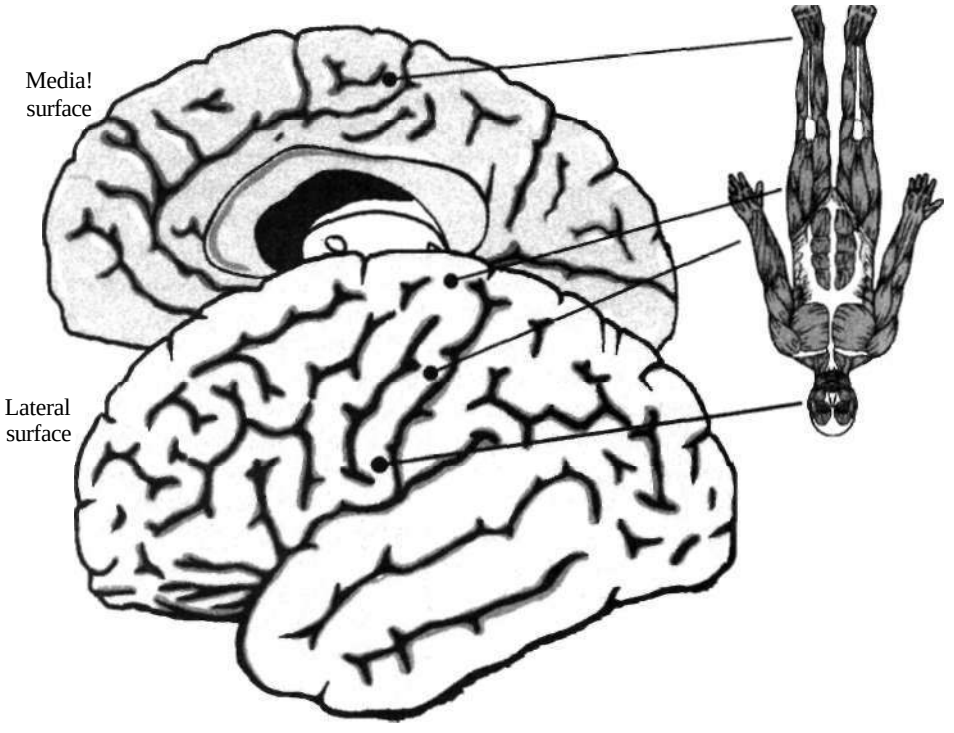

FIGURE 26.1 Representation of the body on the motor cortex. The face and arms are represented laterally, and the legs are represented medially, with the distal legs of the cortex bordering on the central sulcus.

dominant side, speech centers are also supplied—Broca's area in the posterior frontal region and Wernicke's area on the superior aspect of the temporal lobe.

Cortical infarction in the territory of the MCA produces contralateral hemiparesis, usually associated with other signs of cortical dysfunction such as aphasia with left hemisphere lesions, or neglect with right hemisphere lesions. The arm, hand, and face are affected much more than the leg. Diagnosis is suspected with hemiparesis, which affects predominantly the face and arm. Aphasia or neglect is confirmatory of the cortical localization.

Anterior Cerebral Artery. The anterior cerebral artery (ACA) supplies the inferior frontal and parasagittal regions of the frontal and anterior parietal lobes. This region is responsible for leg movement and is important for bowel and bladder control. Infarction in the ACA distribution produces contralateral leg weakness. The arm may be slightly affected, especially the proximal arm, with sparing of hand and face. Diagnosis is suspected when a patient presents with leg weakness and CST signs. The leg weakness can be bilateral if both ACAs arise from the same trunk; this situation can he mistaken for myelopathy.

Posterior Cerebral Artery, The posterior cerebral arteries (PCAs) are the terminal branches of the basilar artery. They supply most of the occipital regions and the medial temporal regions. PCA infarction is not expected to produce weakness but produces contralateral hemianopia, often with memory deficits. Diagnosis may be missed, because the examiner may not look for hemianopia in a patient who otherwise may present only with confusion. The visual complaints may be vague or nonexistent.

Subcortical Lesions

Subcortical lesions are more likely to produce equal weakness of the face, arm, and leg on the contralateral side, because the descending axons that project to the brainstem and spinal cord converge into a small volume in the internal capsule to ultimately form the CST, Lesions of sudden onset are most likely to be stroke, usually lacunar infarction, but hemorrhage can occur. Demyelinating disease has a subacute onset. Tumors have a slower onset and can get quite large in subcortical regions before reaching medical attention.

Infarction, Infarction is usually a clinical diagnosis but can be confirmed by CT or MRI scans, as discussed (see Cortical Lesions, Infarction, earlier in this chapter).

Lenticulostriate Arteries. These small penetrating arteries arise from the proximal MCA and supply the basal ganglia and internal capsule. Infarction commonly produces contralateral hemiparesis with little or no sensory involvement ("pure motor hemiplegia," which can also be due to a brainstem lacuna).

Thaiamoperforate Arteries. These small penetrating arteries arise from the PCAs and supply mainly the thalamus. Infarction in this distribution produces contralateral sensory disturbance but can also cause movement disorders such as chorcoathetosis or hemiballismus; hemi paresis is not expected.

Demyelinating Disease. Demyelinating disease is a group of conditions whose pathophysiology implicates the immune system. Diagnosis is based on clinical grounds for most patients but is suggested by finding areas of increased signal intensity on T2-weighted images of the MRI. Active demyelinating lesions often show enhancement on Tl-weighted gadolinium-enhanced images. Cerebrospinal fluid (CSF) examination is usually performed and can be normal or show elevated protein, a mild lymphocytic pleocytosis, and/or oligoclonal bands of immunoglobulin G (IgG) in the CSF.

Multiple Sclerosis. Multiple sclerosis (MS) presents with any combination of white matter dysfunction, Hemiparesis can develop especially if there are large plaques affecting the CST fibers in the hemispheres. However, hemiparesis is even more likely with brainstem or spinal demyelinating lesions, because smaller lesions can produce more profound deficits in these areas.

The diagnosis is suspected by the progression over days and a history of episodes of relapsing and remitting neurological deficits. Episodes of weakness that last for only minutes are likely not to be due to demyelinating disease, but to be vascular or a migraine equivalent.

Parainfectious Encephalomyelitis, Parainfectious encephalomyelitis (acute disseminated encephalomyelitis) is a demyelinating illness that is monophasic but in other respects presents like a first attack of MS. Symptoms and signs at all levels of the central nervous system (CNS) are common, including hemiparesis, paraplegia, ataxia, and brainstem signs.

Diagnosis is based on clinical grounds because MRI scans cannot distinguish between MS and parainfectious encephalomyelitis. CSF may show a mononuclear pleocytosis and elevation in protein, but these findings arc neither always present nor specific. Even the presence or absence of oligoclonal IgG in the CSF cannot differentiate between this and MS, When a patient presents clinically with this, the patient should be warned of the possibility of recurrent events.

Progressive Multifocal Leukocnccphalopathy. Progressive multifocal leukocnccphalopathy (PML) is a demyelinating disease caused by reactivation of the JC virus, especially seen in immunodeficiency. Patients with acquired immunodeficiency syndrome, leukemia, lymphoma, tuberculosis, and sarcoidosis are predisposed to develop PML.

Visual loss is the most common symptom and weakness is the second most common. MRI scan shows multiple

white matter lesions. CSF is either normal or shows a lymphocytic pleocytosis and/or elevated protein. Brain biopsy is required for specific diagnosis.

Migraine. Migraine is often associated with an aura of visual symptoms (classic migraine), but motor and sensory symptoms can also develop (complicated or hcmiplegic migraine). Sensory symptoms may include loss of sensation or paresthesias. Motor symptoms can include hemiparesis. The deficit progresses across the extremities in a manner that looks like the spreading of cortical localization. Headache does not always follow the neurological deficit, making the diagnosis even more difficult.

Diagnosis is suspected when the patient is young, has few risk factors, and the deficit marches in a manner that can be visualized as a migration of spreading electrical depression across the cerebral cortex. Imaging is often necessary to rule out hemorrhage, infarction, and demyelinating disease.

Tumors. Tumors affecting the cerebral hemispheres commonly present with progressive deficits including hemiparesis. Cortical dysfunction is also commonly present, such as aphasia with dominant hemisphere lesions. Other signs of expanding tumors may include headache, seizures, confusion, and visual field defects. The hemiparesis often is manifest as a disorder of coordination developing before the weakness.

Diagnosis is suspected in a patient with progressive motor deficit over weeks, especially if there are coexistent seizures and/or headache. MRI with contrast enhancement is more sensitive for identification of tumors than CT

Alternating Hemiplegia of Childhood. Alternating hemiplegia of childhood is characterized by attacks of unilateral weakness, often with signs of other motor deficits (e.g., dyskinesias or stiffness) and oculomotor abnormalities (e.g., nystagmus). Attacks begin in young childhood, usually before age 18 months; they last hours, and deficits accumulate. Initially, patients are normal, but with time, neurological deficits, including motor deficits and cognitive decline, become obvious. Diagnostic studies show no abnormalities, including MRI, electroencephalography, and angiography.

Hemiconvulsion-Hemiplegia Syndrome. Young children with this rare condition develop unilateral weakness after the sudden onset of focal seizures. The seizures are often incompletely controlled. Neurological deficits ate not confined to the motor system and may include cognitive, language, and visual deficits. Unlike alternating hemiplegia, the seizures and motor deficits are consistently unilateral, although eventually the unilateral seizures may become generalized. Imaging may be normal initially but eventually shows atrophy of the affected hemisphere. CSF analysis is not specific, but a mild mononuclear pleocytosis may develop because of the CNS damage and seizures.

Brainstem Lesions

Brainstem lesions producing hemiplegia are among the easiest to localize, because associated signs of brainstem dysfunction are almost always present.

Brainstem Motor Organization

Figure 26.2 shows the anatomical organization of the motor systems of the brainstem. Discussion of the complex anatomical organization of the brainstem can be simplified by concentrating on some important functions:

- Appendicular motor and sensory function
- Facial motor and sensory function
- Appendicular coordination
- Ocular motor function
- Descending sympathetic tracts

Motor pathways descend to the pyramidal decussation in the medulla, when they cross to innervate the

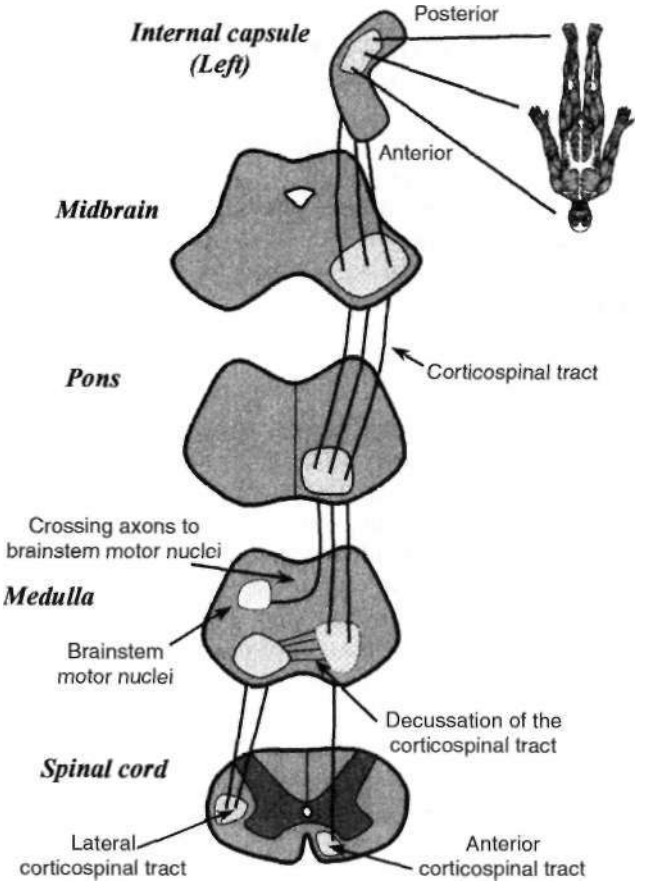

FIGURE 26.2 Brainstem motor organization, beginning with the internal capsule. The corticospinal tract remains topographically organized throughout the brainstem and spinal cord, although isolated lesions below the cerebral cortex are unlikely to produce topographically specific damage.

contralateral body. Lesions of the pons and midbrain above this level produce contralateral hemiparesis, which may involve the contralateral face. Rostral lesions of the medulla produce contralateral weakness, whereas more caudal medullary lesions produce ipsilateral cranial nerve signs with a contralateral hemiparesis and sensory deficit.

Sensory pathways from the nucleus gracilis and nucleus cuneatus cross at about the same level as the motor fibers of the CST, so deficits m light touch and position sense tend to parallel the distribution of the motor deficit. In contrast, the spinothalamic tracts have already crossed in the spinal cord and ascend laterally in the brainstem. Therefore lesions of the lower medulla may produce contralateral loss of pain and temperature sensation and ipsilateral loss of touch and position sense. Lesions above the mid medulla produce a contralateral sensory defect of all modalities indistinguishable from cerebral lesions, yet the clues to brainstem localization can include the following:

- Ipsilateral facial sensory deficit from a trigeminal lesion
- Ipsilateral hemiataxia from damage to the cerebellar hemispheres or nuclei
- Ocular motor weakness, resulting in diplopia
- Ipsilateral Horner's syndrome from damage of the descending sympathetic tracts

Common Lesions

Table 26.2 shows some of the important lesions of the brainstem and their associated motor deficits. Brainstem lesions are usually due to damage to the penetrating branches of the basilar artery. Patients present with contralateral weakness along with other findings that help localize the lesion. Hemiataxia often develops and can be mistaken for hemiparesis, so careful examination is essential; the implications for localization of the differentiation of hemiataxia and hemiparesis are tremendous. Demyelinating disease and tumors are the other most common causes of brainstem dysfunction.

Spinal Lesions

Spinal lesions can produce hemiplegia sparing the face, although they mostly will cause bilateral findings typical of myelopathy. Diagnosis of a spinal cord lesion is suspected in a patient if there is bilateral weakness, bowel- and/or bladder-control deficits, or back pain.

Spinal Hemisection (Brown-Sequard's) Syndrome

Spinal hemisection is seldom seen in clinical practice. However, components of the syndrome are occasionally identified. This is usually seen in intradural tumors, trauma,

Tabic 26.2: brainstem lesions

Named disorder	*Location*	*Signs*
Midbrain		
Weber's syndrome	Cranial nerve III, ventral midbrain, corticospinal tract	Contralateral hemiparesis, third nerve palsy
Benedikr's syndrome	Cranial nerve HI, ventral midbrain, corticospinal tract, red nucleus	Contralateral hemiparesis, third nerve palsy, intention tremor, cerebellar ataxia
Top-of-the-basilar syndrome	Occipital lobes, midhrain oculomotor nuclei, cerebral peduncle, medial temporal lobe, thalamus	Contralateral hemiparesis, cortical blindness, oculomotor deficits, memory difficulty, contralateral sensory deficit
Pons		
Millard-Gubler syndrome	Cranial nerve VI, cranial nerve VII, ventral pons	Contralateral hemiparesis, sixth nerve and seventh nerve palsies
Clumsy-hand syndrome	Corticospinal tract, facial nerve	Contralateral hemiparesis; dysarthria, often with facial weakness
Pure motor hemiparesis with lesion in the pons	Ventral pons	Contralateral hemiparesis with corticospinal tract signs
Ataxic hemiparesis with lesion in the pons	Corticospinal and cerebellar tracts	Contra lateral hemiparesis with impaired coordination
Fovilie's syndrome	Cranial nerve VII, vcnrral pons, paramedian pontine reticular formation	Contralateral hemiparesis, seventh-nerve palsy, gaze palsy to side of lesion
Medulla		
Media! medullary syndrome	Corticospinal tract, medial lemniscus, hypoglossal nerve	Contralateral hemiparesis, loss of position and vibratory sensation, ipsilateral tongue paresis

and inflammatory conditions. Spondylitic myelopathy, disc-disease, and most extradural tumors usually produce symmetrical findings.

Patients with the spinal hcmisection syndrome present with weakness ipsilateral to and below the lesion. In addition, segmental motor loss may be seen wirh involvement of the motoneurons at the level of the lesion. Sensory findings include loss of pain and temperature contralateral to and below the lesion. Position sense may be affected ipsilateral to the lesion.

Transverse Myelitis

Transverse myelitis is an acute myelopathic process that is presumed to be autoimmune in origin. Patients present with motor and sensory deficits below the lesion. Findings are typically bilateral yet may be asymmetrical.

Spinal Cord Compression

Spinal cord compression is usually due to disc protrusion or spondylosis. Neoplastic and infectious causes should always be considered. Disc disease and spondylosis are typically in the midline, so unilateral findings are not expected. Extradural tumors are less likely than intradural tumors to produce unilateral symptoms. Lastly, lesions below the cervical spinal cord would not produce hemiplegia, hut monoplegia of the lower limb or paraplegia.

Spondylosis with cord compression produces lower motor neuron (LMN) weakness at the level of the lesion and CST signs below the level of the lesion. Spinal cord compression resulting in paralysis should be evaluated as quickly as possible with MRI if available. Myelography should be considered if MRI is not urgently available.

Spinal Cord Infarction

Anterior spinal artery infarction usually causes paraparesis and spinothalamic sensory loss below the level of the lesion. Rarely, one segmental branch of the anterior spinal artery can be involved with unilateral spinal cord damage and monoparesis or hemiparesis.

Peripheral Lesions

Peripheral lesions are not expected to produce hemiplegia. However, a pair of peripheral lesions affecting both the arm and the leg oil the same side may occasionally masquerade as hemiplegia. Differentiation depends on identification of the individual lesions as being within the distribution of one nerve, nerve root, or plexus. The tendon reflexes are likely to be depressed in patients with CST lesions. Amyotrophic lateral sclerosis can produce weakness of one limb, followed by weakness of the other limb on the same side, with progression over months or even years. Usually the combined presence of upper motor neuron (UMN) and LMN involvement, without sensory changes, assists in making the diagnosis. If the predominant involvement is UMN in type, the picture can look like a progressive hemiparesis.

Conditions that predispose to separate lesions affecting one arm and leg are disorders producing mononeuropathy multiplex. Diabetes is the most common cause, hut other causes include leprosy, vasculitis, and predisposition to pressure palsies. Diagnosis is by electromyography (EMG), which can differentiate mononeuropathy from polyneuropathy. Radiculopathy would not give hemiparesis but is in the differential diagnosis of monoplegia (see Radiculopathies, later in this chapter).

Functional Hemiplegia

Functional or psychogenic weakness includes both conversion reaction and malingering. In conversion reaction, the patient is not conscious of the nonorganic nature of the deficit, whereas in malingering the patient is making a conscious effort to fool the examiner. In both circumstances, there is some secondary gain for the patient, whether psychological or economic. In malingering, the secondary gain is usually more obvious and includes disability payments, litigation, family attention, and avoidance of stressors or tasks.

Clues to functional weakness include the following:

- Improvement in strength with coaching
- Give-way weakness
- Inconsistencies in examination, for example, inability to extend the foot but able to walk on toes
- Hoover's sign: The patient lies supine on the bed and lifts one leg at a time. If the leg is truly paralyzed, the examiner should feel effort to press down with the opposite heel. Failure to do so is a positive Hoover's sign.
- Paralysis in the absence of other signs of motor system dysfunction, including tone and reflex changes

Diagnosis of functional weakness is based on consistencies on examination and elimination of the possibility of organic disease. Functional weakness should be diagnosed with caution. It is easy to dismiss the patient's complaints after an inconsistent feature is seen, especially if some secondary gain is obvious. Unfortunately, the diagnosis of functional weakness is difficult, because a patient with organic problems may have a functional overlay, which may exaggerate an otherwise subtle clinical finding. For example, weakness and incoordination of the hand may seem subtle on examination and may be missed completely if the patient gives incomplete effort with the extremity.

Some diagnostic testing is often required to rule out neurological disease, although this should be kept to a minimum. Prescription of multiple tests and treatments may serve to reinforce the presumed presence of illness, and thereby augment illness behavior. Psychological evaluation and treatment can be key.

MONOPLEGIA

Cerebral Lesions

Cerebral lesions more commonly produce hemiplegia than monoplegia, but isolated limb involvement can occasionally occur, especially with cortical involvement. The arm segment of the motor sensory cortex lies on the lateral part of the hemisphere, adjacent to the sylvian fissure.

Subcortical infarction is less likely to produce monoplegia than cortical lesions because of the dense packing of the fibers of the CST in the internal capsule. The internal capsule is generally organized with the arm segments represented anteriorly in the capsule relative to the leg sections. Infarction in the distribution of the lenticulostriate arteries, however, usually affects both divisions.

Infarction

The arm region of the cerebral motor cortex is supplied by the MCA. Infarction of a branch of the MCA can produce isolated arm weakness, although facial involvement and cortical signs are expected—language deficit with left hemisphere lesions and neglect with right hemisphere lesions. With more extensive lesions, visual fields can be abnormal because of infarction of the optic radiations. Mild leg weakness can also occur. The leg segment lies in the parasagittal region and is supplied by the ACA. ACA infarction produces weakness of the contralateral leg,

Migraine

Migraine can produce sensation that marches along one limb, usually the arm. The progression through the limb differs from the abrupt onset of stroke. Involvement of only the leg is unusual. The headache phase typically begins as the neurological deficit is resolving. Weakness can develop as part of the migraine aura, but this is much less likely than sensory disturbance.

Seizure and Transient Ischemic Attacks

Seizure can rarely produce negative motor symptoms rather than positive symptoms. Episodic paralysis can seem like a transient ischemic attack (TIA), and evaluation for vascular disease is often indicated. Focal seizure activity may be suggested by subtle twitching or disturbance of consciousness associated with the episodes. Seizures are usually more frequent and have a shorter duration than TIAs.

Multiple Sclerosis

MS can produce monoplegia through a discrete white matter plaque, but hemiparesis is more common.

Tumors

Tumors deep to the cortex rarely produce monoplegia because the involvement is not sufficiently discrete to affect only one limb. Cortical involvement makes single limb involvement more likely. Parasagittal lesions often produce leg involvement, which can be initially unilateral. Meningiomas often arise from one side of the falx, so they predominantly affect one leg. The presentation is of CST findings referable to only one leg. The single leg weakness could be mistaken for a thoracic spinal lesion, although paraparesis is more common in such a situation.

Metastatic tumors are often found at the gray-white junction and as such are in position to produce focal cortical damage. Early on, the lesion may be too small to produce definite neurological symptoms, but with increasing growth, the lesion is more likely to produce focal seizures or loss of function.

Brainstem Lesions

Brainsrem lesions seldom produce monoplegia because of the tight packing of the fibers of the CSTs in the brainstem. Unilateral cerebellar hemisphere lesions may produce appendicular ataxia, which is most obvious in the arm, although this should be distinguished from monoparesis by the absence of weakness and the presence of ataxia.

Spinal Lesions

Spinal lesions can produce weakness from segmental damage to nerve roots, or CSTs. CST signs below the level of the lesion are expected. Weakness in one leg can develop from damage ro the spinal nerve roots, and in this case, the weakness is associated with muscle wasting and lost reflexes in a radicular distribution.

Peripheral Lesions

Peripheral lesions usually produce monoparctic weakness in the distribution of a single nerve, nerve root, or plexus. A few conditions, such as amyotrophic lateral sclerosis and focal spinal muscular atrophy, may produce weakness in a monomelic (monopk'j;ic) distribution.

Pressure Palsies

Intermittent compression of a peripheral nerve can produce transient paresis of part of a limb. The patient may think the entire limb is paralyzed, but detailed examination shows that the paresis is limited. The weakness usually improves so quickly that examination is often not possible before the improvement. Predisposition to pressure palsies can be seen in two main circumstances: on a hereditary basis and in the presence of peripheral polyneuropathy.

Hereditary Neuropathy Ptcd is position to Pressure Palsies. Hereditary neuropathy with predisposition to pressure palsies is associated with episodic weakness and sensory loss associated with compression of isolated nerves. Nerve conduction studies may show distal slowing of conduction velocities.

Pressure Palsies in Polyneuropathy. Patients with polyneuropathy may have an increased susceptibility to pressure palsies. Areas of demyelination are more likely to have a depolarizing block produced by even mild pressure,

Mononeuropathies

Table 26.3 shows some important peripheral nerve lesions of the arm. Table 26.4 shows some important peripheral nerve lesions of the leg.

Median Nerve

Carpal Tunnel Syndrome. Carpal tunnel syndrome is the most common mononeuropathy. The median nerve is compressed as it passes under the flexor retinaculum at the wrist. Patients present with numbness on the palmar aspects of the first through third digits. Fotccd flexion or extension of the wtist commonly exacerbates the sensory symptoms. Weakness of the abductor poilicis brevis may develop in advanced cases.

This condition would not normally be considered in the differential diagnosis of monoparesis, but because the patient can complain of weakness that is more extensive than the actual deficit, it is considered here. Nerve conduction studies show slow motor and sensory velocities through the carpal tunnel. KMG shows denervation in the abductor poilicis brevis muscle with severe disease.

Table 26.3: Peripheral nerve lesions of the arm

Lesion	*Clinical findings*	*EM.G findings*
Median neuropathy		
Carpal runnel syndrome	Abductor poilicis brevis wasting and weakness when severe. Sensory loss on palmar aspect of the first through third dibits	Slow motor and sensory NCV through carpal tunnel; abductor poilicis brevis denervation if severe
Anterior interosseous syndrome	Weakness of flexor digitorum profundus, pronator titiadratus, flexor poilicis longus	Denervation in flexor digitorum profundus, flexor poilicis longus, pronator quadratus
Pronator teres syndrome	Weakness of distal median-innervated muscles; tenderness of pronator teres	Slow median motor NCV through proximal forearm; denervation of distal median-innervated muscles
Compression at the ligament of Strurhers	Weakness of distal median-innervated muscles	As for pronator teres syndrome, with the addition of denervation of pronator teres
Ulnar neuropathy		
Palmar branch damage	Weakness of dorsal interossei; no sensory loss	Normal ulnar NCV; denervation of first dorsal intcrosseus but not abductor digiti minimi
Entrapment at Guyon's canal	Weakness of ulnar intrinsic muscles; numbness over fourth and fifth digits	Slow ulnar motor and sensory NCV through wrist
Entrapment at or near the elbow	Weakness of ulnar intrinsic muscles; numbness over fourth and fifth digits	Slow ulnar motor NCV across elbow, denervation in abductor digiti minimi and ulnar half of flexor digitorum profundus
Radial neuropathy		
Posterior interosseous syndrome	Weakness of ringer and wrist extensors; no sensory loss	Denervation in wrist and finger extensors; supinator and extensor carpi radialis spared
Compression at the spiral groove	Weakness of finger and wrist extensors; triceps spared; sensory loss on dorsal aspect of first digit	Slow radial motor NCV across spiral groove; denervation in distal radial-innervated muscles; triceps may be affected with proximal lesions

NCY = nerve conduction velocity.

Table 26.4: Peripheral nerve lesions of the leg

Lesion	*Clinical findings*	EMG *findings*
Sciatic neuropathy	Weakness of tibial- and peroneal-innervated muscles with sensory loss on posterior leg and foot	Denervation distally in tibial- and peroneal-innervated muscles; contralateral muscles normal
Peroneal neuropathy	Weakness of foot extension and eversion and of toe extension	Denervation in peroneal-innervated muscles; conduction across fibular neck may be slowed
Tibial neuropathy	Weakness of foot plantar flexion	Denervation in gastrocnemius and soieus
Femoral neuropathy	Weakness of knee extension; weakness of hip flexion if psoas involved	Denervation in quadriceps, and sometimes psoas

Anterior Interossetts Syndrome. The anterior interosseous nerve is a branch of the median nerve in the forearm that supplies some of the forearm muscles. Damage can occur distal to the elbow, producing a syndrome that is essentially purely motor. Weakness of finger flexion is prominent. Affected muscles include the flexor digitorum profundus to the second and third digits (the portion to the fourth and fifth digits is innervated by the ulnar nerve). The distal median nerve entering the hand is unaffected, because the anterior interosseous nerve arises from the main trunk of the median nerve.

Diagnosis is suspected by weakness of the median-jj-mervared finger flexors with sparing of the abductor pollicis brevis and ulnar-innervated flexors. EMG can confirm the diagnosis, but because this entrapment is not commonly looked for by many electromyographers, study of the appropriate muscles must be specifically requested.

Pronator Teres Syndrome. The median nerve distal to the elbow can be damaged as it passes through the pronator teres muscle. All median-innetvated muscles of the arm are affected except for the pronator teres itself. The clinical picture looks like an anterior interosseous syndrome plus distal median neuropathy. The pronator teres may be tender, and palpation may exacerbate some of the distal pain.

Ulnar Nerve. Ulnar entrapment is most common near the elbow and at the wrist, Entrapment at the elbow produces weakness of the ulnar-innervated intrinsic muscles. Weakness of long flexors of the fourth and fifth digits also can develop. When the entrapment is at the wrist, the weakness is isolated to the intrinsic muscles of the hand, and more proximal muscles are unaffected. Although most of the intrinsic muscles of the hand are ulnar innervated, a few arc median innervated and arc unaffected in ulnar neuropathy.

Diagnosis of ulnar neuropathy is suspected when a patient complains of pain or numbness on the ulnar aspect of the hand. The diagnosis is reinforced when the patient has weakness and wasting of the intrinsic muscles of the hand, which is especially easy to see in the first dorsal interosseous.

Radial Nerve Palsy. Radial neuropathy is most commonly seen above the elbow, such that wrist and finger extensors are mainly affected. The triceps can also be affected. This is most commonly a pressure palsy seen in alcoholic intoxication. Peripheral neuropathy makes the development of pressure neuropathy of the radial nerve more likely.

Femoral Neuropathy. Femoral neuropathy can occur from compression by intra-abdominal contents (fetus or neoplasm), but we have also seen it from damage around the time of angiography or surgery. Patients present with pain in the thigh and weakness of knee extension. The complaint is usually not so specific but is of the leg "giving out" during walking or of the patient being unable to get out of a chair without using the arms. Examination may show quadriceps weakness, but this muscle group is so strong that the examiner may not be able to detect the weakness. Lower leg muscles must be examined to ensure that muscles in the sciatic distribution arc normal.

Diagnosis is confirmed by EMG, showing denervation confined to the femoral nerve distribution. Unfortunately, electrical signs of denervation may not be obvious for up to 4 weeks after the injury.

Sciatic Neuropathy. Sciatic neuropathy can have multiple causes, including acute trauma and chronic compressive lesions. The term *sciatica* describes pain in the distribution of the sciatic nerve in the back of the leg. It is usually due to radiculopathy (see Radiculopathies, later in this chapter). An intramuscular injection into the sciatic nerve rather than the gluteus is an occasional cause of sciatic neuropathy and is characterized by initial severe pain followed by a lesser degree of pain and weakness. Pyriformis syndrome is an uncommon condition in which the sciatic nerve is compressed by the pyriformis muscle. This is a difficult diagnosis to make, requiring demonstration of increased pain on tensing the pyriformis muscle by flexing and adducting the hip.

Diagnosis of sciatic neuropathy is considered when a patient presents with pain and/or weakness of the lower leg muscles. EMG can confirm the distribution of denervation. Nerve conduction studies are usually normal. MRI of the lumbosacral plexus is occasionally needed to look for

tumors and other causes of sciatic nerve or plexus compression.

Peroneal Neuropathy. Peroneal neuropathy can develop from a lesion at the fibular neck, the popliteal fossa, or even ihi[1] sciatic nerve in the thigh. The peroneal division of rhe sciatic nerve is more susceptible to injury than the tibial division, so incomplete sciatic injury affects predominantly the peroneal innervated muscles.

The peroneal nerve innervates the tibialis anterior, extensor digitorum brcvis, and pcronei muscles. In addition, the peroneal division innervates the short head of the biceps femoris in the distal posterior thigh. This is an important muscle to remember, because distal peroneal neuropathy spares this muscle, whereas a proximal sciatic neuropathy, a peroneal division lesion, or a radiculopathy is expected to cause denervation not only in the tibialis anterior but also the short head of the biceps femoris.

Radiculopathies

Radiculopathy produces weakness of one portion of a limb. Common radiculopathies are summarized in Table 26.5. Complete paralysis of all of the muscles of an arm or leg is not caused by radiculopathy, other than traumatic avulsion of the nerve roots, which may occur in the upper limbs with distraction injuries of the arm from the neck. Roots serving arm power include chiefly C5 to T1. Roots serving leg power are chiefly L2 to SI. A lesion at the L5 level often elicits a complaint of the entire limb being weak because of the footdrop, which interferes with gait.

Reflex abnormalities are often present early in a radiculopathy and are a manifestation of the sensory component. Motor deficits develop with increasingly severe radiculopathy.

Diagnosis of radiculopathy can be facilitated by EMG, which is an aid to localization and helps determine whether acute changes are developing. V1RI shows the structural cause of a definite radiculopathy in most patients, although the diagnostic yield in patients with back pain without clear radicular symptoms is far less (see Chapter 34). Myelography with post-myelographic CT scanning is still more sensitive for structural imaging, although it is not performed as a first-line investigation because of the invasive nature of the procedure.

Plexopathies

Brachial and Lumbar Plexitis (or Piexopathy). Brachial plexitis is an acute neuropathic syndrome of presumed autoimmune etiology. Patients present with shoulder and arm pain followed by weakness as the pain abates. Eventually the weakness improves, although this takes months and is occasionally incomplete. Brachial plexitis is somewhat more common than lumbar plexitis. The upper plexus, C5-C6, is most commonly affected, although the lower plexus can be involved. Lumbar plexitis has a similar clinical course to brachial plexitis.

Diagnosis of plexitis is considered when a patient presents with single limb pain and weakness, which docs not follow a single root or nerve distribution. MRI of the region is normal, unless there is neoplastic infiltration, Nerve conduction studies may be normal distally in the limbs, but F waves will be slowed or absent. EMG may be normal initially but eventually shows denervation in the distribution of the affected portion of the plexus.

Differentiation of plexitis from radiculopathy is made on the basis of not only the more extensive deficits in patients with plexitis, but also the time course of pain followed by weakness as the pain abates; this pattern is not expected in patients with radiculopathy.

Neoplastic Plexus Infiltration, The brachial and lumbar plexuses are in proximity to the areas that can be infiltrated by tumors, including those involving the lymph nodes, lungs, kidneys, and other abdominal organs. The first symptom of tumor infiltration is usually pain. Weakness and sensory loss are less common symptoms. Neoplastic plexus compression or infiltration presents as a progressive

Table 26,5: Radiculopathies

Level	*Motor findings*	*Sensory findings*
Cervical radiculopathy		
C5	Deltoid, biceps	Lateral upper arm
C6	Biceps, brachioradialis	Radial forearm and first and second digits
C7	Wrist extensors, triceps	Third and fourth digits
C8	Intrinsic hand muscles	Fifth digit and ulnar forearm
Lumbar radiculopathy		
L2	Psoas, quadriceps	Lateral and anterior upper thigh
L3	Psoas, quadriceps	Lower medial rhigh
L4	Tibialis anterior, quadriceps	Medial lower leg
L5	Peroneus longus, gluteus medius, tibialis anterior, extensor ballucis longus	Lateral lower kg
SI	Gastrocnemius, gluteus maximus	Lateral foot and fourth and fifth digits

painful monoparesis. Limb movements that stretch the plexus elicit pain, and the patient tends to hold the limb immobile to avoid exacerbating the pain.

Neoplastic infiltration of the brachial plexus usually involves the lower plexus, C8-T1. Lung cancer and lymphoma are the most common tumors to cause this, Horner's syndrome can develop with lower brachial plexus involvement. The main differential diagnosis is radiation plexopathy.

Diagnosis is suspected as a result of the severe pain and weakness. EMG often shows denervation that spans single nerve and root distributions. Detailed knowledge of the plexus anatomy is essential during examination and EMG. MRI usually shows the infiltration or compression of the plexus.

Radiation Plexopathy, Radiation therapy in the region of the plexus can produce progressive dysfunction. The upper brachial plexus is especially susceptible because of the lesser amount of surrounding tissues to attenuate the radiation. Symptoms are dysesthesias and weakness. The dysesthesias may be uncomfortable but are seldom described as painful. This is one key to differentiation from neoplastic plexus infiltration, which is typically quite painful.

Diagnosis is suspected in the clinical setting of progressive painless weakness in a patient with cancer who has received radiation to the region, MRI is essential to rule out tumor infiltration. EMG shows denervation, which is not a differentiating feature, but myokymia is more commonly seen in patients with radiation plexopathy than in those with neoplastic infiltration.

Plexus Hematomas. Hematomas can develop adjacent to and compress the brachial and lumbosacral plexuses producing motor and sensory findings. Brachial plexus hematomas are usually from bleeding disorders or instrumentation such as central line placement. Lumbosacral plexus hematomas can also develop from coagulopathies including anticoagulant treatment, and after procedures such as abdominal surgeries or after femoral arterial catheterization. In the latter circumstance, blood leaking from the puncture site can flow proximally, and a substantial amount of blood may be lost without a clinically obvious hematoma.

Hematomas interfere with the function of the peripheral nerves and plexus by blocking conduction. The prognosis is generally good as long as the plexus or nerve has not been directly injured, because the condition is usually neurapraxia rather than neurotmesis, and conduction is usually restored when the blood is resorbed. Large hematomas should be evacuated if severe plexopathic damage is present.

Plexus Trauma. A history of trauma makes the etiology of the plexopathy quite obvious. The main difficulty is differentiating plexopathy from radiculopathy (nerve root avulsion) or peripheral nerve damage. Also, spinal cord damage must be considered, because cord contusion and hemaromyelia may present with weakness that is more prominent in one extremity. Motor vehicle accidents, deliveries, and occupational injuries arc the most common causes of traumatic plexopathy. In many cases of plexus stretch, the mechanism is forced extension of the arm over the head or forced downward movement of the shoulder. Forced extension of the arm over the head damages the lower plexus, with the intrinsic muscles of the hand being especially affected *(Klumpke's palsy).* Forced depression of the shoulder produces damage to the upper plexus, giving prominent weakness of the deltoid, biceps, and other proximal muscles *(Erb's palsy).*

Diagnostic studies should include imaging not only of the plexus but also of the proximate spinal cord, looking for disc herniation, spondylosis, subluxation, or other anatomic deformity. Plain radiograph should always be performed. MRI and/or CT of the region is also helpful.

Trauma includes not only stretch injury, but also penetrating injury, such as knife and bullet wounds. Knife wounds are less likely to affect the lumbar plexus, but downward strike with a knife can easily affect the brachial plexus and nearby vessels. Gunshot wounds may directly affect the plexus, and the shock waves of high-velocity bullets may damage the plexus without direct involvement. Unfortunately, the speed and effectiveness of recovery from these types of injuries is poor.

Thoracic Outlet Syndromes, Thotacic outlet syndrome is an overdiagnosed condition characterized by weakness of muscles innervated by the lower trunk of the brachial plexus. The motor axons in the lower trunk supply both the median- and ulnar-innervated intrinsic muscles of the hand, Finger and wrist flexors may occasionally be affected, causing marked impairments in use of the hand, which is not restricted to a single nerve distribution. This must be differentiated from a cortical lesion. Sensory loss is mainly in an ulnar distribution because the sensory fibers of the median nerve ascend through the middle trunk rather than the lower trunk.

Diagnosis of thoracic outlet syndrome depends on demonstration of low-amplitude median and ulnar nerve compound motor action potentials and ulnar sensory nerve action potentials. Median sensory nerve action potentials are normal. Cervical ribs are usually asymptomatic, so their presence does not confirm the diagnosis of thoracic outlet syndrome. MRI of the plexus may be necessary to rule out infiltration by nearby tumor.

Diabetic Amyotrophy. *Diabetic amyotrophy* is the term given to the syndrome of damage to the proximal lumbar plexus, serving mainly the femoral nerve, seen in diabetics. Patients present with weakness and pain in a femoral nerve distribution. Although there may bq an additional

length-dependent diabetic peripheral neuropathy, the femoral distribution symptoms and signs overshadow the other findings. Patients eventually improve, although the recovery is often prolonged and incomplete.

It is difficult to study the nerve conduction of the femoral nerve. EMG usually shows denervation with chronic lesions, although up to 4 weeks may pass before electrical signs of denervation are seen.

Neuronnpathies

Neuronal degenerations usually affect multiple individual nerve distributions and more than one limb. However, a few focal motor neuropathies can produce single limb defects. Monomelic amyotrophy is a condition in which motoneurons of one limb degenerate; often the distribution suggests involvement of specific motoneuron columns in the spinal cord.

Monomelic Amyotrophy. Monomelic amyotrophy is a degenerative condition that affects only one limb, usually an arm. The opposite limb can be affected to a much lesser extent. There is no pain or sensory loss. Progressive weakness develops over months to years and may eventually produce weakness that plateaus.

Onset is usually in young adult life, about the age of 20 years, and men are predominantly affected. Diagnosis is confirmed by clinical presentation and EMG findings of active and chronic denervation without sensory abnormalities.

Poliomyelitis. Poliomyelitis is now uncommon but still occurs in some parts of the world. A poliomyelitis-like syndrome can result from viruses other than the poliovirus itself. The illness usually presents with acute asymmetrical weakness after an initial phase of encephalitic symptoms, including headache, meningeal signs, and possibly confusion or seizures. The paralysis may involve only one limb but is more commonly generalized. After recovery, only one limb may remain weak (monoparesis).

PITFALLS IN THE DIAGNOSIS OF HEMIPLEGIA AND MONOPLEGIA

Diagnosis of hemiplegia and monoplegia can always be a challenge, but some diagnoses can be especially difficult.

Weakness in Intrinsic Muscles of the Hand: Median, Ulnar, Plexus, or Small Cerebral Cortical Lesion?

Most of the intrinsic muscles of the hand arc innervated by the ulnar nerve, so an isolated distal ulnar lesion produces profound loss of use of the hand. This lesion must be differentiated from a lateral frontocentral cerebral lesion, which if located in the hand region produces prominent loss of independent digit use.

A median nerve lesion produces impaired hand function because of loss of function of the finger and wrist flexors more than of the intrinsic muscles of the hand. With stabilization of the hand, intact function of ulnar- and radial-innervated muscles can be demonstrated to rule out lesions at or above the plexus.

Lower brachial plexus lesions produce dysfunction of the median- and ulnar-innervated intrinsic muscles of the hand and may also affect the long finger flexors. This dramatic loss of function can be mistaken for central weakness, because the deficit spans peripheral nerve distributions. EMG usually documents the axonal damage.

A small cerebral cortical lesion can produce disuse of the hand without signs of other deficit. Reflexes should be exaggerated, although acutely they may not be. Cupping of the outstretched hand and pronator drift strongly suggests a central lesion. EMG cannot rule out a peripheral nerve lesion, because several weeks may be required before signs of axonal damage are evident on needle study. MRI of the brain is the most sensitive imaging study for a small cerebral lesion.

Radial Neuropathy or Small Cerebral Cortical Infarcts?

Radial neuropathy presents with weakness of the wrist extensors, which if severe can result in destabilization of the intrinsic muscles of the hand and long finger flexors, because opposition from the radial-innervated extensors is required for these median- and ulnar-innervated muscles to work well. Therefore the deficit seems more extensive than would be expected on the basis of a radial lesion alone. A cerebral lesion is suggested. Although cerebral lesions span neural distributions, wrist extension may be more obviously affected than grip and/or finger flexion.

Differential diagnosis of radial neuropathy from cerebral lesion depends on the examiner stabilizing the finger flexors and wrist to demonstrate intact median and ulnar nerve function. Also, CST signs and other signs of cortical damage (aphasia or neglect) should be looked for in a patient with a possible cerebral infarct.

Leg Weakness: Peroneal Nerve Palsy or Paramedian Cerebral Cortical Lesion?

Peroneal nerve palsy results in weakness of foot dorsiflcxion and eversion with relative preservation of other motor functions. Small lesions of the leg region of the homunculus on the medial aspect of cerebral hemispheres cause weakness that is most prominent in the same distribution as a peroneal nerve palsy. Differentiation is by absence of inverter weakness with peroneal palsy. EMG signs of

denervation do not develop with cerebral lesions. Cerebral causes of lower leg weakness also cause upgoing plantar response and hyperactivity of the Achilles tendon reflex, despite little clinical evidence of gastrocnemius muscle involvement.

Leg Weakness: Cauda Equina Lesion, Myelopathy, or Paramedian Cerebral Cortical Lesion?

This chapter discusses monoplegia rather than paraplegia (Chapter 27), but it is important to differentiate between lower spinal cord dysfunction and cauda equina compression; between upper spinal cord involvement and cervical spondylotic myelopathy; and between these problems and midline cerebral lesions producing leg weakness.

Cauda equina lesions are usually due to acute disc herniations, spondylosis, or tumors in the lumbosacral spinal canal. The lumbar and sacral nerve roots are compressed, resulting initially in a depolarizing block but later axonal degeneration, which produces motor and sensory loss. With the syndromes of intermittent claudication of the cauda equina, repetitive nerve action potentials result in severe pain that is relieved by rest only after a few minutes and that may be accompanied by neurological dysfunction. Pain, sensory loss, and weakness are typically worsened by standing and relieved by flexing the lumbar spun-.

Spondylotic myelopathy is compression of the spinal cord by degenerative spondylosis above the cauda equina. Compression of the CSTs produces weakness of the legs. Pain is usually near the level of the lesion, although the localizing value is not precise. Midline cerebral lesions produce unilateral or bilateral leg weakness, depending on the cause and exact location, with CST signs. Spine pain is not expected.

Differentiation between these three lesion locations (cauda equina, spinal cord, and cortical) can be tricky, but in general the following apply:

- Bowel and bladder incontinence can develop with all three locations but is more common with cauda equina lesions.
- Cauda equina lesions are associated with depressed reflexes, whereas spinal cord and cerebral lesions have hyperactive reflexes and upgoing plantar responses.
- Sensory loss is more prominent with cauda equina lesions than higher lesions.
- Pain in the spine is approximately at the level of the lesion, although the localization is not exact.

FURTHER READING

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Chapter 27
Paraplegia and Spinal Cord Syndromes

Thomas N. Byrne and Stephen G. Waxman

The clinical presentations of spinal cord disease are diverse, The protean manifestations of spinal cord disease may mislead even the most astute clinician. Patients may present with vague numbness or weakness. Alternatively, their first complaint may be pain without neurological signs, which may he incorrectly attributed to musculoskeletal disease or visceral pathology. Because it is essential to evaluate and treat such patients with spinal cord compression expeditiously, a thorough understanding of the clinical manifestations of spinal cord diseases and those of the n on-neurological diseases that may mimic spinal disease is necessary. The purpose of this chapter is to provide an understanding of the clinical pathophysiology of the spinal cord and to demonstrate the methods of history taking and physical examination that are helpful in assessing the patient suspected of suffering from spinal cord disease.

The localization of spinal cord pathology is described by the following three coordinates. The first two are anatomical: (1) the level in the rostrocaudal axis and (2) the extent in the transverse plane of spinal cord involvement, These coordinates are determined by clinically assessing neurological functions served by both nerve roots and spinal cord tracts. The third coordinate is the time course of evolution of spinal cord dysfunction, which is often important in predicting the etiology, the physiological response of the cord to the disease, and the prognosis (Byrne, Benzel, and Waxman 2000),

SEGMENTAL INNERVATION

Ventral Root Dysfunction

Ventral root dysfunction is manifested by characteristic motor disturbances that are usually quite distinct from those arising from corticospinal tract disease or from plexus or peripheral nerve disease. Important aspects of the physical examination are the assessment of the distribution of abnormalities of muscle strength, tone, and bulk. The pattern of weakness is often the most important physical finding that distinguishes root disease from peripheral nerve disease.

Muscle strength or power may be determined by individual muscle testing or by functional assessment. Because each muscle usually is innervated by several nerve roots, complete lower motor neuron (LMN) paralysis of a muscle or muscle group typically signifies plexus or peripheral nerve disease, rather than a monoradiculopathy. The lattet usually produces partial weakness of a muscle. Despite this fact, with a monoradiculopathy, a single muscle often suffers greater dysfunction than others. Such muscles have been termed *segment-pointer* muscles. Table 27,1 lists a group of muscles that may point the examiner to a specific nerve root. This listing, however, should not be considered infallible, because some individuals have prefixed or postfixed plexuses (i.e., are one nerve root higher or lower than the usually described anatomical localization).

Table 27.1: S eg me nr-pointer muscles

Root	*Muscle*	*Primary function*
CA	Diaphragm	Respiration
CA	Diaphragm	Respiration
CS	Deltoid	Arm abduction
CA	Biceps	Forearm flexion
C6	Brachioradialis	Forearm flexion
C7	Triceps	Forearm extension
C8	Intrinsic hand muscles	Finger adduction/abduction
Tl	Intrinsic hand muscles	Finger adduction/abduction
LI	Iliopsoas	Hip flexion
L3	Quadriceps femoris	Knee extension
14	Quadriceps reiuoris	Knee extension
14	Tibialis anterior	Foot dorsiflexion
L5	Extensor hallucis longus	Great toe dorsiflexion
SI	Gastrocnemius	Plantar flexion

Source: Modified with permission from Schliack, H. 1969, "Segmental innervation and the clinical aspects of spinal nerve root syndromes," in *Handbook of Clinical Neurology,* vol. 2, eds P. J. Vinken, G. *8c* W. Rruyn, North! lolhuul Publishing, Amsterdam.

Denervation of a muscle causes muscular atrophy (neurogenic atrophy). Other common causes of muscular atrophy are disuse, endocrinological disturbance, and malnutrition. Neurogenic atrophy develops in cases of radiculopathy. With a monoradiculopathy, however, the atrophy is not as prominent as that occurring with peripheral nerve injury because most muscles receive innervation from several nerve roots. In cases of chronic radiculopathy, such as that caused by cervical spondylosis, atrophy may precede weakness. Alternatively, in cases of acute radiculopathy, for instance, caused by acute disc herniation, weakness may ptecedc atrophy.

Neurogenic atrophy may be associated with fasciculations, which represent spontaneous contraction of a group of muscle fibers innervated by a single motor neuron (a motor unit). Usually, they are seen as a twitching or rippling movement just beneath the skin. Exercise, cold, medications, and metabolic derangements often cause similar movements. Fasciculations are seen commonly in motor neuron disease but are widesptead in this case. In cases of compressive root lesions, fasciculations may be tcstricted to the myotomal distribution of the compressed root. These fasciculations are different from those seen in antctiot horn cell disease in that they occur tepetitively in the same fasciculus during minimal contraction and are usually absent during complete test. The syndtome of benign fasciculations is more diffuse and is not associated with weakness or atrophy.

Muscle tone is often a valuable sign in distinguishing the site of a lesion causing weakness. When measuring muscle tone, the clinician must ensure that the patient's muscles are relaxed, and it is often helpful to distract the patient's attention. In cases of radiculopathy, either muscle tone is not affected ot tone is decteased unless there is muscle spasm, as often occurs if there is severe pain. Alternatively, *spasticity* and *rigidity* refer to common fotms of incteased muscle tone caused by central nervous system disease. In spasticity, the increased rone is caused by an exaggeration of the sttetch reflex and accordingly is dependent on stretch rate. Thus if the muscle is slowly stretched, tone may be normal; however, if the muscle is stretched more rapidly, increasing amounts of resistance occur. Spasticity has been referred to as *rate sensitive* for this teason. The weakness of upper motor neuron (UMN) damage preferentially involves the deltoid, triceps and wrist extensors in the upper limbs, and the iliopsoas, hamsttings, and tibialis anterior muscles in the lower extremities, whether caused by cortical or corticospinal tract disease. Spasticity usually results from dysfunction of the descending spinal tracts, including but not limited to the corticospinal ttact (Ditunno and Formal 1994).

Rigidity refers to increased muscle tone, which does not depend on the fate of movement. Unlike spasticity, it is found equally in both extensors and flexors. Rigidity is commonly caused by extrapyramidal disease or is a side effect of antidopamincrgic drugs (e.g., halopcridol).

Dorsal Root Dysfunction

Disturbance of dorsal root function most commonly produces pain and to a lesser extent sensory impairment. The pain may be local or projected elsewhere in a tadiculat or nonradicular distribution (referred pain).

Local Pain

Local or regional back or neck pain is usually secondary to irritation or damage of innervated structures of the spine. The periosteum, ligaments, dura, and apophyseal joints are innervated structures. The clinical characteristics of local pain are that it is appreciated in the local tcgion of the spine

and that it is deep, aching, and exacerbated by activity that places an increased load on the diseased structures. Patients suffering from pain caused by an epidural tumor often report that their pain is made worse by the supine position, wiu-RMs those sntiering from spondylosis and musculoligamentous strain generally favor bed rest. Palpation or percussion of the spinal column may exacerbate the local pain regardless of the cause. Irritation of local innervated structures also causes secondary muscle spasm and local or somewhat diffuse pain.

Projected Pain

Projected pain is pain that arises from one anatomical site but is projected to a site some distance from the location of the pathology. When the spine is the source, the projected pain may be either radicular or nonradicular. Projected pain that arises from irritation of posterior nerve roots is of a radicular type, whereas that caused by irritation of other spinal structures is usually of a nonradicular type, herein termed *referred pain.* Although these forms of pain are not always easy to differentiate, it is important to distinguish between them because radicular pain has strong localizing value and nonradicular pain does not.

Referred Pain. The pain in normal volunteers after injection of 6% saline into the facet joints of L1-L2 and L4-L5 is cramping and aching in quality. As shown in Figure 27.1, there is overlap in the regions of pain referral from upper and lower lumbar injections, with most of the pain being referred to the flanks, buttocks, groins, and thighs. It is of clinical interest that referred pain in normal volunteers does not project below the knee despite rhe fact that the L4-L5 level is stimulated, whereas it can radiate below the knee in symptomatic individuals. It appears that unlike tadicular pain, referred pain does not follow segmental dermatomes and is not usually helpful in localization.

Although there may be paresthesias in the cutaneous area of pain referral, as well as tenderness to deep palpation of the muscles, no neurological abnormalities are found in cases of referred pain of nonradicular origin. This situation is in contrast to cases of radicular pain, in which disturbance of the nerve root often may be present in the form of sensory loss, hyporcflexia, ventral root dysfunction, or a combination of these. Referred pain generally is aggravated and relieved by the same maneuvers that alter local pain.

Radicular Pain. Radicular pain, which has great localizing value, arises from irritation of dorsal roots, with pain being projected to the dermatome of the nerve root. Tables 27.2 and 27.3 list the differential diagnoses of lesions of the cervical and lumbosacral nerve roots and the common sites to which pain of radicular origin is projected.

Radicular pain often has a sharp, stabbing quality. Maneuvers that stretch or further compress the nerve root, such as Valsalva maneuver, coughing, straight-leg raising, and neck flexion, generally aggravare the pain. The patient may avoid certain activities and postures that place further strerch on the nerve. For example, in the case of sciatica (pain in the distribution of the sciatic nerve) caused by a compressive SI radiculopathy (Figure 27,2), the patient may maintain the leg in a flexed posture at the hip and knee and plantar flex the foot. Such a posture may result in

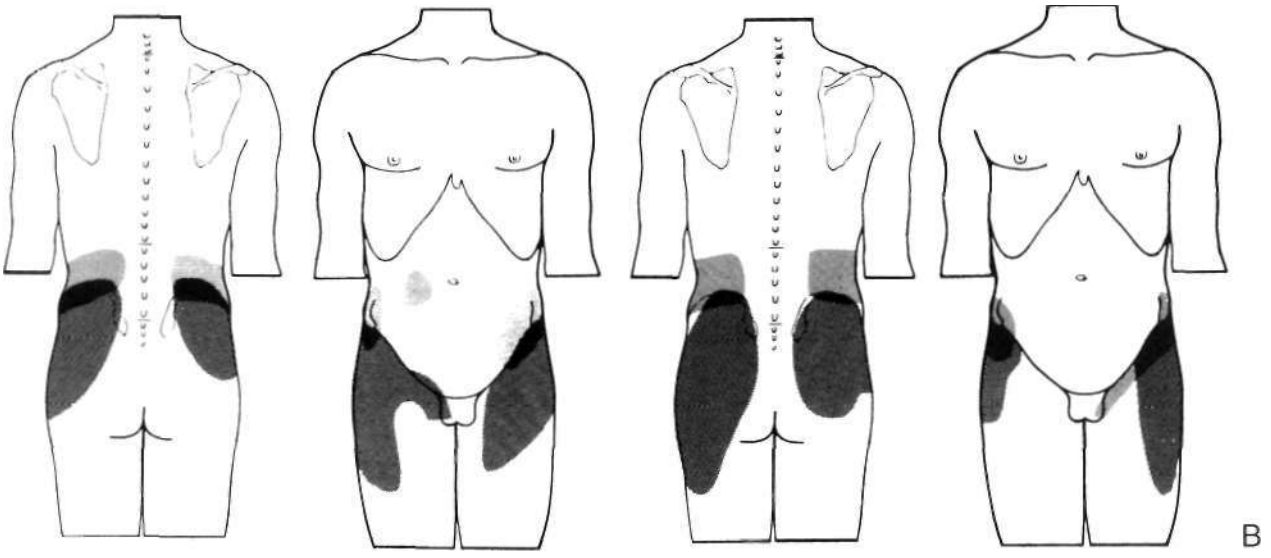

FIGURE 27.1 Patterns of referred pain. The distributions of pain referral from L1-L2 *(diagonal Shies)* and L4-L5 *(crosshatching)* are superimposed following (A) intracapsular and (B) pericapsular injections of 6% saline into the apophyseal joints. Overlap of the patterns is shown in the region of the iliac crest and groin. (Reprinted with permission from Mccall, J. W,, Park, W.M., & O'Brien, J, P. 1979, "Induced pain referral from posterior lumbar elements in normal subjects," *Spine,* vol. 4, pp. 441-446.)

Table 27.2; Differential diagnosis of lesions of the cervical nerve roots

Roots	*C5*	C6	*C7*	*C8*	*Tl*
Sensory supply	Lateral border upper arm	Lateral forearm including thumb	Over triceps, mid forearm, and middle finger	Medial forearm to include little finger	Axilla down to the olecranon
Sensory loss	As above	As above	Middle fingers	As above	As above
Area of pain	As above, and thumb and index finger	As above, especially thumb and index finger	As above, and medial scapula border	As above	Deep aching in shoulder and axilla to olecranon
Reflex arc	Biceps jerk	Supinator jerk	Triceps jerk	Finger jerk	None
Motor deficit	Deltoid	Biceps	Latissimus dorsi	Finger flexors	All small hand muscles in some via C8
	Supraspinatus	Rrachioradialis	Pectoralis major	Finger extensors	
	Infraspinatus	Brachialis (pronators and supinators of forearm)	Triceps	Flexor carpi ulnaris (thenar muscles in some patients)	
	Rhomboids		Wrist extensors Wrist flexors		
Some causative lesions	Brachial neuritis	Acute disc lesions	Acute disc lesions	Rare in disc lesions or spondylosis	Cervical rib
	Cervical spondylosis	Cervical spondylosis	Cervical spondylosis		Thoracic outlet syndromes
	Upper plexus avulsion				Pan coast's tumor
					Metastatic-carcinoma in deep cervical nodes

Source: Adapted from Patten, J. 1977, *Neurological Differential Diagnosis,* Springer-Verlag, New York.

Table 27.3: Differential diagnosis of lesions of the lumbosacral nerve roots

Roots	*L2*	*I ≻*	*IA*	*U*	*SI*
Sensory supply	Across upper thigh	Across lower thigh	Across knee to medial malleolus	Side of leg to dorsum and sole of foot	Behind lateral malleolus to lateral foot
Sensory loss	Often none	Often none	Medial leg	Dorsum of foot	Behind lateral malleolus
Area of pain	Across thigh	Across thigh	Down to medial malleolus	Back of thigh, lateral calf, dorsum of foot	Back of thigh, back of calf, lateral foot
Reflex arc	None	Adductor and knee reflex	Knee jerk	None	Ankle jerk
Motor deficit	Hip flexion	Knee extension	Inversion of the foot	Dorsiflexion of toes and foot (latter L4 also)	Plantar flexion and eversion of foot
Some causative lesions		Neurofibroma		Disc prolapse	Disc prolapse
		Meningioma		Metastases	Metastases
		Metastasis		Neurofibroma	Neurofibroma
		Intervertebral disc prolapse (infrequent)		Meningioma	Meningioma

Source: Adapted from Patten, J. 1977, *Neurological Differential Diagnosis,* Springer-Verlag, New York.

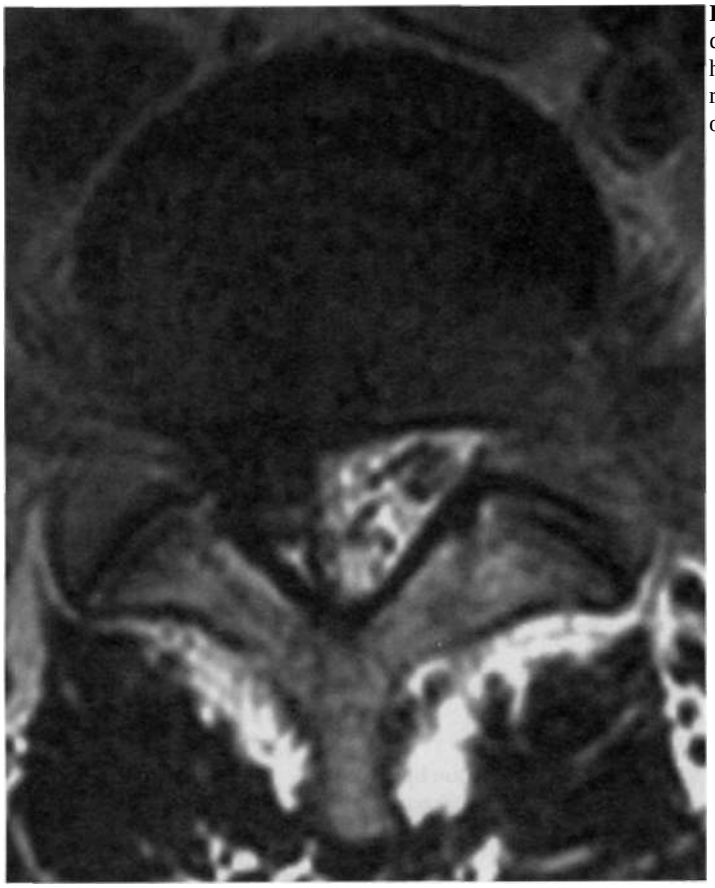

FIGURE 27.2 MRI (axial image) of the lumbar spine demonstrating a right-sided herniated L5-S1 disc (Note: The herniated disc is on rhe left side of the figure). The patient had right-sided sciatica and an absent ankle reflex and sensory loss ot 1111 L- lateral foot.

a characteristic gait. As with referred pain, cutaneous paresthesias and tenderness of tissues in the region of pain projection are common. However, in radicular pain, unlike referred pain, there may be sensory disturbances and at times reflex and motor abnormalities corresponding to the injured nerve root.

SENSORY DISTURBANCES

Dermatomes

A knowledge of the dermatomal map is valuable in recognizing and localizing radicular syndromes, A currently recognized dermatomal map is shown in Chapter 31 {see Figure 31.4). A few points deserve emphasis:

- On the trunk, the C4 and T2 dermatomes are contiguous.
- The thumb, middle finger, and fifth finger are innervated by C6, C7, and C8, respectively.
- The nipple is at the level of T4.
- The umbilicus is at the T10 level.
- In the posterior axial line of the leg {medial thigh), the lumbar and sacral dermatomes arc contiguous.

Finally, it should be recognized that there arc variations in dermatomal innervation between individuals that may make it difficult to base clinical conclusions on sensory testing alone.

DEEP TENDON REFLEXES

In addition to motor and sensory disturbances, deep tendon reflex abnormalities can be of precise localizing value. When deep tendon reflexes are segmentally hypoactive, they can be sensitive indicators of specific root disturbance. When they arc hyperactive below a specific spina! level, they may indicate a myelopathy at or above that level. The combination of hypoactive tendon reflexes at a segmental level with hyperactive reflexes caudal to that level is found commonly with cervical spine disease. For example, cervical spondylosis may cause hyporcflcxia of the biceps, brachioradialis, or triceps because of impingement on C5, C6, or C7 roots, respectively, and hyperreflexia below this level secondary to an associated myelopathy. At times, attempts to elicit the brachioradialis reflex produce no direct response but paradoxically cause contraction of the finger flexors rather than flexion and supination of the **hand. Such** a response is called *inversion of the radial reflex.*

NERVE ROOT VERSUS PERIPHERAL NERVE LESION

Monoradiculopathies rarely cause complete paralysis of *a* single muscle or muscle group. In contrast, with peripheral nerve disease, it is common for paralysis of such muscle groups to occur. A knowledge of innervation of muscle groups is important in making the distinction between peripheral nerve, plexus, or nerve root lesions. The sensory examination may be helpful in distinguishing peripheral nerve lesions from radiculopathies.

Autonomic disturbances may also be valuable in distinguishing peripheral nerve lesions from root disturbances. Ordinarily, mo no radiculopathies are not associated with autonomic disturbances such as sweat loss, whereas peripheral nerve injuries often arc associated with autonomic complaints. Tables 27.2, 27.3, 27,4, and 27.5 review the locations of sensory loss, projected pain, reflex loss, motor deficit, and some causative lesions of the more common radiculopathies and peripheral neuropathies.

Electrodiagnostic studies are often helpful in differentiating radiculopathies from peripheral neuropathies. With radiculopathies, the sensory action potentials are unaffected, whereas they are typically decreased in amplitude or absent in petiphcral nerve disease. Motor conduction

Tabic 27.4: Differential diagnosis of lesions of upper limb peripheral nerves

Nerves	*Axillary*	*Musculocutaneous*	*Radial*	*Median*	*Ulnar*
Sensory supply	Over deltoid	Lateral forearm	Lateral dorsal forearm and back of thumb and index finger	Lateral palm, thumb, and lateral two fingers	Medial palm, fifth finger, and medial one half of ring finger
Sensory loss	Over deltoid	Lateral forearm	Dorsum of thumb and index finger	As above	As above
Area of pain	Across shoulder tip	Lateral forearm	Dorsum of thumb and index finger	Thumb, index, finger(s) and middle fingers Often spreads up forearm	Ulnar-supplied fingers and palm distal to wrist Pain occasionally along course of nerve
Reflex arc	Nil	Biceps jerk	Triceps jerk and supinator jerk	Finger jerks {flexor digitorum sublimis)	Nil
Motor deficit	Deltoid	Biceps	Triceps	Wrist flexors	All small hand muscles, excluding abductor pollicis brevis
		Brachial is	Wrist extensors	Long finger flexors (thumb, index fingers, and middle fingers)	Flexor carpi ulnaris
			Finger extensors	Pronator* of forearm	Long flexors of ring and little fingers
			Brachioradialis	Abductor pollicis b rev is	
			Supinator of forearm		
Some causative lesions	I'IMCUllVtl llec'k of humerus	Rarely damaged	Crutch palsy	Carpal tunnel syndrome	Elbow: trauma, bed rest, fractured olecranon
	Dislocated shoulder		Saturday night palsy	Direct trauma to wrist	Wrist: local trauma, ganglion of wrist joint
	Deep intramuscular injections		Fractured humerus		
			Entrapment in supinator muscle		

Source: Adapted from Patten, J. I 977, *Neurological Differential Diagnosis,* Springer—Verlag, New York.

Tabic 27,5: Differential diagnosis of lesions of lower limb peripheral nerves

			Sciatic nerve	
Nerves	*Obturator*	*Femoral*	*Peroneal division*	*Tibial divisio?t*
Sensory supply	Medial surface of thigh	Anteromedia! surface of thigh and leg to medial malleolus	Anterior leg, dorsum of ankle and foot	Posterior leg, sole, and lateral border of foot
Sensory loss	Often none	As above	Often just dorsum of foot	As above
Area of pain	Medial thigh	Anterior thigh and medial kg	Often painless	Often painless
Reflex arc	Adductor reflex	Knee jerk	None	Ankle reflex
Motor defieir	Adduction of thigh	Extension of knee	Dorsiflexion and eversion of the foot (plus lateral ham strings)	Plantar flexion and inversion of foot (plus medial ham strings)
Some causative lesions	Pelvic neoplasm	Diabetes	Pressure palsy at fibula neck	Rarely injured, even in buttock
	Pregnancy	IVmoral hernia	Hip fracture or dislocation	Peroneal division more sensitive to damage
		Pregnancy	Penetrating trauma to buttock	
		Pelvic hematoma	Misplaced injection	
		Posterior abdominal neoplasm		
		Psoas abscess		

Source: Adapted from Patten, J. 1977, *Neurological Differential Diagnosis,* Springer-Vcrlag, New York.

studies and patterns of denervation also may be helpful (see Chapter 36B). In dorsal root ganglionopathics, the sensory axons degenerate, often causing loss of sensory nerve action potentials in the affected segment.

LOCALIZATION OF LESIONS IN THE TRANSVERSE PLANE

Motor Disorders

As mentioned previously, the abnormalities on neurological examination of LMN dysfunction are weakness associated with atrophy, hypotonia, fasciculations, and depressed reflexes. In contrast, corticospinal tract disease often manifests with spasticity, hyper-reflexia, and Babinski's sign (except during the early phase of spinal shock), as well as weakness that usually involves more than a single extremity. In cervical spine disease, one may find a combination ot IAIN disturbance involving the upper extremity and UMN findings in one or both lower extremities. UMN disease usually affects the distal extremity more prominently than the proximal. For example, hand and foot dexterity are usually more impaired with UMN lesions than are shoulder and hip strength.

Perhaps the most important clue suggesting a spinal origin to weakness is the pattern of weakness. Hemiparesis involving the face, arm, and leg usually localizes the problem to the brain. Proximal muscle weakness of the arms and legs with intact sensation and notmal deep tendon reflexes directs the examiner to myopathic disorders. When the pattern is distal and associated with stocking-glove sensory loss and decreased deep tendon reflexes, peripheral neuropathies are considered. In patients with paraparesis or quadriparcsis, the examiner usually is directed to the spinal cord. Monoparesis creates the greatest diagnostic confusion. Early in the development of spinal cord disease, the patient may present with unilateral leg weakness, and examination may not reveal findings in the contralateral leg or the arms.

Lesions of the cranioccrvical junction and cervical spine often present with a pattern of unilateral arm weakness before progressing to ipsilateral leg weakness, and then contralateral involvement. However, although weakness involving an ipsilateral arm and leg with sparing of the face suggests a high cervical lesion, it should be recognized that cerebral disturbances or lacunar infarction in the internal capsule or medullary pyramidal may cause this pattern of involvement. Babinski's response is a sign of corticospinal tract disease. Plantar stimulation therefore helps differentiate UMN causes from othet etiologies in patients with leg weakness.

Sensory Disturbances

Subjective sensory complaints generally precede objective sensory signs, and therefore sensory complaints without abnormal sensory signs may be the first sign of serious underlying neurological disease. One corollary is that in the absence of sensory complaints, the sensory examination is usually normal.

Dysfunction of the dorsal (or posterior) columns and of the lateral spinothalamic pathways usually causes characteristically different symptoms. Tingling paresthesias, which may be vibratory in nature, are sometimes reported below the level of a dorsal column lesion. Subjective reports of the skin being "too tight" or an extremity or trunk being "wrapped in bandages" also may be caused by dorsal column disturbances. Spinothalamic tract disturbance is often first manifested by pain that is poorly characterized and localized. It should be recognized that many of the complaints of patients with imiMinediiihii'v lesions are nut-associated with any abnormal signs early in their course, so the complaints may be dismissed inappropriately after a negative sensory examination.

Pain sensation, usually measured by pinprick, and temperature sensation are conveyed via the lateral spinothalamic tract. These pathways are somatotopically organized so that the sacral fibers are most peripheral and the cervical fibers are most central. Because a laterally placed extramedullary lesion compresses the peripheral fibers before the more centrally located fibers, a compressive lesion in the rostral spine may give rise to an apparency ascending loss of pain and temperature sensation (Adams et al. 1996). These findings underscore the importance of recognizing that a rostral lesion may give rise to a sensory level *far below the site of the compression.* In practical terms therefore when spinal cord compression is suspected, one may need to image the entire spine rostral to the sensory level to exclude a lesion above the sensory level.

Position and vibration sensation classically arc thought to be transmitted through the posterior columns. However, both modalities of sensation also probably travel in other pathways (Glendinning and Vierck 1993). Spinal cord impairment of position and vibration sensation generally arc easily evaluated. Ataxia caused by spinal lesions is not as readily recognized. Disturbances of posterior columns or possibly the spinocerebellar tracts may result in an ataxic gait. This may be particularly evident in vitamin B_{12} deficiency. Light touch is conveyed by both lateral and posterior columns and usually is not impaired as early in spinal cord disease as the more specific modalities described previously.

Several incomplete lesions of the spinal cord result in characteristic sensory signs. A hemisection of the spinal cord results in a Brown-Sequard syndrome, in which there is loss of appreciation of pain and temperature contralateral to the lesion, loss of sensation for position and vibration, and UMN paralysis ipsilateral to the lesion (Figure 27.3).

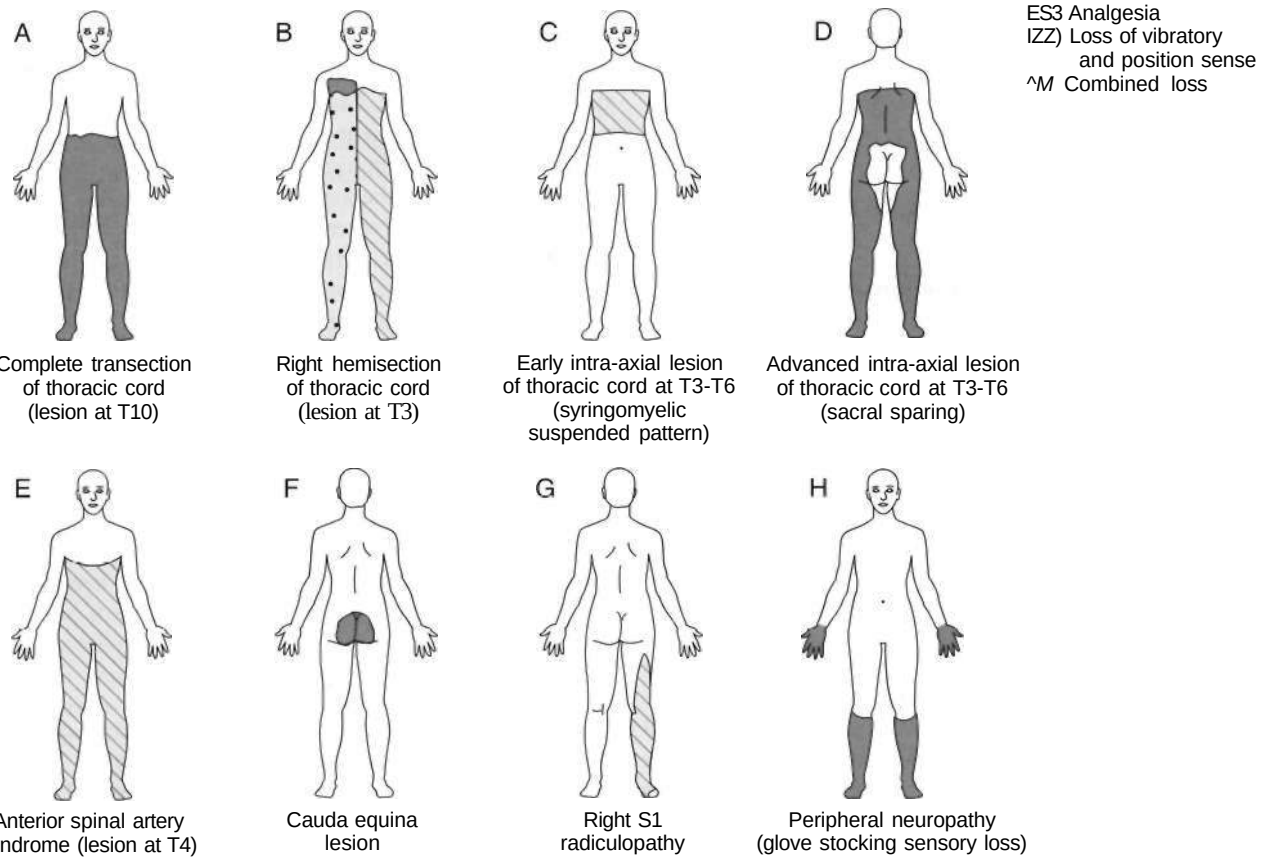

FIGURE 27.3 Characteristic sensory disturbances found in various spinal cord lesions in comparison with peripheral neuropathy.

An early intramedullary lesion such as a syrinx, intramedullary tumor, or contusion may give rise to a *dissociated sensory loss* in which damage to the decussating fibers at the level result in sensation of pain and temperature being lost or decreased, whereas the position and vibratory sensibilities remain unimpaired. Central cord lesions also may result in a suspended sensory level (see Figure 27.3). In such cases, sacral sensation is preserved until late in the course because these fibers are most peripheral in the lateral spinothalamic tracts and they tend to be involved later.

AUTONOMIC AND RESPIRATORY DISTURBANCES

Dysfunction of the spinal cord and cauda equina is often manifested as symptoms and signs of bladder, bowel, and sexual dysfunction (see Chapter 42). A high cervical cord lesion may cause respiratory compromise. Although the diaphragm, intercostal muscles, and abdominal muscles are used for normal respiration, individuals may ventilate adequately with only the diaphragm intact (see Tabic 27.1). In cases of complete cord transection above the C3 level, respiration cannot be maintained. Trauma, foramen magnum tumors, atlantoaxial dislocation, and congenital disturbances of the craniocervical junction are common causes of upper cervical spine injury,

The urinary bladder and its sphincters are innervated by (1) sympathetic nerves beginning in the intermediolateral cell column at the lumbar level (primarily LI and L2); (2) parasympathetic nerves exiting at S2-S4; and (3) somatic efferent nerves to the skeletal muscles of the external urethral sphincter exiting at S2-S4 to form the pudendal nerves. In complete transverse lesions of the cord, the bladder immediately becomes flaccid. In unilateral lesions, voluntary control of micturition is not lost. This corresponds to the clinical observation in spinal cord compression in which it is unusual to have sphincter function disturbed early when there is only unilateral or equivocal bilateral lower extremity weakness or sensory disturbance. The most common exception is when the conus medullars or sacral nerve roots arc compressed.

Immediately after acute spinal cord injury, there is often an initial period of *spinal shock,* which is often accompanied by urinary retention and overflow incontinence (as well as flaccid areflexia); Liter, a reflex (neurogenic or spastic) bladder typically develops (see Chapter 42). If the disturbance of UMN function evolves slowly, then the reflex bladder may develop without a preceding period of spinal shock and flaccid bladder. The reflex bladder is characterized by overactivity of both the detrusor muscle and the external sphincter. This causes incontinence of urine. In addition, the bladder capacity is diminished because of the detrusor contraction. The sensation of bladder distention may be lost if ascending tracts are involved. The anal reflex is often intact in cases of reflex bladder. On cystometry, the detrusor muscle demonstrates excessive contraction to small increments of fluid volume.

In contrast to the reflex bladder, when the damage occurs in the region of the conus medullaris or the cauda equina, a decentralized or autonomous flaccid bladder develops (see Chapter 42), Voluntary control over bladder function is impaired or abolished entirely. In such cases, detrusor tone is lost and the bladder distends to the point that overflow incontinence occurs. Bladder sensation is impaired. Control over the anal sphincter and the anal reflex usually is lost. A region of saddle anesthesia may be present (see Figure 27.3). Unlike the situation in the reflex bladder, cystometrography usually demonstrates diminished or absent contractions of the detrusor muscle.

The anatomical pathways subserving bowel function are similar to those controlling the urinary bladder. Spinal shock generally is associated with ileus, and a neurogenic megacolon may develop. The anal reflex usually is lost in cases of spinal shock. In lesions above the sacral level that evolve slowly, voluntary control of the sphincter ani may be lost, but in such cases, the anal reflex remains intact unless complete cord transection occurs, in which case it may be absent. In disturbances of the conus medullaris and cauda equina {nerve roots S3-S5), fecal incontinence and a flaccid anal sphincter with loss of the anal reflex may be a presenting manifestation of neurological disease. Saddle anesthesia (i.e., loss of sensation in the perianal area) is often seen in such cases. Partial impairment may be present in any of these syndromes before frank paralysis and a flaccid sphincter ensue,

Disturbances of sexual function arc common in spinal cord disease, especially in men. The descending pathways from the neocortex, limbic system, and hypothalamus course adjacent to the corticospinal tracts in the lateral funiculi. Penile erection occurs via the sacral parasympathetics {S3 and S4), the pudendal nerves, and nervi erigenres, and via inhibition of the sympathetic vasoconstrictor center located in the intermediolateral cell column at L1-L2, and then through the superior hypogastric plexus. Ejaculation is performed via the reflex arc beginning with the afferent limb arising in the genital epithelium and passing centrally via the dorsal nerve of the penis and pudendal nerve to the S3 and S4 dorsal roots. The perineal branch of the pudendal nerve is an important peripheral efferent pathway.

COMMON SPINAL CORD SYNDROMES

Spinal Shock

A complete transverse lesion of the spinal cord results in total loss of motor and sensory functions below the level of the lesion. If the lesion is slow in development, such as may occur with a benign tumor or cervical spondylosis, or if it is

incomplete, then spinal reflexes such as hyperactive deep tendon reflexes and Eabinski's signs genetally arc present. Alternatively, if the lesion is acute, a condition known as *spinal shock* ensues, in which there is temporary loss of all spinal reflex activity below the level of the lesion along with motor paralysis and sensory loss. Spinal shock is characterized by flaccid, areflexic paralysis of skeletal and smooth muscles. A complete loss of autonomic functions occurs below the level of the lesion, which results in a loss of urinary bladder tone and paralytic ileus. Sweating and piloerection also are diminished or absent below the level of the lesion. Because vasomotor tone is lost, dependent lower extremities may become edematous and temperature regulation may be a major problem. Genital reflexes such as penile erection, the cremasteric reflex, and bulbocavernosus reflexes are losr. Sensation below the level of the lesion is completely absent.

Incomplete Lesions of the Spinal Cord

Unilateral Transverse Lesion

A unilateral lesion or hemisection of the spinal cord produces a Brown-Scquard syndrome. In reality, pure unilateral lesions are rare, and therefore most clinical cases are described as a *modified* or *partial Brown-Sequard syndrome.* The clinical presentation of pure Brown-Sequard's syndrome is that of ipsilatcral weakness and loss of position and vibration below the level of the lesion, as well as contralateral loss of pain and temperature caudal to the lesion. The loss of pain and temperature usually is manifest a few segments below the level of the lesion because the decussating fibers enter the spinothalamic tract a few segments rostral to the level of entry of the nerve root. At the level of the insult, there may be a small ipsilateral area of anesthesia, analgesia, and LMN weakness because the segmental afferent and efferent pathways arc disrupted (see Figure 27.3).

Trauma such as a bullet or stab wound is probably the most common cause of a Brown-Scquard syndrome. Spinal metastases rarely present with a Brown-Sequard syndrome. In the large series of spinal metastases, fewer than 2% of patients with signs of myelopathy have a pure Brown-Sequard syndrome. Approximately 8% have greater weakness ipsilateral to the lesion and more marked pain and temperature loss contralateral to the lesion, without dorsal column signs (modified Brown-Sequard's syndrome). Radiation necrosis also has been reported to presenr with Brown-Sequard's syndrome.

Central Cord Syndrome

The central cord syndrome is caused by an jntra-axial lesion disturbing the normal structures of the central or paracentral region of the spinal cord. Such disturbances are either acute, in which case they are usually caused by hemorrhage or contusion following trauma (see Chapter 56C), or chronic, in which case they may be caused by tumor or syringomyelia. A demyelinating process occasionally may cause *a* similar syndrome, but it usually is not confused with the other more typical causes. Though clinically distinct, the presentations of these disorders share some common features. Contusions following trauma and syringomyelia often occur in the cervical spine and cervicotboracic junction. Spontaneous hematomyelia generally presents with the acute onset of severe back or neck pain followed by paralysis.

When the cervical spine or cervicothoracic junction is the site of a central cord syndrome, the upper extremities show weakness of an LMN type. Characteristically, there is loss of sensation in the upper extremities of a dissociated type, with loss of pain and temperature sensation and preservation of position and vibration sensation. This is caused by the decussating fibers destined for the spinothalamic tracts being interrupted, whereas those projecting within the dorsal columns are spared (see Figure 27.3). As a result of the laminated structure of the spinothalamic tract, sensation from the more caudal regions is preserved, with a capelike distribution of sensory loss in some patients with sacral sparing of pain and temperature sensation being the rule (Figure 27.4).

Anterior Spinal Artery Syndrome

Spinal cord infarction has been seen more frequent!) in recent years, in part because of an increased number of invasive procedures such as vascular and thoracoabdominal surgery and improved survival after cardiac arrest and hypotension. The anterior horns and anterolateral tracts are involved in this syndrome (see Chapter 57F). The thoracic vascular watershed zone at about T6 is especially susceptible. Corticospinal deficits develop below the level of the infarction; dysfunction of autonomic pathways occurs, causing loss of bowel, bladder, and sexual functions; and a sensory disturbance develops in which posterior column function remains intact and the spinothalamic tracts arc disrupted. Initially spinal shock with areflexia is expected, followed later by spasticity.

Anterior spinal artery syndrome is differentiated from acute central cord syndrome, as occurs in traumatic contusions and hematomyelia, by the sacral sensory sparing that tends to occur in the latter. Moreover, the anterior spinal artery syndrome can be differentiated from that of acute complete transverse myelopathy caused by the loss of posterior column function in the latter.

Anterior Horn and Pyramidal Tract Syndromes

Disturbances of the anterior horns and pyramidal tracts alone with sparing of the sensory functions and autonomic nervous system are seen in motor neuron disease. Clinically,

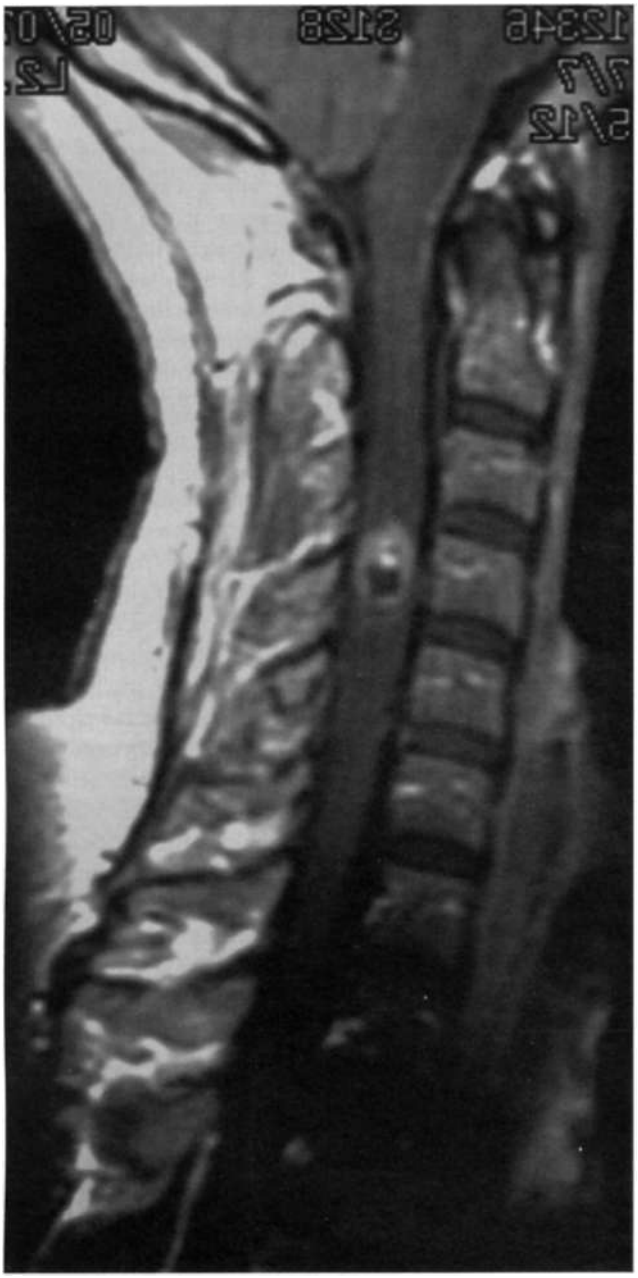

FIGURE 27.4 Magnetic resonance imaging scan of the cervical spine showing a contrast-enhancing mass. The patient presented with a capclike sensory loss to pain and temperature. Resection of the mass revealed a glioma.

one typically finds a combination of both LMN weakness with its attendant atrophy and fasciculations (and fibrillations and dcncrvation/reinnervatlon on electromyography) and upper motor weakness with spasticity, hyperrcflcxia, and Babinski's signs. Virtually diagnostic is the presence of LMN and UMN signs in the same muscle group. Alternatively, either the LMN or the UMN disturbance may predominate for months or years. Ultimately, as the LMN disease progresses, increasingly severe atrophy and evolution from hyperreflexia to hyporeflexia occur.

Combined Posterior and Lateral Column Disease

The clinical presentation of loss of posterior column and lateral column (pyramidal! (unction is that ot spastic ataxic gait. The ataxia is of a sensory type and may be bizarre in appearance. Although Friedreich's ataxia may cause such a syndrome, the classic cause for this is subacute combined degeneration associated with vitamin B_L2 deficiency.

CHARACTERISTIC CLINICAL FEATURES OF LESIONS AT DIFFERENT LEVELS

Spinal lesions at different levels often present with characteristic symptoms and signs referable to the segmental levels involved. In cases of extramedullar compression, disturbances at the segmental level (i.e., nerve root signs) usually herald the presentation. Conversely, intramedullary diseases frequently do not present with segmental disturbances but rather with tract dysfunction.

Foramen Magnum

Lesions of the foramen magnum, which include trauma, tumors, syringomyelia, multiple sclerosis, Arnold-Chiari malformation, atlantoaxial dislocation, and other bony abnormalities of the craniocervical junction, present a most challenging diagnostic problem for the clinician because symptoms are often vague or may be distant from the foramen magnum. Occipital or neck pain, often increased by neck movement, is a common initial manifestation. The pain may radiate also into the shoulders or the ipsilateral arm. In the latter situation, the pain may be similar to that of cervical spondylosis. The neurological signs associated with foramen magnum tumors also may be perplexing. Cranial nerve symptoms and signs are inconstant; nystagmus, often downbeating, impaired sensation over the upper face (caused by involvement of the descending tract of cranial nerve V), and dysarthria, dysphonia, and dysphagia arc present in some patients. Motor system involvement characteristically presents as spastic weakness. The corticospinal tract compression causes weakness that typically begins in the ipsilateral arm and is loll owed by weakness of the ipsilateral leg, spreading to the contralateral leg and then the arm,

Alternatively, foramen magnum tumors may cause signs of LMN weakness, atrophy, and depressed reflexes in the arms and hands. The mechanism of this LMN disturbance well below the level of the tumor is uncertain but possibly is secondary to circulatory disturbances affecting the (descending) distribution of the anterior spinal artery.

Sensory disturbances consisting of pain and numbness are early manifestations of foramen magnum tumors. Pain and paresthesias affecting the same upper extremity first

involved by spastic weakness is an early finding. The sensory disturbances in these patients are often of the dissociated type so patients suffer from loss of pain and temperature sensation but have preserved tactile sensation. In addition, a suspended sensory loss also has been reported in some cases and vibratory sensory loss over the clavicles in others. This pattern of sensory loss may be caused by a secondary syrinx, which may direct attention away from the causative lesion at the cervicomedullary junction. Magnetic resonance imaging (MRI) has become the test of choice for imaging the craniocervical junction.

Upper Cervical Spine

Compressive lesions of the upper cervical spine have similar clinical characteristics to those arising at the foramen magnum. Pain in the neck, occipital region, or shoulder is a common presenting complaint. The second cervical root innervates the posterior aspect of the scalp, which explains the pattern of radicular pain. If the compression is at the third or fourth cervical level, radicular pain may be projected to the neck or top of the shoulder. When pain does occur, it is usually provoked by neck movements, resulting in marked limitation of head turning and nodding.

With progressive compression, upper extremity weakness usually becomes apparent on the side of pain. The weakness may be of a UMN or LMN type. Some patients therefore may have spasticity and hyper-reflexia and others may have atrophy and hyporeflexia of a portion or the entire upper extremity including the hand. When UMN findings develop in the ipsilateral leg, a spinal hemiplegia is present. Weakness may then progress to the contralateral lower extremity and then the contralateral upper extremity.

Lower Cervical and Upper Thoracic Spine

Spinal cord and root compressions at the levels of C5-T1 most frequently betray their presence by radicular symptoms at the affected level in the shoulder or upper extremity in the form of pain and later reflex, motor, and sensory disturbances. With lesions at the C4-C6 level, pain and sensory disturbances are frequently reported along the radial aspect of the arm, forearm, and thumb (see Table 27.2). With intramedullary neoplasms, pain is also common at these levels, but the localization is usually more diffuse and less typically radicular.

At the C7-T1 level, pain and sensory symptoms often are localized to the ulnar aspect of the arm, forearm, and hand. Tumors at the Tl and T2 levels often cause pain to radiate into the elbow and hand, together with sensory complaints along the ulnar border of the hand. As at other locations, intramedullary neoplasms usually give rise to more diffuse symptoms, which are often bilateral. Conversely, extramedullar)' compression often presents with exquisite localizing symptoms.

Weakness usually follows pain, particularly at the affected segmental level. As might be expected based on the myotomal map of the upper extremity, intramedullary and extra medullary lesions at the C4-C6 level show a predilection to involve the muscles in the shoulder and upper arm (see Table 27,2), Atrophy and weakness of the hand can rarely occur with lesions at the C4-C6 level. This may be caused by vascular factors affecting the lower cervical segments. Such a pattern of weakness and atrophy is usually caused by a lesion at the C7-T2 level.

The pattern of extremity weakness may be a guide in distinguishing intramedullary from extramcdullary disorders. Although exceptions are encountered, extramedullary lesions tend to affect the ipsilateral upper and lower extremity before involving the contralateral side. In contrast, intramedullary lesions may involve both upper extremities before the lower extremities are affected or show bilateral arm and leg involvement from the onset.

The deep tendon reflexes are helpful in localizing the segmental level of involvement in the cervical spine. Disease at the C5-C6 level is often associated with depressed biceps (C5), brachioradialis reflex (C6), or both (see Table 27.2). Alternatively, one may encounter depressed biceps and brachioradialis reflexes associated with a hyperactive triceps reflex if there is a compressive myelopathy at the C5-C6 level. Suggestive of cervical spondylosis is a depressed brachioradialis (C6) reflex with hyperactive finger flexors (C8-T1), indicaring a C6 radiculoneuropathy with myelopathy; neoplasms or other diseases at the C6 level may cause a similar clinical presentation. When the lesion is at the C7 level, the triceps reflex may be depressed.

With lesions at C8 and T1, the finger flexor response may be impaired. Hoffmann's sign is performed by dorsiflexing the patient's wrist and then flicking the distal phalanx of the middle finger with the examiner's thumb. The patient's middle finger is thus flexed and suddenly extended. When Hoffmann's sign is present, this maneuver is followed by reflex flexion of the patient's thumb and other fingers. When present bilaterally, Hoffmann's sign is usually an indication of hyperactive deep tendon reflexes. Although disease of the pyramidal pathways may be responsible, healthy individuals with hyperactive reflexes may have bilateral Hoffmann's signs such as in the case of anxiety, hyperthyroidism, and stimulatory drugs. When Hoffmann's sign is present unilaterally, it usually signifies disease of the nervous system.

Thoracic Levels

The thoracic dcrmatomal landmarks that guide the examiner ro the level of involvement are the nipple (T4),

Table 27.6: Differentiation of con us lesions from cauda equina lesions

	Cotius medullar is	*Cauda equina*
Spontaneous pain	Unusual and not severe; bilateral and symmetrical in perineum or thighs	Often very prominent and severe, asymmetrical, radicular
Motor findings	Not severe, symmetrical Fibrillary twitches are rare	May be severe, asymmetrical, fibrillary twitches of paralyzed muscles arc common
Sensory findings	Saddle distribution, bilateral, symmetrical, dissociated sensory loss (impaired pain and temperature sensibility with sparing of tactile sensibility)	Saddle distribution, may be asymmetrical, no dissociation of sensor; loss
Rdk'\ dump's	Lpiconus: only Achilles reflex absent Conns: Achilles and patellar present	Patellar and Achilles reflexes may be absent
Sphincter disturbance	Early and marked (both urinary and fecal incontinence)	Late and less severe
Male sexual function	Impaired early	Impairment less severe
Onset	Sudden and bilateral	Gradual and unilateral

Source: Modified with permission from Dejong, R. N. 1979, *The Neurologic Examination,* 4th ed, Harper & Row, Hagerstown, Md; Haymaker, W. 1969, *Bmg's Local Diagnosis in Neurological Disease,* 15th ed, Mosby, St. Louis.

the umbilicus (T10), and the inguinal ligament (LI). Pain or sensory alterations in a radicular distribution are localized to a specific dermatome using these levels as points of reference. The relatively small vertebral canal and the vascular watershed area of the spinal cord at about T6 in the thoracic region make the thoracic spinal cord extremely vulnerable to injury from compression. Consequently, the temporal course of symptoms of cord compression is often shorter in this region than elsewhere in the spine. Thus pain often evolves rapidly into weakness, sensory loss, and reflex abnormalities caudal to the lesion. Sphincter disturbances ultimately develop.

Conus Medullaris and Cauda Equina

Lesions of the cauda equina and conus medullaris (Table 27.6) cause similar symptoms and signs including local, referred, and radicular pain, sphincter disturbances, loss of buttock and leg sensation, and leg weakness. Although it may be relatively easy to establish the level of a single radiculopathy based on sensory, motor, and reflex changes, it is much more difficult to assign the cause and localization when several lumbosacral levels are involved. In such situations, one must consider the possibility of a lower spinal cord lesion or a cauda equina syndrome. Although there has been a long effort to differentiate conus medullaris lesions from those of the cauda equina, it is not always possible to accurately discriminate between them. Although rare in its pure form, the conus medullaris syndrome presents with sphincter disturbances, saddle anesthesia (S3-S5), impotence, and absence of lower extremity abnormalities. If the cauda equina is involved, patients may experience difficulty with external rotation and extension of the thigh at the hip, flexion of the knee, and weakness of all muscles below the knee.

DISTINGUISHING INTRAMEDULLARY FROM EXTRAMEDULLARY LESIONS

The earlier sections of this chapter describe several features that help distinguish between intramedullary lesions and extra medullary compressive lesions of the spinal cord. However, as stressed earlier, this may be a vexing clinical problem that ultimately requires elucidation by imaging techniques. The explanation for this clinical experience has been provided by clinicopathological studies of extra-medullary spinal neoplasms. It has been demonstrated that extramedullary compression can cause ischemia and demyelination in the posterior and lateral column, with relative sparing of the anterior columns regardless of the location of the extramedullary tumor. Both coup and contrccoup injuries occur in the spinal cord. The areas of infarction and demyelination are often deep and do not follow a specific pattern. In some instances, the pathological findings are more marked ipsilatcral to the tumor, and in other cases, they are primarily contralateral to the mass. It follows therefore that stereotypical clinical patterns of evolution cannot be expected.

CLASSIFICATION OF DISEASES AFFECTING THE SPINAL CORD

This chapter emphasizes the clinical pathophysiology of spinal cord disorders. Table 27.7 lists a classification of disorders that may cause a spinal cord syndrome; discussion of specific diseases can he found elsewhere in

Table 27.7: Differential diagnosis of diseases affecting the spinal cord

Compressive lesions
- Non-neoplastic
  - Trauma
  - Spondylosis
  - Intervertebral disc herniation
  - Spinal stenosis
  - Infectious disorders (e.g., abscess, tuberculosis)
  - Inflammatory (e.g., rheumatoid arthritis, ankylosing spondylitis, sarcoid)
  - Spinal hemorrhage
  - Syringomyelia
  - Congenital disorders
  - Arachnoid cysts
  - Paget's disease
  - Osteoporosis
- Neoplastic
  - Epidural
  - Intradural extramedullar (e.g., meningioma, neurofibroma, and leptomeningeal metastasis)
  - Intramedullary

Noncompressive myelopathies
- Demyelinating (e.g., multiple sclerosis, acute disseminated encephalomyelitis)
- Viral myelitis (e.g., roster, acquired immunodeficiency syndrome-related myelopathy, human T-lymphotropic virus type 1)
- Vitamin B12 deficiency and other nutritional deficiencies
- Infarction
- Ischemia and hemorrhage resulting from vascular malformations
- Spirochetal diseases (syphilis and Lyme disease)
- Toxic myelopathies (e.g., radiation induced)
- Autoimmune diseases (e.g., lupus, Sjogren's syndrome)
- Paraneoplastic
- Neuronal degenerations
- Acute and subacute transverse myelitis of unknown cause

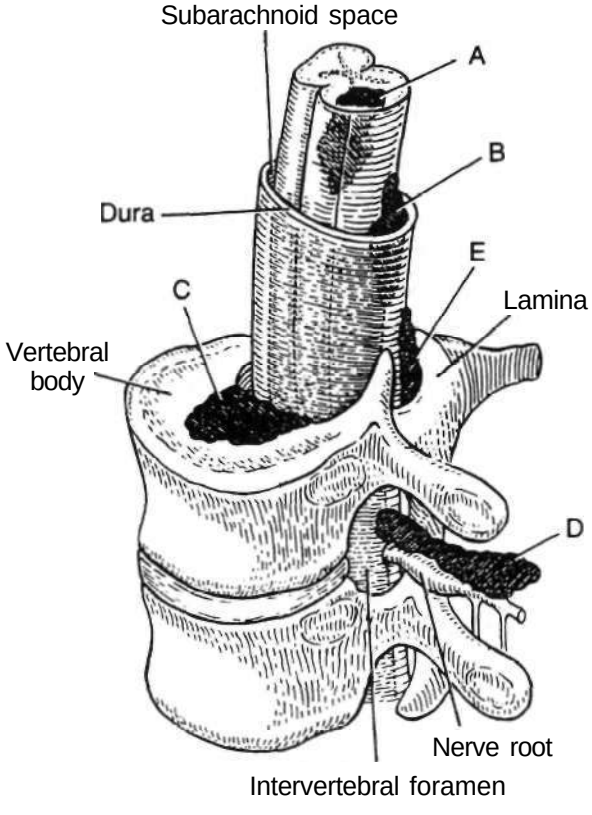

FIGURE 27.5 Anatomical locations of spine metastases. (A) Intramedullary metastasis is located within the spinal cord. (B) Leptomeningeal metastasis is in the subarachnoid space and is extra medullary and intradural. Epidural metastases arise from the extension of metastases located in one of the adjacent structures: (C) vertebral column; (D) paravertebral spaces via the intervertebral foramina; or rarely, (E) the epidural space itself. As these epidural metastases grow, they compress adjacent blood vessels, nerve roots, and the spinal cord, resulting in local and referred pain, radiculopathy, and myelopathy. (Reprinted with permission from Byrne, T. N. 1992, "Spinal cord compression from epidural metastases," N *Engl J Med*, vol. 327, pp. 615.)

this book. Diseases arc classified according to their etiology and location. With the availability of MRI, this classification permits the clinician to consider the differential diagnosis before and after the imaging has been obtained. Furthermore, because compressive lesions may be surgical emergencies, this classification considers the therapeutic nature of many of the diseases that must be considered.

METASTATIC EPIDURAL SPINAL CORD COMPRESSION

Metastatic epidural spinal cord compression (MESCC) deserves special comment because it affects approximately 20,000 patients with cancer in the United Stares annually. Figure 27.5 demonstrates the location of tumors of the spine, distinguishing among intramedullary, extramedullar, intradural, and extradural tumors. As with **other** causes of spinal cord compression, the major presenting clinical signs and symptoms of MESCC are pain, weakness, sensory loss, and autonomic disturbance. In approximately 95% of adults and 80% of children, progressive axial, referred, radicular, or all three kinds of pain are the most common initial complaint of both vertebral metastasis and MESCC, Because the neurological prognosis depends directly on the level of neurological function at the time of initiation of therapy, there is a great incentive to make an early diagnosis while the patient is still ambulatory.

The imaging test of choice in evaluating patients for MESCC is MRI when available in a timely fashion. Alternatively, myelography should be performed when management is delayed by inability **to** obtain an MRI, in patients unable to undergo MRI (e.g., those with pacemakers and pain precluding recumbency) or when a technically adequate **MRI** cannot be obtained. The mainstays of treatment include corticosteroids, radiotherapy, and, in selected patients, surgical decompression of the cord. Approximately 80% of patients who arc ambulatory at the initiation of radiotherapy remain so at the end of treatment, whereas fewer than 10% who are paraplegic at the beginning of radiotherapy recover ambulation.

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Chapter 28
Proximal, Distal, and Generalized Weakness

David C. Preston, Barbara E. Shapiro, and Michael H. Brooke

Muscle weakness may be due to disorders of the central or peripheral nervous system (CNS and PNS, respectively), the neuromuscular junction, or the muscle. The neurological examination allows separation of weakness arising from these different locations. If the pattern of weakness is characteristic of upper motor neuron (UMN) weakness {i.e., weakness of the extensors of the upper limbs and the flexors of the lower limbs), together with hyper-reflexia and an extensor plantar response, weakness is clearly of CNS origin. If there is clear sensory impairment, the weakness is likely to arise from dysfunction of the peripheral nerves, nerve roots, or CNS. If there is marked fatigue and weakness involves the extraocular, bulbar, and proximal upper limb muscles, the diagnosis is likely to be myasthenia gravis.

If weakness is not accompanied by sensory loss, marked fatigue, or signs of CNS involvement, then it is likely to be due to a disorder of the motor unit. The motor unit includes the anterior horn cell, the motor nerve, rhe neuromuscular junction, and the muscle itself. This chapter concentrates on disorders of the motor unit, discussing disorders of the neuromuscular junction and PNS as they enter into the differential diagnosis.

The clinical features of motor unit disorders arc determined mostly by which muscles are weak. Muscle weakness changes functional abilities that are more or less specific to the muscle groups affected. Recognizable patterns of symptoms and signs often allow a reasonable estimation of the anatomical involvement. Recognizing these patterns is the first step in the differential diagnosis of weakness, as certain disorders have a predilection for certain muscle groups. This chapter begins with a discussion of symptoms of muscular weakness, depending on which muscle groups are affected. This is followed by a discussion of the bedside and functional physical examinations and comments on laboratory tests often employed in patients with muscle weakness. The chapter concludes with an approach to the diagnosis of muscle weakness, based on which muscle groups are weak, whether the muscle weakness is constant or fluctuating, and whether the disorder is acquired or inherited.

SYMPTOMS OF WEAKNESS

As muscles begin to weaken, symptoms depend more on which muscles are involved than on the cause of involvement. A complicating factor in evaluating weakness is the difference in the patient's interpretation of the word *weak.* Although physicians use the word to denote a loss of muscle power, the patient may use the word more loosely. Even more confusing, many people use the words *numb* and *weak* interchangeably. Thus the complaint of weakness should not be taken at face value but should be questioned until it is clearly shown to mean a loss of muscle strength. If the patient has no objective weakness when examined, the clinician must rely on the history. Patients with weak

muscles have a fairly stereotypical set of symptoms depending on which muscle groups are weak (see the following sections). The patient whose weakness is caused by depression or malingering will have much more vague symptoms, and if leading questions are avoided, the stereotypical symptoms of weakness are seldom volunteered. Instead, patients make statements such as, "I have no strength to do the housework,[1]" "I just can't do the task," and "I can't climb the stairs because I get so tired and have to rest." When ptcsscd regarding these symptoms, it soon becomes apparent that specific details are lacking. Patients who cannot get out of a low chair because of real weakness explain exactly how they have to maneuver themselves into an upright position (e.g., pushing on the chair arms, leaning forward in the seat, and bracing their hands against the furniture). The examiner should avoid providing patients with the details for which they are searching. Asking patients whether they have to push on the arms of the chair to stand up provides patients with information that can be used later in response to the questions of baffled successive examiners. In addition, it is often difficult to differentiate true muscle weakness from apparent weakness that accompanies tendon or joint contractures or that occurs secondary to pain. For example, patients with primary orthopedic conditions often complain of weakness. However, in these situations, pain with passive or active motion is often a prominent part of the symptoms.

In evaluating weakness, the first key task is to discern which muscle groups are affected. In this regard, it is helpful to divide the symptoms of weakness into the following body regions: ocular; facial and bulbar; neck, diaphragm, and axial; proximal upper extremity; distal uppet extremity; proximal lower extremity; and distal lower extremity.

Ocular Muscles

Extraocular muscle weakness results in ptosis and/or diplopia. Drooping of the eyelids may be noticed by the patient when looking in the mirror or may be pointed out by family and friends. It is important to keep in mind that older patients occasionally develop ptosis as a consequence of aging (i.e., partial dehiscence of the levator muscles) or as a consequence of ocular surgery (e.g., lens implanrs for cataracts). To differentiate between acute and chronic ptosis, it is often helpful to look at prior photographs or because the ocular myopathies are often familial to look at family photographs. Bilateral ptosis may result in compensatory backward tilting of the neck to look ahead or upward. Rarely, this may lead to neck pain and fatigue as the prominent symptoms. In addition, true ptosis often results in compensatory contraction of the frontalis muscles to lessen the ptosis, resulting in a characteristic pattern of a droopy eyelid with prominent contraction and furrowing of the frontalis muscle above. Weakness of extraocular muscles may result in diplopia. However, mild diplopia may cause only blurring of vision, sending the patient to the ophthalmologist for new eyeglasses. It is also worth asking the patient if closing one eye corrects the diplopia, because neuromuscular weakness is not among the causes of monocular diplopia.

Facial and Bulbar Muscles

Facial weakness is usually experienced by the patient as a feeling of stiffness or sometimes as a twisting or altered perception in the face (note that patients often use the word *numbness* in describing facial weakness). Drinking through a straw, whistling, and blowing up balloons are particularly difficult tasks and may be sensitive tests for facial weakness, parricularly when such weakness dates from childhood. Acquaintances may notice that the patient's expression is somehow changed. A pleasant smile may turn into a snarl because of weakness of the levator anguli oris muscles in myasthenia gravis. In lower facial weakness, patients may have difficulty with drooling and retaining their saliva, often requiring them to carry a tissue in their hand (so-called "napkin sign," which often accompanies bulbar involvement in amyotrophic lateral sclerosis |ALS|). A common observation in mild long-standing facial weakness, for instance, in facioscapulohumeral (FSH) muscular dystrophy, is a tendency for the patient to sleep with the eyes open from weakness of the orbicularis oculi. Weakness of masticatory muscles may result in difficulty chewing, sometimes with a sensation of fatigue and discomfort, as may occur in myasthenia gravis. Pharyngeal, palatal, and tongue weakness disturbs speech and swallowing. A flaccid palate is associated with nasal tegurgitation, choking spells, and aspiration of liquids. Speech may become slurred, nasal, or hoarse. In contrast to central lesions, there is no problem with fluency or language function.

Neck, Diaphragm, and Axial Muscles

Neck muscle weakness is first noticed in situations in which the patient is called on to stabilize the head. Riding as a passenger in a car when the brake or the accelerator is used, particularly in an emergency situation, may be disconcerting for the patient with neck weakness because the head tocks forward or backward. Similarly, when the patient is stooping or bending forward, weakness of the posterior muscles may cause the chin to fall on the chest. A patient with neck flexion weakness often notices difficulty lifting the head off the pillow in the morning. As neck weakness progresses, patients may develop the L'dtopped head" syndrome, in which they can no longer extend the neck and their chin rests against the chest (Figure 28.1).

FIGURE 28.1 Dropped head syndrome. In severe weakness of the neck extensor muscles, patients can no longer extend the neck and their chin rests against the chest.

This posture leads to several secondary difficulties, especially with vision and swallowing.

When diaphragm muscles weaken, patients often develop shortness of breath, especially when lying flat or with exertion, and these symptoms can be mistaken for lung or heart disease. Severe diaphragmatic weakness leads to hypoventilation and carbon dioxide retention. This may first manifest as morning headaches and/or vivid nightmares. Latet, hypercapnia results in sedation and a depressed mental state.

Rarely, axial and trunk muscles can be involved early in the course ol a neuromuscular disorder. Weakness ol the abdominal muscles may make sit-ups impossible. Focal weakness of the lower abdominal muscles results in an obvious protuberance that superficially mimics an abdominal hernia. Patients with weakness of the paraspinal muscles are unable to maintain a straight posture when sitting or standing as compared to lying on the bed (so-called "bent spine" syndtome).

Proximal Upper Extremity

A feeling of tiredness is often the first expression of shoulder weakness. The weight of the arms is sufficient to cause fatigue. Eatly on, the patient expetiences fatigue on performing sustained tasks with the hands held up, especially over the head. The most problematic activities include painting the ceiling, shampooing ot combing the hair, shaving, or simply trying to lift an object off a high shelf.

Distal Upper Extremity

Hand and forearm weakness is easily noticed because it interferes with so many common activities of daily living. Difficulty with activities that require dextetity is often noticed first, such as buttoning and using a zipper. With further decreased hand strength, other activities are affected, especially opening a jat, turning on a faucet or the car ignition, using a key, holding silvetware, writing, or opening a car door.

Proximal Lower Extremity

Weakness of the proximal lower extremity is often responsible for the earliest symptoms experienced by patients who develop weakness. Patients notice that they have difficulty arising from the floor or horn a low chair and have to use the support of the hands ot knees. Getting out of a bath or a toilet without handrails is particularly difficult. Older patients may interpret this as arthritis or some similar minor problem. Walking becomes clumsy, and the patient may stumble. In descending stairs, people with quadriceps weakness tend to keep the knee locked and stiff. If the knee bends slightly as the weight of the body is transferred to the lower stair, the knee may collapse. Greater problems coming down staits than going up suggest quadriceps weakness, whereas the reverse is true for hip extensor weakness. Once patients with hip-girdle weakness are up and on level ground, they feel more secure. Howevct, others will often notice an obvious change in their gait. Patients with hip-girdle weakness often develop a waddling gait, because weakness of the hip abductors of the weight-bearing leg results in the hip falling as the patient walks (a *Trendelenburg* gait).

Distal Lower Extremity

Weakness of the distal lower extremity is most often manifested by symptoms of the antetiot compartment (i.e., peroneal) muscles. Weakness of the anterior tibial and ankle evertor muscles often results in tripping, even over small obstacles, and an increased tendency to sprain the ankle repeatedly. If the weakness becomes severe, a footdrop is noted, and the gait assumes a slapping quality. To compensate for a dropped foot, patients must raise their knee higher when they walk, so the dropped ankle and toes cleat the floor (i.e., steppage gait). Weakness of both anterior and postetiot muscles of the lower leg often makes the stance unstable, which causes the patient to complain of poor balance. Isolated weakness of the posterior calf makes standing on tiptoes impossible.

BEDSIDE EXAMINATION OF THE WEAK PATIENT

The neurological examination of patients with muscle weakness is the same as that used for patients with other

neurological problems. However, special attention to the observation and functional evaluation of the patient are particularly rewarding in the patient with weakness.

Observation

It is useful to spend a few moments observing the patient and noting natural posture and motion. When patients, particularly children, are aware that they arc being examined, they often concentrate on performing as normally as possible. When unaware of scrutiny, their posture and movements may be more natural. At one time or ::.n(>iikT, wc ha\e heard the parents' exasperated cry, "He never does it that way at home." For example, ptosis may be obvious on inspection of the head and neck. The more severe the ptosis, the greater is the patient's tendency to throw the head backward. The eyebrows are elevated and the forehead is wrinkled in an attempt to raise the upper lids. This is sometimes so successful that ptosis is apparent only when the examiner smooths out the wrinkled forehead and allows the eyebrows to assume a more normal position, Psychogenic ptosis is easy ro detect because raising of the lower lid (due to contraction of both parts of the orbicularis oculi muscle, i.e., blepharospasm) accompanies the lowered upper lid.

Weakness of the face that has been present since childhood may give a smooth, unlined appearance to the adult face. In addition, facial expression is diminished or altered. A smile may become a grimace or snarl, with eversion of the upper lip. The normal blink may be slowed or eyelid closure may be incomplete so the sclera is always visible. The normal preservation of the arch of the upper lip may be lost, and the mouth may assume either a tented or a straight-line configuration. Actual wasting of the facial muscles is difficult to see, but temporal and massctcr atrophy produces a characteristic scalloped appearance above and below the cheekbone. Because the hairstyle may be rearranged to cover the wasting, the examiner should make a conscious effort to check the upper portion of the face. The tongue should be inspected for atrophy and fasciculations. This is best accomplished by inspecting the tongue at rest with the mouth open looking for random, irregular twitching movements of fasciculations. When the tongue is fully protruded, many patients will have some normal quivering movements. It is wise to diagnose fasciculations of the tongue only when atrophy is associated,

Facial weakness causes the normal labial sounds (that of *p* and *b)* to be softened. The examiner with a practiced car can detect other alterations of speech. Lower motor neuron (LMN) involvement of the palate and tongue gives the speech a hollow, nasal, echoing timbre, whereas UMN dysfunction causes the speech to be monotonous, forced, and strained. Laryngeal weakness may also be noticed in speech when the voice becomes harsh or brassy, often associated with the loss of the glottal stop {the small sound made by the larynx closing, as at the start of a cough).

Weakness of the shoulder muscles causes a characteristic change in posture. Normally, the shoulders are braced back by the tone of the muscles, so the thumbs tend to face forward when the arms are held by the side. As the shoulder muscles lose their tone, the point of the shoulder rotates forward. This forward rotation of the shoulder is associated with a rotation of the arm, so that the backs of the hands now face forward. Additionally, the loss of tone causes a rather loose swinging movement of the arms in normal walking. When shoulder weakness is severe, the patient may fling the arms by using a movement of the trunk, rather than lifting the arms in the normal fashion. In the most extreme example, the only way the patient can get the hand above the head is to use a truncal movement to throw the whole arm upward and forward so the hand rests on the wall, and then to creep the hand up the wall using finger movements.

Atrophy of the pectoral muscles leads to the development of a horizontal or upward sloping of the anterior axillary fold. This is particularly seen in FSH muscular dystrophy,

The examiner may observe winging of the scapula, a characteristic finding in weakness of muscles that normally fix the scapula to the thorax {i.e., the serratus anterior, rhomboid, or trapezius). As these muscles become weak, any attempted movement of the arm causes the scapula to rise off the back of the rib cage and protrude like a small wing. The arm and shoulder may be thought of as a crane: The boom of the crane is the arm and the base is the scapula. Obviously, if the base is not fixed, any attempt to use the crane results in the whole structure falling over. This is how it is with attempts to elevate the arm; the scapula simply pops off the back of the chest wall in a characteristic fashion. In the most usual type of winging, the entire medial border of the scapula protrudes backward. In some diseases, particularly FSH muscular dystrophy, the infero-medial angle juts out first, and the entire scapula rotates and rides up over the back. This is often associated with a trapezius hump, in which the middle part of the trapezius muscle, in the web of the neck, is mounded over the upper border of the scapula (Figure 28.2). A word of caution pertains to the examination of the slender person or a child, in whom a prominent shoulder blade is often seen. The shoulder configuration returns to normal, however, when the individual attempts to use the arm forcibly, as in a push-up.

Muscle Bulk **and** Deformities

The examination of muscle bulk, looking both for atrophy and hypertrophy, is an important part of the neuromuscular examination. Prominent muscle wasting usually accompanies neurogenic disorders associated with axonal loss. However, severe wasting can also be seen in chronic

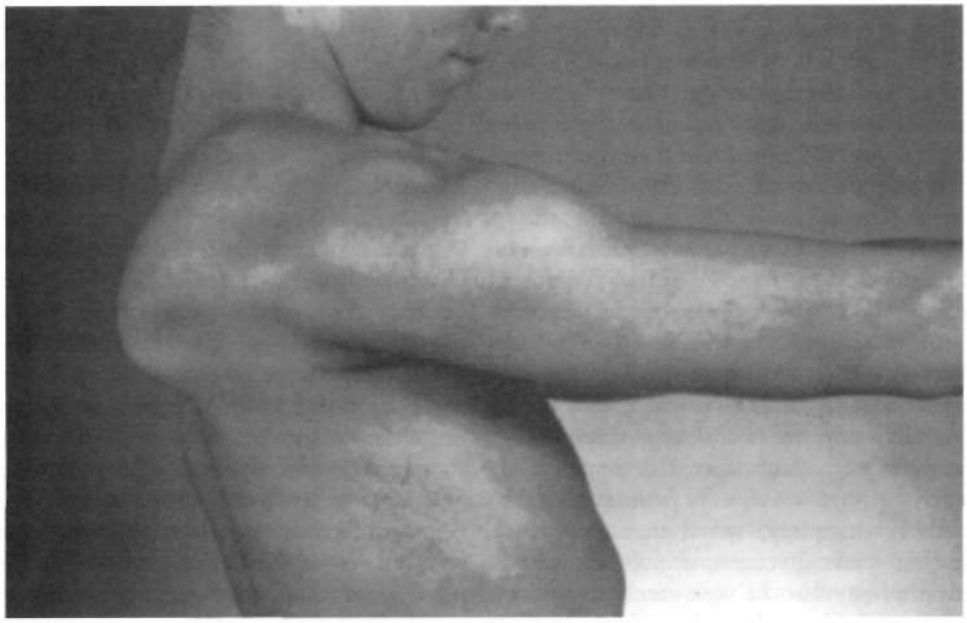


FIGURE 28.2 The scapular winging of facioscapulohumeral muscular dystrophy is distinguished by the prominent protrusion of the inferior medial border of the scapula. When viewed from the front, the elevation of the scapula under the trapezius muscle produces the trapezius hump.

myopathic conditions. Wasting is most often best appreciated in the distal hand and foot muscles and around bony prominences. In the upper extremity, wasting of the intrinsic hand muscles produces the characteristic claw hand, in which the thumb rotates outward so that it lies in the same plane as the fingers; the interphalangeal joints are slightly flexed and the metacarpophalangeal joints are slightly extended (the simian hand). Wasting of the small muscles leaves the bones easily visible through the skin, resulting in the characteristic guttered appearance of the back of the hand. In the foot, one of the easier muscles to inspect is the extensor digitorum brevis, a small muscle on the lateral dorsum of the foot that helps to dorsiflex the toes (Figure 28.3). It often wastes early in neuropathies and anterior horn cell disorders. In myopathic conditions in which proximal muscles are affected more than distal muscles, the extensor liis'jtoiuni brevis may actually hypertrophy to try to compensate for weakness of the long toe dorsiflexors above.

Muscle mass of the leg is so variable among people that it is sometimes difficult to decide whether the muscles are wasted. Any marked asymmetry indicates an abnormality, but distinguishing a slender thigh from quadriceps muscle atrophy is often difficult. One way to try to distinguish these conditions is to ask the patient to tighten the knee as firmly as possible. The firm medial and lateral bellies of the normal quadriceps that bunch up in the distal part of the thigh just above the knee fail to appear in the wasted muscle. The same technique may be used to evaluate anterior tibial wasting. In a severely wasted muscle, a groove on the latetal side of the tibia (which should be filled by the anterior tibial muscles) is apparent. A moderate degree of wasting is difficult to distinguish from a thin leg, but if the patient is asked to dotsiflcx the foot, the wasted muscle fails to develop the prominent belly seen in a normal muscle.

Abnormal muscle hypertrophy is uncommon but may be a key finding when present. Beyond the expected increase in muscle bulk that accompanies exercise, generalized muscle hypertrophy is seen in patients with myotonia congenita

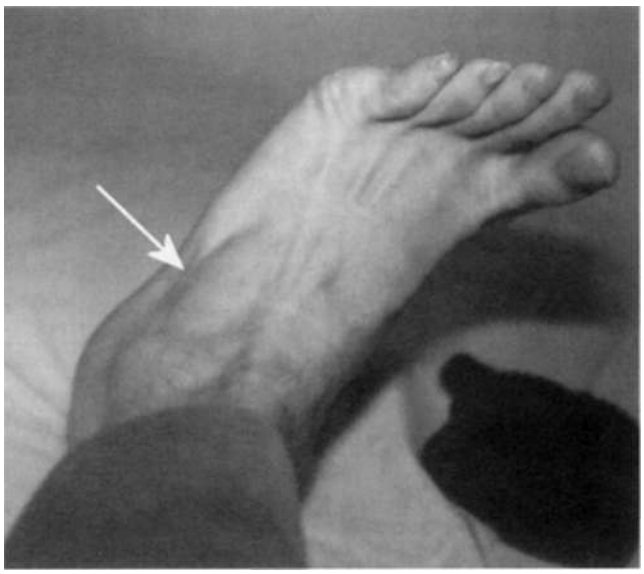


FIGURE 28.3 Extensor digitorum brevis (EDB) muscle *{arrow)* is a small muscle on the lateral dorsum of the foot, which helps dorsiflex the toes. It often wastes early in neuropathic conditions but may become hypcrtrophicd in proximal myopathic conditions.

and paramyotonia congenita, giving them the appearance of weight lifters. Hypertrophy is a common finding in the rare syndrome of acquired ncuromyotonia, in which the continuous discharge of motor axons results in the muscle effectively exercising itself. Exceptionally, hypertrophy can be seen in chronic denervating disorders, especially in the posterior calf muscle in SI radiculopathies. Electromyography (EMG) of these patients often reveals spontaneous discharges in these muscles (usually complex repetitive discharges) as a consequence of the chronic denervation. In contrast, there are conditions in which muscle hypertrophy is not from true muscle enlargement but from infiltration of fat, connective tissue, and other material (i.e., pseudohypertrophy). Focal hypertrophy may be seen in calf muscles of patients with Duchenne's and Becker's muscular dystrophy, as well as in patients with the limb-girdle muscular dystrophies, spinal muscular atrophies (SMA), and in some glycogen storage disorders. Similarly, hypertrophy may also be seen rarely in sarcoidosis, cysticercosis, amyloidosis, hypothyroid myopathy, and focal myositis. Palpable masses in muscles may be seen with muscle tumors, ruptured tendons, or muscle hernias.

Several bony deformities are often important clues in neuromuscular conditions. Proximal and axial muscle weakness often leads to scoliosis. Intrinsic foot muscle weakness, present from childhood, often leads to the characteristic foot deformity of pes cavus, in which the arch is high, the foot is foreshortened, and hammer toes, where the toes are cocked up (Figure 28.4). Pes cavus is a sign that weakness has been present at least since early childhood and implies a genetic disorder in most patients. Likewise, a high-arched palate often develops from chronic neuromuscular weakness present from childhood,

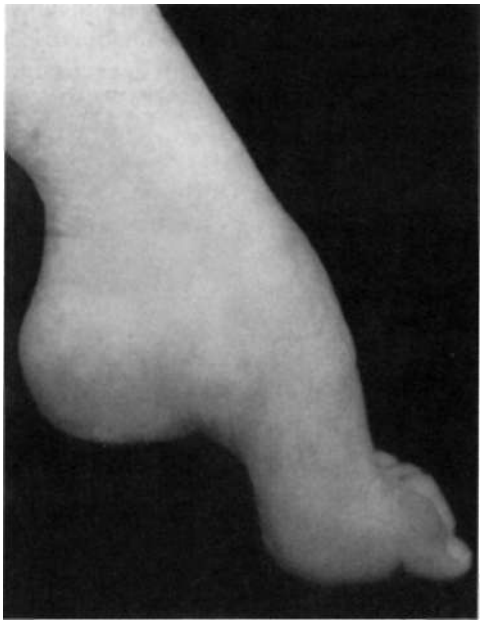


FIGURE 28.4 Pes cavus is caused by intrinsic foot muscle weakness present as a child develops. It is recognized as a high arch, foreshortened foot, and hammer toes. It is often a sign that weakness has been present since early childhood and implies an inherited disorder in most patients.

Muscle Palpation, Percussion, and Range of Motion

Palpation and percussion of muscle provide additional information. Fibrotic muscle may feel rubbery and hard, whereas denervated muscle may separate into separate strands that can be rolled under the fingers. Muscle in inflammatory myopathies or rheumatologic conditions may be tender to palpation, but severe muscle pain on palpation is unusual. An exception to this is the patient experiencing an acute phase of viral myositis or rhabdomyolysis, whose muscles may be very sensitive to either movement or touch. Percussion of muscle may produce the phenomenon of myotonia, in which a localized contraction of the muscle persists for some seconds after percussion. This is best noted percussing the thenar eminence and watching for a delayed relaxation of the thumb abductors. This phenomenon, which is characteristic of myotonic dystrophy and myotonia congenita, is to be distinguished from myoedema, which is found occasionally in patients with thyroid disorders and other metabolic problems. In myoedema, the percussion is followed by the development of a dimple in the muscle, which then mounds to form a small hillock.

In addition to its diagnostic value, the presence of muscle contracture across a joint may cause disability, even in the absence of weakness. Thus an evaluation of range of morion at major joints is an important part of the cluneal examination. In a standard examination, contractures are evaluated at the fingers, elbows, wrists, hips, knees, and ankles. Wrist and finger flexor contractures can be evaluated only with the fingers extended; otherwise, the dorsiflcxion of the wrist is compensated for by flexion of the fingers. At the hips, both flexion and iliotibial band contractures should be evaluated.

Strength

Evaluation of individual muscle strength is an important part of the clinical examination. Many methods are available. Fixed myomctry has become popular with the research community. This uses a strain gauge attached to a rigid supporting structure, often integrated into the examining couch on which the patient lies. The patient then uses maximum voluntary contraction, which can be quantitated in Newtons. The merits of this method are debated, and for the average clinician, the expense of the machinery is prohibitive. In an office situation, and in many clinical drug trials, manual muscle testing gives perfectly adequate results and is preferable to fixed myometry in young children. It is based on the Medical Research Council grading system with some modification (Table 28.1).

Table 28.1: The Medical Research Council scale for grading muscle strength

0	No contraction
1	Flicker or trace of contraction
2	Active movement, with gravity eliminated
3	Active movement against gravity
4	Active movement against gravity and resistance
5	Normal power

This is adequate for use in an office situation, particularly if it is supplemented by the functional evaluation. A scale of 0-5 is used. Grade 5 is normal strength. A grade 5 is used only if the examiner is certain that a muscle is normal and should not be used for muscles that are slightly weak. Muscles that can move the joint against resistance may vary quite widely in strength; grades of 4+, 4, and 4— are often used to indicate differences, particularly between one side of the body and the other. Grade 4 represents a wide range of strength, from slight weakness to moderate weakness, which is a disadvantage. For this reason, the scale has been more useful in following the average strength of many muscles during the course of a disease, rather than the course of a single muscle. Averaging the scores of many muscles smooths out the stepwise progression noted in a single muscle and may demonstrate a steadily progressive decline in an illness. Grade 3+ is used when the muscle can move the joint against gravity and can exert a tiny amount of resistance but then collapses under the pressure of the examiner's hand. It is not used to denote the phenomenon of sudden give way, which occurs in conversion disorders and in patients limited by pain. Grade 3 indicates that the muscle can move the joint throughout its full range against gravity, but not against any added resistance. Sometimes, particularly in muscles acting across large joints like the knee, the muscle is capable of moving the limb partially against gravity, but not through the full range of movement. A muscle that cannot extend the knee horizontally when in a sitting position but can extend the knee to within 30-40 degrees of horizontal is graded 3—. Grades 2, 1, and 0 are as defined in Table 28.1.

Although it is commendable and sometimes essential to examine each muscle separately, most of us test muscle groups rather than individual muscles. In our clinic, we test neck flexion, neck extension, shoulder abduction, internal rotation, external rotation, elbow flexion and extension, wrist flexion and extension, finger abduction and adduction, thumb abduction, hip flexion and extension, knee flexion and extension, ankle dorsiflexion and plantar flexion, and dorsiflexion of the great toe.

Fatigue

Fatigue is a common symptom in many neuromuscular disorders and in many medical conditions. Anemia, heart disease, lung disease, cancer, poor nutrition, and depression are among the many disorders that can result in fatigue. However, in certain neuromuscular conditions, strength is normal at rest but progressively worsens with use. This most often occurs in the postsynaptic neuromuscular transmission disorders, especially myasthenia gravis. Repetitive or sustained muscle resting brings out true muscle fatigue. In patients with a suspected neuromuscular transmission disorder, fatigue should be formally tested. Ptosis may be provoked by sustained upgaze for 2-3 minutes. Counting out loud from 1-100 may result in the voice becoming slurred, nasal, or hoarse. Repetitively testing the strength of shoulder abduction or hip flexion may result in progressive weakness in patients with myasthenia gravis.

Reflexes

In disorders of the motor unit, reflexes are either normal, reduced, or absent. ALS is the exception because both UMN and LMN dysfunction coexist and hyperreflexia and spasticity often accompany signs of LMN loss. In neurogenic disorders, demyelinating conditions tend to lose reflexes early, as occurs in Guillain-Barre syndrome from blocking and desynchronization of muscle spindle afferents and motor efferents. Disorders resulting in axonal loss depress reflexes in proportion to the amount of axonal loss. As most axonal neuropathies predominantly affect distal axons, the distal reflexes (ankle reflexes) are depressed or lost early and the more proximal ones remain normal. In myopathies, reflexes tend to be diminished in proportion to the amount of muscle weakness. The same is true for postsynaptic neuromuscular transmission disorders. Presynaptic neuromuscular transmission disorders (e.g., Lambert-Eaton myasthenic syndrome) tend to have depressed or absent reflexes at rest that can be elicited after brief (10 seconds) periods of exercise.

Sensory Disturbances

Disorders of the motor unit are generally not associated with disturbances of sensation unless there is a second superimposed condition. Motor neuron disorders, neuromuscular transmission disorders, and myopathies generally follow this rule. Among the few exceptions is the minor sensory loss in patients with X-linked spinobulbar muscular atrophy (Kennedy's disease) and inclusion body myositis, in which some coexistent degeneration of the peripheral nerves and dorsal root ganglion cells may occur. In **the** paraneoplastic Lambert-Faton myasthenic syndrome, patients often have minor sensory signs reflecting a more widespread paraneoplastic process.

Sensory findings often accompany peripheral neuropathies that are predominantly motor and usually thought of

as motor ncuroparhies. These include the Guillain-Barre syndrome, multifocal motor neuropathy with conduction block, Charcot-Maric-Tooth disease, and some toxic neuropathies (e.g., lead). In these conditions, sensory abnormalities on examination and/or electrophysiological testing help identify the disorder as a neuropathy and thus limit the differential diagnosis.

Peripheral Nerve Enlargement

Palpation of peripheral nerves may yield important information in several neuromuscular conditions. Diffusely enlarged nerves occur in some patients with chronic demyclinating peripheral neuropathies, especially Charcot-Marie-Tooth disease type 1, Dejerine-Sottas disease, chronic inflammatory demyelinating polyneuropathy (CIDP), and Refsum's disease. In addition, nerves may be focally enlarged in the presence of a nerve sheath tumor (neurofibromatosis) or with infiltrative lesions (e.g., amyloidosis, leprosy). Nerves that are often easily palpated include the greater auricular nerve in the neck, the ulnar nerve at the elbow, 111L- superficial radial sensory nerve ;i\ il crosses the extensors to the thumb distal to the wrist, and the peroneal nerve at the fibular head at the knee.

Fascicurations, Cramps, and Other Abnormal Muscle Movements

All limbs should be examined to determine the presence or absence of fascicular ions. Fasciculations are brief twitches caused by the spontaneous firing of one motor unit. Fasciculations may be difficult or impossible to see in infants or obese individuals. They can be present in normal people, so their presence in the absence of wasting or weakness is probably of no significance (benign fasciculations). Fasciculations that are widespread and seen on every examination may indicate denervating disease, particularly anterior horn cell disease. Mental or physical fatigue, caffeine, cigarette smoking, or drugs such as amphetamines exacerbate fasciculations. Patients whose fasciculations appear benign should be re-evaluated after avoiding exposure to exacerbating factors. Abundant fasciculations may be difficult to differentiate from myokymia, which is a more writhing, bag of worms-like motion of muscle. Myokymia is caused by repetitive bursting of a motor unit (i.e., grouped fasciculations) and is characteristically associated with certain neuromuscular conditions (e.g., radiation injury and Guillain-Barre syndrome).

Similar to fasciculations, cramps may be a benign phenomenon or accompany a variety of neuropathic conditions. Cramps are painful and occur when a muscle is contracting in a shortened position. During a cramp, the muscle becomes hard and well defined. Stretching the muscle relieves the cramp. Superficially, a muscle contracture that occurs in a metabolic myopathy may resemble a cramp, although it is completely different on electrophysiological testing. Electrical silence occurs during a contracture and numerous motor units fire at high frequencies during a cramp.

Functional Evaluation of the Weak Patient

Walking

Gait is altered by weakness of muscles of the hip and back, leg, and shoulder. In normal walking, when the heel hits the ground, the shock is taken up by the action of the hip abductors, which stabilize the pelvis. In a sense, the hip abductors act as shock absorbers; their weakness disturbs the normal fluid movement of the pelvis during walking so when the heel hits the ground, the pelvis dips to the other side; when the weakness is bilateral, this results in a waddle. Additionally, weakness of the hip extensors and back extensors makes it difficult for the patient to maintain a normal posture. Ordinarily the body is carried so the center of gravity is slightly forward of the hip joint. To maintain an erect posture, the hip and back extensors are in continual activity. If these muscles become weak, the patient often throws the shoulders back so the weight of the body falls behind the hip joints. This accentuates the lumbar lordosis. Alternatively, if there is much weakness of the quadriceps muscles, the patient stabilizes the knee by throwing it backward. When the knee is hyperextended, it is locked; it derives its stability from the anatomy of the joint, not from the support of the muscles. Finally, weakness of the muscles of the lower log may result in a steppage gait, in which dorsiflexion of the foot is affected by a short throw at the ankle midswing. The foot is then brought rapidly to the ground before the toes fall back into plantar flexion. Shoulder weakness may be noted as the patient walks; the arms hang loosely by the sides and tend to swing in a pcndular fashion, rather than with a normal conrrolled swing.

Arising from the Floor

The normal method for arising from the floor depends, to a certain extent, on the age of the patient. The young child can spring rapidly ro his or her feet without the average-observer being able to dissect the movements. The elderly patient may turn to one side, place a hand on the floor, and rise to a standing position with a deliberate slowness. In spite of this vatiability, abnormalities caused by muscle weakness are easily detected. The patient with hip muscle weakness will turn to one side or the other to put the hand on the floor for support. The degree of turning is proportional to the severity of the weakness. Some patients have to turn all the way around until they are in a prone

position before they draw their feet under them to begin the standing process. Most people arise to a standing position from a squatting position, but the patient with hip extensor and quadriceps muscle weakness finds it easier to keep the hands on the floor and raise the hips high in the air. This has been termed the *butt-first maneuver;* the patient forms a triangle, with the hips at the apex and the base of support provided by both hands and feet on the floor, and then laboriously rises from this position, usually by pushing on the thighs with both hands to brace the body upward. The progress of recovery or progression of weakness can be documented by noting whether the initial turn is greater than 90 degrees, whether unilateral or bilateral hand support is used on the floor and thighs, whether this support is sustained or transitory, and whether there is a butt-first maneuver. The entire process is known as *Gower's maneuver,* but it is useful to break it up into its component parts (Figure 28.5).

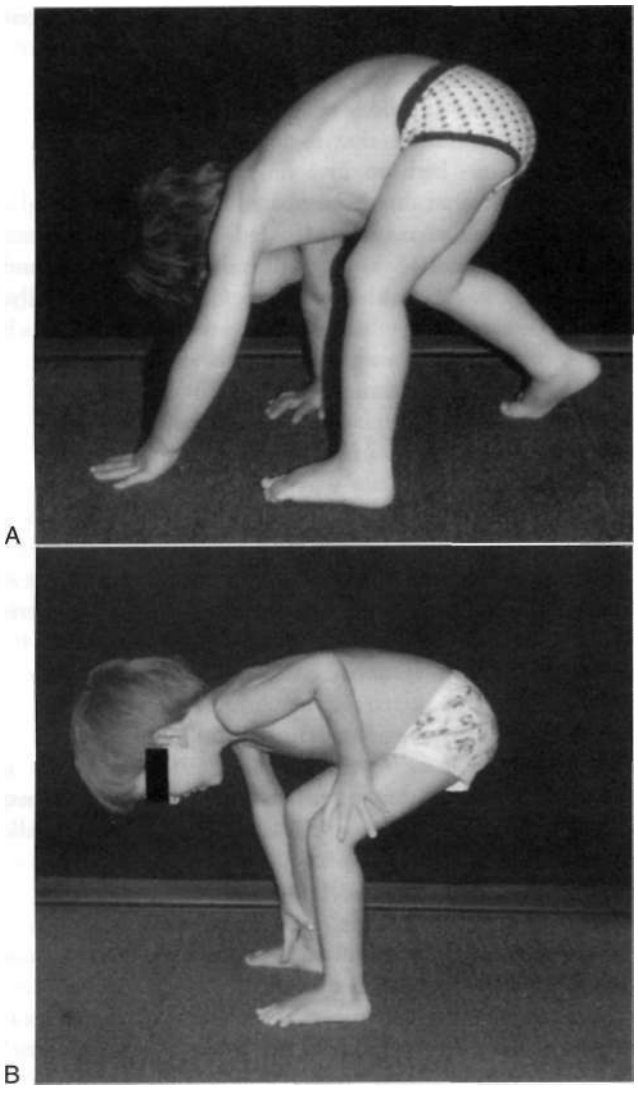


FIGURE 28.5 Gowers' maneuver. (A) Butt-first maneuver as the hips are hoisted in the air. (B) Hand support on the thighs.

Stepping onto a Stool

For a patient with hip and leg weakness, stepping onto an 8-inch-high footstool is equivalent in difficulty to a normal person's stepping onto a table. This analogy is apt because similar maneuvers are performed in both cases. Whereas the patient with normal strength readily approaches a footstool and easily steps onto it, the patient with weakness often hesitates in front of the stool while contemplating the task, There then occurs a curious little maneuver that is known colloquially as the *fast-foot maneuver.* Normal individuals can easily take the weight of their body on one leg, straightening out the knee as they stand on the footstool. Patients with weakness feel unsafe. They like to get both feet under them before straightening the knees and arising to their full height. To accomplish this, they place one foot on the footstool. While the knee of this leg is still bent, they quickly transfer the other foot from the floor to the footstool and then straighten the knees. This gives the impression of a hurried transfer of the trailing foot from floor to footstool, hence the name *fait foot.* As the weakness increases, the pelvis may dip toward the floor as the leading leg takes up the straiti and the patient's weight is transferred from the foot on the floor to the foot on the stool, the so-called *hip dip.* Finally, if the weakness is severe, patients may either use hand support on the thighs or gather themselves in and throw their bodies onto the footstool. Analysis of the various components, the hesitation, fast foot, hip dip, and throw, together with the presence or absence of hand support, may provide a sensitive measure of changes in an illness.

Psychogenic Weakness

An experienced examiner should be able to differentiate real weakness from psychogenic weakness. The primary characteristic of psychogenic weakness is that it is unpredictable and fluctuating. Muscle strength may suddenly give out when being evaluated. The patient has a difficult time knowing exactly how much strength is expected and therefore cannot adequately counter the examiner's resistance. This gives rise to a wavering, collapsing force. Tricks may be used to bring out the discrepancy in muscle performance when the patient is being tested and not aware of being observed. For example, if the thigh cannot be lifted off the chair in *a* seated position because of weakness, then the legs should not be able to swing up onto the mattress when the patient is asked to sit on the examining table. When an examiner suspects that weakness of shoulder abduction is feigned, the patient's arm can be put in abduction, with the examiner's hand on the elbow, and the examiner can instruct the patient to push toward the ceiling.

At first, the downward pressure is kept very light and the patient is unable to move the examining hand toward the ceiling. However, the arm does not fall down either, and as the downward pressure is gradually increased, continued exhortation to push the examiner's hand upward results in increasing resistance to the downward pressure. The examiner ends up putting maximum weight on the outstretched arm, which remains in abduction. The examiner concludes that the strength is normal. Patients do not realize this because they believe that because they did not move the examiner's hand upward, they must be weak.

INVESTIGATING THE WEAK PATIENT

In the investigation of diseases of the motor unit, the most helpful tests are measurement of the serum concenrration of creatine kinase (CK), elec trod i a gnosis, and muscle biopsy, which are available to virtually all physicians. Genetic testing is being used increasingly for definitive diagnosis. In addition, if facilities are available, exercise testing can provide useful information.

Serum Creatine Kinase

The usefulness of measuring the serum CK concentration in the diagnosis of neuromuscular diseases is to differentiate between neurogenic disease, in which there may be normal or mild to moderate elevations of CK, and myopathics, in which the CK concentration is often markedly increased. Serial CK measurements may be used to follow the progress of the disease. Both of these uses have problems. Foremost is the determination of the normal level. A survey of 250 hospitals in Ontario, Canada, showed a surprising ignorance of the basic mechanisms involved in the test and the way in which normal values were derived. Some hospital laboratories were unaware that race, gender, age, and activity level must be taken into account in determining normal values. When blood samples are obtained from truly normal controls and not from inactive hospital patients who happen not to have overt muscle disease, the normal serum CK concentration is higher than anticipated. Furthermore, all studies on CK concentration show that values are affected by gender and race. A log transformation does much to convert this to a normal distribution curve, but even then the results are not perfect. In a survey of 1500 hospital employees, using carefully standardized methods, it was possible to detect three populations, each with characteristic CK values. The upper limits of normal (97.5 percentile) are as follows:

Black men only: 520 U/liter
Black women, non-black men: 345 U/liter
Non-black women: 145 U/liter

The non-black population included Hispanics, Asians, and whites. Because the upper limit is expressed as a percentile of the mean, it must be understood that by definition 2.5% of the normal population will be above that. Although this does not seem to be a large number, in a town of 100,000, it means that 2500 would be considered abnormal. The point is that the upper limit of normal CK concentration is not rigid and should be interpreted intelligently. The serum CK concentration can be useful in determining rhe course of an illness, although again judgment should be used because changes in CK values do not always mirror the clinical condirion. In treating inflammatory myopathies with immunosuppressive drugs Or corticosteroids, a steadily declining CK concentration is a reassurance, whereas concentrations that are creeping back up again when the patient is in remission are not.

Serum CK concentrations also can be used to determine whether an illness is monophasic. A bout of myoglobinuria may be associated with very high concentrations of CK. The concentration then declines steadily by approximately 50% every 2 days. This indicates that a single episode of muscle damage has occurred. Patients with CK concentrations that do not decline in this fashion or that vary from high to low on random days have an ongoing illness that should be treated as such. Interestingly, CK concentrations may be elevated as high as 10 times normal in patients with spinal muscular atrophy and occasionally in those with ALS (see Chapter 80). Finally, exercise may cause a marked elevation in CK, which usually peaks 12-18 hours after the activity but may occur days later. CK concentrations are more likely to increase in people who are sedentary and then undertake unaccustomed exercise than in a trained individual.

Electromyography

The EMG is an observer-sensirive study, and an experienced electromyographer is essential to interpret EMG correctly. The principles of EMG are discussed in Chapter 36B. The EMG may provide much useful information. An initial step in the assessment of the weak patient is determination of whether the disease is caused by a neuropathic, myopathic, or neuromuscular junction transmission disorder. Nerve conduction studies and needle electrode examination arc particularly useful for identifying neuropathic disorders and localizing the abnormality to anterior horn cells, roots, plexus, or peripheral nerve territories (see Chapters 80-82). Repetitive nerve stimulation and single-fiber EMG can aid in elucidating disorders of the neuromuscular junction. Needle electrode examination may help establish the presence of abnormal muscle activity, including acute and chronic denervation, myotonia, neuromyotonia, fascicular ions, cramps, and myokymia.

Muscle Biopsy

The use of muscle biopsy is important for establishing the diagnosis in most disorders of the motor unit. Histochemistry evaluation is available at most hospitals and is particularly useful, and electron microscopy may provide a specific diagnosis. An important newer aspect of the muscle biopsy is the analysis of the muscle proteins. Individual muscle proteins, including dystrophin, sarcoglycans, and other structural proteins, may be missing in specific illnesses, and diagnosis is definitive with these analyses.

The details of muscle biopsy are reviewed in Chapter 85, but a word about the selection of the muscle to be biopsied is appropriate here. In all biopsies, there is a risk of sampling error. Not all muscles are equally involved in any given disease, and it is important to select a muscle that is likely to give the most useful information. The gastrocnemius muscle, which is often chosen for muscle biopsy, is not ideal because it has the disadvantage of demonstrating type 1 fiber predominance in the normal individual and often shows denervation changes caused by minor lumbosacral radiculopathy. Also, it has more than its fair share of random pathological changes, such as fiber necrosis and small inflammatory infiltrates, even when no clinical suspicion of a muscle disease exists. For this reason, it is preferable to select either the quadriceps femoris or the biceps brachii if cither of these muscles is weak. Never perform a biopsy on a muscle that is the site of a recent EMG or intramuscular injection, because these produce focal muscle damage. If such a muscle has to be biopsied, allow at least 2-3 months after the procedure before performing the biopsy.

In the patient with a relatively acute (duration of weeks) disease, it is wise to select a muscle that is obviously clinically weak. In patients with long-standing disease, it may be better to select a muscle that is clinically fairly normal to avoid an end-stage muscle. Sometimes an apparently normal muscle is selected for biopsy. For example, in a patient who is suspected of having motor neuron disease and who has wasting and weakness of the arms with EMG changes of denervation in the arms but no apparent denervation of the legs, biopsy of the biceps muscle would show the expected denervation and would add no useful information. If a biopsy of a quadriceps muscle showed denervation, this would provide support for widespread denervation, supporting the diagnosis of motor neuron disease. However, if the biopsy from the quadriceps muscle was normal, this would make the diagnosis of ALS less likely, because even strong muscles in patients with ALS usually show some denervation. Biopsies are generally not indicated in patients with ALS, unless the diagnosis is in question.

Genetic Testing

The details of genetic testing and counseling are covered in Chapter 44. Genetic analysis has become a routine part of the clinical investigation of neuromuscular disease and in many situations has supplanted muscle biopsy and other diagnostic tests. This is a distinct advantage to the patient if a blood test may be substituted for a muscle biopsy. The use of genetic testing for diagnosis in an isolated individual implies that the gene is well characterized and that intragenic probes are available that allow the determination of whether the gene in question is abnormal. Examples of such abnormalities are deletions in the dystrophin gene seen in many cases of Duchenne's muscular dystrophy and the expansion of the triplet repeat in the myotonic dystrophy gene.

Linkage studies can be used when the location of the gene is known, but tests for mutations of the gene itself arc not available. The success of such studies depends on having probes that are close to the gene. By using these closely situated probes, one can often demonstrate that the individual is or is not carrying the part of the chromosome (in which ;ui involved gene must have occurred in another affected family member. For linkage studies to be successful, a sufficient number of family members must be available for testing, both with and without the illness, to allow an identification of the segment of the chromosome at fault. This type of study is hampered by the tendency of parts of the chromosome to become detached during mciosis and to be exchanged with parts of another chromosome, a phenomenon known as *recombination.* The closer the probe is to the actual gene, the less likely recombination is to separate them. Genetic counseling based on linkage studies is less likely to be successful when only one or two patients with the illness and few family members are available. It is difficult to keep up with the mushrooming list of genes known to be associated with neuromuscular diseases, and yet it is imperative if we are to provide suitable advice for our patients. Useful references arc found in the journal *Neuromuscular Disorders,* which carries a list of all known neuromuscular generic abnormalities each month, and the Web sites Online Mcndelian Inheritance in Man (www.ncbi.nlm.nih.gov/omim/) and GeneTests-GeneClinics(www.genetests.org),

Exercise Testing

Exercise testing may be an important part of the investigation of muscle disease, particularly in metabolic disorders. The two primary types of exercise tests that are used are forearm exercise and bicycle exercise. Forearm (grip) exercise has been designed ro provide a test of glycolytic pathways, particularly those involved in power exercise. Incremental bicycle ergometry gives additional information regarding the relative use of carbohydrates, fats, and oxygen.

Forearm exercise is performed according to several schedules. The traditional method is to ask the patient to

grip a dynamometer repetitively, with a blood pressure cuff on the upper arm raised above systolic pressure. If the work performed by rhe patient is sufficiently strenuous, the cuff is unnecessary, because the muscle is working at a level that surpasses the ability of blood-borne substances to sustain it. An adequate level of forceful exercise is maintained for 1 minute, and then venous blood is drawn at intervals after the exercise to monitor changes in metabolites. In the norma] individual, the energy for such short-duration work is derived from intramuscular glycogen. Lactate is formed when exercise is relatively anaerobic, as it is when the exercise is strenuous. Additionally, serum concentrations of hypoxanthinc and ammonia are elevated. Patients with defects in the glycolytic pathways produce normal to excessive amounts of ammonia and hypoxanthine, but no lactate. Patients with adenylate deaminase deficiency show the reverse situation; ncithet ammonia nor hypoxanthine appears, but lactate production is normal. In patients who cannot cooperate with the testing and whose effort is poor, neither lactate nor ammonia concentrations are very high.

In mitochondrial disorders and other instances of metabolic stress, the production of both lactate and hypoxanthine is excessive. More recently, a modification of the ischemic forearm test has been reported as a sensitive and specific screen fot mitochondrial disorders. During exercise in normal individuals, mitochondrial oxidative phosphotylation increases 100-fold from that measured during rest. In mitochondrial disorders, the disturbed oxidative phosphorylation results in an impaired systemic oxygen extraction. In one study, 12 patients with mitochondrial myopathy were compared with 10 patients with muscular dystrophy and 12 healthy subjects. Cubital venous oxygen saturation was measured after 3 minutes at 40% of maximal voluntary contraction of the exercised arm. Oxygen desaturation in venous blood from exercising muscle was markedly lower in patients with mitochondrial myopathy than in patients with othct muscle diseases and healthy subjects.

Incremental bicycle ergometry allows one to measure the oxygen consumption and carbon dioxide production associated with varying workloads. The patient pedals a bicycle at a steady rate. The workload is increased every minute or two. Excessive oxygen consumption for a given work level suggests an abnormality in the energy pathway in muscle. In addition, the respiratory exchange ratio (RER), the ratio of carbon dioxide produced to oxygen consumed, is characteristic for various fuel sources. Carbohydrate metabolism results in an RER of 1.0. Fat, on the other hand, has an RER of 0.7. The resting RFR in normal individuals is approximately 0.8. For complex reasons, at the end of an incremental exercise test, the RFR is often as high as 1.2 in the normal individual. Patients with disorders of lipid metabolism often have an unusually high RFR because they preferentially metabolize carbohydrates, whereas patients with disorders of carbohydrate metabolism may never increase RER to more than 1,0 because they preferentially metabolize lipids.

APPROACH TO THE PATIENT WITH WEAKNESS

Once it is established that a patient has weakness, either by history or examination, the clinical features may be so characteristic that the diagnosis is obvious. At other times, the clinician may be uncertain. Figure 28.6 displays an outline of diagnostic considerations based on the characteristics of the weakness, such as whether it is fluctuating or constant. The following sections amplify this approach,

Disorders with Prominent Ocular Weakness

In oculopharyngeal muscular dystrophy, a slowly progressive weakness of the eye muscles causing ptosis and external ophthalmoplegia is associated with difficulty in swallowing. This disorder is an autosomal dominant trait and does not seem to shorten life. A number of patients also have facial weakness and hip and shoulder weakness. Swallowing difficulty may become severe enough to necessitate gastrostomy tube placement.

The Kearns-Sayre syndrome is a distinctive collection of physical findings, including ptosis, extraocular muscle palsies, pigmentary degeneration of the retina, cerebellar ataxia, pyramidal tract signs, short stature, mental retardation, and cardiac conduction defects. These findings accompany an abnormality of the mitochondria in muscle and other tissues. It may be slowly progressive or nonprogressive.

In addition, several other disorders may display prominent extraocular muscle involvement. Among these is centronuclear myopathy, one of the congenital myopathics. However, this condition is not restricted to the eye muscles and has prominent involvement of the limbs as well. Lastly, myasthenia gravis often, and occasionally Lambert-Eaton myasthenic syndrome, presents with isolated ptosis or extraocular muscle weakness. A subset of patients with myasthenia gravis will never generalize to other muscles and remain in the restricted ocular group.

Disorders with Distinctive Facial or Bulbar Weakness

FSH muscular dystrophy may nor be noted until early adult life. Weakness of the face may lead to difficulty with whistling or blowing up balloons and may be severe enough to give rhe face a smooth, unlined appearance with an abnormal pout to the lips (Figure 28.7A). Weakness of the muscles around the shoulders is always seen, although the deltoid muscle is surprisingly well preserved and even pseudohypertrophic in its lower portion. When the patient attempts to hold the arms extended in front, winging of the scapula occurs that is quite characteristic. The whole scapula may slide upward on the back of the thorax. The inferomedial border always juts backward, producing the appearance of a triangle at right angles to the back, with the

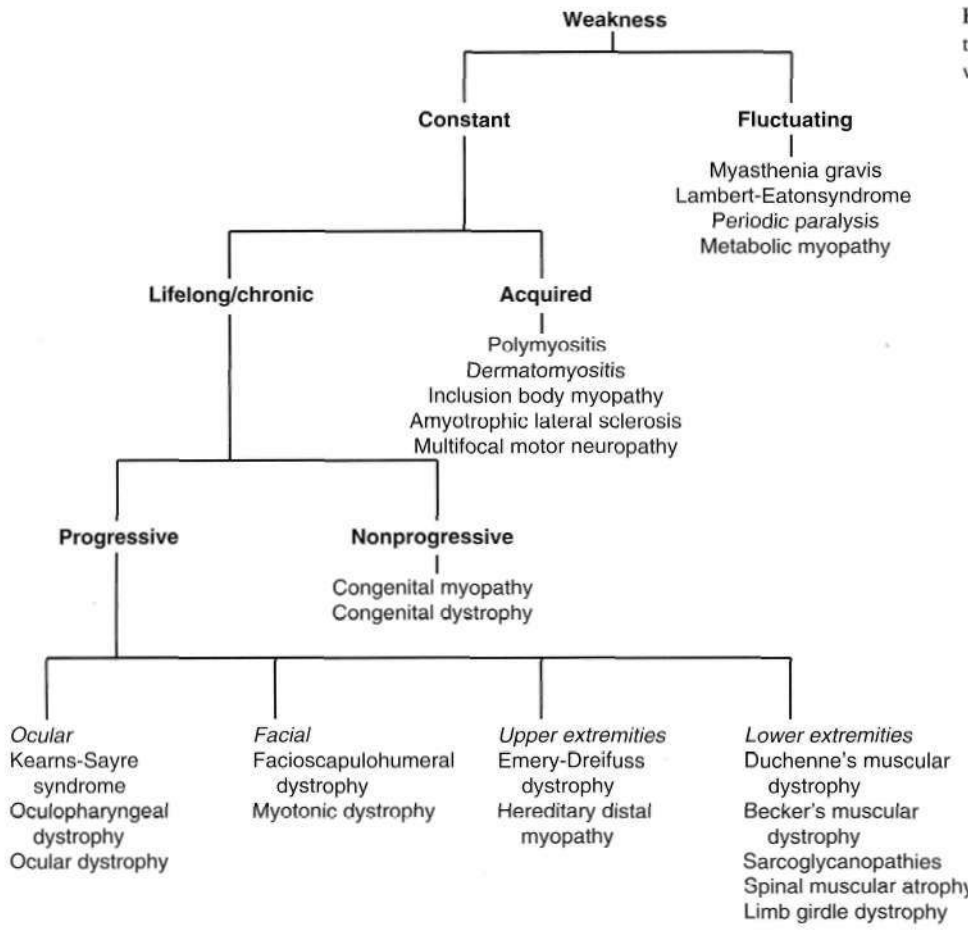


FIGURE 28.6 An algorithm for the approach to the patient with weakness.

base of the triangle still attached to the thorax. In addition, a discrepancy in power is often seen between the wrist flexors, which are strong, and the wrist extensors, which are weak. Similarly, the plantar flexors may be strong, whereas the dorsiflexors of the ankles are weak. It is common for the weakness to be asymmetrical, with one side much less involved than the other (Figure 28.8). The disorder is inherited as an autosomal dominant trait, although mild forms of the illness may be missed in the parents.

Myotonic dystrophy type I is a common illness with distinctive features, including distal predominance of weakness. It is inherited as an autosomal dominant trait, but often no family history is reported because the patients may be unaware that other family members have the illness. This is due to the phenomenon of anticipation, whereby successive generations are more severely affected, because of the expansion of the trinucleotide repeat. The diagnosis may be suspected in any patient with muscular dystrophy and predominantly distal weakness. The neck flexors and temporal and masseter muscles are often wasted. More charactetistic than the distribution of the weakness is the long, thin face with hollowed temples, ptosis, and frontal balding (Figure 28.7B). Percussion myotonia and grip myotonia are seen in most patients after age 13 years. An EMG can be diagnostic. Muscle biopsy may also show characteristic changes, and genetic testing shows the characteristic trinucleotide repeat in the myotonin gene on chromosome 19.

A subset of patients with ALS present with isolated bulbar weakness of LMN type (i.e., progressive bulbar palsy) or UMN type (i.e., progressive pseudobulbar palsy). Frequently the condition shows a combination of UMN and LMN involvement. In these patients, dysarthria, dysphagia, and difficulty with secretions are the prominent symptoms. On examination, the tongue is often atrophic and fasciculating (Figure 28.9), and the jaw and facial reflexes are exaggerated- The voice is often harsh and strained as well as slurred, reflecting the coexistent UMN and LMN dysfunction. In patients with X-linked spino-bulbar muscular atrophy {Kennedy's disease), bulbofacial muscles are also affected prominently. Patients often have a characteristic finding of chin fascial kit ions.

Disorders with Distinctive Shoulder-Girdle or Arm Weakness

In Emery-Dreifuss muscular dystrophy, an abnormal gene on the X chromosome produces wasting and weakness of muscles around the shoulders, upper arms, and lower part

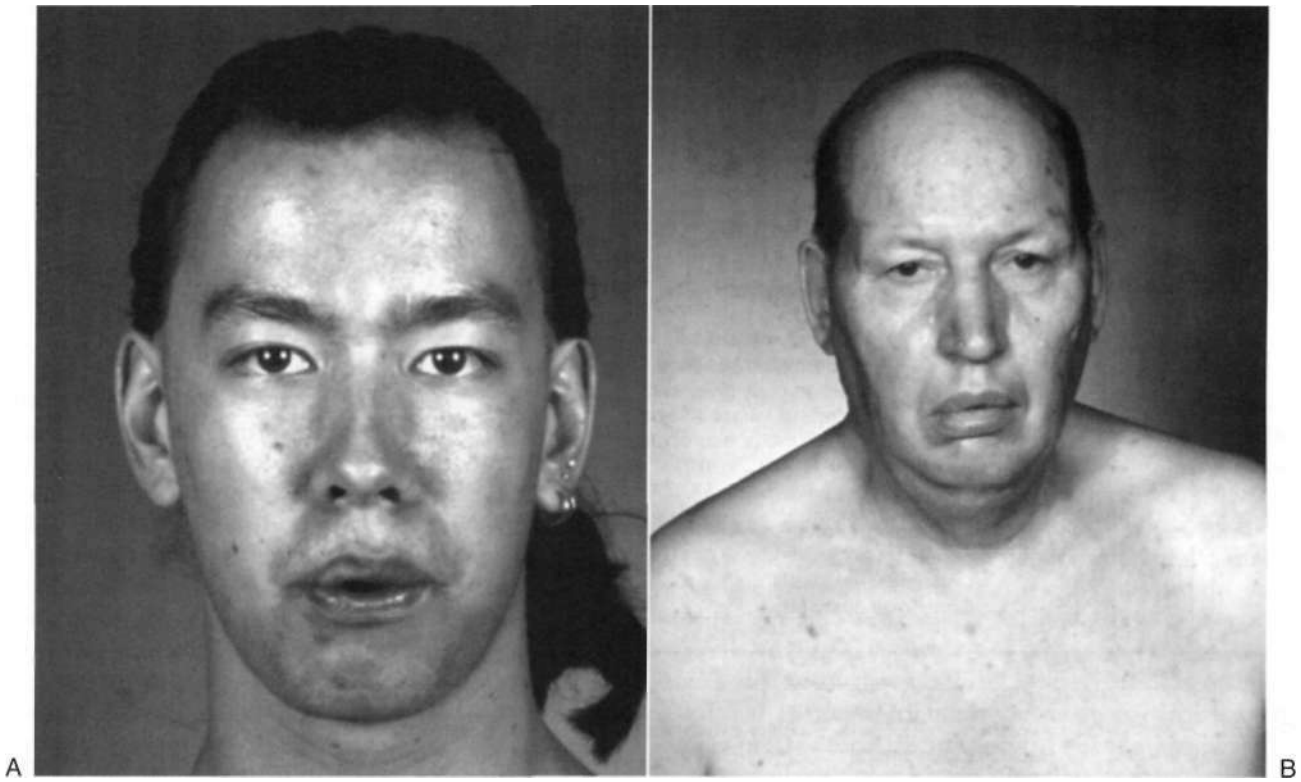


FIGURE 28.7 Facial weakness is a prominent feature of both facioscapulohumeral dystrophy (FSH) and myotonic dystrophy. However, the characteristic features are so distinctive that they are readily recognizable and not easily confused. (A) The patient with FSH dystrophy is unable to purse his or her lips when attempting to whistle. (B) The typical appearance of a patient with myotonic dystrophy includes frontal balding, temporalis muscle wasting, ptosis, and faeial weakness. Related to F5H dystrophy is scapuloperoneal dystrophy, which has similar fearures but lacks the facial weakness. The two are differentiated because the scapuloperoneal distribution of weakness may be seen in some other congenital nonprogressive myopathies, which may lead to some confusion in the diagnosis.

of the legs, with contractures of the elbow, posterior neck, and Achilles tendon. Cardiac conduction abnormalities are **common,** and death may occur as a result of acute heart block.

Distal muscular weakness and atrophy are most commonly seen in neurogenic disorders. Among these **is** Charcot-Marie-Tooth disease, which is almost always characterized by distal weakness and wasting that starts

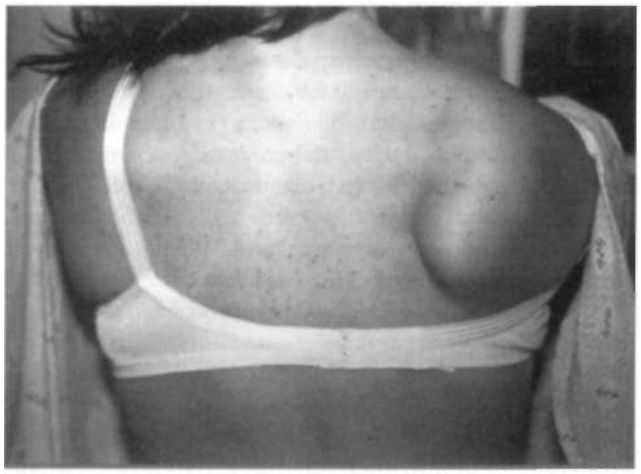


FIGURE 28.8 Asymmetrical scapular winging in facioscapulohumeral muscular dystrophy.

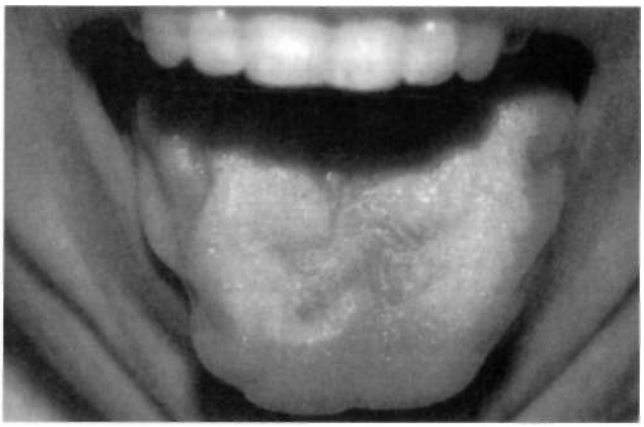


FIGURE 28.9 Tongue atrophy in a patient with amyotrophic lateral sclerosis. (Reprinted with permission from Katirji, B., Kaminski, H. J., Preston, D. C, et a1, eds, *Neuromuscular Disorders in Clinical Practice,* Buttcrworth-Heincmann, Boston.)

in the distal lower limbs before involving the hands. ALS often begins as weakness and wasting in one distal limb. More important because it is treatable is multifocal motor neuropathy with conduction block, a rare demyelinating polyneuropathy that may be confused clinically with I.iVIN ALS. The initial features are often weakness, hyporcflexia, and fasciculations, especially of the hands. Clues to the diagnosis are a slow indolent coutse, weakness out of proportion to the amount of atrophy, and asymmetrical involvement of muscles of the same myotome but with a different peripheral nerve supply (e.g., weakness of ulnar-innervated C8 muscles out of proportion to weakness of median-innervated C8 muscles). Benign focal amyotrophy (Sobue's syndrome) presents with the insidious onset of weakness and atrophy of the hand and forearm muscles, predominantly in men between the ages of IS and 22.

Two muscular dystrophies that are predominantly distal may affect the upper extremity: myotonic dystrophy, which has been discussed earlier in this chapter, and the hereditary distal myopathics. The hereditary distal myopathies are a heterogenous group of disorders. Welander's myopathy, transmitted as an autosomal dominant trait, is one of the more common forms. Ir has a predilection for the intrinsic hand and wrisr extensor muscles.

In the older individual, involvement of the finger flexors with relative preservation of the finger extensors is commonly seen in inclusion body myositis. However, in these latter cases, weakness is also prominent in the lower extremities, especially die quadriceps.

Disorders with Prominent Hip-Girdle or Leg Weakness

Although patients with these disorders often have more diffuse weakness, including arm and shoulder-girdle weakness, it is the hip and leg weakness that brings them to medical attention. Acute infantile spinal muscular atrophy (Werdnig-Hoffmann disease) is a severe and usually fatal illness with marked weakness of the limbs and respiratory muscles. Children with the intermediate form of spinal muscular atrophy (chronic Werdnig-Hoffmann disease or spinal muscular atrophy type 2) also are severely affected, rarely maintaining the ability to walk for more than a few years, so they are confined to a wheelchair in adult life. The progression of the illness is not steady; plateaus last for some years, interspersed with more rapid deterioration. Scoliosis is common. In the intermediate form of spinal muscular atrophy, a fine tremor of outstretched hands is characteristic.

In juvenile spinal muscular atrophy the muscle weakness is more severe proximally, and the term *pseudomyopatbic spinal muscular atrophy* has been applied. The illness begins sometime during the first decade of life, and patients walk well into the second decade or even into early adult life. Scoliosis is less common than in the infantile form.

The inherited muscular dystrophies cause progressive, nonfluctuating weakness. Duchenne's muscular dystrophy-is an X-linked recessive disorder associated with an absence of dystrophin. Clinically, the combination of proximal weakness that is greater than distal weakness with hypertrophic calf muscles and contractures gives the clue to the diagnosis. The serum CK concentration is markedly elevated, and the muscle biopsy is diagnostic (see Chapter 85}. The clinical features of Becker's muscular dystrophy are identical except for later onset and slower progression.

Severe childhood autosomal recessive muscular dystrophies, also known as *sarcoglycanopathies,* arc caused by deficiency in muscle of one of rhe dystrophin-associated glycoproteins (sarcoglycans) and have been linked to chromosomes 4, 5, 13, and 17. Severe childhood autosomal recessive muscular dystrophy is phenotypically similar to Duchenne's muscular dystrophy, including the calf hypertrophy, but affects both boys and girls. Cardiac involvement is rare, and mental retardation is not seen.

The limb-girdle dystrophies are a well-accepted diagnostic classification, despite their clinical heterogeneity. Weakness begins in the hips, shoulders, or both and spreads gradually to involve the rest of the limbs and the trunk. The diagnosis is often established by exclusion of everything else. The most helpful test is the muscle biopsy, which shows dystrophic changes, separating limb-girdle dystrophy from other (inflammatory) myopathies and from denervating diseases. Immunohistochcmical analysis of dystrophic muscle will further clarify the diagnosis, followed by genetic analysis of the sarcoglycan genes.

In patients with inclusion body myositis, the quadriceps and forearm ulnar finger flexor muscles are often preferentially involved. In some patients, this may be asymmetrical at the onset. The other inflammatory myopathies, polymyositis and dermatomyosiris, affect proximal, predominantly hip-girdle muscles in a symmetrical fashion, Though rare, the Lambert-Eaton myasthenic syndrome can also present with proximal lower extremity weakness, similar to a myopathy. Hyporeflexia and autonomic and sensory symptoms may suggest the diagnosis. EMG is often diagnostic.

Distal muscle weakness and atrophy are most often caused by neurogenic disorders. In Charcot-Marie-Tooth disease of both the demyelinating form (type 1) and the axonal form (type 2) the problem in the legs antedates that in the hands. In ALS, the weakness is often asymmetrical and may be combined with UMN signs.

As mentioned earlier, the last group is the hereditary distal myopathics. Distal leg weakness is usually the initial featute. Among these disorders are the Markesbcry-Griggs/Udd, Nonaka, and Laing myopathies, which affect anterior compartment muscles, and Miyoshi myopathy, which affects predominantly the posterior calf muscles.

Disorders with Fluctuating Weakness

The first step is to determine whether the weakness is constant or fluctuating. Even constant weakness may vary somewhat depending on how the patient feels. We are all capable of better physical performance on the days when wc feel energetic and cheerful and do less well on days when we are depressed or sick. Such factors also affect the patient with neuromuscular weakness. Specific inquiries should be made to determine how much variability exists. Is the fluctuation related to exercise or time of day? Symptoms and signs that are provoked by exercise imply a disorder in the physiological or biochemical mechanisms governing muscle contraction, l'ain, contractures, and weakness after exercise are often characteristic of abnormalities in the biochemistry of muscle contraction. Pathological fatigue is the hallmark of neuromuscular junction abnormalities.

Factors other than exercise may result in worsening or improvement of the disease. Some patients notice that fasting, carbohydrate loading, or other dietary manipulations make a difference in their symptoms. Such details may provide a clue to underlying metabolic problems. Patients with a defect in lipid-based energy metabolism are weaker in the fasting state and may carry a candy bar or sugar with them. The patient with hypokalemic periodic paralysis may notice that rest after a high-carbohydrate meal precipitates an attack.

Weakness that fluctuates markedly on a day-to-day basis or within .1 space of several hours is more often caused by a defect in neuromuscular transmission or a metabolic abnormality (e.g., periodic paralysis} than by one of the muscular dystrophics. Most neurologists recognize that the cardinal features of myasthenia gravis arc ptosis, ophthalmoparesis, dysarthria, dysphagia, and proximal weakness (see Chapter 84). On clinical examination, the hallmark of myasthenia gravis is pathological fatigue. Normal muscles fatigue if exercised sufficiently, but in myasthenia gravis, fatigue occurs with little effort. Failure of neuromuscular transmission may prevent maintenance of the arms in an outstretched position for more than a few seconds or maintenance of sustained upgaze. One of the problems with the diagnosis of myasthenia is that the patient may be relatively normal when examined in the office; the history and ancillary studies (acetylcholine receptor antibodies and EMG with repetitive stimulation or single-fiber EMG) must be relied on to establish the diagnosis.

In the Lambert-Eaton myasthenic syndrome, fluctuating weakness may also occur but is less marked than in myasthenia gravis. Weakness of the shoulder and especially the hip girdle predominates, with the bulbar, ocular, and respiratory muscles relatively spared. There are exceptions to this latter rule, with few patients with Lambert-Eaton myasthenic syndrome mimicking myasthenia gravis. Reflexes are typically reduced or absent at test. After a brief exercise, weakness and reflexes are often improved {facilitation), which is the opposite of the situation in myasthenia gravis. The electrophysiological correlate of this phenomenon is the demonstration of a marked incremental response to rapid, repetitive nerve stimulation. The underlying pathophysiology of Lambert-Easton myasthenic syndrome is an autoimmune or paraneoplastic process mediated by anti-voltage-gated calcium channel antibodies; commercial testing for these antibodies is available.

Patients with periodic paralysis note attacks of weakness, typically provoked by rest after exercise (see Chapter 85), In the primary periodic paralyses, the disorder is inherited as an autosomal dominant trait, secondary to a sodium or calcium channel defect (see Chapter 70), In the hyperkalemic (sodium channel) form, patients experience weakness that may last from minutes to days, beginning in infancy to early childhood, which is provoked by rest after exercise or potassium ingestion. Potassium levels are generally high during an attack. In the hypokalemic (calcium channel) form, weakness may last hours to days, is quite severe, beginning in the early teens, and is provoked by rest after exercise or high-carbohydrate ingestion. Potassium levels are generally low during an attack. In both types, patients may become totally paralyzed, although notably sparing bulbofacial muscles. Rarely, respiratory muscles are affected in hypokalemic periodic paralysis. Patients with paramyotonia congenita may also experience attacks of weakness, especially in the cold.

Disorders Exacerbated by Exercise

Fatigue and muscle pain provoked by exercise, the most common complaints in the muscle clinic, are often unexplained, and diagnoses such as fibromyalgia and the aches, cramps, and pain syndrome are used to cloak our ignorance (see Chapter 29). Biochemical defects are being found in an increasing number of patients with exercise-induced fatigue and myalgia. The metabolic abnormalities that impede exercise are disorders of carbohydrate metabolism, lipid metabolism, and mitochondrial function. The patient's history may give some clue to the type of defect.

Fatty acids provide the main source of energy metabolism for resting muscle. The initiation of vigorous exercise requires the use of intracellular stores of energy, because blood-borne metabolites are initially inadequate. It takes some time for the cardiac output to increase, for capillaries to dilate, and for the blood supply to muscle to be increased, and .111 even longer time for fat stores in the body to be mobilized so the level of fatty acid increases in the blood. Muscle must use its glycogen stores in this initial phase of heavy exercise. Thus defects of glycogen metabolism cause fatigue and muscle pain in the first few minutes of exercise. As exercise continues in the normal individual, the blood supply increases, resulting in an increased supply

of oxygen, glucose, and fatty acids. After 10-15 minutes, the muscle begins to use a mixture of fat and carbohydrate. The use of carbohydrate cannot be tolerated for long periods, because it would deplete the body's glycogen stores and might result in hypoglycemia. After 30-40 minutes of continued endurance exercise, the muscle is chiefly using fatty acids as an energy source. Patients with a defect of fatty acid metabolism can exercise in the initial phase easily but may become incapacitated with endurance exercise lasting 30-60 minutes. Similarly, in the fasting state, the body is more dependent on fatty acids, which it uses to conserve glucose. Thus the patient with a disorder of fatty acid metabolism may complain of increased symptoms when exercising in the fasting state. Ingestion of a candy bar may give some relief, because this boosts the blood sugar level. Patients with fatty acid metabolism defects often have well-developed muscles, because their favorite exercise is relatively intense, brief power exercise, such as weight lifting,

Disorders of mitochondrial metabolism are varied in presentation. In some types, recurrent eneephaloparhic episodes occur, often noted in early childhood and resembling Reye's disease (see Chapter 69). In others, there is particular weakness of the extraocular and other skeletal muscles. In some types, usually affecting young adults, the symptoms are predominantly of exercise intolerance. Defects occur in the electron transport system or cytochrome chain that uncouples oxygen consumption from the useful production of adenosine triphosphate. This causes metabolic pathways to run at their limit, even to keep up with the demands of a light exercise load. Resting tachycardia, high lactic acid levels in the blood, excessive sweating, and other indications of hypermetabolism are noted. This may lead to an erroneous diagnosis of hyperthyroidism. It is always worth measuring the scrum lactic acid concentration if a mitochondrial myopathy is suspected. In addition to lactate, ammonia and hypo-xanthine concentrations also may be elevated. Patients with suspected metabolic defects require forearm exercise and bicycle exercise tests. Myoglobinuria may occur during an exercise test, so the patient should be cautioned about the possibility.

Disorders with Constant Weakness

With constant weakness, the course is one of stability or steady deterioration. Without treatment, the periods of sustained, objective improvement or major differences in strength on a day-to-day basis are lacking. The division of this group into subacute and chronic also needs clarification. *Subacute* means that weakness appeared over weeks to months in a previously healthy person. In contrast, *chronic weakness* implies a much less definite onset and prolonged course. Although the patient may say that the weakness came on suddenly, a careful history elicits symptoms that go back many years. This division is not absolute. Patients with polymyositis, usually a subacute disease, may have a slow course, mimicking a muscular dystrophy. Patients with a muscular dystrophy may have a slow decrease in strength but suddenly lose a specific function, such as standing from a chair or climbing stairs, and believe their disorder to be acute.

Acquired Disorders Causing Weakness

Acquired disorders producing weakness are usually either motor neuron diseases, inflammatory, toxic, or endocrine disorders of muscle, neuromuscular transmission disorders, or peripheral motor neuropathies. The first task is to determine whether the weakness is neuropathic, myopathic, or secondary to a neuromuscular transmission defect. In some cases, this is straightforward clinically; in others, it may be very difficult. For instance, some cases of predominantly LMN ALS may mimic inclusion body myositis; Lambert-Easton myasthenic syndrome may mimic polymyositis. If fasciculations are present, the disorder must be neuropathic. If reflexes arc absent and clearly out of proportion to muscle bulk, one should suspect a demyelinating neuropathy, although presynaptic neuromuscular junction disorders may also have hypore-flexia. The presence of sensory signs or symptoms, even if mild, may indicate a peripheral neuropathy or involvement of the CNS. Often, serum CK concentration, EMG, and sometimes muscle biopsy are needed to separate these conditions.

ALS is the most common presentation of an acquired motor neuron disease. Although more common in the 55-65-year-old age-group, it can occur at any adult age. It often follows a relatively rapid course, often preceded by cramps and fasciculations. Examination shows wasting and often widely distributed fasciculations. If the bulbar muscles are involved, difficulty with swallowing and speaking are also present. The diagnosis is relatively simple if unequivocal evidence of UMN dysfunction accompanies peripheral wasting and fasciculations. These signs include slowness of movement, hyper-reflexia, Babinski's signs, and spasticity. A weak wasted muscle, associated with an abnormally brisk reflex, is almost pathognomonic of ALS. The electrophysiological diagnosis is supported by the finding of widespread denervation on needle electrode examination in the absence of any sensory abnormalities or demyelinating features on nerve conductions. In all patients without bulbar involvement, it is important to rule out spinal pathology because the combination of cervical and lumbar stenosis may occasionally mimic the clinical and electrophysiological findings of ALS. In patients with only LMN dysfunction, it is essential to exclude the rare diagnosis of multifocal motor neuropathy with conduction block, a condition that is usually treatable with intravenous gammaglobulin. Parients with multifocal motor neuropathy with conduction block

usually have no bulbar features or UMN signs and have characteristic findings of demyelination (i.e., conduction block) on motor nerve conductions. Although most adults with motor neuron disease have ALS or one of its variants, sporadic forms of adult-onset spinal muscular atrophy and especially X-linked spinobulbar muscular atrophy (Kennedy's disease) can occur as well. In these cases, the progression of weakness is much slower and UMN involvement is absent. Of importance, these latter cases, especially Kennedy's disease, often have elevated CK levels in the 500-1500 range.

If the patient is shown to have an acquired myopathy, one must consider inflammatory myopathies, including polymyositis, dermatomyositis, or inclusion body myopathy, in addition to a large number of toxic, drug-induced, and endocrine disorders. Inflammatory myopathies, as exemplified by polymyositis, often run a steadily progressive course, although some fluctuation may be noted, particularly in children. If an associated skin rash is present, there is little doubt about the diagnosis of dermatomyositis. In its absence, polymyositis may be difficult to differentiate from any of the other causes of proximal weakness. Sometimes the illness occurs as part of an overlap syndrome, in which fragments of other autoimmune diseases, such as scleroderma, lupus, or rheumatoid arthritis, are involved. Polymyositis is sometimes difficult to differentiate from a limb-girdle muscular dystrophy, even after a muscle biopsy; some inflammatory changes may be seen in the latter. Other signs of systemic involvement, such as malaise, transient aching pains, mood changes, and loss of appetite, are more common in polymyositis than in limb-girdle dystrophy.

Inclusion body myopathy also may mimic polymyositis clinically. More often it may mimic LMN ALS. Clues to the diagnosis are male gender, age older than 40 years, slower progression, and characteristic involvement of certain muscles, especially the quadriceps and long finger flexors. Some patients may have proximal muscle weakness, similar to polymyositis, whereas others may have predominantly distal weakness mimicking ALS and other neuropathic conditions. Scrum CK is generally elevated but may occasionally be normal. Like other chronic inflammatory myopathics, the interpretation of the EMG study may be difficult and requires an experienced examiner, because inclusion body myopathy often shows a combination of myopathic and neuropathic features. Inclusion body myopathy, unlike polymyositis, is often unresponsive to immunosuppressive therapy and has rimmed vacuoles and intracytoplasmic and intranuclear filamentous inclusions in muscle fibers on biopsy.

Toxic, drug-induced, and endocrine disorders must always be considered in acquired myopathies. Among toxins, alcohol is still the most common and may produce both an acute and a chronic syndrome. A large number of prescription medicines are associated with myopathies. Most prominent are corticosteroids, cholesterol-lowering agents (the statins), and colchicine.

Although neuromuscular transmission disorders arc most often considered with disorders with fluctuating symptoms, the Lambert-Faton myasthenic syndrome may be an exception and often presents similar to a myopathy with progressive proximal lower extremity weakness. Clues to the diagnosis include a history of cancer, especially small cell lung cancer (although in many patients the myasthenic syndrome may predate the discovery of the cancer), hyporeflcxia, facilitation of strength and reflexes after brief exercise, and coexistent autonomic symptoms, especially urinary and sexual dysfunction in men.

Most peripheral neuropathies are easily separated from disorders of the motor unit by the presence of clear-cut sensory symptoms and signs. The notable exception is multifocal motor neuropathy with conduction block discussed earlier. Other neuropathies may also present with predominantly motor symptoms. Among these are toxic neuropathies (dapsone, vincristine, lead, acute alcohol-related neuropathy) and some variants of the Guillain-Barre syndrome (especially the acute motor axonal neuropathy syndrome).

Lifelong Disorders

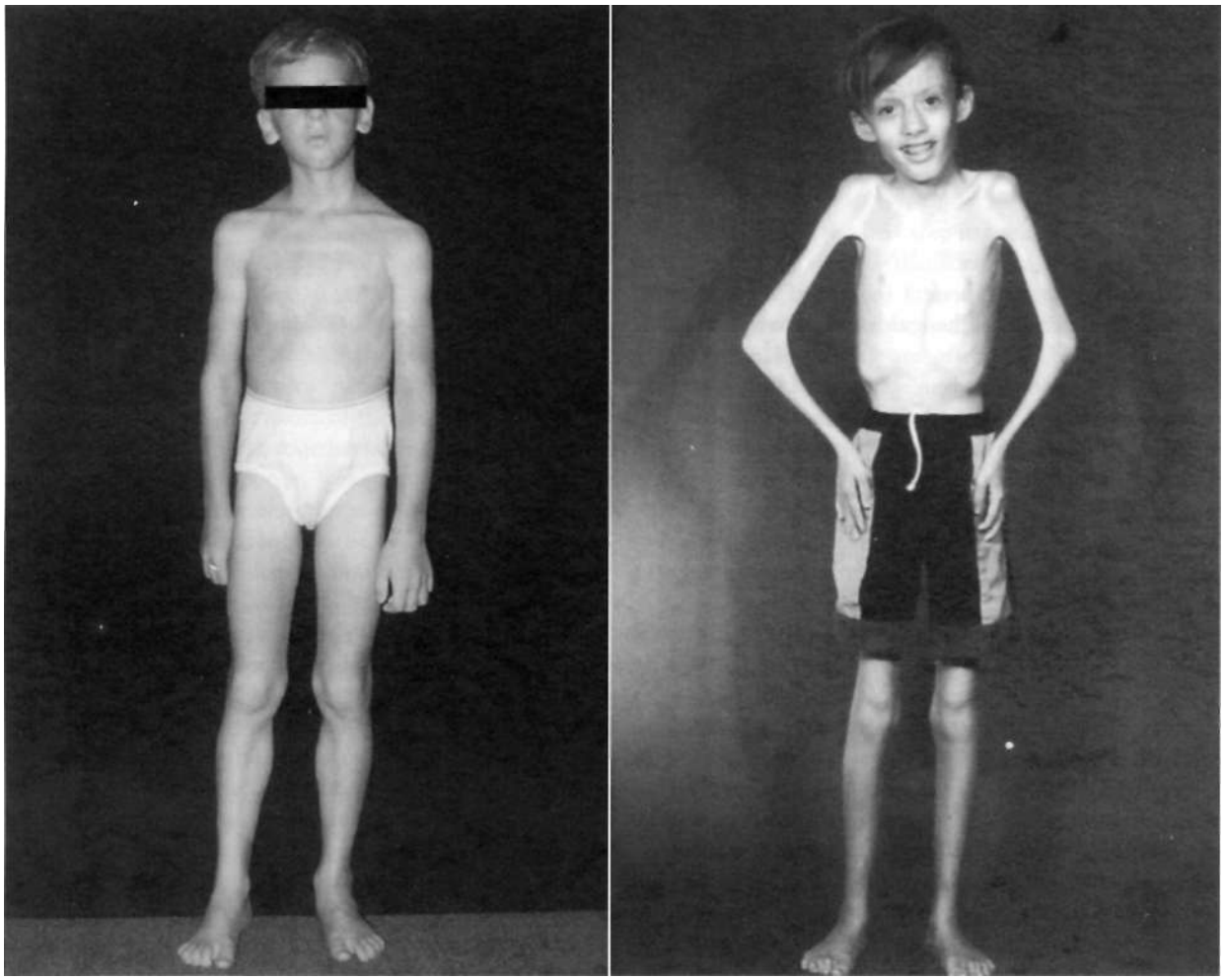
Most patients in the neuromuscular clinic have lifelong or at least very chronic, presumably inherited disorders. These include inherited disorders of muscle (e.g., dystrophies, congenital myopathies), anterior horn cell (e.g., spinal muscular atrophies), peripheral nerves (e.g., Charcot-Marie-Tooth polyneuropathy), or very rarely neuromuscular transmission (e.g., congenital myasthenic syndromes). In some, the responsible genetic abnormality has been identified. An important point in the differential diagnosis is to determine whether the weakness is truly progressive. The examiner should ask questions until the progressive or nonprogressive nature of the disease is certain. The severity of the disease is often taken as proof of progression. It is difficult to imagine that a 16-ycar-old girl, confined to her wheelchair with spinal muscular atrophy and scoliosis and having difficulty breathing, has a relatively nonprogressive disorder, but careful questioning may show that there has been no loss of function for the last several years. Further, it is not sufficient to ask the patient in vague and general terms whether the illness is progressive. Questioning should be specific, such as "Arc there tasks that you cannot perform now that you could perform last week, month, or year?" One must also be alert for denial, which is common in young patients with increasing weakness. The 18-year-old boy with limb-girdle dystrophy-may claim to be the same now as in years gone by, but questioning may reveal that he was able to climb stairs well when he was in high school, whereas he now needs assistance in college.

Lifelong, Nonprogressive Disorders. Some patients complain of lifelong weakness that has been relatively

unchanged over many years. Almost by definition such disorders have to start in early childhood. Nonprogression of weakness does not preclude severe weakness. Later-life progression of such weakness may occur as the normal aging process further weakens muscles that have little functional reserve. One major group of such illnesses is the congenital nonprogressive myopathies, including central core disease, nemaline myopathy, and congenital fiber-type disproportion. The typical clinical picture in these diseases is that of a slender dysmorphic individual with diffuse weakness {Figure 28.10A). There may be associated skeletal abnormalities, such as high-arched palate, pes cavus, and scoliosis. Deep tendon reflexes are depressed or absent. Though unusual, severe respiratory involvement has been noted in all of these diseases. The less severe (non-X-1 inked) form of myotubular (centronuclear) myopathy may be suspected because of the occurrence of ptosis, extraocular muscle weakness, and facial diplegia. Muscle biopsy usually can be relied on to provide the diagnosis in the congenital myopathies.

Several varieties of congenital muscular dystrophy are recognized. The weakness in congenital muscular dystrophy is usually severe, contractures are prominent, and there may be associated findings. For example, in Fukuyama's muscular dystrophy, there are associated mental retardation and seizures. Other signs of damage to the CNS may be present, such as increased tendon reflexes and extensor plantar responses. Most patients with Fukuyama's dystrophy are severely disabled, both physically and intellectually. The serum CK concentration may be elevated markedly. The muscle biopsy is different from that in the congenital nonprogressive myopathies and shows fiber necrosis with fibrosis and phagocytosis.

There are also patients whose biopsies show dystrophic changes but whose illnesses are much milder. One such illness has been termed *stick man dystrophy* because of the almost skeletal appearance of the limbs, with severely atrophic muscles (Figure 28.10B). Although there is diffuse weakness, the atrophic muscles generate more force than one would expect on the basis of their bulk. Patients also



B

FIGURE 28.10 The patient with a congenital myopathy is slender, without focal atrophy. Shoulder-girdle weakness is apparent from the horizontal scr of rhe clavicles. (B) The patient with congenital muscular dystrophy of the "stick man" type is distinguished by his skeletal appearance and the presence of the prominent contractures.

have severe heel cord contractures and often have contractures of the posterior cervical muscles.

Lifelong Disorders Characterized by Progressive Weakness. Most diseases in this category are inherited progressive disorders of anterior horn cells, peripheral motor nerve, or muscle. Among these are the spinal muscular atrophies, Charcot-Marie-Tooth polyneuropathies, and muscular dystrophies. Mild day-to-day fluctuations in strength may occur, but the overall progression is steady (i.e., the disorder is slowly progressive from the start and it remains that way); it will not suddenly change course and become rapidly progressive. As mentioned earlier, patients may experience long periods of stability when their disease is seemingly nonprogressive.

Attempts to categorize disorders have traditionally been based on whether the disorder was caused by anterior horn cell, peripheral motiir nerve, or muscle disease, along with .1 specific pattern of muscle weakness. Certain characteristic patterns of weakness often suggest specific diagnoses. For example, FSH and oculopharyngeal muscular dystrophies are so named because of their selective involvement of muscles. In the modern day, all of these disorders are being further redefined and categorized based on their specific genetic abnormality and in some the specific structural protein the involved gene encodes.

Other Conditions

No scheme of analysis is perfect in clinical medicine, and many exceptions exist to the guidelines provided earlier. Most notable are disorders that are restricted to various parts of the body. The etiology and the reasons for such localized illness are not clear, but examples include branchial myopathy and quadriceps myopathy, as well as the focal form of motor neuron disease, which often remains in one segment of the body for years to decades (benign monomelic amyotrophy). These diseases are often "benign" in that they do not shorten life. The weakness may cause disability, although it is usually mild.

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Chapter 29
Muscle Pain and Cramps

Waqar Waheed and Alan Pestronk

Pain is an uncomfortable sensation with sensory and emotional components. Short episodes of muscle pain or discomfort are a universal experience. Common causes of short-term muscle discomfort are unaccustomed exercise, trauma, cramps, and systemic infections. Chronic muscle discomfort is also relatively common. In the U.S. population between the ages of 25 and 74 years, 10-14% complain of chronic pain rehired to the joints and musculoskeletal system. Pain localized to muscle may be caused by noxious stimuli in muscle but also may be referred from other structures, including connective tissue, joints, and bone. The referral of pain may involve secondary contraction of muscle during the pain or indirect neural activation evoked by the noxious stimulus. Some patients with small-fibet polyneuropathies have spontaneous pain that is localized to muscle.

Pain in muscle and other tissues can be categorized according to temporal and qualitative features. Pain elicited by noxious stimulation of normal tissue has an early ("first") phase that is perceived as sharp and well localized and that lasts as long as the stimulus. This is followed by a somewhat delayed ("second") phase of pain that is dull, aching or burning, and more diffuse. Second-phase pain has both sensory and affective components and may predominate with visceral and chronic pain. Pain from stimulation of diseased tissue is often associated with *hyperalgesia,* in which a noxious stimulus produces an exaggerated pain sensation, or with *allodynia,* in which pain is induced by a normally innocuous stimulus. Neuropathic pain is associated with incteased activity in abnormal afferent axons and occurs spontaneously or after peripheral stimuli.

MUSCLE **PAIN:** BASIC CONCEPTS

Nociceptors

Many of the afferent nerve fibers that transmit painful stimuli from muscle (nociceptors) have small unmyelinated (free) axon terminals (Graven-Nielsen and Mense 2001; Julius and Basbaum 2001). These terminal axons (nerve endings) are mainly located near blood vessels and in connective tissue but do not contact muscle fibers. Free nerve endings have a small diameter (0.5 *jim)* with varicosities (expansions). They contain glutamate and neuropeptides. Noxious stimuli produce graded receptor potentials in nerve endings, with the amplitude dependent on strength of the stimulus. If the amplitude is large enough to reach threshold, an action potential is generated. Action potentials arising in nociceptor terminals play two roles in inducing pain. Direct centripetal conduction along afferent axons brings nociceptive signals to the central nervous system (CNS). Indirect effects occur when action potentials are conducted centrifugally, invading other nerve terminals, which then release glutamate and neuropeptides into the extracellular medium. These algesic substances can stimulate or sensitize terminals on other nociceptive axons.

Nociceptor Stimulation and Sensitization

Muscle pain is induced by chemical or mechanical stimuli. The specific chemical factors that are involved in the peripheral generation of pain arc better defined in tissues other than muscle. Intramuscular injections of hypertonic saline arc used experimentally to induce pain that is similar to acute clinical muscle pain, without producing associated morphological abnormalities in muscle. Increased levels of glutamate in muscle correlate temporally with the appearance of pain due to hypertonic saline and after exercise. Other possible chemical algesic stimuli in muscle include ions (acid pH and potassium |high|), and neurotransmitters (adenosine triphosphate |ATP|, bradykinin, 5-hydroxytryptamine [5-HT], and adrenaline).

Sensitization of nociceptive axon terminals is defined as reduction, into the innocuous range, of the threshold for their stimulation. Vanilloid receptors and tetrodotoxin-rcsistant sodium channels can play roles in the sensitization of nerve terminals. The reduction in threshold of axon

terminals is induced by factors released during muscle damage or repetitive stimulation. Stimuli implicated in the sensitization of terminals include algesic substances (5-HT, prostaglandin E_z [$PGE_2$1, and bradykinin), nerve growth factor, and repeated stimulation {heat, protons, or capsaicin via vanilloid receptors). Effects of stimuli may be mediated intracellularly by calcium and kinases. Sensitization of nociceptor terminals can increase the frequency of action potentials in normally active nociceptors or induce new action potentials in a population of normally silent small axons that is especially prominent in viscera. Substance P induces a low-frequency discharge in afferent axons that could contribute to spontaneous pain. Lcukotriene D_4 may have a desensitizing effect on muscle nociceptors. The depression of muscle nociceptor activity by aspirin may reflect inhibition of the effects of PGE_2.

Afferent Axons Involved in Nociception

AS group III and C group IV class axons play important roles in the conduction of pain-inducing stimuli from muscle to the CNS. The ability to detect acute noxious stimuli is largely eliminated by blockade of both *AS* and C class axons. *AS class nociceptive axons* are thinly myelinated, conduct impulses at moderately slow velocities (3-13 m per second), and have membrane sodium channels that are tetrodotoxin sensitive. AS axons are high-threshold medianoceptors that are stimulated by strong local pressure and mediate rapid, acute, sharp ("first") muscle pain. Spontaneous pain and dysesthesias are probably mediated by A3 class axons. C *class nociceptive axons* are unmyelinated, conduct impulses at very slow velocities (0.6-1.2 m per second), and have membrane sodium channels that are tetrodotoxin resistant. C class axons in muscle are often poly modal, responding to a range of stimuli, but stimulus-specific axon terminals are also present. C fibers mediate somewhat delayed, diffuse, dull, or burning ("second") pain evoked by noxious stimuli. Constituents of muscle nociceptor C axons include substance P, calcitonin gene-related peptide, and somatostatin. These constituents may place the nociceptive axons in a subgroup of C fibers that mediate hyperalgesia in response to inflammation. *AS class axons* are large and myelinated and conduct impulses at rapid velocities. They normally mediate innocuous stimuli and stimulation may reduce the perception of pain, liitlaiiiin.ivion or repetitive stimulation can sensitize *AS* axons, which then mediate mechanical allodynia in some tissues. This "phenotypic switch" in *AS* axons may be mediated by uprcgulation of neuropeptide Y and sprouting of terminals in the spinal cord from lamina III and IV into lamina II, with subsequent stimulation of ascending central pain pathways.

Central terminations of nociceptive axons from muscle are located in lamina I in the dorsal horn of the spinal cord. Ascending central neurons, with cell bodies in lamina I or II, are stimulated by glutamate from the terminals of primary afferent axons and convey sensory pain modalities via the contralateral spinothalamic tract to thalamic nuclei (Ren and Dubncr 2002). Transmission of affective features of pain may involve other pathways to the parabrachial nucleus, amygdala, thalamic intralaminar nucleus, and anterior cingulate gyrus. Inrerncurons and descending CNS pathways modulate afferent input, especially with chronic pain. Central sensitization to pain is associated with neurons containing substance-P receptors. Glutamate acting at N-mcthyl-D-aspartate (NMDA) receptors is essential for the initiation of central sensitization and for the hyperexcitability of spinal cord neurons and persistent pain. Facilitation via descending CNS pathways may lead to allodynia and the maintenance of hyperalgesia. Inhibitory descending pathways are associated with increased opioid sensitivity and may provide a system of endogenous analgesia. There is enhanced net descending inhibition at sites of primary hyperalgesia associated with inflammation.

Pathological Conditions Producing Muscle Pain

Episodes of pain originating in muscle are commonly associated with exercise, inflammation, and trauma. Exercise can produce muscle pain by several pathways, including exhaustion of fuel supply (with lack of training, vascular insufficiency, or metabolic detect-,;, cramps, or injury to muscle fibers or tendons. When muscle contracts while it is being stretched (eccentric contraction), damage and pain are especially likely. During exercise with eccentric contraction, the shearing forces on connective tissue may directly activate muscle nociceptors. Similar painful shearing forces occur during cramps, when the contracting segment stretches the remainder of the muscle. Delayed-onset muscle soreness (DOMS) may be due to several factors, including muscle fiber and connective tissue damage, inflammation, and edema. Pain with DOMS is associated with increased levels of glutamate in muscle.

In damaged muscles, tenderness, a decrease in pressure pain threshold, and pain with movement are due to sensitization of muscle nociceptors. The sensitized nociceptors have a lowered threshold of excitation and a greater response to noxious stimuli. With muscle inflammation, pain at rest may be due to nociceptive axons that develop a raised level of background discharge. Mediators of this phenomenon could include algesic substances including substance P, bradykinin, and serotonin. Pain during muscle ischemia may also be related to accumulation of algesic substances, but probably not to lactate accumulation. It has been suggested that myofascial (trigger-point) pain syndromes arc associated with hypercontraction of muscle fibers. However, this has not been well documented and the possible afferent pathway is unclear because muscle fibers are not innervated by nociceptive axons. A more objective

definition of clinical and pathophysiological features of myofascial and fibromyalgia syndromes would be helpful.

CLINICAL FEATURES OF MUSCLE **PAIN**

General Fearures of Muscle Pain

Muscle discomfort is described using several different terms, including *pain, soreness, aching, fatigue, cramps,* or *spasms.* Pain that originates from muscle is perceived to arise from deep tissues. This property of muscle pain may reflect convergent afferent axons from various tissues that mask identification of a specific source by higher centers. Chronic muscle pain may be poorly localized, referred to another (usually deep) location, and associated with autonomic and affective symptoms. Pain with muscle cramps has an acute onset and short duration. Cramp pain is associated with palpable muscle contraction and is immediately relieved by stretching the muscle. Pain originating from fascia and periosteum is relatively precisely localized. Cutaneous pain differs from muscle or fascial pain by its distinct localization and sharp, pricking, stabbing, or burning nature. In fibromyalgia syndromes, patients commonly complain that fatigue accompanies their muscle discomfort. Depression is approximately twice as common in patients with chronic musculoskeletal pain (18%) than in a population without chronic pain (8%).

Evaluation of Muscle Discomfort

Disorders underlying muscle discomfort can be classified based on anatomy, temporal relation to exercise, muscle pathology, and the presence or absence of active muscle contraction during the discomfort {Kincaid 1997; Pestronk 2003). Evaluation of muscle discomfort typically begins with a history, including the type, localization, inducing factors and evolution of the pain, drug use, and mood disorders. The physical examination is conducted with special attention to the localization of weakness. However, accurate assessment of strength may be difficult in the presence of pain. The sensory examination is important because small-fiber sensory neuropathies commonly cause discomfort with apparent localization in muscle. A general examination is important to evaluate the possibility that pain may be arising from other tissues, such as joints. Blood studies may include a complete blood cell count, erythrocyte sedimentation rate, creatine kinase (CK), potassium, calcium, phosphate, and lactate levels, thyroid functions, and evaluation for systemic immune disorders. Urine myoglobin concentration should be evaluated in patients with a high CK level and severe myalgias, especially when they are related to exercise. Electromyography (EMG) is a sensitive test for myopathy. A normal EMG result suggests that muscle pain is arising from other anatomical loci. Nerve conduction evaluation may detect an underlying neuropathy, but objective documentation of small-fiber adenopathies can require quantitative sensory testing or skin biopsy with staining of distal nerve fibers (generally a research technique). Magnetic resonance imaging or radionuclide scans may reveal focal or diffuse anomalies in muscle, joints, or fascia and can be used to guide biopsy procedures. Phosphorous magnetic resonance spectroscopy may become useful in the evaluation and monitoring of some metabolic myopathies, but its specific utility is not yet determined. Muscle biopsy is most often useful in the presence of another abnormal test result, such as a high scrum lactate or CK level or an abnormal EMC. However, important clues to treatable disorders, such as fasciitis or systemic immune disorders (perivascular inflammation or granulomas), may be present in muscle in the absence of **other** positive testing. The yield of muscle biopsy in syndromes with muscle discomfort is increased if both muscle and connective tissue are examined. There is increased diagnostic yield from muscle biopsies if histochemistry includes staining **for** acid phosphatase, alkaline phosphatase, esterase, mitochondrial enzymes, glycolytic enzymes, and myoadenylate deaminase, in addition to routine morphological analysis and processing. **Ultra**-structural examination of muscle rarely provides additional information.

MUSCLE DISCOMFORT: SPECIFIC CAUSES

Muscle pain can he broadly divided into groups depending on its origin and whether it occurs at the time of muscle contraction. Myopathies may be associated with muscle pain without associated muscle contraction (myalgias) (Tables 29.1 and 29.2). Muscle pain during muscle activity (Tables 29.2 and 29.3) may occur with muscle injury, myopathy, cramps, or long-term tonic contraction. Some pain syndromes that are perceived as arising from muscle originate in other tissues or have no clear morphological explanation for the pain (Table 29.4).

Myopathies with Muscle Pain

Myopathies that produce muscle pain (see Table 29,1) are usually associated with weakness, a high serum CK level, and an abnormal EMC; (Griggs, Mendel I, and Miller I 995; Pestronk 2003). Only a minority of inflammatory myopathies are associated with pain and muscle tenderness. Pain is a typical feature of childhood dcrmatomyositis, immune myopathies with systemic disorders, eosinophilia myalgia syndromes, and infections. Myopathies caused by infections, including bacterial, viral, toxoplasmosis, and trichinosis, are usually painful. Metabolic myopathics, including phosphorylase and carnitine palmitoyltransferase II deficiencies, typically produce muscle discomfort or fatigue

Table 29.1: Pain syndromes, myopathic"[1]

- Inflammatory
  - Inflammatory myopathics
    - Systemic connective tissue disease
    - Transfer ribonucleic acid synthetase antibodies
    - Childhood dcrmatomyositis
  - Muscle infections
    - Viral myositis
    - Pyomyositis
    - Toxoplasmosis
    - Trichinosis
- Rhabdomyolysis ± metabolic disorder
  - Myophosphorylase—McArdle's
  - Phosphof r ucro kinase
  - Carnitine palmitoyltransferase II
  - Mitochondrial myopathies
  - Malignant hyperthermia syndromes
- Other myopathics with pain
  - Myoadenylate deaminase
  - Myopathy with focal depletion of mitochondria
  - Myopathy with tubular aggregates ± cylindrical spirals
  - Myopathy with tubulin-rcactive crystalline inclusions
  - Neuromyopathy wirh internalized capillaries
  - Myoronias: PROMM; dominant myotonia congenita (occasional)
  - Selenium deficiency
  - Toxic myopathy: Eosinophilia myalgia; rhabdomyolysis
  - Hypothyroid myopathy
  - Mitochondrial disorders
  - Camurati-F.ngelmann syndrome
- Drugs and toxins

'Usual features: weakness, high serum crearine kinase level, and abnormal electromyogram.

Table 29.2: Muscle discomfort associated with drugs and toxins

- Inflammatory myopathy
  - Definite
    - Hydralazine
    - Penicillamine
    - Procainamide
    - L-Tryptophan (impurity)
  - Possible
    - Cimetidine
    - Ipecac
    - Lansoprazole
    - Leuprolide
    - L-Dopa
    - Penicillin
    - Phenytoin
    - Propylthiouracil
    - Sulfonamide
- RliaKlomyolysis + chronic myopathy
  - Alcohol
  - "^-Aminocaproic acid
  - Ampheramines
  - Cocaine
  - Cyclosporine
  - Hypokalemia
  - Isoniazid
  - Lipid-lowcring agents*
    - Bezafibrate
    - Clofibratc
    - Gemfibrozil
    - Lovasrarin
    - Simvastatin
    - Pravastatin
    - Fluvastatin
    - Atorva statin
    - Ccr vista tin
    - Red yeast rice
  - Lithium
  - Propofol
  - Zidovudine
- Painful myopathy ± rhabdomyolysis
  - Colchicine
  - Emetine
  - Germanium
  - Hypervitaminosis E
  - Taxenes
  - Zidovudine
- Myalgia ± myoparhy
  - All rrans-retinoic acid
  - Azathioprinc
  - Bryosratin 1
  - Captopril
  - Ciguatoxin
  - Corticosteroid withdrawal
  - Cytotoxics
  - Danazol
  - Enalapril
  - Gemcitabine
- Cold
  - Interferon-a; 2 a and 2b
  - Isotretinoin
  - Kerorolac
  - Labetalol
  - Methotrexate*
  - Metolazone
  - Mycophcnolate mofctil
  - Paclitaxel
  - Retinoids
  - Rifampin
  - Spanish toxic oil
  - Suxamethonium (succinylcholine)
  - Vinca alkaloids
  - Zimeldine
- Cramps
  - Albuterol
  - Anticholinesterase
  - Bergamor (bergapten)
  - Caffeine
  - Clofibrate
  - Cyclosporine
  - Diuretics
  - Laberalol
  - Lithium
  - Nifedipine
  - Terburaline
  - Tetanus
  - Theophylline
  - Vitamin A

'"Especially with concurrent: Cyclosporine A, Danazol, Erythromycin, Gemfibrozil, Niacin.
[+]With concurrent pantoprazole.

that arises toward the end or after the completion of exercise and is less prominent at rest. As a general rule, disorders of carbohydrate use produce pain and fatigue after short intense exercise, whereas lipid disorders cause muscle discomfort with sustained exercise. Rhabdomyolysis is usually associated with muscle pain and tenderness that can persist for days after the initial event. It may occur with a defined metabolic or toxic myopathy or sporadically, in the setting of unaccustomed exercise, especially with hot weather. Because rhabdomyolysis may produce renal failure—a life-threatening complication—diagnosis, treatment, and avoidance of further precipitating factors should be aggressively pursued. Medications, including "'*[s]-aminocaproic acid and cholesterol-lowering agents, may produce a painful necrotic myopathy that can be associated with rhabdomyolysis. Muscular dystrophy and mitochondrial disorders are usually painless, but a small proportion of patients, including some with mild Becker's muscular dystrophy with minimal or no weakness, may experience myalgias and cramps or rhabdomyolysis. Several myopathies defined by specific morphological or physiological changes in muscle commonly have myalgias or exercise-related discomfort as part of their associated clinical syndrome. Features of these myopathies include tubular aggregates with or without cylindrical spirals, focal depletion of mitochondria, internalized capillaries, and proximal myotonic myopathy (myotonic dystrophy type 2, DM2).

Muscle Overuse Syndromes

Cramps (see Table 29.3) are a localized form of muscle contraction and overuse. Pain syndromes associated with cramps include discomfort during a muscle contraction and soreness after the contraction due to muscle injury. Cramps

Table 29.3: Cramps*

- Cramp syndromes
  - Ordinary
    - Common in normal subjects, especially gastrocnemius
    - Pregnancy
  - Systemic disorders
    - Dehydration: Hidrosis; diuretics; hemodialysis
    - Metabolic: Low Na^+, Mg^+, Ca^{2+}, glucose levels
    - Endocrine: Thyroid (hyper or hypo); adrenal insufficiency
  - Drug induced
  - Cramp faseiculation
  - Contractures: Glycolytic disorders; Brody's syndrome; rippling muscle
  - Neurogenic: Cramps and spasms
    - Central disorders: Stiff person syndrome; spasticity
    - Neuromyotonia
    - Denervation, partial: Neuropathy; radiculopathy
  - Familial syndromes
- Familial cramp syndromes
  - Myopathic: Becker's muscular dystrophy; limb girdle muscular dystrophy (LGMD) 1C
  - Myotonia: Congenita; occasionally dystrophy
  - Contractures
    - Brody's syndrome
    - Glycogen disorders: Phosphorylase deficiency, etc.
    - Rippling muscle syndrome
  - Neuropathic
    - Cramps: Autosomal dominant
    - Dwarfism and muscle spasms
    - Neuromyotonia
- Treatments for cramps
  - Normalize metabolic abnormalities
  - Quinine sulfate, 260 mg qhs or bid
  - Carhamazepine, 200 mg bid or tid
  - Phenytoin, 300 mg qd
  - Tocainide, 200-400 mg bid
  - Verapamil, 120 mg qd
  - Amitriptyline, 25-100 mg qhs
  - Vitamin E, 400 1U qd
  - Riboflavin, 100 mg qd
  - Diphenhydramine, 50 mg qd
  - Calcium, 0.5-1.0 g elemental Ca^{2+} qd

*Usual features: sudden involuntary painful muscle contractions; usually involve single muscles, especially gastrocnemius; local cramps in other muscles often associated with neuromuscular disease. Precipitants: muscle contraction; occasionally during

Tabic 29.4: Pain syndromes without chronic myopathy*

- Pain of uncertain origin
  - Polymyalgia rheumatica
  - Fibromyalgia
  - Chronic fatigue syndrome
  - Infections
    - Viral and postviral syndromes
    - Brucellosis
  - Endocrine
    - Thyroid: increased or decreased
    - Parathyroid: increased or decreased
  - Familial Mediterranean fever
- Pain with defined origin
  - Connective tissue disorders
    - Systemic
    - Fasciitis
  - Joint disease
  - Bone: osteomalacia; fracture; neoplasm
  - Vascular: ischemia; thrombophlebitis
  - Polyneuropathy
    - Small-fiber polyneuropathies
    - Cm Ham-Bane
  - Radiculoneuropathy
  - Central nervous system: restless legs syndrome; dystonias (focal)
- Pain of muscle origin without chronic myopathy
  - Muscle ischemia: atherosclerosis; calciphylaxis
  - Muscle overuse syndromes
    - Drugs and toxins
  - Delayed-onset muscle soreness (DOMS)
    - Cramps
  - Muscle injury (strain)

""Usual features: muscle pain; may interfere with effort, but no true weakness; present at rest, may increase with movement; muscle morphology and serum creatine kinase level normal.

are common in normal people in the gastrocnemius muscle and in patients with fasciculations. They usually atisc duting sleep or exercise and are more likely to occur when muscle is contracted while in a shortened posirion. Relief of cramps is often obtained rapidly by stretching the affected muscle. Active stretching, by contracting the antagonist, may be especially effective treatment because it evokes reciprocal inhibition. Cramps that occut ftequcntly in muscles othet than the gastrocnemius usually herald an underlying neuromuscular disorder.

The EMG is useful for defining the specific type of cramp. Cramps of muscular origin include electrically acrive contractions, electtically silent contractures and myotonic types. Electrically active muscle cramps due to myopathy are manifest by itrcgular triphasic action potentials occurring at a rate of 40-60 Hz. They may be a feature of Becker's muscular dystrophy and thyroid disorders. Muscle contractures are active muscle contractions in the absence of electrical activity. These electrically silent muscle contractions occur in myophosphorylase deficiency and other glycolytic disorders, Brody's syndrome, rippling muscle disease, and hypothyroidism (myoedema). Contractures in myophosphorylase deficiency are typically provoked by exercise and may be prolonged and painful. Myotonia appears on EMG as repetitive bursts of action potentials in individual muscle fibers that last 1-30 seconds and have a variable frequency. The action potentials may be triggered by mechanical or electrical stimulation. Myotonic cramps are frequently not painful. Patients with recessive myotonia congenita often note fatigue.

Neurogenic cramps may arise from peripheral nerves or the CNS, They often ptoduce discomfort. The common muscle cramp usually arises from motor netve terminals. EMG shows irregular triphasic action potentials at 40-150 Hz that increase and then decrease during the course of the ctamp. Several drugs may precipitate cramps

(see Table 29.2). Muscle spasms are defined as intense painful muscle contractions that are more persistent than a cramp. There is often palpable tightness and resistance to movement in muscle. Occasionally there is distortion of posture. EMG shows tonic firing of motor unit action potentials. Neurogenic disorders that are associated with cramps, painful muscle spasms, or muscle discomfort include amyotrophic lateral sclerosis, neuromyotonia, spinal stenosis, stiff person syndrome, spasticity, restless legs syndrome, and focal dystonias. Treatment of cramps involves remedy of the underlying disorder or symptomatic trials of a variety of medications. Quinine was effective in treating nocturnal muscle cramps in a double-blind, placebo-controlled trial.

Diffuse muscle contraction syndromes are often related to CNS disorders associated with drugs or toxins (see Table 29.2). They include malignant hyperthermia, neuroleptic malignant syndrome, and toxic disorders related to phencyclidine, amphetamine, tetanus, and strychnine. Diffuse contraction syndromes produce great discomfort in the awake patient. In the postoperative period, myalgia and fasciculations often occur after the use of succinylcholinc (suxamethonium).

Myalgia Syndromes without Chronic Myopathy

Polymyalgia syndromes (see Table 29.4) are characterized by pain localized to muscle and other structures without muscle weakness. The pain may produce the appearance of weakness by preventing full effort. This type of "weakness" is characterized on examination by sudden reductions in the level of effort, rather than the smooth movement through the range of motion that is detected with true muscle weakness. Polymyalgic pain is often present at rest and is variably affected by movement. Serum CK levels and EMG are normal. There are no major pathological changes jn muscle unless the discomfort produces disuse and atrophy of type II muscle fibers. Muscle biopsies may show changes associated with systemic immune disorders, including inflammation around blood vessels or in connective tissue. Many polymyalgia syndromes have clear underlying disorders, including systemic immune disease, drug toxicity, and small-fiber polyneuropathies.

Some syndromes associated with muscle discomfort, such as polymyalgia rheumatica, fibromyalgia, and chronic fatigue syndrome, are defined by a series of clinical criteria and have no well-defined pathophysiology. Polymyalgia rheumatica usually occurs after age 50 years and manifests with pain and stiffness in joints and muscles, weight loss, and low-grade fever. The pain is symmetrical, involves the shoulder, neck, and hip girdle, and is greatest after inactivity and sleeping. Polymyalgia rheumatica can be associated with temporal arteritis. Patients often have an elevated erythrocyte sedimentation rate (>40 mm/hour). Pain improves within a few days after treatment with corticosteroids (prednisone, 20 mg/day). The diagnosis of fibromyalgia depends on a history of widespread musculoskeletal pain, most commonly around the neck and shoulders, for 3 months or more, and examination findings of tender points on the extremiries and trunk. Patients also may note fatigue and disturbed sleep, headache, irritable bowel syndrome, and aggravation of symptoms by exercise, anxiety, or stress. The diagnosis of chronic fatigue syndrome requires symptoms of muscle fatigue for at least 6 months. Myalgias, paresthesias, headache, dizziness, diaphoresis, fainting, and memory loss may also be noted. Findings on examination may include a low-grade fever, pharyngitis, and enlarged cervical or axillary lymph nodes. Many patients with chronic fatigue syndrome improve spontaneously over time. Treatment of both fibromyalgia and chronic fatigue syndrome frequently includes the use of tricyclic antidepressants. Among controversial syndromes that include myalgias are myoadcnylatc deaminase deficiency, adjuvant breast disorders, Gulf War syndrome, and multiple chemical sensitivity,

Pain or discomfort localized to muscle may arise in other structures. For example, hip disease can be misdiagnosed as a painful proximal myopathy with apparent leg weakness. In this situation, external or internal rotation of the thigh commonly evokes proximal pain. Radiological studies confirm the diagnosis. Disorders of bone and joints, connective tissue, endocrine systems, vascular supply, peripheral nerve and roots, and the CNS may also present with discomfort localized to muscle.

Pain originating from muscle, often acute, may occur in the absence of a chronic myopathy. Muscle ischemia causes a squeezing pain in the affected muscles during exercise. Ischemia produces pain that develops particularly rapidly (wirhin minutes) if muscle is forced to contract at the same time and subsides quickly with rest. Cramps and overuse syndromes are associated with pain during or immediately after muscle use. DOMS occurs 12-48 hours after exercise and lasts for hours to days. It is most commonly prccipiratcd by eccentric contraction or unaccustomed exercise.

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Chapter 30
The Floppy Infant

Thomas O. Crawford

The floppy infant is one of the more common neurological syndromes encountered in the premature neonate (<37 weeks' gestational age), full-term neonate (birth to 30 days), and infant (1 month to 1 year). The terms *hypotonic infant* or *weak infant* are often applied to this syndrome, but each has both a distinct technical meaning and an accepted common usage. The more colloquial term *floppy* may be a better generic definition for the syndrome because it carries no such ambiguity. The differential diagnosis of the floppy infant is broad and includes many rare disorders and syndromes, some with precise nosologic definitions and others with only vague descriptive value (Table 30.1). As in all of neurology, the differential diagnosis is first narrowed by localization of the problem to a portion of the nervous system on the basis of the history and the physical examination. Once the site of dysfunction is suspected, a specific diagnosis can often be reached with a small number of confirmatory tests that may include an imaging study, electromyography (EMG) and nerve conduction study, muscle biopsy, or molecular genetic test.

Normal movement and tone depend on the coordinated fusion of multiple hierarchical and parallel central nervous system (CNS) pathways acting on an adequate number and distribution of functioning motor units. Each motor unit consists of a motor neuron, its peripheral nerve fiber consisting of an axon and the surrounding Schwann cell-produced myelin sheath, and the multiple muscle fibers connected with the motor neuron through the neuromuscular junction. Fortunately for the process of differential diagnosis, a disturbance in function at different locations within the CNS or the motor unit is often associated with a characteristic clinical syndrome of disturbed power and tone. The cardinal features that characterize these syndromes in the floppy infant are tone, power, range of movement, reflexes, endurance, muscle bulk, sensation, and associated CNS or systemic abnormalities (Table 30.2).

CARDINAL SIGNS

Tone

Muscle tone is defined by different authors in different ways; these definitions often are not easily translated from **one** discussion to another. In general, *tone* can be defined as the unconscious and automatic induction of muscle power in response to an applied load. Different, nonexclusive forms of tone can be distinguished and elicited by various **tests.** Resting tone is that which is present with the subject in an awake, alert state at rest. It is generally assessed by inspection, as for example when evaluating a neonate or premature infant before handling (Figure 30.1). Static or passive tone is that which is induced by passive movement of an otherwise immobile muscle. The subject must be awake, cooperative, and voluntarily nonresisting during the assessment, a state that is not common in the examination of infants. Postural tone involves resistance to gravity and is important to the maintenance of stable

Table 30.1: Important differential diagnoses of the floppy infant (excluding syndromes in which features of cerebral degeneration precede hypotonia or weakness)

- Cerebral hypotonia
  - Chromosomal disorders
    - Trisomy
    - Partial chromosome deletion/duplication
    - Prader-Willi syndrome*
  - Static encephalopathy
    - Cerebral malformation
    - Perinatal distress
    - Postnatal cerebral injury
    - Idiopathic disorders
  - Single gene disorders
    - Zellweger syndrome (peroxisome biosynthesis, multiple)
    - Neonatal ad re no leukodystrophy (multiple)
    - Oculocercbral renal syndrome (Lowe's syndrome) (OCRL, Xq26.1)
    - Acid maltase (c*2,4 glucosidase deficiency, 17q25.2-q25.3)
    - Carbohydrate-deficient glycoprotein syndrome (unknown)
- Spinal cord disorders
  - Hypoxic-ischemic myelopathy
  - Trauma
  - *i*Congenital malformation
- Motor neuronopathies
  - Spinal muscular atrophy (SMA) (SMN, 5qll-13)»
  - Congenital cervical spinal muscular atrophy (unknown)
  - Infantile neuronal degeneration (some have SMA)
  - Neurogenic arthrogryposis (some have SMA)
  - Vaccine-associated poliomyelitis
  - Incontinentia pigmenti (unknown, Xq28)
- Polyneuropathies
  - Congenital hypo myelinating polyneuropathy (myelin P_0 |MPZ1, lq22)
  - Dejerine-Sottas syndrome (myelin $P_{(l}$ |MPZ], lq22; PMP22, lq22)*
  - Idiopathic (heritable) motor sensory polyneuropathies
- Disorders of neuromuscular transmission
  - Congenital (genetic) defect of neuromuscular junction (multiple)
  - In utero passive transfer of maternal antijunction antibodies
  - Autoimmune myasthenia gravis
  - Infantile botulism
- Myopathies
  - Genetic myopathies
  - Central core disease (ryanodine receptor, 19ql3.1)
  - Congenital fiber type disproportion myopathics
  - X-linked myotubular myopathy (MTM1, Xq28)*
  - Autosomal dominant nemaline myopathy (tropomy osin-3,1 q22-q23)
  - Autosomal recessive nemaline myopathy [Nebulin{?), q21.2-q22]
  - Congenital myotonic dystrophy (myoronin protein kinase, 19ql3.2-ql3.3)
  - Other congenital myopathies (nosologically indistinct)
- Infantile myositis
- Metabolic myopathies
  - Acid maltase deficiency (a2,4 glucosidase deficiency, 17q25.2-q25.3)
  - Cytochrome-c-oxidasc deficiency (multiple, autosomal, and mitochondrial)
- Metabolic myopathies
  - Carnitine dependency with impaired cellular carnitine uptake (unknown)
  - Multisystem phosphofructokinase deficiency (unknown)
- Congenital muscular dystrophics
  - Fukuyama's (fukutin, 9q31)
  - Merosm/(*2-laminin deficiency (a2 laminin, 6q22-q23)
  - Walker Warburg (unknown)
  - Muscle-eye-bra in (Ip32-p34)

Note: Gene and location, respectively, indicated in parentheses.
'Indicates whether DNA test is practical for diagnosis.

posture in space. It is evoked in response to the pull of gravity and testable at diffctcnt ages by different methods, such as in infants by withdrawing head support, applying traction to the arms to pull to a sitting position from a supine position (Figure 30.2), ot simply by axillary support in vettical suspension (Figure 30.3). Dynamic tone, which is closely telated to postutal tone, is that which is evoked in a phasic manner during automatic movements such as walking. At each stage of human development each of these diffetent foims of tone is assessed easily (Table 30.3).

At all stages diminished tone in the setting of normal muscle power implies involvement of the CNS. Increased tone can be further subdivided by characteristics of the resistance into the categories of spasticity, rigidity, or dystonia. Hypertonia always implies involvement of the

Table 30.2: Cardinal features for evaluation of the floppy infant

Feature	*Increased*	*Decreased*
Tone	Hypertonia: spasticity, rigidity, dystonia	Hypotonia*
Power	Normal	Weakness*
Range of movement	Laxity	Contracture*
Reflexes	Increased tendon reflexes	Decreased tendon reflexes*
Endurance	Fatigue resistant	Abnormal fatigue**
Muscle hulk	Hypertrophy*	Atrophy*

* Commonly associated with motor unit origin.
Commonly associated with central nervous system origin.

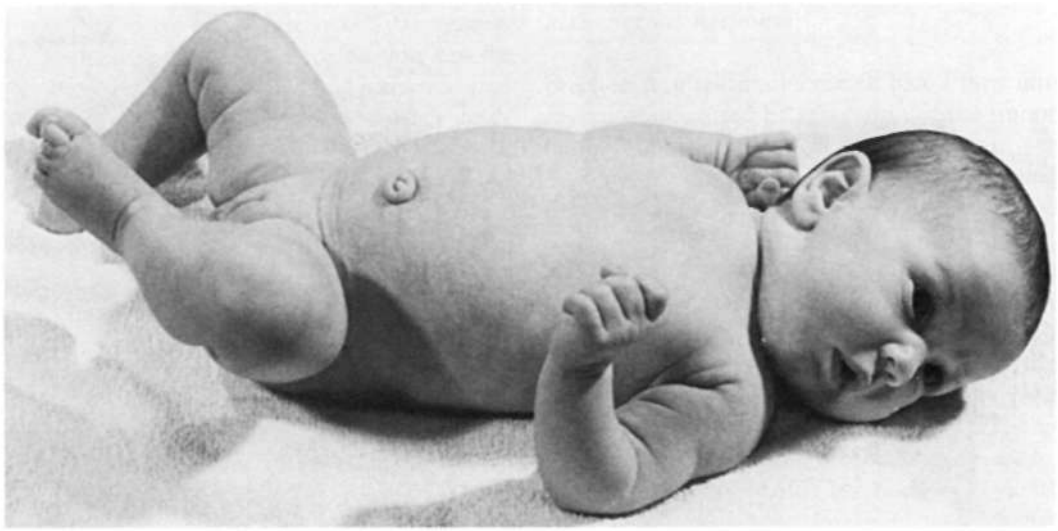

FIGURE 30.1 Normal resting tone. Note flexion at knees, hips, and elbows; hips are partially internally rotated to lift knees off of the surface and shoulders arc neutral to internal rotation.

CNS. Diminished muscle power (weakness) limits the appreciation of increased, normal, or diminished tone. Thus to the degree to which weakness is present, less can be inferred about motor pathways of the CNS.

Power

Muscle power (strength) is more easily defined than is muscle tone, and, in most cases, more easily evaluated. It is the maximum force that can be generated by any stimulus or provocation, whether voluntary or reflexive, normal or pathological. Attention is generally focused on states of diminished power, because increased muscle power is never pathological. Occasionally, infants and children with profound hypotonia cannot or will not express their available power by the usual examination methods but may do so duting phlebotomy or other painful procedures. Weakness in infants and children is usually best assessed in relation to develop mentally appropriate skills and behaviors, because maximum strength in isolated muscles may be difficult to elicit and grade according to the traditional five-point measures used in older children and adults. Certain skills that are often assessable and useful for the evaluation of infants and children are noted in Table 30.4, Diminished muscle power is substantial but not conclusive evidence of involvement of the motor unit; rare patients may have diminished muscle power on a central basis.

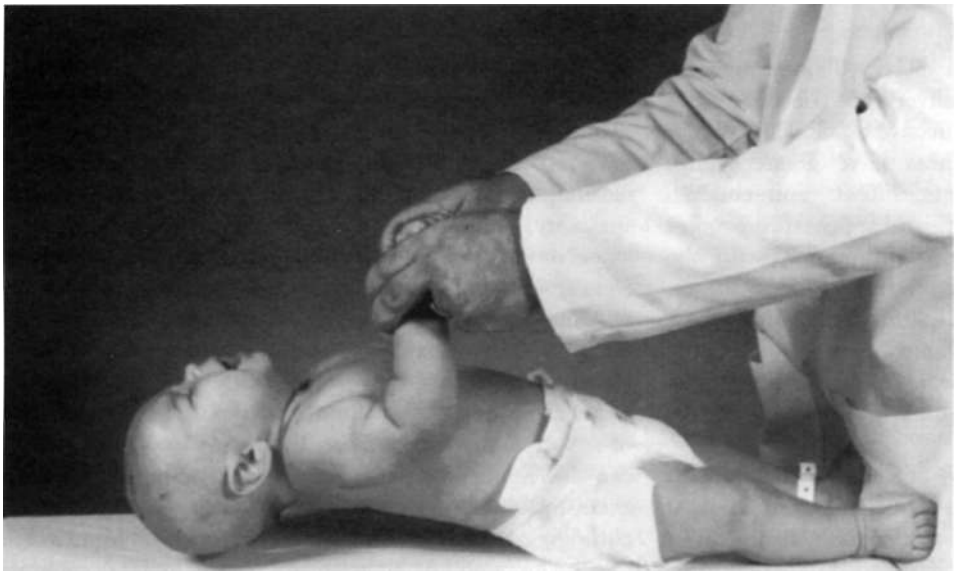

FIGURE 30.2 Abnormal traction response with a mixture of increased and decreased postural tone. The head sags, yet legs extend, manifesting a tendency to "pull to stand."

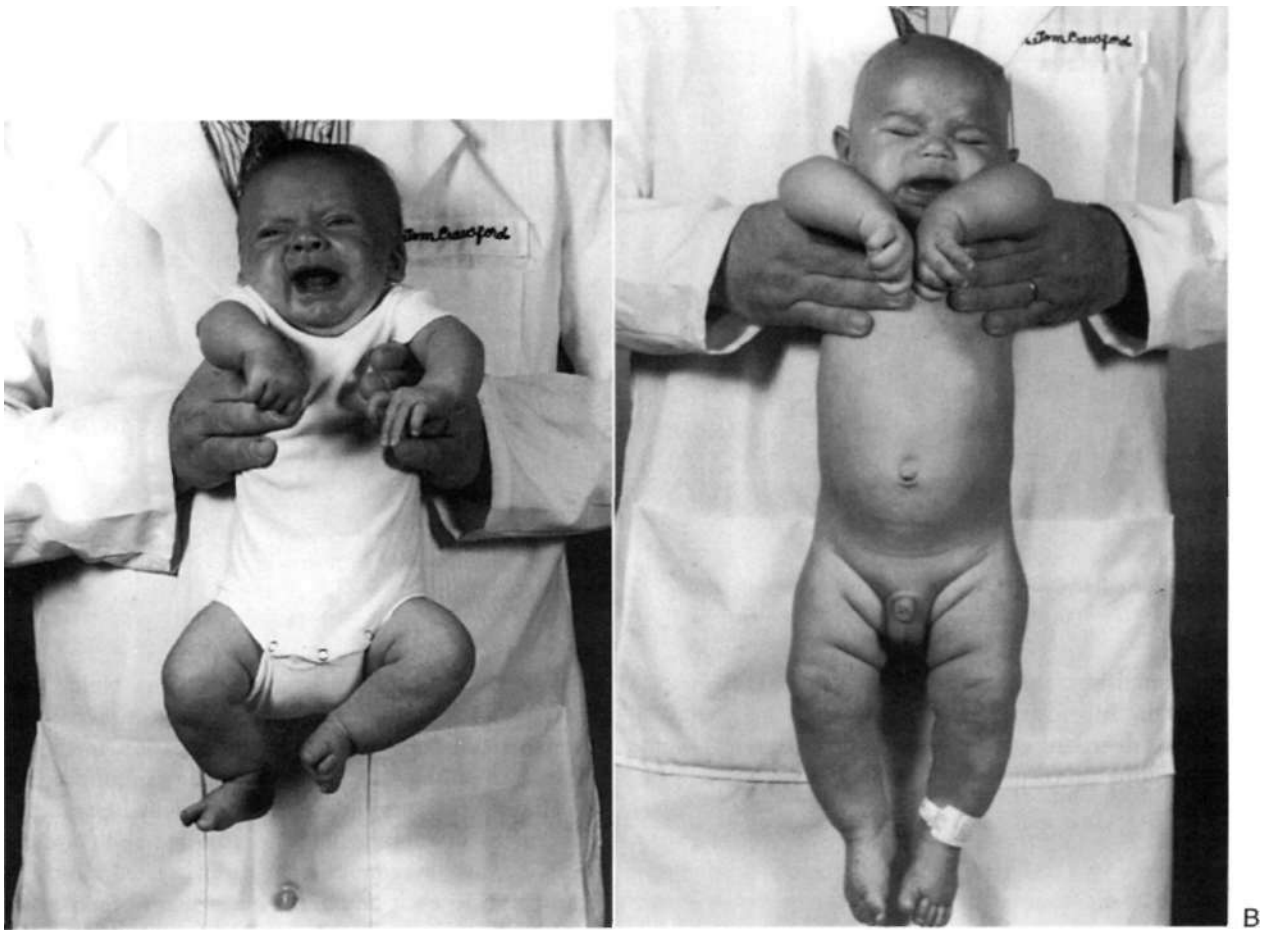

FIGURE .10.3 Vertical suspension: (A) Normal response. The head is erect, shouklers resist elevation, and arms remain adducted to counter slip-through while the legs are mostly flexed. (B) Abnormal response with a mixture of increased and decreased postural tone. Shoulders and arms elevate, requiring the examiner to clasp the chest to prevent slip-through. Legs are extended with a tendency for scissoring.

Range of Movement

Newborn infants often have an increased range of joint movement for a few days after delivery, the consequence of maternal hormone-mediated connective tissue relaxation to aid parturition. Premature infants have greater range of motion than do term infants. Infants and children with hypotonia or weakness have the appearance of joint laxity and may be referred for consultation with the presumptive diagnosis of a connective tissue disorder. However, children with isolated pathological joint laxity, such as those with the Ehlcrs-Danlos disorders, generally have normal strength and tone and thus appear quite different from children with primary disorders of the motor unit.

Joint range can be restricted by one or mure factors that include muscle fibrosis with an associated restriction of maximum length of the muscle tendon unit, ligamentous restrictions, and fibrosis of the joint capsule and associated structures. If acquired prenatally, a restriction of joint range is termed *arthrogryposis* and may be associated with underdevelopment of the joint itself. If acquired postnatally, a restriction in joint mobility is termed a *contracture.* Demonstration and measurement of a contracture require sufficient relaxation of the muscles surrounding a joint so that the connective tissue restrictions, and not active muscle tension, are the limiting factor being measured. With spasticity, contractures are often present but difficult to assess or measure because passive stretch stimulates muscle contraction.

Arthrogryposis is caused by a wide range of disorders and may affect a single joint or many joints. Multiple joint involvement is called *arthrogryposis congenita multiplex.* The least severe end of the arthrogryposis spectrum is the observation that main normal term or posi-tcrin infants can have mild and transitory restriction of full hip extension in the neonatal period. The most common pathologic expression of arthrogryposis is clubfoot, which may be unilateral or bilateral and usually involves multiple joints of the ankle and foot. The differential diagnosis

Tabic 30.3: Useful characteristics of tone at different stages of development

	Resting tune	*Static and passive tone*	*Postural and dynamic tone*
Premature	Increasing flexor tone associated with gestational age: lower extremities (30-32 wks), elbow flexion (34-36 wks), shoulder elevation (37-38 wks)*	Hypertonic states rarely expressed	Elastic recoil (36-40 wks)*; minimal postural reflexes
Neonate	Flexor tone prominent*	Hypertonic states rarely expressed	Traction response*; vertical suspension*; ventral suspension* ; head support emerges*
Infant	Decreasing resting tone; opisthotonus posture at rest	Emergence of spasticity with corticospinal tract injury; mixed tone; increased deep tendon reflexes	Traction response*; vertical suspension* ; luiri/nnial suspension '; good head support*; emergence of parachute responses**
Early childhood (approximately 15 yrs)	External rotation of hips and arms*; extensor posturing of lower extremities, flexor or extensor posturing of upper extremities**	Developing spasticity; increased deep tendon reflexes; rigidity (rare); dystonia	Gait analysis: symmetry, toe walking**; reciprocal upper extremity movements* ; spastic posturing of upper extremities*'
Adulthood	KM una I rotation tit hips and arms"; extensor posturing of lower extremities, flexor or extensor posturing of upper extremities**	Spasticity*; increased deep tendon reflexes ; rigidity ; dystonia	Gait analysis* : symmetry, toe walking*; reciprocal upper extremity movements* ; spastic posturing of upper extremities ; diminished checking with cerebellar disease*

* Features useful for assessment of decreased tone.
*Features useful for assessment of increased tone.

of arthrogryposis is summarized in Table 30.5. Many nongenetic and nonorthopedic causes of arthrogryposis are considered to be a nonspecific consequence of fetal immobility and may be the result of obstetrical complications such as uterine abnormalities, abnormal fetal positioning, diminished volume of amniotic fluid, or twinning, Curiously, among the several disorders that significantly decrease fetal movement, arthrogryposis is frequently associated with some but rarely so in others. In many cases in which arthrogryposis appears to be attributable to abnormal fetal development, a specific diagnosis cannot be made. One reason for this difficulty is found in the developmental interplay of trophic support between the fetal motor neuron and muscle; early injury to one or the other tissue may lead to resorption of both, thereby removing the evidence that can localize the primary insult.

Acquired contractures can be a consequence of either weakness or spasticity but are rarely seen in patients with primary central hypotonia. Although some association exists between the type and distribution of contractures and the underlying pathology, the overlap is sufficient to limit the usefulness of these distinctions to aid differential diagnosis.

Reflexes

Tendon reflexes involve a monosynaptic connection between afferent and efferent arms of the peripheral nervous system. The knee tendon reflexes usually can be elicited shortly after birth; ankle and biceps reflexes are more inconsistent but become more easily demonstrated with each succeeding month. Tendon reflexes are easiest to elicit when the limb is relaxed and are difficult to obtain in an agitated child. In younger infants, care should be taken to maintain the head in a midline position because of the asymmetrical effect of the tonic neck reflex (see discussion in this section of the chapter). Attention should be paid to the amount of stimulus necessary to evoke a reflex and to response symmetry and proportionality, comparing the vigor of reflexive responses between distal and proximal sites and between the arms and legs. Some overall change in the briskness of the tendon reflexes can be expected with change of state, but the relationships between body-locations should remain constant.

To produce a tendon reflex, the pulse of excitation elicited by tendon percussion must ascend the sensory nerve to the spinal cord in a coherent phasic pulse. Any neuropathy with

Tabic 30.4: Practical in-office measures of strength in infants and young children

! lend and mink
- Upright head stability
- Traction response
- Ability to recover head stability from progressively greater deflections laterally or anterior/posteriorly
- Independent sitting with or without hand propping, slumped or upright sitting posture
- Ability to reach overhead without lateral propping and tilting head back

Proximal arm strength
- Arms overhead *{"So* big")
- Reaching overhead to defined height (top of head, eye level, and so forth)
- Height of reach with arm outstretched at elbow
- Toy rings over post at defined heights
- Length of ball throw
- Combat crawling
- Wheelbarrow walk (with horizontal body position at defined level of support: hips, thighs, knees, ankles)

Distal arm strength
- Ability to grasp and elevate defined objects of various size and weight

Proximal leg strength
- Movement of legs against gravity while supine
- Kneeling, quadrupedal stance, or crawl
- Gower's maneuver (roll to prone, push to quadrupedal stance, walking up knees and trunk with hands to elevate torso)
- Stance
- Gait, Trendelenburg's waddle
- .Stoop and recover (squat stanee)
- Standing broad jump
- Time to run 30 yd

Distal leg strength
- Motion against gravity
- Steppage gait with slapping feet

associated abnormality of myelin spreads out arrival of the signal between different sensory nerve fibers, which in turn blunts the phasic motor response. The vigor of the reflexive response is related both to the phasic nature of this signal on arrival at the spinal cord as well as the excitability of the motor neuron pool. Chronic decreases in corticospinal tract input, inhibition of local inhibitory interncuronal circuits, isometric strain of other limbs (Jendrassik's maneuver), head position in infants (the tonic neck reflex), and some stimulatory drugs can increase motor neuronal excitability and increase the vigor of response. Acute inhibition of the corticospinal tract (spinal shock) and some other complex

Table 30.5: Differential diagnosis of arthrogryposis congenita multiplex

Non-neurological causes
- Oligohydramnios/polyhydramnios: upper gastrointesrinal malformations
- Oligohydramnios/polyhydramnios: urinary malformations
- Twinning
- Uterine abnormalities
- Chromosomal disorders
- Prader-Willi syndrome
- Other rare genetic syndromes
- Severe maternal illness

Central nervous system disorders
- Oligohydramnios: neurological swallowing defect
- Cerebral malformation
- Chromosomal disorders
  - Spina bifida or occult spinal dysraphism

Motor unit disorders
- Spinal muscular atrophy/infantile neuronal degeneration (deletion of SMN)
- Congenital segmental spinal muscular atrophy (non-SMN)
- Congenital hypo myelinating polyneuropathy
- Genetic myasthenic syndromes
- Passive transfer of maternal acetylcholine receptor antibodies (neonatal myasthenia gravis)
- Fiber disproportion myopathics
- Neurogenic arthrogryposis (non-*SMN)*

central disorders can decrease motor neuron excitability and inhibit the tendon reflex,

The importance of the tendon reflexes is always related to context. Absent or increased reflexes with normal coordination and power are likely to be of little importance. Normal reflexes in the setting of hypotonia or weakness imply localization to the CNS. Decreases in the number of motor neurons or contractile ability of muscle generally decrease the reflexes commensurate with the loss of power. Increased ease of reflex elicitation with a normal or diminished response, for example, percussion below the tibial tuberosity provoking reflexive knee extension in a weak limb, suggests simultaneous CNS and motor unit involvement. Disorders of the neuromuscular junction usually spare tendon reflexes, at least early in the course, because the first impulse of a series of depolarizations is relatively unaffected. Slowing of nerve conduction with dispersion of the phasic afferent signal, even though all impulses arrive at the spinal cord and are sensed normally, blunts stimulation of the reflex, which is why demyelinating neuropathy diminishes reflexes out of proportion to clinical weakness or loss of sensation.

Extension of the great toe and flaring of the other toes with plantar stimulation, Babinski's response, is suggestive of CNS ilvstunction at any age. hi younger children, infants, and newborns, however, extension of the great toe in response to plantar stimulation is common and likely to be complicated by other responses; in the absence of other signs of central involvement the value of plantar stimulation as a diagnostic clinical test is probably not worth the infant's annoyance.

Certain postural responses elicited in infancy may have predictive value. The Moro reflex and tonic neck reflex may be elicited in newborns and infants with cerebral hypotonia even when there is a paucity of spontaneous movement (Fenichel 1993). Their presence shows that the motor unit is intact. The Moro reflex is elicited by startle and is normally present in its full expression up to 6 months, but can be seen in fragmentary form in adults. It allows for observation of coordination and symmetry of extension. The best stimulus for startle is the sensation of falling. With the child held in the supine position, the head is allowed to fall a few centimeters rapidly, but gently, into the examiner's hands. The first response is a spreading movement, with the arms abducted and extended and the hands open. This is followed by a clutching movement of the arms adducting and flexing over the torso with fists closed. Absence of a Moro reflex is always abnormal and suggests severe central or motor unit dysfunction. Asymmetry of the response also may be either central or peripheral in origin.

The tonic neck reflex is a primitive vestibular reflex that is present from birth to 3 months of age. It must be suppressed before the child can learn to turn over. In the supine position the normal resting position of arms and legs is in flexion. With head rotation to one side, the ipsilateral arm and leg extend and contralateral limbs remain flexed. The tonic neck reflex should be variable, unsustained, **and** nonobligatory, with other responses easily dominating. An asymmetrical tonic neck response suggests injury to the contralateral hemisphere; a persistent or obligatory tonic neck response bilaterally suggests bihemispheric injury. In some infants turning the head from one side to the other can alter the vigor of tendon reflexes on one and then the other side, likely by a means analogous to the effect of Jcndrassik's maneuver.

Endurance

The concept oi latiguc ⊱. at least as complicated, and as confusing, as that of muscle tone. Many different competing definitions of fatigue exist among neurologists as well as the lay public. One form of fatigue can be a result of central perception of mood, weariness, or sleepiness. At the other end of the neuraxis, a different form of fatigue is demonstrable in the progressive loss of contractile force to tetanic direct muscle stimulation. Muscle fibers fatigue at differing rates, depending on the type and concentration of contractile proteins, energy substrate and supply, gas exchange, and the clearance of toxic metabolites.

The form of fatigue that is of greatest interest to most neuromuscular clinicians is that associated with progressive conduction failure of the neuromuscular junction. This manifests as an abnormal diminution of power in a muscle under a continuous load; it requires that the subject sustain maximum effort despite the associated discomfort. The assessment that effort is indeed maximum requires clinical judgment and is a common source of error in mistaken diagnosis, both in the misdiagnosis of myasthenia as psychogenic weakness and the reverse.

Disorders of the neuromuscular junction are not common in infants, but the appreciation that weakness has a fatigable component may be even more difficult because infants do not ordinarily exercise to the point of mental or physical exhaustion, except possibly while crying vigorously. Thus neuromuscular junction fatigue is best appreciated in those with difficulty in sucking or possibly swallowing. An infant who appears alert and hungry and has normal oral motor coordination but only sucks briefly may have bulbar fatigue. When junctional function is severely compromised, fatigue is manifested as variable weakness without sustained effort. In infants with junctional disorders, this is most often exhibited in restricted extraocular movement, ptosis, and bulbar and facial weakness but can eventually also cause generalized weakness.

Bulk

Severe loss of muscle bulk follows denervation and is most extreme in spinal muscular atrophy. Diminished bulk

of muscle may be obscured in infants by abundant subcutaneous fat and is thus sometimes better appreciated by palpation of long bones rather than by inspection. With severe muscle atrophy it is possible to outline the bony contour in a way that is not possible when muscle mass is more normal. Chronic denervating weakness without loss of muscle bulk is a characteristic of chronic conduction block in adults, but there arc no descriptions of disorders specific to children with well-characterized and long-standing conduction block. Some congenital myopathies also manifest with significant loss of muscle mass. Commensurate decreases in muscle bulk and power occur in severe malnutrition and some poorly characterized developmental myopathies that mostly have stable function over time. Though muscle atrophy suggests motor unit disease, it also occurs infrequently with purely central disorders.

Sensation

The sensory examination is difficult to evaluate in infants. It requires a lot of time, and small differences in sensibility almost never have diagnostic value. Thus the general sensory examination is limited; more extensive probing is necessary and appropriate only when there is a specific question and the answer is important. The different modalities of sensory testing have differing value for answering specific questions (Table 30.6). In evaluating the floppy infant, the sensory examination is of greatest value in the evaluation of those with spinal injury or peripheral polyneuropathy, in which sensory and motor fibers are equally affected. In polyneuropathy, changes in sensibility are most apparent in long fibers to the distal portions of extremities. In children old enough to report their experience reliably, the appreciation of vibratory stimuli should be roughly equal between distal and proximal bony prominences of both the arms and the legs. It is not as easy to relate the degree of the impairment of joint position sense between distal and proximal sites unless the changes with location are more extreme. Pin sharpness and temperature should be equal at distal and proximal sites, although care should be taken to compare extensor surfaces with extensor surfaces and flexor surfaces with flexor surfaces of the limb.

Associated Features

Long-standing immobility in the fetus may produce a scries of deformations. Such infants may have, in addition to arthrogryposis, a narrow, high-arched palate with mandibular underdevelopment, a short umbilical cord, and demincralizariou of bones with thinning on ribs notable on chest radiography. In addition, the hip acetabulum may be shallow, with dislocated or easily dislocated hip joints. If there is difficulty with swallowing, polyhydramnios may ensue. Babies with significant weakness are more likely to be breech at presentation.

CLINICAL TESTS USEFUL IN THE EXAMINATION

Traction Response

The traction response is a sensitive measure of postural tone. The response is initiated by grasping the hands and pulling the child to a sitting position. Ry 1 month, normal infants lift the head immediately and maintain it in line with the trunk. When the sitting position is attained, the head is erect in the midline. During traction, the examiner should feel the child pulling back against traction, and there is flexion at the elbows, knees, and ankles. A traction response is not present in premature infants of less than 33 weeks' gestation. After 33 weeks, there is considerable head lag, but the neck flexors consistently respond to traction by lifting the head. At term, only minimal head lag is present, but when the sitting posture is attained, the head may continue to lag or may become erect momentarily before falling forward (see Figure 30.2). The presence of more than minimal head lag and failure to counter traction by flexion of the limbs is abnormal and indicates weakness or postural hypotonia in full-term newborns and infants.

Table 30.6: Modalities of sensation most useful in the evaluation of neuromotor disorders

Modality	*Central pathway*	*Transverse spinal level*	*Dorsal spinal cord defect*	*Ventral spina! cord defect*	*Unilateral spina! cord defect*	*Poly-neuro pathy*	*Radiculopathy/ plexopathyl mononeuropathy*
Vibration	Dorsal column	—	tt	—	ttt	Ttt	—
Position	Dorsal column	—	ttt	—	ttt	T	—
Pin	Spinothalamic	m	—	t	Ttt	TTT	i ' 1
Temperature	Spinothalamic	t	—	ttt	ttt	ttt	—
Light touch	Spinothalamic and others	—	—				

t t t = very useful; ft = moderately useful; T = *ot* some value.

Vertical Suspension

To test vertical suspension, the examiner places both hands in the child's axillae and without grasping the thorax lifts straight up. Normal full-term newborns and infants respond with shoulder fixation sufficiently strong to suspend themselves vertically without falling through. With weakness or postural hypotonia, the infant needs to be grasped around the trunk to prevent falling, or the shoulders elevate excessively with internal rotation of the arms (see Figure 30.3). While the infant is in vertical suspension, the head is held erect in the midline and the legs are kept flexed at the knee, hip, and ankle. Sustained extension and adduction of the legs is abnormal and suggests regional hypertonicity (see Figure 30.2).

Horizontal Suspension

A normal infant suspended horizontally in the prone position keeps the head erect, maintains a straight back, and demonstrates flexion at the elbow, hip, knee, and ankle. A healthy term newborn makes intermittent efforts to maintain the head erect, the back straight, and the limbs flexed against gravity. Hypotonic and weak newborns and infants drape over the examiner's hands, with the head and legs hanging limply.

Fetal Posture

The favored posture that a fetus assumed in utero can often be inferred by the ease of folding of arms and legs into that position, a phenomenon that is generally observable for the first week or two of postnatal life. This natural asymmetry can at times be quite unusual, for example, a leg with extended knee across the chest, but is normal if the ease of folding into this posture diminishes steadily and quickly after release from the confinement of the womb.

Assessment of the Mother

In some disorders of the floppy infant, significant information can be discerned from a careful review of the mother (Table 30.7). Maternal percussion myotonia or the inability to relax quickly a tightly clenched fist might suggest the floppy infant has congenital myotonic dystrophy. Bulbar weakness, ptosis, or diplopia with sustained upgaze, or early arm ptosis with sustained forward arm abduction may suggest unappreciated maternal myasthenia, which can be transferred passively to an infant, producing more obvious signs and symptoms, l.ong-since resolved congenital limb deformities or a narrow, high-arched palate may suggest a dominantly inherited developmental anomaly of power or tone. The age of first walking of both parents, often remembered accurately by the newborn's grandparents, may be a clue to early dominantly inherited weakness.

Table 30.7; Disorders in which features in the parents may have diagnostic value

Neonatal myasthenia gravis (passive transfer of maternal antibody)
Congenital myasthenia syndromes, dominantly inherited
Congenital myopathy, dominantly inherited
Fiber typo disproportion syndromes
Central core disease
(Congenital) myotonic dystrophy
Other channelopathies

CHARACTERISTIC SYNDROMES AND DIFFERENTIAL DIAGNOSIS

Injury to each portion of the motor unit produces a characteristic clinical syndrome that is often sufficiently-distinctive to have significant localizing value (Table 30.8, see also Table 30.1). Once a location is suspected a specific differential diagnosis often follows naturally.

Cerebral Disorder

Floppincss attributable to a cerebral cause is often marked by the prominence of hypotonia out of proportion to weakness. Many infants with hypotonia on a central hasis also have regional signs of hypertonia at the same time. One common combination of this mixture of increased and decreased tone is the infant with obligatory trapping of thumbs into the hand, excess pronator tone of the forearms, and excess extensor and adductor tone of the legs on vertical suspension (see Figure 30.3B), combined with axial and appendicular hypotonia at rest. Infants with a combination of increased and decreased tone likely will develop more diffuse spasticity later. Increased or "inappropriately normal" tendon reflexes in the setting of hypotonia have the same implication. Other features that indicate brain involvement are seizures, alterations in level of consciousness, or abnormalities of head size or shape. The appearance of other unexplained unusual physical features raises the concern about occult brain malformations, hut the potential for in utero deformation with long-standing weakness should not be overlooked. It is notable that many well-characterized syndromes combine central with peripheral weakness.

Chromosomal disorders associated with hypotonia usually are associated with other dysmorphtsms. Careful chromosomal studies are warranted in any floppy infant with dysmorphic features of hands or face or with other major organ malformation, but the yield is low in the absence of any of these abnormalities.

Table 30.8: Classic clinical syndromes that characterize the floppy infant

	Examples	*Characteristic features*
Corticospinal tract	.Stroke	Regional spasticity (diplegia, hemiplegia, quadriplegia)
Diffuse central nervous system	Down syndrome, Prader-Willi syndrome	Diffuse hypotonia more than weakness
High cervical spinal cord	Birth injury	Quadriplegia sparing the face, arms, and legs; impaired sphincter function; possible diaphragm weakness
Motor neuron	Spinal muscular atrophy	Diffuse weakness, legs > arms > diaphragm > face
Nerve	Congenital hypomyelmating neuropathy	Distal weakness of extremities, legs > arms; sensory impairment, distal I iinbs>proximal
Neuromuscular junction	Congenital myasthenic syndromes; infantile botulism	Prominent involvement of bulbar muscles with impaired suck and swallow; extraocular muscle weakness
Muscle	Congenital myopathy	Diffuse weakness including face, proximal limbs > distal

Chronic nonprogressive encephalopathy may be caused by genetic or acquired influences and may or may not be associated with anatomical deformations of the CNS. Known or unknown toxins may be responsible for cerebral dysgenesis, but the etiology of most cerebral palsy is unknown. Most cases of hypotonic cerebral palsy evolve to forms of increased tone, either with spasticity, dystonia, or a mixed hypertonic and hypotonic state.

Perinatal brain injury leading to a chronic encephalopathy and weakness is never an occult event. Seizures, coma, or other features of an acute encephalopathy shortly after birth suggest petinatal traumatic injury, hypoxia-ischemia, infection, or withdtawal from maternal placental "dialysis" of small toxic molecules that may build up after delivery as **a** consequence of an inborn error of metabolism. Perinatal asphyxia sufficient to cause brain injury leads to sustained very low Apgar scores and obvious signs of an acute encephalopathy or evidence ot other organ damage. All newborns with an acute encephalopathy should be evaluated immediately for sepsis or other occult infection and treated presumptively. In the absence of obvious infection or perinatal injury, however, the newborn who appears vigorous at birth but then becomes weak or encephalopathy should be assessed for inborn errors with blood tests for metabolic acidosis, glucose, electrolytes, serum lactate, and ammonia, and urine tests for reducing substances and abnormal amino acids. Feedings should be suspended temporarily until these studies are demonstrably normal. Because inborn errors are complex and rare, when they are suspected, early consultation with centers expert in their care is essential.

Chronic progressive encephalopathy may be caused by identifiable inborn errors of metabolism or unknown causes. In general, diagnosable conditions involve large insoluble molecules of peroxisomal metabolism or lysosomal storage disorders. In most of these disorders, hypotonia is less prominent as a presenting feature than is developmental regression. *Benign congenital hypotonia* is a term applied to a group of infants in whom early hypotonia gives way to more normal motor development, implying that there is a developmental anomaly of motor control. Family histories are often positive and reassuring, particularly if a similarly affected first-degree relative later did well. Most clinicians agree that cognitive impairment is common in this group, but the incidence is unknown because of the difficulties in case definition.

Combined cerebral and motor unit disorders may have features of both and can present especially challenging diagnostic problems. Degeneration of white matter of the brain and peripheral nerve myelin combined is a feature of Krabbe's and metachromatic leukodystrophies. Mitochondrial disorders may affect both cerebral and muscular metabolism. Congenital myotonic dystrophy produces an unusual developmental delay with both hypotonia and weakness but without myotonia until later years; school-aged children are often more impaired by mental subnormality than by weakness. Many children with hypotonia or weakness who have an abnormal muscle biopsy characterized by only a predominance of rype 1 fibers have associated cognitive subnormality manifest in later years (Kyriakidcs et al. 1993). Acid maltase deficiency (Pompc's disease) produces both an encephalopathy and a distinctive vacuolar myopathy, as well as congestive cardiac failure with cardiomegaly. Congenital muscular dystrophy now has four forms that include cerebral dysgenesis with myopathy. Various acquired insults, particularly hypoxia-ischcim.i, can injure brain and motor neurons within the spinal cord. Severe weakness from any defect in the motor unit can lead to perinatal asphyxia if respiration is impaired for too long. Finally, some patients have a combination of motor neuron or nerve disease with CNS dysfunction that has no other distinctive features and thus falls into an idiopathic group of ncurodysplasia or neurodegeneration.

High Cervical Spinal Cord

Fortunately, congenital or acquired high cervical myelopathies are now rare. Affected infants may have many features of motor unit dysfunction, especially before the

development of spasticity. Such miauls have an active facial expression and frog-leg posture of the body and limbs that resemble that seen with spinal muscular atrophy. Additional features may include diminished responsiveness to pin, weakness of sphincters with continuous urinary leakage or abnormal retention, variable diaphragmatic weakness and ventilatory dependence, and a different clinical course. Infants with a high cervical myelopathy often have prominent weakness at birth, whereas those with severe infantile spinal muscular atrophy are often progressively weaker over weeks or months.

Motor Neuron op athy

Infantile spinal muscular atrophy is the most common neuronopathy causing a floppy infant. It is characterized by an active face with diffuse weakness of legs more than arms, normal sphincter tone, and paradoxical breathing with a strong diaphragm but weak chest and abdominal wall musculature. Other motor neuronopathies are rare and generally have other associated features that are important to the diagnosis. Spinal muscular atrophy has traditionally been divided into several clinical subgroups ranging from the severe acute infantile to milder chronic forms appearing later in childhood (Crawford and Pardo 1996). Identification of the pathogenic survival motor neuron (.SMN) gene has now led to recognition of a broader expression of phenotypes, with a severe form associated with widespread neuron degeneration, arthrogryposis, and an early demise after birth. Spinal muscular atrophy affects approximately I in 10,000 infants. Most of those with the sevete form develop evident weakness before 6 months of age and succumb to respiratory insufficiency at a median of 8 months and *95%* mortality by the second birthday. However, the course of weakness is unusual for a degenerative disease, with the greatest losses occurring at the outset of the disease and increasingly slower loss of power with the passage of time. This course has led to speculation that the underlying defect is related to a distortion of naturally occurring motor neuron cell death (apoptosis). The pathogenic *SMN* gene appears lo k imolvi.\l in nuclear UNA processing; how ibis relates to motor neuron survival is at present beyond speculation.

Other motor neuronopathies of infancy are recognized usually by context. Vaccine-acquired poliomyelitis is rare but persists with a meningoencephalitic illness leading to characteristic regional weakness and paralysis and slow recovery. A predominantly cervical, nun .S'.U.V spinal muscular atrophy-like syndrome is now distinguished from the more common disorder by the unusual segmental distribution of weakness and a normal genetic test. A rare X-linked form of infantile spinal muscular atrophy also exists. Incontinentia pigmenti and GM2 gangliosidosis (Tay Sachs disease) have been associated with motor neuron dropout. Occult spinal cord deformities may be associated with segmental loss of motor neurons.

Infantile Polyneuropathy

Infantile polyneuropathy, a rare syndrome in infants, is characterized most often by weakness and insensibility concentrated distally in the limbs, combined with loss of deep tendon reflexes. The only specific neuropathies that may present in the first year as a floppy infant are congenital hypomyelinating neuropathy and Dejerine-Sottas syndrome (hereditary motor and sensory neuropathy, type III); others may have their onset in early childhood years or infancy (Ouvrier 1996). Polyneuropathies are divided into two categories: those in which the primary defect is in the myelin- forming cells, and those in which the primary defect is in the integrity of the axon (Table 30.9). In the very young, the demyelinating polyneuropathies also include those disorders that might be more properly termed *dysmyelinating* and *hypomyelinating polyneuropathies*^ in which myelin is abnormally formed or diminished in abundance as a developmental defect.

Disorders of the Neuromuscular Junction

Most congenital and acquired disorders of the neuromuscular disorders, including infantile botulism, are characterized by weakness of bulbar, facial, and oculomotor muscles, alone or in combination with weakness of the limbs. Abnormal fatigue with sustained maximum effort is difficult to discern in infants except when the severity is just sufficient to limit the duration of sucking followed by hungry irritabiliry and weak attachment to the nipple. In most cases, fatigue manifests as baseline weakness of swallowing, crying, or facial or extraocular movement. In some of the congenital myasthenic syndromes, particularly when myasthenia coexists with myopathy, appendicular weakness can exist independent of facial, ocular motor, or bulbar weakness.

The congenital myasthenic syndromes constitute a heterogeneous group of defined genetic disorders that have a common physiologic disturbance of the neuromuscular junction. They can be classed into disorders of presynaptic acetylcholine (ACh) release, receptor binding of ACh molecules, kinetics of receptor-mediated opening of the sodium channel (slow channel syndrome), and a disturbance of junctional acetylcholinesterase. Many patients who are not the product of a consanguineous relationship have a complex junctional physiology that results in a loss of safety factor for neuromuscular transmission that arises from a compounding of heterozygous mutations. Diagnosis can be suspected by fatigable weakness, responsiveness to cholincstcrasc-inhibiting drugs or a-adrencrgic agents, characteristic decremcntal responses to repetitive stimulation

Table 30.9: Named polyneuropathies with possible onset in infancy

Demyclinating
Congenital hypomyelinating polyneuropathy
Dejerine-Sottas syndrome (HMSN III)
Charcot-Mane-Tooth disease, type 1 (HMSN 1)
Globoid cell leukodystrophy (Krabbe's disease)
Metachromatic leukodystrophy
Acute inflammatory demyclinating polyneuropathy
Chronic inflammatory demyelinating polyneuropathy
Axonal
Charcot-Marie-Tooth disease, type 2 (HMSN II)
Spinal muscular atrophy with widespread neuronal degeneration
Familial dysautonomia
Idiopathic

HMSN = hereditary motor and sensory neuropathy.

testing, or a "double hump" compound muscle action potential with single stimulation of a motor nerve, and absence of detectable ACh receptor antibodies. Diagnosis can be confirmed only with more sophisticated in vitro testing of the neuromuscular junction.

Passive transfer of maternal ACh receptor antibody may cause more profound weakness in the newborn infant than in the mother; this weakness improves with time, but rare infants are profoundly weak. Infantile onset of the adult form of autoimmune myasthenia gravis is at most very rare,

Infantile botulism can present as young as 2 weeks of age or as old as 1 year, with a median peak of onset in the second month, A history of decreased stooling frequency followed by decreasing feeding in a previously normal infant is common. Affected infants often have relative appendicular strength at a time of substantial bulbar, extraocular, and intraocular weakness, but may then progress to quadriparesis. Early diagnosis can be suspected with a characteristic EMG and incremental nerve conduction velocity responses to repetitive stimulation at high rates. Such infants should be watched carefully because respiratory failure caused by collapse of the airway can be seen at a time of relative appendicular strength. Full recovery is usual with only supportive therapy.

Myopathy

In infants, myopathic weakness often involves facial, appendicular, and axial muscles equally, although loss of strength is easier to demonstrate in the largest muscles proximally in the limbs. Many have an associated reduction in muscle mass, although this may not be apparent in the young infant with normally abundant baby fat. Severe facial and extraocular weakness can lead to the false impression of mental subnormality or inattentiveness; however, this distinction is both important and difficult to make because several congenital myopathies are associated with widespread cerebral disease.

The diagnosis of congenital myopathy depends on the muscle histology (Goebel 1996). However, some of the distinctive abnormalities of muscle histology are seen in a variety of clinical settings, which diminishes the predictive value of the histological diagnosis alone. Three disorders of infants are nosologically distinct. X-linked myotubular myopathy is associated with severe weakness, limitation of extraocular movements, respiratory insufficiency, and mental subnormality. Severe infantile nemaline myopathy is an autosomal recessive disorder associated with significant facial and axial weakness with a high-arched narrow palate. Both of these severe infantile disorders have a defined gene mutation, but the histologic features are shared with milder conditions that do not share the same mutation (Wallgren-Pettersson 1998). Central core disease is a dominantly inherited disorder involving mutation of the calcium-release channel of skeletal muscle sarcoplasmic reticulum, the ryanodine receptor. It is not clear how often a floppy baby's histological features of central core myopathy are attributable to mutation of the same gene. Abnormalities in the ryanodine receptor are present in less than one half of older individuals with a malignant hyperthermia response to anesthesia.

The congenital muscular dystrophies are characterized by severe weakness at birth, elevated levels of creatine kinase, and muscle biopsy features of a necrotizing myopathy with significant fibrosis and fatty replacement of muscle. Four nosologically distinct entities, each associated with abnormalities of the brain, have emerged in recent years (Voit 1998). The best understood of these involves mutation of the a2-laminin gene, also known as *tnerosin,* an extracellular constituent of the muscle basal lamina that is linked to dystrophin through a transmembrane dystroglycan. Infants with this form of congenital muscular dystrophy have associated profoundly abnormal white matter signal on magnetic resonance imaging (MRI), but have no important functional cerebral deficits. The Fukuyama form of congenital muscular dystrophy, mostly seen in Japan, is associated with cerebral and cerebellar micropolygyria and leptomeningeal fibrogliosis and severe cognitive subnormality. The responsible gene, fukutin, appears to be a secreted protein but its function is otherwise unknown. The Walker-Warburg syndrome, characterized by lissencephaly, hydrocephalus, microphthalmia, and retinal dysplasia may or may not be distinct from the Finnish muscle-eyc-brain syndrome, which is characterized by severe congenital myopia, retinal hypoplasia with congenital glaucoma, hydrocephalus, myoclonic jerks, and mental retardation.

LABORATORY TESTS

A limited number of confirmatory tests, or a screening test within a restricted range of differential possibilities, is generally possible in the final diagnostic steps of the

differential diagnosis. Laboratory diagnosis has changed significantly in the last decade because of specific DNA tests for several of the better characterized disorders that can obviate the need for biopsy; EMG and nerve conduction velocity studies; or other painful, expensive, or ambiguous tests (see Table 30.1). Because DNA test availability is likely to change rapidly between editions of this textbook, the reader is directed to the Web-based Online Mendclian Inheritance in Man for up-to-date information on specific disorders.

Neuroim aging

T1 -weighted MR! of the brain is useful for the detection and characterization of occult cerebral malformations. However, care should be taken with sedation for this or any other procedure in rhe floppy infant, because respiratory and airway muscles may be easily compromised because of weakness. If cerebral malformation is suspected, careful evaluation of skin and eyes may produce clues to the underlying diagnosis. T2-weightcd imaging best displays the abnormal white matter signal associated with *ot2*-laminin deficiency in congenital muscular dystrophy. More specialized MRI studies may demonstrate abnormal spectra associated with the mitochondrial encephalomyopathies.

Nerve Conduction Studies and Electromyography

Nerve conduction studies and EMG are most useful in focusing attention on a portion of the motor unit for further study. The value of the study is related directly to the skill and experience of the physician performing the test, the quality of the question being posed, the age of the infant being studied, the setting in which the study is performed, and the presence of a disorder of the motor unit. EMG is able to discern myopathic from neuropathic weakness in most cases in which one of the two is present. Nevertheless, profound hypotonia on a central basis, in very young infants, or studies taken in the neonatal intensive care unit with significant background electrical noise degrade the quality of information obtained. Specific studies with repetitive stimulation are especially valuable in the diagnosis of the myasthenic syndromes and infantile botulism (Jones, Bolton, and Harper 1996).

Muscle Biopsy

Muscle biopsy is essential to the diagnosis of congenital myopathies and muscular dystrophies, but like neurophysiological studies, biopsies are most useful when the question being asked is sharply focused and the center obtaining and interpreting the tissue is experienced, especially in the handling of infant muscle. Histochemical evaluation of quickly frozen muscle tissue is essential to diagnosis. If possible, delay of muscle biopsy beyond the newborn period or later improves sensitivity for a number of disorders in which the persistence of characteristic features of muscle immaturity is helpful to diagnosis. The best anatomical sites for biopsy are those muscles free of myotendinous insertions in which the histochemical fiber types ate normally equal in abundance. Muscles that best fit these criteria are the deltoid, biceps, triceps, and rectus femoris. The muscle selected for biopsy should be mild to moderately weak and not recently needled by EMG, Adequate tissue can be obtained either by needle biopsy or by open biopsy depending on physician experience, However, careful thought should be given prospectively to the amount of tissue that will be necessary for the potentially relevant histochemical, electron microscopic, enzymatic, or DNA tests.

Nerve Biopsy

Biopsy of the sural nerve is indicated in the setting of unexplained neuropathy when other tests for specific candidate neuropathies are either not available or are normal. Nerve biopsies should be done only in centers with significant experience, particularly because, if done poorly, they can be repeated only once. Nerve biopsies can reveal features of primary demyelination or axonal degeneration, the presence of abnormal abundant inflammation suggesting an acquired pathophysiology, and on occasion, specific features within myelin or axon that can have specific diagnostic import. Samples for electron microscopy should be obtained routinely. New techniques in the visualization of small myelinated and unmyelinated axons in skin biopsies may expand the role of nerve pathology in the evaluation of neurodegenerative disorders.

Edrophonium (Tensilon) Test

Edrophonium chloride (Tensilon) is a rapid-acting anticholinesterase that produces a temporary reversal of weakness in patients with many of the myasthenic syndromes. It is most useful when change can be assessed in a chronically weak muscle that is tonically activated. In practice, this is generally confined to eyelid ptosis or restriction of eye movement. A false impression of significantly increased appendicular muscle strength sometimes results from the limb movements generated by an uncomfortable feeling accompanying Tensilon infusion. Rare patients, especially those with a defect of the junctional acetylcholinesterase or vagal sensitivity, may be paralyzed or stop breathing with Tensilon infusion. Thus the test should only be done where defense of the airway, breathing, and circulation can be ensured. In newborns and infants the total dose is

0.15-0.20 mg/kg; one fourth of this dose is given intravenously each minute until a response is seen or the total dose is given,

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Chapter 31
Sensory Abnormalities of the Limbs, Trunk, and Face

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Clinical evaluation of sensory deficits is inherently more difficult than evaluation of motor deficits because of the subjective nature of the examination. Although we try to make the sensory examination as precise as possible, there is commonly inconsistency in reporting by the patient. Also, the types of sensory abnormality may differ greatly among patients. Nevertheless, identifying sensory deficits is of importance in localization of the lesion.

Accurate localization begins with a foundation of detailed anatomy. Of course, the presence or absence of motor deficits also aids with anatomical localization. Therefore the sensory data are always considered in association with other neurological functions.

ANATOMY

Sensory **Transduction**

Activation of sensory end organs produces a generator potential in the afferent neurons. If the generator potential reaches threshold, an action potential is produced. The action potential is conducted to the spinal cord by action-potential propagation.

Sensory transducers are seldom directly affected by neuropathic conditions, although peripheral vascular disease can produce dysfunction of the skin sensory axons, and systemic sclerosis can damage skin sufficiently to produce a primary deficit of sensory transduction {Table 31.1).

Sensory Afferents

The rate of action-potential propagation differs depending on the diameter of the axons, and whethet the fibers are myelinated or unmyelinated. In general, nociceptive afferents are small myelinated and unmyelinated axons. Non-nociccptivc afferents are large-diameter myelinated axons. Afferent fiber characteristics are shown in Table 31.2.

Spina! Cord Pathways

Sensory afferent information passes through the dorsal root ganglia to the dotsal horn of the spinal cord. Some of the axons pass through the dorsal horn without synapsing and ascend in the ipsilateral dorsal columns; these serve mainly joint position and touch sensations. Other axons synapse in the dorsal horns, and the second-order sensory neurons cross in the antetior white commissure of the spinal cord to ascend in the contralateral spinothalamic tract. Although this tract is best known for conduction of pain and temperature information, some non-nociceptive tactile sensation is conducted as well.

The dorsal column tracts ascend to the cervicomedullary junction where axons from the leg synapse in the nucleus gracilis and axons from the arms synapse in the nucleus cuneatus. Figure 31.1 shows the ascending pathways through the spinal cord to the brain.

Brain Pathways

Brainstem

Axons from the nucleus gracilis and cuneatus cross in the medulla and a seen d in the medial lemniscus (from a Greek word meaning *ribbon).* The spinothalamic tracts in the brainstem are continuations of the same tracts in the spinal cord and ascend lateral to the medial lemniscus in the brainstem.

Table 31.1: Sensory receptors

Receptor	? !•/><•	*Afferent axon*	*Modality*
Pacinian corpuscle	Multilayeted capsule around a nerve terminal, producing a rapidly adapting mecbanoreccptor	Large-diameter myelinated axons	Touch and vibration
Golgi's tendon organ	Specialized organs in the tendons near joints	Large-diameter myelinated axons	Joint position and rate of movement
Free nerve ending	Branched terminal endings of axons	Small myelinated and unmyelinated axons	Strong tactile and thermal stimuli, especially painful inputs
Me rk el's discs	Slowly adapting mcchanorcccptor	Large- to medium-diameter myelinated axons	Touch and pressure. Slowly adapting
Meissner's corpuscle	Specialized quickly adapting mechanorecepror	Myelinated axons	Touch
Krause's end bulbs	Specialized terminal axon ending	Small myelinated axons	Thermal sensation
Muscle spindles	Specialized organ involving intrafusal muscle fibers and the associated nerves	Large-diameter myelinated axons	Sensation of muscle length and contraction

Table 31.2: Sensory afferent axons

Class {older terminology)	*Diameter*	*Conduction velocity*	*Modalities*
la (Aa)	12-20 microns	70-100 m/sec	Proprioception (muscle spindles)
lb (Aa)	12-20 microns	70-100 m/sec	Proprioception (Golgi's tendon organs)
ii ***tm***	5-12 microns	30-70 m/sec	Touch and pressure from skin; proprioception from muscle spindles
III (AS)	2-5 microns	10-30 m/sec	Pain and temperature; sharp sensation; joint and muscle pain sensation
IV (C, unmyelinated)	0.5-2.0 micron	0.5-2.0 m/sec	Pain, temperature

Note: The terminology of sensory afferents has changed through the years. The older terminology *{Act,* A/J, *Ay, AS,* B, C) spans motor and sensory modalities, so the newer classification presented here for sensory fibers should be used nowadays. The corresponding older terms are placed in parentheses in the table for reference.

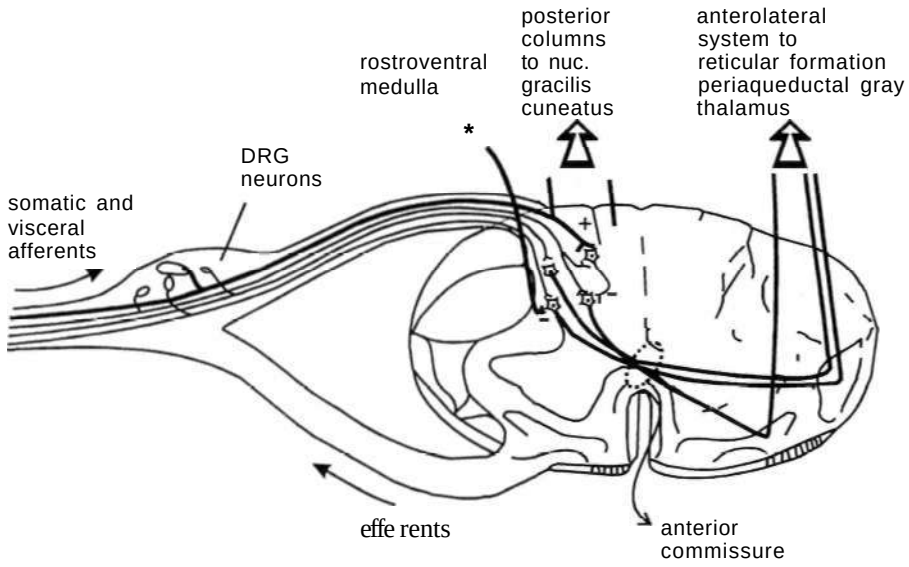

FIGURE 31.1 Axial section of the spinal cord showing dorsal and ventral roots forming a spinal nerve. Sensory afferents give rise to two major ascending pathways: the anterolateral system (nociceptive, thermal sensation primarily) and posterior columns (large-fiber modalities primarily, including touch, vibration, and proprioception). Inhibitory input derives from descending fibers as well as collaterals, via interneurons, from meehanoreceptive fibers. DRG = dorsal mot ganglion; dashed circle anterior white commissure. (Modified with permission from Rizzo, M. A., Kocsis, J. D. & Waxman, S. G. 19%, "Mechanisms of paresthesiae, dysesthesiae, and hypcresthesiac: Role of Na^+ channel heterogeneity," *Eur Neurol,* vol. 36, pp. 3-12.)

Thalamus

lesions of the thalamus rarely affect only a single region, but there is functional organization, which may affect clinical findings. The ventroposterior (VP) complex is the main somesthetic receiving area and includes the ventroposterior lateral nucleus, which receives information from the body, and the ventroposterior medial nucleus, which receives sensory input from the head and face. Projections are to the primary somatosensory cortex

on the postcentral gyrus. The posterior nuclear group receives nociceptive input from the spinothalamic tract and projects mainly to the secondary somesthetic region on the inner aspect of the postcentral gyrus, adjacent to the insula.

Cerebral Cortex

Classic neuroanatomical teaching presents a picture of the central sulcus hounded by the motor strip anteriorly and the sensory strip posteriorly. This division was derived largely from study of lower animals where the separation between these functions is marked. As we ascend the evolutionary ladder, this division becomes less prominent, and many of us refer to the entire region as the motor sensory strip. In general, sensory function is served prominently on the postcentral gyrus. The mapping of the cortex follows the same homunculus presented in Chapter 26, with the head and arm portions laterally on the hemisphere and the leg region superiorly near the midline and wrapping onto the parasagittal cortex.

SENSORY ABNORMALITIES

Sensory perception abnormalities are varied, and the pattern of symptoms is often a chic to diagnosis.

- Loss of sensation (numbness)
- Neuropathic pain
- Dysesthesia and paresthesia
- Sensory ataxia

Patients often use the term *numbness* to mean many different abnormalities, including weakness. Strictly speak ing, numbness is loss of sensation, usually manifest as decreased sensory discrimination and elevated sensory threshold; these are negative symptoms. Some patients use the term *numbness* to mean positive symptoms, such as dysesthesia and paresthesia.

Dysesthesia is an abnormal perception of a sensory stimulus, such as when pressure produces a feeling of tingling or pain. If large-diameter axons are mainly involved, the perception is typically tingling; if small-diameter axons are involved, the perception is commonly pain. *Paresthesia* is an abnormal spontaneous sensation of similar quality to dysesthesia. Dysesthesias and paresthesias are usually seen in localized regions of the skin affected by peripheral neuropathic processes, such as polyneuropathy or mononeuropathy. However, these can also be seen in patients with central conditions such as myelopathy or cerebral sensory tract dysfunction.

Neuropathic pain can result from damage to the sensory nerves of any cause. Peripheral neuropathic conditions result in failure of conduction of the sensory fibers giving decreased sensory function, plus pain from excessive electrical discharge. The pathophysiology of neuropathic pain is interesting. Part of its basis is lowering of the membrane potential of the axons so that minor deformation of the nerve can produce repetitive action-potential discharges. There also appears to be membrane potential instability with neuropathic conditions, so that the crests of the fluctuations of depolarization can produce action potentials. Lastly, cross talk *(epbaptic transmission)* between damaged axons allows an action potential in one nerve fiber to be abnormally transmitted to an adjacent nerve fiber. These pathophysiological changes produce exaggerated sensory symptoms including hyperesthesia and hyperpathia. *Hyperesthesia* is increased sensory experience with a stimulus. *Hyperpathia* is augmented painful sensation.

Sensory ataxia is the difficulty in coordination of a limb that results from loss of sensory input, particularly proprioceptive input. The resulting deficit may resemble cerebellar ataxia until detailed neurological examination is performed.

LOCALIZATION OF SENSORY ABNORMALITIES

A general guide to sensory localization is presented in Table 31.3. Guidelines for diagnoses of these sensory abnormalities are summarized in Tabic 31.4. Details of specific sensory levels of dysfunction are subsequently discussed.

Peripheral Sensory Lesions

Lesions of peripheral nerves and the plexuses produce sensory loss, which follows the peripheral anatomic distribution. Exact mapping of sensory deficit is commonly difficult because sensory testing is subjective. Also, there are differences between individuals in sensory peripheral anatomy, including distribution and overlap of sensory fields.

Peripheral sensory loss produces a multitude of potential complaints. Clues to localization are as follows:

- Distal sensory loss and/or pain in more than one limb suggests peripheral neuropathy.
- Sensory loss in a restricted portion of one limb suggests a peripheral nerve or plexus lesion, and mapping of the deficit should make the diagnosis.
- Sensory loss affecting an entire limb is rarely due to a peripheral lesion, because even proximal plexus lesions rarely affect the entire limb. A central lesion should be sought.

Unfortunately, there is often a discrepancy between the complaint and the examination, especially with peripheral lesions. The patient may complain of sensory loss affecting an entire limb, when the examination shows a median or

Table 31.3: General guidelines to sensory abnormality localization

Level of lesion	*Features and location of sensory loss*
Cortical	Sensory loss in contralateral body, restricted to the portion of the homunculus affected by the lesion. If the entire side is affected (with large lesions), either the face and arm or the leg tends to be affected to a greater extent.
Internal capsule	Sensory symptoms in contralateral body, which usually involve head, arm, and leg to an equal extent. Motor findings commonly present, though not always.
Thalamus	Sensory symptoms in contralateral body including head and may split the midline. Sensory loss without weakness highly suggestive of lesion here.
Spinal transection	Sensory loss at or below a segmental level, which may be slightly different for each side. Motor examination is also key for localization.
Spinal hemisection	Sensory loss ipsilateral for vibration and proprioception (dorsal columns), contralateral for pain and temperature (spinothalamic tract).
Nerve root	Sensory symptoms follow a dcrmatomal distribution.
Plexus	Sensory symptoms span two or more adjacent root distributions, corresponding to the anatomy of the plexus.
Peripheral nerve	Distribution follows peripheral nerve anatomy or involves nerves symmetrically.

ulnar distribution of sensory loss. Alternatively, the patient may complain of sensory loss when examination fails to reveal a sensory deficit. This is mote likely to be due to Iimirations on the examination than malingering. Also, patients may have significant sensory complaints as a result of dysfunction of the afferent axons when the conducting function is still intact, so the examination shows no loss of sensoty function. Figure 31.2 summarizes the peripheral nerve anatomy of the body. Figure -SI.} shows the detmatomal disttibution.

Table 31.4: Guidelines to diagnosis of sensory abnormalities

Abnormality	*Features*	*I .ftion*	*Cause*
Distal sensory deficit	Sensory luss with or without pain distal on the legs; arms may also be affected	Peripheral nerve	Peripheral neuropathy
Proximal sensory deficit	Sensory loss on the trunk without limb symptoms	Neuropathy with predominantly proximal involvement	Porphyria, diabetes, other plexopathics
Dcrmatomal distribution of pain and/or sensory loss	Pain or sensory loss in the distribution of a single nerve root	Nerve root	Radiculopathy due to disc, osteophyte, tumor, herpes zoster
Single-limb sensory deficit	Loss of sensation on one entire limb that spans neural and dermatomal distribution	Plexus or multiple single nerves	Autoimmune plexitis, hematoma, tumor compression or infiltration
Hemisensory deficit	Loss of sensation on one side of the body, may be associated with pain; face is involved in brain lesions but not with spinal lesions	Thalamus, cerebral cortex, or projections less likely to be brainstem lesion if face im ⊱K i'd; spinal cord it face not involved	Infarction, hemorrhage, demyelinating disease, tumor, infection
Crossed sensory deficit: unilateral facial and contralateral body	Unilateral loss of sensation on the face and contralateral body	Lesion of the uncrossed trigeminal fibers and the crossed spinothalamic fibers	Lateral medullary syndrome
Crossed sensory deficit: pain/temperature and vibrarion/proprioce prion on opposite sides	Loss of pain and temperature inivmon on one side and vibration and proprioception on the other	Spinal cord lesion ipsilatcral to the vibration and proprioception deficit and contralateral to the pain and temperature deficit	Disc protrusion, spinal stenosis, intraspinal tumor, transverse myelitis; intra parenchyma I lesions more likely to produce dissociated sensory loss
Dissociated suspended sensory deficit	Loss of pain and temperature sensation on one or both sides, with normal sensation above and below	Syringomyelia in cervical or thoracic spinal cord	Chiari malformation, hydromyelia, central spinal cord tumor, or hemorrhage
Sacral sparing	Preservation of perianal sensation with impaired sensation in the legs and trunk	I esion ot tin' cord with mainly central involvement, sparing the peripherally located sacral ascending fibers	Cord trauma, intrinsic tumors of the cord

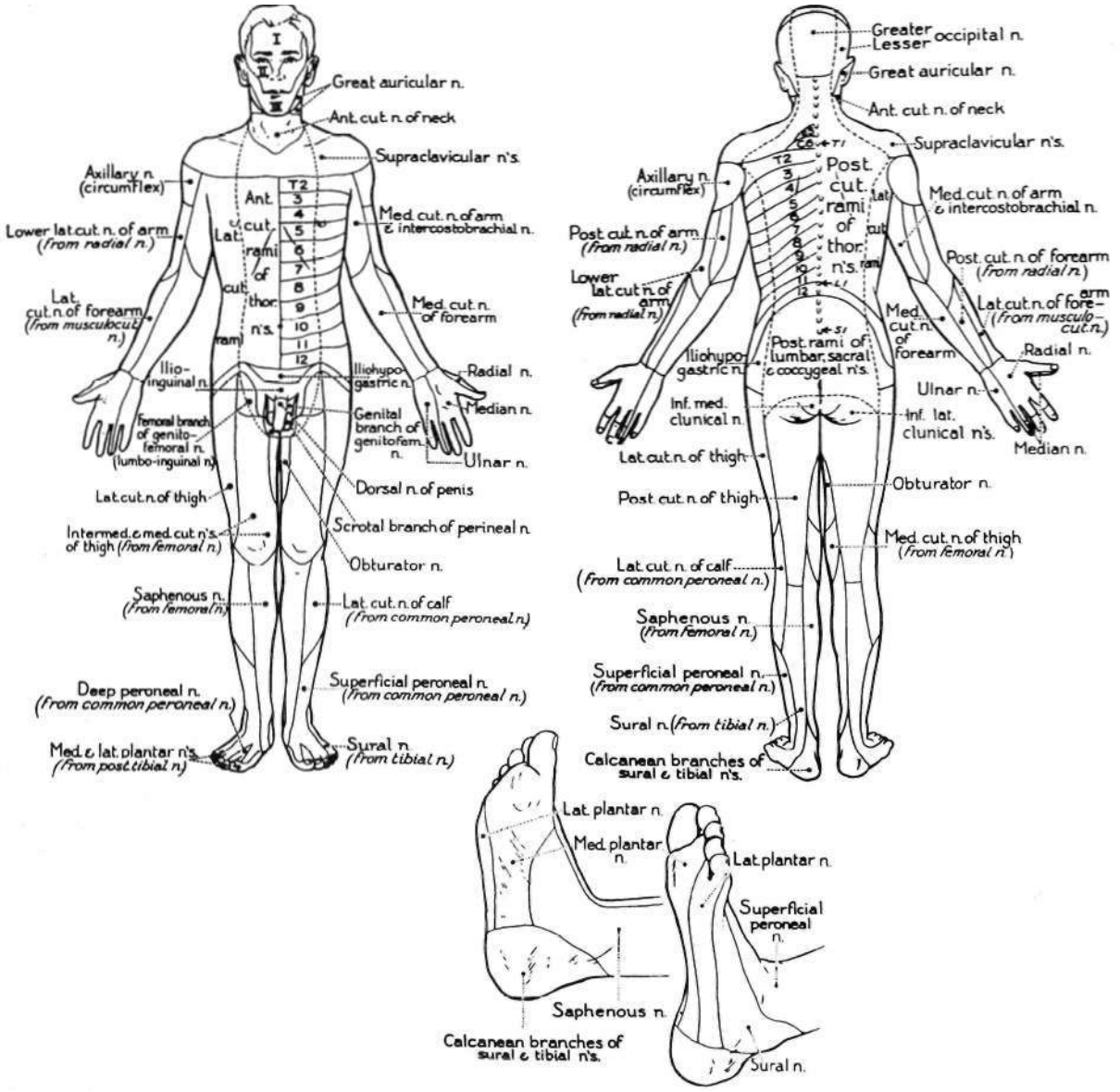

FIGURE 31.2 Cutaneous *(cut)* fields of peripheral nerves *(>:).* Note that the thoracic dermatomes are innervated by the primary anterior and posterior rami of the spinal nerves from the respective level. The spinous processes of T1, LI, and SI are indicated. Inf. = inferior; Lat. = lateral; Med. = median. (Reprinted with permission from Haymaker, W. & Woodall, B. 1953, *Peripheral Nerve Injuries: Principles of Diagnosis,* WB Saunders, Philadelphia.)

Spinal Sensory Lesions

Some sensory syndromes suggest a spinal lesion:

- Sensory level
- Dissociated sensory loss, sparing face
- Sacral sparing

Sensory Level

A spinal localization is suggested by loss of sensation below a certain spinal level (termed the *presence of a sensory level).* Loss of sensation in a myelopathic distribution without weakness and reflex abnormalities would be very unusual. Sensory symptoms with incipient myelopathy are more often positive than negative, with Lhcrmitte's sign being a common presentation of cervical myelopathy. Although we commonly think of Lhermitte's sign as being associated with inflammatory conditions such as multiple sclerosis, we more commonly see it with cervical spondylotic myelopathy.

Diagnosis of a spinal source of sensory abnormalities is suspected in a patient with a "sensory level." The level of the sensory loss may be slightly different between the two sides, and this should not suggest a functional sensory loss. Magnetic resonance imaging (MRI) is the best noninvasive

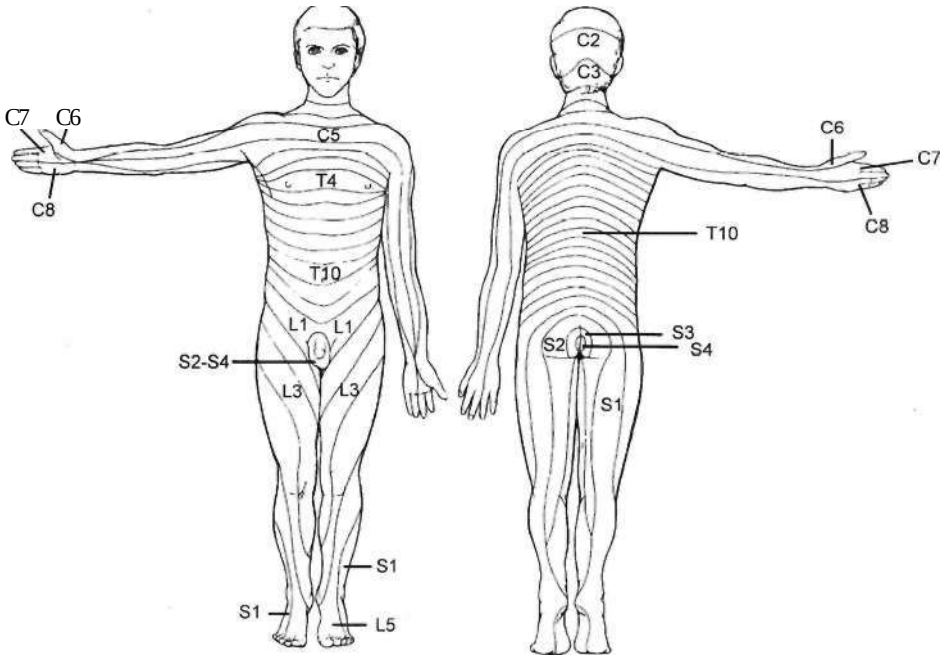

FIGURE 31.3 The dermatomes: (C) cervical, (T) thoracic, (L) lumbar, (S) sacral. The boundaries are not quite so distinct because of overlapping innervation and variability among individuals. (Reprinted with permission from Martin, J. H. & Jessell, T. M. 1991, "Anatomy of the somatic sensory system," in *Principles of Neural Science,* eds E. R. Kandcl et al, Appleton Sc Lange, Norwalk, Conn.)

test for sensory loss of spinal origin. Note that demyelinating disease and other inflammatory conditions of the spinal cord may not be visualized on MRI.

Dissociated Sensory Loss

Pain and temperature fibers cross shortly after entering the spinal cord and ascend contralaterally in the spinothalamic tract, whereas vibration and proprioception ascend uncrossed in the dorsal columns. Therefore unilateral lesions of the spinal cord can produce loss of vibration and proprioception ipsilateral to the lesion and loss of pain and temperature sensation contralateral to the lesion. This is most prominent with patients with intrinsic spinal cord lesions such as tumors but can also be seen with focal extrinsic compression. MRI usually shows the spinal lesion.

A second form of dissociated sensory loss can arise from selective lesion of the dorsal or ventral parts of the cord. Anterior spinal artery syndrome produces infarction sparing the dorsal columns, so there is deficit of pain and temperature below the level of the lesion but vibration and proprioception are spared. Selective lesion of the dorsal columns is less likely, but predominant dorsal column deficits can occur in patients with tabes dorsalis, multiple sclerosis, subacute combined degeneration, Friedreich's ataxia, and occasionally in focal spinal cord mass lesions.

A third form of dissociated sensory loss, with loss of pain and temperature sensation, sparing touch and joint position sensation, usually affecting the upper limbs with normal sensation above and below the lesion is seen in syringomyelia (see Syringomyelia, later in this chapter).

Sacral Sparing

Ascending spinal afferents are topographically organized, with caudal fibers peripheral to more tostral fibers. Therefore centtal cotd lesions can affect the higher fibers before the lower fibers, so that there may be sensory loss throughout the legs yet sparing of perianal sensation. In some patients with severe cord lesions, this may be the only neurological function below the level of the lesion. Cause is usually trauma, but intrinsic mass lesions can also produce this.

Brainstem Sensory Lesions

Brainstem lesions uncommonly affect sensory function without affecting motor function. The notable exception is *trigeminal neuralgia,* where there is characteristic lancinating pain without sensory loss in the distribution of a portion of the trigeminal nerve. Diagnosis is clinical, and studies serve to eliminate other possibilities,

Lateral medullary syndrome typically results from occlusion of the posterior inferior cerebellar artery, produces sensor) lus-. on the ipsilateral face from trigeminal involvement and loss of pain and temperature sensation from the contralateral body from damage to the ascending spinothalamic tract. However, the motor findings eclipse the sensory findings; these include ipsilateral ataxia, bulbar weakness giving dysarthria and dysphagia, and Horner's syndrome.

Medial medullary syndrome typically results from occlusion of a branch of the vertebral artery and is less common than lateral medullary syndrome. Patients have loss of contralateral position and vibration sensation, but again,

the motor findings predominate, including contralateral hemiparesis and ipsilateral paresis of the tongue.

Ascending damage in the brainstem from vascular and other causes can also produce contralateral sensory loss, but again, the sensory findings are trivial compared with the motor findings.

Cerebral Sensory Lesions

Thalamic Lesions

Pure sensory deficit of cerebral origin usually arises from damage to the thalamus. The thalamus receives vascular supply from the thalamoperforate arteries, branches of the posterior cerebral arteries, often with some contribution from the posterior communicating arteries. In some patients, both thalami are supplied by one posterior cerebral artery, so bilateral thalamic infarction can develop from unilateral arterial occlusion. Thalamic pain syndrome is an occasional sequela of a thalamic sensory stroke and is characterized by spontaneous pain localized to the distal arm and leg. exacerbated by contact and stress.

Cortical Lesions

Lesions of the postcentral gyrus produce more sensory symptoms than motor symptoms. Infarction of this region involving a branch of the middle cerebral artery can produce sensory loss with little or no motor loss. More posterior lesions may spare the primary modalities of sensation (pain, temperature, touch, and joint position) but instead impair higher sensory function, such as graphesthc-sia, two-point discrimination, and the perception of double simultaneous stimuli.

COMMON SENSORY SYNDROMES

Some common sensory syndromes are outlined in Table 31.5. Many of these have motor deficits as well.

Peripheral Syndromes

Sensory Polyneuropathy

The most common presenting complaint of a patient with distal symmetrica] peripheral polyneuropathy is sensory disturbance. The disturbance can be negative (decreased discrimination and increased threshold) and/or positive (neuropathic pain, paresthesias, dysesthesias}. Most neuropathies involve motor and sensory fibers, although the initial symptoms are usually sensory.

Nerve conduction studies can evaluate the status of the myelin sheath, thereby identifying patients with predominantly dcmyclinating polyneuropathies, including acute inflammatory dcmyclinating polyneuropathy (AIDP) and chronic inflammatory demyelinating polyneuropathy (CIDP). The electromyographic (EMG) study can identify denervation and hence axonal damage, thereby identifying the motor involvement of many neuropathies with predominantly axonal features. Cerebrospinal fluid (CSF) study is rarely performed for isolated neuropathy but when examined in patients with autoimmune demyelinating neuropathies shows increased protein. Increased cellularity suggests an inflammatory cause. Muscle biopsy is usually performed for evaluation of myopathy but in neuropathy may show denervation and reinnervation. Nerve biopsy can show several of the important causes of neuropathy, including inflammatory infiltrates, segmental demyelination, amyloid deposition, and axonal dropout. Nerve and muscle biopsy should be left to those who have expertise in the performance and interpretation of the data.

Diabetic Neuropathies. Diabetic sensory neuropathy-affects mainly small myelinated and unmyelinated axons, thereby producing disordered pain and temperature sensation. The findings often appear to be a paradox to the patients: loss of sensation yet with burning pain. Pathophysiological, this makes perfect sense. The damaged axons cannot carry the patterns of action potentials, which would give intact sensation, yet spontaneous action potentials from damaged nerve endings, plus increased susceptibility to discharge from mechanical stimuli, cause the perceived neuropathic pain.

Painful neuropathy in diabetics is so common that when present, other potential causes may be overlooked. When neuropathy is present, basic laboratory studies for other causes should be performed, even when the diagnosis is most likely diabetes.

Acquired Immunodeficiency Syndrome-Associated Neuropathies, Human immunodeficiency virus type 1 (HIV-1) infection can produce a variety of neuropathic presentations. One of the most common is a painful, predominantly sensory polyneuropathy. Diagnosis can be confirmed by nerve conduction studies, EMC, and the appropriate clinical setting. CSF analysis and biopsy are usually not necessary, unless there is an HlV-l-associated vasculitis or infection (such as cytomegalovirus).

Toxic Neuropathies. Some toxic neuropathies can be predominantly sensory. We see this most commonly in patients with chemotherapy-induced peripheral neuropathy. Although motor abnormalities do occur, the sensory symptoms eclipse the motor symptoms for most patients. Patients develop dysesthesias, burning, and loss of sensation. The neuropathy can be severe enough to be dose limiting for some patients. The neuropathy may continue to progress for a couple of months following the cessation of

Table 31.5: Common sensory syndromes

Syndrome	*Localization*	*Sensory features*	*Associated findings*
Acute inflammatory demyelinating polyneuropathy	Demyelinating lesion of peripheral nerves and roots	Dysesthesias and paresthesias, which may be painful, along with sensory loss	Areflexia is common early in the course; motor findings are predominant
Sensory polyneuropathy	Axonal or neuronal damage involving predominantly sensory axons	Burning pain, often with superimposed dysesthesias and paresthesias	Reflexes often suppressed distally early in the course
Carpal tunnel syndrome	Compression of the median nerve at the wrist	Numbness on the thumb, index and middle fingers	Weakness and wasting of the abductor pollicis brevis may develop in advanced cases
Ulnar neuropathy	Ulnar nerve compression is most likely near the elbow and at the wrist	Loss of sensation on the fourth and fifth digits	Weakness of the interossei is often evident with advanced cases
Syringomyelia	Fluid-filled cavity, which expands the spinal cord damaging segmental neurons and eventually also white matter tracts	Loss of pain and temperature at the levels of the lesion (capelike distribution; suspended sensory loss); dissociated sensory loss (i.e., affecting spinothalamic sensation and sparing posterior column sensation)	Weakness at the levels of the lesion can develop with motoneuron damage; spasticity below the lesion can develop in severe cases
Thalamic infarction	Infarction of the territory of the thalamoperforate arteries	Sensory loss and sensory ataxia involving the contralateral body	Weakness may develop; aphasia or neglect suggesting cortical damage can rarely develop with involvement of the thalamocortical connections
Thalamic pain syndrome	Previous sensory stroke in thalamus produces neuropathic pain of central origin	Burning dysesthetic pain in the contralateral body, especially distally in the limbs	Other signs of the thalamic damage are typical, including sensory loss
Trigeminal neuralgia	Dysfunction of the trigeminal nerve root	Paroxysms of lancinating electric shock–like neuropathic pain	No sensory loss or motor findings are seen; no other cranial nerve abnormality is seen

chemotherapy administration ("coasting"), after which time some recovery is expected.

Patients with neuropathy that develops during chemotherapy can be presumed to have toxic neuropathy. However, if the association is not clear, then other possibilities should be considered, including paraneoplastic and nutritional causes. Atypical features of chemotherapy-induced ncuropathy would be development of symptoms clearly after cessation of the administration or development of prominent neuropathy with administration of agents that are seldom neurotoxic.

Amyloid Neuropathy, Primary amyloidosis can produce 1 predominantly sensory neuropathy in about one third of patients. Familial amyloid polyneuropathy is a dominantly inherited condition. Patients present with painful dysesthesias, phis loss of pain and temperature sensation. Weakness develops later. Autonomic dysfunction is typical. Eventually, the sensory loss can be severe enough to make the affected extremities virtually anesthetic. Diagnosis can be suspected on clinical grounds, and confirmation requires nerve biopsy. Nerve conduction studies and LMG findings are not specific.

Proximal Sensory Loss. Proximal sensory loss involving the trunk and upper aspects of the arms and legs is uncommon but can be seen in patients with porphyria, diabetes, and with restricted distributions in some patients with proximal plexopathies. Other rare causes of proximal sensory loss include Tangier disease, Sjogren's syndrome, and paraneoplastic syndrome. These neuropathic processes can be associated with pain in addition to the sensory loss. Motor deficit is also common with weakness in a proximal distribution. Patients with thoracic sensory loss should also be evaluated for thoracic spinal cord lesion, which may not always be associated with corticospinal tract signs.

Temperature-Dependent Sensory Loss. Leprosy can produce sensory deficits that predominantly affect cooler

regions of the skin, including the fingers, toes, nose, and ears. Temperature sensation is initially impaired with subsequent involvement of pain and touch sensation in the cooler skin regions. The deficit gradually ascends to warmer areas. Distribution is typically in a stocking-glove distribution and with ftequent trigeminal and ulnar nerve involvement. Diagnosis is by suspicion and can be confirmed by additional testing including antibodies to phenolic glycolipid-I (PGL-I) and nerve biopsy.

Acute Inflammatory Demyelinating Polyradiculoneuropathy

AIDP (Guitlain-Barre syndrome) is an autoimmune process characterized by rapid progression of inflammatory demyelination of the nerve roots and peripheral nerves. Patients present with generalized weakness that may spread from the legs upwards or occasionally from cranial motor nerves downwards. Sensory symptoms are generally overshadowed by the motor loss. Tendon reflexes are lost as the weakness progresses.

Diagnosis is suspected in a patient who presents with progressive weakness with areflcxia. Nerve conduction studies can confirm slowing, especially proximally (F waves are particularly affected}. CSF analysis shows increased protein level without a prominent cellular response (albuminocytological dissociation).

Mononeuropathy

There are many mononeuropathies, the most common of which is carpal tunnel syndrome, with ulnar neuropathy being a close second. Although not classically considered a mononeuropathy, radiculopathy falls into this categoty, because one peripheral nerve unit is affected.

Carpal Tunnel Syndrome. Compression of the median nerve at the wrist produces sensory loss on the palmar aspects of the first thtough third digits. Motor symptoms and signs can develop with increasing severity of the mononeuropathy, but the sensory symptoms predominarc, especially early in the course. Weakness and wasting of the abductor pollicis brcvis can develop.

Nerve conduction studies usually show slowing of sensory and motor conduction of the median nerve through the carpal tunnel at the wrist. The slowing is ptcseut when conduction elsewhere is normal or at least when the distal slowing is far out of proportion to the slowing from neuropathy elsewhere. EMG is usually normal, bur denervation in the abductor pollicis brcvis may develop with severe disease.

Ulnar Neuropathy. Ulnar neuropathy is commonly due to compression in the region of the ulnar groove. Patients present with numbness in the ulnar two fingers (fourth and fifth digits). Weakness of the interossei develops, with advanced ulnar neuropathy of any location, but sensory symptoms predominate, especially early in the course.

Nerve conduction studies show slowing of motor conduction across the elbow or wrist—the two most common sites for ulnar entrapment. Sensory nerve conduction studies will also be abnormal if the lesion is at the wrist. EMG can show denervation in the ulnar-innervated intrinsic muscles of the hand; the muscle easiest to examine and study is the first dorsal interosseous muscle.

Radiculopathy. Radiculopathy commonly produces pain and/or sensory loss in the distribution of one or more nerve roots. Motor symptoms and signs develop with increasing severity, but sensory symptoms (usually pain) may be ptesent for years without motor symptoms.

Reflex abnormalities ate common in radiculopathy, but this should be considered a sensory finding, rather than a motor finding. Prominent weakness would need to be present to suppress a reflex, whereas mild sensory dysfunction may supptess or abolish the reflex.

Table 31.6 presents clinical features of common radiculopathies. Although cervical and lumbar radiculopathies are discussed here, any level can be affected. Diabetic tadiculopathy and herpes zoster commonly affect thoracic dermatomes, as well as cervical and thoracic dermatomes unaffected by spondylosis or disc disease.

Radiculopathy is best studied using MRL In patients younger than 45 years, the most common etiology is disc disease. In older patients, spondylosis and osteophyte formation predominate. The lattet is slower to progress

Table 31.6: Radiculopathies

Nerve root	*Sensory loss*	*Motor loss*	*Reflex abnormality*
C5	Radial forearm	Deltoid, biceps	None
C6	Digits 1 and 2	Biceps, brachioradialis	Biceps
C7	Digits 3 and 4	Wrist extensors, triceps	Triceps
C8	Digit 5	Intrinsic hand muscles	None
L2	Lateral and anterior upper thigh	Psoas, quadriceps	None
L3	Lower medial thigh	Psoas, quadriceps	Patellar (knee)
L4	Medial lower leg	Tibialis anterior, quadriceps	Patellar (knee)
L5	Lateral lower leg	Peronei, gluteus medius, tibialis anterior, toe extension	None
S1	Lateral foot, digits 4 and 5, outside of sole	Gastrocnemii, gluteus maximus	Achilles (ankle)

and less likely to have spontaneous remissions and exacerbations. EMG can be helpful to determine whether there has been any axonal damage from radiculopathy, which may help determine rhc need, location, and timing of decompressive surgery.

Spinal Syndromes

Myelopathy

Myelopathy typically produces sensory loss, although the motor and reflex findings eclipse the sensory findings for most patients. Nevertheless, when a patient presents with back pain with or without leg weakness, a sensory level should be sought. There are some basic pearls regarding sensory testing in patients with suspected myelopathy.

- A defined linclike level is not expected. The sensory mapping is not as precise as that shown on dermatome charts.
- The sensory loss is seldom absolute, which makes precise localization even more difficult.
- The sensory level may not be at the same level on the two sides of the body—a discrepancy of up to several levels can be seen.
- The sensory level may be much higher than might be expected from motor examination or pain. This is because the lesion may be much higher than the lower levels of clinical findings, reinforcing the pearl that one must start from the level of the symptoms and look up!

Syringomyelia

Syringomyelia is due to a syrinx, or fluid-filled space, in the spinal cord that extends over several to many segments. This is most commonly associated with a Chiari malformation. The theory is that partial obstruction to (:Sl flow plus pressure waves in the CSF produce rupture of the central canal into the parenchyma of the spinal cord, which then produces symptoms by mechanical effects. The mass effect of the syrinx produces damage to the fibers crossing in tlic anterior whin.- commissure and destined for die spinothalamic tract that convey pain and temperature sensation. With more severe enlargement of the syrinx, there can be damage to the surrounding ascending tracts affecting sensation below the level of thi[1] lesion, By the riuntil is develops, segmental motoneuron damage and descending corticospinal tract damage are almost always present, and clinical signs of these can be seen.

Spinal Hemisection

The spinal hemisection (Brown-Sequard) syndrome is classically described as the result of surgical or traumatic hemisection of the cord, but this presentation is rarely, if ever, encountered in clinical practice. Below the level of the lesion, there are ipsilateral deficits in vibration and proprioception from dysfunction of the dorsal columns, as well as contralateral deficits in pain and temperature from damage to the spinothalamic tracts. Ipsilateral weakness is also seen from damage to the corticospinal tracts.

Diagnosis is suspected by clinical presentation. This is a condition that can be easily missed if individual sensory modalities are not examined. Merely testing for pinprick will not identify this syndrome. V1R1 is usually performed to look for inflammatory or structural causes of the condition.

Tabes Dorsalis and Related Disorders

Tabes dorsalis is due to involvement of the dorsal roots by late neurosyphilis. Patients present with sensory ataxia, lightning pains, and often with a slapping gait. Tendon reflexes are depressed. Diagnosis is confirmed by serological testing.

Syphilitic myelitis is a rare complication of neurosyphilis, characterized by progressive weakness and spasticity. Moror symptoms dominate in this condition, with lesser sensory symptoms than with tabes dorsalis. MRI of the spine must be performed to look for other structural causes of myelopathy.

Brain Syndromes

Thalamic infarction and Hemorrhage

Thalamic infarction typically produces contralateral hemisensory loss and is the main cause of a pure sensory stroke. All modalities are affected to variable degrees. The thalamus and its vascular supply arc not organized so that specific portions of the sensory system are affected without dysfunction of other sensory systems and regions.

Emergent computed tomographic (CT) scanning is performed on patients with sudden onset of sensory symptoms. This can differentiate infarction from hemorrhage, which has implications for emergent medical management. CT may not show infarction early in stroke, so repeated scanning or MRI should be performed after 2-3 days.

Thalamic Pain Syndrome

Thalamic pain syndrome is an occasional sequela to thalamic infarction that usually affects the entire contralateral body, from face through arm, trunk, and leg. The pain is present mainly distal in the limbs at rest but is exacerbated by sensory stimulation. Sensory detection thresholds arc increased. Involvement of the posterior ventrobasal region is thought to be necessary for production of thalamic pain,

When the patient is known to have had a thalamic infarction, additional study is usually not needed when the patient develops thalamic pain. If the pain develops long after the infarction, then repeated scanning is warranted to look for new pathology, such as recurrent infarction, hemorrhage, or less likely tumot.

Trigeminal Neuralgia

Trigeminal neuralgia is a painful condition that produces lancinating pain in the distribution of part of the trigeminal nerve. This is prototypical neuropathic pain. Patients have paroxysms of pain, which last for seconds at the most. Sensory loss does not occur and when present encourages further search for other diagnoses. Imaging studies arc commonly performed in trigeminal neuralgia **but** are seldom revealing.

Cortical Infarction

Infarction of the sensoty cortex serving the face and arm is due to thromboembolism of branches of the middle cerebral artery. Infarction of the anterior cerebral artery produces sensory loss affecting the leg. Motor symptoms and signs are usually present, as well as the sensory findings; howevet, if the region of infarction is limited, the sensory findings may be much more prominent than the motor findings.

Functional (or Psychogenic) Sensory Loss

Functional sensory loss is less common than other positive functional neurological symptoms such as seizures or paralysis. In fact, it is easy to mistakenly ascribe a pattern of sensory loss as being nonanatomical, when in fact true disease damage is present. This is particularly common in thalamic infarction and plexus dysfunction. As one last precaution, embellished sensory and/or motor loss may be obvious to an examiner but may be superimposed on a real neurological deficit. The patient may be unintentionally helping the examiner and rather ruining the credibility of the report.

With these cautionaty notes, clinical presentations suggesting functional sensoty loss include the following:

- Sensory loss exactly splitting the midline, with a transition zone of millimeters
- Circumferential sensory loss around rhe body or an extremity
- Failure to perceive vibration with a precise demarkation
- Loss of vision ot hearing on the same side of the body as the cutaneous sensory deficit
- Total anesthesia

The discrepancies in total anesthesia can be failure to perceive any sensory stimulus on an extremity that moves perfectly well. This degree of sensory loss would be expected to produce sensory ataxia. Another trap for the patient with an anesthetic limb is movement of the limb when it is tapped while the eyes are closed. Third, if the anesthetic limb is an arm, asking the patient to fold the arms across the chest and then examining sensory abnormality can be confusing, especially if peiformed quickly.

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Chapter 32
Neurological Causes of Bladder, Bowel, and Sexual Dysfunction

Clare J. Fowler

Because of their anatomical proximity and shared peripheral innervation, it might reasonably be assumed that the bladder, bowel, and organs of sexual function are neurological ly similar. Although the organs share the same nerve roots and have common peripheral nerves within the pelvis, each is controlled by its own unique set of central nervous system reflexes. In this chapter, a brief account ni the neurophysiological control of the bladder, bowel, and sexual responses is given, followed by a description of the functional consequences for each organ of neurological damage in different parts of the nervous system.

THE FUNCTION OF PELVIC ORGANS AND THEIR NEUROLOGICAL CONTROL

Bladder

The bladder performs only two functions: storage and emptying. The modern view of the control of these two mutually exclusive activities is that neural programs for each exist in centers in the dorsal tegmentum of the pons and that supra pontine influences switch from one state to the other (Morrison et al. 2002).

The frequency of micturition of a person with a bladder capacity of 400-600 mL is once every 3-4 hours, depending on fluid intake. Because voiding takes 2-3 minutes, this means that for more than 98% of life, the bladder is in storage mode. The decision as to when to switch to voiding is determined by the perceived state of bladder fullness and an assessment of the social appropriateness to do so. To effect both storage and voiding, connections between the pons and the sacral spinal cord must be intact, as must the peripheral innervation that originates from the most caudal segments of the cord.

During the storage phase, raised pressure in the bladder outlet is maintained by sympathetic influences on the smooth muscle of the detrusor in the bladder neck region and by pudendal nerve activation of the striated muscle of the urethral sphincter and the pelvic floor. Inhibition of the parasympathetic outflow prevents detrusor contraction. At the start of voiding, the reciprocal activation-inhibition of the sphincter-detrusor reverses. Relaxation of the striated muscle of the sphincter is followed seconds later by contraction of the smooth muscle of the detrusor, effecting bladder emptying.

Positron emission tomography (PET) studies of male and female subjects voiding have demonstrated that neurological control of the bladder in humans is essentially similar to that demonstrated in experimental animals (Blok et al. 1997, 1998). Right-handed volunteers were trained to void while lying in the scanner, but some subjects, botb male

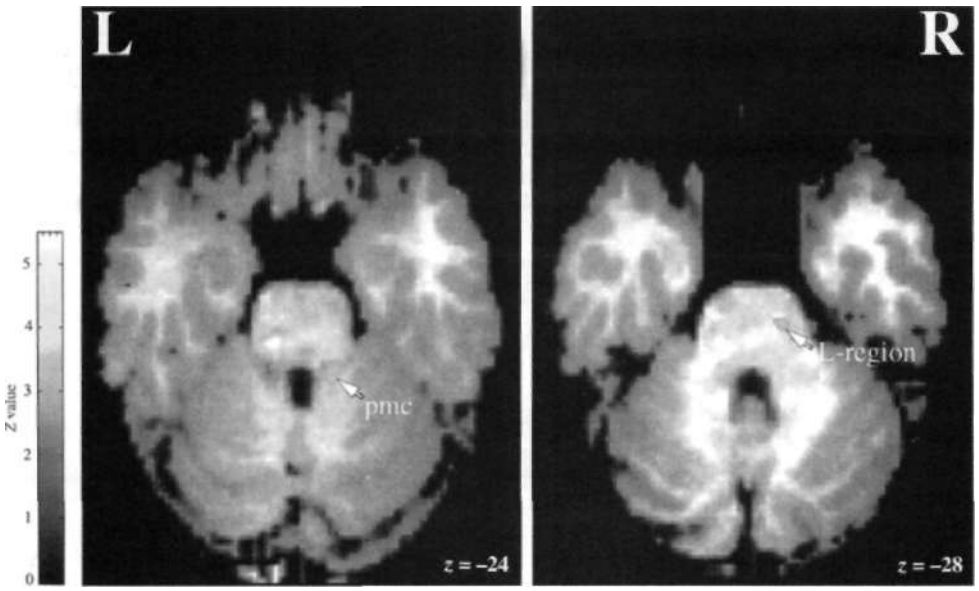

FIGURE **32.1** PET scanning images of the pontine region in subjects who could micturate in the scanner (left) and those who could not (right), compared with empty bladders. In those who could void, activation is seen in the pontine micturition center (pmc), whereas in those unable to void and still storing urine, activation is seen in a lateral part of the pons (L-region). (Reprinted with permission from lilok, P. I'., Sturm-,. [. M.. 8i Holstege, (I. 1998, "Brain activation during micturition in women," *Hmin,* vol. 121, pp. 2U33-2042.)

and female, were unable to do this. In successful voiders, activity was shown in a region of the medioposterior pons. In the unsuccessful voiders, when the subjects were attempting to void hut failing, a region in the ventrolateral pontine tegmentum was activated (Figure 32.1). It had been demonstrated in cats that separate pontine nuclei exist for the storage and voiding phases of bladder activity. In the cortex, the PET scans showed significant activity in the right inferior frontal gyrus and the right anterior cingulatc gyrus during voiding that was not present during the withholding phase.

A PET study of cortical activation with bladder filling showed increased brain activity with increasing bladder volume in the periaqueductal gray matter in the midline pons, in the mid-cingulate cortex, and bilaterally in frontal lobe area (Figure 32.2). Increased brain activity relating to decreased urge to void was seen in a different portion of the cingulate cortex, in the premotor cortex, and in the hypothalamus. These findings supported the hypothesis that the PAG receives information about bladder fullness and relays this information to areas involved in the control of bladder storage and that a network of brain regions is involved in modulating the perception of the urge to void that is distinct from that associated with the appreciation of bladder fullness (Athwal et al. 2001).

Bowel

Similarly, lower bowel function exists mostly in the storage mode. Continence is maintained by a combination of the acute anorectal angle, caused by puborectalis contraction,

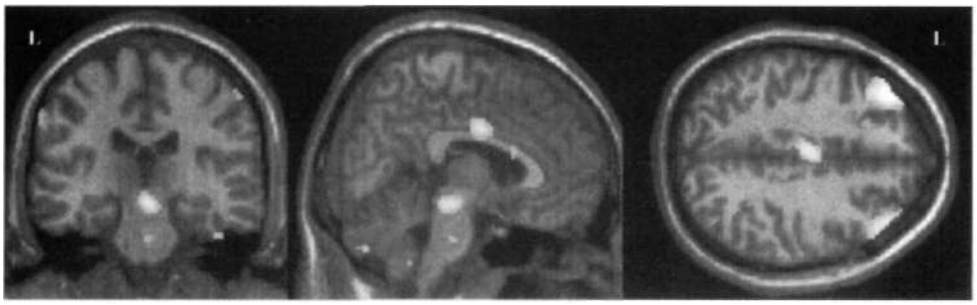

FIGURE 32.2 PET scanning images showing increasing activity in the periaqueductal gray, pons, and cingulate gyrus with increasing bladder volume in health; male volunteers. [Reprinted with permission hum Athwal, 11. S.. link lev, K. | , f lussam,]., el al. 2001, "Brain responses to changes in bladder volume and urge, to void in healthy men," Bram, vol. 124, pp. 369-377.)

and internal anal sphincter tone, determined by sympathetic activity. In neurological health, defecation can be delayed if necessary by contraction of the external anal sphincter and pelvic floor, which requires sensory feedback from the anorcctum. Functional imaging has shown differences between cortical processing of distention of the rectum and the anal canal, as would be expected because the former is a visceral structure and the latter receives somatic innervation (Hobday et al. 2001).

The process of defecation involves a series of neurologically controlled actions that begin in response to the conscious sensation of a full rectum. When this is perceived and if it is judged to be appropriate, defecation is initiated by raising the intra-abdominal pressure and by straining down, causing descent of the pelvic floor. The internal anal sphincter pressure falls due to the rectoanal inhibitory reflex, and the pubococcygeus and striated external sphincter muscles relax (Craggs and Vaizey 1999).

Sexual Function

Physiological sexual response in men and women has been divided into four phases: excitement, plateau, orgasm, and resolution (Masters and Johnson 1970). Excitation occurs in response to either physical or psychologic stimulation and results in clitoral or penile tumescence and erection and vaginal lubrication. The plateau phase is accompanied by the various physical changes of high sexual arousal in anticipation of orgasm. Orgasm, an intensely sensory event, is usually associated in women with rhythmic contraction of the pelvic floor and in men with ejaculation. During resolution, the increased genital blood flow resolves.

Much remains to be discovered about cortical control of sexual function. Although it is thought that cerebral processing determines libido and desire, the ability to effect a sexual response is determined by spinal, autonomic reflexes (Lundberg and Brattbcrg 1993). Libido is hormone dependent, with a major hypothalamic component, and loss of libido may be the earliest symptom of a pituitary tumor.

In experimental animals, the deep anterior midline structures that form the limbic system have been shown to be important for sexual responses, and the medial preoptic-anterior hypothalamic area has an integrating function (Andersson 2001), Electrical stimulation of the hypothalamic and limbic pathways in experimental animals results in erection. Brain stimulation in awake men has been carried out as part of various forms of stereotaxic neurosurgery, but there are no reliable reports of erection occurring during such surgery. Recent functional imaging experiments have demonstrated a number of areas of brain activation (Figure 32.3) with penile turgidity during sexual arousal in healthy men (Arnow et al. 2002).

Male Sexual Response

Erection results from increased blood flow into the corpus cavernosum caused by relaxation of the smooth muscle in the cavernosal arteries and a reduction in venous return. The major peripheral innervation determining this is the parasympathetic, which arises from the S2-S4 segments and travels to the genital region in the pelvic nerves **(Lue** and Tanagho 1987). Sympathetic input is also important: The sympathetic innervation of the genital region originates in the thoracolumbar chain (T11-L2) and rravels through the hypogastric nerves to the confluence of nerves that lies on either side of the rectum and the lower urinary tract: the pelvic plexus. The pelvis plexus also receives input from the pelvic nerves. It is from the pelvic plexus that the cavernous nerves pass to innervate the corpora cavernosa. Although erection is induced by-para sympathetic activiry, the effective neurotransmitter is not acetylcholine because erection in humans is not blocked by atropine. Nitric oxide has been identified as important in causing relaxation of the corporeal blood vessels and the increase in penile blood flow that causes erection,

Psychogenic erection requires cortical activation of erectogenic pathways via the spinal cord, and the preservation of this type of responsiveness in men with low spinal cord lesions suggests that sympathetic pathways can mediate it. Reflex erections occur as the result of cutaneous genital stimulation. Preservation of reflex erections in men with lesions above T i l indicates that the response is the result of spina! reflexes with afferent impulses conveyed in the pudendal nerve, the S2-S4 roots, and efferent traffic through the same sacral roots. In health, reflex and psychogenic responses are thought to reinforce one another. In men, orgasm and ejaculation arc not the same process: Ejaculation is the release of semen, and orgasm consists of the sensory changes accompanied by pelvic floor contractions. Ejaculation involves emission of semen from the vas and seminal vesicles into the posterior urethra and closure of the bladder neck. The latter processes are under sympathetic control, whereas the contraction of the pelvic-floor muscles is under somatic nerve control, innervation being from the perineal branch of the pudendal nerve. Afrer ejaculation, a period of resolution is necessary before sexual activity can be reinitiated.

Female Sexual Response

Lundberg (1999) has written a detailed account of the neurology of the female sexual response. The neurological control of sexual function in women is less well understood than that of men, but similarities exist: The main para-sympathetic innervation is from the pelvic nerves, the sympathetic innervation from the hypogastric nerves, and bilateral somatic innervation from the pudendal nerves. The finding of acetylcholincstcrasc-positivc nerves around

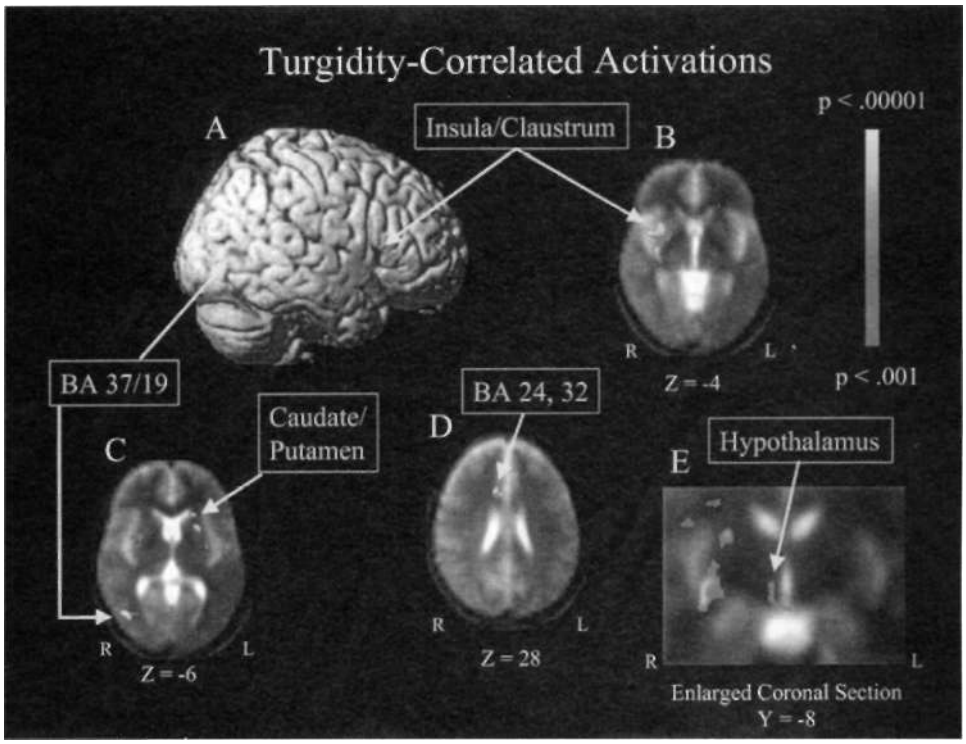

FIGURE 32.3 Magnetic resonance images showing brain activation correlated with penile turgidity in 11 subjects. (A) SPM99 surface reconstruction depicting projections of activation on right side of brain, (B-D) axial sections, and (E) a coronal section. (With permission from Arnow, *R.* A., Desmond, J. E., Banner, L. L., ct al. 2002, "Brain activation and sexual arousal m healthy, heterosexual males," Brain, vol. 125, pp. 1014-1023.)

blood vessels in the vagina suggests that there is parasympathetic control of vaginal vasodilation secretomotor function. It seems likely that increased vaginal blood flow, erection of the cavernous tissue of the clitoris and around the outer part of the vagina, and lubrication are brought about through similar neural mechanisms to those that control erection in men.

The lubrication that occurs as part of sexual arousal results from transudation through the vaginal walls and fluid from Bartholin's glands. There are no actively secreting gland cells in the vaginal walls, and the formation of vaginal lubricant is thought to be the result of a nonsecretory process entirely dependent on increased vaginal blood flow, with the slippery quality of the vaginal fluid resulting from its sialoprotein content. Sexual arousal, either through direct stimulation of the genital region or through cerebral mechanisms, can result in very rapid vaginal lubrication (i.e., within 30 seconds). Normal lubrication depends on both intact innervation and normal estrogen levels.

During orgasm, there may be a scries of synchronous contractions of the sphincter and vaginal muscles. As many as 20 consecutive contractions have been registered, lasting for 10-50 seconds. The sensory changes generally are described as an intensely pleasurable pelvic event. Discussion continues as to whether there is any physiological difference between clitoral or vaginal orgasm. Unlike men, some women are able to have multiple orgasms without a resolution phase.

EFFECT OF CORTICAL LESIONS ON PELVIC ORGAN FUNCTION

Bladder Dysfunction

That anterior regions of the frontal lobes are critical for bladder control has been known since the 1960s. Series of patients with disturbed bladder control were reported with various frontal lobe disturbances, including intracranial tumors, damage after rupture of an aneurysm, penetrating brain wounds, and prefrontal lobotomy (leukotomy) subjects (Andrew and Nathan 1964). The typical clinical picture of frontal lobe incontinence is of a patient with severe urgency and frequency of micturition and urge incontinence but without dementia; the patient is socially aware and embarrassed by the incontinence. Micturition is normally coordinated, indicating that the disturbance is in the higher control of these processes. Urinary retention has also been described in patients with brain lesions. There are a small number of case histories of patients with right frontal lobe disorders who had urinary retention and

in whom there was restoration of voiding when the frontal lobe disorder was treated successfully (Fowler 1999).

After stroke, some patients develop urinary incontinence. This has been studied in two ways: with urodynamic studies and epidemiological^. Urodynamic studies of many incontinent patients have been carried out, and the general conclusion drawn from studying patients with disparate cortical lesions is that voiding is mostly normally coordinated, The most common cystometric finding is of detrusor hypcr-reflexia (Sakakibara et al. 1996). It has not been possible to demonstrate a correlation between any particular lesion site and urodynamic findings.

In terms of the epidemiological approach to stroke and urinary incontinence, the presence of urinary incontinence within 7 days after a stroke appears to be a more powerful prognostic indicator for poor survival and eventual functional dependence than does a depressed level of consciousness in this period. It was suggested that incontinence was the result of severe general loss of function or that those who were incontinent were less motivated to recover both continence and general function (Wade and Langton Hewer 1985).

The cause of urinary incontinence in dementia probably is multifactorial. Not all incontinent older adults are cognitively impaired, and not all cognitively impaired older adults are incontinent. In a study of patients with progressive cognitive decline, incontinence was associated with severe mental failure in pure Alzheimer's disease but was preceded by severe cognitive impairment in diffuse Lewy body disease {Del Ser, Munoz, and Hachinski *1996).*

A much less common cause of dementia is normal-pressure or low-pressure hydrocephalus, of which incontinence is a cardinal feature. Improvement in urodynamic function has been demonstrated within hours of lumbar puncture in patients with this disorder,

Bowel Dysfunction

Articles describing the effects of frontal lobe disorders on micturition note that defecation was generally affected much less often (Andrew and Nathan 1964). Cases of impaired defecation were always accompanied by urinary dysfunction. Only one study has concentrated primarily on the anorectal abnormalities of patients with frontal lobe damage of various types. The conclusion was that the frontal lobe is involved in neurological control of anorectal motility as it is for bladder function, but the lack of correlation between urinary and anorectal abnormality in individual cases suggests that these functions depend on distinct areas of the frontal lobes (Weber et al, 1990).

So far, PET studies of the areas of brain activation after rectal distention have compared responses in healthy control subjects with those of a group of patients with irritable bowel syndrome. It was hypothesized that hyperalgesia of visceral events would occur in the Iattet group. Using a balloon catheter inserted into the rectum, different degrees of distention were applied at timed intervals and the subjects asked to rate any discomfort. Differences between the control subjects and patients were found both on maximal filling and in anticipation of filling, but in healthy subjects activation of the anterior cingulate cortex could be demonstrated only on filling to pressures that were perceived as painful (Silverman et al, 1997).

Sc\ual Dysfunction

Before functional imaging experiments all that was known about human cerebral control and sexuality came from observations of patients with brain lesions, particularly those affecting temporal or frontal regions. These areas can be involved by disorders that cause epilepsy or by trauma, tumors, cerebrovascular disease, or encephalitis.

It has long been observed that sexual dysfunction is more common in men and women with epilepsy. Although various sexual perversions and occasionally hypersexuality have been described in patients with temporal lobe epilepsy, the picture most commonly seen is that of sexual apathy (Shukla, Srivastava, and Katiyar 1979). From studies comparing sexual dysfunction in generalized epilepsy with that in focal temporal lobe epilepsy, there is sufficient evidence to suggest that the deficit is a result of the specific temporal lobe involvement rather than a consequence of epilepsy, psychosocial factors, or antiepileptic medication. The problem is usually that of a low or absent libido, of which patients may not complain. The role of hormonal dysfunction has yet to be fully determined. Based on measurements of sex hormones and pituitary function, it has been suggested that the hyposexuality of temporal lobe epilepsy results from a subclinical hypogonadotropic hypogonadism and that dysfunction of medial temporal lobe structures may dysmodulate hypothaiamic-pituitary secretion (Murialdo et al. 1995).

Erectile dysfunction (ED) with preserved libido, of which some patients complain, can also occur in men with temporal lobe damage with and without epilepsy and may be characterized by loss of nocturnal penile tumescence. Surgery for epilepsy rarely restores erectile function, although a survey of operated patients showed a higher level of satisfaction with sexual function among those who were free of seizures. Sexual dysfunction is not uncommon after head injury, particularly if there has been cognitive damage. A study of people who were admitted to hospital for a minimum of 24 hours after a closed head injury found significant dysfunction in 50% during a 15-year follow-up period (O'Carroll, Woodrow, and Maroun 1991). Hypersexual behavior may occur after frontal lobe damage. Lesions of the frontal lobes, the basal-medial part in particular, may lead to loss of social control, which may also affect sexual behavior.

BASAL GANGLIA

Bladder Symptoms in Patients with Parkinsonism

There are several possible causes of urinary symptoms in a patient with parkinsonism, which include neurogenic causes as well as local urological problems. In Parkinson's disease (PD), bladder symptoms usually occur at an advanced stage of the disease (Araki and Kuno 2000), and prostatic outflow obstruction is a more common cause of problems in older men. In a patient with severe urinary symptoms but mild parkinsonism, a diagnosis of multiple-system atrophy (MSA) should he considered. The onset of urogenital symptoms in MSA may precede overt neurological involvement by years. A study that looked at the duration of symptoms before the diagnosis of MSA found that ED and bladder symptoms began 4-5 years before the diagnosis and, on average, 2 years before more specific neurological symptoms appeared. Almost half the male patients had had a transurethral prostatectomy, from which few benefited (beck, Herts, and bowler 19941.

The neuronal degeneration of MSA probably affects the central nervous system at several locations that are important for bladder control, which explains why urinary complaints occur early and are so severe. It is thought rh.ir detrusor hyper-reflexia is cruised bv neuronal loss in the pontine region, whereas incomplete bladder emptying is caused by loss of parasympathetic innervation of the detrusor after neuronal degeneration in the intermediolateral cell columns of the spinal cord. In addition, anterior horn cell loss in Onufs nucleus results in denervation of the urethral sphincter so that the patient has a combination of bladder overactivity, incomplete emptying, and a weak sphincter. Bladder dysfunction may change during the progression of MSA: Although patients often present with detrusor hypcr-rcflcxia, over the ensuing months or years, impaired bladder emptying may develop so that the postmicturition residual volume increases.

Bladder symptoms in other parkinsonian syndromes are less prominent than m MSA, and although they may occur as part of the patient's general disability, they are rarely so severe or occur at a stage of the disease when a neurological cause is not evident.

In patients with PD and urinary symptoms, it may be difficult to establish the exact cause of the bladder dysfunction, and its treatment often is problematic. Typically, patients present with advanced neurological disease and describe how the bladder symptoms came on many years after treatment for PD started (Chandiramani et al. 1997). They complain of urgency and frequency and urge incontinence if poor mobiliry complicates their bladder overactivity. Urodynamic studies in series of patients with PD have found that the most common urodynamic abnormality is detrusor hyper-reflexia (Araki et al. 2000). There arc several possible explanations for this. The hypothesis most often proposed is that in healthy individuals the basal ganglia have an inhibitory effect on the micturition reflex, and with neuronal loss in the substantia nigra, detrusor hyper-reflexia develops. Experimental data support this theory because marmosets with toxin-induced parkinsonism were found to have detrusor hyper-reflexia, and stimulation of the substantia nigra in cats inhibited distention-induced rhythmic contractions of the bladder. Additional studies on anesthetized cats demonstrated that rhythmic contractions were inhibited by inrracerebrovenrricular administration of a dopamine D| receptor agonist but were not affected by a D_2 receptor agonist. From this, it was concluded that the D, receptor is the main inhibitory influence on the micturition reflex in the cat. Studies in marmosets with toxin-induced parkinsonism confirmed that the same was true for the primate model {Yoshimura et al. 1992).

The results of clinical studies that have looked at the effect of i.-dop.i or apomorphinr on bladder behavior in patients with PD have produced conflicting results. In patients showing the on-off phenomenon, cystometry done in both states showed a lessening of hyper-reflexia with L-dopa in some patients and a worsening in others. A similar unpredictable effect was found on detrusor hyper-reflexia when subcutaneous apomorphine was given in one study, although in another series, all patients with detrusor hypcr-rcflcxia improved. From the results of the animal studies, it seems sensible to treat patients with bladder symptoms with a D] receptor agonist. Pergolide, with its dual D! and D_2 receptor activity, has been tried, with significant symptomatic and urodynamic improvement. The reputation for poor outcome after prostatic surgery in patients with PD may well have resulted from the inclusion of patients with MSA in some of the published studies of PD and the bladder. Nevertheless, if there is convincing evidence of an irreversible outflow obstruction presumed to be caused by prostatic enlargement {rather than a fluctuating, possibly neurogenic disorder), a prostatectomy should be considered.

Bowel Dysfunction

There are several possible causes for the constipation of which many patients with PD complain. A slow colonic transit time has been demonstrated in a number of studies, and it has been suggested that this is caused by a reduction in dopaminergic myenteric neurons, the colonic myenteric plexus being involved by the PD process. An abnormality of the defecation process has also been demonstrated in some patients with PD, with paradoxical contraction of the external anal sphincter and pubococcygcus causing outlet obstruction. This has been called *anismus* and is thought to be a form of focal dystonia.

Bowel dysfunction appears earlier and progresses faster in patients with MSA than in those with PD (Stocchi et al. 2000).

Sexual Dysfunction

Experimental animal and human evidence shows that dopaminergic mechanisms are involved in determining libido and inducing penile erection. In animal studies, the medial preoptic area of the hypothalamus has been shown to regulate sexual drive, and selective stimulation of D_2 dopaminergic receptors in this region increases sexual activity in rats (Andersson 2001). An increase in libido in some patients with PD treated with L-dopa is a well-known phenomenon, although its incidence is uncertain.

The cause of ED in PD is unclear, but it is a significant problem, affecting 60% of a group of men compared with 37.5% of an age-matched healthy nonparkinsonian group in one study. ED usually affects men with PD years after the neurological disease has been established. A survey of young patients with PD (mean age, 49.6 years) and their partners revealed a high level of sexual dysfunction, with the most severely affected couples being those in which the patient was male. ED and premature ejaculation were complaints in a significant proportion, although in general terms sexual dysfunction appeared to be multifactorial, with no single cause identified (Brown etal. 1990).

Dopaminergic agonists induce erection in rats and monkeys, and spontaneous erections have been reported in patients treated with L-dopa. Subcutaneous injections of apomorphine used to treat complicated motor fluctuations in patients with PD have been found to benefit sexual function in a small series (O'Sullivan and Hughes 1998), but sublingual apomorphine is now available to treat general patients with ED and is claimed to be particularly effective in men with mild dysfunction (Heaton 2001).

ED may be the first symptom in men with MSA, predating the onset of any other neurological symptoms by several years. The disorder appears chronologically to be distinct from the development of postural hypotension (Kirchhof et al, 2002). The reason for the apparently early selective involvement of neural mechanisms for erection is not known. Preserved erectile function strongly contradicts the diagnosis of MSA. Nothing yet is known about the sexual dysfunction of women with MSA.

BRAINSTEM

Pelvic Organ Dysfunction

Voiding difficulty is a rare but recognized symptom of a posterior fossa tumor and has been reported in series of patients with brainstem disorders (Fowler 1999). An analysis of urinary symptoms of 39 patients who had had brainstem strokes showed that lesions that resulted in micturition disturbance usually were dorsally situated (Sakakibara ct al. 1996), consistent with the known location of the brainstem centers involved with control of the bladder. The proximity of the pontine micturition center in the dorsal pons to the medial longitudinal fasciculus means that a disorder of eye movements, such as an internuclear ophthalmoplegia, is highly likely in patients with a pontine disorder causing a voiding difficulty.

There has been a single report suggesting that neurological control of anorectal reflexes can be affected by pontine disease, based on the observation of severe constipation in patients after brainstem strokes.

No isolated dysfunction of sexual response has been described specifically associated with brainstem disease.

SPINAL CORD

Bladder Dysfunction

Spinal cord disorders are the most common cause of neurogenic bladder dysfunction. Trans-spinal pathways connect the pontine micturition centers to the sacral cord. Intact connections are necessary to effect the reciprocal activity of the detrusor and sphincter needed to switch between storage and voiding. After disconnection from the pons, this synergistic activity is lost. The result is that the sphincter tends to contract when the detrusor is contracting, a condition known as *detrusar-sphmcter dyssynergia.* In addition, new reflexes emerge to drive bladder emptying and cause detrusor hyper-reflexia. Immediately after spinal cord transection and during the phase of spinal shock, the bladder is not contractile, but gradually over the course of weeks, reflex detrusor contractions develop in response to low filling volumes. The neurophysiology of this recovery has been studied in cats. It has been proposed that after spinal injury, C fibers emerge as the major afferents, forming a spinal segmental reflex that results in .uiiimutic voiding. It is assumed that the same pathophysiology occurs in humans. In support of this assumption is the observed response to intravesical capsaicin (a C-fiber neurotoxin) of patients with acute traumatic spinal cord injury (SCI) or chronically progressive spinal cord disease from multiple sclerosis (MS) (see Chapter 42).

The abnormally overactive, small-capacity bladder that characterizes spinal cord disease causes patients to experience urgency and frequency. If the detrusor hyper-reflexia is severe and if there is also a spastic paraparesis, urge incontinence is highly likely. Poor neural drive on the detrusor muscle during attempts to void, together with an element of demisor-splnncter dyssynergia, likely indicates incomplete bladder emptying. This may exacerbate the symptoms caused by detrusor hyper-reflexia. Although the neurological process of voiding may have been as severely disrupted as the process of storage, the symptoms of difficulty emptying can be minor compared with those of urge incontinence. Only on direct questioning might the patient admit to having difficulty initiating micturition,

an interrupted stream, or possibly a sensation of incomplete emptying.

Because bladder innervation arises more caudally than innervation of the lower limbs, any form of spinal cord disease that causes bladder dysfunction is likely to produce clinical signs in the lower limbs unless the lesion is limited to the conus. This rule is sufficiently reliable to be of great value when considering whether a patient has a neurogenic bladder caused by spinal cord disease.

Spinal Cord Injury

After SCI, detrusor hyper-reflexia, loss of compliance, and dctrusor-sphmcier dyssynergia can be of such severity as to cause ureteric reflux, hydronephrosis, and eventual upper renal tract damage. Before the introduction of modern treatments, renal failure was a common cause of death after SCI. The bladder problems of those with SCI therefore muse be managed aggressively to lessen the possibility of upper tract disease and to provide the patient with adequate bladder control for a fully rehabilitated life. Those with SCI often are young and otherwise fit, and it may be best for them to undetgo surgery on their lower urinary tract with a view to fulfilling these two aims father than to be treated medically.

Multiple Sclerosis

The pathophysiological consequences for the bladder of progressive MS affecting the spinal cord are similar to those of SCI, but the medical context of increasing disability is such rhat management must be quite different. The incidence of bladder dysfunction in MS is estimated to be approximately 75%, similar to the incidence of spinal cord involvement. There is a strong association between bladder symptoms and the presence of clinical spinal cord involvement, including paraparesis and upper motor neuron signs on examination of the lower limb in patients with MS (Betts, D'Mellow, and Fowler 1993). The most common urinary symptom is urgency. All series of urodynamic studies of patients with MS have shown that this is caused by underlying detrusor hyper-reflexia (Chancellor and Blaivas 1995). Patients may volunteer or admit on direct questioning to hesitancy of micturition, but the more disabled may find themselves unable to initiate micturition voluntarily, emptying their bladders only with an involuntary hypcr-rcflcxic contraction and an interrupted urinary flow. Evidence of incomplete emptying may come not from a sensation of continued fullness after voiding but rather from the need to pass urine again within 5-10 minutes.

As the neurological condition progresses, the bladder dysfunction may become more difficult to treat. This is caused by both worsening detrusor hyper-reflexia and decreasingly efficient emptying in the context of worsening paraparesis, spasticity, and general immobility and possibly also cognitive impairment. Unlike the bladder dysfunction that follows SCI, however, progressive neurological diseases very rarely cause upper urinary tract involvement. This is true even when long-standing MS has resulted in severe disability and spasticity. The reason for this is not known, but it means that in such patients, management must emphasize symptomatic relief.

Bladder Dysfunction in Other Nontraumatic Causes of Spinal Cord Disease

Various other forms of nontraumatic spinal cord disease are likely to cause bladder dysfunction, and a more detailed description of these is available (Fowler 1999). Early reviews stated that bladder disturbance was rare in patients with cervical spondylosis, but more recent studies have refuted this. A variable combination of detrusor hyper-reflexia and detrusor sphincter dyssynergia is the most common urodynamic finding, and the majority of patients with bladder dysfunction also have long-tract symptoms and signs.

A consistent feature of transverse myelitis is that although there may be an excellent clinical recovery from **a (.|uadnp:)ivsis of siieh** severity rhat at **its nadir** artificial ventilation was necessary, bladder dysfunction may be the sole residual neurological sequela (Sakakibara et al. 1996). The explanation for this is not known, but it may tclatc to the emergence of spinal segmental reflexes during the period of spinal shock, which then persist as a dominant functional mechanism.

Detrusor hyper-reflexia occurs as an early feature and may even be a presenting symptom in patients with tropical spastic paraparesis, the progressive myelopathy caused by infection by human T-cell lymphotropic virus 1.

Once a common cause of bladder dysfunction, neurosyphilis is now rare. Tabes dorsalis was classically said to result in an areflexic, hyposensitive bladder through involvement of the dorsal columns and roots. Studies of small groups of patients with tabes have demonstrated a variety of abnormal urodynamic findings.

Arteriovenous malformations of the spinal cord may be difficult to recognize clinically but common!) cause bladder disturbance as a prominent, early feature. Although the majority of arteriovenous malformations occur in the thoracolumbar tegion, alterations to cord blood flow and subsequent ischemia of the conus mean that the patient may present with what appears to be a conus or cauda equina lesion. Symptoms of voiding difficulty arc common at an early stage, followed by urinary retention.

A mixture of upper and lower motor neuron signs in the legs together with urinary symptoms is characterisric of a tethered spinal cord. Typically asymmetrical wasting of the calves and intrinsic muscles of the feet occurs, but the prominent bladder symptoms and possibly extensor plantar

responses suggest a diagnosis of a conus lesion rather than peripheral neuropathy or previous poliomyelitis. Although the majority of cases present in childhood, tethered spinal cord is a condition that should be considered in adults with the appropriate clinical features. Urodynamic studies show a mixed picture of detrusor hyper-reflexia and incomplete bladder emptying. Although an improvement in bladder function after a detethering procedure has been claimed, the operation usually is carried out to treat pain or prevent progression of neurological deficit.

Bowel Dysfunction

Only about one third of patients achieve fecal autonomy after SCI, and half of patients need help with bowel management. A questionnaire survey of patients with SCI found that bowel dysfunction was a major problem, rated as only slightly less serious than loss of mobility ((Hickman and Kamm 1996). Bowel management may be equally problematic for patients with progressive spinal cord disease, such as MS. The loss of rectal sensation and the normal desire to defecate mean that bowel emptying must be induced at a convenient time by digital anal stimulation, the use of suppositories or enemas, or manual evacuation (Norton and Henry 1999). The loss of ability to postpone bowel emptying, because of both impaired sensation of impending defecation and the inability to voluntarily contract the anal sphincter means that fecal incontinence is common.

Sexual Dysfunction

Male Sexual Dysfunction

The level and completeness of a lesion determine erectile and ejaculatory capability after SCI. With a complete cervical lesion, psychogenic erections are lost, but the capacity for spontaneous or reflex erections may be intact. In low spinal cord lesions, particularly if the Cauda equina is involved, there may be little or no erectile capacity (Bors and Comarr I960). Theoretically, a lesion below spinal level L2 leaves psychogenic erections intact, but in practice it is uncommon for men with such a lesion to have erections adequate for intercourse. Psychogenic erections arc more likely to be preserved in incomplete lesions. Preserved ejaculation function after a spinal cord lesion is unusual.

Studies of men who underwent bilateral anterolateral cordotomies for pain relief reported loss of orgasmic sensation, which suggests that erotica I ly colored sensation travels in close proximity to the spinothalamic tracts, and a study of patients with anorgasmia after an anterior cord syndrome demonstrated loss of small nerve fiber-media ted function, whereas large-fiber, dorsal column functions were preserved.

Although earlier studies indicated a much lower figure, 60-65% of men with MS have ED. ED usually occurs in men with urinary symptoms, the majority having urodynamically demonstrable hype r- re flex i a (Belts et al. 1994). Typically, in the early stages of MS, the chief complaint is of difficulty sustaining an erection for intercourse. Penile erections occurring during rhe night and on morning waking and normal nocturnal penile tumescence tests have been demonstrated in men with MS who complain of erectile difficulties. These features may have contributed in the past to a misapprehension that the problem was not organic. Wirh advancing neurological disability, erectile function may cease, and there may be difficulty with ejaculation. A study of the pudendal evoked potentials in men with MS found that those with a severe delay (i.e., those with more severe spinal cord disease) were more likely to be unable to ejaculate (Betts et al. 1994). It has been said that a diagnosis of MS should be considered in a young man presenting with impotence, but in the absence of clinical spinal cord disease, this seems unlikely. In one series only, a single patient had erectile difficulties in association with the firsr symptoms of MS, and no man presented with ED and then developed neurological disease.

Female Sexual Dysfunction

A remarkable recent study of female sexual function after SCI showed that a proportion of women, particularly with higher cord lesions, had preserved orgasmic capacity (Sipski, Alexander, and Rosen 2001). Sexual dysfunction in women with MS is common, affecting 50-60%, with the incidence increasing with increasing disability. Reduced sexual desire is the most common complaint. Presumed neurogenic problems with intercourse include decreased lubrication and reduced orgasmic capacity. In women with advanced disease, there may be additional problems of lower limb spasticity, loss of pelvic sensation, genital dysesthesia, and fear of incontinence (Hulter and Lundberg 1995). Little research has been done to date, although female sexual dysfunction is now being recognized as a significant problem and treatment trials of various therapies are in progress.

SYMPATHETIC THORACOLUMBAR OUTFLOW

The fibers that travel from the thoracolumbar sympathetic chain emerge from spinal levels T10-L2 and course rhrough the retroperitoneal space to the bifurcation of the aorta, from which they enter rhe pelvic plexus. Loss of sympathetic innervation of the genitalia causes disorders of ejaculation, with cither failure of emission or retrograde ejaculation; the ability to experience the sensation of orgasm may be retained. The sympathetic thoracolumbar fibers are particularly likely to be injured by the procedure

of retroperitoneal lymph node dissection, and complaints of loss of ejaculation are common after such surgery (Fowler 1998).

CONUS AND CAUDA EQUINA

The cauda equina contains the sacral parasympathetic outflow together with the somatic efferent and afferent fibers. Damage to the cauda equina therefore results in sensory loss as well as a parasympathetic defect. After such a lesion, both men and women complain of perineal sensory loss and loss of erotic genital sensation, for which there is no effective treatment. In men, ED is also a complaint.

Damage to the cauda equina leaves the detrusor decentralized rather than denervatcd because the postganglionic parasympathetic innervation is unaffected. This may explain why the bladder dysfunction after a cauda equina lesion is unpredictable and why even detrusor hyperrcflexia has been described. Inability to evacuate the bowel may be a severe problem, and manual evacuation may be necessary for the long term. Additional denervation of the anal sphincter can result in incontinence of flatus or liquid motions.

Loss of control over bladder and bowel and loss of sexual function are patticularly difficult for patients to bear psychologically when they are otherwise ambulant and mobile. Although there are a number of scries reporting the urodynamic changes that can occur after a cauda equina lesion, there has been no analysis of the effect a cauda equina lesion can have on the quality of life. The levels of compensation awarded in medicolegal cases reflect the fact that loss of control of the pelvic organs is a catastrophe.

Contact with other patients similarly affected may prove supportive (see www.caudaequina.com or www.cauda-cquina.org).

PERIPHERAL INNERVATION

Diabetic Neuropathy

Bladder involvement was once considered an uncommon complication of diabetes, but the greater use of techniques for studying bladder function has shown that the condition is common, although often asymptomatic. Bladder dysfunction does not occur in isolation, and other symptoms and signs of generalized neuropathy must be present in affected patients. The onset of the disorder is insidious, with progressive loss of bladder sensation and impairment of bladder emptying over years, eventually culminating in clironic low-pressure urinary retention (Frimodt-Moller 1980). Urodynamic studies demonstrate impaired detrusor contractility, reduced urine flow, increased postmicturition residual volume, and reduced bladder sensation (Kaplan, Alexis, and Blaivas 1995). It seems likely that vesicle afferent and efferent fibers are involved, causing reduced awareness of bladder filling and decreased bladder contractility.

Diabetes is the most common cause of ED. Surveys of andrology clinics have found that 20-31% of men attending arc diabetic. The prevalence of ED increases with age and duration of diabetes, and the problem is known to be associated with severe retinopathy, a history of peripheral neuropathy, amputation, cardiovascular disease, raised glycosylated hemoglobin, and the use of antihypertensives (Kolodny et al. 1974). A large population study of men with early-onset diabetes found that 20% had ED. Whether its pathogenesis in diabetic patients results mainly from neuropathy, there is a significant microvascular contribution, or rhe two processes are codependent is not yet resolved. At a cellular level, however, the evidence suggests a depletion of neurotransmitters.

Age-matched studies of women with and without diabetes suggest that diabetic women may also be affected by specific disorders of sexual function, including decreased vaginal lubrication and capacity for orgasm (Jensen 1986).

Amyloid Neuropathy

Autonomic involvement occurs early both in inherited familial amyloid polyneuropathy (FAP) and in amyloidosis secondary to myeloma or benign plasma cell dyscrasia. Typically, there are features of somatic sensory involvement, such as loss of pain and temperature sensation in the feet, by the time the disease has advanced to produce pelvic autonomic deficits. A study of the urogenital complaints of 12 patients with FAP type I amyloidosis showed reduced bladder contractility and a reduced flow rate in most of them, and two patients had a significant postmicturition residual. Five had ED, and one also had retrograde ejaculation (Villaplana et al. 1997). Although the patients in this series generally were at an advanced stage (undergoing liver transplantation), ED is often reported early in the course of FAP when fewer systemic symptoms are present.

Immune-Mediated Neuropathies

About one fourth of patients with Guillain-Barre syndrome have bladder symptoms. These symptoms usually occur in patients with more severe neuropathy and appear after limb weakness is established. Both detrusor areflexia and bladder overactivity have been described (Zochodne 1994).

It is likely that acute distal autonomic neuropathy is a form of Guillain-Barre syndrome, and there have been a

number of reports of distal autonomic neuropathy affecting both the sympathetic and parasympathetic systems. Painful urinary retention usually occurs in both cholinergic and pandysautonomia.

Injury to Pelvic Nerves

Extirpating pelvic surgery, such as resection of rectal carcinoma, radical prostatectomy, or radical hysterectomy, can damage the peripheral innervation of the pelvic organs. The dissection necessary for rectal cancer surgery is likely to damage the parasympathetic innervation to the bladder and genitalia because the pelvic nerves take a mediolateral course through the pelvis on either side of the rectum and the apex of the prostate. The nerves may be removed together with the fascia that covers the lower rectum or may be damaged by a traction injury as the rectum is mobilized before excision (Mundy 1982).

Urinary incontinence after a radical prostatectomy or a radical hysterectomy that includes the upper part of the vagina probably is also caused by damage to the parasympathetic innervation of the detrusor and, in the case of radical prostatectomy, direct damage to the innervation of the striated urethral sphincter. Much has been written about the importance of sparing nerves during a radical prostatectomy to preserve erectile function {Walsh and Donker 1982), but ED occurs in a significant proportion of patients postoperatively. Ejaculation can also be affected after this operation.

Myotonic Dystrophy

Although myotonic activity has not been found in the sphincter or pelvic floor of patients with myotonic dystrophy, bladder symptoms may be prominent and difficult to treat, presumably because bladder smooth muscle is involved. With advancing disease, megacolon and fecal incontinence may also become an intractable problem (Herbaut et al. 1992),

Urinary Retention in Young Women

Urinary retention or symptoms of obstructed voiding in young women in the absence of overt neurological disease have long puzzled urologists and neurologists alike, and in **the** absence of any convincing organic cause, the condition was often said to be hysterical. Typically, the clinical history is of a young woman aged 20-30 years who presents with retention and a bladder capacity greater than 1 liter. The history is often that over the preceding 12 hours she has found herself unable to void and, although by the time of presentation she may be very uncomfortable, she does not have the sensations of extreme urgency that might be expected. Many of the women have previously had an interrupted urinary stream but are unaware that this is abnormal; therefore, a voiding history can be misleading unless taken carefully (Swinn et al. 2002). There are no other clinical neurological features or laboratory investigations to support a diagnosis of MS, and magnetic resonance images of the brain, spinal cord, and cauda equina are normal. The lack of sacral anesthesia makes a cauda equina lesion improbable. In some young women with urinary retention, concentric needle electrode examination of the striated muscle of the urethral sphincter reveals a striking electromyographic abnormality (Fowler et al, 1988) (see Chapter 42). Until recently, management was symptomatic only, and patients had to perform intermittent self-catheterization indefinitely. However, it appears that these patients respond particularly favorably to sacral nerve stimulation. The mechanism of action of this therapeutic intervention is being researched (Swinn et al. 2000).

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Chapter 33
Arm and Neck Pain

Michael Ronthal

The evaluation of the patient with arm or neck pain depends on a careful history and clinical examination. Almost always, the diagnosis of the common causes can be made in the office before seeking laboratory investigation, but these may be required if the patient fails to improve with treatment or has other specific indications for imaging or electrophysiological studies.

A useful approach is to consider the problem in terms of pain-sensitive structures in the neck and in the upper limb. These structures may be part of the nervous system (neurological) or part of the joints, ligaments, muscles, and so on (non-neurological). Neurological causes involve the innervation of the structures in the neck and arm, and non-neurological causes are based on dysfunction of other anatomical structures of the arm or neck. Nerve root irritation frequently generates neck muscle spasm, which is therefore classified in the "neurological" category. Some essentially non-neurological conditions have neurological complications and are grouped in this chapter as "in between" disorders.

CLINICAL ASSESSMENT

History

Neurological Causes of Pain

Muscle Spasm. Spasm of posterior cervical muscles causes local pain that is aggravated by neck movement. The diagnosis is supported by the finding of palpable spasm and tenderness of the neck and shoulder muscles. The pain may radiate upwards to the occipital region and over the top of the head to the bifrontal area. It is usually described as constant, aching, and bursting or as a tight band or pressure on top of the head. Pain with similar characteristics can be triggered by abnormalities of the facet joints of the cervical spine, of the vertebrae, and even of the intervertebral discs.

Neck mobility is restricted as a result of muscle spasm. It should be assessed by testing for movement in each of the main planes, flexion and extension, lateral flexion to the right and left, and rotation to right and left. Normally in flexion the chin can touch the sternum and in rotation the chin should be able to approximate the point of the shoulder.

Central Pain, Central dysfunction affecting sensory tracts in the spinal cord may generate pain or paresthesias in the arm or down the trunk and lower limbs. An electric-like sensation spreading to the arms, down the spine, and even into the legs that is provoked by neck flexion is thought to originate in the posterior columns of the cervical spinal cord (Lhermittc's sign). Although it is common in patients with multiple sclerosis, it is nonspecific and simply denotes a pathological process in the cervical cord. Sharp superficial burning or itching pain suggests dysfunction in the spinothalamic system, whereas deep aching boring pain with paresthesias and sensations of tightness, squeezing, or swelling suggest dysfunction in the posterior columns.

Nerve Root Pain. If the damage involves nerve roots, it is referred down the limb more or less in dermaromal distribution. Brachialgia (arm pain) aggravated by neck movement, coughing, or sneezing indicates a cervical radiculopathy, hut ihis pathognomonic symptom may not

he present. Nerve root pain is classically lancinating bur can be a dull ache in the arm,

Plexus Pain. Pain in the arm can result from damage to the brachial plexus or individual nerves in the arm. Infiltrative or inflammatory lesions of the brachial plexus produce severe brachialgia radiating down the arm and spreading also to the shoulder region. Radiation to the ulnar two fingers suggests origin in the lower brachial plexus, and radiation to the upper arm, forearm, and thumb suggests an upper brachial plexopathy. Patients with a thoracic outlet syndrome complain of brachialgia and numbness or tingling in the upper limb or hand when working with objects above the head.

Ulnar Nerve Pain. Ulnar nerve entrapment produces numbness or pain radiating down the medial aspect of the arm to the little and ring fingers. The symptoms are often worse at night when the patient sleeps with a flexed elbow and may be the cause of interrupted sleep. They are also worse when the patient rests the elbow on the arm of a chair or desk.

Median Nerve Pain, Median nerve entrapment in the carpal tunnel will often wake the patient from sleep with numbness and tingling in the thumb, index and middle fingers, which is relieved by "shaking out" the hand. Pain generated in the median nerve can be sharp and lancinating and radiates to the thumb and index and middle fingers.

Non-Neurological Causes of Neck Pain and Brachialgia

Pain arising in muscles is described as deep aching and boring. In the cervical region, it is localized to the shoulders and sometimes radiates down the arm. Patients with fibromyalgia ma] have pain in the neck, shoulders, and arms, with trigger spots that are exquisitely render even to light pressure.

Joint and tendon pain has the characteristic of being initiated and aggravated by movement of the joint involved or tension of a specific tendon. Particular attention should be paid to these precipitating factors. Pain on shoulder joint movement is unlikely to be neuropathic. Although the pain of epicondylitis may radiate down the forearm in a pseudoneuralgic fashion, precipitation of pain by movement at fingers or wrist generally indicates an arthropathy cause.

Examination

The physical examination is designed to localize a neurological deficit related to spinal cord, nerve roots, or peripheral nerves. At the same time, evaluation for non-neurological pathology is important because orthopedic and rheumatological problems often simulate or complicate neurological presentations. A detailed knowledge of motor and sensory neuroanatomy is required for accurate localization.

Motor Signs

The examination begins with inspection. Particular attention is paid to atrophy of the muscles of the shoulders and arms, as well as the small muscles of the hands. Fasciculations are often due to anterior horn cell disease, but they are not uncommon in patients with cervical spondylosis and radiculopathy. A good confirmatory sign of cervical radiculopathy is in the Spurling sign. The patient's head is inclined towards the painful side, and pressure is applied downwards from the crown. This may produce sharp pain radiating down the arm and forearm. Although the specificity for radiculopathy is in the range of 93%, sensitivity is only around 30% (Tong, Haig, and Yamakawa 2002).

Muscles in the various cervical and upper thoracic myotomes must be tested individually. When there is unilateral weakness, the contralateral side can act as a control. A standard measure of strength is necessary for accurate evaluation when bilateral weakness is present. If the examiner can overcome the action of a patient's muscle by resisting or opposing its action using an equivalent equipotcnt muscle (fingers test fingers, whole arm tests biceps), then that muscle in the patient is by definition weak. The amount of weakness present can be graded, and the 5-point Medical Research Council (MRC) grading scale is often used. Grade 5 represents normal strength. Grade 4 represents "weakness" somewhere between normal strength and the ability to move the limb only against gravity (grade 3). Grade 4 covers such a large range that it should be expanded. One simple expansion is into mild, moderate, or severe. When the muscle can move the joint with the effect of gravity eliminated, it is graded at 2, and grade 1 is just a flicker of contraction.

The distribution of weakness helps localize the problem to the nerve root, peripheral nerve, muscle, or even the upper motor neuron. It is useful to use a simplified schema of anatomical localization in the evaluation of weakness due to nerve root lesions because overlap of myotomes can complicate the analysis (Table 33.1}.

The lower limbs need to be examined even when the patient complains of symptoms only in the upper limbs, because evidence of a myelopathy and the finding of sensory or motor dysfunction in the lower limbs, when combined with the presence of radicular signs in the upper limbs, indicates a spinal cord lesion.

The thoracic outlet syndrome is an overdiagnosed condition. Maneuvers designed to test for compromise of the neurovascular structures passing through the thoracic outlet are often difficult to interpret. In these maneuvers, the arm is extended at the elbow, abducted at the shoulder, and then rotated posteriorly. The examiner palpates the radial

Table 33.1:

Segment level	*Muscle(s)*	*Action*
C4	Supraspinacus	First 10 degrees of shoulder abduction
C.5	Deltoid	Shoulder abduction
	Biceps/brachialis	Elbow flexion
C6	Extensor carpi radialis longus	Radial wrist extension
C7	Triceps	Elbow extension
C7	Extensor digitorum	Finger extension
C8	Flexor digitorum	Finger flexion
Tl	Interossei	Finger abduction and adduction
	Abductor digiti minimi	Little finger abduction

Nore: This is a somewhat schematic representation of the main segmental innervation of the muscles of the upper limbs. It is clinically useful in localizing a single radicular level and although not entirely correct, it usually "works," If we were to be absolutely anatomically correct, because virtually all muscles are of multisegmental innervation, clinical localization would be more complicated and imprecise.

pulse and listens over the proximal and distal brachial artery with a stethoscope. The patient takes a deep inspiration and turns the head to one and the other side. Many normal individuals lose the radial pulse with these maneuvers, but the development of a bruit does suggest the presence of at the least vascular entrapment (Adson's test). The patient then exercises the hands held above the bead with extended elbows; the development of numbness, pain, or paresthesias, often with pallor of the hand, supports the diagnosis of a thoracic outlet syndrome (Roos test).

Light tapping over an accessible plexus or peripheral nerve may elicit distal tingling in the distribution of the plexus or nerve {Tinel's sign). This may be positive over the brachial plexus in the supraclavicular fossa, the ulnar nerve at the elbow, or the median nerve at the wrist.

Sensory Signs

Sensation is tested in a standardized manner starting with pinprick appreciation at the back of the head (C2), followed by testing the cervical dermatomes proceeding stepwise down the shoulder, over the deltoid down the lateral aspect of the arm to the lateral fingers, and then proceeding to the medial fingers and up the medial aspect of the arm ifigure ,i.>. I I. The procedure is repeated with a wisp of cotton, and test tubes filled with cold and warm water to test temperature sensation. Vibration sense is tested in the fingers. Position sense in the distal phalanx of a finger is tested by immobilizing the proximal joint and supporting the distal phalanx on its medial and lateral sides. Then the terminal phalanx is moved up and down, and the patient reports movement and its direction. Loss of position sense in the fingers usually indicates a high cervical cord lesion.

Tendon Reflexes

Examination of the tendon reflexes helps localize segmental nerve root levels affected. An absent or decreased biceps reflex localizes the root level to C5, and an absent triceps reflex localizes the level to C6 or C7. In patients with cervical spondylosis who have both a radiculopathy and an associated myelopathy, the reflexes may be preserved or even increased despite the radiculopathy. The most common disc prolapse at C5-C6 may result in a radiculopathy and myelopathy at that level, which manifests with absent or decreased biceps and brachiuradialis reflexes, an increased triceps reflex, and spread of the brachioradiahs reflex to the finger flexors to produce a finger jerk. There may be a Hoffman reflex.

Non-Neurological Signs

The arm is passively abducted and internally and externally rotated at the shoulder. The complaint of pain on movement or at a point in the abductor arc indicates local shoulder joint pathology. This is usually due to shoulder tendonitis or pcricapsulitis. The tendons anteriorly and at the lateral point of the shoulder may be tender to pressure. More diffuse tenderness anterior to the shoulder joint indicates bursitis. Tenderness over the medial or lateral epicondyle at the elbow indicates local inflammation, and pain on active or passive wrist or finger joint movement suggests tendonitis or arthritis.

CLINICAL SYNDROMES AND DIFFERENTIAL DIAGNOSIS

Spinal Cord

Primary intramedullary spinal cord lesions may be neoplastic, inflammatory, or developmental. The most common presenting symptom of spinal cord tumor is pain that is present in about two thirds of patients, usually radicular in distribution, often aggravated by coughing or straining, and worse at night (Alter 1975), A minority of patients show dissociated sensory signs (segmental suspended [i.e., has an upper and lower border] loss of pinprick and temperature sensation with preserved

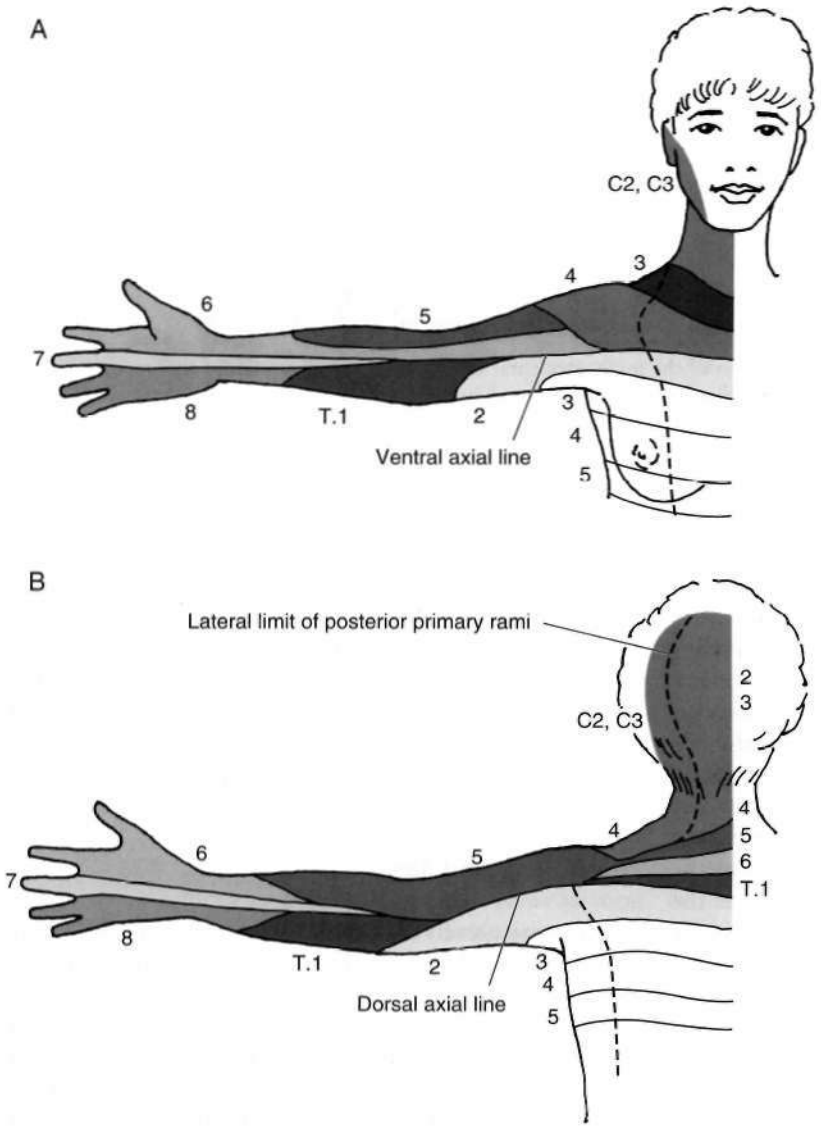

FIGURE 33.1 Diagram of the dermatomes in the upper limbs. (**A**) Anterior aspect. Although there is variability and overlap across the interrupted lines, there is little or no overlap across the continuous lines (i.e., the dorsal and ventral axial lines). The examiner should routinely choose one spot in the "middle" of a dermatome and test at that point in all patients. C4 usually terminates at the point of the shoulder, T3 is almost always in the axilla, and T4 spreads across the chest so that C4 abuts T4 approximately at the nipple line. (**B**) Posterior aspect.

light-touch, vibration, and position sense) in the upper limbs to suggest a central cord lesion. Long tract signs in the lower limbs will develop sooner or later. Imaging with magnetic resonance reveals swelling of the spinal cord. The most common tumors arc glioma, lymphoma, and ependymoma.

Cervical myelitis may sometimes present with rapid onset of radicular and long tract symptoms and signs, although commonly radicular signs are absent. This may be due to multiple sclerosis or postinfectious acute dcmyclinating encephalomyelitis, or it may be without clear cause (idiopathic).

Syringomyelia, a cystic intramedullary lesion of variable and unpredictable progression, may present with deep aching boring pain in the upper limb said to be characteristically referred to the ear. Asymmetrical lower motor neuron signs in the upper limbs with dissociated suspended sensory loss is very suggestive of a syrinx. However, the most common cause of intramedullary cord dysfunction is extrinsic spinal cord compression.

Extramedullar? Lesions

Extramedullar lesions may result in any combination of nerve root, central spinal cord, and long tract signs and symptoms. The most common cause of extrinsic nerve root and spinal cord compression is cervical spondylosis (Ronthal 2000). This is a degenerative disorder of the cervical spine characterized by disc degeneration with disc-space narrowing, bone overgrowth producing spurs and ridges, and hypertrophy of the facet joints, all of which can compress spinal cord or nerve roots. Hypertrophy of the spinal ligaments with or without calcification may contribute to compression. However, hypertrophic osteophytes

are present in approximately 30% of the population, and the incidence increases with age. Hence, the presence of such degenerative changes docs not indicate that the patient has symptoms caused by these changes and acumen is needed in the diagnosis to ensure that the abnormalities seen on imaging are responsible for the patient's signs and symptoms. The osteophyte is sometimes referred to as a "hard disc" as opposed to an acute disc herniation or "soft disc," in which the onset is acute with severe neck pain and brachialgia.

Patients with cervical spondylosis often awake in the morning with a painful stiff neck and diffuse nonpulsatile headache that settles in a few hours. Cervical spondylosis is most commonly found at C5-C6 and C6-C7, and focal signs are likely to be at these levels. Wasting and weakness of the small muscles of the hands may occasionally be seen in cervical spondylotic radiculomyelopathy with no observable anatomical change at the C8-T1 level, when it is referred to as a *fake localizing sign.* However, most commonly, the intrinsic muscle wasting in the hand is due to another disease, such as amyotrophic lateral sclerosis (ALS).

Restricted neck movement is always present with significant cervical spondylosis. Bladder dysfunction, indicated by frequency, urgency, and incontinence, ot the finding of long tract signs or symptoms indicate the need for imaging of the cervical spine both to exclude a disease othet than cervical spondylosis and to define the severity of the spinal cord compression. Immobilization in a cervical collar often helps with the symptoms and signs of cervical spondylosis. The role of surgery in treatment is discussed in Chapter 79.

Extramedullar compression, usually in the extradural space is usually due to primary or metastatic tumors. Of the primary tumors commonly encountered, a schwannoma produces signs and symptoms telatcd to the nerve root on which it arises, and as it enlarges a progressive myelopathy develops. X-rays of the cervical spine may demonstrate an enlarged intervertebral foramen at the level of the nerve root schwannoma, bur magnetic resonance imaging (MRI) is usually diagnostic. A meningioma may present in a somewhat similar fashion, but without foramina! enlargement; this is more common in the thoracic region.

Epidural spinal cord compression due to metastatic malignancy presents initially with spine pain in more than 90% of patients (Gilbert, Kim, and Posner 1978). Malignant bone pain is usually localized to the vertebra involved and percussion tenderness is a good localizing sign, even in the neck. As the metastasis spreads to the epidural space, radicular pain appears. X-rays of the cervical spine may show bony erosion with preservation of disc spaces, and the imaging modality of choice is MRI. The whole spinal column should be scanned because metastases are often at multiple sites, some of which may be subclinical (Chamberlain and Kormanik 1999). Spinal cord compression resulting from metastatic disease is a neurological emergency requiring treatment with immediate high-dose corticosteroids and local irradiation. Few patients arc referred for surgery.

Epidural infection (abscess) may be either acute and pyogenic or more chronic when the organism is likely to be mycobacterial or fungal (Mackenzie et al. 1998; Sampath and Rigamonti 1999). Pyogenic epidural abscess usually presents acutely with fever, severe pain localized to a rigid neck, radicular pain, and rapidly progressing nerve root and myelopathic signs. Sometimes the presentation is more subacute with less systemic evidence of infection. Imaging will usually reveal early destruction of the intervertebral disc with spread into the epidural space. Only later is there spread to bone with vertebtal collapse. Optimal therapy is surgical decompression and evacuation, combined with 6-12 weeks of appropriate antimicrobial therapy for pyogenic infections and more prolonged treatment for tuberculosis.

The differential diagnosis of a very rapidly progressing painful epidural lesion includes spinal epidural abscess and spinal subarachnoid, subdural or epidural hemorrhage (Henderson et al. 2001). The latter is usually associated with some form of coagulopathy, including iatrogenic anticoagulant therapy, and sometimes with vascular anomalies or trauma. The sudden onset of severe pain in the neck with or without radicular pain suggests the diagnosis of hemorrhage. Reversal of the coagulation deficit if present should be followed by decompression.

The sudden onset of pain at the back of the neck with associated posterior fossa signs suggests vertebral artery dissection {Caplan, Zarins, and Hemmati 1985). The diagnosis is nowadays easily made with MR] and fat suppression sequences.

Repetitive sudden shooting pains radiating from the occipital region to the temporal areas or vertex suggest the diagnosis of occipital neuralgia. There may be local tenderness over the greater or lesser occipital nerve, and a local injection of corticosteroid and local anesthetic is both diagnostic and therapeutic. Failure to respond suggests that the cranioverrebral junction area should be imaged.

Radiculitis

Herpes-zoster virus may infect cervical sensory root ganglia (Kleinschmidt-DcMastcrs and Gilden 2001). The pain is typically radicular and the diagnosis becomes clear when, after 2-10 days, the typical vesicular rash appears. Motor involvement occasionally occurs. Myelitis with long tract signs is seen in fewer than 1% of patients. If the pain lasts longer than 3 months after crusting of the skin lesions, postherpetic neuralgia has developed. The pain is described as constant nagging, burning, aching, tearing, and itching, upon which are superimposed electric shocks and jabs.

Treatment of postherpetic neuralgia pain (Bajwa and Ho 2001) is discussed in Chapters 50 and 81.

Brachial Plexopathy

Brachialgia and signs not respecting a single nerve root with tenderness to palpation in the supraclavicular fossa should arouse suspicion of a brachial plcxopathy.

Brachial Neuritis (Neuralgic amyotrophy, Parsonage-Turner syndrome)

Brachial neuritis is characterized by the abrupt onset of severe pain in one shoulder and arm, which is constant and unrelenting, worse at night, and rarely bilateral, and the syndrome afflicts mainly young adult men (Kim 1996). Within a week or so, muscle weakness atrophy and fasciculations are evident, mainly in the shoulder girdle but at times more distally and not in one particular myotome. There is usually little or no sensory loss despite the pain. The pathogenesis is thought to be autoimmune/ inflammatory and a number of antecedent inciting events have been described, including immunization, prior infections, and trauma. The syndrome is associated with autoimmune diseases and Hodgkin's disease. There is no proven specific treatment, but a short course of corticosteroid is usually given. Treatment should be directed to relief of pain, which often runs its course in 6-8 weeks. In some patients, paralysis can take up to 2 years to recover and occasionally there is some permanent weakness.

A subset of patients have a familial history of recurrent attacks. Hereditary neuralgic amyotrophy is an autosomal dominant trait, and many patients have deletions of the **PMP-22** gene on the distal long arm of chromosome 17 (Chance and Windcbank 1996).

Brachial Plexopathy in Cancer Patients

Plexopathy in patients with cancer, particularly those with breast cancer or lymphoma who have been irradiated poses a diagnostic problem: Is this radiation plexopathy or malignant infiltration of the brachial plexus? Malignant infiltration is more likely to trigger severe brachialgia and a Horner syndrome and to affect the lower plexus. Irradiation damage is less likely to cause severe pain and often affects the upper plexus. Both are slowly progressive, but radiation plexitis is more likely to be of longer duration. Electrophysiological studies (see Chapters 17B and 81) are helpful, because myokymia and fasciculations support the diagnosis of radiation plexitis (Harper ct al. 1989). MRI for infiltration with tumor has a sensitivity of *96%,* a specificity of 95%, and a positive predictive value of 95% (Qayyum ct al. 2000). Occasionally, a locally malignant, recurrent schwannoma occurs in a brachial plexus that has been irradiated many years before.

Thoracic Outlet Syndrome

Brachial plexus involvement as an entrapment syndrome in the thoracic outlet is rare. The very existence of this entrapment remains open to debate, partly because n is difficult to diagnose, and partly because it is often used in disability claims, often in the absence of proof. Consequently questions remain about diagnosis and the efficacy of surgical treatment (Landry et al. 2001). Entrapment may involve the brachial plexus, the subclavian artery, or both. Sagging musculature with postural abnormalities including droopy shoulders and a long neck contributes to the predisposition to develop the thoracic outlet syndrome.

A supernumerary cervical rib or simply an elongated transverse process of the seventh cervical vertebra may be seen on x-rays. The rib may articulate with superior surface of the first true rib or a fibrous band may extend from its tip or the tip of the abnormal transverse process connecting to the first true rib. The abnormal structure compresses the brachial plexus, particularly when the upper limb is elevated above head level. Pain and paresthesias radiate to the ulnar side of the hand and fingers, and weakness and wasting of the intrinsic muscles of the hand, secondary to lower plexus compression, may be evident. Thoracic outlet maneuvers described earlier are generally considered to be unreliable, but do raise suspicion of the presence of the syndrome. The examination may be normal, or there may be weakness of abductor digiti minimi and hypothenar sensory loss. Occasionally, the abductor pollicis brevis muscle is particularly atrophic and weak.

The diagnosis is often one of exclusion; imaging of the cervical spine is normal and nerve conduction studies below the clavicle are also normal. Venous and arterial anatomy can be studied by catheter angiography, Doppler flowmetry, or magnetic resonance angiography (Napoli et al. 1993; Dymarkowski et al. 1999). Electrophysiological studies that show partial denervation of the small muscles of the hand and a decreased sensory nerve action potential amplitude from the fifth digit are compatible with the diagnosis of thoracic outlet syndrome (Smith and Trojaborg 1987).

In all cases, a conservative approach should be tried initially. Postural exercises and thoracic outlet muscle strengthening exercises, instructions in proper sitting at work, and correction of unusual sleep positions should provide relief in 50-90% of patients, usually **within** 6 weeks (Tyson and Kaplan 1975). Failure of conservative treatment prompts consideration of a surgical opinion (Leffert, Perlmuttcr 1999; Sheth and Belzberg 2001).

Suprascapular Nerve Entrapment

The nerve may be entrapped or injured as it passes through the suprascapular notch (see Chapter 82). It is occasionally

cut in the process of lymph node biopsy. The branch to the infraspinatus muscle can be entrapped at the spinoglenoid notch by a hypertrophicd inferior transverse scapular ligament. The patient complains of deep pain at the upper border of the scapula aggravated by shoulder movement and there may be atrophy and weakness of the supraspinatus and more commonly the infraspinatus muscles. The supraspinatus muscle accounts for the first 10 degrees of shoulder abduction and the infraspinatus muscle externally rotates the arm.

Carpal Tunnel Syndrome

Carpal tunnel syndrome, the most common entrapment neuropathy, is more common in women (Atroshi et al. 1999). It is now an accepted occupational hazard secondary to repetitive stress and occasionally is the presenting symptom of underlying systemic disease. The nerve is entrapped in the bony confines of the carpal tunnel, which is roofed by the ttansverse carpal ligament. Pregnancy, diabetes, rheumatoid arthritis, hypothyroidism, sarcoidosis, acromegaly, and amyloid infiltration of the ligament are possible predisposing factors, and appropriate screening studies should be performed on all patients with a carpal tunnel syndrome. Numbness or pain radiating to the thumb, index, and middle fingers often wakes the patient at night. At times, there is diffuse brachialgia. Atrophy of the abductor pnllicis brcvis muscle may be marked, but the motor deficit is rarely the cause of disability. Significant sensory loss in the median nerve distribution can be a handicap because of poor feedback when using the hand out of sight.

Examination reveals, in advanced cases, atrophy of abductor pollicis brevis muscle, which produces a longitudinal furrow in the thenar eminence. There is weakness of thumb abduction. In theory there is also weakness of **the** opponens, but patients recruit the long flcxot tendons when testing opposition so that weakness is hard to define. The palmar cutaneous branch leaves the median nerve proximal to the flexor retinaculum and supplies the skin over the thenar eminence and proximal palm on the radial aspect of the hand. Hence, sensoty loss secondary to dysfunction of the median nerve in the carpal tunnel, if present, is likely to involve the distal thumb, index, and middle fingers but not the thenar eminence, a diagnostic point helpful in localization of the lesion. Phalen's test is performed by holding the wrist in complete flexion, when numbness or tingling in a median nerve distribution is seen within 20 seconds, but latency before the sensory symptoms occur can be up to a minute. Sensitivity is about 74% and the false-positive rate is about 25% (Salerno et al. 2000). The Tinel's sign may be elicited by producing distal tingling on tapping the median nerve at the wrist (Kuhlman and Hennessy 1997). Confirmation of the diagnosis is provided by nerve conduction studies and electromyography (EMG). Distal motor and sensory latencies are prolonged, and polyphasic reinnervation potentials are seen in the abductor pollicis brevis muscle (Kimura 1979), More extensive and expensive investigations are not warranted, but sonography and MR scanning have been utilized (Swen et al. 2001; Horch et al. 1997). **Initial** relief of the sensory symptoms can be obtained with the use of wrist splints, but patients with unremitting pain or significant motor and sensory signs, with confirmatory nerve conduction studies, should be offered decompressive surgery, which can now be undertaken using fiberoptic techniques. This can be curative. The surgeon should always send the flexor retinaculum for histopathological examination to search for amyloid deposition.

Occasionally carpal tunnel syndrome may be mimicked by entrapment of the median nerve more proximally at the elbow. Here, it passes beneath the thick fascial band between the biceps tendon and the forearm fascia and then between the two heads of the pronator teres muscle. As the nerve passes between the heads of the pronator teres, it supplies that muscle, as well as the flexor carpi radialis (which flexes and abducts the hand at the wrist) and the flexor digitorum superficialis (which flexes the fingers at the interphalangeal joints with the proximal phalanx fixed) muscles. After it passes between the two heads of the pronator teres muscle, it supplies the flexor pollicis longus muscle (which flexes the distal phalanx of the thumb with the proximal phalanx fixed), the flexor digitorum profundus muscle to the first and second digits (which flexes the distal phalanx with the middle phalanx fixed), and the pronator quadratus muscle (which pronates the forearm with the elbow completely flexed). Nerve conduction studies may localize the site of pathology and the EMG precisely defines which muscles are involved.

Ulnar Entrapment at the Elbow

The ulnar nerve may be entrapped proximal to the epicondylar notch or as it passes through tin- cubital tunnel at the elbow, a fibro-osseous canal formed by the medial condyle, ulnar collateral ligament, and flexor carpi ulnaris muscle (Campbell etal. 1991). Structural narrowing of the canal aggravated by occupational stress and a sustained flexion posture, especially when sleeping, as well as repetitive flexion-extension movements contribute to entrapment. Although numbness and tingling is more common than pain, both are referred to the hypothenar eminence and little and ring fingers. A positive Tinel's sign at the elbow over the ulnar nerve helps to localize the site. In severe cases, there is wasting and weakness of the small muscles of the hand (excluding the abductor pollicis brevis and opponens muscles, which are median nerve innervated). There is decreased sensation over the palmar aspect of the ring and little finger and there may be decreased sensation on the media] dorsal aspect of the hand and ulnar two fingers

because of involvement in the distribution of the dorsal branch of the ulnar nerve. In severe chronic cases, clawing of the fourth and fifth digits results from weakness of the third and fourth lumbrical muscles. Nerve conduction studies localize the area of entrapment, and if the symptoms do not settle by avoiding prolonged elbow flexion and the physical signs are significant, surgical decompression may be considered (see Chapter 82).

Radial Nerve and Posterior Interosseus Nerve Syndrome

Having passed round the spiral groove of the humerus, the radial nerve pierces the lateral intermuscular septum to lie in front of the lateral condyle of the humerus between the brachialis and brachioradialis muscles. There, it bifurcates to form the superficial branch, which is sensory to the lateral dorsal hand, and the deep branch, referred to as the *posterior interosseus nerve.* This branch supplies the finger and thumb extensors and the extensor carpi radialis brevis muscle, which is of lesser importance for radial wrist extension (extensor carpi radialis longus is dominant and its nerve supply comes off slightly more proximally, so radial wrist extension is spared in lesions of the posterior interosseus nerve). The deep branch passes through the fibrous edge of extensor carpi radialis muscle through a slit in the supinator muscle (arcade of Frohse |Papadopoulos, Paraschos, and Pelekis 1989]). Entrapment of the posterior interosseous nerve produces symptoms similar to those of lateral epicondylitis, namely lateral arm pain, or a dull ache in the deep extensor muscle area, which radiates proximally and distally and is increased with resisted active supination of the forearm. Extension of the elbow, wrist, and middle fingers against resistance increases the lateral elbow pain. Tenderness may be elicited over the posterior interosseous nerve just distal and medial to the radial head. Pain secondary to posterior interosseous entrapment is typically seen in manual laborers and occasionally in typists. The site of pathology is easily localized by EMG and nerve conduction studies, and surgical decompression is usually successful (Lawrence, Mobbs, and Forrcms 1995). Occasionally, a neoplasm of the nerve causes the same symptoms and some surgeons prefer MRI before surgery (Rosenberg, Bencardino, and Beltran 1997).

Complex Regional Pain Syndromes

Complex regional pain syndromes include syndromes previously called *reflex sympathetic dystrophy* (RSD), causalgia, shoulder-hand syndrome, Sudeck's atrophy, transient osteoporosis, and acute atrophy of bone (see Chapters 50, 82, and 83). By consensus, the syndrome requires the presence of regional pain and sensory changes following a noxious event (Stanton-Hicks et al. 1995). The pain is of a severity greater than that expected from the inciting injury and is associated with abnormal skin color or temperature change, abnormal sudomotor activity or edema. Type I refers to patients with RSD without a definable nerve lesion, and type II refers to patients in whom a definable nerve lesion is present and was formerly called *causalgia.*

A soft tissue injury is the inciting event in about 40% of patients, a fracture in 25%, and myocardial infarction in 12% (Paketal. 1970).

The pathophysiology is unclear, but because it used to be thought that many patients respond to sympathetic block and autonomic features are prominent, it has been suggested that there is an abnormal reflex arc that follows the routes of the sympathetic nervous system and is modulated by cortical centers. There is decreased sympathetic outflow to the affected limb and autonomic manifestations previously ascribed to sympathetic overactivity are now thought to be due to catecholamine hypersensitivity (Wasucr et al. 2001). Significant emotional disturbances at the time of onset occur in many patients and stress may be a precipitating factor (Geertzen et al. 1994).

Pain can be progressive and three stages of progression have been described (Veldman et al. 1993):

Stage I: There is diffuse burning, throbbing, aching sensations, sensitivity to touch or cold, and localized edema. Vasomotor disturbances produce altered skin color and temperature.

Stage II: There is progression of soft tissue edema with thickening of skin and articular soft tissues and muscle wasting. This may last 3-6 months.

Stage III: There is now limitation of movement, often with a frozen shoulder, contractures of the digits, waxy trophic skin changes, and brittle ridged nails. X-rays show severe demtneralization of the adjacent bones.

Motor impairment is not necessary to make the diagnosis, but weakness, tremor, or dystonia is sometimes present.

The diagnosis is essentially clinical. Diffuse severe nonsegmental pain with cyanosis, or mottling, increased sweating and shiny skin, swollen nonarticular tissue, and coldness are characteristic. Hypersensitivity to pinprick may preclude precise sensory testing. There may be associated myofascial trigger points and tendonitis around the shoulder,

Autonomic testing may help with the diagnosis; the resting sweat output and quantitative sudomotor axon reflex test used together are 94% sensitive and 98% specific and are excellent predictors of a response to sympathetic-block (Chelimsky et al. 1995). Bony changes including osteoporosis and joint destruction may be seen. Bone scintigraphy is more sensitive in stage I, though less useful in later stages (Lee and Weeks 1995). A stellate ganglion block may be useful both therapeutically and diagnostically (see Chapter 82).

These patients require a good deal of support, as well as trials of symptomatic medication. Drugs that sometimes work are prazosin, propranolol, nifedipine or verapamil, guancthidine or phenoxybenzamine, and antidepressants. Bisphosphonarcs may prevent bone resorption and are helpful with pain control. A trial of stellate ganglion block, which can be repeated if successful, is worthwhile. Sympathectomy has been used for progressive disease in patients who previously responded to sympathetic block.

"In Between" Neurogenic and Non-Neurogenic Pain Syndrome: Whiplash Injury

Whiplash is an acceleration-deceleration mechanism of energy transfer to the neck. It may result from rear-end, or side-impact motor vehicle collisions bur can also occur during diving or other mishaps. The impact may result in bony or soft tissue injuries (whiplash injury), which in turn may lead to various clinical manifestations (whiplash-associated disorders) (Spitzer et al. 1995). Rear-end motor vehicle collisions are responsible for 85% of whiplash injuries, and about one million such injuries occur in the United States every year. Severe injuries can cause rupture of ligaments, avulsion of vertebral endplates, vertebral fractures, and intervertebral disc herniations, sometimes associated with cervical nerve root or spinal cord damage.

The severity of injury can he graded:

- Grade I injuries: pain and stiffness and tenderness in the neck with no physical signs
- Grade II injuries: as noted above, together with physical signs of decreased range of movement and point tenderness
- Grade III injuries: neurological signs, including weakness, sensory loss, absent reflex, or long tract signs.

The prognosis is related to the severity of injury:

- Neck pain for more than 6 months after injury: grade I, 44%; grade II, 81%; grade III, up to 90%
- Headache for more than 6 months after injury: grade I, 37%; grade II, 37%; grade III, 70%.

In general about 40% of patients report complete recovery at 2 years, and about 45% continue to have major complaints more than 2 years after the collision.

The cause of persistent symptoms in patients with minor injuries is unknown and little evidence exists for a structural basis for chronic whiplash pain in this group. The difference between a trivial injury and one of more significance should be based on the presence or absence of neurological signs.

About 20% of patients complain of cognitive symptoms after whiplash, which is likely to be functional or malingering (Alexander 1998).

The influence of compensation and legal action in whiplash-associated disorders remains controversial. Two studies from Lithuania, where only a minority of car drivers are insured for personal injury, demonstrated both retrospectively and prospectively significantly less symptomatology than for similar accidents in the United States; at 1 year there was no significant difference between collision and control groups (Obelieniene et al. 1999). The Quebec Task Force emphasized that whiplash is essentially a benign condition with most patients recovering, but it is the refractory minority that accounts for an inordinate proportion of the costs (Spitzer et al. 1995).

Support, physical therapy, muscle relaxants, and antidepressants are the main therapeutic options, but if neurological signs are present, imaging of the cervical spine with magnetic resonance is indicated. Persistence of pain for more than 6 weeks should indicate referral to a more specialized center, and often a multidisciplinary team approach is best.

Rheumatoid Arthritis of the Spine

Rheumatoid arthritis in the cervical spine involves all the synovial joints but is particularly dangerous when it involves the atlantoaxial articulation. Local inflammation and pannus formation cause pain on neck movement and rupture of the transverse ligament, which holds the odontoid process in place. This may cause atlantoaxial subluxation. Pain is referred to the neck below the carlobe, and there may be a high myelopathy or even sudden death, Spine x-rays show excessive space between the anterior arch of the atlas and the odontoid process (Dreyer and Boden 1999).

Non-Neurological Neck/Arm Pain Syndromes

Patients with n on-neurological causes for acute, subacute, or chronic neck and arm pain are often referred for neurological opinion. They may have no focal neurological deficits, or they may have minor nerve root or peripheral nerve signs, which arc incidental to their main complaint. Usually, the clue to diagnosis is to be found in the history of movement aggravating or triggering the pain.

Fibromyalgia and Myofascial Syndrome

Within this group of rheu ma to logical disorders, fibromyalgia is considered the most common cause of gcnctalized musculoskeletal pain in women between the ages of 20 and 55 years; its prevalence is approximately 2% (Goldenberg 1999). The pain may be initially localized to the neck and shoulders but can spread diffusely over the body (see Chapter 79), It may follow an episode of physical or

emotional trauma or an influenza-like illness. It is associated with depression, which is present in more than 90% of cases, but chronic pain cannot be regarded as a manifestation of depression. Many patients have a sleep disorder. A host of somatic symptoms may accompany the pain: fatigue and a feeling of weakness, paresthesias, memory complaints, "allergies,'" palpitations, and irritable bowel syndrome.

The only physical sign is muscle tenderness and the finding of "trigger spots"—tender palpable nodules in the muscles. The diagnostic criteria are widespread musculoskeletal pain and excess tenderness in at least 11 of 18 predefined anatomic sites (Wolfe et al. 1990). Myofascial pain is considered a localized form of fibromyalgia with pain in one anatomic region such as in the right or left neck and shoulder with local tenderness.

Although litigation issues may drive the concept of causality and permanent tissue damage, there is no good evidence to support the notion that minor trauma induces a persistent source of noxious stimuli, and the 1994 Fibromyalgia Consensus Conference recommended that the terms *reactive* and *post-traumatic* fibromyalgia be eliminated.

The cause and pathology of the condition are unknown. Some evidence is accumulating to implicate stress as a mediator of disturbed hypotha la mic-pituitary-adrenocortical function in fibromyalgia and chronic pain. Neurally mediated postural hypotension is present in some patients. "Resetting" of central pain pathways has been postulated as a factor in increasing pain sensitivity and prolonging it. Maladaptive coping mechanisms certainly play ii role,

Adequate office management of the patient with fibromyalgia is time consuming and not cost effective for treating individual patients, so group clinics are often used. Lducniion of the patient is followed by recommendations for therapy. Most patients are tried on analgesics, muscle relaxants, and antidepressants, combined with a regimen of physical therapy and exercise. Low doses of fluoxetine and amitriptyline are more effective than either medication alone (Goldenberg ct al. 1996). If a sleep hygiene disorder is diagnosed, treatment of this can alleviate the symptoms of muscle pain. Failure to tespond suggests the need for a trial of trigger point injections of local anesthetic with or without corticosteroid.

Polymyalgia Rhcumatica

Usually seen in patients older than 50 years, severe aching pain and tenderness in the neck and shoulder-girdle muscles in association with a markedly elevated erythrocyte sedimentation rate responds dramatically to small doses of oral corticosteroid (Cohen and Abril 2001). Sometimes this is associated with temporal arteritis. If there is weakness, the diagnosis is more likely to be polymyositis and the serum creatine kinase concentration should be estimated,

Tendonitis, Bursitis, and Arthritis

Shoulder

Pain triggered by shoulder joint movement suggests tendonitis, peri capsulitis, or an internal derangement of the joint. Flexion and elevation of the shoulder, which evokes pain, is often called the *impingement sign.* Patients with a painful arc syndrome often respond to local corticosteroid injections into the tender tendons. Tenderness anterior to the shoulder joint suggests butsitis, which also will usually respond to local corticosteroid injections. Weakness is said to indicate a rotator cuff tear, but pain on movement makes evaluation difficult and MRI of the shoulder may be needed to establish the diagnosis. Acromioclavicular joint arthritis causes a more diffuse shoulder pain aggravated by arm elevation; diagnosis requires x-rays of the shoulder joint. Nonsteroidal anti-inflammatory medications help. In patients with such marked limitation of shoulder joint movement that the scapula moves en bloc with the humerus, together with movement-evoked pain, a diagnosis of "frozen shoulder" or adhesive capsulitis is made. Treatment of adhesive capsulitis is often unsatisfactory. Analgesics and physical therapy help in a limited way, but the course is likely to consist of many months of discomfort,

Elbow

Epicondylitis. Pain in the elbow region triggered by clenching the fist, which tenses the extensor muscles and irritates their points of origin, or pain that is increased with resisted finger and/or wrist extension and flexion suggests epicondylitis. Local tenderness will be found medially or laterally over the distal end of the humerus. Lateral epicondylitis is known as *tennis elbow,* and medial epicondylitis as *golfer's elbow.* F.xercises designed to strengthen the muscles that attach to these tendons arc helpful in many patients. Treatment with a firm elbow support can be supplemented by local corticosteroid injections. Occasionally these patients come to surgery.

Olecranon Bursitis. Local tenderness and swelling, which can be extreme (Popcye joint) at the point of the elbow, makes the diagnosis. The condition may follow local irritation but can be part of gout and occasionally represents a pyogenic infection. The bursa may need to be aspirated for diagnosis.

Wrist

Tendonitis. Wrist tendonitis is diagnosed by finding local tendon tenderness and by evoking the pain by stretching the tendon in question. Thus De Quervain's tenosynovitis is diagnosed by finding tenderness over the radial aspect of the wrist and by evoking pain by ulnar flexion with the thumb held in the closed fist (Finklestein test). Splinting or

casting and the use of local corticosteroid injections usually produce relief.

Hands

Arthritis of the fingers and hands leads to the complaint of pain on finger joint movement, and there may be swelling of the joints and inflammation as indicated by rubor. Pain and stiffness in the fingers, worse in the morning and not associated with numbness as in carpal tunnel syndrome, suggest rheumatoid arthritis. Spindling of the fingers or other joint deformity can often be seen. Distal arthritis in the terminal intcrphalangeal joints suggests osteoarthritis or psoriatic arthropathy. Bony swelling of the terminal phalanges (Hebcrden's nodes) is likely to be due to osteoarthritis, which can also cause local pain and tenderness.

Red, hot painful extremities, which are sensitive to heat, suggest the diagnosis of erythromelalgia. This may represent abnormal sensitization of thermal receptors or abnormal platelet function and is sometimes associated with blood dyscrasias. It responds, usually, to aspirin (Kalgaard, Seem, and Kvernebo 1997).

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Chapter 34
Lower Back and Lower Limb Pain

Karl E. Misulis

Lower kick pain is one of the most common causes of neurological and neurosurgical consultation. The cost to society is huge, with estimates of up $80 billion per year in direct and indirect health care costs and loss of productivity. Many of the patients who present with lower back pain have either developed or exacerbated their pain as a result of their occupations. Lower limb pain is a common accompaniment to lower back pain but can occur independently.

The differential diagnosis of lower back and lower leg pain is huge, including neural, bony, and non-neurological causes. Although we usually think of lower back pain as being either radiculopathy or mechanical low back pain, we cannot forget other possible sources of pain, including urolithiasis, tumors, and other intra-abdominal processes.

ANATOMY

The lumbosacral spinal cord terminates in the conus medullaris at the level of the body of LI vertebra (Figure 34.1). The motor and sensory nerve roots from the lumbosacral cord form the cauda equina. The individual motor and sensory lumbosacral nerve roots unite at the dorsal root ganglion to form the individual spinal nerves. These anastomose in the lumbosacral plexus (Figure .34.2), from which run the major nerves supplying the leg (Table 34.1).

Pain in the lower back can have many origins. The differential diagnosis can be narrowed depending on whether the leg also has pain. A factor complicating this simple differential diagnosis is that local spine pain can cause referred pain, that is, pain felt at a distance, because of the common nerve root innervation of the spinal location of the pain and a distant part of the leg.

Causes of lower back pain without leg involvement include ligamentous strain, facet pain, muscle strain, bony destruction, and inflammation. Causes of lower back plus lower limb pain include radiculopathy and plexopathy. Important causes of leg pain without low back pain include sciatic neuropathy, femoral neuropathy, peroneal neuropathy, meralgia paresthetica, and peripheral neuropathies.

Isolated tibial neuropathy is uncommon. Individual peripheral nerve lesions usually arc caused by local trauma, entrapment by connective tissue, or involvement with mass lesions.

Lower back pain is occasionally caused by non-neurological and nonskeletal lesions, with some of the most important being urolithiasis, ovarian cysts and carcinoma, endometriosis, and bladder infection.

DIAGNOSIS

The first step to diagnosis is establishing the localization. History and examination usually allow differentiation between mechanical, neuropathic, and non-neurological pain.

History and Examination

History

History should focus on the following features of the pain; lower back and leg pain should be evaluated separarely.

- Mode of onset
- Character
- Distribution
- Associated motor and sensory symptoms
- Bladder and bowel control
- Exacerbating and remitting factors
- History of predisposing factors (e.g., cancer, osteoporosis)

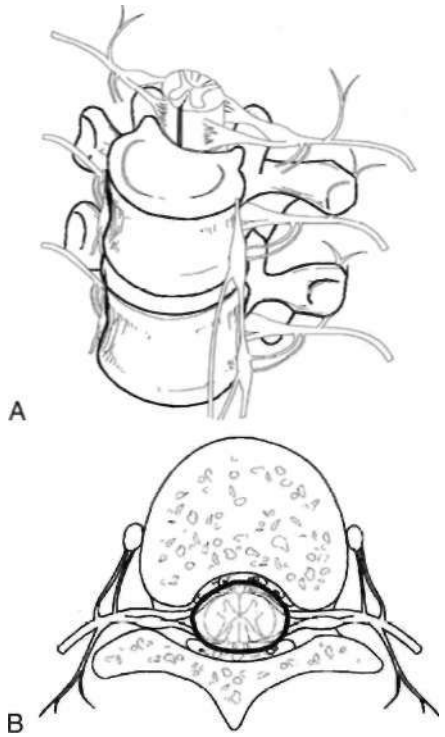

FIGURE 34.1 Oblique (A) and axial (B) views of the spine showing iiiKitomioil rdutionsliips licrwi'i'n ru-nr.il unil lionv elements.

For example, the acute onset of lower back pain radiating down the leg suggests a lumbosacral radiculopathy. Onset with exertion suggests a herniated disc as a cause of the radiculopathy. Onset with a motor vehicle accident could also be caused by a disc herniation, although contusion of a nerve root without ongoing compression is more common after this type of trauma. Progressive symptom development can be from any expanding lesion, such as a tumor, or a gradually expanding disc extrusion.

Symptoms in patients with lower back and leg pain usually are more prominent than the signs of neurological dysfunction. Therefore, if examinations shows sensory and motor signs in a specific radicular or neural distribution, this mandates evaluation for a structural lesion.

Examination

The neurological examination is targeted to determine whether the symptoms are accompanied by abnormal neurological signs. General examination of the lower limb is important. Muscle groups to be tested include the following:

- Hip girdle muscles:
- Hip flexors (psoas, sartorius)
- Hip extensors (gluteus maximus, semitendinosus, semimembranosus, biceps femoris}
- Hip adductors (adductor group: longus, brevis, magnus)
- Hip abductors (gluteus medius, gluteus minimus, piriformis)
- Knee muscles:
- Knee extension (quadriceps)
- Knee flexion {semitendinosus, semimembranosus, biceps femoris}
- Ankle and foot muscles:
- Foot plantar flexion (gastrocnemius)
- Foot dorsiflexion (tibialis anterior}
- Foot everters (peroneii)
- Foot inverters (tibialis posterior)
- Toe extension (extensor digitorum)
- Great toe extension (extensor hallucis longus)
- Toe plantar flexion (flexor digitorum longus)
- Great toe flexion (flexor hallucis longus)

Sensory examination should examine the important nerve roots and peripheral nerve distributions: the femoral, peroneal, tibial, and lateral femoral cutaneous, lumbar roots L2-L5, and sacral root SI. Reflexes to be studied include the Achilles, patellar, and plantar reflexes.

Exacerbation of pain with some maneuvers can also be revealing. Stretch of damaged nerves results in increased pain by deforming the axon membrane, thereby increasing membrane conductance and producing repetitive action potentials. Straight leg raising augments pain in a lumbosacral radiculopathy. Hip extension exacerbates pain of upper lumbar radiculopathy or damage to the upper parts of the lumbar plexus, such as from carcinomatous infiltration or inflammation.

Armed with the abnormalities recognized from this history and examination, the neurologist may come to a conclusion about the localization of the lesion. This narrows the differential diagnosis.

THE DIFFERENTIAL DIAGNOSIS OF LOWER BACK AND LEG PAIN

Differential diagnosis of lower back and leg pain can be addressed as shown in Tables 34.2 through 34.5, Classification into mechanical and neuropathic pain narrows the differential diagnosis. The possibility of non-neui ologic causes should always lie remembered.

Some basic guidelines for differential diagnosis are as follows:

- Pain confined to the lower back generally is caused by a low back disorder.
- Pain confined to the leg usually is caused by a leg disorder, although neuropathic pain from lumbar spine disease can radiate down the leg without back pain in a minority of patients.
- Pain in both the low back and the leg usually is caused by lumbar radiculopathy or, less commonly, lumbosacral plexopathy,

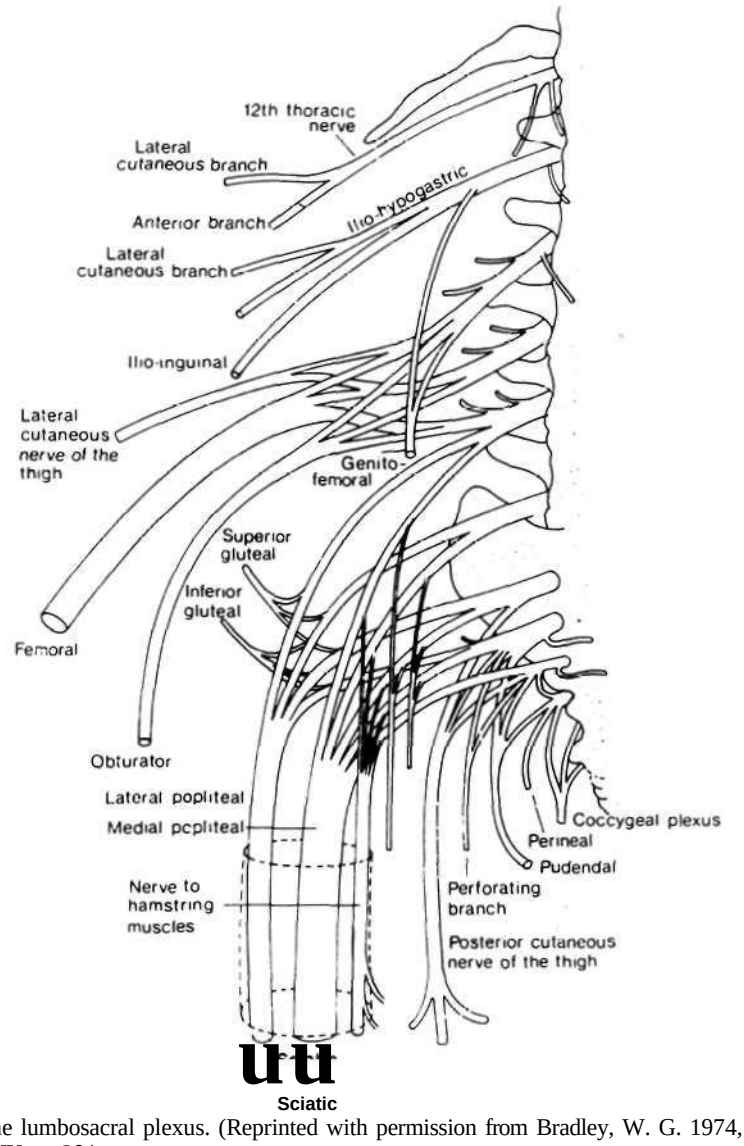

FIGURE 34.2 Anatomy of the lumbosacral plexus. (Reprinted with permission from Bradley, W. G. 1974, *Disorders of the Peripheral Nerves,* BlackweU, Oxford, UK, p. 29.)

- Clinical findings confined to one nerve root distribution usually are caused by intervertebral disc disease or lumbosacral spondylosis producing radiculopathy.
- Clinical findings that involve several nerve distributions usually are caused by plexus lesions, with cauda equina lesions being the alternative diagnosis.
- Bilateral lesions suggest proximal damage in the spinal canal, affecting the roots of the cauda equina.
- Impairment of bladder control indicates either a cauda equina lesion or, less commonly, a bilateral sacral plexopathy.
- More than one lesion may complicate neurological localization.
- Non-neurological causes of lower back pain are possible.

Multiple lesions can make differential diagnosis more difficult. For example, radiculopathies at two or more levels may look like a plexopathy or peripheral neuropathic process.

Non-neurological causes of lower back pain include urolithiasis; ovarian cysts; pelvic carcinoma; bladder infection; and other retroperitoneal lesions including tumor, abscess, and hematoma. These conditions produce pain that does not radiate unless neural structures arc involved. Early involvement of bowel or bladder function and abdominal pain suggests one of these non-neurological conditions.

Evaluation

Diagnostic evaluation of lower back and lower leg pain begins with proper clinical localization and classification of the complaint. Diagnostic tests are summarized in Table 34.6.

Table 34.1: Motor and sensory function of lumbosacral nerves

Nerve	*Origin*	*Motor function*	*Sensory function*
Femoral	Lumbar plexus, L2–L4	Extension of the knee, flexion of the thigh	Anterior thigh
Saphenous	Distal sensory branch of the femoral nerve	None	Inside aspect of the lower leg
Lateral femoral cutaneous	Branch of the lumbar plexus, L2–L3	None	Lateral thigh
Obturator	Lumbar plexus, L2–L4	Adduction of the thigh	Medial aspect of the upper thigh
Sciatic	Combined roots from the lumbosacral plexus, partially separated into tibial and peroneal divisions	Foot plantar and dorsiflexion, foot inversion and eversion	Lateral, anterior, and posterior aspects of the lower leg and foot
Tibial	Lumbosacral plexus, L4–S3	Plantar flexion and inversion of the foot	Posterior lower leg and sole of the foot
Peroneal	Lumbosacral plexus, L5–S2	Dorsiflexion and eversion of the foot	Dorsum of the foot and lateral lower leg
Superficial peroneal	Distal sensory branch of the peroneal nerve	None	Dorsum of the foot
Sural	Cutaneous branches of the peroneal and tibial nerves	None	Lateral foot to sole

Table 34.2: Classification of lower back and lower limb pain

Type	*Examples*
Mechanical pain	Facet pain
	Bony destruction
	SI joint inflammation
	Osteomyelitis
	Lumbar spondylosis
Neuropathic pain	Polyneuropathy
	Radiculopathy from disc disease, zoster, and diabetes
	Mononeuropathy, including sciatic, femoral, lateral femoral cutaneous, and peroneal neuropathies
	Plexopathy from cancer, abscess, hematoma, and autoimmune processes
Non-neurological pain	Urolithiasis
	Retroperitoneal mass
	Ovarian cyst or carcinoma

Table 34.3: Differential diagnosis of lower back and leg pain

Disorder	*Clinical features*	*Diagnosis*
Radiculopathy	Back pain radiating into the leg in a dermatomal distribution. Sensory loss and motor loss are in a root distribution. Increased pain with coughing or straining.	Suspected when neuropathic pain radiates from the back down into the leg in a single nerve distribution. Disc or mass can be seen on MRI or CT. Zoster and diabetes can cause radiculopathy without abnormal studies.
Plexopathy	Back and leg pain with a neuropathic character, dysesthesias, burning, or electric sensation. Back pain can develop when the cause is mass lesion in the region of the plexus.	Suspected when patient has leg pain in more than one peripheral nerve distribution. MRI of the plexus or CT of the abdomen and pelvis can show mass or hematoma.
Spinal stenosis	Pain in the lower back, buttocks, and legs, especially with standing, walking, and lumbar spine extension.	MRI or CT shows obliteration of the subarachnoid space.

CT = computed tomography; MRI = magnetic resonance imaging.

Table 34.4: Differential diagnosis of isolated lower back pain

Disorder	*Clinical features*	*Diagnosis*
SI joint inflammation	Pain lateral to the spine as the sacrum inserts into the top of the iliac bone. Pain is exacerbated by movement and pressure but does not radiate down the leg.	Clinical diagnosis. Radiographs can show degenerative changes in the joint. Bone scan shows increased uptake in the region.
Facet pain	Unilateral or bilateral paraspinal pain without radiation, increased by spine motion, especially extension. No motor, sensory, or reflex deficits.	Clinical diagnosis. Radiographs can show facet degeneration.
Ovarian cyst or cancer	Pain in the hip and lower back, often but not always extending to the lower quadrant. Bowel disturbance may develop with advanced disease.	Abdominal and pelvic CT shows mass lesion in the ovary.
Retroperitoneal mass, abscess, hematoma	Pain in the back, lateral to the spine. May be associated with superimposed neuropathic pain if there is plexus or proximal nerve involvement.	CT or MRI shows hematoma or mass in the abdomen.
Urolithiasis	Pain in the upper- to mid-back laterally, which may radiate to the groin. No radiation down the leg.	Radiographs may show stones. Intravenous pyelography typically shows obstruction of flow. Contrasted abdominal CT usually shows the stone and any obstruction.

CT = computed tomography; MRI = magnetic resonance imaging.

Table 34.5: Differential diagnosis of isolated leg pain

Disorder	*Clinical features*	*Diagnosis*
Peroneal neuropathy	Loss of sensation on the dorsum of the foot. Weakness of foot and toe dorsiflexion.	Slowed nerve conduction velocity across the region of entrapment, usually at the fibular neck. EMG may show denervation in peroneal-innervated muscles, especially tibialis anterior without involvement of the short head of the biceps femoris.
Femoral neuropathy	Pain and sensory loss in the anterior thigh, often with weakness of the quadriceps and suppression of the knee reflex.	NCS can sometimes be performed but may be technically difficult. EMG may show denervation in a distribution limited to the femoral nerve.
Piriformis syndrome	Pain from the back or buttock down the posterior thigh. Exacerbation by sitting or climbing stairs. Stretch of the piriformis (flexion and adduction of the hip) worsens pain.	Clinical diagnosis. Pain radiating down the leg in a sciatic nerve distribution, exacerbation of the pain by flexion and adduction of the hip. EMG and NCS can show proximal sciatic nerve damage.
Meralgia paresthetica (lateral femoral cutaneous nerve dysfunction)	Pain and loss of sensation in the distribution of the lateral femoral cutaneous nerve on the lateral aspect of the thigh.	Clinical diagnosis. Nerve conductions are difficult to perform on this nerve.
Claudication	Pain in the thigh and lower leg with exertion, not so with lumbar spine extension. Ischemic changes in the legs distally.	Suspected with exertional leg pain without back pain. Ultrasound or angiography confirms the arterial insufficiency.
Plexopathy	Back and leg pain that has a neuropathic character, dysesthesias, burning, or electric sensation. Plexitis has no associated back pain.	Suspected when patient has leg pain in more than one peripheral nerve distribution. Magnetic resonance imaging of the plexus or computed tomography of the abdomen and pelvis can show cause.

EMG = electromyography; NCS = nerve conduction study.

Table 34.6: Diagnostic studies for lower back and lower limb pain

Diagnostic test	*Advantages*	*Disadvantages*
Magnetic resonance imaging	Sensitive for identification of lumbar disc herniation, spinal stenosis, paravertebral mass in the region of the plexus, and perineurial tumors.	May overemphasize structural lesions. May miss vascular lesions of the spinal cord. The radiologist may not notice paravertebral disorders because they are not the focus of interest. Cannot be performed on patients with some implanted metallic and electrical equipment.
Noncontrast CT	Shows osteophytes and lateral disc herniations best. Can show bone fractures and extension of fragments into regions that may contain neural elements.	Cannot identify neural elements without intrathecal contrast. Disc herniations without bony involvement may be missed.
Myelography with postmyelographic CT	Definitive test for identifying lumbar disc herniation, osteophytes, and intervertebral foraminal stenosis. Very sensitive when combined with postmyelographic CT scanning, and this sequence should be routine.	May miss far-lateral disc herniations. Is invasive, with a small risk of serious adverse effects.
Nerve conduction studies and electromyography	Sensitive for identification of specific nerve, root, or peripheral neuropathic involvement.	Patients may have clinically significant radiculopathy without electromyographic evidence of denervation (or vice versa if the radiculopathy is old).
Discogram	Can identify disc anatomy in comparison to bony and neural anatomy. May confirm disc level if it produces pain that reproduces patient's complaints.	Invasive test, but risk of serious complications is low. Seldom performed in routine practice.

CT = computed tomography,

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is commonly performed to assess the lumbosacral spine and the lumbosacral plexus. It also can be used to evaluate the peripheral nerves in the pelvis and lower limbs.

MRI of the lumbosacral spine has the highest yield when the patient has back pain associated with radicular distribution of pain. Isolated back pain with no clinical symptoms or signs in the leg is seldom associated with significant findings on MRI. Intraspinal disorders that may not be revealed by MRI without contrast enhancement include neoplastic meningitis and some chronic infectious meningi tides.

MRI of the lumbosacral plexus and peripheral nerves is still a developing field. It can reveal masses, infiltration, and even inflammatory lesions but can miss other disorders.

Nerve Conduction Study and Electromyography

Nerve conduction study (NCS) and electromyography (EMG) are performed for two main purposes. First, these studies are an important aid to the neurological examination of the peripheral nervous system and can help neurological localization. Second, EMG can determine whether there are signs of denervation that indicate nerve damage. In relation to nerve root injury, this information may help to determine whether surgery will be performed. EMG can show signs of active and chronic denervation in all neuropathic conditions, but fibrillation potentials and positive sharp waves do not appear for up to 4 weeks after a nerve injury.

Entrapment neuropathy or nerve root compression, which can be responsible for lower limb pain, is likely to slow nerve conduction velocity across the region of the compression. Conduction velocities proximal and distal to the compression usually are normal, so conduction across the affected nerve segment must be studied. Radiculopathy typically is associated with normal NCS in the peripheral branches of the nerves, but the F wave is slowed. Normal NCS and EMG do not rule out the presence of a radiculopathy.

Mechanical lower back pain is associated with no EMG or NCS alterations. Therefore, these studies usually are not indicated unless there are symptoms or signs of neural involvement.

Myelography and Postmyelographic Computed Tomography

With the advent of **MRI,** myelography has been performed less commonly. If adequate information is not obtained from noninvasive studies, myelography may be indicated.

Lumbar puncture is performed and radio-opaque dye is infused into the cerebrospinal fluid (CSF). Conventional radiographs arc performed as the dye is manipulated through the CSF pathways. Postmyelographic computed tomography (CT) is performed in most instances,

Radiography

Plain radiographs arc performed for patients with acute bony trauma and for almost all patients with isolated lower back pain. Among the potential findings are degenerative joint disease, vertebral body collapse, bony erosion, subluxation, or other fracture. Radiographs of the pelvis and long bones arc also performed and may show fractures and destructive lesions.

Bone Scan

Bone scan is important, especially when there is suspicion of neoplastic bone involvement, to examine multiple bone regions. Multifocal involvement makes neoplastic causes more likely than infectious causes for the destruction.

SYNDROMES

Lower Back and Leg Pain

Lumbar Spine Stenosis

Lumbar spine stenosis is a disorder that affects mainly late-middle-aged and older adults. The cause is multifactorial, with disc disease, bony hypertrophy, and thickening of the ligamentum flavum being the most important. Some of the symptoms are undoubtedly caused by direct pressure of these tissues on the cauda equina and exiting nerve roots, but a major contributor appears to be compression of the vascular supply of the nerve roots. Standing is associated with extension of the lumbar spine, which causes protrusion of the ligamentum flavum. Compression of the vascular supply creates nerve root ischemia, which can produce severe pain and weakness.

Diagnosis is suspected in patients with lower back pain that is exacerbated by standing and walking and relieved promptly by sitting. Lying down, especially in the prone position, may exacerbate the pain, again through lumbar extension, a feature that helps to differentiate lumbar spine stenosis from lumbar radiculopathy.

Diagnosis is confirmed by **MRI** or CT of the lumbar spine, which shows obliteration of the subarachnoid space at the level of the lesion. The hypertrophied ligamentum flavum and osteophyte formation usually is evident on these studies. If there is doubt about the diagnosis, myelography with postmyelographic CT scanning can be performed, but this invasive test is seldom needed.

Treatment usually is surgical decompression, which usually improves the exertional back and leg pain, Conservative management with symptom control often is ineffective. Weakness or sphincter disturbance means that conservative measures should be abandoned.

Lumbosacral Radiculopathy

Lumbosacral radiculopathy usually is caused by either herniated disc material or osteophytes infringing on the neural foramen. Herniated disc is most common in young patients; osteophyte formation is more common in older patients.

Patients present with back pain radiating down the leg in a distribution appropriate to the involved nerve root. The most common lumbosacral radiculoparhy is of the SI nerve root, produced by a lesion at the 1,5-Sl interspace. Table 34.7 presents the typical motor, sensory, and reflex deficits associated with lumbosacral radiculopathy at individual levels.

Radiculopathy is suspected in the presence of lower back pain with radiating pain in a nerve root distribution. Motor, sensory, and reflex deficits are not always present, so the diagnosis is suspected on the basis of symptoms without objective signs.

Diagnosis is confirmed by MRI, which can show disc protrusion or osteophyte encroachment with nerve root compression. Myelography with posrmyclogram CT is still considered the gold standard for diagnosis of radiculopathy, although the noninvasive MRI is used much more often. Myelography is especially common for patients with implanted electronic devices and metallic heart valves, who cannot undergo MRI. NCS usually is normal in patients with lumbosacral radiculopathy. EMG can reveal denervation in a nerve root distribution and usually can differentiate peripheral neuropathic processes from radiculopathy. EMG can also determine whether there is denervation with radiculopathy, which can help the physician determine whether surgery is necessary.

Management of lumbosacral radiculopathy depends on the severity of symproms, including pain and weakness. If the symptoms are mild, anti-inflammatory agents may suffice. Muscle relaxants can produce short-term relief of muscle spasm and pain.

Table 34.7: Lumbosacral radiculopathy

Roof	*Motor deficits*	*Sensory deficits*	*Reflex deficits*
L2	Psoas, quadriceps	Lateral and anterior upper thigh	None
L3	Psoas, quadriceps	Lower medial thigh	Patellar
L4	Tibialis anterior, quadriceps	Medial lower leg	Patellar
L5	Tibialis anterior, peroneus longus, gluteus medius	Lateral lower leg	None
S i	Gastrocnemius, gluteus maximus	Lateral foot, digits 4 and 5, outside of sole	Achilles

Surgical options for lumbosacral radiculopathy are considered when the patient has intractable pain, refractory to conservative care; when weakness is prominent, especially if it is unresponsive to conservative management; and when sphincter disturbance is present. Sphincter disturbance caused by lumbar disc disease or spondylosis often necessitates urgent surgery. Such patients should not be given a trial of conservative therapy,

How much conservative treatment should be given to patients with weakness before surgical options are considered? In general, weakness should prompt at least consideration of surgery. Patients may have mild and transient weakness that responds to conservative therapy, but if weakness is prolonged or severe, the expected recovery is compromised. Increasing evidence for success of conservative treatment will make surgery less common (Rust and Olivero 1999).

Intractable pain without motor loss and with or without sensory loss can be treated sutgically, but treatment effectiveness is limited.

Plexopathy

Neoplastic Lumbosacral Plexopathy

Neoplasms affecting the lumbosacral plexus can be solid or infiltrating. Infiltrating tumors such as lymphoma usually are treated by radiation therapy, which is commonly followed by chemotherapy for the systemic cancer.

Solid tumors affecting the lumbosacral plexus rarely can be completely surgically excised without producing severe damage to the plexus. Radiation therapy is given initially.

Pain often is relieved shortly after the radiation therapy has begun. Duting initial treatment, anticonvulsants often are used to relieve the neuropathic pain. Pure analgesics also are used often, and sustained-release opiate formulations arc effective in treating this condition.

Plexus Injury [ruin Retroperitoneal Abscess

Retroperitoneal abscess usually is caused by peritonitis from gastrointestinal neoplasms or follows surgery, Retroperitoneal abscess can affect the lumbosacral plexus. Patients present with abdominal and flank pain, often with overt signs of systemic infection, with fever, malaise, elevated white blood cell counts, and elevated C-rcactive protein. Diagnosis is confirmed by CT of the abdomen.

Management usually begins with surgical drainage followed by long-term antibiotics. Narcorics usually are needed for the pain of retroperitoneal abscess.

Plexus Injury from Retroperitoneal Hematoma

Retroperitoneal hematoma usually is caused by a bleeding disorder, a pelvic fracture, or abdominal surgery. Occasionally, bleeding around the site of arteriography can result in tracking of blood into the region of the lumbosacral plexus. Diagnosis is suspected in patients with leg motor and sensory symptoms who are at risk for intra-abdominal hemorrhage. Diagnosis is confirmed by CT of the abdomen, which can show blood in the region of the plexus.

Treatment of plexus hematoma is supportive. Evacuation of the hematoma is seldom needed, and surgery is commonly reserved for patients in whom there is continued blood loss, which must be corrected.

Leg Pain without Lower Back Pain

Peripheral Nerve Syndromes

Peripheral nerve palsy is commonly caused by sustained com press i mi. ['en meal palsy is rhe nuisr common lower extremity syndrome, caused by pressure at the fibular neck. Femoral neuropathy commonly results from intra-abdominal causes and can be difficult to differentiate from upper lumbar plexopathy. Some individual peripheral nerve palsies are discussed in this section,

Diagnosis of peripheral nerve palsy is clinical, with symptoms and signs confined to one neural distribution. Patients usually present with neuropathic pain and sensory loss. Dysesthesias and paresthesias in the affected distribution are common. Reflex abnormalities depend on the individual nerve affected.

Definitive treatment of peripheral nerve entrapment is surgical release. Surgery is not always necessary, and conservative management may be successful. Tumor infiltration of peripheral nerve can be treated surgically, but radiation therapy can shrink the tumor and relieve pain. Conservative management includes physical therapy to improve pain and function, anti-inflammatory agents to improve pain, anticonvulsants to improve pain, and counseling on methods to avoid subsequent damage. The counseling includes prevention of nerve compression and nerve stretch. For example, peroneal nerve compression at the fibular neck can be improved by avoiding pressure on the posterior knee with the knee extended and avoiding squatting with the knee acutely bent.

Femoral Neuropathy

The femoral nerve usually is injured in the pelvis, as it passes beneath the inguinal ligament, or in the leg. Intra-abdominal disorders including mass lesions and hematoma are commonly implicated. Femoral artery puncture for angiography may also be a cause, either directly or via the resultant hematoma. Patients present with weakness that is most easily detected in the psoas because the quadriceps is so strong. Sensory loss is over the anterior thigh and medial

aspect of the calf; this loss has a saphenous nerve distribution (the terminal sensory branch of the femoral nerve). This distribution of sensory loss is helpful to differentiate femoral neuropathy from lumbar radiculopathy. The patellar reflex usually is depressed.

Diagnosis can be supported by electromyographic evidence of denervation in the quadriceps but not in the lower leg or posterior thigh muscles; the adductors are especially important to test because they are innervated by the same nerve roots as the femoral nerve but by the obturator nerve. A normal elcctromyogram cannot rule out this diagnosis because many patients do not have active or chronic denervation. NCS of the femoral nerve is difficult, especially in large patients, who are predisposed to development of femoral neuropathy.

Treatment is seldom surgical, except for the removal of a massive psoas or iliacus hematoma. Weight loss and avoidance of marked hip flexion can reduce the chance of persistent damage. Physical therapy will aid recovery of motor power. Femoral neuropathy usually improves.

Meralgia Paresthetica

Dysfunction of the lateral femoral cutaneous nerve is commonly caused by compression as it passes beneath the inguinal ligament. Obesity and pregnancy predispose to this disorder.

Meralgia paresthetica is the sensory syndrome of pain and sensory loss on the lateral thigh. Patients present with numbness and often pain on the lateral thigh. There are no motor deficits. Mcralgia paresthetica is differentiated from femoral neuropathy by the lateral distribution of the sensory findings and the absence of motor and reflex abnormalities.

NCS can be performed of the lateral femoral cutaneous nerve, but this is technically difficult even in the best circumstances. It is even more difficult in obese patients, wini arc at risk for entrapment of the lateral femoral cutaneous nerve.

Treatment is conservative. Weight loss usually is effective in preventing recurrence. Anticonvulsants and tricyclic antidepressants are effective for the neuropathic pain. Surgery is rarely performed, and there is controversy about its indications and effectiveness.

Sciatic Neuropathy

The sciatic nerve is most likely to be injured as it leaves the sciatic notch and descends into the upper leg. Compression can occur in patients suffering prolonged coma, especially in very thin patients. The sciatic nerve is also susceptible to injury from pelvic and sacral fractures, hip surgery or dislocation, needle injection injuries, and any penetrating injury.

Patients present with pain that is usually close to the level of the sciatic nerve lesion, although there may be substantial radiation of the pain. Loss of sensation is prominent below the knee, sparing the medial lower leg (the territory of the saphenous branch of the femoral nerve). Weakness can affect all muscles of the lower leg, but peroneal-innervated muscles are more likely to demonstrate weakness for two reasons. First, tibial-innervated foot extensors are so strong that substantial weakness would have to be present for weakness to be evident on examination. Second, the peroneal division of the sciatic nerve is more susceptible to compression injury than the tibial division, even high in the thigh.

Diagnosis is clinical, although EMG can show denervation in sciatic-innervated muscles; signs of denervation may not be seen until 4 weeks after injury. NCS usually is normal, but F-wave study may show slowing.

Treatment of sciatic compression is supportive, with avoidance of recurrent compression. Tricyclic antidepressants and anticonvulsants are commonly used for the neuropathic pain, and in some patients with acute sciatic injury, opiates are needed to deal with the pain in the short term. Surgical exploration and decompression are performed only when there is a clear structural lesion such as neural or perineural tumor.

Piriformis Syndrome

Piriformis syndrome is an uncommon condition in which the sciatic nerve is compressed by the piriformis muscle in the posterior glureal area. Hypertrophy of the piriformis muscle and other anatomic variants predispose to piriformis syndrome. This condition may affect not only the main sciatic trunk but also the superior gluteal nerve. Patients present with pain in the buttock radiating down the leg that is exacerbated by adduction and flexion of the hip. Pain tends to be aggravated by prolonged sitting, climbing steps, and other maneuvers that irritate the piriformis muscle.

Diagnosis is clinical. A patient with symptoms of sciatic neuropathy has typical clinical features on examination and no signs of radiculopathy or spinal stenosis. Spinal claudication can be confused with piriformis syndrome, so imaging of the spine is commonly performed and would be unremarkable.

Piriformis syndrome usually is managed with anti-inflammatory agents for acute exacerbations and physical therapy, which can be tailored to piriformis syndrome. Local injections of corticosteroids are given occasionally. Surgical treatment is rarely performed, and there is controversy about the indications and expected effectiveness of surgical treatment.

Peroneal Neuropathy

Peroneal neuropathy is commonly caused by compression of the nerve as it passes from the popliteal fossa across the fibular neck into the anterior compartment of the lower leg.

Patients often present with foot drop from weakness of the tibialis anterior. Diagnosis is confirmed by NCS and EMG, with slowing of peroneal nerve conduction across the region of entrapment, usually across the fibular neck. EMG shows active and chronic denervation in many patients because the common presenting complaint of foot drop indicates axonal damage.

Peroneal neuropathy may be produced by prolonged bed rest; hyperflexlon of the knee, usually from an occupational activity; coexisting peripheral neuropathy, predisposing to pressure palsy; fibrous band attached to the peroneus longus, predisposing to nerve compression; pressure in obstetric stirrups; prolonged crossed legs; and stretch and compression by the contracted tibialis anterior muscle in ballet dancers. A fibrous band beneath the superficial head of the peroneus longus is found in a much larger proportion of patients with peroneal entrapment than in normal patients (Dellon, Ebmer, and Swier 2002}.

Polyneuropathy

Peripheral neuropathy is a common cause of lower extremity pain and has a wide differential diagnosis. Among the most common causes are diabetes mellitus, familial neuropathy, metabolic neuropathies, and vasculitis.

Patients present with pain, which has a differing character depending on the type of neuropathy. Small fiber neuropathies present with burning pain that is often worse in the evening. Large fiber neuropathies present with dysesthesias and paresthesias, often with electric-shock-likc pains.

Diagnosis usually is confirmed by NCS and EMG. Axonal neuropathy is more common than demyelinating neuropathy. Occasionally, patients with a predominantly small fiber sensory neuropathy have a normal NCS. Laboratory studies for peripheral neuropathy typically are performed as outlined in Chapter 82.

Treatment is with tricyclic antidepressants or anti-convulsants. Amitriptyline is commonly used for patients with small fiber neuropathic pain. Anticonvulsants are predominantly used for patients with large fiber neuropathic pain. When patients have symptoms of both, treatment with gabapentin or oxearba/epinc can be helpful. Combination therapy with a tricyclic and anticonvulsant is occasionally beneficial. Pure analgesics occasionally are used on a nightly basis to assist with sleep.

Plcxopathy

Lumbosacral Plexitis

Lumbosacral plexitis is similar to brachial plexitis, a presumed autoimmune process, but may be less common. Management of idiopathic lumbosacral plexitis is supportive, with no medical intervention known to alter the course of the disease.

Anticonvulsants are commonly used. Corticosteroids and high-dose intravenous immunoglobulin are also used occasionally, although it is not clear that their benefits outweigh the risks. This is one situation m which pure opiates are commonly used because the duration of the pain usually is weeks rather than months. As the pain abates and the weakness is more prominent, the analgesics usually can be tapered and discontinued. Sustained-release opiates are especially helpful for patients with plexitis.

Diabetic Amyotrophy

Diabetic amyotrophy is lumbosacral plexopathy seen in diabetics. The disorder is thought to be an inflammatory vasculopathy, with damage that is probably immune mediated. Patients present with pain in the hip and thigh associated with weakness of the quadriceps, psoas, and adductors. The plexopathy is more often unilateral than bilateral,

Diagnosis is suggested by the proximal pain and weakness in a patient with known diabetes. This must be differentiated from lumbar radiculopathy and other structural lesions in the region of the plexus. NCS and EMG show coexistent peripheral polyneuropathy and denervation in proximal muscles including quadriceps, psoas, and adductors. MRI and CT do not show a structural lesion,

Treatment is symptomatic. Immune-modulating treatment with immune globulin may reduce the duration of the deficit but is not routinely administered. Most patients improve, although recovery is incomplete for most. The pain abates before the weakness.

Herpes Zoster

Reactivation of the varicella zoster virus produces pain in a single nerve root distribution. Patients present with severe neuropathic pain confined to one root distribution. Most patients develop a vesicular rash in the same cutaneous distribution, but the pain often begins before development of skin changes, and the skin changes are variable. Eventually, the rash crusts over and leaves some pigmentary changes. The pain abates as the inflammation recedes, although the patient may be left with sensory or motor deficit. Weakness can be evident in muscle innervated predominantly by a single nerve root.

Diagnosis is clinical, and when the rash is present at onset, structural imaging usually is not necessary. NCS and EMG often are not needed, but they may show denervation in affected muscles if there is persistent nerve root damage. Differential diagnosis is broader before development of the rash and includes radiculopathy from other causes including disc disease and osteophytes.

Treatment with antiviral agents such as acyclovir or famciclovir should begin within 72 hours of onset of symptoms. This may help to hasten recovery and reduce the incidence of postherpetic neuralgia. Corticosteroids often are used, and the chance of disseminated zoster is not appreciably higher in immune-competent patients. Corticosteroids reduce acute neuropathic pain and may reduce the incidence of postherpetic neuralgia. Corticosteroids are more important for zoster ophthalmicus than for lower limb zoster.

Claudication of Leg Arteries

Arterial claudication is discussed here because it is an important element in the differential diagnosis of spinal stenosis. Vascular disease of the iliac arteries and terminal branches produces marginal perfusion of lower limb muscles. Walking and other moderate activities exacerbate the ischemia, producing pain and weakness with exertion. In this feature, it may resemble spinal stenosis, but it is distinguished from vascular ischemia by a lack of back pain with claudication, lack of exacerbation of leg pain by recumbent lumbar extension, and vascular changes in the leg that should be absent in spinal stenosis.

Claudication is diagnosed by vascular imaging. Ultrasound can be a good screening test, but angiography can provide the definitive diagnosis and, in some people, treatment through angioplasty.

Lower Back Pain without Leg Pain

Mechanical Lower Back Pain

Mechanical lower back pain usually is caused by strain of paraspinal muscles and ligaments, with local inflammation. Muscle tears may also cause acute lower back pain. Therefore, mechanical lower back pain usually is a combination of bony, muscular, and connective tissue pain. Patients present with pain in the lower back without radicular symptoms and show no motor, sensory, or reflex abnormalities oil examination.

Diagnosis is by clinical features and exclusion of other causes. In the absence of objective neurological deficits, spinal MRI usually is not needed initially, but radiography may be performed to look for bony fractures or erosion, NCS and EMG usually are not indicated. In the absence of signs of bony or neural desttuction, conservative management may begin. If the patient does not respond to initial treatment, further study with MRI can be performed.

Mechanical lower back pain usually is treated by an initial period of rest of about 2 days followed by an increase in activity. Physical therapy can be very helpful during this initial treatment period. After the initial treatment, self-help guidelines are followed to reduce the likelihood of recurrent lower back pain. Muscle relaxants can help reduce the tightness of the muscles, which impedes movement and successful physical therapy.

Patients who do not respond to conservative management may benefit from epidural blocks. Surgery for "bulging discs" is occasionally performed on patients who have clinically apparent mechanical back pain, but the likelihood of response is not high.

Facet Pain Syndrome

Pain from the facet joints of the lumbosacral spine usually is not an isolated entity but rather a component of mechanical back pain. Pain results from long-term degenerative changes in the facet joints, usually caused by strain. Repetitive strenuous activity, excessive weight, and abnormal posture may predispose to facet pain. Acute trauma to the back may produce active joint inflammation that can be self-limited.

Facet pain usually is lateral to the spine and exacerbated by extending the spine or bending toward the affected side. Facet pain often is bilateral. Prolonged sitting or walking up steps, as well as retaining one position for a prolonged time, tend to exacerbate the pain.

Patients present with pain without motor, sensory, or reflex deficit unless there is coexistent radiculopathy or spinal stenosis. Diagnostic studies usually are normal. Chronic degenerative changes may be seen in radiographs, but with acute facet damage even radiographs may be unremarkable.

Facet pain usually is treated with anti-inflammatory agents and physical therapy. Change in exacerbating activity usually is helpful. Facet blocks can be performed but often are not necessary. As part of physical therapy, traction can change the character of weight bearing on the joints. Physical therapy can strengthen paraspinal muscles and improve posture.

Lumbar Spine Osteomyelitis

Vertebral osteomyelitis is most common in the lumbar region and may develop as a sequela of trauma, urinary tract infection, respiratory infections, and other causes of sepsis. Patients present with lower back pain, which may develop weeks after the inciting infection has abated. There is limitation of the motion of the spine and tightness of the paraspinal muscles. There is local lumbar spine pain with percussion tenderness.

Diagnosis is suspected in patients with lower back pain without radiation associated with systemic signs of infection {fever, elevated C-rcactivc protein, and elevated white blood cell count). MRI shows changes in the vertebral body and often in adjacent psoas muscle. Radiographs show degeneration of the disc margin of the vertebral body and disc space narrowing. Needle biopsy usually can reveal the

causative organism in most patients. Open biopsy usually is not necessary.

Treatment is with antibiotics and bed rest. Surgical debridement is needed for patients who do not respond to antibiotics.

Lumbar Spine Compression

Compression of the lumbar vertebral bodies occurs in the setting of acute trauma, osteoporosis, infection, or tumor. The latter may predispose the lumbar vertebrae to collapse with minimal trauma or stress. Patients present with severe lower back pain, usually without radicular symptoms. If the collapse results in bone compressing the nerve roots, radicular pain may develop in addition to the lower back pain. If there is compression of the cauda equina, diffuse weakness of the legs with sphincter disturbance can develop.

Diagnosis is suspected when a patient presents with lower back pain, which is exacerbated by movement, jarring, or certain postures such as bending or twisting. Radiographs and CT scan can easily show the bony destruction. Bone scan confirms the damage and can screen for other regions of damage. However, these studies usually cannot differentiate the cause of the compression. MRI is better able to make this differentiation, but it is not exact (Tan, Tsou, and Chee 2002).

Treatment consists of immobilization of the fracture site, which may include bracing. Pure analgesics often are needed, especially at night. Corticosteroids should be avoided if the cause is osteoporotic but can be very helpful for malignant vertebral collapse. Malignant collapse usually is treated by radiation therapy; surgery is performed if the spine is unstable because of the destruction or if there is no known primary tumor in a patient with presumed neoplastic cord involvement. The benefits of acute surgical decompression for neoplastic cauda equina compression are controversial.

/.*innl*w *Discitis*

Discitis is an inflammatory process affecting the intervertebral discs of any level, often occurring in the lumbar spine. Discitis usually is a benign nonbacterial process in children. In adults, bacterial infection is more common, especially mycobacterial. Discitis caused by recent lumbar surgery is likely to be caused by resistant bacteria.

Patients present with lower back pain with marked restriction of flexion of the spine because flexion increases pressure on the disc and disc space. Patients with benign discitis have no systemic symptoms, but patients with postoperative infection have overt signs of infection associated with elevated erythrocyte sedimentation rate and white blood cell count.

Diagnosis is suggested by the presence of severe lower back pain without a radicular component, with tenderness and spasm of the paravertebral muscles, associated with willingness of the patient to flex the hips but not the spine, The erythrocyte sedimentation rate usually is increased, even in benign discitis. Diagnosis can be confirmed by MRI, which shows decreased signal intensity of the disc on Tl-weighted images and increased signal on T2-weighted images. Bone scan shows increased uptake in the region of the infected disc. Radiographs show disc space narrowing. Adults with discitis may progress to fusion of the adjacent vertebral bodies. MRI is the most sensitive test for discitis but cannot differentiate septic from aseptic discitis. Therefore biopsy is needed if there is any reasonable concern that there is active bacterial infection.

Treatment begins with bed rest, and antibiotics are given to most patients. Surgery usually is not necessary; even tuberculous discitis is successfully treated with antibiotics in more than 80% of cases (Bhojraj and Nene 2002). The treatment is age-dependent, with resistant bacteria being more likely to be the cause of the discitis in older patients and benign discitis more likely in younger patients.

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Part II

Neurological Investigations and Related Clinical Neurosciences

Chapter 35
Laboratory Investigations in Diagnosis and Management of Neurological Disease

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The history and examination are the keys to making the diagnosis in a patient with neurological disease (see Chapter 1), However, laboratory investigations are becoming increasingly important in diagnosis and management. A test may be diagnostic (e.g., the finding of cryptococci in the cerebrospinal fluid of a patient with a subacute meningitis, a low vitamin E level in a patient with ataxia and tremor, or a low serum vitamin $B|_2$ level in a patient with a combined myelopathy and neuropathy). A test may help assess the extent to which the nervous system is functioning normally. For instance, the finding of an abnormally delayed visual evoked response in one eye in a patient with possible multiple sclerosis will show that there has been demyelination in that optic nerve and may help confirm the diagnosis.

Laboratory tests should be directed to prove or disprove the hypothesis that a certain disease is responsible for the condition in the patient. They should not be used as a fishing expedition. Sometimes, a physician who cannot formulate a differentia] diagnosis from the clinical history and examination is tempted to order a wide range of tests to see what is abnormal. This approach is likely to add to the confusion because "abnormalities" may be found that have no relevance to the patient's complaints. For instance, many patients are referred to neurologists to determine whether they have multiple sclerosis because their physicians requested magnetic resonance imaging (MRI) of the brain for some other purpose, such as the investigation of headaches. If the MRI shows small T2-weightcd abnormalities in the centrum semiovale (changes that are seen in a proportion of normal older adults and in those with hypertension and diabetes), the neuroradiologist will report that the differential diagnosis includes multiple sclerosis, despite the fact that the patient has no multiple sclerosis symptoms.

Results of laboratory tests can be used to determine response to treatment. For instance, the high erythrocyte sedimentation rate in a patient with cranial arteritis falls with corticosteroid treatment and control of the condition. A rising erythrocyte sedimentation rate as the corticosteroid dosage is reduced indicates that the condition is no longer adequately controlled and that headaches and the risk of loss of vision will soon return,

It is important to use laboratory tests judiciously and to understand their sensitivity, specificity, risks, and costs. The physician must understand the hematological, biochemical, and bacteriological studies and the specific ncurodiagnostic investigations. These include clinical neurophysiology, neuroimaging, neurogenetic DNA testing, and the neuropathological study of biopsied tissue. The neurologist must also have a working knowledge of a number of related disciplines that bring specific investigations to aid in neurological diagnosis. These include neuroendocrinology, neuroepidemiology, neuroimmunology and ncurovirology, neuropsychology, nenro-ophthalmology, neuro-otology, and neurourology. Chapters 36 to 47 describe these disciplines and the investigations they offer.

Biopsy of skeletal muscle or peripheral nerve may be needed to diagnose neuromuscular diseases. A brain biopsy may be needed to diagnose a tumor, infection, vasculitis, or rarely degenerative disease of the nervous system (see Chapter 52).

USE OF LABORATORY TESTS IN DIAGNOSIS

The investigations used to diagnose neurological disease change rapidly. Genetic studies of DNA mutations in the blood now allow the diagnosis of Huntington's disease, a

growing number of spinocerebellar ataxias, a form of autosomal dominant dystonia (DYT1), Duchenne and other muscular dystrophies, many forms of Charcot-Marie-Tooth disease, Rett's syndrome, fragile X premutation, and a variety of other neurogenetic disorders (see http://www.genetests.org; http://www.geneclinics.org).

Blood tests for human immunodeficiency virus, Lyme disease, other infections, and various paraneoplastic syndromes affecting the nervous system can also be diagnostic. For example, there are three types of anti-Purkinje cell antibodies: anti-Yo (PCA-I), seen with tumors of breast, ovary, and adnexa; atypical anti-cytoplasmic antibody (anti-Tr or PCA-Tr), seen with Hodgkin's disease and tumors of the lung and colon; and PCA-2, identified mostly with lung tumors. In addition, there are three antineuronal antibodies: anti-Hu (ANNA-1), seen in possible conjunction with encephalomyelitis, small cell lung tumor, and tumors of breast, prostate, and neuroblastoma; anti-Ri (ANNA-2), found with tumors of breast and ovary; and atypical Anti-Hu, seen with tumors of lung, colon, adenocarcinoma, and lymphoma. Anti-CV2 (CRMP) antibody, expressed by oligodendrocytes, is associated with a syndrome of ataxia and optic neuritis and has been seen with small cell lung carcinoma.

Antibodies directed to a serum protein, Ma (anti-Mai and anti-Ma2), have been seen in patients with limbic encephalitis associated with testicular and other rumors. Antibodies directed to amphiphysin have been detected in patients with a cerebellar syndrome and small cell lung carcinoma. Antibodies against a glutamare receptor are rarely seen in patients with a pure cerebellar syndrome associated with cancer and a variety of autoimmune diseases. Antibodies against glutamic acid decarboxylase (anti-GAD) have been seen in patients with the stiff man syndrome and in patients with ataxia in a setting of an autoimmune disease such as diabetes, thyroid disease, and vitiligo. Antigliadin antibodies are helpful in evaluating patients with unexplained ataxia. As a result of advances in laboratory technology, genetic, immunological, and other blood tests arc expanding our ability to confirm the diagnosis of an increasing number of neurological disorders, obviating more invasive studies.

MRI is replacing computed tomography for most conditions, and magnetic resonance angiography and venography have largely replaced conventional arteriography. Many older investigations have been abandoned in favor of the newer, less invasive tests, as in the case of pneumoencephalography and direct puncture carotid angiography. The neurologist must know enough about each laboratory test to request it appropriately and to interpret the results intelligently. As a rule, it is unreasonable to order a laboratory test if the result will not influence diagnosis or management. Tests should be used to diagnose and treat patients, not to protect against litigation. When used judiciously, laboratory investigations serve both purposes; when ordered indiscriminately, they serve neither.

DIAGNOSTIC **YIELD** OF LABORATORY TESTS

When choosing tests, one must decide what information will help distinguish between the diseases on the differential diagnostic list. A test is justified if the result will confirm or rule out a certain disease or alter patient management, provided it is not too risky or painful. A lumbar puncture (LP) is justified if the patient has a clinical picture of meningitis, when it may confirm the diagnosis and probably reveal the responsible organism. However, one should not order culture and sensitivities on every sample of cerebrospinal fluid (CSF) sent to the laboratory if meningitis is not in the differential diagnosis. LP is not justified unless an abnormal finding will aid in the diagnosis.

The physician should provide full clinical information and highlight the questions for which answers are being sought from the investigations. The electrophysiologist will look more carefully for evidence of denervation in a certain myotome if the patient has a syndrome suggesting herniation of that disc. The neuroradiologist will take additional views to search for evidence of a posterior communicating artery aneurysm if the neurologist says there is a third nerve palsy in the patient with a subarachnoid hemorrhage.

INTERPRETATION OF **RESULTS** OF **LABORATORY INVESTIGATIONS**

Every biologic measurement in a population varies over a normal range, which usually is defined as plus or minus two or three standard deviations *(SD)* from the mean value. Two .SDs encompass 96% and three *SDs* encompass 99% of the measurements from a normal population. Even with three *SDs,* 1 normal person in 100 has a value outside the normal range. Therefore an abnormal result may not indicate the presence of a disease. It is also important to know the characteristics of the normal population used to standardize a laboratory test. Ranges that were normalized using adults are almost never correct for newborns and children. Ranges that were normalized using a hospital population may not be accurate for ambulatory people.

An abnormal test result may not be caused by the disorder under investigation. For example, an elevated serum creatine kinase concentration can result from recent electromyography or intramuscular injection, liver disease, or myocardial infarction, in addition to a primary muscle disease. A common problem for pediatric neurologists is centrotemporal spikes on the electroencephalogram (EEG) in a child with headache or learning disability who has never had a seizure. The EEG probably should not have been ordered in the first place. To give such a patient anticonvulsant drugs would compound poor judgment in diagnosis with worse judgment in management.

The neurologist should personally review test results that are ordered. In most instances, imaging studies should be reviewed, and where appropriate the neuroradiologist should participate. Similarly, for those experienced in pathology, biopsies may he reviewed with the neuropathologist. The neurologist who knows the patient may be of great help in interpreting the imaging or the pathologic study.

RISK AND COST OF INVESTIGATIONS

If two different tests provide equivalent informarion, the physician should choose the one that causes the least pain and risk. The costs of the two tests also should be considered. However, the diagnostic capability of the two tests may not be identical, and the more expensive test may not be better. The cost of a test must he considered in the context of the total cost of the illness. An expensive test that shortens a hospital stay may be cost-effective. The selection of laboratory tests and the sequence in which they are performed are important components of good medical practice.

Risk-to-Benefit Analysis

The neurologist makes judgments about the risk-to-henefit ratio of tests every day. The following examples can help clarify the principles used in making these decisions.

Lumbar Puncture

The risks and benefits of LP must be weighed in every patient. The LP may yield a specific diagnosis, such as subarachnoid hemorrhage or bacterial meningitis. It may help confirm the diagnosis, such as by showing raised intracranial pressure in benign intracranial hypertension. The LP may yield information that is not specific but aids in confirming the diagnosis. A fourfold increase in the CSF protein concentration (without an increase in the cell count) suggests one of the following diagnoses: an acute or chronic inflammatory demyelinative polyradiculoneuropathy, schwannoma or meningioma in the CSF pathways, or spinal compression that obstructs the flow of CSF (Froin's syndrome). A moderately increased number of lymphocytes, an increased *y*-globulin concentration, and oligoclonal bands in the CSF point to an immunologic process in the central nervous system, such as multiple sclerosis.

LP carries significant risks, the most disastrous being cerebral or cerebellar herniation. The LP may suddenly release elevated CSF pressure produced by an expanding supra tentorial lesion and may force the medial temporal lobe through the tentorium cercbelli to compress the midbrain or an expanding infratentorial lesion to push the cerebellar tonsils through the foramen magnum and compress the cervicomedullary junction (see Chapter 56B). These herniations can be fatal, and an LP should never be performed in a patient in whom there is a possibility of a space-occupying lesion without examination of the fundi for evidence of papilledema or of a recent computed tomography scan or MRI, at least in adult patients. LP is justified in some situations despite increased intracranial pressure. The prime example is acute meningitis, in which CSF examination is essential to establish the diagnosis and identify the organism. Other risks of LP include the production of meningitis as a result of contamination of the needle, a post-LP (low-pressure) headache, a spinal epidural hematoma in a patient with a coagulopathy, or the later development of an implantation dermoid (if the needle is inserted without the trocar).

Cerebral Arteriography

The question of whether to request percutaneous cerebral arteriography (see Chapter 37C) entails analysis of the risks and benefits for each patient. In a stroke patient, the study may show thrombotic or embolic occlusion of arteries and abnormalities of the arterial wall, including arteriosclerotic plaques, fibromuscular hyperplasia, medial dissection, and arteritis. It also may demonstrate an intracranial aneurysm or arteriovenous malformation. Any of these findings can clarify the diagnosis, treatment, and prognosis.

However, arteriography has risks. These include thrombosis of the artery at the site of puncture, dissection of a vessel wall, and cerebral infarction from thrombosis, embolism, or dissection. The likelihood that a patient being considered for cerebral arteriography will experience a particular complication is influenced by patient-specific factors, including age and the presence of arteriosclerosis and other diseases. These patient-specific probabilities of risk must be balanced against the potential benefits the angiographic information may provide, specifically the likelihood of demonstrating a treatable condition. Arteriography is definitely indicated in a previously healthy 55-year-old woman with an acute transient right hemiplegia and aphasia and a left carotid artery bruit, especially when carotid ultrasound studies suggest a 75% internal carotid artery stenosis. Invasive angiography clearly is not indicated in a 75-year-old woman with unstable congestive cardiac failure and advanced carcinoma of the breast who suffers a similar transient ischemic attack. Noninvasive techniques may he adequate for revealing the cause of the patient's symptoms, thereby avoiding the risks of catheter cerebral angiography. Carotid Doppler ultrasound and transcranial Doppler studies can be as reliable as angiography for demonstrating extracranial occlusive disease (Chapter 37D). Magnetic resonance angiography, a technique that images the main extracranial and intracranial vessels noninvasively, may obviate invasive angiography in patients with extracranial occlusive disease,

arteriovenous malformations, or a family history of intracranial aneurysms,

Craniotomy and Brain Biopsy

Brain biopsy carries significant risks that always necessitate discussion of the risk-to-benefit ratio with the patient and family. There are four main situations in which a brain biopsy may be considered: intraparenchymal brain tumor, intraparenchymal infectious lesion, intracranial vasculitis, and cerebral degenerative disease. The risk-to-be nef it analysis is influenced by the availability of computer-assisted stereotactic technology to obtain a biopsy through a burr hole. This allows tissue to be obtained for pathological and bacteriological study with little risk.

Open craniotomy for brain biopsy is significantly more risky. The patient's age, the presence of other diseases, lesion location, and the patient's wishes must all be taken into account when considering open brain biopsy. Hemorrhage, infection, postbiopsy epileptic seizures, and the production of a neurological deficit are the main risks of the procedure. The risk of a permanent neurological deficit is slight if the biopsy is from a "silent" area of the brain, such as the nondominam frontal lobe. It has a high risk of worsening the neurological deficit {unless that deficit is already total) if the lesion is located in the sensorimotor cortex, Bioca's speech area, or the internal capsule.

The treatability of the possible cause of the disease is the crucial benefit for inclusion in the risk-to-benefit analysis. If the neuroimaging study suggests a malignant glioma, for which treatment is ineffective, biopsy may not be considered justified. If it suggests a primary lymphoma of the brain, which is likely to respond to radiotherapy, then confirmatory biopsy may be recommended. If the differential diagnosis in a patient with acquired immunodeficiency syndrome includes toxoplasmosis or lymphoma, it may be reasonable to give antitoxoplasma therapy rather than perform a brain biopsy. Biopsy is needed only if the lesions do not respond to 2-3 weeks of treatment. Figure 35.1 presents a risk-to-be nef it analysis and prioritization of investigations for an 80-year-old man with a possible cerebral degeneration.

Cost-to-Benefit Analysis

Cost-to-benefit analysis often presents the physician with an ethical dilemma. The patient and family want everything possible done, no matter what the cost. Society complains that health care costs arc skyrocketing. Any effort at cost containment may place society's interests in conflict with those of the patient. MRI and magnetic resonance angiography are safer procedures than arteriography for diagnosing an arteriovenous malformation but may be more costly. Where only limited funding is available for health care, the money must be used to purchase the most cost-effective care for the greatest number of people. Clearly, physicians should acquaint themselves with the costs of the tests they order.

PRIORITIZATION OF TESTS

The order in which to undertake tests depends on their diagnostic specificity, invasiveness, and benignity. Therefore most blood studies are performed before neuroimaging and LP. Sometimes a therapeutic trial is used as an investigation. For instance, in a patient with possible herpes simplex encephalitis, risk-to-benefit analysis indicates that an FFG, an MRI scan of the brain, and an LP with polymerase chain reaction study of the CSF for *Herpes simplex* are better than a brain biopsy. With typical changes of herpes simplex encephalitis and a response to a therapeutic trial of acyclovir, brain biopsy may be avoided. Time may be used as an investigation. For instance, occasionally it may be difficult to differentiate a stroke from a tumor on the basis of clinical history, examination, and neuroimaging studies. A reasonable plan is to follow the patient and repeat the scan in 2-4 weeks rather than immediately performing a brain biopsy.

QUANTITATIVE DIAGNOSTIC METHODS

When a new laboratory test is developed, its sensitivity (the frequency with which the test is abnormal in patients with a particular disease) and specificity (the frequency with which the test is abnormal in people without the particular disease) must be determined. If a test is very sensitive but has poor specificity, then it may not be useful for diagnosis. For instance, the erythrocyte sedimentation rate is very sensitive in cranial arteritis, but is elevated in so many other conditions that it cannot be used to diagnose the condition. Of more use is a test that is highly specific even if it has a lower sensitivity. For instance, the acetylcholine receptor antibody titer is raised in only about 60% of patients with myasthenia gravis but in almost no other condition. The specificity and sensitivity can be used to quantitate the extent to which a test result makes a diagnosis of a certain disease more or less likely.

DECISION ANALYSIS

Diagnostic acumen and treatment success are the hallmarks of the experienced neurologist. This acumen can be taught and can be learned from years of practice. Decision analysis is a method developed to provide insight into the processes of diagnosis and management of a

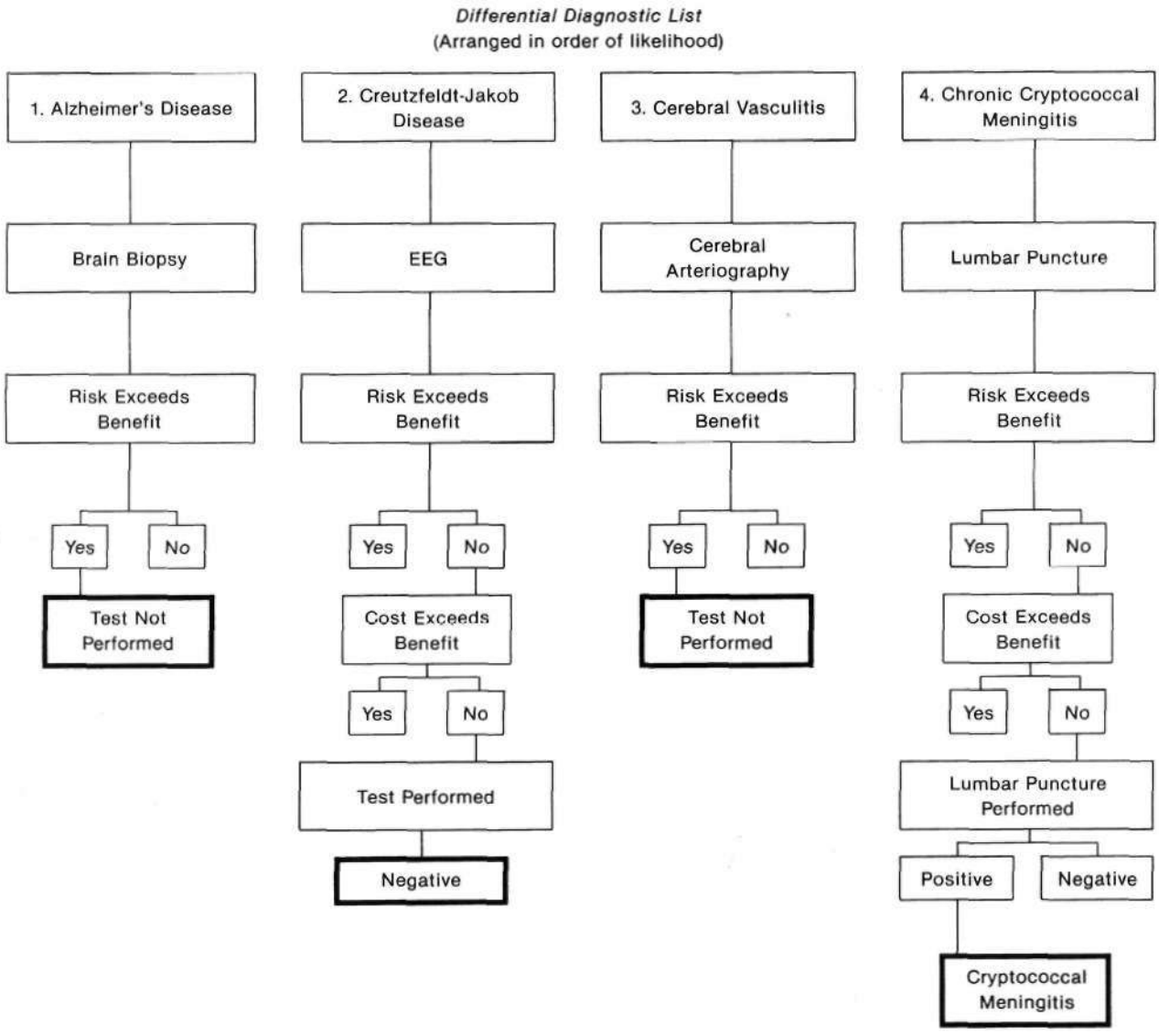


FIGURE 35.1 Flowchart of the decision process involved in choosing investigations to elucidate the diagnosis in an 80-year-old man with a 3-month history of a progressive dementia. The differential diagnosis includes Alzheimer's disease, Creutzfcldr-Jakob disease, cerebral vasculitis, and cryptococcal meningitis. A brain biopsy was not performed, and an electroencephalogram (EEG) did not show typical changes of Creutzfeldt-Jakob disease. The analysis suggests that arteriography is justified to look for a vasculitis, but the lumbar puncture revealed cryptococcal meningitis before the angiography was performed.

complex disease, where often insufficient data are available. Plame reviewed Bayesian methods and decision analysis in the first edition of this textbook (Plante 1991). Decision analysis can help identify areas of uncertainty in currently accepted diagnostic and management methods. Decision analysis forces the clinician to make quantitative estimates of each of the many factors entering into a clinical decision and to calculate the risk-to-bene fit ratio of each management decision. Decision analysis is an excellent teaching tool. Because crucial quantitative data often ate not available, this necessitates a search for such data, either from the literature or through new research.

RESEARCH INVESTIGATIONS AND TEACHING HOSPITALS

Because many readers are neurologists in training, we shall briefly mention the use of investigations in teaching and research centers. Clinical research is closely regulated in most parts of the world, and research investigations cannot be performed until the protocol is approved by an institutional review board or an ethics-in-research committee. The peer review process is designed to ensure that the risks of the research study are justified, taking into account thk- patient's particular disease and the likely benefits of the research. The institutional review board ensures that the

patient receives full information contained in an informed consent form and understands the risks of the study and what is likely to he learned from the research. No patient should be coerced, knowingly or unknowingly, into participating in a research procedure. Once the institutional review hoard gives permission for a research project, it continues to monitor the study to ensure that the research conforms to the protocol.

In a teaching hospital, the attending or consultant physician is legally and ethically responsible for the care provided to a patient by physicians in training. The attending neurologist must ensure that every investigation is justified for diagnostic and management purposes. We are all legally and ethically bound to ensure that the patient understands the reason for each investigation and gives informed consent. The neurologist in training must learn to use tests judiciously and not to perform them simply for curiosity ot education. The two-way discussion with more senior neurologists about the rationale, risk-to-bene fit, and cost-to-benefit analyses of each investigation is an important part of the learning process.

PATIENT CONFIDENTIALITY

Some diagnostic tests, such as the DNA genetic test for Huntington's disease, and the test for human immuno-deficiency virus 1, necessitate prior counseling about the implications of these tests for the individuals and their families. Results of such tests should be kept separate from the rest of the chart to maintain strict confidentiality for the patient.

PLACE OF LABORATORY INVESTIGATIONS IN NEUROLOGICAL DISEASE MANAGEMENT

The standard neurological examination is designed more to detect abnormal function for diagnostic purposes than to quantify the neurological abnormalities. One would like to use laboratory investigations to measure the response of the disease to treatment. Laboratory investigations usually are quantitative and may be helpful in managing disease. Generally, abnormal laboratory values return toward normal as a disease improves or become increasingly abnormal as it worsens. The vital capacity in a patient with (luillam-Barre syndrome is an example in which the impairment in vital capacity decreases as the disease improves. This is not always true, however. In Duchenne's muscular dystrophy, the scrum creatine kinase concentration decreases as the disease worsens because fewer muscle fibers remain to release enzyme inro the scrum. In myasthenia gravis the patient's condition can go from minimal weakness to total paralysis unrelated to the titers of acetylcholine receptor antibodies in the blood. Therefore monitoring laboratory values cannot always be used as an index of disease severity or response to treatment. Other limitations on the use of laboratory tests to monitor disease progression include sampling errors and test sensitivity and specificity.

Quantitative tools provide important information for measuring a patienr's status objectively during the course of a disease. They can be as simple as visual acuity measurement, how many serial numbers from 1 to 100 a patient can count on a single breath, or the frequency and severity of headaches each month. Alternatively, they can be sophisticated measurements, such as the force of maximum voluntary muscle contraction or the temperature perception threshold for an area of skin. They can be Eliminated scores of semiquantitative assessments such as the Kurtzke scale devised to follow patients with multiple sclerosis, the Norris score for amyotrophic lateral sclerosis, or the Z scores of muscle strength. Quantitative measures of neurological function allow much better assessment of the response of a disease to treatment than does the routine neurological examination.

FURTHER READING

Genetic testing: http://www.genetests.org; http://www.geneclinics.org

PET scans: http://www.crump.ucla.edu/software/lpp/clinpcmciiro/spasms.html

Plante, D. 1991, "Quantitative diagnostic methods and decision analysis," in *Neurology in Clinical Practice,* eds W. G. Bradley, R. B. Daroff, G. M. Fenichel *Sc* C. D. Marsden, Butterworth-Heiiiemann, Boston, Mass

Chapter 36
Clinical Neurophysiology

A. ELECTROENCEPHALOGRAPHY AND EVOKED POTENTIALS

Ronald G. Emerson and Timothy A. Pedley

The techniques of applied electrophysiology are of practical importance in the diagnosis and management of certain categories of neurological disease. Modern instrumentation pi: mi its the selective investigation oi various functional aspects of the centra! and peripheral nervous systems. Electroencephalography (EEG) and evoked potentials are measures of electrical activity generated by the central nervous system. Despite the introduction of positron emission tomography, functional magnetic resonance imaging, and magnetoencephalography (MEG), EEG and evoked potentials are the only readily available laboratory tests of brain physiology. As such, they are generally complementary to anatomical imaging techniques such as computed tomography (CT) or magnetic resonance imaging, especially when it is desirable to document abnormalities that are not associated with detectable structural alterations in brain tissue, furthermore, EEG provides the only continuous measure of cerebral function over time.

This chapter is not intended as a comprehensive account of all aspects of EEG and evoked potentials. Rather, it describes the scope and limitations of electrophysiological testing as currently used.

ELECTROENCEPHALOGRAPHY

Physiological Principles of EEG

Electroencephalographic signals are generated by the cerebral cortex. Spontaneous electroencephalographic activity is a reflection of currents flowing in the extracellular space. These currents are generated by the summation of excitatory and inhibitory synaptic potentials occurring on thousands or even millions of cortical neurons. Individual action potentials do not contribute directly to electroencephalographic activity. Conventional EEG is a continuous graph of the spatial distribution of changing voltage fields at the scalp surface recorded over time that result from ongoing synaptic activity in the underlying cortex.

In addition to reflecting the spontaneous intrinsic activities of cortical neurons, EEG depends on important afferent inputs from subcortical structures, including the thalamus and brainstem reticular formation. For example, thalamic afferents probably are responsible for entraining cortical neurons to produce the rhythmic oscillations that characterize such normal patterns as the alpha rhythm and sleep spindles. Similarly, an electroencephalographic abnormality may result directly from disruption of cortical neural networks or indirectly from modification of subcortical inputs onto cortical neurons.

EEG is not the same as electrocorticography because not all potentials recorded at the cortical surface are detectable at the scalp. In the case of epileptiform activity, it has been estimated that 20-70% of cortical spikes do not appear on the electroencephalogram, depending on the region ot cortex involved. This is largely because of the pronounced voltage attenuation that occurs in overlying cerebrospinal fluid and dura. Large areas of cortex must be involved in similar activity for a discharge to appear on the electroencephalogram. Furthermore, potentials involving surfaces of gyri are recorded more readily than are potentials arising in the walls and depths of sulci. Activity generated over the lateral convexities of the hemispheres is recorded more

accurately than is activity coming from interhemispheric, mesial, or basal areas.

The following considerations limit the usefulness of EEC First, surface recordings cannot be used to determine unambiguously the nature of synaptic events contributing to a particular electroencephalographic wave. Second, EEG is rarely specific as to cause because different diseases and conditions produce similar electroencephalographic changes. In this regard, EEG is analogous to findings on the neurological examination; hemiplegia caused by a stroke cannot be distinguished from one caused by a brain tumor. Third, many potentials occurring at the brain surface involve such a small area or are of such low voltage that they cannot be detected at the scalp. EEG results may be normal despite clear indications from other data of focal brain dysfunction. Finally, abnormalities in brain areas inaccessible to EEG electrodes (some cortical areas and almost all subcortical and brainstem regions) do not affect EEG directly but may exert remote effects on patterns of cortical activity.

Normal Electroencephalographic Activities

Spontaneous fluctuations of voltage potential at the cortical surface are in the 100- to 1000-mV range but at the scalp arc only 10-100 uV. Different parts of the cortex generate distinct potential fluctuations, which also differ in the waking and sleep states.

In most normal adults, the waking pattern of electroencephalographic activity consists mainly of sinusoidal oscillations occurring at 8-12 Hz, which are most prominent over the occipital area (alpha rhythm) (Figure 36A.1A). The alpha rhythm is attenuated (or blocked) by eye opening, mental activity, and drowsiness. Activity faster than 12 Hz (beta activity) normally is present over the frontal areas and may be especially prominent in patients receiving barbiturate or benzodiazepine drugs. Activity slower than 8 Hz is subdivided into delta activity (1-3 Hz) and theta activity (4-7 Hz). Adults normally may show a small amount of theta activity over the temporal regions; the percentage of intermixed theta frequencies increases after age 60. Delta activity is not present normally in adults when they are awake but appears when they fall asleep (Figure 36A.1B). The amount and amplitude of slow activity (theta and delta) correlate closely with the depth of sleep. Slow frequencies are abundant on the electroencephalograms of newborns and young children, but they disappear progressively with maturation.

Common Types of Electroencephalographic Abnormalities

Focal Arrhythmic (Polymorphic) Slow Activity

Polymorphic slow activity is irregular or amorphous activity in the delta (1-4 Hz) or theta (4-7 Hz) range, which, when continuous, has a high correlation with a localized cerebral lesion such as infarction, hemorrhage, tumor, or abscess. Intermittent focal slow activity also **may** indicate localized parenchymal dysfunction but is less predictive than polymorphic slow activity.

Intermittent Rhythmic Stow Waves

Paroxysmal bursts of generalized, bisynchronous rhythmic theta or delta waves usually indicate thalamocortical dysfunction and arc seen with metabolic or toxic disorders, obstructive hydrocephalus, and deep midline or posterior fossa lesions and also as a nonspecific functional disturbance in patients with generalized epilepsy. Focal bursts of rhythmic waves laterali/ed to one hemisphere usually indicate deep (typically thalamic or periventricular) abnormalities, often structural.

Generalized Arrhythmic (Polymorphic) Slow Activity

Diffuse disturbances in background rhythms marked by excessive slow activity and disorganization of waking EEG patterns are seen in encephalopathies of metabolic, toxic, or infectious origin and in people with brain damage caused by a static encephalopathy.

Voltage Attenuation

Voltage attenuation is caused by cortical disease. Generalized voltage attenuation usually is associated with diffuse depression of function such as after anoxia or with certain degenerative diseases (e.g., Huntington's disease). The most severe form of generalized voltage attenuation is electrocerebral inactivity, which is corroborative evidence of brain death in the appropriate clinical setting. Focal voltage attenuation reliably indicates localized cortical disease such as porencephaly, atrophy, or contusion or an extra-axial lesion, such as a meningioma or subdural hematoma.

Epileptiform Discharges

Epileptiform discharges are spikes or sharp waves that occur interictally in patients with epilepsy and sometimes in people who do not have seizures but have a genetic predisposition to epilepsy. Epileptiform discharges may be focal or generalized depending on the seizure type.

Recording **Techniques**

The following section summarizes the recording methods in common use. Details are provided in the American EEG Society's guidelines (1994).

A series of small gold, silver, or silver-silver chloride discs are symmetrically positioned over the scalp on both

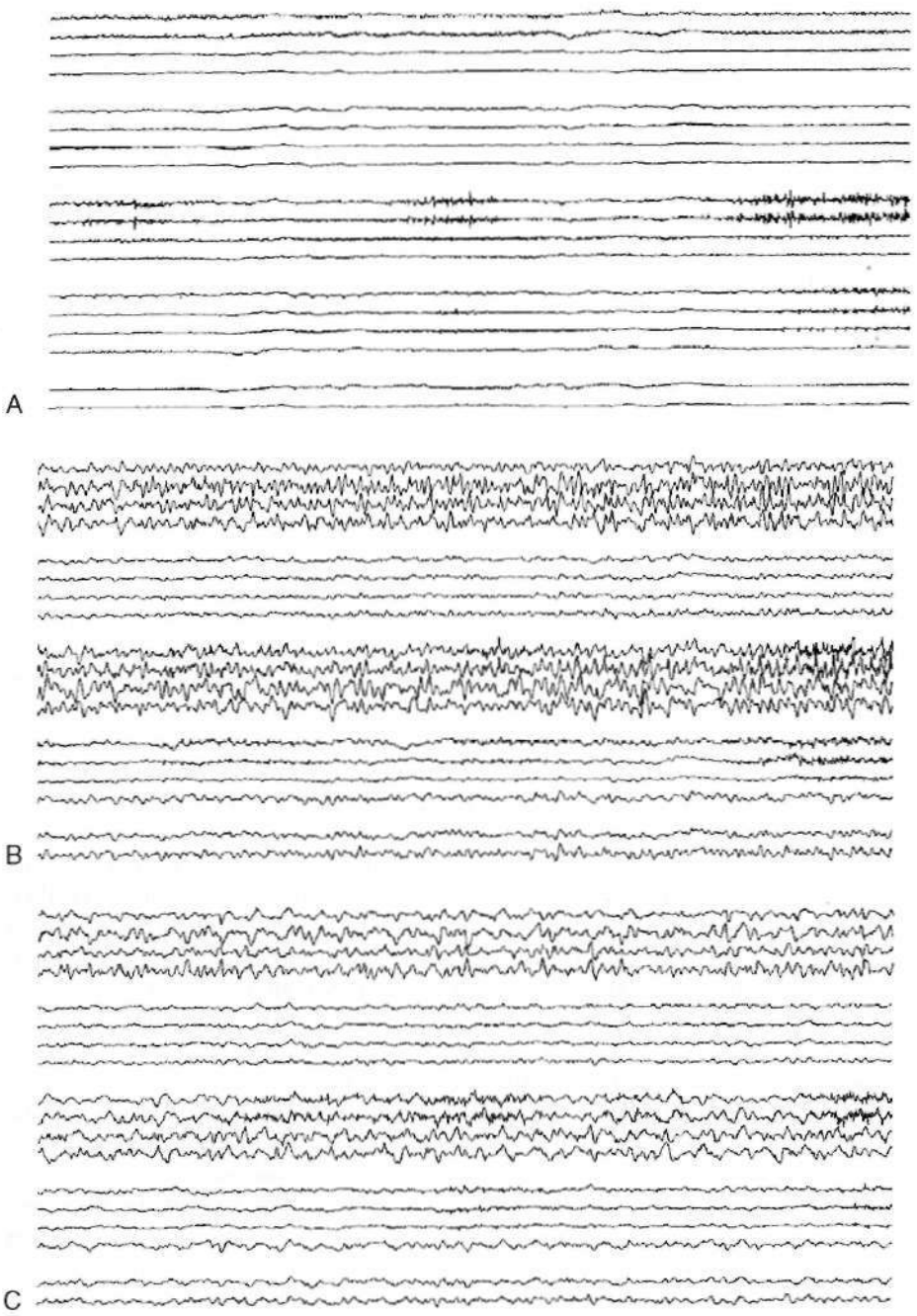


FIGURE 36A.1 Samples of normal electroencephalography from two patients. (**A**) Waking activity is characterized by a 9-Hz alpha rhythm that attenuates when the eyes are opened (EO) and returns when eyes are closed (EC). (**B**) Stage 2 sleep is characterized by 2- to 5-Hz background activity, on which are superimposed vertex waves and sleep spindles.

sides of the head in standard locations (the International Ten-Twenty system).

These recording electrodes are interconnected in chains, and the potential difference between pairs of electrodes is recorded. In practice, 16 or more channels (one pair of electrodes equals one amplifier channel) of electroencephalographic activity arc recorded simultaneously. Electrode pairs are interconnected in different arrangements called montages to permit a comprehensive survey of the brain's electrical activiry. Typically, montages are designed to compare symmetrical areas of the two hemispheres or anterior and posterior regions or parasagittal and temporal areas in the same hemisphere.

Spontaneous brain wave activity is recorded for 30-45 minutes. In addition, most patients are routinely subjected to two types of activating procedures: hyperventilation and photic stimulation. In some patients, these techniques provoke abnormal focal or generalized alterations in activity that are of diagnostic importance and would otherwise go undetected (Figure 36A.2),

Sleep, sleep deprivation, and placement of additional electrodes at other recording sites are useful in detecting specific kinds of epileptiform potentials.

Other maneuvers are carried out depending on the clinical question posed. For example, epileptiform activity may occasionally be activated only by movement or specific

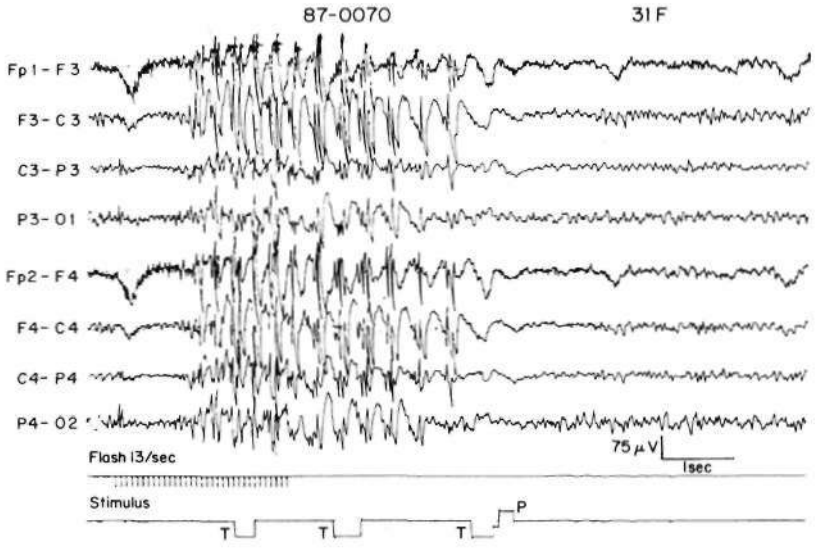


FIGURE 36A.2 Intermittent stroboscopic light stimulation at 13 per second elicited generalized bursts of 4- to 5-Hz spike-wave activity, called a photoparoxysmal (photoconvulsive) response. The spike-wave paroxysm was associated with a brief absence, as documented by the patient's (P) inability to respond to a tone given by the technologist (T). Normal responsiveness returned immediately on cessation of the spike-wave activity. The remainder of the electroencephalogram was normal.

sensory stimuli. Vasovagal stimulation may be important in some types of syncope.

Clinical Uses of Electroencephalography

EEG assesses physiological alterations in brain activity. Many changes are nonspecific, but some are highly suggestive of specific entities (epilepsy, herpes encephalitis, or metabolic encephalopathy). EEG is useful also in following the course of patients with altered states of consciousness and in certain circumstances may provide prognostic information. It can be important in determining brain death,

EEG is not a screening test but is ordered to answer a particular problem posed by the patient's condition. Sufficient clinical information must be provided so that an appropriate test can be designed that allows a meaningful electrographical clinical correlation. The question to be addressed by EEG should be specifically stated on the request.

EEG interpretation should be rational and based on a systematic analysis that uses consistent parameters that permit comparisons to be made with findings expected from the patient's age and circumstances of recording. High-quality recording is needed for accurate interpretation. Trained technologists understand the importance of meticulous electrode application, proper use of instrument controls, recognition and elimination of artifacts where possible, and appropriate selection of recording montages to allow optimal display of cetebral electrical activity.

Epilepsy

EEG usually is the most helpful laboratory test when a diagnosis of epilepsy is considered. Because the onset of seizures is unpredictable and their occurrence is infrequent in most patients, EEG usually is obtained when the patient is not having a seizure. Fortunately, electrical abnormalities in EEG occur in most patients with epilepsy even between attacks. However, interictal findings must be interpreted with caution. Although certain patterns of abnormality may support a diagnosis of epilepsy, most epileptiform discharges correlate poorly with the frequency and likelihood of recurrence of epileptic seizures. In certain cases, they may not even help in distinguishing epilepsy from other paroxysmal but nonepilcptic conditions. Furthermore, a substantial number of patients with unquestionable epilepsy have consistently normal electroencephalograms. The most convincing proof that a patient's episodic symptoms are epileptic is obtained by recording an electrographical seizure discharge during a typical behavioral attack. Although ictal tracings greatly increase EEG sensitivity in assessing the pathophysiology of specific behavioral episodes, the clinician must still be aware of limitations inherent in such recordings.

The only elcctroenccphalographic finding that has a high correlation with epilepsy is epileptiform activity, consisting of spikes and sharp waves that arc clearly distinct from ongoing background activity. Both clinical and experimental evidence supports a specific association between epileptiform discharges and seizure susceptibility. Only 2% of nonepilcptic patients have epileptiform electroencephalograms, whereas as many as 90% of patients with epilepsy show epileptiform activity, depending on the circumstances of the recording and the number of studies obtained.

In addition to epileptiform patterns, electroencephalograms in patients with epilepsy often show excessive focal or generalized slow-wave activity. Less often, asymmetries of frequency or voltage exist. These findings are not unique to epilepsy and may be seen in other conditions such as static encephalopathies, brain tumors, migraine, and trauma. In patients with unusual spells, nonspecific changes

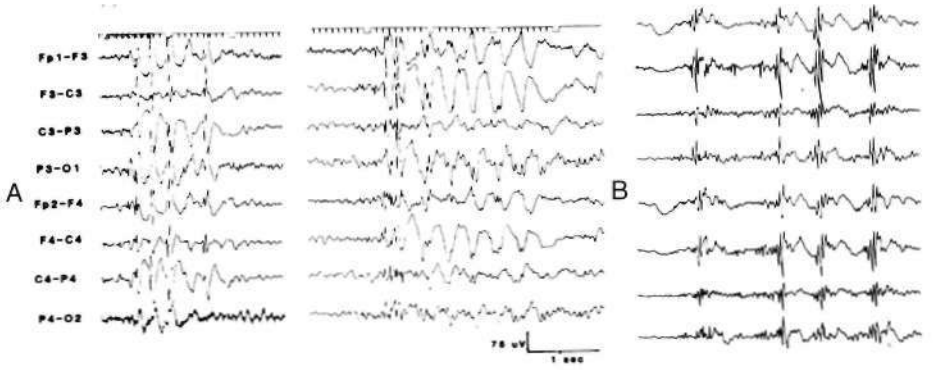


FIGURE 36A.3 Examples of generalized spike-wave patterns from different patients with primary generalized (idiopathic) epilepsy. The patient in (**A**) had mainly tonic-clonic seizures, with occasional absence attacks. The patient in (**B**) had juvenile myoclonic epilepsy.

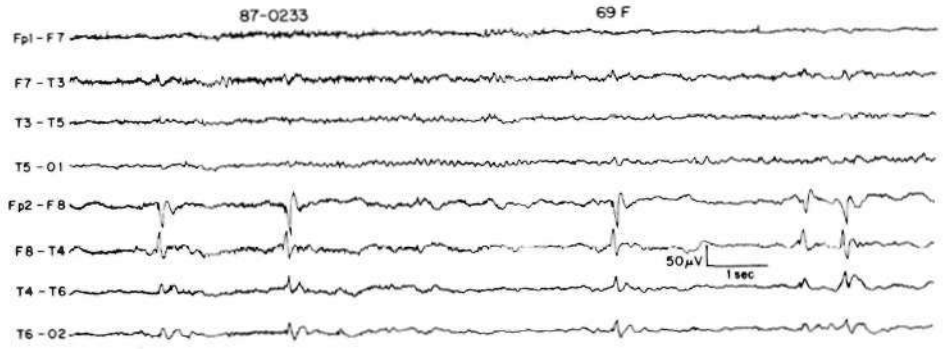


FIGURE 36A.4 Focal right anterior temporal spikes occurring in a 69-year-old woman with complex partial seizures after a stroke involving branches of the right middle cerebral artery.

on EEG should be weighed cautiously and not considered direct evidence for a diagnosis of epilepsy. On the other hand, when clinical data are unequivocal or when epileptiform discharges occur as well, the degree and extent of background electroencephalographic changes may provide information important for judging the likelihood of an underlying focal cerebral lesion, a more diffuse encephalopathy, or a progressive neurological syndrome. Additionally, electrocncephalographic findings may help determine prognosis and aid in the decision to start or discontinue antiepileptic medication.

The type of epileptiform activity on EEG is helpful in classifying a patient's seizure type correctly and sometimes in identifying a specific epileptic syndrome (see Chapter 73). Clinically, generalized tonic-clonic seizures may be generalized from the outset or secondary to spread from a focus. Lapses of awareness with automatisms may be a manifestation of a generalized nonconvulsive form of epilepsy (absence seizures) or of focal epileptogenic dysfunction (temporal lobe epilepsy). The initial clinical features of a seizure may be uncertain because of postictal amnesia or nocturnal occurrence. In these and similar situations, EEG can provide information crucial to the correct diagnosis and appropriate therapy.

In generalized seizures of nonfocal origin, KEG typically shows bilaterally synchronous diffuse bursts of spikes and spike-wave discharges (Figure 36A.3). All generalized epileptiform patterns share certain common features, although the exact expression of the spike-wave activity varies depending on whether the patient has pure absence, tonic-clonic, myoclonic, or atonic-astatic seizures. EEG also may distinguish between primary and secondary generalized epilepsy. In primary generalized epilepsy, no demonstrable cerebral disease exists, whereas in secondary generalized epilepsy, evidence of brain damage can be found. Typically, primary (idiopathic) generalized epilepsy is associated with normal or near normal electroenccphalographic background rhythms, whereas secondary (symptomatic) epilepsy is associated with some degree of generalized slow-wave activity.

Consistently focal epileptiform activity is the signature of pun nil (focal) epilepsy (Figure 36A.4). With the exception of the benign focal epilepsies of childhood, focal epileptiform activity results from neuronal dysfunction caused by demonstrable brain disease. The waveform of focal epileptiform discharges is largely independent of localization, but a reasonable correlation exists between spike location and the type of ictal behavior. Anterior temporal spikes are almost always associated with complex partial seizures, rolandic spikes with simple motor or sensory seizures, and occipital spikes with primitive visual hallucinations or diminished visual function as an initial feature.

In addition to distinguishing epileptiform from non-epilcptiform abnormalities, electroencephalography analysis sometimes identifies specific electroclinical syndromes such as hypsarrhythmia associated with infantile spasms (West's syndrome) (Figure 36A.5); 3-Hz spike-and-wave

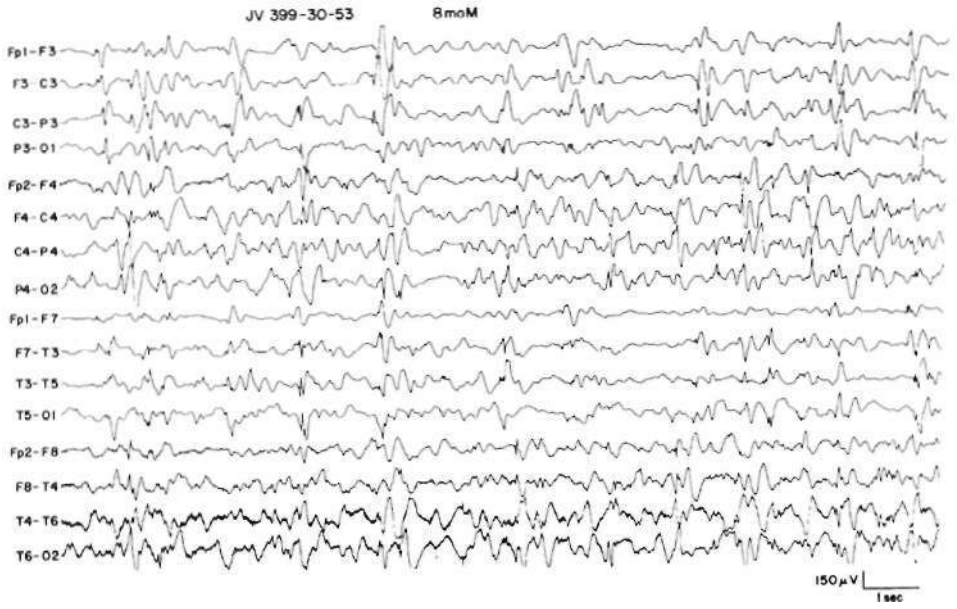


FIGURE 36A.5 Electroencephalographic pattern, called hypsarrhythmia, from an 8-month-old boy with infantile spasms. Background activity is high voltage and unorganized with abundant multifocal spikes.

activity associated with typical absence attacks (petit mal epilepsy) (Figure 36A.6); generalized multiple spikes and waves (polyspike wave) associated with myoclonic epilepsy, including so-called juvenile myoclonic epilepsy of Janz (see Figure 36A.3B); generalized sharp and slow waves (slow spike and wave) associated with Lennox-Gastaut syndrome (Figure 36A.7); central-midtcmporal spikes associated with benign rolandic epilepsy (Figure 36A.8); and periodic lateralized epileptiform discharges associated with acute destructive cerebral lesions including hemorrhagic cerebral infarction, a rapidly growing malignancy, or herpes simplex encephalitis (Figure 36A.9).

The increased availability of special monitoring facilities for simultaneous video and EEG recording and ambulatory EEG recorders has improved diagnostic accuracy and the reliability of seizure classification. Prolonged, continuous recordings through one or more complete sleep-wake cycles are the best way to document ictal episodes and should be considered in patients whose interictal electroencephalograms are normal or nondiagnostic and in clinical dilemmas that can be resolved only by recording actual behavioral events. Although electroencephalograph ic documentation of an ictal discharge establishes the epileptic nature of a corresponding behavioral change, the converse is not necessarily true. Sometimes the recording is so obscured by muscle or movement artifacts that it is impossible to know whether any electroencephalographic change has occurred. In these circumstances, postictal slowing usually indicates an epileptic event if similar slow waves are not present elsewhere in the recording and if the electroencephalogram subsequently returns to its baseline condition. In addition, focal seizures that are not accompanied by altetation in consciousness occasionally have no detectable scalp correlate. On the other hand, persistence of alpha activity and absence of slowing during and after an apparent convulsive episode are inconsistent with an epileptic generalized tonic-clonic seizure.

Focal Cerebral Lesions

The use of FKG to detect focal cerebral disturbances has declined because of the development and widespread availability of computerized anatomical imaging techniques. Nonetheless, EEG has a role in documenting focal physiological dysfunction in the absence of

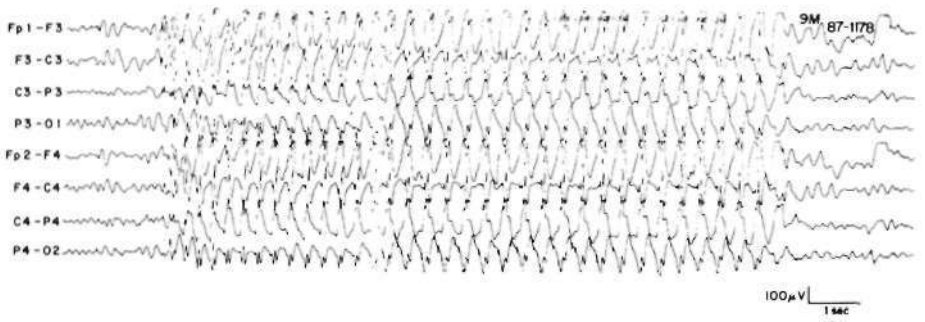


FIGURE 36A.6 A 3-Hz spike-and-wave paroxysm from a 9-year-old boy with absence seizures (petit mal epilepsy). During this 12-second discharge, the child was unresponsive and had rhythmic eye blinking.

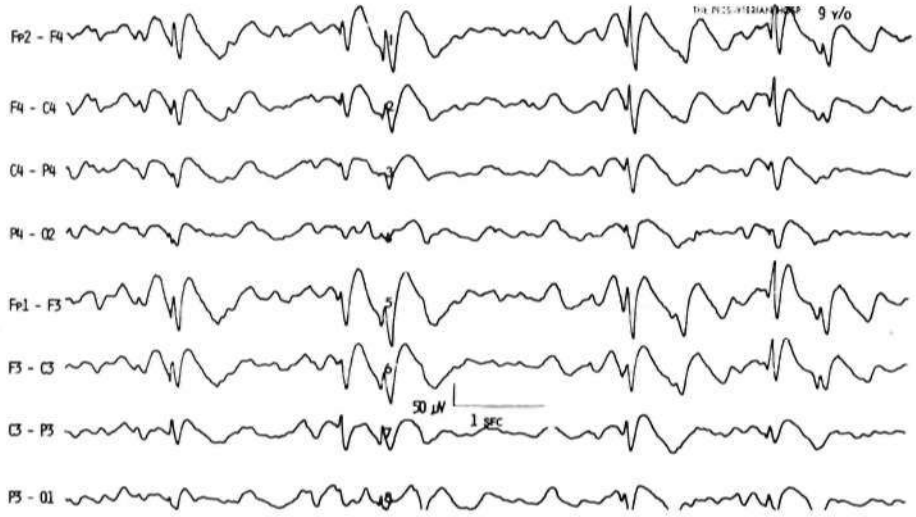


FIGURE 36A.7 Generalized sharp- and slow-wave discharges in a 9-year-old child with mental retardation and uncontrolled typical absence, tonic, and atonic generalized seizures. This constellation of clinical and electroencephalographica I features constitutes the Lennox-Gastaut syndrome.

discernible structural disorders and in evaluating the functional disturbance produced by known lesions.

Focal delta activity is the usual electroencephalographic sign of a focal brain disturbance. A structural lesion is likely if the delta activity is continuously present; shows variability in waveform, amplitude, duration, and morphology (known as arrhythmic or polymorphic activity); and persists during changes in wake-sleep states (Figure 36A, 10). The localizing value of focal delta is increased when it is topographically discrete or associated with depression or loss of superimposed faster background frequencies. Superficial lesions tend to produce limited electroencephalographic changes, whereas deep cerebral lesions produce hemispheric or even bilateral delta activity.

Bilateral paroxysmal bursts of rhythmic delta waves with frontal predominance (Figure 36A.11) were once attributed to subfrontai, deep midline, or posterior fossa lesions. They are now known to be nonspecific and seen mote often with diffuse encephalopathies. Focal or lateralized intermittent bursts of rhythmic delta waves as the prominent electroencephalographic abnormality suggest a deep supra tentorial (periventricular or diencephalic) lesion.

The character and distribution of the electroencephalographic changes caused by a focal lesion depend on its size, its distance from the cortical surface, the specific structures involved, and its acuity. A small stroke critically located in the thalamus may produce widespread hemispheric slowing and alteration in sleep spindles and alpha rhythm regulation. The same sized lesion located at the cortical surface produces few or no electroencephalographic findings.

Single lacunae usually produce little or no change in the electroencephalogram. Similarly, transient ischemic attacks not associated with chronic cerebral hypoperfusion or imminent occlusion of a major vessel do not significantly

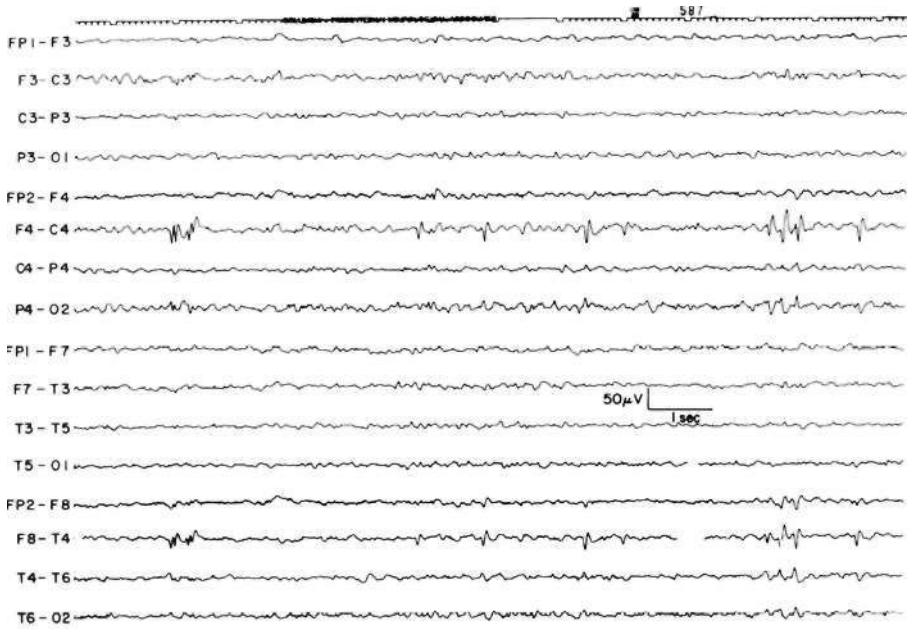


FIGURE 36A.*8* Electroencephalogram obtained during drowsiness in a 10-year-old hoy with benign rolandic epilepsy. Stereotyped diphasic or triphasic sharp waves occur in the right centtal-parietal and midtemporal regions.

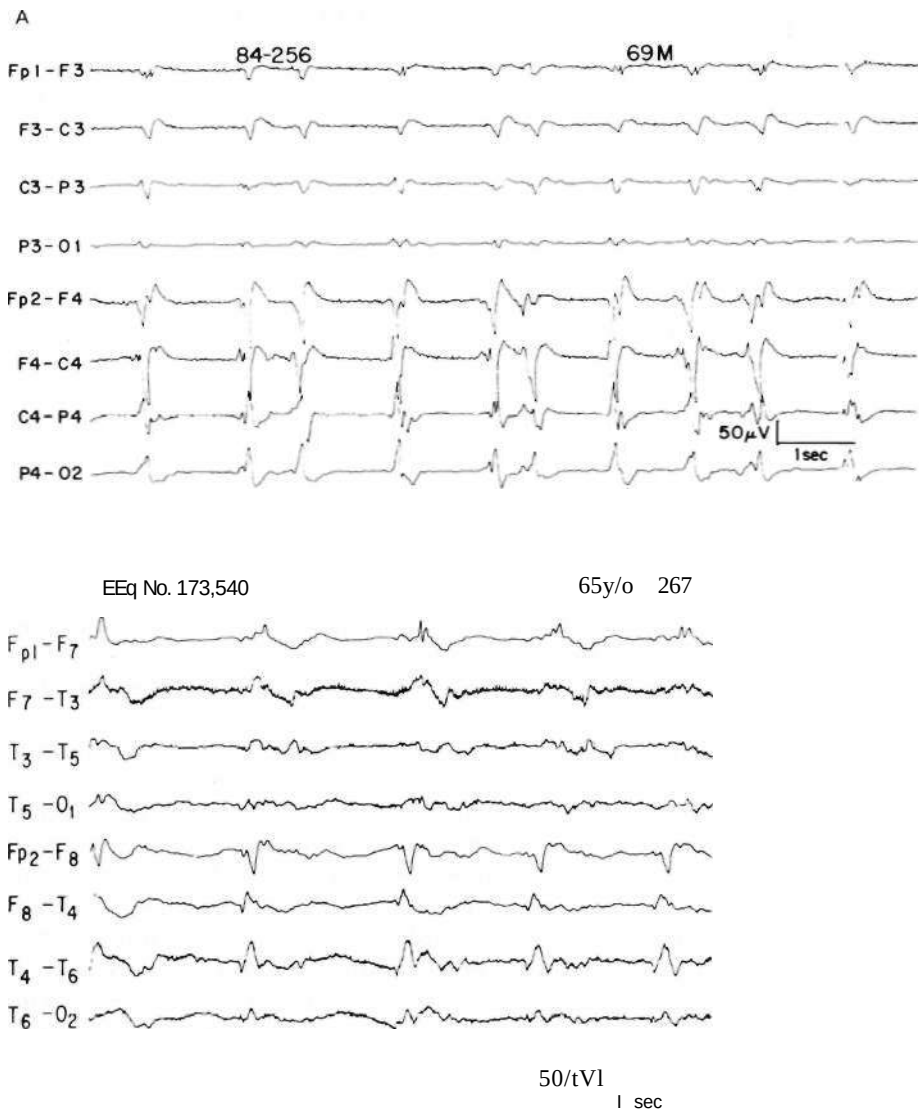


FIGURE 36A.9 Two examples of periodic lateralized epileptiform discharges (PLEDs). (A) Right parasagittal I'LEDs in a 69-year-old man with severe brain damage caused by meningitis with multiple cerebral infarctions. (B) A 65-year-old woman with herpes simplex encephalitis. PLEDs ate bilateral but have *a* right-sided predominance.

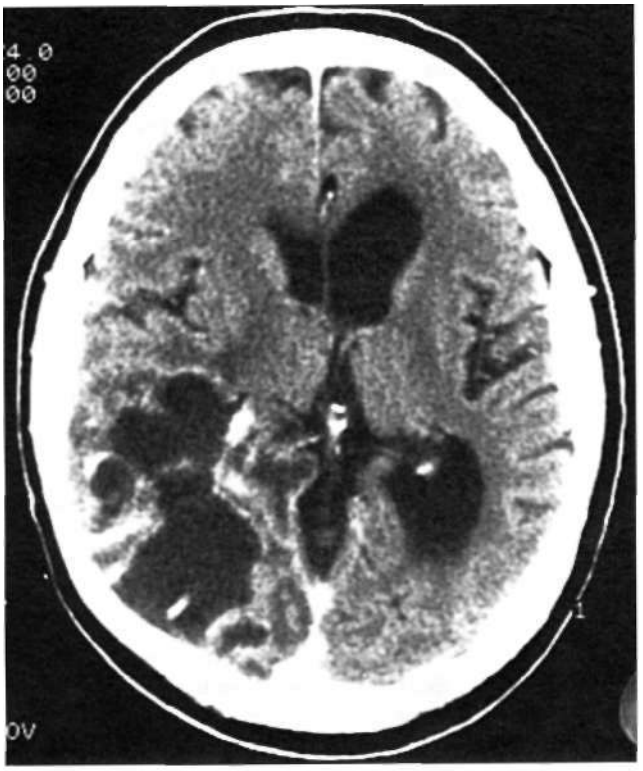
affect the electroencephalogram outside the symptomatic period. Superficial cortical or large, deep hemispheric infarctions usually are associated with localized electro-encephalograph ic abnormalities.

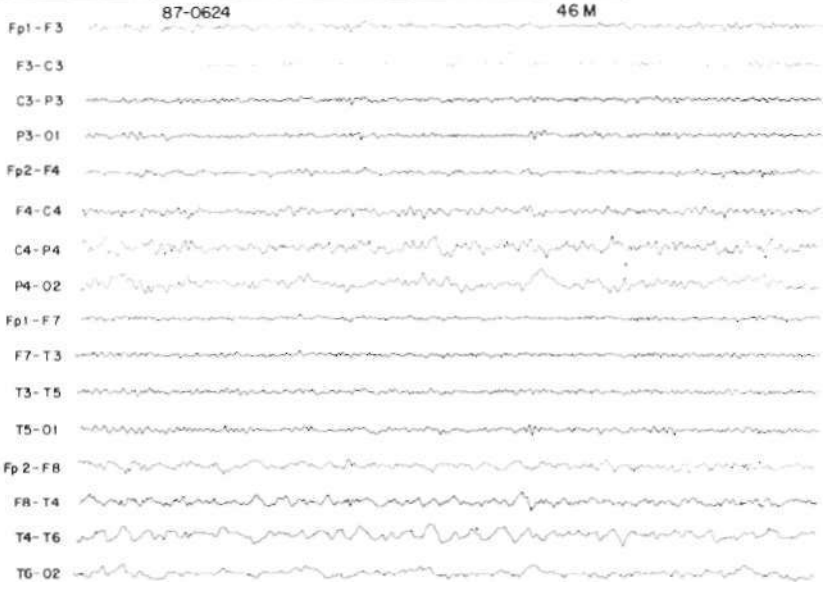
Focal electroencephalographic changes (and other non-epileptiform abnormalities) are common in migraine. The likelihood of an abnormal electroencephalogram and the severity of the abnormality are related to the timing and character of the migraine attack. Focal clectrocnccphalo-graphic abnormalities are more likely with complicated rather than with common migraine and during rather than between headaches, Electroencephalographic changes seen with brain tumors arc caused by disturbances in bordering brain parenchyma; tumor tissue is electrically silenr. Focal electroencephalographic changes are caused by interference with patterns of normal neuronal synaptic activity, by destruction or alteration of the cortical neurons, and by metabolic effects caused by changes in blood flow, cellular metabolism, or the neuronal microenvironment. More diffuse elrerriH'iiu/pha log rapine changes are the consequence of increased intracranial pressure, shift of midline structures, or hydrocephalus. EEG is especially helpful in following the extent of cerebral dysfunction over time, distinguishing between direct effects of the neoplasm and superimposed metabolic or toxic encephalopathies, and differentiating among epileptic, ischemic, and noncercbral causes of episodic symptoms.

The role of EEG in treating patients with head injuries is limited. Transitory generalized slowing is common after concussion. A persistent area of continuous, localized slow-wave activity suggests cerebral contusion even in the absence of a focal clinical or CT abnormality, and unilateral voltage depression suggests subdural hematoma. EEG in the first 3 months after injury does not predict post-traumatic epilepsy.

Altered States of Consciousness

EEG has a major role in evaluating patients with altered levels of consciousness. EEG complements the clinical





B

FIGURE 36A.10 (At A 46 year-old man with a glioblastoma involving the right Temporal and parietal lobes. (B) The electroencephalogram demonstrates continuous arrhythmic slowing over die right temporal and paricto-occipital areas. [11 addition, loss of the alpha rhythm and overriding faster frequencies are seen in corresponding areas of the left cerebral heinisplu'iv.

examination when consciousness is depressed significantly because EEG permits a reasonably critical assessment of supratentorial brain function. Abnormalities typically are nonspecific in origin. However, a generally good correlation exists with the clinical state. Some findings are more suggestive of particular causes than of others and occasionally are prognostically useful. Specific questions that EEG may help answer, depending on the clinical presentation, include the following:

Are psychogenic factors playing a major role?
Is the process diffuse, focal, or multifocal?
Is unrecognized epileptic activity depressing consciousness (nonconvulsive status cpilcpticus)?

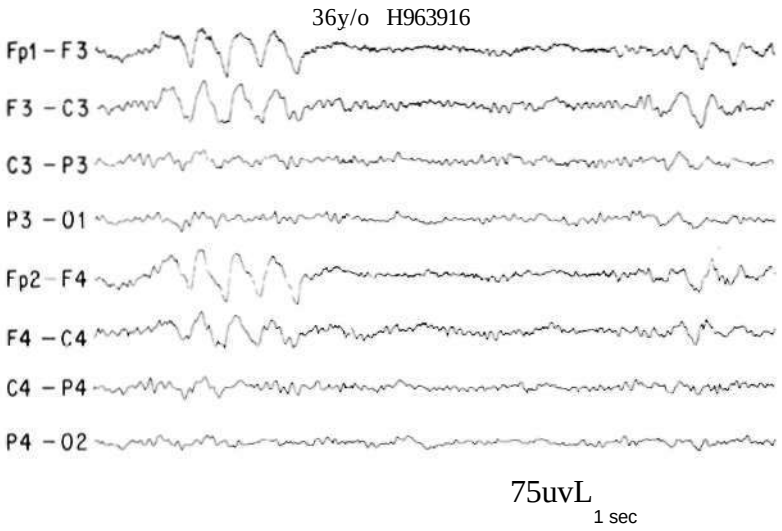


FIGURE 36A.11 Bursts of intermittent rhythmic-delta waves in a 36-year-old man with primary generalized epilepsy and tonic-clonic seizures. Generalized spike-wave activity occurred elsewhere in the electroencephalogram. The intermittent rhythmic delta waves are a nonspecific manifestation of his generalized epileptic disorder. (Courtesy Dr. Bruce J. Fisch,)

- Is there evidence of improvement despite little change in the clinical picture?
- Arc there findings that assist in assessing prognosis?

Metabolic Encephalopathies

Metabolic derangements affecting the brain diffusely are one of the more common causes of altered mental function in a general hospital. Generalized slow-wave activity is the main electroencephalographic indication of decreased consciousness. The degree of electroencephalographic slowing parallels closely the patient's mental status and ranges from only minor slowing of alpha rhythm frequency (slight inattentiveness and decreased alertness) to continuous delta activity (coma). Slow-wave activity sometimes becomes bisynchronous and assumes a high-voltage and sharply contoured triphasic morphology, especially over the frontal head regions (Figure 36A.12). These triphasic waves were originally considered diagnostic of hepatic failure but are now known to occur with equal frequency in several metabolic disorders. The value of triphasic waves is that they suggest a metabolic cause in an unresponsive patient.

Some electroencephalographic features increase the likelihood of a specific metabolic disorder. Prominent, generalized rhythmic beta activity raises the suspicion of drug intoxication in a comatose patient. Severe generalized voltage depression indicates impaired energy metabolism and suggests hypothyroidism if anoxia and hypothermia can be excluded. A photoconvulsive response is seen more often with uremia than with other causes of metabolic encephalopathy. Focal seizure activity is common in patients with hyperosmolar coma.

Hypoxia

Hypoxia, with or without circulatory arrest, produces a wide range of electroencephalographic abnormalities depending on the severity and reversibility of the brain

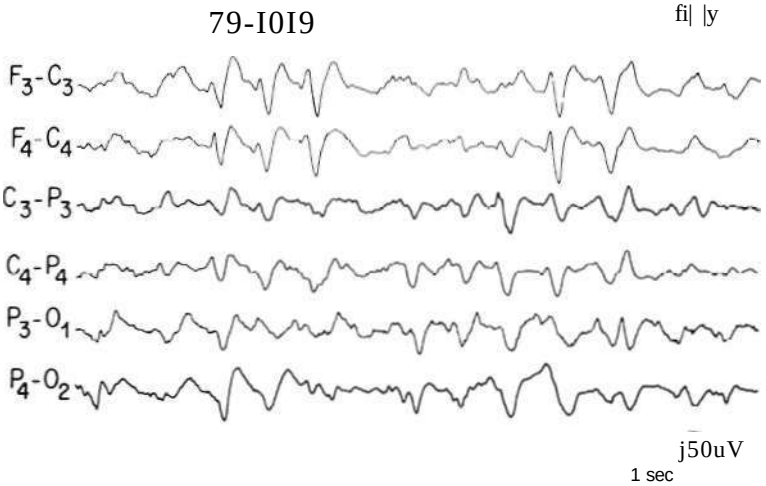


FIGURE 36A.12 Triphasic waves in a 61-year-old man with hepatic failure. (Courtesy Dr. Bruce J. Fisch.)

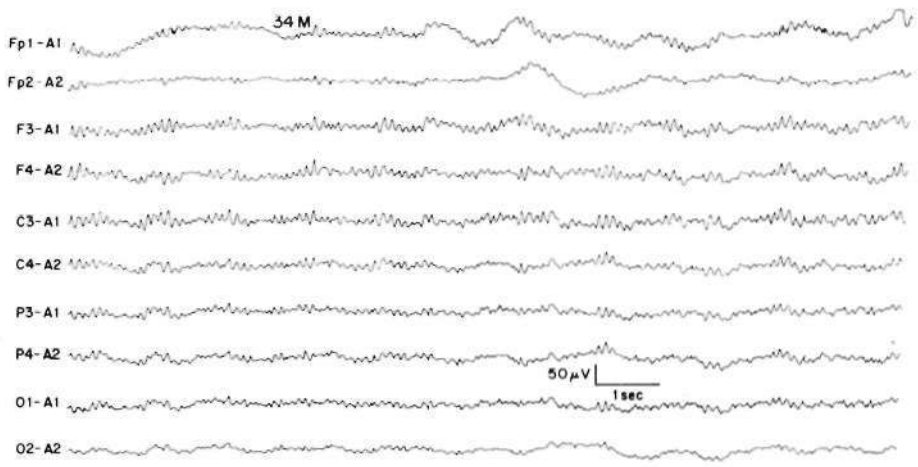


FIGURE 36A.13 Alpha coma in a 34-year-old man with severe hypoxic-ischemic brain damage after subarachnoid hemorrhage with diffuse prolonged cerebral vasospasm. Unlike the normal alpha rhythm, the alpha-range activity in this comatose patient is widespread but maximal frontally, unrcactive, and superimposed on low-voltage arrhythmic delta frequencies.

damage. An electroencephalogram obtained *6* hours or more after the hypoxic insult may show patterns that have prognostic value. The validity of such findings is strengthened if sequential electroencephalograms are obtained, Electroencephalographs: abnormalities associated with poor neurological outcome are alpha coma, burst suppression, and periodic patterns.

The term *alpha coma* refers to the apparent paradoxical appearance of monorhythmic alpha frequency activity in the electroencephalogram of a comatose patient; the electroencephalogram may appear normal to the inexperienced observer (Figure 36A.13). In contrast to normal alpha activity, the alpha pattern of alpha coma is generalized, often maximal frontally, and unreactive to external stimuli.

The burst suppression pattern consists of occasional generalized bursts of medium- to high-voltage mixed-frequency slow-wave activity, sometimes with intermixed spikes, with intervening periods of severe voltage depression or cerebral inactivity {Figure 36A.14). The bursts may be accompanied by strong myoclonic body jerks.

The periodic pattern consists of generalized spikes or sharp waves that recur at a fixed interval, typically 1-2 per second {Figure 36A. 15). Sometimes the periodic shatp waves occur independently over each hemisphere. A postanoxic periodic pattern usually is accompanied by myoclonic jerks of the limbs or whole body.

The prognostic value of these patterns is related exclusively to cause. Similar findings are seen with potentially reversible causes of coma including deep anesthesia, drug overdose, and severe liver or kidney failure.

Infections Diseases

Herpes simplex encephalitis is the one infectious disease for which EEG is useful in initial assessment. Early and accurate diagnosis is important because the response to acyclovir is best when treatment is started early. Although a definitive diagnosis is made only by brain biopsy, characteristic clcctrocncephalographic changes in the clinical setting of encephalitis help select patients for early treatment and biopsy. The electroencepbalographic result usually is abnormal and suggests the diagnosis of herpes infection before CT lesions are recognized.

Other forms of viral encephalitis are expected to cause diffuse polymorphic slow-wave activity, and a normal electroencephalogram result raises doubt about the diagnosis. With herpes simplex encephalitis, the majority of

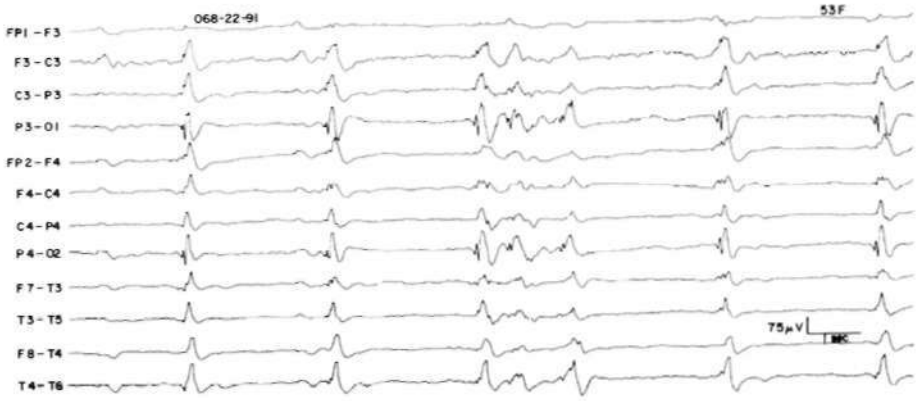


FIGURE 36A.14 Suppression burst pattern in a 53-year-old woman with anoxic encephalopathy after cardiorespiratory arrest. The patient died several days later. (Courtesy Dr. Barbara S. Koppel.)

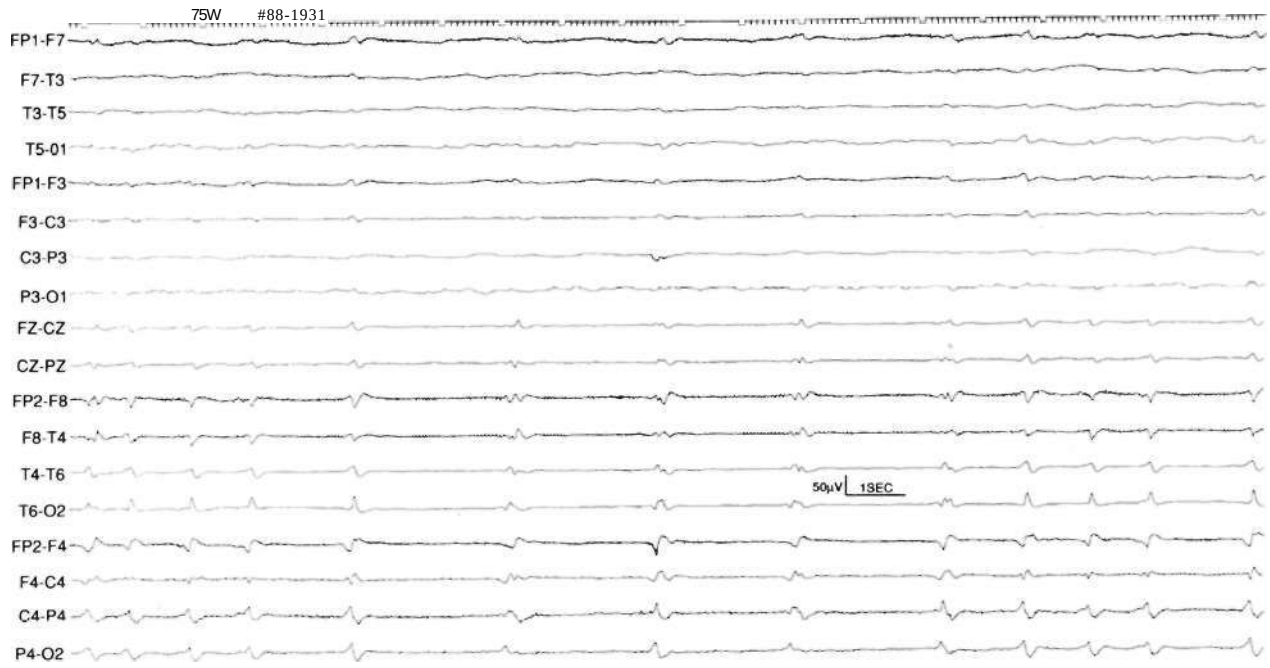


FIGURE 36A.15 Periodic partem in a patient witli anoxic encephalopathy after cardiorespiratory arrest. The patient was paralyzed with pancuronium because of bilateral myoclonus.

patients show focal temporal or frontal temporal slowing that may be unilateral or, if bilateral, asymmetrical. Periodic sharp-wave complexes over one or both fronto-temporal regions (occasionally in other locations and sometimes generalized) add additional specificity to the electroencephalographic findings (see Figure 36A.9B). These diagnostic features usually appear between the second and fifteenth day of illness and are sometimes detected only with serial tracings.

Bactetial meningitis causes severe and widespread electroencephalographic abnormalities, typically profound slowing and voltage depression, but viral meningitis produces few significant changes. Although CT has replaced EEG in evaluating patients with suspected brain abscess, focal electroencephalographic changes may be seen in the early stage of cercbritis, before an encapsulated lesion is demonstrable on CT,

Electroencephalographic abnormalities usually diminish as the patient recovers, but the rate of resolution of clinical deficits and the elcctrographic findings may be different. It is not possible to predict residual neurological morbidity or postencephalitic seizures by electroencephalographic criteria. An early return of normal electroencephalographic activity does not preclude persistent neurological impairment.

Brain Death

The diagnosis of bram death rests on strict clinical criteria that, when satisfied unambiguously, permit a conclusive determination of irreversible loss of brain function. In the United States, brain death usually is defined as irreversible cessation of all functions of the entire brain, including the brainstem. Because EEG is a measure of cerebral (especially cortical) function, it has been widely used, in association with clinical evaluation, to provide objective evidence that brain function is lost. Several studies have demonstrated that enduring loss of cerebral electrical activity (called electrocerebral inactivity or electrocerebral silence) accompanies clinical brain death and is never associated with recovery of neurological function. Determination of electrocerebral inactivity is technically demanding and requires a special recording protocol. Reference should be made to criteria established by the American EEG Society (1994).

Temporary and reversible loss of cerebral electrical activity can be seen immediately after cardiorespiratory resuscitation, drug overdose from central nervous system depressants, and severe hypothermia. Therefore, accurate interpretation of an electroencephalogram demonstrating electrocerebral inactivity must take into account these exceptional circumstances. The clinical criteria for establishing the diagnosis of brain death are summarized in Chapter 5 1.

Aging and Dementia

Because EEG is a measure of cortical function, theoretically it should be useful in the diagnosis and classification of dementia. However, the utility of single

electroencephalographic examinations in evaluating patients with known or suspected dementing illnesses often is disappointing. Two important reasons for this are problems in distinguishing the effects on cerebral electrical activity of normal aging from those caused by disease processes and the absence of generally accepted quantifiable methods of analysis and statistically valid comparison measures.

With increasing age over 65, a slight reduction in the total amount of alpha activity and in the alpha rhythm frequency is normal. Normal older adults also show slightly higher amounts of theta and delta activity, especially over the temporal and frontoremporal regions, and changes in sleep patterns. Early in the course of some dementing illnesses, there may be no apparent electroencephalographic abnormality (this is the rule with Alzheimer's disease), or the normal, age-related changes may become exaggerated, differing more in degree than in kind.

In practice, EEG can assist in evaluating suspected dementia by confirming abnormal cerebral function when the possibility of a psychogenic disorder exists and by delineating whether the process is focal or diffuse. Sequential electroencephalograms usually are more helpful than a single tracing, and a test early in the course of the illness may provide more specific information than one performed later. Overall, the degree of electroencephalographic abnormality shows a good correlation with the degree of dementia.

Electroencephalographic findings in Alzheimer's disease are highly dependent on timing. The electroencephalogram initially is normal or shows an alpha rhythm at or just below the lower limits of normal. Generalized slowing appears as the disease progresses. In patients with focal cognitive deficits, low-frequency activity is accentuated over the corresponding brain area. Continuous focal slowing is sufficiently unusual to suggest the possibility of another diagnosis. Prominent focal or bilateral independent slow-wave activity, especially in company with a normal alpha rhythm, favors multifocal disease, such as multiple cerebral infarcts. A specific cause sometimes is suggested. For example, an electroencephalogram showing generalized typical periodic sharp wave complexes in a patient with dementia is virtually diagnostic of Creutzfeldt-Jakob disease (Figure 36A.16).

Event related evoked potentials have been applied to the study of dementia. These are long-latency events (i.e., potentials occurring more than 150 milliseconds after the stimulus) that are heavily dependent on psychic and cognitive factors. Ideally, they measure the brain's intrinsic mechanisms for processing certain types of information and arc potentially valuable in the electrophysiologic assessment of dementia. The best known of the event-related potentials is the P300, or P3, wave. The place of these long-latency evoked potentials in evaluating dementia is still under investigation, but it may be possible to help distinguish between types of dementia by the pattern of electrophysiological abnormality (Goodin 1999).

Computerized Electroencephalography

For decades, electroencephalographic recording instruments were simple analog devices consisting of banks of amplifiers connected to a multichannel strip chart recorder. In recent years, electroencephalographic recording technology has shifted to digital paperless systems in which amplified electroencephalographic signals are converted to a digital format and stored on a computer disc rather than printed on paper. The electroencephalographer interprets the electroencephalogram by viewing it on a computer display rather than on paper. Fundamentally, routine interpretation of EEG, as well as its clinical significance

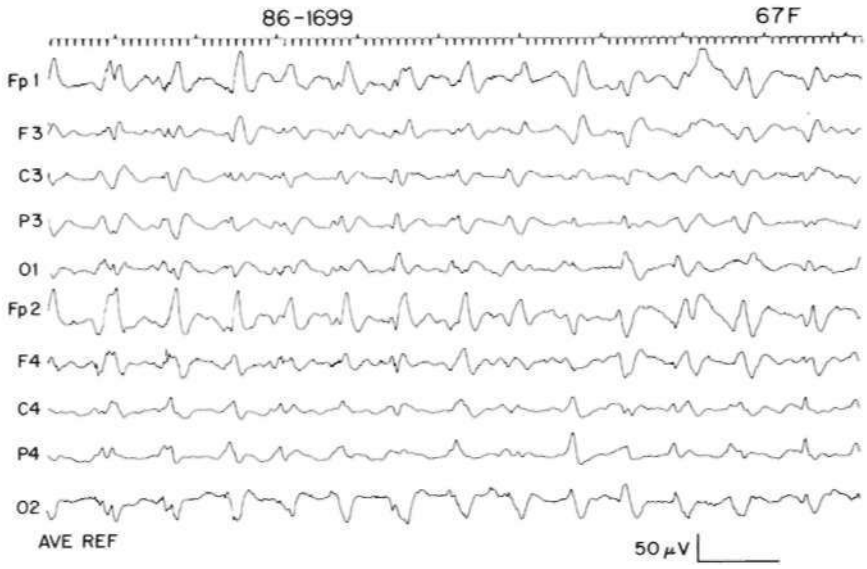


FIGURE 36A.16 Periodic sharp-wave pattern in a 67-year-old woman with Creutzfeldt-Jakob disease. Generalized bisynchronous diphasic sharp waves occur approximately L5-2.0 per second.

and applications, has not been altered by this change in recording technology. However, digital recording systems have facilitated electroencephalographic interpretation and made it possible for the clectroencephalographer to use a variety of signal-processing and display techniques that greatly supplement standard methods of analysis.

In a conventional paper-based EEG system, all recording variables, including sensitivity, filter settings, and the manner in which scalp-recorded signals are combined and displayed (montages), are fixed by the technologist when the KEG is recorded. In digital EEG systems, the electro-cncephalographer can adjust all these parameters when the electroencephalogram is interpreted. Thus a given wave-form or pattern can be examined using a number of different instrument settings. In addition, digital EEG systems permit the use of certain sophisticated montages (e.g., Laplacian montage) that are not available using analog recording systems. Although this flexibility does not change the interpretive strategies used to read an electro-encephalogram, it does allow them to be used much more effectively than was possible using paper-based recording systems.

Although conventional paper recording techniques generally are adequate for standard 20- or 30-minute EEG, they are poorly suited to long-term or continuous EEG. For example, a 24-hour electroencephalographic recording could produce a stack of paper more than 1 foot high. In contrast, digital EEG recording systems are well suited to storage and rapid review of lengthy recordings. For patients undergoing long-term electroencephalographic recordings as part of the diagnosis or management of epilepsy, a time-locked digital video image of the patient generally is recorded along with the electroencephalogram, and the data can be processed automatically to detect most interictal and ictal epileptiform activity. Automatic spike and seizure detection software is now a standard component of commercial epilepsy monitoring systems.

Computerized recording techniques have also made continuous electroencephalographic monitoring practical in inrensive care units. A growing body of literature supports the utility of continuous electroencephalographic monitoring for patients with nonconvulsive seizures, threatened or progressing cerebral ischemia, severe head trauma, and metabolic coma. Furthermore, new insights are emerging concerning the clinical significance of certain periodic electroencephalographic patterns as long-term monitoring becomes routine in the intensive care unit (Brenner 2002). Fully automated, robust systems analogous to those used for cardiac monitoring are not yet available. However, compressed spectrograms, which graphically summarize the frequencies present in several hours of EEG on a single screen, can be used to facilitate the interpretation of continuous electroencephalographic recordings by allowing the elcctrocnccphalographer ro rapidly pinpoint important changes in the electroencephalogram and sometimes to spot patterns or trends that might otherwise go unnoticed (Plate 36A.I) (Scheuer 2002), It must be emphasized that although frequency spectral analysis and similar mathematical methods can be very useful adjunctive techniques, they are properly used in clinical practice only in conjunction with standard EEG. The very data reduction th.it makes them useful also makes them LIHSLJiC;I1>1L- lor stand-alone use.

Topographical mapping displays can be useful in depicting spatial relationships and electroencephalographic features in a graphical manner similar to brain scans. For example, topographical maps can show electroencephalographic voltage distributions over the scalp at a particular point in time (Plate 36A.II). They also may be used to illustrate the distributions of particular frequencies in the electroencephalographic background.

In addition to facilitating EEG interpretation, mathematical techniques can be applied to extract attributes that are not apparent from visual inspection of raw electroencephalographic waveforms. Averaging techniques, useful in improving the signal-to-noise ratio of electroencephalographic transients such as spikes and sharp waves, reveal field distributions and timing relationships that cannot otherwise be appreciated. Recently, dipole source localization techniques have been used to characterize interictal spikes and ictal discharges in patients with epilepsy. Although these methods may contribute to localization of the seizure focus (Ebersole 2000), they are based on several critical assumptions that, when applied without recognition of their limitations, can result in anatomically and physiologically erroneous conclusions (Emerson et al. 1995). Finally, some success has been reported in the application of a variety of linear and nonlinear mathematical techniques to seizure prediction, or at least the detection of preictal changes minutes, or even longer, before any change is observable either clinically or in the routine electroencephalographic display {Jcrgcr et al. 2001; Lift and Lehnertz 2002). Although it is too early to assess their ultimate utility, these techniques are likely to provide important insights into the physiology of the interictal and preictal states, and they could also lead to important therapeutic advances.

M ag n etoen ceph a lo g rap h y

Magiu-rocncephalograpliy (MEG) is a measure of brain function equivalent to EF,G. The same neuronal sources that generate electrical activity also give rise to magnetic-fields. However, MEG differs from EEG in several ways that are theoretically useful. Electroencephalographic potentials are attenuated substantially by the overlying cerebrospinal fluid, dura, and skull. Magnetic fields are less affected by these structures. In addition, EEG measures cortical current sources oriented in all directions but emphasizes radially oriented dipoles. MEG more accurately measures tangential dipoles that are parallel to the cortical

surface. However, the limitations that apply to dipole source localization of elcctrocncephalographic signals apply similarly to magnet oencephalographic signals.

To date, MEG has been used mainly to localize sources of evoked potentials and focal epileptiform activity {Baumgartner et al. 2000). It also has been applied, in a more limited way, to investigations of patients with psychiatric disorders, stroke, and migraine. Because of the shielding requirements and the complex and costly instrumentation necessary to measure neuromagnetic fields, MEG has been and is likely to remain limited to research applications.

EVOKED POTENTIALS

Evoked potentials are electrical signals generated by the nervous system in response to sensory stimuli. The timing and location of these signals arc determined by the sensory system involved and the sequence in which different neural structures are activated. The stimulus paradigms used in clinical practice are chosen so that the responses they evoke arc sufficiently stereotyped to allow the limits of normal to be clearly defined. Violation of these limits indicates dysfunction of the sensory pathways being studied. An overview of recording methods, criteria for abnormality, and [imitations of use is provided by the American EEG Society's guidelines (1994).

Because of their low voltage, evoked potentials generally are not discernible without computer averaging to distinguish them from ongoing elcctrocncephalographic activity and other sources of electrical noise. Exceptions are the visual responses evoked by transient flash stimuli, which are seen in routine EEG as photic driving. Typically, however, it is necessary to present the stimulus repeatedly, averaging the time-locked brain or spinal cord responses to a series of identical stimuli while allowing unrelated noise to average out.

In the clinical setting, evoked potential studies are viewed properly as an extension of the neurological examination. Like any neurological sign, they help reveal the existence and often suggest the location of neurological lesions. Evoked potentials therefore are most useful when they detect clinically silent abnormalities that might otherwise go unrecognized or when they assist in resolving vague or equivocal symptoms and findings. Like EEG, evoked potentials are tests of function; they are not usually etiologically specific.

Visual Evoked Potentials

Cerebral visual evoked potentials (VEPs) are responses of the visual cortex to appropriate stimuli. The composite retinal response to visual stimuli, electroretinography, may he recorded separately, and the procedure may lie indicated

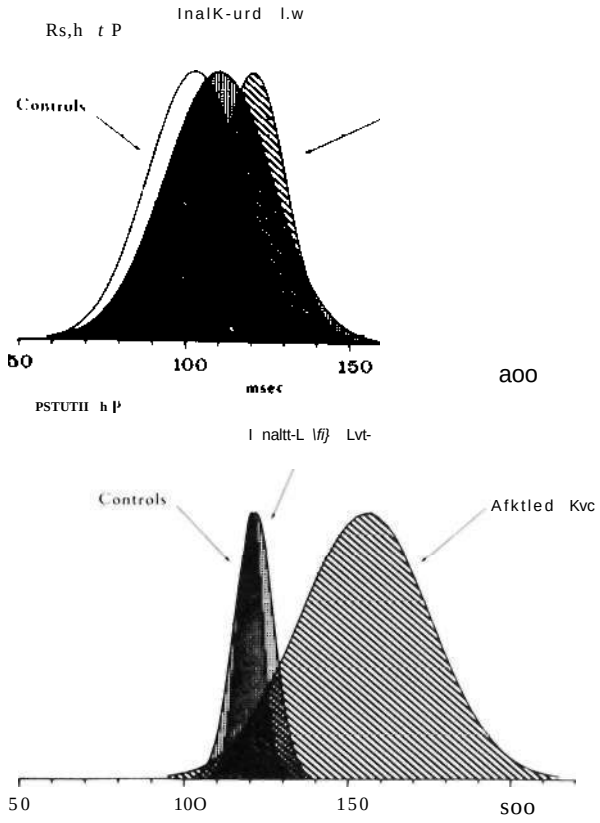


FIGURE 36A. 17 Distributions of latencies of the major occipital positivity to flash (A) and pattern shift (B) stimulation in healthy controls and in the affected and unaffected eyes of patients with optic neuritis. The superior sensitivity of pattern shift visual evoked potentials (EP) to dcmyclinating lesions is clearly demonstrated. (Reprinted with permission from Halliday, A. M. 1982, "The visual evoked potential in the investigation of diseases of the optic nerve," in *FA'oked Potentials in Clinical Testing,* ed A. M. Halliday, Churchill Livingstone, New York.)

in certain clinical situations. The cerebral VEP is obtained by averaging the responses from occipital scalp electrodes generated by 100 or more sequential stimuli. Stimulus characteristics arc critically important in determining what portion of the visual system will be tested by the VEP and what the sensitivity of the test will be to the presence of lesions. Initial clinical applications of VEPs used a stroboscope flash stimulus, but the utility of the flash-evoked VEP is severely limited by the great variability of responses among normal individuals and its insensitivity to clinical lesions (Figure 36A.17). Occasionally, flash VEPs may provide limited information about the integrity of visual pathways when the preferred patrcrn reversal stimulus cannot be used, as in infants or other patients unable to cooperate for more sensitive testing methods.

Normal Visual Evoked Potential

More sensitive and reliable responses are obtained using ;i pattern reversal stimulus. The subject focuses on

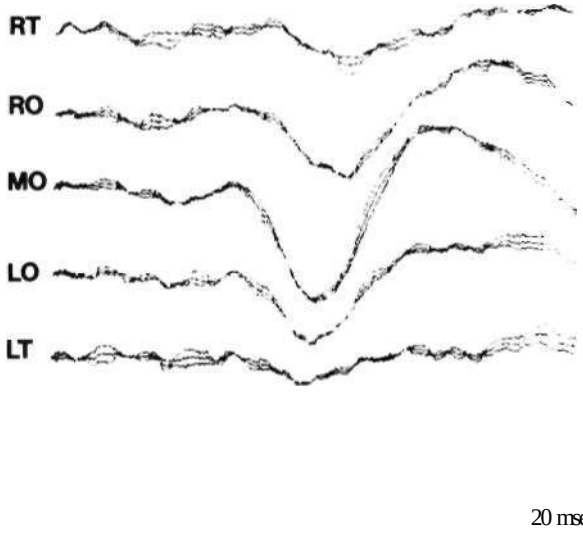


FIGURE 36A.18 Normal pattern reversal visual evoked potentials to full-field monocular stimulation. The MO electrode is in the posterior midline over the occiput. RO and RT are 5 and 10 cm, respectively, to the right of MO, and LO and I.T are 5 and 10 cm, respectively, to the left of MO. All electrodes are referred to Fpz (a midline frontopolar electrode). The response is largest at MO and symmetrically distrihutcd left and right of midline.

a high-contrast checkerboard of black and white squares displayed on a video or optical projection screen. The stimulus is the change of black squares to white and white squares to black (pattern reversal). When appropriate check sizes are used (15—40 minutes of arc at the subject's eye), the VF.P is generated primarily by foveal and parafoveal elements. Monocular full-field stimulation is almost always used so that the test is most sensitive to lesions of the optic nerve anterior to the chiasm. However, it is possible to modify the stimulus presentation so that only selected portions of the visual field are stimulated, permitting detection of postchiasmatic abnormalities as well. VEPs elicited by pattern reversal stimuli show less intersubject variability than do flash VEPs and are much more sensitive to lesions affecting the visual pathways.

A few investigators have further refined the pattern shift stimulus by using a black and white sinusoidal grating rather than a checketboard pattern. This appears to enhance test sensitivity by permitting selective stimulation of retinal elements responsive to specific spatial frequencies and of cortical elements sensitive to both spatial frequency and orientation.

A normal pattern reversal VEP to full-field monocular stimulation is illustrated in Figure 36A,18. The VEP waveform is deceptively simple. It is the sum of many waveforms generated simultaneously by various areas of the retinotopically organized occipital cortex. By selectively stimulating portions of the visual field, it is possible to dissect the full-field VEP into its component waveforms. For example, Figure 36A.19, recorded from the same person as Figure 36A.18, illustrates VEPs to nght and left hemifield stimulation. It is apparent that the full-field VEP is the sum of the two hemifield responses. In principle, it is possible to divide the visual fields into progressively smaller components and to record the VEP to each independently.

Clinical interpretation of the pattern reversal VEP is based primarily on measurement of the latency of the PI 00 component (the major positive wave having a nominal latency of approximately 100 milliseconds in normal

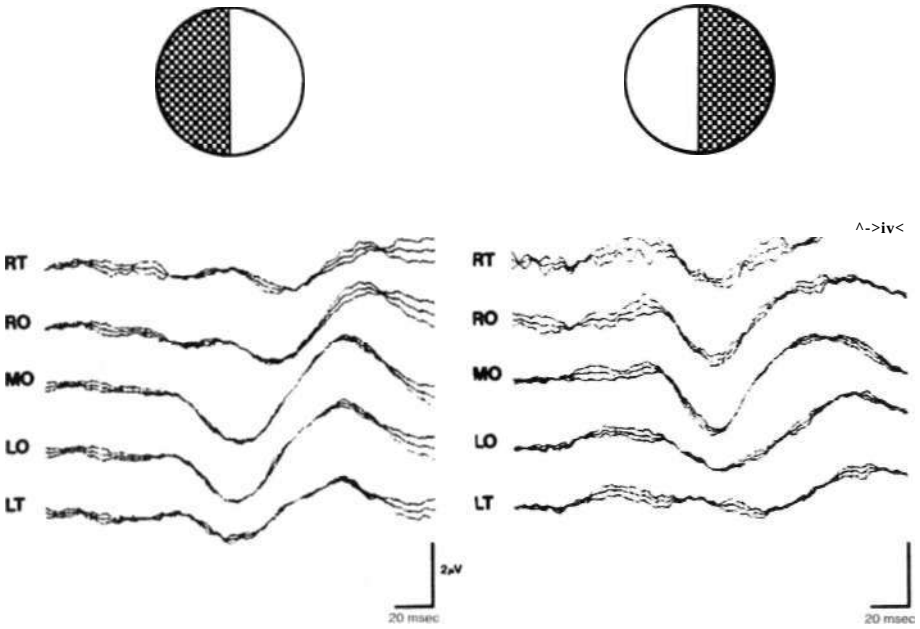


FIGURE 36A.19 Normal pattern shift visual evoked potentials to right and left hemifield stimulation of one eye in the same subject as shown in Figure 36A.I8. Partial field responses arc asymmetrical about the midline, with the largest positivities ipsilateral to the stimulated field.

subjects) after stimulation of each eye separately. Less emphasis is placed on measurement of P100 amplitude, although intereye differences of more than 50% may be significant. The absolute PI00 latency is measured for each eye, and then the intereye PI00 latency difference is determined. These values are compared with the laboratory's normative data and a conclusion reached regarding whether the responses arc normal or abnormal. Finally, the clinical significance of the findings should be interpreted, whenever possible, in the context of other relevant clinical data.

Because optic nerve fibers from the temporal retina decussate at the chiasm, unilateral prolongation of P100 latency after full-field monocular stimulation implies an abnormality anterior to the optic chiasm on that side. Bilateral delay of the P100, demonstrated by separate stimulation of each eye, can be caused by bilateral lesions either anterior or posterior to the optic chiasm or by a chiasmal lesion. Unilateral hemispherical lesions do not alter the latency of the full-field PI00 (because of the contribution from rhe intact hemifield) but do alter the scalp topography of the response.

Visual Evoked Potentials in Neurological Disease

Acute optic neuritis is accompanied by marked attenuation or loss of Pi00 amplitude after pattern reversal stimulation of the affected eye. After the acute attack, the VEP shows some recovery, but P100 latency almost always remains prolonged, even if functionally normal vision is restored. In patients with a history of optic neuritis, P100 latency typically is prolonged, but waveform amplitude and morphology often are well preserved (Figure 36A.20). Factors contributing to changes in PHK) probably include the combined effects of patchy conduction block, areas of variably slowed conduction, temporal dispersion of the afferent volley in the optic nerve, loss of some components

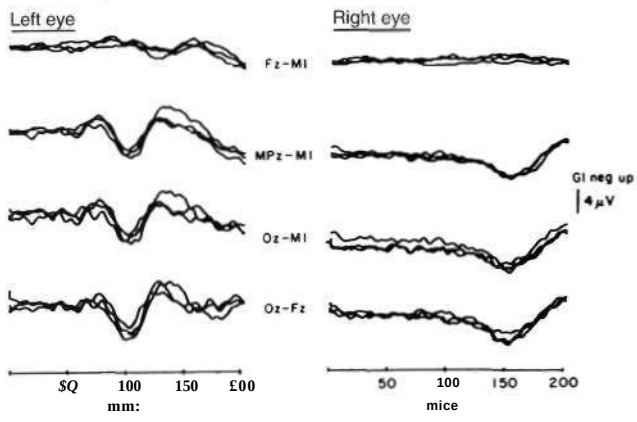


FIGURE 36A.20 Pattern shift visual evoked potentials in a patient with right optic neuritis iUustrating marked delay of the PI00 component from the right eye. As is typical of demyelinating optic neuropathies, the waveform is largely preserved.

Table 36A.1: Some causes of abnormal visual evoked potentials

Ocular disease
- Major refractive error
- Lens and media opacities
- Glaucoma
- Retinopathies

Compressive lesions
- Extrinsic tumors
- Optic nerve tumors

Noncompressive lesions
- Demyelinating disease
- Ischemic optic neuritis
- Nutritional and toxic amblyopias (including pernicious anemia)
- Leber's hereditary optic atrophy

Diffuse central nervous system disease
- Adrenoleukodystrophy
- Spinocerebellar degenerations
- Parkinson's disease

of the normal VEP, and the appearance of previously masked components.

Pattern shift VEPs are abnormal in nearly 100% of patients with a definite history of optic neuritis. More important, the pattern shift VEP is a sufficiently sensitive indicator of optic nerve demyelination that it can reveal asymptomatic and clinically undetectable lesions. Therefore 70-80% of patients with definite multiple sclerosis but no history of optic neuritis or visual symptoms have abnormal VEPs. Many patients with abnormal VF.Ps have normal neuro-ophthalmological examination results.

Pattern reversal VEPs arc highly sensitive to demyelinating lesions but are not specific for multiple sclerosis. A partial list of other causes of abnormal VEPs is given in Table 36A.1.

VEPs may be helpful in distinguishing hysteria or malingering from blindness. A normal pattern reversal VEP is strong evidence of psychogenic illness. However, rare cases have been reported in which essentially normal VEPs were present in cortical blindness because of bilateral destruction of area 17, wirh preservation of areas 18 and 19, or bilareral occipital infarcts with preservation of area 17 (Epstein 2000).

Brainstem Auditory Evoked Potentials

Brainstem auditory evoked potentials (BAEPs) are signals generated in rhe auditory nerve and brainstem by an acoustical stimulus. A brief stimulus, usually a sharp click, is given to one car through an earphone, while the opposite ear is masked with white noise to prevent its stimulation by transcranial!)' conducted sound. The normal BAEP consists of a series of waves that occur within the first 10 milliseconds after the stimulus. The BAEP is extremely low voltage (only approximately 0.5 uV), and typically 1000-2000 recordings are averaged to resolve the BAEP waveform.

Normal Brainstem Auditory Evoked Potentials

Unlike VEPs, which are cortical responses, BAEPs are generated in or caudal to the mesencephalon. BAEPs characteristically resist the effects of metabolic disturbances and pharmacologic agents. Indeed, in the absence of anatomical lesions, BAEPs persist essentially unchanged into deep coma or in the presence of general anesthesia.

A normal BAEP is illustrated in Figure 36A.21. The components designated by roman numerals are produced by summated neuronal activity in anatomical structures that are activated sequentially by the afferent sensory volley. Uncertainty exists regarding the relative contributions to the scalp-recorded BAEP of synaptic potentials occurring in nuclear structures and compound action potentials in fiber tracts. Although the following electro-anatomical relationships may be somewhat oversimplified, they are useful for purposes of clinical localization. Wave I, corresponding to Nl of the electrocochleogram, represents the auditory nerve compound action potential and arises in the distalmost pottion of the nerve. Wave II is generated mainly in the proximal eighth nerve but probably also includes a contribution from the intra-axial portion of the nerve and perhaps the cochlear nucleus as well. Wave III is generated in the lower pons, in the region of the superior olive and trapezoid body. The generators of waves IV and V lie in rhe upper pons and the midbrain, as high as the inferior colliculus. Waves II and IV are inconsistently identified in some normal individuals, so clinical interpretation of BAEPs is based primarily on latency measurements of waves I, III, and V. Despite decussation of brainstem auditory pathways at multiple levels, clinical experience indicates that unilateral BAEP abnormalities usually reflect lesions ipsilateral to the stimulated car.

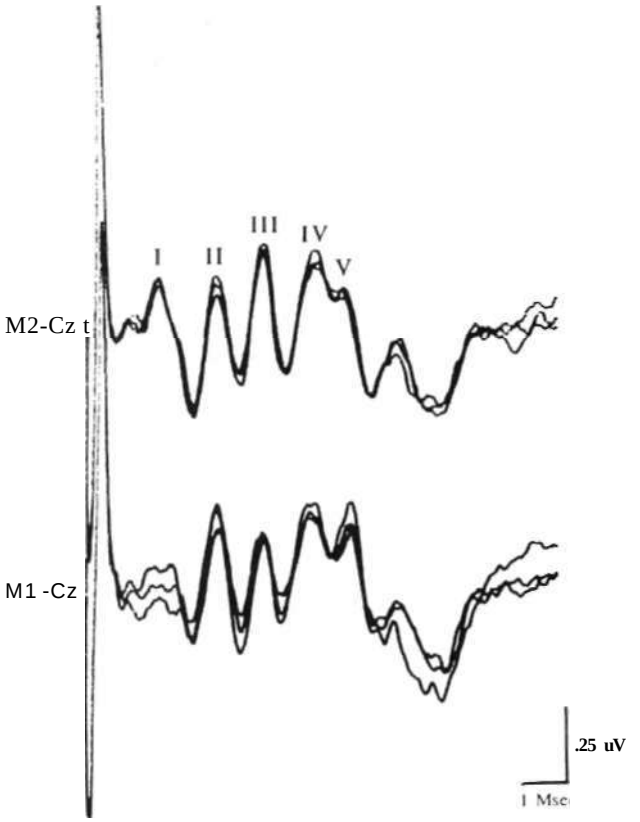


FIGURE 36A.21 Normal brainstem auditory evoked potentials. .Major components are labeled with roman numerals and discussed more fully in the text. M2 is an electrode over the mastoid process ipsilatcral to the stimulated car, in this case the right. Left and right mastoid electrodes are connected to an electrode at the vertex (Cz).

Brainstem Auditory Evoked Potentials in Neurological Disease

Auditory nerve disorders have several effects on the BAEP, in part related to the nature and size of the lesion. Findings range from prolongation of the I-III imerpcak interval, to preservation of wave I with distortion or loss of later components, to loss of all BAEP components. Any of these abnormalities can be seen with acoustic neurinomas and other cerebellopontine angle tumors (Figure 36A.22). In fact, the BAEP may be the most sensitive screening test for acoustic neurinoma, detecting abnormalities in more than 90% of patients. The sensitivity of the test can be further extended by using a range of stimulus intensities and evaluating the effect on components of the BAEP (the latency intensity) (Figure 36A.23).

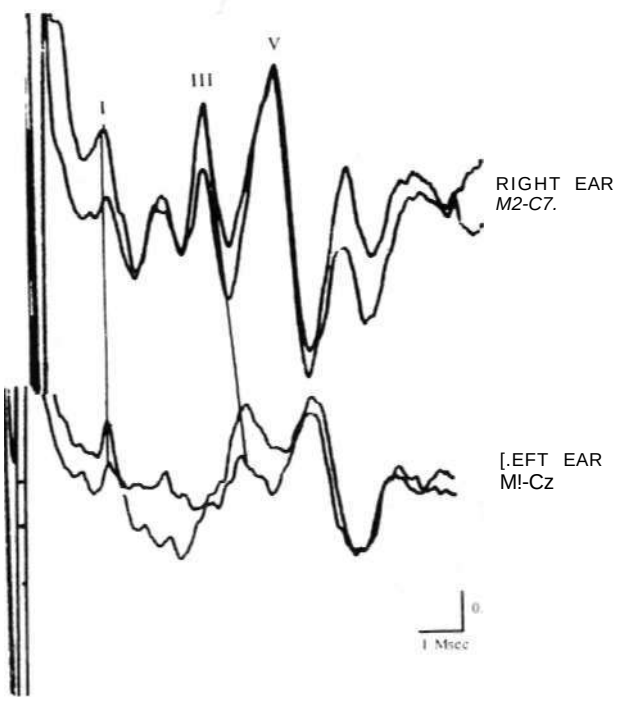


FIGURE 36A.22 Brainstem auditory evoked potentials in a patient with a left acoustic neurinoma. There is prolongation of the I-1II interval on that side, and the overall response is not as well formed as that from the normal ear.

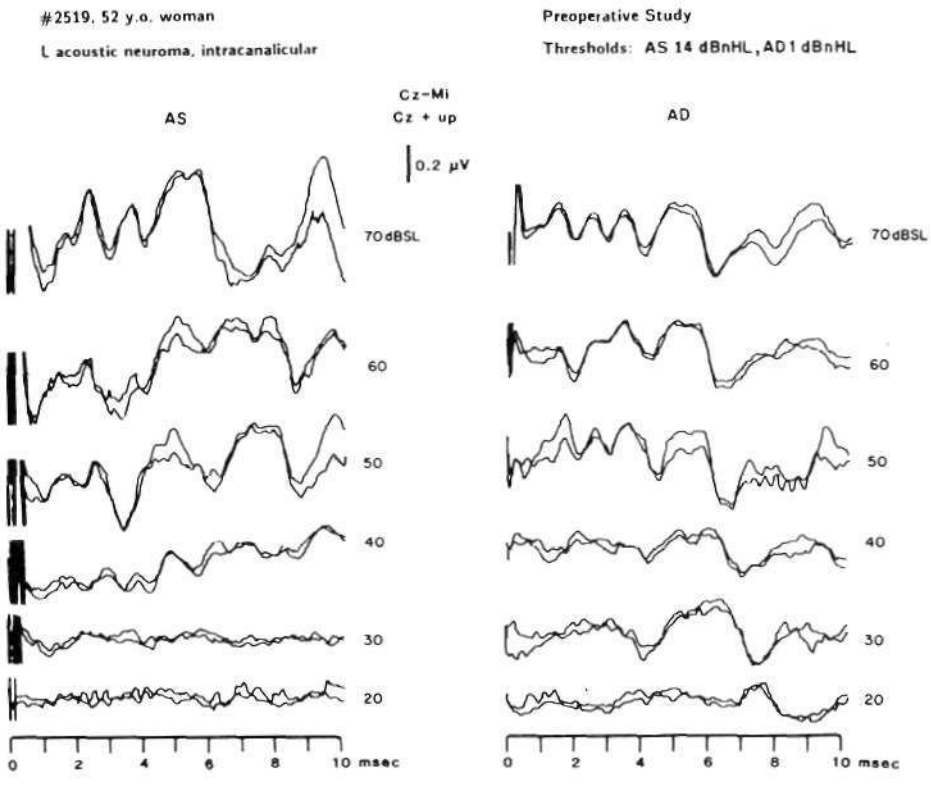


FIGURE 36A.23 Brainstem auditory evoked potential wave V latency plots as a function of increasing stimulus intensity from 20 to 70 dBSL (decibels sound level) in a woman with a left intracanalicular acoustic neurinoma. Brainstem auditory evoked potentials at 70 dBSL are normal bilaterally, but responses at lower intensities are asymmetrical, and the response threshold is elevated on the left.

In patients with focal brainstem lesions that impinge on the auditory pathways, the BAEP is abnormal, and the type of abnormality reflects the lesion's location and extent. For example, Figure 36A.24 illustrates a BAEP obtained from a patient with a brainstem hemorrhage that involved the rostral two thirds of the pons but spared the caudal one third. Waves IV and V are absent, but waves I, II, and III are normal. BAEPs are normal when brainstem lesions do not involve auditory pathways, as is often the case in the locked-in syndrome produced by ventral pontine infarction, or with Wallenberg's lateral medullary syndrome. In contrast, pontine gliomas nearly always produce abnormal BAEPs.

Nearly 50% of patients with definite multiple sclerosis have abnormal BAEP results. Of greater clinical importance, approximately 20% of patients with possible or

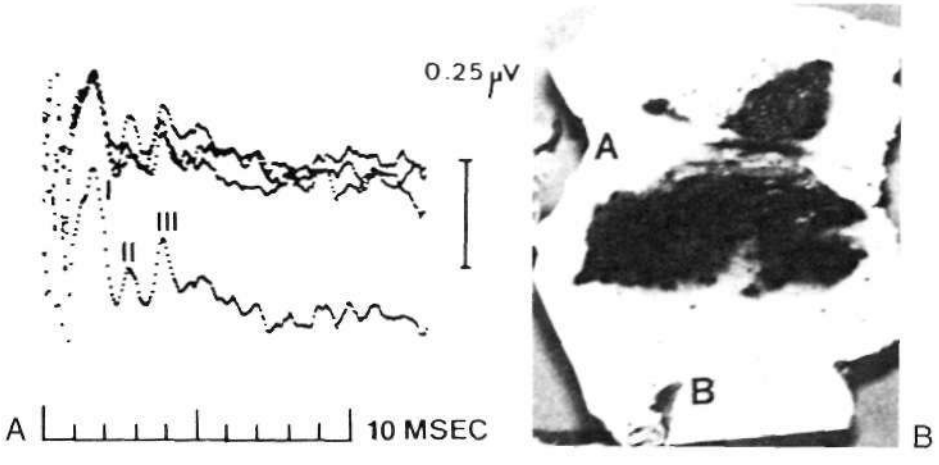


FIGURE 36A.24 Brainstem auditory evoked potentials recorded from a patient with a brainstem hemorrhage sparing the lower one third of the pons. Waves I, II, and III are preserved, but later components are lost. The figure shows a coronal section through the pons. (A) Pontomesencephalic border. (B) Pontomedullary border. (Reprinted with permission from Chiappa, K. H. 1985, "Evoked potentials in clinical medicine," in *Clinical Neurology*, eds A. B. Baker & L. H. Baker, Harper & Row, New York.)

probable multiple sclerosis have an abnormal 15 A HP result, even in the absence of clinical signs or symptoms referable to the brainstem. In such cases, abnormalities usually consist of absence or decreased amplitude of BAEP component waves, most often of waves IV and V, or increased 111—V interpeak latency. Occasionally, prolongation ot the I-III interpeak interval occurs, probably reflecting involvement of the central myelin, which covers the proximal and immediately intra-axial portion of the auditory nerve.

BAEPs may document brainstem involvement in patients with nonfocal neurological diseases, especially those affecting myelin such as metachromaric leukodystrophy and adrenoleukodystrophy. In such diseases, the BAEP also may show electrophysiologic abnormalities in clinically asymptomatic heterozygotes.

BAEPs ate used to assess hearing in young children and in patients otherwise unable to cooperate with standard audiologicnl testing. A latency intensity study, discussed previously, permits characterization of the response threshold for wave V and the relationship between wave V latency and stimulus intensity. Such testing allows estimation of hearing threshold and may distinguish between conductive and sensorineural types of hearing impairment. However, brainstem audiometry is not really a hearing test per se but a measure of the brainstem's sensitivity to auditoty input. The BAEP is normal in the rare patient with deafness resulting from bilateral cortical lesions. On the other hand, patients with multiple sclerosis or a pontine glioma often have abnormal BAEP results but normal hearing (although their ability to localize sound accurately in space may be diminished). One limitation to using BAEPs to test hearing is that the brainstem must be intact, so that BAEP alterations teflect dysfunction in the peripheral hearing apparatus (Lueders and Terada 2000).

Somatosensory Evoked Potentials

After electrical stimulation of a peripheral nerve, recordings from electrodes placed over [lie spine and scalp reveal a series of waves that reflect sequential activation of neural structures along the afferent somatosensory pathways. The dorsal column-lemniseal system is the major substrate of the somatosensory evoked potential (SEP), although other nonlcmniscal systems, such as the dorsal spinocerebellar tract, have been shown to contribute to SEP generation. In clinical practice, SEPs usually arc elicited by stimulation of the median nerve at the wrist, the common peroneal nerve at the knee, or the posterior tibial nerve at the ankle.

Normal Median Nerve Somatosensory Evoked Potentials

Figure 36A.25 shows a normal SEP elicited by median nerve stimulation. The accompanying diagram indicates presumed generator sources for the various components of

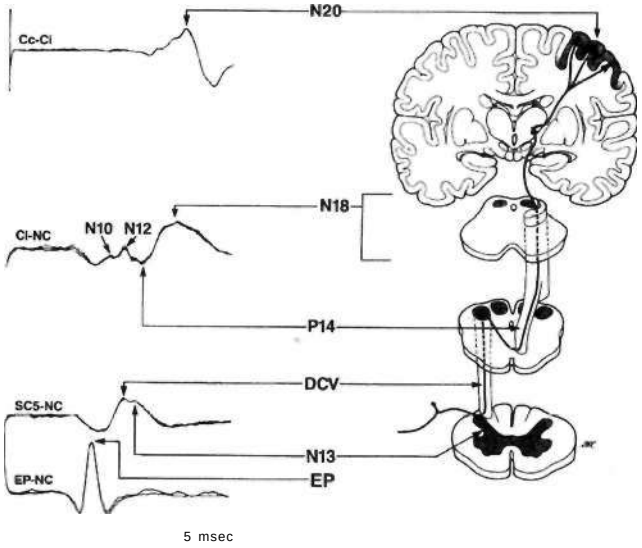


FIGURE 36A.25 Presumed generator sources of median nerve somatosensory evoked potential. Cc and Ci are central-parietal scalp locations contralateral (Cc) and ipsilateral (Ci) to the stimulated nerve. They are 2 cm posterior to the C3 and C4 placements of the International Ten-Twenty System. EP and SOS are electrodes located over Erb's point and the spinous process of the fifth cervical vertebra, respectively. NC is a noncephalic (such as elbow) reference.

rhe SEP. An electrode at Erb's point ipsilateral to the stimulated arm registers the afferent volley as it passes through the brachial plexus. The Erb's point potential serves as a reference point against which the latencies of subsequent components are measured. Electrodes ovet the midcervical dorsal spine record two independent but partially overlapping waveforms that reflect local activity in the spinal cord. The first of these, designated DCV (dorsal column volley), is the afferent volley in the cuneate tract. The second, N13, represents postsynaptic activity in the central gray matter of the cervical cord generated by input from axon collaterals off the primary large-fiber affcrents. Nl.i is accompanied by a simultaneous potential of opposite polarity (PI3) over the anterior neck. Lesions such as syringomyelia, which disrupt the central gray matter, may selectively affect the N13/P13.

SEP components generated in the brainstem are best recorded by an electrode placed on the scalp away from the primary sensory area. This electrode "sees" subcortical activity that is volume conducted to the scalp surface. The P14 wave is generated in the cervicomcdnllaiy region, probably by the caudal medial lemniscus. This is followed by a long-duration negative wave, N18, whose origin is uncertain but probably includes postsynaptic activity from multiple generators in the brainstem. Figure 36A.26 illustrates preservation of the P14 but loss of the N18 and all later waves in a patient with an arteriovenous malformation of the right pons. This is probably the electrophysiological equivalent of functional transection of the medial lemniscus at a pontine level.

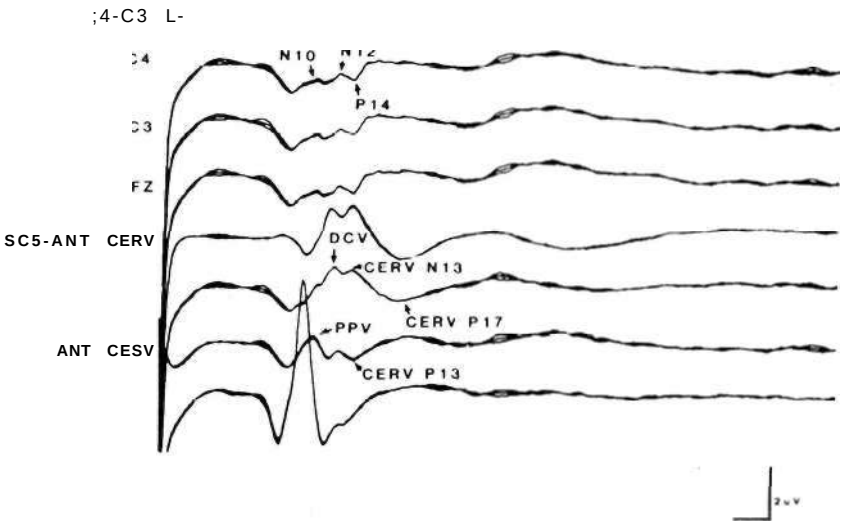


FIGURE 36A.26 Left median nerve somatosensory evoked potentials in a patient with a right pontine arteriovenous malformation. All components after P14 (cervicomedullary potential) arc absent. Unless otherwise labeled, a right elbow reference was used.

The initial cortical response to the afferent sensory volley is designated N20 and is best recorded by a scalp electrode placed directly over the primary sensory cortex contralateral to the stimulated side. The N20 is also a composite waveform made up of signals from mulriple generators within or close to the primary cortical receiving area. This can be demonstrated by selective stimulation of cutaneous and muscle spindle afferent fibets in the median nerve, which are known to project to adjacent but distinct cottical regions, or by observation of state-dependent changes in the N20 (Figure 36A.27). Sleep, for example, attenuates small inflections that are often present on the waking N20, a phenomenon probably caused by downward modulation of some genetators contributing to N20 and to alterations in thalamic input to cortex during sleep.

Normal Posterior Tibia! Nerve Somatosensory Evoked Potentials

In many ways, SEl's to posterior tibial nerve stimulation are analogous to median nerve SEPs, When the posterior tibial nerve is stimulated, tecordings from electrodes over the lumbar spine show two distinct potentials (Figure 36A.28). One (PV) is produced by the afferent volley in the lumbar nerve roots and gracile tract, and the other (N22) is a SLimmated synaptic potential generated in the gray matter of the lumbar cord. Because of its stability, fixed latency, and high voltage, the N22 lumbar potential is used clinically as a reference point against which latencies of subsequent components are measured. Additionally, determination of the spinal level where N22 voltage is maximal

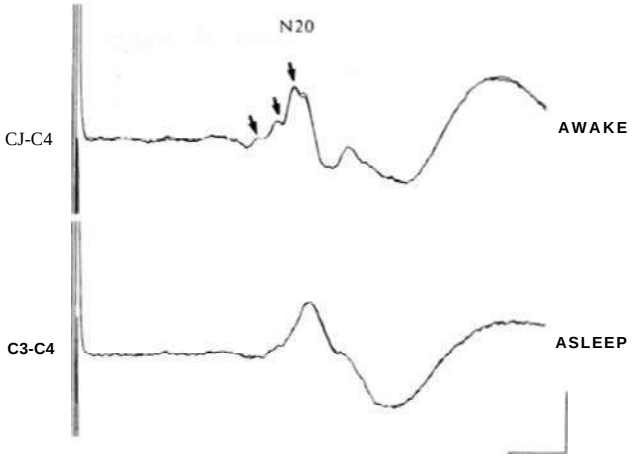


FIGURE 36A.27 Right median nerve somatosensory evoked potentials recorded in a normal subject awake and asleep after sedation with diazepam. Note the state-dependent change in morphology of the N20. Multiple small inflections present on the rising limb of N20 during wakefulness disappear during sleep.

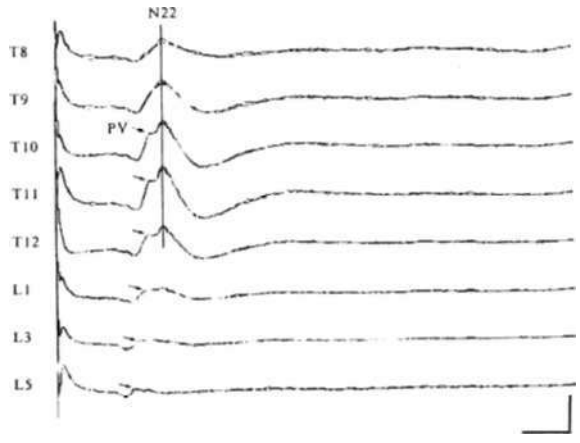


FIGURE 36A.28 Recordings over the lumbar and lower thoracic spine after posterior tibial nerve stimulation. Recording electrodes are referenced to the iliac crest. Note the increasing latency of the propagated volley (PV) and the appearance at T12 of a second, stationary potential (N22). See text for details.

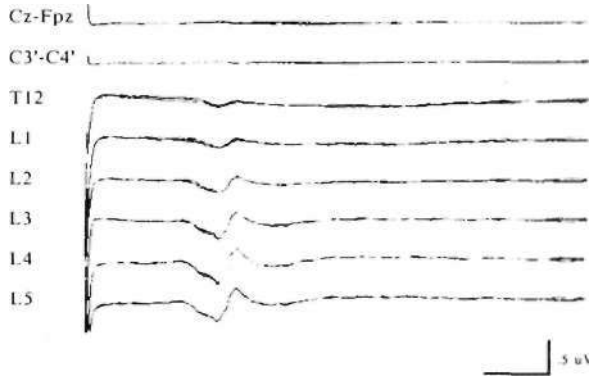


FIGURE 36A.29 Posterior tibial nerve somatosensory evoked potentials in a patient with a tethered spinal cord. The maximal amplitude of the lumbar potential, normally between T10 and T12, is caudally displaced. The cortical response is absent also. Unless labeled otherwise, an iliac crest reference was used.

provides an approximate indication of the position of the lumbar cord enlargement. Tins is sometimes clinically useful if there is a question of spinal cord tethering (Figure 36A.29).

Subcortical activity from posterior tibial nerve stimulation consists of a positive wave, P31, followed by a long-duration negative wave, N34 (Figure 36A.30). These components are analogous to the P14 and N1S following median nerve stimulation and probably are generated by the afferent volley in the caudal medial lemniscus and by postsynaptic activity in the rostral brainstem, respectively.

The initial cortical response to posterior tibial nerve stimulation is .1 prominent positivity (P3S) that is recorded from scalp electrodes placed at the vertex and central parasagittal regions, close to the cortical areas representing the leg (Figure 36A.30). This positive potential usually is maximal just lateral to the

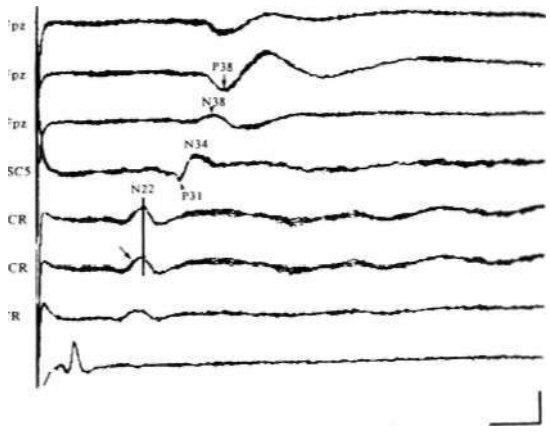


FIGURE 36A.30 Normal posterior tibial somatosensory evoked potentials. The lower channel is a bipolar recording between two electrodes over the popliteal fossa.

stimulated nerve. This apparently paradoxical localization of the P38 reflects the mesial location of the primary sensory area for the leg and foot within the interhemispheric fissure.

Somatosensory Evoked Potentials in Neurological Disease

SEP abnormalities arc produced by a wide variety of conditions that disturb conduction m the somatosensory system. These include focal lesions (tumors, strokes, cervical spondylosis) and diseases that affect the nervous system more diffusely (hereditary ataxias, subacute combined degeneration, vitamin E deficiency). Ninety percent of patients with definite multiple sclerosis have either upper- or lower-limb SEP abnormalities. Furthermore, an abnormal SEP is found in 50-60% of patients with multiple sclerosis even in the absence of symptoms or signs referable to the large-fiber sensory system. Other diseases that affect myelin, such as Pelizaeus-Merzbacher disease, metachromatic leukodystrophy, ad re no leukodystrophy, and adrenomyeloncLiropathy, also produce SEP abnormalities. In cases of adrenoleukodystrophy and adrcnomycloncuropathy, SEP abnormalities can be demonstrated in heterozygotes.

Many lesions alter the SEP by producing a conduction delay or block. This results in prolonged interpeak latencies or attenuation or even loss of one or more SEP components. Abnormally large SEPs, involving exaggeration of cortical components occurring after N20 (median nerve), are characteristic of patients with progressive myoclonus epilepsy, some patients with photosensitive epilepsy, and children with late infantile ceroid lipofuscinosis (Figure 36A.31) (Emerson, 2003).

Motor Evoked Potentials and Magnetic Coil Stimulation

It is possible to assess the functional integrity of the descending motor pathways using motor evoked potentials (MEPs). MEP studies generally entail stimulating the motor cortex and recording the evoked compound motor action potential over appropriate target muscles. The motor cortex may be stimulated either by directly passing a brief, high-voltage electrical pulse through the scalp or by using a time-varying magnetic field to induce an electrical current in the brain.

Whereas transcranial electrical stimulation is painful, magnetic coil stimulation is essentially painless. Therefore, whereas transcranial electrical stimulation is used for intraoperative motor system monitoring in anesthetized patients, magnetic stimulation generally is used in studies of waking subjects and patients.

Direct electrical stimulation of the motor cortex produces a series of signals that are recordable from the pyramidal tract. The earliest wave, the D (direct) wave, results from direct activation of the pyramidal axons. Subsequent

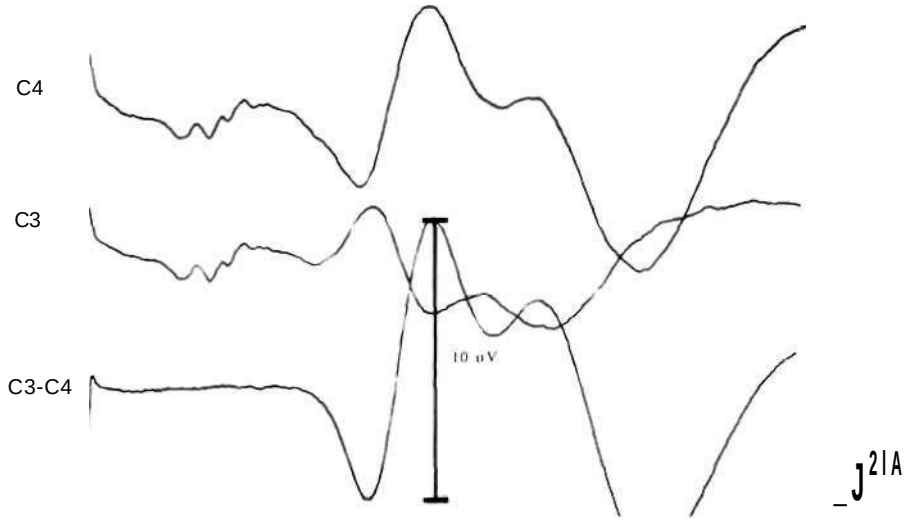


FIGURE 36A.31 Recording from central-parietal scalp electrodes after median nerve stimulation in a patient with cortical myoclonus. Marked exaggeration of later cortical components exists. A noncephalk reference was used in the upper two tracings.

signals, the I (indirect) waves, are thought to reflect indirect trans-synaptic activation of pyramidal cells. Transcranial electrical stimulation is capable of eliciting both D and I waves, but transcranial magnetic stimulation generally elicits only I waves. For this reason, MEPs evoked by transctanial magnetic stimulation occur at slightly greater latency and are less stable than those evoked by trans-cranial electrical stimulation.

It is possible to measure the central motor conduction time by subtracting the latency of the MEP elicited by cervical or lumbar stimulation from that obtained by transcranial stimulation. For MEPs elicited by transcranial magnetic stimulation, this interval encompasses the time needed for activation of cortical interneurons, trans-synaptic activation of pyramidal neurons, conduction of the efferent volley through the pyramidal tract, and depolarization of the spinal motor neuron.

Although the clinical utility of MEPs is not fully defined, they provide information about motor pathways that complements data about sensory pathways obtained from SEPs. MEPs often are abnormal in patients with mye-lopathies caused by cervical spondylosis (Figure 36A.32), where they appear to be sensitive to eatly, preclinical spinal cord compression. They are often delayed in parients with multiple sclerosis and may he more sensitive to demyelinat-ing lesions than VEPs or SEPs. In motor neuron disease, pyramidal tract conduction delays can be demonstrated in patients without upper motor neuron signs.

MEPs also offer insights into the pathophysiology and evolution of disorders affecting the motor system. Patients with cerebral palsy may demonstrate enhanced MEPs in some muscle groups because of aberrant corticospinal projections. In Parkinson's disease, MEP latencies are normal, but their amplitudes may be elevated, possibly because of spinal disinhibition or corticomotoneuronal hyperexcitability. MEPs have been used to study brain plasticiry and to document cortical reorganization after spinal cord injury and amputation.

Transcranial magnetic coil stimulation provides a means to study normal cortical physiology by transiently inter-rupting the regional function. Disruption of cortical processing produced by single or repetitive magnetic stimuli has been used to study not only the function of motor system but also cortical somatosensory, visual, and language processing function. Finally, potential therapeutic uses for transcranial magnetic stimulation in parkinsonism,

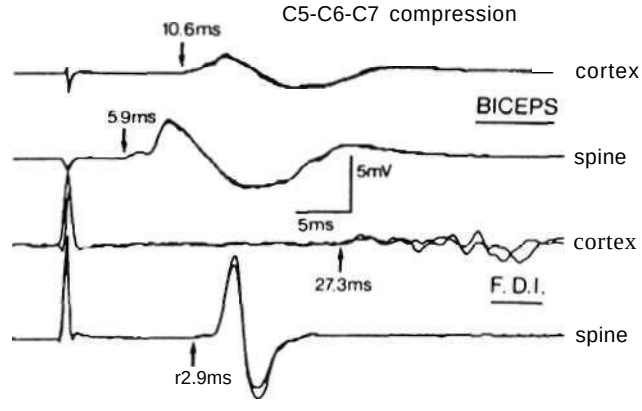


FIGURE 36A.32 Motor evoked potentials (MEPs) recorded from biceps and first dorsal interosseous (FDI) muscles in a patient with cervical spondylosis producing C5-C7 spinal cord compression. MEPs recorded from biceps are normal after magnetic stimulation over both motor cortex and cervical spine. MEPs recorded from FDI are normal after stimulation over the cervical spine but are of abnormally low voltage and polyphasic after cortical stimulation. (Reprinted with permission from Macrtens de Noordhout, A., Remade, J. M., Pepin, J. L., et al. 1991, "Magnetic stimulation of the motor cortex in cervical spondylosis," *Neurology,* vol. 41, p. 75-80.)

dystonia, and depression have been proposed (Cracco and Cracco 1999; Hallett 2000; Mills 1999).

Intraoperative Monitoring

Electrophysiological monitoring to assess the functional integrity of the brain and spinal cord during neurosurgical and orthopedic procedures has become routine in many centers. Such monitoring reduces neurological morbidity by detecting adverse effects at a time when prompt correction of the cause can prevent permanent neurological injury. In addition, monitoring may provide information about the mechanisms of postoperative neurological abnormalities and occasionally lead to changes in surgical approach or technique.

Monitoring can be done using EEG, sensory evoked potentials (usually BAEPs or SEPs), and MEPs. Which monitoring modality or combination of modalities is used depends on the type of surgery, the neural structures judged to be most at risk, and previous experience with complications of the particular surgical procedure. Because neurological injury can occur suddenly and may be irreversible, the ideal monitoring method is one that detects impending, not permancnr, damage. A certain percentage of false-positive results therefore is highly desirable. Experienced monitoring teams learn that small changes in recorded signals are common during surgery because of clinical and technical factors that have negligible effects on outcome. Other variables that affect electrical signals are the type of anesthesia, temperature, blood pressure, and neuromuscular blockade. Detetmining what constitutes a significant and reproducible change that warrants alerting the surgeon or anesthesiologist is a critical aspect of monitoring.

Patients occasionally experience a new postoperative neurological abnormality despite uneventful monitoring. It is rare for a major neurological complication ro occur in a part of the nervous system that was monitored directly and accurately judged to be normal throughout the operation. More often, complications arise when structures not monitored directly arc involved (e.g., infarction of the ventral spinal cord when only dorsal column function was monitored using SEPs) or when a significant pre-existing abnormality masks even moderate changes from baseline. Minor and usually transient neurological symptoms and signs (e.g., sensory dysesthesias, mild weakness, temporary neurogenic bladder) occur occasionally with stable intraoperative electrophysiological measures.

Klectrucneephalographic monitoring lias been used extensively in patients undergoing carotid endarterectomy, during embolization of arteriovenous malformations, and for clipping or removal of some aneurysms. Computer-assisted methods are used commonly to process primary Electroencephalographic data to compress what is otherwise an unmanageable amount of information and to present the data in a more easily interpretable manner. Monitoring is especially helpful in selecting patients for shunting during occlusion of the carotid artery. With monitoring, overall intraoperative major morbidity for endarterectomy can be as low as 1%.

Monitoring auditory nerve function using BAEPs, with or without electrocochleography, is useful in any neurosurgical or neuro-otological procedure that risks injury to the eighth cranial nerve. Risk of hearing loss is minimized in patients with small, especially intracanalicular, acoustic neurinomas and other cerebellopontine angle tumors, and in patients undergoing microvascular decompression for hemifacial spasm or trigeminal neuralgia. Monitoring facial nerve function by recording compound nerve or muscle action potentials after direct stimulation of the intracranial portion of the seventh nerve has greatly reduced the incidence of permanent facial palsy after cerebellopontine angle sutgety.

SEPs are used routinely to monitor baseline and spinal cord function during neurosurgical and orthopedic procedures. They provide useful and sensitive feedback information about the integrity of the dotsal column somatosensory system. MEPs are particularly sensitive to the effects of spinal cord ischemia, compression, distraction, and blunt trauma and are used also to monitor spinal cord function during surgical procedures. They complement SEPs because SEPs may not detect surgical injuries that are limited to the lateral and anterior spinal cord (Emerson and Adams 1999).

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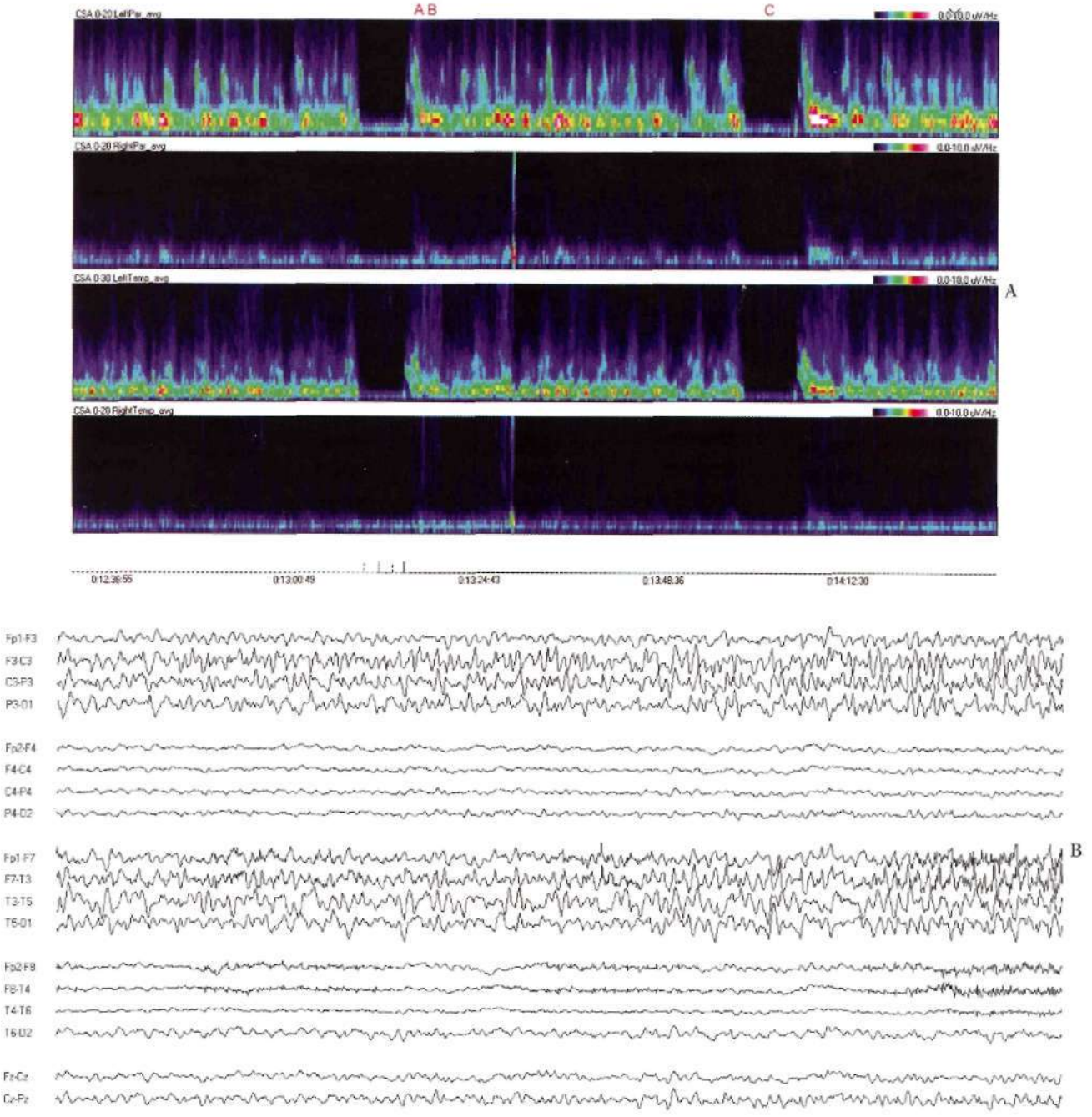

PLATE 36A.I Frequency spectrograph depicting 2 hours of electroencephalographic (EEG) recordings from a patient in focal status epilepticus. (A) The upper two panels show activity in right and left parasagittal electrode derivations, respectively; the lower two panels depict activity in temporal derivations. Time is represented on the horizontal axis. The vertical axis on each panel corresponds to frequency, from 1 Hz on the bottom to 20 Hz at the top. The colors indicate EEG voltage at a given frequency; from black for 0 μV/Hz to purple for 10 μV/Hz. This spectrograph shows bursts of high-voltage, high-frequency (*green*) activity recurring approximately every 5 to 7 minutes, most prominent in the left parasagittal panel. This EEG demonstrates a pattern of recurring electrographic seizures, as illustrated by representative EEG traces B and C, corresponding to points A and B on the spectrograph. Additionally, there are two quiescent periods with no activity (*black*) at most frequencies, corresponding to periods of postictal voltage depression, also illustrated in trace D.

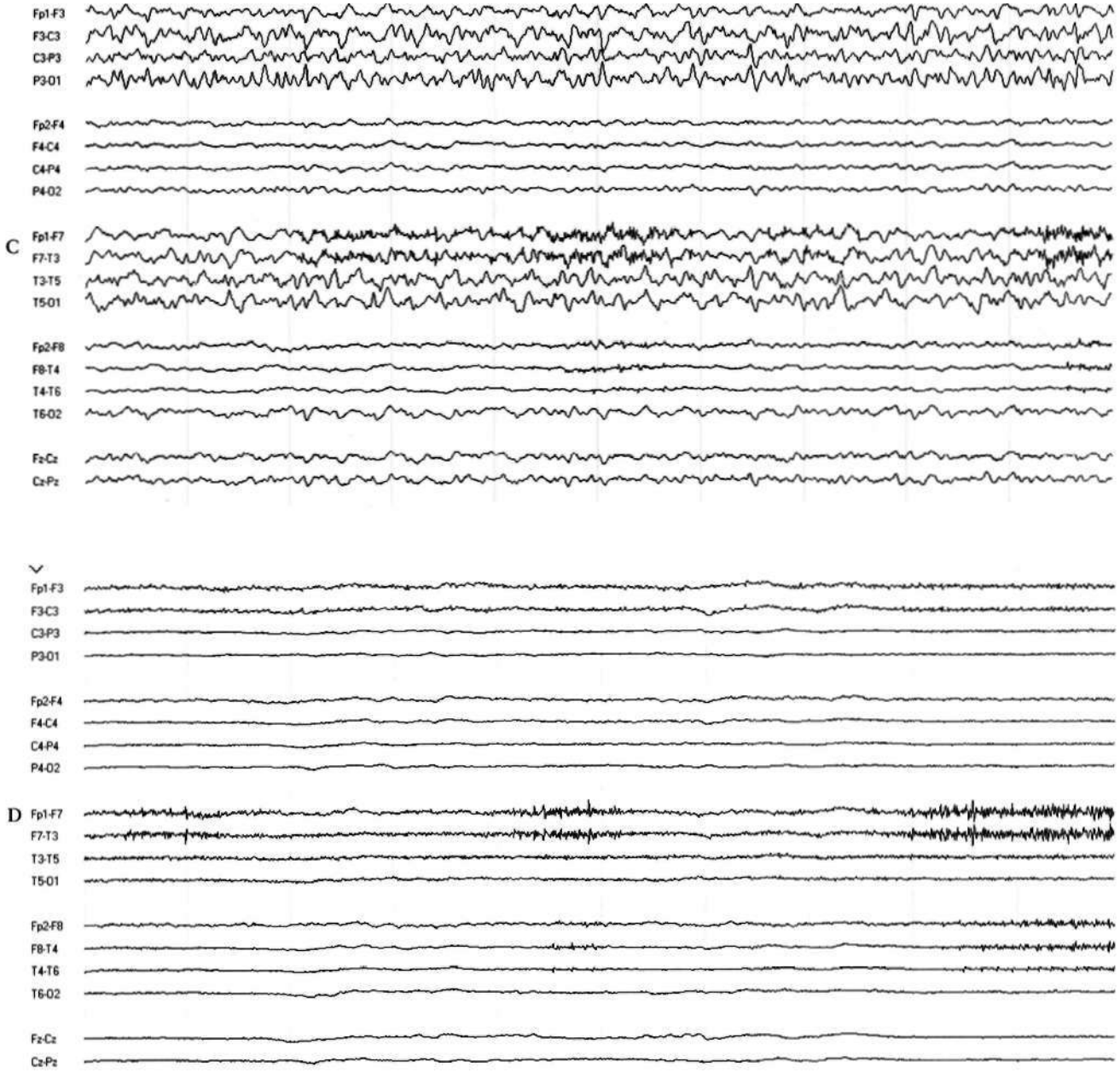

PLATE 36A.I, cont'd

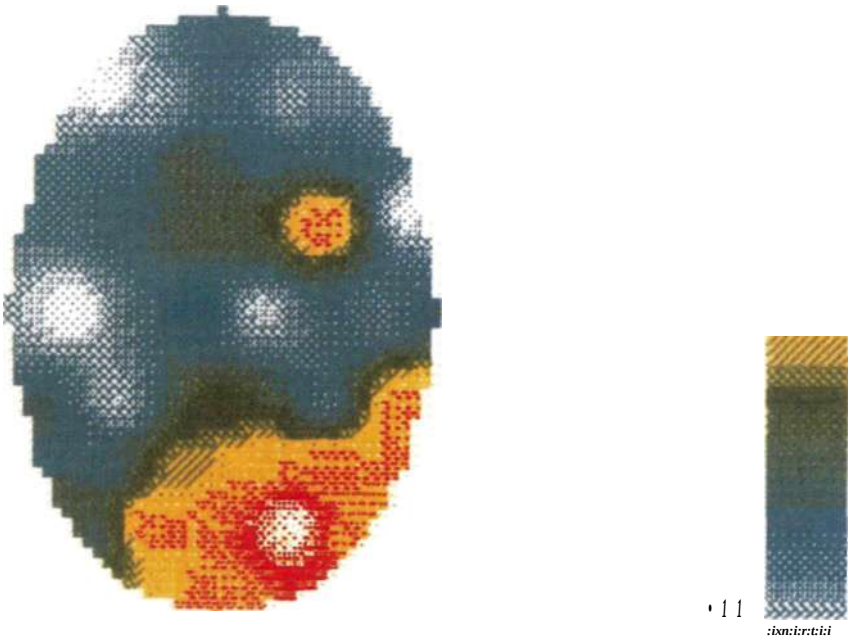

PLATE 36A.II Frequency domain topographic brain map obtained from a 32-channel bipolar elecrroencephalographic (EEG) recording. The patient was a 53-year-old man with hemodynamically significant left carotid stenosis. This map demonstrates an asymmetry over the occipital regions during eye opening, reflecting relative failure of left hemisphere alpha activity to attenuate normally. The color scale at the right reflects percentage change in EEG activity going from the eyes-closed to eyes-open state. (Courtesy Dr. Bruce J. Fisch.)

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Chapter 36
Clinical Neurophysiology

B. CLINICAL ELECTROMYOGRAPHY

Bashar Katirji

Clinical electromyography (EMG), also called *electradtagnostic examination,* is a distinct medical discipline that plays a pivotal role in the diagnosis of neuromuscular disorders. The F.MG study should be preceded by a detailed neurological examination, although it should serve as an independent procedure to provide the referring physician with an objective assessment of the neuromuscular system.

The EMG examination is composed of two main tests: nerve conduction studies (NCSs) and needle EMG. These tests complement each other and often are necessary to make a final diagnosis. The electromyographer must first obtain a focused history and examination to design the best electrodiagnostic study (Katirji 2002). The electromyographer must know the normal nerve conduction values, normal values of motor unit action potentials (MUAPs) in different muscles, how needle EMG findings differ in different diseases, and how to differentiate between specific and nonspecific findings. Additional electrodiagnostic procedures include F waves, H reflexes, blink reflexes, repetitive nerve stimulation, and single-fiber EMG.

NERVE CONDUCTION STUDIES

Principles

Electrical stimulation of nerve fibers initiates impulses that travel along motor, sensory, or mixed nerves and evoke a compound action potential. There arc three types of NCS: motor, sensory, and mixed. Conduction characteristics of motor fibers are assessed indirectly by studying the compound muscle action potential (CMAP) recorded from the muscle; sensory fibers are assessed by analyzing the sensory nerve action potential (SNAP) recorded from the nerve. Mixed NCSs assess directly the sensory and motor fibers simultaneously by recording from mixed nerve action potential (MNAP). The use of standard NCSs allows precise lesion localization and accurate characterization of peripheral nerve function.

Stimulators

Two different kinds of surface (percutaneous) electric stimulators are used in NCSs. Constant voltage stimulators regulate voltage output so that current varies inversely with the impedance of the system including the skin and subcutaneous tissues. Constant current stimulators change voltage according to impedance so that the amount of current that reaches the nerve is specified within the limits of skin resistance. As the current flows between the cathode (negative pole) and anode (positive pole), negative charges accumulate under the cathode, depolarizing the nerve, and positive charges under the anode hyperpolarize the nerve. In bipolar stimulation, both electrodes are placed over the nerve trunk, with the cathode closer to the recording site. If the cathode and anode of the stimulator are inadvertently reversed, anodal conduction block of the propagated impulse may occur. This is caused by hyperpolarization at the anode, which may prevent the nerve

impulse evoked by the depolarization occurring under the cathode from proceeding past the anode,

Supramaximal stimulation of a nerve that results in depolarization of all available axons is a paramount prerequisite to all NCS measurements. To achieve supramaximal stimulation, current (or voltage) intensity is slowly increased until it reaches a level at which the recorded potential docs not increase. Then, the current should be increased an additional 20-30% to ensure that the potential does not change further.

Recording Electrodes

Surface electrodes are used for recording the CMAP, SNAP, or MNAP. The advantages of surface recording are that these evoked responses are reproducible and change only slightly with the position of the electrodes in relation to the recording muscle or nerve. In contrast, needle electrode recording registers only a small portion of the muscle or nerve action potentials, but with less interference from neighboring discharges. Needle recordings improve the recording from small atrophic muscles or a proximal muscle not excitable in isolation. Ring electrodes are convenient to record the antidromic sensory potentials from digital nerves over the proximal and distal interphalangeal joints.

Recording Procedure

A pre-pulse preceding the stimulus triggers the sweep on a storage oscilloscope. The amplifier sensitivity determines the size (amplitude) of the potential. Overamplification truncates the response, and underamplification prevents accurate measurements of the takeoff from baseline. Digital averaging is a major improvement in recording low-amplitude responses. Signals time-locked to the stimulus summate at a constant latency and appear as an evoked potential, distinct from the background noise. The signal-to-noise ratio increases in proportion to the square root of the trial number. For example, four trials give twice as big a response as a single stimulus, and nine trials give three times the amplitude. Modern instruments digitally indicate the latency and amplitude when the desired spot on the waveform is marked.

Motor NCSs

Motor NCSs are performed by stimulating a motor or mixed peripheral nerve while recording the CMAP from a muscle innervated by that nerve. A pair of recording electrodes consists of an active lead (Gl) placed on the belly of the muscle and an indifferent lead (G2) on the tendon (belly-tendon recording). The propagating muscle action potential, originating under Gl located near the motor point, gives rise to a simple biphasic waveform with initial negativity. Initial positiviry suggests incorrect positioning of the active electrode or a volume-conducted potential from distant muscles activated by anomalous innervation or by accidental spread of stimulation to other nerves.

The nerve is stimulated at two or more points along its course. Typically, it is stimulated distally near the recording electrode and more proximally to evaluate its proximal segment. Several measurements are evaluated with motor NCSs (Figure 36B.1):

CMAP amplitude. This is usually measured from baseline to negative pink and expressed in millivolts, When recorded with surface electrodes, CMAP amplitude is a semiquantitative measure of the number of axons conducting between the stimulating and the recording points. CMAP amplitude also depends on the relative conduction speed of the axons, the integrity of the neuromuscular junctions, and the number of muscle fibers that are able to generate action potentials.

CMAP duration. This is usually measured as the duration of the negative phase of the evoked potential and is expressed in milliseconds. It is a function of the conduction rates of the various axons forming the examined nerve and the distance between the stimulation and recording electrodes. **The** CMAP generated from proximal stimulation has a longer duration and a lower amplitude than **that** obtained from distal stimulation.

CMAP area. This is usually limited to the negative phase area under the waveform and shows linear correlation with the product of the amplitude and duration. It is measured in millivolts per millisecond and requires electronic integration using computerized equipment. The ability to measure CMAP area has replaced the need to measure its duration.

Latencies. This is the time interval between nerve stimulation (shock artifact) and the onset of the CMAP. It is expressed in milliseconds and reflects the conduction rate of the fastest-conducting axon. Whenever it is technically possible, the nerve is typically stimulated at two points: a distal point near the recording site (distal latency) and a more proximal point (proximal latency). Both latencies depend mostly on the length of the nerve segment and, to a much lesser extent, on neuromuscular transmission time and propagation time along the muscle membrane.

Conduction velocity. This is a computed measurement of the speed of conduction and is expressed in meters per second. Measurement of conduction velocity allows the comparison of the speed of conduction of the fastest fibers between different nerves and subjects, irrespective of the length of

the nerve. It is calculated after the length of the nerve segment is incorporated between distal and proximal stimulation sites. The nerve length is estimated by measuring the surface distance along the course of the nerve and should be more than 10 cm to improve the accuracy of surface measurement.

$$\text{Motor conduction velocity} = \frac{\text{Distance}}{\text{Proximal latency} - \text{Distal latency}}$$

As with latencies, motor conduction velocity measures the speed of conduction of the fastest axon. However, in contrast to motor latencies, motor nerve conduction velocity is a pure nerve conduction time because neuromuscular transmission time and muscle fiber propagation time are common to both stimulation sites, and the latency difference between two points is the time for the nerve impulse to travel from one stimulus point to the other.

Sensory NCSs

Sensory axons are evaluated by stimulating a nerve while recording the transmitted potential from the same nerve at a different site. Therefore, SNAPs arc true nerve action potentials. Antidromic sensory NCSs are performed by recording potentials directed toward the sensory receptors, whereas orthodromic studies arc obtained by recording potentials directed away from these receptors. Sensory latencies and conduction velocities are identical with either method, but SNAP amplitudes generally are higher in antidromic studies. Because the thresholds of some motor axons are similar to those of large myelinated sensory axons, superimposition of action potentials from distal muscles may obscure antidromically recorded SNAPs. Fortunately, latencies can still be measured accurately because the large-diameter sensory fibers conduct 5-10% faster than motor fibers. This relationship may change in disease states that selectively affect different fibers.

SNAPs may be obtained by stimulating and recording a pure sensory nerve (such as the sural and radial sensory nerves), stimulating a mixed nerve while recording distally over a cutaneous branch (such as the antidromic median and ulnar sensory responses), or stimulating a distal cutaneous branch while recording over a proximal mixed nerve (such as the orthodromic median and ulnar sensory-studies). Similar ro their motor counterparts, several measurements are recorded with sensory NCS (Figure 36B.2):

SNAP amplitude. This is a semiquantitative measure of the number of sensory axons that conduct between the stimulation and recording sites. It is calculated from the baseline to negative peak or from negative peak to positive peak and expressed in microvolts.

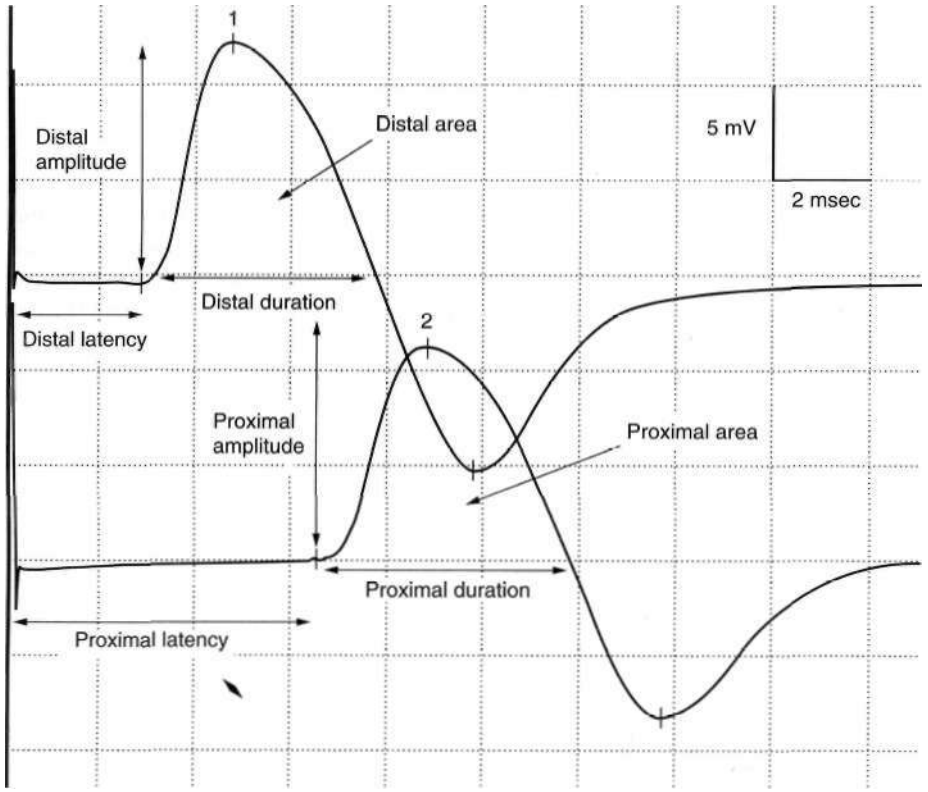


FIGURE 36B.1 Motor nerve conduction study of the median nerve showing a typical compound muscle action potential (CMAP) with distal and proximal stimulations, showing the distal and proximal latencies and CMAP amplitudes, durations, and areas. The proximal CMAP has a lower amplitude (12.6 mV vs. 11.3 mV) and atea (37.3 mV/ms vs. 34.50 mV/ms) than the distal CMAP because of tempotal dispersion and phase cancellation.

SNAP duration and area may be measured but are not useful because of significant temporal dispersion and phase cancellation.

Latencies. With sensory NCSs, often only a single distal site is stimulated. Sensory distal latencies may be measured (in milliseconds) from the stimulus artifact to the peak of the negative phase (peak latency) or from the stimulus artifact to the onset of the SNAP (onset latency). Onset latency may be obscured by a large shock artifact, a noisy background, or a wavy baseline. Although peak latency does not reflect the fastest-conducting sensory fibers, it is easily defined and more precise than onset latency.

Conduction velocity. This requires stimulation at a single site only because the latency consists of only the nerve conduction time from the stimulus point to the recording electrode. It may be also done with distal and proximal stimulation sites. Sensory conduction velocities are calculated similarly to their motor counterparts; only onset latencies (not peak latencies) are used to calculate the speed of the fastest conducting fibers.

$$\text{Sensory conduction velocity} = \frac{\text{Distance}}{\text{Proximal onset latency} - \text{Distal onset latency}}$$

$$\text{Sensory conduction velocity} = \frac{\text{Distance}}{\text{Onset latency}}$$

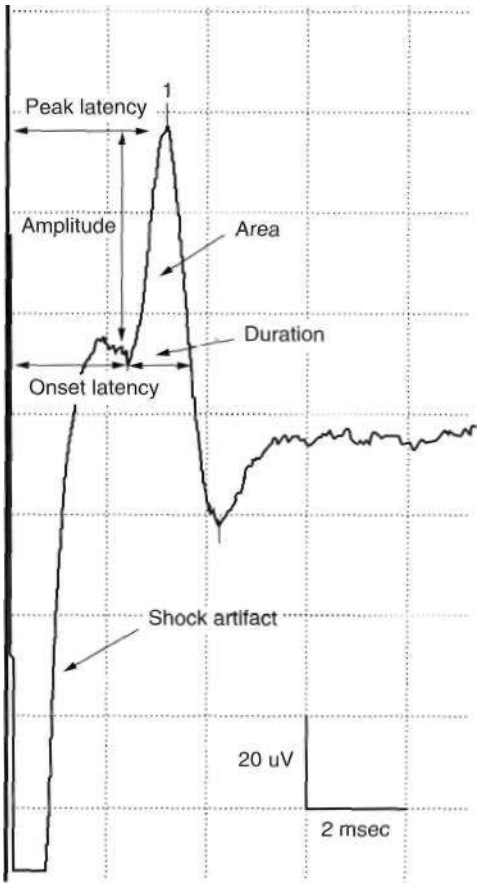


FIGURE 36B.2 Antidromic median sensory nerve conduction study after stimulation at the wrist, revealing peak and onset latencies and sensory nerve action potential amplitude, duration, and area. The shock artifact interferes with the accurate determination of onset latency, whereas peak latency is easily-determined.

Mixed NCSs

Mixed NCSs are performed by stimulating and recording from nerve trunks with sensory and motor axons. Often, these tests are done by stimulating a nerve trunk distally and recording more proximally because the reverse is often contaminated by large CMAPs that obscure the lower-amplitude MNAPs. When the nerve is deep (as at the elbow or knee), the MNAP may be very low in amplitude ot unelicitable because tissue interposes between the nerve and recording electrode. Therefore, these studies are limited to evaluating mixed nerves in distal nerve segments, such as in the hand or foot during the evaluation of carpal tunnel syndrome and tarsal tunnel syndrome, respectively.

Segmental Stimulation in Short Increments

Routine NCSs are sufficient to localize the site of involvement in entrapment neuropathies. However, during the evaluation of a focal demyelinating lesion, inclusion of the unaffected segments in conduction velocity calculation dilutes the effect of slowing at the injured site and decreases the sensitivity of the test. Therefore, incremental stimulation across shorter segment helps localize an abnormality that might otherwise escape detection. More precise localization entails inching the stimulus in short increments along the course of the nerve. The study of short segments provides better resolution of restricted lesions. Assume a nerve impulse conducting at a rate of 1,0 cm per 0.2 millisecond (50 m per second); for a 1-cm segment there is dcmyelination that doubles the conduction time to 0.4 millisecond per cm. In a 10-cm segment, normally covered in 2.0 milliseconds, a 0.2-millisecond increase would constitute a 10% change, or approximately one standard deviation, well within the normal range of variability. However, the same 0.2-millisecond increase would represent a 100% change in latency if measured over a 1-cm segment. The large per-stcp increase in latency more than compensates for the inherent measurement error associated with stimulating multiple times in short increments.

The inching technique is particularly useful in assessing sensory conduction in patients with carpal tunnel syndrome (Kimura 1979). With stimulation of a normal median nerve in 1-cm increments across the wrist, the latency changes

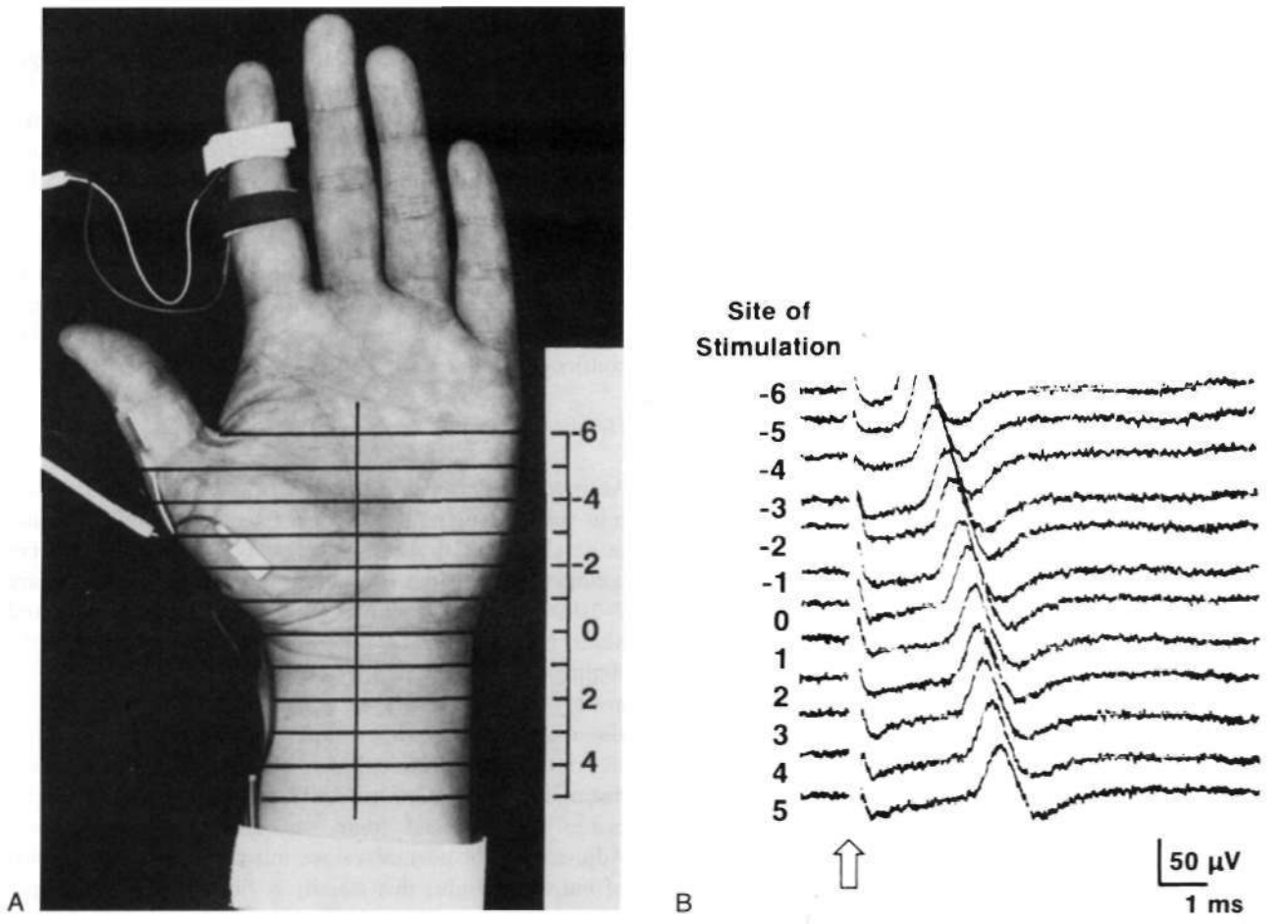


FIGURE 36B.3 (A) Twelve sites of stimulation in 1-cm increments along the length of the median nerve. The 0 level is at the distal crease of the wrist, corresponding to the origin of the transverse carpal ligament. Sensory nerve action potentials (SNAPs) and compound muscle action potentials are recorded from the second digit and abductor po I lie is brevis, respectively. (B) SNAPs in a normal subject recorded after stimulation of the median nerve at multiple points across the wrist. The site of each stimulus is indicated on the left. The latency increased linearly as the stimulus site was moved proximally in 1-cm increments. (Reprinted with permission of the author and publisher from Kimura, J. 1979, "The carpal tunnel syndrome: Localization of conduction abnormalities within the distal segment of the median nerve," Brain, vol. 102, pp. 619-635. By permission of Oxford University Press, Inc.)

approximately 0.16-0.21 millisecond per centimeter from midpalm to distal forearm (Figure 36B.3). A sharply localized latency increase across a 1-cm segment indicates a focal abnormality of the median nerve (Figure 36B.4). An abrupt change in waveform usually accompanies the latency increase across the site of compression. Segmental stimulations are useful in other focal mononeuropathies such as ulnar neuropathies at the elbow or wrisr (Campbell, Pridgeon, and Sahni 1992; Mcintosh, Preston, and Logigian 1998).

Physiological Variability and Common Sources of Error

The major pitfalls in NCSs usually result from Technical errors in the stimulating or recording systems (Kimura 1997}. They result from spread of the stimulating current to a nerve not under study; eliciting an unwanted potential from distant muscles; anomalous innervation; the effect of temporal dispersion; or errors in the measurement of nerve length and conduction time.

Temperature

Nerve impulse propagation slows by 2.4 m per second, or approximately 5% per degree centigrade from 38^{c} to 29"C of body temperature. Also, cooling results in a higher CMAP and SNAP amplitude and longer duration, probably because of accelerated and slowed Na^{+} channel inactivation (Rutkove, Kothari, and Shefner 1997). Therefore a CMAP or SNAP with high amplitude and slow distal latency or conduction velocity should raise the suspicion of a cool limb.

To reduce this type of variability, skin temperature is measured with a plate thermistor; this measurement correlates linearly with the subcutaneous and intramuscular

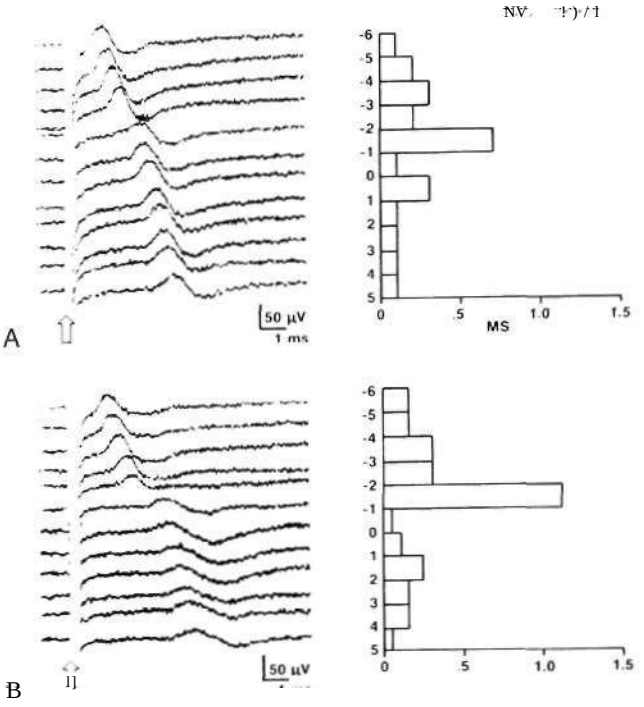


FIGURE 36B.4 Sensory nerve action potentials in a patient with the carpal tunnel syndrome. A sharply localized showing was found from -2 to -1 in both hands, representing a segmental conduction velocity of (A) 14 m per second on the left and (B) 9 m per second on the right. Note a distinct change in waveform of the sensory potential at the point of localized conduction delay. Double-humped appearance at -2 on the left suggests sparing of some sensory axons at this level. (Reprinted with permission of the author and publisher from **Kimura,** J. 1979, "The carpal tunnel syndrome: Localization of conduction abnormalities within the distal segment of the median nerve," *Brain,* vol. 102, pp. 619-635. By permission of Oxford University Press, Inc.)

temperatures. If the skin temperature falls below 33°C, it is necessary to warm the limbs by immersion in warm water. Warming packs or a hydrocollator can also be used, particularly in bedridden or intensive care units patients. Adding 5% of the calculated conduction velocity for each degree below 33°C theoretically normalizes the result. However, such conversion factors are based on experience with healthy subjects and may not apply to patients with abnormal nerves.

Age

because myelination is incomplete at birth, nerve conduction velocities are roughly one half the adult value in full-term newborns and one third that of term newborns in 23- to 24-week premature newborns. They reach adult values at 3-5 years (Thomas and Lambert I960). Motor and sensory nerve conduction velocities tend to increase slightly in the arms and decrease in the legs during childhood up to 19 years. With aging, conduction velocities slowly decline after 50 years of age, so that the mean conduction velocity is reduced about 10% at 60 years of age.

Aging also causes a diminution in SNAP and CMAP amplitudes, which decline slowly after the age of 60 years. This affects SNAP amplitudes more prominently, so much that normal upper limb SNAP amplitude drops up to 50% by age 70, and lower limb SNAPs in many healthy subjects above the age of 60 years are low in amplitude or unevokable. Therefore absent lower extremity SNAPs in older adults must always be interpreted with caution and are not necessarily considered abnormal without other confirmatory data.

Height and Nerve Segment Lengths

An inverse relationship between height and nerve conduction velocity suggests that longer nerves generally conduct more slowly rhan shorter nerves. For example, the nerve conduction velocities of the peroneal and tibial nerves are 7-10 m per second slower than those of the median and ulnar nerves. This cannot be explained entirely by the slightly lower temperature of the legs as compared with the arms. Possible factors to account for the length-related slowing include abrupt distal axonal tapering, progressive reduction in axonal diameter, or shorter internodal distances. For similar reasons, nerve impulses propagate faster in proximal than in distal nerve segments. Adjustments of normal values must be made for patients of extreme height; this usually is no more than 2 m per second below the lower limit of normal.

Anomalies

Two anomalous peripheral innervations are important to recognize because they have a significant effect on NCSs. These are the Martin-Gruber anastomosis and the accessory deep peroneal nerve.

In the Martin-Gruber anastomosis, anomalous fibers cross from the median to the ulnar nerve in the forearm. The communicating branches usually consist of motor axons that supply the ulnar-innervated intrinsic hand muscles, particularly the first dorsal interosseous muscle, the hypothenar muscles (abductor digiti minimi), the thenar muscles (adductor pollicis, deep head of flexor pollicis brevis), or a combination of these muscles (Gutmann 1993). Martin-Gruber anastomosis occurs in approximately 15-20% of the population and is sometimes bilateral. On **ulnar** NCS recording from the abductor digiti minimi or first dorsal interosseous, this anomaly manifests as a drop in the ulnar CMAP amplitude between distal and proximal stimulation sites (simulating the appearance of conduction block). With distal stimulation (at the wrist), the CMAP reflects all ulnar motor fibers, whereas proximal stimulation activates only the uncrossed fibers, which are fewer in number. This anomaly can be confirmed by median nerve stimulation at the elbow that evokes a small CMAP from the

abductor digiti minimi or first dorsal interosseous, which is not present on median nerve stimulation at the wrist. When anomalous fibers innervate the thenar muscles, stimulation of the median nerve at the elbow activates the nerve and the crossing ulnar fibers, resulting in a large CMAP, often with an initial positivity caused by volume conduction of action potential from the ulnar thenar muscles to the median thenar muscles. In contrast, distal median nerve stimulation evokes a smaller thenar CMAP without the positive dip because the crossed fibers are not present at the wrist. Also, the median nerve conduction velocity in the forearm is spuriously fast, particularly in the presence of carpal tunnel syndrome, because the CMAP onset represents a different population of fibers at the wrist than at the elbow. An accurate conduction velocity may be obtained by using collision studies that abolish action potentials of the crossed fibers (Kimura 1976; Sander, Quinto, and Chockroverty 1997).

The accessory deep peroneal nerve is present in 20-30% of the population. It is a branch of the superficial peroneal nerve that usually arises as a continuation of the muscular branch that innervates the peroneus longus and hrevis muscles. It passes behind the lateral malleolus and terminates in the extensor digirorum brevis on the dorsum of the foot. During peroneal motor NCS recording from the extensor digitorum hrevis, the peroneal CMAP amplitude is larger stimulating proximally than distally because the anomalous fibers arc not present at the ankle (Gutmann 1993). This anomaly can be confirmed by stimulation behind the lateral malleolus, which yields a small CMAP that approximately equals the difference between the CMAP amplitudes evoked with distal and proximal peroneal nerve stimulations.

Temporal Dispersion and Phase Cancellation

The CMAP, evoked by supramaximal stimulation, represents the summation of all individual MUAPs directed to the muscle through the stimulated nerve. Typically, as the stimulus site moves proximally, the CMAP slightly drops in amplitude and area and increases in duration. This is caused by temporal dispersion, in which the velocity of impulses in slow-conducting fibers lags increasingly behind those of fast-conducting fibers as conduction distance increases. With dispersion, there is also a slight positive and negative phase overlap and cancellation of MUAP waveforms (Figure 36B.5). The final result of temporal dispersion and phase cancellation is a reduction of CMAP amplitude and area and prolongation of its duration.

Physiological temporal dispersion affects the SNAP more than the CMAP (Figure 36B.6). This difference is related to two factors. First is the disparity between sensory fiber and motor fiber conduction velocities. The range of conduction velocities between the fastest and slowest individual human myelinated sensory axons is almost twice that of the motor

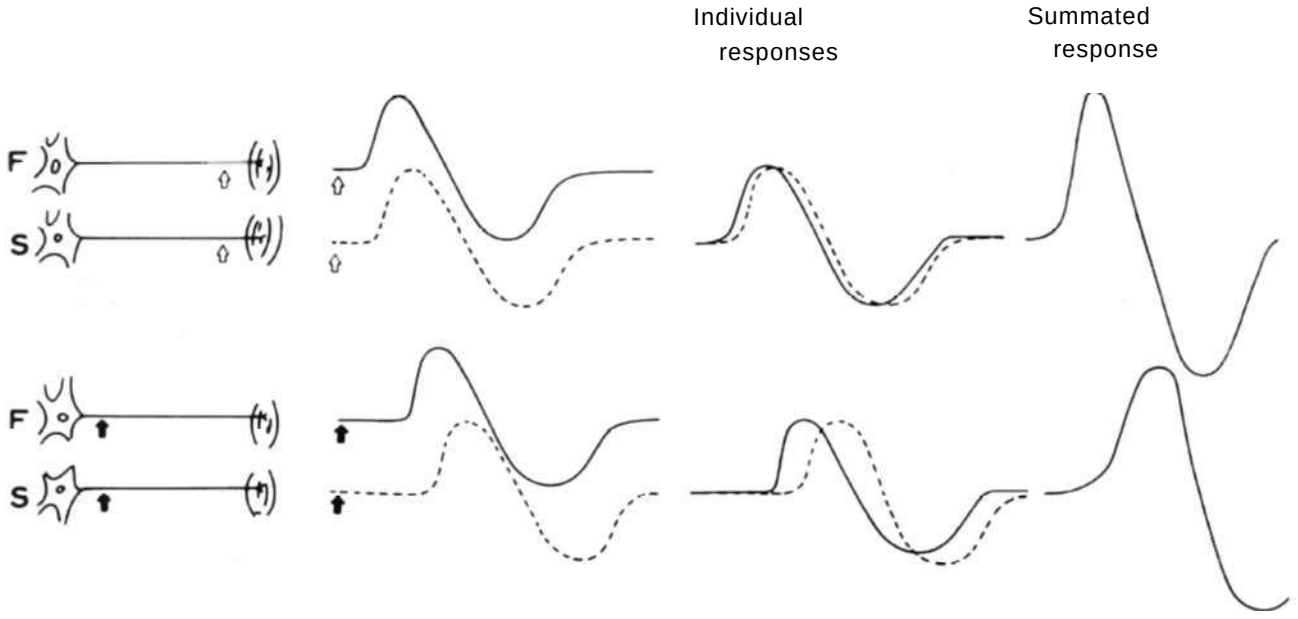


FIGURE 36B.S Compound muscle action potentials showing the relationship between fast-conducting (F) and slow-conducting (S) motor fibers. With distal stimulation, two unit discharges representing motor unit potentials sum to produce a muscle action potential twice as large. With proximal stimulation, motor unit potentials of long duration still superimpose nearly in phase despite the same latency shift of the slow motor fiber. Thus, a physiological temporal dispersion alters the size of the muscle action potential only minimally, if at all. Phase cancellation increases substantially when the latency difference between fast- and slow-conducting fibers is increased by a demyelinating neuropathy. This gives the false impression of motor conduction block, (Reprinted with permission from Kimura, J-, Machida, M., Ishida, T., et al. 1986, "Relation between size of compound sensory or muscle action potentials and length of nerve segment," *Neurology,* vol. 36, pp. *647-652.)*

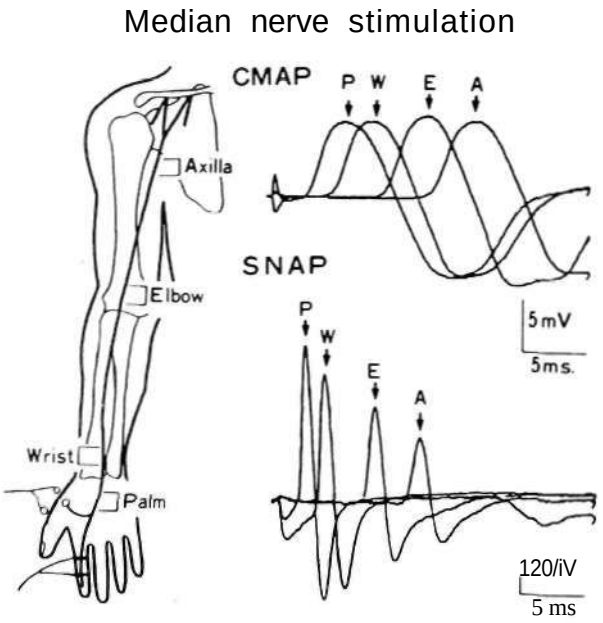


FIGURE 36B.6 Simultaneous recordings of compound muscle action potentials (CMAPs) from the thenar eminence and sensory nerve action potentials (SNAPs) from index and middle fingers after stimulation of the median nerve at palm (P), wrist (W), elbow (E), and axilla (A). With progressively more proximal stimulation, CMAPs remained nearly the same; for SNAPs, however, both amplitude and the area under the waveform became much smaller.

axons (25 m per second and 12 m per second, respectively). The second factor is the difference in duration of individual unit discharges between nerve and muscle. With short-duration biphasic sensory spikes, a slight latency difference could line up the positive peaks of the fast fibers with the negative peaks of the slow fibers and cancel both (Figure 36B.7). In longer-duration MUAPs, the same latency shift would only partially superimpose peaks of opposite polarity, and cancellation would be less of a factor.

Intertrial Variability

Principal factors contributing to an intertrial variability include errors in determining surface distance and measuring latencies and amplitudes of the recorded response. Amplitudes vary most, probably reflecting a shift in the recording site. NCSs are more reproducible when done by the same examiner, and there is a significant degree of interexaminer difference (Chaudhry et al. 1991).

Electrodiagnosis by NCS

Although it is often necessary to obtain both the NCS and needle EMG on most patients in order to make a final eleetrodiagnostic impression, certain neuromuscular diagnoses may be evident on NCSs.

Focal Nerve Lesions

Nerve fibers may be injured by a variety of mechanisms, including compression, ischemia, traction, and laceration. Anatomically, nerve lesions are classified as *neurapraxia* (first-degree injury), in which distortion of myelin occurs near the nodes of Ranvicr, producing segmental conduction block without wallerian degeneration; *axonotmesis* (second-degree injury), in which the axon is interrupted

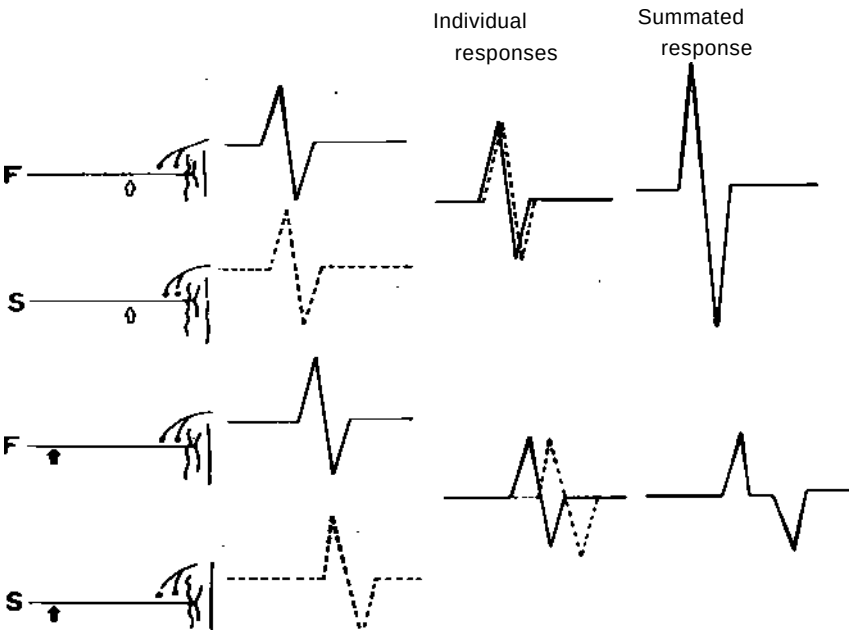


FIGURE 36B.7 Sensory nerve action potentials. A model for phase cancellation between fast-eonducting (F) and slow-conducting (S) sensory fibers. With distal stimulation, two unit discharges sum in phase to produce a sensory action potential twice as large. With proximal stimulation, a delay of the slow fiber causes phase cancellation between the negative peak of the fast fiber and positive peak of the slow fiber, resulting in a 50% reduction in *si/.e* of the summated response. (Reprinted with permission from Kimura, J., Machida, M., Ishida, T., et al. 1986, "Relation between size of compound sensory or muscle action potentials and length of nerve segment," *Neurology,* vol. 36, pp. 647-652.)

but all the supporting nerve structures remain intact; and *tieurotmesis,* in which the nerve injury is severe, resulting in complete disruption of the nerve with all the supporting structures (Seddon 1943; see Chapter *56D),* The latter category is often subdivided into three categories: a third-degree injury, in which the endoncurium is disrupted with intact pefineurium and epineurium; a fourth-degree injury, in which all neural elements are disrupted except the epineurium; and a fifth-degrec nerve injury, in which the nerve is transected, resulting in complete discontinuity of the nerve. However, the clectrodiagnostic studies alone cannot accurately distinguish between the five degrees of nerve injuries that involve axonal degeneration but can separate the first level, demyelination (ncurapraxia), from the other five levels (Wilbourn 2002).

Demyelinativc Mononeuropathy. When focal injury to myelin occurs, conduction along the affected nerve fibers may be altered. This may result in conduction slowing or block along the nerve fibers. *Conduction block* is caused by interruption of action potential transmission across the nerve lesion and is the electrophysiological correlate of ncurapraxia. It is usually the result of loss of several myelin segments (segmental or internodal demyelination). A nerve lesion manifesting with conduction block is best localized when it can be bracketed by two stimulation points, one distal to the site of injury and one proximal. In conduction block, it is characteristic to find that stimulation distal to the lesion elicits a normal CMAP, whereas proximal stimulation elicits a response with reduced amplitude (partial conduction block) or absent response (complete conduction block; Figure 36B.8A).

There are several limitations to the diagnosis of demyelinative conduction block. First, reduced CMAP size may result from phase cancellation between peaks of opposite polarity because of abnormally increased temporal dispersion. Such excessive desynchronization often develops in acquired demyelinativc neuropathies. If the distal and proximal responses have dissimilar waveforms, the discrepancy in amplitude or area between the two may represent in part a phase cancellation rather than true conduction block. Therefore, for a diagnosis of partial conduction block, there should be a significantly lower CMAP amplitude and smaller area with stimulation proximal to the injury site, when compared with the CMAP distal to it, without evidence of significant prolongation of CMAP duration. More than 50% decrement of the CMAP amplitude and area across the lesion usually is the criterion for definite conduction block. Second, distal demyelinating lesions, causing conduction block of the nerve segment between the most distal stimulating point and the recording site, manifest as unelicitable or low CMAP amplitudes at both distal and proximal stimulation sites. This finding mimics the NCSs seen with axonal degeneration. Third, the prominent temporal dispersion normally seen in evaluating SNAPs precludes the use of these potentials to diagnose conduction block. Fourth, conduction block may also follow axonal loss before the completion of wallerian degeneration.

Focal slowing of conduction usually is the result of widening of the nodes of Ranvier (paranodal demyelination). Slowing often is synchronized and affects all large myelinated fibets equally. This results in prolongation of distal latency (if the focal lesion is distal) or slowing in conduction velocity (if the focal lesion is proximal; Figure 36B.8B). However, CMAP amplitude, duration, and area are normal and do not change when the nerve is stimulated proximal to the lesion. *Desynchronized slowing {differential slowing)* occurs when conduction velocity is reduced at the lesion site along a variable number of the medium or small nerve fibers (average or slower conducting axons). Here, the CMAP is dispersed with prolonged duration on stimulations proximal to the lesion. The speed of conduction along the injury site (latency or conduction velocity) is normal because at least some of the fastest-conducting axons are spared (Figure 36B.8C). When both synchronized and desynchronized slowing coexist, the dispersed CMAP with prolonged duration is also accompanied by slowing of distal latency or conduction velocity.

Axon Loss Mononeuropathy. After acute focal axonal damage, the distal nerve segment undergoes wallerian degeneration. Characteristically, unelicitable or low CMAP amplitudes with distal and proximal stimulations are signs of complete or partial motor axonal loss lesions. The CMAP amplitudes are a reliable estimate of the amount of axonal loss except in the chronic phase, in which reinnervation via collateral sprouting often increases the CMAP and gives a misleadingly low indication of the extent of original axonal loss.

In partial axon loss lesions, distal latencies and conduction velocities are normal or borderline. Selective loss of fast-conducting fibers associated with more than a 50% reduction in mean CMAP amplitude can slow conduction velocity up to 80% of normal value because the velocity represents the remaining slow-conducting fibers. Motor conduction velocity may be slowed to 70% of normal value, with reduction of CMAP amplitude to less than 10% of normal.

Soon after axonal transaction (i.e., for the first 48 hours), the distal axon remains excitable. Therefore stimulation distal to the lesion elicits a normal CMAP, whereas proximal stimulation elicits a response with reduced amplitude (conduction block pattern; Figure 36B.8D). This has been called *axonal noncontinuity, early axon loss,* or *axon-discontinuity conduction block.* However, soon the distal axons undergo wallerian degeneration, and the distal CMAP decreases and reaches its nadir in *5-6* days; the distal SNAP lags slightly behind and reaches its nadir in 10-11 days (Figure 36B.9). The difference between the decline of the SNAP and CMAP amplitudes after axon loss nerve lesions probably is related to neuromuscular

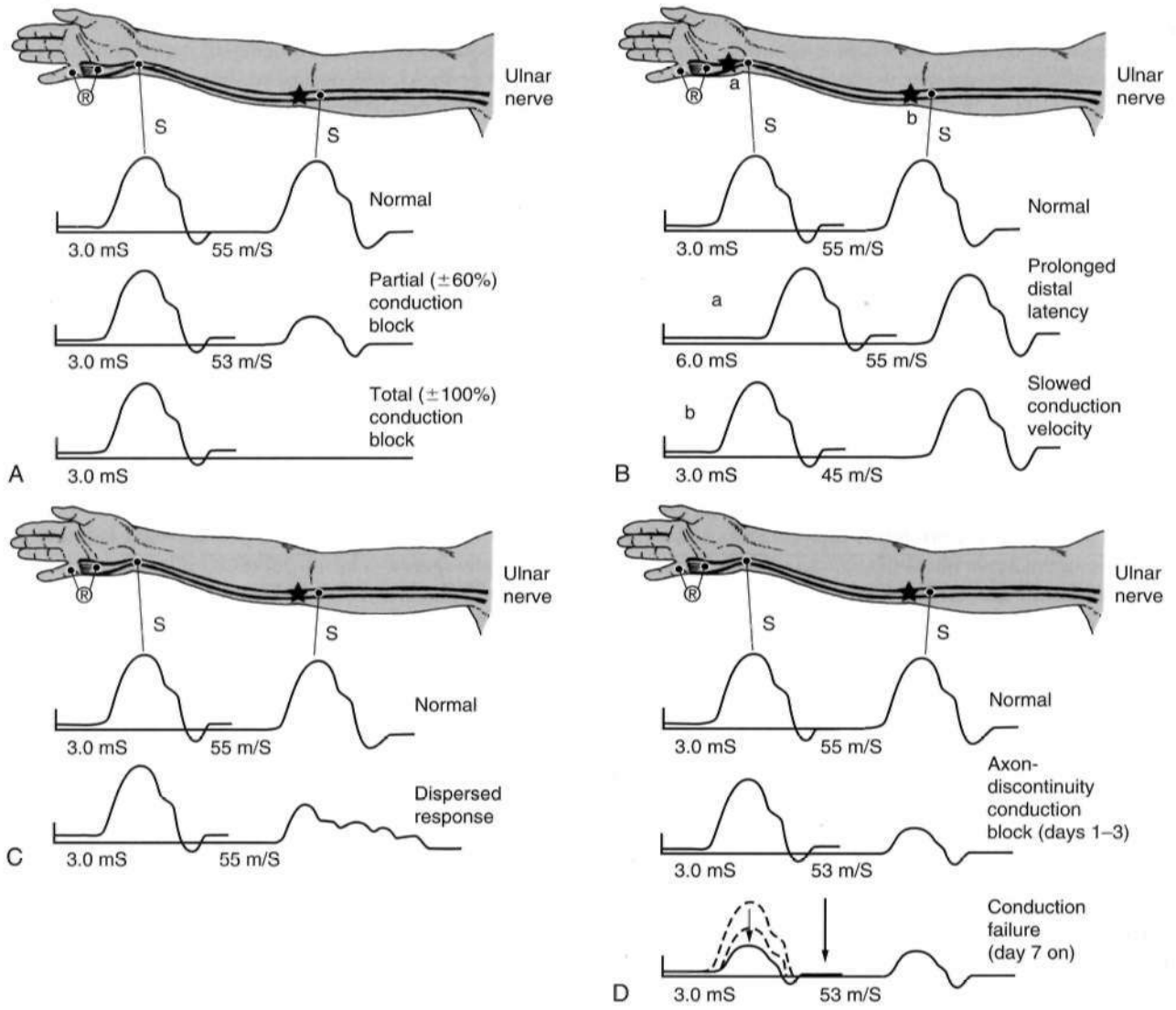


FIGURE 36B.8 Nerve conduction studies. (A) Demyelinative conduction block. (B) Focal synchronized slowing. (C) Focal desynchronized slowing (dispersion). (D) Axon loss. R = recording; S = stimulation. (Reprinted with permission from Wilbourn, A. J. 2002, "Nerve conduction studies. Types, components, abnormalities and value in localization," *Neurol Clin*, vol. 20, pp. 305-338.)

transmission failure, which affects only the CMAP amplitude. This is supported by the fact that mixed nerve action potentials, recorded directly from nerve trunks, follow the time course of SNAPs.

To distinguish between conduction blocks caused by demyelination and those caused by axon loss, the nerve is stimulated beiow the lesion after 11 days, when tJL^aiLTJiiiiL; axons would have lost their excitability. A reduced amplitude of the evoked potential from stimulation above and below the lesion indicates axonal loss (Figure 36B.8D). In contrast, if the distally evoked CMAP still has higher amplitude than the proximally elicited response, this indicates partial segmental demyelination.

The identification of conduction block in the early days of axonal loss is extremely helpful in localizing a peripheral nerve injury, particularly the closed type, in which the exact site of lesion is not apparent. Awaiting the completion of wallerian degeneration results in diffusely low or unevok able CMAPs (regardless of stimulation site), which does not allow accurate localization of the injury site. Needle EMG is useful, but localization by this method is suboptimal because peripheral nerves may not have motor branches from long segments (such as the median and ulnar nerves in the arms),

Preganglionic (Intraspinal Canal) Lesions. Damage to the sensory axons in the nerve roots located proximal to the dorsal root ganglion does not affect the SNAP amplitude because the peripheral sensory axons originating from the unipolar dorsal root ganglion neurons remain intact. Because the dorsal root ganglia usually are located outside

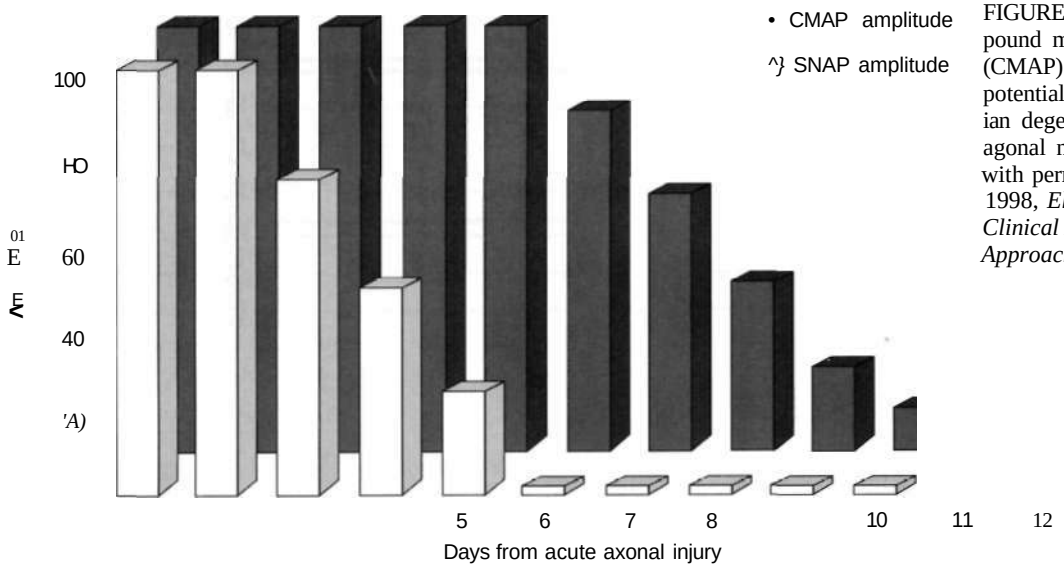


FIGURE 36B.9 Distal compound muscle action potential (CMAP) atid sensory nerve action potential (SNAP) during wallerian degeneration after an acute agonal nerve injury. (Reprinted with permission from Katirji, B. 1998, *Electromyography in Clinical Practice: A Case Study Approach*, Mosby, St Louis.)

the spinal canal and within the intervertebral foramina, axon loss intraspinal canal lesions (such as radiculopathies or root avulsions) have no effect on SNAP amplitudes. However, these nerve root lesions often result in motor axon degeneration as reflected by abnormal needle EMG and, when severe, by low-amplitude CMAP. In contrast to intraspinal canal lesions, axon loss extraspinal lesions (such as plexopathies) affect the CMAP as well as the SNAP amplitudes when mi\ed nerves undergo walk-nan degeneration.

Generalized Neuropathies

NCSs are essential in diagnosing peripheral polyneuropathies. They are very useful in confirming the diagnosis and establishing the types of fibers affected (large fiber sensory, motor, or both). Most importantly, NCSs often can identify the primary pathological process of the various polyneuropathies: axonal loss or segmental demyelination.

Demyelinating Polyneuropathies. The hallmark of demyelinating polyneuropathies is a widespread increase in conduction time caused by impaired saltatory conduction. Therefore, the NCSs are characterized by significant slowing of conduction velocities (<75% of lower limit of normal) and distal latencies (>130% of upper limit of normal).

With distal stimulation, the CMAP amplitude is mildly or moderately reduced because of abnormal temporal dispersion and phase cancellation, and the distal latency is delayed by demyelination. With more proximal stimulation, the CMAP amplitude is lower because of temporal dispersion and conduction block along some fibers. The proximal conduction velocity is markedly slowed because of increased probability for the nerve action potentials to pass through demyelinated segments (Figure 36B.10C).

Chronic demyelinating polyneuropathies may be further distinguished by NCSs into inherited and acquired polyneuropathies. Inherited demyelinaring polyneuropathies such as Charcot-Marie-Tooth disease type I are characterized by uniform slowing without conduction blocks, and the abnormalities usually are symmetrical. In contrast, acquired demyelinating polyneuropathies, such as chronic inflammatory demyelinating polyneuropathy, often have asymmetrical nerve conductions, even when there is no apparent clinical asymmetry. In addition, multifocal conduction blocks and excessive temporal dispersions at nonentrapment sites are characteristic of acquired demyelinating polyneuropathies.

Axonal Polyneuropathies. Axonal polyneuropathies produce length-dependent dicback degeneration of axons. The major change on NCS is a decrease of the CMAP and SNAP amplitudes, more marked in the lower extremities. In contrast, conduction velocities and distal latencies are normal (Figure 36B.10B). As with mononeuropathics, selective loss of many fast-conducting fibers associated with more than a 50% reduction in mean CMAP amplitude can slow conduction velocity to 70-80% of normal value.

NEEDLE ELECTROMYOGRAPHIC EXAMINATION

Principles and Techniques

The motor unit consists of a single motor neuron and all the muscle fibers it innervates. A single motor unit consists of either type I or type II muscle fibers, but never both. All muscle fibers in one motor unit discharge simultaneously when stimulated by synaptic input to the lower motor neuron or by electrical stimulation of the axon. The ratio of muscle fibers per motor neuron (motor unit or innervation ratio) is variable and ranges from 3 to I for extrinsic eye

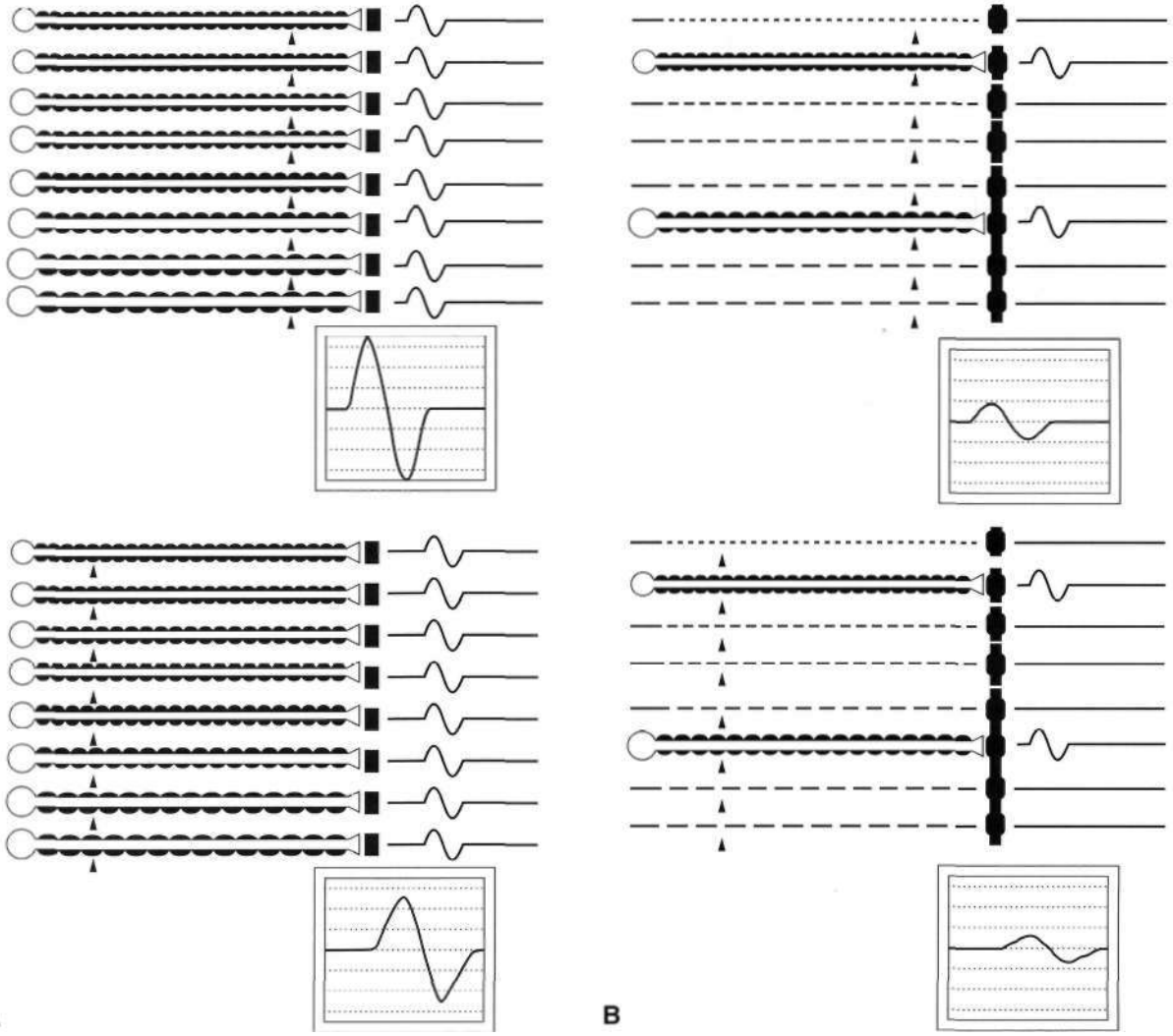


FIGURE 36B.10 Computerized model of peripheral motor nerve: (A) normal, (B) axonal degeneration, and (C) segmental demyelination. (Reprinted with permission from Brown, W, F. & Bolton, C. F. (eds) 1989, *Clinical Electromyography*, Butterworth-Heiiiem;inn, Boston.)

muscles to several thousand to 1 for large limb muscles. The smaller ratio generally occurs in muscles that perform fine gradations of movement. The distribution of muscle fibers in a muscle is wide, with overlap between different motor units.

The muscle fiber has a resting potential of 90 mV, with negativity inside the cell. The generation of an action potential reverses the transmembrane potential, which then becomes positive inside the cell. An extracellular electrode, as used in needle **EMG,** records the activity resulting from this switch of polarity as a predominantly negative potential (usually triphasic, positive-negative-positive waveforms). However, when recording near a damaged region, action potentials consist of a large positivity followed by a small negativity,

Concentric and Teflon-coated monopolar needle electrodes are equally satisfactory in recording muscle potentials, with little appreciable difference. Although monopolar needles are less painful, an additional reference electrode must be placed nearby, which often results in greater electrical noise caused by electrode impedance mismatch between the intramuscular active electrode and the surface reference disk.

The electromyographer first identifies the needle insertion point by recognizing the proper anatomical landmark and the activation maneuver for the sampled muscle. EMG evaluation is performed in four steps (Daube 1991):

1. Inserting or slightly moving the needle causes insertion a 1 activity that results from needle injury of muscle fibers.
2. Spontaneous activity is assessed in relaxed muscle by moving the needle a small distance and pausing a few seconds. The needle is relocated in four quadrants of the muscle from a single insertion to make these evaluations.

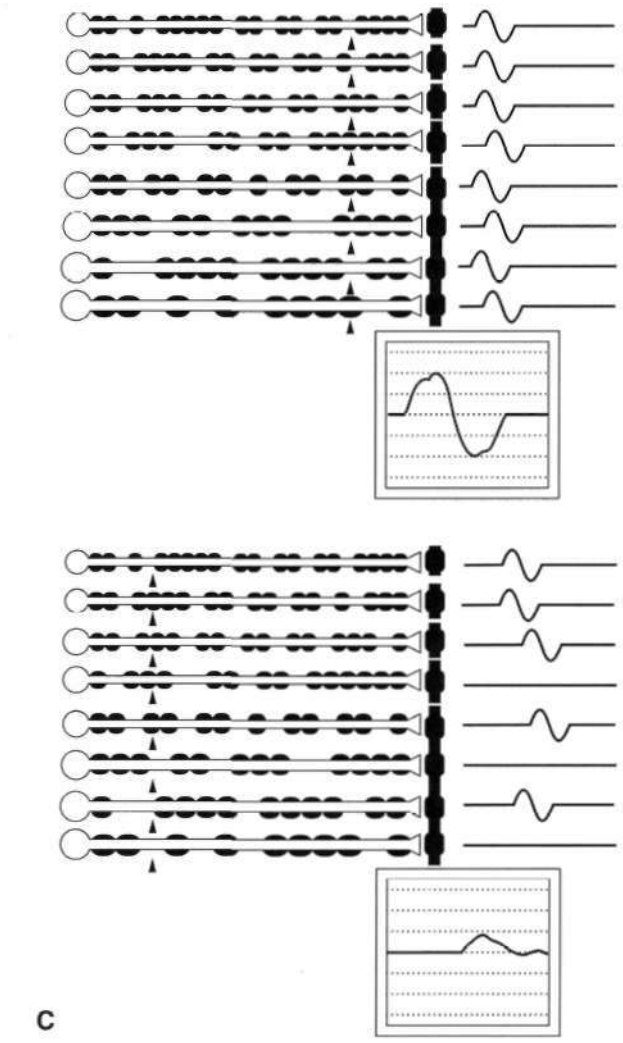


FIGURE 36B.10, cont'd.

3. A minimal contraction is obtained to assess the morphology of several MUAPs that are measured on the oscilloscope or hard copy.
4. The intensity of muscle contraction is increased to assess the recruitment pattern of MUAPs, Maximal contraction normally fills the screen, producing the interference pattern,

Oscilloscope sweep speeds of 10 milliseconds per division best define spontaneous and voluntary activities. Most laboratories use an amplification of 50 pV per division for insertional and spontaneous activity and 200 pV per division for voluntary activity.

Insertional and Spontaneous Activity

Normal Insertional and Spontaneous Activity

Brief bursts of electrical discharges accompany insertion and repositioning of a needle electrode into the muscle, slightly outlasting the movement of the needle. On average, insertional activity lasts for a few hundred milliseconds. It appears as a cluster of positive or negative repetitive high-frequency spikes, which make a crisp static sound over the loudspeaker.

At rest, muscle is silent, with no spontaneous activity except in the motor endplate region, the site of neuromuscular junction, which is usually located near the center of rhe muscle belly. Normal and abnormal insertional and spontaneous activities are listed in Table 36B.1 (Preston and Shapiro 2002). Two types of normal endplate spontaneous activity occur together or independently: endplate noise and endplate spikes.

Endplate Noise. The tip of the needle approaching the endplate region often registers recurring irregular negative potentials, 10-50 uV in amplitude and 1-2 milliseconds in duration. These potentials are the extracellularly recorded miniature endplate potentials, nonpropagating depolarizations caused by spontaneous release of acetylcholine quanta. They produce a characteristic sound on loudspeaker much like a scashell held to the ear.

Endplate Spikes, These are intermittent spikes, 100-200 pV in amplitude and 3-4 milliseconds in duration, firing irregularly at 5-50 impulses per second. Their characteristic irregular firing pattern distinguishes them from the regular firing fibrillation potentials. They have a clacking or buzzing sound on the loudspeaker. The waveform of the endplate spike is also distinguished by its initial negative deflection. The endplate spikes arc discharges of single muscle fibers generated by activation of intramuscular nerve terminals irritated by the needle. The similarity of the firing pattern of endplate spikes to discharges of muscle spindle afferents suggests that they may otiginatc in the intrafusal muscle fibers.

Abnormal Insertional and Spontaneous Activity

Prolonged versus Decreased Insertional Activity. An abnormally prolonged (increased) insertional activity indicates instability of the muscle membrane, often seen in conjunction with denervation, myotonic disorders, or necrotizing myopathies such as inflammatory myopathies. Insertional positive waves, initiated by needle movements only and identical to the spontaneous discharges, may follow the increased insertional activity, lasting few seconds. This isolated activity usually signals early denervation of muscle fibers, such as 1-2 weeks after nerve injury. A marked reduction or absence of insertional activity suggests either fibrotic or severely atrophied muscles or functionally incxcitable muscles, such as during the attacks of familial periodic paralysis.

Fibrillation Potentials. Fibrillation potentials are spontaneous action potentials of denervated single muscle fibers

Table 36B.1: Insertional and spontaneous activity

Potential	*Source generator and morphology*	*Sound on loudspeaker*	*Stability*	*Firing rate*	*Firing pattern*
Endplate noise	Miniature endplate potentials (monophasic negative)	Seashell	—	20–40 Hz	Irregular (hissing)
Endplate spike	Muscle fiber initiated by terminal axonal twig (brief spike, diphasic, initial negative)	Sputtering fat in a frying pan	—	5–50 Hz	Irregular (sputtering)
Fibrillation (brief spike)	Muscle fiber (brief spike, diphasic or triphasic, initial positive)	Rain on a tin roof or tick-tock of a clock	Stable	0.5–10 Hz (occasionally up to 30 Hz)	Regular
Positive sharp wave	Muscle fiber (diphasic, initial positive, slow negative)	Dull pops, rain on a tin roof, or tick-tock of a clock	Stable	0.5–10 Hz (occasionally up to 30 Hz)	Regular
Myotonia	Muscle fiber (brief spike, initial positive, or positive wave)	Revving engine	Waxing and waning amplitude	20–150 Hz	Waxing and waning
Complex repetitive discharge	Multiple muscle fibers time-linked together	Machine	Usually stable, may change in discrete jumps	5–100 Hz	Perfectly regular (unless overdriven)
Fasciculation	Motor unit (motor neuron or axon)	Corn popping		Low (0.1–10 Hz)	Irregular
Myokymia	Motor unit (motor neuron or axon)	Marching soldiers		1–5 Hz (interburst), 5–60 Hz (intraburst)	Bursting
Cramp	Motor unit (motor neuron or axon)		—	High (20–150 Hz)	Interference pattern or several individual units
Neuromyotonia	Motor unit (motor neuron or axon)	Pinging	Decrementing amplitude	Very high (150–250 Hz)	Waning

Source: Reprinted with permission from Katirji, B., Kaminski, H. J., Preston, D. C., et al. (eds) 2002, *Neuromuscular Disorders in Clinical Practice*, Butterworth–Heinemann, Boston.

that result from the resting membrane potential of the denervated fiber being reduced to the level at which it can fire spontaneously. Fibrillation potentials have two types of waveforms: brief spikes and positive waves. Brief spikes usually arc triphasic, with initial positivity {Figure 36B.11 A). They range from 1 to 5 milliseconds in duration and 20 to 200 pV in amplitude when recorded with a concentric needle electrode. If the needle electrode is placed near the endplatc zone, brief spike fibrillation potentials resemble physiological endplate spikes with an initial negativity. Positive waves have an initial positivity and subsequent slow negativity and have a characteristic sawtooth appearance (Figure 36B.11B). Recording near the damaged part of the muscle fiber incapable of generating an action potential accounts for the absence of negative spike. Although usually seen together, positive sharp waves tend to precede brief spikes after nerve section, possibly because they can be triggered by the insertion of a needle in already irritable muscle membrane.

Fibrillation potentials are triggered by spontaneous oscillations in the muscle fiber membrane potential. They typically fire in a regular pattern at a rate of 1-30 Hz. The sound produced by fibrillation potentials is crisp and clicking, reminiscent of the sound caused by ram on the roof or the tick-tock of a clock.

Fibrillation potentials are the electrophysiological markers of muscle denervation. Based on their distribution, they are useful in localizing lesions to the anterior horn cells of the spinal cord, root, plexus, or peripheral nerve. Insertional positive waves may appear within 2 weeks of acute denervation, but fibrillation potentials do not become full until about 3 weeks after axonal loss. Because of this latent period, their absence does not exclude recent denervation. Also, late in the course of denervation, muscle fibers that are remnervated, fibrotic, or severely atrophied show no fibrillation potentials. A numerical grading (from 0 to 4) is used to semiquantitate fibrillation potentials because their density is a rough estimate of the extent of denervated muscle fibers: 0, no fibrillations; +1, persistent single trains of potentials (>2 seconds) in at least two areas; +2, moderate number of potentials in three or more areas; +3, many potentials in all areas; +4, abundant spontaneous potentials nearly filling the oscilloscope.

Fibrillation potentials are also seen in necrotizing myopathies, such as the inflammatory myopathies and muscular dystrophics. Tins is probably caused by segmental necrosis of muscle fibers, leading to effective denervation of the distant segments as they become physically separated from the neuromuscular junction, or by the resting membrane potential of partially damaged fibers being reduced to the level that allows spontaneous discharges to occur. Also, damage to the terminal intramuscular motor axons, presumably by the inflammatory process, may also result in muscle fiber denervation. In disorders of the neuromuscular junction such as myasthenia gravis and botulism, fibrillation potentials are rare, but when they occur they are explained by a neuromuscular transmission blockade, resulting in effective denervation of muscle fibers.

Fasciculation Potentials. Fasciculation potentials are spontaneous discharges of a motor unit. They originate from the motor axon anywhere along its length and may stem also from the spinal cord. Fasciculation potentials fire randomly and irregularly and undergo slight changes in amplitude and waveform from time ro time, giving them a corn popping sound on the loudspeaker. They have a much lower firing rate than voluntary MUAPs and are unaffected by slight voluntary contraction of agonist or antagonist muscles.

Fasciculation potentials are most common in diseases of anterior horn cells but also occur in radiculopathies, entrapment neuropathies, peripheral polyneuropathies, and the cramp fasciculation syndrome. They are seen also in tetany, thyrotoxicosis, and overdose of anticholinesterase medication. In addition, they may occur in healthy people. There is no reliable method of distinguishing "benign" from "malignant" fasciculation potentials except that the benign discharges tend to fire more quickly, whereas grouped fasciculation potentials from multiple unirs are more common in motor neuron disease. Most importantly, the association of fasciculation potentials with fibrillation potentials or other neurogenic MUAP changes is strong evidence of a lower motor neuron disorder.

Myotonic Discharges. Myotonic discharges, a special type of abnormal insertional activity, appear either as a sustained run of sharp positive waves, each followed by a slow negative component of longer duration, or as a sustained run ot negative spikes with a small initial positivity iFigure 36B.11C). Myotonic discharges are recurring single-fiber potentials, showing, as with fibrillation potentials, two types of waveforms depending on the spatial relationship between the recording surface of the needle electrode and the discharging muscle fibers. Of the two types, the positive sharp waves are initiated usually by needle insertion injuring muscle membrane, whereas the negative spikes, resembling the brief spike form of fibrillation potentials, tend to occur at the beginning of slight volitional contraction. Both positive sharp waves and negative spikes typically wax and wane in amplitude over the range of 10 LIV to 1 mV, varying inversely to the rate of firing. Their frequency ranges from 20 to 150 Hz and gives rise to a characteristic noise over the loudspeaker, simulating an accelerating or decelerating motorcycle or chainsaw.

Myotonic discharges may occur with or without clinical myotonia in the myotonic dysttophies (types I and II), myotonia congenita, and paramyotonia congenita. They may also accompany other myopathies, such as acid maltasc deficiency, polymyositis, colchicine myopathy, and myotubular myopathy, as well as hyperkalemic periodic paralysis.

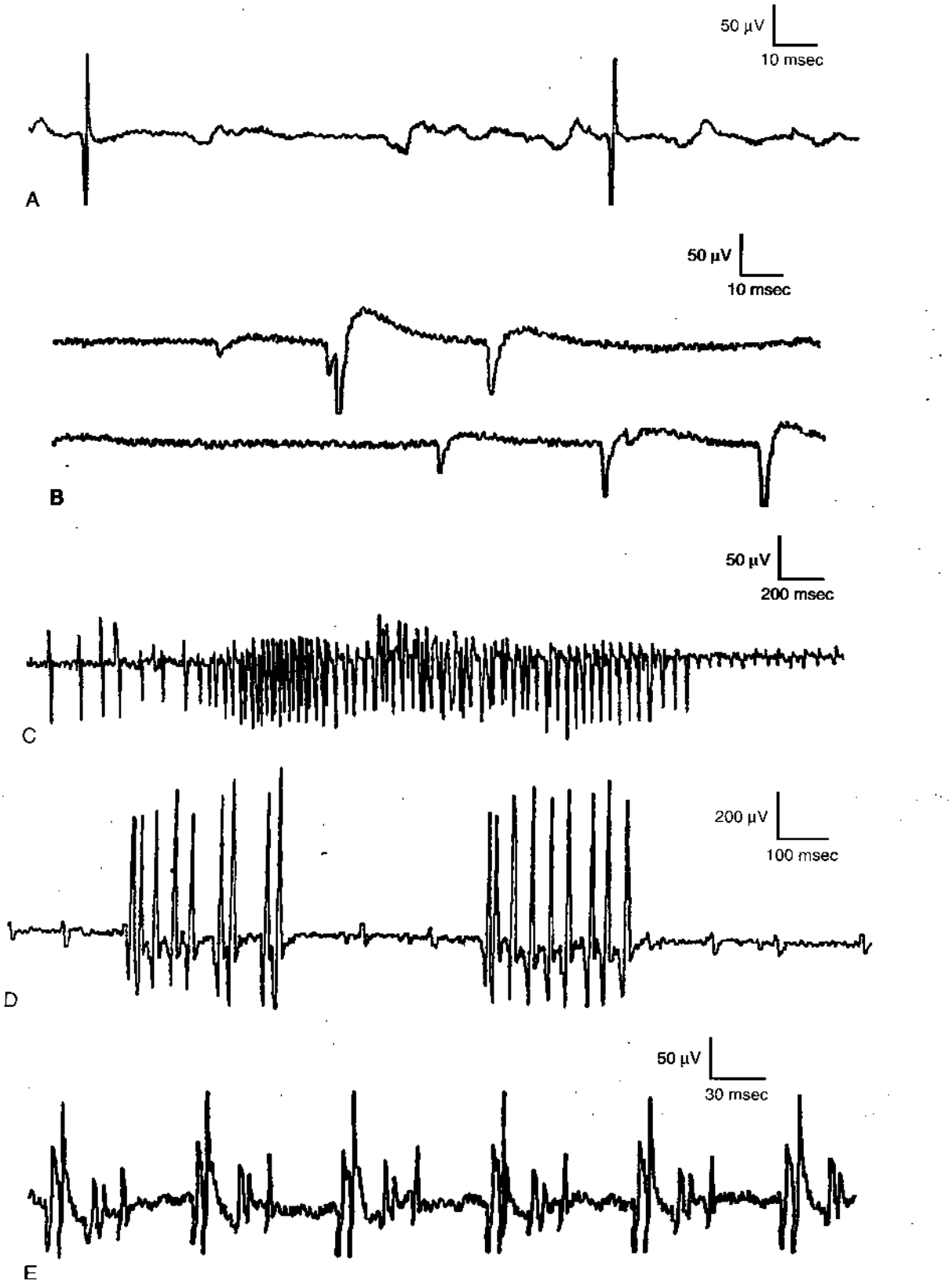


FIGURE 36B.11 Abnormal insertional activities. (A) Brief spike fibrillation potentials. (B) Positive waves. (C) Myotonic discharge. (D) Myokymic discharge. (E) Complex repetitive discharge. {Reprinted with permission from Preston, D. C. 8c Shapiro, B. E. 2000, *EMG Waveforms,* Butter wort h-Heinemann, Boston.)

Myokymic Discharges. Myokymia results from complex bursts of grouped repetitive discharges in which motor units fire repetitively, usually with 2-10 spikes discharging at a mean of 30-40 Hz (Figure 36B.11D). Each burst recurs at regular intervals of 1-5 seconds, giving the sound of marching soldiers on the loudspeaker. Clinically, myokymic discharges often give tise to sustained muscle contractions, which have an undulating appearance beneath the skin ("bag of worms"). Myokymic discharges probably originate ectopically in motor nerve fibers and accordingly arc amplified by increased axonal excitability, such as after hypcrvcntilation-induced hypocapnia.

Myokymic discharges in facial muscles suggest a brainstem glioma or multiple sclerosis, wheteas those occurring in limb muscles are seen with radiation plcxopathies, Guillain-Bane syndrome, and carpal tunnel syndrome.

Complex Repetitive Discharges. A complex repetitive discharge results from the nearly synchronous firing of a group of muscle fibers. One fiber in the complex serves as a pacemaker, driving one or several other fibers ephaptically so that the individual spikes in the complex fire in the same order as the discharge recurs. One of the late-activated fibers reexcites the principal pacemaker to repeat the cycle. The entire sequence recurs at slow or fast rates, usually in the range of 5-100 Hz. The discharge ranges from 50 pV to 1 mV in amplitude and up to 50-1000 milliseconds in duration. The complex waveform contains 10 or more distinct spikes and remains uniform from one discharge to another (Figure 36B.11E). These discharges typically begin abruptly, maintain a constant rate of firing for a short period, and cease as abruptly as they started when the chain reaction eventually blocks. They produce a noise that mimics the sound of a machine gun on a loudspeaker.

Complex repetitive discharges are abnormal discharges but are nonspecific because they are seen in many chronic disorders, including chronic neuropathies and myopathies. They may also be found in the iliopsoas or cervical pataspinal muscles of apparently healthy people, probably implying a clinically silent neuropathic process.

Neuromyotonic Discharges. Neuromyotonic discharges are rare discharges in which muscle fibers fire repetitively at high frequency (150-250 Hz), either continuously or in recurring decrementing bursts, producing a pinging sound on the loudspeaker. The discharge continues during sleep and diminishes in intensity with progressively distal nerve blocks, implicating the entite axon as the site of generation (Harik et al. 1976). Many cases of neuromyoronia are associated with the syndtome of continuous motor unit activity (Isaac's syndrome), which may have an autoimmune origin, with the target antigen probably peripheral nerve potassium channels (Hart et al. 1997). Other conditions associated with neuromyoronia include anticholinesterase poisoning, tetany, and chronic spinal muscular atrophies.

Cramp Discharges. A muscle cramp is a sustained involuntary muscle contraction. On needle FMG, ctamp discharge consists of MUAPs usually firing at a rate of 40-60 Hz, with abrupt onset and cessation. Cramps most often occur in healthy people but ate exaggerated by hyponatremia, hypocalcemia, myxedema, pregnancy, postdialysis state, and the early stages of motor neuron disease. Clinically, cramps may resemble muscle contractures that accompany sevetal of the metabolic muscle diseases and are characterized by complete electrical silence on needle F.MG.

Voluntary MUAPs

MUAP Morphology

The MUAP is the exttacellular electrode recording of a small portion of a motor unit. The waveform is dictated by the inherent properties of the MUAP and the spatial relationships between the needle and individual muscle fibers. Slight repositioning of the electrode causes major changes in the electrical profile of the same motor unit. Therefore, one motor unit can give rise to MUAPs of different morphology at different recording sites. The amplitude, dutation, and number of phases charactetize the MUAP.

Amplitude. MUAP amplitude is the maximum peak-to-peak amplitude and tanges from several hundred microvolts to a few millivolts with a concentric needle and is substantially greater with a monopolar needle. The amplitude of an MUAP decreases to less than 50% at a distance of 200-300 pm from the source and to less than 1% a few millimeters away. Therefore, only a small number of individual muscle fibers located near the tip of the tecording electrode determine the amplitude of an MUAP (probably less than 20 muscle fibers lying within a 1-mm radius of the electrode tip). In general, amplitude indicates muscle fiber density and not the motot unit territory.

Duration, MUAP duration reflects the activity from most muscle fibers belonging to a motor unit because potentials generated more than 1 mm away from the electrode contribute to the initial and terminal low-amplitude portions of the potential. The duration indicates the degree of synchrony among many individual muscle fibers with variable length, conduction velocity, and membrane excitability. A slight shift in needle position or rotation influences duration much less than the amplitude. MUAP duration is a good index of the motor unit tetritory and is the parametet that best reflects the number of

muscle fibers in a motor unit. It is measured from the initial deflection away from baseline to the final return to baseline and normally varies from 5 to 15 milliseconds, depending on the sampled muscle and the age of the subject.

Long-duration MUAPs often show high amplitude and arc the best indicators of reinnervation. They occur with increased number or density of muscle fibers or a loss of synchrony of fiber firing within a motor unit, as seen with lower motor neuron disorders. Short-duration MUAPs often have low amplitude. They occur in disorders associated with loss of muscle fibers, as seen with myopathies {Figure 36B.12).

Phases. A phase constitutes the portion of a waveform that departs from and returns to the baseline. The number of phases equals the number of negative and positive peaks extending to and from the baseline, or the number of baseline crossings plus one. Normal MUAPs have four phases or less, but about 5-15% of MUAPs have five phases or more, and tins may he up to 25% in proximal muscles, particularly the deltoid and iliacus. Increased polyphagia is a nonspecific MUAP abnormality seen in myopathics and neuropathies. An increased number of polyphasic MUAPs suggests desynchronized discharge, loss of individual fibers within a motor unit, or temporal dispersion of muscle fiber potentials within a motor unit. Excessive temporal dispersion, in turn, results from differences in conduction time along the terminal branch of the nerve or over the muscle fiber membrane. In early reinnervation after severe denervation in which the newly sprouting axons only begin to leinnervate few muscle fibers, the MUAP may also be polyphasic, with short duration and low amplitude ("nascent" MUAP).

Some MUAPs have a serrated pattern, making several turns or directional changes without crossing the baseline; this also indicates desynchronization among discharging muscle fibers. Satellite potential {linked potential or parasite potential) is a late spike of MUAP, which is distinct but time-locked with the main potential. It implicates early reinnervation of muscle fibers by collateral sprouts from adjacent motor units.

MUAP Stability

Motor units normally discharge semirhythmically, with successive potentials showing nearly identical configuration

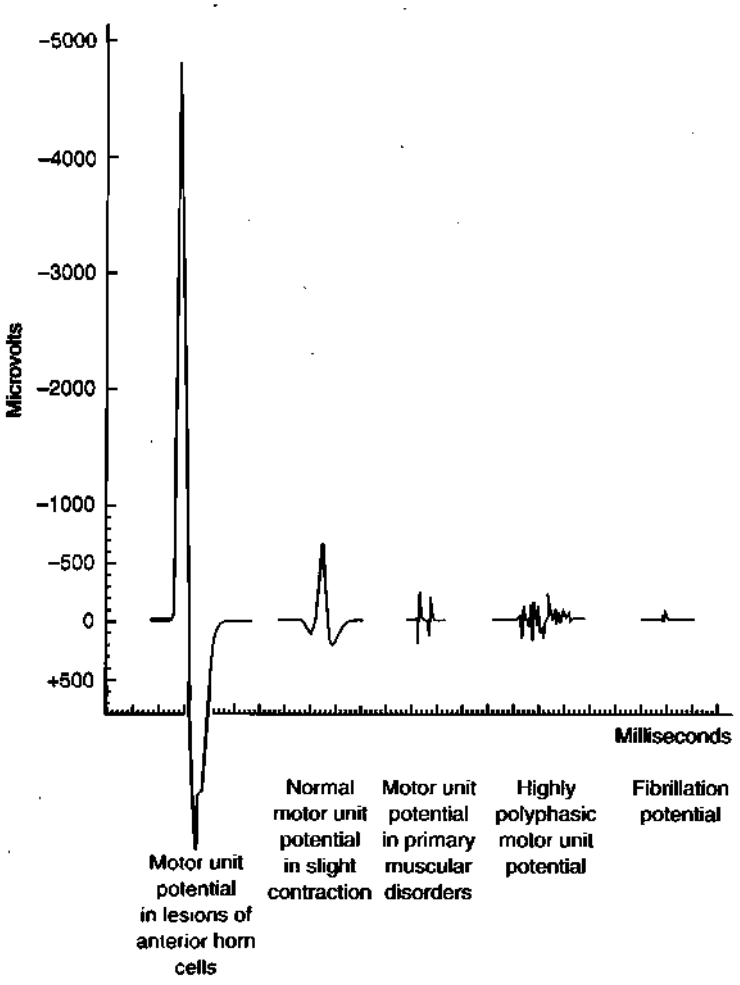


FIGURE 36B.12 Motor unit action potentials in health and disease, (Reprinted with permission from Daube, J. 1991, "Needle electromyography in clinical electromyography," *Muscle Nerve,* vol. 14, pp. 685-700.)

because all muscle fibers of the motor unit fire during every discharge. The morphology of a repetitively firing unit may fluctuate if individual muscle fibers intermittently block within the unit. Moment-to-moment MUAP variability indicates deficient neuromuscular transmission as recurring discharges deplete the store of immediately available acetylcholine (Figure 36B.13). This instability is consistent with not only a neuromuscular junction disorder, such as myasthenia gravis, the myasthenic syndrome, or botulism, but also with motor neuron disease, subacute radiculopathy, or polyneuropathy, and with the early stages of reinnervation.

MUAP Firing Patterns

During constant contraction, a healthy person initially excites only 1 or 2 motor units semirhythmically. The motor units activated early are primarily those with small, type I muscle fibers. Large, type II units participate later during strong voluntary contraction. Greater muscle force brings about not only recruitment of previously inactive units but also more rapid firing of already active units, with both mechanisms operating simultaneously (Erim et al. 1996).

Recruitment frequency is a measure of motor unit discharge, defined as the firing frequency at the time an additional unit is recruited. In normal muscles, mild contraction induces isolated discharges at a rate of 5-10 Hz. This depends on the sampled muscle and the types of motor units studied. The reported ranges for healthy people and those with neutomuscular disorders overlap. *Recruitment ratio* is the average firing rate divided by the number of active units. This ratio normally should not exceed five, for example, with thtee units each firing less than 15 Hz. A ratio of 10, with two units firing at 20 Hz each, indicates a loss of motor units.

Activation is the central control of motor units that allows an increase in the firing rate and fotce. Failure of descending impulses also limits tecruitment, although here the excited motor units discharge more slowly than expected for normal maximal contraction. Thus, a slow rate of discharge (poor activation) in an upper motor neuron disorder (such as stroke or myelopathy) or in volitional lack of effort (such as that caused by pain, hysterical paralysis, or malingering) stands in sharp contrast to a fast rate of dischatge of a lower motor neuron weakness (decreased recruitment).

With greater contraction, many motor units begin to fire rapidly, making recognition of individual MUAPs difficult, hence the name *interference pattern. A* number of factors influence the spike density and the average amplitude of the summated response. These include descending input from the cortex, number of motor neurons capable of discharging, firing frequency of each motor unit, wavefoim of individual potentials, and phase cancellation. An incomplete interference pattern may be caused by poor activation or reduced recruitment. Recruitment may be assessed during maximum contraction by examination of the interference pattern, or during moderate levels of contraction by estimation of the number of MUAPs firing for the level of activation. Evaluating maxima! compaction is most valuable in excluding mild degrees of decreased recruitment.

In myopathy, low-amplitude, short-duration MUAPs produce a smaller force per motor unit than normal MUAPs. Many units must be recruited instantaneously to support a slight voluntaty effort in patients with moderate to severe weakness (early recruitment). With early recruitment, a full interference pattern is attained at less than maximal contraction, but its amplitude is low because fiber density is low in individual motor units. In advanced myopathies with scvetc muscle weakness, loss of muscle fibers is so extensive that whole motor units effectively disappear, resulting in a decreased recruitment and an incomplete interference pattern, mimicking a neuropathic change.

Electrodiagnosis by Needle EMG

Upper Motor Neuron Lesions

Patients with uppet motot neuron lesions have normal inscrtional activity, no spontaneous activity at rest, and

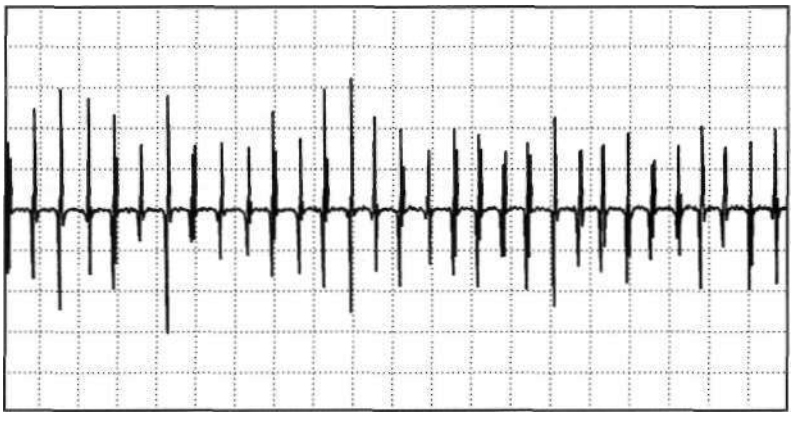


FIGURE 36B.13 Motor unit action potential instability (moment-to-moment variation) in a patient with myasthenia gravis. (Reprinted with permission from Katirji, B. 1998, *Electromyography in Clinical Practice: A Case Study Approach,* Mosby, St Louis.)

normal MUAP morphology. The only abnormality is a reduced interference pattern and a poor activation (slow rate of motor unit discharge; Figure 36B.14). Recruitment, measured by either recruitment frequency or ratio, is normal. Hysterical weakness or poor effort produces a similar pattern, except that motor unit firing may be irregular.

Lower Motor Neuron Lesions

I he fust needle FMG change occurring after an acute lower motor neuron insult is an abnormal recruitment pattern. Recruitment frequency and ratio increase in lower motor neuron lesions because fewer motor units fire for a given strength of contraction. Also, interference pattern with maximal contraction decreases, and in the extreme case, only a single motor unit fires rapidly, producing a picket fence-like pattern.

Insertional activity is increased after the first week, and insertional positive waves may appear within 2 weeks after acute denervation. However, spontaneous fibrillation potentials become present in all abnormal muscles after only .3 weeks. Kasciculation potentials accompany electrical denervation changes in diseases of the anterior horn cells, roots, and peripheral nerves but do not have pathological significance when they appear alone. Limb myokymic discharges may be seen, usually with entrapments, radiation plexopathy, or Guillain-Barre syndrome. Complex repetitive discharges denote a chronic disorder and accompany lower motor neuron disorders as well as myopathies.

MUAPs are normal in morphology in the acute phase of denervation, but signs of reinnervation become apparent as early as 1 month later. Reinnervation causes first an increased number of MUAP turns and phases and then an increased amplitude and duration. Amplitude generally reflects fiber density, and duration reflects motor unit territory. The expected MUAP from lower motor neuron lesions is a long-duration, high-amplitude polyphasic unit (see Figures 36B.12 and 36B.14). The exceptions are MUAPs seen in early reinnervation in which motor units acquire few muscle fibers, resulting in brief, small polyphasic MUAPs ("nascent" MUAPs), mimicking myopathic processes.

Radiculopathies. Needle EMG is the most sensitive and specific clcctrodiagnostic test for identifying cervical and lumbosacral radiculopathies, particularly those associated with axon loss. Needle EMG is useful in the accurate localization of the level of the root lesion. Finding signs of denervation (fibrillation potentials, decreased recruitment, and long-duration, high-amplitude polyphasic MUAPs) in a segmental myoromal distribution (i.e., in muscles innervated by the same roots via more than one peripheral nerve), with or without denervation of the paraspinal muscles, localizes the lower motor neuron lesion to the root level (Wilbourn and Aminoff 1998). A normal SNAP of the corresponding dermatome ensures that the lesion is within the spinal canal (i.e., proximal to the dorsal root ganglia}. For example, in an *IS* radiculopathy, the tibialis anterior (peroneal nerve) and tibialis posterior (tibial nerve) may be abnormal on needle EMG, as may the lumbar

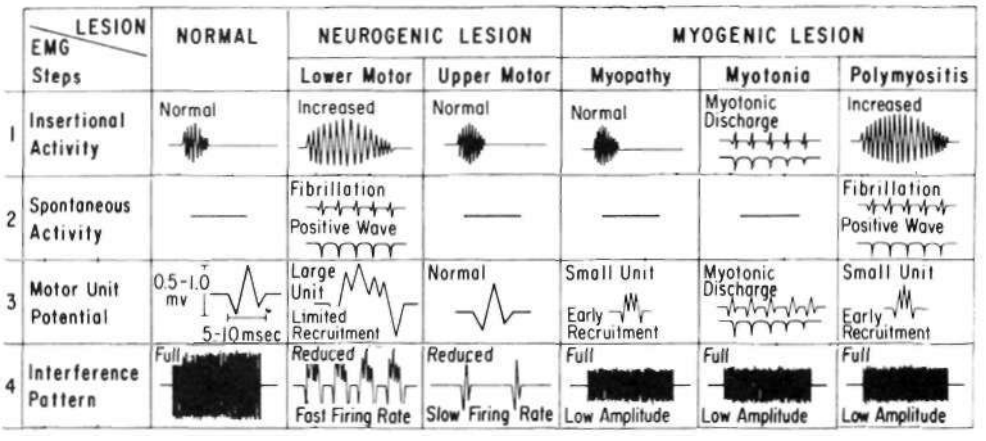


FIGURE 36B. 14 A summary of characteristic electromyographic (EMG) findings in normal subjects, patients with neurogenic lesions, and those with myogenic lesions. Insertional activity is greater in lower motor neuron lesions and polymyositis and consists of myotonic discharges in myotonia. Spontaneous activity generally occurs in lower motor neuron disorders and in inflammatory myopathy. Motor unit action potentials usually are large and polyphasic, with reduced recruitment in lower motor neuron conditions; in myopathics and polymyositis motor units are small with early recruitment. Interference pattern is reduced in both upper and lower motor neuron lesions, as well as in hysterical weakness; however, firing rate is rapid in lower motor neuron lesions and normal in upper motor neuron lesions and hysteria (m which the rate may be irregular also). Interference pattern is full but of low amplitude in myopathic lesions. (Reprinted from Kimura, J. 1989, *Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practices*, 2nd ed, FA Davis, Philadelphia.)

paraspinal muscles, but the superficial peroneal SNAP is normal.

Plexopathies. The diagnosis of brachial and lumbosacral plexopathies requires a solid knowledge of peripheral nerve anatomy. Brachial plexus anatomy is particularly complex, so multiple NCSs or muscle EMGs are needed to evaluate it. An important task of the elcctrodi a gnostic evaluation is to differentiate between lesions affecting the brachial plexus (postganglionic) and those involving the roots (preganglionic). This is parricularly important in brachial plexus traction injuries, which may mimic root avulsions (Ferrante and Wilbourn 2002), In avulsions, the dorsal root ganglia remain intact, and their peripheral axons do not undergo walletian degeneration. Therefore the SNAPs in root avulsions are spared, whereas they are low in amplitude or absent in brachial plexopathies when studied after the completion of wallerian degeneration (more than 10 days from injury),

Mononeuropathies. The needle EMG is most useful when axon loss mononeuropathies are examined after the completion of wallerian degeneration. These lesions cannot be localized by NCSs because they are not associated with focal conduction slowing or conduction block, as seen with demyelinating mononeuropathies. The NCSs in axon loss lesions often show low-amplitude or absent CMAPs, and SNAPs with normal or slightly slowed distal latencies and conduction velocities.

The principle of localizing an axon loss mononeuropathy by needle EMG is similar to manual muscle strength testing on clinical examination. Typically, the needle EMG reveals neurogenic changes (fibrillation potentials, reduced MUAP recruitment, or chronic neurogenic MUAP morphology changes) that are limited to muscles innervated by the involved nerve and located distal to the site of the lesion. However, localization of axon loss peripheral nerve lesions by needle EMG is suboptimal because some nerves have very long segments from which no motor branches atise (such as the median and ulnar nerves in the aim). Also, needle EMG may falsely localize a partial nerve lesion more distally along the affected nerve because of fascicular involvement of nerve fibers or effective reinnervation of ptoximally situated muscles (Wilbourn 2002).

Needle EMG is particularly useful in assessing the progress of reinnervation occurring spontaneously or after nerve repair. MUAP recruitment and morphology help in assessing the process of muscle fiber reinnervation that occuts after proximodistal regeneration of nerve fibers from rhe site of the injury or collateral sprouting. Early proximodistal regeneration of nerve fibers in severe axon loss lesions often manifests as brief, small, polyphasic (nascent) MUAPs. Collateral sprouting causes an increased number of MUAP turns and phases followed by an increased duration and amplitude of MUAPs.

Peripheral Polyneuropathies. Peripheral polyneuropathies are indicated by characteristic widespread abnormalities on NCSs, and the needle EMG is most useful in depicting the temporal profile of the illness. In demyelinating polyneuropathies, the needle EMG may show signs of mild axonal loss, not suspected on clinical examination, with fibrillation potentials and tcinncrvated MUAPs. In axon loss polyneuropathy, fibrillation potentials typically develop within 2-3 weeks, and reinnervated MUAPs become apparent within 1-2 months. In acute polyneuropathies, such as the Guillain-Barre syndrome, needle EMG during the acute phase of illness may show only reduced recruitment of MUAPs in weak muscles with normal MUAP morphology and no spontaneous activity. In active and progressive axon loss polyneuropathies, a combination of fibrillation potentials with reduced recruitment of reinnervated MUAPs is most prominent distally. In chronic and very slowly progressive polyneuropathies, reinnervation may completely keep pace with active denetvation, yielding few or no fibrillation potentials but reduced recruitment of reinnervated MUAPs.

Anterior Horn Cell Disorders. Needle EMG is the most important electrodiagnostic study for providing evidence of generalized lower motor neuron degeneration, even early in the course of the illness in apparently unaffected limbs. Needle EMG often shows signs of active denervation (fibrillation potentials), chronic denervation (reinnervared and unstable MUAPs), and reduced MUAP recruitment.

The electrodiagnostic studies can evaluate only lower motor neuron degeneration, whereas upper motor neuron degeneration must be assessed clinically. Therefore the diagnosis of amyotrophic lateral sclerosis (ALS) is based on clinical evaluation, with the electrodiagnostic studies playing a supporting role. There are three reasons ro perform electrodiagnostic studies in patients with suspected ALS: (1) to confirm lower motor neuron dysfunction in clinically affected regions, (2) to detect electrophysiological evidence of lower motor neuron dysfunction in clinically uninvolved regions, and (3) to exclude other pathophysiological processes (Chad 2002).

Although lower motor neuron degeneration may ultimately affect almost the entire neuraxis (brainstem and cervical, thoracic, or lumbosacral segments of spinal cord) in ALS, there is an increasing need to establish the diagnosis of ALS eatly in the illness so that patients can participate in clinical trials. Lambert's initial criteria of detecting fibrillation and fasciculation potentials in muscles of the lower as well as the upper extremities or in the extremities as well as rhe head are stringent. These criteria have evolved into denervation in at least three extremities or two extremities and cranial muscles (with the head and neck considered an extremity). Recently, the revised El Escorial criteria recommended

that needle EMG signs of lower motor neuron degeneration should be present in at least two of the four central nervous system regions (i.e., the brainstem, cervical, thoracic, or lumbosacral regions; Brooks ct al. 2000).

In patients with suspected motor neuron disease, NCSs are useful mostly in excluding other neuromuscular diagnoses such polyneuropathies. Sensory NCSs usually are normal in anterior horn cell disorders, whereas motor NCSs are either normal or yield low CMAP amplitudes consistent with motor neuronal loss. Motor conduction velocities are normal or slightly slowed but never below 70% of the lower limits of normal. Also, the NCSs do not show other demyelinating features, such as conduction blocks that are characteristics of multifocal motor neuropathy, a treatable disorder that may mimic lower motor neuron disease.

Myopathic Disorders

Insertional activity usually is normal except in the late stage of the disease, when it is reduced by atrophy and fibrosis. Spontaneous activity is absent except in necrotizing myopathies (such as inflammatory myopathics and muscular dystrophies). MI JAP amplitude and duration are reduced by random loss of fibers from the motor unit (see Figure 36B.I2). Regeneration ol muscle fibers sometimes gives rise to long-duration spikes and satellite potentials. Early recruitment is the rule because more motor units are needed to maintain a given force in compensation for the small size of individual units (see Figure 36B.14).

A disadvantage of the electrodiagnosis of myopathies is that the EMG findings in myopathy are not always specific enough to make a final diagnosis. Exceptions include myotonia, which occurs in myotonic dystrophies, myotonia congenita, paramyotonia congenita, hyperkalemic periodic paralysis, acid maltasc deficiency, and some toxic myopathies (such as due to colchicine); and fibrillation potentials, which occur in inflammatory myopathies and progressive muscular dystrophies (such as Becker and Duchenne muscular dystrophy; Table 36B.2), Another disadvantage of the needle EMG is that it is either normal or has subtle abnormalities in some myopathies, such as the metabolic and endocrine myopathics (Lacomis 2002). Therefore, a normal needle EMG does not exclude a myopathy.

In polymyositis and dermatomyositis, it is essential to recognize the changing pattern on needle EMG at diagnosis, after treatment, and during relapse. Fibrillation potentials appear first at diagnosis or relapse and disappear early during remission. Abnormal MUAP morphology becomes evident later and takes longer to resolve (Wilbourn 1993). The presence of fibrillation potentials is also helpful in differentiating exacerbation of myositis from a corticosteroid-induced myopathy.

SPECIALIZED ELECTRODIAGNOSTIC STUDIES

F Wave

A supramaximal stimulus applied at any point along the course of a motor nerve elicits a small late motor response (F wave) after the CMAP (M response). This long-latency F wave is a very small CMAP that results from backfiring of antidromically activated anterior horn cells, averaging 5-10% of the motor neuron pool. The F wave's afferent and efferent loops arc the motor neuron, with no intervening synapse (Fisher 2002). The F wave latencies measured from the stimulus artifact to the beginning of the evoked potential vary by a few milliseconds from one stimulus to the next. Therefore, an adequate study requires **that** about 10 F waves be clearly identified. If the stimulator is moved proximally, the F wave latency decreases because the action potential travels a shorter distance (Figure 36B.15).

The minimal F wave latency is the most reliable and useful measurement and represents conduction of the largest and fastest motor fibers. The most sensitive criterion of abnormality in a unilateral disorder affecting a single nerve is a minimum latency difference between the two sides or between two nerves in the same limb. Absolute latencies are useful only for sequential reassessment of the same nerve. The F wave conduction velocity provides a better comparison between proximal and distal (forearm or leg) segments. F wave chronodispersion reflects the degree of scatter among consecutive F waves, is determined by the difference between the minimal and maximal F wave latencies, and indicates the range of motor conduction velocities in the nerve. F wave persistence is a measure of the number of F waves obtained for the number of stimulations and usually is greater than 50% except when one stimulates the peroneal nerve while recording the extensor digitorum brevis.

F wave latencies arc prolonged in most polyneuropathies, particularly the demyelinating type. In the early phases of Cuillain-Barre syndrome, the routine motor nerve studies may be entirely normal, with prolonged or absent F responses, which implies proximal demyelination (Gordon and Wilbourn 2001). F wave latencies in radiculopathies have a limited use; they may be normal despite partial motor axonal loss, and most muscles have multiple root innervation (Wilbourn and Aminoff 1998).

H Reflex

The H reflex, named after Hoffmann for his original description, is an electrical counterpart of the stretch reflex elicited by a mechanical tap to the Achilles tendon (Katirji and Weissman 1994). The group 1A sensory fibers and alpha motor neurons form the respective afferent and efferent arcs of this predominantly monosynaptic reflex.

Table 36B.2: Needle electromyographie findings in myopathies

Normal	*Myopathic MUAPs with fibrillation potentials*	*Myopathic MUAPs only*	*Fibrillation potentials only*	*Man*
Metabolic myopathics	Inflammatory myopathies	Muscular dystrophics	Inflammatory myoparhies[+]	
McArdle's disease	Polymyositis	Facioscapulohumeral	Polymyositis	
Tartu's disease	Dermato myositi s	Limb girdle	D e rma romy o skis	
Brancher deficiency	Inclusion body myositis	Oculopharyngeal	Sarcoid myopathy	
Debrancher deficiency	Sarcoid myopathy	Congenital	HIV-associated myopathy	
Carnitinepalmitoytransferase deficiency	HIV-associated myopathy			
Carnitine deficiency				
Adenylate deaminase deficiency				
Mitochondrial myopathies	Muscular dystrophies	Congenital myopathies	Others	
Kearns-Sayrc syndrome	Duchenne	Central core	Acute rhabdomyolysis	
Mitochondrial myopathy, encephalopathy, lactacidosis, and stroke	Becker	Nemaline rod	Chloroquine	
	Distal			
Myoclonic epilepsy with ragged red fiber myopathy				
Endocrine myopathies	Others	Endocrine myopathies		
Corticosteroid (mild)	Critical illness myopathy	Steroid (severe)		
Hypothyroid	Myo tubular myopathy	Hypothyroid		
Hyperthyroid	Parasitic infections (trichinosis)	Hyperthyroid		
Hyperpara thyroid		Hyperparathyroid		
Cushing's				
Others		Toxic myopathies		
Fiber type disproportion		Alcohol		
Periodic paralysis*		Emetine		

* Between attacks.
Early or mild.
HIV = human immunodeficiency virus; MUAP = motor unit action potential.
.*Source:* Reprinted with permission from Katirji, B., Kaminski, H, J., Preston, D. C. et al. (eds) 2002, *Neuromuscular Disorders in*

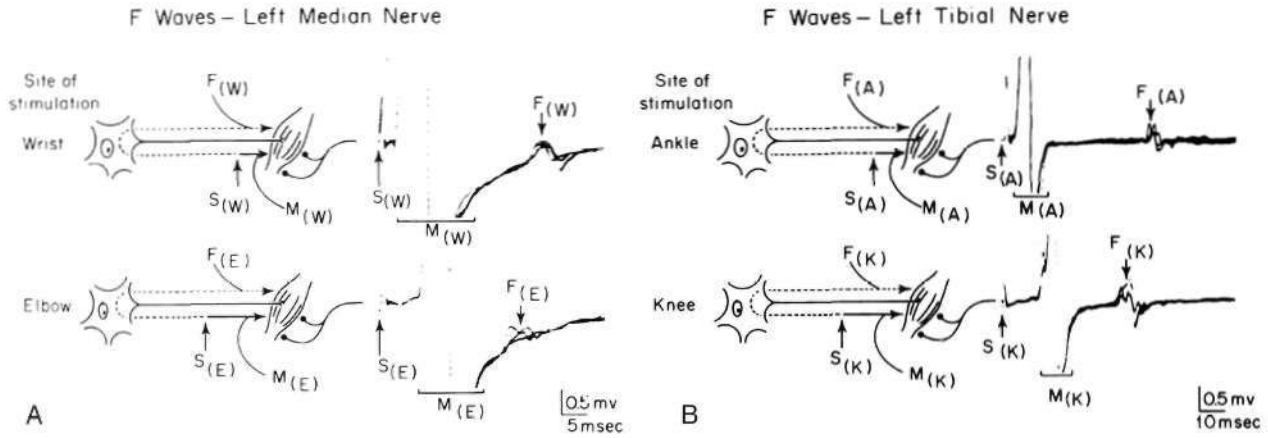


FIGURE 36B.1S (A) Normal *M* response *{horizontal brackets)* and F wave *{small arrows)* recorded from the thenar muscles using surface electrodes. Sites of supramaximal stimulus (S) to the median nerve are shown, with these consecutive traces superimposed for each. As the stimulus was moved from the wrist (W) to the elbow (E), the latency of the M response increased, whereas that of the F wave decreased. The figures on the left are schematic illustrations showing the centrifugal *(solid arrows)* and centripetal *{dotted arrows)* impulses carrying the M response and F wave, respectively. (Modified from Kimura, J. 1974, "F-wave velocity in the central segment of the median and ulnar nerves: A study in normal subjects and patients with Charcot-Marie-Tooth disease," *Neurology* [Minneapolis], vol. 24, pp. 539-546.) (B) Normal M response *{horizontal brackets)* and F wave *[smalt arrows)* recorded from the abductor hallucis using surface electrodes. Supramaximal stimulus (S) was delivered to the tibial nerve at the ankle (A) and knee (K). Three consecutive traces are superimposed for each. As the stimulus was moved ftom ankle to knee, the latency of the M response increased, whereas that of the F wave decreased. (Reprinted with permission from Kimura, J., Bosch, P., & Lindsay, G. M. 1975, "F-wave conduction velocity in the central segment of the peroneal and tibial nerves," *Arch Pbys Med Rebabil,* vol. 56, pp. 492-497.)

The H reflex and F wave can be distinguished by increasing stimulus intensity. The H reflex is best elicited by a long-duration stimulus, submaximal to produce an M response (Figure 36B.16), whereas the F wave requires supramaximal stimulus intensity. In contrast to the F wave, which can be elicited from any limb muscle, the H reflex stimulating the tibial nerve while recording the soleus muscle is the most reproducible and commonly used in clinical practice. The H reflex latency and amplitude, determined by the sensory and motor conduction of the nerve, are better than routine NCSs in the early phases of Guillain-Barre syndrome (Gordon and Wilbourn 2001) and in the diagnosis of mild polyneuropathy or mild SI radiculopathy (Nishida et ah 1996).

Blink Reflex

The blink reflex generally evaluates the trigeminal and facial nerves and their connections in the pons and medulla. It has an afferent limb, mediated by sensory fibers of the supraorbital branch of the ophthalmic division of the trigeminal nerve, and an efferent limb, mediated by motor fibers of the facial netve.

With two-channel recording, the blink reflex has two components: an early Rl and a late R2 response. The Rl response is present only ipsilateral to the stimulation and usually is a simple triphasic waveform with a disynaptic pathway between the main trigeminal sensory nucleus in the midpons and the ipsilateral facial nucleus in the lower pontine tegmentum. The R2 response is a complex waveform and is the electrical counterpart of the corneal reflex. It is typically present bilaterally, with an oligosynaptic pathway between the nucleus of the trigeminal spinal tract in the ipsilatetal pons and medulla and interneurons forming connections to the ipsilatetal and contralateral facial nuclei.

The blink reflex is most useful in unilateral lesions such as facial palsy, trigeminal neuropathy, or pontine or medullary lesion (Kimura 1983). With facial nerve lesions, the Rl and R2 potentials are absent ot delayed with supraorbital stimulation ipsilateral to the lesion, whetcas the R2 response on the contralateral side is normal. With trigeminal nerve lesions, the ipsilateral Rl and R2 and contralateral R2 ate absent or delayed, whereas all responses arc normal with contralateral stimulation. With a midpontine lesion involving the main sensory trigeminal nucleus or the pontine interneurons to the ipsilateral facial netve nucleus, supraorbital stimulation on the side of the lesion results in an absent or delayed Rl but an intact ipsilatetal and contralateral R2. Finally, with a medullary lesion involving the spinal tract and trigeminal nucleus or the medullary interneurons to the ipsilateral facial nerve nucleus, supraorbital stimulation on the affected side results in a normal Rl and contralateral R2 but an absent ot delayed ipsilateral R2. In demyelinating polyneuropathies such as Guillain-Barre syndrome or Charcot-Marie-Tooth disease type 1, all the blink responses may be markedly delayed, reflecting slowing of motor fibcts ot sensory fibers,

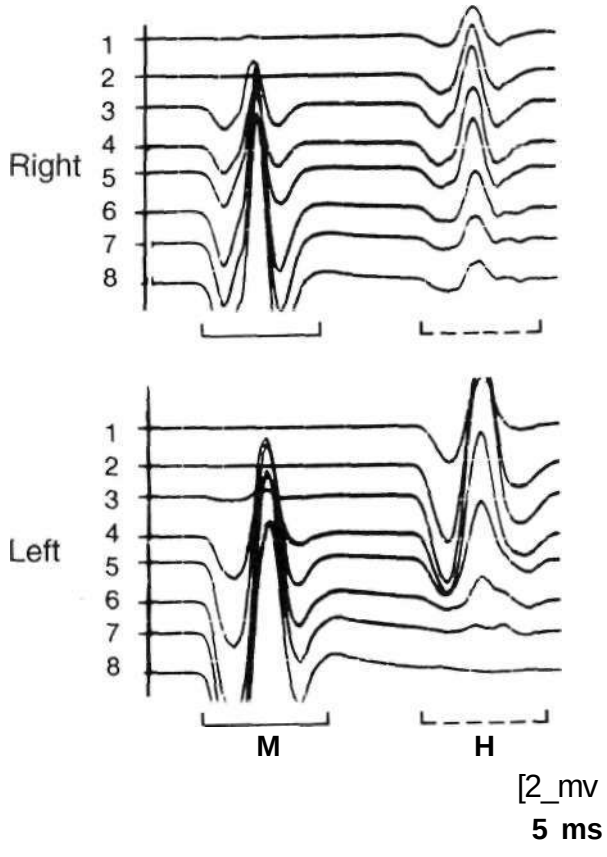


FIGURE 36B.16 H reflex recorded from the solcus after stimulation of the tibial nerve at the knee. Shock intensity was gradually increased from subthreshold level (1) to supramaximal stimulation (8}. Note initial increase and subsequent decrease in amplitude of the reflex potential with successive stimuli of progressively higher intensity. The 11 reflex normally disappears with shocks of supramaximal intensity that elicit a maximal M response.

Repetitive Nerve Stimulation

Principles

Repetitive stimulation of motor or mixed nerves is performed to evaluate patients with suspected neuromuscular junction disorders, including myasthenia gravis, Lambert-Eaton myasthenic syndrome, botulism, and congenital myasthenic syndromes. The design and plans for repetitive nerve stimulation depend on physiological facts inherent to the neuromuscular junction that dictate the type and frequency of stimulations used in the diagnosis of neuromuscular junction disorders. The CMAP obtained during routine NCSs represents the summation of all muscle fiber action potentials generated in a muscle after supramaximal stimulation of all motor axons while recording via surface electrode placed over the belly of a muscle.

- A quantum is the amount of acetylcholine in a single vesicle, which contains approximately 5000-10,000 acetylcholine molecules. Each quantum (vesicle) released results in a 1-mV change of postsynaptic membrane potential. This occurs spontaneously during rest and forms the basis of the miniature endplate potential.
- The number of quanta released after a nerve action potential depends on the number of quanta in the immediately available (primary) store and the probability of release: $m = p$ x «, where m = the number of quanta released during each stimulation, p = the probability of release (effectively proportional to the concentration of calcium and typically about 0.2, or 20%), and n = the number of quanta in the immediately available store. In normal conditions, a single nerve action potential triggers the release of 50-300 vesicles (quanta) with an average equivalent to about 60 quanta (60 vesicles). In addition to the immediately available store of acetylcholine located beneath the presynaptic nerve terminal membrane, a secondary (or mobilization) store starts to replenish the immediately available store after 1-2 seconds of repetitive nerve action potentials. A large tertiary (or reserve) store is also available in the axon and cell body.
- The endplate potential is the potential generated at the postsynaptic membrane after a nerve action potential. Because each vesicle released causes a 1-mV change in the postsynaptic membrane potential, this results in about a 60-mV change in the amplitude of the membrane potential.
- In normal conditions, the number of quanta (vesicles) released at the neuromuscular junction by the presynaptic terminal far exceeds che postsynaptic membrane potential change necessary to reach the threshold needed to generate a postsynaptic muscle action potential. This safety factor results in an endplate potential that is always above threshold and results in muscle fiber action potential. In addition to quanta! release, several other factors contribute to the safety factor and endplate potential, including acetylcholine receptor conduction properties, acetylcholine receptor density, and acetylcholinesterase activity (Boonyapisit, Kaminski, and Ruff 1999).
- After depolarization of the presynaptic terminal, voltage gated calcium channels open, leading io calcium influx. Through a calcium-dependent intracellular cascade, vesicles are docked into active re lease zones, and acetylcholine molecules are released. Calcium then diffuses slowly out of the presynaptic terminal in 100-200 milliseconds. The rate at which motor nerves arc repetitively stimulated dictates whether calcium accumulation plays a role in enhancing the release of acetylcholine. At slow rate of repetitive nerve stimulation (i.e., a stimulus every 200 milliseconds or more, or a stimulation rate <5 Hz), the calcium role in acetylcholine release is not increased, and subsequent nerve action potentials reach the nerve terminal long after calcium has dispersed. In contrast, with rapid

repetitive nerve stimulation (i.e., a stimulus every 100 milliseconds or less, or a stimulation rate >10 Hz), calcium influx is greatly increased, and the probability of release of acetylcholine quanta increases.

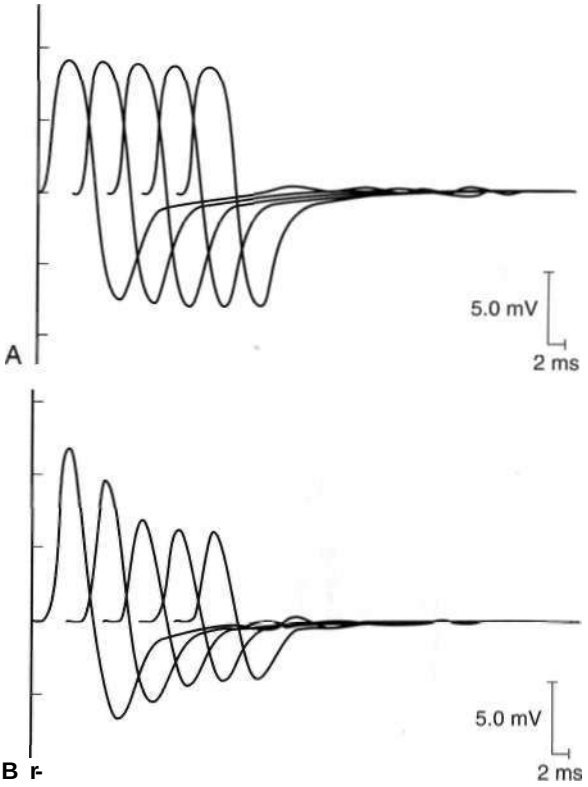
Slow Repetitive Nerve Stimulation

Slow repetitive nerve stimulation usually is performed by application of three to five supramaximal stimuli to a mixed or motor nerve at a rate of 2-3 Hz. This rate is **low** enough to prevent calcium accumulation but high enough to deplete the quanta in the immediately available store before the mobilization store starts to replenish it. Three to five stimuli is adequate because the maximal decrease in acetylcholine release occurs during the first three to five stimuli.

Calculation of the decrement with slow repetitive nerve stimulation entails comparing the baseline CMAP amplitude with the lowest CMAP amplitude (usually the third or fourth). The CMAP decrement is expressed as a percentage and calculated as follows:

$$\% \text{ Decrement} = \frac{\text{Amplitude (1st response)} - \text{Amplitude (3rd or 4th response)}}{\text{Amplitude (1st response)}} \times 100$$

In normal conditions, slow repetitive nerve stimulation does not cause a CMAP decrement. Although the second through fifth endplate potentials fall in amplitude, they remain above threshold (because of the normal safety **factor)** and ensure generation of muscle fiber action potential with each stimulation. In addition, the secondary store begins to replace the depleted quanta after the first few seconds, with a subsequent rise in the endplate potential. Therefore, all muscle fibers generate muscle fiber action potentials, and the CMAP docs not change. In postsynaptic neuromuscular junction disorders (such as myasthenia gravis), the safety factor is reduced because there are fewer available acetylcholine receptors. Therefore, the baseline endplate potential is reduced but usually still above threshold. Slow repetitive nerve stimulation results in a decrease in endplate potential amplitudes at many neuromuscular junctions. As endplate potentials decline below the threshold, there is a decline in the number of muscle fiber action potentials produced, leading to a CMAP decrement (Figure 36B.17). In presynaptic disorders (such as Lambert-Eaton myasthenic syndrome) the baseline endplate potential is low, with many endplates not reaching threshold. Therefore, many muscle fibers do not fire, resulting in a low baseline CMAP amplitude (Table 36B.3). With slow repetitive nerve stimulation, there is further CMAP decrement, caused by the further decline of acetylcholine release with the subsequent stimuli, resulting in further loss of many endplate potentials and muscle fiber action potentials (Katirji and Kaminski 2002).



FTGURE 36B.17 Slow (2-Hz) repetitive nerve stimulation (A) in a healthy control subject and (B) in a patient with generalized myasthenia gravis showing compound muscle action potential decrement. (Reprinted with permission from Katirji, B. 1998, *Electromyography in Clinical Practice: A Case Study Approach,* Mosby, St Louis.)

In myasthenia gravis, the diagnostic yield of slow repetitive nerve stimulation increases if the following recommendations are applied:

1. Obtain slow repetitive nerve stimulation at rest and after exercise. If there is a reproducible CMAP decrement (>10%) at rest, slow repetitive nerve stimulation should be repeated after the patient exercises for 10 seconds to demonstrate repair of the decrement (post-tetanic facilitation). If there is no or equivocal decrement (<10%) at rest, the patient should perform maximal volunrary exercise for 1 minute. Then, slow repetitive nerve stimulation should be repeated every 30 seconds afterward and for *3-5* minutes after exercise. Because the amount of acetylcholine released with each stimulus is at its minimum 2-5 minutes after exercise, slow repetitive nerve stimulation after exercise increases the chance of detecting a defect of neuromuscular transmission at the neuromuscular junction by demonstrating a worsening CMAP decrement (postcxercise exhaustion).
2. Record from clinically weakened muscles. Most technically feasible nerves for slow repetitive nerve stimulation are the median, ulnar, and spinal accessory

Table 36B.3: CMAPs and RNS in neuromuscular junction disorders

Neuromuscular junction defect	*Disorder*	*CMAP*	*Slow RNS*	*Rapid RNS'*
Postsynaptic	Myasthenia gravis	Norma]	Decrement	Normal or decrement
Presynaptic;	Lambert-Eaton myasthenic syndrome	Low	Decrement	[ncri'iiinn

*Or post-brief exercise CMAP.
CMAP = compound muscle action potential; RNS = repetitive nerve stimulation.

nerves. Facial repetitive nerve stimulation is indicated in patients with oculobulbar weakness, but this study is difficult and often associated with a large stimulation artifact. The diagnostic sensitivity is clearly higher for slow repetitive nerve stimulation recording in proximal muscles than in distal muscles.

3. Warm the extremity studied (skin temperature should be above 32^{C}C). This decreases false negative results because cooling improves neuromuscular transmission and may mask the decrement.
4. Discontinue all cholincsterase inhibitors for 12-24 hours (if clinically possible). This also decreases the false negative rate of slow repetitive nerve stimulation.

Rapid Repetitive Nerve Stimulation

Rapid repetitive nerve stimulation is most useful in patients with suspected presynaptic neuromuscular junction disorders such as Lambert-Eaton myasthenic syndrome or botulism. The optimal frequency is 20-50 Hz for 2-10 seconds. A typical rapid repetitive nerve stimulation applies 200 stimuli at a rate of 50 Hz (i.e., 50 Hz for 4 seconds). Calculation of CMAP increment after rapid repetitive nerve stimulation is as follows:

$$\%\ \text{increment} = \frac{\text{Amplitude (highest response)} - \text{Amplitude (First response)}}{\text{Amplitude \{first response)}} \times 100$$

A brief (10-sccond) period of maximal voluntary isometric exercise is much less painful and has the same effect as rapid repetitive nerve stimulation at 20-50 Hz (Tim and Saunders 1994). A single supramaximal stimulus is applied to generate a baseline CMAP. Then, the patient performs a 10-second maximal isometric voluntary contraction, which is followed by another stimulus that produces the postexercise CMAP.

With rapid repetitive nerve stimulation or postexercise CMAP evaluation, two competing forces act on the nerve terminal. First, stimulation tends to deplete the pool of readily available synaptic vesicles. This depletion reduces transmitter release by reducing the number of vesicles that are released in response to a nerve terminal action potential. Second, calcium accumulates in the nerve terminal, thereby increasing the probability of synaptic vesicle release. In a normal nerve terminal, the effect of depletion of readily available synaptic vesicles predominates, so that with rapid repetitive nerve stimulation, the number of vesicles released decreases. However, the cndplate potential docs not fall below threshold because of the safety factor. Therefore the supramaximal stimulus generates muscle fiber action potentials at all endplates, and no CMAP decrement occurs. In fact, rapid repetitive nerve stimulation or brief (10 seconds) exercise in normal subjects often leads to a slight physiological increment of the CMAP that does not exceed 40% of the baseline CMAP. This is probably-caused by increased synchrony of muscle fiber action potentials after tetanic stimulation (post-tetanic pseudo-facilitation).

In a presynaptic disorder (such as Lambert-Eaton myasthenic syndrome), very few vesicles are released and many muscle fibers do not reach threshold, resulting in low baseline CMAP amplitude. With rapid repetitive nerve stimulation, the calcium concentrations in the nerve terminal can rise high enough to stimulate synaptic vesicle fusion for a sufficient number of synaptic vesicles to result in an endplate potential capable of action potential generation. This leads to many muscle fibers reaching threshold and firing and results in a CMAP increment (see Table 36B.3). The increment often is higher than 200% in Lambert-Eaton myasthenic syndrome and is 30-100% in patients with botulism (Figure 36B.18).

In a postsynaptic disorder (such as myasthenia gravis), rapid repetitive nerve stimulation causes no change of CMAP because the depleted stores are compensated by the

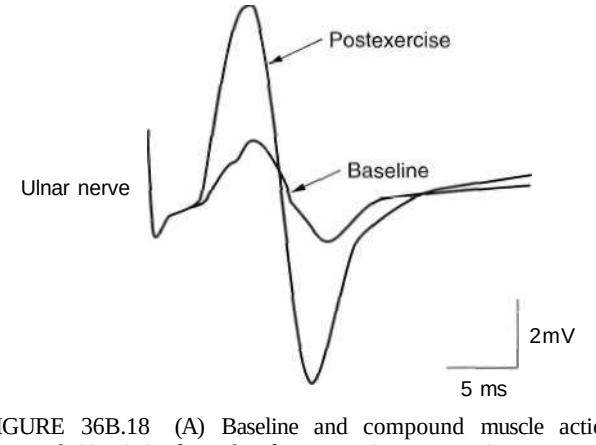


FIGURE 36B.18 (A) Baseline and compound muscle action potential (CMAP) after a brief exercise (postexercise) in a patient with Lambert-Eaton myasthenic syndrome. Note the significant CMAP increment (294%) after exercise.

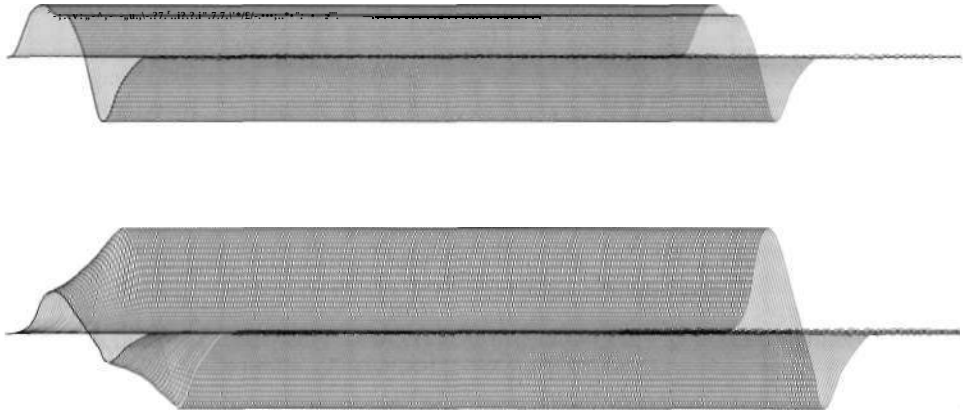


FIGURE 36B.18, cont'd. (B) Rapid (50-Hz) repetitive nerve stimulation in a control subject *{upper panel)* and in a patient with Lambert-Eaton myasthenic syndrome *{lower panel).* There is no CMAP increment in the control, whereas a significant (250%) increment is apparent in the patient. (Reprinted with permission from Katirji, B, 1998, *Electromyography in Clinical Practice: A Case Study Approach,* Mosby, St Louis.)

calcium influx. In severe postsynaptic blockade (such as during myasthenic crisis), the increased quantal release cannot compensate for the marked neuromuscular block, resulring in a drop in endplate potential amplitude, Therefore fewer muscle fiber action potentials are generated with an associated CMAP decrement.

Single-Fiber Electromyography

There are several technical requirements for performing single-fiber EMG, First, a concentric single-fiber needle electrode allows the recording of single-muscle fiber action potentials. The small side port on the cannula of the needle serves as the pickup area. A single-fiber needle electrode records from a circle of 3O0-|4irj radius, as compared with the 1-mm radius of a conventional EMG needle. Second, the amplifier must have an impedance of 100 megohms or greater to counter the high electrical impedance of the small lead-off surface, the gain is set higher for single-fiber EMG recordings than for conventional EMG, the sweep speed is faster, and the filter should have a 500-Hz low frequency to attenuate signals from distant fibers. Third, an amplitude threshold trigger allows recording from single muscle fiber, and a delay line permits the entire waveform to be viewed even though the single-fiber potential triggers the sweep. Fourth, computerized equipment assists in data acquisition, analysis, and calculation.

Voluntary {recruitment) single-fiber EMG is a common method for activating muscle fibers. A mild voluntary contraction produces a biphasic potential with a duration of approximately 1 millisecond and an amplitude that varies with the recording site. Single-fiber potentials suitable for study must have a peak-to-peak amplitude greater than 200 uV, rise time less than 300 ps, and a constant waveform. The needle is rotated, advanced, and retracted until a potential meets these criteria. *Stimulation single-fiber EMG* is a newer technique performed by inserting another monopolar needle electrode near the intramuscular nerve twigs and stimulating at a low current and constant rate. This method does nor require patient participation and therefore may be performed on children or on uncooperative or comarose patients. Single-fiber EMG is useful in assessing fiber density or in jitter analysis.

fiber Density

Fiber density is calculated as the number of single-fiber potentials firing almosr synchronously with the initially identified single-fiber potential. Increased muscle fiber clustering indicates collateral sprouting. Simultaneously firing single-fiber potentials within 5 milliseconds after the triggering single-fiber unit are counted at 20-30 sites. For example, in the normal extensor digitorum communis muscle, single fibers fire without nearby discharges in 65-70% of random insertions, with only two fibers discharging in 30-35% and with three fibers discharging in 5% or fewer. An average number of single-muscle fiber potentials per recording site can be calculated. In conditions producing loss of the normal mosaic distribution of muscle fibers from a motor unit, such as reinncrvation, fiber density increases.

Jitter

Jitter is the variability of the time interval between two muscle fiber action potentials (muscle pair) innervated by the same motor unir, that is, it is the variability of the interpotential intervals between repetitively firing paired single-fiber potentials (Stalberg and Trontelj 1997; Figure 36B.19). Jitter can be determined by using a commercially available computer program. It is calculated as the mean

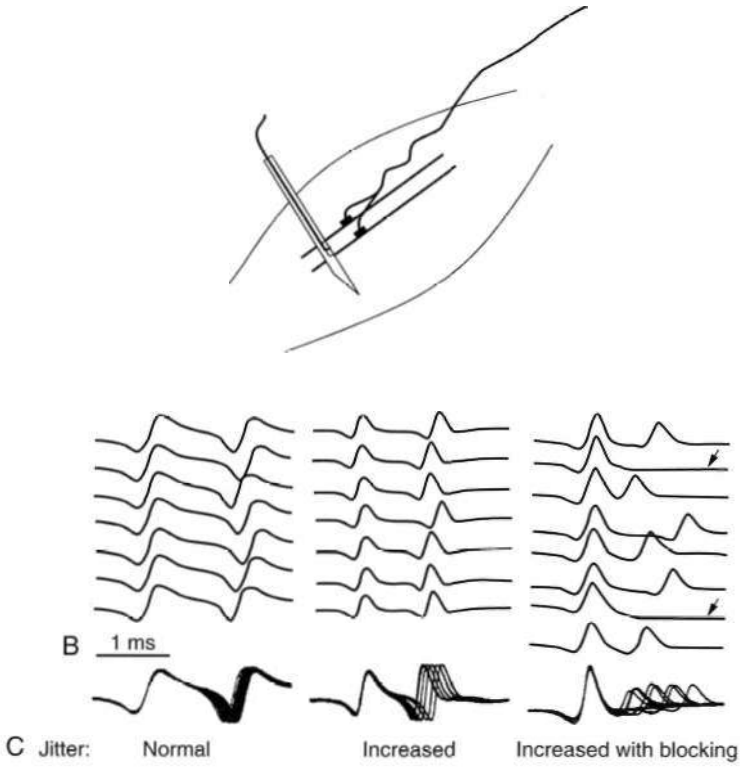


FIGURE 36B.19 Voluntary single-fiber electromyographic jitter study (A). The jitter is measured between two single-muscle fiber action potentials innervated by the same motor unit. Normal, moderately increased jitter in a patient with myasthenia gravis, and greatly increased jitter with intermittent blocking *(arrows)* in a patient with myasthenia gravis. The upper tracings (B) are shown in a raster mode, and the lower tracings (C) are superimposed. (Reprinted from Stalberg, E. & Trontelj, J. V. 1997, "The study of normal and abnormal neuromuscular transmission with single fibre electromyography," / *Neuroses Methods,* vol. 74, pp. 145-154, with permission from Elsevier Science,)

value of consecutive interval differences over a number of 50-100 discharges, as follows:

$$MCD = [IPI\ 1 - IPI\ 2] + [IPI\ 2 - IPI\ 3] + \text{-•-} + [IPI(N-1) - IPIN]/N - 1.$$

where MCD is the mean consecutive difference, **IPI** 1 is the intetpotential interval of the first discharge, IPI 2 of the second discharge, etc., and N is the number of discharges recorded.

Neuromuscular blocking is the intermittent failure of transmission of one of the two muscle fibct potentials. This reflects the failure of one of the muscle fibers to transmit an action potential caused by the failure of the cndplate potential to reach threshold. Blocking is the most extreme abnormality of the jitter and is measured as the percentage of dischatges of a motor unit in which a single-fibet potential does not fite. For example, in 100 discharges of the pair, if a single potential is missing 30 times, the blocking is 30%. In general, blocking occurs when the jitter values are significantly abnormal.

The results of single-fibet EMG jitter study are expressed by the mean jittet of all potential pairs, the percentage of pairs with blocking, and the percentage of pairs with normal jittet. Because jitter may be abnormal in 1 of 20 recorded potentials in healthy subjects, the study is considered to indicate defective neuromuscular transmission if the mean jitter value exceeds the upper limit of the normal jitter value for that muscle, more than 10% (more than two pairs) exhibits jitter values above the upper limit of the norma! jittet, or there is any neuromuscular blocking.

Jitter analysis is highly sensitive but not specific. Although it is often abnormal in myasthenia gravis and other neuromuscular junction disorders, it may also be abnormal in a variety of neuromuscular disorders including motor neuron disease, neuropathies, and myopathics. Thetefore the diagnostic value of jitter must be considered in light of the patient's clinical manifestations, and NCSs and needle EMG findings.

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Chapter 37
Neuroimaging

A. STRUCTURAL NEUROIMAGING

Evelyn M. L. Sklar, Armando Ruiz, Robert M. Quencer, and Steven F. Falcone

Major technological developments in neuroimaging have resulted in the detection and characterization of neurological diseases that were not demonstrated by earlier imaging methods. Magnetic resonance imaging (MRI) in particular has had the greatest effect on the practice of neurology since the advent of computed tomography (CT) in the 1970s.

This chapter reviews the basic principles of CT and MRI, discusses other imaging techniques, and illustrates and describes the findings in neurological diseases.

BASIC PRINCIPLES OF NEUROIMAGING PROCEDURES

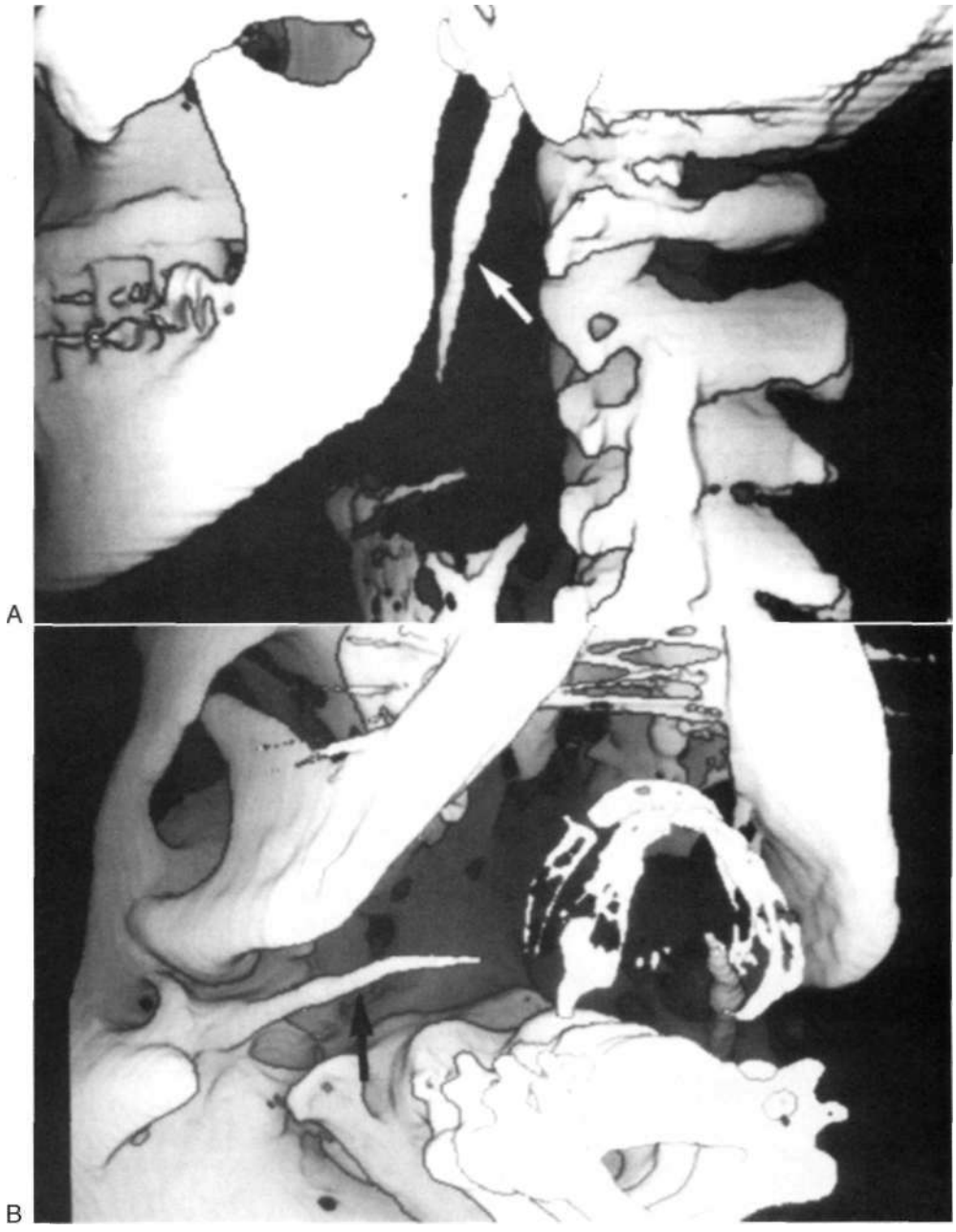
Computed Tomography

CT provides a cross-sectional image of the body. The images produced are based on the principle of tissue absorption of x-rays. A beam of x-rays is transmitted through the body, and the x-ray attenuation of a volume of tissue (voxel) is recorded. Shades of gray then are applied to the voxels, depending on the amount of x-ray absorption. A scan is produced as shades of black and white. Differences in the shades of gray directly reflect the differences in x-ray attenuation of different tissues. Tissues have different attenuation properties depending on the atomic number of their constituent atoms and physical density. The attenuation of a material can be described as an attenuation coefficient, which is then translated to a CT number on an arbitrary scale (Hounsfield units). The images are acquired in an axial or coronal plane and then may be reformatted in any desirable plane.

Contrast agents have increased the sensitivity and specificity of CT, The mechanism of enhancement is based on disruption of the blood-brain barrier by disease processes. This barrier normally restricts the movement of many substances from the bloodstream to the brain. On CT and MRI, only areas where the blood-brain barrier is damaged, such as tumors and inflammatory processes, enhance.

In 1989, spiral CT (helical or volume acquisition) was introduced clinically. With spiral CT, instead of by movement of the patient through the CT gantry at discrete intervals, each representing a slice, data are acquired continuously by constant rotation of the x-ray tube-detector system and the constant movement of the patient through the gantry. With spiral CT a long segment of the body (e.g., chest and abdomen) can be scanned during a single 20- to 30-second breath hold, eliminating problems of misregistration. A major advantage of spiral CT over conventional CT is the optimization of contrast administration. With short scanning times, less contrast material may be needed. Spiral CT also allows one to time the contrast administtation, optimizing the enhancement.

If the volumetric imaging capabilities of spiral CT are combined with optimal contrast enhancement, spiral CT angiography can be performed. Spiral CT also allows the acquisition of multiplanar two-dimensional (2D) and thtee-dimcnsional (3D) images, particularly for evaluating the carotid vessels both intracranially and at the neck level. Helical CT also creates 3D refotmations of the skeletal structutes of the calvatium, facial bones, and spine (Figure 37A.1),



F1GURE37A.1 Thi-to-diiiH'iisioiuiltL-fdniiattedeoniputcdtomogrrtphicima^c.l'arientwithF.agle'ssyndrome.Theseimagesareuseful in demonstrating rlic base of the skull skeletal anatomy. NOIL- the long styloid processes *[arrows).*

Magnetic Resonance Imaging

In MRI, the images result from the varying intensities of radio wave signals emanating from the tissue where hydrogen nuclei have been excited by a radio frequency (RF) pulse. Contrast in the MRI is the result of these differences in signal intensities. The initial level of intensity and its rate of decay depend on different physical properties of tissues, so different tissues show different intensity signals depending on the time between RF excitation and the sampling time chosen. Hydrogen is the most commonly used nucleus for MRI because of its abundance in biological tissues and the physical properties of the field sttcngths of the magnets available for clinical use.

When placed in a magnetic field, the majority of the hydrogen atoms align in the direction of the field. A 90-degree pulse produced by an RF transmitter then causes the net magnetization vector to rotate away from its primary alignment to produce net magnetization in a different plane. The resulting transverse component of the field is responsible for producing the MRI signal.

The loss of magnetization from the transverse plane occurs by two distinct relaxation processes: spin-lattice and spin-spin. Spin-lattice telaxation is the return of magnetization to equilibrium with the applied magnetic field *(z*-direction). This process is represented by the time constant T1. One Tl period is the amount of time in which 63% of the longitudinal magnetization has been regained. Spin-spin relaxation is the loss of nuclear spin phase coherence. The protons dcphase, resulting in a decrease in the transverse magnetization, causing a decrease in signal. Dephasing caused by molecular interaction alone is called *T2.* Dephasing produced by molecular interactions and spatial variation of the external magnetic field is called *T2 *.* Signal is measured at a time interval, echo time (TF), after the RF excitations. The time between excitations is called *repetition time* (TR).

The previous steps are the basis for the acquisition of spin-echo sequences. In Tl-weighted images, tissues with short relaxation times appear bright, whereas tissues with long Tl relaxation times (e.g., cerebrospinal fluid [CSF], cyst, edema) appear dark. In T2-weighted images, tissues with long T2 relaxation times (e.g., fluids) appear bright. In general, Tl-weighted images provide excellenr anatomical details whereas T2-wcighted images provide information about pathological conditions.

The four major types of magnets are permanent, hybrid, resistive, and superconducting. The field sttength achievable with a resistive magnet is limited, whereas it is possible to achieve magnetic fields of much greater strength with superconductive magnets. A set of coils called *sbitn coils* is used to adjust the static field to establish a high degree of homogeneity in the magnetic field.

Contrast agents have been used widely in MRI. As in CT, the enhancement of central nervous system (CNS) pathology is based on disruption of the blood-brain barrier. Unlike conventional contrast agents used in CT that are directly visualized, those used in MRI (called *paramagnetic contrast agents)* produce local alterations in the magnetic environment that influence the MRI signal intensity. It is the effect on proton relaxation that appears on the MRI, not the contrast material itself.

Fat Suppression Techniques

The fat suppression technique suppresses the normal bright signal of fat on Tl-weighted images to improve the visualization of enhancing lesions located in fatty areas such as the neck, orbits, and skull base and those in the spinal canal (e.g., to differentiate between normal epidural fat and enhancing scar in patients with previous spinal surgery). This technique takes advantage of the fact that water and fat protons resonate at different frequencies. The application of an additional 90-degree pulse sequence allows a chemical saturation of fat protons, nulling its signal.

Fast Spin-Echo Sequences

Fast spin-echo sequences are intended to acquire images (proton density, T2-weighted) in a fraction of the time needed by the conventional spin-echo sequences. The sequence is acquired by phase encoding of several echoes during a particular TR (echo train) instead of the traditional single echo during a conventional spin-echo sequence. The reduction in scan time improves image quality by increasing the signal-to-noise ratio or the spatial resolution of the scan. There are two main disadvantages to fast spin-echo techniques. First, a "true" proton density-weighted image cannot be obtained. The signal of CSF is brighter than in a conventional spin-echo proton density sequence; therefore, lesions adjacent to brain surface and the ventricular edges arc inconspicuous and difficult to detect. Furthermore, with fast spin-echo T2-weighted images there is less loss of signal intensity from fat, a fact that limits the evaluation of bright lesions against a fatty background.

Additional advantages of fast spin-echo sequences include less loss of signal intensity and susceptibility effect seen when dealing with ferromagnetic substances or materials (e.g., evaluation of spine lesions in patients with orthopedic metallic instrumentation),

Gradient-Recalled Echo Sequences

Gradient-recalled echo sequences are faster than spin-echo sequences. The MRI signal is produced by using a dephasing and a readout gradient without a 180-degree

RF pulse. The images acquired are noisier than spin-echo images and include more artifacts because of changes in magnetic susceptibility between tissues. The gradient-recalled echo "T2-like" images are useful in detecting blood-containing lesions or collections in early and chronic-stages (deoxyhemoglobin and hemosiderin, respectively). Tl-weighted gradient-recalled echo sequences with thin slices arc used to generate Tl-weighted 3D volume data acquisition. These data can be reformatted to generate images in any plane.

Magnetization Transfer Contrast Imaging

In magnetization transfer contrast imaging, the magnetization transfer pulse selectively saturates prorons bound to tissue macromolccules, which typically have restricted motion. Later, the magnetization is transferred from the bound protons to the unbound water protons surrounding these macromolecules. Magnetization transfer pulses can be obtained with Tl-weighted images, thus decreasing the white matter signal, which in turn allows enhancing lesions to become more conspicuous on postcontrast Tl-weighted images (e.g., brain merastasis, multiple sclerosis [MS] plaques). Magnetization transfer conrrast pulses are used also to suppress the background signal when performing time-of-flight magnetic resonance angiography (MRA) studies.

Diffusion-Weighted Magnetic Resonance Imaging

Diffusion-weighted MRI (DWI) of the brain is a new method based on echo-planar imaging. To date, this sequence has been used primarily to detect cerebral ischemia. This technique is not widespread because specialized hardware and software are needed. Given the potential of DWI to improve acute stroke management and the increase in the number of MRI systems that perform this sequence, diffusion-weighted imaging of the brain will certainly become a staple in the workup of acute cerebral ischemia.

Physics

Diffusion is the process of random molecular motion (Brownian motion). Free diffusion in biological systems usually occurs in CSF. Isotropic restricted motion occurs in a homogeneous medium and is directionally invariant, as in gtay matter. White matter is inhomogeneous; it contains cell membranes, myelin, and nerve fibers. Therefore diffusion of water in the whire matter is an orientation-dependent (anisotropic) phenomenon. The measured value of the mobility of water is known as the apparent diffusion coefficient (ADC). Alterations in the restriction of water movement that are central in the pathophysiological changes that occur in ischemia result in changes in the ADC of water.

DWI is designed to detect the random movement of water protons. Noninvasive spatially varying magnetic gradients that label water protons ate applied. The technique generates a series of images with various degrees of diffusion encoding, from very little to intense diffusion encoding. The degree of diffusion encoding is indicated by the b value. A b value of zero indicates no diffusion encoding and essentially corresponds to a conventional T2-weightcd image in which the CSF is high signal, with white matter appearing dark and gray matter appearing brighter than white matter. In images with higher b values (greater degrees of diffusion encoding), both the CSF and the brain parenchyma become darker, the former at a more rapid rate because of the free diffusion of water protons in CSF. When large b values are applied in a particular direction, diffusion can be made the dominant image contrast mechanism, enabling variations in diffusion to be visualized, including their directional dependence.

The differences in the rate of change of signal intensiry at different b values allow calculation of ADC, which is a quantitative measure of water diffusion. Normal white matter regions in the brain, which have unrestricted water movement (high diffusion rates) along the orientation of their fibers, have high ADC values and appear bright on the calculated ADC image. In contrast, gray matter regions, with restricted water movement (low diffusion rates), have low ADC values and appear dark on the calculated ADC image. A typical protocol generates diffusion-weighted images with multiple b values.

Diffusion images ate best obtained by applying the diffusion gradient in three orthogonal axes *{x, y, z)* because water movement in the brain parenchyma is anisotropic. The individual images generated from the application of the diffusion gradients in the three otthogonal axes are summed and displayed as a trace image for both the calculated ADC images and the diffusion-weighted images. This allows the cancellation of high-signal regions on the diffusion-weighted images and low-signal regions on the ADC images that would result from normal white matter tracts when diffusion is applied perpendicular to the white matter tracts.

Clinical Application

How does ischemic tissue affect the contrast of a diffusion-weighted image? It is thought that acute ischemia induces a shift of water from the unconstrained extracellular space to the more constrained intracellular space (cytotoxic edema), This results in a 33-60% decrease in ADC as early as 4 minutes after ischemia in overall models that results in a hypointense region on the calculated ADC map and a hyperinrensc region on the diffusion-weigh ted image (Figures 37A.2 and 37A.3). It is unclear whether changes in diffusion are an early indication of infarction or

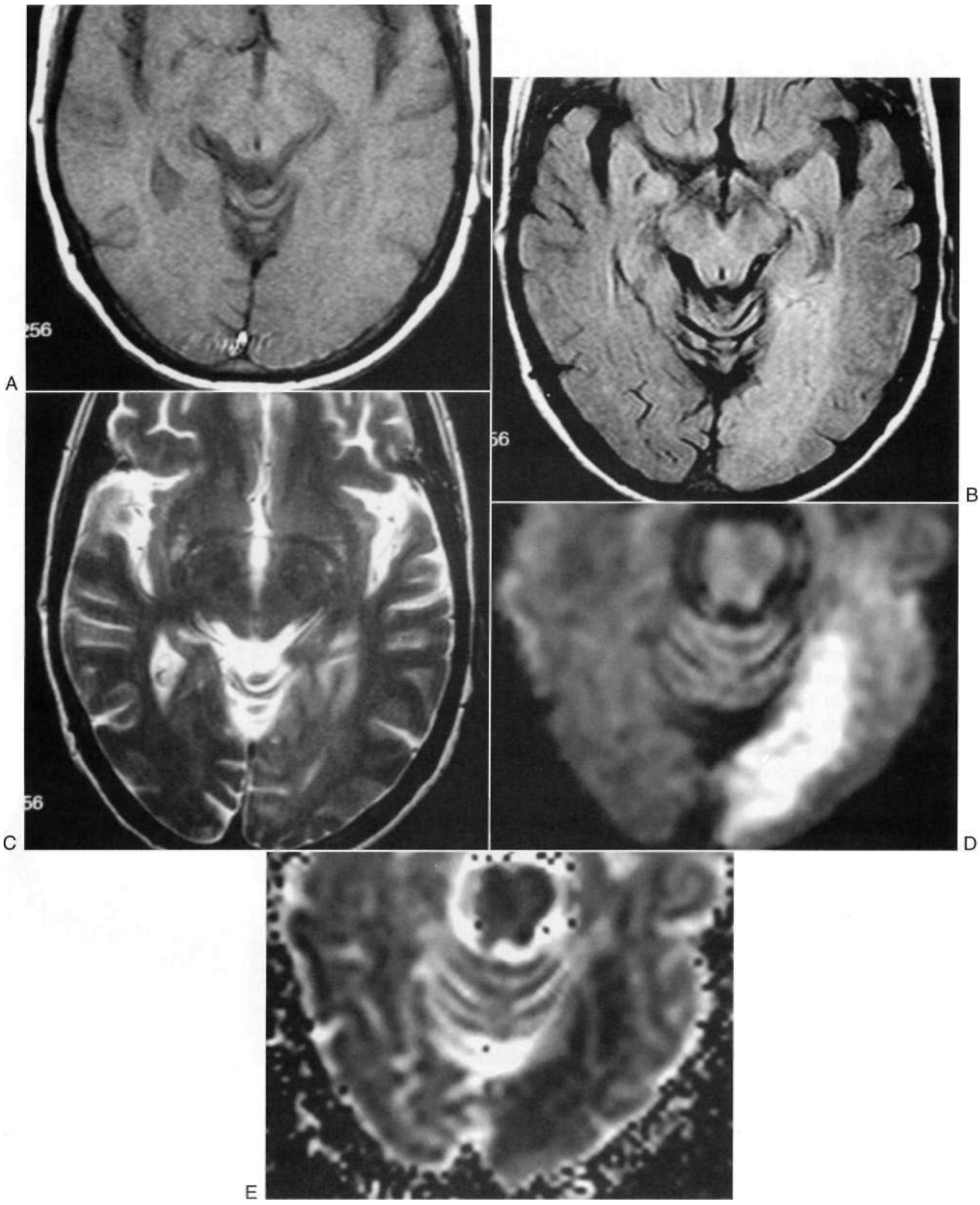


FIGURE 37A.2 Stroke. (A) Axial Tl-weighted image shows subtle effacement of sulci in the left occipital lobe. (B) Axial fluid-attenuated inversion recovery and (C) T2-weighted images show subtle hyper in tensity in the left occipital lobe. (D) Diffusion-weighted image (DWI) and (E) apparent diffusion coefficient (ADC) map demonstrate a matched defect (high signal on DWI and low signal on ADC) consistent with restricted diffusion.

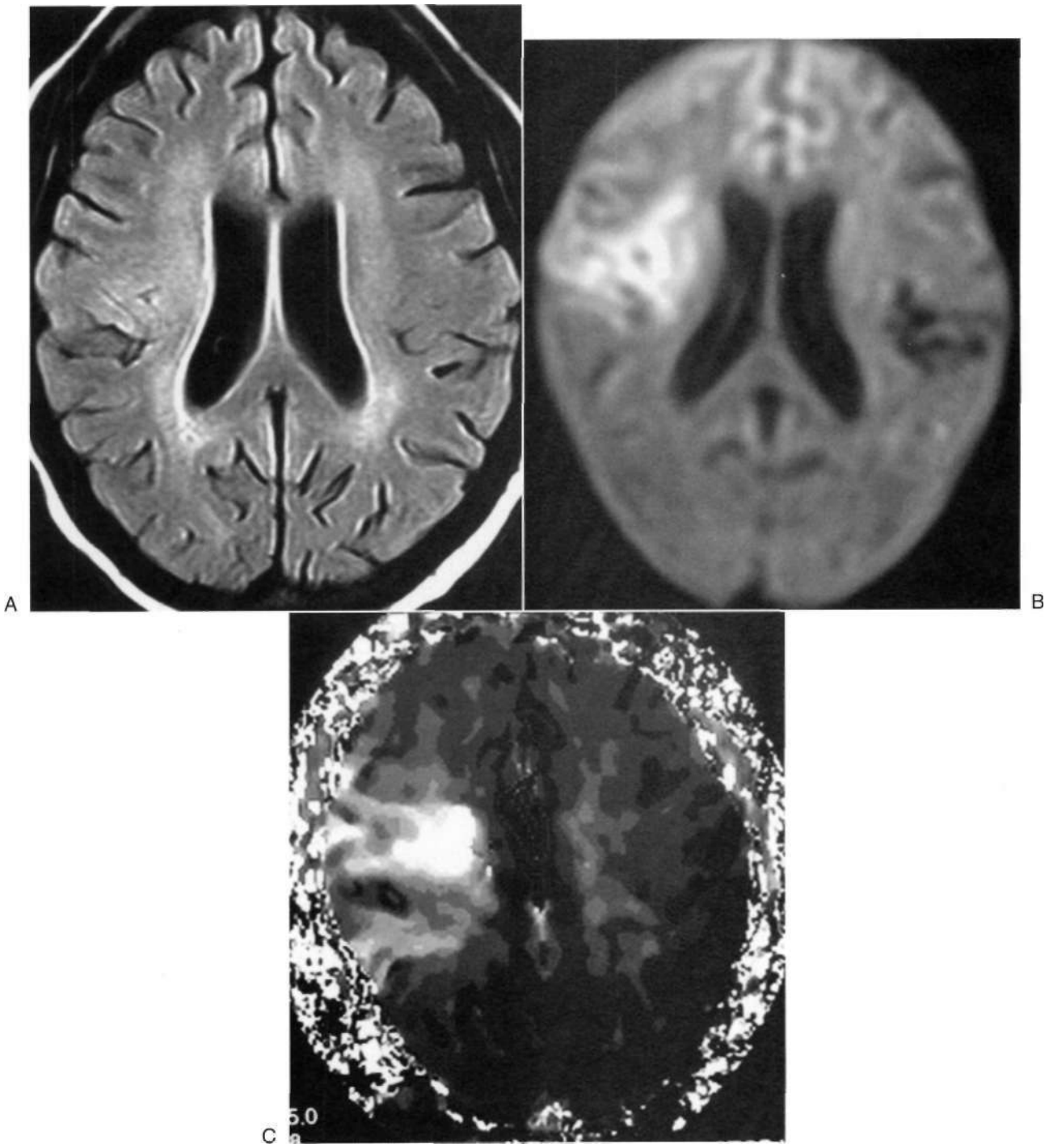


FIGURE 37A.3 Stroke. (A) Fluid-attenuated inversion recovery axial image shows very subtle hyperintensity in the right frontotemporal region. (B) Diffusion-weigh ted image (DWI) shows an area of increased signal, which had a correspondingly low apparent diffusion coefficient (not shown). (C) Time-to-peak (TTP) perfusion map shows an increase in the TTP consistent with a perfusion deficit, which was slightly larger than the DWI deficit. The mismatch is consistent with tissue at risk or the ischemic penumbra.

irreversible ischemia because reversibility has been demonstrated in animals but not in humans. When interpreting these images, one must remember that a T2 component is always present in the diffusion-weighted image contrast even with a large b value. This can result in a phenomenon known as T2 *skine-througk.* Evaluation of the diffusion image along with the calculated ADC maps is necessary to avoid misinterpreting an area of T2 shine-through as a region of restricted diffusion. A true region of restricted diffusion will appear hypcrintense on the DWI but

hypointense on the ADC map (see Figures 37A.2 and 37A.3).

Once infarction occurs, there is an eventual increase in the ADC, which returns to normal and then increases when compared with unaffected tissue. This increase in the ADC is presumably related to an increase in extracellular water in an area of chronic infarction. The time course of elevation of depressed ADC as it relates to a stroke signature is unclear. It is likely that depressed ADCs persist to the end of the second week after the acute ischemic event.

It is still unclear what role diffusion imaging will play in acute stroke management. To date, diffusion imaging has been of value in improving the detection of acutely ischemic brain regions, identifying ischemic regions in patients with multiple white matter abnormalities, identifying acutely ischemic regions adjacent to chronic infarcts, and increasing clinical confidence in diagnosis. It is likely that diffusion-weighted images and magnetic resonance perfusion imaging will play a vital role in diagnosing and managing acute stroke.

It is also important to remember that restricted diffusion may be seen in conditions other than stroke. It may also be seen in abscesses (Figure 37A.4), some infections such as Creutzfeldt-Jakob disease (Figure 37A.5), and other entities such as an epidermoid cyst (Figure 37A.6). In the latter case, it is helpful in distinguishing this entity from an arachnoid cyst because arachnoid cysts do not have restticted diffusion and instead have CSF characteristics.

Perfusion-Weigh ted Magnetic Resonance Imaging

Perfusion-weighted MRI (PWI) of the brain is a functional imaging method that provides physiological information. Although the anatomical information provided by conventional MRI sequences is sensitive in detecting pathological changes, it is not specific. In addition, some neurological diseases including dementia and psychiatric illnesses may have a normal appearance on conventional imaging. PWI may provide clinically useful information differentiating between tumor and radiation necrosis, grading gliomas, detecting perfusion changes in anatomically normal regions in patients with dementia and psychiatric illnesses, and detecting the ischemic penumbra around an area of acute cerebral infarction.

Physics

PWI is sensitive to microvascular tissue-level blood flow. Most clinical experience is with gadolinium-based relative cerebral blood volume (rCBV) perfusion imaging, but techniques are available to obtain information about perfusion without the use of contrast (spin-labeled perfusion). The following is a summary of the physics behind gadolinium-based perfusion imaging.

Gadolinium is a suitable agent for use in perfusion imaging because of the susceptibility effects of gadolinium on $T2^{"1}$, not the 11 shortening effects that are routinely associated with contrast enhancement. In rCBV perfusion imaging, the T2* MRI signal dropoff in a perfused region of brain caused by rapid passage of gadolinium through the capillary bed is used to compute the relative perfusion to that region. This signal drop depends on both the vascular concentration of contrast agent and the density of small (3- to 10-/im) vessels per voxel of tissue. This gadolinium-based rCBV mapping technique also requires quick, susceptibility-sensitive ($T2^{S}$) scanning capabilities. The technique is optimized through fast scanning techniques such as gradient-echo echoplanar MRI. To produce a high intravascular concentration and limit recirculation, contrast should be administered as a tight bolus. We typically inject 5 mL per second with a power injection. A double dose of contrast can improve signal changes, producing a 2()-30% peak signal drop in gray matter at a TE of 100 milliseconds. rCBV maps are constructed using tracer kinetic principles by integrating the signal-time curve for each voxel. Maps are relative in that the arterial input function is not typically measured, so true quantitative volumes are not routinely calculated.

One can envision that a problem will arise in highly permeable regions of severe blood-brain barrier breakdown. In this situation, the Tl shortening effects of gadolinium predominate in lowering the T2* signal of gadolinium, resulting in falsely low rCBV values. This can occur with enhancing tumors and subacute infarcts. To limit the Tl shortening effects of gadolinium, rCBV maps must be mathematically corrected for Tl enhancement. Spin-labeled techniques are not susceptible to this problem but are fraught with other limitations such as long imaging times.

Clinical Applications

As seen with non-magnetic resonance perfusion techniques, PWI can identify an ischemic penumbra in acute stroke. The advantage of magnetic resonance techniques is the improved spatial resolution and the ability to coregister PWIs with DWIs. This is important in distinguishing between irreversible infarcted tissue and ischemic but potentially salvageable tissue. However, this distinction assumes that the DWI abnormalities define the minimal infarct volume.

In humans, three general patterns of DWI and rCBV abnormalities in acute stroke have been described: matched abnormalities, larger rCBV abnormality with the final infarct size greater or equal to the rCBV abnormality, and larger rCBV abnormality with final infarct size between the DWI and rCBV abnormality. Comparing DWI, rCBV, relative cerebral blood flow, mean transit time, and time to peak, rCBV probably is the best predictor of final infarct volume. Relative cerebral blood flow and mean transit time maps overestimate final stroke volume. The identification

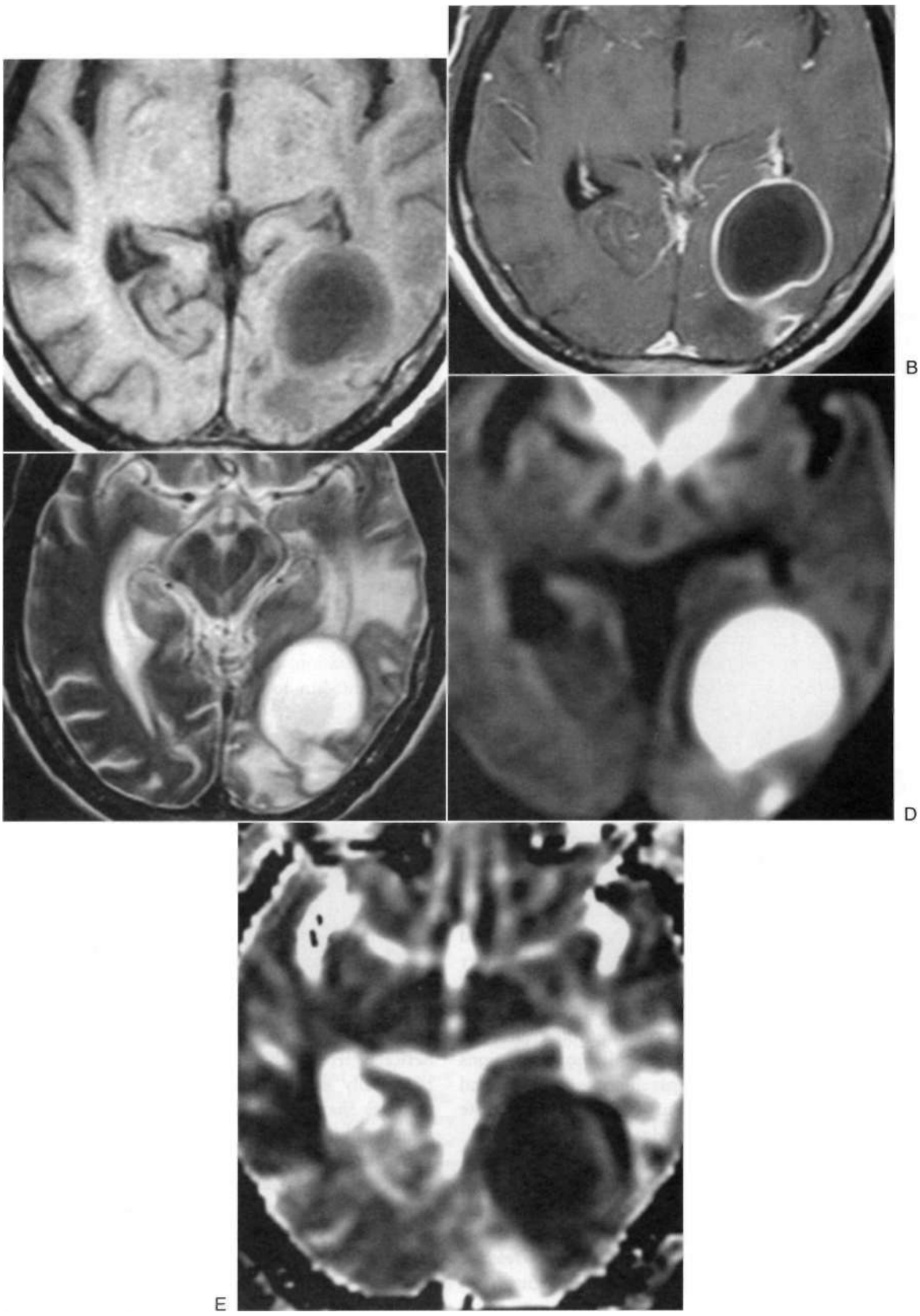


FIGURE 37A.4 Abscess. Tl-weighted axial images (A) before and (B) after contrast administration demonstrate a ring-enhancing lesion in the left occipital lobe. (C) This lesion is hypenntense on T2-weighted image and shows some surrounding edema and mass effect. (D) Diffusion-weighted image and (E) apparent diffusion coefficient map show restricted diffusion in this lesion.

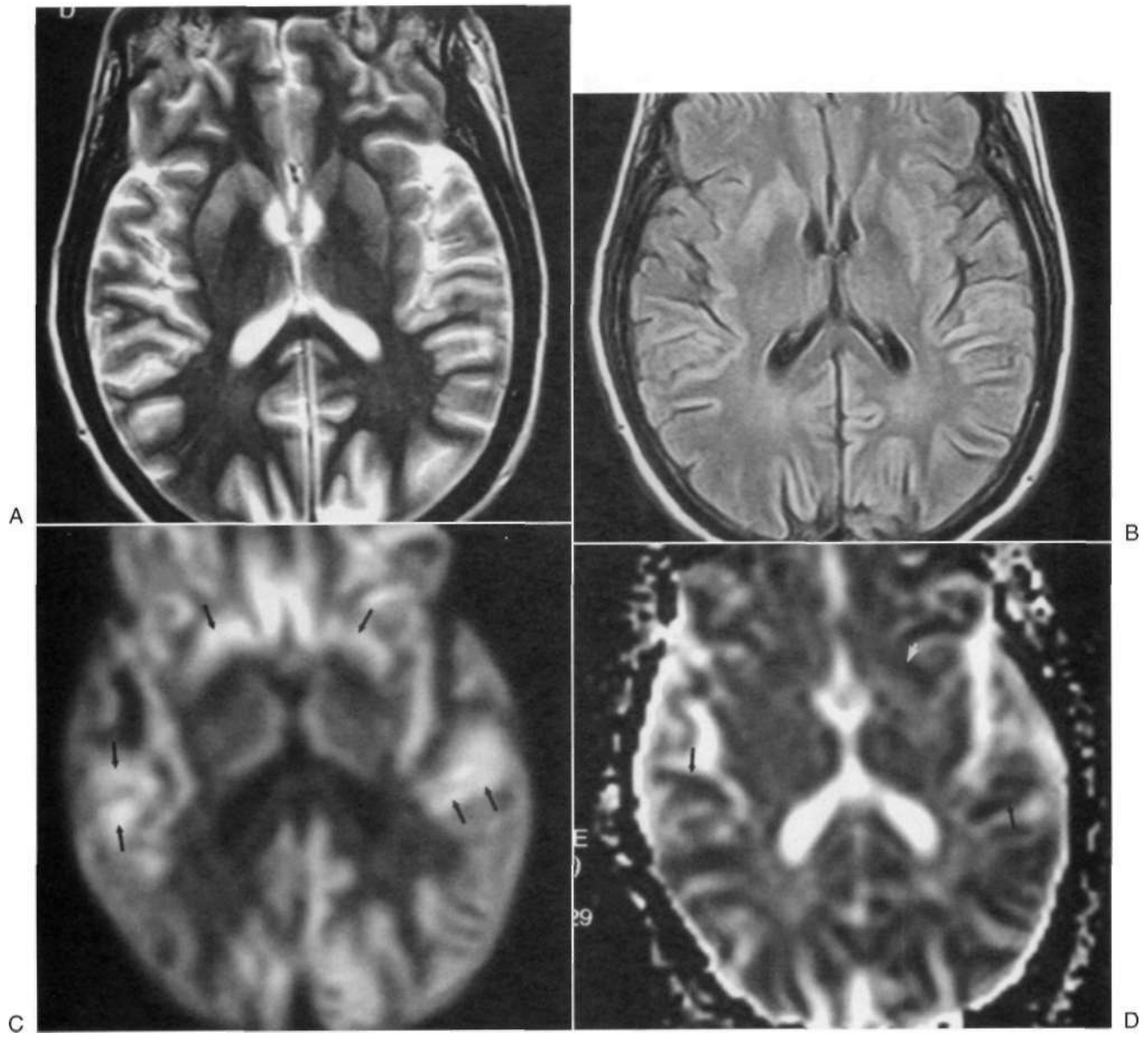


FIGURE 37A.5 Creutzfeldt-Jakob disease. (A) T2 axial and (E) fluid-attenuated inversion recovery axial images show very subtle hyperintensity involving the basal ganglia bilaterally. (C) Diffusion-weighted image and (D) apparent diffusion coefficient map show restricted diffusion in both temporal lobes *(arrows)* and basal ganglia bilaterally *(arrows).*

of rCBV abnormalities greater than DWI probably will be one of the key factots in determining which patients ate most likely to benefit from thrombolysis.

So far, the most extensive clinical application of magnetic resonance perfusion imaging has been in tumor imaging, Potential uses include tumor grading, determining potential biopsy sites, distinguishing recurrent tumor from radiation necrosis, and following response to treatment. In untreated gliomas, rCBV imaging has a high negative predictive value because the absence of incteascd rCBV excludes high-grade tumor irrespective of the enhancement characteristics of the lesion. However, gadolinium-based perfusion imaging is problematic because of blood-brain barrier breakdown ptesent in many tumors. Non-gadolinium-based methods may turn out to be a valuable alternative and ultimately more accurate.

PWI has shown some promise in evaluating dementia and psychiatric illnesses, migtaine, and trauma, but it is too early to know whether any of these applications will result in daily clinical use.

Flu id-Attenuated Inversion Recovery Imaging

In fluid-attenuated invctsion recovery (FLAIR) imaging, a radiofrequency pulse is applied during a chosen inversion time before the conventional spin-echo sequence. With FLAIR, the CSF signal is sttongly attenuated without

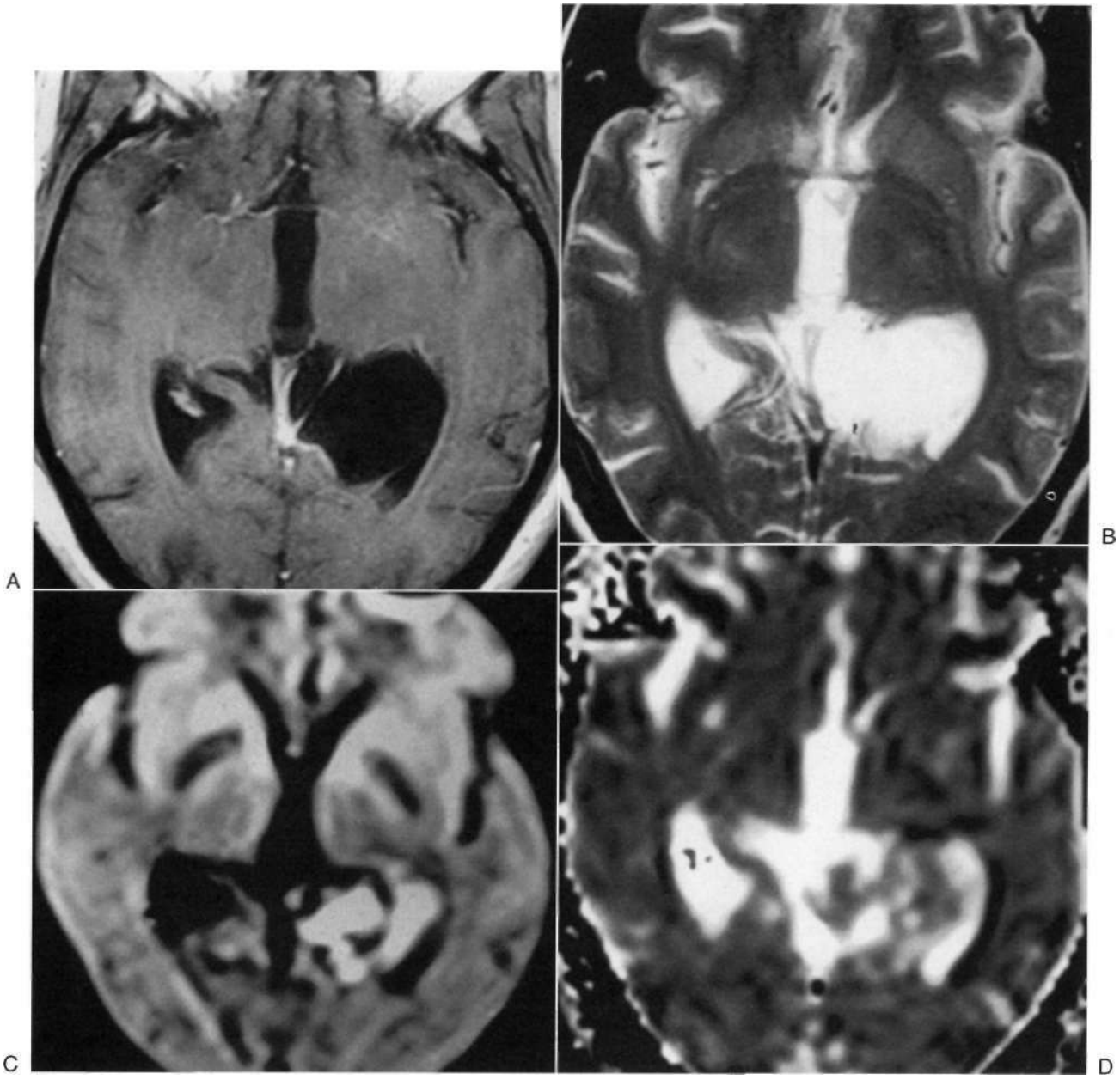


FIGURE 37A.6 Epidermoid tumor. (A) Tl- and (B) T2-weighted axial images show an intraventricular cystic lesion, which has signal intensity similar to that of cerebrospinal fluid (CSF). (C) Diffusion-weighted image and (D) an apparent diffusion coefficient map show that this lesion does not follow CSF characteristics and instead is restricted.

affecting the brain signal. In other words, a T2-like image is obtained in which the CSF appears black. With this technique, pathological lesions, particularly in the periventricular regions, extra-axial collections, and lesions near the brain surfaces, appear more conspicuous (Figure 37A.7).

Echoplanar Imaging

Echoplanar imaging is a fast imaging technique that allows collection of all the data needed to reconstruct an image in a brief interval (30-100 milliseconds). Rapid acquisirion of multiple rows of K space is the fundamental principle for this technique. Echoplanar imaging is ideal for evaluating uncooperative patients, mapping rCBV, and performing functional task activation studies.

Angiography

Many indications exist for cerebral angiography, including the investigation of patients with subarachnoid hemorrhage and intracerebral hemorrhage in whom the cause has not

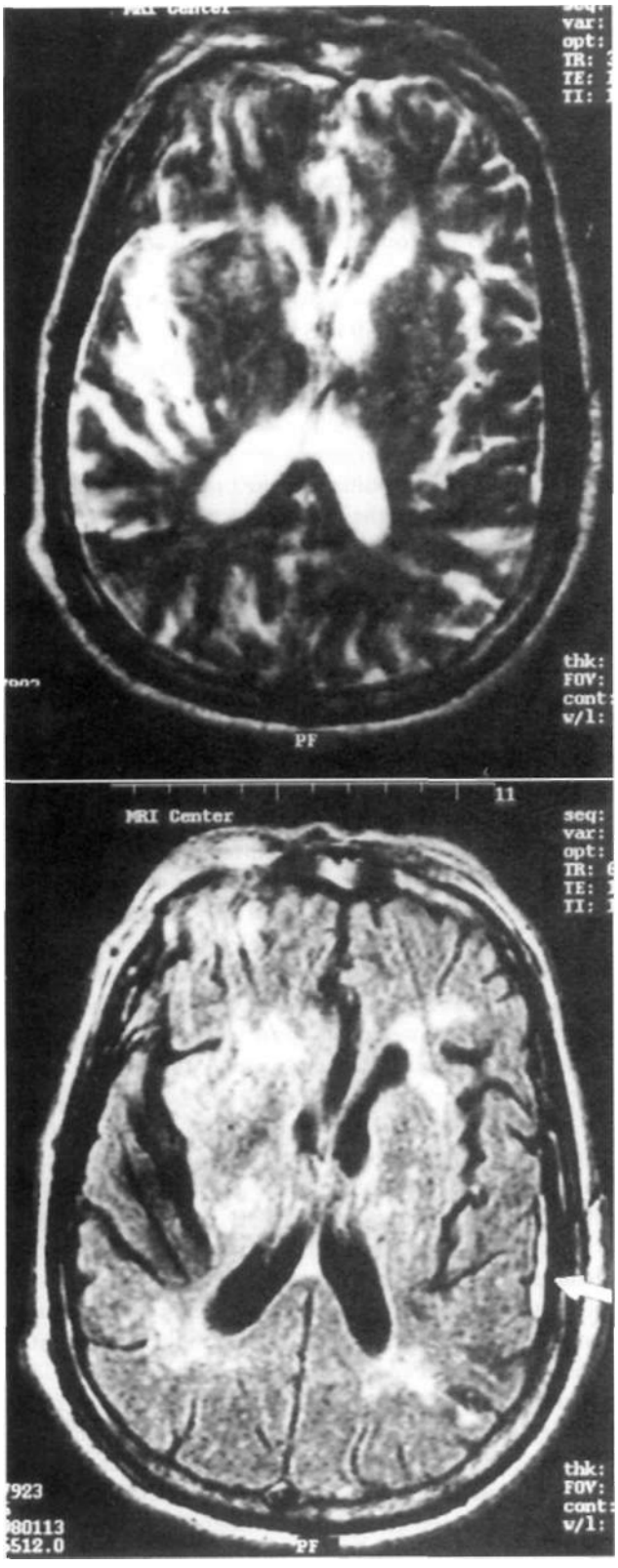


FIGURE 37A.7 Axial T2-weightcd *{top)* and axial fluid-attenuated inversion recovery {FLAIR) image *{bottom)* in an older adult with periventricular white matter ischemic changes. The white matter changes are more conspicuous in FLAIR, as is the incidental small left temporal subdural collection *{arrow).*

been determined clinically or with CT or MRI. Angiography is used also in patients with thromboembolic stroke, especially to evaluate the carotid vessels in the neck and the intracranial vasculatute. In patients with arterial dissections, vasculitis, or tumors at the base of the skull, angiography is indicated also.

Currently, angiography is performed by puncturing the femoral artery and threading a catheter up the iliac artery and into the aortic arch, with subsequent selective catheterization of the carotid or vertebral arteries (see Chaptet 37C). After the desired vessel is entered, an iodine-containing contrast agent is injected and serial films of the vasculatute are obtained for approximately 10 seconds to demonstrate arterial, capillary, and venous phases of the cerebral circulation. More recently, digital subtraction angiography has been substituted for cut-film angiography, in which a computer subtracts the background image and transmits it to a television monitor.

In addition, newer advances in angiographic techniques have allowed expansion in the field of interventional neuroradiology. These procedures include embolization of vascular malformation and tumors, occlusion of cavernous carotid fistulas by detachable balloons, and angioplasty. The advent of the tracker catheter system and its variants has greatly promoted this field. MRA and magnetic-resonance venography offer the advantage of being noninvasive, although they have somewhat lower resolution than catheter angiography (sec Chapter 37B).

Myelography

Myelography is still used in certain cases in which MRI cannot be performed, such as in postoperative patients in whom multiple clips or metallic hardware may produce too many artifacts. CT myelogtaphy also may define nerve root avulsions or dura! tears better than MRI. An iodinated water-soluble agent is injected into the subarachnoid space and roentgenographical images of the spine are obtained. Tilting the myelogram table moves the contrast throughout the spine. The contrast agents can be introduced by a lumbar, C1-C2, or cisternal puncture.

Intraoperative Neurosonography

The field of neurosonology for imaging the cerebral vasculature is reviewed in Chaptet 37D. A high-resolution, portable, real-time sonographic scanner that can be used in the operating room allows the visualization of intraspinal or intracranial abnormalities and permits the surgeon **and** radiologist to assess the progress and final result of surgety before the operation is completed.

The images are obtained using a 7.5-MHz or 5.0-MHz in-line ttansducer, with the optimal focus varying depending on the transducer's RF. The transducer is placed most

commonly in a water bath at the laminectomy site in the case of intraoperative spinal sonography or at the craniotomy or burr hole site in the case of intraoperative cranial sonography.

Intraoperative neurosonography is performed in multiple planes. Images are obtained in each plane by gradually moving the transducer across the operative field. Filmed images are obtained throughout the study.

Magnetic Resonance Angiography

MRA is a very sensitive method for detecting and characterizing blood flow. It produces a blood flow map in which the vessel visualization is based on the physical differences between moving and stationary protons (see Chapter 37B). Image intensity reflects velocity and flow patterns.

There are two major MRA techniques: time-off light angiography and phase contrast angiography. The differentiation between moving and stationary protons depends on the degree of longitudinal or transverse magnetization. Time-of-flight angiography deals with longitudinal magnetization and is sensitive to amplitude, whereas phase contrast angiography deals with transverse magnetization and is sensitive to phase.

Time-of-flight angiography relies on inflow of unsaturated protons into an imaging plane. A volume is repeatedly pulsed, and because stationary nuclei are unable to remagncrizc fully when the repetition period is smaller than the relaxation timeTl, their signal is smaller than that of the fully magnetized nuclei flowing into the excited volume. Therefore inflowing blood has a higher signal than stationary tissue, and the difference between the signals of stationary and flowing protons produces a time-of-flight MRA.

Phase contrast MRA relies on velocity-induced phase shifts of moving protons. A bipolar gradient is applied, and if the proton is stationary, there is no phase shift. However, if the proton is moving, a phase shift occurs. The faster the proton moves, the greater the phase shift. Velocity-induced changes in the transverse magnetization distinguish moving from stationary protons.

MRA can be performed with either a 2D or 3D Fourier transformation (2DFT or 3DFT) gradient-echo technique. In 2DFT techniques, each slice is individually acquired, and even slow flow is identified. In 3DFT or volume acquisition, data are acquired from an entire volume simultaneously. Very thin sections can be obtained with 3DFT, so high resolution can be attained.

The maximal intensity projection is a ray-tracing technique performed at a specific angle. It processes a series of acquired slices by projecting a straight line through these slices. It selects only the pixels along the ray with the highest signal intensity, so only vascular structures are represented in the final image. The procedure is repeated using parallel rays until a full 2D projection is generated. The use of MRA with arteriovenous malformations (AVMs) is illustrated in the following section on vascular malformations.

The source images are the individually reconstructed 2DFT or 3DFT partitions, whereas the collapsed view refers to the maximal intensity projection that "pancakes" all the images into one,

INTRACRANIAL LESIONS

Intra-Axial Brain Tumors

Supratentoriai Tumors

Primary cerebral gliomas make up 40-45% of all intracranial tumors; their incidence peaks in the second decade of life. In adults, most of these are supratentorial, whereas in children, they are mostly located in the posterior fossa. The degree of malignancy is variable, ranging from low-grade pilocytic astrocytomas to glioblastomas.

MRI is more sensitive than CT for tumor detection and delineation, even after contrast administration.

Oligodendrogliomas. Oligodendrogliomas usually have a heterogeneous signal on MRI, with small cystic regions and areas of hemorrhage. Edema usually is not significant, Calcification on CT has been reported in 50-90% of these tumors. One half of the cases demonstrate contrast enhancement (Figure 37A.8).

Low-Gradc Astrocytoma. Low-grade astrocytoma (grades I and II) is an irregular nonhomogeneous lesion, and calcifications are present in approximately 15% of cases. Usually, there is little edema around the lesion, and in general it is noncncapsulated and poorly demarcated from the surrounding parenchyma. With contrast, grade I astrocytomas may show minimal or no enhancement, and grade II astrocytomas enhance in approximately 90% of cases.

Pleomorphic Xanthoastrocytoma. Pleomorphic xanthoastrocyroma is a distinct astrocytoma subtype, more common in children and young adults. Presentation typically occurs in the second or third decade of life. The patient may present with symptoms of seizures. Histologically, the tumor consists of a cyst with lipid vacuoles, fibrillary astrocytes, and multinucleated giant cells. A typical location for this tumor is the temporal region, and an enhancing mural nodule usually is seen. Calcifications occasionally are present.

Dyscmbryoplastic Neuroepithelial Tumor. This benign neoplasm may be the underlying tumor in up to 23% of patients with temporal lobe epilepsy. The neoplasm contains ganglioneuronal elements and may be associated

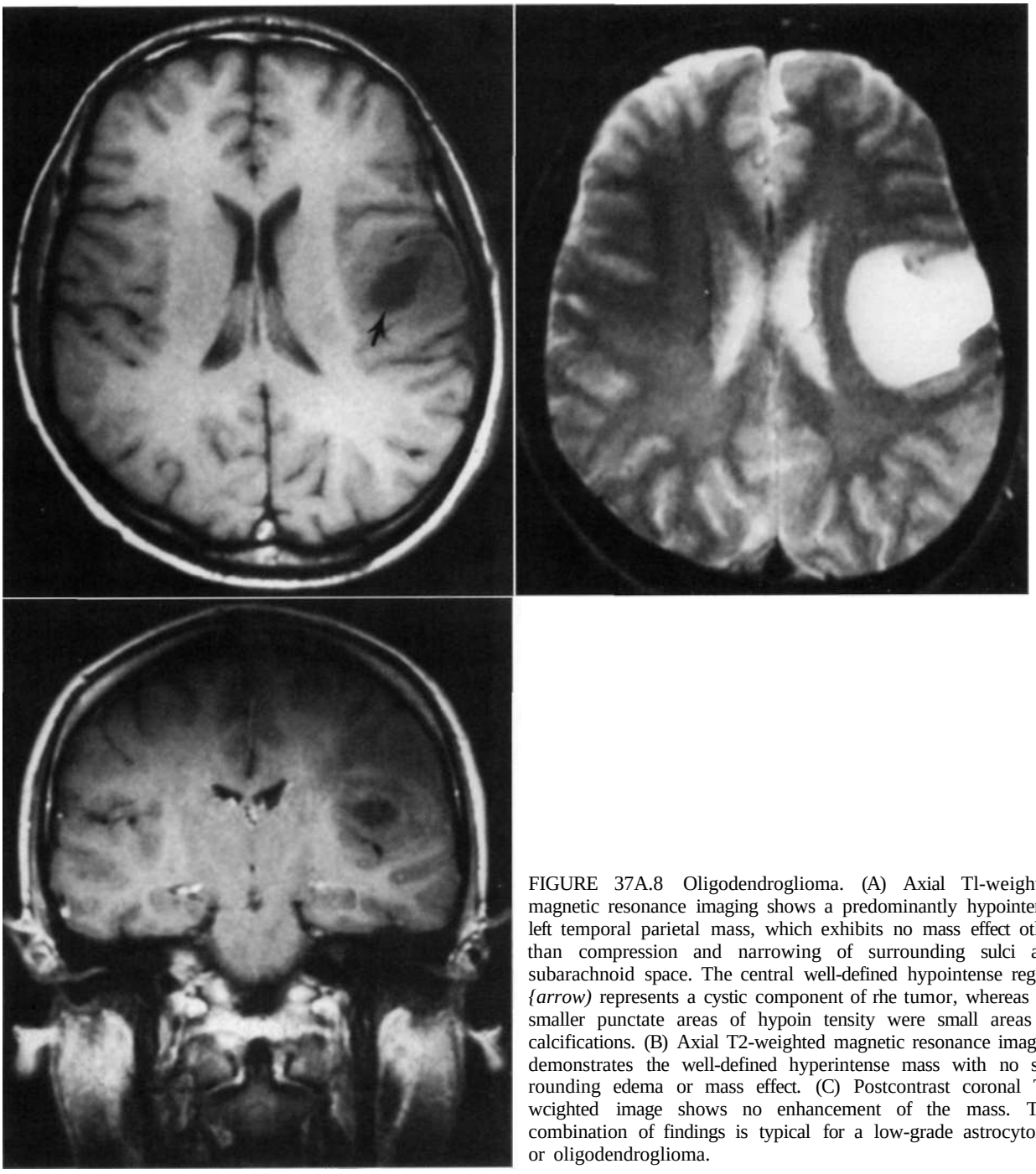


FIGURE 37A.8 Oligodendroglioma. (A) Axial Tl-weighted magnetic resonance imaging shows a predominantly hypointense left temporal parietal mass, which exhibits no mass effect other than compression and narrowing of surrounding sulci and subarachnoid space. The central well-defined hypointense region *{arrow)* represents a cystic component of rhe tumor, whereas the smaller punctate areas of hypoin tensity were small areas of calcifications. (B) Axial T2-weighted magnetic resonance imaging demonstrates the well-defined hyperintense mass with no surrounding edema or mass effect. (C) Postcontrast coronal Tl-wcighted image shows no enhancement of the mass. This combination of findings is typical for a low-grade astrocytoma or oligodendroglioma.

with cortical dysplasia. A cystic lesion may be seen on CT or **MRI,** with or without enhancement.

Ganglioglioma. Ganglioglioma affects mostly children and young adults and contains both neural and glial elements. Most gangliogliomas are supratentorial, with the temporal lobe the predominant site. In imaging studies, they are well circumscribed and typically cystic and often have calcification (Figure 37A.9).

Glioblastoma **Multiforme.** Glioblastomas represent the most malignant end of the spectrum of glial tumors. They represent 15-20% of all intracranial tumors, arc the most common supratentorial neoplasm in adults, and show a male predominance. Peak incidence is between 45 and *55* years of age. They arc located most commonly in the frontal lobe, followed by the temporal lobe. A **"butterfly"** pattern is the characteristic distribution in those glioblastomas, with bihemispheric involvement and infiltrarion of

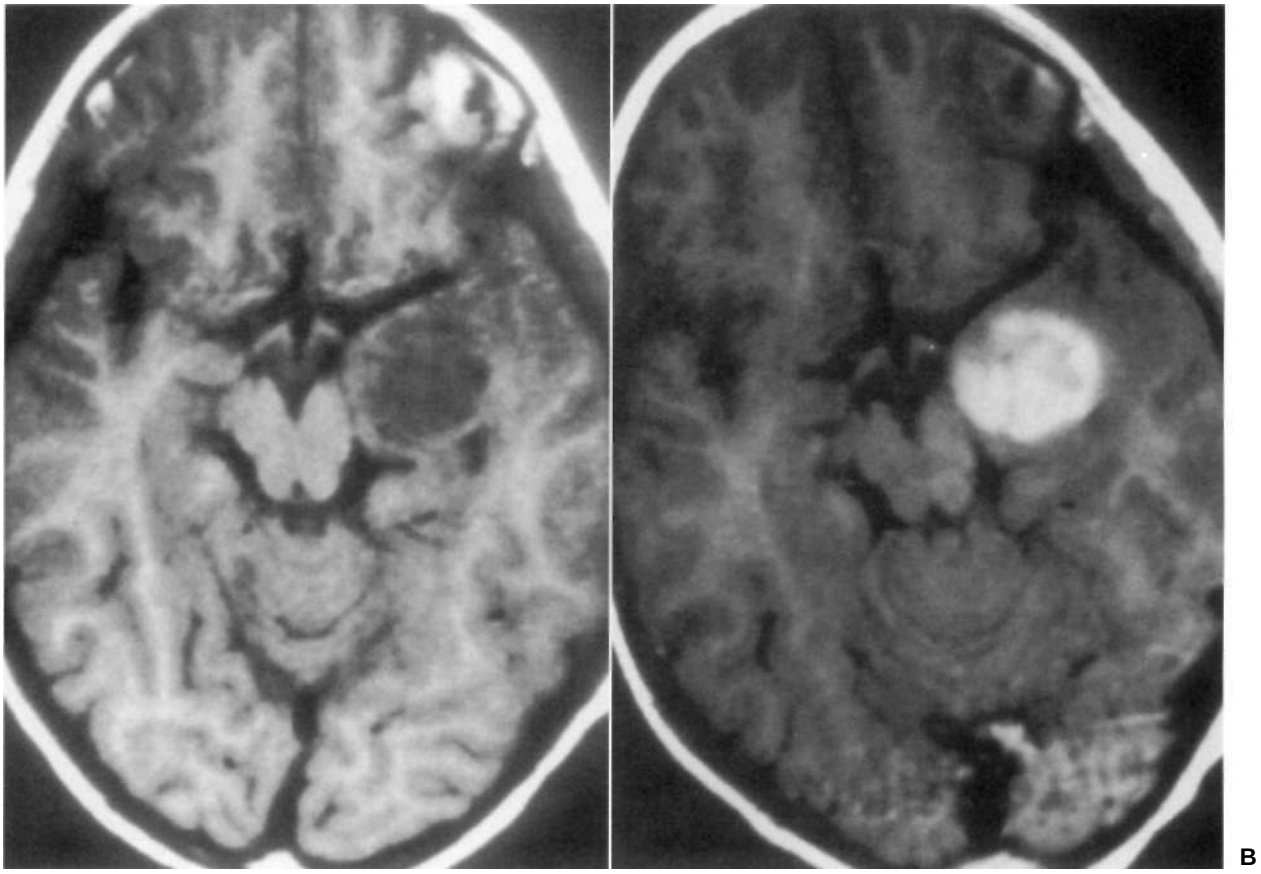


FIGURE 37A.9 Left temporal lobe ganglioglioma. Patient with history of temporal lobe seizure. (A) Axial Tl-weighted image demonstrates a low-signal mass lesion in the medial portion of the left temporal lobe. (B) The lesion enhances nearly homogeneously with gadolinium.

the intervening corpus callosum. Glioblastomas tend to invade the leptomeninges and dura.

MRI usually shows marked tumoral heterogeneity (Figure 37A.10), with necrosis and cystic changes. These tumors tend to bleed, but calcification is rare. The majority of these lesions enhance with contrast, and the enhancement pattern is heterogeneous. One can see ringlike enhancement with thick, irregular nodular areas surrounding necrotic regions {see Figure 37A.10). Regions that enhance correlate with areas of viable tumor tissue at pathological examination, so enhancement is helpful in guiding surgical biopsy. It should be emphasized that one cannot distinguish the exact margins of the tumor from edema. As with all infiltrative gliomas, there is no clear margin microscopically that separates tumor cells from reactive gliosis, edema, or normal brain.

Lymphoma and Metastatic Disease. Primary CNS lymphoma represents approximately 1% of all primary brain tumors, although this incidence has been steadily increasing in the past decade because of its frequent occurrence in patients with acquired immunodeficiency syndrome (AIDS). Focal intracerebral masses arc the most common initial presentation of primary CNS lymphoma, and multiplicity is common. Intracranial metastases from systemic (nonprimary CNS) lymphoma tend to involve the leptomeninges (with or without parenchymal involvement). The appearances of parenchymal lymphoma on neuroimaging studies include masses that involve the deep gray matter structures, periventricular regions, and corpus callosum. The amount of edema seen on MRI varies. Signal intensity also varies, but when these lesions are deep they are often isointense to gray matter on T2-weighted images. In the majority of lymphomas, enhancement is dense and homogeneous (Figures 37A.11 and 37A.12). Secondary brain involvement is indistinguishable from primary CNS lymphoma, but parenchymal as opposed to meningeal involvement is more common with primary lymphoma. Postcontrast MRI is more sensitive than CT for detecting leptomeningeal seeding. Lymphoma in patients with AIDS tends to have more necrosis than in those without AIDS and therefore appears as lesions with ring enhancement and more prominent edema.

Cerebral metastases account for 26% of all clinically detected brain tumors, and 80-85% of them arc supratentorial in location. The optimal screening examination

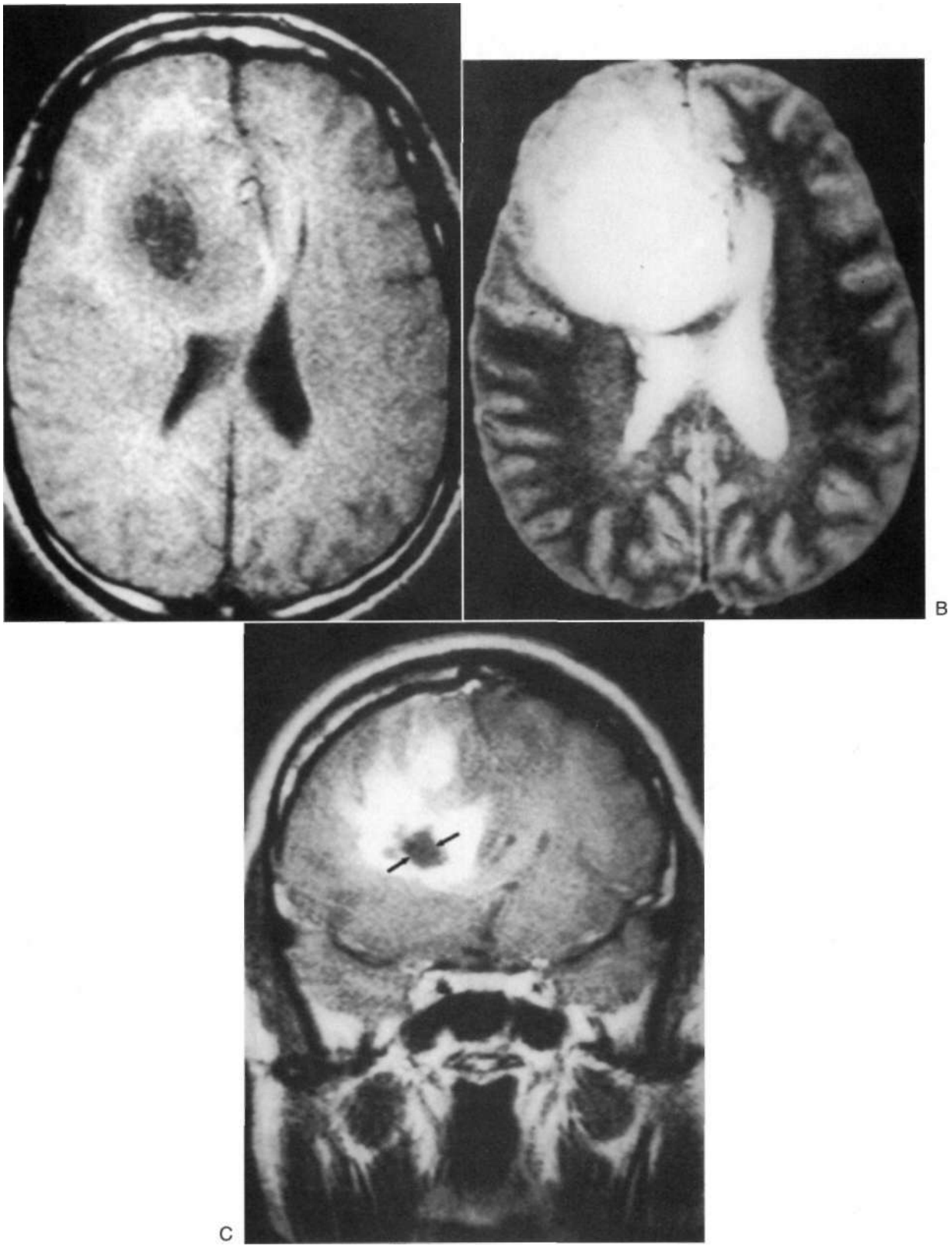


FIGURE 37A.10 Glioblastoma multiforme. (A) Axial T1-weighted image and (B) T2-weighted image reveal a mass lesion compressing the frontal horn and producing shift of the midline. This lesion is isointense to hypointense on Tl weighting and becomes hyperintense on T2 weighting. (C) l'ostcontrast Tl coronal image shows irregular enhancement of this lesion with a central area of hypo in tensity representing a tumor cyst or necrotic tissue *[arrows).*

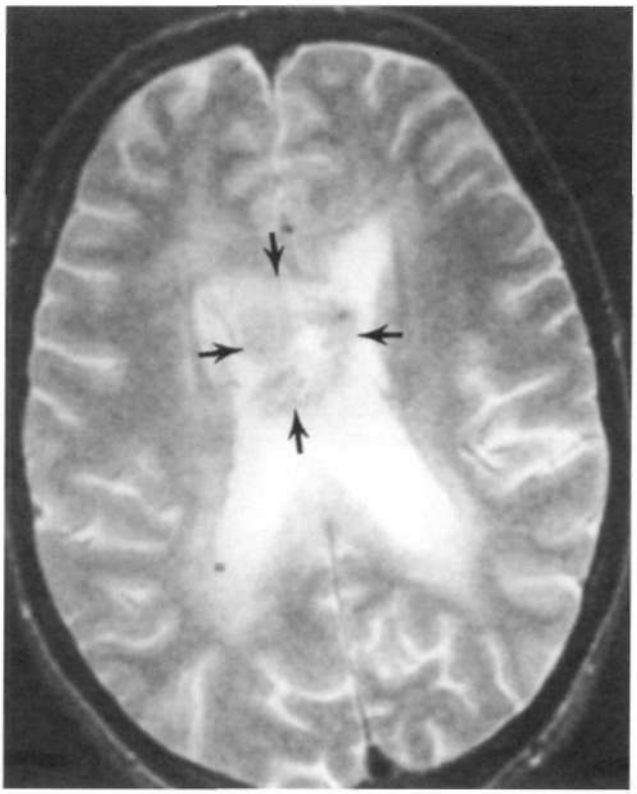


FIGURE 37A.11 Lymphoma. Mass involving the body of the corpus callosum *{arrows)* is isointense to gray matter on this T2-weighted axial image.

for detecting intracerebral metastases is the postcontrast MRI. Intra parenchymal metastases are most common, with tumors of the king and breast the most common primary sites. Most intracerebral metastases are multiple, but solitary metastases are common (30-50% of cases of metastases). They are found at the gray-white junction, are usually well circumscribed and round, and often are surrounded by edema (Figure 37A.13). The extent of edema bears no relationship to the size of the metastasis or the clinical status of the patient.

On MRI, metastases can be distinguished from edema on T2-weighted images because the metastasis is of variable intensity within an area of high-intensity edema. Peritumoral edema usually is prominent and is identified as fingerlike projections following white matter boundaries. lntratumoral hemorrhage occurs in 20% of metastases.

Contrast increases the ability to detect metastases. CT is highly sensitive to intra parenchymal metastatic disease, but contrast-enhanced MRI detects many lesions that are not detected on CT. In one study, high-dose (triple-dose) gadolinium-enhanced MRI examinations had advantages over the standard gadolinium-enhanced (0.1 mmol per kilogram) examinations in detecting small metastases. In addition, magnetization transfer (a technique that uses special saturation pulses to produce greater than normal enhancement of cortical and subependymal veins and other gadolinium-containing structures) with single-Jose gadolinium-enhanced MRI improves sensitivity to

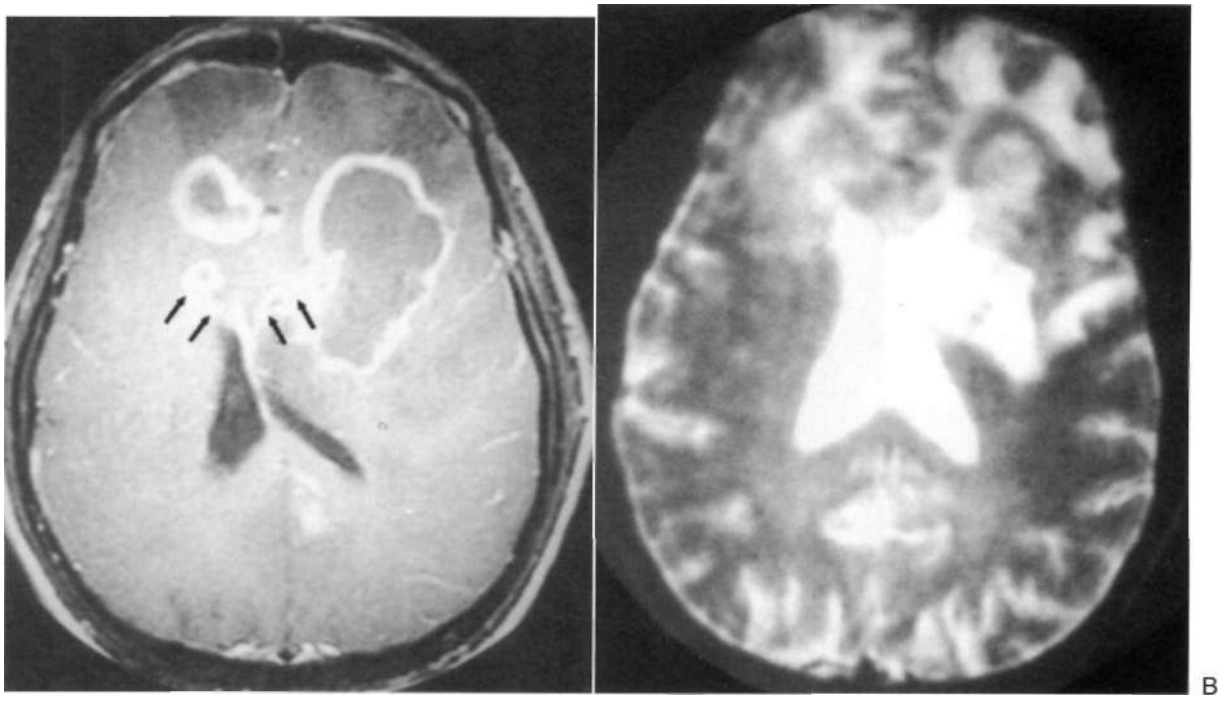


FIGURE 37A.12 Lymphoma. (A) Postgadolinium Tl-weighted image in a patient with lymphoma shows multiple ring-enhancing lesions in the frontal lobes and one lesion in the left occipital parasagittal location. Arrows indicate subependymal enhancement. (B) Axial T2-weighted image demonstrates isointense to hyperintense lesions in the frontal lobes bilaterally corresponding to the ring-enhancing lesions.

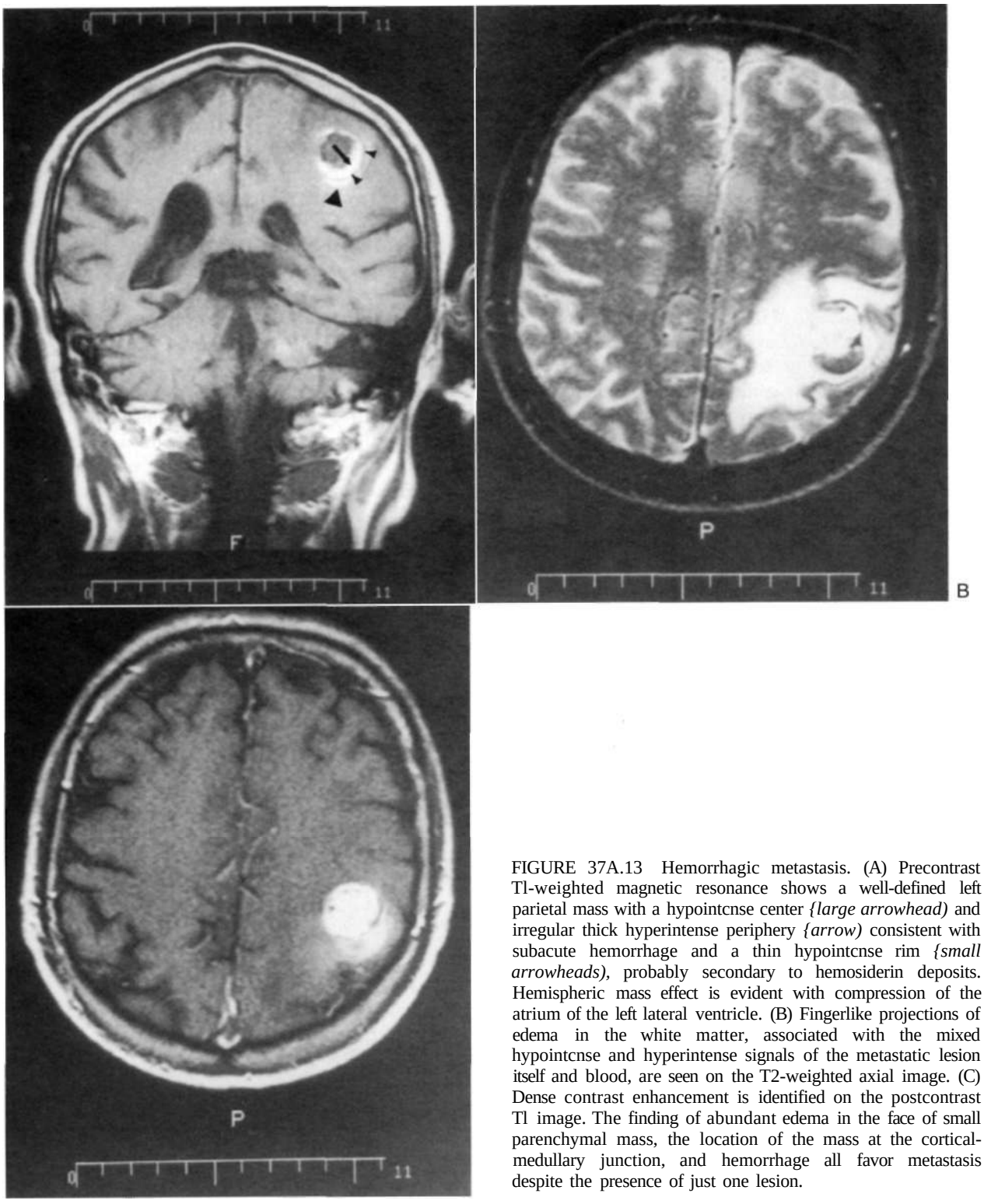


FIGURE 37A.13 Hemorrhagic metastasis. (A) Precontrast Tl-weighted magnetic resonance shows a well-defined left parietal mass with a hypointcnse center *{large arrowhead)* and irregular thick hyperintense periphery *{arrow)* consistent with subacute hemorrhage and a thin hypointcnse rim *{small arrowheads),* probably secondary to hemosiderin deposits. Hemispheric mass effect is evident with compression of the atrium of the left lateral ventricle. (B) Fingerlike projections of edema in the white matter, associated with the mixed hypointcnse and hyperintense signals of the metastatic lesion itself and blood, are seen on the T2-weighted axial image. (C) Dense contrast enhancement is identified on the postcontrast Tl image. The finding of abundant edema in the face of small parenchymal mass, the location of the mass at the cortical-medullary junction, and hemorrhage all favor metastasis despite the presence of just one lesion.

metastases and doubles the relative contrast of enhancing brain lesions. In general, metastases have mote edema and mass effect than inflammatory processes and primary gliomas, a sign that can be helpful in differential diagnostic considerations.

Infrcttentorial Tumors

The postetior fossa is the most common site of primary intracranial tumors in children. The most common tumors of the posterior fossa seen in children are, in order

of decreasing frequency, cerebellar astrocytomas, primitive neuroectodermal tumors (PNETs), ependymomas, and brainstem gliomas. In the adult, infra tentorial tumors make up only 15-20% of all intra-axial brain tumors, the most common being hemangioblastoma and metastasis.

Cerebellar Astrocytoma. The cerebellar astrocytoma is the most common posterior fossa neoplasm in children and also occurs in adults. The typical findings of a cerebellar astrocytoma on MRI include a mass made up of a single large cyst with a solid nodular portion in the wall of the cyst. The solid portion of the tumor enhances with contrast, whereas the cyst wall may or may not enhance. The solid portion is hyperintense to normal brain on T2-weighted sequences, whereas the cystic portion is isointense to CSF. Cerebellar astrocytomas may not be cystic, and if solid they are usually homogeneous in signal intensity. Twenty percent calcify.

Primitive Neuroectodermal Tumors. PNETs are a group of CNS tumors thought to originate from primitive or undifferentiated neuroepithelial cells. The prototype of these tumors is the medulloblastoma. Other tumors included in this category are ependymoblastoma, cerebral neuroblastoma, pinealoblastoma, medulloepithelioina, and pigmented medulloblastoma.

The cerebellar PNET, the medulloblastoma, makes up 25% of all intracerebral tumors in children, second only to cerebellar astrocytoma. The tumors originate most often in the midline, filling the fourth ventricle. These malignant tumors tend to invade the leptomeninges and seed the CSF. On CT, these tumors are high-density lesions that enhance and produce hydrocephalus. On MRI, they have homogeneous to mixed signal intensity {Figure 37A.14). On T2-weighted images, the lesions are nearly isointense to brain parenchyma. These tumors enhance intensely after contrast administration.

Ependymoma. Ependymomas are common tumors in children (10% of pediatric CNS neoplasms), and two thirds are located in the posterior fossa. They are usually intimately associated with the fourth ventricle or its outlet foramina and tend to arise from the floor and track along its lateral recesses into the cerebellopontine angle. The next most common location is the body of the lateral ventricle, although they may be found also in the brain parenchyma, outside the ventricular system.

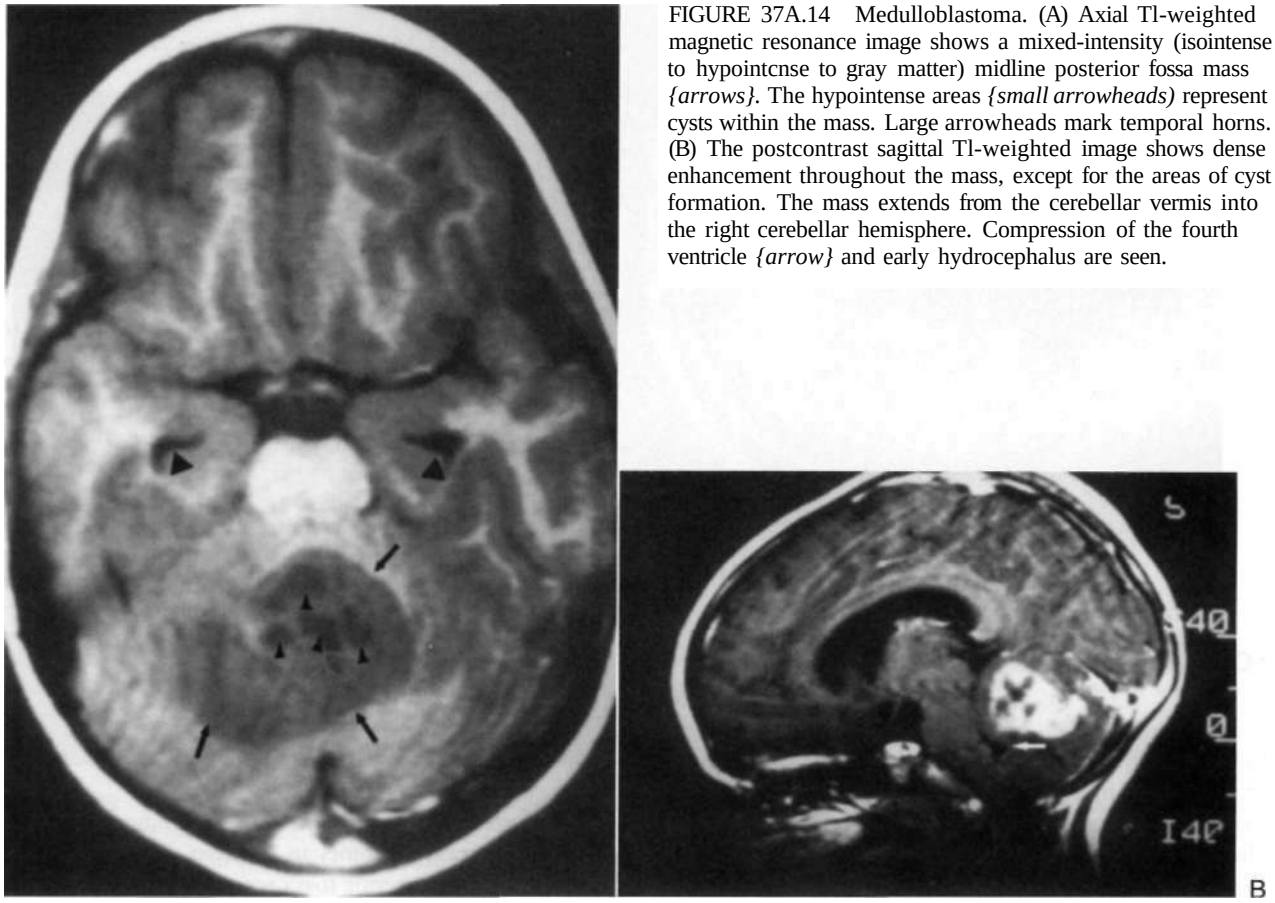
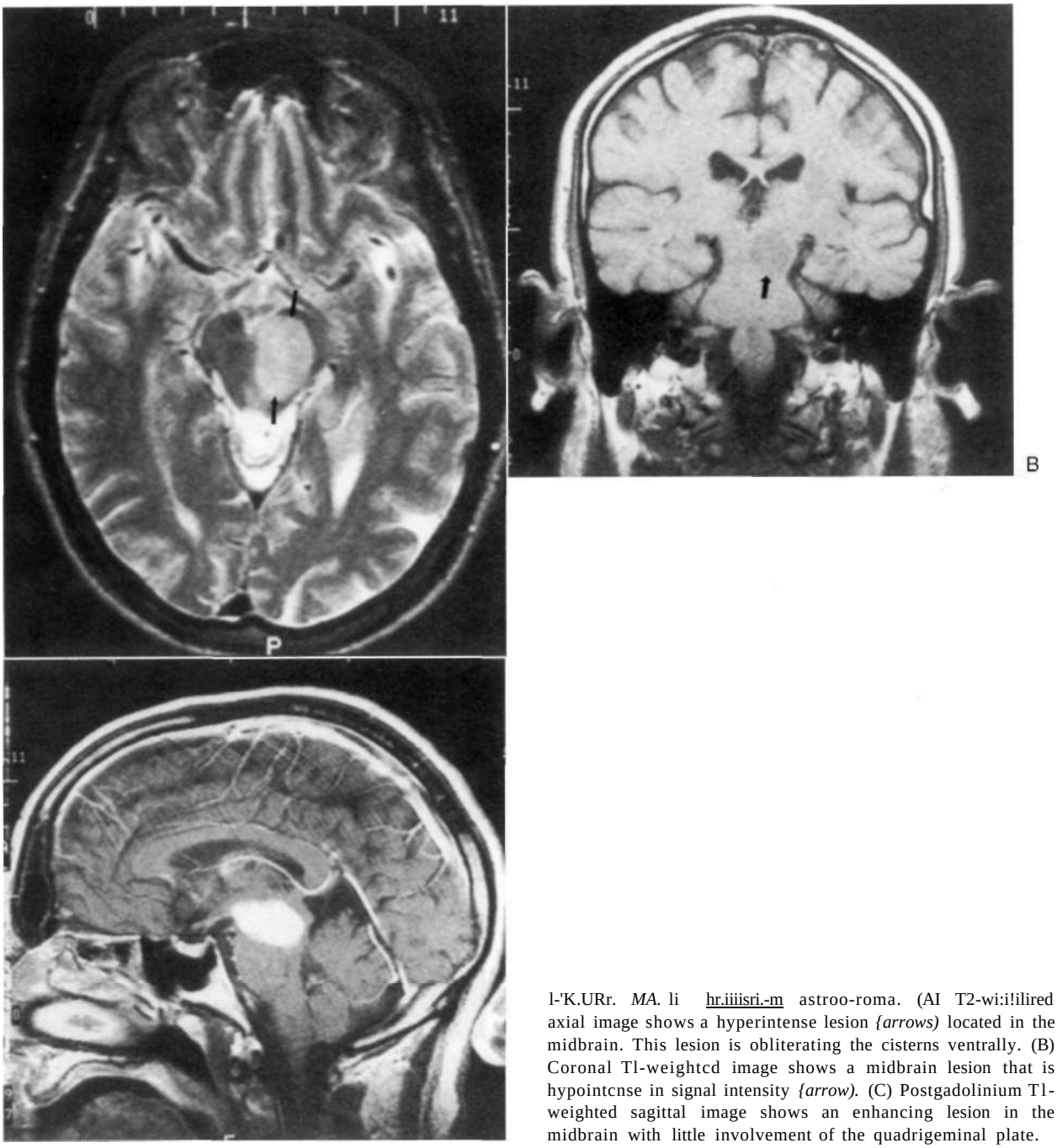


FIGURE 37A.14 Medulloblastoma. (A) Axial Tl-weighted magnetic resonance image shows a mixed-intensity (isointense to hypointcnse to gray matter) midline posterior fossa mass *{arrows}*. The hypointense areas *{small arrowheads)* represent cysts within the mass. Large arrowheads mark temporal horns. (B) The postcontrast sagittal Tl-weighted image shows dense enhancement throughout the mass, except for the areas of cyst formation. The mass extends from the cerebellar vermis into the right cerebellar hemisphere. Compression of the fourth ventricle *{arrow}* and early hydrocephalus are seen.

Ependymomas most often present as partially cystic, calcified, and sometimes hemorrhagic masses. They can extend through the foramen magnum and compress the dorsal aspect of the spinal cord (aplastic ependymoma). Almost all enhance with contrast. Seeding of the CSF occurs less often than with the PNF.T lesions.

Brainstem Astrocytoma. Brainstem astrocytomas make up 10% of all childhood brain tumors. The tumor is characteristically located in the pons. The majority are of the diffuse (infiltrative) fibrillary type, and a small minority constitute the more benign juvenile pilocytic astrocytoma. The MRI appearance of brainstem astrocytoma is variable with regard to signal intensity and enhancement. MRI demonstrates these lesions as poorly defined areas of high intensity on long TR-long TE images (Figures 37A.15 and 37A.16). MRI is much better for demonstrating this lesion than CT. When gross enlargement of the brainstem occurs, the size of the cisternal spaces decreases, and when the growth becomes exophytic there may be encasement of



l-'K.URr. *MA.* li hr.iiiisri.-m astroo-roma. (AI T2-wi:i!ilired axial image shows a hyperintense lesion *{arrows)* located in the midbrain. This lesion is obliterating the cisterns ventrally. (B) Coronal Tl-weightcd image shows a midbrain lesion that is hypointcnse in signal intensity *{arrow).* (C) Postgadolinium T1-weighted sagittal image shows an enhancing lesion in the midbrain with little involvement of the quadrigeminal plate.

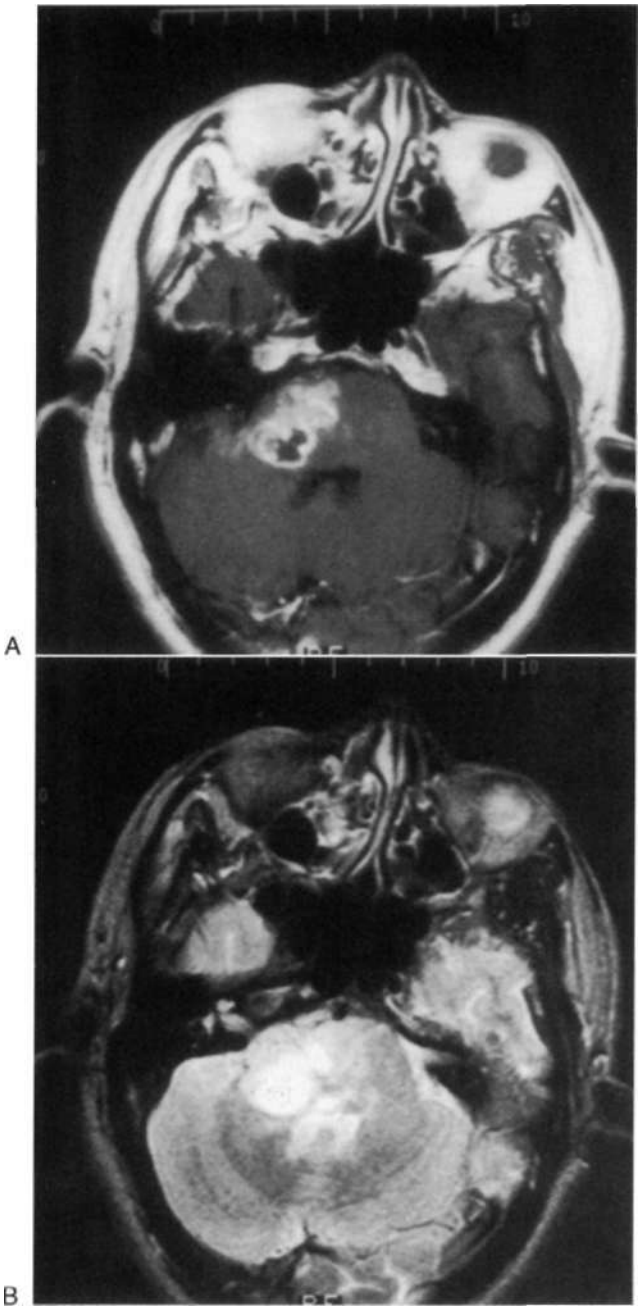


FIGURE 37A.16 Pontine astrocytoma. (A) Axial magnetic resonance imaging scan after gadolinium administration demonstrates a lesion on the right side of the pons, with irregular borders and inhomogeneous enhancement, which is producing enlargement of the pons. (B) The T2-weighted image shows a high-intensity lesion with heterogeneous signal.

the basilar artery. Contrast enhancement occurs in approximately one half of patients and is often **irregular** (see Figure 37A.16).

Hemangiobiastoma. Hemangiobiastoma is the most common primary posterior fossa intra-axial neoplasm in adults. This lesion has a high association with von Hippel-Lindau disease, in which retinal angiomas, cysts and angiomas of the liver and kidney, renal cell carcinoma, and pheochromocytoma occur. Although the cerebellum is the most common site of involvement, supratentorial hemangiobiastoma may be seen occasionally.

Pathologically and in imaging studies, hemangioblastomas are commonly well-demarcated cystic masses with highly vascularized nodules in the wall of the cyst. Importantly, the cyst wall is not tumorous. The vascular nidus always abuts pia mater, giving rise to the alternate theory of origin that rhis is primarily a meningeal-based tumor (Figure 37A.17). Entirely solid hemangioblastomas occur in 30-40% of cases, especially in the supratentorial compartment.

On MRI, the majority of these lesions are cystic and have a peripheral pial-based mural nodule of solid tissue that enhances markedly, and there may be large vessels in or at the periphery of the mass. The cysts can be isointense to CSF on all sequences or slightly hyperintensc to CSF on T1-weighted images, a fact rclared to their high protein content. The mural nodule is slightly hyperintense to gray matter on long TR images.

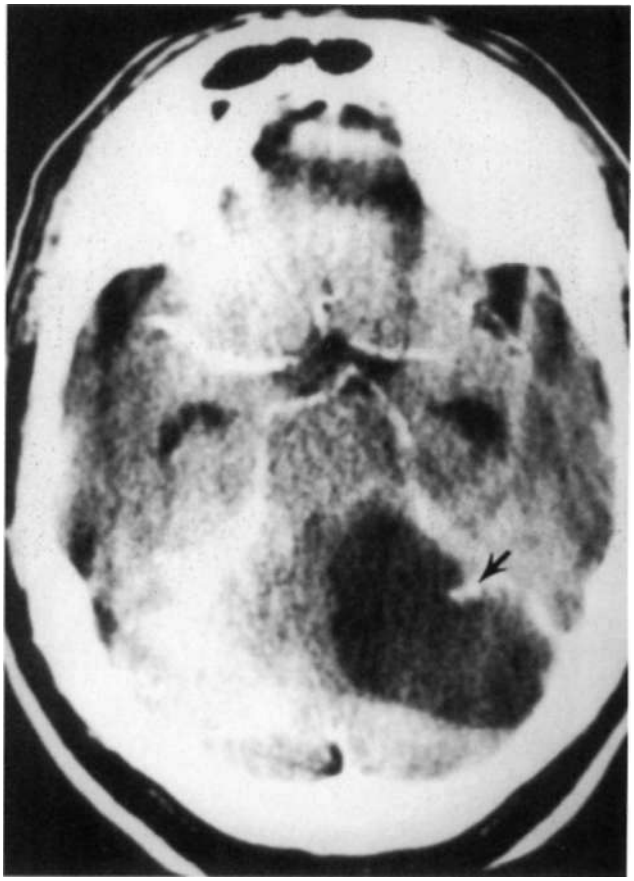


FIGURE 37A.17 Hemangiobiastoma. Contrast-enhanced computed tomographic scan demonstrates a cystic lesion with an enhancing mural nodule *(arrow),* which is peripheral and pial-based.

Extra-Axial Brain Tumors

Several criteria help establish rhc location of a lesion as extra-axial. A broad dural-based margin strongly suggests an extra-axial lesion. Other characteristics of extra-axial tumors include bony hyperostosis, invasion of the bone, displaced gray matter, buckled white matter, inwardly displaced pial vascular structures, and CSF clefts.

Subependymal Giant Cell Astrocytoma

The classic setting of a subependymal giant cell astrocytoma is a mass in the region of the foramen of Monro in a young adult with tuberous sclerosis. The mass is an astrocytic neoplasm projecting into the ventricle from a subependymal location. It is found in up to 10% of patients with tuberous sclerosis, and it is rare outside the clinical setting of this disease. MRI and CT findings in subependymal giant cell astrocytoma include the typical location, a heterogeneous hyperintense mass with evidence of contrast enhancement, and hydrocephalus (Figure 37A.18). Central regions of hypointensity on MRI may be caused by calcifications.

Central Neurocytoma

This is an intraventricular neoplasm of neuronal origin formerly called intraventricular oligodendroglioma. The lesion usually is located in the lateral ventricular wall, near the foramen of Monro anterior fornices or septum pellucidum. On CT or MRI the lesion appears as a we 11-cireuinscribed nonhomogeneously enhancing mass containing cystic spaces. On CT calcifications may be seen. On plain MRI the lesion is of intermediate signal on Tl andT2 (Figure 37A.19}.

Pineal Tumors

Pineal tumors are uncommon, representing 1% of all intracranial tumors. MRI is excellent at distinguishing true pineal masses from parapineal masses, a differentiation that has clear surgical relevance. Two major groups of pineal tumors are recognized: germ cell tumors and tumors derived from pineal parenchymal cells.

Germ Cell Tumors. The majority of pineal tumors are of germ cell origin. These include the germinoma, teratoma, embryonal carcinoma, choriocarcinoma, and mixed types. Of these, germinomas are the most common. They often seed the subarachnoid space and invade adjacent brain parenchyma. The second most common pineal germ cell tumor is the teratoma, occurring in an earlier age group than germinomas. These can contain hair, reerh, bone, and fat.

Pineal germinomas are well-circumscribed, homogeneous lesions. Nonhemorrhagic germinomas can be of low signal intensity on T2-wcighted image, and they enhance markedly with intravenous contrast. Teratomas, on the

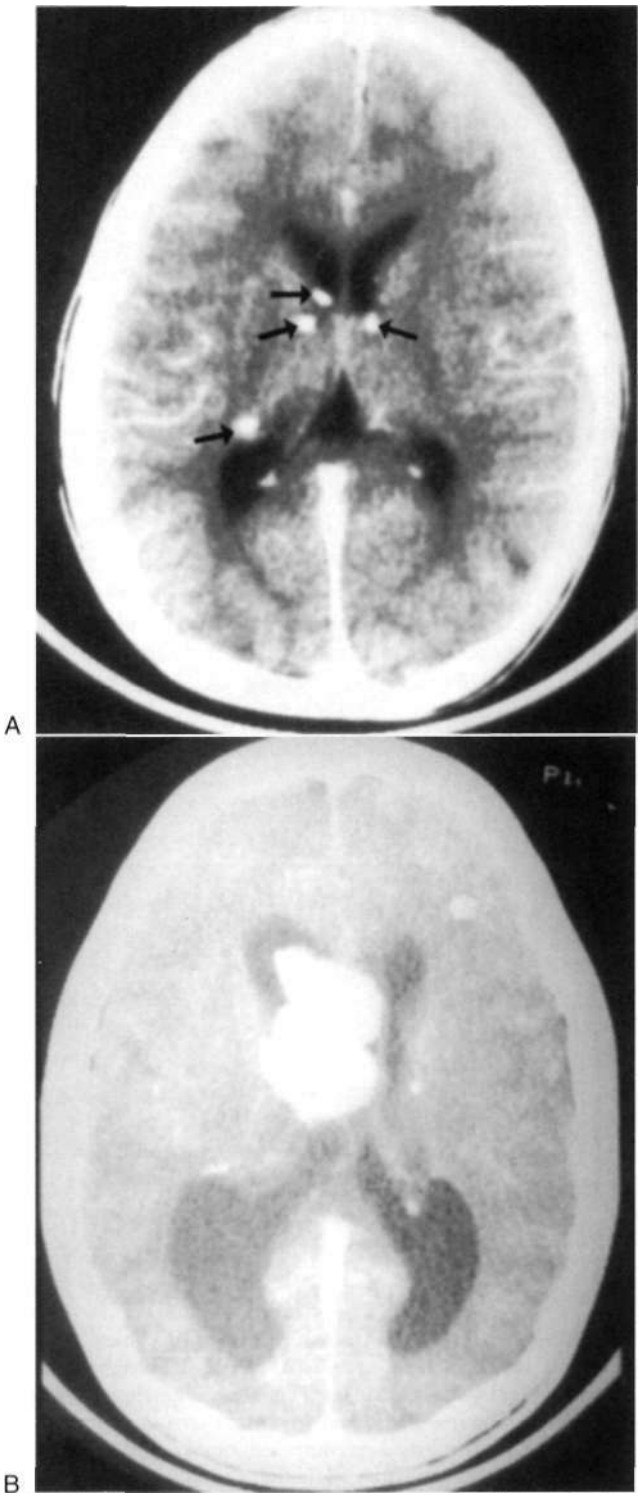


FIGURE 37A.18 Tuberous sclerosis. (A) Multiple calcified periventricular lesions *(arrows)* are seen on this computed tomographic axial scan. (B) In another patient, an enhancing mass lesion is noted in the region of the foramen of Monro with associated hydrocephalus. The diagnosis was subependymal giant cell astrocytoma.

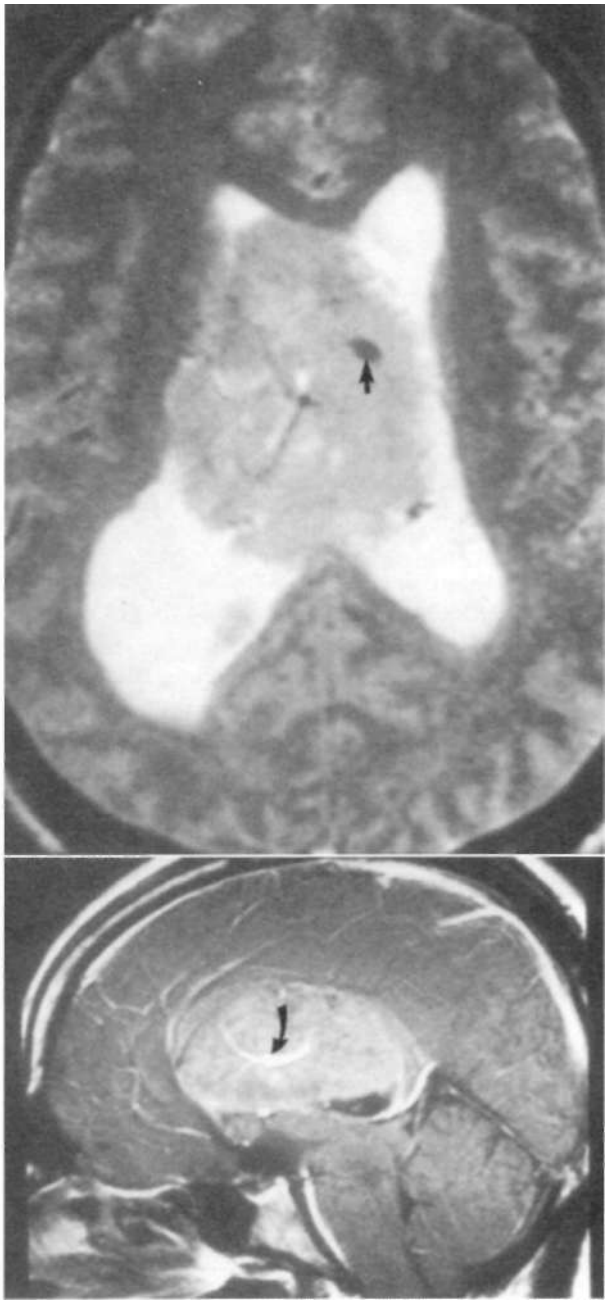


FIGURE 37A.19 Neurocytoma. Patient with clinical signs of increased intracranial pressure. (A) Axial T2-weighted image shows a lateral ventricular mass. The lesion is nearly isointense to gray matter. The rounded signal void areas *{arrow)* represent foci of calcifications continued on computed tomography (not shown). (B) The mass enhances with gadolinium and fills a great portion of the lateral ventricles. Note the enhancing tubular feeding vessel *{curved arrow).*

other hand, are heterogeneous, and their enhancement is variable.

Pineal Ceil Tumors. Pinealoblastoma (a PNKT) is a highly cellular tumor that tends to disseminate early through the subarachnoid pathways with leptomeningeal and subependymal seeding (Figure 37A.20). Pinealoblastoma tends to be isointense to gray matter on Tl-wcighted images (similar to othet PNET tumots) and to enhance densely with contrast.

Pinealocytoma is a tumot of adults that is more benign than pinealoblastoma. It is a well-differentiated, densely enhancing mass that has a high signal on T2-wcightcd sequences. Calcifications are more commonly with pinealocytoma s.

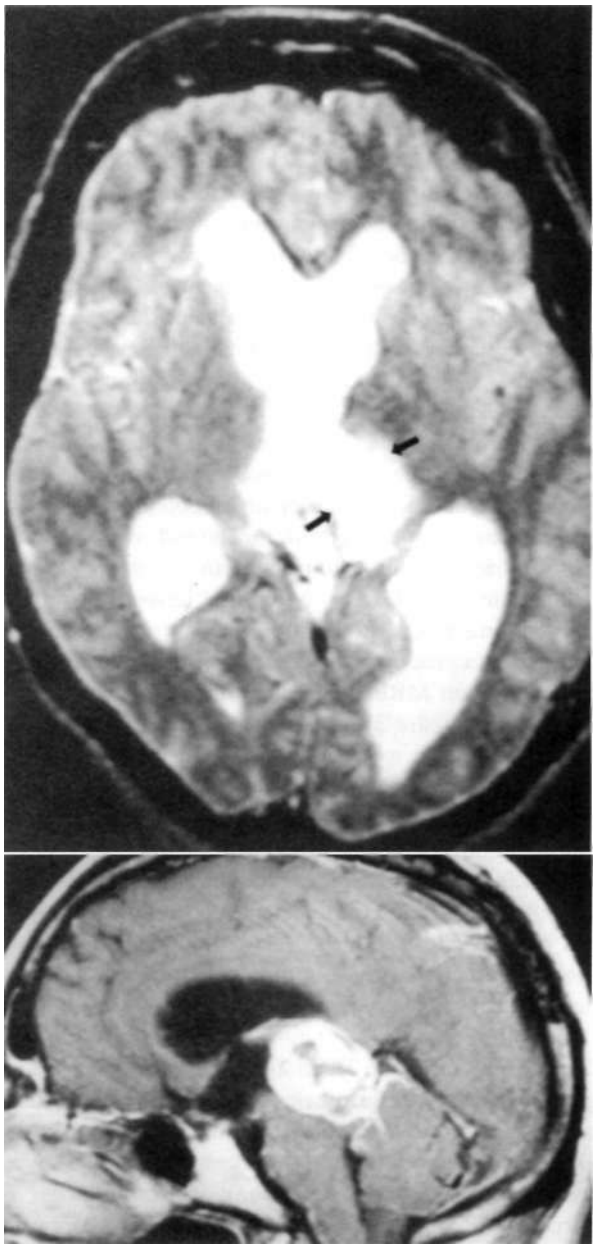


FIGURE 37A.20 Pinealoblastoma. (A) Axial T2-weighted image shows a mass *{arrows),* which is hyper in tense and produces mass effect on the posterior portion of the third ventricle. (B) Postcontrast-enhanccd magnetic resonance sagittal image demonstrates the mass and its effect on the colliculi and on the aqueduct of Sylvius, with resultant hydrocephalus.

Colloid Cysts

Colloid cysts arc benign lesions derived from infolding of the neuroepithelium, which is probably developing choroid plexus. The majority of these lesions are located in the anterosuperior aspect of the third ventricle. They are the most common form of neuroepithelial cysts and contain dense mucoid material and various ions, some of which are paramagnetic.

On MRI, colloid cysts are varied in their signal, ranging from hypoinrense to markedly hyperintense on both Tl- and T2-weighted images. Peripheral contrast enhancement may occur (Figure 37A.21).

Meningiomas

Meningiomas, rhe most common primary nonglial intracranial tumors, have a peak incidence in the middle and later decades of life. Meningiomas have a predilection for cerrain locations: parasagittal plane, cortical convexity, sphenoid wings, tuberculum sellae, parasellar region, olfacrory groove, cerebellopontine angle, clivus, and tentorium. They are usually broad-based and are attached to the adjacent dura.

If high-field strength magnets are used, the detection rate on noncontrast MRI for the meningiomas is comparable to that of contrast CT. **MRI** is superior to CT in determining dural sinus invasion with occluded venous flow and in defining tumor vascularity and arterial encasement. On Tl-weighted images, meningiomas are isointense to hypointense to gray matter, and on T2-weighted images approximately one half are isoinrense and one half are hyperintense to gray matter (Figure 37A.22). There is a good correlation between tumor histology and tumor intensity on T2-weighted images, although exact histological typing by MRI is not possible. Almost all meningiomas that are hyperintense to gray matter on T2-weighted images are of the syncytial or angioblastie type, whereas fibroblastic and transitional cell types are hyperintense to gray matter on T2-weighted images. The majority of meningiomas demonstrate a heterogeneous intensity pattern. Tumor vascularity has been identified in approximately one third of cases, seen as punctate and curvilinear hypointensities. Calcification, seen in 20% of meningiomas, appears as coarse, irregular regions of hypointensity on both T1 - and T2-weighted sequences. Routine MRI may not distinguish complete from near total venous sinus obstruction, and MRA or routine angiography may be needed in these cases for proper surgical planning.

Brain edema is seen in approximately 50% of meningiomas, with the most significant edema associated with meningiomas of the syncytial or angioblastie cell types. Angioblastie meningiomas are considered hisrologically identical to hcmangioblastomas and show tumor neovascularity. A less common variety of meningioma that is clinically more aggressive is histologically similar to the extracranial hemangiopericytoma.

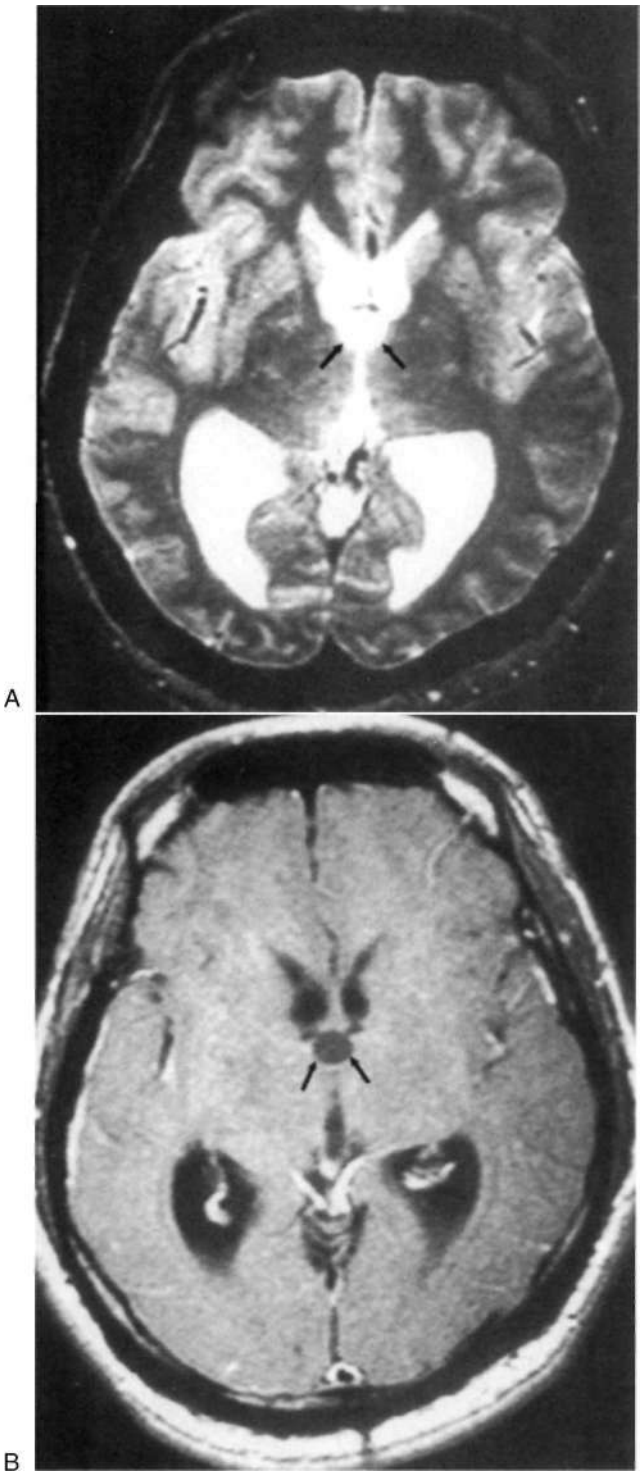


FIGURE 37A.21 Colloid cyst. (A) There is a rounded lesion in the region of the foramen of Monro, which is hyperinrense **on T2-**wcighted image *(arrows).* There is associated hydrocephalus. **(B) Postcontrast Tl-weighted** image shows a hypointense lesion with slight peripheral enhancement *{arrows).*

Hemangiopericytoma

Hemangiopericytoma is a tumor of uncertain origin. It is believed to arise from hemangiopericytes (cells located in vessel walls and responsible for the contraetibility of the vessel). The age of presentation is the fifth decade, The tumot affects mote male than female subjects. The clinical presentation is related to the extra-axial location of the mass.

On imaging, the lesion, when small, is well circumscribed. When large, it tends to be lobulatcd, with cystic spaces that are hyperintense on T2-weighted images. The lesion enhances intensely with gadolinium or iodinated intravenous contrast. In angiography a pial vascularization with intense blush may be seen, although sometimes pial, dural, or both kinds of blood supply may be seen. If the tumor is tescctcd incompletely, it tends to recur. Extracranial metastases from hemangiopericytoma ate not uncommon (Figure 37A.23).

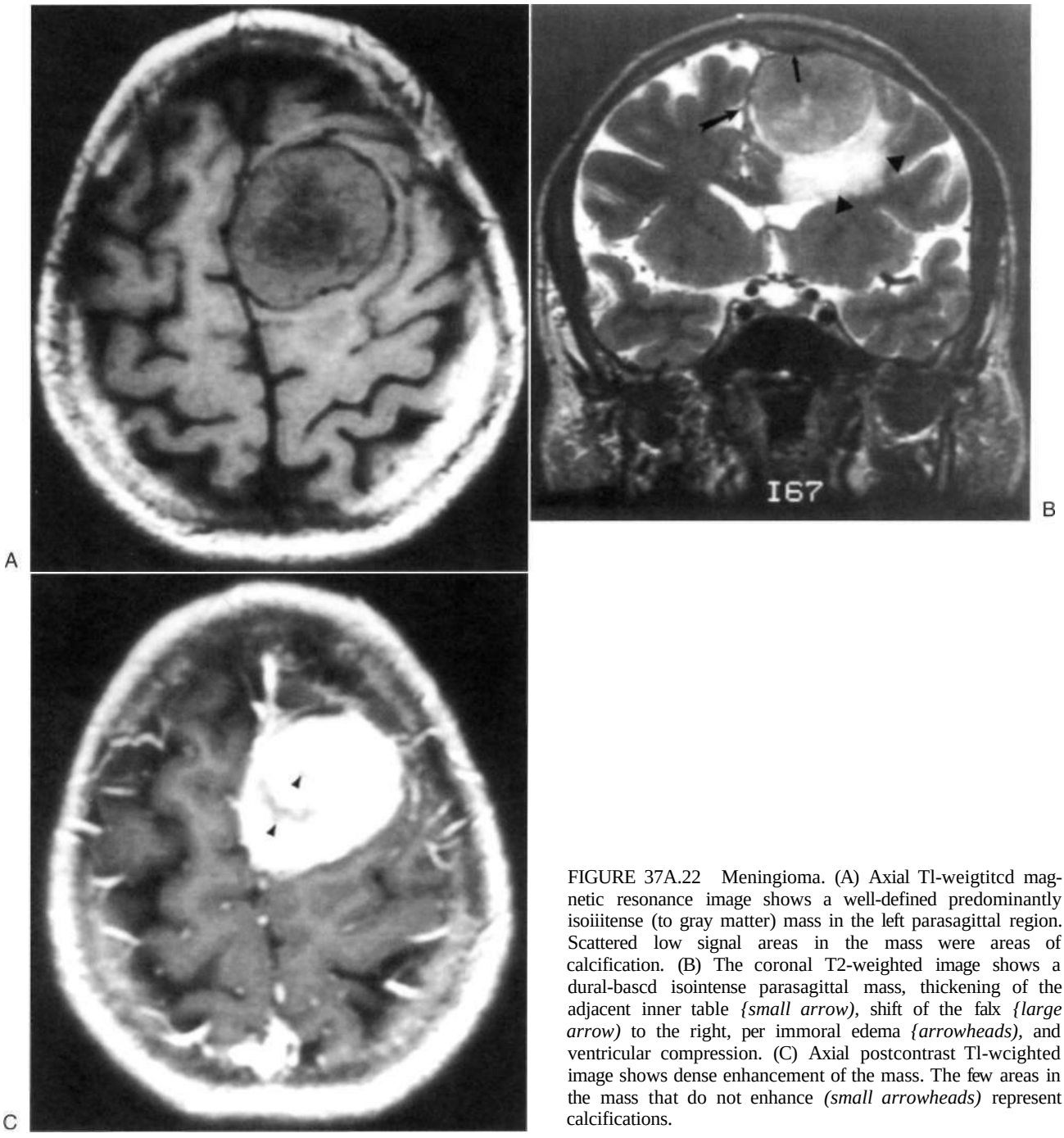


FIGURE 37A.22 Meningioma. (A) Axial Tl-weigtitcd magnetic resonance image shows a well-defined predominantly isoiiitense (to gray matter) mass in the left parasagittal region. Scattered low signal areas in the mass were areas of calcification. (B) The coronal T2-weighted image shows a dural-bascd isointense parasagittal mass, thickening of the adjacent inner table *{small arrow)*, shift of the falx *{large arrow)* to the right, per immoral edema *{arrowheads)*, and ventricular compression. (C) Axial postcontrast Tl-wcighted image shows dense enhancement of the mass. The few areas in the mass that do not enhance *(small arrowheads)* represent calcifications.

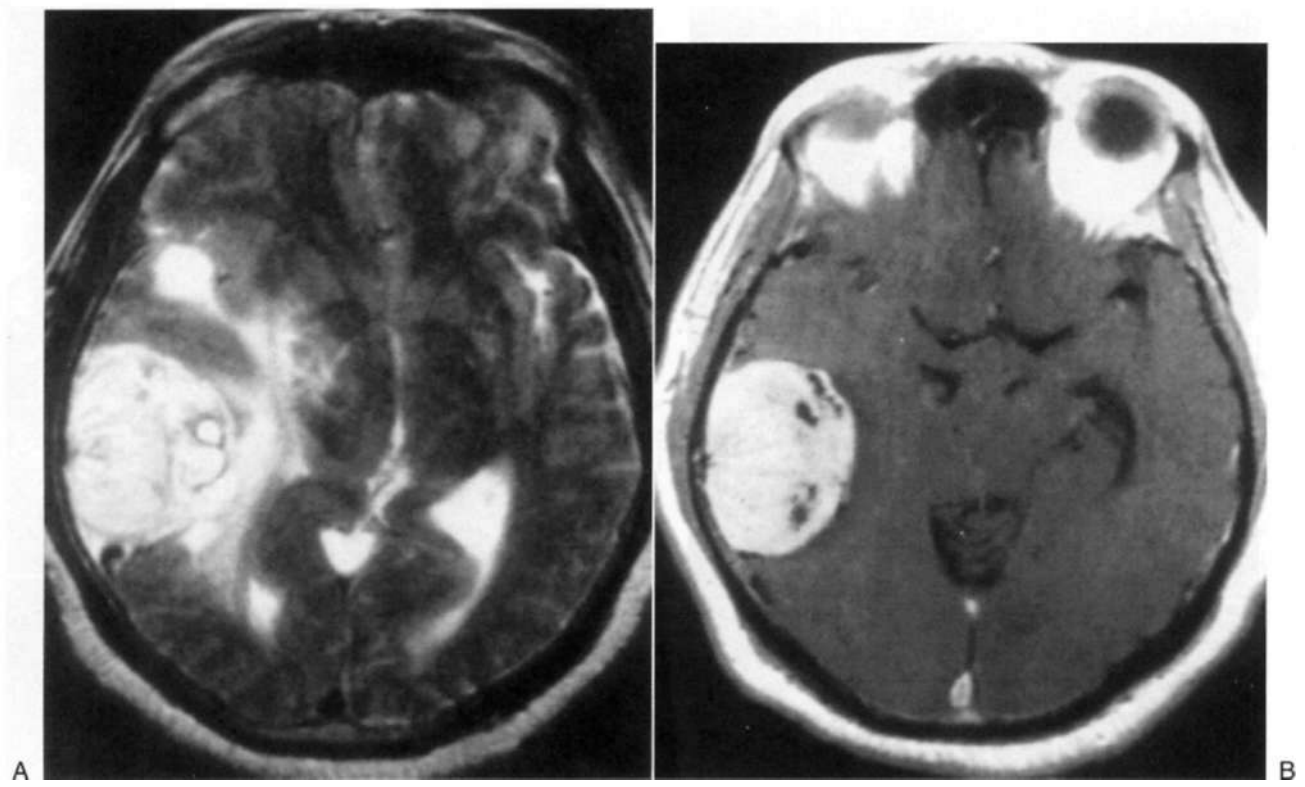


FIGURE 37A.23 Hemangiopericytoma. (A) Axial T2-wcightcd image demonstrates a right temporal extra-axial hyperintense mass containing peripheral cysts. The mass compresses the surrounding edematous brain parenchyma. (B) The tumor enhances with gadolinium.

Meningeal Sarcoma

This malignant neoplasm arises from the meninges. It is more common in children (mean age, 2 years). The lesion is not encapsulated and usually infiltrates the brain. On imaging, a large mass with intense enhancement in an extra-axial location is seen. On noncontrast CT the lesion is isodense to brain. On MRI it is isointense on Tl-weighted images and mildly hyperintense on T2-weighted images. A characteristic finding is a rapid rate of growth of the tumor in a short inrerval of rime.

Settar and Parasetlar Tumors

Pituitary Adenoma. Pituitary adenomas of less than 10 mm are called *microadenomas,* and those greater than 10 mm are called *macroadenomas.* The most common of the actively secreting adenomas is the prolactinoma. Nonfunctional pituitary adenomas present with signs and symptoms caused by compression or invasion of structures adjacent to the adenoma, such as the optic chiasm and the cavernous sinus.

Most commonly, the MRI image of the pituitary adenoma shows low signal intensity on Tl-weighted images and high signal intensity on T2-wcightcd images when compared with normal pituitary tissue. Hyperinrensity on Tl-weighted images most often represents subacute collections of blood (Figure 37A.24). This hemorrhage usually is subclinical but may indicate that a significant bleed into the pituitary tumor occurred. Gadolinium enhancement can detect adenomas that otherwise would be occult by differentially enhancing the normal gland tissue and the nonenhancing microadenoma (Figure 37A.25). Enhanced MRI is the best way to detect small adenomas found in Cushing's disease. Delayed images sometimes can demonstrate a reversal of the image contrast because of accumulation of gadolinium in the adenoma and washout from the rest of the normal gland.

A macroadenoma characteristically is seen as a hypointense mass on Tl-weighted images. The visualization of the cavernous carotid arteries and the middle and anterior cerebral arteries obviates preoperative angiography. Lateral extension of the tumor into the cavernous sinus is common and may be associated with extremely high prolactin levels. It is often impossible to determine whether the cavernous sinus is invaded or compressed by the adenoma because the medial wall of the cavernous sinus is very thin. However, the placement of abnormal tissue between the lateral wall of the cavernous sinus and the cavernous carotid is a reliable indicator of cavernous sinus invasion. Marked constriction or occlusion of the cavernous carotid artery by a pituitary adenoma is rare.

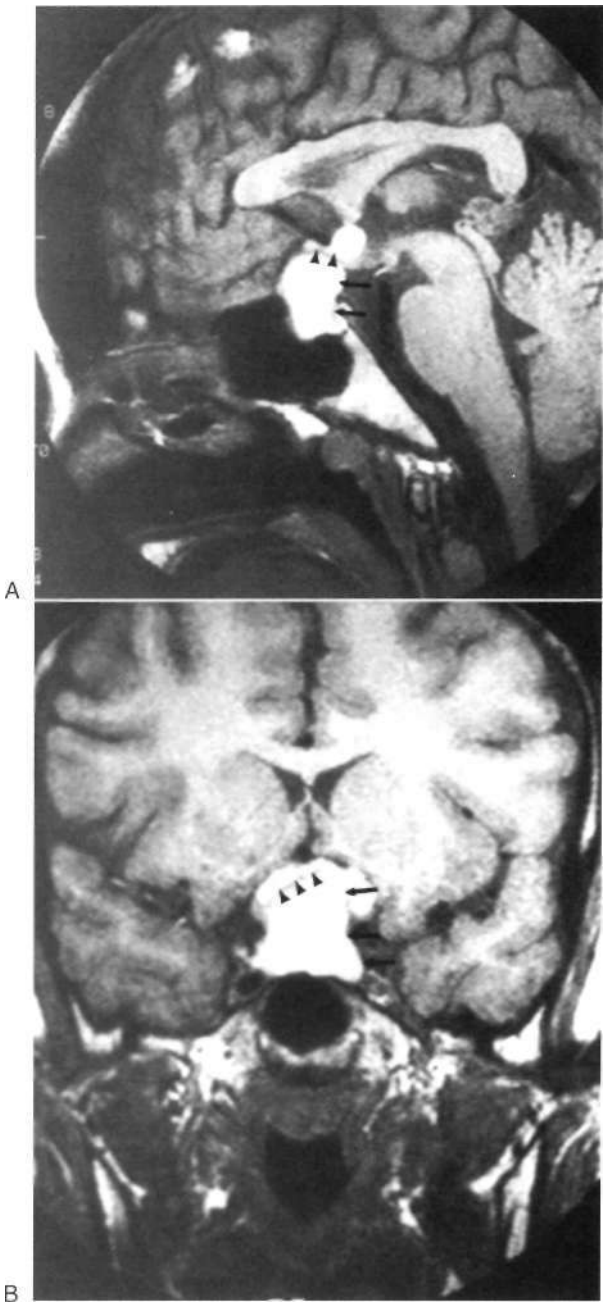


FIGURE 37A.24 Hemorrhagic pituitary macroadenoma. (A) Sagittal and (B) coronal noncontrast Tl-wcightcd images show a hyperintense signal (subacute blood) in a sellar and suprasellar mass *(arrows).* This patient presented with pituitary apoplexy and sudden vision loss, which is explained by the compression of the optic chiasm and hemorrhage into the chiasm *{arrowheads).* Incidentally noted is the multicystic pineal gland in A (pineal cyst).

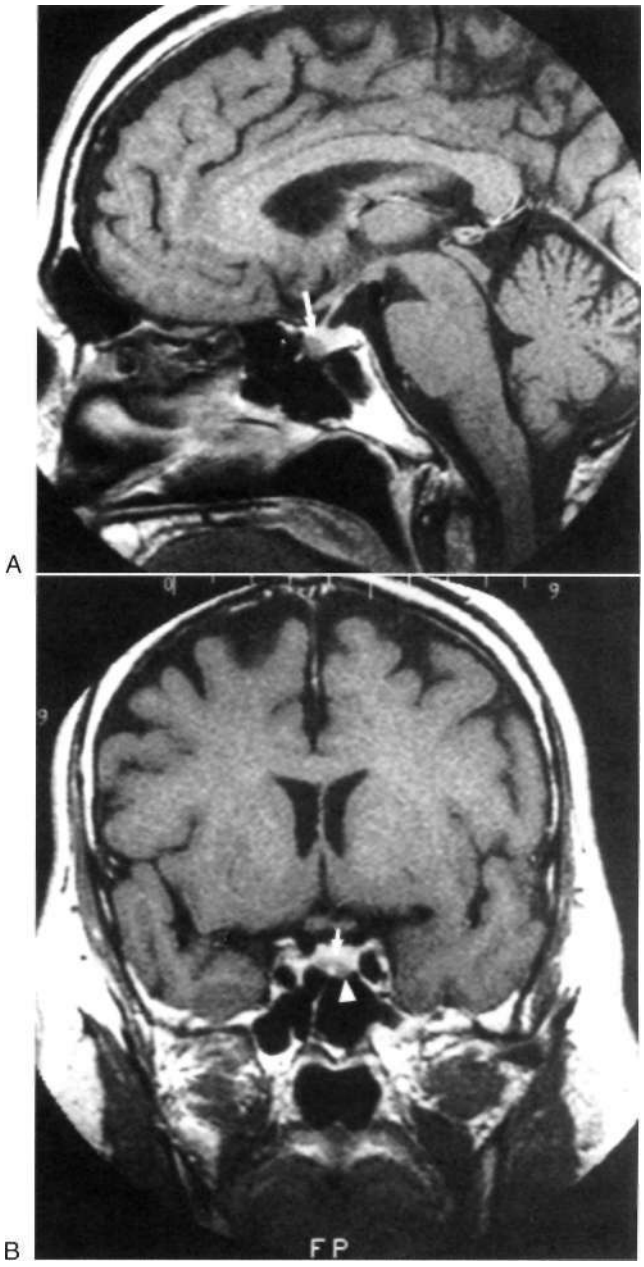


FIGURE 37A.25 Pituitary microadenoma. Postcontrast Tl-weighted images in (A) sagittal and (B) coronal planes show a nonenhancing lesion in the anterior-inferior aspect of the gland *{arrows).* Note the sloping of the floor of the sella *[arrowhead).*

Craniopharyngioma. Craniopharyngiomas commonly present in the suprasellar cistern. However, intrasellar craniopharyngiomas are found occasionally. Craniopharyngiomas may have both solid and cystic components, and calcification is seen in most tumors but is less common in adults.

On **MRI,** craniopharyngiomas are heterogeneous suprasellar masses, with components that may be hyperintense on both Tl- and T2-weighted images. If contrast is given, the solid portions usually enhance moderately (Figure 37A.26). The extension of these masses can be remarkable, growing beneath the frontal and temporal lobes and extending inferiorly along the clivus.

Meningioma. Ten percent of meningiomas occur in the parasellar region. On MRI, they are often isointense relative to gray matter on Tl-weighted images; 50% are

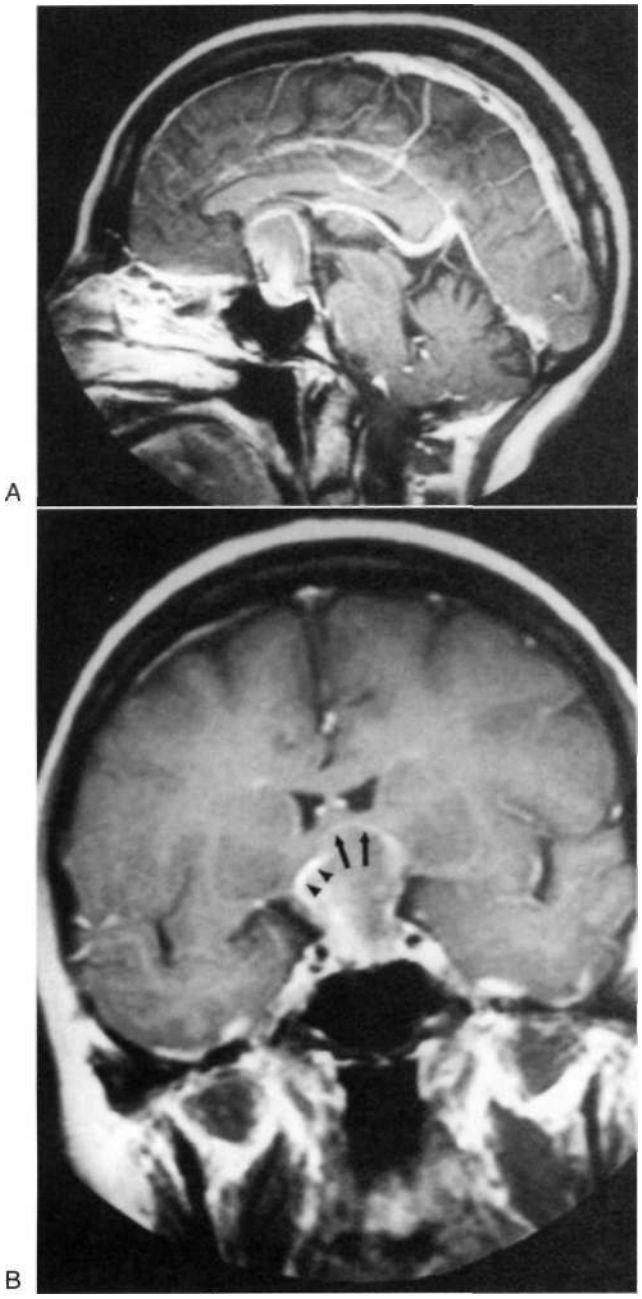


FIGURE 37A.26 Craniopharyngioma. A large suprasellar mass with nonuniform enhancement is seen on these postcontrast Tl (A) sagittal and (B) coronal images. Intense enhancement exists around the periphery of the mass *(arrows),* a portion of which may represent slowed flow in the Al segment of the right anterior cerebral artery *{arrowheads* in B). The cavernous carotid arteries are clearly separated from the mass. The major differential lies between a pituitary adenoma with suprasellar extension and craniopharyngioma. Note in both images that the sella turcica is not enlarged, ;t distinct indication that this is not a pituitary adenoma.

isointense on T2-weighted images, and 40% are hyperintense. Vascular encasement is a common finding with a meningioma in the cavernous sinus. Meningiomas enhance intensely with gadolinium, so those arising from the walls of the cavernous sinus can be difficult to separate from the enhancing venous blood in the cavernous sinus.

Chiasmatic and Hypothalamic Glioma. The distinction between gliomas that arise in the optic chiasm or hypothalamus is arbitrary because the lesion often involves both areas. These gliomas are seen mostly in children, particularly in those with neurofibromatosis (Figure .37A.27). Tumors of the chiasm are more aggressive than those arising from the optic nerves.

On Tl-weighted images, the gliomas usually are isointense and on T2-weighted images they are moderately hyperintense. Because they can extend posteriorly along the optic radiations, T2-weighted images of the entire brain are necessary. If intraorbital extension is possible, then fat-suppressed MRI is helpful.

Acoustic Neurinoma

Acoustic neurinomas (or schwannomas) arise from the vestibular portion of the eighth cranial nerve and are common with type 2 neurofibromatosis (Figure 37A.2S).

On MRI, most tumors are visualized on thin-section Tl-weighted images, where these tumors are well demarcated from CSF. On T2-weighted images the tumors are hyperintense. The signal pattern often is heterogeneous because of their internal composition, which is varied and includes different cells, mucinous and microcystic changes, regions of focal calcification, and blood vessels. Significant heterogeneity on MRI is more typical of acoustic neurinomas than meningiomas, which is the other lesion common in the cerebellopontine angle (Figure 37A.29). Acoustic neurinomas can be demonstrated on noncontrast MRI when they are 5 mm or larger. Usually, an intracanalicular portion of the tumor is associated with a cisternal mass. Approximately 2()"(J ol acoustic neurinomas have no intracanalicular component, and in those cases the differential diagnosis from meningiomas is difficult. Small intracanalicular tumors can be demonstrated with contrast enhancement.

Epidermoid Cysts

Epidermoid cysts are congenital lesions of ectodermal origin and usually do not present until the third or fourth decade of life. They are often located in the cerebellopontine angle, suprasellar and parasellar regions, and middle cranial fossa.

On CT they are hypodense, do not enhance with contrast, and may be difficult to differentiate from arachnoid cysts. However, their external surface is lobulated, unlike the smooth surface of arachnoid cysts. On Tl-weighted images epidermoid tumors arc hypointense, bur internal structure can be seen, and on T2-weighted images the tumors arc markedly hyperintense (Figure 37A.30).

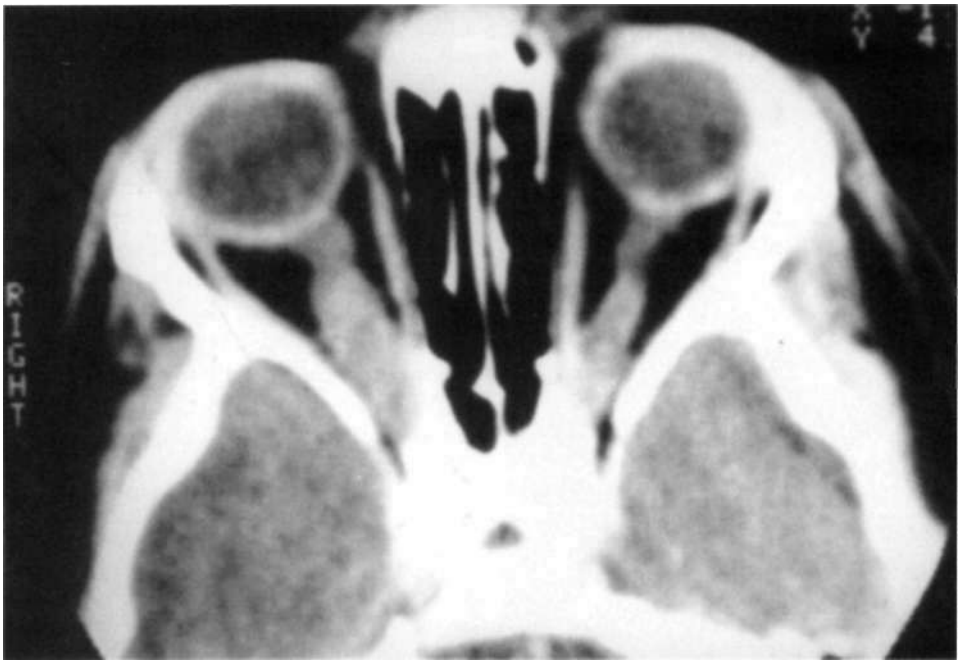


FIGURE 37A.27 Neurofibromatosis. Bilaterally enlarged optic nerves in a patient with neurofibromatosis type 1. The patient also was noted to have an optic chiasm glioma.

Neurodegenerative Disorders

Atrophy

With norma) aging, there is mild to moderate progressive enlargement of the ventricles, sulci, and cisternal spaces. In neurodegenerative disorders, atrophy is excessive and premature.

Periventricular white matter hyperintense lesions range from normal capping of the frontal horns to confluent abnormal high-signal regions extending into the deep white matter. The amount of periventricular hyp erin tensity increases with age and is higher in patients with vascular disease. Subcortical lesions, ischemic in nature, are located outside the periventricular region in the cerebral white

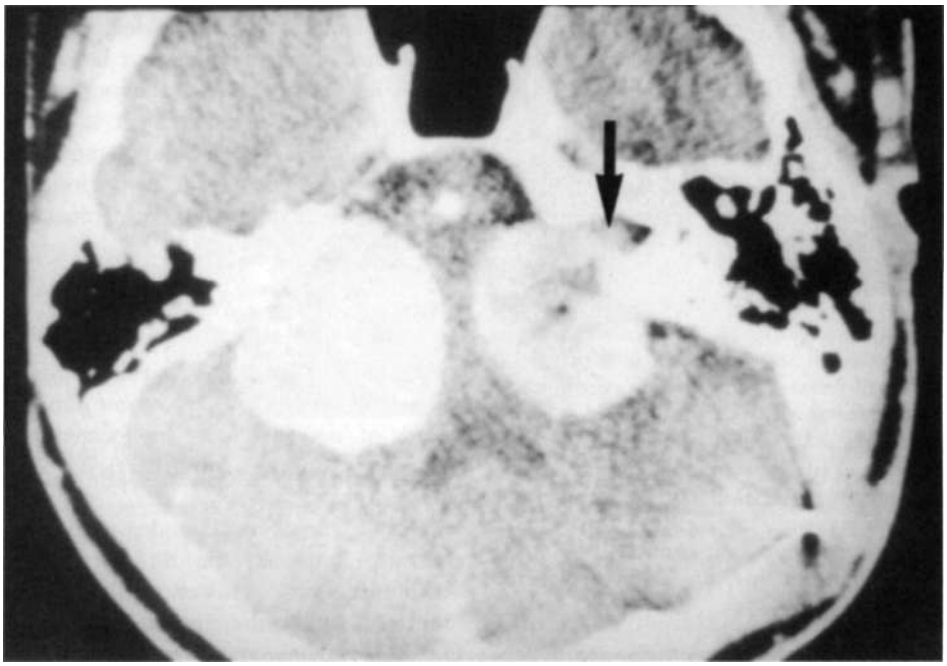


FIGURE 37A.28 Acoustic neurinomas. Bilateral acoustic neurinomas in a patient with neurofibromatosis type 2, Computed tomographic axial scan after contrast administration demonstrates bilateral rounded cerebellopontine angle masses Note the extension of the left cerebellopontine angle mass into a widened internal auditory canal *{arrow).*

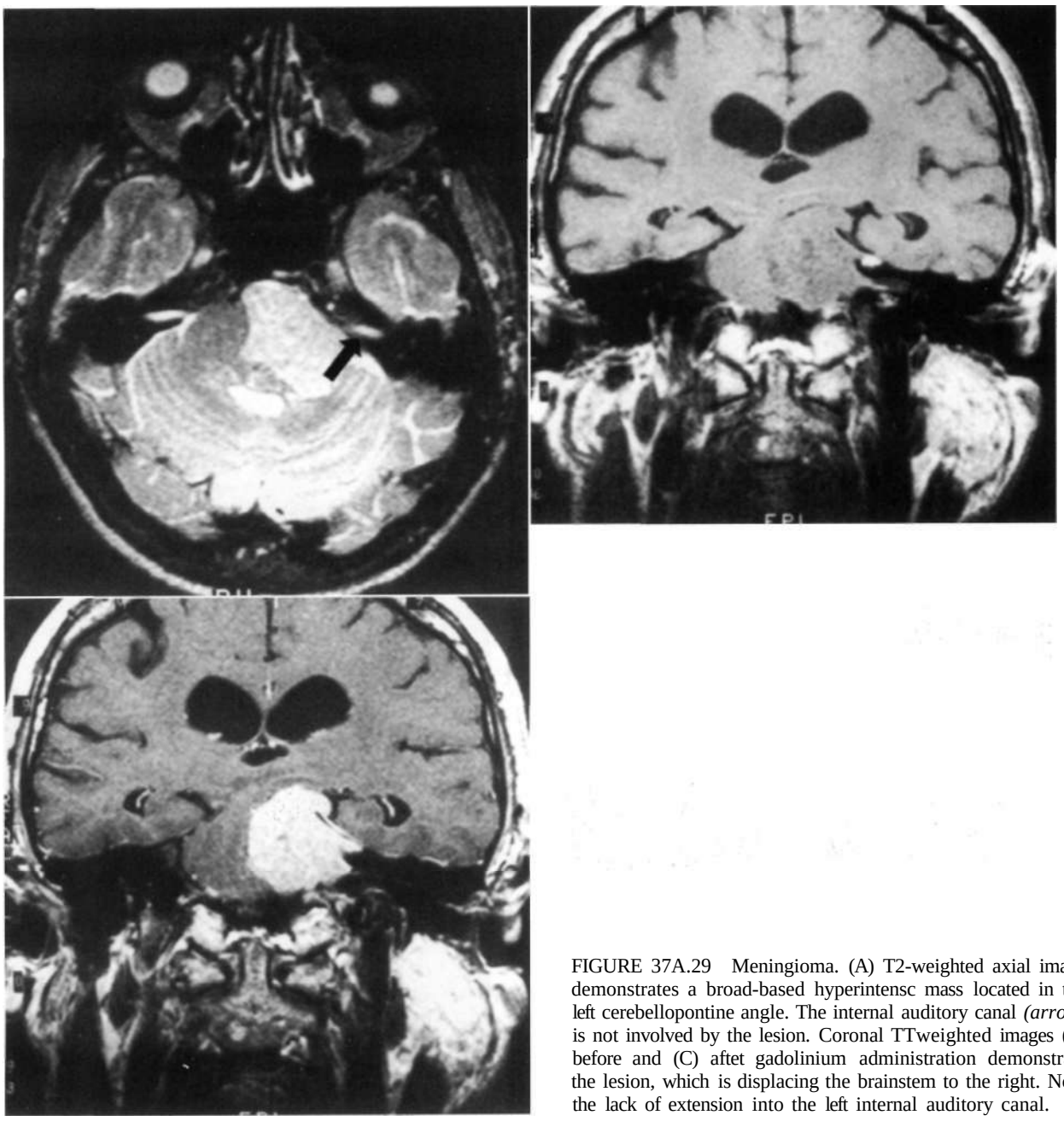


FIGURE 37A.29 Meningioma. (A) T2-weighted axial image demonstrates a broad-based hyperintensc mass located in the left cerebellopontine angle. The internal auditory canal *(arrow)* is not involved by the lesion. Coronal TTweighted images (B) before and (C) aftet gadolinium administration demonstrate the lesion, which is displacing the brainstem to the right. Note the lack of extension into the left internal auditory canal.

matter, deep gray matter (basal ganglia), or pons. The extent of these lesions also increases with age and in patients with disorders such as multi-infarct dementia (MID).

Hypoinrensiry compared with gray matter on T2-weighted images is seen normally in the globus pallidus, red nucleus, substantia nigra, and dentate nuclei because of iron deposition. With aging, a progressive decrease in signal occurs in the putamen and caudate. Many neurodegenerative disorders are associated with excessive signal loss in the extrapyramidal nuclei and thalami.

Dementia

Alzheimer's Disease. In Alzheimer's disease, generalized atrophy is seen on MRI, as is symmetrical or asymmetrical enlargement of the temporal horns, sylvian fissures, and suprasellar cistern. The degree of atrophy generally is greater than in normal aging. Medial temporal lobe atrophy and the number and size of white matter hypcrintense foci are generally greater than in normal aging,

Multi-Infarct Dementia. MID may result from cortical or multiple subcortical infarcts, or both, and is associated with hypertension. Extensive periventricular hyperintensity,

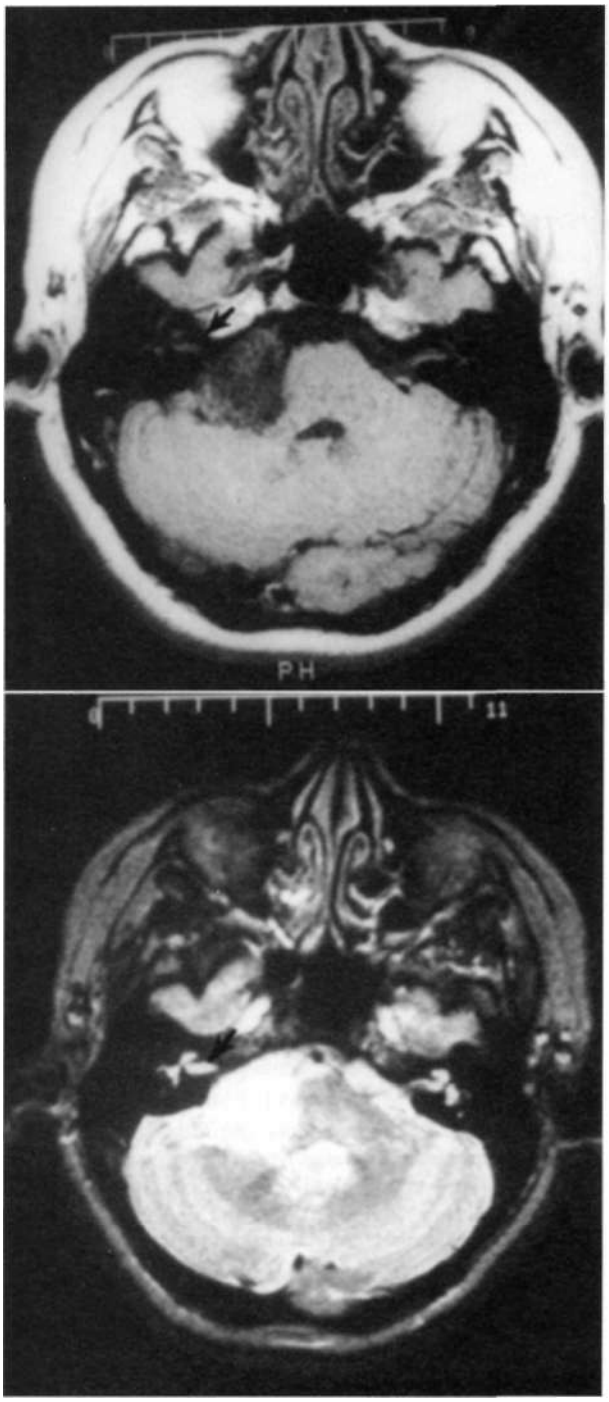


FIGURE 37A.30 Epidermoid cyst. A lesion is located in the right cerebellopontine angle, which is hypointense (slightly higher than cerebrospinal fluid) in (A) Tl-weighted image and hyperintense in (B) T2-wcighted image. The right internal auditory canal is normal *[arrows).*

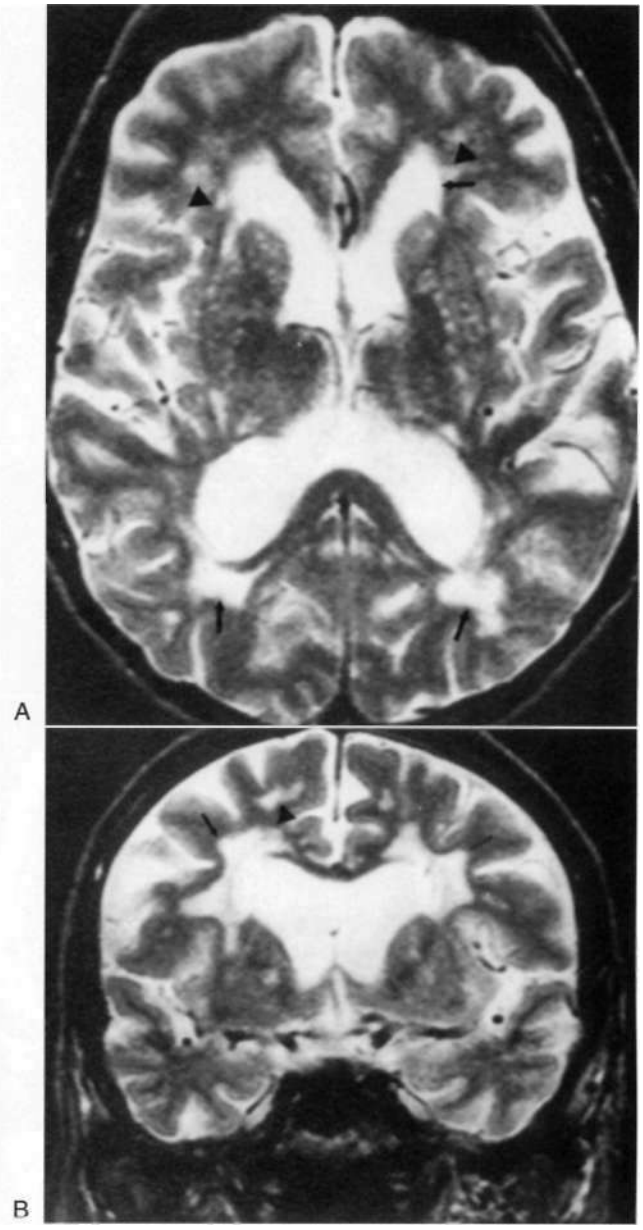


FIGURE 37A.31 Multi-infarct dementia. T2-weighted (A) axial and (B) coronal images demonstrate periventricular hyper in tensity *(arrows)* and multiple subcortical lesions *(arrowheads).* Prominent perivascular spaces are seen in the basal ganglionic region.

cortical infarcts, and basal ganglia lacunar infarcts in a patient with dementia favor a clinical diagnosis of MID or mixed MID and Alzheimer's disease. An MRI scan demonstrating prominent white matter signal changes, particularly subcortical lesions, favors MID over Alzheimer's disease (Figure 37A.31). Lacunar infarcts may be found in all forms of **MID.**

Pick's Disease. Grossly, Pick's disease is characterized by lobar atrophy that may be asymmetrical, with the **frontal** and temporal lobes most commonly affected. This atrophy is well demonstrated on CT and MRI. A similar pattern of atrophy is seen in the other forms of fron totem p oral dementia.

Creutzfeldt-Jakob Disease. CT scanning is used to exclude focal lesions as a cause for the symptoms in patients

with suspected Creutzfcidt-Jakob disease, but CT scanning rarely shows focal parenchymal abnormalities. Most often, CT scans are normal, but in approximately 20% of cases atrophy is present. Approximately one half of the cases demonstrate atrophy only on MRI, whereas in the remaining cases, abnormal high signal intensity is noted on T2-weighted images in the caudate nuclei, striatum, thalamus, cortex, basal ganglia, and periventricular white matter. Cortical gray matter involvement without diffuse cerebral atrophy may represent an early phase of the disease.

Movement Disorders

Parkinsonism. Parkinsonism includes several conditions, such as Parkinson's disease, multisystem atrophy including Shy-Drager syndrome, olivopontocerebellar atrophy, progressive supranuclear palsy, striatonigral degeneration, and corticobasal ganglionic degeneration (see Chapter 76}.

Parkinson's Disease. The imaging findings in Parkinson's disease often are indistinguishable from normal aging. There may be decreased width of the pars compacta of the substantia nigra or decreased signal in the putamen. The latter finding is more likely to be observed in patients with Parkinson's-phis syndromes. Patients with Shy-Drager syndrome associated with striatonigral degeneration have MRI findings that show this (Figure 37A.32}, whereas those with pure autonomic failure have normal MRI results. Neuroimaging and pathological examination in striatonigral degeneration show atrophy of the striatum with signal changes in the putamen. Specifically, at 1.5 T, the signal of the putamen is as hypointcnse as the globus pallidus, and the width of the pars compacta is diminished. The MRI in olivopontocerebellar atrophy shows atrophy and abnormal signal in the pons and cerebellum (Figure 37A.33). There is atrophy of the pons, middle cerebellar peduncles, cerebellum, and inferior olives. On long TR images, slight hyperintensity is seen involving the pontocerebellar pathways and olives.

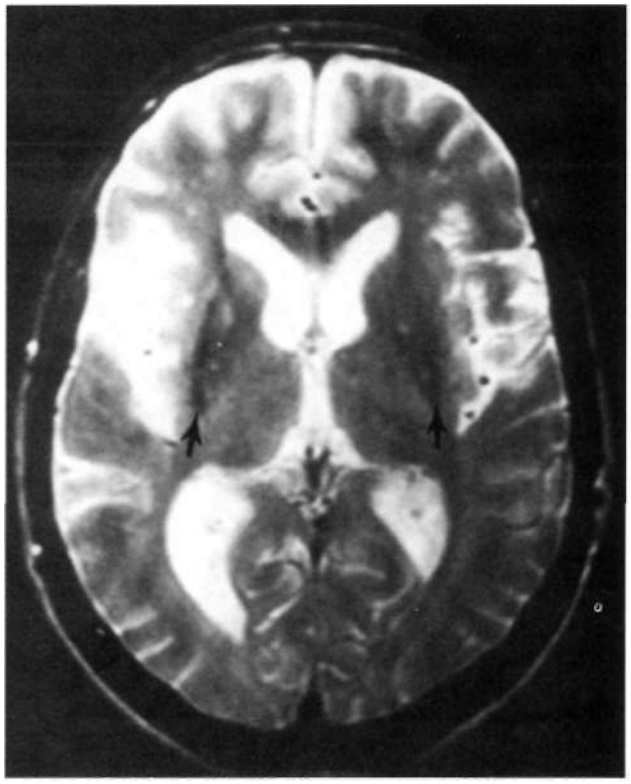


FIGURE 37A.32 Shy-Drager syndrome. This T2-weighted axial image shows hypointensity in the region of the putamen *{arrows).* Right temporal lobe atrophy (widened sylvian fissure} and ven triai I omega ly are present.

Mitochondrial Encephalopathies

Several syndromes of mitochondrial dysfunction with neurological involvement have been described, including myoclonus epilepsy with ragged-red fibers (MERRF); mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); Kearns-Sayre syndrome; and subacute necrotizing encephalomyetopathy, or Leigh's disease, which is a severe and often fatal mitochondrial disease (see Chapter *69).* In Leigh's disease, necrosis and capillary proliferation occur in the basal ganglia, spinal cord, and brainstem. CT scans usually show low-density areas in the putamen and caudate nuclei that do not enhance after contrast administration. T2-wcightcd MRIs show striking symmetrical hyperintense foci in the globus pallidus, putamen, and caudate. The imaging changes most commonly seen in the brain in MELAS arc those of cerebral infarcts. Both large and multifocal infarcts occur, and the occipital lobes arc the most common sites of involvement. Imaging findings in MFRRF may be similar to MELAS or may show atrophic changes in the cerebral cortex, brainstem, and cerebellum.

White Matter Disease

Demyeiinating Diseases

Demyelinating diseases cause normal myelin to be destroyed. There may be additional loss of axons and secondary gliosis. MS is the most common demyelinating disease.

Multiple Sclerosis. On MRI, MS plaques appear as rounded areas of increased signal on T2-weighted images (Figure 37A.34; see Chapter 60). Gadolinium enhancement is present in many acute plaques and probably disappears within a few days. A small number of plaques show a mass effect during the acute phase. In time, the area

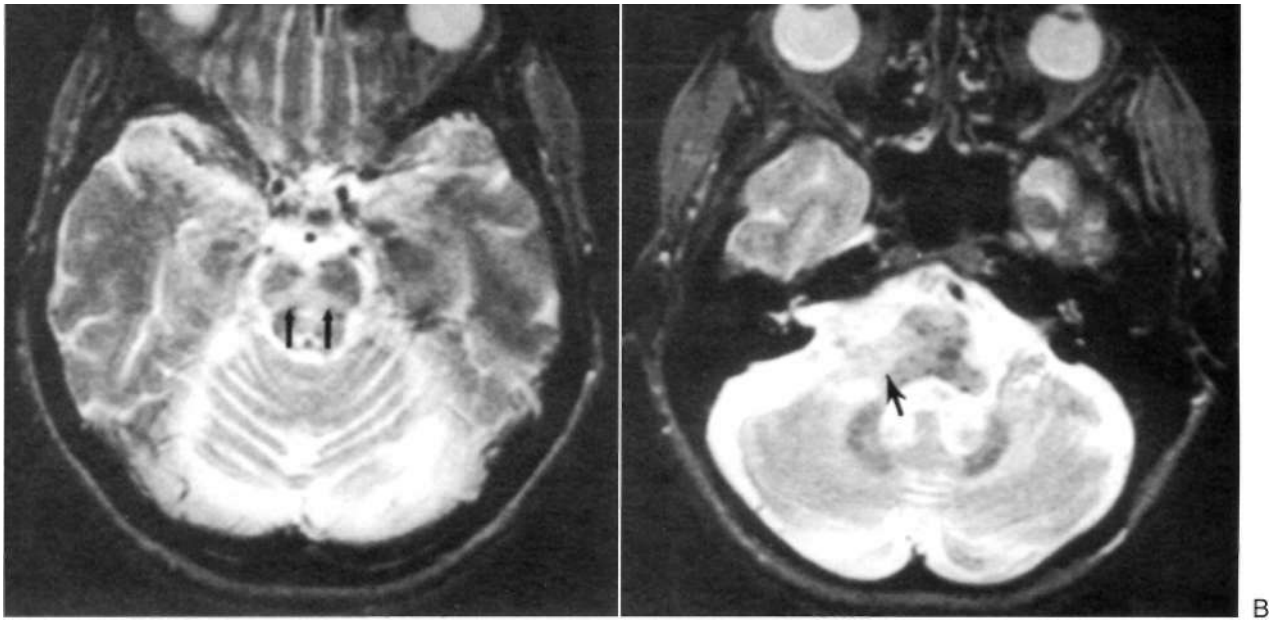


FIGURE 37A.33 Olivopontocerebellar atrophy. (A) Axial T2-weighted image through the pons shows abnormal hyperintense signal of transverse pontine fibers (between the tegmentum and the base of the pons) *(arrows).* Cerebellar atrophy is present. (B) A more inferior section shows abnormal hyperintense signal of the right middle cerebellar peduncle *(arrow).* Also note atrophy of the brainstem with enlargement of the cisterns and the fourth ventricle.

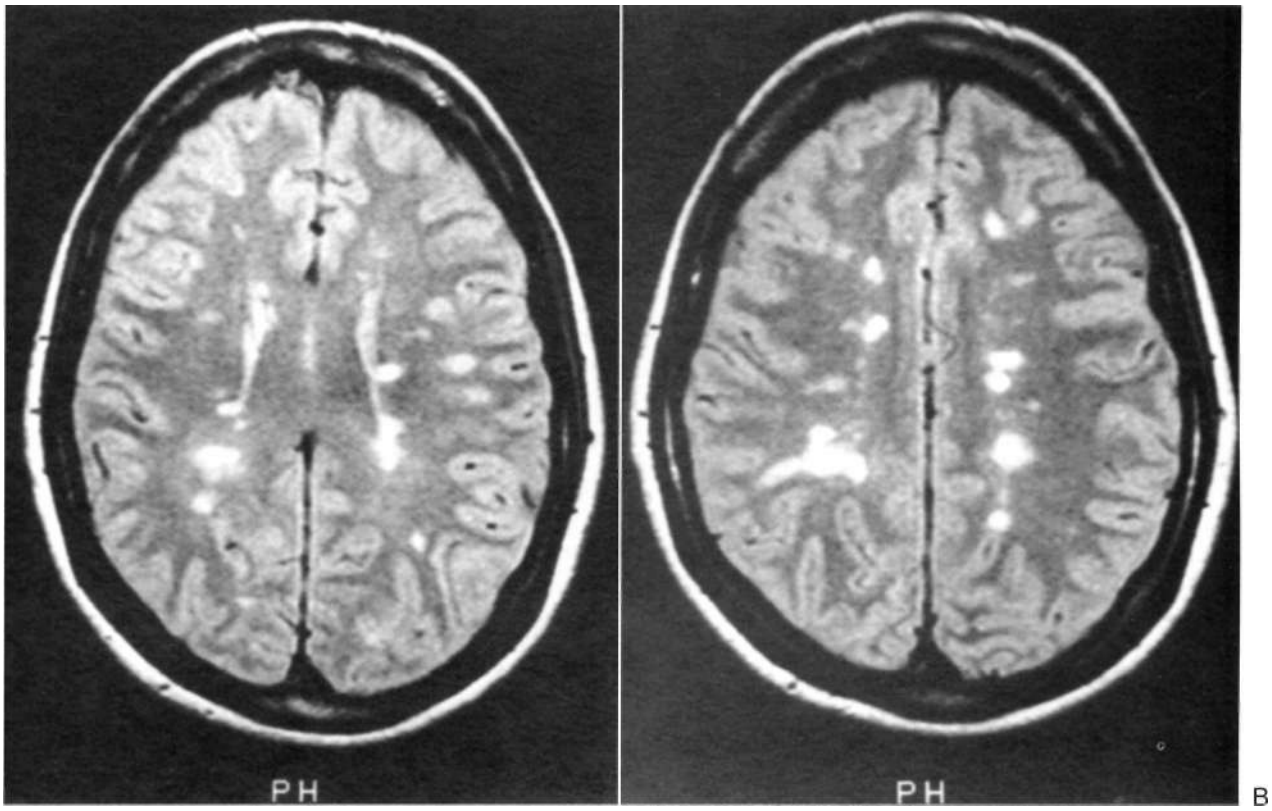


FIGURE 37A.34 Multiple sclerosis. Proton-weigh ted axial images demonstrate hyperintense lesions (A) in the periventricular region and (B) in the centrum semiovale in a patient with multiple sclerosis.

of inflammation decreases in size and leaves a plaque of high intensity on T2-weighted images. Plaques are common in the periventricular regions, internal capsule, corpus callosum, pons, and brachium pontis. Plaques located in the periventricular region may not he well seen on long 1 R-long TE images, where CSF in the ventricles is bright and may obscure the plaques. Proton density images (long TR-short TE) better define the MS lesions. Axon loss in chronic plaques is recognized by magnetic resonance spectroscopic loss of N-acety(aspartate and is responsible for the low signal in these areas in Tl-weighted images.

Acute Disseminated Encephalomyelitis. In acute disseminated encephalomyelitis, the MRI shows bright lesions on T2-weighted images, most in the subcortical white matter with relative symmetrical involvement of both hemispheres {Figure 37A.35; see Chapter 60). Enhancement can be seen with acute disseminated encephalomyelitis, and lesions usually regress in response to corticosteroid treatment.

Central Pontine Myelinolysis. On MRI, in central pontine myelinolysis the typical finding is a hyperintense lesion in T2-weighted images of the central pons, with sparing of the periphery of the pons. High-intensity lesions may also be seen more extensively throughout the brain in areas whert white and gray matter lie in proximity, including the subcortical regions and the thalamus.

Leukodystrophies

The MRI picture is that of progressive white matter lesions and diffuse cerebral atrophy (see Chapter 67), Some features distinguish between the different leukodystrophies early in the course of the disease.

Krabbe's Disease. In Krabbe's disease, on CT, increased density occurs in the thalami, caudate, and corona radiata. On MRI, lesions involve the basal ganglia and white matter in a symmetrical fashion.

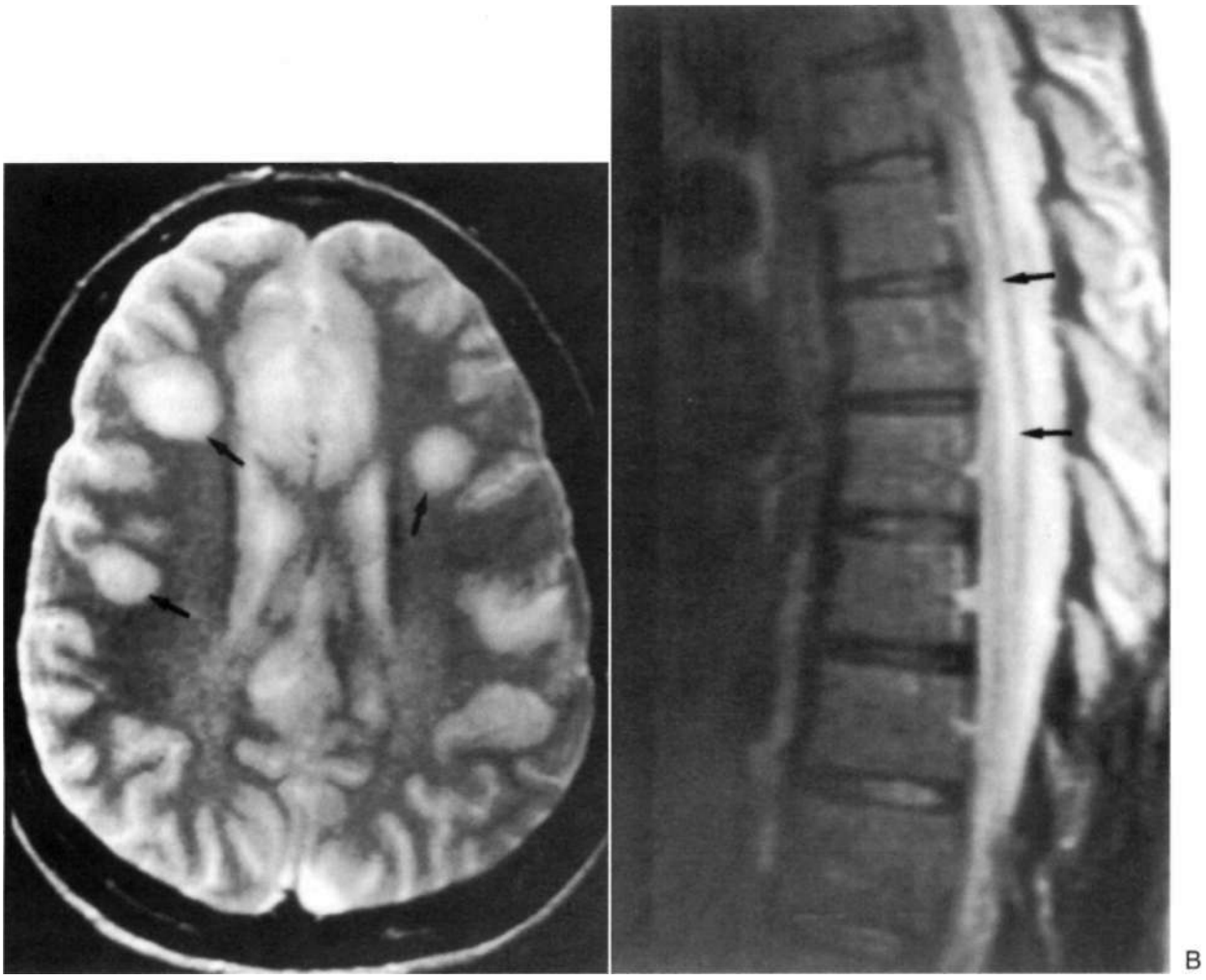


FIGURE 37A.35 Acute disseminated encephalomyelitis. (A) T2-weighted axial image shows multiple hyperintense subcortical white matter lesions *(arrows).* (B) T2-weighted sagittal image of the thoracic spine shows abnormal high signal with the cord *(arrows).*

Metachromatic Leukodystrophy. CT and MRI reveal diffuse white matter lesions (Figure 37A.36) in metachromatic leukodystrophy.

Adrenoleukodystrophy. On CT and MRI in adrenoleukodystrophy, symmetrical areas of white matter abnormality surround the atria of the lateral ventricles and span the splenium of the corpus callosum. At the lateral margin of the zones of demyelination, contrast enhancement may occur. Demyelination along certain tracts, such as the lateral lemniscus, occasionally is identified.

Miscellaneous Lesions of White Matter

Arteritis and secondary ischemic lesions of the brain may result from chemotherapy and radiation treatment. Determining whether a patient's symptoms are caused by an exacerbation of the neoplasm or the effects of treatment (i.e., radiation necrosis) can be difficult. Most recurrent or residual tumors appear as focal areas of enhancement with surrounding edema. The white matter lesions caused by radiation endarteritis may be transient or permanent

Areas of radiation necrosis can be focal or disseminated within the white matter. Radiation necrosis is seen on T2-weighted images as an area of high-intensity signal with variable gadolinium enhancement on T1-weighted images. Mass effect and edema are common early in radiation necrosis, although later atrophy predominates.

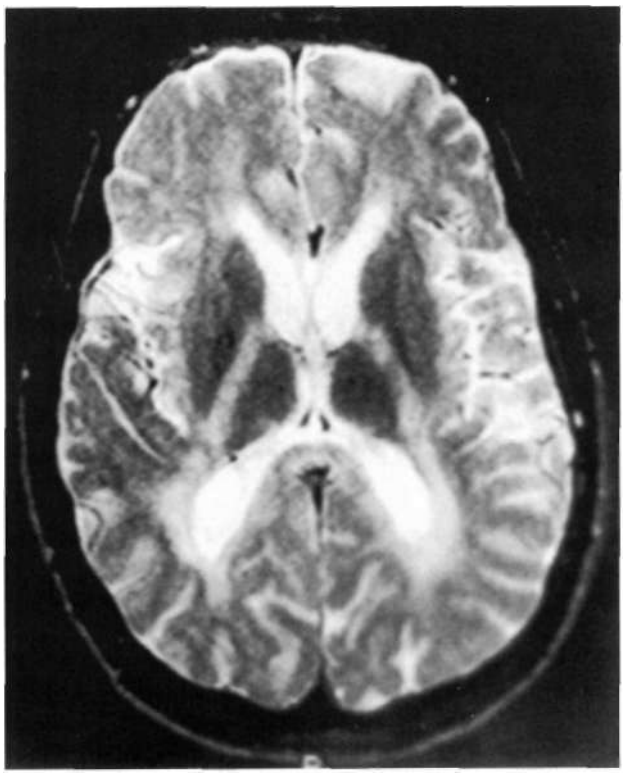


FIGURE 37A.36 Metachromatic leukodystrophy. A 26-year-old patient with progressive neurological deterioration. Diffuse high-intensity signal is noted in the periventricular white matter and internal capsule bilaterally in this T2-wcighted axial scan. The absolute symmetry of the abnormal high signals is a clue that a white matter disease other than multiple sclerosis or vascular myelopathy is responsible.

Head Trauma

CT is obtained in the initial evaluation of the acutely unstable patient who has a head injury to determine whether there is a surgical lesion, such as a subdural or epidural hematoma. However, many lesions are identified by MRI, such as cortical contusions, small subdural hematomas, and diffuse axonal injury, that may not be seen on CT examination. In addition, MRA can play an important role in evaluating trauma, identifying vascular abnormalities such as arterial occlusion and dissecrion, arteriovenous fistula (AVF), and venous sinus occlusion.

Diffuse Axonal Injury

Diffuse axonal injury occurs when the brain has been subjected to an angular acceleration force, causing the hemispheres to move in relation to more fixed structures such as the btainstem, thus tearing white matter fibers (axons). Diffuse axonal injury or shear injury is a common post-trauma tic lesion and is seen well on MRI. Lesions commonly are less than 1 cm in diameter and are seen in the lobar white matter, corpus callosum, and dorsolateral aspect of the tostral brainstem and at the corticomedullaty junction (Figure 37A.37). Patients with such injuries present with loss of consciousness and significant neurological impaitment.

The majority of shear injuries are nonhemorrhagic and MRI, especially the T2-weighted sequence, is more sensitive than CT in detecting them.

Cortical Contusion

Cortical contusions, another common type of traumatic lesion, involve the superficial cortex, tend to be multiple, usually are larger (2-4 cm) than diffuse axonal injuries, are less likely to be associated with severe impairment of consciousness, and most commonly occur in the temporal and frontal lobes. A higher percentage of cortical contusions are hemorrhagic than are those of diffuse axonal injury. MRI and CT are sensitive in detecting hemorrhagic cortical contusions, but MRI, particularly the T2-weighted sequence, is more sensitive in detecting nonhemorrhagic contusions (Figure 37A.38).

Subdural Hematoma

Subdural hematomas evolve in a pattern similar to parenchymal hematomas in the acute and subacute phase but differ from parenchymal hemaromas in the chronic

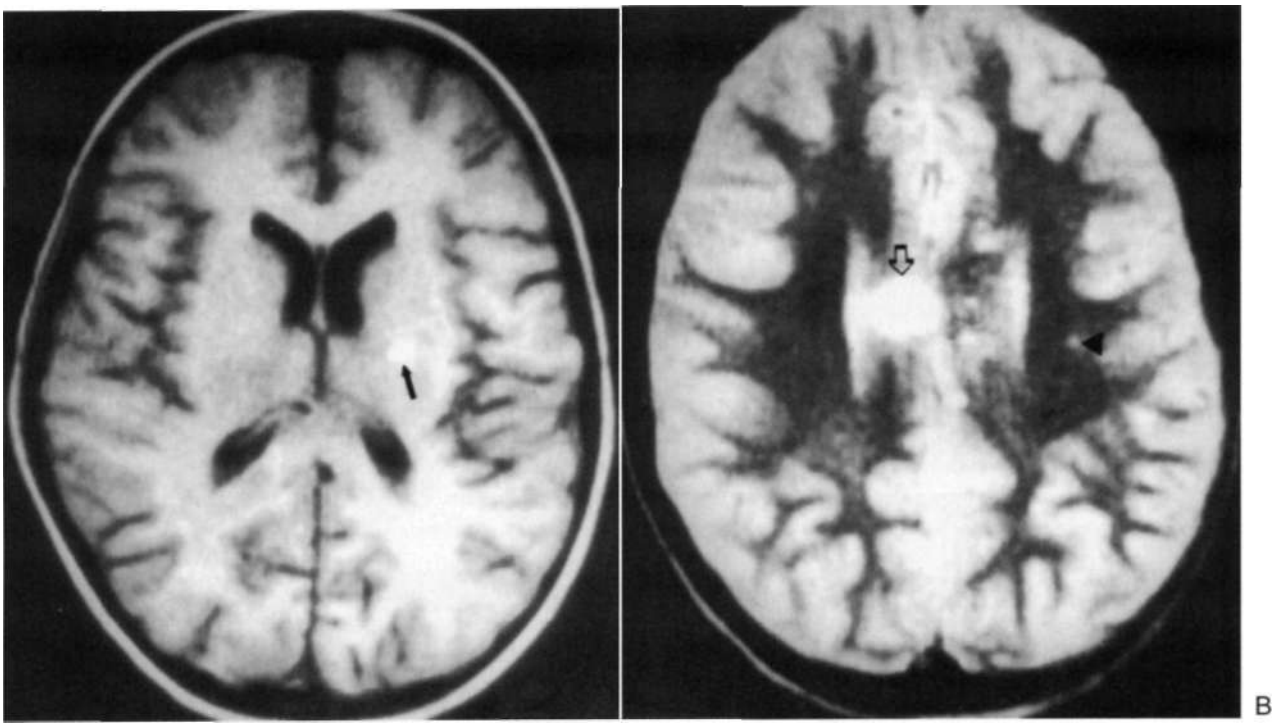


FIGURE 37A.37 Diffuse axonal injury. (A) Axial short repetition time-echo time (TR-TE) magnetic resonance scan of a patient with hemorrhage and nonhemorrhagic diffuse axonal injury. A hemorrhage is seen in the posteriot limb of the left internal capsule *(arrow).* (B) Axial long TR-TE image at a higher level shows a lesion in the corpus callosum *(open arrow)* and a smaller lesion in the left centrum scmiovale *(arrowhead),* (Reprinted with petmission from Sklar, E. M. L, Quencer, R. M., Bowen, B. C, et al. 1992, "Magnetic resonance application in cerebral injury," *Radiol Clin North Am,* vol. 30, pp. 353-366.)

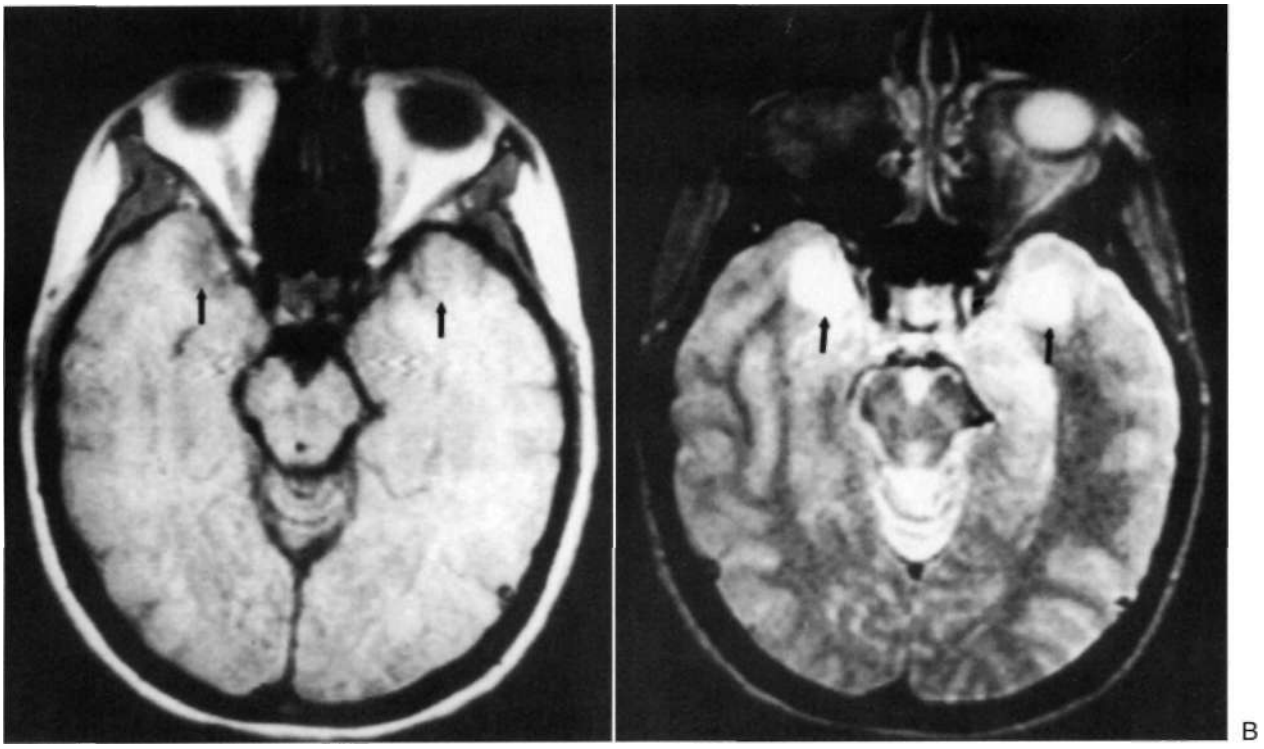


FIGURE 37AJ8 Contusion. Nonhemorrhagic cortical contusions in the temporal lobes *(arrows).* Areas are much more clearly seen in (B) T2-weighted than in (A) Tl-weighted images. (Reprinted with permission from Sklar, E. M. L, Quencer, R. M., Bowen, B. C, et al. 1992, "Magnetic resonance application in cerebral injury," *Radiol Clin North Am,* vol. 30, pp. 353-366.)

phase, as explained later. The time categories used in this discussion are as follows: *Acute* means less than 1 week old, *early subacute* indicates more than 1 week and less than 2 weeks, *late subacute* means more than 2 weeks and less than 1 month, and *chronic* indicates a duration of more than 1 month. The acute subdural hematomas are characterized by hypointensity on T2 weighted images, reflecting the presence of deoxyhemoglobin. A late subacute subdural hematoma shows high signal intensity on all pulse sequences because of the presence of extracellular methemoglobin (Figure 37A.39). Subdural hematomas in a chronic phase are hypointensc on short TR and TE images; this loss of Tl shortening results from a decrease in the concentration of methemoglobin caused by dilution, absorption, or degradation. Enhancement of the periphery of the subdural hematomas is expected in the chronic phase because of the presence of a vascular capsule.

Epidural Hematoma

Epidural (or extradural) hematomas may arise from arterial or venous bleeding. When arterial, they usually are caused by a laceration of a meningeal artery and are associated with skull fractures (Figure 37A.40). On MRI, the dura often can be seen displaced away from the inner table of the skull as a thin low-signal line between the brain and the hematoma.

Subarachnoid Hemorrhage

On CT, subarachnoid hemorrhage is seen as high density in the basal cisterns, sylvian fissures, inter hemispheric fissure, sulci, or some combination of these locations. Most of the increased density rarely lasts more than a few days because the blood becomes diluted in the subarachnoid space and

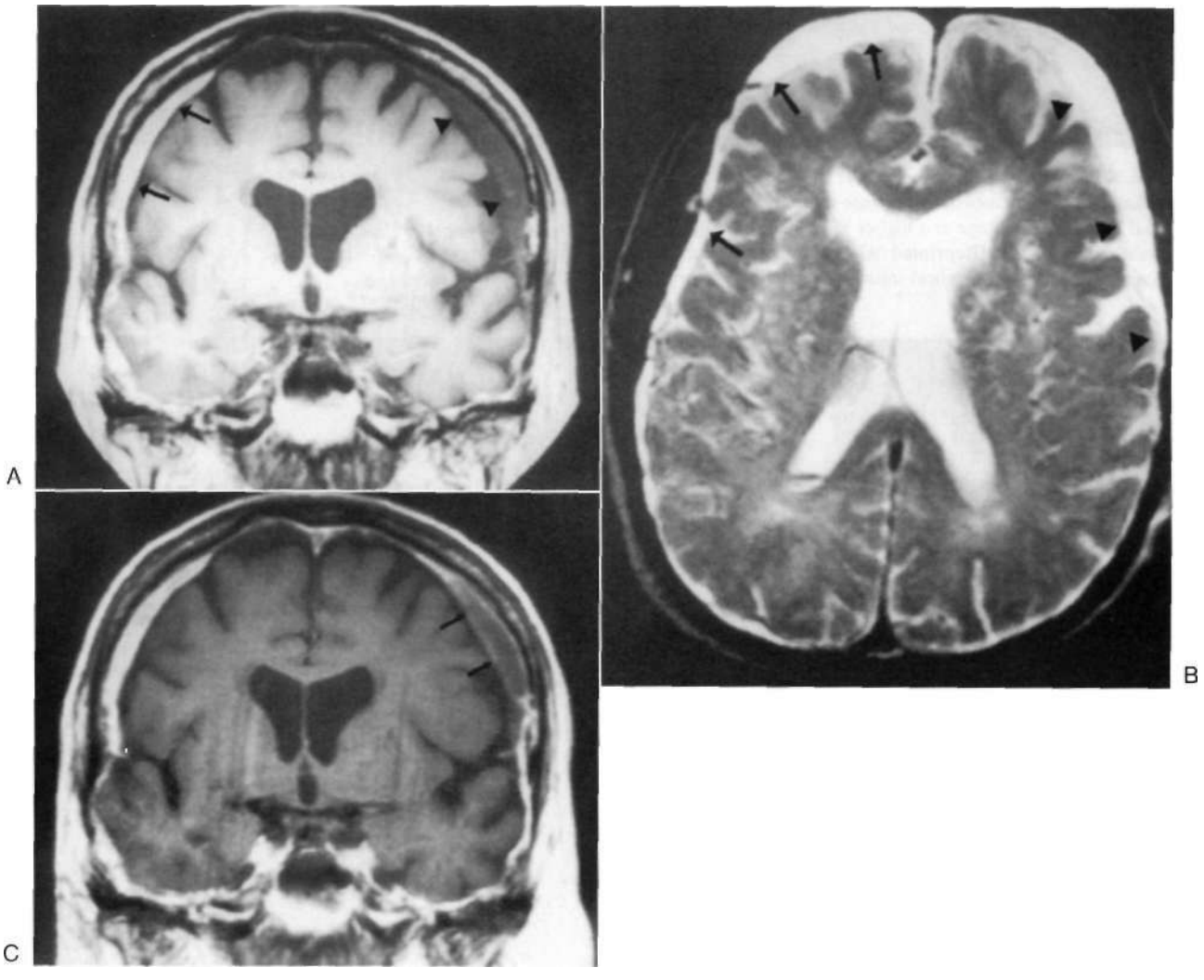


FIGURE 37A.39 Subdural hematoma (SDH). A 76-year-old man who fell 10 days before magnetic resonance imaging. (A) Subacute SDH on right *{arrows)* shows high signal on this IT-weighted coronal image. On the left side, a chronic SDH *{arrowheads)* is shown. (B) T2-weighted axial image shows high signal along the entire collection of right SDH *{arrows).* Also note the chronic SDH on the left, which is iso in tense on T1- and hyperintense on T2-weigh ted image *(arrowheads).* (C) Postcontrast-cnhanced coronal magnetic resonance innigi' liL-tnonsmucH .in enhancing membrane *(arrows)* of the chronic SDH.

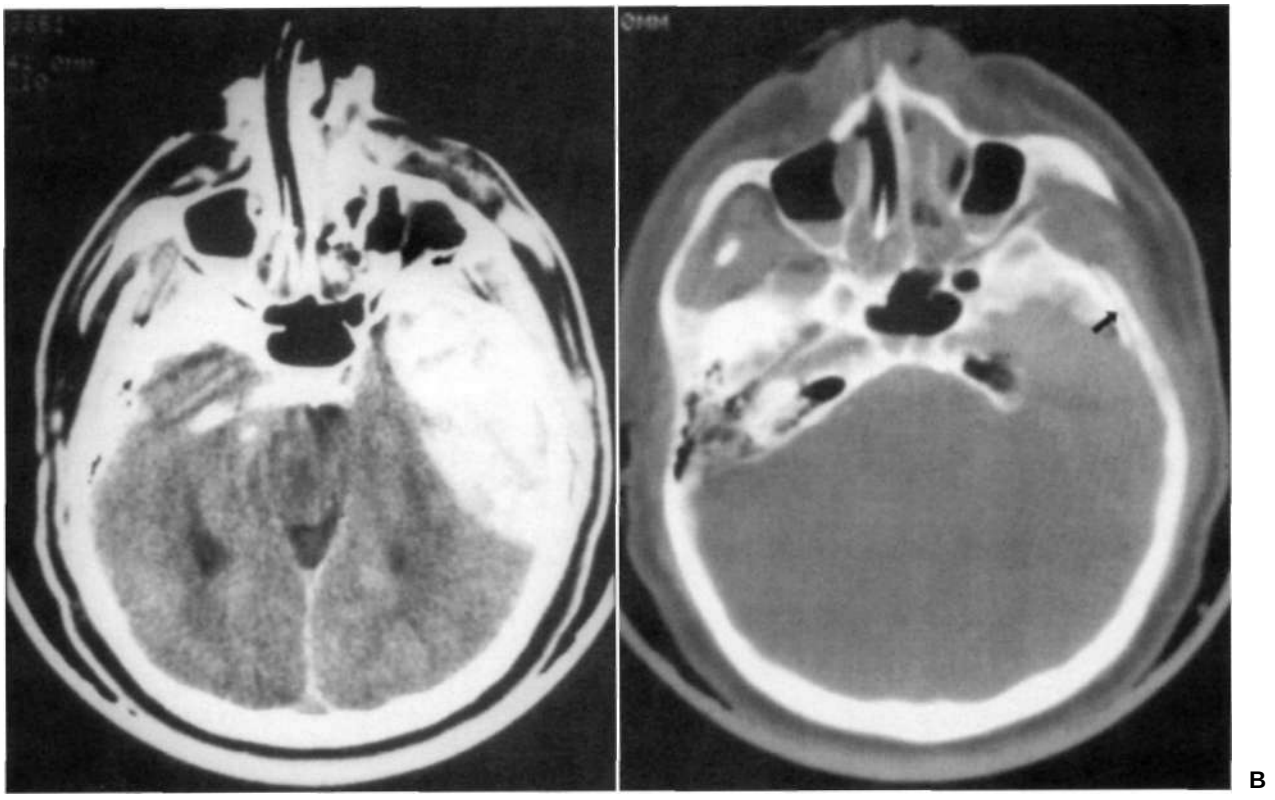


FIGURE 37A.40 Epidural hematoma. (A) Computed tomographic axial section shows a left biconvex peripheral high-density lesion consistent with an epidural hematoma. (B) A fracture *(arrow)* is seen on the bone windows of the same section.

is resorbed over the cerebral convexities. MRI is less successful in depicting acute subarachnoid hemorrhage, so CT is still the preferred study in suspected subarachnoid hemorrhage.

This inscnsitivity of MRI to blood in the subarachnoid space is related to the high Po_2 in the CSF. Conversion of oxyhemoglobin to dcoxyhemoglobin and subsequently to methemoglobin requires a narrow range of oxygen tension. In the CSK, significant quantities of methemoglobin are not formed until several days after the hemorrhage, and if the subarachnoid hemorrhage is mild the red blood cells may be resorbed before significant amounts of methemoglobin are formed. For these reasons, CT is advocated for the early diagnosis of acute subarachnoid hemorrhage. However, for subacute and chronic subarachnoid hemorrhage, MRI may be superior to CT.

Intracerebral Hematoma

Traumatic intracerebral hematomas may range from a few millimeters to several centimeters in diameter. Distinguishing hematomas from hemorrhagic contusions and shear injuries is difficult but important. Unlike intracerebral hematomas, the hemorrhage in the latter two types of injuries is interspersed between areas of edematous brain. Although most of these lesions develop immediately after trauma, some may develop in the first 48 hours after injury. This may be either because the swelling of the brain decreases, thus allowing more capillary bleeding, or because the change in oxygen tension alters the brain perfusion, thus increasing the chances of delayed hemorrhage.

Vascular Injuries: Role of Magnetic Resonance Angiography

Vascular injuries can be either arterial or venous. The most common abnormality of the major arteries after trauma is arterial occlusion, which is attributed to severe spasm and emboli from mural thrombi in areas of intimal disruption. Arterial dissections often occur near the junction of the cervical and petrous segments of the internal carotid artery where it enters the carotid canal. Arterial dissection often is idiopathic, but trauma can be the cause.

Routine spin-echo MRI is useful in imaging carotid-cavernous fistulas. The MRA findings are characteristic even though the exact site and dynamic character of the fistula arc not as well shown as on conventional angiography (Figure 37A.41). A sign of a carotid-cavernous fistula on routine MRI is significant enlargement of a draining vein, such as the superior ophthalmic vein.

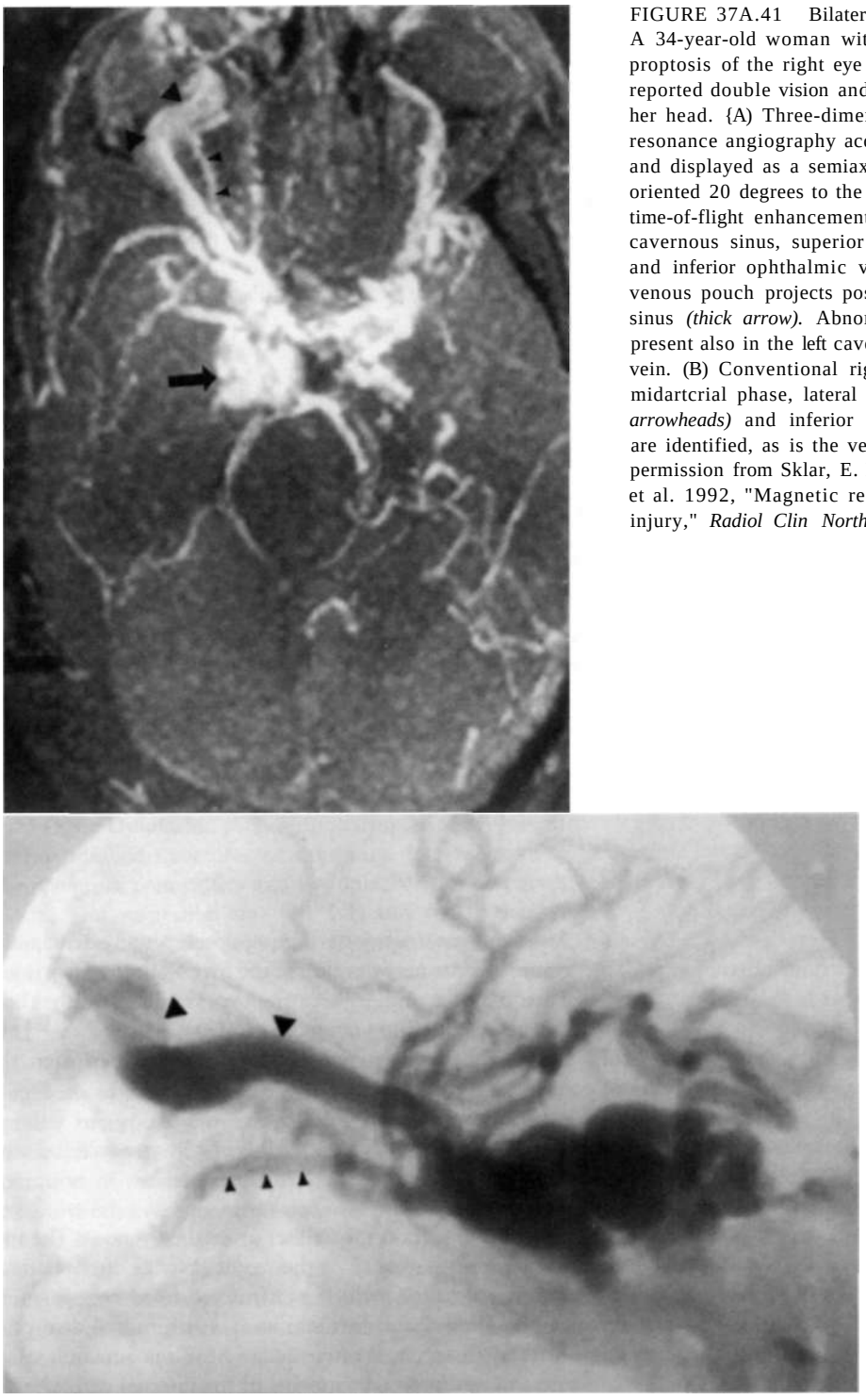


FIGURE 37A.41 Bilateral carotid cavernous fistulas, A 34-year-old woman with extensive facial injuries and proptosis of the right eye after a motor vehicle accident reported double vision and a pulsating noise in the right side of her head. {A) Three-dimensional time-of-flight magnetic resonance angiography acquired as a transaxially oriented slab and displayed as a semiaxial maximal intensity projection oriented 20 degrees to the horizontal plane. There is abnormal time-of-flight enhancement and enlargement of the right cavernous sinus, superior ophthalmic vein *(large arrowheads),* and inferior ophthalmic vein *{small arrowheads).* A large venous pouch projects posteriorly from the right cavernous sinus *(thick arrow).* Abnormal time-of-flight enhancement is present also in the left cavernous sinus and superior ophthalmic vein. (B) Conventional right internal carotid angiogram, midartcrial phase, lateral projection. The superior *[large arrowheads)* and inferior *[small arrowheads)* ophthalmic veins are identified, as is the venous pouch. (Reprinted with permission from Sklar, E. M. L, Quenccr, R. M., Bowen, B. C, et al. 1992, "Magnetic resonance application in cerebral injury," *Radiol Clin North Am,* vol. 30, pp. 353-366,)

Cerebral Infections

MRI is the imaging procedure of choice for CNS infection and inflammation. With intravenous conttast administration, areas of enhancement on MRI indicate sites of blood-brain barrier disruption and meningeal inflammation.

Viral Infections

On MRI in herpes simplex encephalitis, hyperintensiry involving the cortex and white matter in the temporal and inferior frontal lobes is noted on T2-weighted images. The areas of involvement then enlarge and coalesce, MRI often demonstrates bitemporal involvement, and hemorrhage

may be detected (Figure 37A.42). Atrophy is seen late in the course of the disease.

Bacterial Infection (see Chapter 59)

Lyme Disease. North American Lyme disease, or borreliosis, results from infection by the tickborne spirochete *Borrelia burgdorferi.* Lyme disease is endemic in the northeastern United States. Lyme disease has protean clinical manifestations, with involvement of skin, heart, and musculoskeletal and nervous systems. Neurological abnormalities develop in approximately 11% of patients with skin lesions, may occur without a histoty of skin manifestations, and typically occur months to yeats after the initial tick bite. Neurological symptoms may include aseptic meningitis, ctanial neuritis, ataxia, and encephalitis.

MRl scans may be normal or may demonstrate (in advanced stages), multiple bilateral periventricular or subcortical hyperintensc lesions on T2-weighted images without mass effect resembling MS plaques. Brainstem and basal ganglia may be involved. With gadolinium, parenchymal lesions and the meninges may be enhanced.

Cerebritis and Abscess. Cerebritis is a pootly demarcated localized area of parenchymal softening with necrosis, edema, vascular congestion, and perivascular inflammation. A focus of cerebritis may progress to abscess formation, in which a central /.one of necrosis liquefies; the lesion becomes better defined and eventually encircled by an enhancing vascularized fibrotic capsule surrounded by a zone of gliosis. Most abscesses form because of hematogenous spread of organisms at the gray matter-white matter junction, most commonly in the frontal and parietal lobes.

On MRl, an abscess on T1-weighted images has a central cavity, which is hypointensc to brain parenchyma; on T2-weighted images it is hyperintense. The rim, which is isointense to hypointense on Ti-weighted images and is hypointense on T2-wcighted images, is not identical to the ring of enhancement seen with gadolinium. The ring of enhancement usually is smooth and thin walled when compared with the peripheral enhancement seen with malignant tumors; however, occasionally the wall may be thick and simulate a necrotic neoplasm (Figure 37A.43). Edema in the white matter atound an abscess usually is greater in volume than the abscess itself. Abscesses tend to point (i.e., have a thinner wall) toward the ventricle and may ruptute into the ventricle.

Meningitis. In meningitis, unenhanced MRl scans usually show no abnormality. Gadolinium-enhanced MRl scans

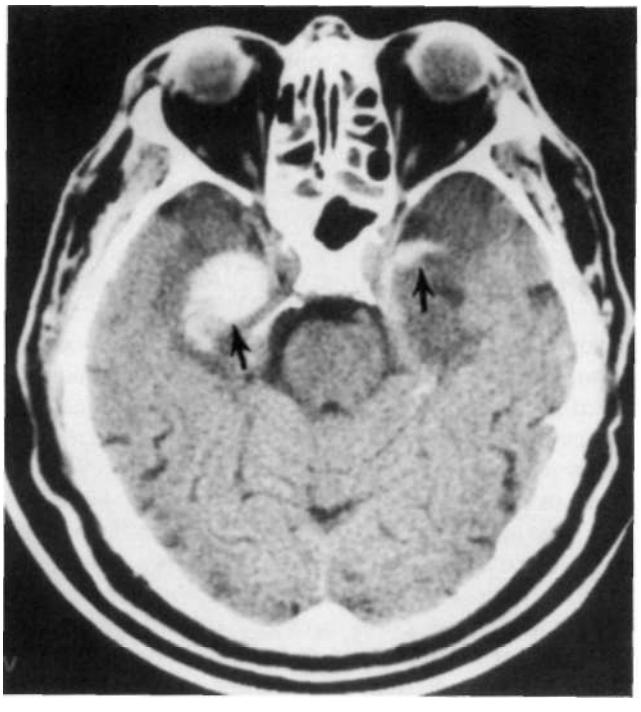


FIGURE 37A.42 Herpes encephalitis. Noncontrast axial computed tomographic scan shows bilateral hemorrhagic lesions *{arrows).* These medial and interiorly located temporal lobelesions consisting of blood, edema, and inflammatory tissue are characteristic of herpes simplex encephalitis.

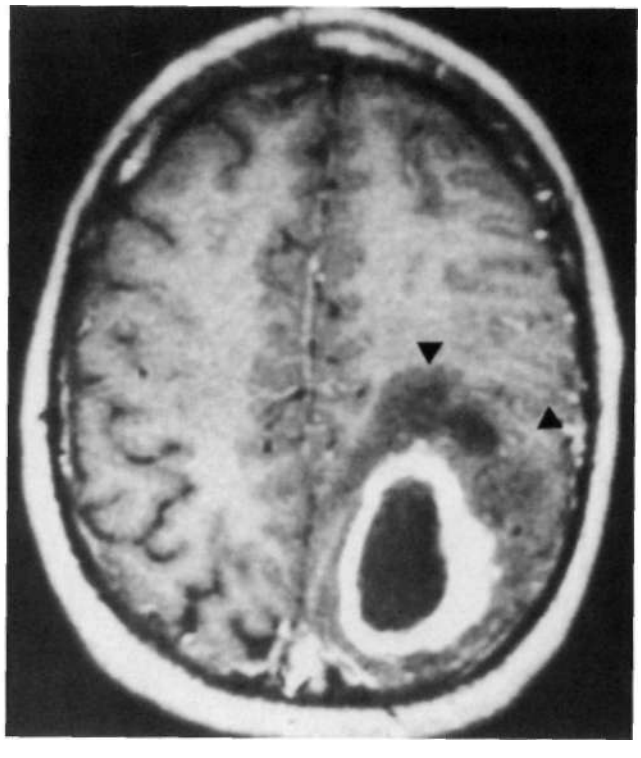


FIGURE 37A.43 Intracerebral abscess. Contrast-enhanced axial Tl-weighted magnetic resonance imaging shows a ring of enhancement surrounded by edema and hemispheric mass effect producing obliteration of sulci and crowding of the gyn *(arrowheads).* Because of the thick rim of enhancement and necrotic center, one would commonly consider a malignancy the primary diagnosis, but this was a surgically proved *Streptococcus viridans* abscess.

may show prominent leptomeningeal enhancement with a gyral pattern in severe cases. Complications of meningitis include cerebral infarction, cerebritis and abscess, subdural empyema, hydrocephalus, and ventriculitis. These complications arc best detected by **MRI.**

Mycobacterium tuberculosis. Infection by *M. tuberculosis* or certain fungi causes a granulomatous inflammatory reaction, which may involve the meninges or hrain parenchyma. Characteristically, a thick gelatinous exudate is found in the basal cisterns. The capsule of the granuloma often is thicker than that of a pyogenic abscess. Tuberculosis may produce a vasculitis due to endarteritis obliterans of the artery passing through the infection that can result in an infarction. Basal cisternal and diffuse meningeal enhancement is a predominant feature of tuberculous meningitis (Figure 37A.44).

Tuberculomas can be located anywhere in the cerebrum or cerebellum and in subarachnoid, subdural, and epidural spaces. Intraparenchymal granulomas are found at the corticomedullary junction and in the periventricular regions. In general, there is less edema in the brain surrounding a tuberculoma than that surrounding a pyogenic abscess. With intravenous contrast administration, tuberculomas enhance intensely in a nodular or ringlike fashion.

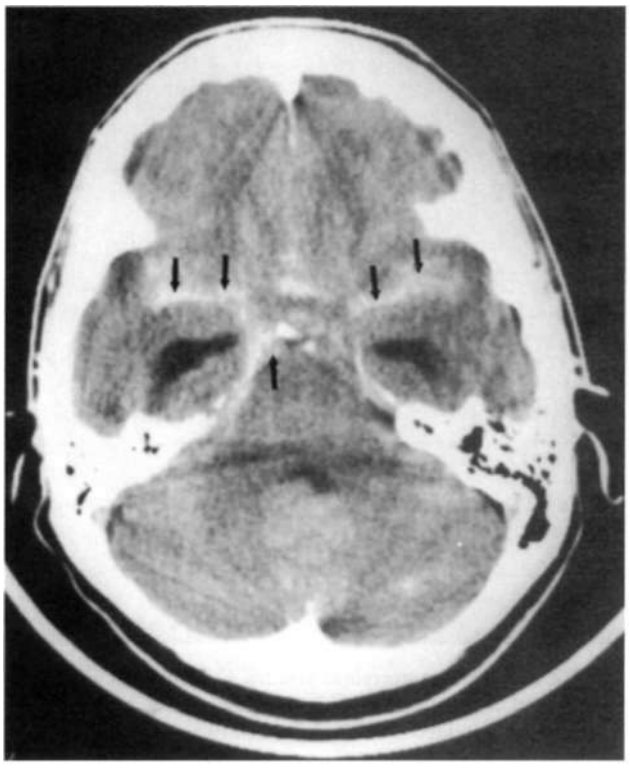


FIGURE 37A.44 Tuberculous meningitis. Postcontrast computed tomographic scan reveals diffuse cisternal enhancement *(arrows)* compatible with diffuse meningitis.

Cysticercosis

Cysticercosis is the most common parasitic infection of the human CNS worldwide. The causative agent is the pork tapeworm, *Taenia solium.* There are four types of neurocysticercosis: parenchymal, subarachnoid, intraventricular, and mixed. After initial infection, the cysticercus develops into a cyst containing the scolcx (Figure 37A.45}. As the organism dies, metabolic products leak from the wall of the cyst and incite an inflammatory reaction. Edema may then develop and the cyst becomes turbid. The cyst then collapses and calcifies. If the cyst becomes nuilriloculated, it resembles a cluster of grapes, known as the *racemose form,* which typically occurs in the basilar cisterns.

Intraventricular and subarachnoid cysts can be difficult to visualize on CT and are better seen on MRI. The fourth ventricle is the most common site of intraventricular cysticercosis (see Figure 37A.45).

Acquired Immunodeficiency Syndrome

Neuroimaging plays a crucial role in the investigation of patients with AIDS and CNS disease (see Chapter 59). CT and **MRI** are the most commonly used modalities in evaluating patients with AIDS and CNS disease; however, nuclear medicine has become an important imaging modality for differentiating inflammatory and neoplastic masses. Specifically, thallium-201 brain single photon emission CT can be used to distinguish toxoplasma encephalitis from CNS lymphoma, the two primary pathological lesions in this population (Ruiz et ai. 1994).

MRI is more sensitive than CT in detecting diffuse white matter disease, which commonly is seen in AIDS. T2-weighted images are necessary in evaluating neurologically symptomatic patients with AIDS.

Toxoplasma Encephalitis

Toxoplasma encephalitis, caused by the intracellular proto/.oan *Toxoplasma gondii,* is the most common infection to affect the brain in AIDS. In noncontrast CT, toxoplasma encephalitis is seen as multiple areas of isodensity or hypodensiry, with a predilection for the corricoiiiedullary junction and basal ganglia. The lesions may vary in size from less than 1 cm to more than 3 cm, and hemorrhage, although unusual, has been reported in both the treated and the untreated patient. Surrounding edema and mass effect occur, and postcontrast CT demonstrates ring, solid, or nodular enhancement {Figure 37A.46), although ring enhancement is most common. Double-dose delayed CT is more effective in detecting these lesions.

After the patient has begun treatment, scans should show a decrease in the number and size of the lesions and a reduction in edema and mass effect within 2-4 weeks after

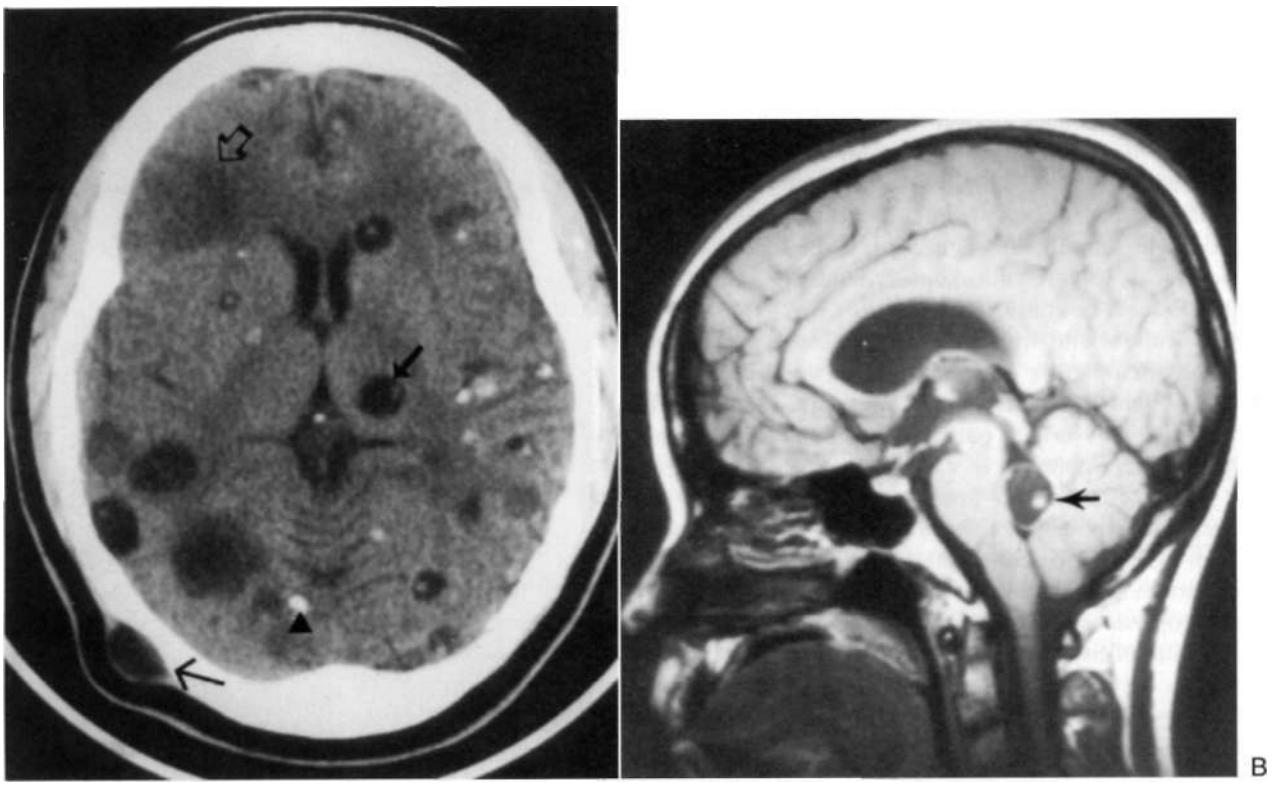


FIGURE 37A.45 Cysticercosis. (A) Noncontrast axial computed tomographic scan demonstrates multiple lesions of cysticercosis in various stages of evolution. Note the multiple cysts with scolices *{arrow)* and the calcified lesion *{arrowhead).* Also, a hypodense lesion in the right frontal lobe represents a degenerating eysticcrcus with edema *{open arrow).* Note scalp lesion *{thin arrow).* (B) Sagittal Tl-weighted magnetic resonance imaging of another patient shows a cysticercosis cyst in the fourth ventricle *{arrow).*

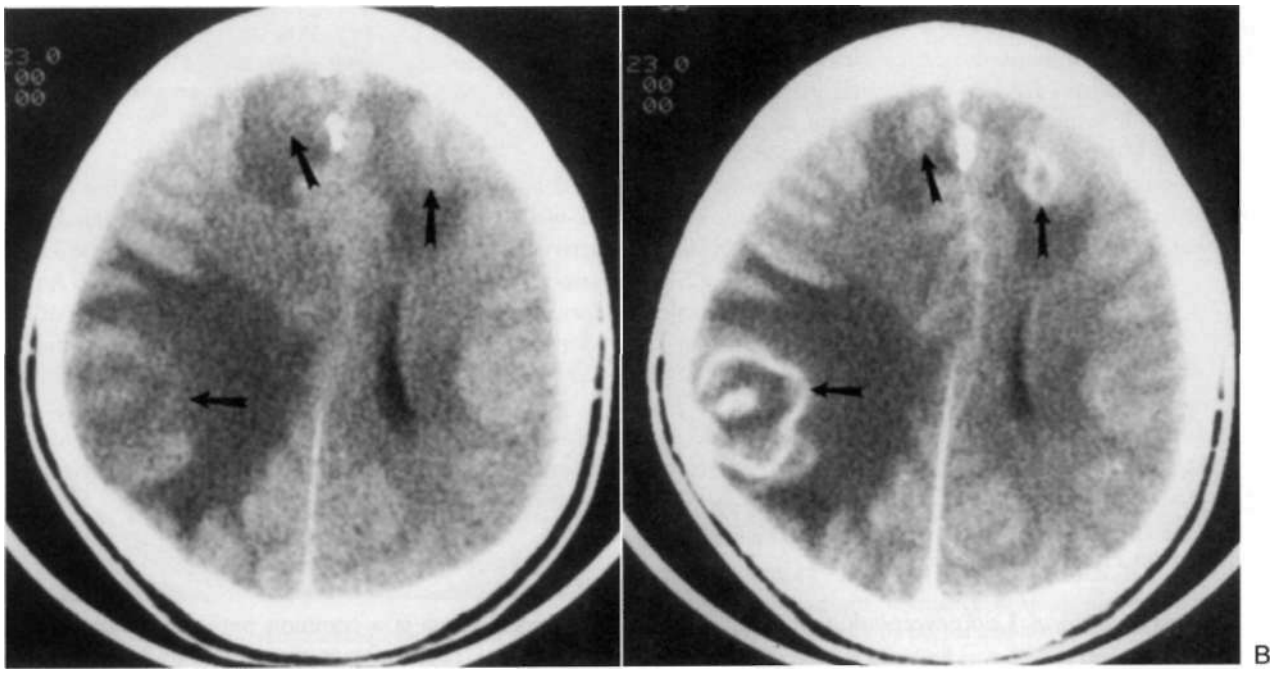


FIGURE 37A.46 Toxoplasma encephalitis. (A) Noncontrast computed tomographic scan of a patient seropositive for human immunodeficiency virus shows lesions *(arrows)* that are isodense to hypodense with extensive mass effect and edema. (B) Postcontrast computed tomographic scan (douhlc-dose delayed technique) reveals multiple enhancing lesions *(arrows).*

treatment hegins. Treated lesions have a variahle appearance on CT, The areas of prior involvement may appear normal, show cncephalomalacia, calcify, or, rarely, show areas of petechial hemorrhage. Reduction or resolution of the lesions on serial scans is presumptive evidence that toxoplasma was the causative agent for the lesions. Toxoplasma encephalitis recurs if treatment is discontinued, so lifelong therapy is needed. If the lesions do not improve with specific antitoxoplasma therapy, alternative diagnoses must be considered.

MRI without and with gadolinium is more sensitive to lesions of toxoplasma encephalitis than postcontrast CT, On Tl-weighted images, the lesions are isointense to hypointense to brain parenchyma. On T2-weighted images, active lesions are of variable intensity. The lesions may be hypcriutense to brain parenchyma or may be isointense to hypointense to brain centrally and surrounded by high-signal edema called the *target sign.* The enhancement pattern is similar to that on CT, Only 14% of patients with toxoplasmosis demonstrate a solitary lesion; therefore, lack of multiplicity should raise the possibility of a different diagnosis.

Primary CNS lymphoma and toxoplasma encephalitis may be difficult to distinguish, and because treatment is different, it is important to distinguish these two lesions. Thallium-201 brain single photon emission CT has become valuable in making this distinction because tumors have increased uptake {Figure 37A.47; Plate 37A.I), whereas infectious lesions do not {Ruiz et al, 1994).

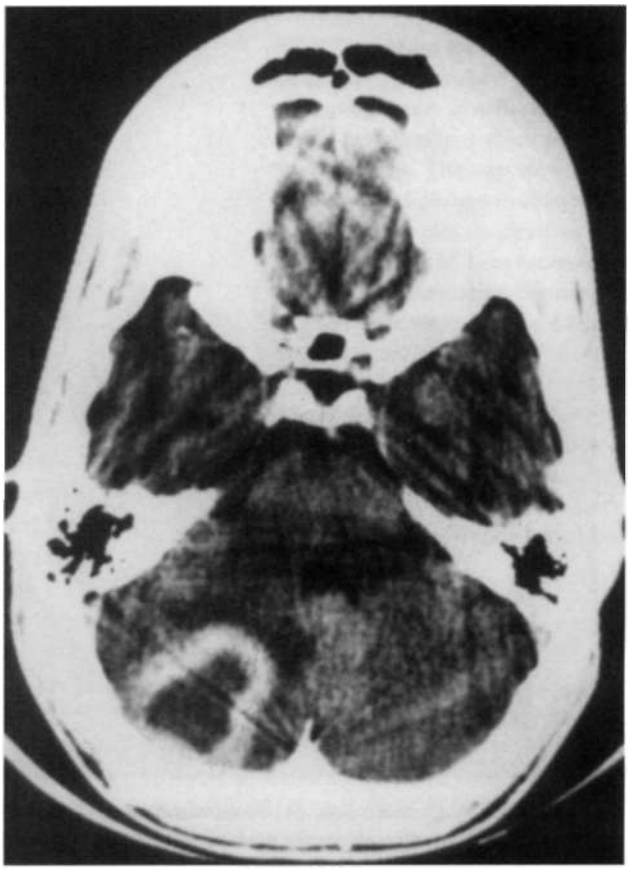


FIGURE 37A.47 Lymphoma. Postcontrast computed tomographic scan demonstrates a ring-enhancing lesion with a necrotic center in the right cerebellar hemisphere. See Plate 37A.I for brain single-photon emission computed tomography images. (Reprinted with permission from Ruiz, A., Ganz, W. L., Post, M. J. D., et al. 1994, "Use of thallium-201 brain SPECT to differentiate cerebral lymphoma from toxoplasma encephalitis in AIDS patients," *Am } Neuroradiol,* vol. 15, pp. 1885-1894. Copyright 1994, American Society of Neuroradiology.)

Human Immunodeficiency Virus Encephalitis

MRI is more sensitive than CT in demonstrating the effects of human immunodeficiency virus (HIV) infection. Hyperintense lesions are seen on T2-weighted images in the periventricular white matter and centrum semiovale and correspond to foci of dcmyelinatioti and vacuo Ian on. MRI may demonstrate atrophy and signal changes in the white matter but does not demonstrate the microglial nodules and multinucleated giant cells seen on histological sections. MRI findings are abnormal in approximately 70% of patients with AIDS, regardless of the presence of neurological symptoms,

Proton MRI spectroscopy also has been used to detect abnormalities in the brains of HIV-infected patients. One study found abnormal spectra in 10 patients with AIDS, whereas routine MRI of these same patients revealed no significant abnormalities. Therefore proton spectroscopy may hold promise of early diagnosis of biochemical alterations in HrV-infected patients.

Progressive Multifocal Leukoencephalopathy

On CT, progressive multifocal leukoencephalopathy (PML) appears as a focal area of hypodensity in the white matter without mass effect and usually without enhancement. MRI has greater sensitivity than CT in imaging PML. On T2-weighted images, PML has increased signal in the periventricular or subcortical white matter (Figure 37A.48}, sometimes with a bilateral multifocal distribution. Any lobe may be affected, but the frontal and pa ric to-occipital locations are most common. PML may be difficult to distinguish from HIV-related demyelination, but the latter is more often diffuse, symmetrical, and periventricular in location, whereas PML is more multifocal and asymmetrical and has a predilection for the subcortical white matter.

Cytom ogd lovirus

Cytomegalovirus is a common pathogen in patients with AIDS. On CT, atrophy is the most frequent finding, and hypodensity of the white matter may be seen. Periventricular and subependymal enhancement may be present, however. CT may grossly underestimate the degree of

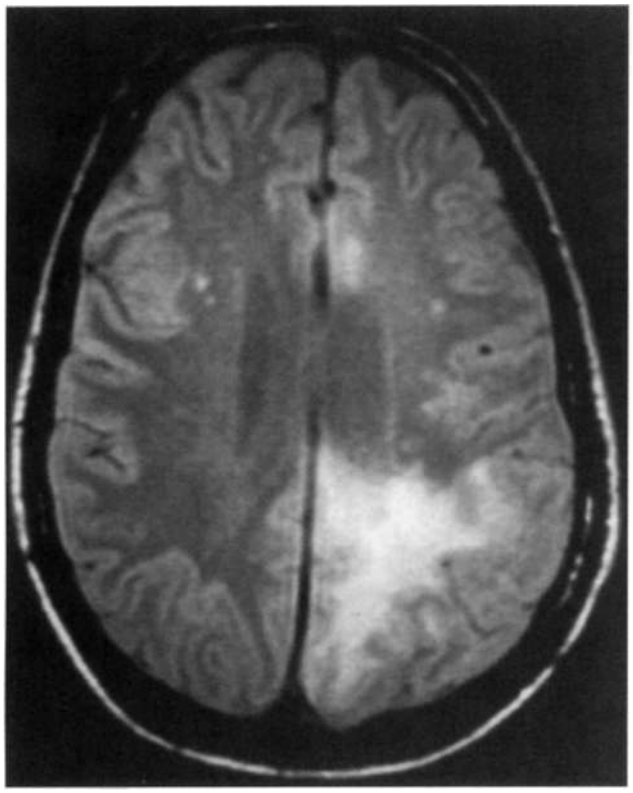
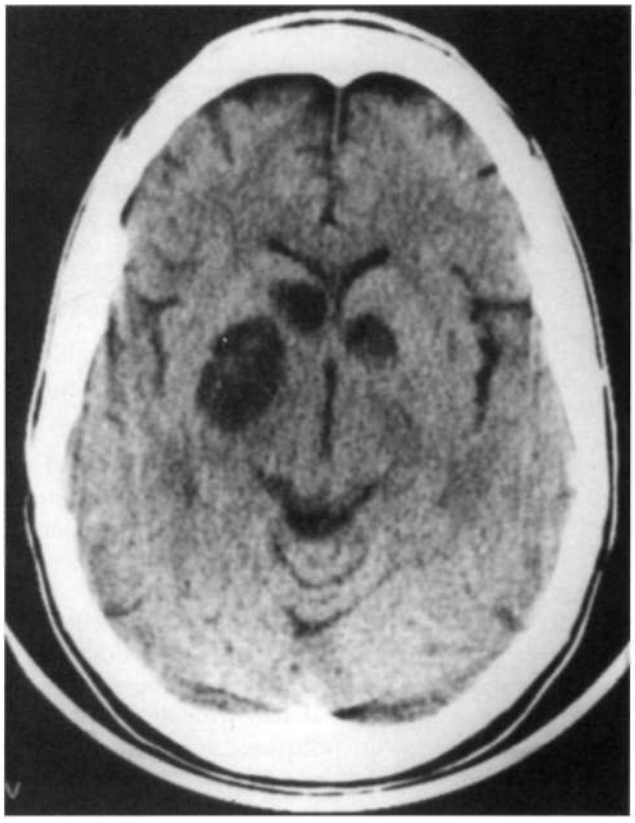


FIGURE 37A.48 Progressive multifocal leukoencephalopathy (PML). Proton density-weigh ted image shows a high-intensity lesion located in the white matter in the left posterior parietal lobe consistent with PML.



HCIJRK 37A.49 Cryprococcal gelatinous pseudocysts. Nioncori-trast computed tomographic scan shows gelatinous pseudocysts in ilu- li.i-iiI s> a nidi a in ,1 patient with acquired immunodeficiency syndrome.

involvement. **MRI** has greater sensitivity than CT in detecting CNS cytomegalovirus and its extent. MRI may demonstrate increased signal in the periventricular white matter on T2-weighted images and subependymal enhancement after contrast administtation.

Cryptococcosis

CNS cryptococcosis is caused by the saprophytic yeastlike fungus *Cryptococcus neaformans.* CNS cryptococcosis is the third most common CNS infection (after HIV encephalopathy and toxoplasma encephalitis) in patients with AIDS and is the most common fungal infection to involve the CNS in patients with AIDS. Cryptococcal meningitis is the sine qua non manifestation of CNS cryptococcosis. In addition, the perivascular (Virchow-Robin) spaces usually are dilatated by cryptococcal spread. Once the perivascular spaces become infected, they tend to become confluent. At that point cystlike lesions, hypodense on CT (Figure .V7A.49) and low on TI-weighted images and bright on T2-weighted images, may be seen in the basal ganglia, mesencephalon, and dentate nuclei. Cryptococcal involvement of the choroid plexus and pituitary gland may occur. In patients with AIDS, cryptococcal meningitis and the other lesions described rarely enhance. This is because of the inability of the patient with AIDS to mount an inflammatory response and the presence of the organism's mucoid capsule, which isolates it from the patient's inflammatory cells. CNS cryptococcomas, lesions invading the brain parenchyma, are rare in patients with AIDS.

Lymphoma

Primary CNS lymphoma is the most common CNS neoplasm seen in HIV-infected patients. AIDS-related CNS lymphomas are more often peripheral in location and tend to demonstrate necrosis more often than non-AIDS-related lymphomas. Up to 25% of CNS lymphomas occur infratentorially. Non-AIDS lymphomas appear as hyper dense masses on noncontrast CT examination, whereas AIDS-related CNS lymphoma lesions may be hypodense, probablj related to a greater degree oi necrosis. On MRI, the dense cellularity of lymphoma renders these lesions isointense to hypoin tense on all sequences. Enhancement in non-AIDS lymphoma may be homogeneous, whereas in AIDS-related lymphoma enhancement may be heterogeneous or ringlike, which again may be related to the greater degree of necrosis (see Figure 37A.47). Brain positron emission tomography and single photon emission CT studies arc helpful in differentiating AIDS-related lymphoma from non-neoplastic brain masses.

Congenital Lesions

Two major types of congenital disorders of the CNS can be described (see Chapter 66). Disorders of organogenesis are those in which an alteration of CNS development occurs. Disorders of histogenesis are those with normal development but with abnormal cell differentiation. The disorders of organogenesis include abnormalities of divcrticulation, closure migration, and CSF flow (Chapter *66).* The disorders of histogenesis include the phakomatoses (see Chapter 71).

Disorders of Diverticulation

Disorders of diverticulation are caused by failure of the primitive prosencephalon to develop into cerebral hemispheres, and various degrees of failure of separation of the brain and ventricles may occur.

Holoprosencephaly. Holoprosencephaly represents absence of cleavage of the forcbrain (prosencephalon). Three types are seen, depending on the severity of the lesion (from most severe to least severe): alobar, semilobar, and lobar. Alobar is the extreme form of holoprosencephaly, resulting in a single monoventricular cavity with thin cortical tissue (Figure 37A.50),

Septo-Optic Dysplasia. Scpto-optic dysplasia involves the anterior midline structures of the brain. It consists of an absent septum pellucidum and hypoplasia of optic nerves, chiasm, and infundibulum. On CT and MRI, there is absence of the septum pellucidum, atrophic optic nerves, and large ventricles.

Disorders of Closure

In agenesis of the corpus callosum, a large bundle of fibers (bundles of Probst) persists, passing anteroposteriorly on the medial aspect of the ventricles. On CT or MRI wide separation of the lateral ventricles occurs, occipital horns may show relative dilatation, and interposition of the third ventricle between the bodies of the lateral ventricles may occur (Figure 37A.51). On sagittal MRI, there is absence of the corpus callosum. In addition, the sulcal markings and gyri in the parasagittal area have a more vertical course.

Disorders of Cerebrospinal Fluid Flow

Chiari Malformations. In the Chiari type I malformation, the cerebellar tonsils are positioned below the foramen magnum, but the cerebellum is normal otherwise and the fourth ventricle is in a normal position. Syringohydromyelia is a common concurrent lesion, with an incidence of 20-25% in Chiari 1 malformation (Figure 37A.52).

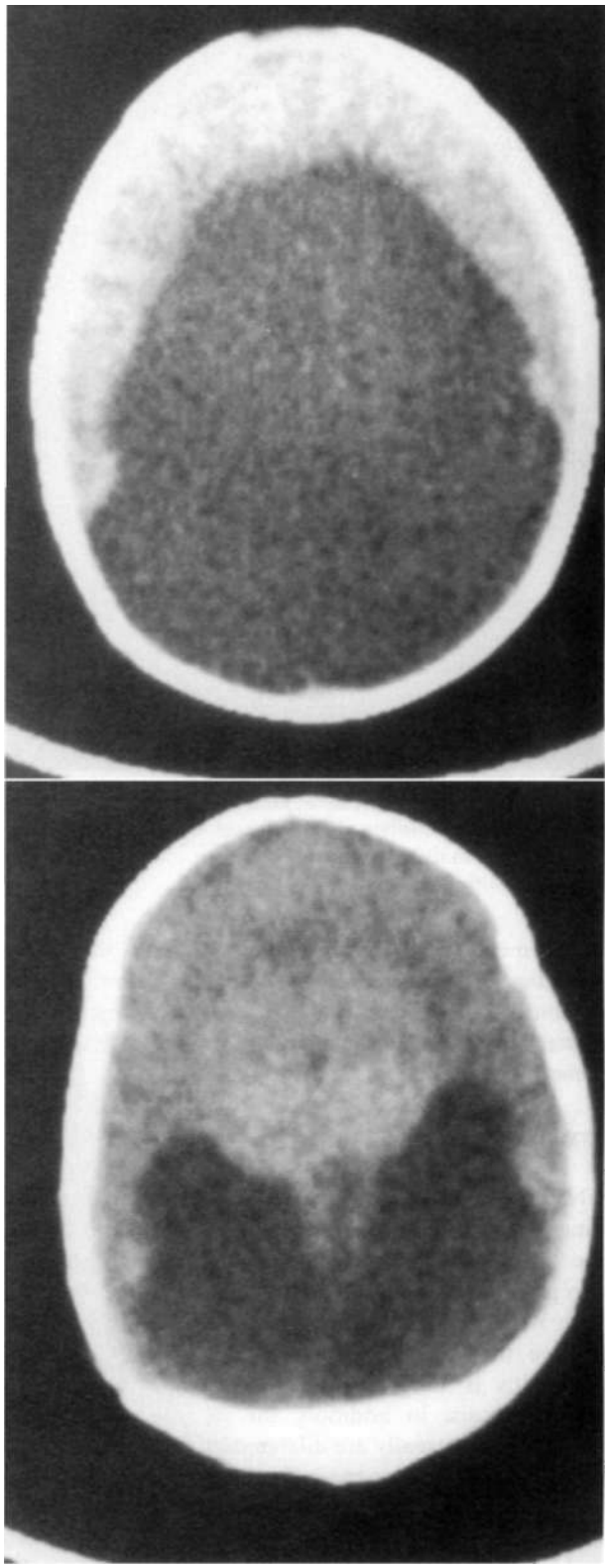


FIGURE 37A.50 Alobar holoprosencephaly. (A) Axial computed tomographic scan demonstrates a large central monoventricular cavity with a peripheral rim of cortical tissue. (B) The thalami are fused, and the third ventricle cannot be identified.

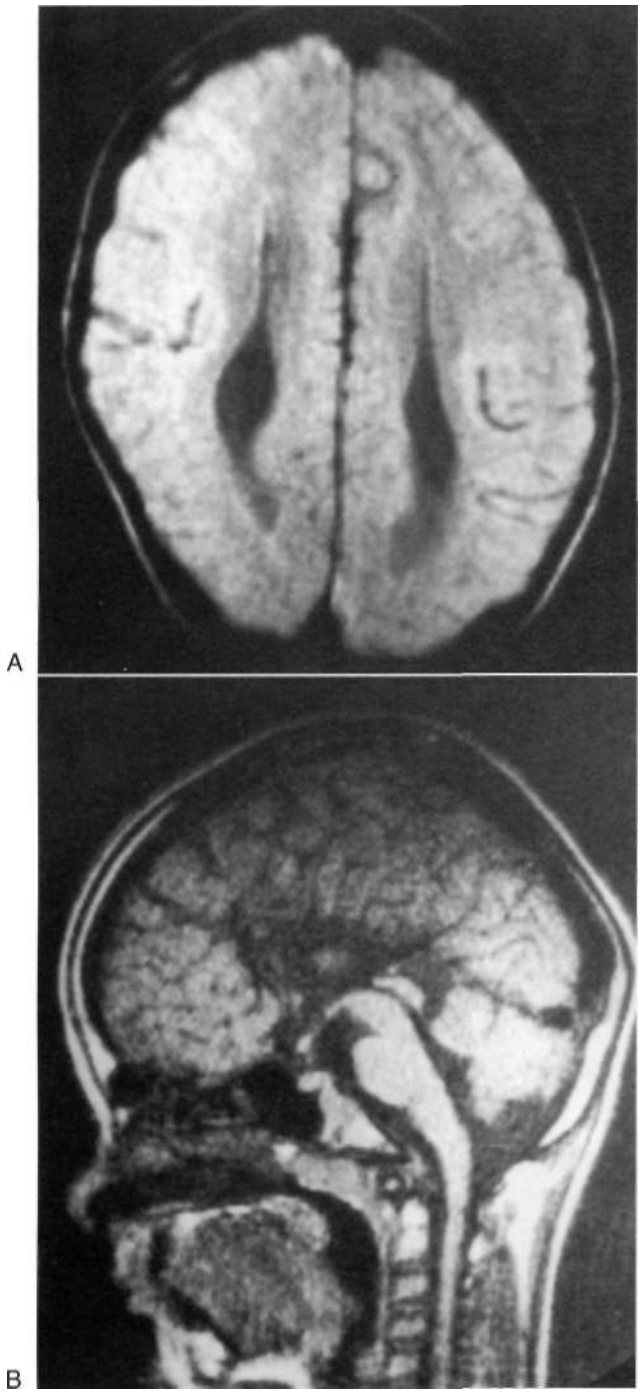


FIGURE 37A.51 Agenesis of corpus callosum. (A) Tl-weighted axial image shows separated and parallel lateral ventricles. (B) Sagittal Tl-wcightcd image shows absence of a midline corpus callosum.

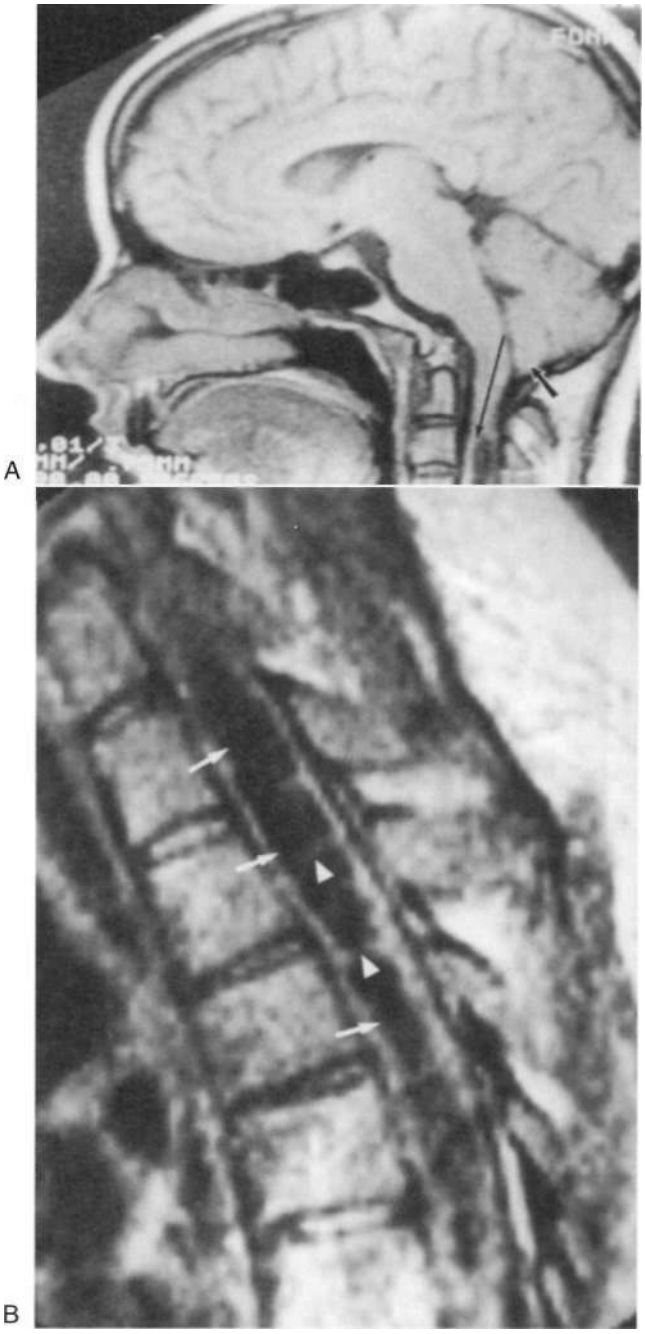


FIGURE 37A.S2 Chiari I malformation with syringohydromyelia. (A) Sagittal Tl-weighted image shows the tonsils extending below the foramen magnum *{arrow).* The very superior aspect of an intramedullary cyst is seen *(long black arrow).* (B) The sagittal T1-weighted image of the cervical spine in the same patient demonstrates a syringohydmniyeliu of the cervical spine *(arrows).* There are multiple scptations within the syrinx *(arrowheads),* and the cord is widened.

The Chiari II malformation is a dysgenesis of the hindhrain that results in a caudally displaced fourth ventricle and medulla. The essential feature is the pathologic downward displacement of the fourth ventricle extending into the cervical canal so that nonvisualization of the fourth ventricle is common. Anomalies associated with Chiari II include lukcnschadel skull (pitting of the skull), clivus and petrous scalloping, enlarged foramen magnum, myelomeningocele, dural anomalies (widened tentorial incisura), hindhrain and midhrain

anomalies (bcaking of the tectum; Figure 37A.53), and forehrain anomalies.

Dandy-Walker Syndrome. In Dandy-Walker syndrome, there is cystic enlargement of the fourth ventricle and hypoplasia of the vermis (Figure 37A.54). The tentorium, torcula, straight sinus, and vein of Galen arc displaced superiorly.

Aqucductal Stenosis. The causes of aqueductal stenosis include infection, Chiari II malformation, and neoplasm, although many cases are idiopathic. Chiari II malformation is the most common cause of hydrocephalus and aqueductal stenosis in early childhood. The lateral and third ventricles are moderately to severely enlarged (Figure 37A.55A). If Chiari II malformation is not present, the fourth ventricle usually is normal in size (Figure 37B.55B).

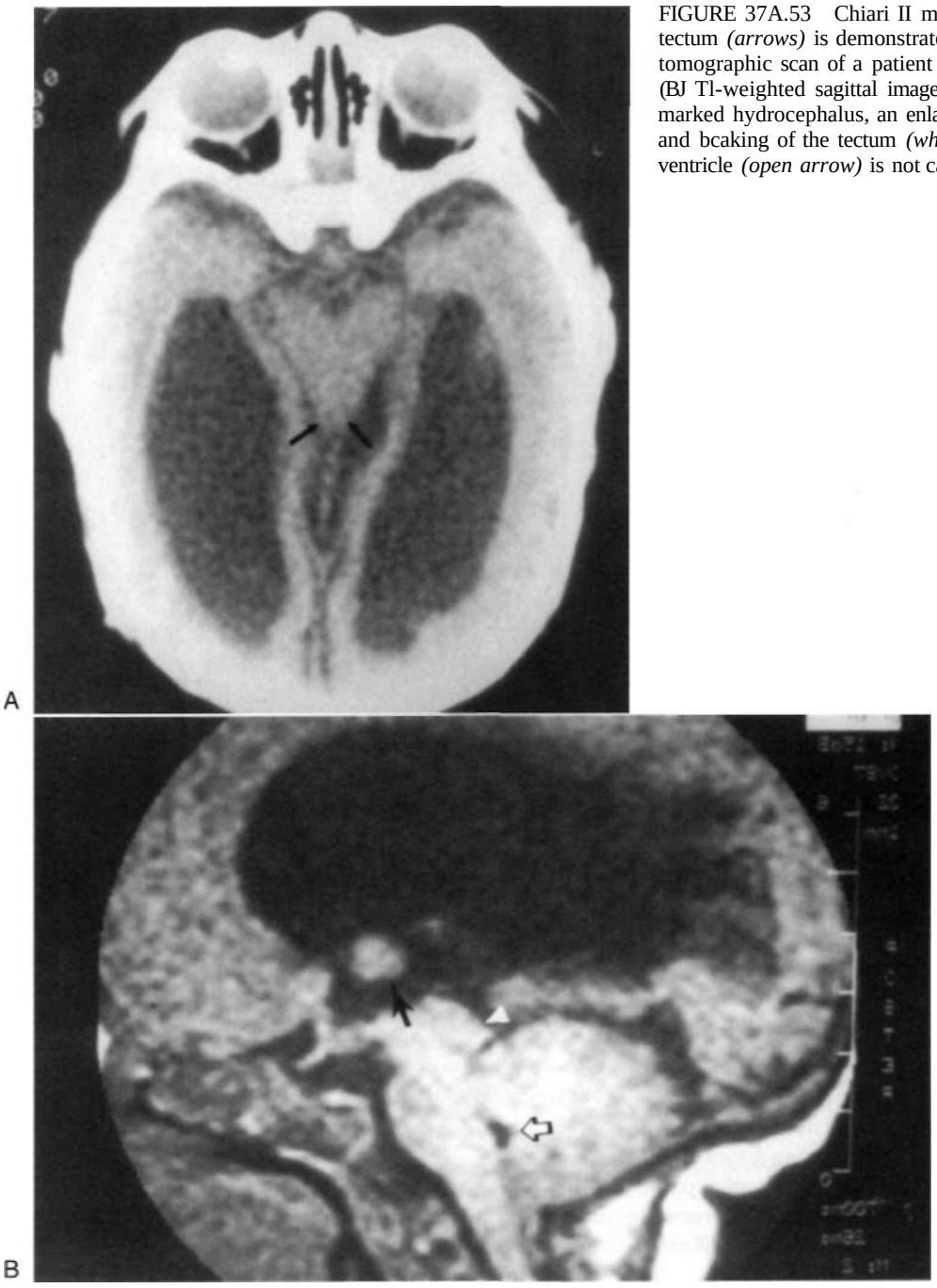


FIGURE 37A.53 Chiari II malformation. (A) Beaking of the tectum *(arrows)* is demonstrated in the axial computed tomographic scan of a patient with a Chiari II malformation. (BJ Tl-weighted sagittal image in another patient shows marked hydrocephalus, an enlarged massa intermedia *(arrow)*, and bcaking of the tectum *(white arroivhead)*. The fourth ventricle *(open arrow)* is not caudally displaced in this patient.

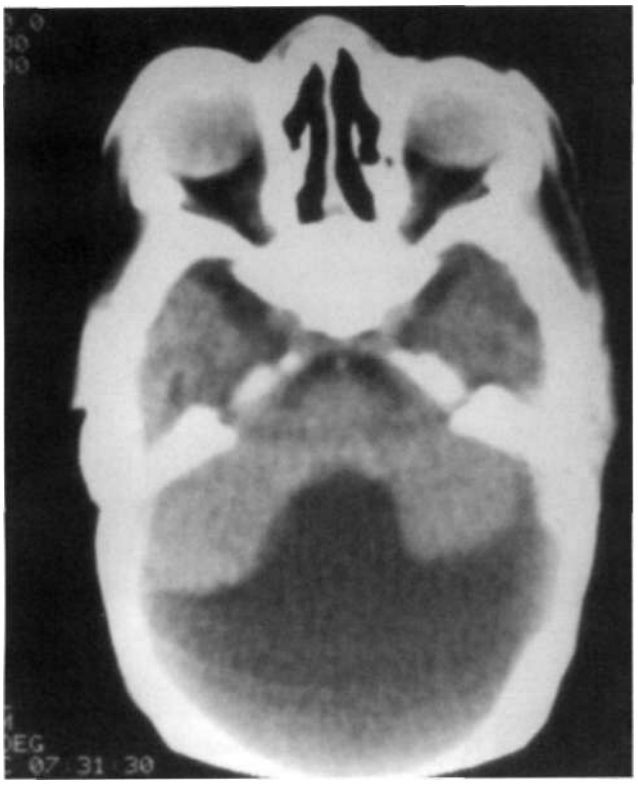


FIGURE 37A.54 Dandy-Walker syndrome. The fourth ventricle is replaced by an enlarged midline cyst in the axial computed tomographic scan. Note the hypoplasia of the vermis.

Disorders of Sulcation and Migration

Heterotopias. Heterotopias have classically been separated into three forms:

- The nodular form consists of subependymal nodules of gray matter that arc usually bilateral.
- The bulk form consists of islands of gray matter that are usually isolated in the hemispheric white matter (Figure 37A.56).
- In band heterotopia, alternating layers of gray and white matter are symmetrical throughout both hemispheres.

Schizencephaly. Schizencephaly is a disorder in which there are clefts spanning the cerebral hemispheres. Pathologically, these clefts are characterized by an infolding of the gray matter along the cleft from the cortex into the ventricles. There are two groups: those in which the walls of the cleft are fused (closed lip schizencephaly; Figure 37A.57) and those in which the walls of the cleft are separated (open lip schizencephaly).

Destructive Lesion

Hydranencephaly. In hydranencephaly, there is virtual absence of the cerebral hemispheres except for the basal ganglia. The infra tentorial structures are intact (Figure 37A.58). A severe and early intrauterine vascular accident is the presumed cause.

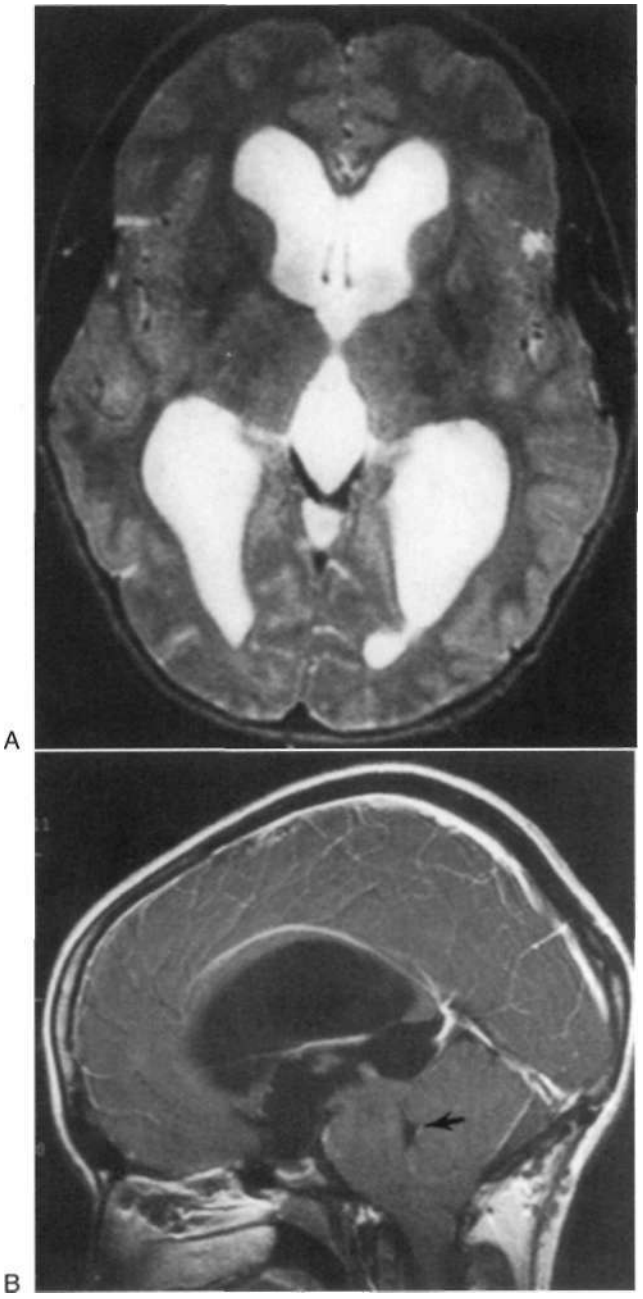


FIGURE 37A.55 Aqucductal stenosis. (A) T2-weighted axial magnetic resonance imaging demonstrates markedly dilatated lateral and third ventricles. (B) The sagittal TI-weighted image (postcontrast) shows the marked dilatation of the lateral and third ventricles hut a small fourth ventricle *{arrow).* The posterior fossa is small, and the aqueduct is not well seen.

Disorders of Histogenesis

Tuberous Sclerosis. Hamartomas, the most common lesions seen on MRI in patients with tuberous sclerosis,

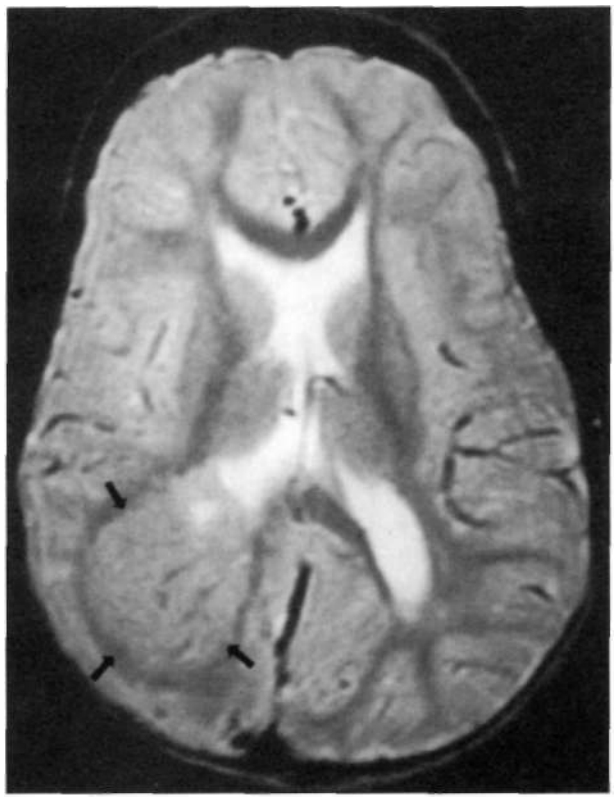


FIGURE 37A.56 Heterotopia. Bulk form of heterotopia is seen as an island of gray matter that is isolated in the hemispheric white matter. This island of tissue *{arrows)* has the signal characteristics of gray matter on this T2-weighted image.

are isointense on T1- and hyperintense on T2-weightcd images (see Chapter 71). Subependymal nodules usually are multiple and bilateral; they often calcify and usually are isointense to hyperintense on Tl-weighted images and hyperintense on T2-weighted images. These subependymal hamartomas may degenerate into a giant cell astrocytoma (see Figure 37A.11), which is most often found near the foramen of Monro.

Neurofibromatosis. Neurofibromatosis is the most common of the neurocutaneous syndromes. There are two genetically distinct types: neurofibromatosis type 1 and type 2.

Neurofibromatosis Type 1. Neurofibromatosis type 1 is inherited as an autosomal dominant disease and is also called *peripheral neurofibromatosis* or *von Recklinghausen's disease.* The CNS and calvarial manifestations are diverse and include gliomas of the optic nerves and chiasm (see Figure 37A.27); gliomas in other areas of the brain; neurinomas and neurofibromas of the cranial, spinal, and peripheral nerves; dysplasia of the sphenoid bone and orbit; plexiform neurofibromas of the scalp and elsewhere; and hyperintense brain lesions demonstrated on MRI with T2-weighted images.

Neurofibromatosis Type 2. Neurofibromatosis type 2, also called *central neurofibromatosis,* is inherited as an

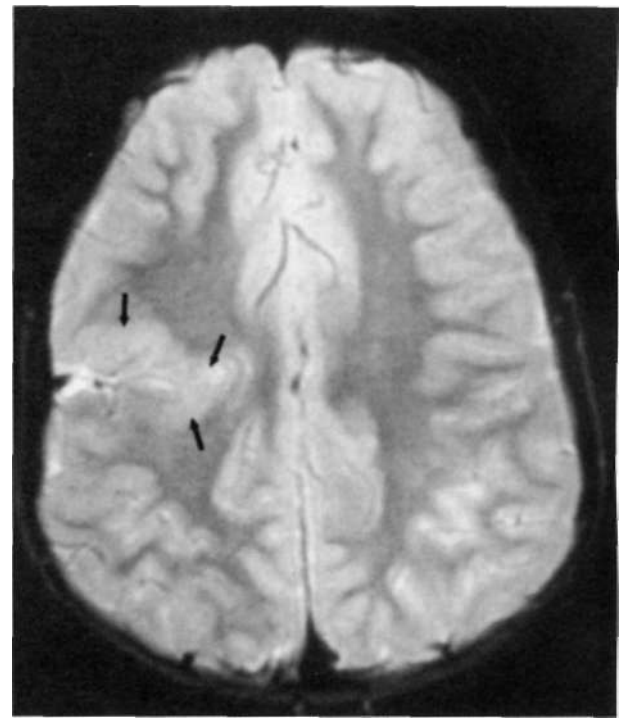


FIGURE 37A.57 Schizencephaly. Closed lip schizencephaly appears as a cleft lined by gray matter extending through the full thickness of the cerebral mantle. The island of tissue has the signal characteristics of gray matter on this T2-weighted image *(arrows).*

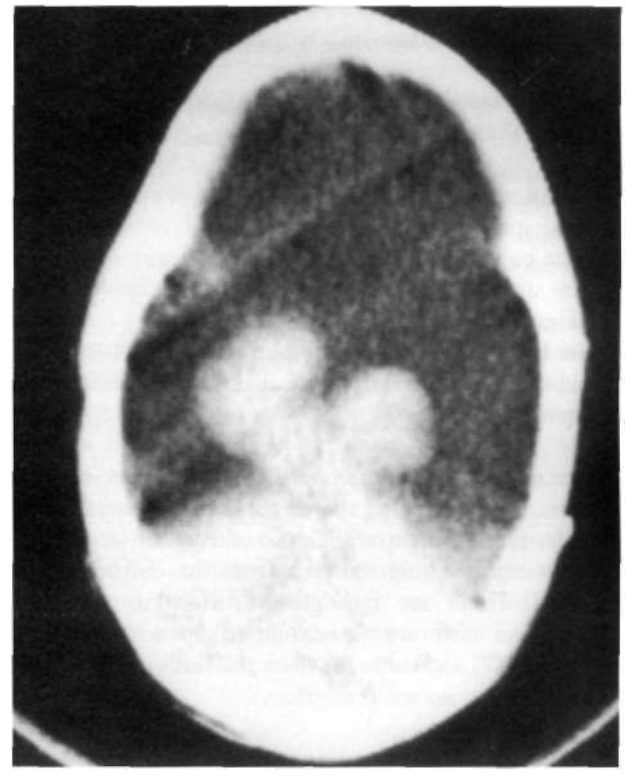
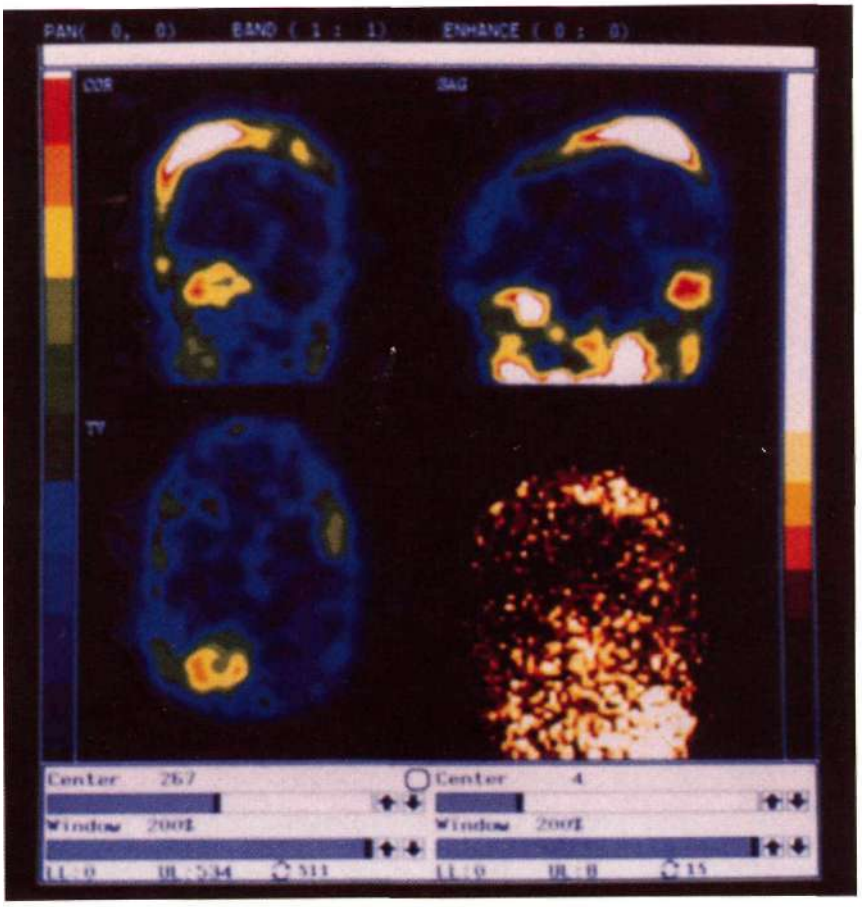


FIGURE 37A..S8 Hydranencephaly. Absence of the cerebral hemispheres, with intact basal ganglia and infratentorial structures.

PLATE 37A.I Brain single photon emission computed tomographic images with thallium-201 demonstrate a focal region of increased uptake corresponding to the same location as the lesion seen on computed tomographic scan (see Figure 37A.47). This is a biopsy-proven lymphoma. (Reprinted with permission from Ruiz, A., Ganz, W. L., Post, M. J. D., et al. 1994, "Use of thallium-201 brain SPECT to differentiate cerebral lymphoma from toxoplasma encephalitis in AIDS patients," *Am J Neuroradiol*, vol. 15, pp. 1885-1894.)



autosomal dominant disease. The diagnostic criteria for neurofibromatosis type 2 include bilateral eighth nerve schwannomas (see Figure 37A.28) or a unilateral eighth nerve schwannoma with two of the following: neurofibroma or schwannoma in a different location, meningioma, glioma, or a relative with neurofibromatosis type 2, This entity is genetically different from that of neurofibromatosis type 1 and hence optic nerve gliomas, skeletal dysplasias, and cutaneous neurofibromas are rare.

Vascular Disorders

Vascular Malformations

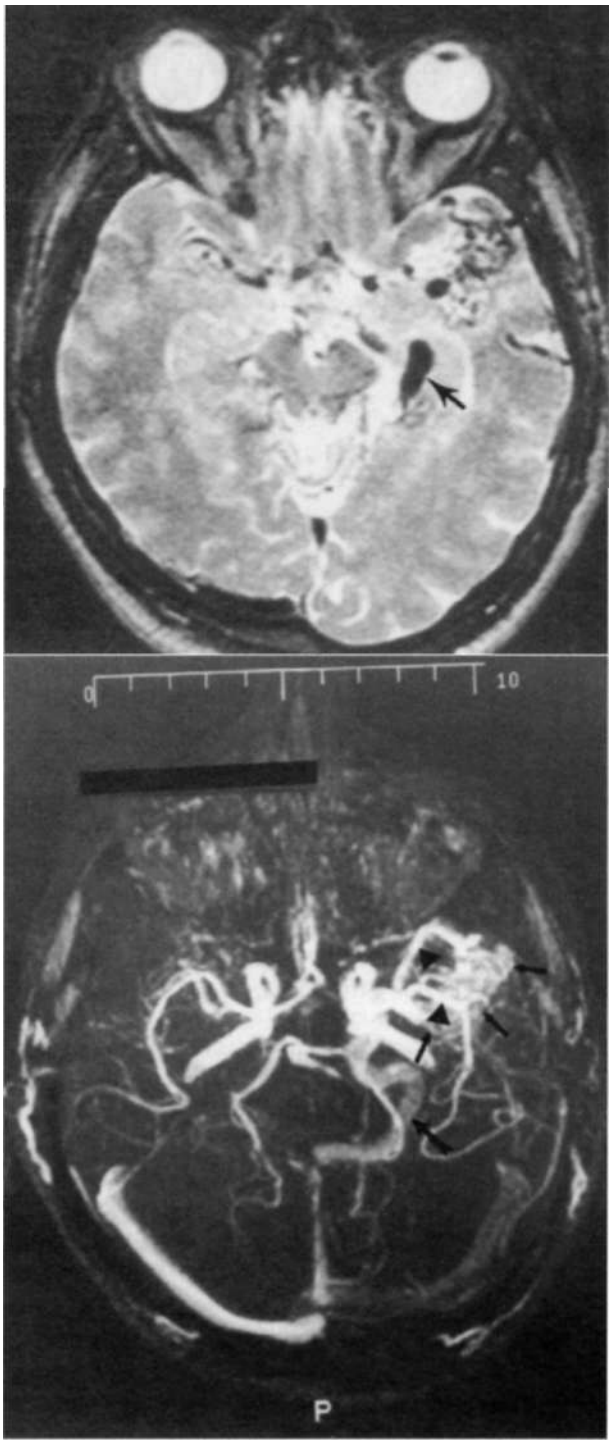
Vascular malformations have been divided into four major types: AVM, cavernous angioma, capillary telangiectasia, and venous angioma (see Chapter 57D).

Arteriovenous Malformation. Cerebral angiography is the definitive method of accurately delineating the vascular supply and venous drainage of intracranial AVMs. Morphologically, AVMs appear as wedge-shaped clusters of vessels with the apex directed toward the ventricular surface. The typical AVM appears on spin-echo MRI as a cluster of focal round lesions or serpentine areas of signal void (Figure .37A.59). At this time, conventional angiography is superior to MRA in depicting the arterial supply and venous drainage of the AVM.

Cavernous Angioma. Cavernous angiomas are discrete, multilobulated, berrylike lesions rhat contain hemorrhage in various stages of evolution. They may be found in any part of the brain; most are supra tentorial and are generally in the frontal and temporal lobes. In the posterior fossa, the pons and cerebellar hemispheres are the most common sites. Most are not detected by angiography, but occasionally a faint blush can be seen in the late capillary or venous phase. On CT, these lesions may be isodense to hyperdense in noncontrast scans, and calcification is common. MRI is the best modality for demonstrating cavernous angiomas, showing a popcorn-like lesion of mixed signal consistent with hemorrhage in different stages.

Capillary Telangiectasia. Capillary telangiectasias are small, angiographically silent or occult vascular malformations, usually revealed on magnetic resonance gradient-echo sequences by the presence of small punctate or nodular areas of dark signal ("blooming") due to the susceptibility effect caused by the presence of hemosiderin in the lesion. They may be single or multiple and may cause seizures. Capillary telangiectasias may be associated with neurocutaneous syndromes such as those of Rendu-Osler-Weber and Wyburn-Mason.

Venous Angioma. Venous angiomas are clinically silent malformations of venous drainage without an arterial



B

FIGURE .17A.59 Arteriovenous malformation (AVM). (A) Long repetition time-echo time spin-echo magnetic resonance image shows a wedge-shaped cluster of vessels in tlie left temporal lobe seen as linear and round areas of signal void. Note enlarged draining vein *{arrow).* (B) Magnetic resonance angiogram formed by a three-dimensional rime-of-flight volume slab through the base of the skull and circle of Willis shows an AVM *(small black arrows)* in the left temporal lobe. Feeding vessels arise from the left middle cerebral artery *{arrowheads).* A large medially draining vein is seen (probably a peri mesencephalic vein; *large arrow).*

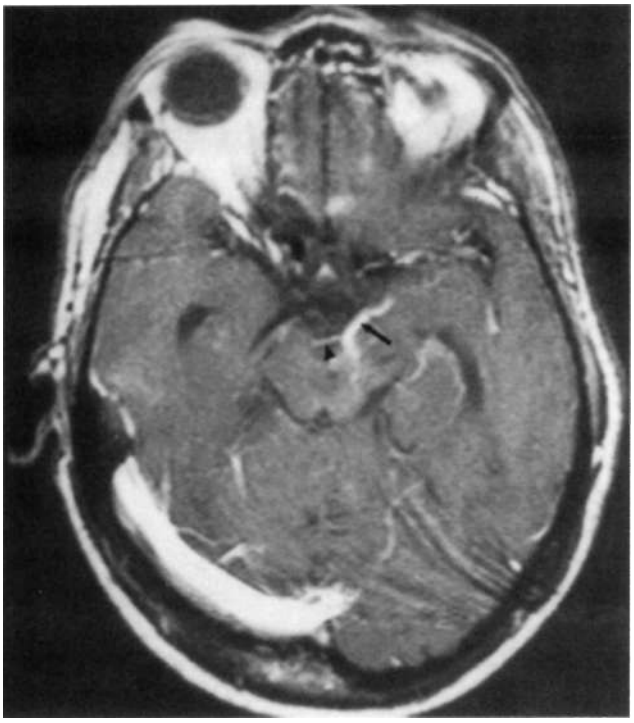


FIGURE 37A.60 Venous angioma. Postcontrast axial Tl-weighted image shows a prominent vein coursing within the left crural cistern *{arrow).* It is receiving multiple small feeding veins from within the substance of the midbrain *{arrowhead}.* These findings are typical of a venous angioma.

component. Imaging studies delineate typical curvilinear vascular channels receiving drainage from a spoke wheel-appearing collection of small tapering veins arranged in a radial pattern (Figure 37A.60). The larger draining veins empty into a targe cortical vein, a dural sinus, or a subependymal ventricular vein.

Spinal Arteriovenous Malformations

Most spinal vascular malformations are AVMs or AVFs. AVMs have a nidus of vessels and arc fed by enlarged feeding arteries and drain via large veins. AVFs drain directly into enlarged venous outflow tracts. Spinal vascular malformations have been subdivided into four groups. Type I are dural AVFs, which are found mostly in the dorsal aspect of the lower thoracic spine. Type II are intramedullary AVMs that drain into a venous plexus that surrounds the cord and usually are located in the cervicomedullary junction. Type III are larger vascular masses that involve the cord and often have extramedullary extension. Type IV are intradural extramedullary AVFs. Most are anterior to the spinal cord and occur near the conus mcdullaris.

MRI may show foci of flow void in enlarged vessels. The cord may be atrophic and often has high signal intensity on T2-weighted images. MRA is a good modality for evaluating these lesions, although spinal angiography has been the definitive diagnostic procedure for evaluating spinal AVMs. Myelography may show filling defects caused by the enlarged vessels, but since the advent of MRI, the flow voids, flow enhancement in enhanced veins, and flow-related enhancement on MRA make myelography unnecessary in the majority of cases.

Cerebral Infarction

In the first 24 hours after an arterial occlusion with infarction, 80% of **MRI** scan results are positive, compared with 50% of CT scans. These infarcts are seen as regions of subtly increased signal on T2-weighted images. At this stage the abnormalities arc mostly in the gray matter. In infarcts 2 days to 3 weeks old, the subtle signal intensity changes seen initially become more obvious with increasing signal intensity on long TR images. White matter and gray matter abnormalities then are seen. In 20% of cases there is a hemorrhagic component with increased signal seen on Tl-weighted images if the stroke is greater than approximately 48 hours old. More acute hemorrhagic strokes reveal hypointense to isointense areas on MRI, with factors such as field strength and pulse sequence playing an important role in the appearance. MRI is the most sensitive, accurate, and practical means of imaging acute strokes.

The MRI of an infarct 3-6 weeks old is characterized by a smaller and better-defined zone of signal changes. The signal intensity on T2-weighted images is greater because of cystic cavitation. Focal atrophy is also present due to a loss of tissue volume.

A crucial factor in stroke management is the determination of a hemorrhagic component in the infarct (Figure 37A.61). Acute hemorrhage may not be as obvious on MRI as on CT, especially if gradient-echo scans have not been done. Hyperacute hemorrhagic lesions may not have adequate time for the accumulation of dcoxyhcmoglobin, so CT scans may be more revealing in the early stroke period.

The pattern of cerebral infarction resulting from blood vessel occlusion depends on vascular anatomy, and the signal changes closely follow the anatomical distribution of the arteries (Figure 37A.62). In the case of proximal disease and infarcts caused by systemic hypotension, the anastomotic border zones {watershed zones) between major vascular territories are involved most severely.

MRI is superior to CT in evaluating infarcts in posterior fossa structures because CT resolution is limited by skull-base artifacts. Infarcts in the brainstem are small in relation to the extent of clinical damage. The small size of these lesions, in addition to the fact that these patients may be neurologically devastated and therefore poor candidates for MRI, sometimes make these lesions difficult to evaluate.

The vessel most often involved in embolic disease is the middle cerebral artery. Smaller, more peripheral infarcts are common with embolic disease. If emboli are multiple, more

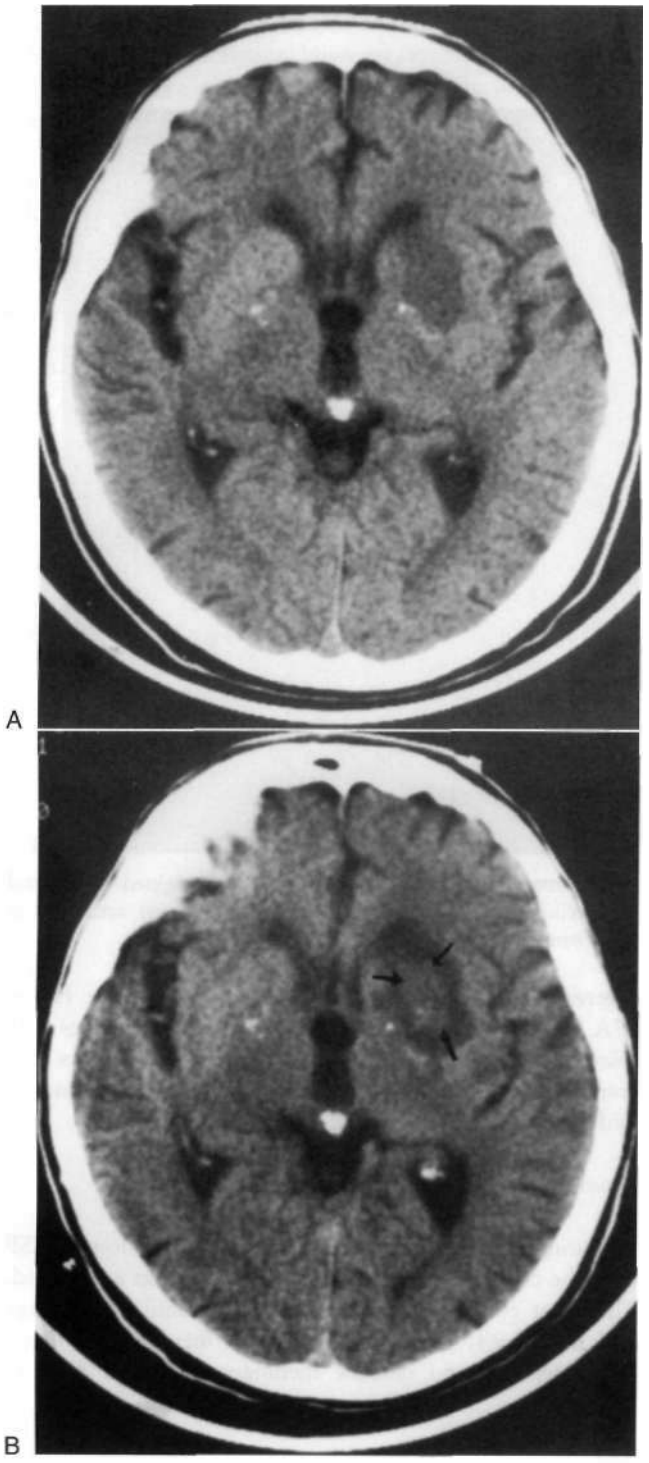


FIGURE 37A.61 Cerebral infarct. (A) Noncontrast computed tomographic scan shows infarct involving left basal ganglia. Incidental basal ganglionic calcifications are seen. (B) Three days later the computed tomographic scan shows hemorrhage (*arrows*) in the area of infarction.

than one vascular territory may be involved. The origin of small, deep infarcts in the capsular and ganglionic regions is unclear. During the chronic stage, these small infarcts resolve to become small cystic lesions, the typical lacunae.

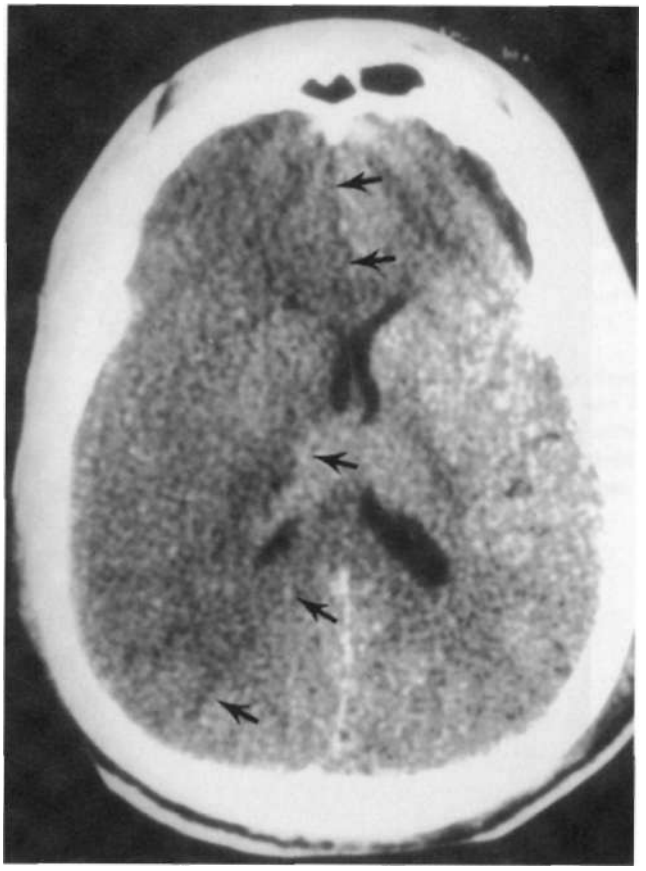


FIGURE 37A.62 Right hemisphere infarct. Noncontrast computed tomographic scan demonstrates a low-density lesion *(arrows)* involving the right frontal, temporal, and parietal lohes in a patient who sustained a hullet injury to the skull, with injury to the right internal carotid artery.

Hemorrhage and Magnetic Resonance Imaging

Acute hemorrhage consists of intact red blood cells and plasma. Intracellular oxyhemoglobin is converted to deoxyhemoglobin (Figure 37A.63), which is then oxidized to methemoglobin (from the periphery to the center). Subsequently, as a result of red blood cell lysis, intracellular methemoglobin becomes free methemoglobin, and hemosiderin concomitantly appears in the periphery. Eventually, methemoglobin is resorbed, and only a hemosiderin cleft remains. As the hemorrhage evolves, each of the stages has unique Tl and T2 relaxation times on MRI, This allows us to determine the age of the hematomas (Table 37A.1).

Hydrocephalus

Hydrocephalus is considered to be present when there are enlarged ventricles in the absence of atrophy or dysgenic brain (see Chapter 65). Therefore, a clear difference exists between hydrocephalus and ventriculomegaly

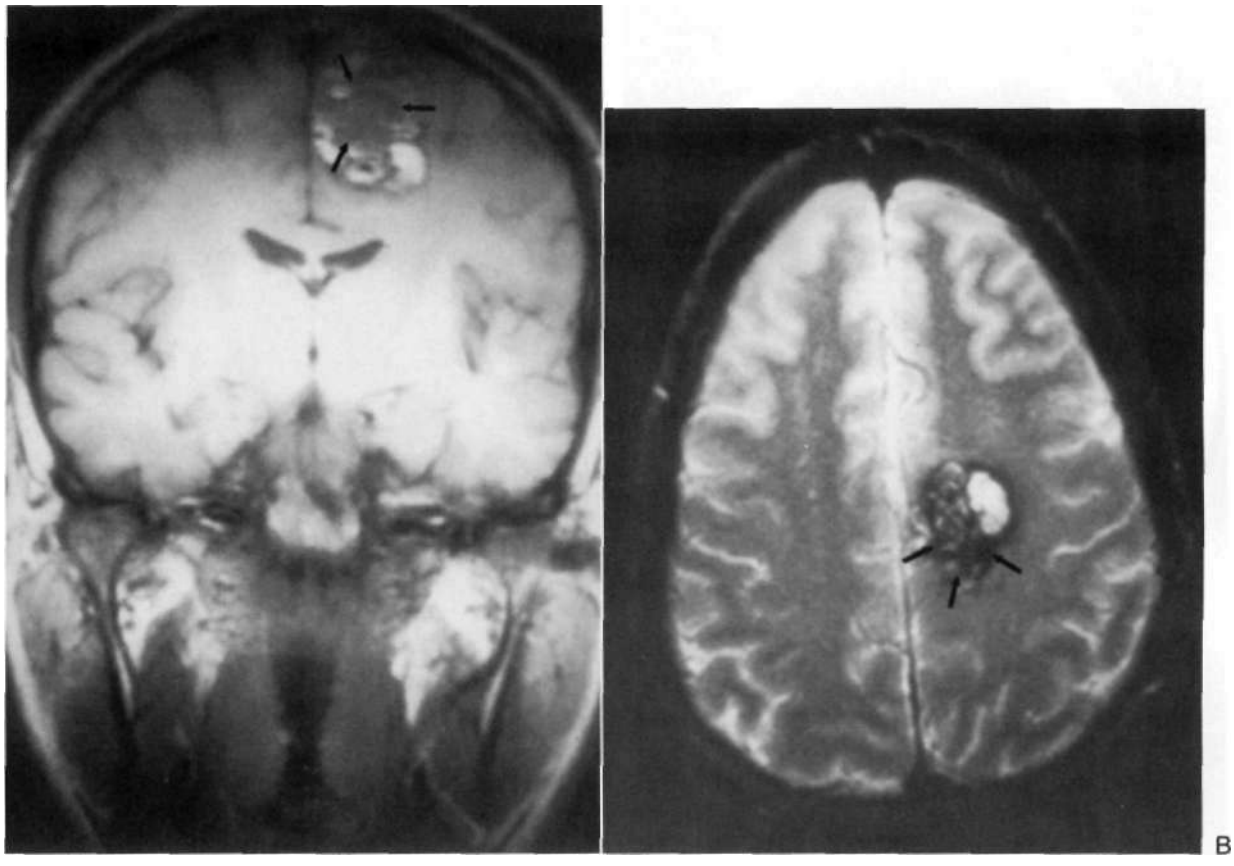


FIGURE 37A.63 Acute hematoma. There is a central area that is isointcnse to brain *{arrows)* in (A) Tl-weighted image and hypointcnsc *{arrows)* in {B) T2-weighred image, consistent with intracellular deoxy hemoglobin, and a peripheral area that is hyperintense in both Tl and T2 images, consistent with extracellular met hemoglobin,

because the latter indicates large ventricles regardless of the cause, CT and MRI can characterize the different patterns of ventricular enlargement to determine the cause,

Obstructive or Noncommunicating Hydrocephalus

The hallmark of obstructive noncommunicating hydrocephalus is ventriculomegaly proximal to the site of obstruction with the common associated finding of periventricular edema secondary to transependyma! flow of CSF. The site of obstruction is determined by the characteristic ventricular dilatation. Aqucductal obstruction produces dilatation of the third and lateral ventricles, whereas the fourth ventricle remains normal (see Figure 37A.55). A colloid cyst of the third ventricle produces only dilatation of both lateral ventricles. Cerebellar tumors may compress the fourth ventricle and cause obstructive hydrocephalus.

Communicating Hydrocephalus

In communicating hydrocephalus, the normal flow of CSF over the cerebral convexities and its resorption arc altered. The most common causes are subarachnoid hemorrhage and meningitis. However, seeding of meninges by metastatic diseases and chronic meningoencephalitic diseases

Table 37A.1: Blood breakdown products in intracerebral hemorrhages

		Signal intensity	
Time	*Type of blood product*	*T1 weighting*	*T2 weighting*
0–24 hr	Oxyhemoglobin	–/=	+
First 24 hr to 3–5 days	Deoxyhemoglobin	–/=	–
3–7 days	Intracellular methemoglobin	+	–
1 wk to months	Extracellular methemoglobin	+	+
1–2 wk to years	Hemosiderin	=	–

= decreased; – = marked decrease; + = increased; = = unchanged.

such as sarcoidosis may result also in hydrocephalus. On imaging, all the ventricles are dilatated and the sulci are effaced.

Normal Pressure Hydrocephalus

The classic clinical triad of normal pressure hydrocephalus (NPH} is dementia, gait apraxia, and urinary incontinence (see Chapter 65). Positive isotope cisternography of NPH shows reflux of the isotope into the ventricles after injection of the isotope into the lumbar thecal sac but no passage of isotope over the cerebral convexities. However, degenerative disorders also may show abnormal CSF flow, so this study is not entirely conclusive. The distinction on MRI or CT of atrophy from NPH is difficult. NPH usually causes uniform thinning and elevation of the corpus callosum and distention of the third ventricle, dilatating the optic and infundibular recesses. The normal CSF flow void in the aqueduct may be accentuated in NPH. There may or may not be periventricular transudation of fluid into the parenchyma in NPH.

SKULL BASE LESIONS

MRI has become an essential part of the evaluation of skull base lesions; it can show the margin of the tumor relative to vital structures such as the cavernous sinus and the relationship to the carotid artery. Often, it can differentiate tumor from an obstructed paranasal sinus. Fat is found between the various muscle groups beneath the skull base. As the tumor invades this fat, the normal high signal on Tl-weigbted images is obliterated by the intermediate signal of the tumor. This is especially important in detecting tumor extension through the various neural foramina. For definition of fine cortical bony erosion at the base of the skull, CT is needed.

Nasopharyngeal Carcinoma

Squamous cell carcinoma, the most malignant tumor seen in the nasopharynx, tends to be locally invasive and erode through the skull base into the intracranial cavity {Figure 37A.64). Tumor may extend through the petroclival suture and foramen lacerum into the posterior fossa and into the inferior aspect of the cavernous sinus.

Petrous Apex Lesions

The two major lesions occurring in the pettous apex are the primary cholesteatoma, or epidermoid tumor, and the granulomatous cholesterol cyst. The latter results from air cells that have been partially obstructed by chronic otitis media and filled with liquid cellular debris and hemorrhage. An epidermoid (pearly) tumor tends to be low signal on Tl-weighted images and bright on T2-wcighted images.

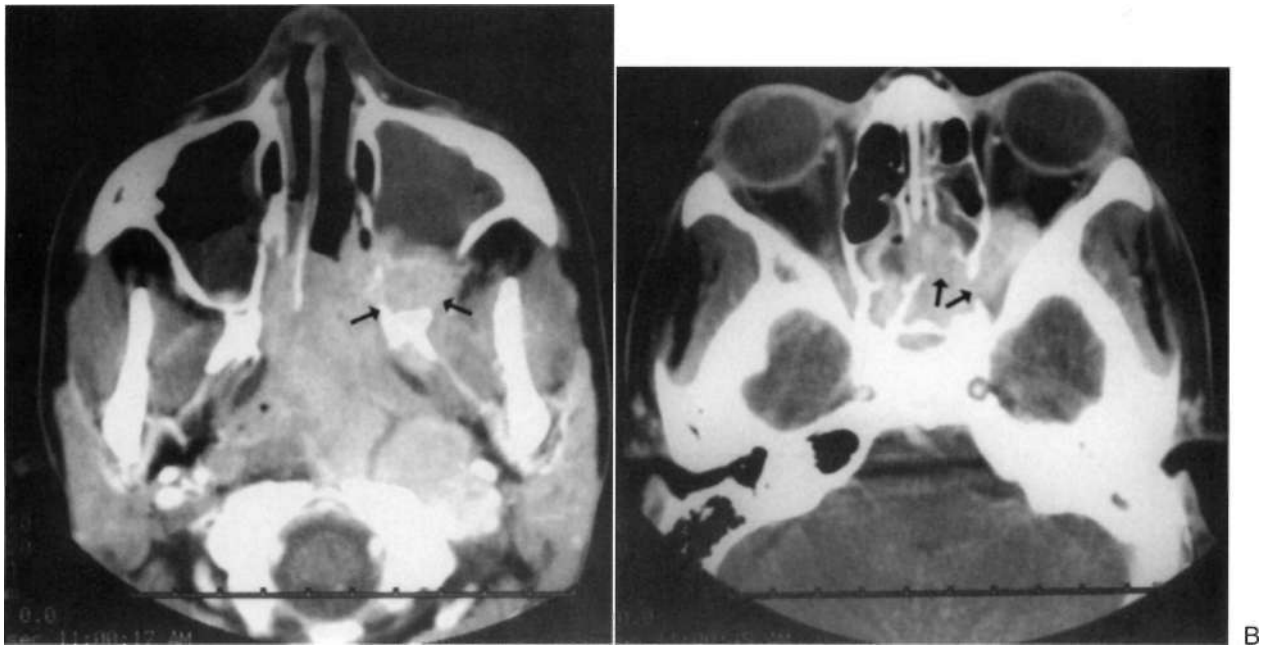


FIGURE 37A.64 Nasopharyngeal carcinoma. (A) Axial computed tomographic scan after contrast administration demonstrates a mass in the nasopharynx, which extends anteriorly to involve the nasal cavity and left maxillary sinus. The lesion is invading the left pterygopalatine fossa *{arrows).* There is bony destruction of the posterior walls of the left maxillary sinus and lateral wall of the nasal cavity. Tin.[1] IIUSS extends posteriorly to the prevertebral space and laterally involves the left carotid space. (B) The mass extends superiorly to involve the ethmoids and left orbit *(arrows).*

The granulomatous cholesterol cyst is bright on both sequences because of the tccurrcnt hemorrhage.

Signal voids representing blood flow scattered throughout the lesion arc characteristic.

Glomus Jugulate Tumor

Glomus jugulare tumor (paraganglioma) arises in the lateral portion of the jugular foramen. There can be significant extension inferiorly beneath the temporal hone and intracranially. On Tl-wcighted images these lesions usually are of intermediate signal intensity, and on Tl-wcighted images they ate hyperintense (Figure 37A.65).

Chordoma

Chordoma is a tumor of notochordal origin that is seen mainly in the sacium and the clivus. Those originating at the clivus level usually grow and spread through the duta into the middle or postetiot cranial fossa and compress the brainstem. They may extend anteriorly into the nasopharynx and often develop calcification,

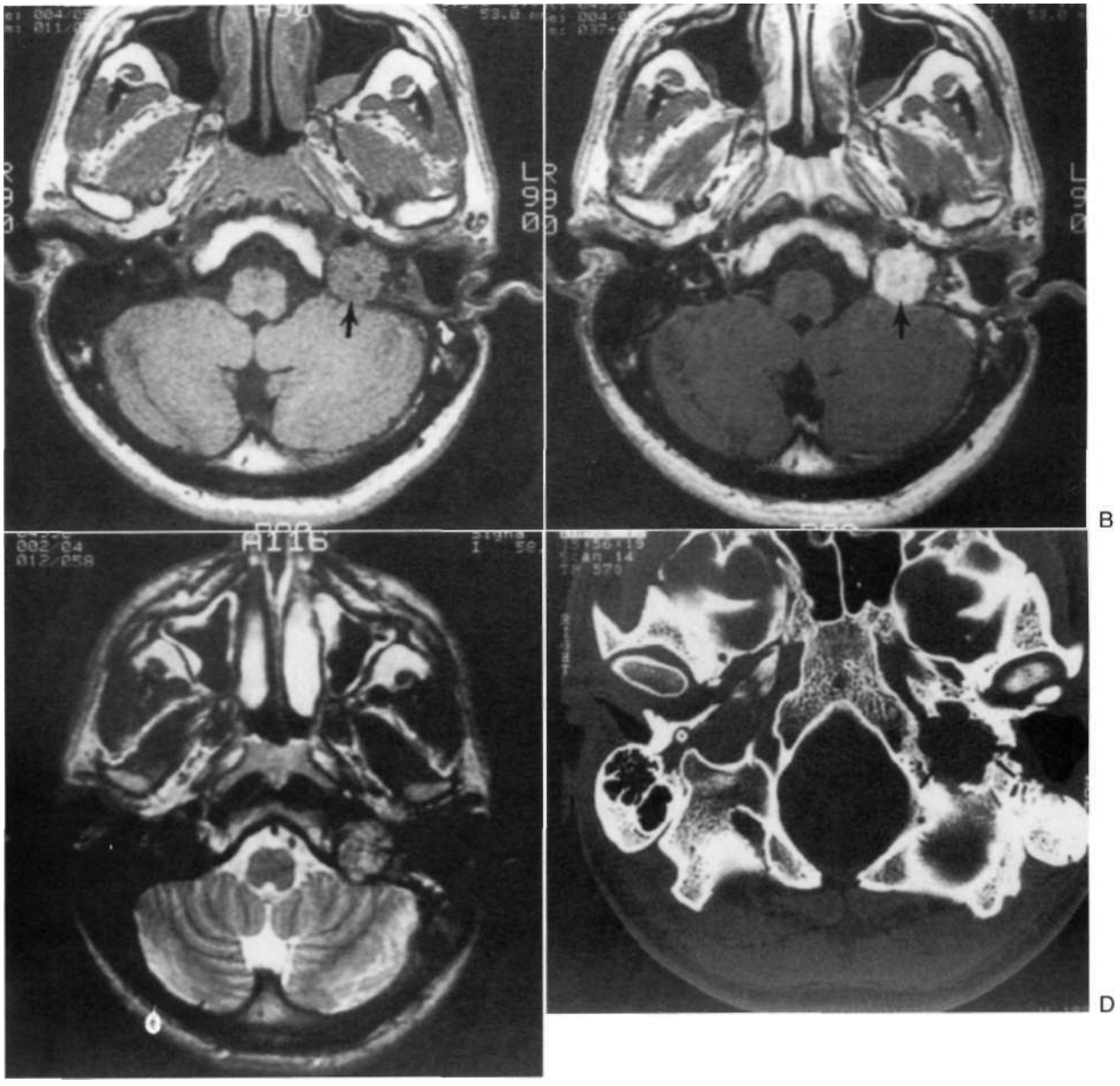


FIGURE 37A.65 Glomus jugulare tumor. Axial Tl-weighted images (A) before and (B) after intravenous administration of gadolinium show a lesion in the region of the jugular foramen, which enhances densely *(arrows).* (C) Axial T2-weighted image demonstrates an isointense to hypointcnse lesion, which has a few signal voids. (D) Computed tomographic scan using bone technique through the skull base shows erosion of the jugular foramen *(arrows).*

On Tl-weighted MRI, a chordoma is seen as a moderately hypointense lesion that replaces the hyperintense clival fat (Figure 37A.66). On T2-weighted images chordomas usually are hyperintense, and calcifications that may be present are seen as hypointensities in the mass (Figure 37A.67). CT shows the bony erosion and calcification to best advantage.

Chondrosarcoma

Chondrosarcoma may arise from the base of the skull, commonly in the region of the petroclival suture. It may have an endochondral hone, cartilaginous, or bony origin. On CT and **MRI,** an erosive, destructive lesion of the skull base or a mass compressing the brainstem may be found. Calcification due to bony lysis or calcium deposition in the tumor may be seen. The tumor spreads by local invasion and rends to recur after surgical removal. The tumor may also arise from the nasopharynx, vomer, and sphenoethmoidal regions and invade the skull base.

ORBITAL LESIONS

Orbital Tumors

Hemangiomas

Hemangiomas are the most common primary tumor of the orbit. Capillary hemangiomas are seen in childhood and cavernous hemangiomas in adults. Capillary hemangiomas appear during the neonatal period and not later than the first 2,5 years of life. They show an infiltrating gtowth (Figutc 37A.68) but may regress spontaneously. Cavernous hemangiomas have an insidious onset and never disappear on their own. They are well circumscribed and have an encapsulated pattern. On imaging, the cavernous hemangioma demonstrates a well-circumscribed intraconal orbital lesion (Figutc 37A.69). On MRI these lesions are of low intensity on Tl-weighted images, are markedly hyperintense on T2-weighted images, and enhance with contrast. With MRI the precise delineation of the mass and its relation to the optic nerve and muscle cone can be determined, which is important in the surgical planning.

Lymphangioma

Lymphangioma is a vascular lesion that is less common than hemangioma. Most of these lesions present at a young age. They show slow progressive growth without regression, and because they ate likely to hemorrhage, sudden symptoms such as proptosis are possible. On MRI these lesions ate hetctogeneous with areas of hemorrhage of varying ages and with regions of cystic change.

Dermoid Lesions

Dermoid lesions are derived from congenital epithelial cell rests. They contain sebaceous glands and other skin appendages. In their growth, they may expand the inner and outer tables of the skull and produce sharply demarcated bone defects with well-defined borders and slightly sclerotic margins. The usual site is in the orbital roof, near the orbital zygomatic suture, and the growth

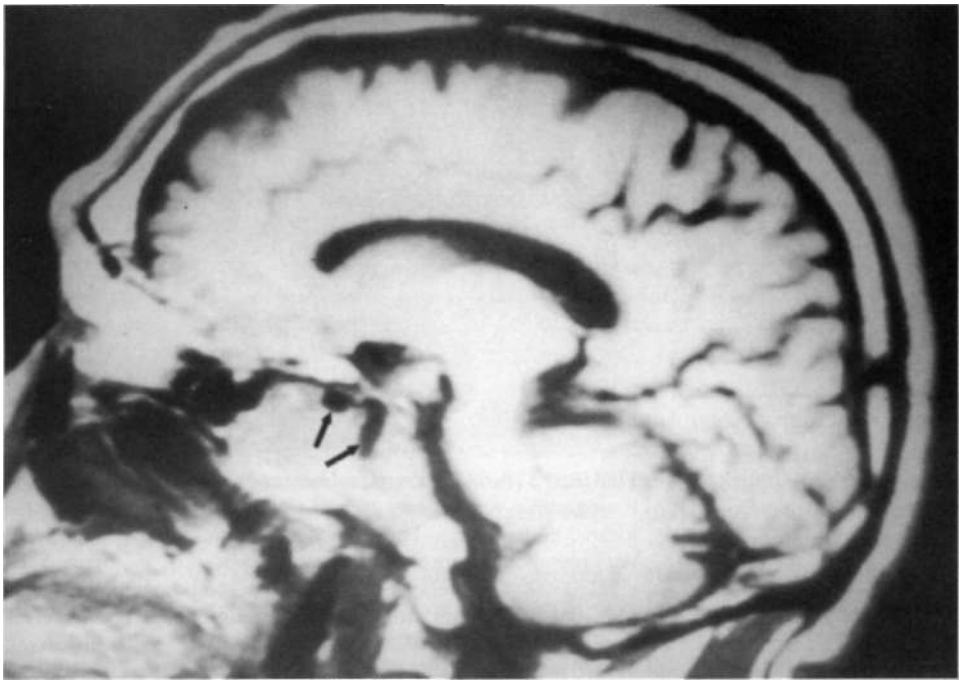


FIGURE 37A.66 Clival chordoma. Sagittal Tl-weighted image demonstrates lesion involving the clivus with destruction of the clivus and extension to the prepontine cistern and apparent encasement of the carotid artery *{arrows).*

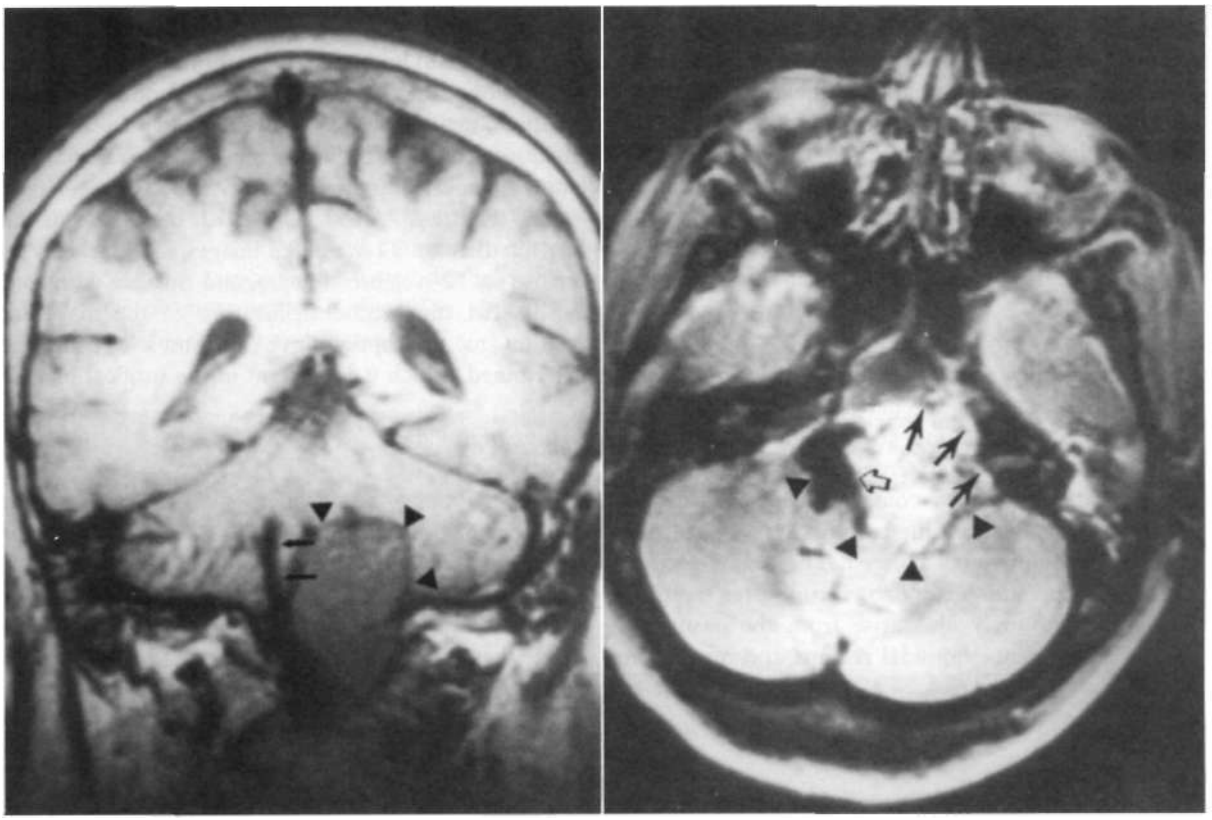


FIGURE 37A.67 Chordoma. Coronal (A) Tl-weighted and (B) T2-weighted axial images show a well-defined mass present in the prepontine cistern *{arrowheads).* Its extra-axial nature is suspected because of the presence of erosion of the clivus and petrous apex (large arrows in B). The small punctate areas that do not enhance are flecks of calcification in the tumor. The displaced basilar artery is outlined with black arrows in A *{white arrow* in B). These findings are typical for a primary clival chordoma. A meningioma is the major differential possibility for an extra-axial mass in this location, but the presence of bone erosion (B) would be atypical.

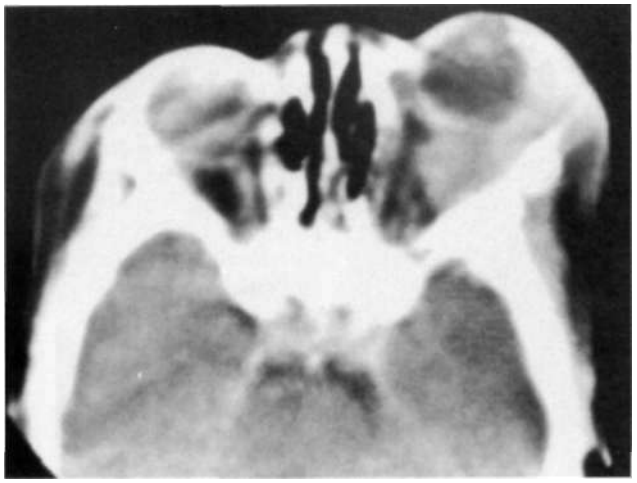


FIGURE 37A.68 Capillary hemangioma. Orbital computed tomographic scan of a capillary hemangioma after administration of contrast material. A large mass is noted, primarily in the left **orbit.** (Reprinted with permission from Sklar, E. M. L., Qucncer, R. M., Byrne, S. F., et al. 1986, "Correlative study of the computed tomographic, ultrasonographic and pathologic characteristics of cavernous versus capillary hemangiomas of the orbit,"/ *Clin NeuroOpbthalmol,* vol. 6, pp. 14-21.)

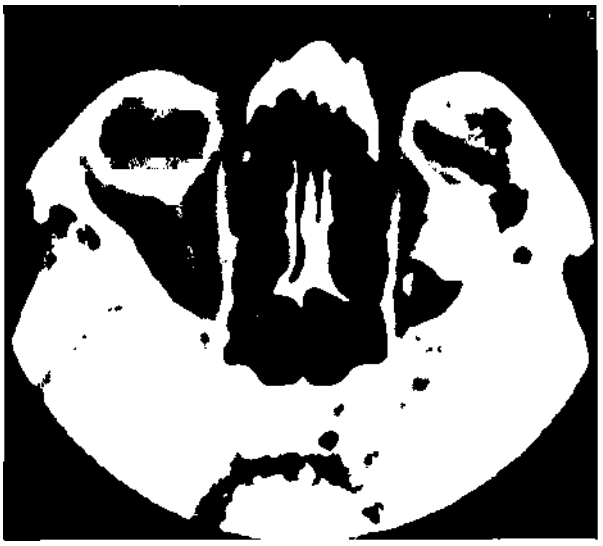


FIGURE 37A.69 Cavernous hemangioma. Orbital computed tomographic scan shows a well-circumscribed intraconal mass located in the temporal portion of the left muscle cone. (Reprinted with permission from Sklar, E. M. L., Qucncer, R. M., Byrne, S. F., et al. 1986, "Correlative study of the computed tomographic, ultrasonographic and pathologic characteristics of cavernous versus capillary hemangiomas of the orbit,'[1] / *Clin NeuroOphthalmol,* vol. 6, pp. 14-21.)

extends to involve the frontal bone. Less often they arise in the lateral wall of the orbit and rarely in the inferior wall. Focal areas of fat are identified easily on MRI. These lesions usually do not enhance.

Orbital Pseudotumor

An inflammatory lesion with acute onset usually occurring in middle age, orbital pseudotumor is difficult to differentiate clinically from a true orbital tumor. Some show spontaneous recovery, whereas others necessitate aggressive therapy, including systemic or local corticosteroid therapy or orbital decompression.

Pseudotumor causes diffuse inflammation and resultant edema. Thickening of the sclera may be seen (uveal-scleral pseudotumor), whereas in other cases there is a mass, extraocular muscle thickening, or diffuse orbital infiltration. Fluid surrounding the optic nerve may be seen as a thickened optic nerve. Obliteration of retrobulbar fat planes, an isolated lacrimal gland, or a retrobulbar mass may be seen. If the insertion of an extraocular muscle into the globe is involved, pseudotumor is a more likely diagnosis than thyroid eye disease.

On MRI, these lesions are isointense to muscle on TI-weighted images, but on T2-weighted images they are hyperintense, making a distinction between pseudotumor and lymphoma possible because orbital lymphoma is most commonly hypointense on T2-weightcd images.

Optic Nerve Glioma

Optic gliomas are low-grade pilocytic astrocytomas, which may be isolated abnormalities or may be associated with neurofibromatosis, especially if bilateral. Three fourths present by age 10 years. Some gliomas have extensive thickening of the pcrioptic meninges (peritumoral arachnoidal hyperplasia), which may be characteristic of patients with neurofibromatosis.

Optic nerve gliomas are isointense to normal white matter on Tl-weighted images, and enhancement with contrast is common. In a patient with an optic glioma, the entire visual pathway must be studied because a large number of these tumors involve the chiasm (see Figure 37A.27) and retrochiasmal pathways, extending to the level of the lateral geniculate bodies. A significant proportion of visual pathway gliomas are limited to the chiasm and retrochiasmal tracts, sparing the intraorbital optic nerve. The signal intensity varies with the site of involvement of the visual pathway. Specifically, intraorbital optic nerve masses are of low intensity on T2-weighted images, which may correlate with arachnoid hyperplasia. The chiasmal and retrochiasmal lesions tend to be hyperintense on T2-weighted images.

Optic Nerve Meningioma

Perioptic meningiomas account for one third of primary tumors of the optic nerve or sheath. Bilateral perioptic meningiomas may be associated with neurofibromatosis. In general, perioptic meningiomas arc most common in adults, and optic nerve gliomas occur in children.

These lesions often calcify and enhance markedly on CT (Figure 37A.70). MRI has a major advantage in evaluating optic nerve lesions; MRI allows visualization of the optic nerve directly and separates it from surrounding subarachnoid space and therefore distinguishes optic nerve

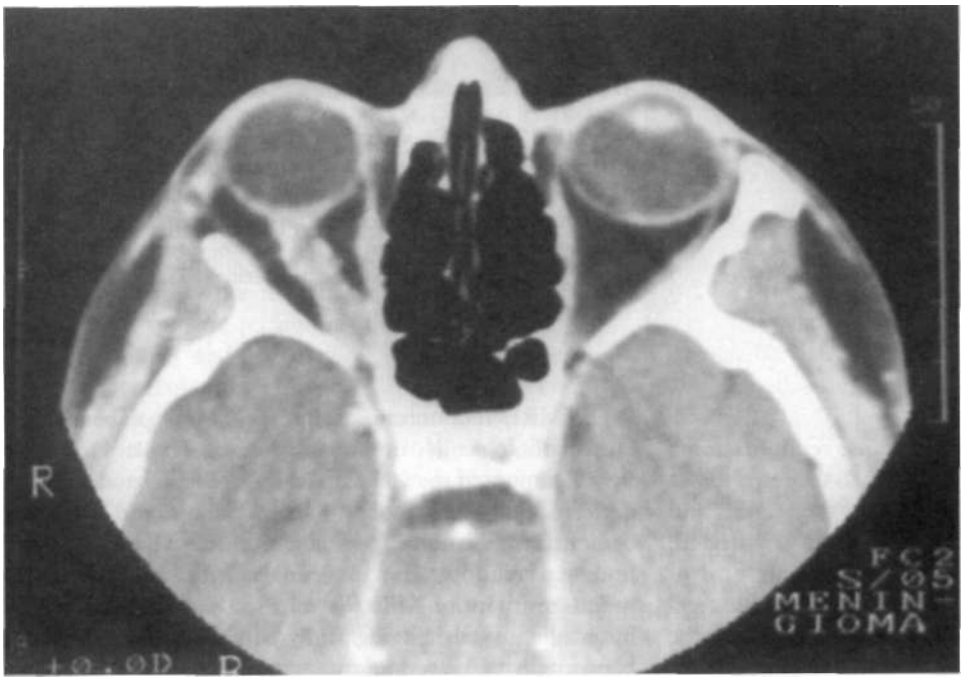


FIGURE 37A.70 Optic nerve meningioma. Con t ra st- e n h a n ccd computed tomographic scan shows the typical thickening and peripheral enhancement of the right optic nerve characteristic of a perioptic meningioma. Extension from die intrascleral portion of the optic nerve posteriorly to the orbital apex is noted.

lesions from sheath lesions. MRI can evaluate also the intracanalicular portion of the optic nerve. MRI signal intensity patterns are variable depending on the site of the lesions (i.e., perioptic versus cxtraconal intraorbital location). The majority of perioptic meningiomas enhance with contrast, and fat suppression techniques with contrast are helpful in delineating regions of gadolinium enhancement.

Ocular Lesions

Melanoma

Malignant melanoma is the most common intraocular malignancy in adults and usually is unilateral. MRI aids in the differential diagnosis of these lesions because there are other entities (such as choroidal metastases, choroidal nevi, choroidal hemangiomas, sarcoidosis, granulomas, and choroidal detachment) that can simulate a melanoma. Also, MRI helps delineate extraocular exrension, **which** occurs in 13% of cases.

On MRI, melanomas are focal masses that extend into the vitreous and enhance afrer contrast, a characteristic common to most ocular neoplasms (Figure 37A.71). In one series, the majority of melanomas were hyperintense on Tl-weighted images and were hypointense on Tl-weighted images because of their content of melanin, which has the paramagnetic characteristic of shortening of Tl and T2 relaxation times. However, melanomas may vary in their degree of pigmentation, and lesions may be amclanotic and then indistinguishable from other ocular lesions.

These lesions can be confusing because they can exhibit varying paramagnetic behavior when they are melanotic or hemorrhagic, and they are often associated with hemorrhagic retinal detachments. In general, MRI can distinguish a melanotic melanoma from an associated hemorrhagic (or nonhemorrhagic) subretinal fluid collection and from an amelanotic neoplasm on the basis of their intensity signals.

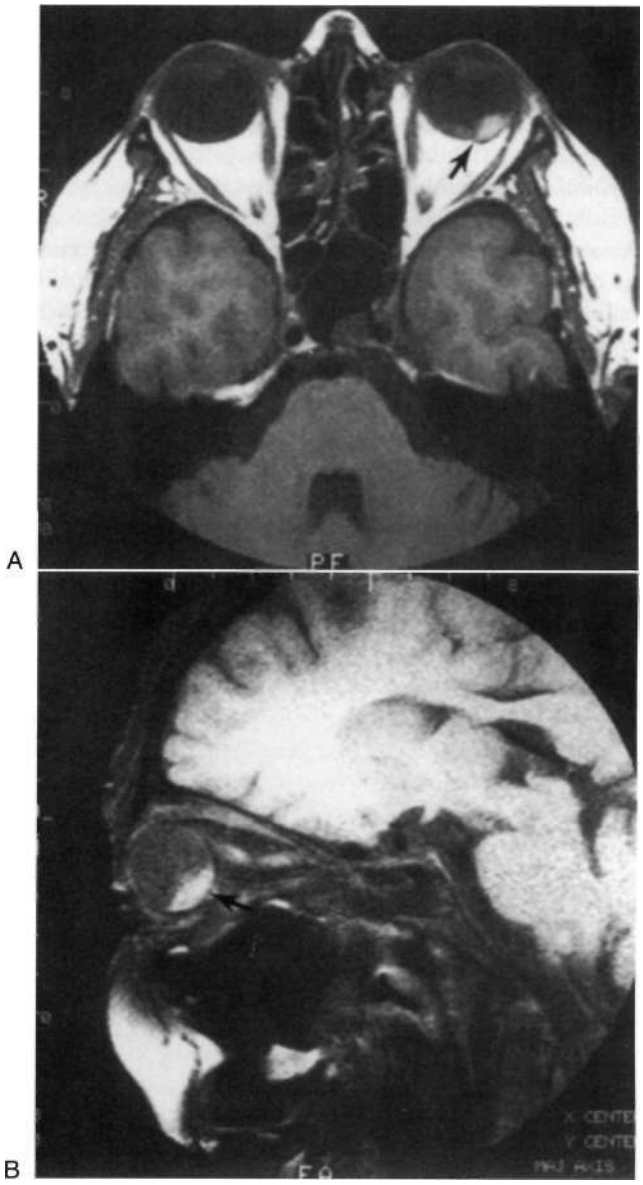


FIGURE 37A.71 Choroidal melanoma. (A) Axial Tl-weighted image demonstrates a lesion in the posterior aspect of the globe, whkh is partially hyperintense *(arrow).* This is consistent with a melanotic melanoma, (B) Sagittal fat-suppressed image shows the hyperintense lesion located in the inferior aspect of the globe *{arrow).* No retrobulbar extension is seen.

Retinoblastoma

Retinoblastoma is the most common intraocular malignancy of childhood. The average age at diagnosis is 18 months. The roles for imaging include limiting the diagnostic possibilities, because the differential diagnosis of leukokoria (reflection from a white mass in the eye, giving the appearance of a white pupil) is extensive; defining the extension of the lesion, because retinoblastoma can spread in a variety of ways, including to the retrobulbar orbit and to the CSF spaces, seeding the CNS; and determining whether the contralateral orbit is affected, because bilateral lesions are common (up to one third of patients). Also, the trilateral retinoblastoma (bilateral retinoblastoma associated with a pineal tumor) can be detected by MRI.

On MRI, retinoblastoma has variable signal intensity. Histopathologically, retinoblastoma is similar to othet PNFT tumors of the CNS and therefore has signal intensity patterns similar to those of these tumors and also may demonstrate hemoirhage and necrosis. The classic CT finding of retinoblastoma is retinal calcification. Because of the insensitivity of MRI for calcification, CT remains the initial diagnostic imaging study of choice when a retinoblastoma is suspected.

SPINAL LESIONS

Spinal Tumors

Extramedullar-)? Intradural Tumors

The two most common extramedullary intradural tumors are the neurinoma (or neurilemmoma) and meningioma. As with any other extramedullar}' intradural mass lesion, these tumors displace the spinal cord and widen the ipsilateral subarachnoid space.

Nerve Sheath Tumors. Nerve sheath tumors are the most common intraspinal neoplasm. Neurinomas can occur at any spinal level, are equally common in both sexes, and often present in the fourth decade of life. Although these tumors are most commonly extramedullary intradural in location, they also can be purely extradural or dumbbell-shaped, with both an intradural and an extradural component, the latter extending through the intervertebral foramen.

On MRI, these tumors tend to have slightly greater intensity than muscle in Tl- and T2-weighted images. These lesions enhance intensely and homogeneously (Figure 37A.72), except when there is an intratumoral cyst.

Meningiomas. Meningiomas typically are found in adults. They usually occur in the thoracic spine or at the foramen magnum and are seen more often in women than men. They are primarily extramedullary and intradural in location, but they can be also both intradural and extradural or purely extradural.

On MRI with short TR images, these lesions are hypointense to isointensc to spinal cord, and T2-weighted images show meningiomas to be slightly hypcrintcnsc to the spinal cord. These lesions enhance homogeneously and intensely after gadolinium administration.

Intramedullary Tumors

In the extradural and extramedullary intradural spaces, MRI has proved to be as effective as CT myelography while being noninvasive. However, for lesions in the cord, **MRI** is superior to CT myelography. Although noncontrast MRI

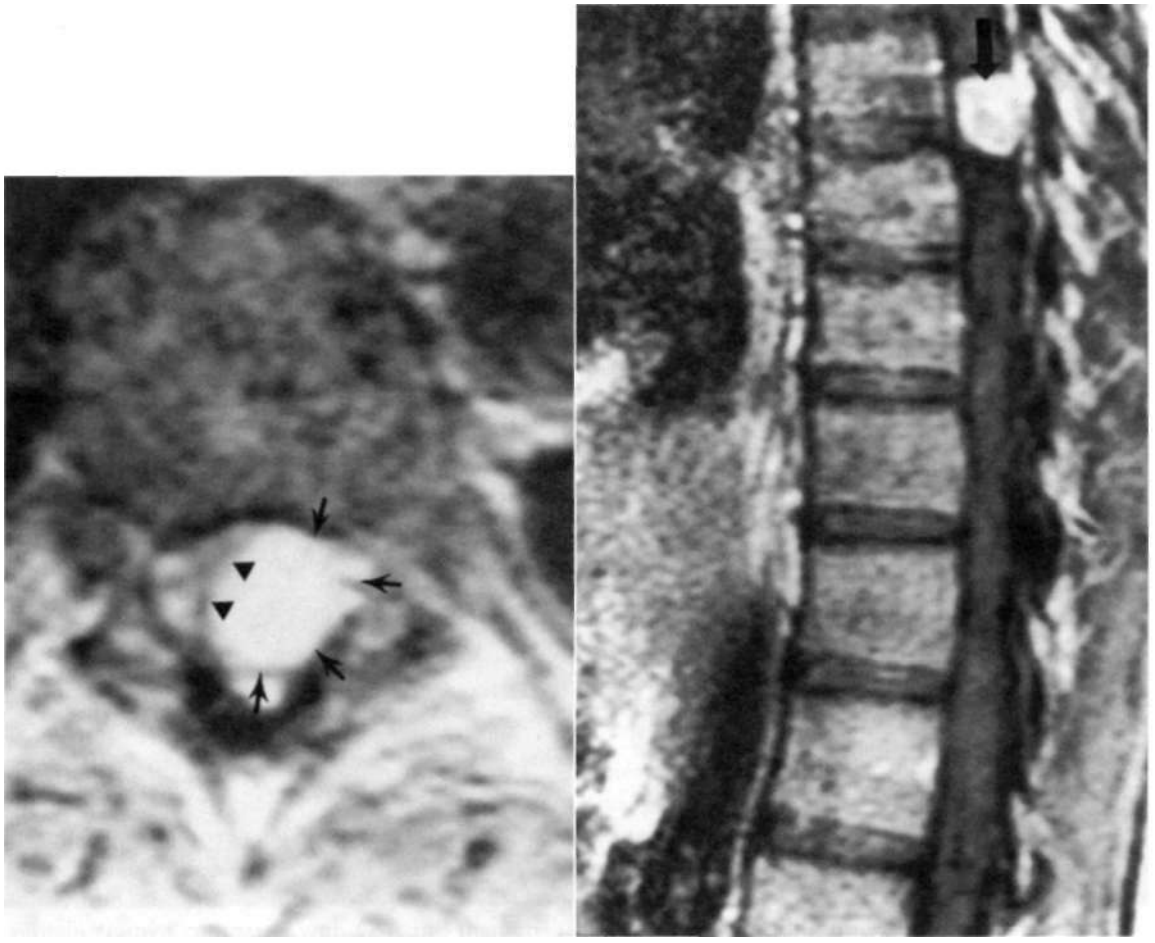


FIGURE 37A.72 Neurofibroma. Postgadolinium Tl-wcighted (A) axial and (B) sagittal images demonstrate an enhancing intradural extramedullary mass *{arrows)* on the left, displacing rhe cord *(arrowheads)* to the right. *Continued*

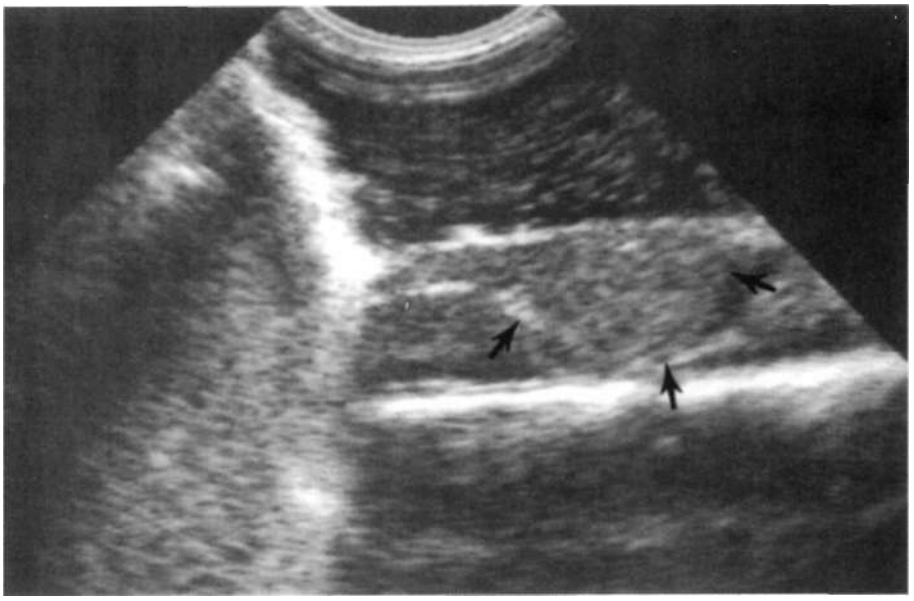


FIGURE 37A.72, cont'd. (C) On intraoperative spinal sonography in a sagittal plane, the mass is noted displacing the cord anteriorly *(arrows).*

scans generally detect lesions, gadolinium can help in further delineating them.

Astrocytomas. The peak incidence of spinal astrocytomas is in the third and fourth decades of life, but they are not uncommon in children. They are most often located in the thoracic cord, but in children holocord involvement can be found.

On MRI with Tl-weighted images astrocytomas are hypointense to normal cord, whereas on T2-weighted images they are hyperintense. The margins of the lesions are poorly defined. After intravenous contrast administration, these lesions almost always enhance, with a homogeneous or in homogeneous pattern. MRI is also helpful in distinguishing tumor cysts from benign cysts associated with tumor; tumor cysts are surrounded by enhancement, whereas the walls of benign cysts lack enhancement.

Ependymomas Ependymomas usually present in patients in the fourth and fifth decades of life, in men more often than women. It is the most common primary cord tumor of **the** lower spinal cord, conus medullaris, and filum terminalc.

Noncontrast MRI demonstrates cord widening (Figures 37A.73 and Figure 37A.74). The lesion is hypointense or hyperintense on T2-weighted images. Areas of hemorrhage may be seen, and intratumoral cysts are common. Hemosiderin deposition is common at the superior and

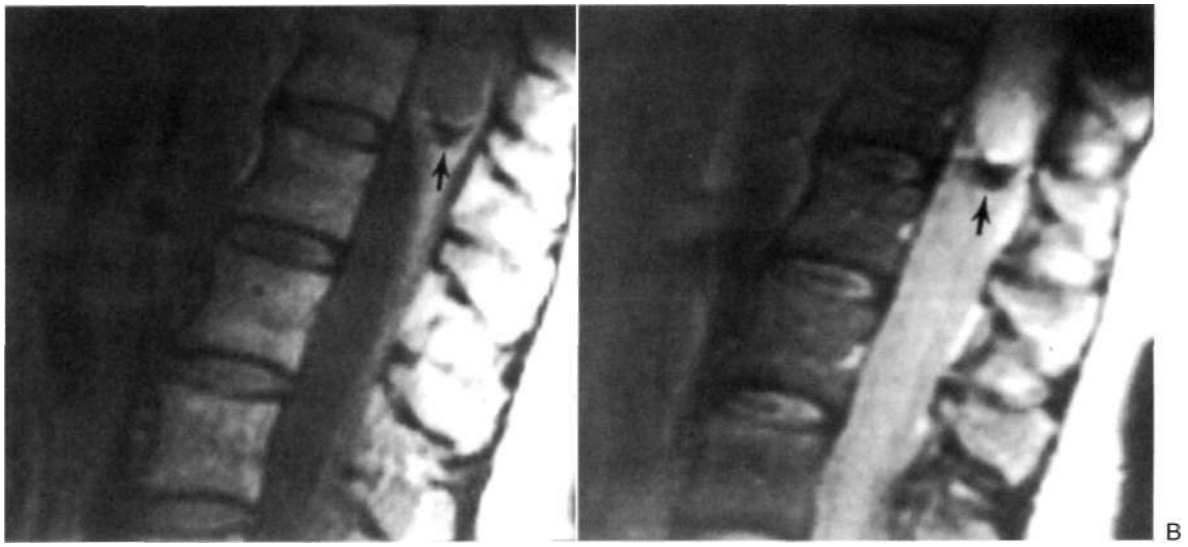


FIGURE 37A.73 Ependymoma. (A) Tl-weighted and (B) T2-weighted sagittal images demonstrate spinal cord widening at the conus. The lesion is hypointense on short repetition time (TR) images and hyperintense on long TR images. Hemosiderin deposition is noted at the inferior borders of the tumor *(arrows).*

inferior borders (see Figures 37A.73 and 37A.74}. After intravenous contrast, ependymomas tend to enhance intensely and homogeneously.

Hemangioblastoma. Hemangioblastoma is an uncommon intramedullary lesion that represents 1-5% of spinal cord tumors. Presentation usually is during the fourth or fifth decade of life, and the cervical and thoracic cord usually are affected. On MRI, a cord cyst with an enhancing nodule and, occasionally, evidence of a prominent enhancing feeding arterial vessel may be seen. Twenty percent of hemangioblastomas are associated with von Hippel-Lindau disease. The tumor may present with hemorrhage.

Extradural Tumors

Metastases are the most common of the extradural tumors. They can destroy the vertebral bodies and extend into the

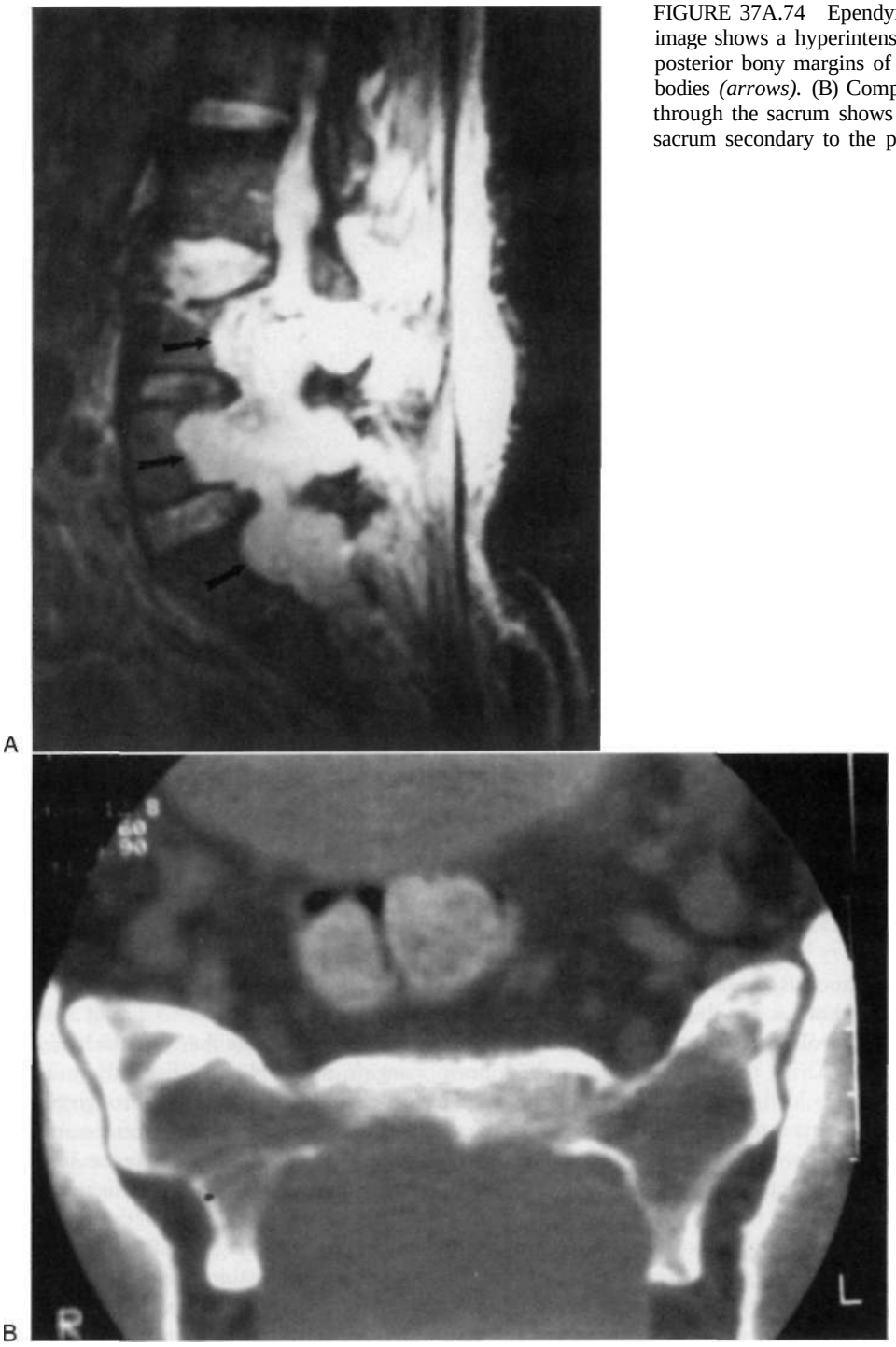


FIGURE 37A.74 Ependymoma. (A) Sagittal T2-weighted image shows a hyperintense lesion, which is scalloping the posterior bony margins of the lumbar and sacral vertebral bodies *(arrows).* (B) Computed tomographic axial image through the sacrum shows the bony erosive changes of the sacrum secondary to the pathologically proven ependymoma,

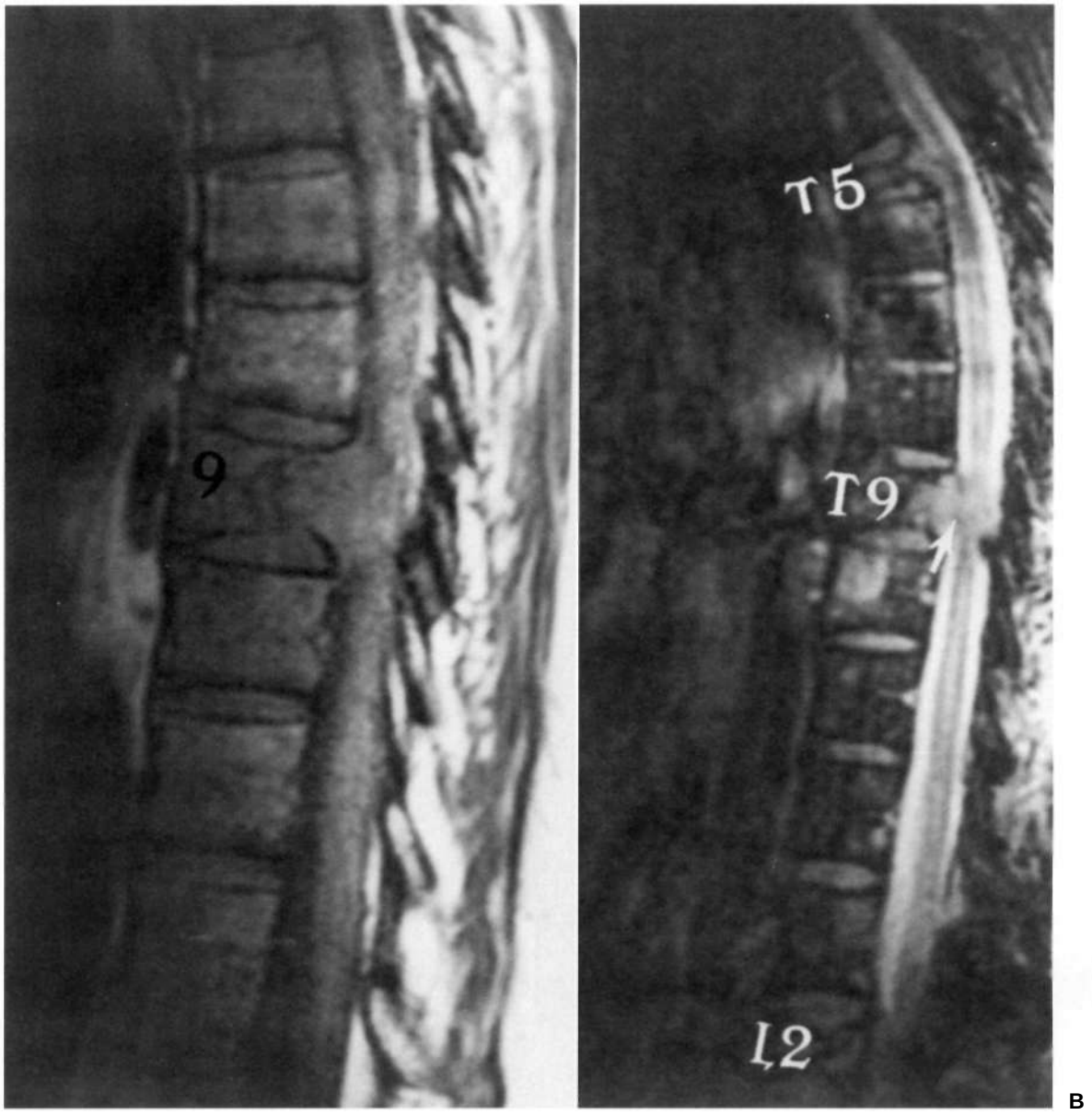


FIGURE 37A.75 Spinal metastases. (A) Sagittal T1-weighted image demonstrates a metastatic lesion involving the T9 body, with epidural extension of soft tissue tumor into the ventral aspect ot the **(.anal.** I Hi ()n l 2-weiiihti'il inias'.e (widl a larger field of 1 iev, | multiple **levels are involved with high signal lesions. Also, compression of T5, T9, and L2 exists. Epidural extension of tumor is noted at T9 with compression of the cord *(arrow).***

spinal canal, displacing the subarachnoid space and spinal cord. The tumor and adjacent bony changes and the extent of the epidural and paraspinal involvement are well demonstrated on MRI (Figure 37A.75).

Degenerative Disease of the Spine

Degenerative Disc Disease

As an intervertebral disc degenerates, it loses water, and fibrous tissue replaces nuclear material as the disc collapses (see Chapter 77). Annular fibers weaken, resulting in disc bulging, and annular tears predispose to disc herniation.

A bulging disc extends diffusely beyond the adjacent vertebral body margins, although the concentric annular fibers are intact. An extruded disc extends through all the layers of the annulus and appears as a focal soft tissue mass (Figure 37A.76). These disc herniations may be subligamentous (anterior to the posterior longitudinal ligament} or may rupture through and be posterior to the posterior longitudinal ligament. A free disc fragment is herniated disc material that has separated from the parent disc and may migrate to a position removed from the original disc space. Approximately 90% of lumbar herniated discs occur

at L4-L5 or L5-S1, 7% at the L3-L4 level, and 3% at L1-L2 or L2-L3.

On MRI, most bulging discs extend beyond the verte bral body margin in a diffuse manner and have decreased signal intensity on T2-weighted images because of disc degeneration and loss of water, whereas a herniated disc is seen as a focal soft tissue mass displacing the epidural fat or thecal sac (see Figure 37A.76) and can show enhancement along the periphery of the disc because of the presence of reactive vascular connective tissue.

Spinal Stenosis and Spondylosis

The most common degenerative process of the spine is spondylosis deformans (osteophytosis). Osteophytes occut because of underlying disc disease. Osteoarthritis is degenerative arthritis involving the synovial joints such as the facet joints. These terms often are used synonymously because the conditions often coexist. Both lead to narrowing of the spinal canal or neural foramina and as a result can cause cord compression or root entrapment.

Lumbar Spinal Stenosis. The term *lumbar spinal stenosis* includes stenosis of the spinal canal, lateral recess, and foramina. Canal stenosis is most common at L2 to L5 levels and causes radiculopathy. Stenosis may be caused by a combination of diffuse disc bulging, facet hypertrophy, and ligamentous thickening.

Cervical Spinal Stenosis. Cervical canal stenosis is most often caused by spondylosis deformans and ligamentous thickening. Foraminal stenosis is caused by hypertrophy of

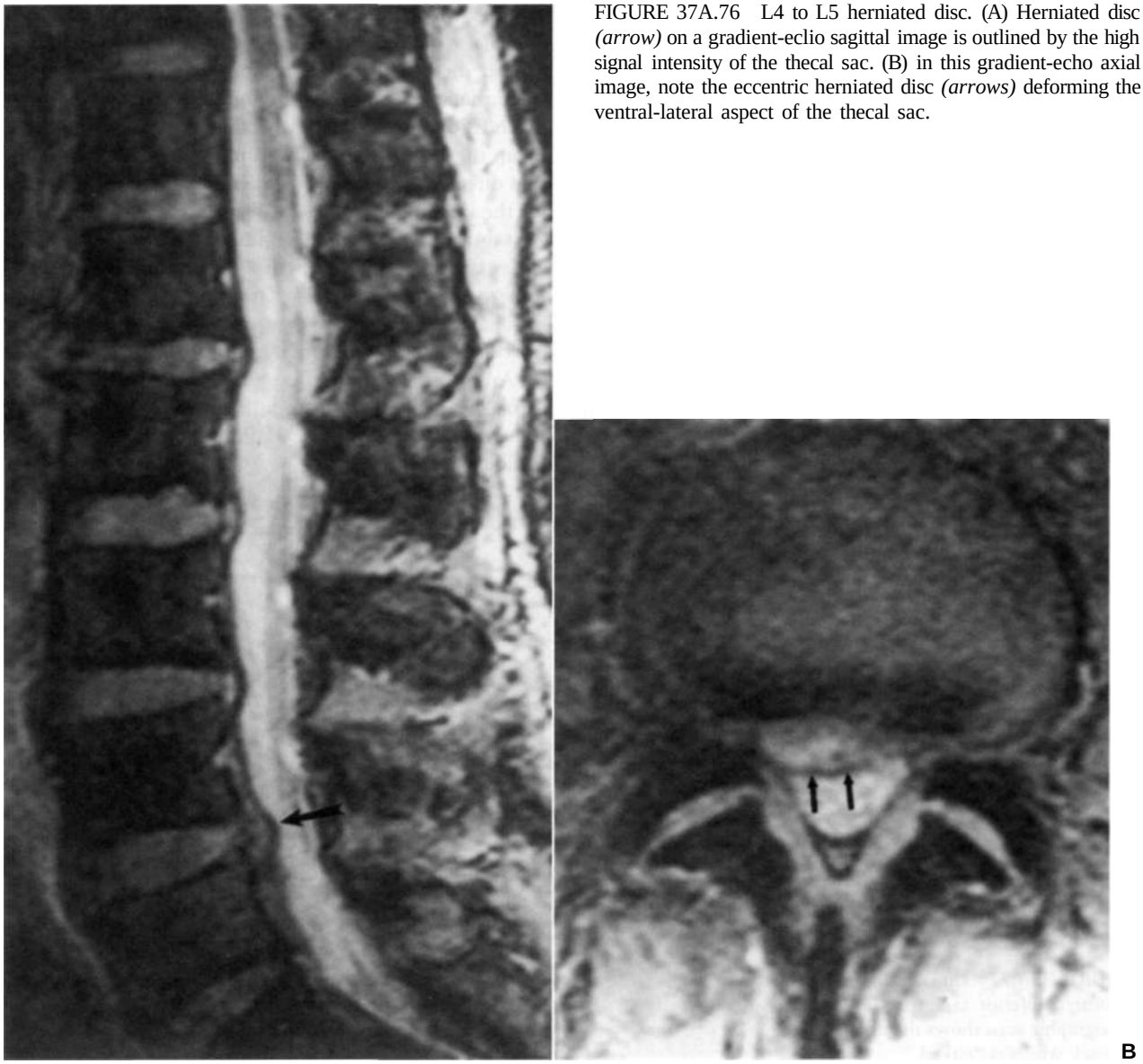


FIGURE 37A.76 L4 to L5 herniated disc. (A) Herniated disc *(arrow)* on a gradient-eclio sagittal image is outlined by the high signal intensity of the thecal sac. (B) in this gradient-echo axial image, note the eccentric herniated disc *(arrows)* deforming the ventral-lateral aspect of the thecal sac.

the uncinate process and superior articular facet. Patients are at particular risk for myelopathy or radiculopathy if the anteroposterior diameter of the cervical canal is less than 11 mm.

T2*-weighted gradient-echo images are most effective for evaluating cervical spondylosis because spurs can be distinguished from discs, and the anteroposterior diameter of the canal can be measured. CT scans have been considered the procedure of choice for diagnosing neural foramina! stenosis. However, with .3D gradient-echo techniques, thin sections may be obtained to evaluate the neural foramina, and the accuracy of these sections approaches that of high-resolution CT myelography.

Spinal Trauma

Spinal trauma is one of the leading causes of disability. Since the 1970s, important imaging developments have improved diagnosis and paralleled the development of better clinical and more aggressive surgical management of spinal injuries. In choosing a particular radiographical protocol, one must take several factors into account, including the neurological status of the patient, level of injury, age of the lesion, and potential henefit that might be derived from each of the different imaging modalities.

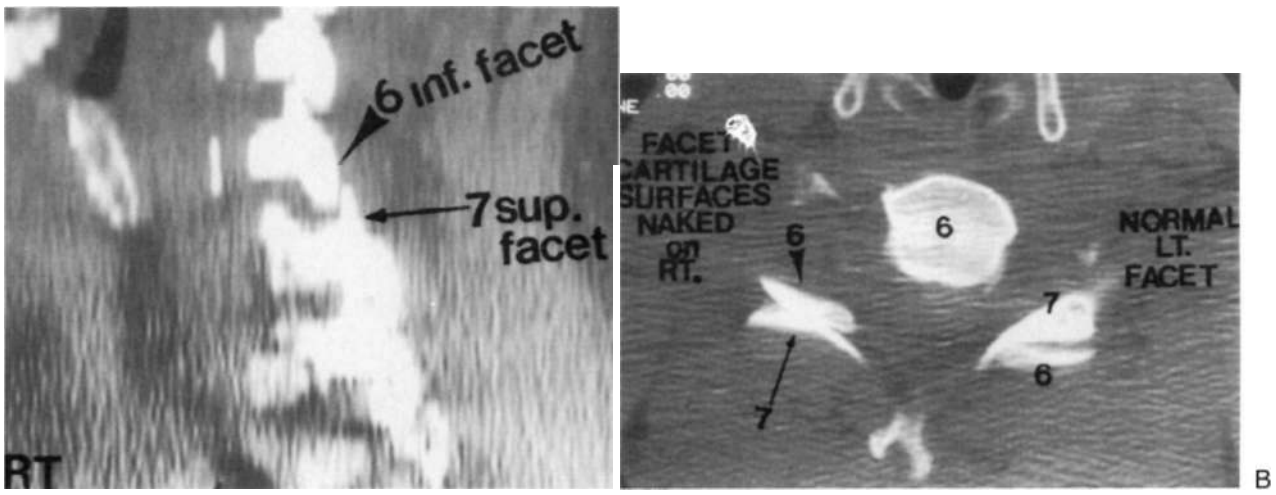
Acute Cervical Spine Trauma

Fractures

Bilateral Interfacetal Dislocation. Bilateral interfacetal dislocation is dislocation of both interfacetal joints at the same level. Interlocking of the articular facets begins with the movement of the inferior articular facets of one vertebra forward over the articular facets of the underlying vertebra. This causes the laminae and spinous processes to distract and the vertebral bodies to sublux. Radiographically, this is characterized by anterior displacement of the dislocated segment. The inferior facets of the dislocated vertebra lie anterior to the superior facets of the adjacent segment. Often this injury is called *double-locked* vertebrae. This lesion is acutely unstable because of skeletal and soft tissue disruption at the level of injury,

Unilateral Interfacetal Dislocation. Unilateral interfacetal dislocation results from simultaneous flexion and roration. The posterior ligament complex and the capsule of the dislocated facetal joint are disrupted. The interfacetal joint on the side of the direction of rotation acts as the pivotal point, whereas the contralateral side including its inferior facet rides upward and forward over the tip of the superior facet of the inferior vertebra. The dislocated facet is locked and fixed. The contiguous facets are no longer in apposition and arc uncovered, or exposed, "naked" facets. There may be fractures of either of the articular facets; tiny fragments have no clinical significance, but large fractures render the interfacetal dislocations unstable.

In the anteroposterior radiograph, unilateral interfacetal dislocation is evidenced by rotation of the spinous processes from the level of the dislocation upward off the midline in the direction of the side of the dislocated interfacetal joint. In the lateral view, forward displacement of the dislocated vertebra is seen. Although the vertebrae below are in the true lateral projection, the vertebrae above are seen obliquely because of the rotational component of the mechanism of injury. This results in a bowtie appearance of the articular pillars of the dislocated vertebra (Figure 37A.77). In the anteroposterior projection the spinous processes are displaced from the midline toward the side of the dislocated interfacetal joint at the level of the dislocation and above.



E1GURE 37A.77 Unilateral interfacetal dislocation. (A) Sagittal reformatted images of computed tomographic scanning show dislocated inferior facet of *C6 {arrowhead)* anterior to the contiguous superior facet of C7 *(arrows).* (B) The axial computed tomographic scan shows the dislocated articular mass of C6 *{arrowhead)* anterior to its subjacent counterpart, the superior facet of C7 *{arrow),* which is "naked."

Continued

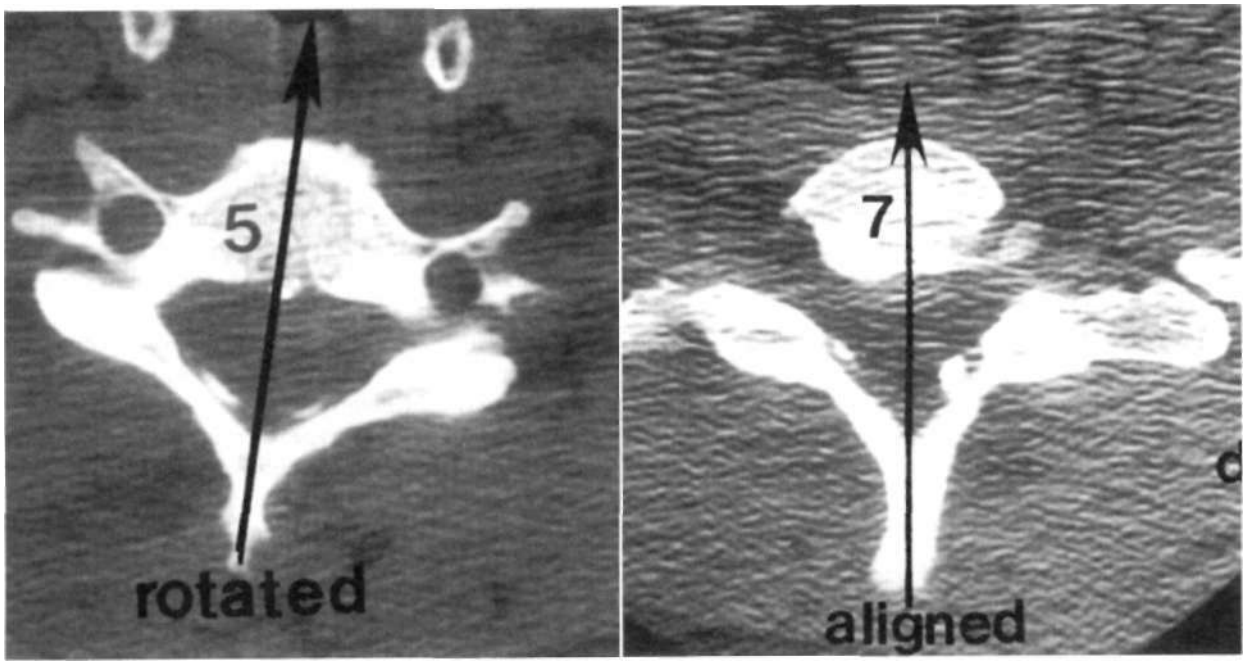


FIGURE 37A.77, cont'd. (C) Axial computed tomographic scan above the level of dislocation shows rotation of the vertebra and spinous process. (D) Axial computed tomographic scan below the level of dislocation shows no rotation.

Clay Shoueler's Fracture. Clay shovcler's fracture is an avulsion of the spinous process of C6, C7, or T1.

Hangman's Fracture. Usually, hangman's fracture represents bilateral fractures of the pars inrerarticularis of the axis. Less commonly, one or both fractures may involve the superior articulating facet or may be more anteriorly located at the junction of the posterior arch and posterior aspect of the body of C2 (Figure 37A.78).

Jefferson Bursting Fracture. The original description of the Jefferson bursting fracture was that of bilateral fractures of both the anterior and posterior arches of CI. However, the Jefferson fracture may result from a single break in each ring. In the frontal projection of plain films, there is bilateral displacement of the articular masses of CI. In the lateral projection, the anterior arch fracture is seen rarely, but the posterior arch fracture ofren is noted. On the

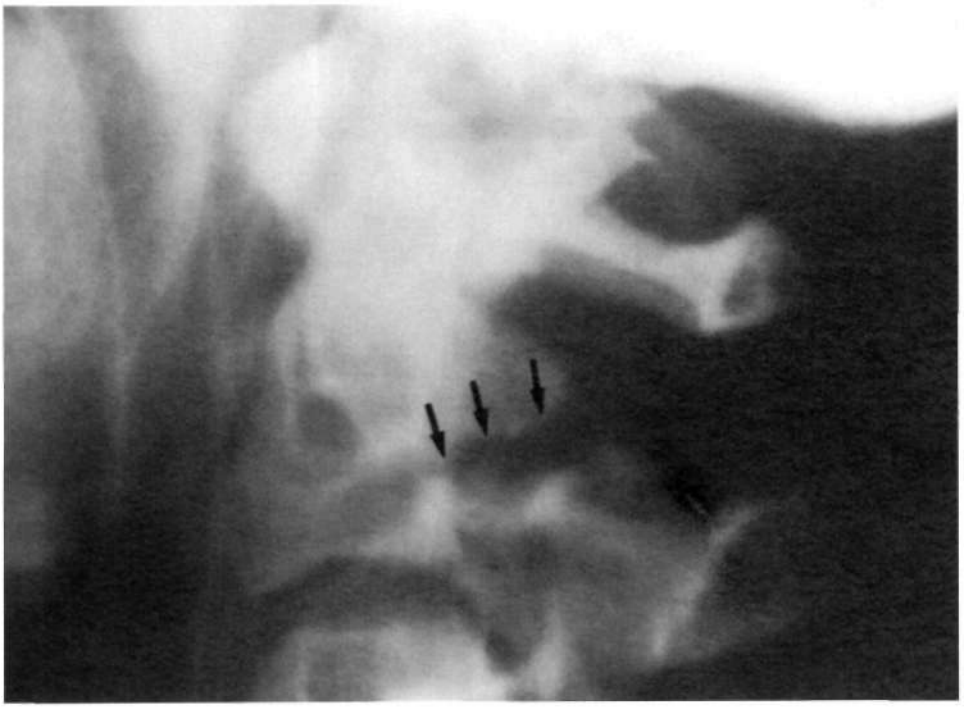


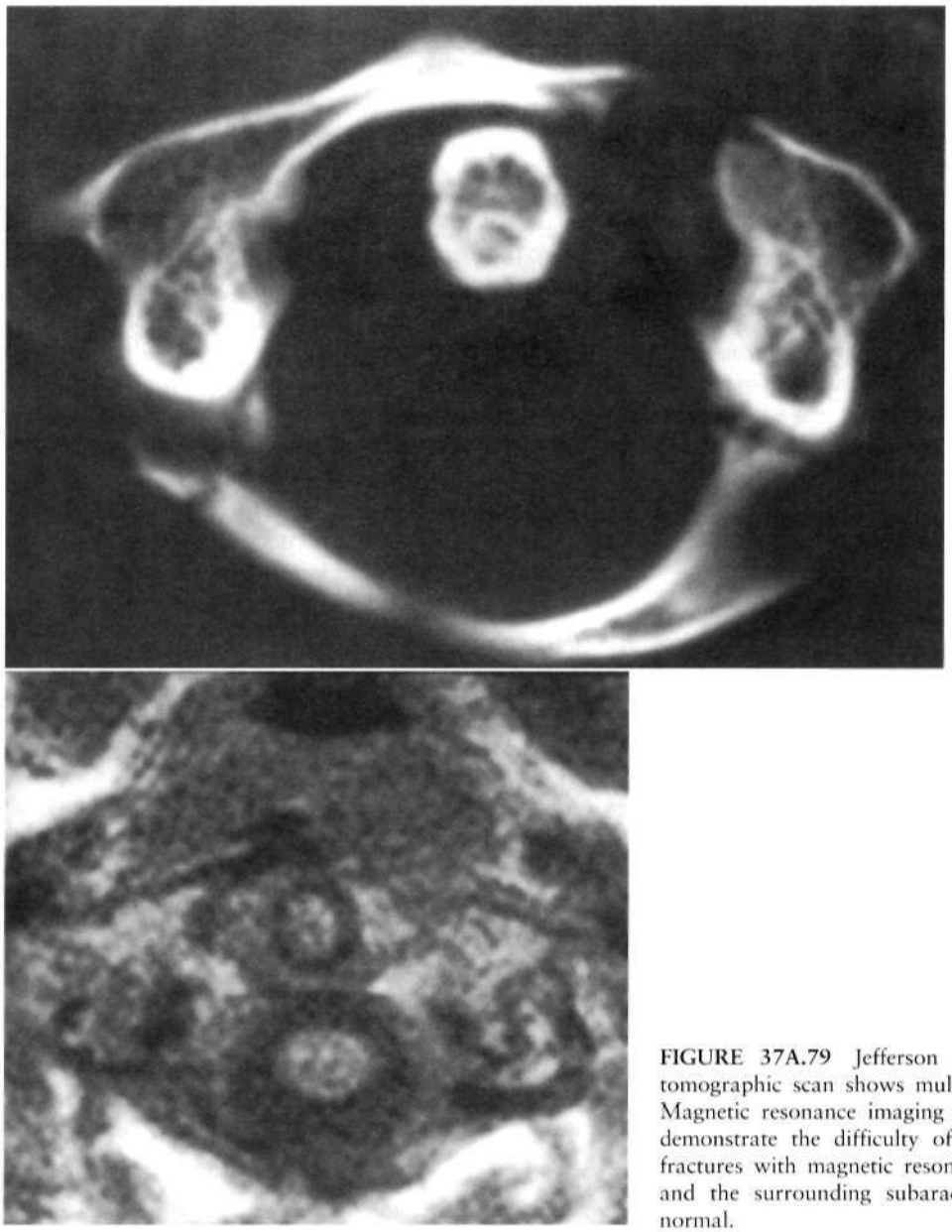
FIGURE 37A.78 Hangman's fracture. Fracture through the pars interarticularis (*arrows*).

lateral projection, the Jefferson fracture cannot be distinguished from an isolated hyperextension of the posterior arch of the atlas. These fractures can be demonstrated on CT and less well on MRI (Figure 37A.79).

Burst Fracture. The burst fracture of the lower cervical spine is a comminution fracture of the vertebral body with retropulsion of bone into the spinal canal, well demonstrated on lateral radiography. CT demonstrates that a posterior arch fracture usually is present. The alignment of the posterior elements is normal. A vertical fracture of the vertebral body is seen on the frontal projection, but the posterior fracture is seen only on CT.

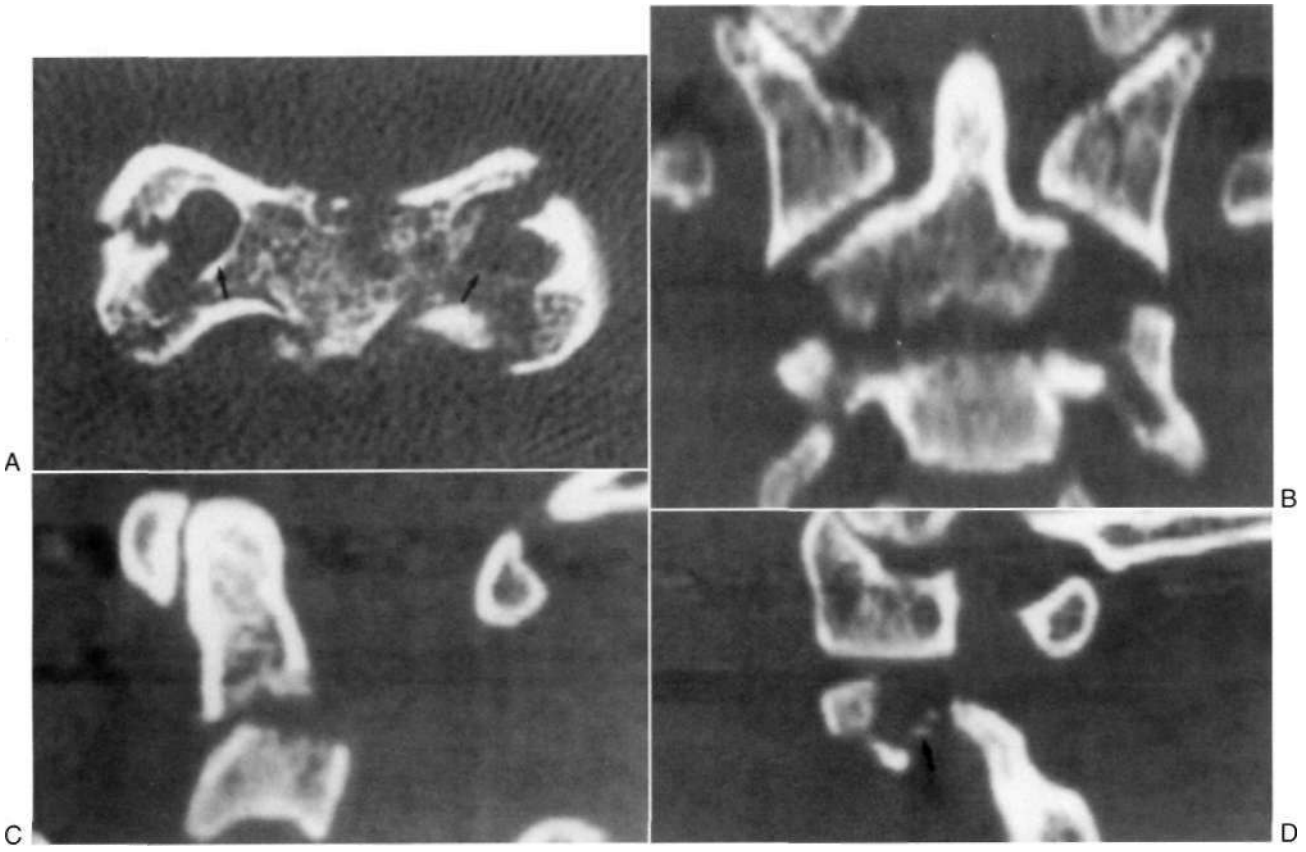
Odontoid bractures. Fractures of the dens can occur with either forced hyperflexion or forced hyperextension of the head or the neck. Hyperflexion injuries cause the dens to be displaced anteriorly, and there is forward subluxation of C1 on C2. Hyperextension injuries cause the dens to be displaced posteriorly, with posterior subluxation of CI on C2. The dens moves with CI unless the transverse ligament is ruptured. Fractures of the dens without displacement of CI on C2 can be most difficult to recognize. Polytomography of the dens may be helpful in detecting these fractures.

Odontoid fractures have been classified into three types. Type I is an avulsion fracture of the top of the dens. Type II is a transverse fracture of the dens above the body of the axis. Type III is a fracture of the superior portion of the axis body that involves one or both articulating facets (Figure 37A.80). This type of fracture is not really a fracture of the dens but a fracture of the superior portion of



B

FIGURE 37A.79 Jefferson fracture. (A) Axial computed tomographic scan shows multiple fractures through C1. (B) Magnetic resonance imaging at the same level is shown to demonstrate the difficulty often encountered in diagnosing fractures with magnetic resonance imaging. The spinal cord and the surrounding subarachnoid space at the level are normal.



HCUR1 37A.*HU* Type **III** odontoid fracture. (A) Axial computed tomographic semi rbroii^h rlu- .ixi— body shows tt-.u-inn- lines lli.n traverse both transverse foramina *{arrows).* (B) Coronal reconstructed image shows fracture through the axis body. (C) Sagittal reconstruction through the midline shows the anterior displacement of the dens. (D) Right parasagittal reconstructed image shows fractures extending through the transverse foramen and therefore not allowing posterior transarticular screw fixation *(arrow).*

the axis body. Because it involves an area of cancellous bone, it almost always heals. Type **III** fracture is considered to be mechanically unstable. The low dens fracture disrupts the axis ring. This ring is composed of the cortex of the junction of the pedicle, the vertebral body, the cortex at the junction of the axis and body superiorly, and the posterior cortex of the axis body.

Spinal Cord. The information that MRI can provide regarding the acutely injured spinal cord is unrivaled, MRI has been found to be superior in detecting spinal cord parenchymal abnormalities compared with myelography and CT myelography. **MRI** is the only imaging study that can directly image the spinal cord parenchyma with sufficient resolution and demonstrate intrinsic signal abnormality even in the absence of cord enlargement. Myelography and CT myelography can provide only information regarding spinal cord size or spinal cord compression. **MRI** can reliably determine whether acute post-traumatic cord enlargement is related to edema or hemorrhage and identify hemorrhage or contusion change in a nonenlarged cord.

Three types of MR! signal patterns in patients imaged 1 day to fi weeks after injury were reported in one study. In 19 patients who demonstrated MRI evidence of cord injury, S had evidence of cord hemorrhage with decreased T2 signal within 72 hours of injury. A peripheral hyperintense rim with persistence of central T2 hypointensity images was seen up to 7 days after injury. In a second group of 12 patients, only cord edema was appreciated (Figure 37A.81). This cord edema showed evidence of some resolution from 7 days to 3 weeks after injury, A mixture of hemorrhage and edema with central hypointensity surrounded by a rim of hyperintensity on T2-weighted images was identified as a third pattern of cord injury in two patients. Resolution of cord lesions with blood products was slower than that of cord lesions that were non hemorrhagic. In I he carh period after injury, Tl-weighred images were useful only in demonstrating cord swelling and failed to reveal significant signal change in the cord parenchyma.

Intramedullary cord hemorrhage and extensive cord edema are poor prognostic indicators for neurological recovery. T2* images are the most sensitive sequences for hemorrhage detection in the acute phase.

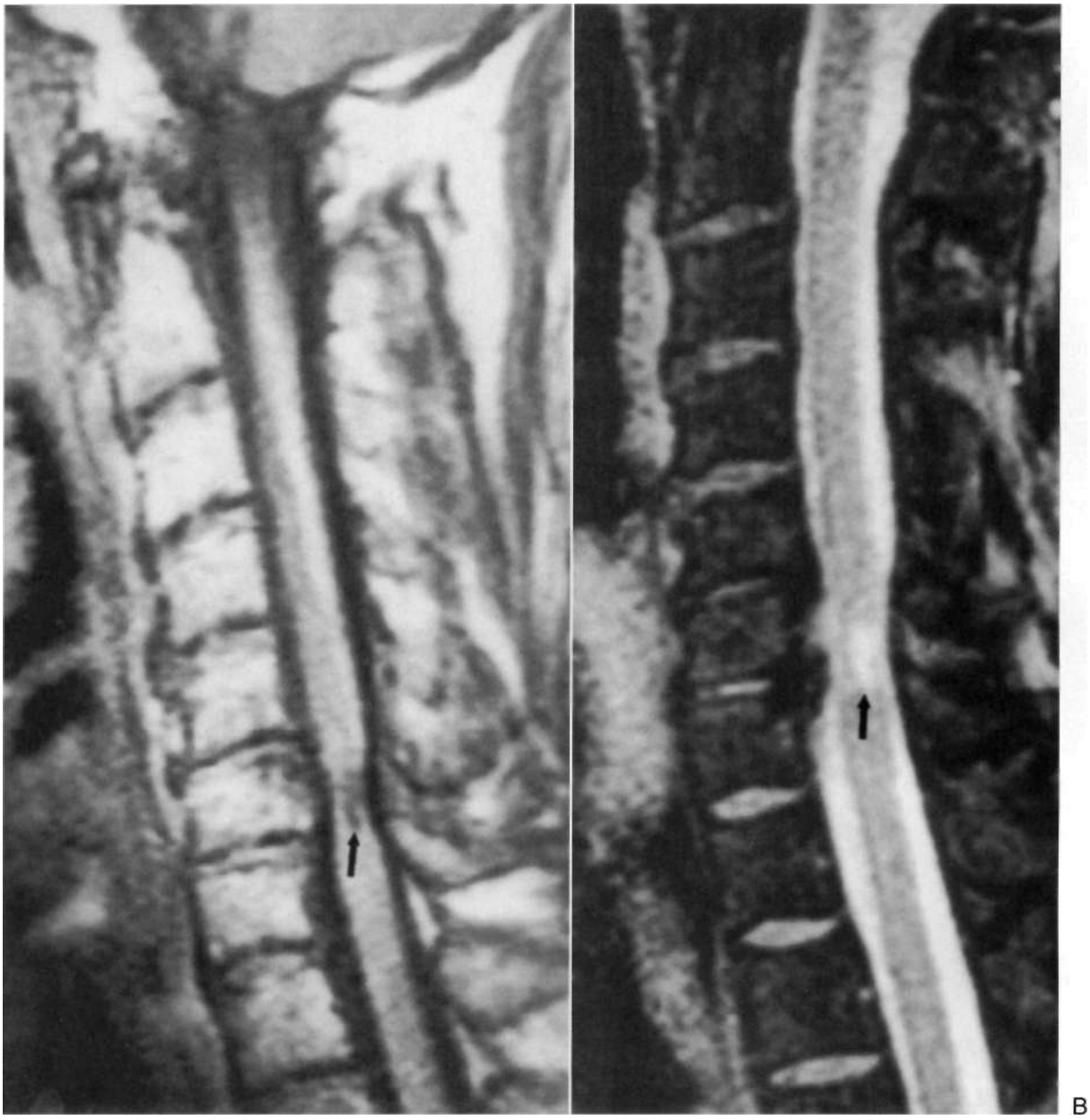


FIGURE 37A.81 Cord edema. Focal lesion in the cord, which is hypointense in (A) T1-weighted image and hyperinrense in (BJ T2-weighted image, is consistent with an area of edema *{arrows)* in a patient with acute spine injury. On the T2-weighted image, the markedly hypointense areas at C5-C6 and C6-C7 disc spaces represent calcified osteophytes.

Deoxyhemoglobin results in signal loss on $T2^{0,}$ images (Figure 37A.82).

Cervical Spine Trauma: Progressive Post-Traumatic Myelopathy

Spinal Cord Cysts. Post-traumatic myelopathy can occur in up to 32% of patients with chronically injured spinal cords. Post-traumatic myelopathy may present as early as 2 months after injury or as late as 36 years afrer injury. Progressive post-trauma tic myelopathy may be related to several conditions. One of the more common treatable parenchymal abnormalities is a spinal cord cyst (Figure 37A.83). Progressive myelopathy also can be seen in the presence of myelomalacia and cord tethering. Cord tethering probably plays a significant role in the development of myelomalacia and spinal cord cysts. There is also evidence that myelomalacia and spinal cord cysts are part of a continuum. Imaging plays a key role in differentiating between spinal cord cyst and myelomalacia because the two are difficult to distinguish clinically. MRI is the modaliry of choice in evaluating patients with a progressive post-traumatic myelopathy. Less common causes of post-traumatic myelopathy that are also detectable by MRI

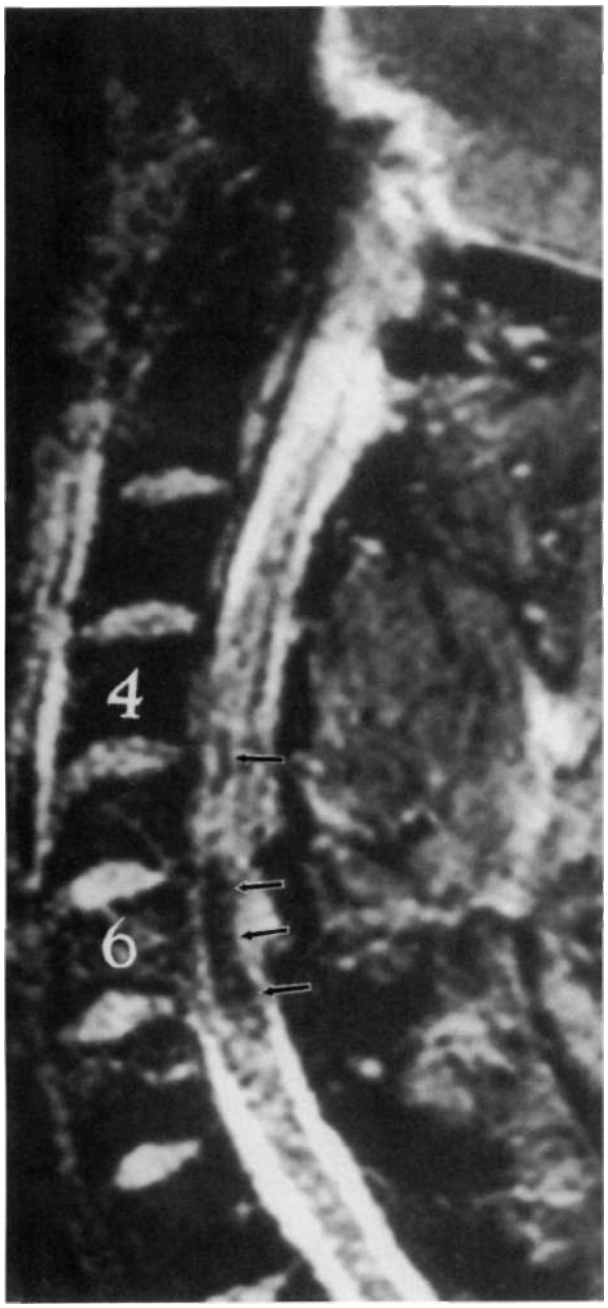


FIGURE 37A.82 Cord hematoma. T2* gradient-echo sagittal image shows hypointensity in the cord from C4 to C7 *{arrows),* consistent with acute hemorrhage (deoxyhemoglobin) in the cord.

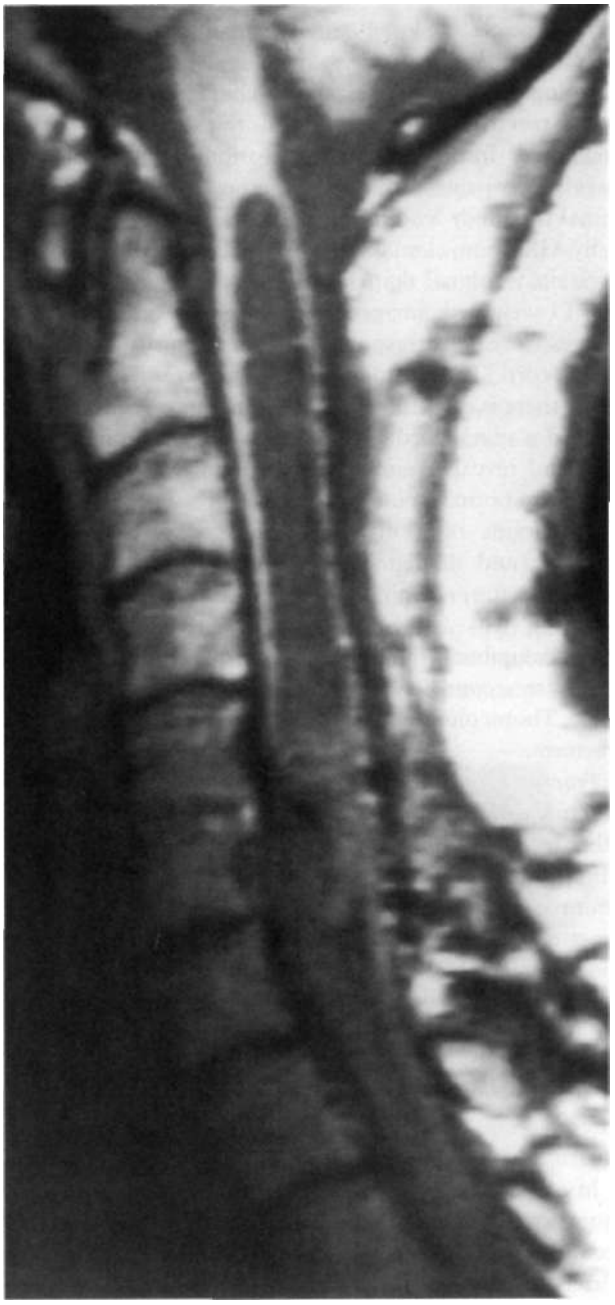


FIGURE 37A.83 Post-traumatic intramedullary cyst. A large multisegmented intramedullary cyst is present from C1 to T1. This patient was worsening n euro logically after a fracture-subluxation in the distant past and had a prior wide posterior laminectomy. Note linear bands in the cyst, which represent fibroglial septa traversing the cyst.

include cord compression from vertebral malalignment, herniated disc or osteophytes, arachnoid cysts, and cord atrophy.

Spinal cord cysts almost always follow CSF signal intensity on MRI (see Figure 37A.83}. CSF pulsation-induced signal loss or flow-related enhancement may be seen in large pulsatile cysts and can alter the MRI appearance. Although cyst contents may contain an elevated protein content compared with CSF and theoretically shorten Tl and T2 relaxation, this is rarely a problem. A well-defined border usually can be traced around the cyst, although when a cyst develops in a region of severely damaged spinal cord tissue the entire border may not be well defined. Post-traumatic spinal cord cysts may be a single cavity or contain septations; they may occur above, below, or at a site of initial injury. Cine images may be helpful in determining cyst pulsatility. Postoperative cine evaluation may help determine whethct shunting of the cyst was successful.

Myelomalacia. Closed spinal cord trauma is a common mechanism leading to a myelomalacia or soft cord. Histologically, myelomalacia is characterized by microcysts, reactive astrocytosis, and thickening of the pia-arachnoid. Intraoperative observations at our institution have always revealed cord tethering. Untethering of the spinal cord may lead to clinical improvement.

By MRI, a myelomalacic cord typically reveals abnormal hypointcnsc signal that is greater in intensity than the CSF on Tl-weighted images (Figure 37A.84). T2-weightcd images reveal corresponding hyperintensity within the spinal cord. The proton density sequence may be helpful when there is difficulty distinguishing between myelomalacia and a spinal cord cyst. Myelomalacia does not parallel CSF and reveals isointense to hyperintcnsc signal change relative to normal spinal cord on the proton density images. The margins of a myelomalacic cord also are usually irregular and ill defined. A myelomalacic cord may be normal in size, atrophic, or expanded.

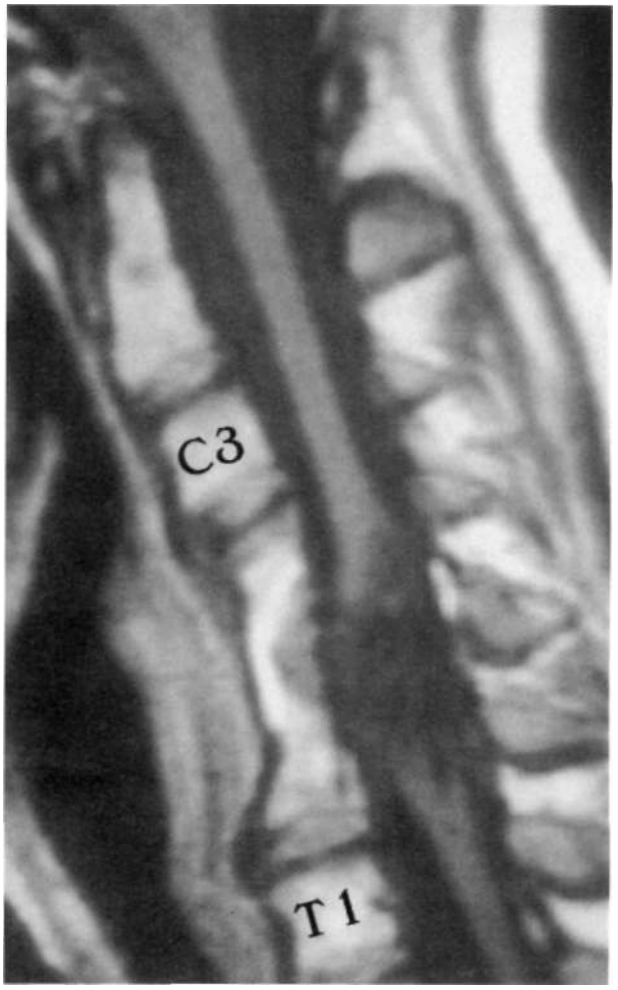


FIGURE 37A.84 Post-trauma tic myelomalacia. Sagittal Tl-weighted magnetic resonance image shows postsurgical anterior cervical decompression and fusion from C4 through C6. The cord at C5 appears expanded, with an ill-defined hypointensity. The differential diagnosis was between a post-traumatic syrinx and a microcystis myelomalacia with tethering of the cord anteriorly and posteriorly to the surrounding dura.

Thoracolumbar Trauma. Fractures of the thoracolumbar spine are second in frequency to fractures of the cervical spine. Thoracolumbar fractures make up one third of spinal fractures.

Fractures of the Upper Thoracic Spine (Tl to T10). Fractures of the upper thoracic spine are different from other levels of spinal fractures because they are stable: The rib cage and the strong attaching costovertebral ligaments limit the degree of motion of this segment of the spine. The most common type of fracture that occurs in the upper thoracic spine is the compression or axial loading fracture, which leads to different degrees of anterior wedging of the vertebral body affected. When neurological deficit occurs, it usually is caused by cord compression secondary to the presence of retropulsed bone in the spinal canal. Alternatively, the cord may be compressed by herniated nucleus pulposus or epidural hematomas.

In addition to the anterior wedging fractures, the upper thoracic spine may be affected by burst fractures, usually secondary to a severe axial loading force applied to the vertebra. Burst fractures of the upper thoracic spine may have associated fractures of the posterior neural arch {Figure 37A.85). Any comminuted retropulsed bone fragment can cause cord compression or cord maceration, a finding that is well demonstrated on MRI.

A third type of post-traumatic upper thoracic spine fracture is the sagittal slice fracture, in which the vertebra above telescopes into the vertebra below with secondary displacement of the latter.

Although most upper thoracic spine fractures are stable, instability necessitating surgical correction is seen in instances of complete dislocations, kyphosis greater than 40 degrees, progressive kyphosis, persistent pain, and progressive neurological deficits. Another indication for surgical intervention in patients with upper thoracic fractures is MRI demonstration of disruption of the spina! supporting ligaments. In the setting of acute trauma, radiographics! findings suggestive of spinal instability include vertebral subluxation, widening of the interspinous or interlaminar distance, disruption of the posterior body line, and vertebral wedging greater than 40%.

Fractures of the Thoracolumbar function (Tl 1 to L2). The thoracolumbar junction is one of the areas most commonly affected during spinal trauma. Most thoracolumbar injuries occur between T12 and L2, the area of transition between a stiff and more mobile segment of the spine. Several authors have creared a mechanistic classification for the thoracolumbar fractures. This classification divides the vertebra into three main regions: the anterior column, middle column, and posterior column (the "three-column" concept}. The anterior column is composed of the anterior longitudinal ligament, the anterior annulus fibrous, and the anterior vertebral body. The middle column

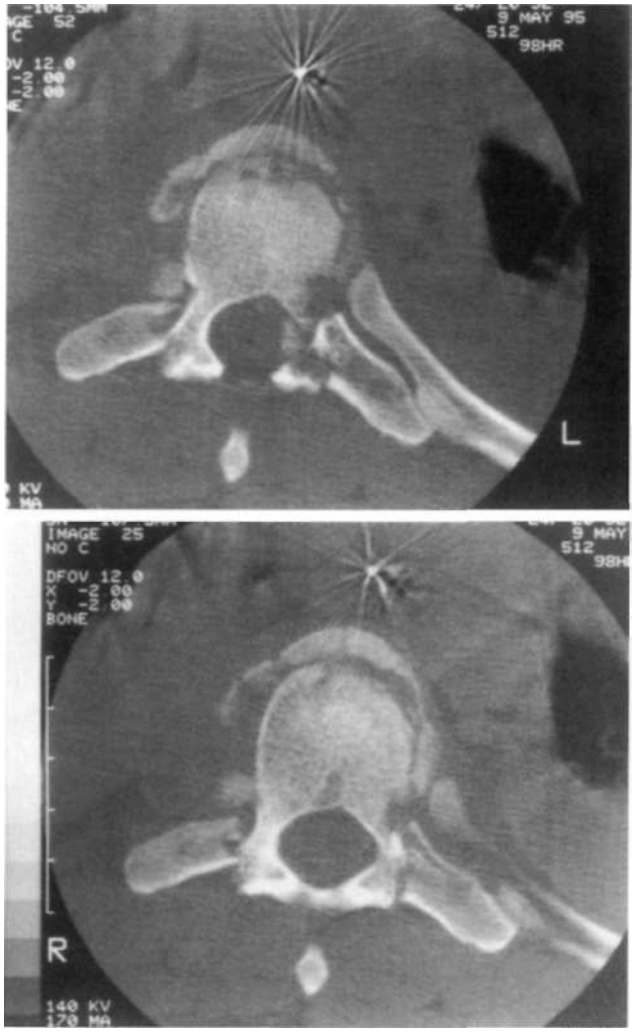


FIGURE 37A.85 Male patient involved in a motor vehicle accident. Two contiguous axial cuts (bone windows! through '17 show the severe nature of the fracture. The burst fracture is associated with fracture of the posterior arch and costotransverse process. There is mild compromise of the canal. (Reprinted with permission from Ruiz, A., Post, J. D., 8c Sklar, E. M. L. 1996, "Traumatic thoracic and lumbar fractures," *Appl Radiol,* Oct, pp. 49-57.)

consists of the posterior longitudinal ligament and the posterior annulus fibrous. The posterior column consists of all structures behind the posterior longitudinal ligament (neural arch). The main purpose of this classification is to predict the stability and neurological sequelae of the fractures of the thoracolumbar region. An intact middle column implies stability and vice versa. Fractures of the anterior column rarely are associated with a neurological deficit.

Three basic forces act to injure the middle column: axial compression, axial distraction, and lateral translation. These vectors of force are applied in the *x*-, *y*-, or ?-axis of the spine, producing the following types of injuries.

Hyperflexion Injuries, Hyperflexion injuries are the most common type of injury affecting the thoracolumbar spine. The anterior column is compressed, whereas the posterior elements arc distracted. There are several types of hypcrflcxion injuries. Hyperflexion compression fractures (Figure 37A.86) commonly affect T12, LI, and L2. The compression force can occur anteriorly or laterally, which becomes manifest on radiography or MRI by loss of height of the vertebral body anteriorly or laterally. There is focal kyphosis and scoliosis, fracture, or all three, usually of the

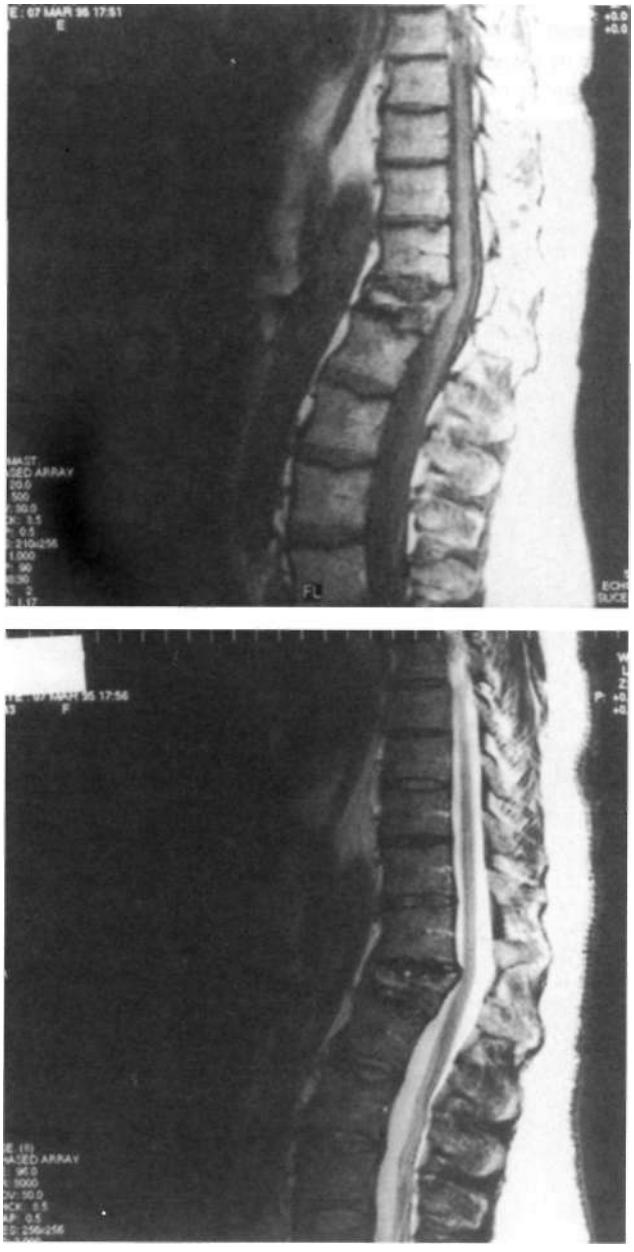


FIGURE 37A.86 Chronic hypcrflcxion compression fracture of T12. Sagirtal Tl- and T2-weighted images. There is severe loss of height of the T12 body anteriorly with associated endplatc disruption. Note the focal kyphos deformity and the degree of retropulsed bone compressing the sac and indenting the cord. (Reprinted with permission from Ruiz, A., Post, J. D., &: Sklar, E, M. I,, 1996, "Traumatic thoracic and lumbar fractures," *Appl Radiol,* Oct, pp. 49-57.)

anterosuperior endplate, and commonly a paraspinal hematoma.

Flexion distraction injury more often occurs from LI to L3. This injury may occur in two different ways. In one instance, the middle and posterior column may be disrupted by the tensional forces applied, with secondary rupture of the annulus fibrosus and subluxation. A second way this type of spinal injury occurs is when the hyperflexion is around an axis anterior to the anterior longitudinal ligament. When this occurs, the entire vertebra is pulled apart or distracted by the tensile force. This type of spinal injury leads then to what is known as a Chance fracture or seat belt injury (Figure 37A.87). Radiographics!ly, a split fracture through the spinous processes, pedicles, and laminae is demonstrated. The fracture line extends upward to involve the vertebral endplate anterior to the neural foramen. There is also severe disruption of the spinal ligaments and distraction of the intervertebral disc and facet joints. The fracture is unstable and usually associated with severe abdominal injuries.

Axial Compression Fracture. The characteristic fracture in this group is the burst fracture (Figure 37A.88). An axial

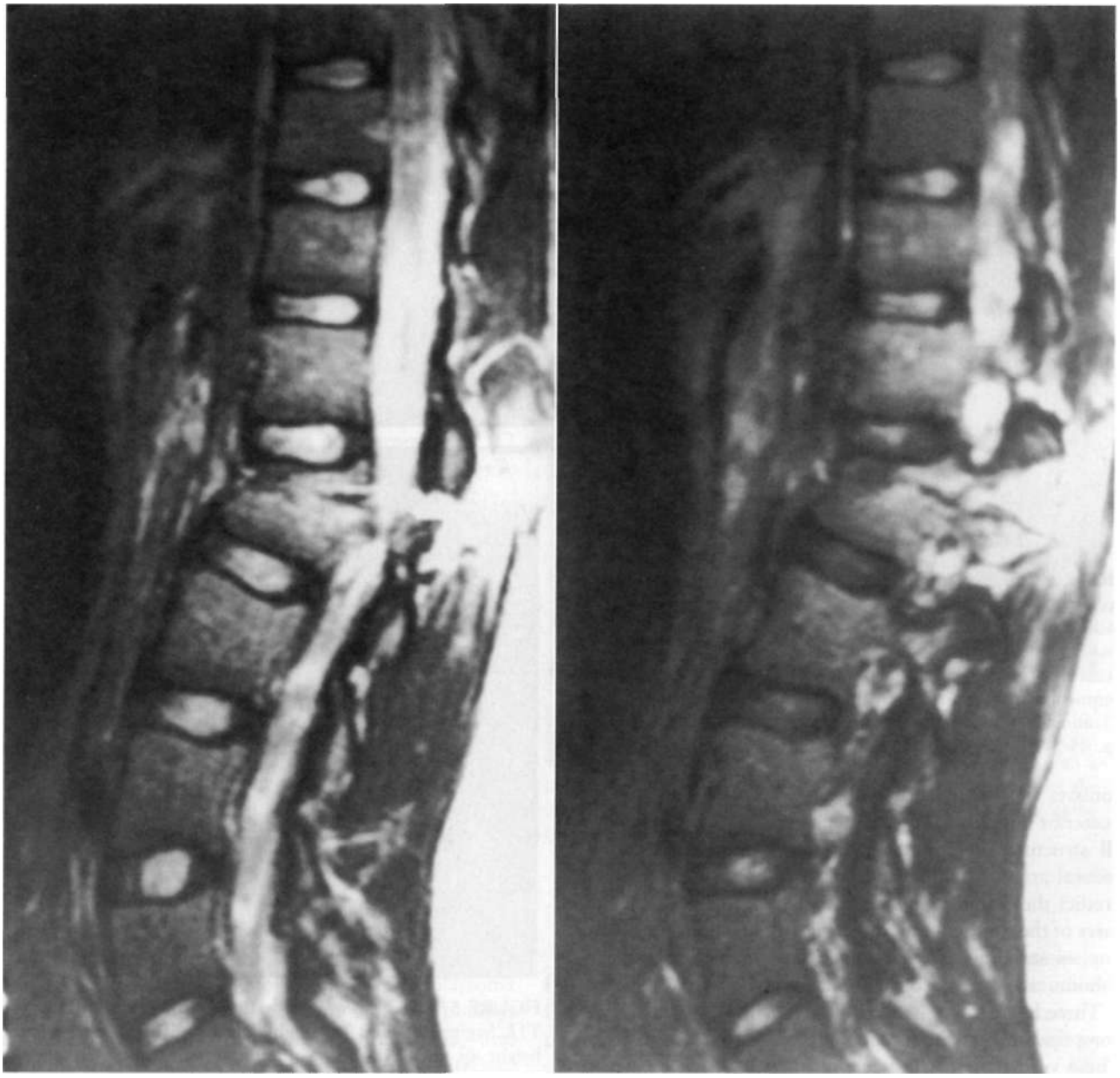


FIGURE 37A.87 Chance fractures. Female adolescent involved in a motor vehicle accident while wearing a lap seat belt. The patient sustained a flexion distraction injury. Contiguous sagittal T2-weighted images demonstrate a split fracture through the posterior elements and posterior 12 body. There is injury to the posterior spinal ligament. (Reprinted with permission from Ruiz, A., Post, J. D., 6c Sklar, E. M. L. 1996, "Traumatic thoracic and lumbar fractures," *Appl Radiol,* Oct, pp. 49-57.)

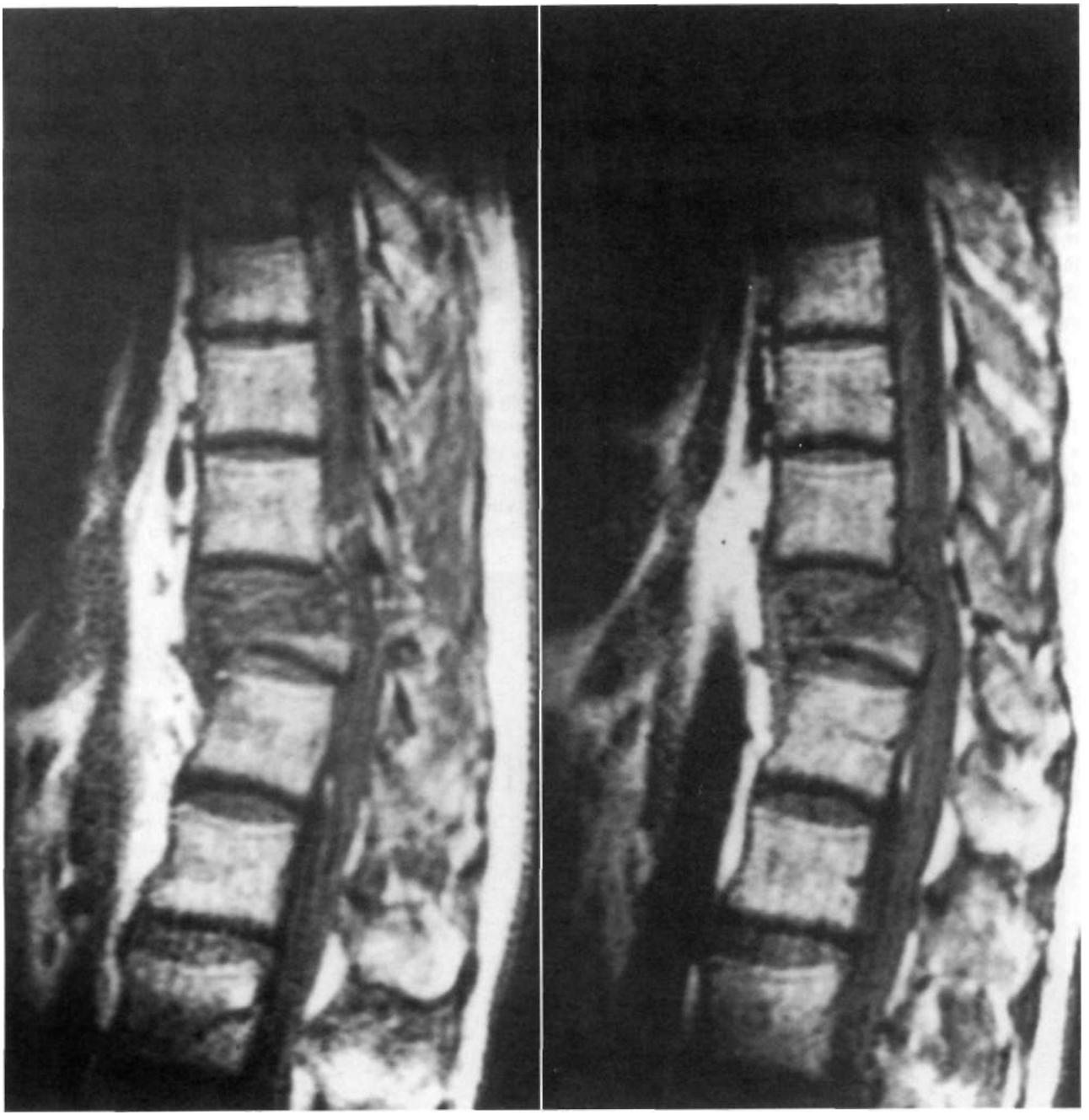


FIGURE 37A.88 Axial compression fracture of T12. Sagittal Tl-weighted images demonstrating superior endplate fracture, wedging deformity, and retropulsion of T12, severely compressing the cord. The decreased signal of T12 vertebra is caused by marrow edema. (Reprinted with permission from Ruiz, A., Post, J. D., 8; Sldar, E. M. L. 1996, "Traumatic thoracic and lumbar fractures," *Appl Radiol*, Oct, pp. 49-57.)

loading force pushes the intervertebral disc through the endplate inferiorly (vertical disc herniation) with secondary comminution of the vertebral body. Approximately 90% of burst fractures occur from T9 to L5. A second burst fracture is present in less than 10% of cases. Radiographic findings characteristic of this fracture are severe anterior vertebral body wedging, bone retropulsion with differenr degrees of neural canal narrowing, neural element compression, increased interpediculate distance, and a vertical fracture through the vertebral body, pedicle, or laminae. Depending on the degree of hone retropulsion and level of injury, different degrees of cord, conus, and cauda equina damage may be present. This injury is unstable. CTand MR! are the best modalities to evaluate this injury. The former demonstrates the degree of bony canal narrowing, whereas the latter provides the best information about the relationship between the retropulsed bone and neural elements, including level and degree of neural damage.

Extradural Lesions

Traumatic disc herniations can occur at the cervical, thoracic, and lumbosacral levels. The thoracic spine is not affected often because the rib cage and thoracic muscles protect this patt of the spine. A herniated disc may be unrecognized if CT or MRI is not used. In patients with fractures or dislocations who are to undergo stabilization, the discovery of one associated herniated disc may indicate the need for a prompt surgical intervention, specifically a decomptession discectomy and fusion.

Spinal epidural hematomas may produce spinal cord and or cauda equina compression. The clinical presentation is that of a sudden acute back or neck pain followed by sensory and motor deficits wirh progression to paraplegia or quadriplegia. Although epidural hemorrhage in the spinal canal has been regarded in the literature as uncommon, with the availability of MRI, this diagnosis is being made mote often. These hematomas may show some compression of the thecal sac and compression of the spinal cotd (Figutc 37A.89). They show variable signal intensity. MRI is an excellent

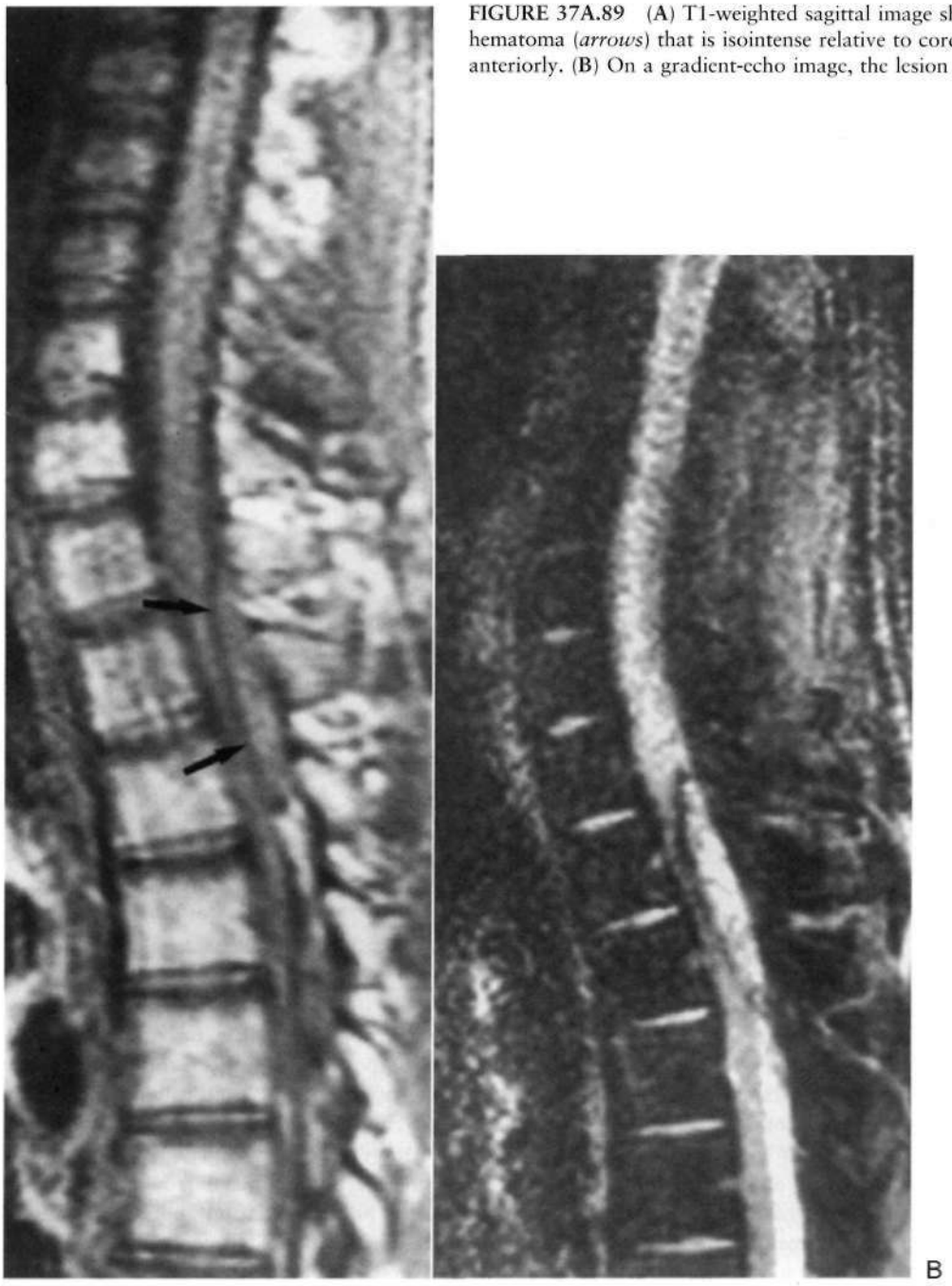


FIGURE 37A.89 (A) T1-weighted sagittal image shows an acute epidural hematoma (*arrows*) that is isointense relative to cord, displacing the sac anteriorly. (B) On a gradient-echo image, the lesion becomes hyperintense.

modality for making the diagnosis ol spinal epidural hematomas.

Chronic Sequelae of Trauma. Post-traumatic spinal cord cysts and myelomalacia can occur in the thoracic spine and in the cervical region. Subarachnoid cysts may follow trauma, and the definitive diagnosis is difficult. Prom our experience, MRI appears to be the most efficient study in diagnosing and characterizing acquired subarachnoid cysts and associated abnormalities.

Infection of the Spine. Infections of the spine often involve the vertebral body or disc space. The organism most often implicated is *Staphylococcus aureus,* responsible for 60% of such infections, even in patients with AIDS. Although CT is useful in detecting bone destruction associated with vertebral osteomyelitis, its depiction of the intraspinal soft tissue structures is limited. Because MRI detects bony changes earlier and shows associated soft tissue abnormalities, it is the imaging study of choice for evaluating inflammatory disease of the spine.

Discitis and Vertebral Osteomyelitis

Pyogenic Infections. Pyogenic infections have a peak incidence in the sixth to seventh decades. Infectious spondylitis involves both the vertebral body and adjacent disc space. The most common site of pyogenic infection is the cancellous bone adjacent to the endplate because of its rich vascularity. The infection then spreads into the disc space. Two thirds of patients have infection limited to the disc space and the adjacent vertebral bodies, and one fourth have involvement at more than one level. MRI detects infection earlier than other imaging modalities. The replacement of marrow by inflammatory tissue is seen as abnormally low signal intensity in the vertebral body on Tl-weighted images (Figure 37A.90). Disc space involvement usually is seen as narrowing of the disc space and a slight loss of signal of the nucleus pulposus on Tl-weighted images and high-intensity signal in the disc on T2-weigh ted images. In many patients these changes in the bone and disc are associated with adjacent inflammatory tissue anteriorly or posteriorly in the epidural space of the spinal canal. After contrast administration, enhancement is seen in the infected disc space and vertebral bodies.

Tuberculous Infections. The most common site of infection of tuberculous spondylitis is at LI; it is much less common in the cervical and sacral regions. Classically, spinal tuberculosis is thought to begin in the anteroinferior portion of the vertebral body. The infection can spread beneath the anterior longitudinal ligament involving adjacent vertebral bodies. Bone destruction typically is more extensive than in pyogenic infections. Contiguous vertebral body involvement with destruction of the disc occurs in one half of cases, and spread of infection beneath the anterior [ongirndin.il ligament may involve noncontiguous vertebral bodies. This multiplicity of vertebral body involvement sometimes makes differentiation from metastatic disease difficult. Paraspinal infection and gibbus deformity are common in tuberculous spondylitis. The size of the paraspinal lesion has been noted to be generally larger in tuberculosis than in pyogenic infections. These paravertebral ahscesses may calcify and thus may be better identified on CT.

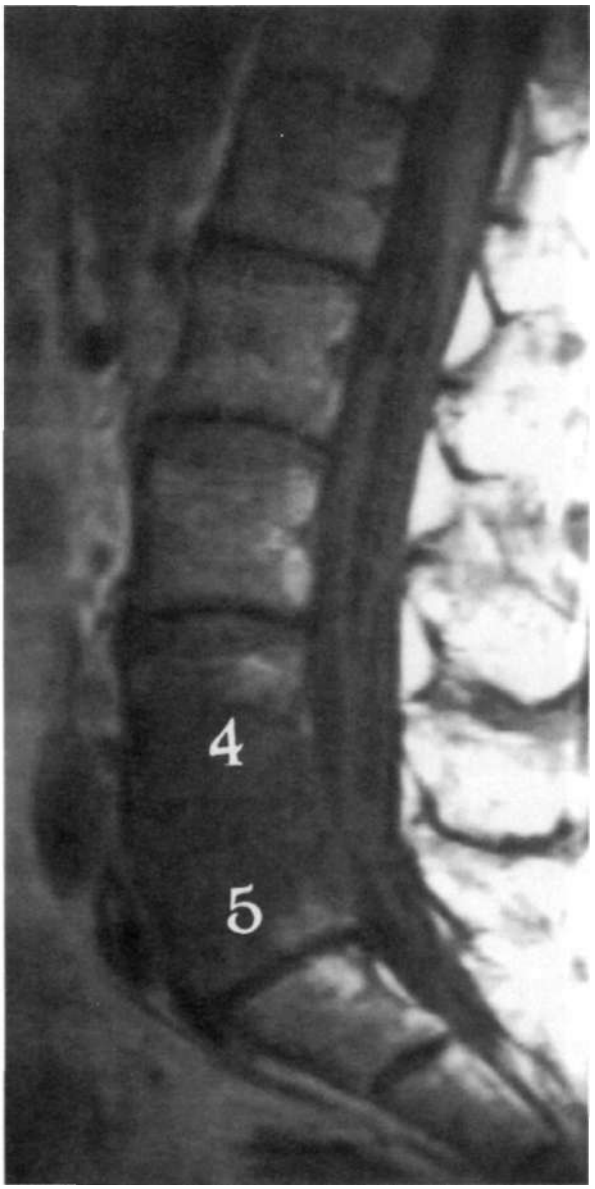


FIGURE 37A.90 Disc space infection. L4-L.S disc space infection in a 65-year-old intravenous drug abuser with blood cultures positive for *Staphylococcus aureus.* Magnetic resonance imaging scans reveal changes consistent with disc space infection and osteomyelitis at L4-L5. (A) Tl-weighted image shows abnormal low signal in the 14 and 15 bodies. *Continued*

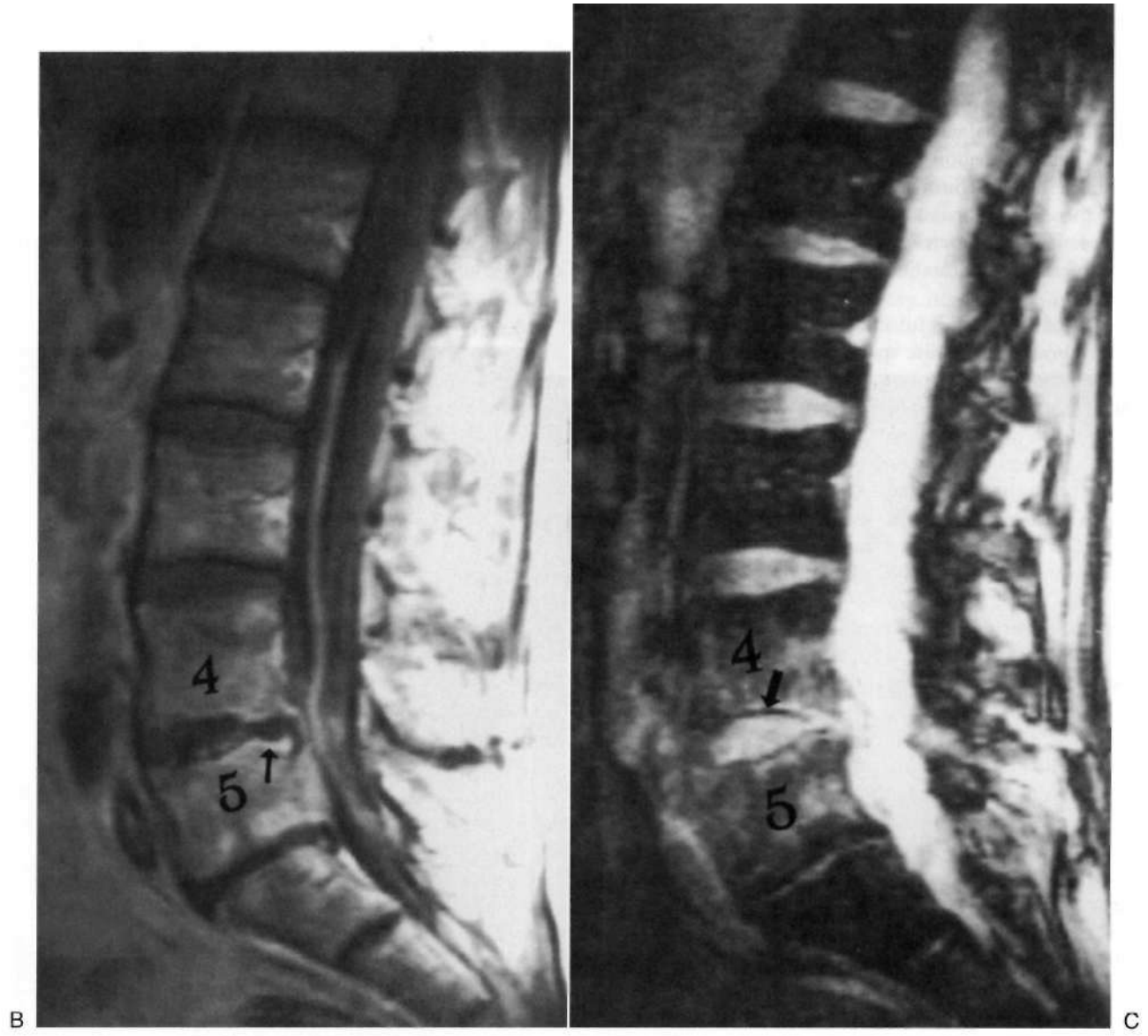


FIGURE 37A.90, cont'd. (B) Postcontrast-enhanced T1-weighted image demonstrates linear enhancement of the L4–L5 disc (*arrow*) and some epidural enhancement. (C) The T2-weighted image shows a uniform hyperintense signal in the disc (*arrow*) with absence of the normal low-signal intranuclear cleft (compare with the other disc spaces).

Epidural Abscess. An epidural abscess, although an uncommon entity when not associated with osteomyelitis or discitis, is important to recognize because early diagnosis greatly improves patient outcome. MRI generally facilitates the diagnosis and may be positive earlier than a radionuclide scan. Early diagnosis is important because timely decompression can save neurological function.

Flexion-rotation injury is unusual but very unstable and often associated with severe neurological damage and sequelae such as paraplegia. The anterior column is compressed during rotation, whereas the middle and posterior columns are disrupted by tensional forces. Subluxation and dislocation are common imaging findings as are widening of the intcrspinous distance and fractures of the laminae and transverse processes, facets, and adjacent ribs

Although MRI and CT myelography are equally sensitive (91% and 92%, respectively) in detecting epidural abscesses, MRI offers the advantage of distinguishing epidural abscesses from other entities, such as herniated discs, spinal tumor, or spinal hematoma (Sklar et al. 1993). Another advantage of MRI over CT myelography is its noninvasive nature, avoiding the potential of spreading the infection and producing meningitis via the spinal puncture needed for myelography. On plain MRI, an epidural abscess appears as a mass that is isointense to spinal cord on Tl-weighted images and often has high-intensity signal on T2-wcighrcd images. The epidural abscess may go

unrecognized if its signal is similar to that of adjacent CSF. With contrast enhancement, however, an epidural abscess can be delineated clearly on MRI. Most epidural abscesses enhance in a homogeneous fashion, occur adjacent to an infected disc space level, and involve two to four spinal segments. The organism most commonly responsible for epidural abscesses is *S, aureus,* as in vertebral osteomyelitis.

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Chapter 37
Neuroimaging

B. COMPUTED TOMOGRAPHIC AND MAGNETIC RESONANCE VASCULAR IMAGING

Brian C. Bowen, Gaurav Saigal, and Armando Ruiz

For the past decade, a major focus of neuroimaging has been the development of noninvasive methods far delecting vascular disease. Three techniques, magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and Doppler sonography (DS), are now used commonly in clinical practice and have progressed to the point that, individually or in combination, these techniques rival catheter angiography in accuracy of detection of certain vascular lesions, such as extracranial carotid stenosis or dural venous sinus thrombosis. Although MRA has been applied more extensively than CTA, the use of CTA is growing rapidly because of the availability of helical computed tomography (CT) scanners. CTA has achieved results comparable to those of MRA in detecting cervical carotid stenosis and intracranial aneurysms (White et ai. 2001; Randoux et al, 2001).

MAGNETIC RESONANCE ANGIOGRAPHY

Traditional Methods

In general, two methods that do not include an injectable contrast agent have been used to generate contrast between flowing blood in a vessel and surrounding stationary tissues. The first and most commonly used method is rime-of-flight (TOF) MRA, and the second is phase contrast (PC) MRA. In both methods, hydrogen nuclei (protons) in a selected volume of interest are excited using a radio-frequency (RF) pulse, which is typically part of a gradient-recalled echo pulse sequence. Before excitation, the nuclei have a net longitudinal magnetization parallel to the main magnetic field. After excitation, the magnetization has been tipped through a small angle (typically 10-40 degrees) so that it now has two components: a transverse magnetization, which produces the detectable magnetic resonance (MR) signal, and some residual longitudinal magnetization. The transverse magnetization is defined by two properties: its magnitude and its orientation (or phase angle). The magnitude produced by nuclei in flowing blood (moving or flowing nuclei) can be made to differ from that produced by nuclei in the adjacent stationary tissue (stationary nuclei). This difference is the basis for vascular contrast in TOF MRA. Alternatively, the orientation produced by flowing nuclei can be made to differ from that of stationary nuclei using a directional flow-encoding magnetic field gradient. This is the basis for vascular contrast in PC MRA.

The difference in magnitude, and hence signal, for flowing nuclei and stationary nuclei in TOF MRA results from the following effects. The stationary nuclei remain in the volume of interest throughout the time of the MR scan and arc repeatedly exposed to an RF excitation pulse at short intervals (recovery time [TR] less than 50 milli-seconds). After a few excitations, the longitudinal magnetization of the stationary nuclei is reduced significantly to a steady-state value, well below the initial value. Consequently, the magnitude of the transverse magnetization on successive excitations is small, resulting in an MR signal from stationary tissue that is markedly reduced, or saturated. Flowing nuclei, on the other hand, do not remain in the volume of interest. Because of continual wash-in and wash-out, the flowing nuclei experience only one or a few excitations (Plate 37B.I). The MR signal from flowing blood therefore is unsaturated (appearing bright on the **MRA** image) and greater than that of stationary tissue (appearing dark). The gradient-recalled echo pulse sequence

parameters that primarily affect vascular signal are the TR and the flip angle. As noted previously, the MR signal also depends on the phase of the transverse magnetization. The TOF method minimizes this dependence by using pulse sequences that compensate for the phase variation caused by position or velocity and by sampling the MR signal as soon as possible after excitation (echo delay time |TE] less than 7 milliseconds}.

In PC MRA, a magnetic field gradient is used to sensitize the phase of the transverse magnetization to the motion (velocity) of flowing nuclei. Two data sets are acquired with opposite sensitization and then subtracted to produce an image. For stationary nuclei, the net phase is zero, and their signal is eliminated in the final image. However, flowing nuclei move from one position in the field gradient to another between the time of the first sensitization and that of the second sensitization. Because phase varies with position in the field, the net phase after subtraction of the two data sets is nonzero, and there is residual signal from flowing blood (Figure 37B.1). To fully characterize the moving nuclei in three dimensions, flow-encoding (sensitizing) gradients must be applied along each of three orthogonal axes (e.g., superior-inferior, right-left, and anterior-posterior). The pulse sequences used in PC studies are designed to impart a phase shift that is proportional to the velocity of the moving nuclei. This phase shift must be between -180 and +180 degrees, and the larger the phase shift within this range, the greatet the vascular signal. Thus before PC angiography data are acquited, the anticipated maximum blood flow velocity (VENC) must be enteted into the pulse sequence protocol. If the flowing blood has velocities that ate the same as or slightly less than the selected VENC, optimal vascular signal results. Blood flow velocities gfcatet than VENC can produce aliasing artifacts, whereas velocities much smaller than VENC tcsult in a weak signal. Saturation effects are less in PC MRA than in TOF MRA because even heavily saturated nuclei in flowing blood generate a phase angle that is latget than that of stationary nuclei.

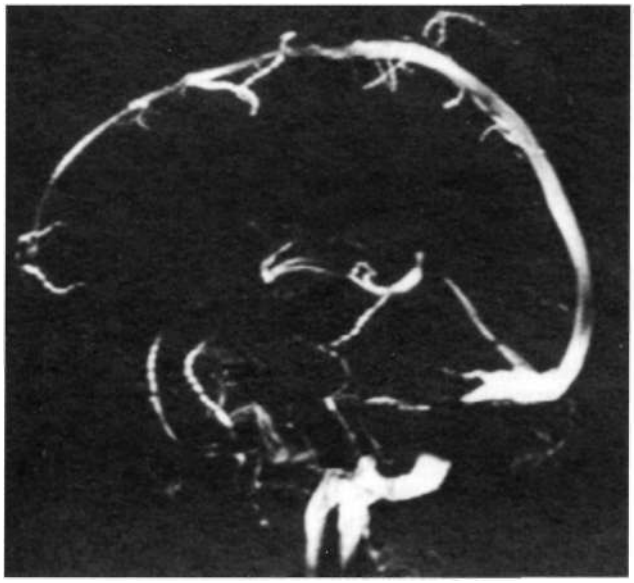


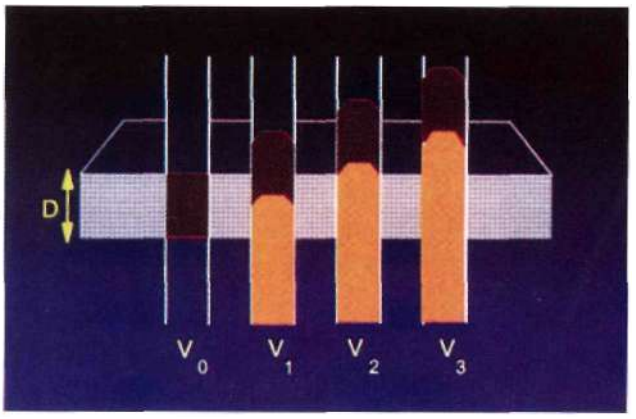
FIGURE 37B.1 Phase contrast method. Flow in the superior sagittal sinus produces bright signal against a dark background of stationary tissue. Elow-encoding gradients were applied along all three axes, with an estimated maximum blood flow velocity of 10 cm per second. The sinus, which has predominantly anterior-posterior and superior-inferior (low, and the cerebral veins, which drain into it and have predominantly right-left flow, all appear bright.

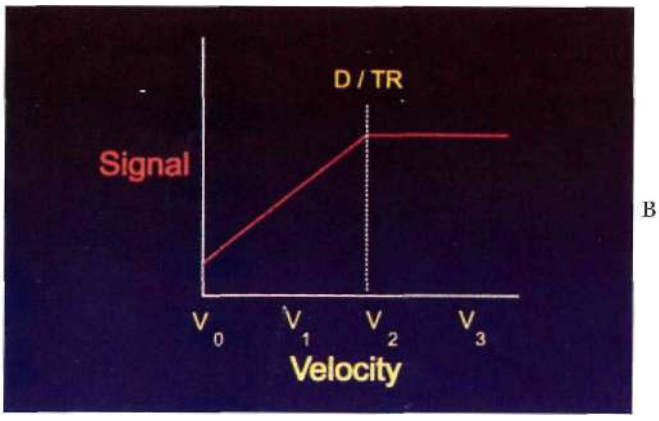
For both the TOF and PC methods, there are two apptoaches to data acquisition and image reconstruction: two-dimensional (2D) and three-dimensional (3D) Fourier transformation techniques. In 2D TOF MRA, a section (approximately 1,5 mm thick) of tissue is excited, the signal data are acquired, and the image is reconstructed. This process is tepcatcd multiple times as sequential sections (typically mote than 50 sections) are acquired, until the volume of interest has been covered (Figure 37B.2), Ideally, the plane of each section is approximately perpendicular to the vessels of interest so that there is inflow of fresh, unsaturated nuclei into each section. This results in high intravascular signal and good sensitivity to slow flow. This method is useful fot differentiating between slow flow and occlusion. If a long segment of the vessel of intetest lies in the section, however, thete can be satutation of the flowing blood and nonvisualization of the vessel.

In 3D TOF MRA, a slab that is a few centimeters thick is excited and partitioned into thin sections (approximately 0.7-0.8 mm). On reconstruction of the 3D data set, a stack of images (partitions or soutce images) is generated (Figure 37B.3). Because these sections ate thinner than the 2D sections, the 3D TOF method has better spatial resolution and is more useful for imaging tortuous and small vessels (e.g., inttactanial arteries). A disadvantage of the 3D method is that flowing blood spends more time in the slab than that in a 2D TOF individual section. Consequently, a vessel passing through the slab may have good vascular contrast on enteting the slab but become barely visible near its exit from the slab. To lessen this saturation effect, multiple thin slabs are used to covet a large region of interest. Additional modifications of the basic 3D TOF method that have been implemented on various MR scanners to improve vessel detection or reduce artifacts include magnetization transfer suppression of stationary tissue, a ramped or tilted optimized nonsaturating excitation (TONE) RF pulse (Atkinson et al. 1994), and a sliding interleaved k_Y acquisition (SLINKY; Liu et al. 1999).

Both the 2D and 3D TOF methods have the disadvantage that stationaty material with high signal intensity, such as subacute thrombus, can mimic blood flow. PC methods are useful in this situation because the high signal from stationaty tissue is eliminated when the two data sets are subtracted to produce the final flow-sensitive images.

A





B

PLATE 37B.I Time-of-flight method. (A) The section (or slab) to be imaged has thickness D. The flowing blood in a vessel that traverses the section may have a mean velocity as low as V_0 (no blood flow) or as high as V_3. At a higher velocity, there is greater wash-in of unsaturated blood *(orange)* and wash-out of partially saturated blood *(brown).* Stationary tissue *(cross-hatched region)* remains in the section and becomes saturated after several radio frequency excitations. (B) As mean blood flow velocity increases, the signal intensity of the vessel increases. Maximum signal is attained at Vi, which corresponds to complete replenishment of the blood in the section in the time (TR) between radio frequency excitations.

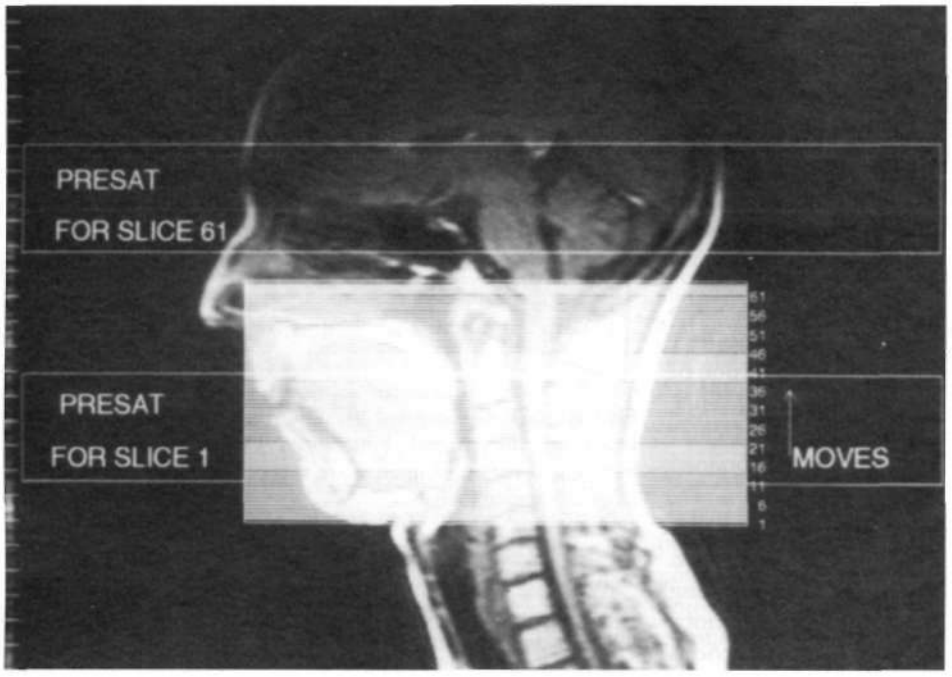


FIGURE 37B.2 Two-dimensional time-of-flight magnetic resonance angiography. Axial (transverse) sections are acquired one at a time from the region of the carotid bifurcation to the skull base. A presaturation band (PRF.SAT) is applied at a set distance above each section as it is acquired and thus "travels" with the section. Signal from the internal jugular veins is suppressed, whereas signal in the carotid and vertebtal arteries is bright.

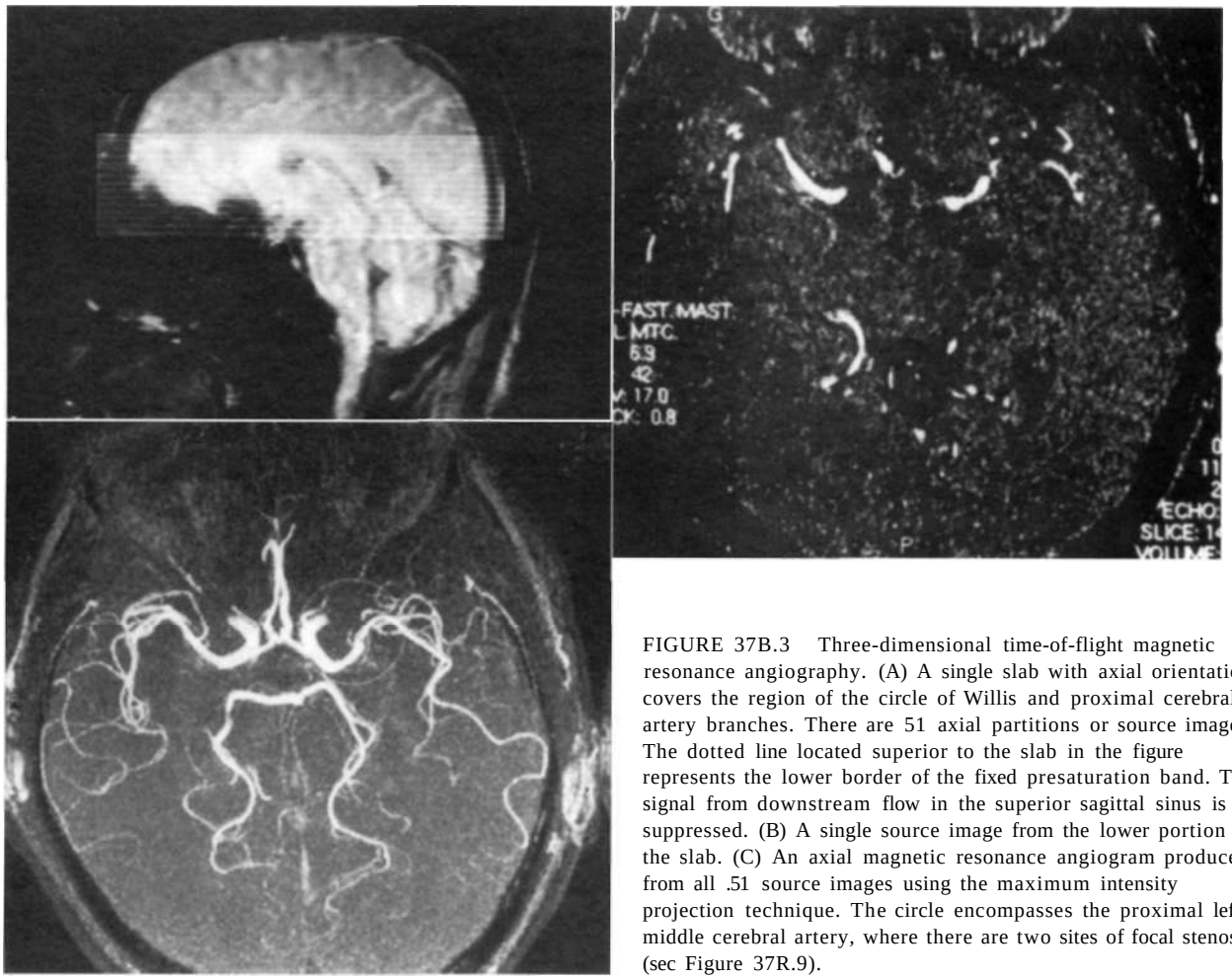


FIGURE 37B.3 Three-dimensional time-of-flight magnetic resonance angiography. (A) A single slab with axial orientation covers the region of the circle of Willis and proximal cerebral artery branches. There are 51 axial partitions or source images. The dotted line located superior to the slab in the figure represents the lower border of the fixed presaturation band. The signal from downstream flow in the superior sagittal sinus is suppressed. (B) A single source image from the lower portion of the slab. (C) An axial magnetic resonance angiogram produced from all .51 source images using the maximum intensity projection technique. The circle encompasses the proximal left middle cerebral artery, where there are two sites of focal stenosis (sec Figure 37R.9).

The PC method also incorporates 2D and 3D Fourier transformation techniques to generate images with vascular contrast. In the 2D PC technique, flow-encoding gradients are applied along two or three axes (see Figure 37B.1). A projection image displaying the vessel against a featureless hackground is produced. As described previously, PC studies are less sensitive to saturation effects than TOF studies. Therefore slow blood flow is more easily detected as long as an appropriately low VF.NC has been selected for the data acquisition. The most common applications of the 2D PC method include rapid acquisition of a localizer image of the carotid bifurcation in the neck and detection of flow in the superior sagittal (or other dural venous) sinus, or in the circle of Willis, in patients with suspected vascular occlusion. IntonthHion on flow dynamics can be obtained by acquiring cardiac-gated 2D images, called cine PC MRA. Compared with the 2D techniques, 3D PC MRA provides higher spatial resolution and information on flow directionality along each of three flow-encoding axes (superior-inferior, right-left, and anterior-posterior). The summed information from all three flow directions is displayed as a speed image, in which the signal intensity is proportional to the magnitude of the flow velocity. In general, the 3D PC method has been used less often in clinical studies than the 3D TOF method, primarily because of the longer time needed for data acquisition and uncertainties associated with the choice of VENC.

The data set that is acquired in a 3D TOF, 3D PC, or sequential 2D TOF study may be envisioned as a 3D array of pixels corresponding to the stack of partitions or sections. To display the course of a vessel, the hyperintense signal from the vessel-containing pixels is mapped onto a desired viewing plane using a maximum intensity projection (MIP) algorithm, producing a projection image. To obtain an overview of the vascular architecture, MIP images are generated in several viewing planes and then evaluated together. Targeted MIP images are produced from a region of interest within the full 3D volume (Figure 37B.4). On the MIP images, called *angiograms* because they show the courses of vessels, hyperintense signal from blood flow in both arteries and veins can cause confusion. To simplify interpretation in TOF studies, presaturation bands often are applied during data acquisition. Usually located on one side of the imaging volume, the presaturation band is a zone in which both flowing and stationary nuclei are saturated by an RF pulse that is added to the gradient-recalled echo pulse sequence. The downstream signal of a vessel that passes through the presaturation /one is suppressed because of the saturation of the flowing nuclei. In TOF studies, the location of the presaturation band may be fixed (see Figure 37B.3), or the presaturation band may travel, keeping the same distance from each imaging section or slab (see Figure 37B.2) as it is acquired. In general, the placement of presaturation bands can be chosen so as to identify flow directionality (e.g., subclavian steal),

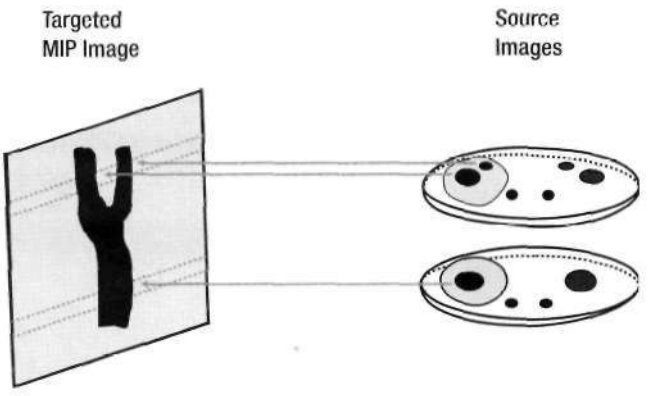


FIGURE 37B.4 Targeted maximum intensity projection (MIP) image of the carotid bifurcation. Only the vessels in the highlighted region of interest are mapped onto the viewing plane from the source images.

With the widespread clinical use of TOF MRA to assess neurovascular disease, it has become evident that two effects can limit the method's accuracy (Saloner et al. 1996}. The first effect is intravoxel phase dispersion: the presence of flowing nuclei with different phases in a single voxel. This effect is the result of a complex or disordered fluid flow pattern (acceleration, pulsatility, or turbulence). The net MR signal from the nuclei in the voxel is diminished by cancellation of the diffetcnt phases. This phenomenon is often tesponsiblc for the signal loss in an artery at a site of stenosis or marked curvature or at a bifurcation. This effect is reduced as the TE is shortened. The second effect that can limit the accuracy of the TOF method is saturation of flowing nuclei, which is most sttiking on 3D studies of small vessels. Saturation is lessened by the use of a longer TR, lower flip angle, thinner slab, or the presence of an exogenous paramagnetic contrast agent (gadolinium chelate). Gadolinium lowers the proton Tl relaxation time, preferentially increasing intravascular signal intensity for approximately 30 minutes after infusion.

3D Contrast-Enhanced MRA

The simplest type of 3D contrast-enhanced MRA (CE-MRA) uses values for TR, TE, and flip angle (e.g., 30-50 milliseconds, 5-7 milliseconds, 20 degrees) and other scan parameters that are typical of the traditional 3D TOF method and is sometimes called contrast-enhanced 3D TOF MRA. The scan time pet 3D volume is on the order of 5-10 minutes, and data are acquired in the first 10-15 minutes after the bolus infusion of a gadolinium contrasr agent (0.1-0.2 mmol per kilogram). Under these steady-state conditions, small intracranial arteries are somewhat better seen, and there is a marked improvement in the visibility of large and small veins. The use of gadolinium overcomes the problem of saturation of the slow-flowing blood in

intracranial and spinal venous structures that lie within the 3D slab. Presatu ration bands usually are ineffective at suppressing the downstream signal from vessels when gadolinium is present.

In the more technically demanding type of 3D CE-MRA (called fast, dynamic, or time-resolved CE-MRA), TR and TE are much shorter (TR less than 10 milliseconds and TF, less than 3 milliseconds), and the total scan time pet 3D volume (usually about 30-50 partitions) is reduced to 5-50 seconds, depending on hardware (gradient strength and rise time) and software (k-space sampling strategy) capabilities (Levy and Maki 1998; Melhem ct al. 1998; Golay ct al. 2001; Fain et al. 2001; Turski et al. 2001). Data are acquired as the bolus of the gadolinium contrast agent (0.2-0.3 mmol per kilogram and 2-3 mL per second infusion rate) passes through the vessels of interest, taking advantage of the marked increase in intravascular signal (first-pass method). Vessel signal is determined primarily by gadolinium concentration, analogous to conventional angiography, in which vessel detection depends on the concentration of injected contrast. Intravascular signal loss caused by phase dispersion is negligible because the TE is so short. Because the *5T*> CE-MRA method entails more tapid data acquisition, and hence higher temporal resolution, than the traditional TOF method, spatial resolution may be less; however, zero-filling of the data matrix and k-space sampling strategies, such as elliptical centric encoding with sampling of higher spatial frequencies, are used to improve vessel detail.

The 3D CE-MRA method has been applied primarily to evaluating the carotid and vertebral arteries in the neck. These ate imaged during the first pass of the gadolinium bolus, before the jugular and other neck veins are enhanced. Data acquisition in which the central lines of k space are sampled during peak arterial enhancement is key to the success of CE-MRA. The most common approaches to synchronizing the 3D data acquisition with the arrival of the gadolinium bolus in the arteries are measurement of the bolus arrival time for each patient using a small (2 mL) test dose of contrast followed by a separate 3D acquisition incorporating the appropriate time delay, automated detection of bolus attival upstream of the arterial segment of interest followed by triggering of the 3D data acquisition (Foo et al. 1997), and real-time monitoring of the bolus location by the scanner operator, who manually triggers the 3D acquisition (Fain et al. 2001). A separate approach avoids the synchronization steps by rapidly and repeatedly acquiring 3D volumes (less than 10 seconds per volume) in the neck beginning at the time of contrast bolus injection. The very rapid scan time ensures that at least one 3D volume showing only attcries will be acquired (Turski et al. 2001). For all of these techniques, both arterial and venous phase images are acquired. Subtraction of venous source images from arterial images, called digital subtraction MRA, increases vessel-to-background contrast.

APPLICATIONS

Extracranial Circulation: Carotid and Vertebral Arteries

One of the major clinical applications of MRA is the estimation of stenosis in the region of the carotid bifurcation. The attention given to this application is based primarily on the following conclusions:

- The percentage of stenosis, determined by catheter angiography using well-defined criteria, has proved effective at stratifying patients at risk for stroke in several multicentcr trials. The North American Symptomatic Carotid Endarterectomy Trial reported that recently symptomatic patients with 70-99% carotid stenosis who were treated surgically, compared with those treated medically, had an absolute risk reduction of 17% for ipsilateral stroke occurring within 2 years of treatment (Barnett et al. 1998). The European Carotid Surgery Trial showed a similar benefit (European Carotid Sutgcry Trialists Collaborative Group 1998). The Asymptomatic Carotid Atherosclerosis Study found that in asymptomatic patients with more than 60% internal carotid stenosis, carotid endarterectomy reduced stroke risk by 53% over 5 years (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study 1995).
- The risks of death and disabling stroke due to catheter angiography (1.2% in the Asymptomatic Carotid Atherosclerosis Study) can exceed those of surgery itself (1.1%).
- The accuracy of the noninvasive neurovascular imaging techniques (MRA, CTA, and DS) has steadily increased in the last decade and, for concordant MRA and DS results, approaches that of catheter angiography, the gold standard.

Time-of-FUghl MRA

Based on the results of early clinical series, several conclusions may be drawn regarding carotid bifurcation stenosis estimated from TOF MRA images (Bowen et al. 1994; Norris and Rothwcll 2001). First, the degree of stenosis tends to be overestimated by the traditional 2D TOF MRA method (Figure 37B.5). A corollary of this observation is that a 2D TOF study with normal or near normal findings effectively excludes the possibility of severe (70-99%) stenosis. The most accurate results are obtained when short TE and small voxel size are used. Second, a consensus estimate of stenosis derived from a combination of the 2D and 3D TOF methods results in greater specificity than 2D TOF alone. This improvement results primarily from the inclusion of the 3D TOF method, in which stenosis is less likely to be overestimated, particularly if original (Figure 37B.6) or reformatted source images are

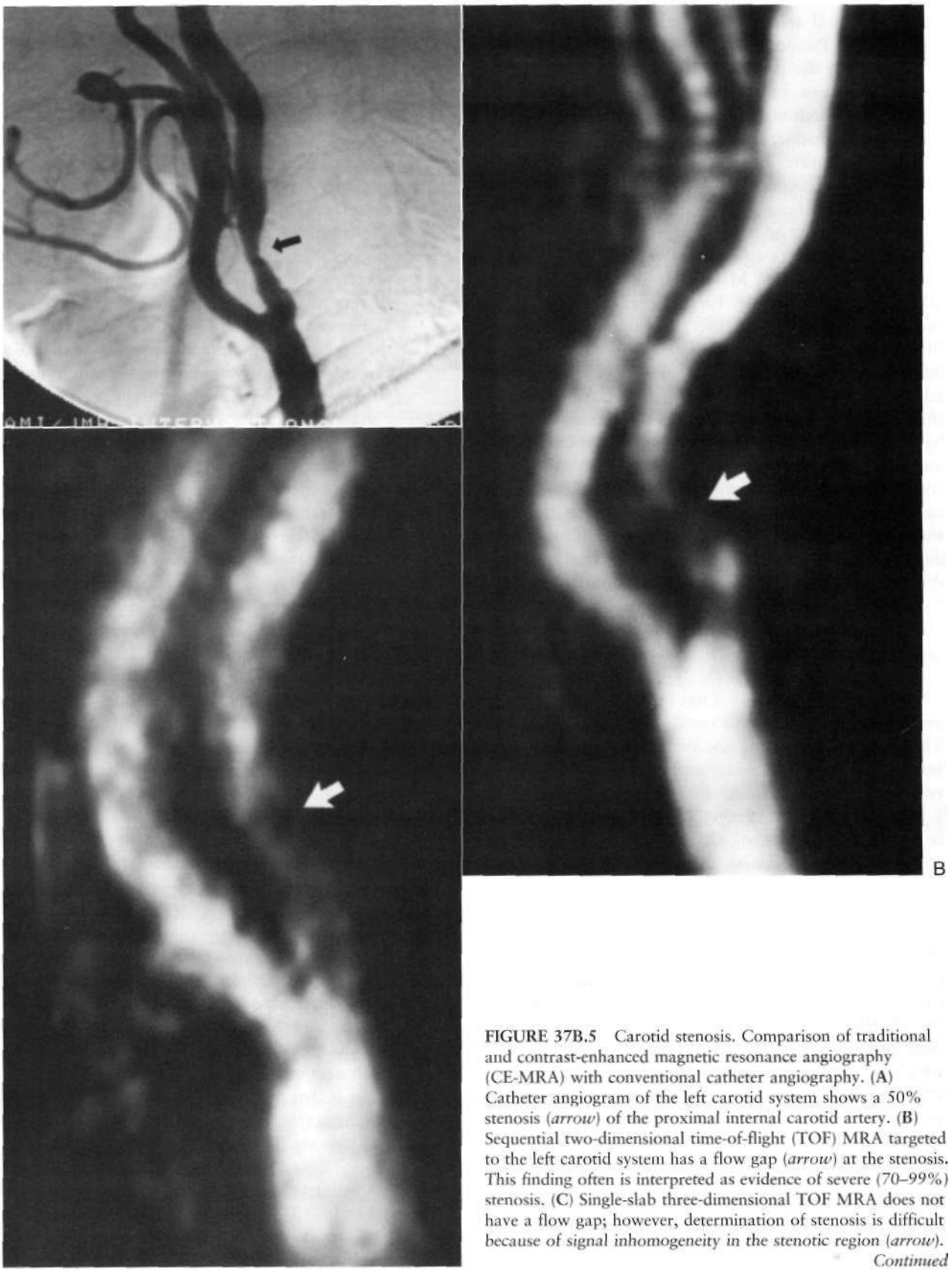


FIGURE 37B.5 Carotid stenosis. Comparison of traditional and contrast-enhanced magnetic resonance angiography (CE-MRA) with conventional catheter angiography. (**A**) Catheter angiogram of the left carotid system shows a 50% stenosis (*arrow*) of the proximal internal carotid artery. (**B**) Sequential two-dimensional time-of-flight (TOF) MRA targeted to the left carotid system has a flow gap (*arrow*) at the stenosis. This finding often is interpreted as evidence of severe (70–99%) stenosis. (**C**) Single-slab three-dimensional TOF MRA does not have a flow gap; however, determination of stenosis is difficult because of signal inhomogeneity in the stenotic region (*arrow*).

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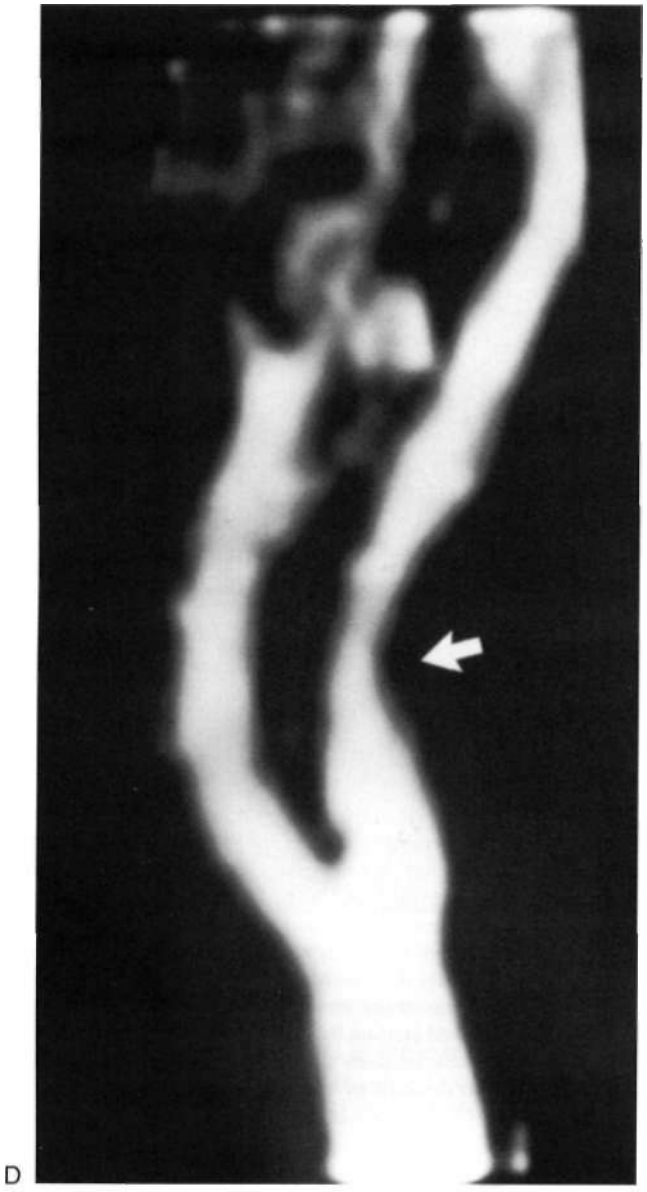


D

FIGURE 37B.5, cont'd. (D) Dynamic CE-MRA has greater vascular contrast than the two-dimensional and three-dimensional TOF techniques and demonstrates an approximately 50% stenosis *{arrow}.*

evaluated rather than the MIP images (Anderson et al. 1994). In the combined TOF approach, the 2D TOF method is used primarily to distinguish slow flow from occlusion, and in general the combined TOF approach is considered superior to DS in differentiating high-grade stenosis from occlusion. A "flow gap," which is a segmental dropout of signal from the carotid (or other vessels) caused by intravoxel phase dispersion or saturation, is often taken as a sign of stenosis measuring 70% or more. This association should be viewed with caution, however, because in one published series of patients, flow gap was observed with the 2D TOF technique at sites of 50-60% stenosis, as determined by catheter angiography (see Figure 37B.5).

Third, in detecting stenosis appropriate for carotid endarterectomy, TOF MRA is less sensitive than DS (75% MRA, 87% DS) but more specific (88% MRA, 46% DS); however, when stenosis estimates by TOF MRA and DS are concordant (Polak et al. 199.3) and then taken together, the combined MRA and DS examination is more sensitive *(96%)* and specific (85%) than either study alone. Furthermore, when patients are classified as to whether carotid endarterectomy is indicated by the noninvasive examination and then judged against the results of catheter angiography, the misclassification rate for the concordant MRA and DS results is much lower than that of cithct test alone (MRA and DS 7.9%, MRA 18%, DS 28%) (Johnston and Goldstein 2001). Therefore surgical decisions are more likely to be correct when based on concordant TOF MRA and DS results.

Three-Dimensional CE-MRA

Compared with 2D and 3D TOF MRA, 3D CE-MRA delineates carotid arterial stenosis better (Willig et al. 1998) (see Figure 37B.5). Surface morphology (e.g., ulcerated plaque) and nearly occluded vessels (e.g., "string sign") are more easily identified, and carotid arterial occlusions are more confidently identified. In recent studies, severe carotid bifurcation stenosis was detected by 3D CE-MRA with high sensitivity (93-100%) and specificity (88-96%) (Remonda et al. 2002; Johnson et al. 2000; Huston et al. 2001; Lenbart et al. 2002; Wutke et al. 2002), using conventional catheter angiography as the gold standard. Two groups of investigators have reported results for 3D CE-MRA and TOF MRA (Houston et al. 1998; Johnson et al. 2000; Huston et al. 2001). Both groups found that CE-MRA had higher sensitivity than TOF MRA in detecting severe stenosis: 93% versus 88% (Houston et al. 2001) and 94% versus 82% (Johnson et al. 2000), respectively. Specificity of CE-MRA was slightly lower thanthatofTOFMRA:88% versus 89% and 95% versus 100%, respectively. Although we are unaware of any published reports of the sensitivity, specificity, or misclassification rate (for carotid endarterectomy) based on concordant results of 3D CE-MRA and DS, such an investigation seems a likely next step in the process of evaluating noninvasive carotid imaging techniques as alternatives to conventional catheter angiography.

Atherosclerotic narrowing of the carotid system less commonly involves the intracranial carotid siphon and the origin of the common carotid artery. Tandem stenosis occurs in approximately 5% of patients with significant bifurcation disease, and the second site usually is the siphon. Although there have been no published reports documenting the accuracy with which MRA detects tandem bifurcation-siphon stenoses, it is sensible to cover the siphon in addition to the bifurcation and cervical internal

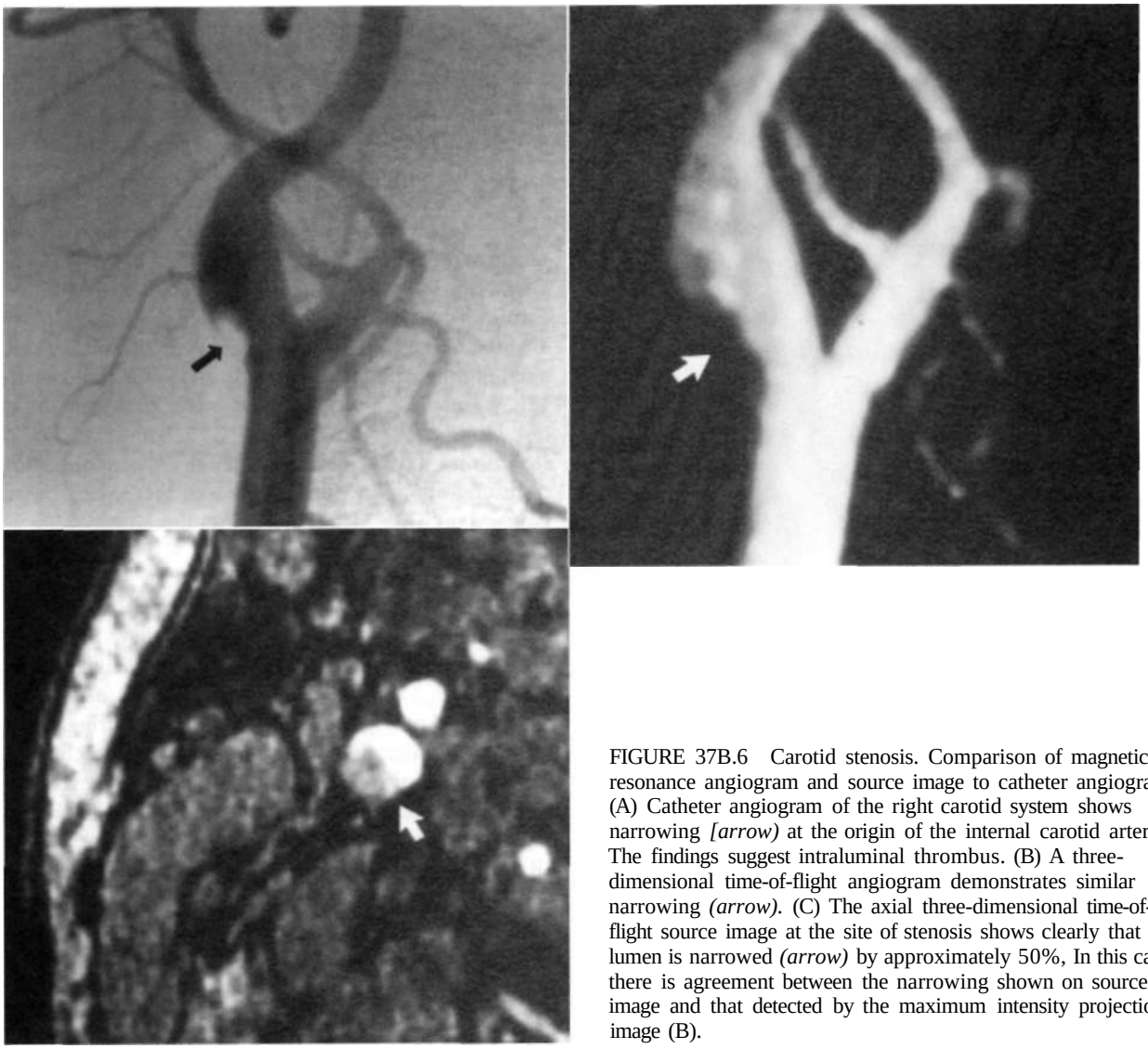


FIGURE 37B.6 Carotid stenosis. Comparison of magnetic resonance angiogram and source image to catheter angiogram. (A) Catheter angiogram of the right carotid system shows narrowing *[arrow)* at the origin of the internal carotid artery. The findings suggest intraluminal thrombus. (B) A three-dimensional time-of-flight angiogram demonstrates similar narrowing *(arrow).* (C) The axial three-dimensional time-of-flight source image at the site of stenosis shows clearly that the lumen is narrowed *(arrow)* by approximately 50%, In this case, there is agreement between the narrowing shown on source image and that detected by the maximum intensity projection image (B).

carotid artery (ICA) during preoperative screening. For 3D TOP MRA with pulse sequences designed to limit saturation effects (described earlier}, the carotid arteries may be satisfactorily imaged from the level of the midportion of rhe common carotid to the circle of Willis. The origin of the common carotid typically is omitted for several reasons, including inadequate RF coil coverage and respiratory motion artifacts. With CE-MRA the entire length of each carotid can be imaged; however, the spatial resolution may be inadequate to allow confident evaluation of even moderate stenosis of the siphons. At our institution, evaluation of the carotid system by MRA involves a 3D TOF study, using SLINKY, from the common carotid bifurcation to the circle of Willis, and a sequential 2D TOF study from the carotid bifurcation to the skull base (see Figure 37B.2). If there is a flow gap, poorly shown surface morphology, or findings indeterminate for near occlusion versus occlusion involving the bifurcation and cervical internal carotid, then a time-resolved 3D CE-MRA is done.

Atherosclerotic narrowing of the vertebral artery commonly involves the origin or distal intracranial portion. For TOF MRA evaluation of posterior circulation cerebrovascular disease, the vertebral origins usually are not evaluated, for the same reasons that the common carotid origins are nor evaluated. Typically, a 3D TOF study covering the vertebral-basilar system from the C2 level to the tip of the basilar artery is done (Wentz et al. 1994). However, sequential 2D TOF MRA of the neck is useful in determining whether proximal occlusion is present and in demonstrating flow direction in the vertebral arteries in patients with suspected subclavian steal. A 2D TOF study obtained with no presaturation band shows flow enhancement in both vertebral arteries, whereas a study obtained with a superiorly located, walking presaturation band

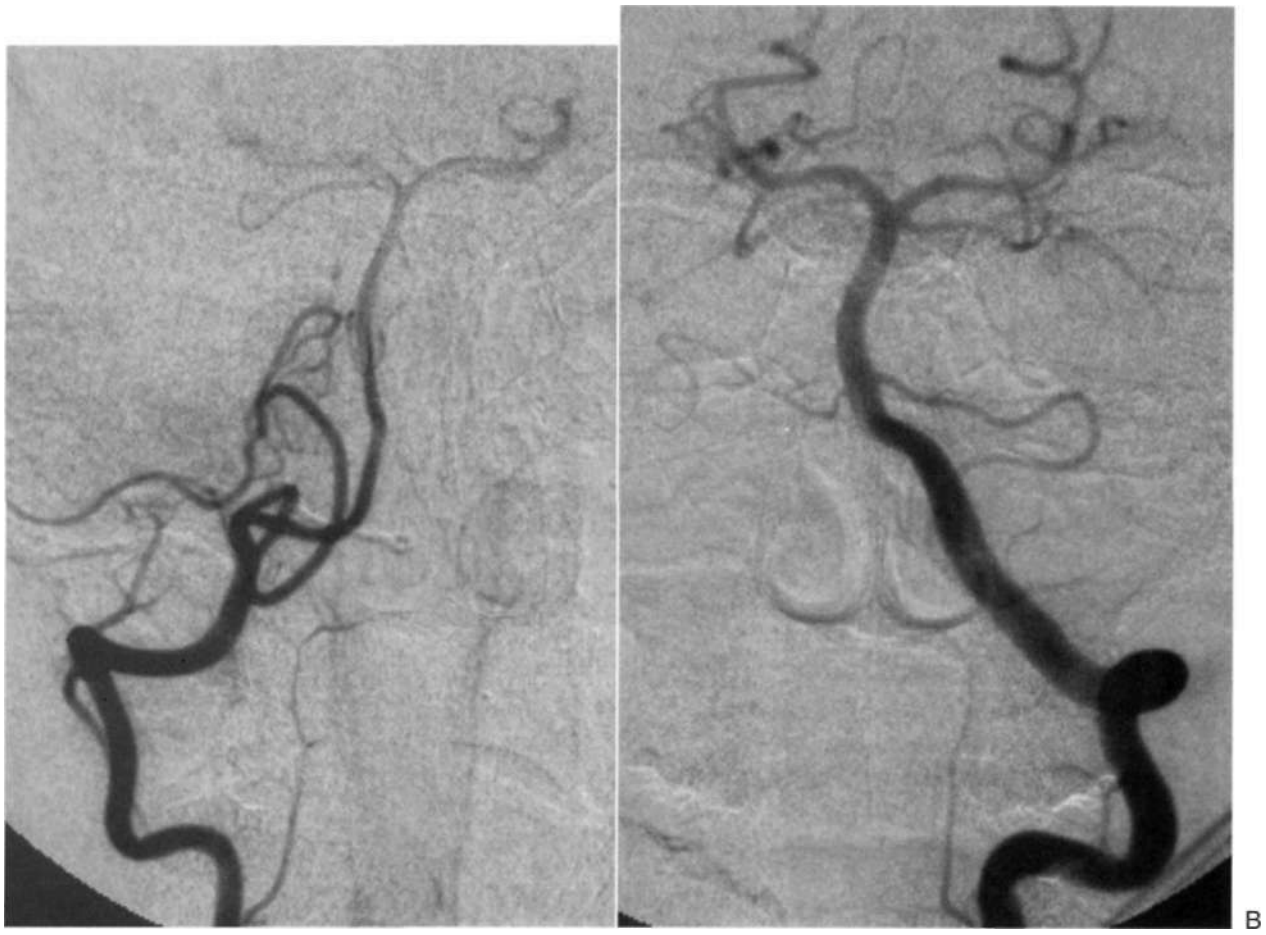


FIGURE 37B.7 Vertebral artery arrifactual signal loss. Comparison of traditional magnetic resonance angiography (MRA) and contra st-en ha need MRA (CE-MRA) with conventional catheter angiography. (A and B) Normal catheter angiograms of the right (A) and left (B) vertebral arteries. The left vertebral artery is dominant in this patient with a history of resection of a foramen magnum meningioma. *Continued*

shows flow only in the vertebral artery with normal antegrade flow. The 3D CE-MRA techniques can display both the origins and distal intracranial portions of the vertebrals in a single acquisition and are particularly useful in evaluating vertebral artery segments with partial or complete signal loss caused by slow flow and in-plane saturation effects (Figure 37B.7). The accuracy of 3D CE-MRA measurements of stenosis at the vertebral artery origin has yet to be reported, although the accuracy is unlikely to equal that of carotid bifurcation measurements because of the smaller size of the vertebral origins (Koliias et al. 1999). Nevertheless, an analysis of the elliptical centric encoding technique predicts that it can achieve an isotropic spatial resolution of 1 mm (before zero filling) in a field of view (FOV) typically used for bilateral carotid and vertebral imaging (Fain et al. 1999). Stenosis or occlusion of the subclavian artery is now routinely evaluated with 3D CE-MRA.

Carotid or vertebral artery dissection may be delected adequately using routine T1- and T2-weighted images; however, subacute, hyper intense thrombus is better seen if fat suppression is implemented on Tl-weigbted acquisitions to eliminate the high signal intensity from perivascular adipose tissue. When the evaluation includes a 2D or 3D TOF combined study or 3D CE-MRA (Koliias et al. 1999), the detection of stenosis (Figure 37B.8), pseudoaneurysm, or occlusion is improved. Also, the presence of a thrombosed false lumen is more convincingly demonstrated when spin-echo images are supplemented with PC or TOF images showing absence of flow in the false lumen.

Intracranial Circulation

Arteries

The accuracy of TOE MRA in detecting stenosis or occlusion of **the** larger intracranial vessels, compared with that of conventional catheter angiography, has been determined by several investigators (Furst ct al. 1996; Stock et a I. 1995). Initially, accuracy was limited by technical shortcomings, such as long TE, lower spatial resolution, and single slab acquisition, that permitted greater loss of vascular signal caused by inrravoxel phase dispersion,

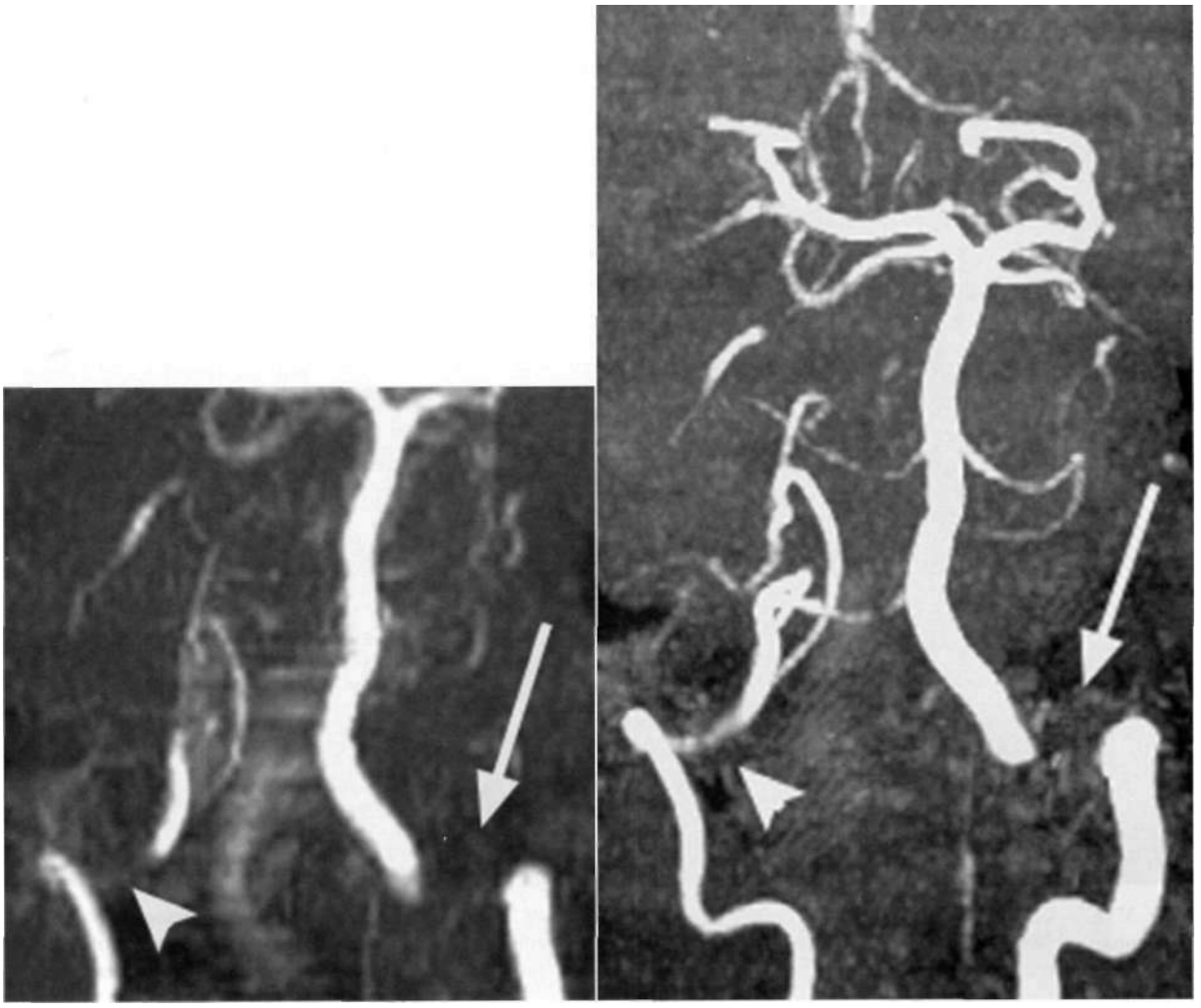


FIGURE 37B.7, cont'd. (C) Two-dimensional time of flight (TOF) MRA shows extensive signal loss involving the horizontal portions of the right *{arrowhead)* and left *(arrow*) vertebral arteries at the level of the foramen magnum. Ill-defined background hyper in ten shy medial to the arrowhead results from cerebrospinal fluid flow in the subarachnoid space. (D) Three-dimensional TOF MRA with higher spatial resolution provides better depiction of small arteries and continuity of the right vertebral artery *{arrowhead),* yet marked signal loss *(arrow)* in the left vertebral artery persists. *Continued*

susceptibility effects, and salutation effects. Signal loss was typically evident in the petrous, cavernous, and supraclinoid segments of the ICA and in the proximal Ml segment of the middle cerebral artery (MCA), Second- and third-order btanches of the cerebral arteries were poorly shown. Later, investigators reported that normal vessels and completely occluded vessels could be graded correctly, when compared with catheter angiogtaphy results; however, stenotic segments wete correctly graded (as cither less than ot more than 50% narrowing) in only about 60% of stenoses. Subsequently, technical improvements in the .3D TOF method (variable flip angle, magnetization transfer suppression, multiple thin-slab acquisitions, and higher spatial resolution [512 matrix or greatet]) improved the accuracy of stenosis grading, with investigators reporting that 80% of stenoses gteater than 70% and 88% of stenoses less than 70% are quantified correctly at MRA. The current approach to evaluating the inttactanial arteries is a multislab 3D TOF acquisition that covets the head from the foramen magnum to the roof of the thitd ventricle. Each slab has a transaxial orientation and may or may not have a superiorly located presaturation band. The axial source images and the rcprojected MIP images (Figure 37B.9) arc reviewed in conjunction with other MR images (e.g., Tl-weightcd, T2-weighted, fluid-attenuated inversion recovery, diffusion-weighted, and susceptibility-weighted [perfusion| images) in an integtated approach to characterizing brain infarction (Wittsack et al. 2002). In the setting of acute infarction with the potential for thrombolytic treatment, protocols often include a rapidly acquired

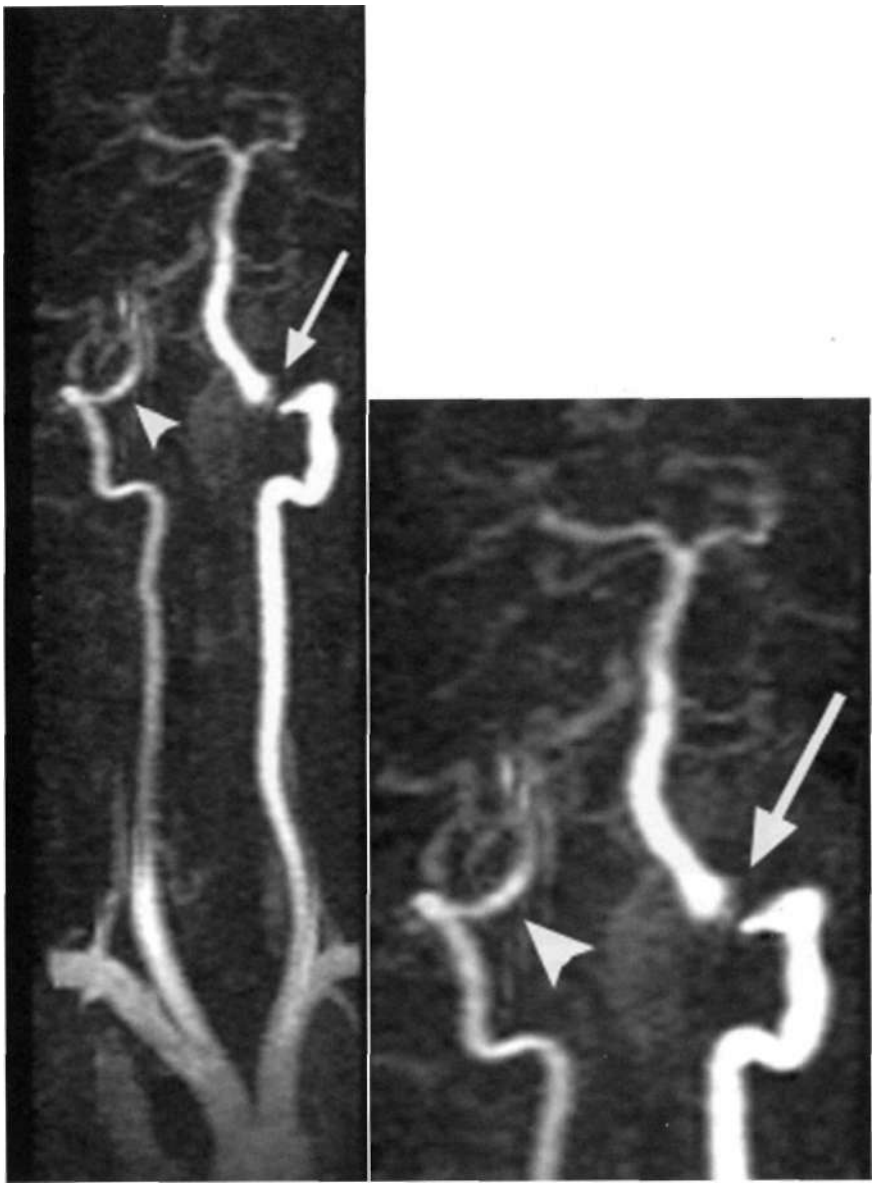


FIGURE 37B.7, cont'd. (E) CE-MRA shows the entire vertebro-basilar arterial system. Spatial resolution is less than in (D). (F) Zoomed view of the distal vertebral arteries from (E) reveals complete restoration of signal in the right vertebral artery *(arrowhead)* and nearly complete restoration of signal in the left vertebral artery *[arrow),* Persistent focal signal loss resulted from a small metal surgical clip adjacent to the left vertebral artery; the clip is obscured by contrast in (B). All MR angiograms were produced with the targeted maximum (pixel) intensity projection technique.

2D PC MR study of the circle of Willis instead of the more time-consuming 3D TOP study. Other clinical settings in which MRA reportedly complements routine MR imaging include sickle cell disease, moyamoya disease, and hemi-facial spasm and ttigeminal neutalgia. **Flow** dynamics (magnitude and direction) in the circle of Willis are more easily determined with the PC method, especially when vessel diameters are 1 mm or more.

As described earlier, the simplest type of 3D CE-MRA technique uses scan parameters typical of 3D TOP MRA acquisitions with scan times on the otder of 5-10 minutes per 3D volume. Under these steady-state conditions, visibility of the small intracranial arteries is greater after intravenous gadolinium administration; however, a much greater increase in visibility occurs for the intracranial veins. Consequently, the MIP images become cluttered with veins, resulting in greater difficulty in identifying and delineating specific arteries. With dynamic 3D CE-MRA, as used for extracranial catotid imaging, temporal resolution is improved, and visibility of arteries is greater than that of veins. However, vascular image detail is variably diminished depending on CE-MRA technique, and temporal resolution usually is incomplete because only about 5 seconds separates the onset of intracranial arterial enhancement from venous enhancement. Some investigators have suggested using careful region-of-intetest MIP postprocessing to further exclude veins from intracranial artery displays. Despite the limits placed on spatial resolution by **the** dynamic 3D CE-MRA technique, Parker and colleagues (1998} have shown that, in theory, imaging with a TR of 7-10 milliseconds (e.g., scan time approximately 1 minute per 3D volume} and a Tl relaxation time of 2.S-50 milliseconds for flowing blood containing gadolinium (first-pass arterial concentration of approximately 5-10 mM) can produce

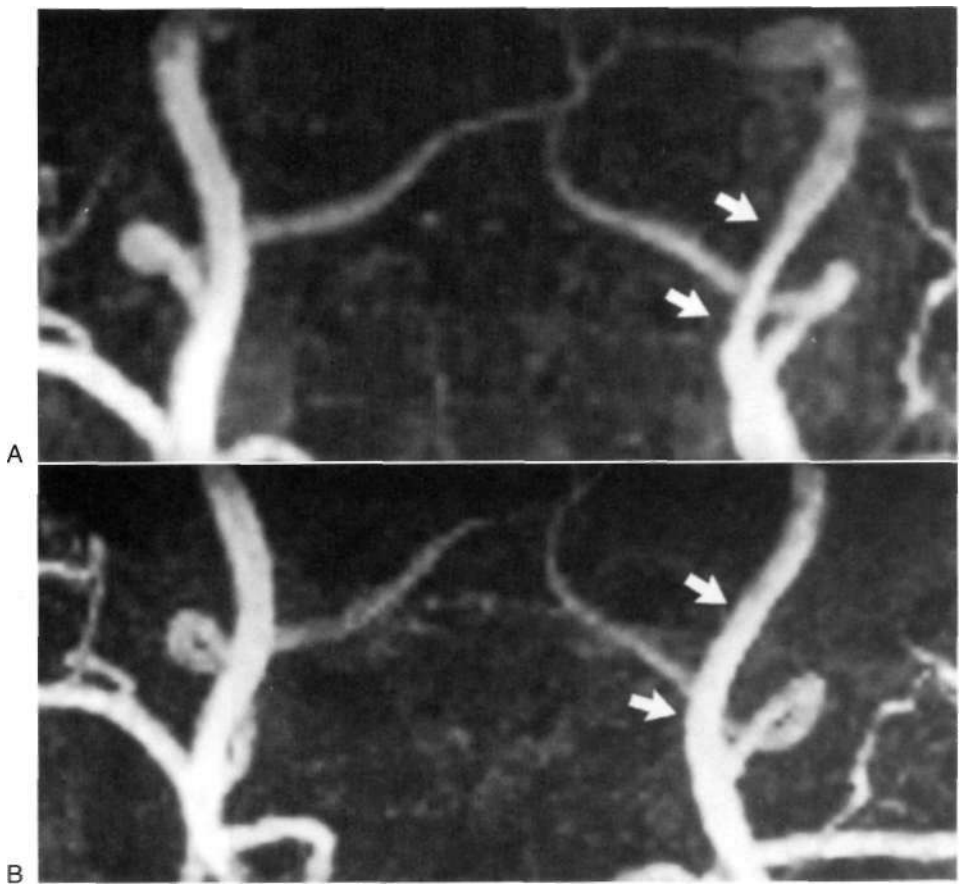


FIGURE 37B.8 Resolution of carotid dissection followed with magnetic resonance angiography. (A) Magnetic resonance angiogram produced by the three-dimensional time-of-flight technique shows a segmental stenosis *[arrows)* involving the distal cervical portion of the left internal carotid artery. (B) A repeat study, obtained after anticoagulant therapy, demonstrates a return to normal caliber of the internal carotid artery segment *(arrows).*

images of the intracranial arteries (approximately 0..S mm diameter) with vascular contrast comparable to that produced by the steady-state 3D CE-MRA technique. Investigational studies indicate that dynamic 3D CE-MRA will play a significant role in evaluating intracranial arterial steno-occlusive disease, but the accuracy, reproducibility, and reliability of CE-MRA measurements compared with those of catheter angiography and TOF MRA in controlled clinical trials have not yet been reported.

3D TOF MRA is now readily accepted as a noninvasive screening tool for familial aneurysmal disease. It has also been used as an alternative to catheter angiography (intra-arterial digital subtraction angiography [IA-DSA]) for the surgical management of ruptured aneurysms. A review of the relevant literature for 1988-1998 found that TOF MRA (and CTA) depicted aneurysms with an accuracy of about 90% (White, Wardlaw, and Easton 2000). Sensitivity was much greater for detection of aneurysms larger than 3 mm (94%) than for detection of aneurysms 3 mm or smaller (38%). Diagnostic accuracy was similar for anterior and posterior circulation aneurysms {Figure 37B.10). In general, noninvasive imaging evaluation includes a review of T1- and T2-weighted (fast) spin-echo images and T2'*-weightcd gradient-echo images, in addition to the source images and MIP images from the MRA acquisition.

The role of 3D TOF MRA in assessing intracranial aneurysms before endovascular treatment is adjunctive to the definitive IA-DSA study (Adams, Lait, and Jackson 2000). Based on a composite assessment that included aneurysm detection rate, aneurysm morphology, neck interpretation, and branch vessel relationship to the aneurysm, Adams and colleagues found MRA to be inferior to IA-DSA overall and to have missed aneurysms smaller than 3 mm. Nevertheless, MRA provided complementary information to IA-DSA in anatomically complex areas or in the presence of intramural thrombus. The authors applied the assessment to four different types of image data display: axial source images, multiplanar reconstruction (MPR) of the source image data, MIP images, and 3D isosurface-rendered images. Among these types of images, the MPR and 3D isosurface images were comparable to the IA-DSA images in all categories of the composite assessment, whereas the MIP images scored poorly in all categories

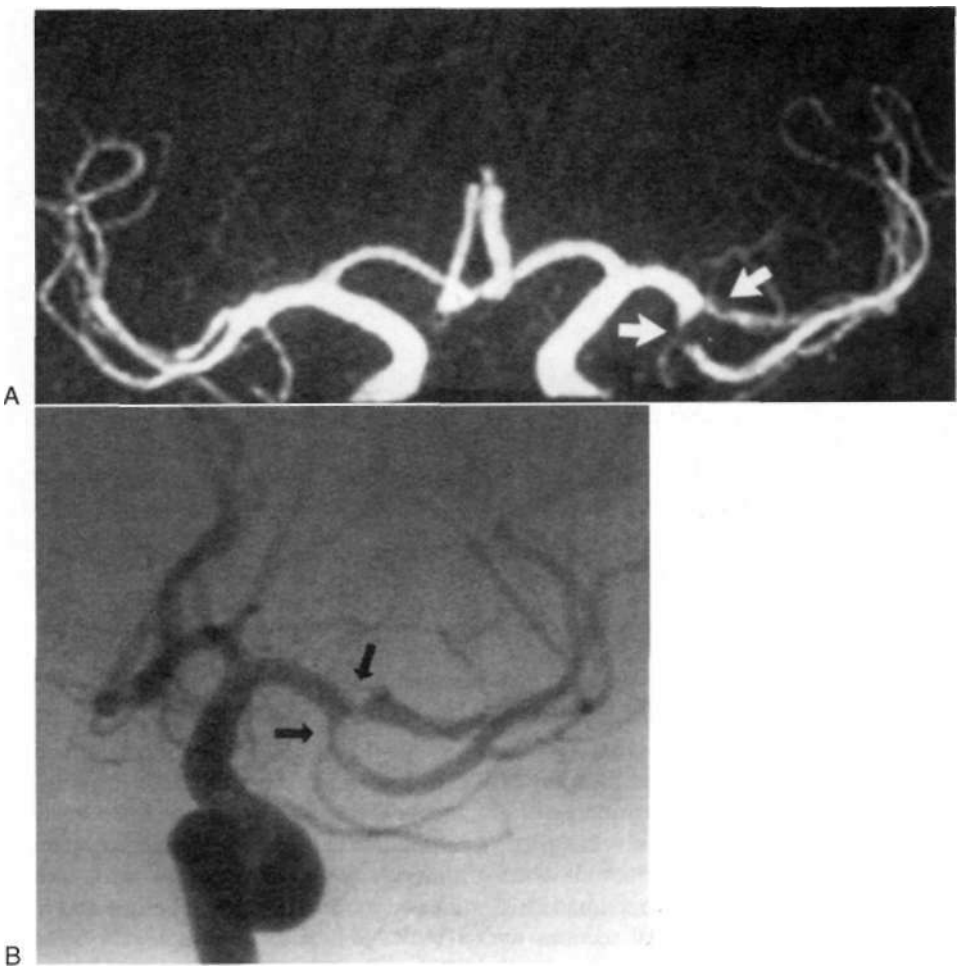


FIGURE 37B.9 Proximal middle cerebral artery (MCAJ stenosis (same patient as in Figure 37B.3). (A) Coronal reprojection magnetic resonance angiogram was produced from die axial source images shown in Figure 37B.3. The coronal view shows better than the axial view (Figure 37B.3C) that there is stenosis *(arrows)* involving both M2 branches of the MCA. (B) Catheter angiography confirms the presence of both stenoses (arrows).

except aneurysm detection. These findings indicate that better noninvasive characterization of aneurysms with TOF MRA can be achieved by adding MPR or 3D isosurface-rendered images to the source and MIP images that are now routinely reviewed in clinical practice.

Although there is no conclusive evidence that CE-MRA is superior to TOF MRA in depicting intracranial aneurysms in general, Jager and colleagues (2000) have shown that 3D CE-MRA is the method of choice for detecting the lumen and connecting vessels of giant cerebral aneurysms {aneurysms larger than 25 mm), Although both the simple steady-state and the dynamic CE-MRA techniques reliably showed the lumen and exiting vessels, the dynamic MRA technique provided superior contrast between flow and background and eliminated the short Tl contamination artifact caused by subacute intraluminal or extraluminal blood clot. Another application of MRA in which CE-MRA shows promise is in the follow-up of intracranial aneurysms treated with detachable coils. In a prospective study of 68 patients, boulin and Pierot (2001) found that the steady-state 3D CE-MRA technique correlated with DSA regarding the presence or absence of residual aneurysm in 90% of cases. In the remaining cases, the primary difference was that MRA failed to detect a remnant lumen measuring less than 3 mm. Because small aneurysm remnants or recurrences were thought not to be clinically significant, the authors concluded that CE-MRA is an option for post-tteatment follow-up and may partly replace IA-DSA.

Veins and Venous Sinuses

The approach to evaluating the intracranial veins and dural venous sinuses differs from that of arteries because of the lower velocity of venous flow and the morphology of the venous sinuses. For suspected dural sinus occlusion resulting from thrombosis or tumor invasion, the primary technique is 2D TOF MRA in conjunction with spin-echo imaging. To establish the diagnosis of venous thrombosis, lack of visualization of a vein or sinus on the source images

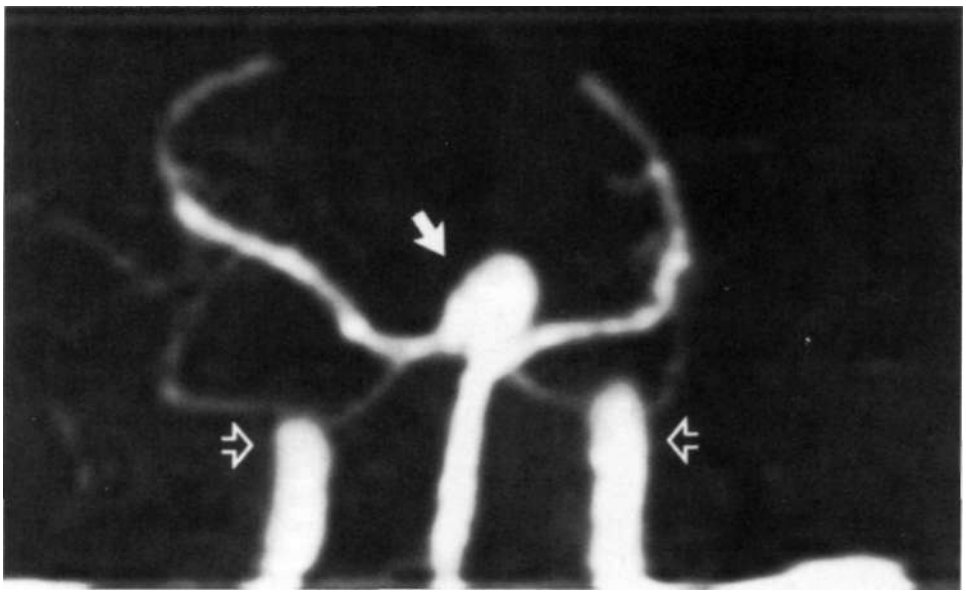


FIGURE 37B.10 Basilar tip aneurysm. Magnetic resonance angiogram (frontal view), produced from a three-dimensional rime-of-flight axial slab acquisition, shows an aneurysm *(closed arrow)* arising from the basilar artery terminus and measuring 9 mm in longitudinal diameter. Although targeted to the posterior circulation primarily, the maximum intensity projection image includes portions of the precavernous internal carotid arteries *{open arrows).*

and angiogram must ⊳L- accompanied by identification of the clot on the spin-echo images at the location of the suspected occlusion (Figure 37B.11). With the 2D TOF technique, optimal flow enhancement is achieved when a section is perpendicular to the flow direction. This condition is best approximated using coronal sections to image the sagittal, straight, and transverse sinuses (as well as the internal cerebral veins, basal veins of Rosenthal, and, to a lesser degree, the vein of Galen). The acquisition of coronal sections can be augmented by the acquisition of oblique sagittal sections to allow better flow enhancement in the postetior portions of the transverse sinuses and the cortical veins draining into the superior sagittal sinus. With the 2D TOF MR venography technique, arterial signal is reduced or eliminated by an axial presaturation band placed across the upper neck below the skull base. A common diagnostic pitfall of the technique is the presence of flow gaps in the transverse sinus. Ayanzen and colleagues (2000) observed these gaps in 31 % of patients with normal MR imaging findings. Flow gaps were not observed in the superior sagittal, straight, or dominant transverse sinuses, so gaps occurring in these locations should raise suspicion of venous obstruction. The authors found that the nondominant transverse sinuses (90% of gaps) or codominant transverse sinuses (10%) that demonstrated the flow gaps were hypoplastic yet patent by conventional catheter angiography,

Alternative techniques for demonstrating intracranial veins and dutal venous sinuses lack the robustness of the 2D TOF technique. The 3D TOF technique suffers from saturation effects and hence frequent signal loss in the veins and dural sinuses. The 2D PC technique is limited by gradient imperfections, eddy currents, aliasing artifacts, and lower spatial resolution. Although the PC technique can be useful in differentiating very slow flow in the dural sinuses from thrombosis, it was recently found to be inferior to the 2D TOF technique and a contrast-enhanced 3D FLASH (fast low-angle shot) MRA technique in displaying the normal septal veins, internal cerebral veins, and the basal veins (Kitchhof er al. 2002), Both the 3D FLASH technique and a 3D magnetization-prepared, rapid-acquisition gradient echo MR imaging technique (Liang et al. 2001) are contrast-enhanced (CE) methods and reportedly are superior to the 2D TOF technique in depicting normal venous structures, especially in overcoming the flow gap artifact. However, these CE techniques have two fundamental limitations: Both techniques involve tapid acquisition (1-2 minutes per 3D volume), so that the intensity of the intravascular signal depends on the timing of the contrast infusion relative to data acquisition, and chronic thrombus enhances with gadolinium and can mimic a patent lumen. Consequently, these two CE techniques should be viewed as adjuncts to the 2D TOF technique.

Vascular Malformations and Tumors

Traditional MRA methods (2D and 3D TOF and PC MRA) have played a secondary role to IA-DSA in evaluating inttactanial arteriovenous malformations (AVMs) because of a lack of consistent and complete demonstration of all components of an AVM: feeding attcrics, nidus, and draining veins. For this reason, and

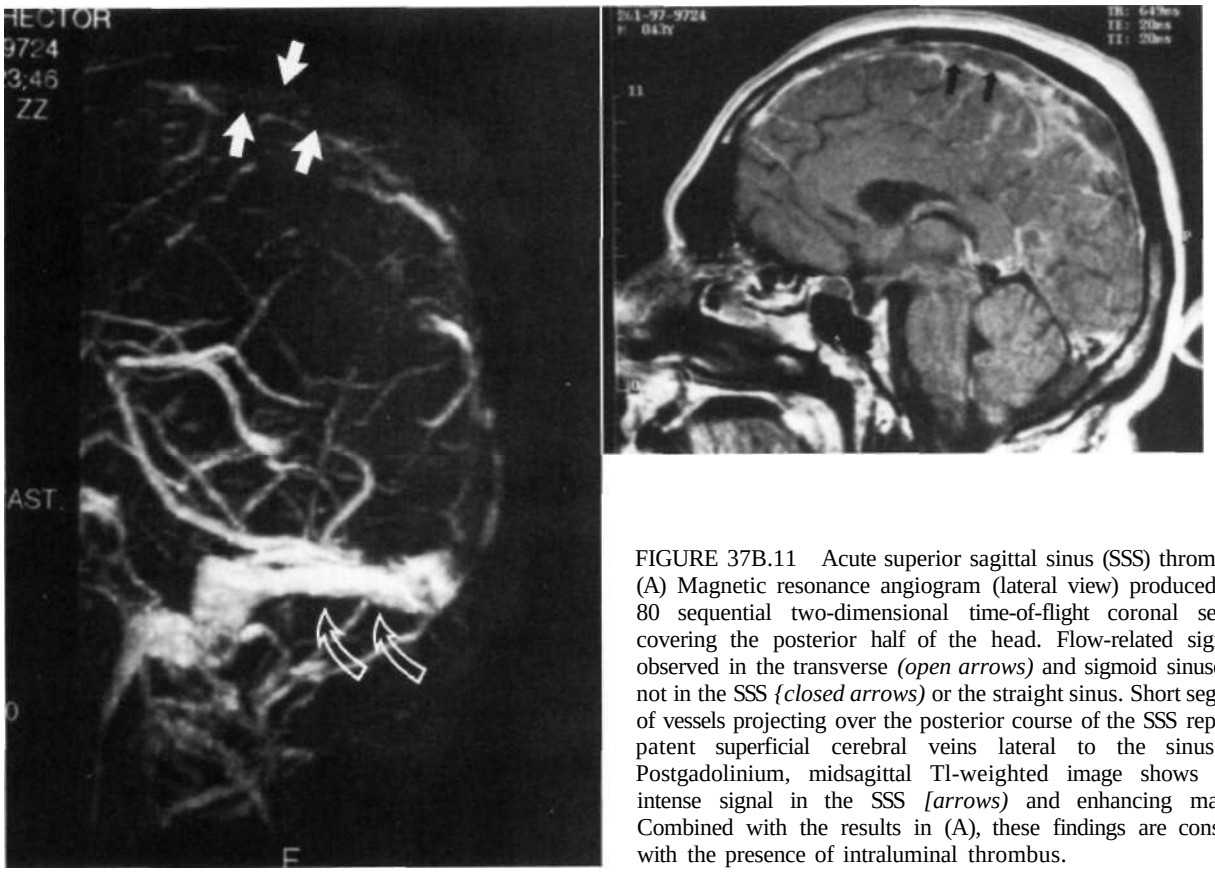


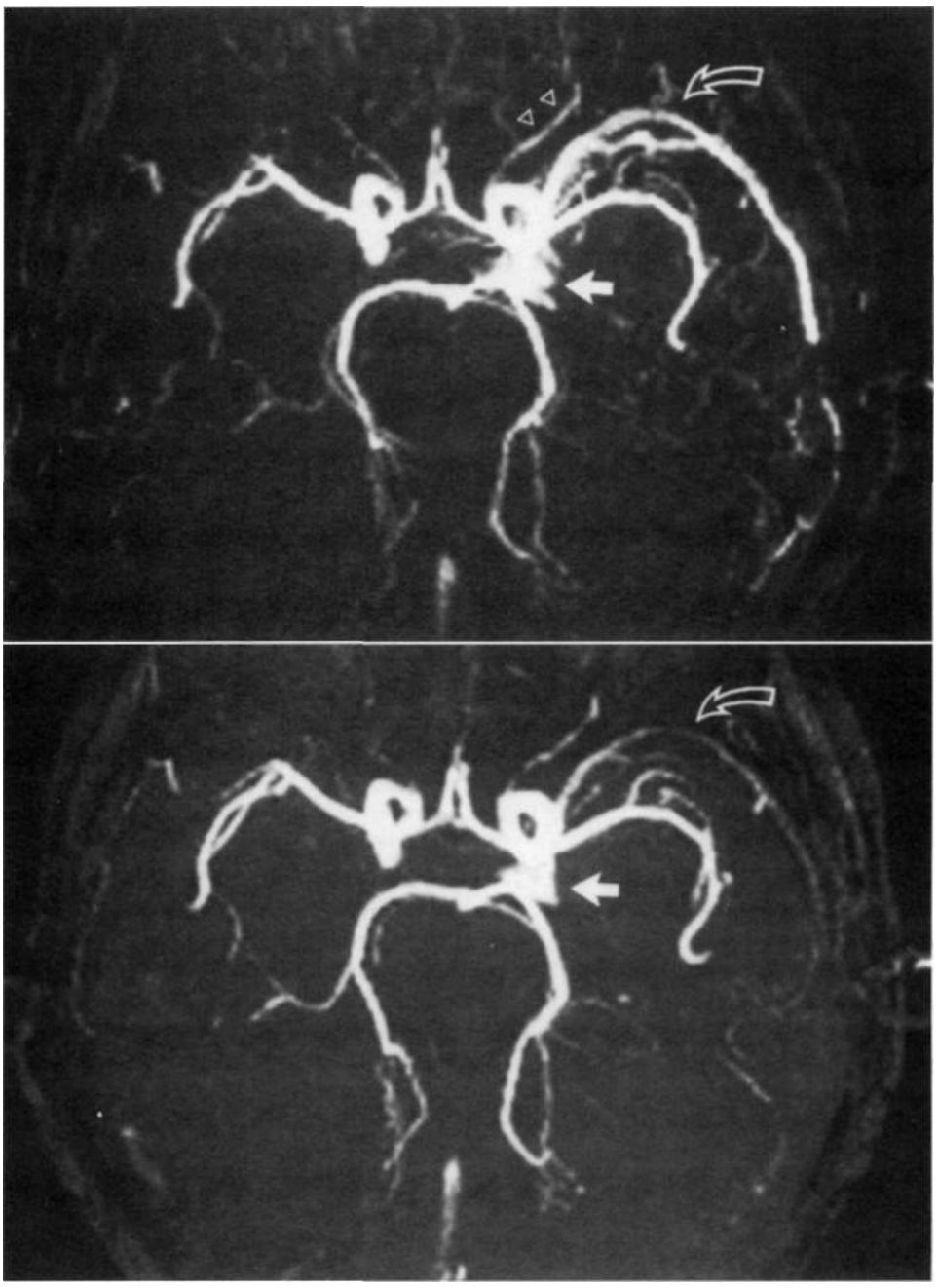
FIGURE 37B.11 Acute superior sagittal sinus (SSS) thrombosis. (A) Magnetic resonance angiogram (lateral view) produced from 80 sequential two-dimensional time-of-flight coronal sections covering the posterior half of the head. Flow-related signal is observed in the transverse *(open arrows)* and sigmoid sinuses but not in the SSS *{closed arrows)* or the straight sinus. Short segments of vessels projecting over the posterior course of the SSS represent patent superficial cerebral veins lateral to the sinus. (B) Postgadolinium, midsagittal Tl-weighted image shows hypo-intense signal in the SSS *[arrows)* and enhancing margins. Combined with the results in (A), these findings are consistent with the presence of intraluminal thrombus.

because of the general impression that TOF MRA adds little to the spin-echo MR imaging findings useful for preliminary staging of an AVM (nidus size and location and central versus peripheral pattern of venous drainage in the Spetzler and Martin criteria) before definitive IA-DSA, many investigators have considered TOF MRA of AVMs superfluous. PC techniques have been used by some investigators to estimate blood flow velocities and volume flow rates in the largest arteries supplying the AVM. A high-resolution 3D gradient-echo technique based on the paramagnetic property of deoxyhemoglobin has been used to detect cerebral veins with submillimeter resolution, resulting in greater sensitivity in identifying the presence of small AVMs compared with TOF MRA; however, the technique provides poorer detection of feeding arteries and is markedly limited in its delineation of nidus size and shape when there are susceptibility artifacts from nearby bone, air, or blood products (hemosiderin) (Essig et al. 1999).

More recently, high-resolution real-time auto-triggered elliptic centtic-ordered 3D CE-MRA (Farb et al. 2001) and lower-resolution time-resolved 2D CF-MRA (Klisch et al. 2000) have been applied to the evaluation of AVMs and the results compared with those of TOP MRA and IA-DSA, In an initial investigation, Farb and colleagues found that their 3D CE-MRA technique was superior to 3D TOF MRA, particularly in depicting nidus and draining veins. The 3D CE-MRA technique consistently showed AVM components and their spatial relationships on MIP images and was equivalent to IA-DSA in depicting AVM components in 70-90% of cases (total patients = 10), based on blinded, independent assessments by two experienced neuroradiol-ogists.

Dural arteriovenous fistulas (AVFs) most commonly involve the cavernous, transverse, and sigmoid sinuses along the skull base. Arterial feeders not seen on spin-echo MR sometimes are detected on 3D TOF MRA but much less often than on catheter angiography. Transverse and sigmoid sinus occlusion and dilated cortical veins are detected better by MRA than spin-echo imaging, yet neither technique achieves the accuracy of carheter angiography. Traditional 3D TOF MRA is useful in detecting cavernous sinus fistulas because flow enhancement in the cavernous sinus and contiguous veins can provide evidence of the fistula (Figure 37B.12). This finding must be regarded with caution because venous flow signal has been observed in the cavernous sinus and inferior pettosal sinus in a variable percentage (from 4% to 36%, depending on unspecified technical differences between MR scanners) of patients without clinical evidence of carotid cavernous fistula (Ouanounou et al. 1999).

The diagnostic imaging features of venous malformations (angiomas, developmental venous anomalies) are well shown on postgadolinium Tl-weighted spin-echo images.



B

FIGURE 37B.12 Spontaneous resolution of a left carotid-cavernous dural arteriovenous fistula. Magnetic resonance angiograms (axial maximum intensity projection images) of the sellar region and the circle of Willis were acquired with rhe three-dimensional time-of-flight technique (no gadolinium enhancement). The studies, performed (A) at the time of clinical presentation, (B) *i* months later, (C) 3 years later, show progressive resolution of the venous drainage from the fistula. Flow-related signal in the left cavernous sinus *[closed arrow),* sphenoparietal sinus *{open arrow),* and cerebral veins results from shunting of high flow rate arterial blood through the fistula. Note the progressive decrease in signal in the sphenoparietal sinus. Flow-related signal in the left orbit is caused by the ophthalmic artery *(arrowheads),* not the superior ophthalmic vein, which was found by catheter angiography to be thromhosed at the time of presentation.

Continued

These features include rhe radially oriented collection of small vessels (medullary veins) that produce a caput medusa or spoke-wheel configuration. This is contiguous with a large trunk vein that drains into cither subependymal or superficial cerebral veins or a dural sinus. The 2D TOF technique and the PC method with low VENC often display these slow-flow malformations without the use of gadolinium and allow determination of flow direction; however, the 3D TOF technique, which provides greater spatial resolution, requires gadolinium to avoid saturation effects. Cavernous malformations and capillary telangiectasias do not show flow enhancement on MRA studies, and

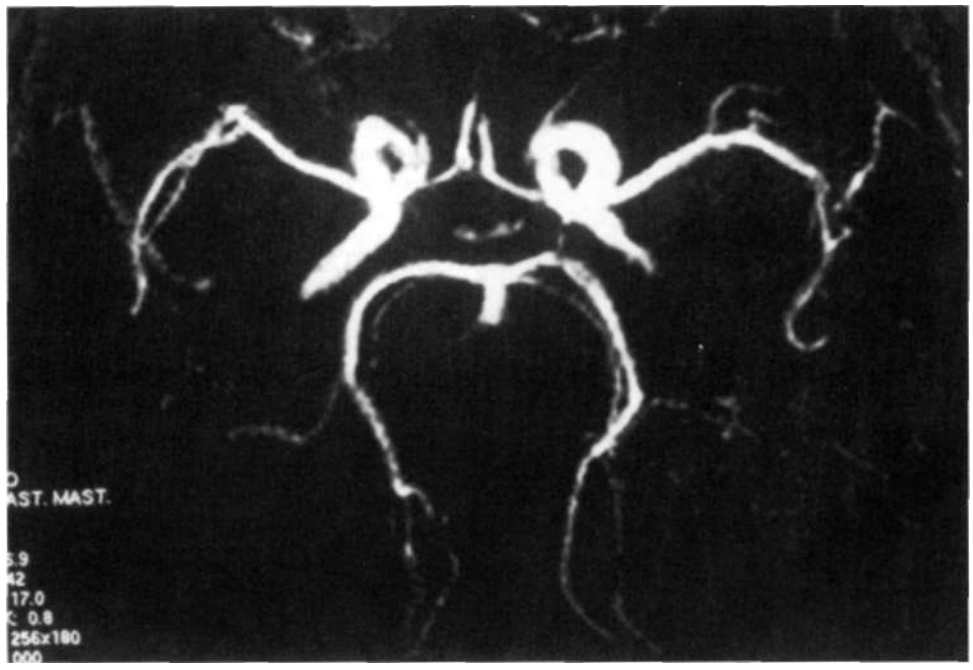


FIGURE 37B.12, cont'd.

the former usually are identified on spin-echo and gradient-echo images by the heterogeneous signal intensity caused hy blood products from prior hemorrhage.

The role of MRA in diagnosing intracranial tumors has yet to be defined, and evaluation more commonly involves bolus-chase susceptibility-weigh ted ("perfusion") MR imaging. In general, tumor-associated neovascularity consists of numerous small vessels, which are poorly delineated on traditional MRA compared with catheter angiography. The 2D TOF technique has been used to document dural sinus invasion or displacement by a neoplasm, and the 3D TOF technique is helpful in distinguishing a parasellar tumor from a patent aneurysm. Steady-state CE-MRA delineates small superficial and deep cerebral veins and has been used for preoperative planning in patients with a proven intracerebral mass.

Extracranial Circulation: Spine

Spinal MRA is used as an adjunct to MR imaging to improve the visibility of the millimeter-sized intradural vessels and to help differentiate abnormal from normal ones. The combined MR examination provides better characterization of spinal vessels and thus more effective noninvasive screening for vascular lesions, such as dural AVFs, than MR imaging alone (Saraf-Lavi et al. 2002). The improved screening facilitates decisions regarding invasive catheter angiography for definitive diagnosis and endovascular treatment. The combined MR examination also allows the largest normal vessels to be localized noninvasively before surgical or endovascular procedures that carry a risk of cord injury (Yamada et al. 2000).

Enhancement of the intradural vessels with gadolinium contrast agents has been found necessary for optimal detection on MRA. The 3D CE-MRA technique with steady-state conditions (i.e., TOF pulse sequence parameters) has been shown to detect the largest intradural veins in healrhy volunteers: the posterior and anterior median veins and the great medullary veins draining from the surface of the cord to the epidural space. This technique, and to a lesser extent the 3D PC technique, also detects the abnormally enlarged and tortuous veins draining dural AVFs (figure 37B.13) and intramedullary AVMs. In detecting the presence of dural AVFs, the steady-state 3D CE-MRA technique combined with spin-echo MR imaging had a sensitivity ranging from 80% to 100%, specificity of 82%, and accuracy of 81-94% in a randomized, blinded review by three neuroradiologists of 11 control subjects and 20 patients with proven dural AVFs (Saraf-Lavi et al. 2002). More importantly, in determining the vertebral level of the fistula, the correct level ± one level was predicted in 73% cases by combined MRA and MRI, representing a significant improvement over MRI alone. Improved noninvasive localization of the fistula level potentially expedites the subsequent invasive catheter angiography study. Preliminary studies of spinal vascular malformations using time-resolved or fast 3D CE-MRA indicate that such first-pass studies may provide better depiction of the dural AVF in the neural foramen because of diminished extradural venous enhancement and improved visibility of the feeding arteries of AVMs (Binkert, Kollias, and Valavanis 1999).

Although intraspinal vascular tumors such as hemangioblasroma, paraganglioma, hemangiopericytoma, and angioblastic meningioma are rare, preoperative imaging findings that suggest this differential diagnosis arc

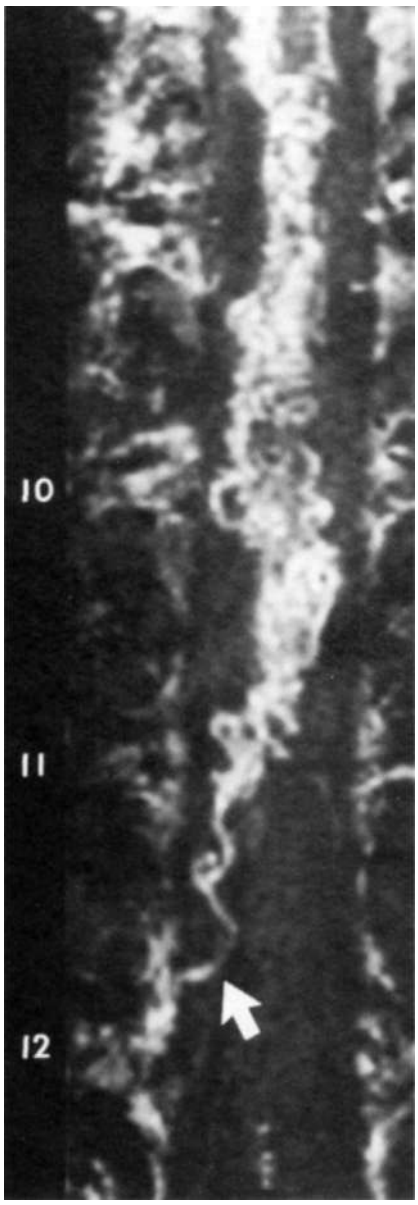


FIGURE 37B.13 Spinal dura] arteriovenous fistula. Gadolinium-enhanced magnetic resonance angiogram (frontal view), targeted to the posterior half of the lower thoracic canal, demonstrates an enlarged and tortuous vessel *(arroiv)* that courses from the region of the right T12 neural foramen to the posterior surface of the spinal cord, where there are numerous abnormal vessels. The enlarged vessel is the right Tl 2 posterior medullary vein, and it is contiguous with the coronal venous plexus around the cord. The veins are enlarged and tortuous because of retrograde filling by the shunted arterial blood from a fistula in the Tl 2 foramen. The right vertebral foramina at T10, Tl 1, and T12 are labeled.

important tor surgical planning and evaluation. In the few cases that have been reported, the steady-state 3D CH-MRA technique detected abnormal intradural vessels (primarily perimedullary veins) associated with these tumors better than did routine spm-echo imaging (Bowen and Pattany 2000). In cases of lumbar paraganglioma or hemangiopericytoma, in which the mass can mimic ependymoma or schwannoma on routine MR imaging, MRA findings suggesting vascular tumor can lead to the performance of catheter angiography and, if indicated, preoperative embolization.

COMPUTED TOMOGRAPHIC ANGIOGRAPHY

Methods

With the advent of helical CT scanning, uninterrupted volume acquisition of data from the head and neck region can easily be obtained in less than 1 minute. In general, data are acquired using a slice (collimated) thickness of 1-3 mm and a pitch of 1-2 as a bolus of iodinated contrast traverses the arteries of interest. For CTA of the carotid and vertebral arteries in the neck, the helical volume extends from the aortic arch to the skull base. Typical acquisition parameters are 7.5 images per rotation of the x-ray tube, 2.5 mm slice thickness, and a reconstruction interval (distance between the centers of two consecutively reconstructed images) of 1.25 mm. For the circle of Willis and proximal cerebral arteries, the helical volume extends from the skull base to the roofs of the lateral ventricles and has a smaller field of view than the neck study. Typical acquisition parameters for this higher spatial resolution scan are 3.75 images per rotation, 1.25 mm slice thickness, and an interval of 0.5 mm,

To produce intravascular enhancement, a volume of contrast ranging from 100 to 150 mL is injected into a peripheral vein at a rate of 2-3 mL per second and followed by a saline chase or flush (20-50 mL). Adequate enhancement of the arteries in the neck or head is obtained approximately 15-20 seconds after injection of the contrast. Most helical scanners have a special feature that allows visual and analytical monitoring of contrast in a chosen vessel upstream from the 3D volume to be scanned. As with CE-MRA, the most common approaches to synchronizing the 3D CT helical data acquisition with the arrival of the contrast bolus are determination of the bolus arrival time using a preliminary test dose, automated detection of bolus arrival and subsequent triggering of data acquisition, and real-time monitoring of bolus arrival and operator-triggered data acquisition. Data from the axial source images typically are postproccssed using one or more of the following techniques: multiplanar reformatting, MIP, and 3D volume rendering.

Applications

Extracranial Circulation

Carotid Artery Stenosis. In evaluating occlusive disease of the carotid bifurcation, CTA complements conventional angiography and is an alternative to DS and MRA

(Figure 37B.14). In the grading of carotid stenosis using North American Symptomatic Carotid Endarterectomy Trial criteria, Randoux and colleagues (2001) found that the rate of agreement between 3D CTA and IA-DSA was 95%. Relative to IA-DSA (the gold standard), severe stenosis (70-99%) was detected with a sensitivity and specificity of 100% and 100% for CTA and 93% and 100% for CE-MRA, respectively. In addition, CTA and CH-MRA were significantly correlated with IA-DSA in depicting the length of the stenotic segment.

Other investigators have reported lower sensitivity (range of 80-89%) yet comparable specificity (range of 96-100%) for CTA in detecting severe stenosis (Magarelli et al. 1998; Binaghi et al. 2001). Those investigatots found that TOF MRA had higher sensitivity (92-93%) than CTA and similar specificity (98-100%). Binaghi and colleagues also compared CTA with DS and showed that the sensitivity was the same *(89%),* whereas specificity was higher fot CTA (100%) than for DS (81%).

CTA has several advantages and disadvantages in comparison to the other techniques. Investigators have noted the following advantages:

- Better visualization of calcifications compared with **IA-DSA**
- Images less affected by carotid kinks and loops compared with TOP MRA, which may show false stenotic lesions or flow gaps at such sites (Link et al. 1995)
- Better localization of the level of carotid bifurcation by including reference points such as the cervical spine and mandible in the image volume
- Better delineation of plaque irregularities and ulceration compared with IA-DSA (Randoux et al. 2001)

Disadvantages of CTA include the following:

- Use of an iodinated contrast agent with its associated risks
- Inability to show the carotid siphon adequately so as to exclude tandem stenosis, which may preclude surgery

Currently, either CTA or MRA is used to evaluate suspected carotid occlusive disease, with the choice of method determined by clinical conditions (e.g., pacemaker), accessibility of CT and MR scanners, and additional imaging capabilities (CT or MR perfusion brain imaging). The advantages of MRA are the availability of both TOF and CE-MRA techniques and the more extensive history of clinical testing, including the validation of combined DS and TOF MRA examinations in which concotdant results correlated highly with IA-DSA results.

Carotid Dissection. Dissections of the extracranial ICA account for up to 20% of ischemic strokes in young adults (Leys et al. 1995). Although catheter angiography has been considered the gold standard for diagnosing ICA dissections, MRI, MRA, and CTA (Leclerc et al. 1996, 1998) have emerged as alternative, noninvasive approaches to the diagnosis and monitoring of acute ICA dissection.

The CTA findings include demonstration of a narrowed eccentric arterial lumen in the presence of a thickened vessel

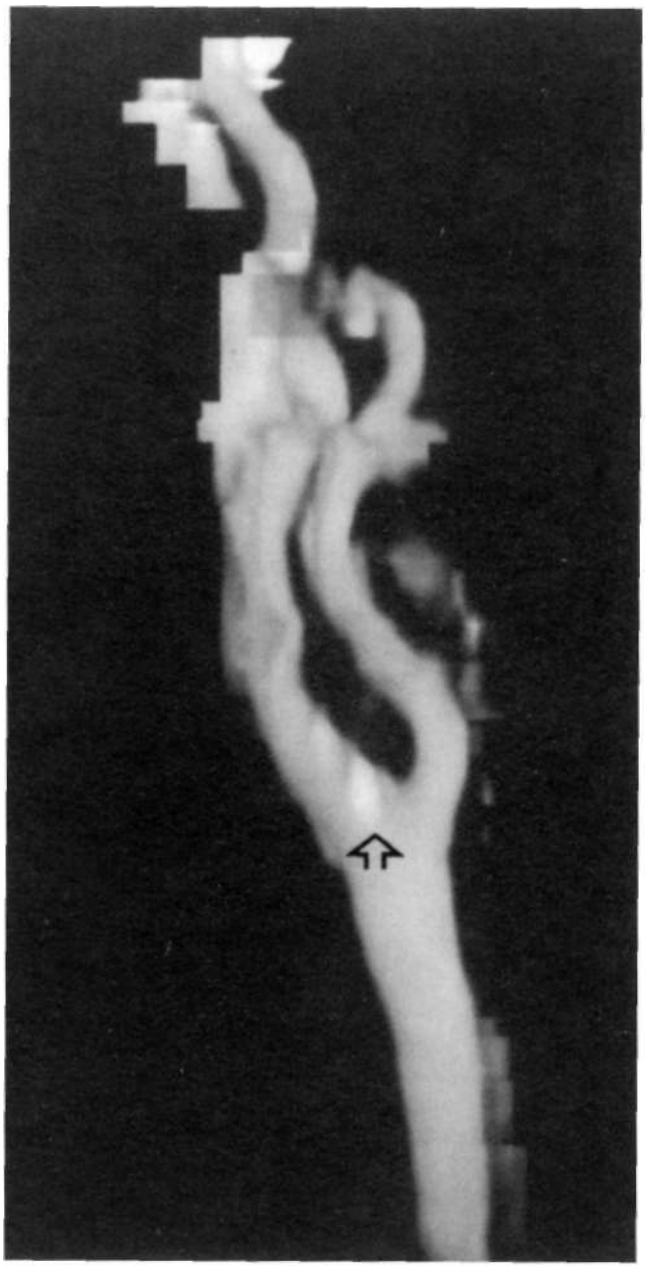


FIGURE 37B.14 Computed tomographic angiography of the cervical internal carotid artery in a patient with a history of transient ischemic attacks. Maximum intensity projection image shows no evidence of stenosis; however, a calcified plaque is demonstrated at the origin of the internal carotid artery *{arrow}.* Large plaques may obscure the arterial lumen. Improved assessment is possible with a virtual endoscopic view of the affected lumen.

wall and occasionally pseudoaneurysm. In subacute and chronic dissection, CTA has been shown to detect a reduction in the thickness of the arterial wall, rccanalization of the arterial lumen, and reduction in size or resolution of pseudoaneurysm. CTA (or MRA) is superior to DS in depicting the middle to distal portions of the cervical ICA, which are commonly involved in dissections (sec Figure 37B.8). CTA is likely to be superior to MR imaging alone in evaluating pseudoaneurysms because MR findings often ate complicated by the presence of flow-related artifacts. CTA usually is inferior to MRI and MRA in depicting dissections at the level of the skull base because CT findings can be masked by beam hardening and other artifacrs and by similarities in the densities of the tempotal and sphenoid bones and the dissected ICA on source and reformatted images.

Intracranial Circulation

Acute Ischemic Stroke. Reports by several investigators (Shrier et al. 1997; Knauth et al. 1997) have shown that CTA is a reliable alternative to MRA in evaluating arterial occlusive disease near the circle of Willis in patients with symptoms of acute stroke (Figure 37B.15). CTA shows clinically televant occlusions of major cerebral arteries and enhancement caused by collateral flow distal to the site of

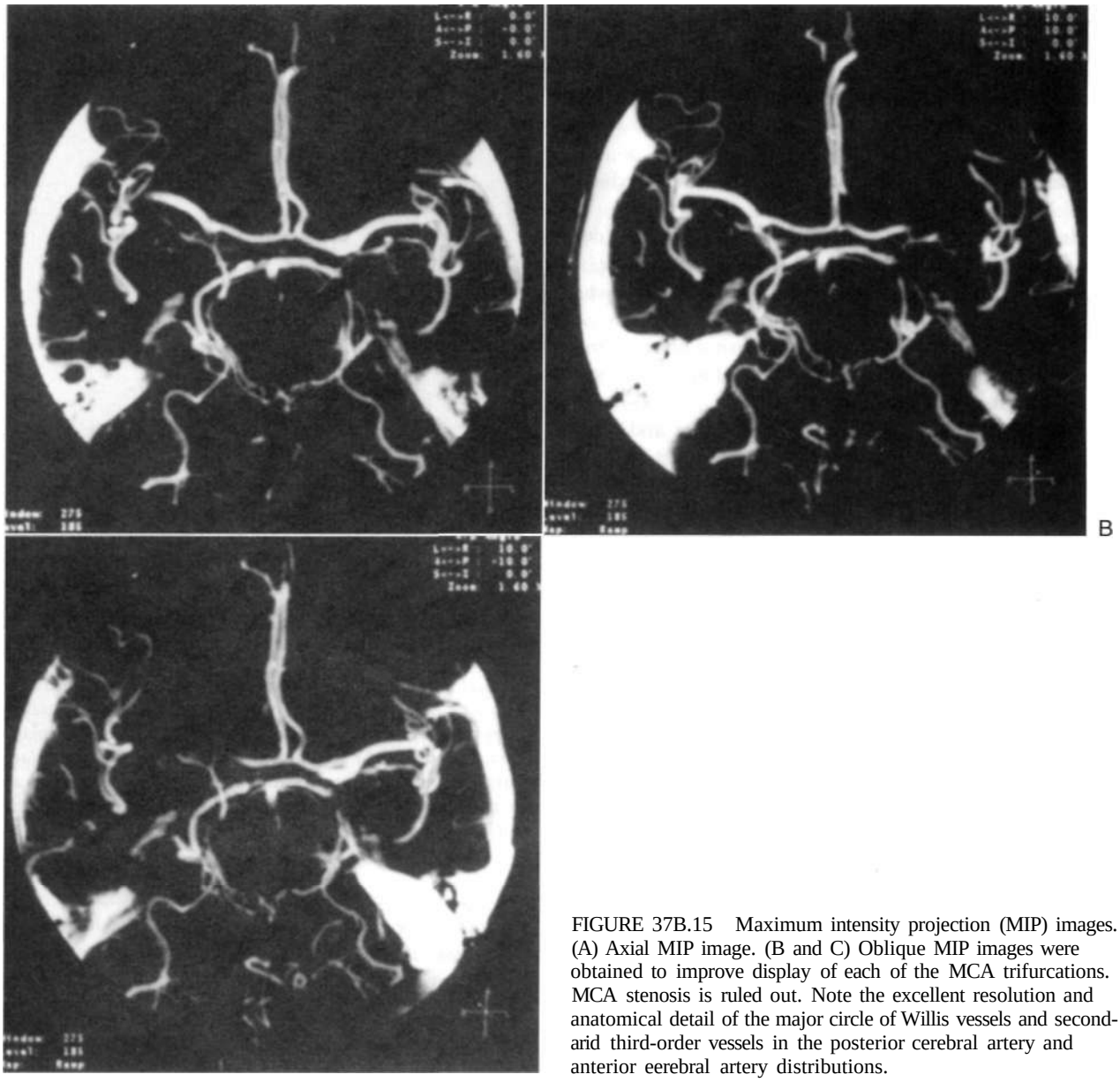
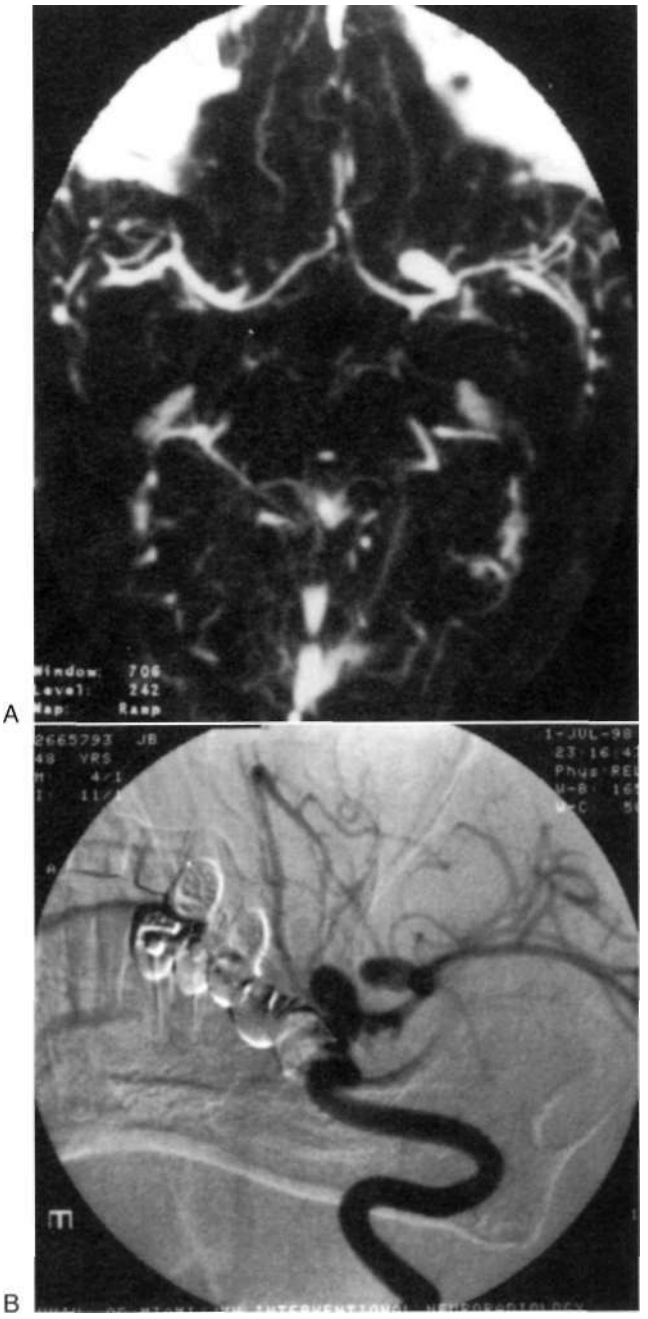


FIGURE 37B.15 Maximum intensity projection (MIP) images. (A) Axial MIP image. (B and C) Oblique MIP images were obtained to improve display of each of the MCA trifurcations. MCA stenosis is ruled out. Note the excellent resolution and anatomical detail of the major circle of Willis vessels and second-arid third-order vessels in the posterior cerebral artery and anterior eerebral artery distributions.

occlusion. In the diagnosis of MCA occlusion, CTA has shown good correlation with transcranial Doppler (TCD) sonography but is inferior to MRA. More recently, CTA was found to be superior to TCD in diagnosing atherothromboric MCA disease in Asian patients presenting with MCA stroke (Suwanwela, Phanthumchinda, and Suwanwela 2002), CTA detected MCA stenosis measuring more than 50% in twice as many patients as TCD. The difference resulted primarily from the improved detection by CTA of distal Ml and M2 stenosis. Because half of the patients studied by Suwanwela and colleagues had distal Ml and M2 disease, the authors concluded that TCD sonography should not be used to screen for MCA stenosis.

In the detection of inttacranial steno-occlusive disease, Hirai and colleagues (2002) have shown that combined CTA and MRA provide substantially higher sensitivity, specificity, and accuracy than MRA alone. Review of the CTA depiction of vessels in conjunction with the 3D TOF MRA display reduced the ftequency of overestimation of stenosis when compared with MRA alone. In the identification of 50% or greater stenosis, the sensitivity, specificity, and accuracy for the combined CTA and MRA evaluation were 100%, 99%, and 99%, respectively, and the values for 3D TOF MRA alone were 92%, 91%, and 91%, respectively. The grading of stenosis by the combined approach agreed with the IA-DSA grading in 98% of cases. In a retrospective review of their cases, the authors found that CTA did not always correctly delineate arterial lumina with circumferential calcification and the cavernous portion of the ICA.

Cerebral Aneurysms. Catheter angiography has been the gold standatd for imaging diagnosis and preoperative evaluation of ruptured and unruptured cerebral aneurysms; however IA-DSA is invasive and subject to complications tesulting from catheter manipulation. Thus in asymptomatic patients at greater risk for cerebral aneurysms, the use of noninvasive techniques such as MRA and CTA to screen for aneurysms is particularly attractive. These techniques have advantages and disadvantages. The most thoroughly investigated MRA technique is 3D TOF MRA, and its main disadvantages arc long scanning times, difficulty in detecting very small aneurysms, difficulty in establishing the relationship of the aneurysm to adjacent (and surgically important) osseous anatomy, and occasional difficulty in distinguishing between patent lumen and thrombus. The main disadvantages of CTA are radiation exposure, the use of iodinated contrast material, and difficulty in detecting very small aneutysms. In a prospective blinded comparison between CTA and 3D TOF MRA (142 patients), White and colleagues (2001) found no significant difference in diagnostic performance between the two techniques. The sensitivity for detecting aneurysms smaller than 5 mm was 57% for CTA and 35% for MRA, compared with 94% and 86%, tespectively, for aneurysms 5 mm or larger (Figures 37B.16 and 37B.17). This is somewhat discouraging because the critical size at which aneurysms are at a significant risk of rupture has been reported to be 4 mm (Crompton 1996). The limited sensitivity of CTA and MRA in detecting small aneurysms has prevented the more widespread application of these techniques for screening



FIGURK 37B.16 Proximal left middle cerebral artery aneurysm. Comparison of computed tomographic angiography (CTA) with conventional catheter angiography, (A) Maximum intensity projection image from CTA of the circle of Willis shows a berry aneurysm of the Ml segment. (B) Catheter angiography submentovertex view, following left internal carotid artery injection, shows excellent correlation,

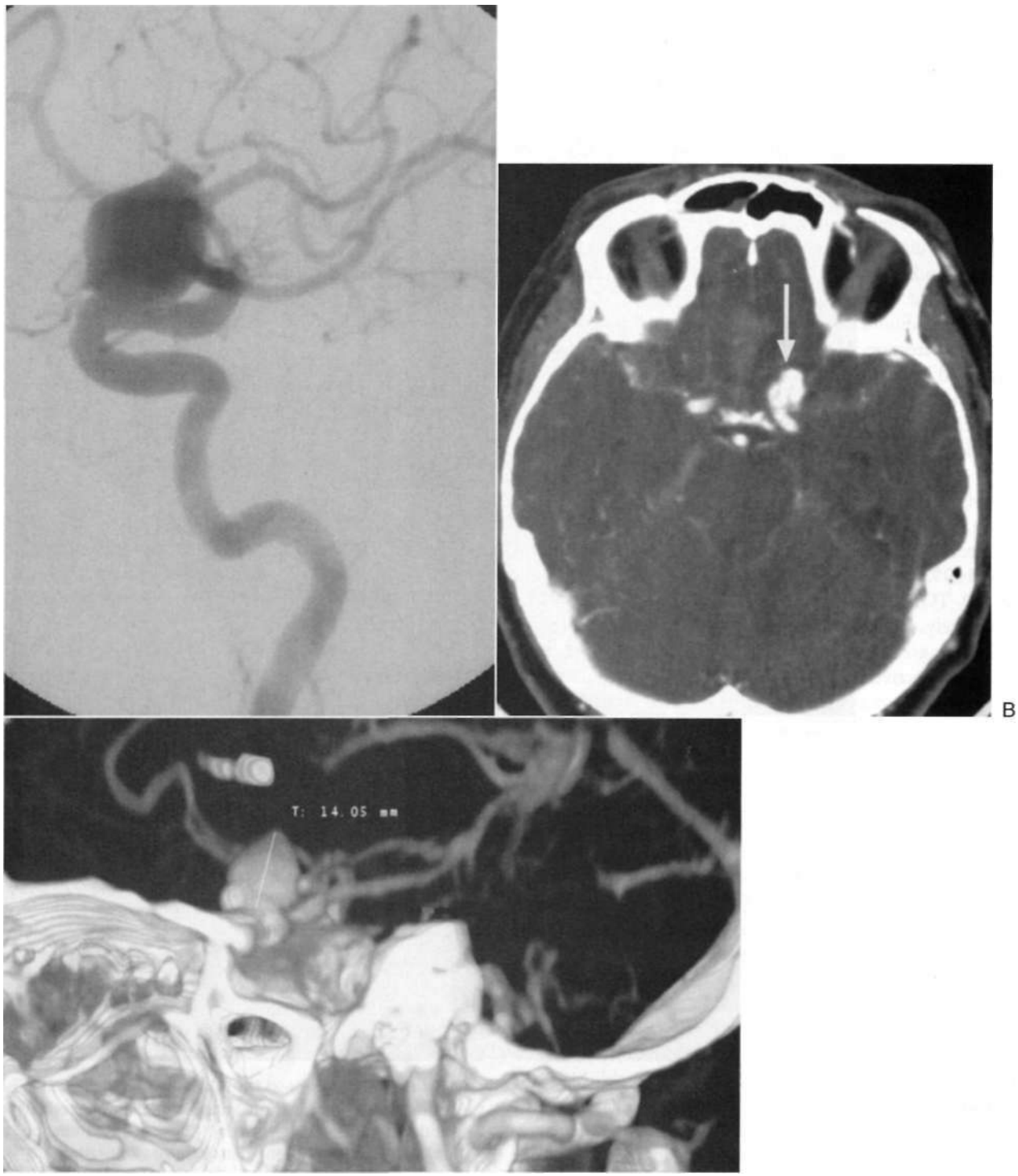


FIGURE 37B.17 Left internal carotid artery aneurysm. Comparison of computed tomographic angiography (CTA) postprocessed images with catheter angiography. (A) Catheter angiography lateral view, following left internal carotid artery (ICA) injection, shows aneurysm originating from the supraclinoid portion of the ICA. (B) CTA axial source image reveals tabulated aneurysm (arrow), (C, D, and E) CTA 3D vol time-rendered images with transparency feature for user-selected tissue regions (called "4D angiography"). (C) Lateral view from the left side of the patient demonstrates the relationship of the aneurysm, measuring 14 mm from neck to dome, to the anterior clinoid process.

Continued

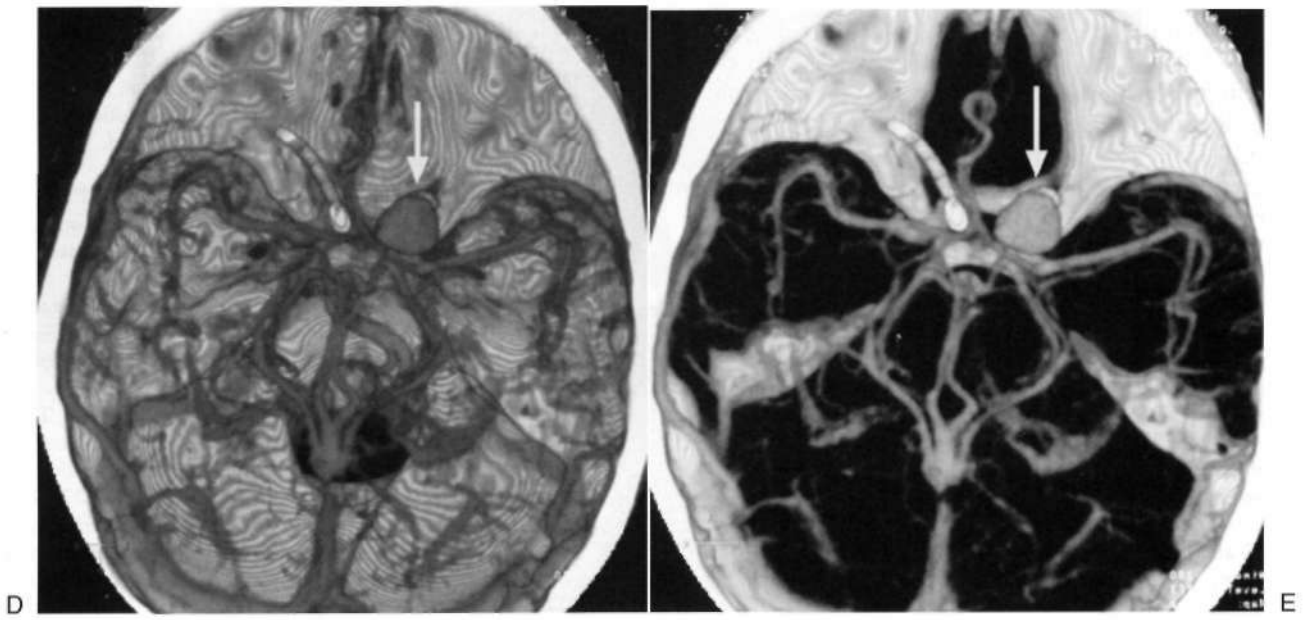


FIGURE 37B.17, cont'd. (D) View of the aneurysm (*arrow*), skull base, and circle of Willis from above. (E) Same view as (D) but edited to remove most of the skull base densities and improve visibility of vessels.

or pretreatment evaluation of aneurysms (Adams, Laitt, and Jackson 2000).

Villablanca and colleagues (2002) have presented promising CTA results for detecting and characterizing very small (less than 5 mm) intracranial aneurysms. Using optimized helical CTA acquisition and postprocessing protocols, which included 3D perspective volume rendered images, 3D thick slab and gray scale 2D single-section images, and thick slab multiplanar reformatted 2D images, the authors reported a sensitivity of CTA for very small aneurysm detection that ranged from 98% to 100%, compared with *95%* for IA-DSA. The specificity of CTA and of IA-DSA was 100%. CTA image analysis times ranged from 6 to 36 minutes (mean = 16 minutes). The smallest aneurysm detected was 1,9 x 1.6 x 1.3 mm', and 48% of aneurysms were detected in the presence of subarachnoid hemorrhage. The sensitivity of CTA exceeded that of IA-DSA primarily because the optimal projection necessary to visualize some aneurysms could be displayed on the postprocessed CTA images but was not or could not be displayed by IA-DSA. Other disadvantages of IA-DSA that have been noted by investigators include superimposition of normal vessels obscuring a small aneurysm and the lack of an internal image scale for estimating the aneurysm sac and neck dimensions. Villablanca and colleagues showed that CTA can provide quantitative information, such as dome-to-neck ratios, and aneurysm characterization, such as the presence of mural thrombi or calcium, branching pattern at the neck, and the incorporation of arterial segments in the aneurysm. The 3D images in particular provided a surgically useful display of the aneurysm sac in relation to skull base structures (see Figure 37B.17). The authors concluded that with adequate attention to detail, all clinically relevant aneurysms can he detected by CTA using routine scanners, protocols similar to those described in the article, and commercially available image-processing workstations. Furthermore, CTA can be a reliable source of information for treatment planning.

Cerebral veins show much more anatomical variation than arteries. The presence of an unexpected vein, or the lack of collateral drainage from a region drained by a vein that may need to be sacrificed during surgery, can alter the approach to resection of an aneurysm. Kaminogo and colleagues (2002) used 3D CTA to demonstrate the venous anatomy accurately. They showed the usefulness of this information in selecting a therapeutic procedure (surgery versus endovascular coiling) and in planning the approach for surgical treatment.

CONCLUSION

Noninvasive imaging of neurovascular disease has progressed greatly in the past decade and is gaining acceptance as the primary approach to screening for several different types of vascular lesions, including atherosclerotic narrowing of the cervical ICA, carotid or vertebral dissection, cerebral aneurysm in the asymptomatic patient at risk, dural venous sinus thrombosis, and spinal dural fistula. The number of indications for noninvasive screening is likely to increase as improvements in MRA (increased field strength to 3 Tesla or more, faster gradient rise times, and improved phased-array technology and k-space sampling techniques) and CTA (greater heat storage capacity and multidetector array helical scanning) result in greater accuracy and reliability of these methods. What remains to be elucidated

are the algorithms that will be followed to diagnose a vascular lesion or category of lesions in the most timely and cost-effective manner for a given clinical presentation. As these algorithms are developed, it seems certain that **MRA** and CTA will play large and complementary roles, with catheter studies reserved for endovascular or intraoperative intervention and evaluation.

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Chapter 37
Neuroimaging

C. NEUROANGIOGRAPHIC ANATOMY AND COMMON CEREBROVASCULAR DISEASES

Johnny S. Sandhu and Ajay K. Wakhloo

Neuroangiography remains the gold standard for diagnostic imaging for most cerebrovascular disorders, even with the advent of magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and three-dimensional (3D) computed tomography (CT) angiography. Despite great advancements in CT and MRA, there are limitations in their sensitivity to detect vascular abnormalities, Although these modalities will undoubtedly improve soon, current indications for diagnostic (catheter) angiography remain extensive (Citron et a). 2000). Furthermore, as other imaging modalities assume a larger role in diagnostic neuroangiography, the applications of neuroendovascular interventions are increasing. Road mapping, digital subtraction angiography, high-resolution flat-panel systems, data acquirement and analysis, and 3D reconstruction (Culham 1996) have all replaced previous methods of acquiring contrast-enhanced images. The importance of understanding normal neurovascular anatomy from an angiographic standpoint remains essential in the diagnosis of neurovascular abnormalities, classification of cerebrovascular pathology, and treatment of disease.

The reported success rate of neuroangiography is 9H% (Vitck 1973; Dion et al. 1987; Citron et al. 2000). The potential risks of angiography and interventional procedures include minor and major stroke (<0.05%, institution dependent) through vessel occlusion and embolic events, contrasr reaction, vessel damage (arterial dissection, pseudoaneurysm, perforation), renal failure, and groin hematoma. Risks increase in patients with severe atherosclerosis, advanced age, pre-existing vascular disease, collagen diseases, dysplasias, and acute subarachnoid hemorrhage, as well as with the length of the procedure, quality of catheters, and the amount of contrast used. Relative contraindications are lodinatcd contrast media allergy, hypotension, severe hypertension, coagulopathy, renal insufficiency, and congestive heart failure. A thorough history and physical examination should precede angiography to allow correction of important pre-existing medical conditions. For example, patients with diabetes mcllitus should discontinue metformin 24 hours befotc undergoing angiography to avoid lactic acidosis. Ir should be withheld for 48 hours after the procedure until their renal function test results return to baseline. Informed consent should be obtained and necessary laboratory work should be documented before performing angiography (Wallace 2000).

FUNCTIONAL NEUROVASCULAR ANATOMY

A thorough understanding of the normal human vasculature and common anomalies is paramount in the practice of safe and effective ncurointervcntional angiography and procedures.

Branches of the Aortic Arch

Generally, three major vessels arise from the aortic arch. The first branch is the *innominate artery* (IA) or *brachiocephalic trunk,* which then branches into the right subclavian artery (SCA) and right common carotid artery

(CCA). The major branches of the right SCA include the right vertebral artery (VA) (dominant vertebral in 25%), the right internal mammary artery, the thyrocervical trunk, and the costoccrvical trunk. An aberrant right SCA arises directly from the aortic arch in 0.5-1.0% of all cases. An irregular right SCA usually presents as the last vessel that arises from the arch (Osborn 1994) and is commonly associated with a right CCA that originates directly from the aortic arch.

The second branch off the aortic arch is the *left* CCA. The most common anatomical variant is a common origin from the aortic arch with the IA (25%). In 5-10% of cases, the left CCA will branch off the proximal IA, termed as the *bovine origin* of the left CCA because of its similarity to bovine anatomy (Figure 37C.1). The left CCA may also be absent, in which case the left external and internal arteries rise directly from the arch.

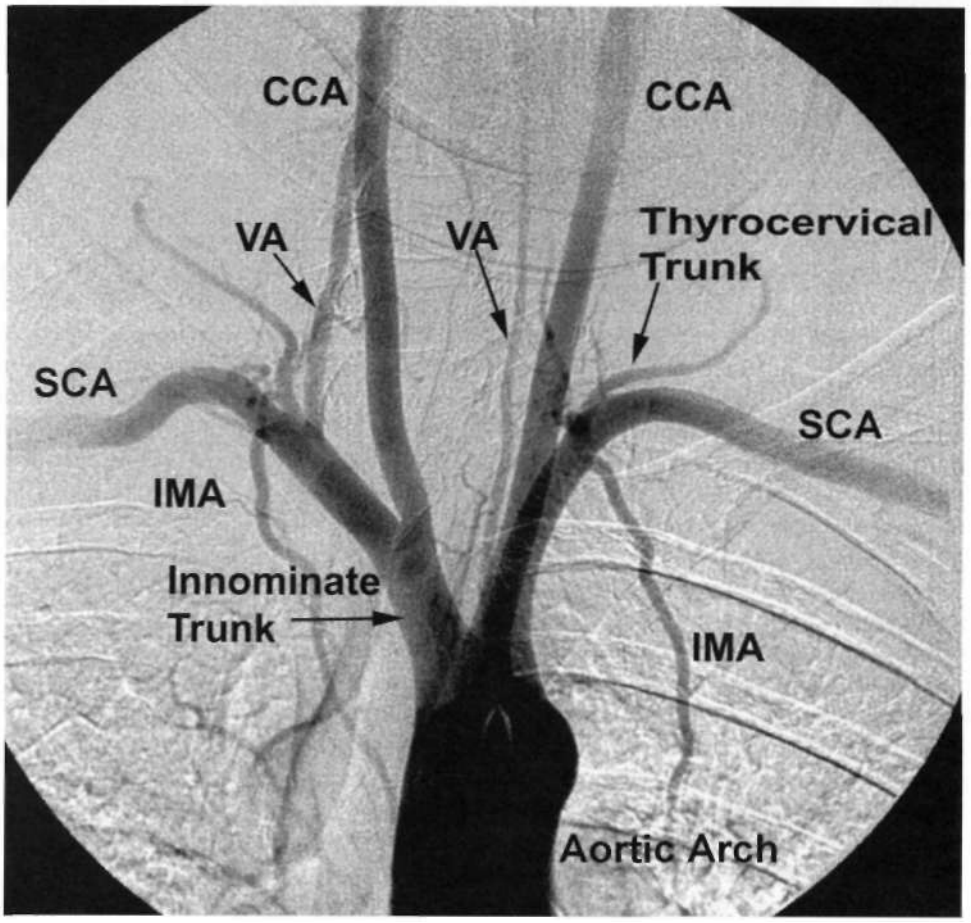
Finally, the third and usually last branch is the *left* SCA. Major branches of the left SCA include the left VA (dominant in 50-60%), the thyrocervical trunk, and the costocervical trunk. The left VA may originate directly from the arch (5%).

Common Carotid Arteries

The right CCA typically arises from the IA; the left CCA usually originates from the aortic arch. The CCA branches into the external and internal carotid arteries approximately at the level of the fourth cervical body (C4). The proximal portion of the internal carotid artery (ICA) runs posterior and lateral to the proximal portion of the external carotid artery (ECA). The carotid bulb is the relatively dilatated proximal portion of the ICA and is significant for disturbed flow that is thought to contribute to endothelial cell damage and subsequent carotid artery plaque formation. There are no significant cervical branches of the ICA.

External Carotid Artery

The smaller ECA in humans, however, gives rise to many hranches of the craniofacial region (Table 37C.1}. Great variability exists in the branches of the ECA, the vascular territories supplied, and the functional significances of those diffetcnecs (Russell 1986; Osborn 1994). Most



A

FIGURE 37C.1 (A) Digital subtraction angiogram of the aortic arch in anteroposterior projection. Note: The left vertebral artery is a variant that originates directly from the aortic arch. CCA = common carotid artery; IMA = internal mammary artery; SCA = subclavian artery; VA — vertebral artery.

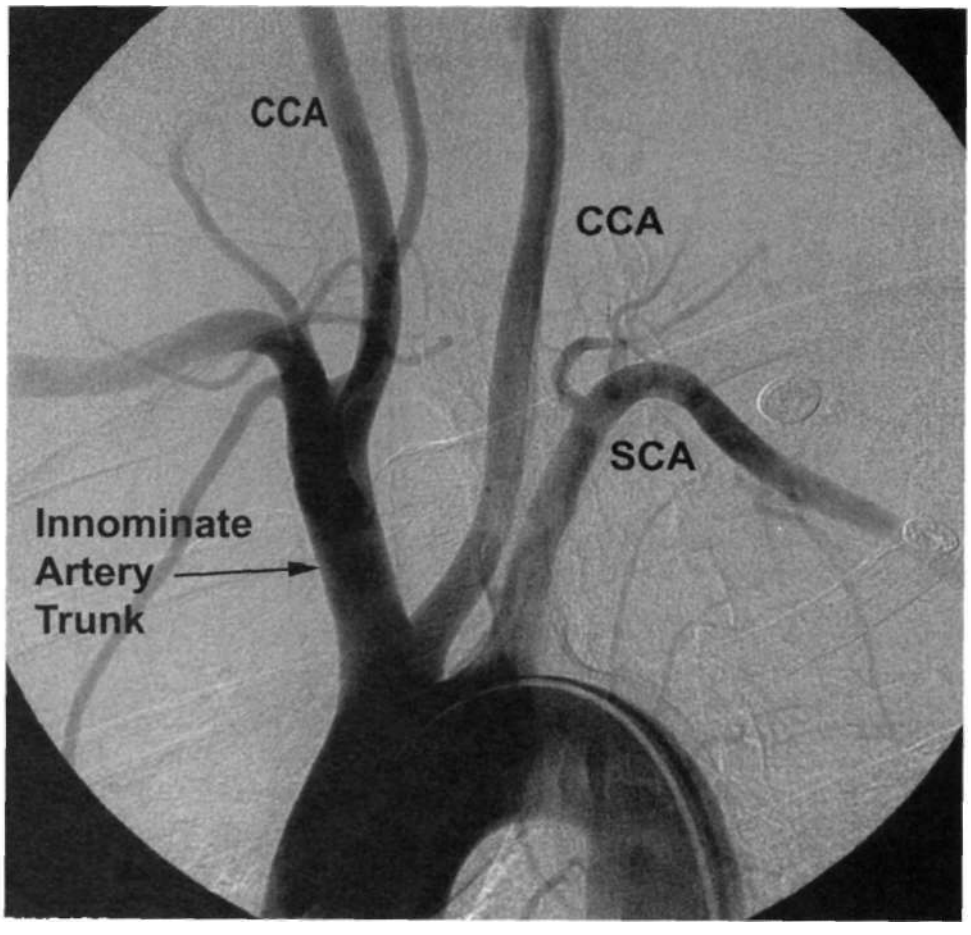


FIGURE 37C.1, cont'd. (B) I.eft antero-oblique (LAO 30-degree) view of the aortic arch. Note the bovine origin of the left common carotid artery.

commonly, the arterial branches of the external carotid are the following in proximal to distal order: superior thyroidal, ascending pharyngeal, lingual, facial, occipital, posterior auricular, superficial temporal, and internal maxillary. In the case of a variant CCA without a bifurcation, all branches may be supplied by the ICA. Key anastomoses of the external and internal carotid arteries are listed because of their significance for embolization in ECA territories and the risk of inadvertent brain stroke resulting from these "dangerous" anastomoses (see Table 37C.1). The maxillary artery has several anastomoses with the ICA. These include the following: infraorbital branch, sphenopalatine artery, middle meningeal artery (meningo-ophthalamic, recurrent meningeal, cavernous ramus), accessory meningeal artery (cavernous ramus), artery of foramen rotundum, anterior deep temporal (orbital branch), anterior tympanic artery, and vidian artery. The ascending pharyngeal artery anastomoses with the petrous ICA through the superior pharyngeal (mandibular anastomosis) and the inferior tympanic artery. The ascending pharyngeal artery anastomoses with the carotid siphon through the superior pharyngeal (carotid branch), the jugular artery (lateral clival branch), and the hypoglossal artery (medial clival branch). The ascending pharyngeal anastomoses with the VA through the hypoglossal artery (odontoid arterial arch), muscular spinal, and lateral spinal artery. The occipital artery meets the VA through CI and C2 anastomotic branches. The posterior cervical artery meets the VA through C2, C3, and C4 anastomotic branches. The ascending cervical meets the VA through C3 and C4 anastomotic branches. The external carotid and vertebral arteries may communicate through C4 collaterals and a type II proatlantal artery.

Commonly associated disorders of the ECA include vascular tumors. Meningiomas, glomus tumors, and juvenile nasopharyngeal angiofibromas are the most commonly discovered vascular tumors supplied by the ECA. The most significant vascular lesions that are supplied by the ECA include pial arteriovenous malformations (AVMs), dural AVMs, capillary telangiectasias, venous angiomas, hemangiomas, carotid-cavernous fistulas, rare aneurysms, and atherosclerotic disease. Commonly, the locus of Kiesselbach that supplies the nasal mucosa will be the source of epistaxis. Traumatic lacctation of the ECA or its branches may also be a source of intractable bleeding.

Table 37C.1: Branches of the external carotid artery, territories supplied, and dangerous anastomoses

	Branch (proximal to distal)	*Territory supplied*	*Cranial nerves*	*Anatomical variants*	*Notes*	*Anastomoses*
1	Superior thyroidal artery	Upper thyroid/larynx		Separate branches for larynx and thyroid directly from ECA		With inferior thyroidal artery
2	Ascending pharyngeal artery	Naso-oropharynx, tympanic membrane, middle ear, some meningeal	V, IX, X, XI, XII: from hypoglossal and jugular branches	Common trunk with occipital artery, also variant branch off ICA		With VA branches through odontoid arcade and neuromeningeal branches
3	Lingual artery	Tongue, floor of mouth, submandibular gland, part of mandible		Common lingual-facial trunk		
4	Facial artery	Face, palate, pharynx, cheek, lip				Angular branch with orbital branches of ophthalmic artery (ICA-ECA)
5	Occipital artery	Posterior scalp, upper cervical musculature, posterior fossa meninges		Variant branch off ICA	Facial nerve palsy not uncommon with embolization of branches of stylomastoid foramen	Numerous with VA branches through distal muscular branches
6	Posterior auricular artery	Scalp, pinna, external auditory canal				With ICA through stylomastoid artery
7	Superficial temporal artery	Scalp, ear, face, buccal		Transverse facial (branch that supplies deep face and cheek) may directly arise from ECA	One of two distal terminal branches, distinguished from middle meningeal artery by hairpin turn across zygomatic arch	
8	Internal maxillary artery	Major distal internal maxillary branches include: Sphenopalatine, descending palatine, and infraorbital arteries. These supply deep facial (muscles of mastication, palate, maxilla, sinuses, teeth, partial nose and orbit including mucous membranes) meninges	Facial nerve through a branch that traverses the petrous bone, also branches with V2		Gives rise to middle meningeal and accessory meningeal branches	With ICA through ethmoidal branches with ophthalmic artery, vidian artery (with petrous ICA), artery of the foramen rotundum (with inferolateral trunk and lateral mainstem in cavernous ICA)

ECA = external carotid artery; ICA = internal carotid artery; VA = vertebral artery.

Internal Carotid Artery

The ICA arises from the bifurcation of the CCA. It consists of four general segments: the *cervical* portion (extracranial), the *petrous* portion (extracranial), the *cavernous* portion (intracranial), and the *cerebral* or *supraclinoid* (intracranial) portion (Hubcr 1982; de Olivcira et al. 1995). The ICA has a typical angiographic appearance (Figure 37C.2) with visible branches that include (proximal to distal) the meningohypophyseal trunk, infcrolateral trunk (lateral mainstem artery), ophthalmic artery (OA), superior hypophyseal artery, posterior communicating artery (PComA), anterior choroidal artery (AChA), anterior cerebral artery (ACA), and middle cerebral artery (MCA), which is the continuation of the ICA.

The *cervical portion* of the ICA includes the carotid bulb and extends to the entrance into the carotid foramen of the petrous temporal bone. Most commonly, the ICA is initially posterolateral to the ECA at the bifurcation; however, the cervical segment subsequently passes medially to the ECA. As stated earlier, anomalous ECA branches may arise from the ICA. Furthermore, persistent embryonic vessels may give rise to vertebrobasilar anastomoses (see Typical Fetal Remnants, later in this chapter).

The *petrous portion* runs within the carotid canal of the petrous bone and ends where the artery enters the cavernous sinus. The petrous portion bends upward toward its posterior bend, or genu, and forms the ascending or vertical segment. The vertical segment runs along the tympanic bone. At the genu, the artery curves anteromedially to the petrous apex and forms the horizontal segment. The distal portion of the horizontal segment runs upward and medially and fills the foramen lacerum to become intracranial. During its run through the petrous, the ICA has several tympanic branches to the middle ear. It is here that the vidian artery, also known as the *artery of the pterygoid canal,* anastomoses with branches of the ECA. Another branch, the caroticotympanic artery, supplies both the middle and the inner ear. It is worthwhile to point out that an aberrant petrous ICA may run posterolaterally rather than anteromedially. It may present in patients as a pulsatile retrotympanic mass.

The *cavernous portion* or the carotid cavernous segment begins at the exit of the JCA from the petrous apex, runs through the cavernous sinus, ends where it exits at the base of the skull, and enters the subarachnoid space near the anterior clinoid. After it leaves the carotid canal, the ICA curves anteriorly and medially to follow the lateral surface

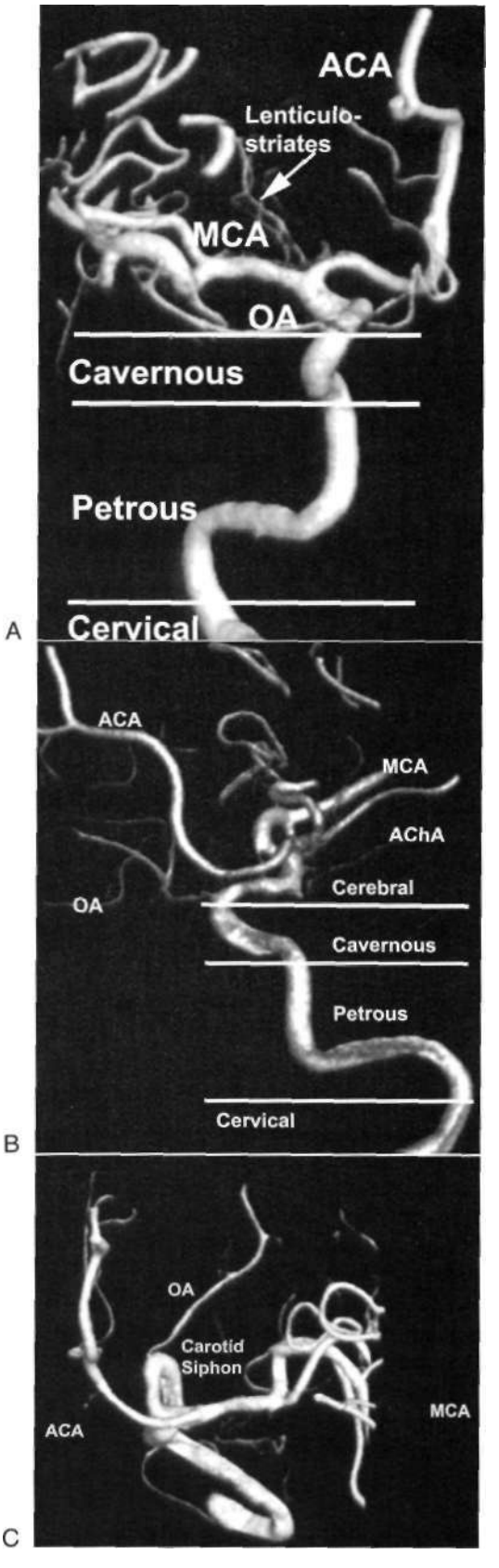


FIGURE 37C.2 Rotational angiogram of the right internal carotid artery with three-dimensional reconstruction. Cervical, petrous, and cavernous segments are demarcated in (A) anteroposterior, (B) lateral, and (C) craniocaudal plane. ACA = anterior cerebral artery; MCA = middlc cerebral artery; OA, ophthalmic artery.

Table 37C.2: Segments of the internal carotid artery and associated branches

Fischer segment (ascending proximal to distal from aorta)	*Named*	*Boundary*	*Common disease findings*	*Branches and vascular territory*	*Anastomoses*
C5 "gassenan segment"	Cavernous between the apex of petrosal pyramid and posreroinferior aspect of the sellar region	Endocranial opening of carotid canal to the beginning of the first (posterior) ICA genu		.\U'Eiiiij;()hypophyseal artery (posterior trunk) (near C4 and C5) Inferior hypophyseal (pituitary gland) Marginal tentorial or Bernasconi and Cassinari (tentorium) Clival dural branch (cavernous sinus, cranial nerves III through VI)	
C4 "cavernous segment"	[ntracavernous Juxtasellar segment	End of ascending portion and beginning of the horizontal segment	Engorgement of ILT with vascular neoplasms or AVM	lnferolateral trunk—ILT (lateral mainstem artery) supplies cranial nerves III, IV, VI, and gasserian ganglion (cranial nerve V) and cavernous sinus dura, foramen of rotundum	ILT with internal maxillary artery
C3 "carotid knee"	]ntracavernous	Posterior 90-degree bend to anterior *90*-degree bend		Capsular branches (distal C3) supplies pituitary gland	
C2 "cisternal segment"	Cerebral portion	End of horizontal segment to end of cavernous segment CI		Capsular branches (proximal C2) supplies pituitary gland	
C1 "terminal segment": supra clinoid	Cerebral portion			Superior hypophyseal, perforating, ophthalmic, PComA, AChA	

AChA = anterior choroidal artery; AVM = arteriovenous malformation; ICA = internal carotid artery; ILT = inferolateral trunk; PComA = posterior communicating artery.

of the sphenoid. It is separated from the trigeminal ganglion laterally and above. The artery runs vertically above the foramen lacerum within a groove along the lateral surface of the sphenoid body near the frontal pole of the trigeminal ganglion, which may be tefetred to as the *ganglion segment* (i.e., the C5 Fischer classification segment) (Fischer 1938) (Table 37C.2).

The artery then tuns anteriorly as it ascends to the base of the anterior clinoid process that displaces the ICA slightly laterally. This segment is referred to as the *C4 Fischer classification segment,* which is la fetal to the pituitary fossa. Below the base of the anterior clinoid process, the carotid makes a sharp bend that is anterior. This segment is known as the *carotid knee* ot *segment C3,* which is still patt of the inttacavernous portion.

The sinusoidal shape of the ICA and the beginning of the final *intracranial or mpraclinoid segment* make up the carotid siphon. The C2-C4 portion was named the "carotid siphon" by Moniz, a term that is well accepted (Huber 1982). In 90% of patients, the OA is the fitst btanch of the intradural portion of the ICA and serves as the demarcation between the *cavernous* and *cerebral* segments of the ICA. The OA is intradural in 90% of patients and arises from the cavernous segment of the ICA in the other 10%. The OA supplies the globe and the tetina via the central retinal artery. It also supplies the orbit and its contents in conjunction with ECA branches. It may receive important collaterals from the orbital branches of the facial and internal maxillary arteries. Proximal occlusion of the OA is associated with little risk to vision because of these ECA collaterals. Visual acuity can be compromised in the case of central tetinal artety embolization, either through the OA or the ECA collaterals to the OA.

The *cerebral* or *supraclinoid portion* of the ICA begins above the antetior clinoid process and ends at the bifurcation to give rise to the ACA and the MCA. The

artery penetrates the dura and arachnoid membrane at the level of the OA, which is usually located intradurally. The carotid artery then runs posteriorly along the medial margin of the anterior clinoid process and beneath the optic nerve, which is known as the *cisternal segment,* or C2, The terminal carotid segment, or CI, ascends and then divides at the circle of Willis.

The PComA is a collateral pathway of the circle of Willis that connects the internal carotid and vertebrobasilar circulations. It originates between the supraclinoid portion of the ICA and the PI segment of the ipsilateral posterior cerebral artety (PCA). The PComA supplies petforating branches to the thalamus, hypothalamus, and optic chiasm. Anomalies of the PComA include hypoplasia, which is seen in one third of anatomical dissections (Sacki and Rhoton 1977; Osborn 1994}. Another anatomical variant is the fetal origin of the PCA that is seen in 20-25% of all patients.

The AChA originates from the ICA distal to the PComA. It is distinguished into two segments. The proximal or cistern segment travels posteriorly in the crural cistern subjacent to the optic tract and medial to the uncus of the temporal lobe. It then enters the choroidal fissure of the temporal horn of the lateral ventricle where there is a slight kink in its contour that is known as the *plexal point.* Distal to the kink, the second segment is known as the *distal* or *plexal (intraventricular) segment.* This segment runs into the choroid plexus of the temporal horn and curves posterolaterally around the thalamus. It supplies the choroid plexus of the lateral ventricle and anastomoses with the la tero posted or choroidal artery. There are several branches that also anastomose with branches of the PComA, PCA, and MCA. Perforators serve the retrolenticular fibers of the internal capsule, optic tract, globus pallidus, thalamus, hypothalamus, caudate nucleus, red nucleus, parts of the temporal lobe, basal ganglia, a portion of the cerebral peduncle, and substantia nigra. Proximal occlusion of the cisternal part of the AChA may cause hemiplegia, hemiparesis, or homonymous quadrant or hemianopia by thrombosis of minute petforators that arise proximal to the plexal point. Also, patients may present with hemianesthesia, or memory deficits. Embolizations performed distally to the plexal point are considered safe. However, because of flow reduction, retrograde thrombosis of the entire AChA may occur.

The cavernous and *cerebral* (supraclinoid) segments of the ICA may undergo distal narrowing secondary to athetosclerotic disease. Other nondegenerative disorders that may cause arterial narrowing include spasm, tumor encasement, dissection, and radiation-induced vasculitis. The most important vascular lesions in this area are aneurysms, carotid-cavernous fistulas, dural fistulas, moyamoya disease, fibromuscular dysplasia (FMD), and AVM. Highly vascularized tumors that may present in this area include meningiomas, juvenile nasopharyngeal angiofibromas, and pituitary adenomas.

The terminal ICA bifurcates into the MCA and the ACA. The PCAs typically originate from the basilar artery but rarely branch off the ICA, which is known as a *fetal origin* (see Typical Fetal Remnants, later in this chapter).

The ACA supplies the anterior two thirds of the medial portions of the cetebral hemispheres and approximately 1 cm of the superolateral surface of the brain convexity. Its caliber is smaller than the MCA (Muller et al. 1991) and it provides several vital branches. The ACA major branches include the following: orhitofrontal, frontopolar, callosomarginal, pcricallosal, anterior (internal) frontal, middle (internal) frontal, posterior (internal) frontal, paracentral, parietal (internal) superior, parietal (internal) inferior, and splenial arteries (Figure 37C.3).

The Al or horizontal segment is the first branch of the ACA and runs medially from its origin, giving rise to the medial lcnticulostriate arteties, which are deep perforating branches that supply the head of the caudate nucleus and the anterior limb of the internal capsule (Ghika, Bogousslavsky, and Regli 1990). The ACA then joins the anterior communicating artery (AComA). The AComA is actually a part of the circle of Willis but is usually considered part of one complex with the ACA (Damasio 1983; van der Zwan et al. 1992; Osborn 1994). Small perforating branches of the AComA may supply the following structures: lamina terminalis and hypothalamus, anterior commissure, fornix, septum pcllucidum, paraolfactory gyrus, the subcallosal region, and the anterior part of the cingulate gyrus.

The A2 segment is the ACA from its connection to the AComA to its bifurcation into the pericallosal and callosomarginal arteries. It runs cephalad in the cistern of the lamina terminalis and courses around the corpus callosum genu. One of the lenticulostriate branches that commonly arise from the proximal A2 segment is the recurrent artery of Heubner (50%), which may originate from the Al segment (44%) and infrequently from the AComA. It supplies the caudate nucleus, the rostral putamen, and the anterior limb of the internal capsule. Infarctions in the vascular territory of the recurrent artery of Heubner result in clinical syndtomes that present with contralateral hemiplegia of face and arm, transcortical motor aphasia, or crural monoplegia.

The medial lenticulostriate arteries from the Al segment supply the basal ganglia, anterior limb of the internal capsule, hypothalamus, optic chiasm, and inmndibulum. The AComA perforators supply the corpus callosum genu, the head of the caudate nucleus, and the basal ganglia. These perforators may be injured during a frontal approach to surgical clipping of AComA aneurysms. Patients may experience short-term memory deficits and complex neuropsychological impairments.

The next two branches of the A2 segment ate the orhitofrontal and frontopolar arteries. The A2 segment runs superiorly within the interhemispheric fissure and ends with the pericallosal and callosomarginal arteries. Table 37C.3 provides an overview of common

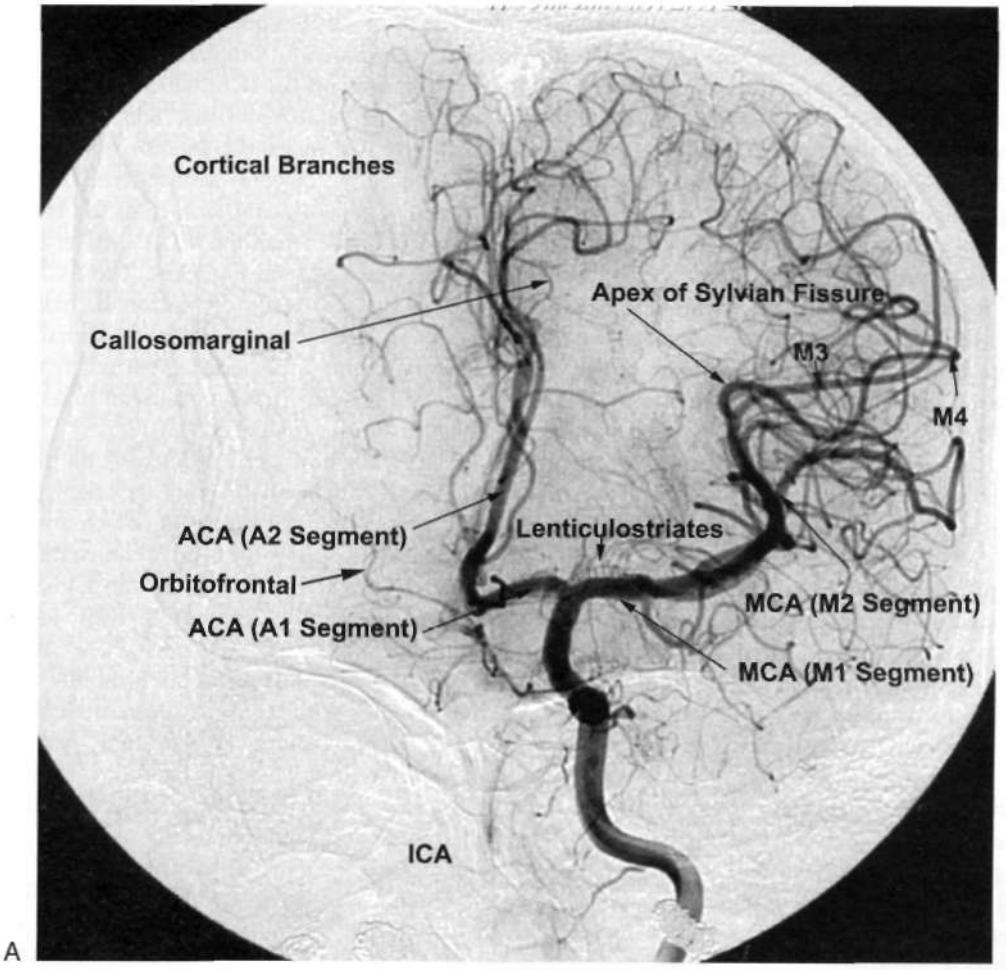


FIGURE 37C3 Anterior (A) and lateral (B and C) views of anterior circulation after contrast injection into the left internal carotid artery. For the purpose of clarity, the middle cerebral artery (MCA) and the anterior cerebral artery (ACA) branches are labeled separately in (B) and (C).

neurological symptoms observed with interruption of blood flow from particular branches. The A3 branches refer to cortical suppliers and have classically been regarded to vascularize the anterior two thirds of the medial hemispheric surfaces in addition to a small area that extends over the convexities. However, variability is common and normal.

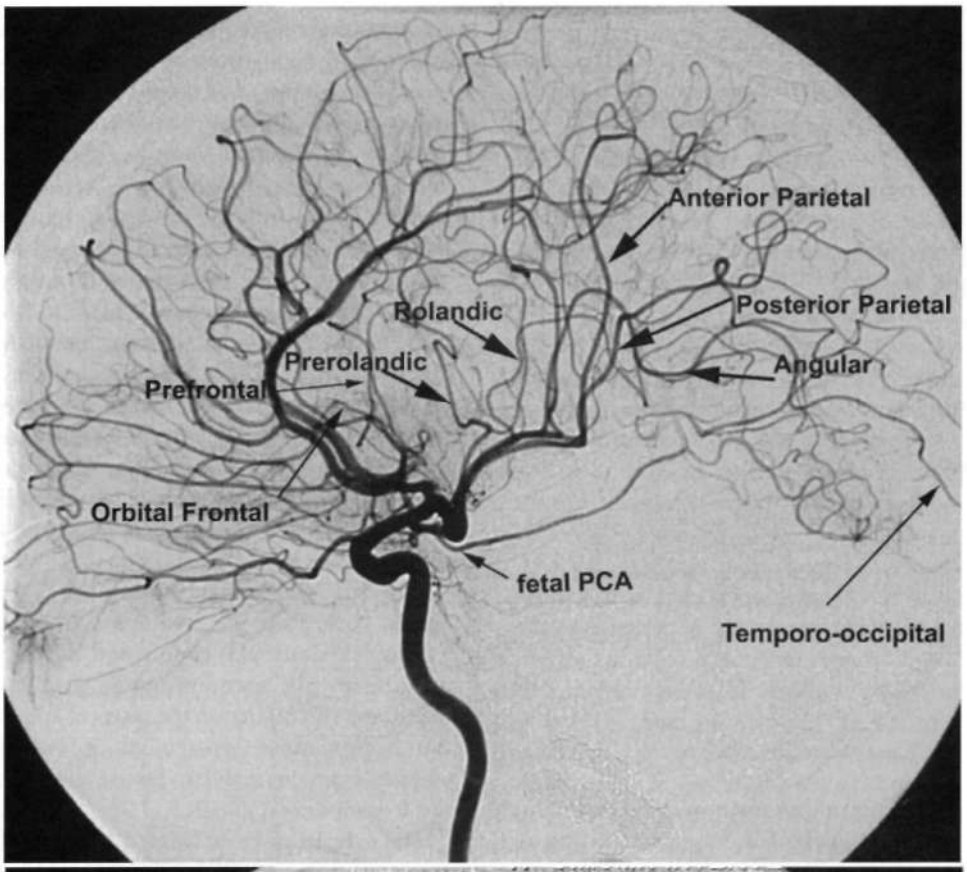
Common anatomical variants include hypoplastic or absent Al (5-18%). Yasargil and Smith (1982) reported that as many as 50% of these patients develop a contralateral Al intracranial aneurysm. A duplicated Al is also seen in approximately 10% of patients. An azygous ACA refers to a solitary and unpaired vessel that arises from the confluence of the Al segments from the left and right ACAs. However, true azygous ACAs are rare and are associated with lobar holoproscnccphaly and saccular aneurysms {Osborn 1994). A bihemispheric ACA sends a variable number of branches to the contralateral side {separate left and right arc present, but one is dominant and sends to both sides). Other ACA variants include infra-optic origin, duplicated ACA, and fusion of associated aneurysms,

Neurological symptoms in the ACA territory include slight impairment of superficial sensation and severe impairment of deep sensation in the contralateral lower limb. If the dominant hemisphere is involved, aphasia resulting from infarction of the supplementary speech areas will occur, although it is usually transient. There may be loss of control of urinary and rectal sphincters. Psychomotor phenomena include catatonic posturing, hypokinesia, and memory loss.

Finally, issues to consider in the endovascular approach of the ACA include recognition of a hypoplastic A1, the hair-pinned origin A1, access through the posterior circulation, and variations of the distal A2 through AComA variations,

The Middle Cerebral Artery

The MCA is the other of two branches of the ICA. It is the larger diameter vessel and is divided into several major segments. Table 37C.4 details its complex course and the large, deep, and cortical territories that are supplied.



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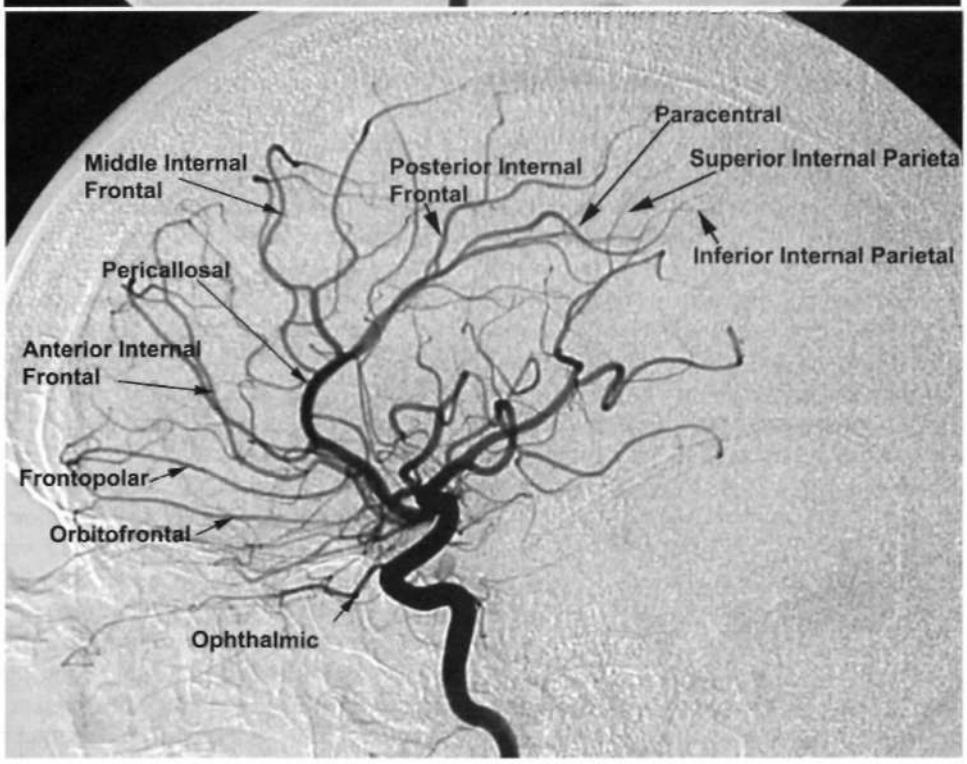


C

FIGURE 37C.3, cont'd.

Tabic 37C.3: Clinical presentation associated with vascular compromise of various anterior cerebral artery territories

Artery	*Associated symptoms*
Orbito frontal	Confabulation, amnesia, cardiovascular instability
Fronto polar	
Callosomarginal	
Pcricallosal	
Anterior (internal) frontal	Eye deviation toward lesions, loss of interest (abulia), and reflex grasping
Middle (internal) frontal	Transcortical motor aphasia (dominant hemisphere), tnniMnii contralateral akinesia, contralateral alien hand syndrome, and contralateral dyspraxia
Posterior (internal) frontal	
Paracentral	Contralateral weakness, numbness of lower extremities, loss of discriminative sensoty modalities, bowel and bladder incontinence
Parietal (internal) superior	
Parietal (internal) inferior	
Splenial	

Great variability exists within the branching of the MCA as it supplies structures in the frontal, parietal, temporal, and lateral occipital lobes. The MCA is the most common site for embolic stroke because it carries almost two thirds of the blood flow from the ICA and presents morphologically a continuation of the ICA. Its branches supply most of the lateral surface of the hemisphere, insula, and anrerior and lateral aspects of the temporal lobe. The variability of the MCA, the bifurcation, and its branches are less frequently seen when compared with rhe other cerebral arteries.

The MCA has been classically described in two major ways: the functional branching approach and the segmental approach. The segmental approach divides the MCA into four major segments according to brain landmarks (Chyatte and Porterfield 2001). The major segments of the MCA are the Ml or sphenoidal segment (origin to limen insulae), M2 or insular segment (runs along the insula), M3 or opercular segment (operculum superior to the insula), and M4 or terminal segment (convex surfaces). The Ml segment is the largest in diameter and gives rise to the lateral lenticulostriate arteries that supply the basal ganglia and the anterior limb of the internal capsule. The Ml segment extends laterally and horizontally for 1-2 cm from its origin at the terminal ICA to the sylvian or lateral cerebral fissure. The lateral lenticulostriate arteries penetrate the inferior surface of the frontal lobe to supply the basal ganglia, caudate nucleus, and internal capsule. The Ml segment may also provide anterior temporal branches that sometimes originate from the proximal M2 segment. The anterior temporal branches supply the temporal tip cortex. At **its** distal portion, the Ml segment curves posterosuperiorly to the insular cortex (island of Reil), where it bifurcates into major anrerior and posterior cortical branches. Between 20% and 30% of all intracranial aneurysms are found at the Ml bifurcation,

Table 37C.4: Branches of the middle cerebral artery and its anatomical course

Segment	*Course*
MCA	
(Ml) sphenoidal	Extends laterally and horizontally from its origin at ICA to sylvian fissure
(M2) insular	At its genu, M2 loops over insula and passes laterally to exit from sylvian fissure
(M4) terminal	Hemispheric surface

ICA = internal carotid arrery; MCA = middle cerebral artery,

The M2 segment has branches that course over the insular cortex and the frontoparietal operculum. It follows a complex sinusoidal course and moves posterosuperiorly to the superior margins of the insular cortex and then passes inferolaterally on the internal and inferior surfaces of the frontoparietal operculum. These multiple branches emerge from the sylvian fissure and run superiorly over the frontoparietal cortex.

The sylvian point is formed by a branch of the angular artery and is the most superior M2 arterial loop on anteroposterior angiographic images. It is at the superior margin of the insula. The sylvian triangle can be noted on lateral angiographic images and is distinguished by the complex array of MCA cortical branches extending over the insular and opercular cortices. Its base is in the frontosellar region and its apex is in the parietal region. Distortions or displacement of the sylvian triangle can be induced by mass effect of intracranial lesions.

The anterior cortical branches of the M2 portion follow the common order: lateral orbito frontal, operculofrontal {ascending frontal or candelabra branch), and central sulcus arteries. The central sulcus arteries are usually called the *precentrai* or *prerolandic* and *central* or *roiandic* branches. They supply the motor and sensory cortical strips. The posterior M2 cortical branches include the anteriot and posterior parietal, angular, and posterior temporal arteries. The M2 cortical branches provide vascular supply to cerebral centers of speech, comprehension, and calculating ability {for the dominant hemi-sphere). It also supplies motor and sensory function of the contralateral face, neck, upper extremities, thorax, and abdomen. Many strokes and transient ischemic events will present with an MCA syndrome with symptoms that reflect consequences of embolic or occlusive events in this vascular territory.

The M4 terminal segment supplies rhe cortex of the frontal and parietal lobes. The superior division includes the orbitofrontal, prefrontal, precentrai, postcentral, anterior and posterior parietal, and angular arteries. The inferior

division supplies the temporal lobe and part of the occipital lobe. Its branches include the temporopolar, anterotemporal, middle temporal, posterotemporal, and tempo ro-occi pita I arteries. Table .>7C..S displays the common neurological presentation of patients with disruption of blood flow from the inferior and superior division,

Aneurysms of the MCA make up approximately 20-25% of all aneurysms and are typically located at the M1-M2 bifurcation. Mycotic aneurysms are generally located in the distal MCA territory, or the M4 branch. Other disorders within the territory of the MCA are commonly seen and include AVM, atherosclerosis, vasculitis, arteritis, and mass effect on the MCA with displacement of the sylvian triangle and point.

Endovascular considerations specific to the MCA include navigation of catheters and devices beyond tin- sylvian triangle where the MCA loops over the surface of the insula, en passage vessels of AVMs, and dominant hemisphere with eloquent brain areas.

VERTEBROBASILAR SYSTEM

The VAs originate from the subclavian arteries adjacent to the origins of the internal maxillary arteries proximal to the thyrocervical and costocervical trunks. In 5% of patients, the VA arises directly from the aortic arch, usually the left side. Also, the thyrocervical and costocervical trunks may anastomose with the extracranial portion of the VA, which may provide branches to the anterior and posterolateral spinal arteries. One of the two vertebral arteries, again usually the left, may be dominant in size. The VA ascends through the transverse foramen of the vertebral body of C6 and passes superiorly through the transverse foramina of C5-C1. The VA then runs posteriorly around the atlanto-occipital joint and ascends through the foramen magnum. This point may be apparent on angiographic images as a decrease in vessel caliber where it penetrates the foramen magnum membrane and the dura, where the origin of the posterior meningeal artery is usually located. The intradural VA travels superiorly and around the lateral aspect of the medulla (Figure 37C.4).

Table 37G5: Clinical presentations associated with vascular compromise of various middle cerebral artery territories

Vessel	*Side*	*Symptoms*
Middle cerebral artery	Dominant hemisphere	Contralateral hemiplegia Hemianesthesia Homonymous hemianopia Conjugate ocular deviation toward the affected side
	Nondominant hemisphere	Contralateral hemineglect, global aphasia
M4 superior		Contralateral sensorimotor deficit and ipsilateral deviation of head and eyes Broca's aphasia in dominant hemisphere (motor)
M4 inferior		Wernicke's aphasia in dominant hemisphere with possible homonymous hemianopia Gerstmann's syndrome (agraphia, acalculia, finger agnosia and right-1 eft confusion, hemisensory deficit if dominant parietal lobe affected) Nondominant hemisphere infarct results in hemineglect and agitated delirium

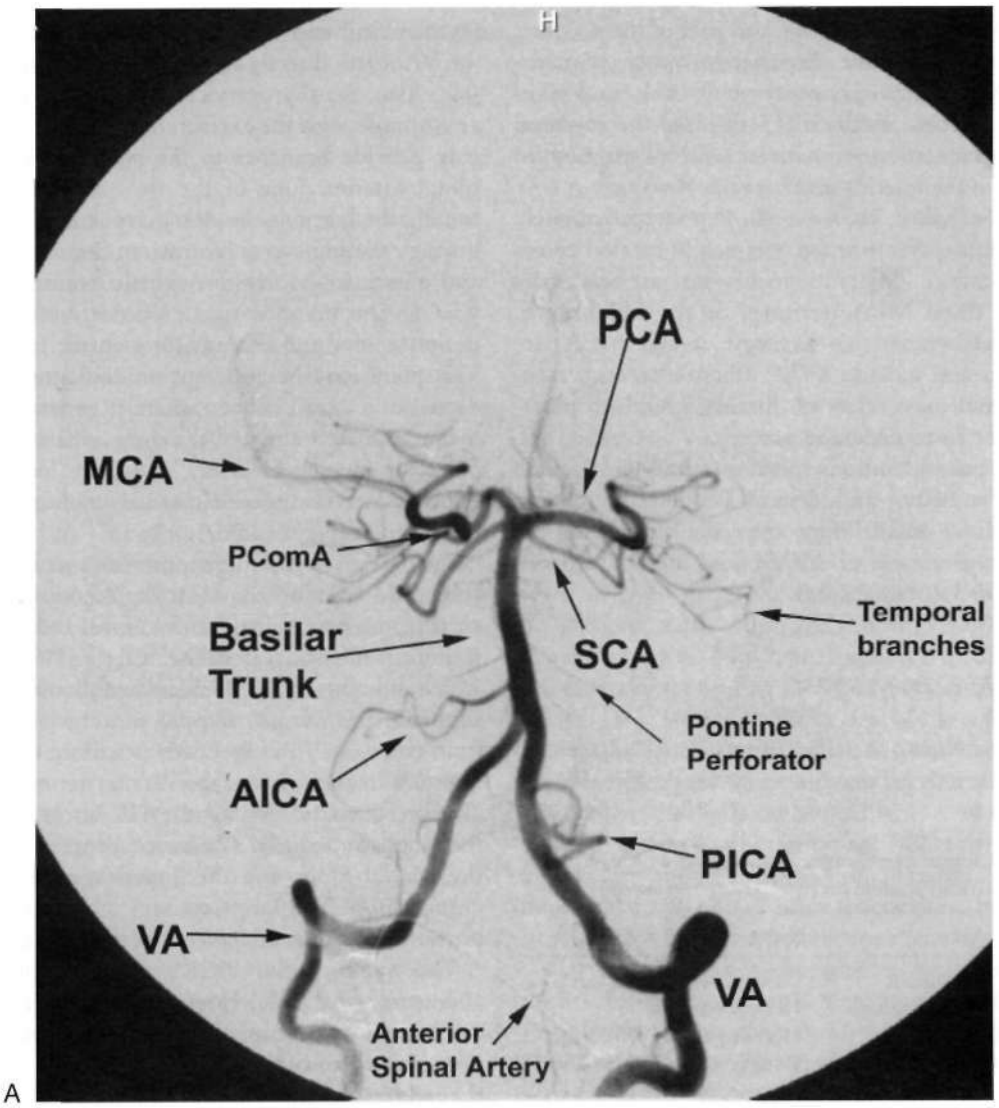
The VA gives rise to the posterior meningeal artery (falx cerebelli), anterior spinal artery (cervical anterior spinal cord), posterior spinal artery (rare and may arise from posterior inferior cerebellar artery [PICA]), and PICA, which runs around the medulla and over the tonsil and supplies the inferior vermis, the choroid plexus of the fourth ventricle, and the inferior surface of the cerebellum.

In 1% of angiograms, the VA may terminate in the PICA. The proximal portion of the PICA travels inferiorly and then loops superiorly. The inferior portion is also known as the *caudal loop,* and the superior portion is called the *cranial loop.* The loops contain the anterior, lateral, and posterior medullary segments of the proximal PICA.

The apex of the PICA'S cranial loop is called the *choroidal point* and defines the floor of the fourth ventricle on lateral angiographic images. It provides the fourth ventricular choroidal branches. After the choroidal point, the supra ton si liar segment of the PICA gives rise to the tonsillohemispheric and inferior vermian branches. The inferior vermian artery anastomoses distally with the superior vermian branch of the superior cerebellar artery and provides a major posterior fossa collateral pathway.

Occlusion of the PICA results in a range of consequences from no symptoms to cerebellar or brainstem infarction that results in severe neurological deficits or even death. Infarction of the lateral medullary segment lying posterior to the inferior olivary nucleus leads to the classic lateral medullary syndrome (Wallenberg's) with nystagmus, ipsilateral ataxia, asynergia, vomiting, dysarthria, dysphonia, singultus, contralateral impairment of pain and thermal sense, hypoacusis, ipsilateral numbness of the face, loss of taste, ipsilateral Horner's syndrome, hoarseness, and dysphagia.

The anterior spinal arteries originate from the VA distal to the PICA origin and course inferomedially in 50% of cases to join the contralateral side along the anterior cord. Normally, a variable degree of hypoplasia may exist distal to the origin of the PICA. Near the pontomedullary junction, the two vertebral arteries join to make up the basilar artery. The basilar artery runs antcrosupcriorly over



FIGUKE 37C.4 (A) Anteroposterior view of the posterior circulation, the left vertebral artery has been injected with contrast. AICA = anterior inferior cerebellar artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; PComA = posterior communicating artery; PICA = posterior inferior cerebellar artery; SCA = superior cerebellar artery; VA = vertebral artery.

the ventral pons. The vertebral arteries and the basilar artery may be fenestrated where they divide into two parallel channels over short distances. Many small pontine perforating branches arise from the basilar artery and supply the following structures: pyramidal tracts, medial Iemnisci, red nuclei, respiratory centers, and all nuclei to cranial nerves II, VI, VII, and XII.

The first major branches of the basilar artery distal to the joining of the vertebral arteries are the paired anterior inferior cerebellar arteries (AICA) that course around the pons and toward the cerebellopontine angle and the internal auditory canal meatus to supply the anterior cerebellar hemispheres, cranial nerve VII, and cranial nerve VIII. The AICA supplies la total pontine structures and gives rise to the labyrinthine artery, which arises directly from the basilar artery in 15% of cases. The PICA and AICA occasionally may originate from the basilar within a common trunk. The labyrinthine artery runs along cranial nerve VIII through the internal auditory canal and supplies the inner ear. Other important basilar artery branches include small pontine perforators that supply the brainstem. The last infratentorial branches of the basilar are the paired superior cerebellar arteries. The superior cerebellar artery runs around the brainstem in the pontomesencephalic groove in the perhne-sencephalic cistern below the oculomotor and trochlear nerves and above the trigeminal nerve to supply the supero-lateral surface of the cerebellar hemisphere. Proximally, it supplies the lateral pontine structures and the sympathetic and spinothalamic tracts. Distally, it branches into the superior vermian artery and cerebellar hemispheric branches, which supply portions of the cerebellar peduncles, dentate nucleus, and superolateral aspects of the cerebellar

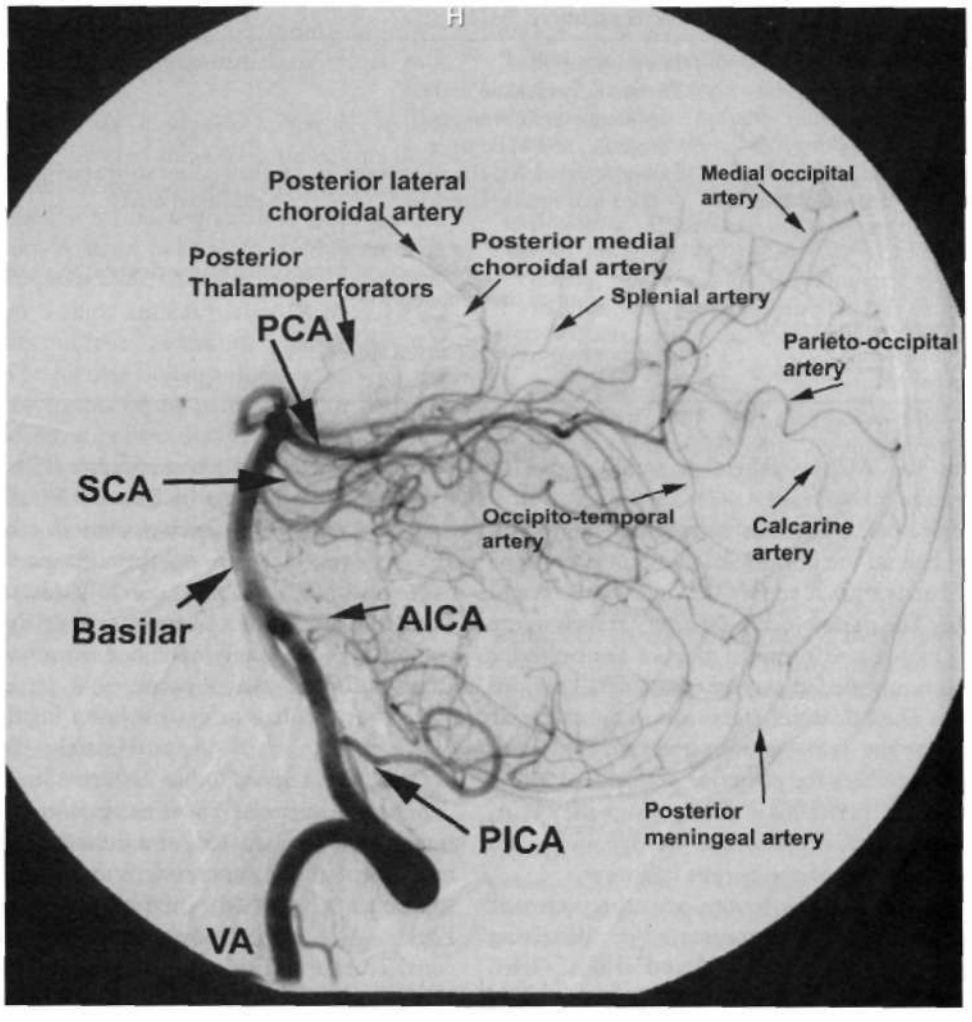


FIGURE 37C.4, cont'd. (B) Lateral view of the posterior circulation.

hemispheres. Duplication of one or both superior cerebellar arteries may be present infrequently.

The distal basilar trunk generally bifurcates into the left and right PCAs at the level of the pontomesencephalic junction, which is superior to the oculomotor nerve and the tentorium. The tentorium separates the proximal PCA from the superior cerebellar artery on both anteroposterior and lateral angiographic images. The proximal PCA is divided into P1 and P2 segments. PI and P2 can often be distinguished during angiography when nonopacified flow fills the transition zone from the ipsilateral PComA. The PCA directly arises from the ipsilateral ICA in approximately 20% of patients, which is also known as the *fetal origin of the PCA.* There is usually marked hypoplasia or complete absence of the PI segment in those cases. Vertebral angiography that reveals unilateral or bilateral absence of the PCA may be due to occlusion of the PCA or secondary to a fetal origin of the PCA. The P2 segment provides many branches with supply to a number of structures (Table 37C.6).

The PCA runs posteriorly around the brainstem in the ambient cistern and then travels medially in the quadrigcminal plate cistern. The distal calcarine cortical branches of the PCAs converge toward the midline on a Towne's projection (caudad angulation of the vertebral angiogram) and arc separated by the falx cerebri.

The PCA has branches that supply the diencephalon, midbrain, posterior one third of the medial hemisphere surface, and occipital lobe.

The peduncular or PI segment is the first part of the PCA. It is characterized as a short segment from the basilar top to the PComA and travels above the third cranial nerve, The thalamoperforating arteries arise from the PComA and PI segment and supply the diencephalon and midbrain. The P2 or ambient segment runs in the ambient cistern from the PComA to the posterior aspect of the midbrain. **Its** branches are the medial PChAs (proximal P2) and supply the colliculi, posterior thalamus, pineal gland, and part of the midbrain. The lateral posterior choroidal arteries pass into the choroid plexus of the lateral ventricle and

Table 37C.6; Branches of the posterior cerebral artery

Proximal segment of P2	*Territory supplied*	*Anastomosis*
Posterior thai a mop erf orating and thalamogeniculate arteries	Thalamus, geniculate body, posterior limb of internal capsule, and optic tract	
Minute branches, medial and lateral posterior choroidal arteries	Cerebral peduncles, choroid plexus of third and fourth ventricles	Collateralizes with anterior choroidal artery
Distal segment of P2		
Splenial artery	Splenium of the corpus callosum	Collatetal with distal ipsilateral pericallosal
Antetiot, middle, and posterior temporal arteries	Undersurface of the temporal lobe	
Parieto-occipital artery	Inner posterior cerebrocortical sutface	
Calcarine artery		Visual cortex

anastomose with the AChAs. There is some degree of variability of supply.

The P3 (quadrigeminal) segment runs within the quadrigeminal cistern behind the brainstem. Its branches are the inferior temporal arteries that supply the inferior surface of the temporal lobe. The parieto-occipital artery travels in the parieto-occipital fissure and supplies most of the posterior one third of the brain's medial surface and a small area of the Literal surface. The calcarine artery runs in the calcarine fissure and supplies the visual cortex and occipital pole. The splenial artery is where the posterior pericallosal artery anastomoses with the pericallosal artery from the ACA, runs adjacent to the corpus callosum at the splenium, and supplies the posterior part of the corpus callosum.

The most important vascular lesions are atherosclerotic changes, rare cases of FMD, traumatic or dissecting aneurysms, moyamoya disease, AVMs, and vein of Galen malformations. Important mass effects and encasements of PCA branches include displacements with brainstem mass, posterior temporal mass, caudal transtentorial herniation, tentorial meningiomas, thalamic mass, suprasellar mass, and posterior fossa mass.

Occlusion of thalamoperforators (P2) results in contralateral hemiplegia, cerebellar ataxia, and rubral tremor associated with ipsilateral oculomotor nerve paresis (Nothnagel's syndrome) (Table 37C.7). If the subthalamus is affected, hemiballism on the contralateral side may result. Occlusion of the thalamogeniculate (P2) arteries results in the thalamic syndrome of Dejerine-Roussy (loss of superficial and particularly deep sensation, with intense intractable hyperpathic pain on the affected side and extreme hypersensitivity to mild touch pain and temperature). Transient contralateral hemiparesis or dystonic movement with possible homonymous hemianopsia may be present. Distortion of taste may occur.

The vertebrobasilar system has a highly variable course of the basilar artery. Approximately 10% of aneurysms occur in this tegion. Other abnormalities include fusiform dilatation (otherwise know as *vertebrobasilar dolichoectasia:* distorted, elongated, and dilatated artery compressing neural structures), atherosclerotic disease, thrombosis with subsequent brainstem infarction, traumatic dissections, FMD, AVM, and metastatic lesions. Endovascular considerations include the tortuosity of the vertebrobasilar system, perforating branches, eloquent areas of the brain supplied, risk of perforation with subsequent hemorrhage, embolic events, en passage vessels, and the proximity of the vascular system to the cranial nerves.

TYPICAL FETAL REMNANTS

Typical fetal remnants include the following vessels: fetal PCA, trigeminal, hypoglossal, otic, proatlamal I, and

Table 37C.7: Clinical presentation associated with vascular compromise of various posterior circulation territories

Vessel	*Clinical symptoms*
P2 peduncular perforators	Contralateral rigor, tremor, chorea, athetosis, ipsilateral oculomotor paresis, and contralateral hemiplegia (Weber's syndrome)
Long circumflex branches (PI, P2)	Damage of oculomotor nuclei and other tectal structures (I'arinaud's syndrome}
Bilateral occlusion of inferior temporal arteries (P2)	Memory loss and Korsakoff-like syndrome, endocrine disturbances
Calcarine	Homonymous hemianopia with central vision pares
Splenial artery (P3)	Dominant occipital lobe leads to dyslexia without dysgraphia
Anterior inferior cerebellar artery	Variable extent of potential infarct dependent on size and territory supplied; large anterior inferior cerebellar artery occlusion can lead to death or infarction of the lateral pons, tegmentum, or medulla
Superior cerebellar artery	Ipsilateral cerebellar ataxia, nausea and vomiting, pseudobulbar speech, contralateral loss of pain and thermal sensation, partial deafness, ipsilateral static tremor, ipsilateral Horner's syndrome, and palatal myoclonus

proatlantal II. Also, a persistent stapedial artery may present as an intra tympanic vascular anomaly that usually ends as a connection to the middle meningeal artery. The fetal PCA may be present in nearly 15% of patients. It originates from the ICA but diminishes in size during development to become the PComA to connect the ICA with the basilar artery. A persistent trigeminal artery may be seen on less than 1% of angiograms and connects the petrous ICA with the distal third of the basilar artery. This embryonic vessel is the most common anastomosis of the carotid to vertebral system caudal to the circle of Willis. The persistent primitive hypoglossal artery connects the cervical ICA to the basilar artery after traversing the hypoglossal canal. The VA is often hypoplastic on the ipsilateral side. The presence of a persistent otic artery is rare. It connects the AICA to the intrapetrous ICA. Intersegmental proatlantal arteries maybe present and connect the cervical ICA {proatlantal I) or the ECA (proatlantal II) to the distal VA before its passage through the foramen magnum. The ipsilateral VA is usually hypoplastic in those cases.

THE CIRCLE OF WILLIS

The circle of Willis connects the anterior and posterior circulations. It has a significant physiological role in providing collateral blood flow to vital brain structures. It is located at the base of the brain, surrounding the optic chiasm and the pituitary stalk. However, there are a large number of bifurcations, multiple flow impingement points, complex flow patterns, and increased wall shear stress within this small region. The higher incidence of cerebral aneurysms within the circle of Willis suggests a strong correlation to these hemodynamic factors (Wakhloo et al. 2003). Most intracranial aneurysms occur within the circle of Willis, with 30% at the AComA and 20-30% at the PComA.

The circle of Willis is composed of the following vessels (posterior to anterior): the basilar artery bifurcation or top, paired proximal PI segments of the PC As proximal to the junction with the PComAs, paired PComAs, paired distal or terminal ICA, paired proximal Al segments of the ACAs, and AComA (Table 37C.8). A complete circle of Willis is present in only 25% of patients, with 75% of patients having hypoplastic or absent segments. Variants include fetal origin of the PCA, hypoplastic or absent Al segments of the ACA, and hypoplastic PComAs.

Branches of the basilar top, PI segments, and the PComAs supply vital structures that include the thalamus, limbic system, reticular activating system, cerebral peduncles, posterior limb of the internal capsule, and oculomotor nerve nucleus.

Other vascular abnormalities that occur at the circle of Willis include atherosclerosis, moyamoya disease, and AVMs. Tumor encasement and displacement of the circle of Willis are also frequently seen. Many facets must be considered in the endovascular treatment of circle of Willis lesions, including the following: obtaining access to the lesion, avoiding perforators, recognizing collateral blood supply, using cross compression or balloon test occlusion, protecting sensitive and eloquent brain areas, and recognizing anatomical variants.

INTRACRANIAL VENOUS DRAINAGE PATHWAYS

The cerebral venous system is highly variable with common anomalies, Ir is composed of Jural sinuses, superficial cortical veins, and deep cerebral and transmedullary veins. It is important to recognize the potential collateral drainage pathways. Cerebral vein and sinus thrombosis can result from, but are not limited to, dehydration, infectious disease, hypcrcoagulable states, and trauma. The venous system of the brain can be fundamentally separated into the supratentorial and infratentorial systems. From there, divisions may be made at deep versus superficial drainage: supratentoiial, infratentorial, deep drainage (including transmedullary veins), cortical drainage, and dural drainage (Figure 37C.5).

Cerebral Cortical Veins

The cerebral cortical veins are highly variable and run in superficial paths along the cortical sulci to drain the cerebral cortex and white matter via transmedullary veins. Multiple cortical veins drain superiorly into the superior sagittal sinus. The superficial middle cerebral vein is within the sylvian fissure and receives drainage from the surrounding opercular cortical regions. It usually runs anteromedially around the temporal tip to empty into the sphenoparietal or cavernous sinus. It may have anastomotic communications with the deep cerebral venous system, the extracranial pterygoid venous plexus, and facial veins.

The posterior portion of the superficial middle cerebral vein communicates with the veins of Trolard (superiorly drains toward the superior sagittal sinus) and Labbe (inferoposteriorly drains toward the ipsilateral transverse sinus). Both of these veins cross the subdural space and enter the dural sinuses. Occlusion of cortical veins during surgical or endovascular procedures may lead to cerebral venous infarction.

Deep Cerebral Veins

Supratentorially, the deep cerebral veins receive their blood supply from white matter, basal ganglia, and thalamus via transmedullary veins. The paired septal veins run posteriorly near the midline along the septum pellucidum. They arc responsible for drainage of the deep white matter of the anterior portions of the frontal lobes. The pair of thalamostriate veins run in a subependymal course

Tabic 37C.8 Vascular components of the circle of Willis territories supplied and clinical symptoms associated with occlusion

Artery	*Variants*	*Branches*	*Neurological deficit*
A Com A		Small perforatots supply the limbic system and optic chiasm	Akinetic mutism, bitemporal hemianopia
Proximal Al	Hypoplasia or absence in Al segment is not uncommon; multiple AComAs in up to 40%, origin of recurrent artery of Heubner (14%)	Medial lenticulostriate branches supply the internal capsule, hypothalamus, and basal ganglia, optic chiasm, and infundibulum Heubner-anterior limb of internal capsule, globus pallidus, and head of caudate nucleus	Motor aphasia, facial weakness, mood changes, impaired judgement
PComA	Hypoplastic in 30% of population, perforators may supply optic chiasm and pituitary stalk	PComA, PI, and basilar provide thalamoperforators: limbic system, midbrain, hypothalamus, reticular activating system, cerebral peduncles, posterior limb of the internal capsule, and the oculomotot nerve nucleus	No specific isolated clinical presentation
Proximal PI	Arises from supraclinoid ICA in 20%, fetal origin, thalamoperforators and thalamogeniculate arteries supply the posterior and lateral thalamus		Memory deficits, homonymous hemianopia, anterolateral and posterolateral thalamic syndromes, contralateral sensory loss
Basilar top			I.ocked-in syndrome, ventral and lateral pontine syndromes, ataxic hemiparesis, cortical blindness

ACA = antcrior cerebral artery; AComA = anterior communicating artery; ICA = internal carotid artery; PCA = posterior cerebral artery; PComA = posterior communicating artety.

anteriorly and medially along the floor of the lateral ventricles. The veins pass between the body of the caudate nucleus and thalamus. They drain the caudate nucleus, the deep white matter of the parietal and posterior frontal lobes, and the internal capsule, and pass anteriorly through the foramina of Monro, where they join with the septal veins to form the paired paramedian internal cerebral veins. The internal cerebral veins run posteriorly within the velum intcrpositum and define the roof of the third ventricle.

The paired basal veins of Rosenthal are formed by the confluence of the deep middle and anterior cerebral veins on the ventral surface of the brain and continue posteriorly around the cerebral peduncles. The basal veins also receive venous drainage from the insula and cerebral peduncles. The basal veins travel posteromedial^ and superiorly, coalescing with the internal cerebral veins (subjacent to the splenium of the cotpus callosum) to form the vein of Galen (great cerebral vein), The midline vein of Galen travels posteriorly approximately 2 cm under the splenium of the corpus callosum within the quadrigeminal plate cistern. It receives the posterior pericallosal, posterior mesencephalic, lateral mesencephalic, internal occipital, and several posterior fossa veins before it joins with the inferior sagittal sinus to form the straight sinus at the junction of the falx and tentorial incisura.

Posterior Fossa Veins

[lu- posterior tossa veins have been divided into four groups: superficial, deep, brainstem, and bridging veins (Rhoton 2000}, The pons is drained by the anterior pontomesencephalic vein and a network of small veins along its ventral surface. Superiorly, the pons drains toward either the basal vein of Rosenthal or the posterior mesencephalic vein. The precentral vein drains a portion of the cerebellar hemispheres and travels posterior to the roof of the fourth ventricle, then superiorly behind the inferior colliculi to drain the vein of Galen. The superior and inferior vermian veins run along the superior and inferior surfaces of the vermis, respectively. These veins

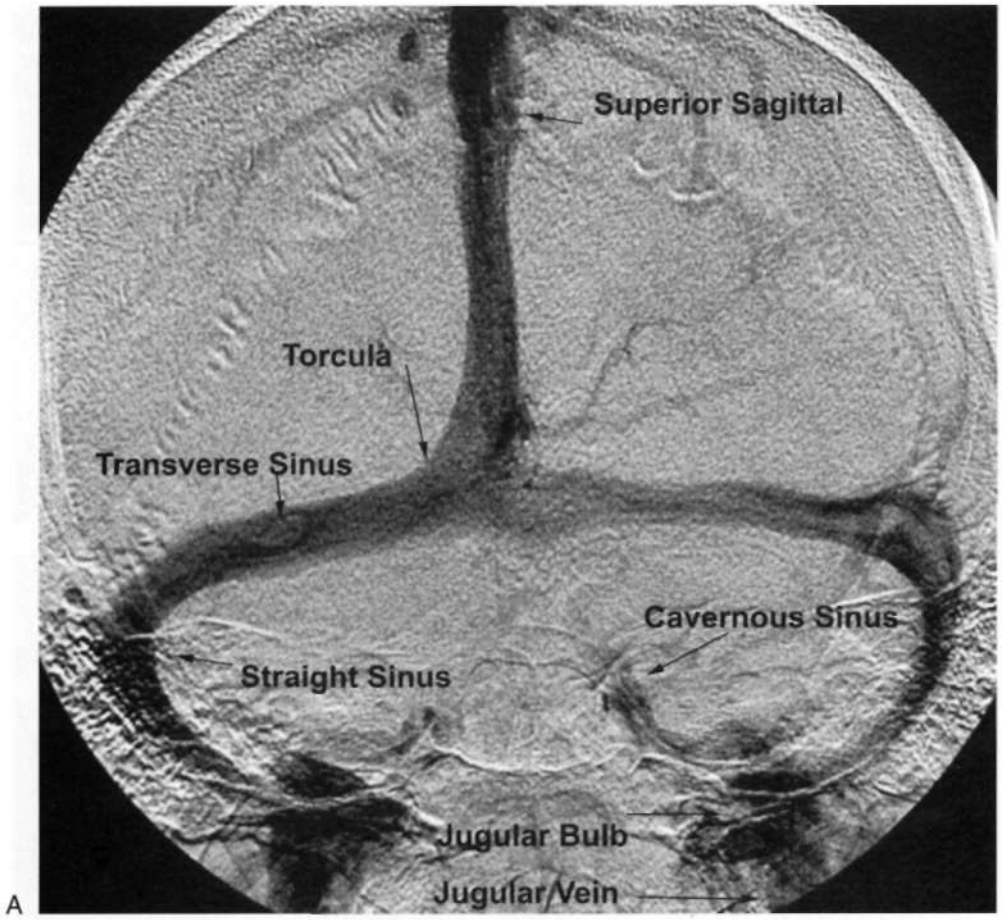


FIGURE 37C.5 Late venous-phase angiogram in anteroposterior (A) and lateral (B) plane. *Continued*

drain the cerebellar vermis and hemispheres. The superior vermian vein drains antcrosupcriorly toward the vein of Galen. The paramedian inferior veins usually drain posteriorly into the straight sinus.

Dural Sinus Network

The dura mater covers the central nervous system and has two layers. The periosteal and meningeal layers of the dura separate to form venous drainage channels or dural sinuses for the brain. The inner meningeal layer forms a reflection onto itself that is known as the falx cerebri {separating the cerebral hemispheres), tentorium (separating the cerebrum from cerebellum), and the falx cerebelli (separating cerebellar hemispheres). Dural sinuses may communicate with veins in the scalp and the diploic space of the calvarium via emissary veins.

The superior sagittal sinus travels along the superior margin of the falx cerebri and receives venous drainage from multiple cerebral cortical veins, the vein of Trolard, and emissary veins. The anterior one third of the superior sagittal sinus may not opacify during late-phase cerebral angiography or may be cnngenitally absent. This midline sinus carries blood flow posteriorly and infcriorly in a creseentie course to the posterior junction point between falx and tentorium containing the confluence of sinuses (also known as the *torcular Heropbili* or *torcuh)* near the occipital protuberance (Table 37C.9),

The inferior sagittal sinus is contained within the lower curvilinear edge of the falx, where it receives venous drainage from the falx and the cerebral hemispheres. This dural channel drains posteriorly in the midline to join with the vein of Galen to form the straight sinus within the intersection between the falx cerebri and the tentorium. The straight sinus drains posteriorly toward the torcula. Occipital sinuses, of variable caliber, are often visualized during cerebral angiography, coursing supramedially within the dura of the posterior fossa, just lateral to the foramen magnum, and draining toward the torcula.

The paired transverse sinuses follow a creseentie course, within the periphery of the tentorium, laterally and anteriorly from the torcula. Usually, the right transverse sinus is dominant or larger than the left. Occasionally, one may be extremely hypoplastic. The transverse sinuses receive drainage from the inferior cerebral veins and vein

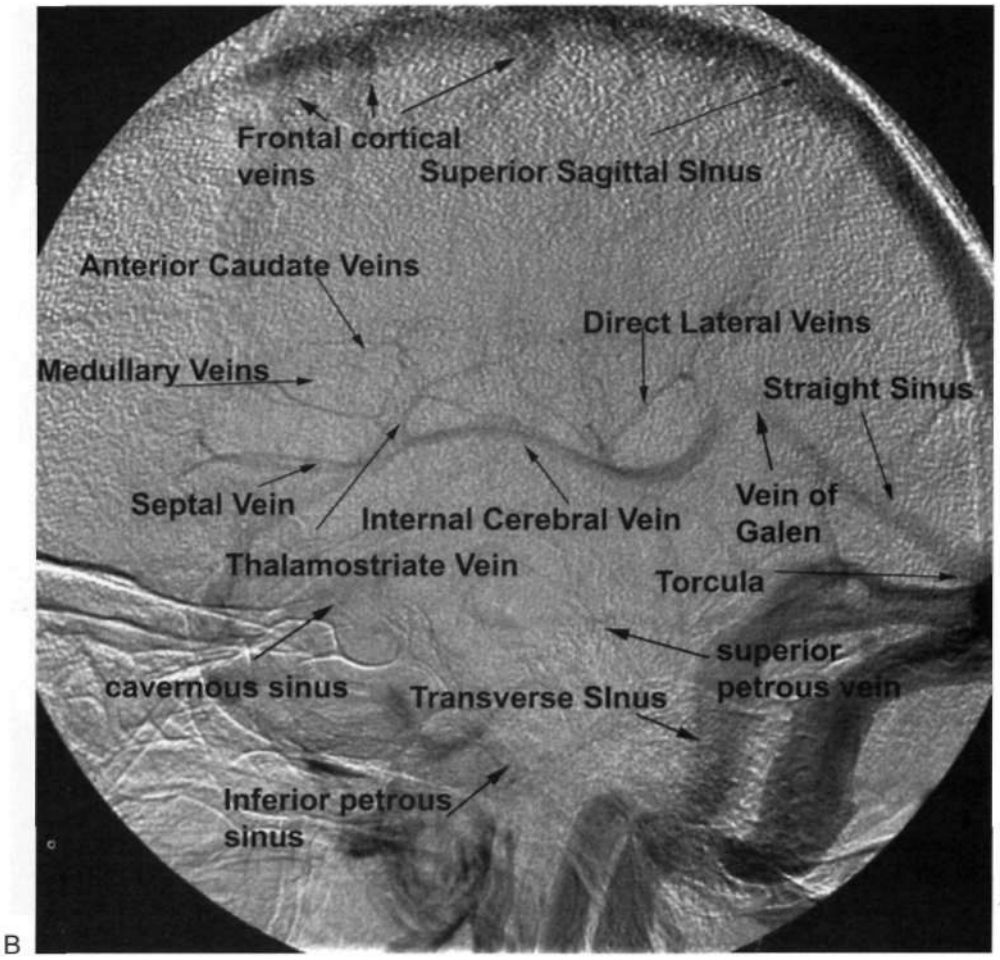


FIGURE 37C.5, cont'd.

Table 37C.9: Major vessels of the venous circulation

Major veins			
Dural sinuses		Deep cerebral vein	
	Superior sagittal sinus		Subependymal veins
	Inferior sagittal sinus		Thalamostriate veins
	Straight sinus		Septal veins
	Torcular herophili (sinus confluens)		Internal cerebral veins
	Transverse sinus		Basal vein of Rosenthal
	Sigmoid sinus		Vein of Galen
	Occipital sinus		Anterior pontomesencephalic veins
	Inferior petrous sinus		Precentral cerebellar vein
	Superior petrous sinus		Superior and inferior vermian veins
	Cavernous sinus	Dural veins	Meningeal vein
Superficial cortical			Emissary veins (connection between sinus and scalp)
	Sylvian veins		
	Veins of Trolard and Labbe	Scalp veins	Occipital vein
	Frontal ascending/descending cortical veins		Temporal vein
	Occipital cortical veins	Cervical veins	Jugular bulb
	Sphenoparietal vein		Internal/external jugular veins

of Labbe, and communicate with the cavernous sinuses via the superior petrosal sinuses, which run along the petrous ridges.

The transverse sinus, as it travels sub]acent to the tentorium, becomes the sigmoid sinus. This sinus, contained within the dura of the posterior fossa, follows a curved course toward the jugular foramen where it empties into the internal jugular vein. A bend in contour at this junction point is termed the *jugular bulb.* Other structures traversing the jugular foramen include cranial nerves IX through XI and small branches of the ascending pharyngeal and occipital arteries. The jugular bulbs communicate with the cavernous sinuses by means of the paired inferior petrosal sinuses, which ascend superomedially from the jugular foramen within the dural flanking the clivus. The inferior petrosal sinuses interconnect through a clival venous plexus.

The cavernous sinuses receive venous drainage from the orbits and their contents via the superior and inferior ophthalmic veins (which in turn communicate with the angular, frontal scalp, and anterior facial veins). This venous drainage pattern may allow intracranial spread of central and deep facial infectious processes.

Arachnoid Granulations

Multiple arachnoid invaginations present along the superior sagittal and the transverse sinuses are known as *arachnoid granulations,* which serve as the sites of cerebrospinal fluid resorption from the subarachnoid space. These structures may appear as filling defects during the venous phase of cerebral angiograms and should not be mistaken for intraluminal thrombi.

Common congenital anomalies found in the venous system include Chiari II malformations with low-lying torcular and transverse sinus, Dandy-Walker malformations with the torcular displaced above lambda, Sturge-Weber syndrome with the lack of superficial cortical veins with dilatated medullary and subependymal veins, and high riding jugular bulb. Variants include venous angiomas (developmental venous anomalies), AVMs, and sinus pericranii (an abnormal communicarion between the intracranial and extracranial venous circulation). Tumor and thrombosis can cause occlusions and displacements.

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Chapter 37
Neuroimaging

D. ULTRASOUND IMAGING OF THE CEREBRAL VASCULATURE

Viken L. Babikian and Charles H. Tegeler

Inttoduced to the clinical neurosciences more than 30 years ago, ultrasound technology is widely used today as a diagnostic modality. Its clinical applications include imaging of the brain parenchyma and assessment of blood flow in the cerebral vasculature in children and adults. Technological advances and a lack of radiation exposure have facilitated this evolution and made it possible for ultrasound to be used not only in the outpatient laboratory hut also at the bedside and in the operating room. The introduction of newer developments is expected to further expand these applications.

A comprehensive review of the principles of physics and the clinical and research applications of ultrasound technology in neurology and neurosurgery can be found in textbooks (Kremkau 2002; Tegeler, Babikian, and Gomez 1997). This chapter presents an outline of ultrasound imaging of the cerebral vasculature.

ULTRASOUND PHYSICS AND PRINCIPLES

Although the end product of ultrasound testing often is condensed into a short report indicating whether a flow velocity measurement suggests the presence of significant vascular stenosis, the clinician must know some basic principles and physics to understand what velocity measurements mean for a specific patient. Even minimal knowledge of these concepts provides valuable insight into the technique's strengths and limitations. This section addresses **the** basic principles and physics of ultrasound that form the basis for understanding its many applications (Kremkau 2002; Tegeler and Ratanakorn 1999a).

Ultrasound Transducers, Frequency, and Units of Measure

All ultrasound devices have a crystal in the transducer that has piezoelectric properties; it rapidly contracts and expands when an alternating electrical current is applied. The rapid expansion and contraction cycle converts electrical energy into acoustic energy, or sound waves. Conversely, when acoustic energy strikes the transducer element, as when sound waves reflected or scattered from the insonated tissues return to the transducer, the conformational change causes the crystal to give off a small electrical current rhat can be analyzed by the instrument. Sound waves are described in terms of their frequency (i.e., the number of cycles per second). The unit used to describe one cycle per second is the Hertz (Hz). The human ear can potentially hear sound at frequencies between 20 and 20,000 Hz. Therefore the term *ultrasound* implies frequencies higher than the human audible range (more than 20,000 1 1/, or 20 kl 1/1. Most diagnostic ultrasound devices operate at frequencies of 2-10 million Hz (2-10 MHz). Ultrasound transducers can have a single crystal or element or many individual elements (up to 256), organized in a variety of arrays. Conventional transcranial Dopplcr (TCD) transducers use a single element, whereas most duplex or color flow transducers are linear arrays in which the

elements fire in specific sequences to steer or focus the ultrasound beam as desired.

Doppler Ultrasonography

Diagnostic ultrasound provides an evaluation of cerebrovascular hemodynamics, structure, and anatomy. Hemodynamic information usually is obtained using Doppler ultrasonography, or derivatives thereof, such as color flow or power Doppler imaging (PDI). Structural and anatomical information is provided by gray-scale B-mode imaging. Doppler ultrasonography often is combined with B-mode imaging as duplex sonography, or duplex color flow imaging (CFI).

The key principle on which vascular ultrasound rests was initially described by Christian Andreas Doppler in 1842. The Doppler effect is the change or shift in the frequency (and thus of the wavelength) of a wave caused by relative movement between the sound source or scattcrer and the receiver (Figure 37D.1). As used in vascular ultrasound, in which moving blood components act as scatterers, this principle holds that the Doppler frequency shift (Fs) depends on the speed of blood flow (v in meters per second), the angle that occurs between the sound beam and the direction of blood flow (angle of insonation, *8),* the transmitted frequency (f[t]), and the speed of sound in soft tissue {C in meters per second).

$$Fs(MHz) = 2 \times v(m/s) \times f(t)(MHz) \times \cos 0/C(m/s)$$

According to the Doppler principle, the change or shift in frequency equals the difference between the transmitted frequency and the frequency that is received by the transducer, having been modified according to the factors in the equation. By convention, blood flowing toward the transducer produces a positive Doppler frequency shift, whereas flow that is farther away from the transducer results in a negative shift.

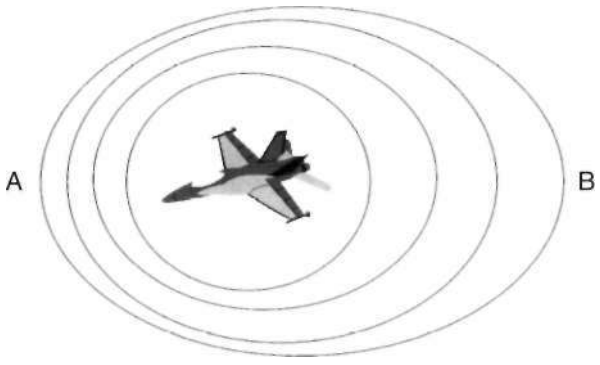


FIGURE 37D.1: Doppler principle. More sound waves per second (higher frequency, higher pitch) hit receiver A than B because of the relative movement of the jet (sound source) toward A and away from B.

$$v\{m/s) = Fs(MHz) \times C\ (m/s)/2 \times f(t)(MHz) \times costf$$

As implemented routinely on newer ultrasound instruments, when both the frequency of the transducer and the angle of insonation arc known, the velocity of the scatterer (flowing blood) can be calculated. For vascular ultrasound, this is the blood flow velocity.

Sound travels through the soft tissues of the body at a speed of 1540 m per second. Thus, the equation is expressed as:

$$v(cm/s) = Fs(kHz) \times 77/f\{t)(MHz) \times \cos 0$$

Because the cosine of the angle of insonation is used in the equation, Fs is greatest as the Doppler angle approaches 0 degrees (direction of the sound beam parallel to the direction of blood flow), and lowest when the angle approaches 90 degrees (right angle to the direction of flow), at which point there is no relative movement toward or away from the transducer and therefore there is no Doppler shift. Although the ideal Doppler angle is 0 degrees, in the body the angle of insonation changes dramatically depending on in situ anatomy.

Use of a standard range for an acceptable angle of insonation increases the reliability and reproducibility of the results. As discussed later in this chapter, carotid ultrasound usually is performed with a 60 degree angle of insonation, whereas conventional TCD instruments assume a 0-degree angle of insonation. Transcranial color flow duplex devices allow angle correction, but criteria and experience with this alternate approach are still emerging.

Current instrumentation almost exclusively uses blood flow velocity {v in centimeters per second) rather than Doppler frequency shift (Fs in kilohertz) to show results. This avoids potential confusion related to variation in f(t) between instruments and laboratories, or cos ft, by correcting for the transducer frequency and the angle of insonation. This approach provides a common language and a measure with which to compare results between different studies. Blood flow velocity is now the most commonly used ultrasound parameter by which to diagnose vascular stenosis and to assess vascular hemodynamics.

Transducers for Doppler ultrasonography can be divided into two broad categories: those that continuously transmit and receive (continuous-wave Doppler) and those that intermittently emit and receive a series of short pulses of sound (pulsed-wave Doppler). The continuous-wave Doppler transducer is sensitive to any moving target along the path of the sound beam. It can accurately identify extremely high-flow velocities. However, continuous-wave Doppler cannot localize the specific depth of the reflector (scatterer) from which a signal arose. Pulsed Doppler transducers emit brief pulses of sound and wait for any scattered signals to return before sending the next pulse. The pulsed-wave Doppler method allows manipulation of the time of sampling to choose a specific depth or a time window for recording. This allows sampling from a specific region or volume of tissue

(sample volume). In addition, because sound travels in soft tissue at a constant speed, the depth of a reflector can be determined, or a desired depth of sampling can be chosen.

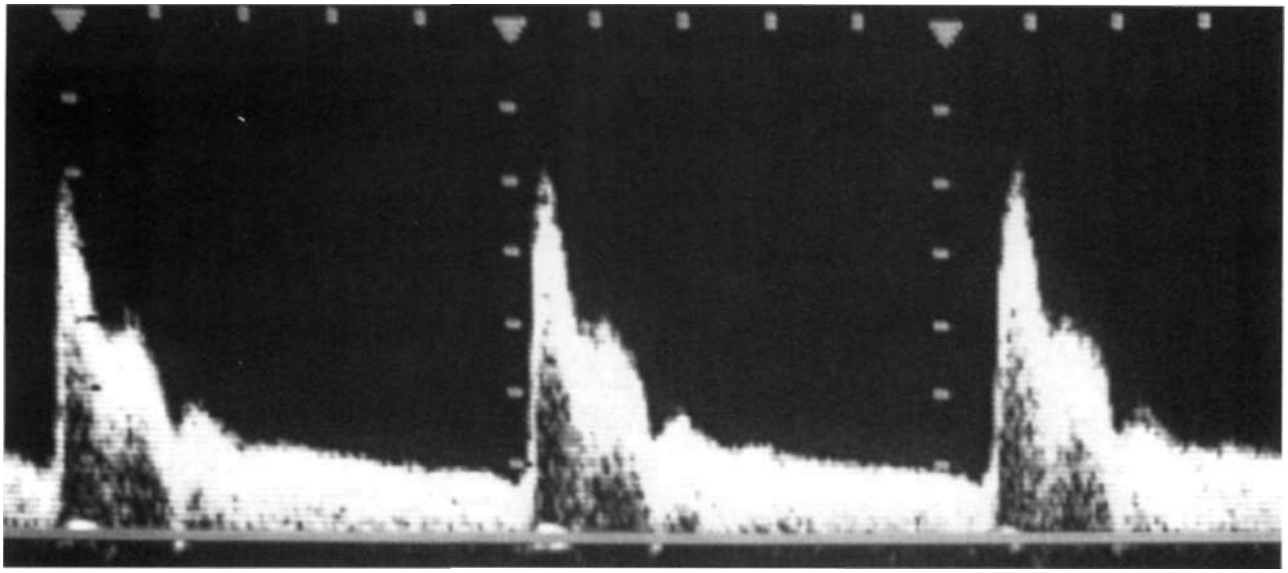
Pulsed-wave Doppler uses a series of sound pulses emitted at a fixed rate (pulse repetition frequency) rather than continuous sampling. It may not be able to accurately assess very high frequency shifts generated by high blood flow velocities. When the frequency shift being sampled exceeds one half the pulse repetition rate, also known as the Nyquist limit, the velocity information is recorded erroneously. The highest velocities, corresponding to frequency shifts higher than one half the pulse repetition frequency, are displayed as flow in the opposite direction, a pattern known as aliasing.

Doppler Spectral Display and Analysis

Because red blood cells flowing in vessels move at a variety of speeds and directions, there is a spectrum of different **blood flow velocities** within any given sample volume at any time. With the hemodynamic changes that occur throughout the cardiac cycle, the spectrum of velocities also changes over time. This diversity of flow velocities within the vessel is displayed visually by use of the fast Fourier transform (FFT) display. Many hemodynamic parameters are derived from analysis of the **FFT** display of the Doppler velocity data. Analysis includes specific objective parameters such as flow direction, peak systolic velocity, and end-diastolic flow velocity, as well as several indirect or derived parameters such as width or spread of the spectral band of velocities, flow acceleration time (systolic acceleration slope), pulsatility, or resistivity index. These latter parameters for spectral analysis provide additional insights into flow characteristics not only at the site of sampling but also proximally and distally.

Norma! vessels have a compact, narrow, smooth flow velocity envelope on **FFT** display of the Doppler velocity data (Figure 37D.2). With arterial stenosis and turbulence, flow is distributed across a broader spectrum of velocities (spectral broadening), reflecting a greater variety of speeds and directions. Turbulent flow, as occurs distal to a tight stenosis, may also produce an irregular margin to the acoustic envelope, resulting in a bubbling or gurgling sound or even flow reversal, displayed below baseline on the **FFT** display, light stenosis can cause vibration of the vessel walls to produce an audible bruit, and the Doppler spectrum can show the ultrasonic equivalent as a low-velocity, turbulent, high-intensity signal on the FFT display. There are also other events, such as cerebral embolism, in which it is crucial to display the intensity of the signals within the Doppler spectrum. An embolic particle passing through **the** Doppler sample volume has a much greater reflectivity or acoustic impedance than the surrounding blood, causing more energy to be scattered back to the transducer. This phenomenon results in transient high-intensity signals, also called microcmbolic signals, to appear in the Doppler spectral display with an accompanying audible sound. These have also been called high intensity transient signals.

Individual vessels also have characteristic spectral appearances, created primarily by the distal peripheral resistance. The internal carotid artery (ICA), supplying a low-resistance vascular system in the brain, has a very different appearance from the external carotid artery, which feeds a high-resistance vascular bed in the face and scalp. The ICA velocity waveform typically has a more gentle systolic upslope, a more rounded peak in systole, a more gradual decrease in velocity, and persistent diastolic



I K.t IU S7D.2 Doppler imaging. Spectral display of normal (low velocities in the common carotid artery as measured by Doppler ultrasound.

flow. The extracranial carotid artery has a sharp upslope, a sharp peak in systole, a rapid fall-off, and little (if any) flow in diastole. Specific spectral patterns, particularly very high- or low-resistance signals, provide indirect clues about hemodynamics and potential pathological conditions both proxiinally and distally.

Brightness-Mode Imaging

B-mode, or brightness-mode, imaging allows anatomical interrogation based on the acoustic properties of the tissue being studied. When an ultrasound beam traverses the tissues, it may be transmitted largely unaltered, or it may be scattered, bent, absorbed as beat, or reflected. The outcome depends on several factors, including the acoustic impedance of the tissue, the differences in acoustic impedance between adjacent tissues, and the angle at which the sound beam strikes the interface. Greater differences in acoustic imped ance between adjacent tissues at an interface or boundary result in greater reflection or scattering. The transducer converts the returning ultrasound energy into electrical impulses that arc then encoded in a digital memory, based on the signal intensity at each point along the ultrasound beam. These data can be displayed visually as varying shades of gray, depending on the signal intensity at each point. When the transducer is mechanically or electronically swept actoss the tissue, in a single plane, the resulting series of scan lines can be used to create a two-dimensional, gray-scale B-mode image. This provides a two-dimensional visual display of a slice of tissue based on the acoustic properties of the tissue (Figure 37D.3). These are static images, but the image can be updated 15-30 times per second so that it appears to be moving in real time. This is the same principle used in making movies: Single frames are displayed in rapid succession to appear as moving reality.

A variety of factors determine the appearance of the B-mode image and the ability to identify structures in the soft tissue. The ability to clearly distinguish two points on the image is called *detail resolution.* This depends on both axial and lateral resolution. Separation of points along the axis of the sound beam (axial resolution) depends mostly on transducer frequency, which improves with higher-frequency transducers. Separation of points perpendicular to the direction of the sound beam (lateral resolution) depends on the width and focusing of the sound beam. Narrower, better-foe used sound beams allow better lateral resolution of points that are side by side. In general, higher

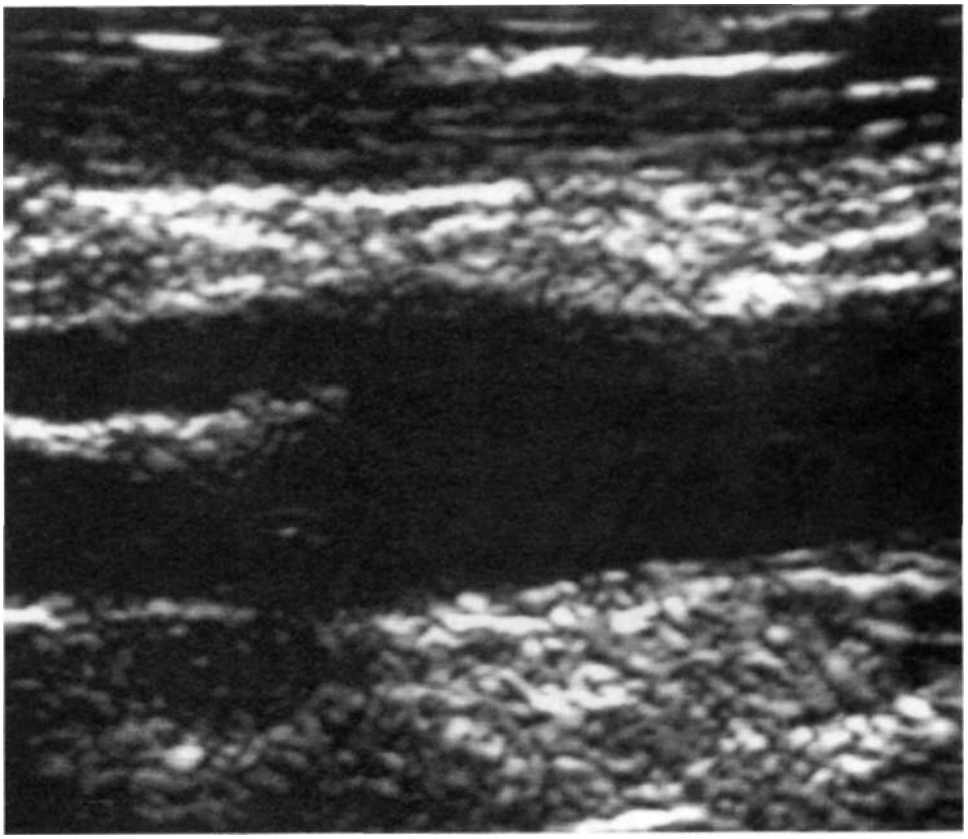


FIGURE 37D.3 B-mode imaging. Longitudinal gray-scale brightness-mode image of a normal carotid bifurcation region, with visualization of the distal common carotid artery, bifurcation, and proximal internal *(below and to the left)* and external *{above and to the left)* carotid arteries.

PLATE 37D.I Colon flow imaging. Duplex color flow imaging superimposes the color-coded velocity information onto the brightness-mode image of the common carotid artery.

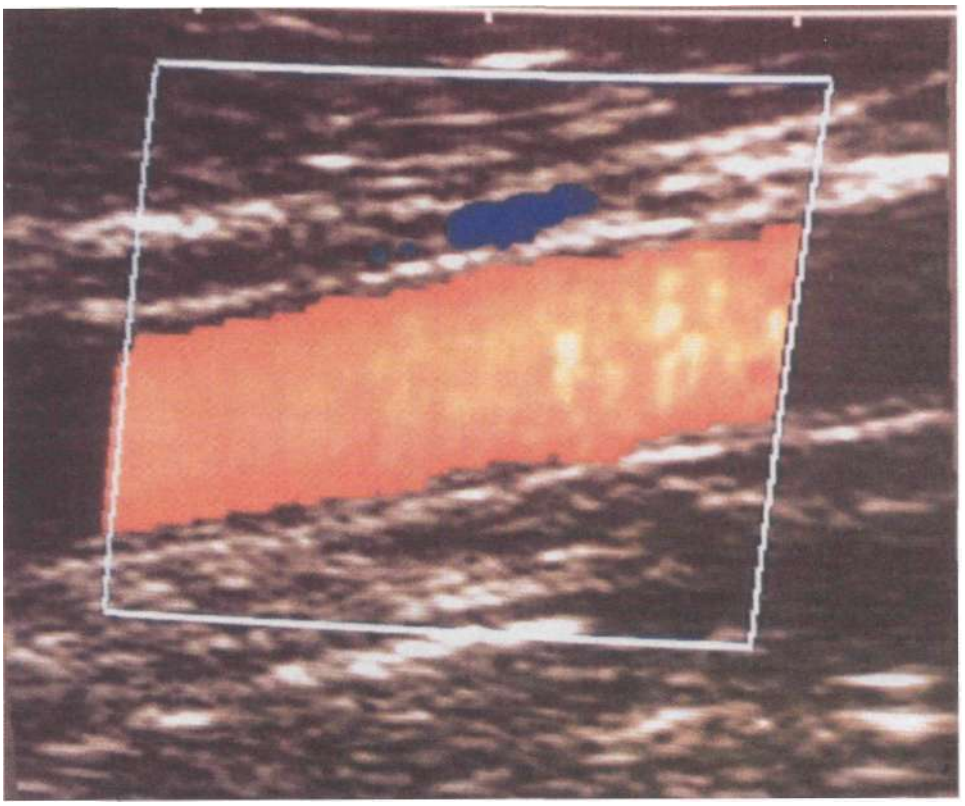
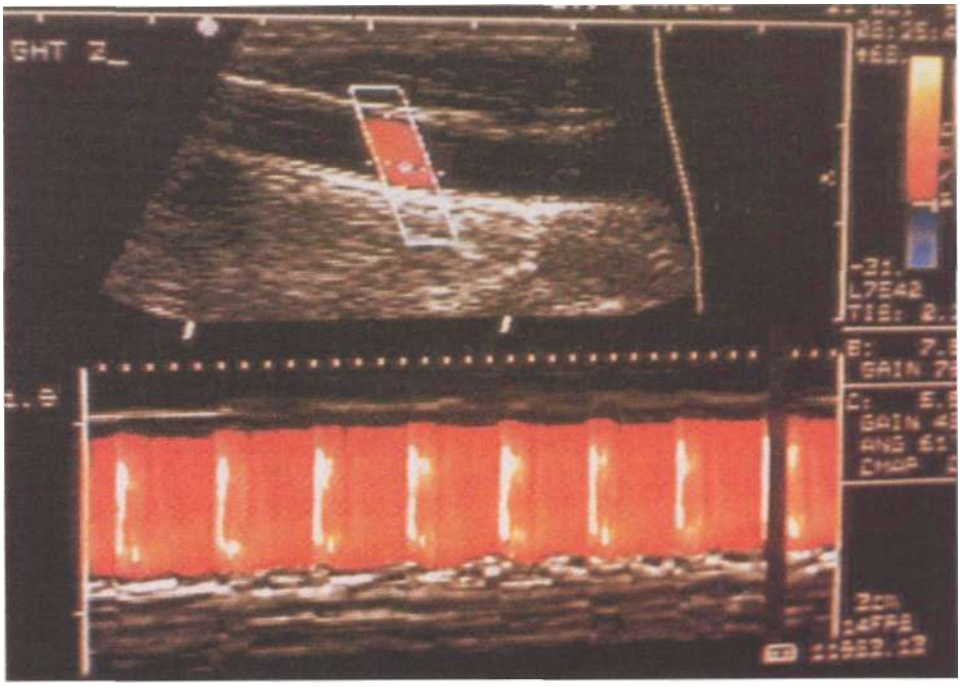
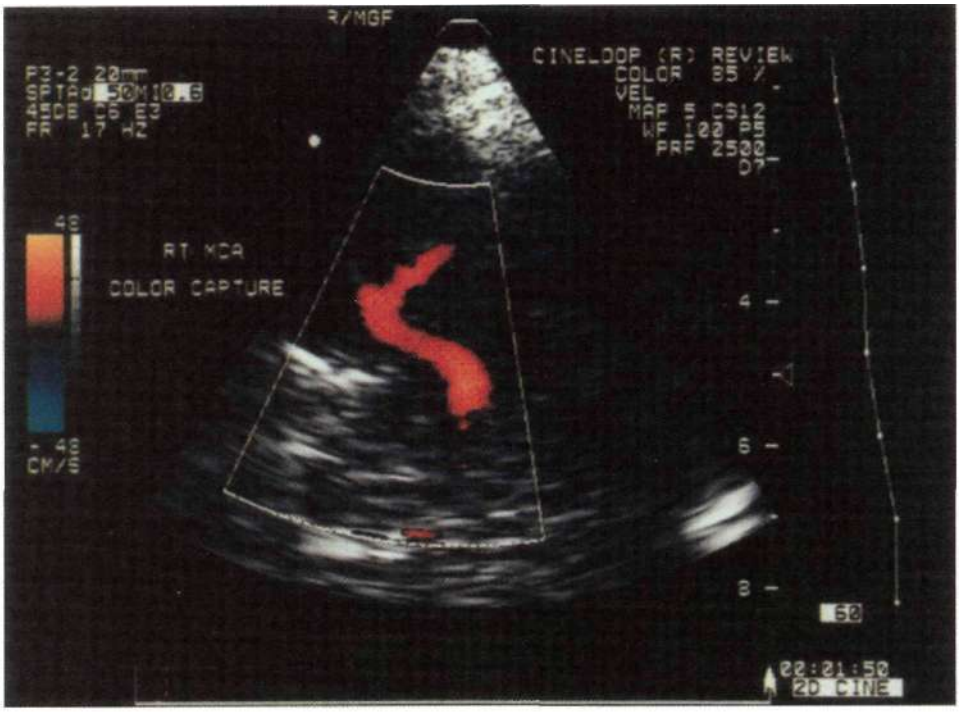


PLATE 37D.II Volume flow rate. Measurement of volume flow rate using Color Velocity Imaging Quantification (Philips Ultrasound International, Irvine, CA) with a color M-mode display of the flow velocities across the common carotid artery and tracking of the vessel diameter is provided. Flow volume is in milliliters per minute.





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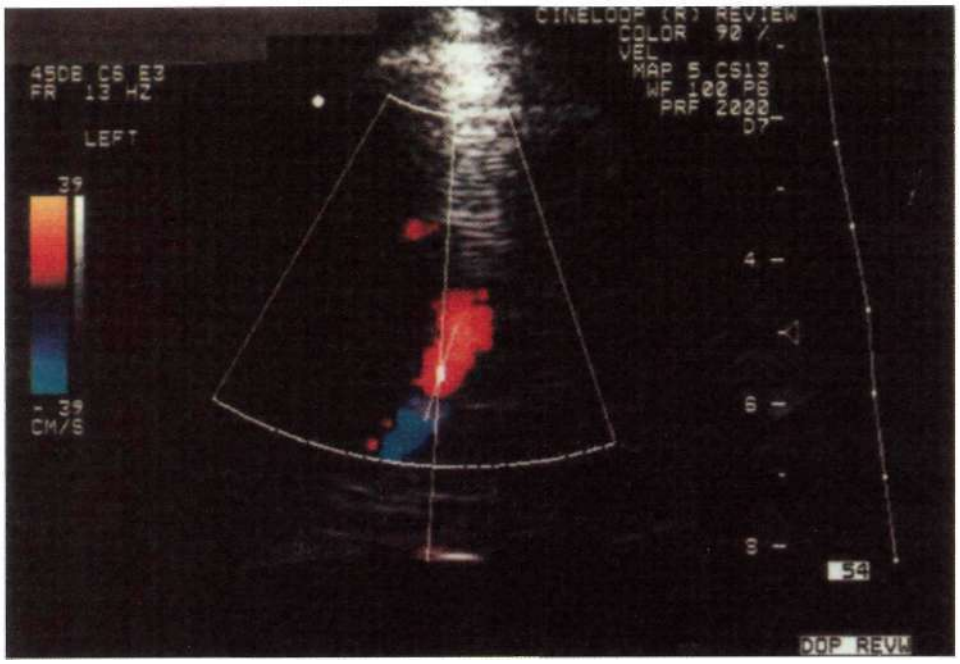
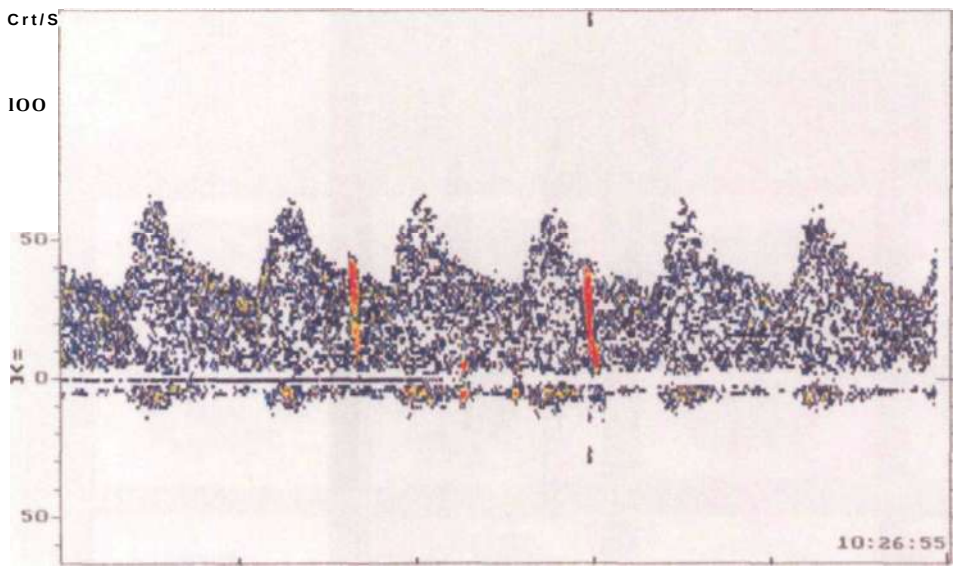


B

PLATE 37D.III Transcranial color-coded duplex imaging. (A) The middle cerebral artery Ml segment is presented in red, indicating flow toward the probe. (B) Imaging of the internal carotid artery bifurcation shows the middle *(red)* and anterior *(blue)* cerebral artery original segments.

PLATE 37D.IV Microembolic signals. Red signals are seen during the third and fifth cardiac heats.



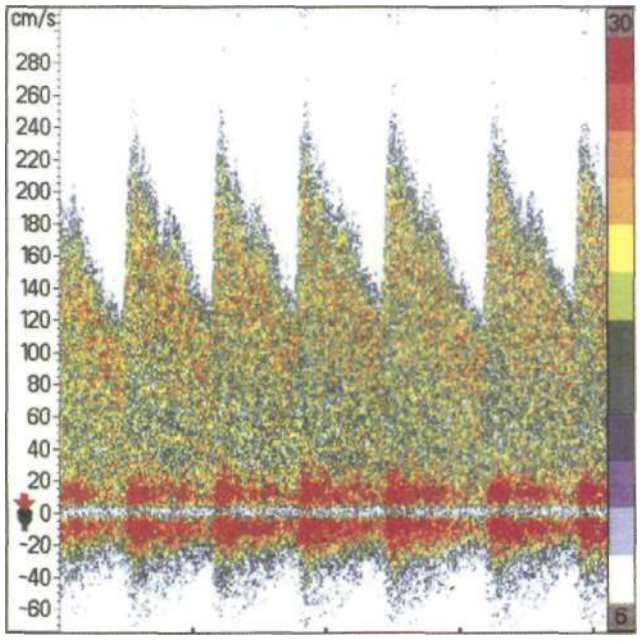


PLATE 37D.V Sickle cell disease. Flow velocities are markedly increased at depths of insonation corresponding to the middle cerebral artery Ml segment.

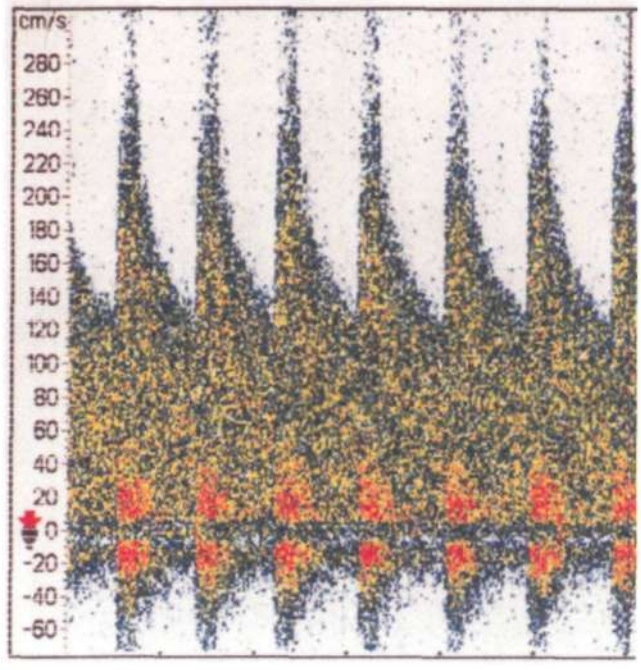


PLATE 37D.VI Subarachnoid hemorrhage. Temporal bone window; depth of insonation of 56 mm. Increased flow velocities indicating moderate to severe vasospasm in the middle cerebral artery Ml segment.

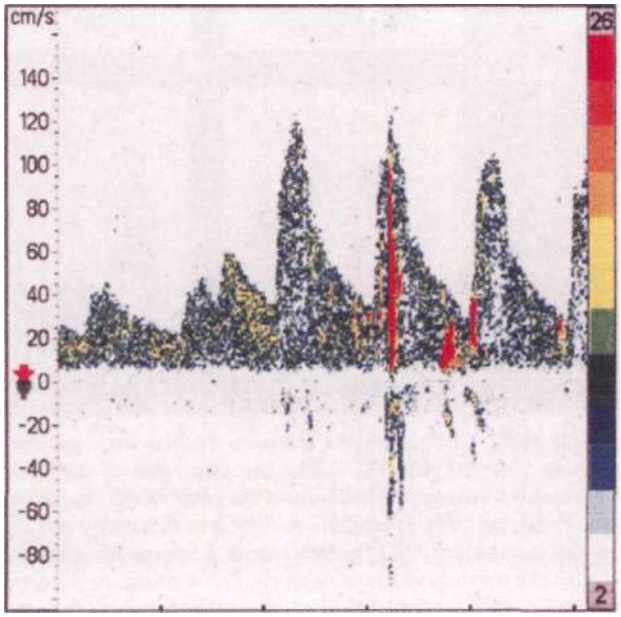


PLATE 37D.VII Carotid cndartercctomy. At clamp release, flow velocities are restored and microembolic signals are seen.

transducer frequencies, with better axial resolution, are desirable to achieve better images. However, attenuation (loss of acoustic energy as sound moves through tissues) is greater with higher frequency transducers, which limits the depth of penetration. Thus, the choice of the best transducer for a specific task must balance the desired depth of penetration against the need for resolution. Modern transducers for extracranial high-resolution B-mode carotid imaging operate ar frequencies of 7.5-10.0 MHz, whereas those used for transcranial CFI operate at 2-3 MHz.

Duplex Imaging

Duplex ultrasonography makes use of both pulsed-wavc Doppler ultrasound and B-modc imaging to obtain both hemodynamic and anatomical information (Figure 37D.4). Now the standard for vascular ultrasound, duplex ultrasound overcomes many prior shortcomings of ultrasound testing by offering image-guided placement of the Doppler interrogation, with correction for the angle of insonation, resulting in more accurate and site-specific velocity measurements.

Color Flow Imaging

CFI uses Doppler flow velocity information obtained from many points (multiple sample volumes) within the image, which is then color coded based on the speed and direction of flow and overlaid onto the appropriate anatomical site in the gray-scale B-mode image {Plate 37D.I). The Doppler data on the color flow image typically represent the mean velocity at each point. This, along with the longer processing time needed to display both Doppler and B-modc data and the resulting slower frame rates, causes CFI to lack the real-time, quantitative hemodynamic accuracy of regular duplex Doppler spectral analysis. However, CFI has many potential advantages compared with conventional duplex ultrasound and is becoming the standard. At least one instrument has used time domain processing, rather than Doppler frequency shift data, to obtain and display velocity information. This approach, known as color velocity imaging, uses the patterns of echoes in the B-modc scan lines, which are cross-correlated with echo patterns from adjacent scan lines, to determine the velocity vector. Although limited in availability, this approach offers several potential advantages over conventional CFI, wirh lower power use, high time and spatial resolution, and the ability to display peak velocity in the color image (Knappertz, Tcgeler, and Myers 1996).

Power Doppler Imaging

Another variation on CFI is PDI, which uses the integrated intensity or amplitude of power in the Doppler spectrum as the basis for displaying color-coded flow on the B-mode

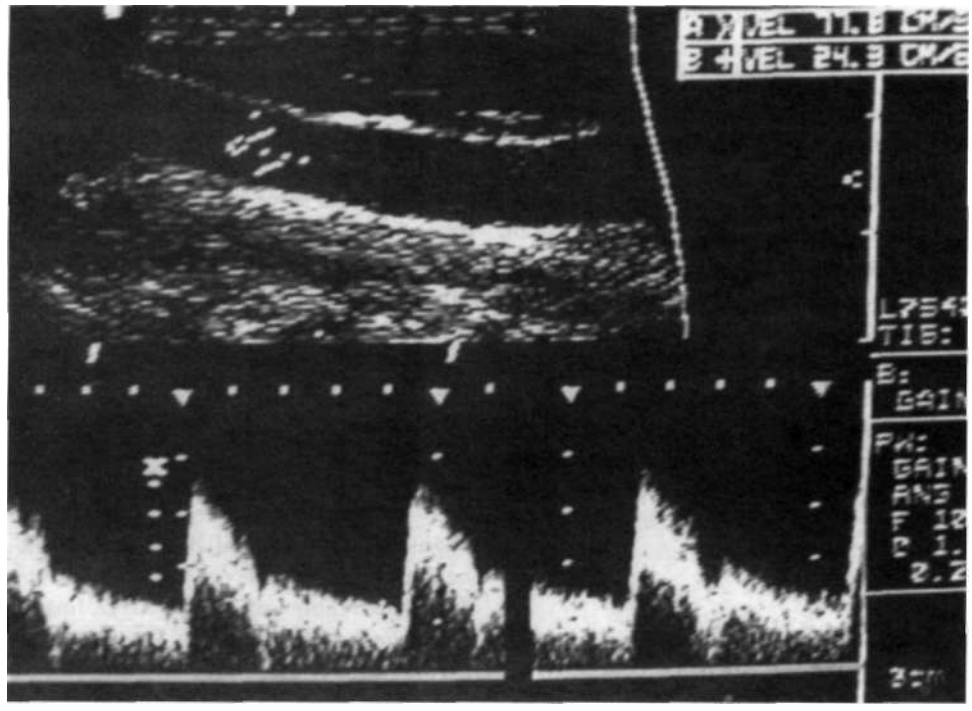


FIGURE 37D.4 Duplex ultrasonography. Combined Doppler velocity spectral display and brightness-mode image guided placement of the sample volume.

image. The data presented on the PDI color display reflect the amount of blood flow detected at each point rather than the mean Doppler velocity (Rubin et al. 1994). PDI is less angle dependent, is not affected by aliasing, and may be more sensitive to flow than conventional CFI, especially with very poor angles of insonation or very little flow in the vessel. Typically, PDI does not display the direction or velocity of flow, so it cannot be used independently to grade stenosis. However, it is complementary to duplex ultrasound and CFI, may improve accuracy in some difficult patients, may be quite useful for screening examinations, and may be particularly helpful with transcranial applications of CFI (Criewing et al. 1996; Bluth et al. 2000).

TECHNICAL CONSIDERATIONS

Extracranial Cerebrovascular Ultrasonography

Interrogation of the carotid arteries is the most common and arguably the most clinically important current application of cerebrovascular ultrasound. Any evaluation of the extracranial cerebral vessels must also include study of the vertebral arteries and usually should be combined with intracranial ultrasound to evaluate the entire cerebral circulation rather than any segment in isolation. As outlined earlier in this chapter, a variety of methods can be used to study the carotid and vertebral arteries. There is great variation across laboratories in the techniques used and in the quality of extracranial testing. This section discusses the essential components for such testing, some additional methods, and the need for quality assurance, certification, and aceteditation.

Any protocol for a carotid or vertebral artery ultrasound study should include duplex ultrasound to evaluate hemodynamic and structural changes, with or without CH. The only exception might be screening situations in which continuous-wave Doppler or PDI might be used alone to assess for hemodynamic changes indicative of significant disease that warrants further study. Real-time recording of the results with videotape is strongly recommended, as opposed to saving only a scries of frozen images. It is important for the reading physician to teview the real-time results to get the most information possible, taking advantage of the real-time capability of ultrasound. CFI, PDI, and volume flow rate measurements provide valuable adjunctive information that can improve understanding and accuracy of interpretation.

Carotid Duplex Examination

Duplex examination of the carotids must include Doppler flow velocity sampling of the proximal, mid-, and distal common carotid (CCA) arteries, proximal and distal ICAs, and external carotid arrerics, bilaterally. The proximal great vessels (innominate and subclavian arteries) are also studied if they can he visualized. If disease is detected, then additional Doppler sampling of the vessel proximal to, at the point of, and distal to the stenosis should be included. Sampling should be across the entire vessel diameter to avoid missing a high-velocity jet along the vessel wall. Sampling should be done using a standard angle of insonation, or at least within a standard range of angles. Most sonographers try to sample at a 60-degree angle, but 45-60 degrees is acceptable. Enough of the study should be videotaped to allow review of both the spectral display and the audible signals from all of rhe target vessels or regions of abnormality. Transducer frequencies for Doppler interrogation usually are between 4.0 and 7.5 MH/..

Because of predictable hemodynamic changes as stenosis develops, duplex Doppler ultrasound can be used to estimate the severity of the stenosis. Very mild degrees of stenosis have little hemodynamic effect and cause little change in flow velocity or in the Doppler spectral waveform. Progressive stenosis first causes increased peak systolic velocity across the narrowed segment. Additional narrow ing causes further increase in the peak systolic velocity, and a disturbed flow pattern, or turbulence, emerges (Figure 37D.5). Severe stenosis prevents adequate blood flow volume across the lesion; despite higher peak systolic velocity values, the end-diastolic velocity also increases. In very tight carotid stenosis approaching occlusion, peak systolic and end-diastolic velocity values may increase even further or may begin to decrease as critical narrowing is reached.

These changes in velocity and flow pattern are used to estimate the severity of stenosis. Most criteria used for interpretation are based primarily on the peak systolic velocity, end-diastolic velocity, and ratios of velocities in the ICA and CCA (Table 37D.1). The ratio of velocities is helpful because the velocity in the stenotic segment remains high when compared with the velocity proximal to the stenosis, even when cardiac dysfunction exists. Any set of criteria should serve as a guideline for interpreting velocity data and should not be considered hard, inflexible rules. Inrerpreters also must consider the overall clinical picture in every patient and exercise judgment and flexibility in reaching conclusions. Current ultrasound laborarories should srrive for an accuracy of approximately 90% for identification of tight carotid stenosis, as documented by a program of ongoing quality assurance.

Carotid B-Mode Imaging

High-resolution carotid B-mode real-time imaging should be done with transducers having frequencies greater than 5 MHz, preferably exceeding 7 MHz. Imaging should include visualization of the CCA; CCA bifurcation; ICA; external carotid artery including anterior, lateral, posterior, and transverse views; or a circumferential scan at each level to include all of these views. Real-time recording of these images allows study of pulsation patterns and movement of

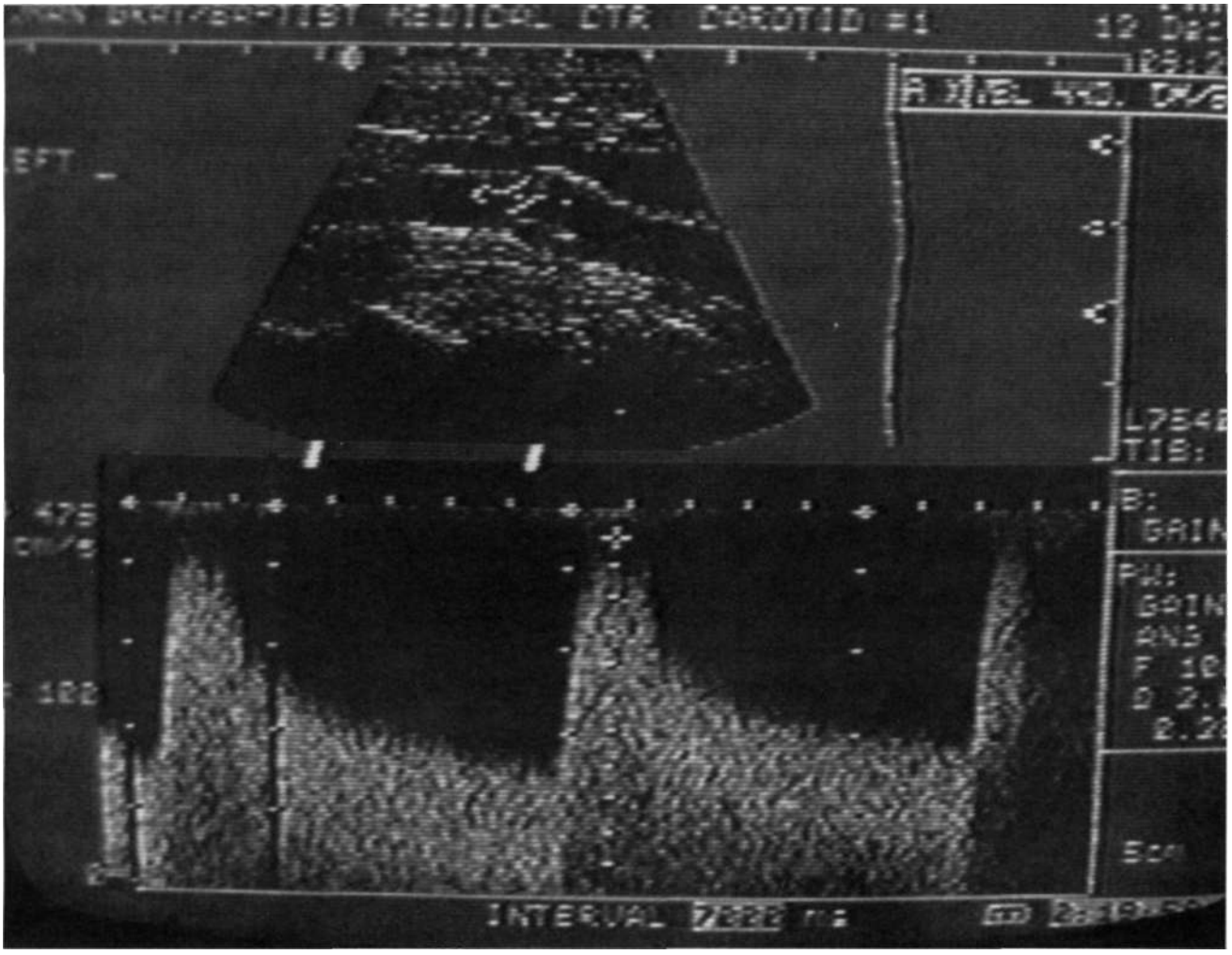


FIGURE 37D.5 Doppter ultrasound with tight stenosis. Spectral display of Doppler flow velocities distal to 75-90% internal carotid artery stenosis, with high systolic (440 cm per second) and diastolic velocities and spectral broadening.

intimal flaps or complex plaques. Measurements of the plaque thickness and residual lumen are performed frequently. Plaque severity can be classified by thickness, with minimal (1.1-2.0 mm), moderate (2.1—4.0 mm), and severe (more than 4.0 mm) categories. The posterolateral approach usually is optimal for measurements of plaque formation and residual lumen because plaques most often occur on the posterior wall of the carotid bifurcation and ICA, and B-mode imaging is most accurate when the sound beam is perpendicular to the interface being imaged.

High-resolution B-mode imaging also has a unique ability to evaluate the specific features of atherosclerotic plaques (Figure 37D.6). Identifiable characteristics include the distribution of plaque (concentric, eccentric; length), the

Tabic 37D.1: Flow velocity criteria for grading carotid stenosis used in the neurosonology laboratory of the Wake Forest University Baptist Medical Center

Stenosis (%)	*Peak systolic velocity (cm/sec)*	*End-diastolic velocity (cm/sec)*	*IC.A/V.VA*
0-49 (no significant stenotic flow)	<140	<40	*<1*
50-74 (moderate)	>140	<1I0	*>1*
75-94 (severe)	>140	>110	***>i***
95-99 (very severe)	Variable	Variable	Variable
Probable occlusion	No flow	No flow	N/A

ICA/CCA = internal carotid artery/common carotid artery ratio of peak systolic velocity; N/A = not applicable.
Source: Reprinted with permission from Tcgeler, C. H. & Ratanakorn, D., 1999, "Ultrasound in cerebrovascular disease," in *Neuroimaging; A Companion to Adams and Victor's Principles of Neurology,* 2nd cd, ed. J Greenberg, McGraw-Hill, New York.

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FIGURE 37D.6 Atherosclerotic plaque. Longitudinal gray-scale brightness-mode image of an atherosclerotic plaque *{arrow)* in the region of the proximal internal carotid artery, with acoustic shadowing.

surface features (smooth, irregular, crater), the echodensity and presence of any calcification producing acoustic shadowing, and the texture (homogeneous, heterogeneous; intraplaque hemorrhage). Hypoechoic plaques and those that are heterogeneous, with prominent hypoechoic regions (complex plaque), indicate an elevated risk of stroke (Polak et al. 1998). High-resolution B-mode imaging is more accurate for defining atherosclerosis of the vessel wall early in the course of the disease than is Dopplcr ultrasound testing. Measurement of the intima-media thickness, **which** increases in the early stages of plaque formation, is used as a surrogate endpoint for clinical trials assessing whether lipid-lowering medications might slow or reverse atherosclerosis. The sensitivity of B-mode imaging for detecting surface ulceration is estimated at 77% in plaques causing less than 50% linear stenosis and 41% for plaques causing more than 50% linear stenosis, with no significant differences between B-mode carotid imaging and arteriography, Although associated with a somewhat worse outcome, surface irregularity or crater formation appears to be a less important morphological risk factor than echodensity and heterogeneity,

Color Plow and Power Doppler Imaging

There is now widespread use of CFI as part of carotid ultrasound testing. Advantages of CFI include rapid determination of the presence and direction of blood flow, with more accurate placement of the Doppler sample volume and determination of the angle of insonation. Absence of color filling in what appears Co be the vessel lumen provides clues about the presence of a hypoechoic plaque, and the contour of the color column can provide information about surface features. If a crater or ulcer is open to the lumen, it is filled in by color. Newer instruments with sensitive CFI designed to detect very low flow velocities are able to accurately differentiate critical stenosis from total occlusion (87-100% sensitivity, 84% specificity compared with angiography), obviating the need for conventional angiography (Sitzer, Siebler, and Steinmetz 1996). The addition of CFI improves understanding of many unusual anatomical configurations such as kinks or coils. Although its contribution is difficult to quantify accurately, CFI probably adds approximately 5% to the overall diagnostic accuracy of carotid duplex ultrasound.

The addition of PDI offers more potential to improve accuracy in some difficult situations. In the setting of high-grade stenosis, PDI improves identification of stenosis and measurement of residual lumen and may improve visualization of plaque surface features, even in the presence of calcification.

Volume Plow Rate Determination

Conventional criteria for reporting carotid stenosis use flow velocity to estimate the linear percentage of stenosis. But flow velocity may be affected by many other factors besides percentage of stenosis. For example, hyper per fusion can

increase flow velocity and might be misconstrued as stenosis. Measurement of actual volume flow rate could help avoid mistakes in such situations, and it is the parameter in which most clinicians treating neurological disorders are interested. Color velocity imaging, as previously described, uses time-domain processing to determine flow velocity. With assumption of a circular vessel and flow symmetrical around the axis of its own direction, the data are integrated to yield the volume flow rate in milliliters per minute. It has been shown to be valid and reliable in vitro and reproducible for studying the CCA in volunteers, and expected normal values have been defined (330 ± 60 mL per minute for women and 375 ± 70 mL per minute for men). Use of the CCA volume flow rate in patients with carotid stenosis reveals characteristic decreases in the rate with progressive stenosis. Measurement of CCA volume flow rate is a standard part of the carotid evaluation in some laboratories, being obtained in patients in whom flow velocity suggests 50% or greater carotid stenosis (Plate 37D.II). This method is also being used in other clinical cerebrovascular diseases and offers a new window for understanding cerebral hemodynamic changes (Knappertz, Tegelcr, and Myers 1996; Tan et al. 2002). Other strategies for measuring volume flow rate are available using traditional Doppler ultrasound instruments.

Vertebral Ultrasonography

Because posterior circulation cerebrovascular disease is common, study of the vertebral arteries is considered a part of the routine extracranial duplex examination. The same techniques described for use in the carotid arteries can be used to study the vertebral arteries and the proximal subclavian or innominate arteries. Therefore duplex Doppler and B-mode imaging of these arterial segments should be performed. CFI is also helpful for visualizing the vertebral arteries. The vertebral artery can almost always be evaluated in the pretransverse and intertransverse cervical segment of C5-C6, whereas the origin can be studied on the right in only 81% and on the left in only *65%* of patients. Because there is mostly a low-resistance distal vascular bed, the vertebral artery usually shows a low-resistance pattern Doppler spectral pattern, similar to that of the ICA. There are no widely accepted criteria for stenosis in the extracranial vertebral artery. As with the carotid system, spectral analysis provides insight into proximal and distal disease.

Technical Limitations

Potentially important limitations of carotid duplex sonography are relared to the patient, instrumentation, sonographer, and interpreter. Patient factors that can preclude an adequate study include the inability to cooperate, neck swelling or other conditions that limit access to the neck, a high carotid bifurcarion, deeply situated vessels, and calcification with acoustic shadowing that blocks the sound beam.

Intracranial Cerebrovascular Ultrasonography

Transcranial Doppler Ultrasonography

Most commercially available TCD instruments use a 2-MHz probe to allow insonation through the cranium. These pulsed-Doppler instruments have an effective insonation depth range of 3.0-12.0 cm or more that can be evaluated by increments of 2 or 5 mm. At an insonation depth of 50 mm, the sample volume usually is 8-10 mm axially and 5 mm laterally. TCD probes differ from the 4- to 10-MHz transducers used to monitor the progress of intraoperative neurosurgical procedures (Unsgaard et al. 2002). Advantages of TCD include the maneuverability of the small probes, the Doppler sensitivity, and, especially when compared with transcranial color-coded duplex and magnetic resonance angiography, the low price of instruments.

Routine TCD testing relies on three natural acoustic windows to study the basal segments of the main cerehral arteries. Insonarion through the temporal bone window allows detection of flow through the middle cerebral artery (MCA) Ml and anterior cerebral artery Al segments. Normal blood flow direction is toward the probe in the MCA and away from it in the anterior cerebral artery. The supraclinoid ICA is also detected, but it may be difficult to distinguish from the MCA. Depending on the position of the window, the probe usually has to be tilted frontally to detect these vessels. A posterior (or occipital) tilt of the probe enables insonarion of the posterior cerebral artery's first segment.

The occipital window takes advantage of the foramen magnum's opening into the skull. Flow in the distal vertebral artery and proximal to midporrions of the basilar artery can be detected; it is away from the probe in these arterial segments. The position and caliber of these arteries vary widely, making insonation occasionally difficult.

The ophthalmic artery and carotid siphon can be studied through the orbital window. Flow in the ophthalmic artery-is toward the probe and has a high resistance pattern. Flow in the ICA siphon can be either toward or away from the probe, depending on the insonated segment of the siphon. The instrument's power output must be decreased when it is insonating through the orbital window because prolonged exposure to high-intensity ultrasound has been associated with cataract formation.

Flow velocities change with age and differ between men and women. Normal values have been reported by several authors. Repeated measurements of flow velocities are highly reproducible.

Based on rhe general knowledge of the location of intracranial arteries and flow direction, a comprehensive map of the basal arteries can be generated. This map is

clinically useful because common pathological conditions affecting the intracranial arteries, such as atherosclerosis, sickle cell disease, and vasospasm associated with aneurysmal subarachnoid hemorrhage, often affect arterial segments that can be insonated. Convexity branches of the cerebral arteries arc beyond the reach of TCD.

Transcranial Color-Coded Duplex Ultrasonography

Examinations performed with 2.25-MHz phased array and 2.5-MHz 90-dcgrcc sector transducers enable color-coded imaging of intracranial arterial blood flow in red *Aiid* blue, respectively, indicating flow toward and away from the probe (Plate 37D.III). The main advantages of transcranial color-coded duplex are the ability to visualize and positively identify the insonated vessel, thus increasing the ultrasonographer's confidence, and the ability to correct for the angle of insonation. In addition, transcranial color-coded duplex provides a limited B-mode image of intracranial structures.

Technical Limitations

A technically adequate study of the anterior circle of Willis cannot be obtained in 2.5-20% of patients studied with TCD. This is due to several factors, including the thickness of the temporal bone. The rate of unsatisfactory studies varies between medical centers and probably relates to the characteristics of the population tested at each neurovascular laboratory. Failure rates are higher in older adults and in African American patients. Restrictions in the emitted power of TCD instruments and limitations secondary to transmission through the skull hone can also result in technically unsatisfactory studies. The immediate cause of this limitation often is an inadequate signal-to-noise ratio. The latter can he improved by enhancing the reflected ultrasound waves with the use of contrast agents. Several echocontrast agents, including lipid-coated microbubbles and galactose microparticlcs, enhance the ultrasound signal in a clinically useful way. A commercially available agent is in use in Germany. Although available for echocardiography, commercial agents are not yet available for **TCD** testing in the United States. Echocontrast agents are especially useful in patients with inadequate temporal bone windows.

Certification and Accreditation

An ongoing program of quality assurance is basic to maintaining the highest quality of testing. Quality assurance is vital to ensure that for specific sonographcrs, using specific equipment, interpreted by specific readers, the criteria arc performing as expected (Gomez et al. 1997; Masdeu 1997; Smith, Anderson, and Gramith 1993). Formal correlation should be sought using any other modalities available, including catheter angiography, magnetic resonance angiography, pathological specimens, clinical outcomes, and repeat examinations.

Certification of sonographcrs and physicians and accreditation of neurovascular laboratories is desirable. In the United States, sonographcrs have access to several certifications that help to demonstrate expertise, The most widely accepted is the registered vascular technologist certification, which requires documented experience in the field, completion of rigorous examinations, and practical application of vascular ultrasound. Guidelines for training physicians have been established by the American Academy of Neurology, the American Society of Ncuroimaging, and other organizations. The Neurosonology Certification offered by the American Society of Neuroimaging is an important mechanism to show additional expertise. It requires documented background training and practical experience. The accreditation offered by the Intersocietal Commission for Accreditation of Vascular Laboratories is the recommended accreditation for neurovascular laboratories and remains the most rigorous of those available. Accreditation is offered for both cerebrovascular extracranial and intracranial testing.

CLINICAL APPLICATIONS

Acute **Stroke**

The 1995 introduction of tissue plasminogen activator (t-PA) to treat acute ischemic stroke (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995) focused the attention of the medical community on acute cerebral ischemia as a treatable emetgency. In the National Institute of Neurological Disorders and Stroke trial, all clinically diagnosed subtypes of stroke benefited from t-PA, and brain computed tomography was the only neuroimaging test obtained to rule out intracranial hemorrhage or other unexpected diagnoses. As a result, imaging of the cerebral vasculature is not currently a prerequisite in initiate intravenous t-PA thrombolytic therapy, although perhaps it should be.

The association of thrombolytic therapy with a 6.4% (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995) or higher risk of symptomatic intracerebral hemorrhage has led some investigators to argue for better patient selection. A belief that the treatment of patients with cerebrovascular disease should be specific to **the** cause of the stroke has prompted the use of technologies such as single photon emission computed tomography, perfusion and diffusion-weighted magnetic resonance imaging, and TCD to better characterize the cause of acute cerebral infarction.

TCD studies obtained within hours from the onset of symptoms of cerebral infarction along the vascular territory of the ICA show stenosis or occlusion of the distal

intracranial ICA or proximal MCA in 70% of patients. **When** compared with cerebral angiography, TCD is more than 90% sensitive and specific in detecting supraclinoid **ICA** or MCA Ml segment lesions. Contrast-enhanced color-coded duplex sonography can he especially useful in this context. Approximately 30% of **TCD** and cerebral angiography studies show no evidence of arterial occlusions during this acute stage, and it is unlikely that this subgroup of patients benefits from thrombolysis.

TCD can monitor the effect of thrombolytic agents. Testing before and after the administration of streptokinase or t-PA o.ni J^SI-SS iIK- agent's efficacy in obtaining arterial patency or ascertain continued patency in the days after treatment (Yasaka et al. 1998). In addition, investigators have adjusted the dosage and duration of intravenous thrombolytic agent administration based on information provided by continuous TCI) monitoring. Rapid arterial I'Lcanalization is associated with better short-term improvement (Alexandrov et al. 2001).

Although the current use of thrombolytic therapy in acute stroke does not necessitate rapid evaluation of the carotid arteries, testing might provide information that would alter therapy. Urgent carotid testing has not been widely available, and the exact clinical utility remains to be defined.

Recent Transient Ischemic Attack or Stroke

Beyond the 3-hour window, t-PA is not an established treatment option for patients with acute or subacute stroke. Antiplatelet agents and heparin or warfarin anticoagulation are prescribed depending on the immediate cause of cerebral ischemia. Atherosclerotic plaques causing moderate or severe stenosis of the ICA origin and siphon; the proximal segments of middle, anterior, and posterior cerebral arteries; the distal vertebral artery; and the basilat artery constitute approximately 20-30% of the causes of cetebral infarction. These lesions can be detected with ultrasound techniques.

Extracranial Internal Carotid Artery

Estimates of how often carotid disease is the primary cause of cerebral infarction vary from 15% to 40%. Although atherosclerosis is by far the most common cause of carotid stenosis or occlusion, other disorders, such as dissection, congenital anomalies, and thrombus that formed locally or arrived from proximal sources, must be sought. In patients with tecent transient ischemic attack or stroke, it is important to identify those with significant carotid stenosis. Not only is carotid endarterectomy (CEA) more effective than the best medical therapy for preventing subsequent stroke in patients with symptomatic tight carotid stenosis (70-99% linear stenosis), but also the absence of significant carotid disease is important in directing further diagnostic testing and treatment. The North **American** Symptomatic Carotid Endarterectomy Trial investigators also showed that patients with 50-69% linear stenosis also have **a** significant but much lower magnitude of benefit from CEA compared with medical therapy (Barnett et al. 1998). Clearly, although every patient with transient ischemic **attack** or stroke is not a candidate for CEA, the treating physician must identify those who might reasonably benefit from such treatment. In addition, new treatments, such as angioplasty with stenting, may offer attractive alternatives, even for those who are not good surgical candidates.

In the setting of recent transient ischemic attack or stroke, as with other cerebrovascular diseases, several key principles should guide the diagnostic evaluation. The physician must first determine whether any testing is warranted. The basic question is whether testing will help with the diagnosis or affect management. If so, safe, accurate, and less costly modalities should be used first, and more risky, invasive, costly methods should be used only when needed. Physicians also must be aware that the services, resources, expertise, and quality of all types of testing available locally may drastically yet appropriately alter the algorithm for evaluating cetebrovascular disease.

Ultrasound testing offers a safe, accurate, noninvasive, and inexpensive way to evaluate for extracranial cerebrovascular disease. It is considered the initial test of choice for identifying significant carotid stenosis in patients with recent transient ischemic attack or stroke (Figure 37D.7; Tegcler and Ratanakorn 1998). For the carotid territory, this should include duplex ultrasonography, with or without CFI. Reports should address the severity of stenosis based on Doppler velocity measurements. They also include information about the presence of any plaque and the morphology, based on high-resolution B-mode imaging. Additional helpful ultrasound tools include PDI and volume flow rate measurement.

Results of carotid ultrasound testing must then be integrated with other available testing modalities if additional information is needed. At present, this often means a combination of ultrasound and magnetic resonance angiography or compured tomographical angiography, with conventional angiography reserved for those in whom the noninvasive testing is technically inadequate, equivocal, or contradictory. The combination of ultrasound and magnetic resonance angiography is more cost-effective than the use of routine conventional angiography in this setting. However, the best algorithm for evaluation may vary depending on the services and expertise available at each medical center.

Intracranial Circulation

Intracranial atherosclerotic lesions account for approximately 5-10% of all cerebral infarcts. They tend to be more common in African Americans and in Japanese and Chinese populations. Intracranial atherosclerotic lesions are

Extracranial Carotid Ultrasonography in Practice

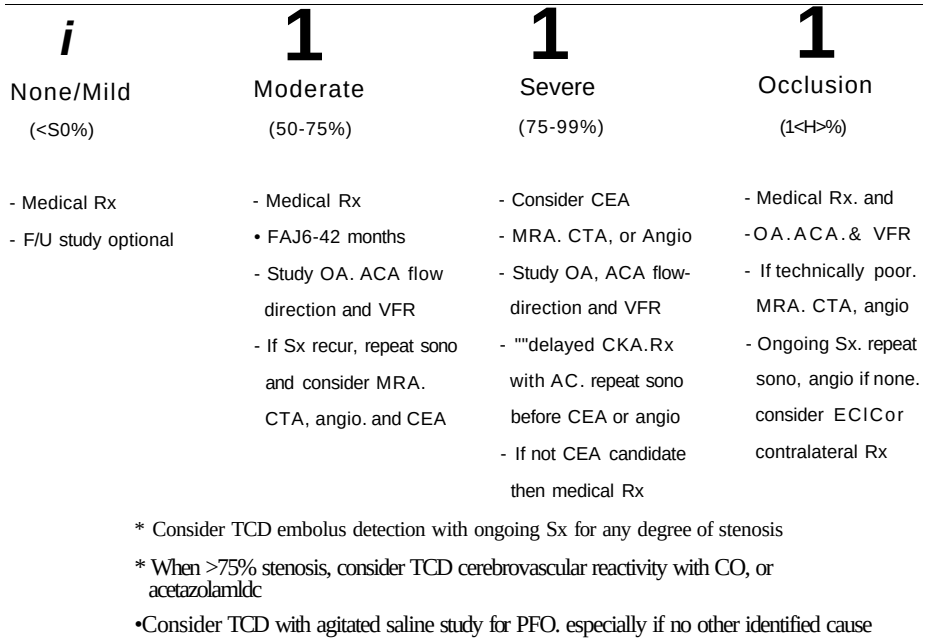


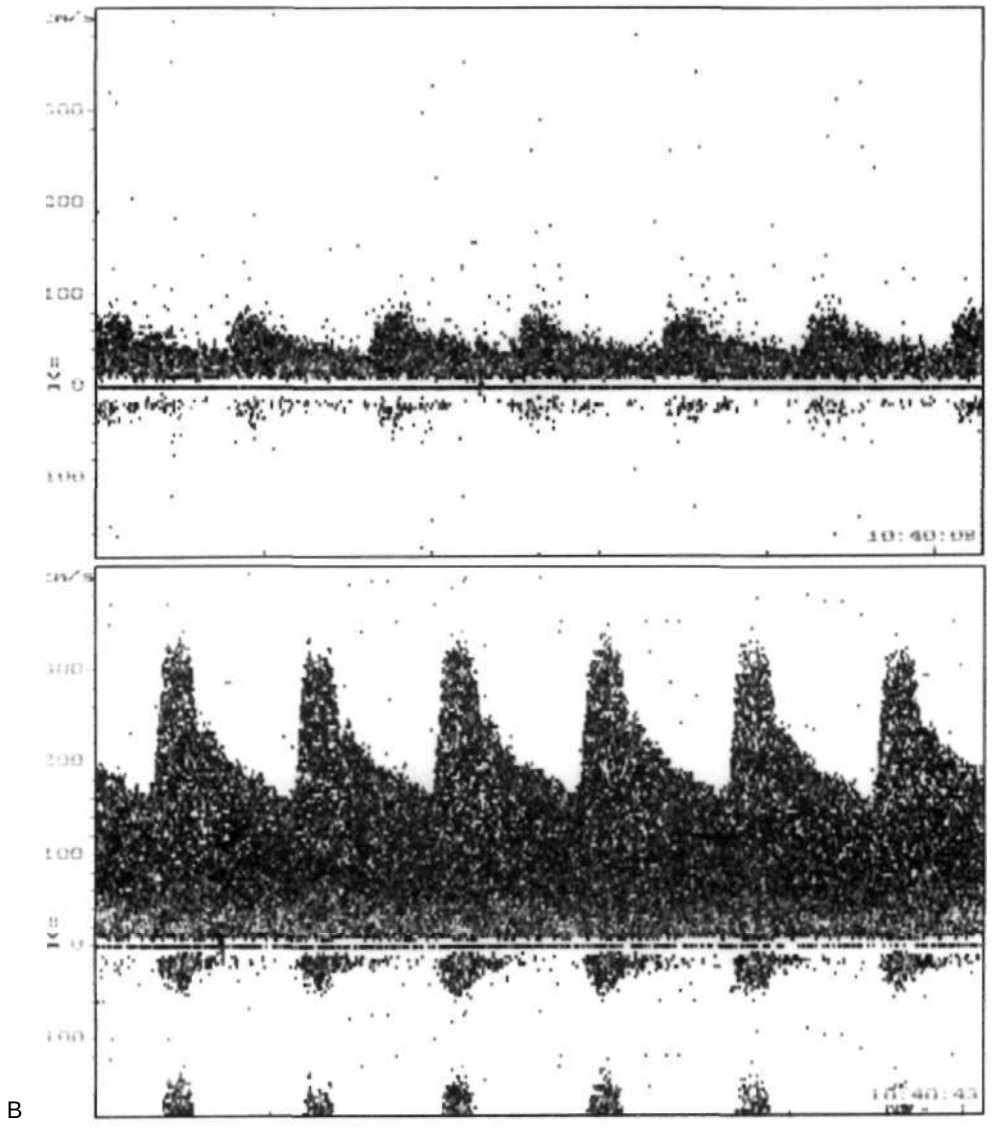
FIGURE 37D.7 Extracranial carotid ultrasonography in practice. Practical importance of carotid ultrasound. The category of stenosis severity influences treatment decisions and provides additional diagnostic information. AC = anticoagulation; ACA = anterior cerehral artery; CEA = carotid end antrectomy; $C0_2$ = carbon dioxide; CTA = computed tomography angiogram; ECIC = extracranial-intracranial bypass surgery; F/U - follow-up; MRA - magnetic resonance angiography; OA = ophthalmic artery; PFO = patent foramen ovale; Rx = treatment; Sx = symptoms; 'LCD = transcranial Doppler; VFR = volume flow rate,

associated with a high risk of cerebral infarction, which varies depending on the location of the lesion. The annual rate of stroke ipsilateral to MCA stenosis is approximately 6-10%. Brain infarction in this setting is caused by occlusion of penetrating arterioles and artery-to-artery embolism {Wong et al. 2002). Pharmacological treatment of vascular risk factors, antiplatelet agents, and anticoagulants often are prescribed to patients with these lesions, but there are no prospective studies showing the efficacy of these regimens. A 1995 retrospective study of symptomatic patients with angiographically demonstrated lesions causing more than 50% stenosis showed that warfarin anticoagulation reduces the risk of recurrent cerebral infarction and has a more favorable risk-to-benefit ratio than aspirin (Chimowitz et al. 1995}. Angioplasty is performed at some centers.

ICA distribution stenoses secondary to atherosclerosis, sickle cell disease, moyamoya disease, and dissection are reliably detected by TCD. As in other arteries, a focal increase of flow velocity is the characteristic finding of ICA siphon and supraclinoid segment as well as MCA Ml stenoses (Figure 37D.8). It is often associated with a decrease in velocity in the arterial segment distal to the stenotic lesion, in addition to low-frequency bidirectional signals during systole and arterial wall covibrations. The diagnostically relevant minimal increase in velocity remains a matter of debate, but most investigators concur that MCA peak systolic and mean velocities exceeding 140 cm per second and 80 cm per second, respectively, are significant. When compared with those of cerebral angiography, TCD findings provide an approximate sensitivity of 85% and specificity of 95% in detecting these lesions. Lower velocity values improve sensitivity, whereas higher values enhance specificity. TCD's accuracy is highest in detecting lesions causing more than 50% stenosis. The technique is less reliable in detecting lesions in the proximal anterior and posterior cerebral arteries, and the MCA M2 segment usually is beyond its reach. The accuracy of cerebral catheter angiography in detecting some itirracranial lesions and in estimating the degree of stenosis has been questioned, however.

MCA or basilar artery occlusion is associated with an absence or severe reduction of the Doppler signal at the appropriate depth of insonation at a time when signals from the other ipsilateral basal cerebral arteries arc detectable. Follow-up studies often show spontaneous recanalization of previously occluded segments. The latter can be detected within hours of the onset of symptoms; the majority of symptomatic occlusions are recanalized within *2* days, followed by a period of hyperpcrfusion.

Collateral flow patterns associated with severe cervical carotid stenosis or occlusion also can be detected. They include retrograde flow of the ophthalmic artery and



B

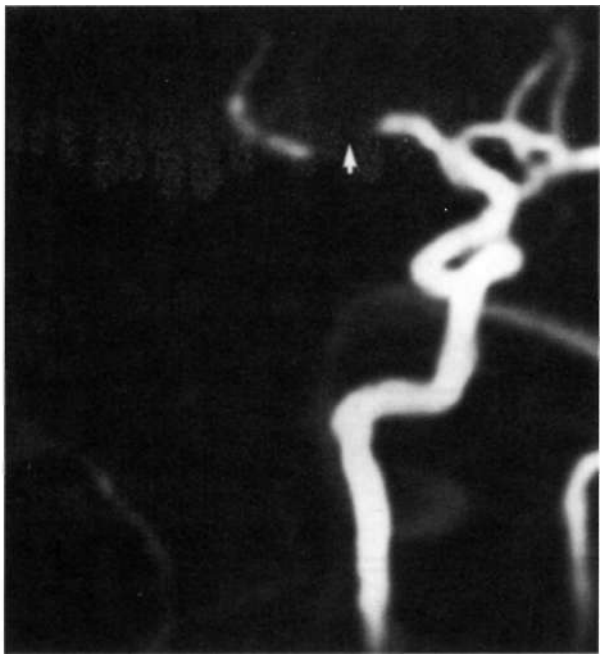
FIGURE 37D.8 Middle cerebral artery stenosis. Focal increase in flow velocities. (A) The peak systolic flow velocity is only 82 em per second, a value within the normal range, at a depth of insonation of 56 mm. (B) At 48 mm, however, the peak systolic velocity is markedly increased at approximately 330 cm per second, indicating a severely stenotic lesion of the Ml segment. *Continued*

anterior or posterior communicating artery flow toward the hemisphere distal to stenosed or occluded ICAs.

Lesions causing stenosis of the V4 segment of vertebral artery and the proximal basilar artery also can be imaged by TCD. Focal increases of the peak systolic and mean velocities to, respectively, 120 cm per second and 80 cm per second or more at depths of insonation corresponding to these arterial segments is considered significant (Figure 37D.9). Velocities often exceed 200 cm per second with lesions causing more than 50% stenosis. When compared with angiography, the sensitivity of TCD is approximately 75% in detecting vertebrobasilar stenotic lesions, and its specificity exceeds 85%. The frequent variation in the size and course of the vertebrobasilar trunk and its contribution of collateral flow to the anterior cerebral circulation are the main reasons for these low figures. Contrast media and transcranial color-coded imaging can be particularly helpful in this setting {Stolz et al. 2002),

Usually a benign condition, the subclavian steal syndrome is characterized by the triad of retrograde flow in one vertebral artery, anterograde flow in the other, and biphasic or retrograde flow in the basilar artery (Figure 37D.10), The surge in interest in this condition stems from the use of angioplasty to treat selected patients with severe symptoms.

Microemholic signals (Plate 371X1V) detected by 1 CI) correspond to gaseous microbubbles or emboli composed of platelets, fibrinogen, or cholesterol moving in intracranial arteries. In patients with extracranial carotid disease, these signals are associated with a history of recent



C

FIGURE 37D.8, cont'd. (C) The magnetic resonance angiogram confirms the presence of the stenotic lesion *{arrowhead}*.

transient ischemic attacks or cerebral infarction in the distribution of the insonatcd artery, and they correlate with the presence of ipsilateral severe stenosis and plaque ulceration. They are detected mainly during the week after symptoms of cerebral ischemia and resolve afterward. Microembolic signals also can be detected in subjects with cardiac prosthetic valves but often correspond to gaseous micro bubbles in that setting. They are less common in adequately anticoagulatcd patients with atrial fibrillation.

The clinical impact of microembolus detection studies remains limited. The presence of these signals in an arterial territory is useful in identifying active lesions. This is especially relevant when a symptomatic patient has more than one potential lesion, such as cervical carotid stenosis and atrial fibrillation, or a suboptimal history. In this situation, laboratory data can help identify the specific cause of cerebral infarction. In addition, because the presence of microembolic signals predicts future cerebral ischemic events in the insonated artery's territory (Babikian et al. 1997), the detection of these signals may tilt therapeutic decisions. In the future, microembolus detection studies may be useful in monitoring the effect of antiplatelet agents or anticoagulation. Microemboli monitoring is also useful in the context of CFA and coronary artery bypass surgery.

Although at some medical cenrers carotid duplex and TCD testing are performed in different laboratories, they are complementary. The accuracy of TCD studies is improved when the condition of the extracranial carotid and vertebral arteries is known. Similarly, in endarterectomy candidates with symptomatic extracranial carotid stenosis diagnosed by duplex scanning, tandem lesions can occasionally coexist and should be ruled out. Therefore duplex and TCD testing should often be obtained together, or in an organized sequence, to answer specific questions or hypotheses developed by the treating physician.

Chronic Ischemic Cerebrovascular Disease

Extracranial Stenotic Lesions

Ultrasound offers a safe, noninvasive way to serially follow patients with carotid or vertebral artery disorders. Periodic evaluation can be helpful for assessing the progression or regression of existing plaques or the development of new lesions, whether symptomatic or asymptomatic. The timing of follow-up carotid testing must be individualized depending on the severity and types of lesions and the onset of new or recurrent symptoms. Asymptomatic stenosis of less than 50% might be initially restudied in 12-24 months, whereas lesions with 50-75% stenosis and uncomplicated plaques might wait 6-12 months. For 50-75% stenosis with complicated plaque features, or for more rh.m 75% stenosis, initial restudy at 3-6 months seems appropriate if CEA is not performed. Lack of progression for several years allows lengthened intervals before restudy. When evidence of asymptomatic progression is present, a shorter interval is recommended. Development of new symptoms should prompt urgent reevaluation. After CEA, repear ultrasound often is done approximately 1 month after surgery and then yearly to look for restenosis.

The identification of asymptomatic carotid stenosis has become an important clinical mandate since the Asymptomatic Carotid Atherosclerosis Study showed the benefit of CEA in asymptomatic individuals with 60-99% stenosis when compared with treatment with 325 mg of aspirin daily (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study 1995). Yet it is not cost-effective to screen the entire population, even with ultrasound. Asymptomatic individuals with cervical bruits should be studied, even though bruits often are due to another cause. Patients with multiple risk factors probably warrant study, but the clinical utility of this has not yet been confirmed. If stenosis is identified, intervals for restudy should be similar to those outlined previously,

Large population studies, such as the Atherosclerosis Risk in Communities and the Cardiovascular Health Study, have documented the association between risk factors and mtima-media thickening in the wall of the carotid artery on B-mode imaging (Howard et al. 1993; Polak et al. 1998). This may be an early stage in the development of atherosclerosis, and the presence of significant thickening correlates with risk of heart attack and with abnormalities

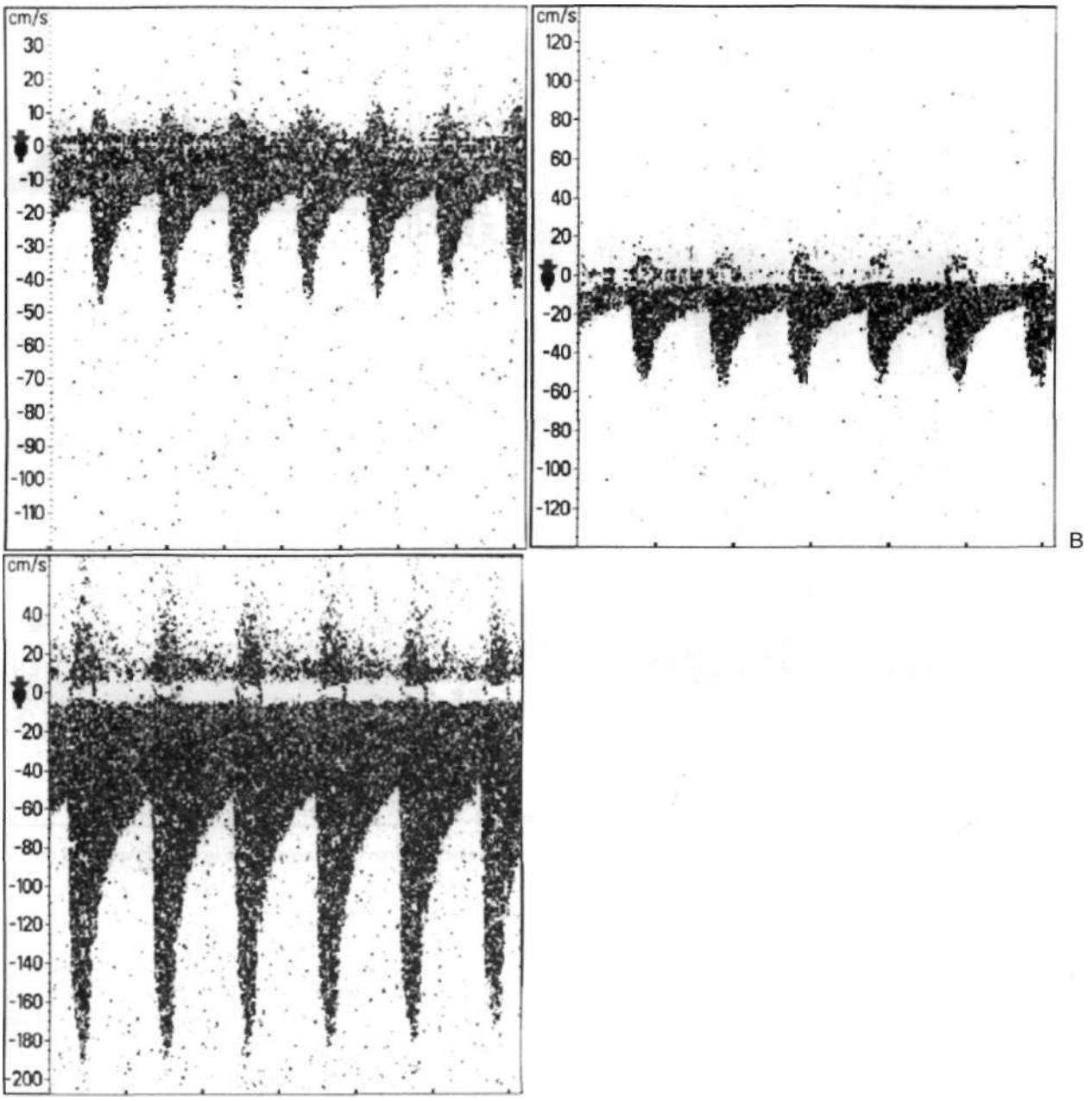


FIGURE 37D.9 Basilar artery stenosis. {A, B) The flow velocities are within the normal range in the vertebral arteries. (C) The peak systolic velocity exceeds ISO cm per second, and the end-diastolic velocity exceeds 45 cm per second at an insonation depth of 100 mm, indicating proximal Basilar artery stenosis.

on magnetic resonance imaging of the htain. Although extensive data to confirm the clinical utility of identifying increased intima-media thickness values are lacking, it has been suggested that B-mode imaging to evaluate intima-media thickness should be used clinically to identify patients with high risk for coronary or cerebrovascular events or to assess responses to risk factor modification (Greenland et al. 2000). It is hoped that such early identification of atherosclerotic changes will allow intervention to prevent later development of clinical events.

Intracranial Stenotic Lesions

Intracranial atherosclerotic plaques are dynamic lesions. Although some lesions progress, causing increasing degrees of stenosis, others may tegress over short periods of time. TCD enables the noninvasive monitoring of the progtession of these lesions. It is often obtained at baseline, in conjunction with cerebral catheter angiogtaphy or magnetic resonance angiography, and is subsequently repeated during the follow-up period (Figure 37D.11), Monitoring also enables detection of new atherosclerotic plaques.

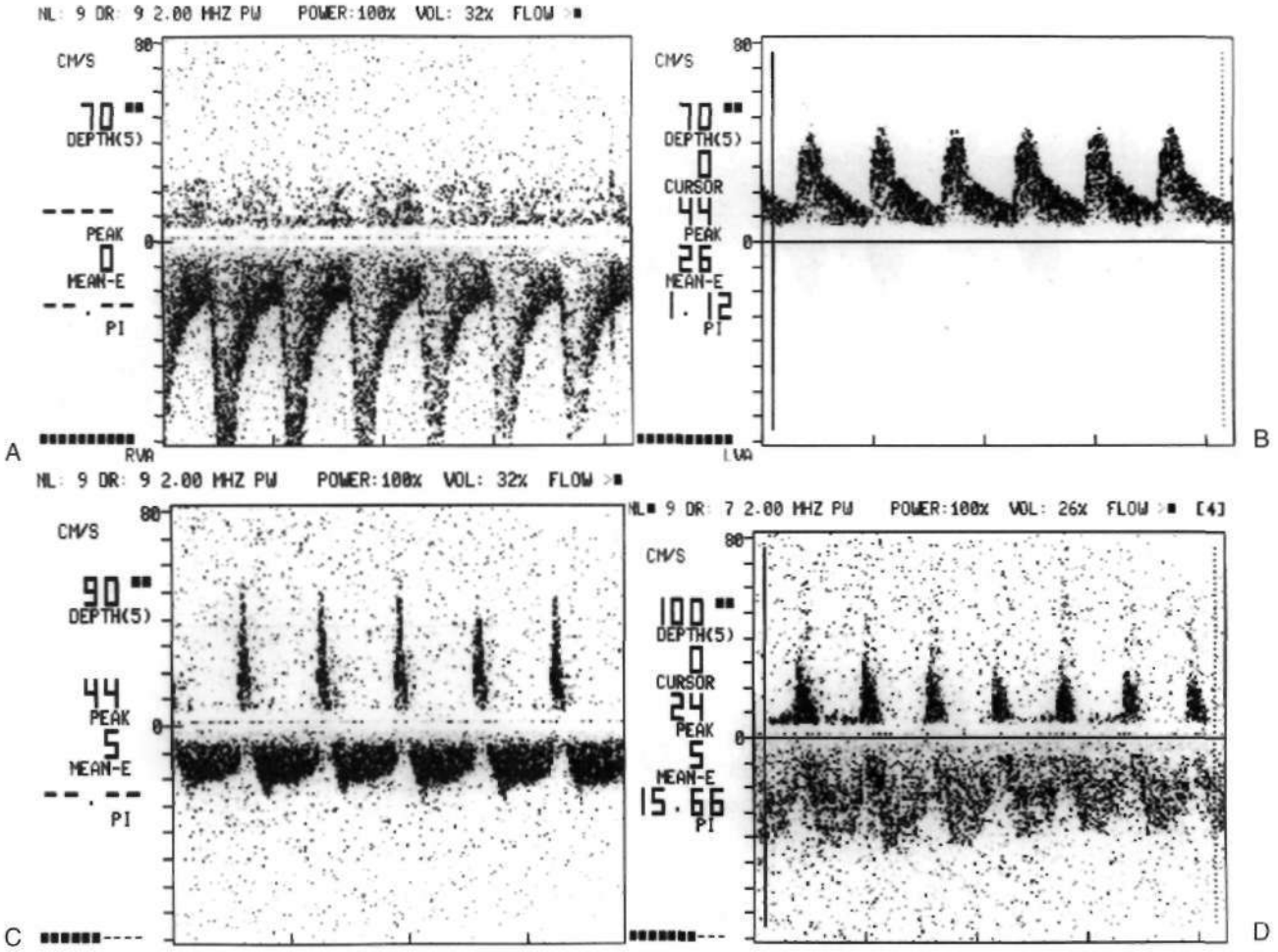


FIGURE 37D.10 Subclavian steal. The flow is anterograde in the right vertebral artery (A), retrograde in the left vertebral artery (B), and biphasic in the basilar artery (C, D).

However, clinical experience is limited, and no published prospective studies exist to make recommendations regarding the frequency and timing of follow-up studies.

Cerebrovascular Reactivity

The annual stroke rate distal to carotid occlusion is approximately 2-5%. Cerebral embolism and hypoperfusion are considered the main causes of recurrent symptoms of cerebral ischemia. Although the ability of abnormal cerebral hemodynamic changes to identify patients at an increased risk of recurrent stroke has been questioned, more recent studies suggest that hemodynamic impairment can be a major cause of cerebral ischemia. In patients with ICA occlusion and impaired cerebrovascular reactivity determined by TCD or xenon computed tomography, the annual rate of distal cerebral ischemic events is approximately 10%. Because a subgroup of patients with impaired cerebrovascular reactivity may benefit from a bypass procedure, a new randomized clinical trial has been organized (Adams et al. 2001).

Both intravenous acetazolamide administration and carbon dioxide inhalation methods are used to assess cerebrovascular reactivity. In patients with exhausted cerebrovascular reactivity, flow velocities fail to adequately increase after the intravenous administration of acetazolamide or have a decreased response to hypercapnia and hypocapnia. TCD testing can provide an estimate of the stroke risk in patients with ICA occlusion. However, the ability of testing to reliably identify patients who might benefit from a revascularization procedure has not been shown.

Sickle Cell Disease

An occlusive vasculopathy characterized by a fibrous proliferation of the intima often involves the basal cerebral arteries of patients with sickle cell disease. Cerebral infarction is a common complication of this vasculopathy and has a frequency of approximately 5-15%.

As in all patients with anemia, flow velocities are diffusely increased in patients with sickle cell anemia.

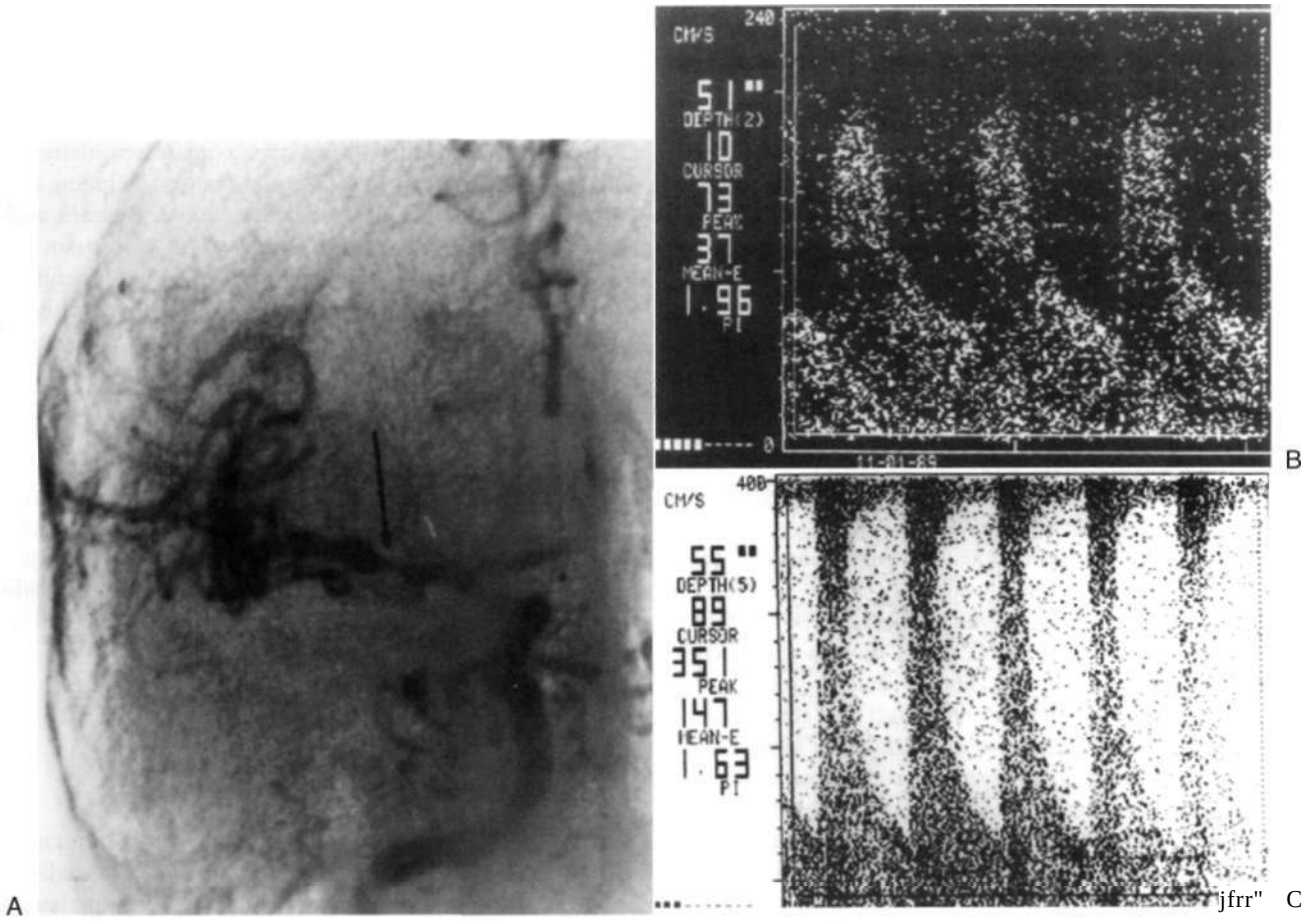


FIGURE 37D.11 Monitoring of intracranial atherosclerotic lesions. (A) Cerebral angiogram shows an area of stenosis *{arrow)* in the Ml segment of the right middle cerebral artery, (B) The first transcranial Doppler study obtained within 48 hours of angiography shows a corresponding peak systolic velocity of 188 cm per second. (C) Repeat transcranial Doppler study .34 months later shows a further increase of the peak systolic velocity to approximately 350 cm per second. (Reprinted with permission from Schwarzc, J. J., Babikian, V., DeWitt, L. D., ct al., 1994, "Longitudinal monitoring of intracranial arterial stenoses with transcranial Doppler ultrasonography," *] Neuroimaging,* vol. 4, pp. 182-187.)

Additional focal velocity increases in the basal cerebral arteries can be detected in some patients (Plate 37D.V}. These increases correlate with 90% sensitivity and more than 95% specificity with stenotic lesions demonstrated by cerebral catheter or magnetic resonance angiography. A time-averaged mean of the maximum velocity of 200 cm per second or greater in the distal ICA and proximal MCA identifies neurologically asymptomatic children at an increased risk for first-time stroke {Adams et al. 1998). Periodic red blood cell transfusion is associated with a 90% reduction in the rate of stroke. A Clinical Alert from the National Heart, Lung and Blood Institute recommended that children with sickle cell disease between ages 2 and 16 receive baseline TCD testing and that those with normal study results be restudied every *6* months {National Heart, Lung and Blood Institute 1997). Red blood cell transfusions reduce some of the abnormalities seen on cerebral angiography.

Aneurysmal Subarachnoid Hemorrhage

Vasoconstriction of intracerebral arteries is the leading cause of delayed cerebral infarction and mortality after aneurysmal subarachnoid hemorrhage. Vasospasm is clinically detected 3 or 4 days after the hemorrhage and usually resolves after day 12. Although the exact cause of vasospasm remains unknown, its presence correlates with the volume and duration of exposure of an intracranial artery to the blood clot. Laboratory and animal models indicate that blood breakdown products can lead to vasoconstriction.

The detection of vasospasm is important because it can be treated. Nimodipine, intravascular volume expansion, and pharmacologically induced relative hypertension are some of the prescribed therapies, and balloon angioplasty and intra-arterial papaverine are experimental therapies increasingly provided at some medical centers.

These treatments are not innocuous, and the ability to noninvasively detect and monitor vasospasm is of clinical interest.

Although vasospasm can he angiographically detected in 30-70% of patients with aneurysmal subarachnoid hemorrhage, only 2CMK)% develop clinical signs of cerebral ischemia. Therefore the presence of vasospasm is not a sufficient condition for developing a clinical focal ischemic deficit, and several factors, including the severity of spasm, presence of collateral flow, condition of patient's intravascular volume, and cerebral perfusion pressure, are considered mitigating factors.

TCD studies show an increase in the flow velocities of basal cerebral arteries, usually starting on day 4 after subarachnoid hemorrhage and peaking by days 7-14 (Plate 37D.VI). Although a diffuse increase in velocities often is detected in patients with severe hemorrhage, arterial segments in close proximity to the subarachnoid blood clot usually have the highest velocities.

Severe vasospasm in an arterial segment can be associated with reduced regional cerebral blood flow in the artery's distal territory. There is a linear, inverse relationship between the severity of vasospasm and the amplitude of flow velocity increase in an arterial segment. It is valid until the vasoconstriction is so severe that the flow volume is reduced, flow velocities drop, and the TCD signal becomes difficult to detect. The linear relationship can also be affected by several factors including the presence of hyperperfusion. Whether there is a critical threshold of flow velocity for cerebral ischemia remains a matter of debate. Angiographic studies confirm the presence of at least some degree of MCA vasospasm when the mean flow velocities are higher than 100 cm per second, but values below 120 cm per second are considered clinically insignificant. Mean velocities between 120 and 200 cm per second correspond to 25-50% angiographically determined diameter reduction, and values exceeding 200 cm per second correspond to more than 50% luminal narrowing (Sloan, Wozniak, and Macko 1999). Based on these and other considerations, some investigators initiate hypertensive therapy at a mean velocity threshold of 120 cm per second, but this is not standard practice. The 200 cm per second threshold and rapid flow velocity increases exceeding 50 cm per second on consecutive days are associated with subsequent infarction. The effect of orally administered nimodipine on flow velocities appears to be minimal.

TCD is used also to monitor the effects of endovascular treatment of vasospasm. Flow velocities decrease after successful angioplasty or papaverine infusion. Persistent increases after treatment indicate either extension of vasospasm to new arterial segments or hyperemia in the treated arterial segment and may constitute a valid reason for repeat cerebral angiography.

The accuracy of TCD in detecting vasospasm depends to some degree on the location of the involved arterial segment. Although TCD criteria are more than 90% specific in detecting MCA and anterior cerebral artery vasospasm, they are, respectively, 80% and less than 50% sensitive in detecting disease in these arterial segments (Sloan, Wozniak, and Macko 1999). Basilar artery vasospasm is detected with an approximate sensitivity of 75% and specificity of 80%. Several factors, including the effects of hyperemia, increased intracranial pressure and blood pressure changes, the presence of vasospasm in convexity branches not accessible by TCD, and difficulties in assessing vasospasm by angiography, contribute to these findings.

Because of these limitations in accuracy, the combined use of TCD and single photon emission computed tomography or xenon-enhanced computed tomography has been advocated, with the expectation that it will provide a more comprehensive and accurate assessment of the clinical condition. Overall, however, TCD is considered to have acceptable accuracy for evaluating vasospasm in aneurysmal subarachnoid hemorrhage. It is a useful tool with limitations that must be taken into consideration in the clinical setting.

Intensive Care Unit and Perioperative Monitoring

Cerebral Circulatory Arrest

A characteristic pattern of changes can be detected by TCD in patients with increased intracranial pressure. Early findings consist of a mild decrease in the diastolic flow velocity and an increase in the difference between peak systolic and end-diastolic velocities. When the intracranial pressure increases further and reaches the diastolic blood pressure level, flow stops during diastole, and the corresponding flow velocity drops to zero; flow continues during systole, and spiky systolic peaks are observed. A further increase of the intracranial pressure is **associated** with a reverberating flow pattern, with forward flow in systole and retrograde flow in diastole (Figure **37D.12).** The net volume of flow decreases and can reach zero. At cerebral perfusion pressure values close to zero, either small systolic spikes are observed (Figure 37D. 12), or no signal at all is detected. This corresponds to a complete arrest of flow as demonstrated by cerebral angiography. The pattern of TCD changes is not specific to a particular neurological disease and can occur in a **variety** of conditions associated with increased intracranial pressure.

The changes described in the preceding paragraphs are also observed in patients clinically diagnosed as brain dead. In one study, a high-resistance waveform pattern consisting of absent or reversed diastolic flow and small early systolic spikes, when present in at least two intracranial arteries, was more than 90% sensitive and 100% specific for brain death. Experience at other centers has been more variable, with some investigators reporting patients who do not

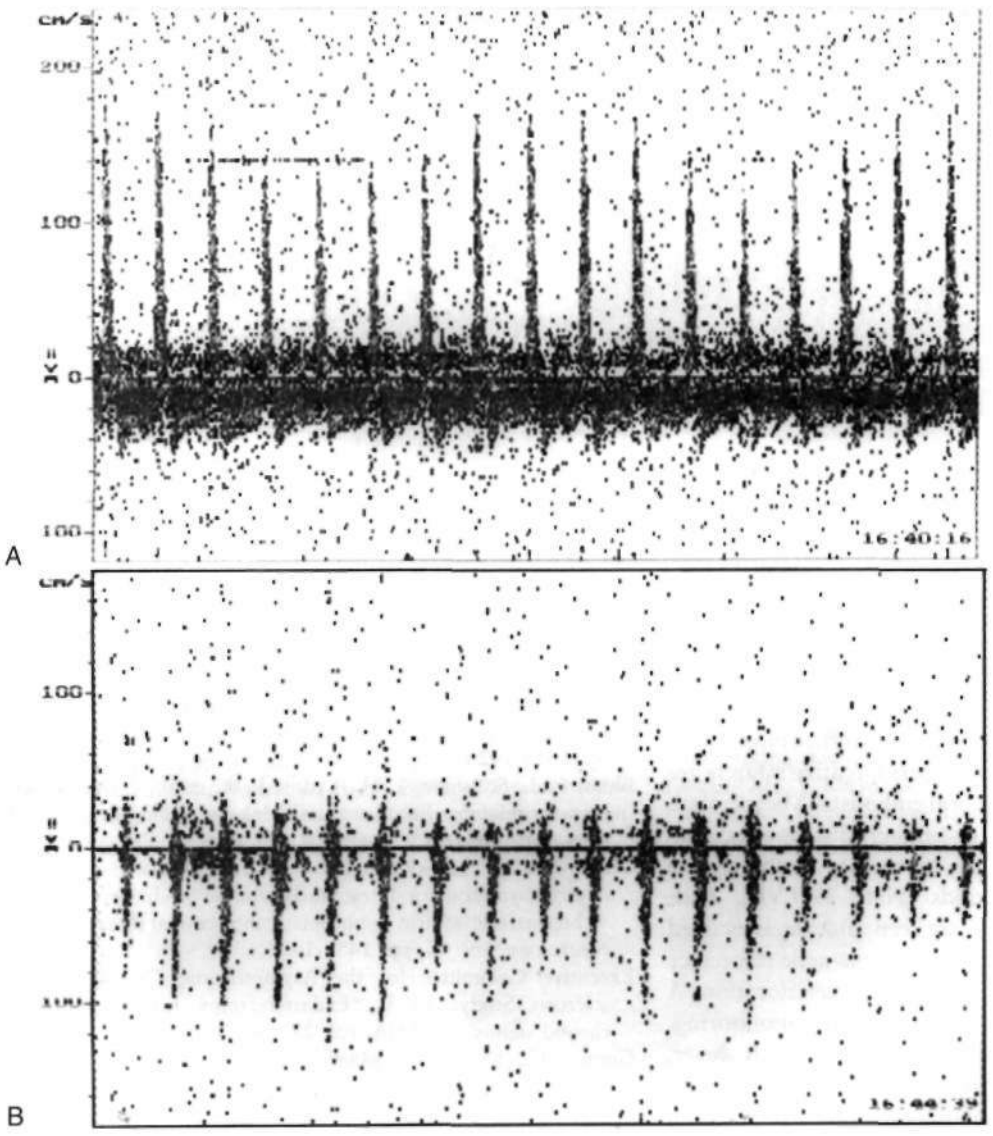


FIGURE 37D.12 Raised intracranial pressure. Reverberating flow pattern (**A**) and small systolic spikes (**B**) seen in a patient with markedly increased intracranial pressure.

satisfy clinical criteria for brain death, even though their TCD studies indicate circulatory arrest in some cerebral vessels. This is not totally unexpected because preserved intracranial circulation has been demonstrated previously in brain-dead patients. Thus although TCD is useful in detecting cerebral circulatory arrest, it cannot be recommended as the sole diagnostic test for diagnosing brain death. The latter must be established based on the clinical presentation and neurological examination findings. TCD and other laboratory tests can help confirm the clinical impression.

Carotid Endarterectomy

As indicated earlier in this chapter, CEA is more effective than medical therapy when it can be performed with a combined mortality and morbidity of less than 6% for symptomatic and 3% for asymptomatic patients. Unfortunately, these results are not achieved at all medical centers (Wennberg et al. 1998).

Monitoring is performed to identify and correct surgical events that can lead to cerebrovascular complications. Monitoring tests currently in use include electroencephalography and stump pressure measurement. These tests are useful in detecting cerebral hypoperfusion or its consequence, cerebral ischemia, but their effectiveness in reducing the perioperative stroke rate has not been demonstrated in prospective studies.

TCD monitoring during CEA shows a consistent pattern of flow velocity changes during endarterectomy, The most significant changes occur at the time of carotid clamping, with persistent and severe velocity decreases to less than 15% of prcclamp values in up to 10% of patients (Figure 37D.13). Patients with velocities decreasing to this level usually are considered candidates for shunting. Although definitive TCD criteria for shunting have not yet been established, a postclamp peak systolic

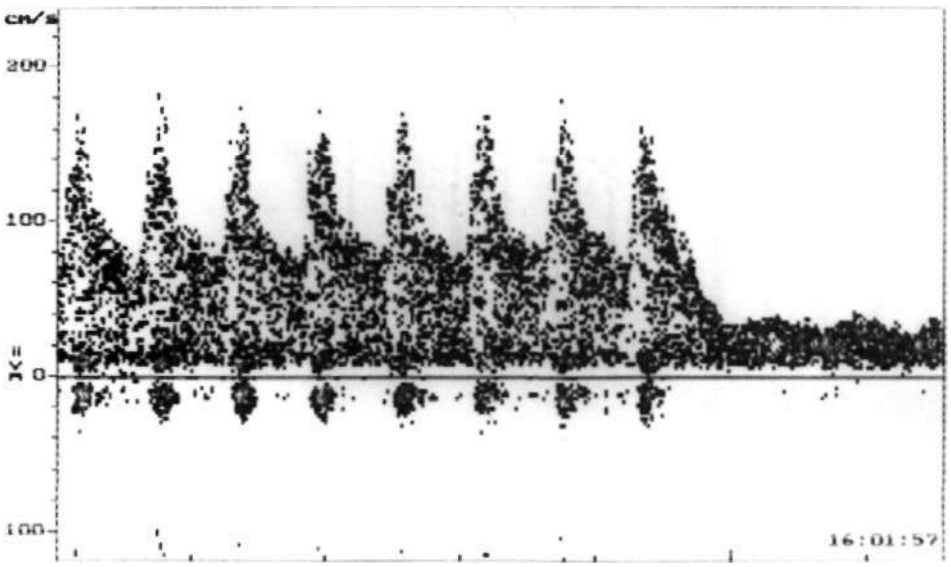


FIGURE 37D.13 Carotid endarterectomy. At clamp insertion, the peak systolic flow velocity decreases from approximately 175 to 35 cm per second.

or mean flow velocity decrease to less than 30% of the preclamp value often is considered an acceptable criterion.

TCD also has the unique ability to detect microembolism as it occurs. This gives TCD an edge over other monitoring techniques because the majority of perioperative infarcts are thought to be secondary to cerebral embolism, Mtcroemholi are detected at specific stages of surgery; dissection, clamp insertion and release, and the immediate postoperative period are rhe high-risk periods (Plate 37D.VII). Roth gaseous and particulate emboli are seen and are associated with small cerebral infarcts detected by magnetic resonance imaging and with postoperative cognitive deterioration. A relative newcomet to the field of intraoperative monitoring, TCD provides useful information to rhe surgeon. However, the characteristics of microembolism associated with cerebral infarction, such as emboli count and composition, remain to be determined. A prospective study to assess the technique's effectiveness is needed.

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Chapter 37
Neuroimaging

E. FUNCTIONAL NEUROIMAGING

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Structural neuroimaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) have been available for several decades and have become invaluable tools in the evaluation of central nervous system (CNS) disease. Functional neuroimaging modalities have been developed more recently. Although CT and MRI provide static, high-resolution images ol die CNS, functional neuroimaging modalities such as positron emission tomography (PET), single-photon emission CT (SPECT), and functional MRI {fMRI) provide dynamic images of brain function. This chapter reviews the various functional neuroimaging modalities. In addition, the clinical utility of these techniques is reviewed and potential clinical and research applications arc discussed.

FUNCTIONAL NEUROIMAGING MODALITIES

Positron Emission Tomography and Single-Photon Emission Tomography

PET and SPECT are radiotracer imaging modalities. A biologically relevant radiotracer is introduced into the subject and its actions can be measured *in vivo.* For example, $^{15}0$ can be incorporated into either CO2 or H2O, The $'^{5}0$ radiotracer can be introduced to the subject cither by inhalation or intravenous injection and serves as an *in vivo* dynamic marker of regional cerebral blood flow (rCBF) in PET studies. PET and SPECT cameras are designed to measure the radiation emitted from radiotracers in a manner that allows for reconstruction of spatial images (tomographs) that provide both qualitative and quantitative measures of brain function. The typical spatial resolution of these images is 3-5 mm for PET and 7-10 mm for SPECT (although advances in technology may ultimately result in comparable spatial resolutions for both modalities). Single functional images may be collected (i.e., "snapshots" of brain function} or multiple serial images may be acquired (i.e., dynamic, "filmstrip-like" images of brain function). However, the temporal resolution of PET and SPECT docs not approach that of fMRI (discussed later in this chapter).

PET and SPECT are primarily used to measure indices of neuronal activity. Regional cerebral metabolic rate (rCMR) and rCBF can be assessed using PET, whereas SPECT can measure only rCBF. ^{IK}F-fluorodeoxygIucosc (FDG) is used to measure rCMR and ^{ts}O is used to measure rCBF with PET. A number of SPECT radiotracers are available to measure rCBE including ^{yym}Tc-hcxamerhylpropyIenearnine oxime (HMPAO), ^{99m}Tc-ethylene cysteinate dimer (ECD), and ^{12}*I-isopropyl iodoamphetamiuc (IMP). Of note, the shorter half-life of $^{15}0$ (about 2 minutes) allows for multiple measures of rCBE during a single PET study, whereas the longer half-life of the SPECT radiotracers typically allows for only one measure of rCBE during a single SPECT session. Thus paradigms requiring multiple acquisitions require multiple visits on separate days if SPECT is to be used.

In addition to the radiotracers designed to measure rCMR and rCBF, there are also a number of agents

Tabic 37E.1: Representative radiotracers

Radiotracer	*What it measures*
Single-photon emission computed tomography	
"Tc-HMPAO	Blood flow
"""Tc-ECD	liluotl flow
^{U,}I-IMP	Blood flow
$^{l;i}$I-altropane	Dopamine transporter
^{u,}I-0CIT	Dopamine transporter/serotonin trans porter
^{123}I-epidipride	Type 2 dopamine (D^) receptor
^{U3}I-IBZM	Type 2 dopamine (D_2) receptor
Positron emission tomography	
$C*0_2$, $H_2{}^{1s}O$	Blood flow
^{la}F-fluorodcoxyglucosc	Glucose metabolism
^{11}C-altropane	Dopamine transporter
^{iii}C-SCH 23,390	Type 1 dopamine (D^ receptor
^{u}C-raclo pride	Type 2 dopamine 2 (D_2) receptor
"C-WAY 100635	Type 1A serotonin (5-HTIA) receptor
F-setoperone	Type 2 serotonin (5-HT2) receptor
C-flumazenil	Benzodiazepine receptor
C-diprenorphine	Opioid receptor (nonselective)
"C-carfentanil	Opioid receptor (mu selective)

designed to measure various aspects of neurochemistry (Table 37E.1). These radiotracers allow for quantification of presynaptic and postsynaptic neuroreceptors and neurotransmitter synthesis. Such neurochemistry studies show promise for assessing conditions in which abnormalities of a single neurotransmitter play a prominent role in the pathophysiology of the disease (e.g., dopamine abnormalities in Parkinson's disease).

Functional Magnetic Resonance Imaging

fMRI studies use unique data-acquisition parameters that differ from those used for conducting structural MRI studies. Structural MRI studies involve placing the subject in a strong magnetic field (see Chapter 37A). This strong magnetic field aligns the resonant spin of a fraction of the hydrogen nuclei in the body. Then, the application of a radiofrequency pulse results in these nuclei changing orientation relative to the pre-existing magnetic field. In time, the hydrogen nuclei begin to return to their initial alignment. It is this relaxation of the hydrogen nuclei that provides the data necessary for construction of structural images, fMRI exploits the fact that deoxyhcmoglobin distorts the magnetic field. Because the local concentration of deoxyhemoglobin varies, the amount of distortion also varies. The local concentrations of deoxyhemoglobin provide an indirect measure of oxygen use. These changes in localized blood oxygenation give rise to the fMRI blood oxygen level-dependent (BOLD) signal change that is related to CBE and cerebral blood volume.

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) also exploits the behavior of endogenous compounds in a magnetic field to measure underlying biological processes. The nuclei of a number of atoms ('H, ^{1y}F, ^{7}Li, ^{2i}Na, and ^{M}P) are excited by the magnetic field. As the energy of these nuclei returns to a baseline state, a "frequency signature" particular to each nucleus can be measured. Simply put, the magnitude of each peak in this "frequency signature" corresponds to the concentration of a particular atom in the brain region being assessed.

MRS studies of the different nuclei allow for quantification of a number of compounds in the brain. MRS studies of the hydrogen nucleus allow for the semiquantitative measurement of a number of endogenous compounds including N-acetyl-aspartate (NAA}, choline, creatine, *y*-aminobutyric acid (GABA), glutamate, glutamine, inositol, and phosphocrcatinc. NAA is purportedly a marker of viable neurons. GABA and glutamate are the main inhibitory and excitatory neurotransmitters, respectively, in the human brain. Creatine and phosphocreatine are involved in neuronal energy metabolism. Choline is involved in membrane metabolism, and inositol is involved 111 second-messenger neurotransmission.

Phosphorus MRS allows for measurement of molecules involved in energy metabolism such as adenosine triphosphate (ATP) and adenosine diphosphate (ADP). Components of neuronal membranes such as phosphomonoesters (PMEs) and phosphodiesters (PDEs) can also be measured using phosphorus MRS. Fluorine MRS and lithium MRS can be used to measure concentrations of exogenous substances (e.g., drugs) in the brain, i.irhium MRS can be used to measure brain lithium levels, and fluorine MRS can be used to measure the concenttation of fluorinated compounds {e.g., fluoxetine).

MRS is being increasingly used to identify neoplasms of brain and to localize areas of tumor involvement (Figure 37E.1).

Electroencephalography and Magneto encephalography

Electroencephalography (EEG) involves measurement of cortical activity via scalp electrodes. Conventional EEG has a multitude of clinical applications and is discussed in detail in Chapter 36A. Other EEG-related methodologies include event-related potentials (ERP) and quantitative EEG (QEEG). *ERP* refers to event-related waveforms in the EEG data that atisc following sensory, motor, or cognitive events. Although HRP lias a wide range ot applications in the research setting, there are currently three major uses of

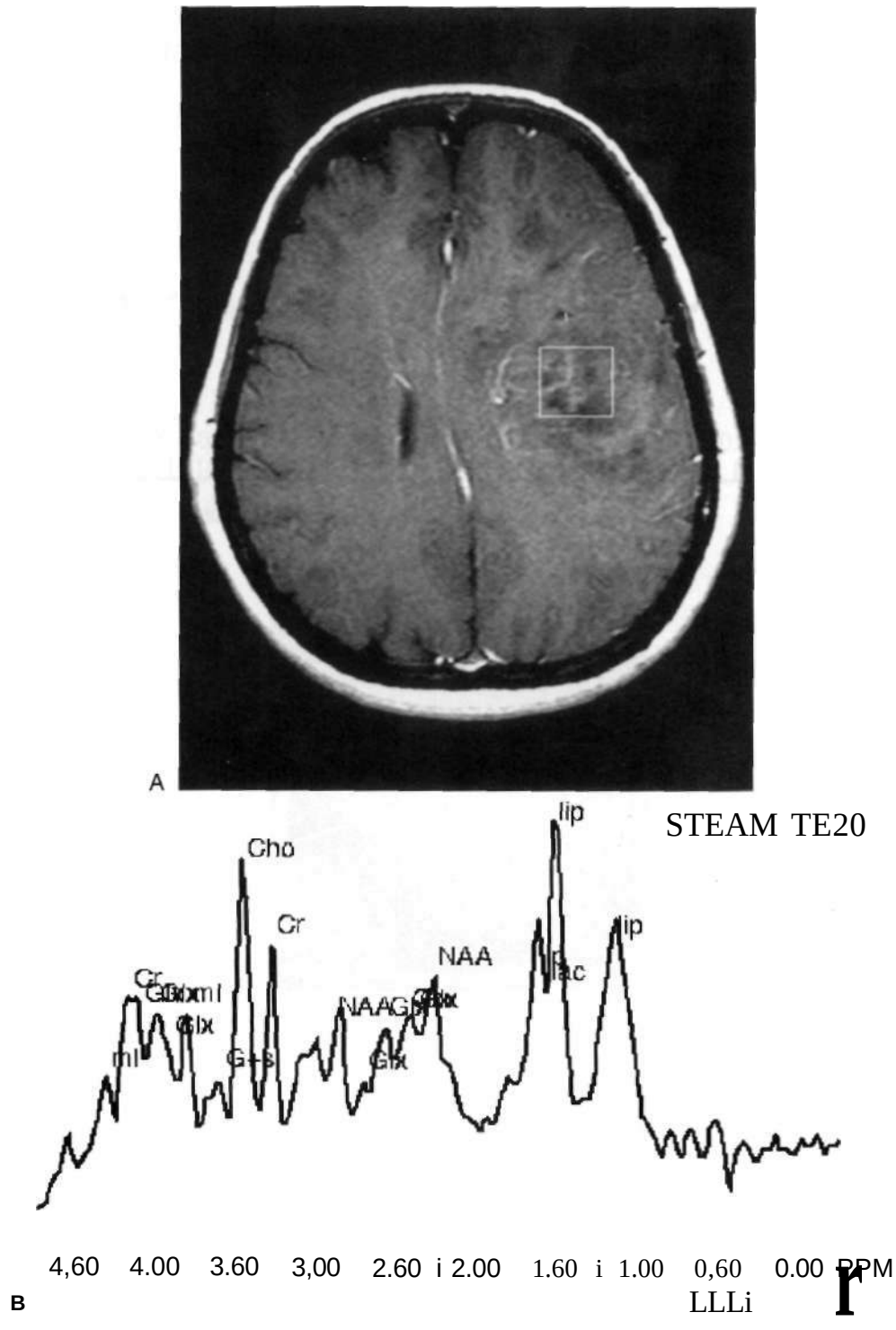

FIGURE 37E.1 Grade III astrocytoma, left frontal lobe, evaluated with single-voxel spectroscopy (SVS) and magnetic resonance spectroscopic imaging (MRSI). The results are typical of a high-grade astrocytoma. (A) Postcontrast Tl-weighted axial image used for localization of an 8-mL single voxel (2 x 2 x 2 cm) in the left frontal lobe. The voxel is positioned in a region of heterogeneous signal intensity with mild enhancement. There is moderate compression and displacement of adjacent brain, (B) SVS at echo time (TF.) of 135 ms: Point-resolved spectroscopy (PRESS) spectrum demonstrates decreased N-acetyl-aspartate (NAA), increased level of choline-con raining small molecules (Cho), and increased lactate (Lac, appears as inverted doublet). Compare the peak heights and areas to those in (E), which were acquired from a region of normal-appearing brain. *Continued*

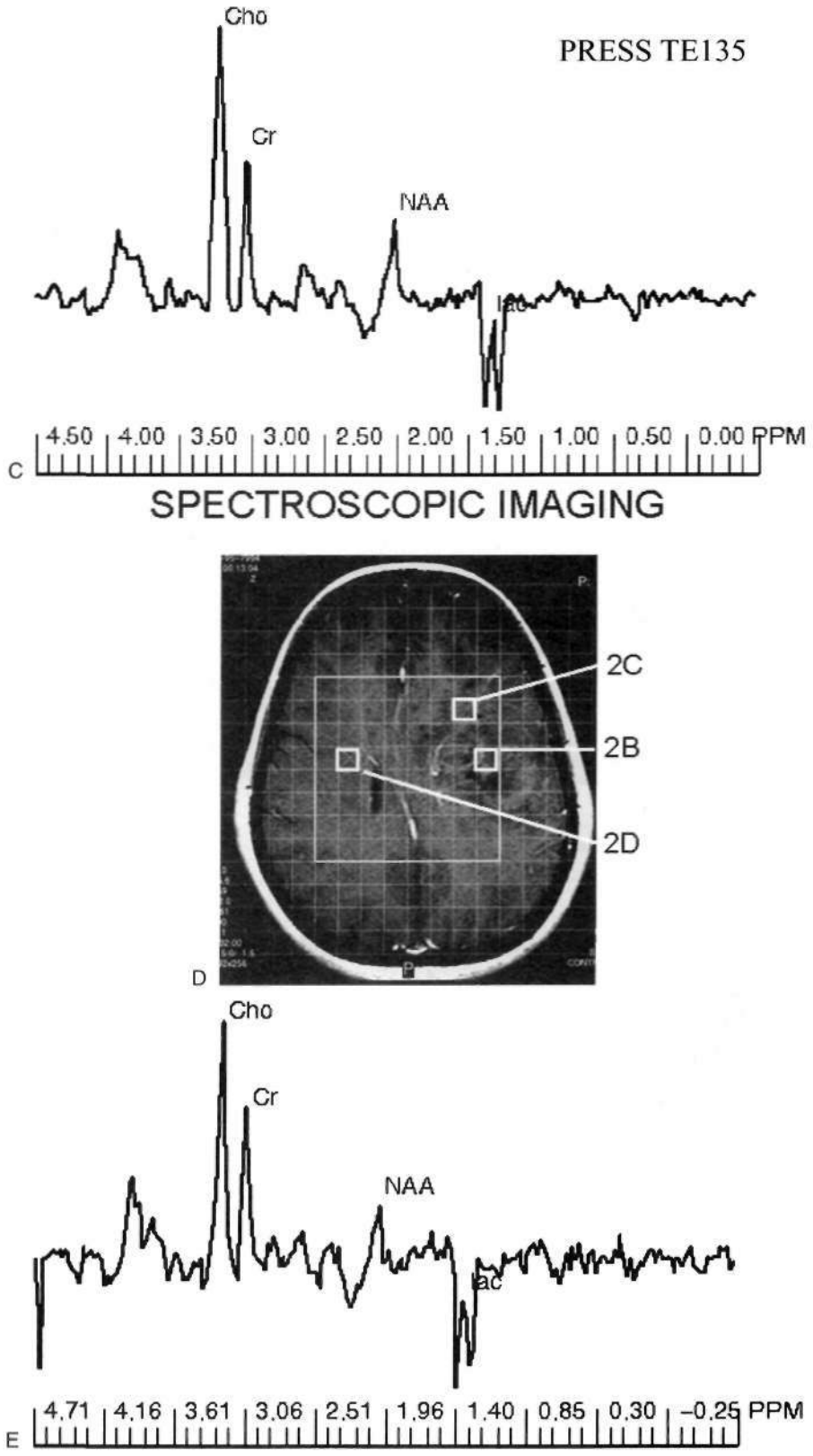

FIGURE 37E.1, cont'd. (C) SVS at TE of 20 ms: Stimulated acquisition mode (STEAM) spectrum acquired with shott TE confirms PRESS findings and reveals prominent lipid (Lip) peaks in the 0.6-1.6 ppm region of the spectrum. (D) Same image as in (A) was also used for placement of a 2-cm thick, single-section, mul ti voxel (16 x 16) grid encompassing the brain at this level. Spectra were generated from the center 8 x 8 subvoxels (each 2.5 ml.) and 3 of the 64 spectra are shown in (E), (F), and (G). (E) MRS! at TE of 135 ms; PRESS specttum from a subvoxel located in the same region as used in (B}. Note the similarity in the MRS] spectra and the SVS spectra in (B).

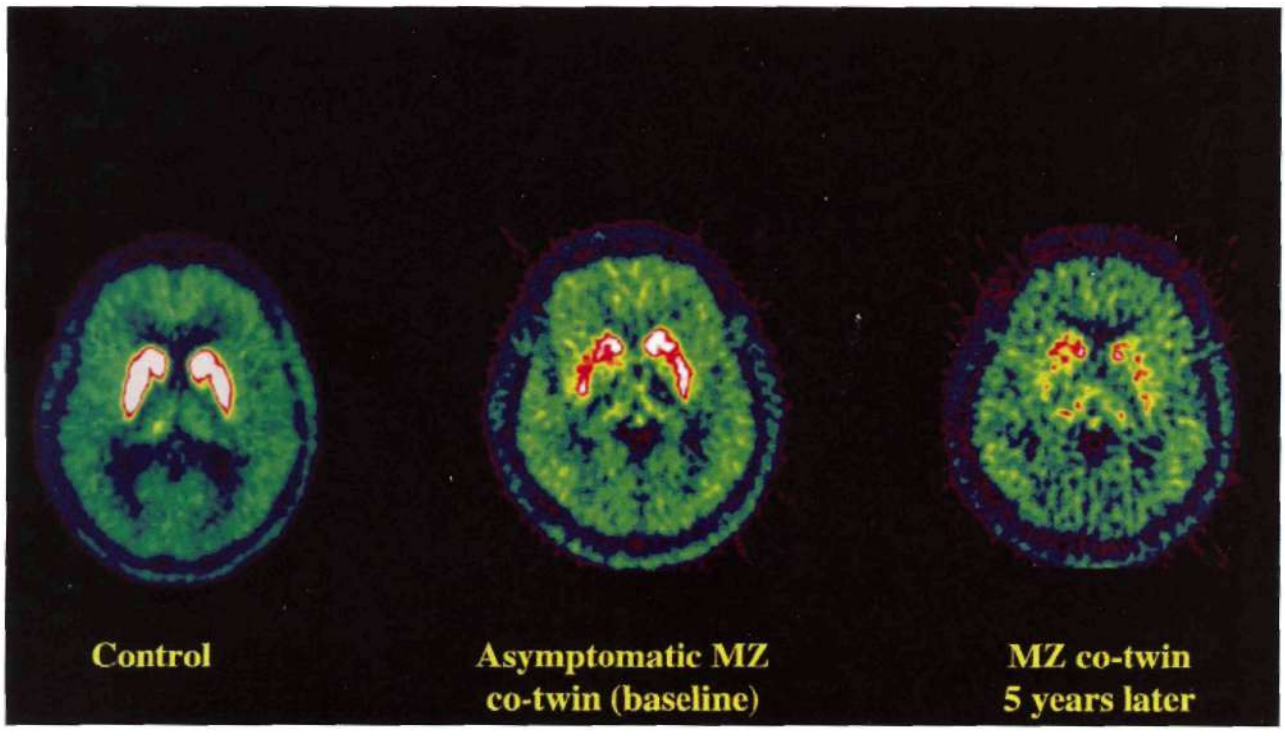

PLATE 37E.I Positron emission tomography images of striatal ^{18}F-dopa uptake in a healthy subject and an asymptomatic monozygotic co-twin of a patient with Parkinson's disease. The co-twin shows reduced putamen ^{18}F-dopa uptake at baseline and more severely 5 years later when symptomatic. (Courtesy Paola Piccini. From Brooks, D. J. 2000, "Morphological and functional imaging studies on the diagnosis and progression of Parkinson's disease," *J Neurol*, vol. 247, suppl. 2, pp. II/11-II/18.)

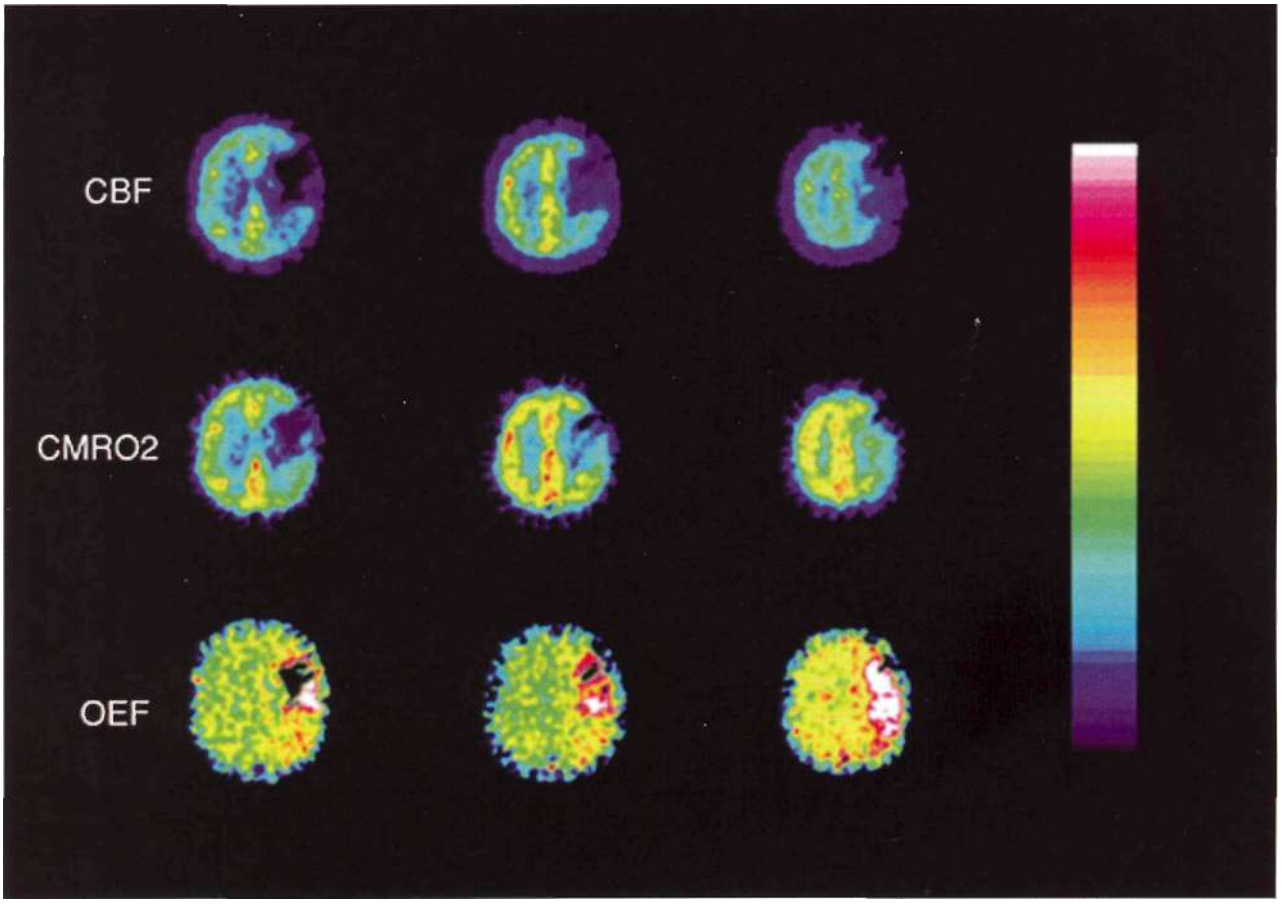

PLATE 37E.I1 $^{L5}0$ positron emission tomography (PET) images of a patient experiencing an acute ischemic event. Note that cerebral blood flow (CBF), cerebral metabolic rate of oxygen (CMRO,), and oxygen extraction fraction (OEF) are all decreased at the site of the ischemic event. These are all indices of neuronal activity that can be measured using "0 PET techniques. (Used with permission from Dougherty, D. D., Rauch, S. L., 8c Fischman, A. J. 2003, "Neuropsychiatric applications of PET and SPECT," in *Essentials of Nmroimaging for the Practitioner,* eds D. **D.** Dougherty, S. L. Rauch, *tk.* J. F. Rosenbaum, American Psychiatric Publishing, Washington, DC.)

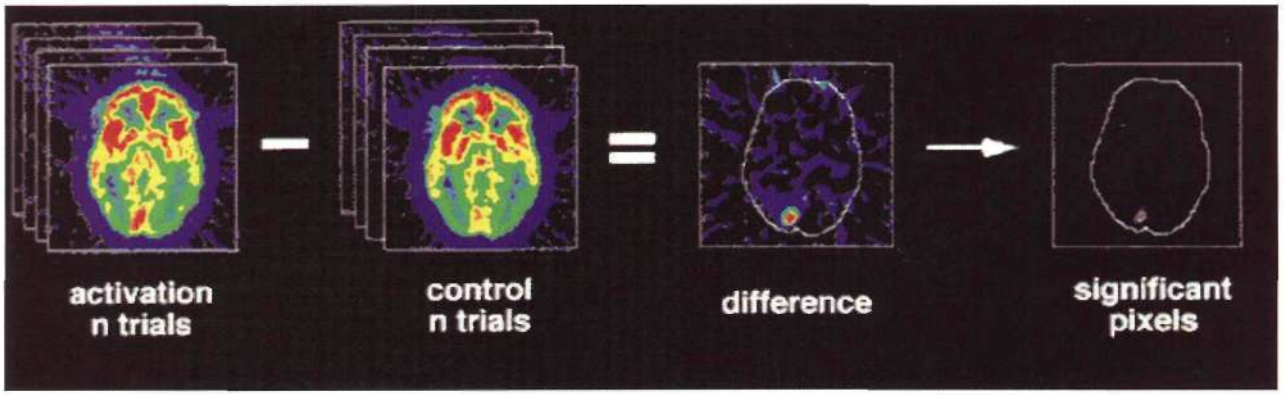

PLATE 37E.III Illustration of the methodology used for functional neuroimaging activation studies. Data are acquired in a serial manner in both activated and control states. By grouping the activation and control data, one can produce a difference image. Statistical tests can be used to determine which differences are statistically significant. This example shows a robust response to a hemifield stimulation of the visual system with a reversing checkerboard pattern using $H_2{}^{15}0$ as the tracer. The activated visual cortex can be clearly seen, even before subtraction. (Used with permission from Cherry, S. R. & Phelps, M. E. 1996, "Imaging brain function with positron emission tomography," in *Brain Mapping: The Methods,* eds A. W. Toga & J. C. Mazziotta, Academic Press, San Diego, Calif.)

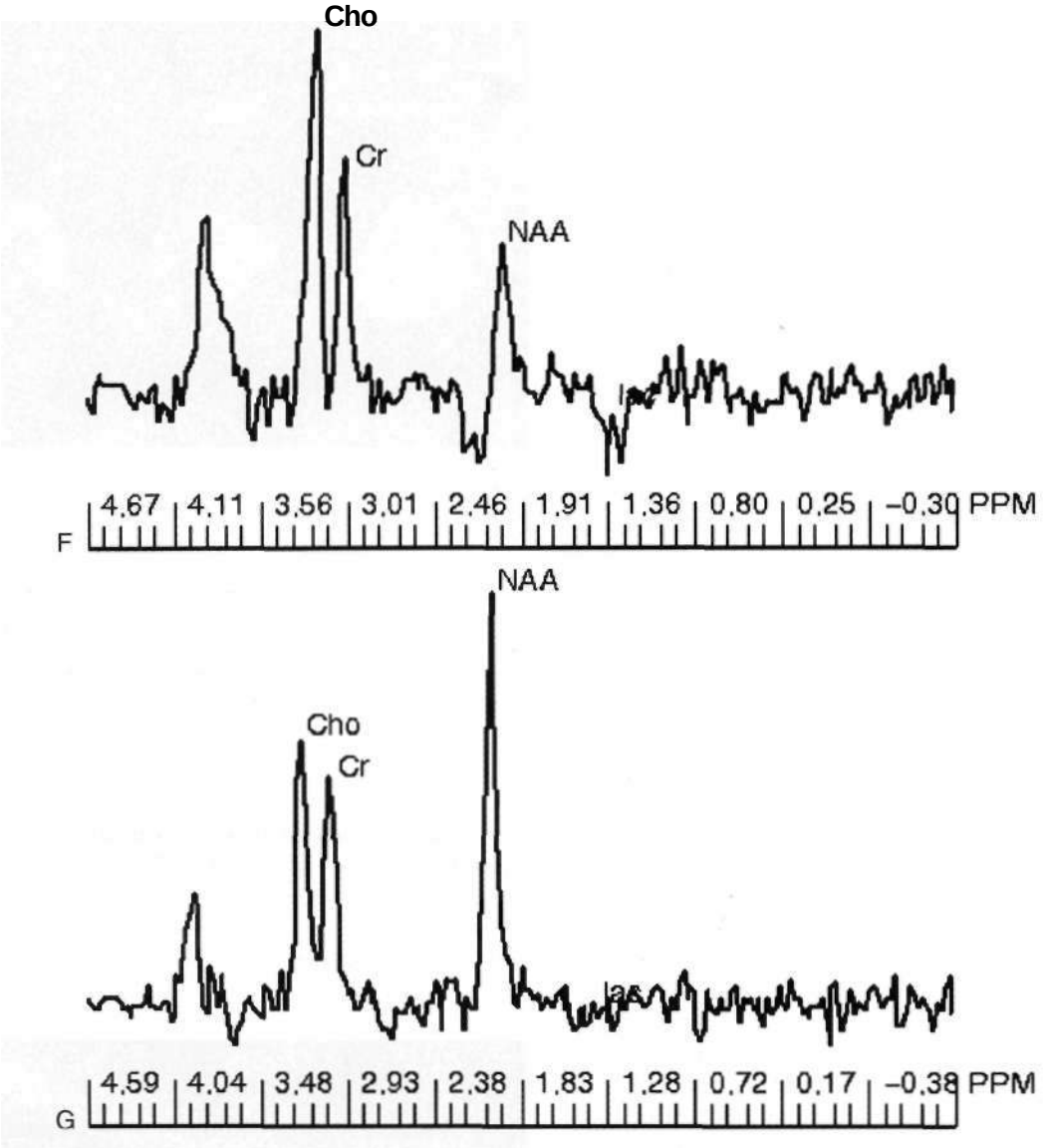

FIGURE 37E.1, cont'd. (F) MRSI at TE of 135 ms: PRESS spectrum from a subvoxel located slightly outside the region of enhancement and necrosis. On routine magnetic resonance imaging (MRI), this area of the hrain might he interpreted as "edema"; however, the elevated Cho, decreased NAA, and evidence of Lac on MRSI suggest that there is tumor infiltration. (G) MRSI at TE of 135 ms: PRESS spectrum from a suhvoxel located in an area of normal-appearing brain. This spectrum serves as a control to which the spectra from abnormal brain can he compared. Note the dominant NAA peak and the similarity of the Cho and Cr peaks in this area of normal brain. (Courtesy Dr. Brian Bowen.)

ERP in the clinical setting. These include brainstem auditory evoked potential, somatosensory evoked potential, and pattern reversal visual evoked potential. QEEG, currently used only in the research setting, involves transforming the LEG data in a manner thai allows for quantitative analysis. Detailed discussion of QEEG and ERP are heyond the scope of this chapter. They are mentioned here because they ate, technically, functional neuroimaging modalities and because they arc increasingly used in conjunction with other functional neutoimaging techniques for research purposes.

Magnetoencephalogtaphy (MEG) is similar to EEG in that it measures surface cortical activity. However, MEG detects the magnetic signal that arises from the electrical current that is measured by EEG. Quantitative and ERP techniques can be applied to MEG data as well. Although fMRI has much better spatial resolution than MEG, the temporal resolution of MEG vastly exceeds that of **fMRI.** Thus fMRI provides spatial information that allows for refinement of MEG data analysis, whereas MEG provides temporal information that allows for tcfinement of **fMRI** data analysis. For these reasons, MEG and fMRI

techniques are increasingly being used in conjunction with each another in the research setting.

CLINICAL UTILITY

Although a number of functional neuroimaging modalities are available for assessing the CNS, currently only PET and SPECT have clinical utility. As such, this section focuses on the clinical uses of PET and SPECT. Potential uses for the remaining functional neuroimaging modalities are currently under investigation.

Dementia

The potential of PET and SPECT in the diagnosis of Alzheimer's disease and other dementias continues to evolve. In fact, recent studies demonstrate that PET and SPECT have sensitivities and specificities of 90% or more in differentiating Alzheimer's disease from other types of dementia. Typically SPECT studies using a variety of blood flow tracers and/or FDG PET studies are ordered as part of a dementia workup. The characteristic "earmuff" pattern of decreased metabolism or blood flow in bilateral temporoparietal and frontal regions with sparing of the somatosensory cortex is associated with the diagnosis of advanced Alzheimer's disease (Figure 37E.2).

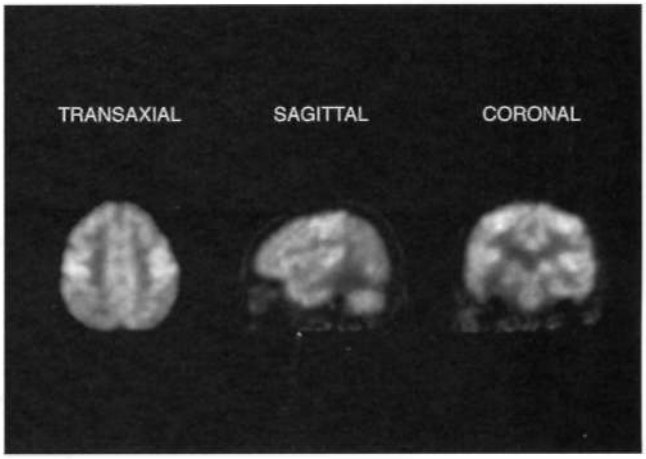

FIGURE 37E.2 Fluorodeoxyglucose positron emission tomography (PET) images of a patient with advanced Alzheimer's disease. Note the characteristic pattern of decreased glucose metabolism in all cortical regions except the somatosensory cortex (the "earmuff" pattern). (Used with permission from Dougherty, D. D., Ranch, S. L„ & Fischman, A. J. 2003, "Neuropsychiatry: applications of PET and SPECT," in *Essentials of Neuroimaging for the Practitioner,* eds D. D. Dougherty, S. L. Rauch, & J. F. Rosenbaum, American Psychiatric Publishing, Washington, DC.)

Seizures

Although EEG is the mainstay for detecting seizure foci, this technique is somewhat limited in that EEG is able to measure only corneal surface electrical activity. **PET** and SPECT are able to measure glucose metabolism or blood flow throughout the brain. Seizure foci demonstrate increased metabolism or blood flow during a seizure and decreased metabolism or blood flow during the interictal period (Figure 37E.3). Thus these functional neuroimaging modalities can be useful in cases with an unclear diagnostic picture, for localization of the seizure focus, and preoperative^ in cases in which neurosurgery is indicated.

Parkinson's Disease

Because Parkinson's disease is caused by degeneration of dopaminergic neurons in the substantia nigra, a means for *in vivo* assessment of dopaminergic function may be of diagnostic value. A number of **PET** and SPECT radiopharmaceuticals arc available to measure presynaptic dopamine synthesis (^{ls}E-dopa) and dopamine transporter density (^{12,}I-/SCIT, "C-CFT, ''C-altropane). These measures serve as markers for the number of intact dopaminergic neurons in the striatum. As Parkinson's disease progresses, binding of these radiopharmaceuticals in the striatum decreases {Plate 37E.I). The clinical use of these techniques is just beginning to emerge. These techniques ultimately may be diagnostically useful not only in situations in which the patient is clinically symptomatic,

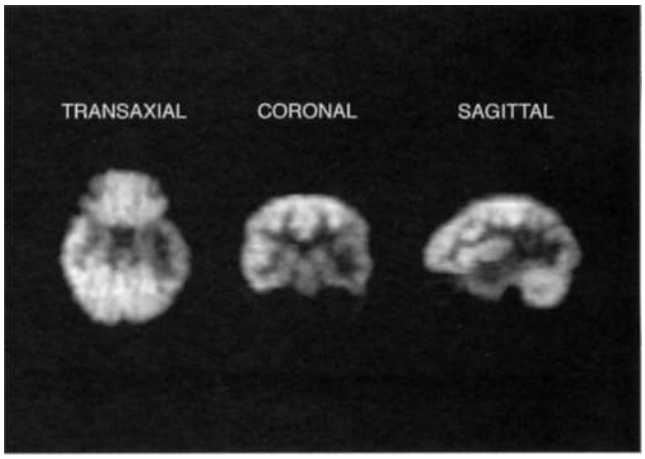

FIGURE 37E.3 Fluorodeoxyglucose positron emission tomography images ol a patient with temporal lobe epilepsy, fk'tausi' this image was acquired during the interictal period, glucose metabolism is decreased at the site of the seizure focus. (Used with permission from Dougherty, D. D., Rauch, S. L., & Fischman, A. J. 2003, "Neuropsychiatric applications of PET and SPECT," in *Essentials of Neuroimaging for the Practitioner,* eds D. D. Dougherty, S. L. Rauch, *&c* J. F. Rosenbaum, American Psychiatric Publishing, Washington, DC.)

but perhaps even for early diagnosis (before symptoms emerge) so appropriate therapeutic interventions may be initiated earlier in the course of the disease. Another potential use is for quantitative measurement of disease progression, both in the standard clinical setting and in the context of clinical trials.

Cerebral Ischemia

Although PET and SPECT are still not widely used in the evaluation of acute cerebral ischemia, there is growing evidence that PET and SPECT may have significant diagnostic value in these clinical situations. In addition, whereas CT and MRI detect structural changes associated with an ischemic event, PET and SPECT can directly measure cerebral perfusion. Thus PET and SPECT can detect hypoperfusion following an acute ischemic event almost immediately, whereas it may take several hours before corresponding structural changes are detected by CT or MRI (Plate 37E.II). Ongoing studies are being conducted that may help define the role of PET and SPECT in the clinical evaluation of cerebral ischemia.

Neoplasms

Most cerebral neoplasms can be detected using CT or MRI. However, because neoplasms typically demonstrate greater metabolism or blood flow than surrounding tissue (Figure 37E.4), PET and/or SPECT studies of glucose metabolism or CBF can provide complementary information in the clinical evaluation of cerebral neoplasms. Importantly, tumor metabolism is thought to be proportional to tumor cell proliferation. Thus PET and SPECT studies provide information thai may be used for rumor classification. Lastly, PET and SPECT data may also be used to follow therapeutic response of cerebral neoplasms, as well as for differentiating radionecrosis from tumor recurrence.

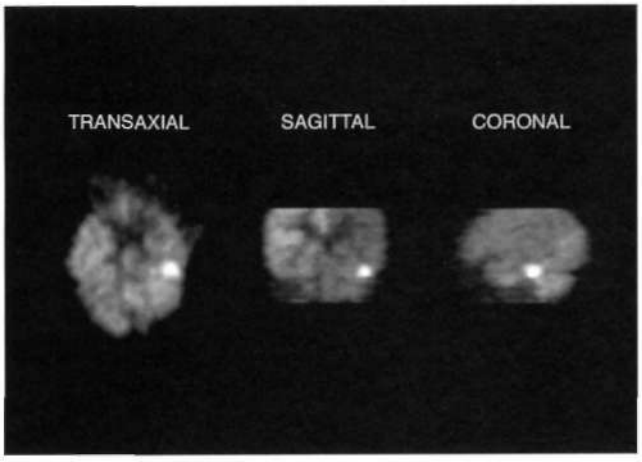

FIGURE 37E.4 Fluorodeoxyglucose positron emission tomography image of a cerebral neoplasm demonstrating the increased glucose metabolism associated with the lesions. (Used with permission from Dougherty, D, D., Rauch, S. L., *He* Fischman, A. J. 2003, "Neuropsychiatric applications of PET and SPECT," in *Essentials of Neitroinhigiiii; for the l'rtiititiancr*, etls D. D. Dougherty, S. L. Ranch, & J. F. Rosen ha uni, American Psychiatric Publishing, Washington, DC.)

RESEARCH APPLICATIONS

All of the functional neuroimaging modalities discussed in this chapter are being used extensively in neuroscience research. Although each of these modalities is capable of measuring different aspects of brain function, the research paradigms used are relatively universal. In this section, we provide a brief description of some of the ways these functional neuroimaging modalities may be used in the research setting.

Neutral State

The simplest type of functional neuroimaging studies involves comparing populations during a resting, or neutral, state. For example, FDG PET studies have been conducted in groups of patients with major depression and in healthy control subjects. These studies have demonstrated that anterior frontal regions, especially on the left side, are hypometabolic in patients with major depression when compared with healthy control subjects. Comparable neutral state functional neuroimaging studies have been conducted in patients with many disorders, including obsessive-compulsive disorder, schizophrenia, and chronic fatigue syndrome.

Activation Studies

Although neutral state functional neuroimaging studies have provided valuable information regarding the pathophysiology of a number of disorders, functional neuroimaging studies conducted during specific tasks may have even greater research use. In functional neuroimaging activation studies, individuals perform tasks designed to assess a particular function (e.g., cognitive, affective, and visual) or to probe the functional integrity of a specific brain region. Brain function during the performance of these tasks is compared with brain function during a neutral condition and the difference is attributed to the performance of the task (Plate 37E.III). This methodology may be more robust than neutral state functional neuroimaging studies. For example, although neutral state functional neuroimaging studies demonstrate minimal abnormalities in patients with attention-deficit/hyper-

activity disorder (ADHD), functional neuroimaging activation studies assessing attention in patients with this condition have demonstrated marked abnormalities in patients with ADHD when compared with healthy control subjects.

Treatment Studies

Functional neuroimaging techniques (eirher neutral state or activation studies) can also be used to assess treatment. There are generally two approaches to these types of studies. The first type, predictors of treatment response studies, involves performing functional neuroimaging studies in patients before initiating a course of treatment. After treatment, correlates between baseline brain function and subsequent treatment response can be ascertained. In this ni.miu • ;, iv possibk' to detect baseline brain function profiles that predict subsequent treatment response. Secondly, functional neuroimaging studies can be performed before and after treatment. Predictors of trearment response analyses can be performed using the baseline functional neuroimaging data. Moreover, a comparison of pretreatment and posttreatment functional neuroimaging data may help to elucidate the mechanism of action of the treatment in question.

Neurochemistry

As described previously PET, SPECT, and MRS can be used to assess neurochemistry *in vivo.* Essentially any functional neuroimaging paradigm that assesses neuronal activity (e.g., neutral state studies, activation studies, and treatment studies) can also be performed using these neurochemistry imaging techniques. Thus dopamine function, for example, can be measured at rest, before and during a specific task, or before and after treatment, and the data can be analyzed using methods similar to those described earlier in this chapter. Thus functional neuroimaging technologies can be used to study indices of neuronal activity, as well as neurochemistry using any of these paradigms.

CONCLUSION

In summary, the application of functional neuroimaging technologies in the clinical evaluation of patients continues to evolve. In addition, functional neuroimaging is a powerful tool for neuroscience research. In the coming years, rhe clinical use of functional neuroimaging technology should continue to expand rapidly.

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Chapter 38
Neuropsychology

Jane S. Paulsen and Karin Ferneyhough Hoth

The assessment of cognitive functioning is a critical part of a complete neurological examination. Whereas the cluneal neurological examination often focuses on the motor and sensory system, the neuropsychological examination focuses on the psychometric assessment of cognition and behavior. The cognitive evaluation can significantly contribute to neurological diagnosis, treatment planning, and monitoring over time. A wide range of intellectual abilities are assessed, and neuropsychological information complements information from electrophysiological techniques and neuroimaging.

In this chapter we describe the neuropsychological evaluation process, including methodological issues that must he considered in test administration, examine the contribution of a comprehensive neuropsychological assessment, and describe the typical patterns of cognitive impairments that are associated with a variety of neurological disorders. Guidelines for brief mental status assessment are also included.

GOALS OF NEUROPSYCHOLOGY

When potential cognitive deficits are noted clinically or during a brief mental status examination, an extended neuropsychology assessment is appropriate. Although the specific goals of a neuropsychological assessment differ depending on the referral question and the context in which the examination is given, several overarching aims can be identified {Table 38.1).

The primary goal oi neuropsychological assessment is to identify and describe the patient's cognitive strengths and weaknesses and characterize impairments and deficits in patients with brain damage. Approximately 30 years ago, the main role of neuropsychology was lesion localization. Although this remains useful, the advent of neuroimaging techniques in the 1970s and 1980s shifted the emphasis of neuropsychology toward describing the patient's cognitive and behavioral profile. Nonetheless, tests of neuropsychological functioning often are able to detect subtle cognitive deficits that are undetected by electrophysiological or neuroimaging methods. Other major goals of neuropsychological assessment concern differentiation between intellectual changes associated with brain damage, cognitive and behavioral impairments resulting from psychiatric illness, and cognitive changes secondary to normal aging.

In addition to offering information regarding diagnosis and neuroanatomical localization of dysfunction, the neuropsychological assessment is unique in its ability to address the patient's functional abilities. Clinicians often are called on to assess a patient's ability to make financial and health care decisions, to drive a car, and to live independently. These decisions can also determine when a patient is able to return to work after injury or what type of job the patient is suited for. A neuropsychological assessment may be used to determine appropriate adjustments to the patient's treatment and develop recommendations regarding activities of daily living.

Repeated neuropsychological evaluation can be invaluable in monitoring cognitive change over time. Repeated assessments can track cognitive decline in a progressive illness, such as dementia or multiple sclerosis, or monitor recovery after acute injury, such as stroke or traumatic brain injury. Evaluating the effectiveness of medical procedures and neurological surgery also entails repeated comprehensive assessment ot cognitive abilities. A comparison ol pre- and post-treatment data offers information about changes in the patient's level of functioning after medical intervention.

Table 38.1: Goais of n euro psycho logy

To identify cognitive strengths and weaknesses
To detect cognitive deficits not evident on the neurological, imaging, and physiological evaluations
To differentiate cognitive impairments due to age, education, socioeconomic status, race, psychiatric symptoms, and personality factors
To predict functional ability in work, driving, and self-care
To monitor cognitive changes associated with recovery, disease progression, **and treatment**

Table 38.2: Heaton adaptation of Halstead-Reitan neuropsychological battery

Tactual Performance Test
Finger Oscillation Test
Category Test
Seashore Rhythm Test
Speech Sounds Perception Test
Aphasia Screening Test
Sensory-Perceptual Examination
Strength of Grip Test
Tactile Form Recognition Test
WVdisliT Adult Intelligence Scale-Revised
Wcchsler Memory Scale-Revised

Source: Adapted from Heaton, R, K., Grant, I., &c Matthews, C. G. 1**991**, *Comprehensive Norms for Expanded Halstead-Reitan Battery: Demographic Corrections, Research Findings, and Clinical Applications,* Psychological Assessment Resources, Odessa, FL.

NEUROPSYCHOLOGICAL ASSESSMENT

The neuropsychological assessment generally involves a clinical interview, review of patient records, test selection, test administration and scoring, test interpretation, diagnosis, and treatment and rehabilitation recommendations. The clinical interview may vary in length given the presenting concerns of the patient. However, a complete interview typically covers the patient's developmental background, personal medical and psychiatric history, family medical history, academic performance, vocational achievements, psychosocial functioning, and activities of daily living. Information obtained from collateral sources such as caregivers or spouses about the patient's medical and psychosocial history often is critical. Behavioral observations of the patient during the examination are an important source of information that can influence test selection and the interpretation of test scores. One of the primary goals of the interview is to develop hypotheses about the patient's cognitive status and guide test selection. Many measures of cognitive functioning are available, and they differ in format, length, complexity, standardization, and quality of normative data. Different tests may be appropriate in different cases, and the test selection process is essential in gathering meaningful information about the patient. In the fixed battery approach, the same tests are given to every patient in a standardized manner. One of the most commonly used fixed batteries is the Halstead-Reitan Battery (Table 38.2}, for which comprehensive norms were published by Heaton and colleagues. An advantage of the **fixed** battery is that the information gathered is comprehensive and systematically assesses multiple domains of cognitive functioning. Additionally, if repeated assessments are available, test scores can be directly compared with baseline information. Drawbacks of the fixed battery approach involve its length (typically *X* hours! because it may be too long for some patients to tolerate and is difficult to afford with limited reirnbursement schedules in managed care. Finally, a comprehensive assessment may not be necessary to address the referral question.

In contrast with a fixed battery, in the flexible (or hypothesis-driven) approach, test selection differs based on the referral question, the patient's history, and the clinical interview. Most neuropsychologists' approach falls somewhere between the use of a set battery and a completely individualized examination. Often called the flexible battery, a brief set of basic tests is initially administered and additional tests of more specific abilities are used to meet each particular patient's needs.

Test interpretation requires the integration of neuropsychological test scores with findings from the clinical interview, the patient's history, the neurological examination, and neurophysiology and neuroimaging data. Before this can be accomplished, however, the raw test scores must be interpreted in the context of an appropriate comparison standard. Several approaches are used in interpreting neuropsychological test scores including the use of normative data, cutting scores, and comparisons with baseline data. Neuropsychological test scores are interpreted most often through the use of normative data obtained by collecting information about test performance from a standardization sample. For instance, Table 38.3 shows the percentage of variance in test raw scores accounted for by the demographic variables age, education, and sex. The test chosen for this example is the Wechsler Adult Intelligence Scale (WAIS), one of the most commonly administered assessments of intellect. As shown in the table, some tests share 38% variance with age (Digit Symbol), others share 4.)'X> variance with education (Information), and others differ with sex (Arithmetic). Interpreting **performances** on these tests without correcting for demographic characteristics of the person of interest would result in inappropriate conclusions.

Normative data provide information about the expected test performance of individuals within a particular group, often stratified based on age or level of education. An individual raw score is compared with the distribution of scores from the person's peer group to determine where it falls within the range of performances. Figure 38.1 and Table 38.4 show guidelines for use in neuropsychological interpretation. The usefulness of normative data depends

Tabic 38.3: Percentage of variance in test scores accounted for by demographic variables

	Base samph raw scores			
	Age	*Education*	*Sex*	*Combined*
Verbal IQ	0	40	I	43 (A, E)
Performance IQ	1	17	i)	22 (A, E)
Full-Scale IQ	0	35	1	40 (A, E)
Information	4	43	2	44 (K, Si
Digit Span	*6*	14	(i	15 (A, E)
Vocabulary	4	42	0	42(E)
Arithmetic	*c*	27	5	31 (E, S)
Comprehension	2	31	0	31 (E)
Similarities	14	36	0	39 (A, E)
Picture completion	10	18	2	23 (A, E, S)
Picture arrangement	20	15	0	26 (A, E)
Block design	17	19	1	28 (A, E, S)
Object assembly	15	10	i)	18 (A, E)
Digit symbol	38	29	4	52 (A, E, S)

A = age; E = education; S = sex.
Source: Adapted from Heaton, R. K., Grant, 1., & Matthews, C. G, 1991, *Comprehensive Norms for Expanded Haistead-Reitan Battery: Demographic Corrections, Research Findings, and Clinical Applications,* Psychological Assessment Resources, Odessa, FL.

strongly on the size and representativeness of the standardisation sample. Clinical utility can be greatly affected by the goodness of the fit between the individual and the sample and the extent to which the norms take demographic factors into account. For example, it would not be appropriate to make determinations about the test performance of an 82-year-old man with 8 years of education by comparing his test score with those of a group of 40-year-olds with an average of 12 years of education. .Significant limitations exist in some normative data including the absence of suitable norms for older adults and heterogeneity of education, ethnicity, and health variables among some standardization samples. Furthermore, it is important to use the most recent norms available because cohort effects may lead to differences between current patients and those from whom data were collected years ago. When appropriate norms are not available, there is a danger of overdiagnosis or undcrdiagnosis of cognitive impairment. Thus the accurate intetprctation of neuropsychological test performance necessarily incorporates information about the sample from which the norms for each test were developed.

Another approach to test interpretation is the use of cutting scores to identify people who demonstrate pathological cognitive symptoms. Some tests ate designed to measure abilities that are largely intact in normal subjects but are impaired in disordered patients. For example, most people are able to bisect a line without difficulty, but patients with left-sided visuospatial neglect typically identify the midpoint of the line to be to the right of the centet. Tests that rely on cutting scores tend to measure performances with low base rates or deficits that very few people demonstrate.

An important component of test interpretation is the comparison of current performance with past test scores. Often no previous data have been collected. Clearly, when one is attempting to identify cognitive decline, a patient's

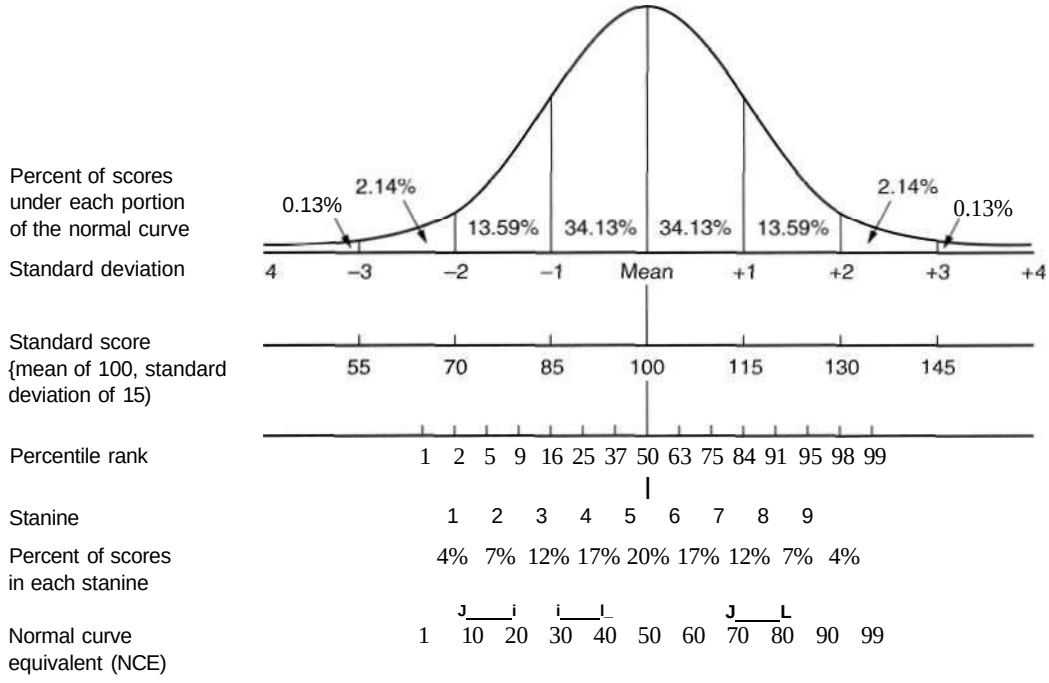


FIGURE 38.1 The normal curve and its relationship to derived scores.

Table 38.4: Descriptive terms associated with performance within various ranges of the normal distribution

Qualitative terms	*Standard deviation score*	*Percentile rank*	*T score*
Severely impaired	**<-3.0**	<l	*<H)*
Moderately to severely impaired	**-3.0 to -2.51**	<1	20-24
Moderately impaired	**-2.5 to** 2.01	1-2	25-29
Mildly to moderately impaired	**-2.0 to -1.51**	3-6	30-34
Mildly impaired	**-1.5 to -1.01**	7-15	35-39
Below average or atypical	**-1.0 to -0.51**	16-30	40-44
Average	**-0.5 to +0.51**	31-69	45-54
Above average	**+0.5 to +0.99**	70-83	55-59
High average	+1.0 **to +1.49**	84-93	60-64
Superior	**+ 1.5 to +1.99**	94-97	65-69
Very superior	**+2.0 to +2.99**	98-99	70-74
Amazingly superior	**- 2.5 ro +2.99**	>99	75-79
God-like	**>+3.0**	>99	>80

Note: The patient's educational history and premorbid level of functioning should be taken into consideration in applying any qualitative label.

previous performance is an ideal comparison standard. When no previous test scores are available, evidence of the patient's premorbid intellectual functioning is used to make an estimate. Demographic factors such as education level can he useful indicators of premorbid level of ability. One rural neuropsychologist used number of acres owned to estimate IQ. A common approach to estimating premorbid intellectual functioning is to rely on specific characteristics of the patient's neuropsychological test performance that arc considered stable, or "hold" tests. Reading ability often is used as an estimate of overall premorbid intellectual ability because it is thought to be resistant to many processes that cause declines in cognitive functioning. Some common measures of reading ability arc the National American Adult Reading Test (Nelson 1982), which measures the ability to read irregularly spelled words, and the Wide Range Achievement Tcst-3 (Wilkinson 1V93), which measures the ability to read aloud. Because demographic variables account for a significant proportion of the variance in neuropsychological test performance, a number of regression equations have been developed using intelligence test standardization samples. Table .38.5 lists some of the demographic regression models used to estimate premorbid intellect. Contemporary neuropsychologists use a combination of these strategies to arrive at the best estimate of premorbid ability.

Factors other than the cognitive ability of interest, including demographic and clinical characteristics, can influence a patient's test scores. Subject characteristics such as age, education, sex, and ethnicity have been shown to affect test behavior (see Table 38.3). Overall, increasing age is associated with more adverse consequences of brain damage, although the relationship is complicated. In terms of test performance, aging has different effects on different cognitive domains. Aging has its most pronounced effects on nonverbal, timed tests, and although ovcrlearned material typically is stable into late life, a generalized slowing of response is the most ubiquitous change. Education level can also influence test performance, which is not surprising given that several neuropsychological tests were developed with the intent to measure intelligence and predict academic success. As mentioned earlier, norms are commonly divided based on age and education. Sex differences on neuropsychological tests of spatial abilities, strength, motor speed, and certain verbal abilities have been observed, although males and females appear to be equivalent in general intelligence. Finally, although research suggests that ethnicity influences performance on some neuropsychological tests, it is clear that more research on the topic is warranted. The clinical myth that ethnicity is important only on verbal or knowledge based tests and not on "culture free" tests such as some abstract reasoning measures is outdated. More recent evidence suggests that this distinction is unclear, and although research on the effect of ethnicity on test performance has been increasing, we still do not understand the complex relationship.

Medication and treatment side effects can complicate the interpretation of test scores. Often patients who are referred for neuropsychological assessment are taking medications or are being treated for a medical disorder. In fact, the action of some drugs or treatments can be the source of a patient's presenting cognitive problems. Gathering treatment information and assessing the potential influence of medications or other inrerventions on cognitive functioning is essential. Older adults and patients with brain damage

Table 38.5: Premorbid verbal IQ estimations

Wilson: V1Q = 0.18 (age) - 2.02 (sex) - 8.99 (race) + 3.09 (education) + 0.97 (occupation) + 70.8

Barona: VIQ = 54.23 + 0.49 (age) + 1.92 (sex) + 4.24 (race) + 5.25 (education) + 1.89 (occupation) + 1.29 (region)

Reynolds: VIQ = 127.85 - 3.7 (parental SES) - 8.86 (race) - 2.40 (sex) - 0.16 (region) - 1.16 (urban or rural residence)

may he particularly susceptible to adverse drug reactions, winch can impair cognitive functioning. For example, anticholinergic drugs used to treat Parkinson's disease can interfere with memory functions and present as exaggerated cognitive dysfunction. When relevant, a neuropsychological examination can help to elucidate potential interactions between brain damage and treatment effects.

THE BRIEF MENTAL STATUS EXAMINATION

zBefore neuropsychological referral the neurologist typically has either clinical or historical evidence of cognitive concerns. The ability to rapidly and reliably assess the nature and extent of cognitive impairments is important in all clinical settings. An important component of the neurological examination is the brief mental status examination. Although the mental status examination often is conducted in a nonstandard manner, neurologists are encouraged to develop a standardized method of mental status examination so that interpretations across time and patients can be made reliably (Table 38.6). Recommended standard examinations arc briefly described in this section.

Mini-Mental State Examination

Although a variety of standardized mental status examinations have been used, a few scales are used more widely than others. One popular mental status examination often administered by neurologists is the Mim-Mcntal State Examination (MMSE; Folstein et al. 1975), an 11-item standardized method assessing orientation, attention, immediate and short-term recall, naming, and the ability to follow simple verbal and written commands. The MMSE has been used with different cultural and ethnic subgroups and has been translated into several different languages. Using a cutoff of 23, the sensitivity and specificity of the MMSE have been reported to he 87% and 82%, respectively, for detecting delirium or dementia in hospitalized patients (Anthony et al. 1982), More recent research has documented the significant associations between MMSE performances and age *[r* — -.38) and education *(r* = .50), suggesting that the utility of the instrument varies greatly depending on demographic factors. The best norms published to dare involve dara from rhc Epidemiologic Catchment Area household surveys and are presented in Table 38.7. Longitudinal studies suggest that people with Alzheimer's disease (AD) show an average annual rate of change of 2.81 points, although change rates are not uniform across illness stages. The item most often missed by people with AD is item 5 (recall three items), whereas the most sensitive item for "subcortical" dementias is item 4 (serial 7s) (Figure 38.2).

Tabic 38.6: Utility of menta! status assessments

Benefits	*Drawbacks*
Standardized format	Reliance on total score
Brevity	Emphasis on verbal tasks
Sensitivity to advanced dementia	Disproportionate weight orinitiition
Test-retest reliability	In sensitivity with above average IQ
	Perceptual deficits = wrong answers
	No consideration of gender, education, or ethnicity

Despite its widespread use, the validity and reliability of MMSE administration and interpretation have received little attention. There are three primary threats to the internal validity of the MMSE: nonorthogonal wotd stimuli allowed fot recall, nonstandard scoring of serial 7s, and nonstandard inclusion of spelling *world* backwards in MMSE total. Because learning and then teaching standard scoring instructions can alleviate the latter two threats, we have included structured scoring criteria in the MMSE shown in Figure 38.3. The primary threat to the internal validity of the MMSE is that most practitioners simply use whatever words come to mind or whatever words they were trained with for the recall of three items. Even the standard MMSE sold by Psychological Assessment Resources (PAR) has only two sets of words. This practice is unsatisfactory for several reasons. Firsr, older adults in a community or hospital quickly learn the local stimuli. For instance, all residents at one university teaching hospital were using "apple, orange, airplane," and many patients had been examined by a medical student, a resident, a fellow, and an attending physician at various times throughout their care. The test is not a measure of learning **and** memory if the patient has **heard it** before. In addition, the wotd stimuli used cannot be associated with one another. For instance, the words in the aforementioned example can easily be associated with one another, such as "orange and apple" (both fruits) or "orange airplane" (a color modifying the airplane). The rest is not a uniform measure of three items if some items are associated with others. Another common problem is the use of words with varying degrees of imageability. For instance, the words "red," "ball," and "happy" are not equivalent in their evocation of images. It may be easy to picture a red ball but more difficult to recall that it is happy. In an effort to encourage residents to vary the word stimuli and avoid "chunked" or "grouped" stimuli, we have selected a list from which words can be selected. We have selected imageablc words with a standard frequency index of U > 60 (approximately 100 per million) that require a reading level not greater than sixth grade. We encourage practitionets to return to the list petiodically and select a new version of three unrelated words to practice standard administration of the MMSE (Table 38.8).

Table 38.7: Mini-Mental State Examination score by ago and educational level, number of participants, mean, standard deviation, and selected percentiles

	Age (years)														
Educational level	18-24	25-29	30-34	.;> 39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	>85	Total
0-4 yr	17	23	41	33	36	28	34	49	88	126	1 *W*	112	105	61	892
Mean	22	25	25	23	23	23	23	2:	23	22	22	21	in	19	22
SD	2.9	2.0	2.4	2.5	2.6	3.7	2.6	***ir***	1.9	1.9	1.7	2.0	2.2	2.9	2.3
5-8 yr	94	83	74	101	100	121	154	208	310	633	533	437	241	134	3223
Mean	27	27	26	26	27	26	27	26	26	26	26	25	25	23	26
SD	2.7	2.5	1.8	2.8	1.8	2.5	2.4	2,9	2.3	1.7	1.8	2.1	1.9	3.3	2.2
9-12 yr or high school diploma	1326	958	822	668	489	423	462	525	626	814	550	315	163	99	8240
Mean	29	29	29	28	28	28	28	28	28	28	27	27	25	26	28
SD	2.2	1.3	1.3	1.8	1.9	2.4	2.2	2.2	1.7	1.4	1.6	*1.5*	2.3	2.0	1.9
College experience	783	1012	989	641	354	259	220	231	270	358	255	181	96	52	5701
Mean	29	29	29	29	29	29	29	29	29	29	28	28	27	27	29
SD	1.3	0.9	1.0	1.0	1.7	1.6	1.9	1.5	1.3	1.0	1.6	1.6	0.9	1.3	1.3
Total	2220	2076	1926	1443	979	831	870	101 1	1294	1931	1477	1045	605	346	18,056
Mean	29	29	29	29	28	28	28	28	28	27	27	26	25	24	28
SD	2.0	1.3	1.3	1.8	2.0	2.5	2.4	2.5	2.0	1.6	1.8	2.1	2.2	2.9	2.0

Source: Data from the Epidemiologic Catchment Area household surveys in New Haven, Connecticut; Baltimore, Maryland; St Louis, Missouri; Durham, North Carolina; and Los Angeles, California, between 1980 and 1984. The data are weighted based on the 1980 U..S. population census by age, sex, and race. Adapted from Crum, R. M., Anthony, J. C, Bassett, S. S., & Eolstein, M. F. 1993,/>1M,4, vol. 269, no. 18, pp. 2386-2391.

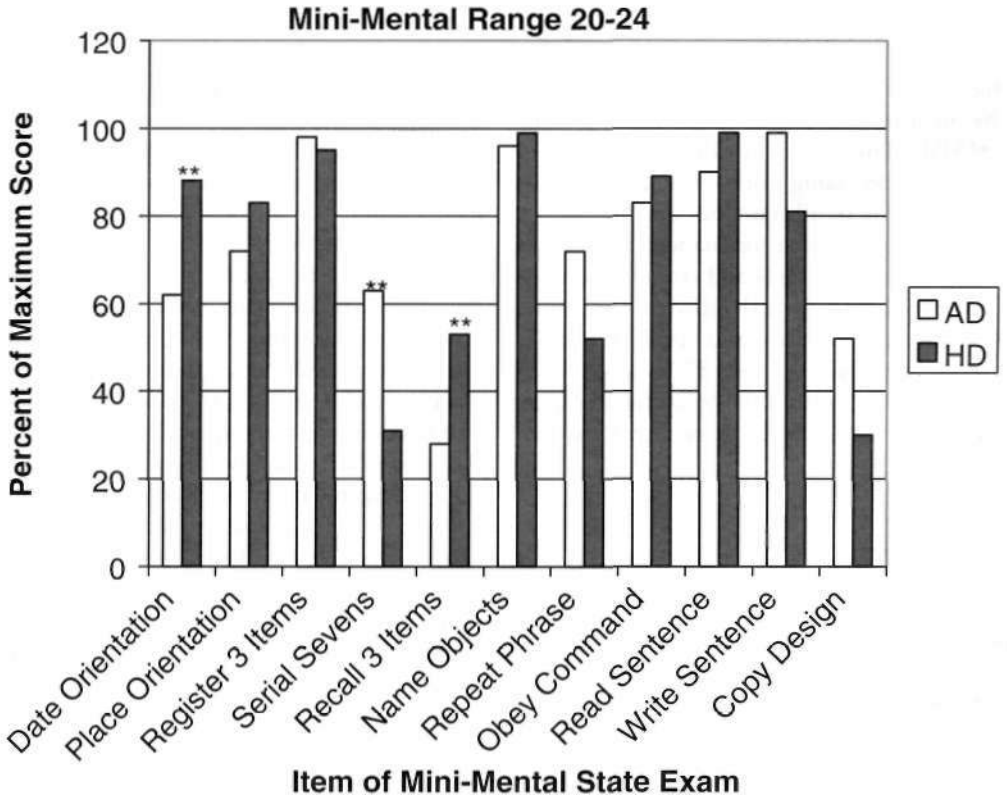


FIGURE 38.2 Mini-Mental State Examination profiles for patients with Alzheimer's disease (AD) and Huntington's disease (1 ID) with total Mini-Mental scores between 20 and 24. (Double asterisk indicates that the difference is significant at $p < .001$.) (Adapted from Brandt, J., Flostein, S. F,„ & Folstein, M. F. 1988, "Differential cognitive impairment in Alzheimer's disease and Huntington's disease," *Ann Neurol,* vol. 23, pp. 555-561.)

1. "What is the year? _____
season? _____
date? _____
day of Week? _____
month? _____
_____/5

2. "Where are we? state? _____
county? _____
town? _____
hospital? _____
floor? _____
_____/5

3. Repeat 3 words: (use list) _____ _____ _____

"Here are three words I want you to remember." Repeat up to 6 times.
words on 1st trial _____
repetitions _____
_____/3

4. Serial 7's: 93 _____
86 _____
79 _____
72 _____
65 _____
_____/5

"Start with 100 and count backward by 7. For example: What is 100–7? Keep subtracting 7. Stop after five responses."

Spell "world" backward:
D _____
L _____
R _____
O _____
W _____
_____/5

5. Recall 3 words: (Set used in #3) _____ _____ _____
_____/3

6. Name a: Pencil _____
Watch _____
_____/2

7. Read and obey _____/1

CLOSE YOUR EYES

8. Copy Design _____/1

(Must have 10 angles and intersect)

9. Write a sentence: _____/1

(Must have subject and verb make sense)

10: Repeat the following:

"no ifs, ands, or buts" _____/1

11. Follow a 3-stage command:
a. take a paper in your right hand _____
b. fold it in half _____
c. put it on the floor _____
_____/3

"Now I will give you some directions to follow. Please listen carefully and do as I say. Take this paper in your right hand, fold it in hand, and put it on the floor."

_____ TOTAL
MAX = 30

FIGURE 38.3 Mini-Mental State Examination. (Adapted from Folstein, M. F., Folstein, S. E., & McHugh, P. R. 1975, "Mini-mental State: A practical method for grading the cognitive state of patients for the clinician," / *Psychiatr Res*, vol. 12, no. 3, pp. 189-198.)

Table 38,8: Mini-Mental State Examination Word Sets For Item #3

hand, snow, telephone	city, nose, salt	school, cotton, lake	eggs, paper, sky	grass, arm, book
eyes, river, newspaper	boy, wheel, meat	house, cross, rock	mouth, wood, key	bus, dog, stone
mountain, door, baby	bag, kitchen, child	Face, valley, dollar	bread, Floor, leaf	dust, sun, hair
garden, drink, teacher	ball, sand, animal	Food, wind, stick	desk, fish, sugar	map, fire, bed
car, moon, breakfast	radio, dinner, hill	milk, tools, plants	horse, world, truck	foot, machine, lunch
window, boat, sheep	farm, ice, children	water, chair, road	teeth, Flowers, ship	girl, star, bird

Dementia Rating Scale

The Dementia Rating Scale (DRS; Mattis 1976) is a 36-item measure of cognitive status with five subscales: Attention, Initiation, Construction, Conceptualization, and Memory. Although administration of the DRS can take 15 minutes for healthy older adults (and up to 40 minutes for people with severe impairment), the scale has clear advantages over the MMSE in some situations. The DRS assesses a greater number of cognitive domains and is less likely to miss impairment. The DRS has a greater range, so measures of change are better documented and interpreted. Finally, the DRS is successful in differentiating between various types of dementia, even in later stages of disease (Paulsen etal. 1995; Figure 38.4).

Using a cutoff of 129, the sensitivity and specificity of the DRS have been reported to he 98% and 97%, respectively, for detecting AD (Monsch et al. 1995). To better account for demographic influences, the following formula is used to determine whether performance is impaired: 0.09 (age) - 0.06 (education) + 0.59 (initialion/petseveration subscale score) + 1.25 (memory subscale score) = *x*. A value of *x* below zero suggests impairment (98% of AD), whereas a score value above zero suggests normal performance (98% of normal controls [NC]). Norms for older adults are provided in Table 38.9. Longitudinal studies suggest that people with AD show an avetage annual rate of DRS change of 11.38 points. The Initiation/ Perseveration subscale is most sensitive for subcortical and white matter dementias, whereas the Memory subscale is most sensitive for AD.

Additional Bedside Evaluation

Despite its advantages, the DRS takes longer to administer and is unlikely to be used at the bedside by neurologists. The 5-minute MMSE is more likely to remain the scale of choice for cognitive screening. Although the MMSE identifies AD, the most prevalent cause of dementia, it does not identify subtle cognitive impairments associated with white matter, subcortical, and cerebellar changes. Because the executive functions involve the most complex forms of human behavior, mild disturbances in their resolution can have significant impact on daily living. It is recommended that bedside executive tasks and careful

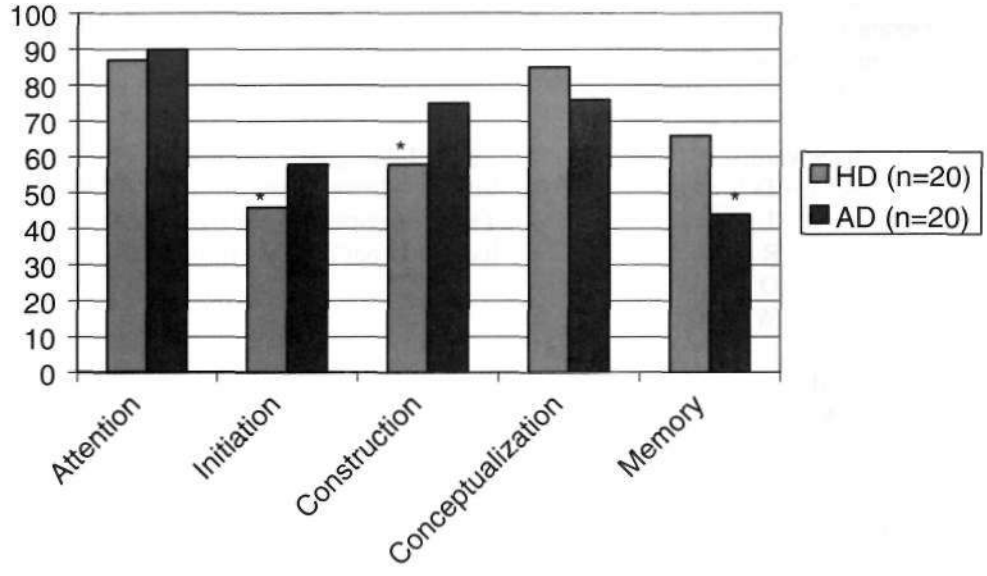


FIGURE 38.4 Dementia Rating Scale (DRS) category scores by Huntington's disease (HD) impairment level. The mean percentage of the maximum possible score obtained on each subscale of the Mattis DRS by the severely impaired patients with HD and Alzheimer's disease (AD). The asterisk (*) indicates significant differences between the groups {p < ,01). (Adapted from Paulsen, J., Butters, N., Sadek, B. S., et al. 1995, "Distinct cognitive profiles of cortical and subcortical dementia in advanced illness," *Neurology,* vol, 45, pp. 951-956.)

Table 38.9: Group means and standard deviations of dementia rating scale scores for older adults

	Age ranges	
DRS scales	62-79	80-95
Total score	*M* = 133.8	**M = 128.2**
	SD = 6.3	***SD* = 8.2**
Attention	**M** = 35.3	**M = *A5.1***
	SD = 1.3	**5D = 2.0**
Initiation/perseveration	**M = 33.9**	**M** = 31.7
	SD = 3.3	**5D = 4.9**
Construction	**M** = 5.5	**M = 5.1**
	SD = 1.3	***SD* = 1.8**
Concept ualization	**M = 35.5**	**M** = 34.7
	SD = 2.8	***SD* = 2.8**
Memory	**M** = 23.4	**M** = 20.7
	SD = **1.8**	***SD* = 3.5**

Source: Adapted from Vangel and Lichtenberg 1995, "'Mattis Dementia Rating Scale: Clinical utility and relationship with demographic variables," *Clin Neurol,* vol. 9, pp. 209-213.

clinical interview accompany the MMSE to provide a comprehensive cognitive screening. Any indication of poor decision making, disinhibition, inflexibility, or slowed processing may warrant a complete neuropsychological assessment. To identify possible weaknesses in this area, many neurologists use fluency, clock drawing, or an evaluation of alternating sets. Healthy older adults should be able to produce about 20 first names in 1 minute, and performances below this cutoff watrant additional evaluation by a neuropsychologist. The alternating patterns shown in Figure 38.5 may be used to document inability to smoothly switch sets. Other bedside mental status examinations include executive items such as proverb interpretation and conceptual teasoning. For example, patients are asked to interpret the meaning of "Rome wasn't built in a day" and "A golden hammer can break down an iron door,"

Draw a Clock

The clock drawing test (CDT) is widely used as a clinical screening tool for cognitive decline in late life. Research indicates that patients with AD commit a greater proportion of conceptual, visuospatial, perseverative, and

FIGURE 38.5 Alternating patterns for bedside cognitive assessment.

stimulus-bound errors while demonstrating better performance when asked to copy a drawing of a clock rather than construct a clock on command (Figure 38.6; Rouleau et al. 1996). Longitudinal study of CDT performance in AD indicates that stimulus-hound errors increase with disease progression. The CDT can effectively differentiate between certain types of dementia syndromes. For instance, people with Huntington's disease (HD) commit more planning errors and tend to have more graphic difficulties than patients with AD (Figure 38.7), whereas people with Parkinson's disease (PD) make a greater proportion of visuospatial errors. Although bedside cognitive examinations have included the clock drawing test for years, little use has been made of the clocks produced in terms of scoring and interpretation. Although originally conceived as a specific test of visuospatial and constructional ability, the CDT has recently gained favor as a quick and easily administered screening instrument for general cognitive dysfunction. The use of the CDT emerged from the realization that the test is sensitive to many fotms of brain dysfunction because it draws on multiple cognitive processes, including auditory comprehension of the instructions, access to the semantic reptesentation of a clock, conceptualization and planning abilities, and visuoperceptual, visuospatial, and visuomotor skills. Numerous studies uniformly demonstrate that patients with AD perform significantly worse than control subjects on the CDT and that the test has clinical utility for detecting dementia. Qualitative analysis of the performance of mildly demented patients indicates that poor performance may be mediated by semantic knowledge deficits tesulting in conceptual errors in AD (e.g., misrepresenting the clock by drawing a face without numbers or with an incorrect use of numbers,

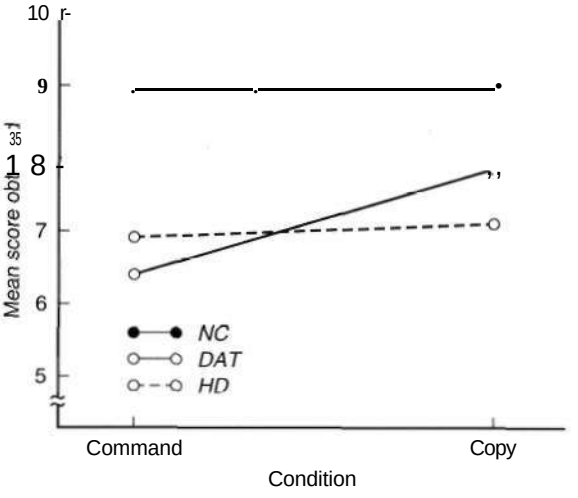


FIGURE 38.6 Scores obtained in the command and copy conditions as a function of diagnostic groups. NC = normal controls; DAT = dementia of the Alzheimer's type; HD = Huntington's disease. (From Rouleau, L, Salmon, D. P., & Burtcrs, N. 1996, "Longitudinal analysis of clock drawing in Alzheimer's disease patients," *Rmin Cngn,* vol. 31, pp. 17-34.)

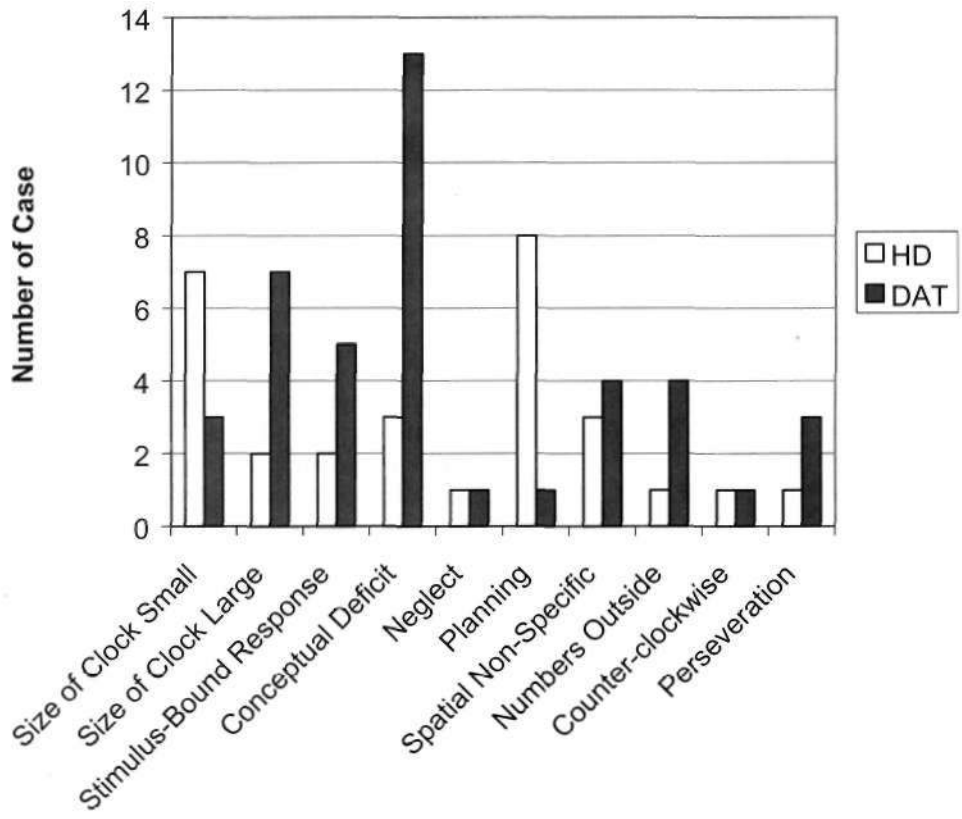


FIGURE 38.7 Distribution of error types in Alzheimer's disease (AD) patient groups in the command condition of the Clock Drawing Test. HD = Huntington's disease. (Adapted from Rouleau, I., Salmon, D. P., Sc Butters, N. 1996, "Longitudinal analysis of clock drawing in Alzheimer's disease patients," *Brain Cogn,* vol. 31, pp. 17-34.)

misrepresenting the time by failing to include the hands, incorrectly using the hands, or writing the time in the clock face; Figure 38.8) or planning or graphic errors in subcortical dementias (Figure 38.9). Conceptual errors on the CDT occur early in AD and increase over time. In addition, the performance of patients with AD often is much worse when they are asked to draw a clock from memory than when they are asked to copy a drawing of a clock.

NEUROPSYCHOLOGICAL CHARACTERISTICS OF NEUROLOGICAL DISEASE

In this section we briefly address the ncuroeognitive sequelae of some of the major neurological disorders. Reference is made to appropriate chapters in this text and to other review articles where appropriate.

Mild Cognitive Impairment

The field of aging and dementia research is increasingly focusing on characterizing the earliest period of cognitive impairment before the development of dementia. Growing evidence points to a long prodromal period in the development of disease, with research suggesting that biochemical and neuropathological changes may occur up to 20 years before the clinical manifestation of disease. Mild to moderate impairment in cognitive functioning, typically memory, with otherwise intact performance has been called mild cognitive impairment (MCI; Petersen et al. 1999). MCI typically refers to a clinical presentation between normal aging and dementia, with greater than expected memory loss in the absence of other cognitive deficits (Figure 38.10). MCI should be differentiated from normal aging and other terms such as "age-associated memory impairment" and "age-associated memory decline," which generally refer to extremes of normal aging rather than a precursor to a pathological condition. Diagnostic criteria for MCI have been formulated by the Mayo Clinic Alzheimer's Research Center (Table 38.10). Estimates of the prevalence of MCI suggest that approximately 5-8% of people in community samples meet criteria for MCI. Several large-scale clinical trials arc under way to identify drugs that can slow cognitive decline among people with MCI, so identifying patients with MCI is imperative.

The clinical outcome of patients with MCI has been investigated in longitudinal follow-up studies. Several reviews of the literature have concluded that patients with MCI are at an elevated risk for developing clinically

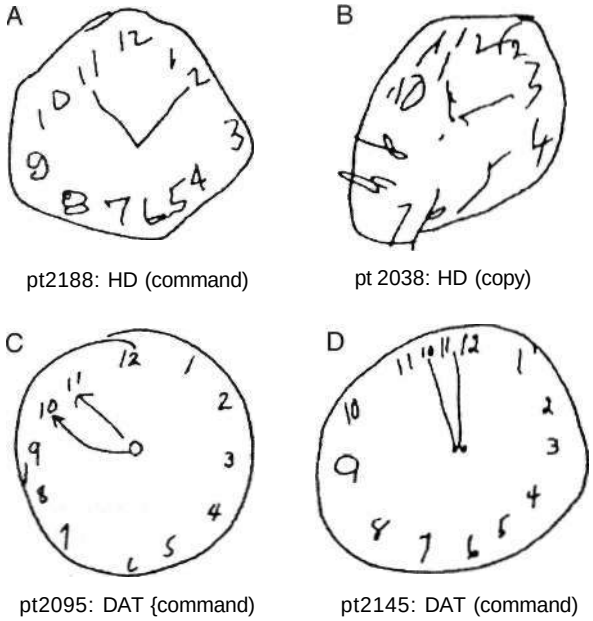


FIGURE 38.8 Sample of command and copy errors observed on the Clock Drawing Test in patients with Alzheimer's disease (dementia of the Alzheimer's type [DAT]) and Huntington's disease (HD). Graphic difficulties; (A) moderate; (B) severe, stimulus-bound response, (C) associated with visuospatial deficit; (D) associated with a conceptual deficit in representing the time on the clock. (Adapted from Rouleau, I., Salmon, D. P., & Butters, N. *1996,* "Longitudinal analysis of clock drawing in Alzheimer's disease patients," *Brain Cogn,* vol. 31, pp. 17-34.)

diagnosed AD. Estimates suggest that approximately 10-15% of patients with MCI will progress to AD per year. Studies have also found that MCI is associated with increased morbidity and a decline in selected cognitive abilities including episodic memory, semantic memory, and perceptual speed.

The heterogeneity of MCI has been acknowledged in the literature. Recently, several subtypes of MCI have been proposed including an amnestic subtype, which emphasizes memory loss, a subtype in which a single nonmemory domain is affected, and a subtype in which multiple domains arc slightly affected (Figure 38.11).

The criteria for MCI require both subjective and objective memory impairment in the presence of normal general cognitive functioning. Overall, deficits on measures of verbal episodic memory and new learning arc reported in patients with MCI, whereas other cognitive functions including language and executive functioning are largely intact (Petersen et al. 2001). The objective memory impairment typically is documented with neuropsychological testing using a cutoff of performance approximately 1.5 standard deviations below the average performance of people of a similar age and education. However, although other aspects of cognitive functioning in these people are largely intact, they may not be completely normal. A study comparing patients with MCI, normal control subjects, and patients with mild AD (characterized by a clinical dementia rating of 0.5 and 1) demonstrated that although the jyucral cognitive function of these subjects was normal, the level of cognitive functioning in other nonmemory domains was somewhat below normal (Petersen 2000).

Several predictors of subsequent cognitive decline among people with MCI and mild AD have been examined. An investigation at the Mayo Alzheimer's Disease Research Center longitudinally examined 155 people with MCI and found that apolipoprotein E4 carrier status, poor performance on a cued recall test, and atrophic hippocampi on magnetic resonance imaging (MRI) predicted more rapid

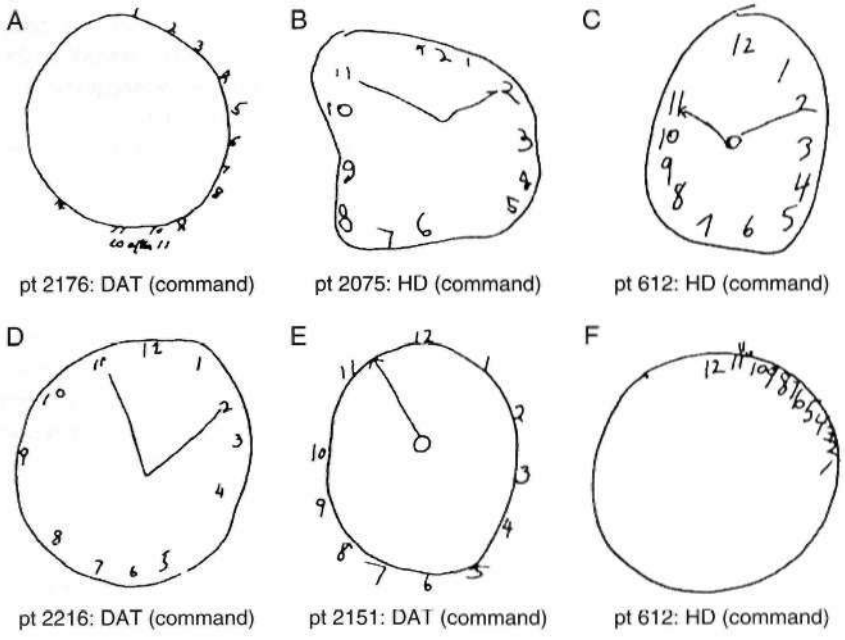


FIGURE 38.9 Samples of visuospatial and planning errors observed on the Clock Drawing Test in patients with Alzheimer's disease (dementia of the Alzheimer's type [DATJ) and Huntington's disease (HD): (A) neglect of the left hemisphere; (B, C) planning deficit; (D) deficit in the spatial layout of numbers; (E) numbers written outside the clock face; (F) numbers written in counterclockwise direction. (Adapted from Rouleau, I., Salmon, D. P., &c Butters, N. 1996, "Longitudinal analysis of clock drawing in Alzheimer's disease patients," *Brain Cogn,* vol. 31, pp. 17-34.)

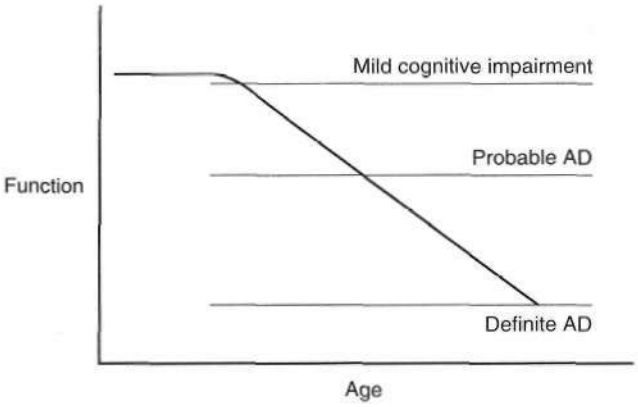


FIGURE 38.10 Theoretical progression of a person developing Alzheimer's disease (AD). (From Peterson, R. C., Doody, R., Kurz, A., et al. 2001, "Current concepts in mild cognitive impairment," *Arch Neurol*, vol. 58, pp. 1985-1992.)

declines (Petersen et al. 2001). Impairment in cognitive domains other than memory may also predict subsequent decline in performance.

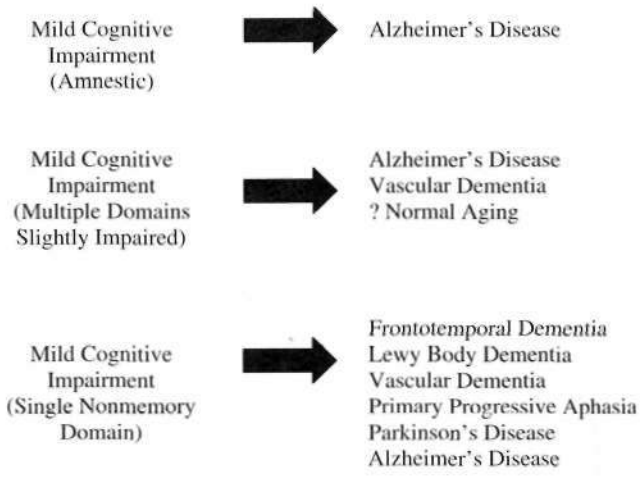


FIGURE 38.11 Heterogeneity of the term *mild cognitive impairment.* (Adapted from Peterson, R. C., Doody, R., et al. 2001, "Current concepts in mild cognitive impairment," *Arch Neurol*, vol. 58, pp. 1985-1992.)

Alzheimer's Disease

Neuropsychological tests, formal or informal, have always been the hallmark of the clinical diagnosis of AD. The recent development of pharmacological treatments for AD and the introduction of new therapies make assessing dementia at its different stages an even greater scientific and public health challenge. Neuropsychological tests at present are the only in vivo screening and diagnostic tools fot AD and related disorders that can establish deficits in more than one domain of cognition. This is required for the diagnosis of dementia and AD by the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (American Psychiattic Association 1994) and the National Institute of Neurological and Communicative Disorders and Srroke/Alzheimer's Disease and Relared Disorders Association (NINCDS-ADRDA) (McKhann et al. 1984) criteria. Although the MMSE is excellent fot identifying AD in mid-stages (i.e., total score of 23), it is insufficient to identify early AD. Several cognitive tasks have been developed to sctccn for AD. Among these additional tests are the Neurobehavioral Cognitive Status Examination (Kiernan et al. 1997) and the 7 Minute Screen (Solomon etal. 1998).

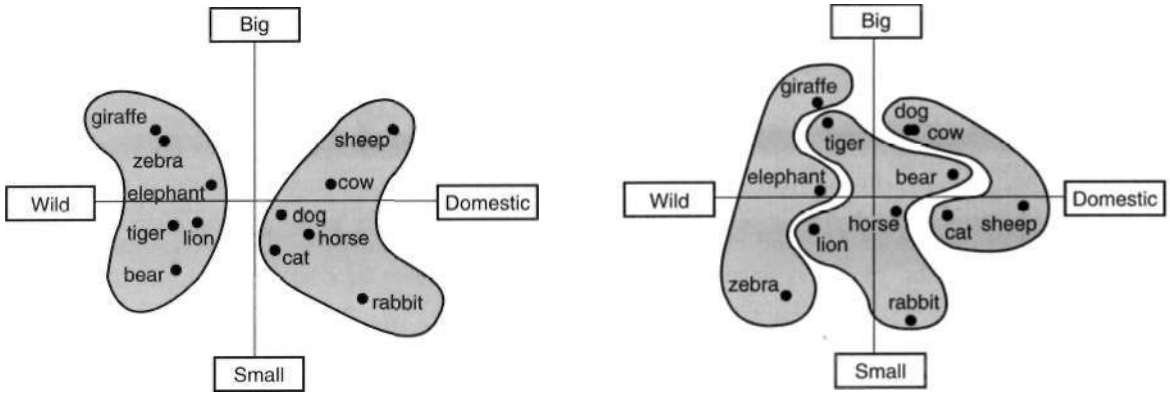
Tabic 38.10: Criteria for amnestic mild cognitive impairment

Memory complaint, preferably corroborated by an informant
impaired memory function for age and education
Preserved general cognitive function
Intact activities of daily living
Not demented

Source; Peterson, R. C, Doody, R., et al. 2001, "Current concepts in mild cognitive impairment," *Arch Neurol*, vol. 58, pp. 1985-1992.

AD results in a global disorder of intellectual functioning that affects a wide variety of cognitive processes. Memory impairment usually is the earliest and most salient fcatute of the disorder, but the particular cognitive processes that are initially affected and the relative seventy of various cognitive impairments can vary from patient to patient. The neuropsychological evaluarion of AD must include a thorough assessment of a wide range of cognitive abilities, including verbal and nonverbal memory, language and semantic knowledge, attention and executive functions, visual perception, and spatial abilities. Numerous studies have shown that measures of the ability to learn and retain new information arc effective in differentiating between mildly demented patients with AD and normal adults. For example, Welsh and colleagues (1991) found that the accuracy of word list recall after a 10-minute delay differentiated patients with very early AD (MMSE > 25) from healthy controls with bettet than 90% accutacy. The abnormally rapid forgetting exhibited by patients with AD on clinical memoty tests suggests that their memory impairment is caused by ineffective consolidation of information (i.e., difficulty transferring information from short-term to long-term memoty).

Because AD results in widespread cortical damage and affects a wide variety of cognitive functions, the memory impairment of these patients may be exacerbated by a number of ancillary deficits. For example, poor attention and weakened semantic memory associations may adversely affect memory performances. One recent report suggests that attention is the first nonmemory domain to be affected in AD, before language and visuospatial functions. Divided attention and aspects of selective attention, such as set-shifting and response selection, are particularly vulnerable, whereas sustained attention is largely preserved in the early stages of AD.



NORMAL ELDERLY CONTROLS ALZHEIMER'S DISEASE PATIENTS

FIGURE 38.12 The cognitive map of normal older adults *{left)* and patients with Alzheimer's disease *(right)* obtained from multidimensional scaling analysis and clustering analysis. (Adapted from Chan, A., Butters, N., Paulsen, J. S., et al. 1993, "An assessment of the semantic network in patients with Alzheimer's disease," *J Cogn Neurosci,* vol. 5, pp. 254-261.)

The nature of language deficits exhibited by patients with Al) Mifi^ests thai these patients MI iter deterioration in the organization of semantic knowledge or a degradation of the knowledge itself. For example, several studies using verbal fluency tests have shown that patients with AD are more impaired when required to generate exemplars from a particular category (e.g., animals) than words beginning with a particular phoneme (e.g., FAS). Chan and her colleagues (1993) used multidimensional scaling analyses to show the distorted semantic network of the patient with AD (Figure 38.12).

Deficits in visuoperceptual abilities and constructional praxis occur in patients with AD, although they usually emerge after the early stages of the disease and may have little to contribute to the differentiation of early dementia from normal aging. Convergent findings from neuropathology, neuroimaging, and neuropsychology indicate that early memory impairments in AD are specifically related to early stage limbic-diencephalic pathology and that nonmnemonic impairment is specifically related to later-stage tcmporal-neocortical pathology.

Vascular Dementia and Vascular Cognitive Impairment

Current estimates of the prevalence of vascular dementia suggest that it accounts for 10-50% of all dementia cases, making it the second most common cause of dementia after AD {see Chapter 72 for a review of the clinical aspects of vascular dementia). The development of the diagnostic criteria for vascular dementia has been heavily based on AD research. This has resulted in a focus on symptoms of memory impairment, progression, and severity of symptoms. Vascular dementia is treated as a largely unitary condition and either implicitly or explicitly includes dementia caused by stroke {see Chapter 72). Several authors argue that this focus is inadequate to capture the range of cognitive impairments that can result from cardiovascular disease (Bowler and Hachinski 2002).

Bowler and Hachinski proposed the broader term *vascular cognitive impairment* (VCI) to encompass the array of cognitive deficits resulting from cerebrovascular disease. Those who may be diagnosed with VCI include patients with early cases of cognitive impairment associated with cardiovascular disease and exclude those with nonischemic cases and major stroke. Future research on VCI may help characterize the range of cognitive impairments that are typically associated with cerebrovascular disease. In the meantime, it is important to recognize that vascular lesions that produce cognitive impairments can have many different origins, including ischemia, incomplete infarction, and major stroke.

Although numerous studies have attempted to identify patterns of cognitive deficits that arc typically associated with cerebrovascular disease, the recognition of characteristic cognitive impairments is influenced by the manner in which the patients are diagnosed. The particular pattern of cognitive deficits varies with the subtypes of vascular dementia, which include subcortical vascular dementia, multi-infarct dementia, hypoperfusion dementia, and single cortical or subcortical infarcts {Desmond and Pasquicr 2002).

Given such a wide range of dementias, a comprehensive description of the corresponding deficits is beyond the scope of this chapter (see Chapter 72). Nonetheless, several commonalities, including an emphasis on impairment of executive functioning with largely intact performance in several aspects of memory, have emerged in the literature.

The most common neuropsychological impairment in patients with cerebrovascular disease, particularly those without a history of major stroke, is subcortical and frontal lobe functioning deficits. Planning and sequencing, speed of mental processing, performance on unstructured tasks, and attention tend to be impaired in vascular dementia

(Desmond and Pasquier 2002). Subcortical lacunar infarctions in the territory near the thalamus, caudate, and globus pallidus may disrupt frontal-subcortical circuits and account for the prevalence of executive dysfunction in these patients.

The presence of memory impairment in vascular dementia is somewhat controversial. Memory impairment is considered a defining feature of AD, and many studies have found more significant memory impairments in AD than in vascular dementia. However, several studies have found evidence of memory impairment in vascular dementia as well. For example, one study found that tests of memory were among those that differentiated between patients with ischemic stroke and control participants.

Findings of memory impairment associated with cerebrovascular disease may result from comorbid cerebrovascular disease and Alzheimer's dementia. Memory impairment may also be a secondary manifestation of cerebrovascular disease from infarcts in the medial temporal lobe or a consequence of executive functioning deficits such as inattention and disorganization (Desmond and Pasquier 2002), Using positron emission tomography, Reed et al. (2000) found that episodic memory failure in patients with subcortical cerebrovascular disease was associated with prefrontal lobe metabolism, whereas memory performance in patients with AD was correlated with left hippocampal and temporal lobe metabolism. The authors suggest that different pathogenic mechanisms underlie episodic memory failure in subcortical vascular disease and AD. Given the current criteria for vascular dementia, which emphasize memory impairment and global cognitive deterioration, it has also been suggested the observed memory deficits in patients diagnosed with vascular dementia may be influenced by selection bias.

A recent review of the literature indicated that patients with AD have greater deficits than patients with vascular dementia in functions mediated by posterior cortical areas including memory deficits (e.g., faster rate of information decay, reduced ability to benefit from retrieval cues, and greater intrusion errors) and particular language deficits such as naming impairment (Desmond and Pasquier 2002). Greater deficits in syntax in vascular dementia, and in accessing lexicon in AD, have also been reported. One study examined the performance of 114 people with probable AD and subcortical ischemic vascular dementia on a variety of tests purported to measure executive abilities. The authors found that patients with AD had more self-monitoring problems than patients with subcortical vascular disease, whereas patients with subcortical vascular disease demonstrated more executive memory search deficits, pointing to differences in the types of executive functioning deficits manifested by the dementia groups (Yuspeh et al. 2002). Despite these observed differences, other recent research has found evidence of similar patterns of deficits when comparing patients with AD and vascular dementia on several neuropsychological tests.

Historically, a patchy, stepwise pattern of cognitive deficits has been associated with vascular dementia, particularly multi-infarct dementia. There is recent evidence that patients with vascular dementia have a higher prevalence of fluctuating cognitive functioning than those with AD. Although this may be the case in some instances, it is clear that the course of cognitive decline may also be continuous and slowly progressive in many patients with multiple vascular disorders,

Fro n to temp oral Dementia

Focal degeneration of the frontotemporal lobes is a common cause of dementia, accounting for about 20% of cases of dementia with presenile onset. Frontotemporal dementia (FTD) encompasses a clinically heterogeneous group of syndromes determined by the distribution of pathological change within the brain. Cases of FTD do not have a common molecular basis, however, and highlight the importance of defining patients on clinical, anatomical, histological, and biological grounds. Three ma]or syndromes can be identified: (1) frontal lobe degeneration of non-Alzheimer type, in which changes in social behavior and personality predominate, reflecting the orbitobasal frontal lobe focus of the pathology; (2) semantic dementia, also known a progressive fluent aphasia, in which there is a breakdown in the conceptual database that underlies language production and comprehension and is associated with asymmetrical anterolateral temporal atrophy with relative sparing of the hippocampal formation; and (3) progressive nonfluent aphasia, the most rare of these syndromes, in which the phonological and syntactic components of language are affected in association with left perisylvian atrophy.

There are three main histological types: microvacuolar, Pick's, or motor neuron disease. It is important to note that each of these FTD syndromes can be associated with motor neuron disease (amyotrophic lateral sclerosis), although the neurological symptoms and signs commence after the development of the dementia and lead to death within 3 years. Although it has been suggested that FTD disorders should be regarded as tauopathies on the basis of the tau pathology seen in a number of cases and the mutations in the tau gene in some familial cases, recent studies have documented only 37% of FTD with tau pathology and 10% with mutations in the tau gene, suggesting that FTD is not a unitary etiological disorder.

Simple cognitive screening tests, such as the MMSF, are unreliable for detecting and monitoring FTD. Performance on the MMSE can remain intact even when institutionalization is needed. Early personality or functioning complaints must be regarded seriously, and a neuropsychological assessment should emphasize executive and social tasks,

The clinical presentation of primary FTD is one of profound alteration in social conduct and personality.

Patients may show a disinhibited, overactive, and restless change reminiscent of orbitofrontal dysfunction or akinesia and apathy accompanied by a lack of concern and insight (Table 38.11). In many patients, stereotypic, ritualistic behaviors are the dominant clinical feature. Such patients may develop elaborate rituals for dressing or toileting, adhere to a rigid daily routine, and experience significant difficulty shifting from one activity to the next. Performances on executive tasks reveal profound abnormalities in abstraction, planning, sequencing, organization, and regulation.

Patients with semantic dementia typically complain of loss of memory for words. They are often painfully aware of their shrinking expressive vocabulary but are strangely oblivious to their impaired comprehension. Caregivers note the increased use of substitute words and phrases such as "thing" and "you know." Patients with primary right-sided atrophy may present with difficulty recognizing and naming faces and become severely prosopagnostic. Day-to-day episodic memory and orientation remain intact.

Progressive nonfluent aphasia presents with a decline in language expression in the relative absence of other cognitive deficits. Speech becomes nonfluent and effortful and may involve stuttering. Word retrieval difficulties are prominent, and repetition is impaired. Spoken and written comprehension remains largely preserved, as do visual perception, spatial abilities, and memory. Social skills typically are well preserved in the early stages, although behavioral changes akin to frontal lobe degeneration emerge later in the disease.

Parkinson's Disease

In addition to motor symptoms, PD is associated with elevated levels of depression and cognitive impairments, Clinical ratings based on the level of clinical disability have become the standard method of measuring PD-related functioning. The Unified Parkinson's Disease Rating Scale {Fahn et al. 1987) is the most widely used scale today and incorporates the Hoehn-Yahr clinical disability stages and the Schwab and Kngland activities of daily living into scores that are used to assess treatments and measure disease stages. Because cognitive and emotional functioning can have a significant impact on functional capacity, these assessments must be a central component of the PD evaluation.

Although cognitive impairment is the rule rather than the exception in PD, there is heterogeneity in presentation and progression of cognitive deficits. The neuropsychological profile of PD includes cognitive slowing, memory impairment, visuospatial deficits (e.g., problems with pattern completion and facial recognition), and a range of executive deficits including impairments in decision making, planning, shifting, and monitoring of goal-directed behaviors. Nearly all patients with PD suffer from a general cognitive slowing, or bradyphrenia.

Several studies suggest that changes in executive functioning may be one of the earliest signs of cognitive decline in PD. Patients with PD often report problems with decision making, planning, and monitoring of goal-directed behaviors. On traditional and computerized neuropsychological tests, even nondemented patients with PD show impaired ability to shift between sets.

Up to 80% of patients with PD experience speech problems beyond production problems related to motor symptoms. They experience problems comprehending and producing syntactically complex sentences. Unlike patients with AD, those with PD generally do not experience problems with name finding.

Memory problems are also commonly reported among patients with PD. In particular, they report difficulty in recalling effortful information but exhibit intact recognition. Several studies have demonstrated that learning and retrieval deficits exist in patients with PD without frank dementia.

Dementia occurs in up to 25% of patients with PD. A number of factors have been implicated as risk factors for dementia in PD, including older age, lower education, and the presence of depression and confusion or psychosis after levodopa treatment.

There is no consensus regarding the effect of pharmacological treatment on cognition in PD. It is clear that for some patients with PD, the gold standard treatment, levodopa, may exert a highly selective and deleterious effect on cognitive function. This is particularly salient given that the cognitive decline observed in PD remains a major source of disability and mortality in PD.

Tabic .18.11: Differentiating Alzheimer-type dementia from frontal lobe dementia

CI mica I variables	*Alzheimer's disease*	*frontal lobe dementia*
Personality	Passive, largely intact	Apathetic, disinhibited, sometimes eccentric
Social skills	Spared early	Early deterioration
Kliivcr-Bucy syndrome	Late	Early
Language	Fluent aphasias	Decreased output, mute
Naming	Lexical anomia	Semantic anomia
Drawing	Impaired early	Largely spared
Calculation	Impaired early	Largely spared
Memory	Impaired early, not helped by cues	Variable, helped by cues

Huntington's Disease

HD is a genetically transmitted neurodegenerative disease of the basal ganglia that is characterized by a triad of clinical symptoms: choreoathctosis, cognitive decline, and psychiatric features. The diagnosis of HD is based on a neurological evaluation and requires the presence of an unequivocal movement disorder, although the cognitive and behavioral alterations are the most debilitating aspect of the disease and place the greatest burden on HD families.

In manifest HD, the most striking cognitive deficit is executive dysfunction (e.g., strategies in planning and problem solving, self-monitoring, and attentional and cognitive flexibility). As expected, cognitive deficits reported in people who are presymptomatic for HD but have the gene mutation also emphasize executive dysfunction. In a meta-analytic review, Zakzanis (1998) concluded that patients with HD are most deficient in the acquisition of new information, delayed recall, cognitive flexibility, manual dexterity, attention, speed of processing, and verbal skill.

Several studies have demonstrated that patients with HD are impaired on tests that require executive functions, such as the Wisconsin Card Sorting Test, the Stroop Color Word Test, and clinical rating scales of executive dyscontrol. In fact, brief tests of executive functions have been suggested as sensitive tools for identifying subcortical dysfunction. That is, the Serial Sevens item on the Mini-Mental State Examination, the Initiation and Perseveration subtest of the Dementia Rating Scale (Mattis 1976), and an abbreviated battery of frontal lobe tests have been demonstrated to be distinctly sensitive to patients with HD.

Some recent research has evaluated the performance of patients with HD on clinically relevant, face-valid tests of judgment and decision making. Stout and colleagues (2001) used a simulated gambling task to quantify decision-making deficits in patients with I ID, Findings showed that patients with HD made fewer advantageous selections than age- and education-matched healthy controls and dementi a-severity-matched patients with PD. Impairments on tasks requiring decision making may result from various cognitive decrements, including learning, attention, inhibition, and appreciation for future consequences. Findings can also be interpreted as further evidence that patients with HD are less able to benefit from feedback and have difficulty varying output based on performance. Despite evidence of explicit knowledge for the tasks, patients with HD were unable to update existing programs based on new experience and to alter their responses. Numerous wide-ranging consequences of these types of executive deficits are self-evident.

Early neuropsychological studies reported that patients with HD perform poorly on subtests requiring attention and working memory. More recent studies have emphasized dysfunction in unique aspects of attention, including resource allocation, response flexibility, and vigilance. For instance, one study reported that patients with HD are able to maintain attention for a previously learned response set but have difficulty shifting attention to a new set. Others have reported that patients with HD are able to maintain alertness when the task involves an external cue but fail when internal self-generated vigilance is required. The clinical implications of the attentional impairment in HD are significant. Many people with HD perform better when they avoid tasks involving divided attention. Patients and families agree that trying to divide the already-compromised attentional resources can contribute to discomfort and increase safety risks. For instance, driving a car while listening to the radio, talking to people in the back seat, or talking on the cell phone is not recommended. To reduce choking risk, the environment should be quiet and calm at mealtimes to emphasize concentration on chewing and swallowing.

Deficits in learning and memory are the most frequently reported cognitive complaints from people with HD and their family members. Patients with HD exhibit verbal learning deficits even in the earliest stages of the illness. The majority of studies describe the memory impairment as a primary encoding and retrieval deficit because recognition memory often is preserved. That is, most studies show that people with HD consistently have problems learning new information and also experience difficulty when asked to use free recall to remember what they have learned; in contrast, they perform near normal when a less-effortful memory strategy is used, such as offering choices of or recognizing possible learned items. Patients with HD manifest intact retention over a delay period, indicating no abnormal forgetting or rapid loss of information. When tested on memory for information acquired long ago, they demonstrate no temporal gradient in performance, indicating that memory performance is equivalent for all periods of their lives.

The memory impairment of HD is characterized by a mild encoding deficit (probably caused by impaired organization of the to-be-learned information and ineffective working memory) and moderately impaired retrieval in the context of largely intact memory storage when measured with a less-effortful strategy (i.e., recognirion). Skill learning can be acquired when external feedback is allowed, but motor programs are not stored for later use, possibly because of the dependence of the striatum in "chunking" components of the motor program.

Several studies have shown olfaction impairments in HD using the University of Pennsylvania Smell Identification Test (Doty 1991). The most comprehensive research to date assessed absolute detection, intensity discrimination, quality discrimination, short-term recognition memory, and lexical- and picture-based identification for odor, using taste and vision as comparison modalities. Results suggested that although odor recognition memory is not affected in patients with I ID, absolute detection, intensity discrimination, quality discrimination, and identification

were significantly impaired. Poor detection sensitivity explained performance on several other olfactory tasks where odor identification was the function most impaired.

Deficits in the ability to copy simple geometric designs, to copy block designs, and to put together puzzles are evident in HD. Although some of these impairments probably reflect motor abnormalities, performance is also impaired on motor-free untimed perceptual tasks. Mohr and colleagues (1997) recently examined whether visuospatial deficits in basal ganglia disease are a nonspecific function of dementia severity or whether they reflect disease-specific impairments. Findings suggested that general visuospatial processing capacity is impaired as a nonspecific dementia effect in both HD and PD, whereas only patients with HD showed specific impairment in person-centered spatial judgment. For instance, people with HI) (but not PD) experience difficulty with map reading, directional sense, and varying their motor responses after alterations in space. People with HD typically misjudge distances and the relationship of their body to walls, curbs, and other potential obstacles.

One of the most prominent features of HD is the motor speech impairment, or dysarthria, that is characteristic of the illness. Early speech changes may include insufficient breath support, varying prosody, increased response latencies, and mild misarticulations. As HD progresses, phrase length decreases, and pauses in speech output lengthen. Performances on tasks of letter and category fluency are impaired early in the disease, although the integrity of word associations remains largely intact, with little evidence of intrusion or perseveration errors. Despite significant impairments in verbal fluency, speed of output, and complexity, syntactic structure remains intact, and speech content usually is appropriate. Although there are some reports in late-stage HD of mild deterioration in semantic knowledge structure, several other studies have shown that errors in confrontation naming are more likely to be caused by visual-perceptual deficits and retrieval slowing. Speech output becomes severely impaired as the disease progresses, typically resulting in a profound communication deficit.

Several studies have relied on the Total Functional Capacity (TFC) scale to quantify disease stages and functional dependence associated with HD. Research has been largely consistent, with most studies demonstrating an average decline of 0.63 ± 0.75 units/year on the TFC. Although controversial, there is some evidence that rate of progression is more rapid in juvenile onset and more gradual in late onset. Marder and colleagues (2000) recently examined the annual rate of functional decline in 960 prospective patients with HD followed an average of 18 months at 43 sites in the Huntington Study Group. Findings were consistent with previous research, suggesting TFC decline of 0.72 units per year and independent-scale decline of 4.52 units per year. Better cognitive status at baseline, lower baseline TFC, and longer disease duration were associated with a less rapid rate of decline, whereas depressive symptoms were associated with more rapid functional decline. Rich and colleagues (1999) assessed flexibility and language functions over 5 years and reported stable semantic clustering (language) performances in patients with HD despite a progressive reduction in shifting. Findings are consistent with a cross-sectional study of 75 patients with HD divided into three stages of illness: early, middle, and advanced. These findings suggested that memory, receptive language, and simple attention remain largely intact throughout the stages of HD. It is important for professionals and family members to educate staff at care facilities regarding the pattern of impaired and preserved cognitive functions in later stages of HD, when verbal output is severely limited.

Tourette's Syndrome

Tourctte's syndrome (TS) is an inherited neuropsychiatric disorder characterized by motor and phonic tics (Jankovic 2001). Diagnostic criteria for TS include the presence of multiple motor tics and one or more vocal tics, both of which must exceed a year's duration. Onset of this disorder occurs in childhood, with an average onset age of 6 to 7 years. AI tin High evidence suggests a genetic transmission of TS, a gene has not yet been identified. Illness course is variable, with some patients experiencing spontaneous remission or significant decrease of symptom severity whereas others experience lifelong presence of symptoms.

Up to 68% of children with TS function below expectations in school. The neuropsychology of TS is incomplete, however, in part because there have been insufficient experimental studies of primary psychological systems and in part because most studies that have been carried out have included a mix of subjects. Because comorbidity in TS is high, subject samples often are heterogeneous with regard to obsessive-compulsive symptoms, attention deficit hyperactivity disorders, mood disorders, coprolalia, age, medication usage, illness duration, and age of onset. In addition, TS children sometimes are distracted by their various motor and vocal tics or use a great deal of resources to suppress these tics, taking attention from their studies. Motor tics may interfere with homework, note taking, or performance on written examinations. Children with TS are clearly seen as different from other children in the classroom and often experience psychological and emotional burdens associated with being perceived as different. Despite these iinutations, some preliminary conclusions may be drawn.

Although some findings suggest that children with TS have executive dysfunction, other reports show that children with pure TS (no comorbid diagnoses) have normal performances on neuropsychological measures or **nearly** normal performances with only subtle slowing or disinhibition. When considered together, findings suggest

that cognitive impairments in pure TS are mild and not easily captured with gross measures. More comprehensive executive evaluations and novel study designs (Cirino et al. 2000) probably are needed to better differentiate the core cognitive component of TS from the cognitive deficits associated with its comorbid disorders.

Children with TS and a comorbid diagnosis of attention deficit hyperactivity disorder (ADHD) demonstrate dysexecutive performances and increased perseverative errors as well as increased incidence of learning disability. Primary cognitive dysfunction associated with frontal systems may impait the planning, organization, and execution of behavioral output for children with TS and ADHD. Compensatory sttategics that might be useful involve increased structure fot problem solving. Children with TS and comorbid obsessive-compulsive symptoms show dysexecutive petformances as well, but performance is mosr severely impaired in children with TS, ADHD, and obsessive-compulsive symptoms. Even after controlling for tic severity, IS children with comorbid ADHD and obsessive-compulsive disorder demonsrrated the most severe cognitive impairments and poorer academic achievement.

Table 38.12: Relative frequency of cognitive deficits in multiple sclerosis

Cognitive deficits	*Frequency \n multiple sclerosis*
Attention	+-H-
Information processing	+++
Encoding memory	+ 4....
Free recall memory	+++
Verbal fluency	+++
Auditory and visual span	++
Recognition memory	++
Executive function	++
Conceptual reasoning	++
Visuoperceptual function	++
Loss of stored factual knowledge	+
Motor learning	+
Apraxia	+
Agnosia	+
Aphasia	+

Note: + indicates frequency from rare (+) to common (+++).
Source: Adapted from Bagart et al. 2002, "Cognitive dysfunction in multiple sclerosis," *CNS Drugs*, vol. 16, pp. 445-455.

Multiple Sclerosis

Cognitive dysfunction is a significant cause of disability in patients with multiple sclerosis (MS). Estimates of the prevalence of cognitive impairment in MS range from 45% to 65%. Cognitive deficits can develop at any time during the course of the disease and can occur in the presence or absence of neurological disability. Although some research suggests that only certain domains of cognition are initially affected and that more widespread cognitive deficits emerge later in the disease, the course of cognitive impairment in MS remains controversial. Although cognitive deficits vary among patients with MS, perhaps because of the inter-individual variability in the nature of the microscopic and macroscopic pathology of MS, several patterns of impairment are evident in the literature {Table 38.12). Patients with MS who have cognitive impairmenr mosr commonly have deficits in memoty, learning, attention, speed of information processing, and verbal fluency. Deficits in conceptual thinking and problem solving, functional language abilities, and spatial reasoning have also been reported in the literature.

As mentioned earlier, memory deficits are one of the most commonly observed cognitive impairments in MS. A meta-analysis of 36 published papets on memoty impairment in MS suggested that patients had significant abnormalities in all aspects of memory functioning, Nonetheless, individual studies have focused on different aspects of the memory deficit. Early studies of memory impairmenr in MS identified rettieval deficits as being important. More recently, several studies have suggested that the memory impairment in MS results primarily from deficits in acquisition rather than recall per se. For example, although people with MS need significantly more learning trials to meet criteria on memory tasks, after a delay they recall similar amounts of information to healthy controls (Demaree et al. 2000). Other studies have suggested that deficits in working memory underlie the short-term memory deficits and verbal dysfluency observed in MS (Janculjak et al. 1999).

Slowed information processing speed among patients with MS has been observed in several studies independent of slowed sensorimotor processing. A recent study compared the neuropsychological performance of 55 inpatients with MS with that of 42 norma) controls (Janculjak et al. 2002). Findings suggested that the major cognitive deficit in MS caused by demyclination is the slowing of information processing, which was found to be related to focused attention and the simplest forms of explicit memory. The transfer of information between hemispheres has also been shown to be slow in patients with MS, and imaging studies have revealed corpus callosum atrophy in MS.

Four subtypes of MS have been defined based on an international survey of specialists: (1) relapsing-remitting, (2) secondary progressive, (3) primary progressive, and (4) progressive-relapsing courses. Primary progressive MS involves continual progression from the onset of the disorder, whereas the relapsing-remitting subtype involves initial petiods of remission that later develop into secondary progressive MS. Some studies on the neuropsychology of MS have attempted to identify differing patterns of cognirive deficits among the subtypes. For example, a study examining explicit and implicit memory found that patients with primary progressive MS exhibited a pattern of memory impairment that was distinct from that of patients

with relapsing-remitting and secondary progressive MS (Figure 38.13}.

Furthermore, a recent meta-analysis of 34 studies comparing patients with MS and healthy controls found that cognitive impairment was evident generally and that distinct patterns of neurocognitive deficits characterized chronic progressive and relapse-remitting subtypes of MS (Kakzanis 2000). Patients with chronic progressive MS presented with more frontal executive impairment, whereas patients with relapsing-remitting MS presented with more memory-related dysfunction.

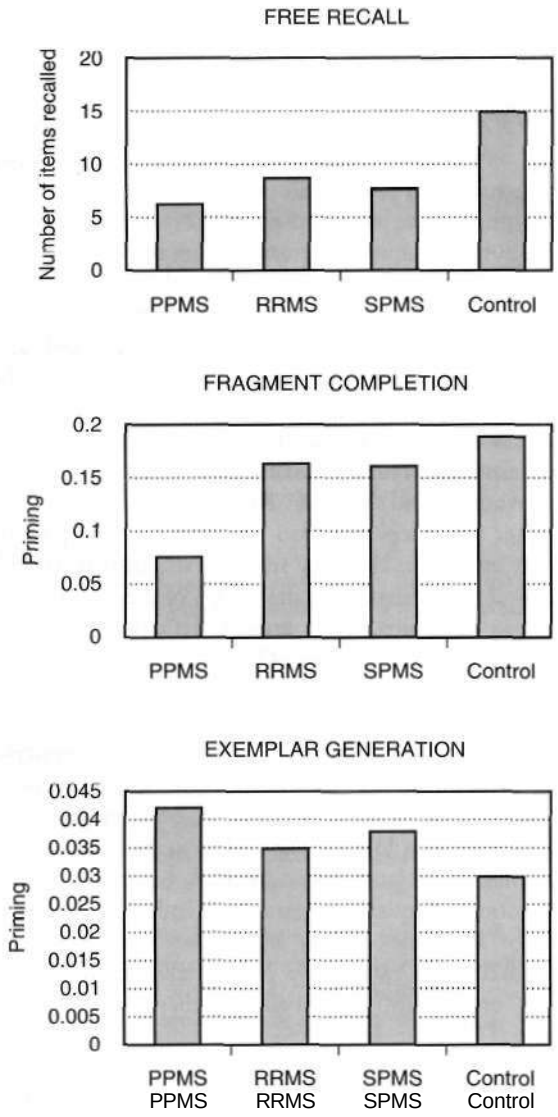


FIGURE 38.13 Free recall performance, word fragment completion priming, and exemplar generation priming in primary progressive multiple sclerosis (PPMS), relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and control subjects. (Adapted from Blum, D,, Yonelinas, A. P., Luks, T., et al. 2002, "Dissociating perceptual and conceptual implicit memory in multiple sclerosis patients," *Brain Cogn,* vol. 50, pp, 51-61.)

A meta-analysis of research on neuropsychological functioning in patients with MS over a 20-year period suggested that interhemispheric transfer, general cognitive ability, and learning and memory were more highly associated with MS than visuoperceptual, visuospatial, and visuoconstructional ability, language, and conceptual ability (Table 38.13). Effect sizes comparing MS and healthy control groups on variables grouped by neuropsychological domain were generally small to moderate. However, in contrast with many previous reports, disease subtype was not related to neuropsychological functioning,

Several studies suggest that lesion burden as measured by brain imaging, including MRI, correlate with cognitive disability. Deficits on neuropsychological measures have been correlated with lesion load, atrophy of the corpus callosum, and magnetization transfer ratio. One study that used MRI found that right and left superior frontal lobes arc the regions of the cortex most susceptible to atrophy and resulting cognitive changes in verbal and spatial learning, attention, and conceptual reasoning (Benedict et al. 2002). Another study examined 28 patients with MS and matched healthy controls using MRI and neuropsychological testing at baseline and 1-year and 4-year follow-up (Sperling et al. 2001). Results of this study suggest that MS lesions demonstrate a propensity for frontal and parietal white matter. Patients with MS showed significant impairments on tasks of sustained attention, processing speed, and verbal memory as compared with the control subjects, which was correlated with MS lesion volume in frontal and parietal regions. The authors concluded that disruption of fronto-parietal subcortical networks might underlie the observed pattern of neuropsychological impairment observed in these patients. In contrast, the authors of a study of cognition using MRI in patients with rare forms of MS (primary progressive and transitional progressive MS) observed modest correlations between MRI lesion measures and a global cognitive impairment index. They concluded that cognitive functioning in primary progressive and transitional progressive MS is multifactorial and is not adequately explained by pathology as demonstrated by conventional MRI (Camp et al. 1999). These authors suggest that advances in imaging and the development of more sensitive cognitive tests will help elucidate the pathophysiology of MS in these subtypes of the disease.

Epilepsy

An epileptic seizure, by definition, involves abnormal activity of the brain; therefore it is commonly acknowledged that the ictal period, before, during, and immediately after a seizure, is associated with cognitive changes including confusion and alterations of consciousness. However, it is important to recognize that epilepsy is also associated with interictal alterations in cognitive abilities {see Chapter 73 for a review of epilepsy).

Table 3S.13: Effect sizes of differences between patients with multiple sclerosis and control subjects

Neuropsychological domain	***k***	N	M_r *(SD)*	$r_{,r}$	$Q_{„}$
Interhemispheric transfer	*7*	798	.46 (.15)	.43*	23.8
Mood Lind psychological status	14	1157	.37 (.21)	.3-1	71.9[s]
General cognitive ability	29	3269	*36* (.20}	.33*	182.7*
Learning and memory	85	7575	.35 (.18)	,32*	414.1*
Attention/executive ability	55	5479	.34 (.26)	.28*	437.6*
Sensory and motor ability	35	3260	.34 (.19)	.30*	109,8*
Visuoperceptual ability	30	3991	.26 (.21)	.24*	159.3*
Language	45	4736	.26 (.21)	.23*	S0.6*
Conceptual ability	22	2733	.22 (.13)	.23*	42.4*

k — number of effect si7.es; N = number of subjects per effect size; M_r — effect size; r_{su} — weighted *r; Q* — homogeneity statistic; Q_w — Q within.

Source: Adapted from Wish art, H. *&c* Sharpc, D. 1997, "Neuropsychological aspects of multiple sclerosis: A quantitative review," *} Clin Exp Ncuropsychol,* vol. 19, pp. 810-824.

There is no one cognitive profile associated with epilepsy, perhaps because the condition has a variety of origins and clinical manifestations. Nonetheless, a substantial body of research suggests that a range of cognitive deficits is related to epilepsy and its treatment,

One of the most often studied neuropsychological variables in epilepsy is overall intellectual functioning. The early clinical literature suggested that epilepsy was commonly associated with overall cognitive deterioration, and several recent studies have also found evidence of overall decrements in intellectual functioning in patients with epilepsy. However, other research suggests that epilepsy does not necessarily lead to overall reductions in cognitive functioning. Research examining the relationship between overall cognitive status and particular clinical characteristics has provided useful information. For example, patients with more generalized seizure activity tend to show more significant and widespread cognitive deficits, There is evidence that people with convulsive seizures have poorer cognitive functioning, whereas generalized non-convulsive and partial seizures are not associated with significant losses in overall intellect. Research on the age of onset shows that the earlier the epilepsy begins, the greater the impact on cognitive abilities. Furthermore, the longer the duration of epilepsy, the lower the patient's overall cognitive functioning. Findings regarding the relationship between the frequency of seizures and cognitive functioning have yielded mixed results. It appears that the type of seizures experienced by the patient, including their cause and whether the patient experiences status epilepticus with repeated seizures concentrated in time, may be more predictive of losses in overall cognitive functioning than seizure frequency alone. Focal seizures typically involve just one side of the brain and are more likely to show a circumscribed pattern of cognitive deficits than more generalized epilepsy. Focal seizures usually are associated with patterns of cognitive performance typically seen with damage to the area of the seizure focus in the absence of epileptic activity.

Memory dysfunction is the most commonly reported cognitive complaint associated with temporal lobe epilepsy (TLE; Ogden-F.pker and Cullum **2001).** Verbal memory deficits typically are reported to be associated with left temporal lobe epilepsy, whereas verbal memory deficits have been emphasized in association with right temporal lobe epilepsy. However, findings regarding the relationship between epilepsy and memory functioning are mixed, and some studies have not found a relationship between the laterality of TLE and material specific memory deficits. Nonetheless, there is evidence that self-reported memory is an important predictor of quality of life in patients with TLE (Giovagnoli and Avanzini 2000).

Language disorders are also associated with epilepsy. One study examined language function in 60 patients with epilepsy and found that more than 30% of the patients had language impairments, with greater deficits in receptive than in expressive abilities. The language abilities of patients with unilateral TLE were studied using a large battery of neuropsychological language tests. Results showed that patients with left temporal lobe epilepsy performed significantly worse on tests of naming, repetition, and language comprehension than patients with right temporal lobe epilepsy. The authors concluded that language problems occur in TLE generally but are more pronounced in left temporal lobe epilepsy. Deficits of the ability to name objects have also been shown to be associated with intractable mesial temporal lobe. For example, one study examined whether object-naming deficits in **TLE** were associated with semantic knowledge deficits (Bell et al. 2001; Figure 38.14). The findings suggested that patients with early-onset TLE have a semantic knowledge deficit that contributes to their confrontation naming problems.

Several studies have demonstrated that deficits in executive functioning are associated with frontal lobe epilepsy. Recently, one study compared the neuropsychological profiles of children with frontal lobe epilepsy and TLE (Culhane Shelburne et al. 2002), Children with frontal lobe

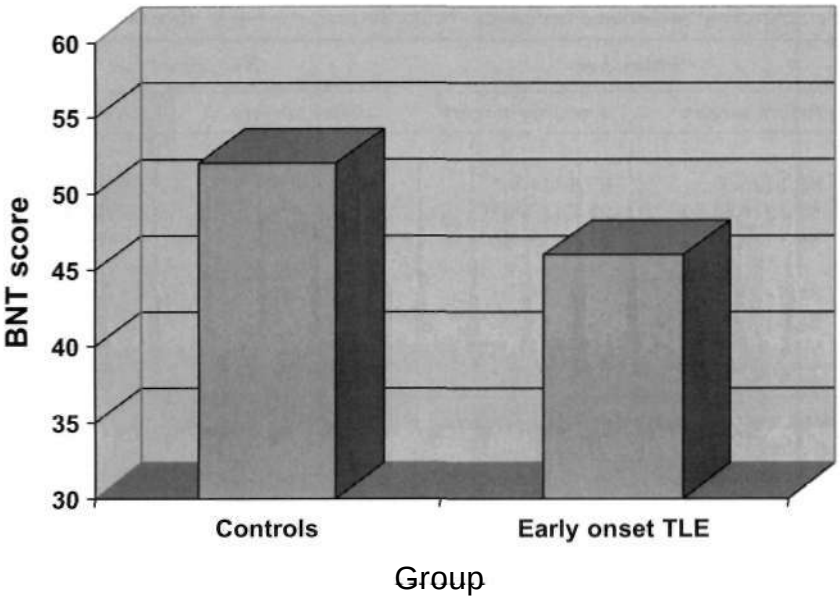


FIGURE 38.14 Boston Naming Test (BNT) results by group (temporal lobe epilepsy [TLF.| versus normal controls). (Adapted from Bell, B. D., Hermann, B. P., Woodard, A. R. 1997, "Object naming and semantic knowledge in temporal lobe epilepsy," *Neuropsychology,* vol. 15, pp. 434-443.)

epilepsy had deficits with planning and executive functions with intact verbal and nonverbal memory, whereas the children with TLE showed the opposite pattern. Another study examined children with TLE, frontal lobe epilepsy, and generalized epilepsy (Hernandez et al. 2002). Findings indicated that children with frontal lobe epilepsy had deficits in planning and impulse control and more coordination problems and motor rigidity than children in the other groups.

A complicating issue in identifying cognitive deficits associated with epilepsy is the fact that the main treatment approaches, including anticonvulsant medications and neurosurgery for intractable seizures, commonly have additional, independent effects on neuropsychological functioning. Therefore treatment must balance seizure relief with adverse side effects of the treatment.

Many patients with epilepsy remain on antiepileptic medication for years. Awareness of the potentially harmful effects of anticonvulsant medications on cognitive functioning is increasing. Many of the older anticonvulsants have been associated with adverse effects on cognition, although their specific patterns of impairments may vary. Reviews of the literature suggest that antiepileptic drugs can decrease performance on tests of motor speed, attention, memory, perceptual functions, and motor coordination. Antiepileptics can also affect cognition by increasing drowsiness and dizziness. However, there is some suggestion in the literature that newer antiepileptic medications such as oxcarbazepinc and vigabatrin have less of an impact on cognitive functioning than older drugs, although this has not been comprehensively studied (see Brunbech and Sabers 2002 for a review). Historically, several methodological problems including selection factors, statistical problems, and inappropriate use of cognitive tests complicate the research. However, it is clear that the consideration of potential side effects of antiepileptic medication is important in treatmenr and that further research as new medications arc developed will be valuable.

The surgical resection of epileptogenic brain tissue can be an effective treatment for inrractable epilepsy; however, preoperative localization of the seizure origin and assessment of cognitive abilities are essential to minimize the adverse consequences that can be associated with the surgery. Surgical resection typically is performed to treat TLE that is resistant to pharmacotherapy and is used less commonly for intractable frontal lobe epilepsy. Neuropsychological evaluation provides important information about localization of seizure onset, lateralization of important cognitive functions, and the risks of surgery to essential psychological functions such as language and memory. Neuropsychological assessment also provides information about psychosocial and cognitive changes after surgery.

The most common neuropsychological finding after surgical resection is a decline in verbal memory after dominant temporal lobe resection and deficits in visual memory after nondominant temporal lobe resection. However, some research suggests that the neuropsychological performance of many patients improves after surgical treatment for TLE. Postoperative improvement appears to be influenced by the reduction in the frequency of seizures after surgery (Wachi et al. 2001; Table 38.14). Engman et al. (2001) found significant variability between individuals in their postoperative cognitive change. The authors point to the importance of considering interindividual and ultraindividual variability. Several factors have been shown to be associated with favorable postoperative outcomes, including interictal electroencephalographic localization to the operated lobe and the absence of secondarily generalized seizures.

Table 38.14: Neuropsychological results of seizure-free and not-seizure-free groups before surgery and 1 year after surgery

	Seizure free		*Not seizure free*	
Test	*Before surgery*	*1 yr after surgery*	*Before surgery*	*1 yr after surgery*
Wechsler Adult Intelligence Scale-Revised				
Verbal IQ	86.1 (15.3)	87.8 (14.8)*	83.4 (10.9)	82.8 (13.3)
Performance IQ	89.2(16.8)	98.7(17.8)**	88.6(14.9)	89.7(18.0)
Full-Scale IQ	86.3(15.9)	91.4(15.4)**	84.1(12.5)	84.1(16.2)
Wechsler Memory Scale-Revised				
Verbal	81.4 (14.7)	91.3 (14.9)**	80.4 (17.3)	88.4 (20.6)
General	88.6 (16.3)	96.1 (18.2)**	85.9 (11.2)	92.0(18.0)
Delayed Paired Associates	90.6 (17.7)	103.7 (17.7)**	89.9 (11.0)	97.7 (18.3)
Raven Progressive Matrices	32.6(3.7)	34.3(2.3)**	32.8(2.4)	34.2 (1.9)[1]

Note: Values represent the means with the standard deviation indicated in parentheses.
*$p < 0.05$, **$p < 0,01$ compared with presurgical scores.
Source: Adapred from Wachi, M., Tomikawa, M., et al. 2002, "Neuropsychological changes after surgical treatment for temporal lobe epilepsy," *Epilepsia,* vol. 42, suppl. 6, pp. 4-8.

Human Immunodeficiency Virus

Overall estimates of the number of people infected with human immunodeficiency virus (HIV) who experience neurocognitive complications of infection range from approximately 30% to 50%. Neuropsychological impairment in HIV-infected patients can be classified into three subgroups (Grant et al. 1999). Patients with subsyndromic neuropsychological impairment show deficits in at least two neuropsychological domains with no evidence of functional impairment. A second ncurobehavioral disorder in HIV has been called mild neurocognitive disorder or minor cognitive/motor disorder and involves deficits in at least two ability domains, confirmed by neuropsychological testing, and impairment sufficient to affect the patient's daily functioning. The most severe neurocognitive manifestation of infection is HIV-1-associated dementia, which is characterized by moderate to severe cognitive and psychomotor slowing, impaired concentration and attention, memory disturbances, and often motor incoordination and weakness.

The neuropsychological profile of patients with HIV, particularly in the later stages of the disease, has been associated with the deficits seen in subcortical dementias (e.g., Huntington's disease), including slowed information processing, reduced fluency, impaired motor skills, and impaired free recall of recently learned information. Indeed, there is evidence that the greatest brain abnormalities occur in subcortical structures and white matter regions. However, the neuropsychological deficits observed in HIV can vary greatly across individuals. Cognitive impairment can be associated with the direct effects of HIV infection or secondary complications, including those resulting from immunodeficiency (e.g., opportunistic infections) and the treatment of the disease.

Although the majority of studies provide evidence of neuropsychological impairments in a subset of patients in the later stages of HIV infection, the prevalence of cognitive symptoms early in the course of HIV infection is more controversial. A meta-analysis of 41 studies examining the neuropsychological sequelae of HIV infection found that cognitive deficits in the early stages of HIV are small and increase in the later phases of the illness (Reger et al. 2002). Overall, the authors concluded that the cognitive decline with disease progression resembled a subcortical pattern; the greatest declines were in motor functioning, executive skills, and information-processing speed.

A literature review of 57 articles on neuropsychological functioning in asymptomatic HIV-infected patients points to inconsistencies in the literature (White et al. 1995). Thirty-two percent of the studies reported increased neuropsychological impairment in HIV-positive subjects, 21% had equivocal results, and 47% found no significant differences in neuropsychological functioning between HIV-infected subjects and seronegative controls. Interestingly, the authors of the review article found that the comprehensiveness of the neuropsychological battery used in the studies was strongly associated with the likelihood of finding group differences, underscoring the importance of a comprehensive assessment approach. The domains of neuropsychological functioning that were most often impaired were attention and speed of information processing, learning, verbal abilities, and motor functioning.

Researchers at the San Diego HIV Neurobehavioral Research Center (HNRC) have been longitudinally assessing the neurocognitive functioning of over 500 HIV-positive men. Findings ftom this group suggest that asymptomatic HIV-positive men have twice the rate of neuropsychological impairment of HIV-negative control subjects and that cognitive impairment increases with disease progression (Figure 38.15). Neuropsychological impairment was found to be more prevalent in later stages of infection, and when it occurred, it affected more cognitive domains than in the asymptomatic stage. Additional research from the HNRC group suggests that

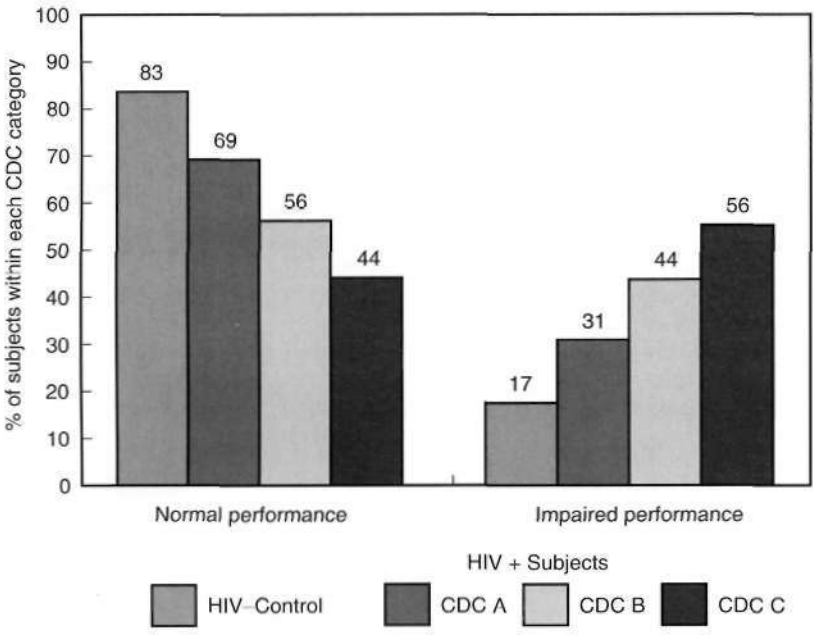


FIGURE 38.15 Clinical rating scores for patients with human immunodeficiency virus (HIV) grouped according to U.S. Centers for Disease Control (CDC) category. Categories **A**, **B**, and **C** refer to clinical levels of HIV infection: asymptomatic, minor symptoms, and AIDS-defining conditions, respectively. (From Kelly, M. D., Grant, I., Heaton, R. K., et al. 1996, "Neuropsychological findings in HIV infection and AIDS," in *Neuropsychological Assessment of Neuropsychiatric Disorders*, eds Grant and Adams, Oxford University Press, New York.)

attention and learning arc the areas impaired in the greatest proportion of HIV-positive men, a finding that is consistent with previous research (Figure 38.16).

Traumatic Brain Injury

Traumatic brain injury (TBI) is one of the most common forms of acquired neurological damage in the United States, particularly in young adults. Cognitive deficits after injury are common. In cases of moderate to severe injury, where head trauma is sufficient to cause loss of consciousness and post-traumatic amnesia, impairment in several cognitive domains including attention, memory, communication skills, and executive functioning may occur. Although more controversial, in some cases mild head injury can also produce alterations in cognitive status (see van der Naalt 2001 for a review of recovery after mild to moderate TBI).

The psychological consequences of injury depend on how the injury occurred, the severity of the injury, the site of the lesion, premorbid personality, and the treatment received after the injury. Therefore the range of deficits that can result from brain injury vary significantly. Brain damage after trauma may involves penetrating or closed injuries, and consequences of both the primary injury and secondary effects influence the clinical presentation. The fact that

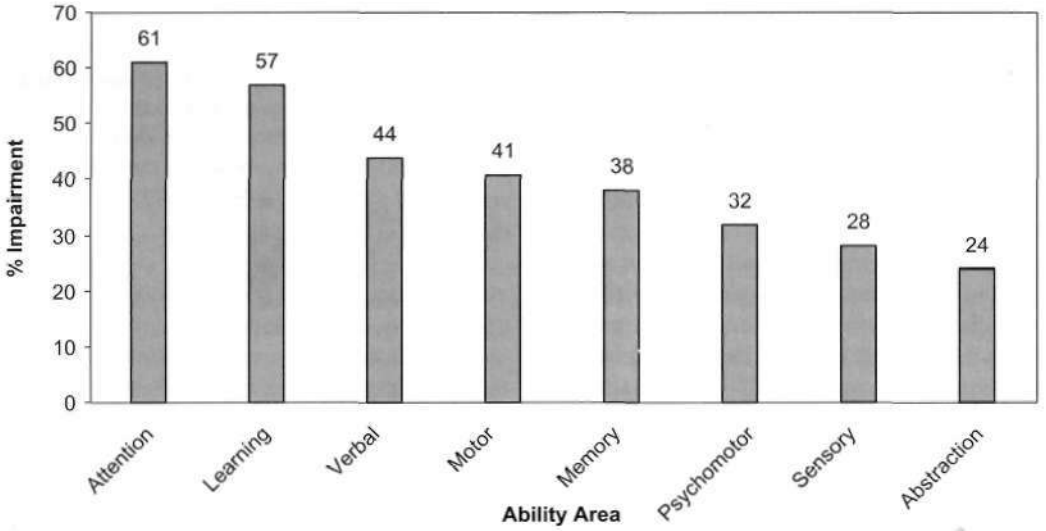


FIGURE 38.16 Prevalence of deficits in each ability area for human immunodeficiency virus–positive subjects rated as neuropsychologically impaired. (Adapted from Heaton, R. K., Grant, I., Butters, N., et al. 1995, "The HNRC 500: Neuropsychology of HIV infection at different disease stages," *J Int Neuropsychol Soc*, vol. 1, pp. 231-251.)

Table 38.15: Common neurocognitive sequelae of moderate to severe traumatic brain injury

Cognitive domain	*Clinical manifestation of the impairment*
Attention	Difficulty with sustained attention
	Poor concentration
	Psychomotor impersistence
Memory	Problems with acquiring and retaining new verbal or nonverbal information
	Problems in retrieving verbal and nonverbal memories
Speed of information processing	Slowed sensorimotor skills and information processing
Executive functioning	Problems in convergent and divergent reasoning
	Poor judgment
	Difficulty planning
	Problems in self-monitoring and self-correcting behavior
Awareness of symptoms	Difficulty recognizing deficits
	Unrealistic expectations concerning the recovery of functions
	Problems related to poor treatment compliance
Language and communication	Problems in word comprehension
	Impaired reading, spelling, and writing ability
	Tendency to become fragmented in free speech
Impaired integrative functions	Problems in adequate or time efficient execution of various pcrccptual-motor-spatial-sequential tasks

brain injury often involves both focal injuries to the brain and diffuse damage (e.g., shearing effects and edema} contributes to variability in the presentation of cognitive impairment.

Despite individual clinical variability, several common neurobehavioral sequelae of moderate to severe TBI can be identified (Table 38.15).

For example, damage to the orbital and polar aspects of the frontal lobe and the temporal poles is likely to result from head trauma given the anatomy of the skull (e.g., orbital plate of the frontal bone and sphenoidal ridge). These injuries can be associated with executive dysfunction and memory deficits.

Immediately after injury, patients may experience loss of consciousness and post-traumatic amnesia. Early recovery is characterized by resumption of basic attentional processes and a return of speech. Patients may go through a period nt confusion during which they confabulate and tail to retrieve new, and often remote, memories. Although attention gradually improves, mental slowness with decreased information-processing speed often persists. Patients may complain of confusion, inability to think clearly, and disorientation. They tend to be distractiblc and unable to maintain focused attention.

After the acute confusional state and post-traumatic amnesia ends, the most common cognitive deficits that persist include disturbances of memory, attention, language, and executive dysfunction. Memory disturbance is one of the most common complaints of patients after TBI and is related to the severity of TBI and the diffuse nature of the injuty. Patients may show problems with acquisition and retention of new verbal and nonverbal information and problems with retrieval. Retrograde memory deficits, for events occurring before the injury, often show a memory gradient so that the most temporally proximate events are the most likely to be forgotten.

After frontal lobe damage, deficits in judgment, planning, organizing and sequencing, concept formation, set shifting, self-monitoring, and self-correcting behavior may occur. The sequelae of moderate to severe traumatic brain injury can also include disturbances in the balance between excitatory and inhibitory processes including impulse control problems, reduced stamina or energy levels, and lowered tolerance for frustration and irritability. Inadequate awareness of deficits may be present such that the patient has difficulty assessing the severity of his or her deficirs, sometimes leading to unrealistic expectations for recovery and poor treatment compliance.

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Chapter 39
Neuro-Ophthalmology: Ocular Motor System

Patrick J. M. Lavin and Sean P. Donahue

Neuro-ophthalmology bridges the disciplines of ophthalmology and neurology. Despite sophisticated technological advances in neuroimaging, competence in neuro-ophthalmological diagnosis still requires basic clinical skills. These include attentive listening; timely, probing questions; knowledge of neuroanatomy and of disorders that affect the afferent and efferent visual pathways; skill in examination of the visual system and the cranial nerves; and experience and expertise in evaluating supplementary investigations, including perimetry, fluorescein angiography, and neuroimaging. Often, a thorough clinical examination and careful thought preempt uncomfortable, invasive, and expensive procedures. The old adage "ears and eyes first and most, hands least and last," still holds true.

This chapter discusses central control mechanisms and disorders of the ocular motor system. Diplopia, nystagmus, and other ocular oscillations are discussed in Chapter 16, and disorders of the ocular motor nerves are discussed in Chapter *76.*

GENERATION AND CONTROL OF EYE MOVEMENTS

A reasonable understanding and interpretation of gaze disorders require an appreciation of the anatomy and physiology of eye movement control. In the words of Hughlmgs Jackson, "The study of the cause of things must be preceded by the study of things caused."

Normal visual behavior is accomplished by a continuous cycle of visual fixation and visual analysis interrupted by saccades (Schall and Thompson 1999). Individuals with intact sensory visual systems (optical and afferent) are capable of discerning small details, comparable to Snellen acuity of 20/13, provided the fovea is maintained on target. However, 10 degrees from fixation, the resolving power of the retina drops to 20/200. Although the peripheral retina has poor spatial resolution capabilities, it is exquisitely sensitive to movement (temporal resolution). The image of an object entering the peripheral visual field stimulates the retina to signal the ocular motor system to make a rapid eye movement (saccade) and fixate it on the fovea: In the words of the American psychologist, William James "The peripheral retina is like a sentinel and when an object of regard falls upon it, it shouts 'hark, who goes there' and calls the fovea to the spot," Visual information concerning spatial resolution (fine detail) and color travels via retinal ganglion (P) cells to the parvocellular layers of the lateral geniculate nucleus (LGN), whereas information concerning temporal resolution (movement) travels via retinal ganglion (M) cells to the magnocellular layer of the LGN. In turn, neurons in the LGN project via the optic radiations to the primary visual area (VI), the striate cortex (area 17). Visual processing in the cortex begins in the primary visual area from which issues two processing streams (Figure 39.1A). One stream (ventral), responsible for form and object recognition and emphasizing foveal representation, projects to the temporal lobe via occipital areas V2 and V4. The second stream (dorsal), responsible for movement recognition, guiding actions in space, and emphasizing peripheral visual field representation, projects to the prestriate cortex. It then relays to the superior temporal sulcus region, which contains cortical areas MT (middle temporal) and MST (middle superior temporal) in monkeys, roughly equivalent

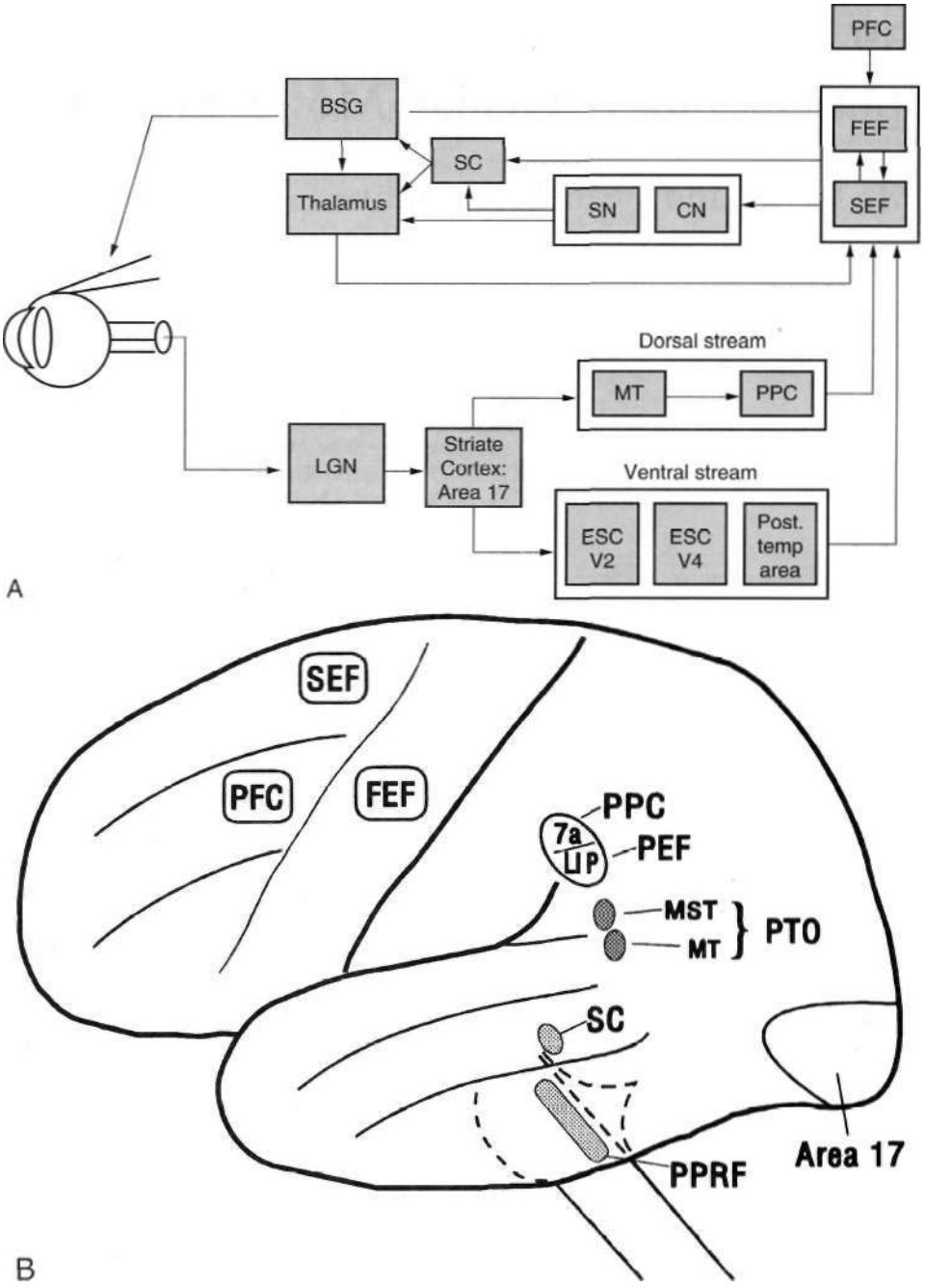

FIGURE 39.1 (A) Overview of the visuo-ocular motor system, (Redrawn from Sruphorn and Schall 2002.) (B) Areas in the human brain that are believed to be important in generating saccades and pursuit. BSG = brainstem saccadic generator; CN = caudate nucleus; ESC = extra striate cortex; FFF = frontal eye field; LGN = lateral geniculate nucleus; IJP = lateral intraparietal area; MST —medial superior temporal visual area; MT = middle temporal visual area; PEF = parietal eye field; PFC = prefrontal cortex; PPC = posterior parietal cortex area; PPRF = paramedian pontine reticular formation; PTO = pa rie to-tempore-occipital junction; SC = superior colliculus; SEF = supplementary eye fields in the supplementary motor area; 7a = area 7a; SN = substantia nigra.

to the parieto-temporo-occipital junction (PTO) in humans, and encodes for location, direction, and velocity of objects. Both streams converge on the FEF (frontal eye field) and are involved in controlling saccades (see later).

The prcmotor substrates for conjugate gaze and vergence eye movements are in the brainstem. The substrates specific for vertical gaze, vergence, and ocular counter-rolling are in the mesodiencephalic region, whereas those for horizontal eye movements are mainly in the pons. The mechanisms for horizontal eye movements are better understood than those for vertical eye movements and are based on clinicoparhological and radiological correlation as well as animal and bioengi nee ring experiments. With the exception of reflexive movements, such as the

vestibulo-ocular reflex (VOR) and fast phases of nystagmus, cerebral structures determine *when* and *where* the eyes move, whereas brainstem mechanisms determine *how* they move: in other words, voluntary eye movements are generated in the brainstem, but are triggered by the cerebral cortex.

Ocular Motor Subsystems

Six ocular motor subsystems enable the fovea to find and fixate a target, stabilize an image of the target on each retina, and maintain binocular foveation during head or target movement, or both. The saccadic system moves the eyes rapidly (up to 800 degrees per second) to fixate new targets (Figure 39.2A). Saccades may be generated voluntarily or in response to verbal commands in the absence of a visible target. Reflex saccades may occur in response to peripheral retinal stimuli, such as visual threat or retinal error signals, or to sound. Saccades are also the fast components of nystagmus.

The pursuit system enables the eyes to track slowly moving targets (up ro 70 degrees per second) to maintain the image stable on the fovea. Specially trained subjects are capable of smooth pursuit eye movements as fast as 100 degrees per second. Pursuit eye movements are limited more by the target's acceleration than by its velocity. If the target moves too quickly or abruptly changes direction, or if the pursuit system is impaired, the eyes are unable to maintain pace with the target and fall behind. Consequently, the image moves off the fovea, producing a retinal error signal that provokes the saccadic system to make a catch-up saccade to refixate the target. The cycle then repeats itself, resulting in saccadic ("cogwheel") pursuit (see Figure 39.2B).

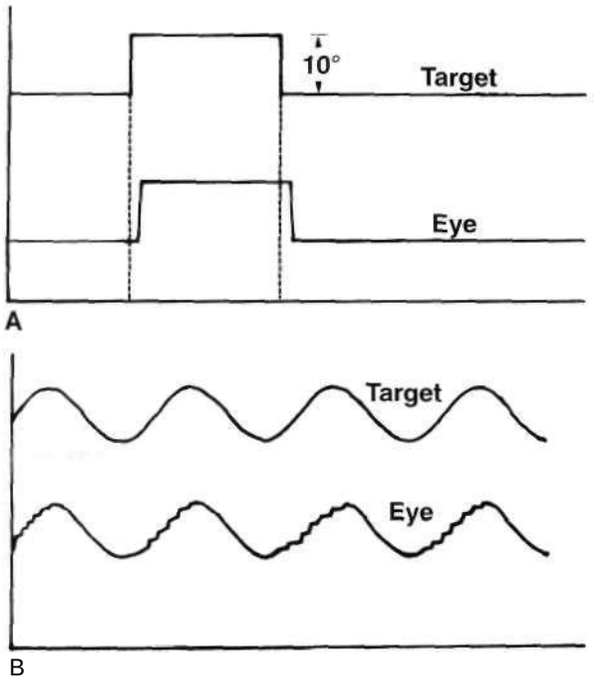

FIGURE 39.2 Simulated eye movement recordings, By convention for horizontal movements, upward deflections represent rightward eye movements, and downward deflections represent leftward eye movements. (A) Saccades. A target moves rapidly 10 degrees to the right. After a latency of about 200 ms, the eye follows. When the target returns to the center, the sequence is repeated in the opposite direction. (B) Pursuit. The target moves in a sinusoidal pattern in front of the patient. The eye follows the target after a latency of about 120 ms, but pursuit movements to the right are defective, resulting in the rightward "cogwheel" (saccadic) pursuit. Pursuit to the left is normal.

Bidircctionally defective pursuit eye movements, a normal finding in infants, are nonspecific and occur under conditions of stress or fatigue, or with sedative medication. Impaired tracking in one direction, however, suggests a structural lesion of the ipsi lateral pursuit system (see Figure 39.2B).

Fixation allows the eyes to maintain an image of a stationary target on each fovea at rest. The fixation subsystem shares neural circuitry with the optokinetic (OKN) and pursuit systems (Leigh and Zee 1999).

The vestibular eye movement subsystem maintains a stable image on the retina during head movements. The semicircular canals respond to rotational acceleration of the head by driving the VOR to maintain the eyes in the same direction in space during head movements. The otoliths (utricle and saccule} are gravity receptors that respond to linear acceleration and static head tilt (gravity), that is, with ocular counter-rolling. The vestibular system is discussed further in Chapter 41.

The optokinetic system uses visual reference points in the environment to maintain orientation. It complements the vestibulo-ocular system, which becomes less responsive during slow or sustained head movements, to stabilize images on the retina in situations such as spinning. When the eyes reach their limit of movement in the orbits, a reflex saccade allows refixation to a point further forward in the direction of bead rotation. The sequence repeats itself, resulting in OKN (see Chapter 16).

In humans, the optokinetic system responds predominantly to fixation and pursuit of a moving target (immediate component), and to a lesser extent velocity storage (delayed component), which involves neural circuitry in the vestibular system. (Velocity storage is a mechanism by which the central nervous system, predominantly the vestibular system including the vestibulo-eerebellum, prolongs or perseverates short signals generated by the vestibular end-organ to enhance orientation in space. Velocity storage is largely involuntary.)

The vergence system enables the eyes to move disconjugarely (converge and diverge) in the horizontal plane to maintain binocular fixation on a rarget moving toward or away from the Subject. Vergence movements are essential for binocular single vision and stereoscopic depth perception.

The different types of eye movements are listed in Table 39.1.

Horizontal Eye Movements

When gaze is redirected from one point to another, a saccade moves the eyes conjugatcly. To enable the small, strap-like extraocular muscles to move the relatively large globes and overcome the elastic recoil of the viscous orbital contents, the yoked agonist muscles require a surge or hurst of innervation (pulse) at the same time their yoked antagonists are reciprocally inhibited (Figure 39.3A). For a leftward saccade, rhe left lateral rectus and the right medial rectus muscles each receive a pulse of innervation while their antagonists, the left medial and right lateral rectus muscles, are reciprocally inhibited. Excitatory burst neurons (EBNs) contained in the ipsilateral paramedian pontine reticular formation (PPRF), just rostral to the abducens nucleus, generate the pulse to initiate the saccade. The EBNs are medium- lead hurst cells that discharge about 10 ms before, and during, all horizontal saccadic eye movements; they preferentially discharge for ipsilateral saccades and create the immediate premotor command generating pulse activity for saccades.

About half the neurons in the abducens nucleus are interneurons (with different morphological and pharmacological features than the neurons of the abducens nerve) that relay, via the medial longitudinal fasciculus

Tabic 39.1: Types of eye movements

A. Saccades (moving eyes from one target to another)
- Intentional saccades (internally triggered, with a goal)
  - Visually guided saccades
  - Memory-guided saccades (with visual/vestibular input)
  - Predictive saccades
  - Target-searching saccades
  - Antisaccades"'
- Reflexive saccades (externally triggered)
  - Visually guided saccades
  - Auditory saccades
- Spontaneous saccades (internally triggered, without a goal)
  - During another motor activity
  - At rest
  - When sleeping
- Quick phases of nystagmus
  - Physiological nystagmus
    - Vestibular nystagmus
    - Optokinetic nystagmus
  - End-point nystagmus
  - Pathological nystagmus (see Chapter 16)

B. Eye movements stabilizing the image of the target on the fovea
- Smooth pursuit
  - Eoveal pursuit
  - Full-Held pursuit (slow phase of optokinetic nystagmus)
- Vesti bu I o-ocular reflex (horizontal, vertical, torsional)
- Convergence

C. Ocular oscillations that may interfere with vision
- Double saccadic pulses
- Macrosaccadic oscillations
- Ocular bobbing
- Ocular dysmetria
  - Ocular hypometria
  - Ocular by per m err ia
  - Ocular lateropnlsioii
  - Ocular torsi pulsion
- Ocular flutter
- Ocular neuromyotonia
- Ocular tics (myoclonic jerks)
- Oculogyric crisis
- Opsoclonus
- Saccadic pulses
- Square wave pulses (previously designated macrosquare wave jerks)
- Square wave jerks
- Superior oblique myokymia
- Torsional saccades (blips)

* Antisaccades are fast eye movements deliberately made away from a new target. It is a laboratory procedure used to investigate frontal lobe or cognitive function.

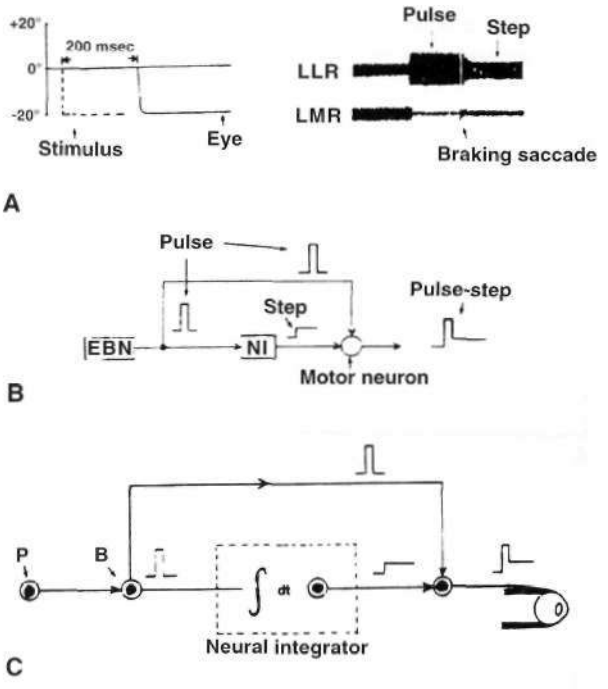

FIGURE 39,3 Ocular motor events on gaze left. (A) After the appearance of a stimulus 20 degrees to the left of fixation (-20 degrees), the eyes move to the target with a saccade after a latency of 200 ms. Idealized electromyography of the left extraocular muscles shows the activity of the agonist (the left lateral rectus [LLR|), and the antagonist (the left medial rectus |I.MR] muscles). (B) The pulse originates in the excitatory burst neurons (EBNs) and is mathematically integrated by the neural integrator (NI); both signals are added to produce the pulse-step of the innervation to the ocular motor neurons. (C) The pause cells (P) discharge continuously, suppressing the hurst cells (B), except during a saccade, when they "pause," allowing the burst cells to discharge and generate a pulse. (Reprinted with permission from P. j. M. Lavin. 1985, "Conjugate and disconjugate eye movements," in *Neitro-opbthaimofoxy: Clinical signs and symptoms,* ed T. J. Walsh, Lea &c Febiger, Philadelphia.)

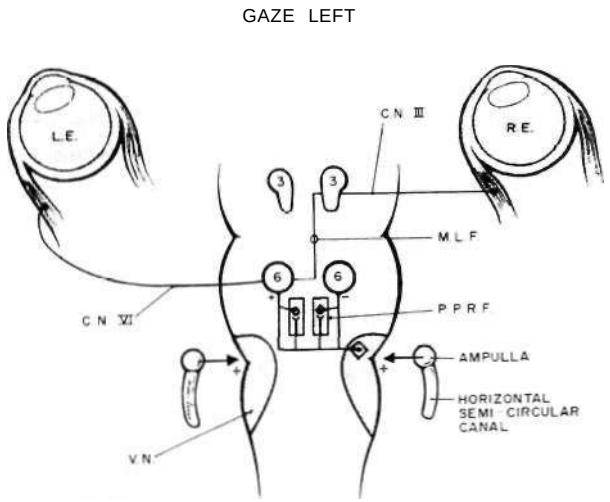

FIGURE 39.4 A lateral head turn induces movement of the cndolymph, in the ipsilatcral horizontal semicircular canal, toward the ampulla (as would warm water caloric stimulation of an ear), and thus excites the contralateral abducens nucleus and inhibits the ipsilateral abducens nucleus via the vestibular nuclei (VN). Each abducens nucleus innervates the ipsilateral lateral rectus muscle via the abducens nerve and the contralateral medial rectus muscle via the abducens nucleus inremeurons, the medial longitudinal fasciculus (MLF), and the neurons for the medial rectus (part of cranial nerve [CN] ill nucleus). Neurons in each paramedian pontine reticular formation (PPRF) also have an excitatory input to the ipsilateral abducens nucleus and an inhibitory input to the contralateral abducens nucleus, for saccades and quick phases of nystagmus, (LE = left eye; RE = right eye. (Adapted from Lavin, P. J. M. 1985, "Conjugate and disconjugate eye movements," in *Neuro-opbtbalmvlogy; Clinical signs and symptoms,* cd T. j. Walsh, Lea *Sc* Febiger, Philadelphia.)

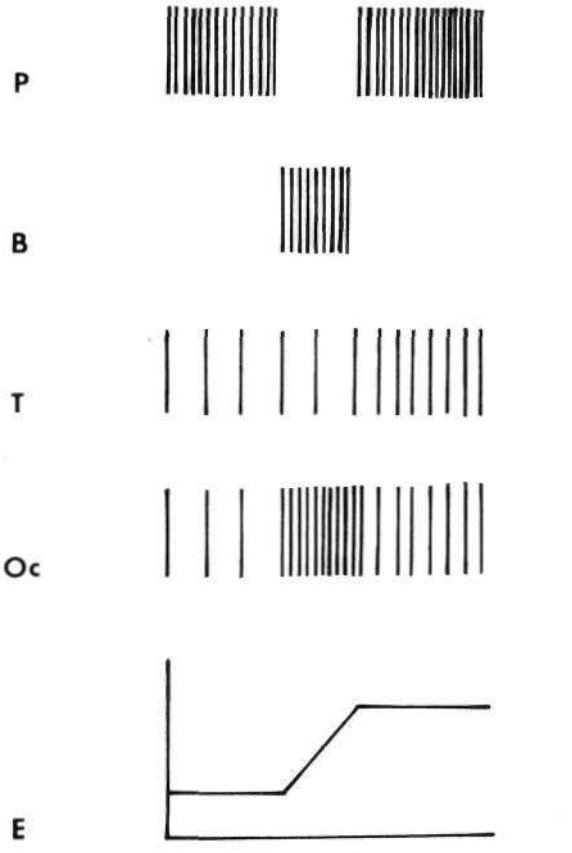

FIGURE 39.5 Electrophysiological events during an eye movement. P represents an intraneuronal recording from a pause cell and demonstrates a constant discharge, which ceases, allowing an excitatory burst neuron (iJ) to discharge during pulse. T represents the discharge in a tonic neuron, which increases after the pulse as a result of integration of the pulse to a step. Both the pulse *[P)* and the tonic output (T) of burst-tonic neurons inncrvare the ocularmoror neurons *(Oc).* The rcsuir is a rapid contraction of the extraocular muscle, which moves the eye from primary position and holds it in an eccentric position (£).

(MLF), to the contralateral medial rectus neurons in the oculomotor nuclear complex (Figure 39.4). The KBNs are tonically suppressed, except just before and during a saccade, by pause cells located in the nucleus raphe inter - positus rostral to the abducens nucleus. Thus the pause cells, which receive input ftom the cerebrum, cerebellum, and superior colliculus (SC), mediate the command for a saccade when they cease discharging and allow the burst cells to fire (Figure 39.5). At the same time the EBNs discharge, a group of inhibitory cell-burst neurons that lie caudal to the abducens nucleus in the medial rostral medulla and project across the midline to the contralateral abducens nucleus, discharge during the saccade to reciprocally inhibit the yoked antagonist muscles (Leigh and Zee 1999).

To maintain the eyes on target in an eccentric position at the end of a saccade, the agonist muscles for a leftward movement (left lateral and right medial recti) now require a new level of tonic innervation—a position command—achieved by a gtoup of neurons referred to as the *neural integrator* (NI). (An integrator converts phasic input to tonic output, mathematically, by using reverberating collateral circuits to rc-excite neurons. The efficiency of an integrator depends on its time constant, that is, the duration it can prolong the activity of the input. The effective time constant is the period necessary for the output to decay to 37% of its initial value after the input signal stops.)

The NI for horizontal gaze, thought to be partly in the rostral perihypoglossal nuclear complex and the adjacent rostral medial vestibular nucleus {Leigh and Zee 1999), receives the velocity command signal (pulse) from the EBNs. The NI then mathematically integrates the pulse to a "tonic" position command (step) before relaying it to the ipsilateral abducens nucleus (see Figures 39.3B and 39,4).

The cerebellum and the PPRF maintain the output of this NI by controlling the gain, via a positive feedback loop, to keep the eyes on target (Figure 39.6). The gain of a system is the ratio of its output to its input. In this case, the output is the innervation required to maintain eccentric fixation, and the input is the pulse signal (see Figure 39.3C). If the NI is unable to maintain the gain at unity (output/input = 1),

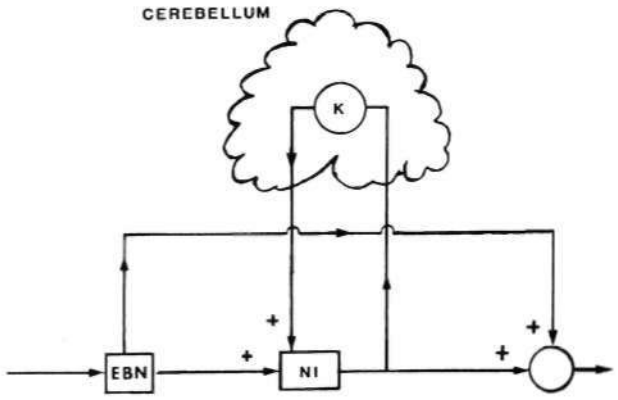

FIGURE 39.6 The time constant of the brainstem neural integrator (Nf), and therefore the fidelity of its output (innervation for gaze holding), is controlled predominantly by the cerebellum. Dysfunction of the gain control *(K)* may cause the integrator output to fall (a shortened time constant causes the signal to decay), allowing the eyes to drift back toward primary position. Conversely, an increase in K may result in an unstable integrator and Cause the eye to drift eccentrically with an increasing velocity waveform. EBN = excitatory burst neuron. (Adapted from Lavin, P.J. M. 1985, "Conjugate and disconjugate eye movements," in *Neuro-ophtbalmology: Clinical signs and symptoms,* eds T. J. Walsh, Lea *&c* Fchigcr, Philadelphia. Reprinted by permission of the author and the publisher.)

the output falls, causing the eyes to drift off target toward primary position. A corrective saccade then refixates the target, resulting in gaze-evoked (gaze-paretic) nystagmus (see Chapter 16). Current evidence suggests that all conjugate eye-movement commands, including saccades, pursuit, the slow phases of OKN, and the VOR, are initiated as velocity commands and mediated by a final common integrator (Figure 39.7),

Although its anatomical borders are not clear, the PPRF is defined functionally with the medial aspects of the nuclei gigantoeellularis, or pontis centralis oralis and caudalis, and is located just ventral and lateral to the MLF, extending from the level of the abducens nucleus almost to the trochlear nucleus. The PPRF innervates the ipsilateral abducens nucleus, the rostral medulla (part of the NI),

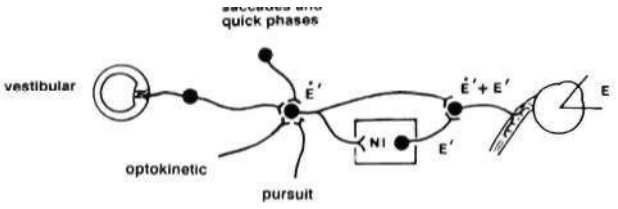

FIGURE 39.7 The final common integrator hypothesis. All conjugate eye movements (£) are initiated as eye, velocity commands (£') that are converted to eye position *(E)* by the neural integrator (N/). Both eye velocity and eye position commands arc relayed to the motor neurons, (Adapted from Cannon, S. C. & Zee, D. S. 1988, "The neural integrator of the oculomotor system," in *Current Neuro-ophthalmalogy,* eds S. Lessell & J. T W. van Dalen, Year Book, Chicago.)

and the midbrain reticular formation (MRF) to coordinate horizontal and vertical eye movements. The PPRF receives direct input from the medial vestibular nucleus, the contralateral frontal eye fields (FEFs), the ipsilateral posterior parietal region, the SC, and the cerebellum.

A lesion of the abducens nucleus produces paralysis of all ipsilateral versional eye movements. Pontine lesions outside the abducens nucleus may selectively involve certain classes of eye movements while sparing others, demonstrating that the neural signals encoding subclasses of eye movements (e.g., saccades, pursuit, VOR, tonic position) project independently to the abducens nucleus (Halmagyi 1994). The PPRF also plays a role in generating vertical eye movements; acute bilateral injury may cause a transient vertical and horizontal gaze palsy. A unilateral lesion, in addition to impairing ipsilateral horizontal saccades, may also cause slowing and oblique misdirection of vertical saccades away from the side of injury (Johnston et al. 1993). With rare exceptions (Miller et al. 2002), lesions of the abducens nucleus that cause an acquired ipsilateral gaze palsy almost always involve the facia! nerve fasciculus as it loops around the abducens nucleus, and result in an associated facial nerve palsy.

The vestibular system stabilizes the direction of gaze during head movements by virtue of changes in its tonic input to the ocular motor nuclei. This is most clearly illustrated by the horizontal VOR (see Figure 39.4). Each horizontal semicircular canal innervates the ipsilateral medial vestibular nucleus to inhibit the ipsilateral and excite the contralateral abducens nucleus. The ampulla of the right horizontal semicircular canal is stimulated by turning the head to the right (or warm caloric stimulation). This mechanical information is transduced by the vestibular end organ to electrical signals and transmitted to the ipsilateral vestibular nucleus. Excitatory information is then relayed to the contralateral abducens nucleus, and inhibitory information to the ipsilateral abducens nucleus, causing the eyes to deviate in the direction opposite to head rotation, thus maintaining the direction of gaze.

Saccades (sec Tabic 39.1), or fast eye movements, are iniriated mainly in the contralateral frontal lobe and may be classified into four broad groups:

1. Internally triggered saccades, which are voluntary (intentional) and include target-searching, memory-guided, predictive (where the appearance of the target is anticipated), intentional visually guided saccades to an existing target in the peripheral visual field, and antisaccades.
2. Externally triggered saccades are reflexively activated by the appearance of a new target or a sound.
3. Spontaneous saccades, which occur in the absence of a target and are triggered internally, by both the FEF and the SC, to repetitively scan the environment; they occur at rest, during other motor activities, and during rapid-eye-movemenr sleep.

4. The quick phases of nystagmus (see Chapter 16).

A number of specialized areas in the cerebral cortex, identified by both experimental and pathologic lesions, and by neurophysiological studies, particularly in monkeys, and by transcranial magnetic stimulation, play a major role in controlling saccades (see Figure 39.IB):

1. The FEF, in the prcccntral gyrus and sulcus (Brodmann's area 6 in humans, and area 8 in monkeys).
2. The supplementary eye field (SEF) on rhe dorsomedial aspect of rhe superior frontal gyrus is anterior to the supplementary motor area.
3. The parietal eye field (PEF), in the lateral intraparietal area (LIP) in monkeys, is equivalent to an area in the intraparietal sulcus near the angular gyrus region (Brodmann's areas 39 and 40) in humans.

Other cortical areas that have a role in controlling saccades include the posterior parietal cortex (PPC), located in Brodmann's area 39 in the upper angular gyrus in humans, equivalent to 7a in monkeys; the prefrontal cortex (PFC), area 46; the vestibular cortex in the posterior aspect of the superior temporal gyrus; and the hippocampus in the medial temporal lobe (Pierrot-Dcscilligny et al. 1995). These cortical areas, and the superior colliculus, are parts of a network that collectively produce saccades and determine when different types of saccades occur and where they go; that is, they calculate their direction and amplitude (accuracy). In summary, this network determines where potential targets for orienting are located; where, whether, and when gaze will shift; and coordinates saccades with visually guided reaching and head movement-,.

The FEF is heavily interconnected, topographically, with areas in both the dorsal and ventral streams of the extrastriate visual cortex (see Figure 39.1A) and participates in the transformation of visual signals into saccadic motor commands (Schall et al. 1995). Being extensively connected with extrastriate visual cortical areas, many neurons in the FEF respond to visual stimuli. The FEF and SC are both activated in the same way at the same time in response to visual stimuli before and during saccades.

The FEF also plays a direct role in producing saccades. Low-intensity microstimulation of the FEF" elicits saccades; this direct influence is mediated by a subpopulation of neurons in FEF that discharge specifically before and during saccades. These neurons that trigger movement-related activity innervate the deeper layers of the SC and neural circuits in the brainstem that generate saccades.

The FEF projects to the SC mainly by three pathways: a direct pathway through the posterior aspect of the anterior limb of the internal capsule near the genu, an indirect pathway via the thalamus, and another indirect pathway via the caudate nucleus to neurons in the substantia nigra pars reticulata (SNr), These neurons in the SNr project, in turn, to the SC and tonically suppress saccades by a *y*-aminobutyric add (GABA)-ergic mechanism. Controlled d is inhibition of this basal ganglia system is important for normal visually and auditory-guided saccades and is probably essential for saccades to remembered targets (Stell and Bronstein 1994). Saccades of different amplitudes and directions are encoded in neurons in the FEF and SC in a retinotopic fashion (i.e., rhe size and direction of a saccade is determined by which neurons are stimulated). The SC also has some role in reflexive and orienting saccades. The basal ganglia are involved in sequencing complex memory-guided saccades and perhaps predictive saccades (Picrrot-Deseilligny et al. 1995).

The SEF parallels the FEF in several respects, and also innervates ocular motor centers in the SC and brainstem. However, the SEF seems to play a less essential or less potent role in saccade production, as ablation of SEF causes only minimal and short-lasting gaze impairment.

The role of the PEF (area LIP in monkeys) is uncertain. Although neural activity in the PEF precedes saccades, the PEF docs not directly control the initiation of saccades, but signals areas such ay the FEE and SC with the location of potential targets for orienting {Colby and Goldberg 1999; Snyder et al. 2000).

The SC has seven alternating fibrous and cellular layers that are broadly divided into a superficial sensory (dorsal) and a deep, predominantly motor (ventral) division. The superficial sensory division receives a direct orderly input from the retina via the accessory optic tract, bypassing the lateral geniculate body, such that the visual field may be mapped on the surface of the SC (retinotopic). Only about 10% of the retinal ganglion cells project to the SC, the remainder project to rhe lateral geniculate bod\ to subserve conscious vision. The deep motor division receives visual input from the striate cortex (area 17) and projects to motor areas in the subthalamic region and brainstem. The deeper division also receives input directly from the FEE and PPC and indirectly via the basal ganglia, as well as somatosensory and auditory input. Stimulation of the SC drives the eyes contralateral^ to a point in the visual field corresponding to the retinal projection lo that site. Thus the SC is essentially a sensory map overlying a corresponding motor map and represents the visual fields (Leigh and Zee 1999). The SC may also play a role in relaying excitatory information from part of the inferior parietal lobule (1PL), which has some influence in initiating saccades. Isolated lesions of the SC produce minimal, but specific, defects of saccades; when combined with experimental lesions of the FEFs; however, significant contralateral saccadic defects result. Purely vertical saccades require bilateral, simultaneous stimulation of corresponding points of the SC or of the FEFs.

Control of smooth pursuit eye movements is also complex (see Figure 39.1) but essentially consists of three components: sensory, motor, and attcntional-spatial. The stimulus for pursuit is movement of an image across the

fovea at velocities greater than 3-5 degrees per second. The sensory component includes the striate cortex (area 17), which receives information from the retinal ganglion (M) cells via the magnocellular layer of the lateral geniculate body (nucleus) and the optic radiations. The striate cortex projects to the prestriate cortex (parieto-occipital areas 18 and 19) and then to the superior temporal sulcus region, which contains cortical areas MT (middle temporal) and MST (middle superior temporal) in monkeys, equivalent to the pariero-temporo-occipital junction (PTO) in humans (Barton et al. 1995). This sensory subsystem encodes for location, direction, and velocity of objects moving in the contralateral visual field and is the major afferent input driving smooth pursuit; it projects bilaterally to the pursuit motor subsystem, which is also located in the PTO region, as well as to the FEF and SFF. This pursuit pathway is indirect and focuses attention on small moving targets. A direct pathway, bypassing the attentional-spatial subsystem, enables large, moving objects, such as full-field OKN stimuli, to generate smooth pursuit contralaterally even when the subject is inattentive. The SC also contributes to pursuit drive. The PTO projects via the internal sagittal stratum and the posterior limb of the internal capsule to the ipsilateral dorsolateral and lateral pontine nuclei (Gaymard et al. 1993). The pursuit pathways control ipsilateral tracking and so must either remain on the same side or undergo a double decussation at least once. In 1992, Johnston and coworkers suggested the pursuit pathways project from the pontine nuclei to the contralateral flocculus and medial vestibular nucleus and then back to the ipsilateral abducens nucleus (Figure 39.8).

Pursuit defects fall into four categories (Morrow and Sharpe 1993):

1, Retinotopic defects: Lesions of the geniculostriatc pathway cause impaired pursuit in both directions in the contralateral visual field defect. Defects also occur with lesions of areas MST or MT; these patients have apparently normal visual fields but selective "blindness" for motion.
2. Impaired pursuit, worse in the ipsilateral direction in both hemifields, occurs with lesions in the lateral aspect of area MST and the foveal representation of area MT in monkeys, similar to a focal PTO lesion in humans. Lesions in the FEFs, posterior thalamus, midbrain, ipsilateral pons, contralateral cerebellum, contralateral pontomedullary junction, and the ipsilateral abducens nucleus can also impair pursuit in both hemifields worse in the ipsilateral direction.

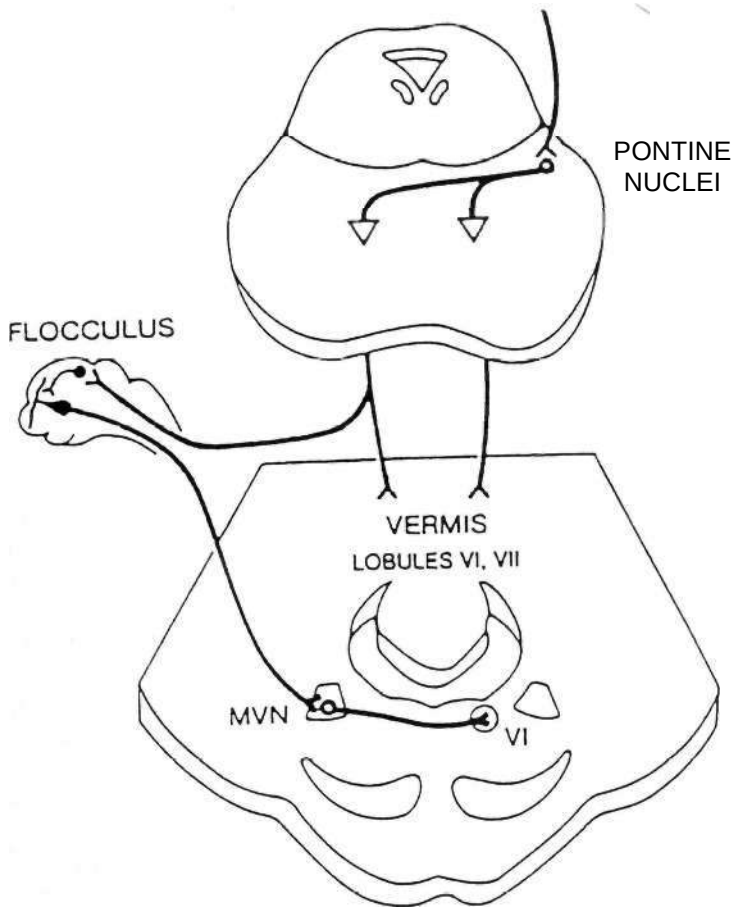

FIGURE 39.8 Postulated double decussation of pursuit pathways in the brainstem and cerebellum. The first decussation consists of excitatory mossy fiber projections from the pontine nuclei to granule cells, which excite basket cells and stellate cells in the contralateral cerebellar flocculus. The basket and stellate cells inhibit Purkinje cells, which in turn inhibit neurons in the medial vestibular nucleus (MVN). The second decussation consists of excitatory projections from the MVN to the opposite abducens nucleus (VI). (Reprinted with permission from Johnston, J. L., Sharpe, J. A., Et Morrow, M. J. 1992, "Paresis of contralateral smooth pursuit and normal vestibulat smooth eye movements after unilateral brainstem lesions," *Ann Neurol,* vol. 31, pp. 495-502.)

3. Symmetrically impaired pursuit in both horizontal directions occurs with focal lesions in the parieto-occipital region {area 39). Medication (e.g., anticonvulsants, sedatives, and psychotropic agents), alcohol, fatigue, inattention, schizophrenia, encephalopathy, a variety of neurodegenerative disorders, and age (infants and the elderly) also cause symmetrically impaired pursuit.
4. An acute nondominant (e.g., parietal or frontal) hemisphere lesion associated with a hemispatial neglect syndrome causes transient loss of pursuit beyond the midline into contralateral hemispace.

The cerebellum coordinates the ocular motor system to drive the eyes smoothly and accurately and is richly supplied by afferent fibers conveying ocular information (such as velocity, position, and neural integration) from the vestibular system, the afferent visual system, the PPRF, and the MRF. The dorsal vermis and fastigial nuclei determine the accuracy of saccades by modulating saccadic amplitude; they also adjust the innervation to each eye selectively to ensure precise conjugate movements. Lesions of the dorsal vermis and fastigial nuclei result in saccadic dysmctna (often, overshoot dysmetria that is greater centripetally) and macrosaccadic oscillations (see Chapter 16).

Selective cerebellar lesions have differential effects on eye movements. Bilateral lesions of the fastigial and globose (interpositus) nuclei cause hypermetria of externally triggered saccades but do not affect internally triggered saccades (Straube et al. 1995). Bilateral lesions of the posterior vermis (lobules VI and VII) cause hypomctric horizontal and vertical saccades and impaired pursuit. Unilateral lesions of the posterior vermis cause hypometric ipsilateral and hypermetric contralateral saccades, whereas unilateral lesions of the caudal fastigial nucleus cause hypermetric ipsilateral and hypometric contralateral saccades (Biittner and Straube 1995; Vahedi et al. 1995).

The flocculus, part of the vestibulocerebellum, is responsible for matching the saccadic pulse and step appropriately and for stabilizing images on the fovea. It adjusts the output of the NI and participates in long-term adaptive processing to ensure that eye movements remain appropriate to the stimulus. For example, the amplitude (gain) and even the direction of the slow phases of the VOR are adjusted by the flocculus. Lesions of the flocculus result in gaze-holding deficits, such as gaze-evoked, rebound, and downbeat nystagmus. Floccular lesions also impair smooth pursuit, cancellation (suppression) of the VOR by the pursuit system during combined head and eye tracking, and the ability to suppress nystagmus (and vertigo) by fixation. The nodulus, also part of the vestibulocerebellum, influences vestibular eye movements and vestibular optokinetic interaction. Lesions of the nodulus in monkeys and humans produce periodic alternating nystagmus (PAN).

Vergence Eye Movements

In humans and other animals capable of binocular fusional vision, dysconjugatc (vergence) eye movements are necessary to maintain ocular alignment on an approaching or retreating object (convergence and divergence, respectively). Electromyography demonstrates that divergence is an active movement, although not as dynamic or as much under voluntary control as convergence. The principal driving stimuli for vergence movements, relayed from the occipital cortex, are accommodative retinal blur (unfocused) and fusional disparity (diplopia). Each of these stimuli can operate independently. During convergence, each eye also extorts, more so in downgaze, to facilitate stereoscopic perception (Brodsky 2002), In addition, the pupils change size, synkinetically, as part of the near reflex to increase the depth of field and to improve the focus of the optical system.

Although the precise locations of the convergence and divergence centers are unknown, two areas, the midbrain prctcctum and the nucleus reticularis teg men ti pontis (NRTP), are important. Lesions in the pretectal region cause accommodative and vergence abnormalities (Ohsuka et al. 2002), and there is a group of neurons that fire in relation to the angle of convergence just lateral ro the third cranial nerve nuclear complex. The NRTP is contiguous with the PPRF and forms part of a feedback loop by relaying visual information to the cerebellum via a cerebro-ponto-ccrcbellar pathway; the NRTP may also function as a vergence integrator. Experimental lesions of the NRTP in monkeys can cause sustained convergence or pendular convergence-divergence oscillations.

Unilateral stimulation of areas 19 and 22 of the preoccipital cortex caused bilateral convergence, accommodation, and miosis in macaque monkeys. The occipito-mesencephalic pathway, involved in vergence, travels more vcntrally in the dienccphalon and midbrain than does the light reflex pathway and is less susceptible to compression by extrinsic lesions (dorsal midbrain syndrome) (see Chapter 22).

Vertical Eye Movements

The pathways involved in controlling vertical gaze arc not fully known, and some of the neural connections discussed below arc speculative.

The third and fourth cranial nerves innervate the extraocular muscles responsible for both vertical and torsional eye movements (see Chapter 16). The pre motor substrate for vertical and torsional eye movements lies in the midbrain reticular formation (MRF); however, some vertical saccades are programmed in the PPRF and relayed to the MRF via a juxta-MLF pathway, presumably to coordinate horizontal, vertical, and oblique trajectories, and head movement. The rostral interstitial nucleus of the medial longitudinal

fasciculus (riMLF) on each side contains EBNS for both upward and downward saccades but only for ipsilateral torsional saccades. The KBNs for upward saccades are probably caudal, ventral, and medial in the riMLF and project to the elevator muscles (superior rectus and inferior oblique) bilaterally, with axons crossing within the oculomotor nucleus (Figure 39.9A) and not in the posterior commissure (PC) as previously thought (Bhidayasiri et al. 2000). The EBNs for downward saccades are more rostral, dorsal, and lateral in the riMLF, and project only to the ipsilateral depressor muscles (inferior rectus and superior oblique) (Figure 39.9B). The EBNs for vertical saccades also project to the interstitial nucleus of Cajal (INC), which plays a major role in neural integration for vertical and torsional gaze (see below) (Bhidayasiri ct al. 2002). From the INC, the pathways project dorsally and laterally to cross in the PC before turning vcntrally to the oculomotor and trochlear nerve nuclei (see Figure 39.9). The axons to the elevator muscles travel more dorsally and thus are more susceptible to extrinsic compression, such as from a pinealoma.

While the riMLF is key for vertical saccades, the MRF also has a role because of its reciprocal connections with the SC. Each riMLF also receives input from the nucleus of the posterior commissure, the FEF, the SC, the fastigial nucleus of the cerebellum and the contralateral riMLF; the latter fibers cross in a commissure ventral to the aqueduct (see Figure 39,9). Each riMLF is supplied by a branch of the proximal posterior cerebral artery, the posterior thalamo-subrhalamic paramedian artery; a single anomalous posterior thalamo-subthalamic paramedian artery (the arrery of Pcrchcron) may supply the riMLF bilaterally. Vertical saccades require bilateral supranuclear innervation from the FEF or SC, or both.

The neural integrator (NI) for vertical and torsional eye movements (Halmagyi et al. 1994) is located in the interstitial nucleus of Cajal (INC). Burst-tonic and tonic neurons in the region of the INC discharge in relation to vertical eye position and play a role in vertical pursuit and eye position. These neurons project to the contralateral INC and the ocular motor nuclei via the PC, which plays a critical role in vertical gaze (see Figure 39.9). Injury to the PC limits all types of vertical eye movements, particularly upward movements, although the vertical VORs and Bell's phenomenon may be relatively spared.

Retinal slip, the sensory stimulus for vertical pursuit, is encoded by the dorsolateral pontine nuclei and relayed to the flocculus and posterior vermis before converging, via the INC, on the midbrain (see Figures 39.8 and 39.9). The commands for vertical pursuit pass through the pons and cerebellum before turning rostrally to reach the relevant ocular motor neurons in the midbrain.

DEVELOPMENT OF **THE** OCULAR MOTOR SYSTEM

At birth, the vestibular system is the most developed of the ocular motor subsystems and is easily tested by rotating the infant, held at arm's length, with the head tilted 30 degrees forward. In normal neonates, the eyes tonically deviate in the same direction as head movement; reflex saccades develop by 2-3 weeks. Smooth pursuit movemenrs may be detected in neonates but only with large targets (such as a human face) at low velocities. These findings, although not well quantified, are consistent with histological maturation of the fovea after at least 8 weeks of age. Neonates can also generate the smooth pursuit component of OKN with full-field stimulation.

Fixation is not well developed until about two months, although some infants younger than 1 month can fixate

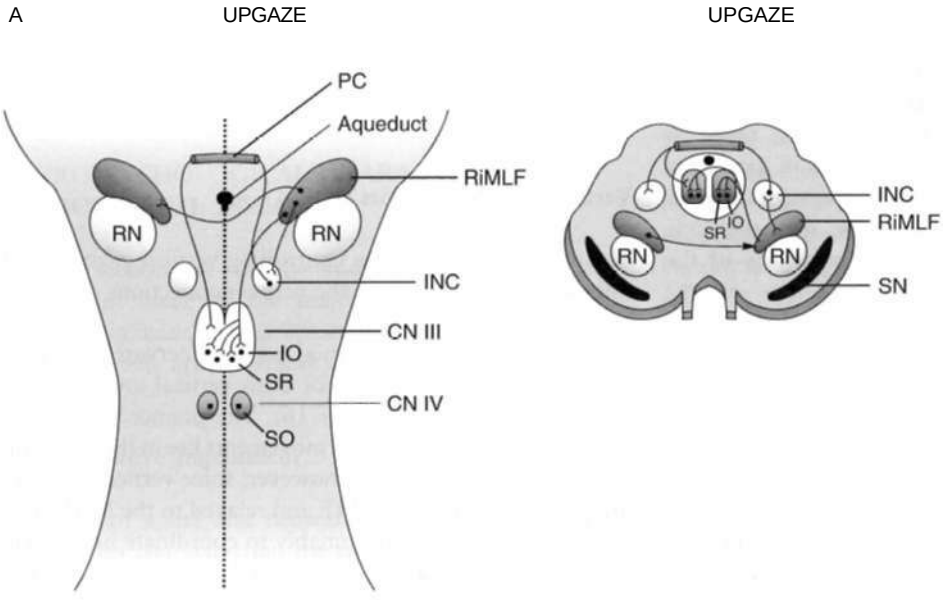

FIGURE 39.9 Hypothetical pathways involved in controlling vertical eye movements, (A) Upward eye movements. Burst neurons for upward saccades are shown projecting from the medial rostra] interstitial nucleus of the medial longitudinal fasciculus (riMLF) to the elevator muscles, superior recti and inferior obliques bilaterally, with axons crossing within the oculomotor nucleus. *Continued*

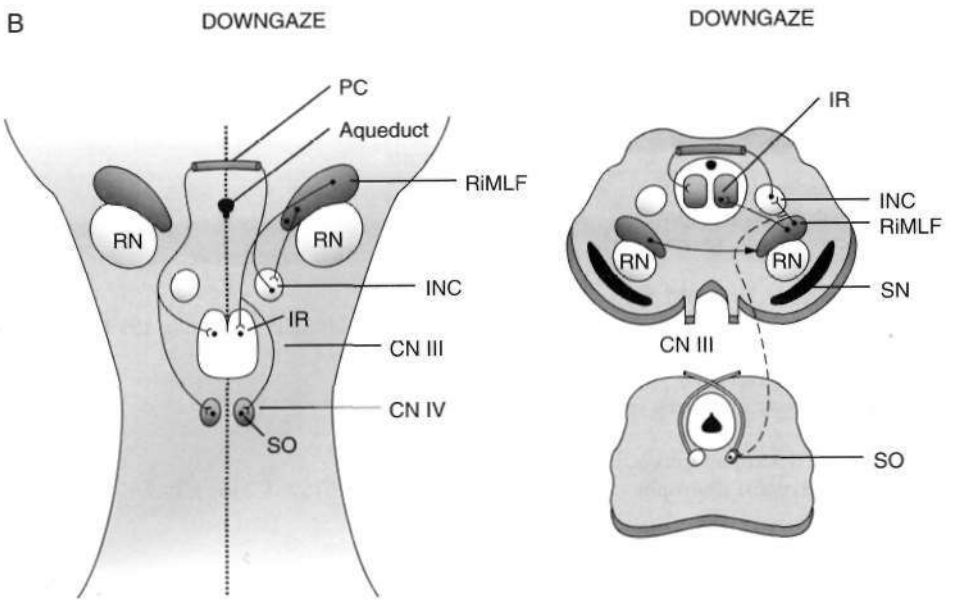

FIGURE 39.9, cont'd. (B) Burst neurons for downward saccades are shown projecting only to the ipsilateral depressor muscles, the inferior rectus and superior ohlique. The axons of the burst neurons for upward saccades also project to the interstitial nucleus of Cajal (INC), which plays a role in tun nil integration tor vertical and torsional gaze. From the INC, the axons project dorsally and laterally to cross in the posterior commissure before turning ventrally to the oculomotor and trochlear nerve nuclei. (CN-II1 = third nerve nuclear complex; CN-IV = fourth nerve nucleus; INC = interstitial nucleus of Cajal; IO — inferior oblique subnucleus; IR = inferior rectus subnucleus; PC = posterior commissure; nMLF = rostral interstitial nucleus of the medial longitudinal fasciculus; RN = red nucleus; SN = substantia nigra; SO = superior oblique nucleus; SR = superior rectus subnucleus.) (Redrawn from Bhidayasiri, R., Plant, G. T,, & Leigh, R. J. 2000, "A hypothetical scheme for the brainstem control of vertical gaze," *Neurology,* vol. 54, pp. 1985-1993.)

targets, provided the stimuli are engaging and the infant is alert. By nine weeks, 90% of full-term infants can fixate and follow the human face. Full-field OKN and larger targets stimulate the parafoveal retina, which matures earlier than the fovea. Stimulation of the saccadic system, also immature in the neonate, is influenced by the infant's attention as well as by the size and appropriateness of the target. Vertical saccades mature more slowly than horizontal saccades and may not he detected for the first month after birth. Vergence movements are also slow to mature but are seen after about the first month.

Ocular alignment in the newborn is usually poor, with transient shifts from esotropia to exotropia during the first few weeks. In most infants, ocular alignment is established by 3-4 weeks but may be delayed as late as five months. Small angle esotropia and intermittent esotropia may spontaneously resolve in infants less than 20 weeks of age; constant esotropia greater than 40 prism diopters is unlikely to resolve spontaneously. Esotropia after 3 months and exotropia after 5 months are considered abnormal and require appropriate evaluation. Large-angle exotropia may be associated with craniofacial, genetic, or other neurological abnormalities.

Paroxysmal phenomena are common in infancy and may be as widespread as one in four (Reerink et al. 1995). Ocular motor anomalies may occur in the neonate without any pathological significance. About 2% of newborns have a tendency for tonic downward deviation of the eyes in the waking state; during sleep, however, the eyes assume the normal position, and the VORs are intact. Other uncommon abnormalities seen in newborns include opsoclonus, which may regress through a phase of ocular flutter, skew deviation, apparent bilateral internuclear ophthalmoplegia; transient downbeat nystagmus; and tonic upward deviation. These findings likely represent delayed maturity of the ocular motor system in neonates.

SUPRANUCLEAR. GAZE DISTURBANCES

Interruption of the saccadic and pursuit pathways before they reach the eye-movement generators in the MRF and PPRF results in a loss of voluntary eye movements but relatively spares reflex movements, such as VOR, optokinetic response and Bell's phenomenon. This constellation of findings is referred to as a *supranuclear gaze palsy* and occurs classically in progressive supranuclear palsy (PSP) as well as a variety of disorders listed in Table 39.2. Technically, skew deviation and the ocular tilt reaction (OTR), which spare the final common efferent pathway

Tabic 39.2: Causes of ophthalmoplegias and gaze palsies (see also Tables 16.8 and 16.3)

Site	*Disorder*
Muscle	Ocular myopathics
	Congenital myopathy
	Central core
	Centronudear (myotubular)
	Fiber-type disproportion
	Multicorc (ptosis, spares EOM)
	Noma line
	Neurocristopathy (EOM fibrosis)
	Ocu lop ha ryngo distal myopathy (Satoyoshi myopathy) (Mastaglia and Laing 1999)
	Autosomal dominant
	Autosomal recessive
	Reducing body myopathy (ptosis, spares EOM)
	Dystrophy
	Myotonic dystrophy (ptosis, usually spares EOM)
	Oculopharyngeal dystrophy
	Inflammatory
	Derma torn yositis
	Giant cell arteritis
	Orbital pseudotumor
	Metabolic and toxic (act at multiple sites, e.g., anticonvulsants)
	Mitochondrial cytopathy
	Kearn-Sayre syndrome
	Chronic progressive external ophthalmoplegia (CPEO)
	Pearson's syndrome
	POLIP syndrome (polyneuropathy, ophthalmoplegia, fcukoencephalopathy, intcstinal pseudo-obstruction)
	High myopia (large globes cause mechanical restriction)
	Infiltrative disorders (thyroid, amyloid, metastases, congenital familial fibrosis, cystinosis)
	Trauma (orbital entrapment)
	Vitamin E deficiency (associated with malabsotption)
Neuromuscular junction	Myasthenia gravis
	Toxins (e.g., botulism, organophosphates)
	Lambert-Eaton syndrome (rarely affects the EOM, mainly causes ptosis)
Ocular motor nerves	See Chapter 76
Gaze palsies	Nuclear and paranuclear
	Brainstem injury (vascular, multiple sclerosis, encephalitis, paraneoplastic, toxins, tumor)
	Familial congenital gaze palsy
	Glycine encephalopathy (nonketotic hypetglycinemia: hiccups, seizures, apneic spells)
	Machado-Joseph disease (SCA3)
	Leigh's disease
	Maple syrup urine disease
	Mobius' and Duane's syndromes (agenesis of cranial nerve nuclei)
	Spinocerebellar degeneration
	Tangier disease
	Vitamin E deficiency
	[nternuclear ophthalmoplegia
	One-and-a-half syndrome
	Prenuclear
	Monocular "supranuclear" elevator palsy
	Ocular tilt reaction
	Skew deviation
	Vertical one-and-a-half syndrome
	Supranuclear (predominantly horizontal)
	Congenital ocular motor apraxia
	Acutely, after hemispheric stroke
	Ipsiversive
	Contravcrsive (wrong-way eyes)
	Gaucher's disease (types 2 and 3)
	Ictal (ttansient, adversive)

Con tinned

Table 39.2, Causes of ophthalmoplegias and gaze palsies (see also Tables 16.8 and 16.9]—conr'd

Site	Disorder
Gaze palsies—cont'd	Juvenile-onset GM2 gangliosidosis (mimics juvenile spinal muscular atrophy)
	Postictal (transient, ipsivcrsive)
	Paraneoplastic (prostatic adenocarcinoma)
	Supranuclear (predominantly vertical)
	Adult-onset CM; gangliosidosis (mimics multiple-system atrophy or spinocerebellar degeneration) (V>H)
	Congenita] vertical ocular motor apraxia (rare)
	Amyotrophic lateral sclerosis (rare, V>H)
	Autosomal dominant parkinsonian-dementia complex with pallido-pontonigral degeneration (dementia, dystonia, frontal and pyramidal signs, urinary incontinence]
	Vitamin B12 deficiency (U>D)
	Cerebral amyloid angiopathy with leukoencephalopathy
	Dentatoruhral-pallidoluysian atrophy (autosomal dominant, dementia, ataxia, myoclonus, choreo athetosis)
	Diffuse Lewy body disease (ophthalmoplegia may be global)
	Dorsal midbrain syndrome (see Chapter 22 and Disorders of Vertical Gaze, later in this chapter)
	Familial Creurzfeldt-Jakob disease (U>D)
	Familial paralysis of vertical gaze
	Fisher's syndrome
	Gcrstmann-Srraussler-Scheinker disease (U>D, dysmetria, nystagmus)
	Guamanian Parkinson's disease-dementia complex (Lyrico-Bodig disease)
	HARP syndrome (^ypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, pallidal degeneration)
	Hydrocephalus (untreated, decompensated shunt)
	Joseph's disease
	Kernicterus (U>D)
	Late-onset cere be 11 o- pontomesencephalic degeneration (D>U)
	Neurovisceral lipidosis; synonyms: DAF syndrome (downgaze palsy-ataxia-foamy macrophages); dystonic lipidosis; Niemann-Pick disease type C (initially loss of downgaze, may become global)
	Pallidoluysian atrophy (dysarthria, dystonia, bradykinesia)
	Paraneoplastic disorders
	Progressive supranuclear palsy (D>U)
	Subcortical gliosis (U>D)
	Variant Creutzfeld-Jakob Disease (U>D)
	Wilson's disease (also slow horizontal saccades) (U>D)
	Supranuclear (global)
	Abetalipoproteinemia
	AIDS encephalopathy
	Alzheimer's disease (pursuit)
	Cerebral adrenoleukodystrophy
	Corticobasal ganglionic degeneration
	Fahr's disease (idiopathic striatopallidodentate calcification)
	Gaucher's disease
	Hexosaminidase A deficiency
	Huntington's disease
	Joubert's syndrome
	Leigh disease [infantile striatonigral degeneration)
	Methylmalonohomocystinuria
	Malignant neuroleptic syndrome (personal observation)
	Neurosyphilis
	Opportunistic infections
	Paraneoplastic disorders
	Parkinson's disease (transient gaze palsy with intercurrent infection)
	Pelizaeus-Merzbacher disease (H>V)
	Pick's disease (impaired saccades)
	Progressive multifocal leukoencephalopathy
	Tay-Sachs disease (infantile GM_2 gangliosidosis) (V>H)
	Wernicke's encephalopathy
	Whipple's disease (V>H)

AIDS = acquired immunodeficiency syndrome; D = loss of downgaze; FLOM = extraocular muscles; g1oba1 = loss of horizontal and vertical gaze; H = loss of horizontal gaze; MNCIE = mitochondrial neurogastrointestinal encephalomyopathy syndrome; OPCA = olivopontocerebellar atrophy; U = loss of upgaze; V = loss of vertical gaze.

for eye movements, are also supranuclear, but because they are dy scon jugate, they are referred to here as prenuclear.

Bilateral lesions of the fronto-mesencephalic pathways cause loss of horizontal saccades in both directions and impair vertical saccades (particularly upward) but spare pursuit, VORs, and the slow phases of OKN. Focal lesions in the PPRF can also cause selective saccadic defects (see Horizontal Eye Movements, earlier in this chapter).

To evaluate disorders of gaze, first determine the range of versions (conjugate eye movements) to a slowly moving target, and then test saccades, as described in Chapter 16. If a dysconjugate defect is observed, check ductions, ocular alignment, and comitance. If a conjugate defect (i.e., a gaze palsy) is present, determine if the eyes move reflexively by testing for the oculoccphalic reflex (doll's eye maneuver) or VOR (calorics), and Bell's phenomenon (ocular deviation, usually upward, on forced eyelid closure); their presence indicates supranuclear dysfunction. With suptanuclcar gaze disorders, saccades may be impaired firsr, then pursuit, followed by loss of VORs. Causes of gaze palsies and ophthalmoplegias are outlined in Table 39.2.

Ocular Motor Apraxia

Ocular motor apraxia is the inability to perform voluntary saccades; spontaneous saccades and reflex eye movements (vestibular and OKN slow phases) are preserved. The term is sometimes used loosely and incorrectly (see below),

Congenital ocular motor apraxia (COMA) is more common in boys than in girls and is characterized by impaired voluntary horizontal pursuit and saccadic movements but preservation of vertical eye movements (Leigh and Zee 1999); teflex saccades may be partly retained. Because random eye movements are also absent in many of these children, the term *apraxia* is strictly incorrect; *congenital saccadic palsy* or *congenital gaze palsy* is more accurate (Leigh et al. 1997), but the term COMA is now established in the literatute. By 4-8 months of age, the child develops a thrusting head-movement strategy, often with ptominent blinking, to ovetcome the eye-movement deficit (see Figure 24.3). Because the VOR prevents a change in direction of gaze on head turning, the child closes the eyes to reduce the degree of reflex eye movement (the gain of the VOR falls with the eyes closed) while thrusting the head beyond the range of the VOR arc to bring the eyes in line with the target. Then, with the eyes open, the child slowly straightens the head while the contralateral VOR maintains fixation. Some patients may use the dynamic head thrust to facilitate saccadic eye movements or reflexively to induce fast phases of vestibular nystagmus.

Because children with COMA cannot easily refixate or pursue new targets, particularly in the first 6 months of life, before they develop the head-thrusting strategy, they arc sometimes initially misdiagnosed as being blind. After *6* months of age, children with COMA present because of the head thrusts. The diagnosis of COMA can be confirmed by demonstrating the inability to make saccades; this is most easily done by spinning the infant, as described in Development of the Ocular Motor System, earlier in this chapter. In normal infants, the eyes tonically deviate in the same direction as head movement; absence of reflex saccades (fast phases in the opposite direction) after 2-3 weeks of age is abnormal and indicates saccadic palsy.

As children with COMA reach school age, pursuit and voluntary saccades variably improve. However, the condition does not completely resolve and can be detected in adulthood. COMA may be associated with hypoplasia of the cotpus callosum, hypoplasia of the cerebellar vermis in as many as 53% of patients (Sargent et al. 1997), occipital porencephalic cysts, and bilateral cortical lesions. It may occasionally be familial. Strabismus, psychomotor developmental delay (particularly reading and expressive language ability), clumsiness, and gait disturbances are often associated.

A similat ocular motor disordet occurs in children with Aicardi's syndrome, ataxia telangiectasia (80%), Cockayne's syndrome, Joubert's syndrome, Pelizaeus-Merzbacher disease, succinic semi-aldehyde dehydrogenase deficiency (Eustace et al. 1994), Wieacker's syndtome, carbohydrate deficient glycoprotein syndrome type la (Stark et al. 2000), and ataxia-oculomotor apraxia syndrome (which mimics ataxia telangiectasia, without the extraneurological features, and is probably autosomal recessive) (Gascon et al. 1995).

Congenital vertical ocular motor apraxia is rare and must be differentiated from metabolic and degenerative disotdets that cause ptogtessive neurological dysfunction, such as neurovisceral lipidosis, and from stable disorders, such as birth injury, perinatal hypoxia, and Leber's congenital amaurosis.

Acquired ocular motor aptaxia occuts in patients with bilateral parietal damage and with diffuse bilateral cerebral disease (see Table 39.2); the head thrusts are not as conspicuous as in the congenital vatiety.

Spasm of Fixation

Spasm of fixation, a term introduced by Gordon Holmes in 1930, describes patients who have difficulty shifting visual attention because of impaired initiation of voluntary saccades when looking at a fixation target but normal initiation of saccades in the absence of such a target. Their saccades have a prolonged latency and may be hypometric in the presence of u a/urr.il visual rarurt; however, Minks or combined eye and head movements may sometimes facilitate normal saccades. Holmes stressed that fixation was an active process and attributed spasm of fixation to "exaggerated" fixation; evidence from other studies supports this concept.

The lesions that cause spasm of fixation may be bi hemispheric and interrupt indirect FEF projections via the caudate nucleus and SNr (see Horizontal Eye Movements, earlier in this chapter) to the SC. Normally, during saccades to auditory, visual, and remembered targets, neurons in the FEFs discharge via these pathways and disinhibit the SC to allow the saccades and disengage fixation. Interruption of these, and perhaps oilier path ways, might contribute to spasm of fixation by maintaining tonic inhibitory suppression of saccades by the SC (Leigh and Zee 1999).

Familial Horizontal Gaze Palsy

Familial horizontal gaze palsy with scoliosis (HGPS) is an autosomal recessive disorder characterized by paralysis of horizontal gaze from birth, impaired OKN and VORs but intact convergence, vertical eye movements, and progressive scoliosis (Leigh and Zee 1999). HGPS maps to chromosome llq23-25 in some kindreds (Jen et al. 2002). Types of nystagmus described in HGPS include a fine pendular horizontal nystagmus, upbeat nystagmus, and see-saw nystagmus (Pieh et al. 2002). Individuals in some families may also have facial myokymia, facial twitching, hemifacial atrophy, and situs invetsus of the optic discs. Neutoimaging may demonstrate brainstem dysplasia, particularly pontine hypoplasia (Pieh et al. 2002). HGPS is one of a spectrum of disorders of maldevelopment of cranial nerve nuclei that include Duane's syndrome (see Chaprer 16), Mobius syndrome, the congenital fibrosis of the extraocular muscles syndromes, and congenital ptosis (Engle and Leigh 2002),

Acquired Horizontal Gaze Palsy

Transient gaze deviation, usually of the head and eyes, occurs in about 20% of patients with acute hemisphere stroke and other insults. The eyes are usually deviated toward the side of the lesion (ipsiversive gaze deviation} because of gaze paresis to the hemiplegic side (i.e., paralysis of gaze and limbs is on the same side). In stroke patients, right-sided lesions are more common but smallet; consequently, patients with left-sided lesions (gaze deviation to the left) have a worse prognosis. Ipsiversive gaze deviation occurs more often when the inferior parietal lobule (IPL) or circuits between the FEFs and the IPL or their projections to the brainstem (SC or PPRF) are involved; the FEFs are usually spared. After about 5 days, the intact hemisphere, which contains neurons for bilareral gaze, takes over; thereafter, subtle abnormalities such as prolonged saccadic latencies and impaired saccadic suppression can be detected only by quantitative oculography.

Because the premotor neural network for voluntary horizontal eye movements in the PPRF is composed of subclasses of neurons with different functions, selective lesions may affect some types of eye movement while sparing others (see Horizontal Eye Movements, earlier in this chapter). A lesion affecting the ipsilateral abducens nucleus or PPRF causes ipsilateral gaze palsy; a rostral PPRF lesion spares the VOR, whereas a caudal lesion does not. Paraneoplastic brainstem encephalitis can cause supranuclear, internuclear, or nuclear damage, resulting in selective loss of voluntary horizontal and vertical saccades (Crino et al. 1996). Patients with prostatic adenocarcinoma may, after an interval of 3–4 years, develop paraneoplastic gaze palsies followed by severe facial and bulbar muscle spasms (probable sustained myoclonus), diplopia, and respiratory insufficiency (Baloh et al. 1993). Other neurological features that may be associated with such paraneoplastic disorders include ataxia, hypcracusis, muscle spasms, myoclonus, periodic alternating gaze deviation (PAGD), and vertigo. Magnetic resonance imaging is often unrevealing, particularly in the early stages, but auditory evoked potentials and cerebrospinal fluid analysis may be abnormal. Clonazepam, valproic acid, and botulinum may help the myoclonus and muscle spasms.

Other causes of horizontal gaze palsies are listed in Table 39.2,

Wrong-Way Eyes

Conjugate eye deviation to the "wrong" side (i.e., away from the lesion and toward the hemiplegia [contraversive gaze deviation]) may occur with supratentorial lesions, particularly thalamic hemorrhage, and, rarely, large perisylvian or lobar hemorrhage. The mechanism is unclear, but possibilities include the following:

1. An irritative or seizure focus causing "contraversive ocular deviation" is unlikely because neither clinical nor electrical seizure activity has been reported in these patients.
2. Because eye movements are represented bilaterally in each frontal lobe, it is conceivable that the center for ipsilateral gaze alone may be damaged, resulting in contraversive ocular deviation.
3. An irritative lesion of the intralaminar thalamic neurons, which discharge for contralateral saccades, could theoretically cause contraversive ocular deviation (Leigh and Zee 1999).
4. Damage to the contralateral inhibitory center could also be responsible.

Postictal "paralytic" conjugate ocular deviation occurs after adversive seizures as part of Todd's paralysis.

Spasticity ol conjugate gaze (lateral deviation ot both eyes away from the lesion) during forced eyelid closure, a variant of Bell's phenomenon, can occur in patients with large, deep parietotemporal lesions; eye

movements are otherwise normal except for ipsilateral saccadic pursuit.

Psychogenic ocular deviation can occur in patients feigning unconsciousness; the eyes are directed toward the ground irrespective of which way the patient is turned.

Periodic Alternating Gaze Deviation

Periodic Alternating Gaze Deviation (PAGD) is a rare cyclical ocular motor disorder in which the direction of gaze alternates every few minutes. Lateral deviation can he sustained for up to \5 minutes; gaze then returns to the midline for 10-20 seconds before changing to the other side. Occasionally, PAGD is associated with structural lesions, such as pontine vascular disorders; Chiari malformations; congenital absence or abnormalities of the inferior cerebellar vermis, the uvula, and nodulus; Creutzfeldt-Jakob disease involving the flocculonodular lobe; spinocerebellar degeneration; occipital cnccphaloceles; and paraneoplastic brainstem encephalitis (Baloh et al. 1993). A reversible form of PAGD occurs with hepatic encephalopathy and is attributed to derangement of GABA metabolism (Averhuch-Heller and Meiner 1995}.

PAN (sec Chapter 16) has a similar time cycle to PAGD and also results from lesions of the uvular and nodular regions. Indeed, PAGD may be PAN with loss of corrective saccades because of concomitant saccadic palsy or immaturity of the saccadic system in infants.

Other cyclical ocular motor phenomena, including cyclical esotropia, cyclical oculomotor palsy, springing pupil, alternating skew deviation, and PAN, are discussed in the appropriate sections.

Ping-Pong Gaze

Ping-pong gaze is a conjugate horizontal rhythmic oscillation that cycles every 4-8 seconds (short-cycle PAGD) and occurs in comatose patients as a result of bilateral cerebral or upper brainstem damage (e.g., disconnection) or metabolic dysfunction. Ping-pong gaze implies that the horizontal gaze centers in the pons are intact. The prognosis for recovery is poor except in patients with a toxic or metabolic cause (Johkura et al. 1998).

Saccadic Lateropulsion

Saccadic lateropulsion is characterized by hypermetric (overshoot) saccades (see Chapter 16, Figure 16.1 SB) to the side of the lesion (ipsipulsion) and hypometric (undershoot) saccades (see Chapter 16, Figure 16.18C) to the opposite side. In darkness or with the eyelids closed, the patient may have conjugate deviation toward the side of the lesion. Saccadic lateropulsion occurs with lesions of the lateral medulla (most commonly ischemic) involving cerebellar inflow (inferior cerebellar peduncle).

Saccadic lateropulsion with a bias away from the side of the lesion (contrapulsion) may occur with lesions involving the region of the superior cerebellar peduncle (outflow tract) and adjacent cerebellum (superior cerebellar artery territory) (Halmagyi 1994),

Pulsion of vertical saccades, with a parabolic trajectory, occurs in patients with lateral medullary injury. Both upward and downward saccades deviate toward the side of the lesion, with corrective oblique saccades, whereas in those with lesions involving cerebellar outflow, vertical saccades deviate away from the side of the injury (Halmagyi 1994).

Torsional Saccades

Pathological rapid torsional eye deviation during voluntary saccades may occur with large lesions involving the midline cerebellum, deep cerebellar nuclei, and dorsolateral medulla. The amplitudes of these torsional saccades (blips) are larger for ipsilesional (hypermetric) than for contralesional (hypometric) horizontal saccades. Eye movement recordings using a scleral search coil (see Eye Movement Recording Techniques, later in this chapter) demonstrated that the "blips" are followed by an exponenrially slow (see Chapter 16) torsional drift toward the initial torsional eye position. These blips may be a form of torsional saccadic dysmetria (Helmchen et al. 1997).

Slow Saccades

Saccades of low velocity result from pontine disease, presumably because of burst cell dysfunction. They occur in patients with olivopontocerebellar degeneration and other disorders listed in Table 39,3. Some patients with hypometric saccades (see Chapter 16, Figure 16.18C), composed of multiple small-amplitude steps (as in myasthenia, Huntington's disease, brainstem encephalitis, and srriatonigral degeneration) appear to have slow saccades clinically (pseudo-slow saccades), but each small saccadc has a normal velocity-amplitude relationship.

Prolonged Saccadic Latency

Disorders of saccadic initiation, resulting in prolonged latencies for voluntary saccades, occur in patients with inattention acquired immunodeficiency syndrome (AIDS)-dementia complex and a variety of encephalopathies and degenerative disorders of the nervous system, such as Alzheimer's, Huntington's, and Parkinson's disease.

Table 39.3; Slow saccades

AIDS-dementi a complex
Amyotrophic lateral sclerosis
Anticonvulsant toxicity (consciousness usually impaired)
Ataxia-telangiectasia
Hexosaminidase A deficiency
Huntington's disease
Internuclear ophthalmoplegia (slow abduction)
Joseph's disease
Lesions of the paramedian pontine reticular formation
Lipid storage diseases
Long-standing cholestasis (proba hie vitamin E deficiency)
Lytico-Bodig disease (Guamanian ALS-PD-dementia complex)
Myotonic dystrophy
Nephropathy cystinosis
Ocular motor apraxia
Ocular motor nerve or muscle weakness
Olivopontocerebellar degeneration (ADCA type I)
Progressive supranuclear palsy
Wernicke's encephalopathy-
Whipple's disease
Wilson's disease

ADCA = autosomal dominant cerebellar ataxia; AIDS = aequired immunodeficiency syndrome; ALS-PD = amyotrophic lateral sclerosis-Parkinson'sdisease.

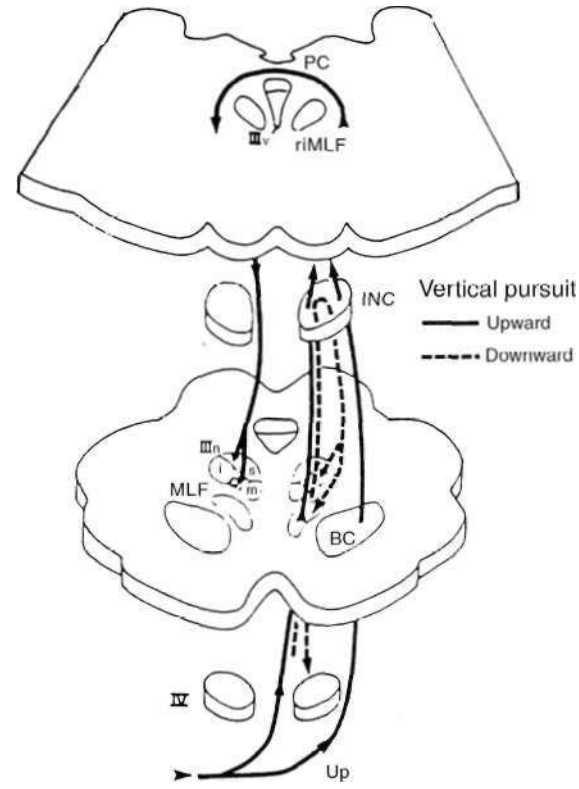

FIGURE 39.10 Vertical pursuit. The hypothetical pathways for pursuit reach the midbrain via the dorsal lateral pontine nuclei and travel upward in the brachium conjunctivum (BQ and the medial longitudinal fasciculus (MLF). The interstitial nucleus of Cajal (INC) is involved in pursuit and may also be the neural integrator for vertical position commands. (Reprinted with permission from Ranalli, P. J., Sharpe, J. A., & Fletcher, W. A. 1998, "Palsy of upward and downward saccadic, pursuit, and vestibular movements with a unilateral midbrain lesion: Pathophysiologic correlations," *Neurology,* vol. 38, pp. 114-123.)

Square Wave Jerks

Square wave jerks (SWJs) (Table 39.4) are spontaneous, small-amplitude paired saccades with an intersaccadic latency of 150-200 ms tbat briefly interrupts fixation (Figure 39.10). They may occur physiologically in normal subjects (particularly in darkness) without fixation and are usually about 2 degrees in amplitude. They are more common in the elderly (Halmagyi 1994) and in carriers of blue-cone monochromatism (Gottlob 1994). SWJs are prominent in PSP, multiple system atrophy, and cerebellar disease; the increased frequency of SWJs in these less dopamine-responsive parkinsonian syndromes, such as olivopontocerebellar atrophy (autosomal dominant cerebellar atrophy), PSP, Lewy body disease, and multiple system atrophy, may distinguish them from Parkinson's disease.

Table 39.4: Square wave jerks

Normal subjects (<2 degrees)
Excitement in normals
Catecholamine depletion in normals
Aging
Carriers of blue-cone monochromatism
Strabismus
Congenital nystagmus
Latent nystagmus
Dyslexia (suppressed by methylphenidate)
Progressive supranuclear palsy
Schizophrenia
Cerebral hemisphere tumors and stroke
Parkinson's disease
Wernicke's encephalopathy
Friedreich's ataxia
Joseph's disease
Gerstmann-Straussler-Scheinker disease
Lithium
Tobacco
AIDS-dementia complex (HIV encephalitis)
Square wave pulses (macrosquare wave jerks)
  Olivopontoccrcbellat atrophy
  Multiple sclerosis (cerebellar dysfunction)

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.

Because of the intersaccadic interval (latency), SWJs arc thought to be triggered supratentorially, whereas other saccadic intrusions (e.g., saccadic pulses) and oscillations (e.g., flutter and opsoclonus) are caused by dysfunction of the pause cells in the brainstem (see Chapter 16).

Square wave pulses (SWPs), previously termed *macro-square wave jerks,* also interrupt fixation but differ from SWJs with larger amplitudes (10-40[11]) and shorter latencies (about 80 ms) before the eyes return to the target; they occur in patients with multiple sclerosis,

olivopontocerebellar degeneration and may accompany rubral tremor. SWJs and SWPs should be distinguished from macrosaccadic oscillations, which wax and wane-across fixation {Figure 39.11), are not present in darkness, and occur with midline cerebellar lesions. These and other saccadic oscillations are discussed in detail elsewhere (Dell'Osso and Daroff 1999a; Leigh and Zee 1999).

In ternu el car Ophthalmoplegia

Damage to the MLF between the third and sixth cranial nerve nuclei impairs transmission of neural impulses to the ipsilateral medial rectus muscle (see Figure 39.4). Adducting saccades of the ipsilateral eye are impaired (either slow or absent), depending on the severity of the lesion. The nystagmus-like movement of the abducting eye typically seen gives the appearance of dissociated nystagmus (see Chapter 16) but is in fact overshoot dysmctria (Halmagyi 1994). Upward-heating and torsional nystagmus is often present. Convergence may be preserved with an INO, but because the patient's attention and effort are necessary for its evaluation, it is not a particularly helpful sign. Patients with bilateral INO may be exotropic, designated the WEBINO (wall-eyed bilateral INO) syndrome (Komiyama et al. 1998), and have slow-abducting saccades because of impaired inhibition of tone in the medial recti. Other clinical features associated with INO include skew deviation (usually ipsilateral hypertropia), and defective vertical smooth pursuit, OKN, and vertical VORs.

A subtle INO may be demonstrated by having the patient make repetitive horizontal saccades, which often discloses slow adduction of the ipsilateral eye. Alternatively, an optokinetic tape may be used to induce repetitive saccades in the direction of action of the suspected weak medial rectus muscle, by moving the tape in the opposite direction and observing for smaller-amplitude adducting saccades.

INO may occur with a variety of disorders affecting the brainstem and must be distinguished from the many, primarily peripheral, causes of pseudo-INO (Table 39.5).

Rarely, patients with small lesions in the rostra! pons or midbrain, remote from the abducens nerve and nucleus, may have a Lutz posterior INO. In this condition, abduction is impaired, but the adducting eye has nystagmus. The mechanism is attributed to impaired inhibition of the antagonist medial rectus muscle because of damage to uncrossed fibers, from the PPRF to the oculomotor nucleus, running close to but separate from the MLF (as discussed by Thomke et al. 1992).

Tabic 39.5: Causes of internuclear ophthalmoplegia

- Brainstem (pontine) stroke—unilateral
- Multiple sclerosis—unilateral or bilateral
- Intrinsic tumor—primary or metastatic
- Meningitis (especially tuberculosis)
- Brainstem eiia/phalim (infective, paraneoplastic)
- Chemotherapy with radiation therapy
- Drug intoxication:
  - (Comatose)—anticonvulsants, phenothiazincs, tricyclics
  - (Awake)—lithium
- Spinocerebellar degeneration
- Fabry's disease (vascular)
- Wernicke's encephalopathy
- Progressive supranuclear palsy
- Syringobulbia associated with a Chiari malformation
- Trauma (closed head injury)
- Hexosaminidase A deficiency
- Maple syrup urine disease
- Cerebral air embolism
- Pseudointernuclear ophthalmoplegia
  - Long-standing exotropia
  - .Myasthenia
  - Myotonic dystrophy
  - Neuromyotonia of the lateral rectus muscle
  - Partial palsy of cranial nerve III
  - Previous extraocular muscle surgery
  - Thyroid orbitopathy (lateral rectus restriction)
  - Orbital pseudotumor
  - Other infiltrative disorders of extraocular muscle (neoplasm, amyloid, and the like)
  - Miller-Fisher syndrome (sometimes may be a true internuclear ophthalmoplegia)

One-and-a-Half Syndrome

A lesion in the caudal dorsal pontine tegmentum involving the ipsilateral PPRF, or the abducens nucleus, and the ipsilateral MLF results in an ipsilateral gaze palsy with an ipsilateral INO (see Figure 39.3) (Komiyama et al. 1998). This is known as the *one-and-a-half syndrome.* Abduction of the contralateral eye is the only intact horizontal movement. Patients who also have facial nerve palsy may later develop oculopalatal myoclonus (see Chapter 16), probably because of the proximity of the central tegmental tract to the facial nerve (Wolin et al. 1996). Ocular myasthenia may cause a pseudo-one-and a-half syndrome.

Disorders of Vertical Gaze

A variety of disorders of conjugate vertical gaze result from discretely placed lesions in the midbrain pretectal region (see Figure 39.9). However, selective deficits of vertical gaze may be overlooked unless the examiner specifically tests for different types of eye movements, particularly saccades.

Paralysis of vertical saccades usually involves loss of downward saccades or combined upward and downward saccades and is often caused by bilateral ischemia of the riMLF, Selective paralysis of downward saccades may occur because the depressor muscles are innervated just unilaterally, whereas the elevator muscles are innervated bilaterally; thus partial riMLF lesions affect the depressor muscles disproportionately (Bhidayasiri et al. 2000).

A unilateral lesion, in the midbrain tegmentum, involving the riMLF can cause impairment of both upward and downward saccades by injuring ipsilateral butst cells, crossing fibers from the contralateral burst cells, and probably neighboring inhibitory pathways. In addition, a unilateral lesion of the riMLF can cause loss of ipsilateral torsional saccades, detected by tilting the patient's head to the shoulder, i.e., in the roll plane. A lesion of the PC limits all types of vertical eye movements, particularly upgaze.

Upgaze paralysis occurs with lesions at or near the posterior commissure, or bilaterally in the pretectal area (see Figure *19.9).*

Downgaze paralysis occurs with bilatetal lesions of the riMLF (Figure 39.11) or its projections, which course caudally and dorsally, bilaterally (see Figure *59.9).* In humans, with the exception of occlusion of the posterior thalamosubthalamic branch of the posterior cerebral artery, such isolated lesions are rare (Green et al. 1993). More commonly, bilatetal involvement of the pathways for downgaze (as well as upgaze) occurs as a part of diffuse disorders, such as P5P, Whipple's disease, neurovisceral lipid storage disorders, and complications of AIDS (see Table 39.2).

Patients with impaired vertical gaze as a result of extrinsic compression of the posterior commissure or pretectal tegion ate more likely to have pupillary light-near dissociation (loss of the pupillary light reflex but preservation of the near reflex) because the light-reflex pathways are more superficial. Intrinsic midbrain lesions cause impairment of convergence and accommodation (the near reflex) while sparing the light reflex. With supranuclear disorders of vertical gaze, saccades are impaired initially, followed by pursuit, and then by loss of verticil VORs. Paralysis of upga/c, light-near dissociation of the pupils, impaired convergence, lid rettaction, and convergence-retraction nystagmus are features of the dorsal midbrain (Parinaud's) pretectal syndrome (see Chaptet 22), which occurs with injury to the PC or both INCs.

Disorders of vertical gaze (see Table 39,2), particularly downgaze and combined upgaze and downgaze paresis, may be overlooked in patients with brainstem vascular disease because of impaired consciousness as a result of concomitant damage to the reticular activating system.

Two forms of the vertical one-and-a-half syndrome occur with discrete lesions in the upper midbrain. One, which consists of bilatetal upgaze palsy associated with monocular paresis of downward movement, can occur with either ipsilateral or contralateral thalamomesencephalic infarctions; the other consists of a downgaze palsy associated with monocular elevator paresis that can occur with bilateral mesodiencephalic lesions.

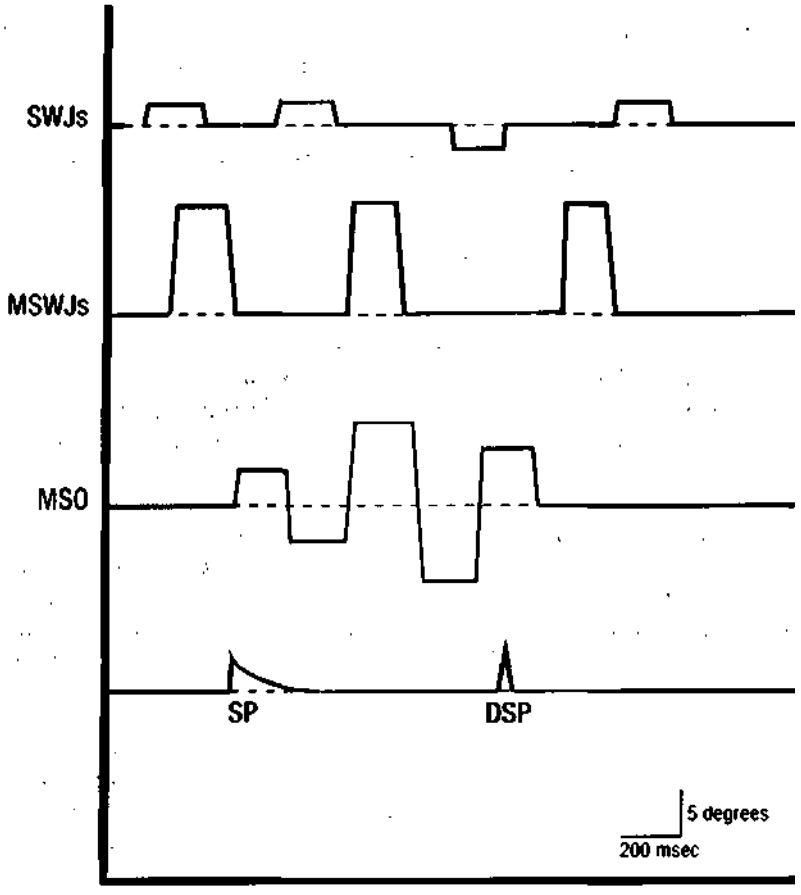

FIGURE 39.11 Simulated eye movement recordings of square wave jerks (SWJs), macrosquare wave jerks or square wave pulses (MSWJs), macrosaccadic oscillations (MSO), a saccadic pulse (SP), and a double saccadic pulse (DSP).

A crossed vertical gaze paresis, with supranuclear weakness of elevation of the contralateral eye and weakness of depression of the ipsilatcral eye, may occur with a lesion involving the me sod i encephalic junction and medial thalamus (Wiest et al. 1996).

Monocular elevator deficiency, also termed *monocular elevator palsy* or *double elevator palsy,* is characterized by limitation of elevation of one eye. The limitation is the same in both adduction and abduction, unlike Brown's superior oblique tendon sheath syndrome, in which rhe limitation is predominantly in adduction. Monocular elevator deficiency can result from paretic or restrictive disorders of the extraocular muscles, such as muscle fibrosis, myositis, myasthenia, infiltrative disease (thyroid orbitopathy, neoplasia), orbital floor fractures, and fascicular lesions of the oculomotor nerve (Gauntt et al. 1995). Some cases may be supranuclear, particularly those with normal ocular alignment in primary position (see below).

When monocular elevator deficiency is congenital, or occurs early in life, it may be associated with abnormalities of convergence, amblyopia, a chin-up head position, and ptosis or pseudoptosis. (Pseudoptosis occurs when a patient with a hypotropic eye fixates with the other eye; the upper lid follows the hypotropic eye and appears ptotic; when the patient fixates with the hypotropic eye the apparent ptosis disappears. Some patients may have both a true ptosis and a superimposed pseudoptosis.) Some congenital cases are supranuclear as a result of congenital unilateral midbrain lesions (e.g., Ziffer et al. 1992) when they are long-standing inferior rectus restriction and fibrosis prevents reflex elevation of the eye (Bell's phenomena). In those cases, primary orbital disorders, such as myositis, thyroid orbitopathy, orbital floor fractures, and infiltrative disease, must be excluded. Corrective surgery is sometimes helpful.

Acquired supranuclear monocular elevator palsy results in limitation of elevation of one eye on attempted upgaze, despite intact downgaze and orthotropia in primary position (unlike patients with monocular elevator deficiency, who have an abnormal head posture). This rare condition occurs with unilateral vascular or neoplastic lesions involving either the ipsilateral or contralateral midbrain. The affected eye can usually be elevated in response to vestibular stimulation or Bell's phenomenon, and ptosis is usually absent.

Tonic upward deviation of gaze {forced upgaze), a rare sign, is seen in unconscious patienrs and must be distinguished from oculogyric crises, petit mal seizures, and psychogenic coma. Comatose patients with sustained upgaze after diffuse brain injury (e.g., hypotension, cardiac arrest, and heatstroke) usually have cerebral and cerebellar hypoxic damage, with relative sparing of the brainstem. **Some of** these patients later develop myoclonic jerks and large-amplitude downbeat nystagmus; their prognosis is extremely poor. Rarely, tonic upward gaze deviation may he psychogenic but can be overcome, indeed cured, by cold caloric stimulation of the eardrums.

"Benign" paroxysmal tonic upward gaze (PTU) may occur in association with ataxia in young children who have downbeat nystagmus on attempted downgaze. The duration of the deviation is variable (seconds to hours) but is usually short, and it occurs frequently throughout the day. PTU usually starts in the first year of life and lasts about 2 years; the onset may be during or shortly after an infection or vaccination. PTU may be exacerbated by fatigue, relieved by sleep, and sometimes provoked by car travel; there is no evidence rhar the episodes are seizures or oculogyric crises. The cause of PTU is unknown, but at follow-up, a significant number of patients have developmental delay, intellectual disability, language delay, or ocular motility disorders; these findings imply that PTU is a marker for underlying neurological or developmental abnormalities (Hayman et al. 1998). The condition is reminiscent of the intermittent or periodic ataxias, which may respond to drugs such as acerazolamide (see Chapter 70).

Tonic downward deviation of gaze (forced downgaze) is associated with impaired consciousness in patients with medial thalamic hemorrhage, acute obstructive hydrocephalus, severe metabolic or hypoxic encephalopathy, or massive subarachnoid hemorrhage. The eyes may also converge, as if looking at the nose. Tonic downward gaze deviation may also occur in psychogenic illness, especially feigned coma, but also can be overcome by caloric stimulation. In young children with acute hydrocephalus, tonic downward deviation may be associated with upper lid retraction; because of its appearance, this is called the *setting sun sign,*

In otherwise healthy neonates, downward deviation of the eyes or tonic upgaze while awake may occur as a transient phenomenon (see Development of the Ocular Motor System, earlier in this chapter); these phenomena may be caused by uneven, delayed development in the vertical otolithic-ocular pathways (Brodsky and Donahue 200 I !. Tonic vertical deviation as a result of ictal activity is rare. A form of paroxysmal ocular downward deviation that lasts seconds and occurs in neurologically impaired infants with poor vision may also be seen in preterm infants with bronchopulmonary dysplasia but subsequent normal development (Kleiman et al. 1994).

Torsional nystagmus with a jerk waveform may be evoked during vertical pursuit eye movements in patients with lesions of the middle cerebellar peduncle {see Chapter 16). The direction of the fast phase is usually toward the side of the lesion on downward pursuit and away from the side of the lesion on upward pursuit {FitzGibbon et al. 1996).

In normal circumstances, a synkinetic movement, ocular counter-rolling, allows people to maintain horizontal orientation of the environment while tilting the head to either side (Figure 39.12A). When the head is tilted to the left, the left eye rises and intorts as the right eye falls and extorts, within the range of the ocular tilt reflex (approximately

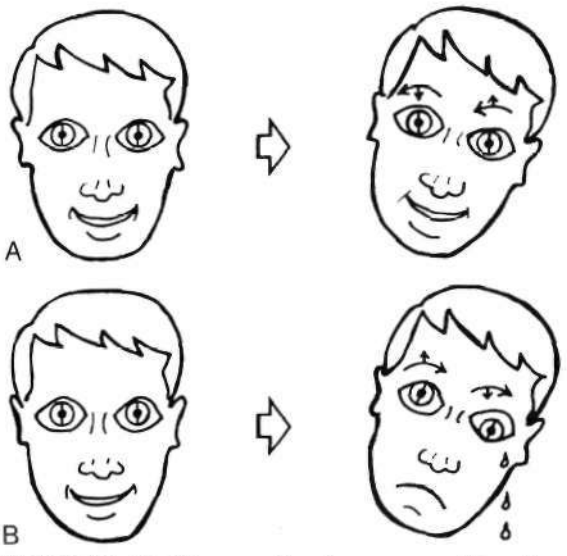

FIGURE 39.12 (A) The normal ocular counter-rolling phenom enon during head tilt. (B) The ocular tilt reaction is a triad o spontaneous skew deviation, cyclotorsion of the eyes, and heac tilt toward the side of the lower eye.

10 degrees from the vertical). The initial transient dynamic (phasic) counter-rolling response results from stimulation of the semicircular canals, whereas the sustained (tonic) response is mediated by the otolith organs and holds the eyes in their new position. Lesions of these pathways result in skew deviation.

Skew deviation is a vertical divergence of the ocular axes caused by a "prenuclear" lesion in the brainstem or cerebellum involving the vertical vestibulo-ocular pathways or, occasionally, the vestibular nerve or end organ. In about 12% of patients, the skew alternates on lateral gaze, or spontaneously. A skew deviation is usually, but not always, comitant (see Chapter 16); when noncomitant, it may mimic a partial third cranial nerve or a fourth cranial nerve palsy. Skew deviation occurs most commonly with vascular lesions of the pons or lateral medulla (Wallenberg's syndrome), presumably because of injury to the vestibular nuclei or their projections. Brandt and Diererich (1998) demonstrated ocular torsion of one or both eyes associated with subjective tilting of the visual vertical toward the lower eye in most patients with skew deviations. With lesions caudal to the lower pons, the ipsilatcral eye was lower (ipsiversive skew), but with lesions rostral to the midpontine level, the contralateral eye was lower (contra-vcrsive skew). Ocular torsion may be present without a vertical deviation and, in either situation, can be detected by blind spot mapping, indirect ophthalmoscopy, fundus photography, or settings of the visual vertical (Halmagyi 1994; Mossman and Halmagyi 1997). Skew deviation with ocular torsion (skew torsion) is a tesult of an imbalance in the tonic vestibulo-oculat pathways, in both the vertical and coronal (roll) planes, which normally stabilize the eyes and head in an upright position to maintain horizontal and vertical orientation.

Alternating skew deviation, in which the hypertropia changes sides, results from vascular or demyelinating lesions at the pretcctal-mesodiencephalic junction, usually involving the INC. This phenomenon, also referred to as *paroxysmal skew deviation* and *periodic alternating skew*, may change spontaneously or with the direction of gaze, in a regular or irregular manner over periods of seconds to minutes. Disorders affecting the cerebellar pathways or cervicomedullary junction cause alternating skew deviation on lateral gaze, in which the abducting eye is hypertropic as a result of presumed superior oblique overaction (Hamed et a I, 1993). This is probably the result of asymmetrical vestibular input to the yoked superiot oblique and contralateral inferior rectus muscles (see Chapter 16, Table 16.2) as a tesult of increased centra) otolithic tone for downgaze (Brodsky and Donahue 2001). Congenital superior oblique overaction causes an A-pattern exotropia (eyes diverge on downgaze) and abducting hypertropia on lateral gaze; it is often associated with disorders of the posterior fossa, such as hydrocephalus and meningomye-locele, and Chiari II malformations. Congenital inferior oblique overaction causes a V-pattern esotropia (eyes converge on downgaze) and is otherwise benign (Brodsky and Donahue 2001).

Bilateral fourth cranial nerve palsies may mimic gaze-dependent alternating skew, in which the adducting eye is hypertropic; however, diplopia is worse on downgaze, with significant excyclotorsion and a V-pattern esotropia,

The OTR consists of the triad of spontaneous skew deviation, cyclotorsion of both eyes, and paradoxical head tilting toward the side of the lower eye (Figure 39.12B) (Arbusow et al. 1998; Ohashi et al. 1998). A tonic (sustained) OTR may occur with a lesion of the ipsilateral utricle, vestibulat nerve, nuclei, or a lesion in the tegion of the contralateral INC and medial thalamus {Halmagyi 1994). A phasic (paroxysmal) OTR occurs with a lesion in the region of the INC, and it may respond to baclofen; when multiple sclerosis is responsible, the OTR also may respond to catbamazepine. An OTR can be induced by sound in patients with perilymph fistulas of the vestibular end organ (Tullio's phenomenon) (Halmagyi 1994).

A partial OTR, in which there is no head tilt, or there is merely ocular torsion, can occur with lesions of the cerebellar nodulus and uvula. This is attributed to an increase in the tonic resting activity of secondary otolithic neutons in the ipsilcsional vestibular nucleus as a result of loss of inhibition from the injured nodulus (Mossman and Halmagyi 1997).

Oculogyric crises are spasmodic conjugate ocular deviations, usually in an upward direction. They occurred in the late stages of postencephalitic Parkinson's disease, aftet the 1918 influenza epidemic, but now are most often caused by neuroleptic medication, particularly halopetidol. They may also occur in patients with head injury,

neurosyphilis, and carbamazepine or lithium carbonate toxicity. Oculogyric crises can also occur in the early stages of autosomal dominant "rapid-onset dystonia-parkinsonism" (Dobyns et al. 1993). A typical attack or crisis lasts about 2 hours, during which the eyes are tonically deviated upward, repetitively, for periods of seconds to minutes. The spasms may be preceded or accompanied by disturbing emotional symptoms, including anxiety, restlessness, compulsive thinking, and sensations of increased brightness or distortions of visual background (similar to occipital lobe seizures). The patient may be able to force the eyes back to the ptimary position temporarily by using voluntary saccades, optokinetic tracking, head rotation, or blinking. Electroencephalograph recordings during the attacks show no epileptiform activity. The eyelids are usually open, although they may rhythmically jerk at times from twitching of the orbicularis oculi. The pupils are not usually involved with mydriasis or aniso-coria. Attacks may be precipitated by excitement. They should be differentiated from benign paroxysmal tonic upward ga2e (see Disorders of Vertical Gaze, earlier in this chapter). Treatment for oculogyric crises includes diphenhydramine, i-dopa, and high-dose trihexyphenidyl.

Disorders of Convergence

Convergence paralysis is usually associated with other features of the dorsal midbrain syndrome (see Chapter 22). Patients with psychogenic convergence paralysis may be distinguished from those with organic disease by absence of pupillary constriction during attempted convergence and preservation of upgaze. Lack of effort is the most common cause of poor convergence, which becomes more difficult with age. Degenerative disorders, such as Parkinson's disease and PSP, are often associated with poor convergence and can be helped with prisms.

Convergence insufficiency, an idiopathic condition that may be partly psychogenic, occurs most commonly in women between the ages of 15 and 45 years (Waltz and Lavin 1993). Symptoms include words running together when reading, occasionally **frank** diplopia at near, and vague symptoms, such as eyestrain, headache, and burning eyes, that are often associated with asthenopia (see Chapter 16). Convergence insufficiency may also be seen after head injury. Because the mechanism of convergence insufficiency is an imbalance between accommodation and convergence, orthoptic exercises (pencil pushups), less commonly prisms, and myopic correction are useful in management.

Spasm of the near reflex, a disorder characterized by intermittent episodes of convergence, miosis, and accommodation, may mimic bilateral, and occasionally unilateral, abducens paresis. The patient may complain of double or blurred vision and is esotropic, particularly at distance; prominent miosis, however, is the due. Spasm of the near reflex may occasionally occur in patients with organic disorders (Goldstein and Schneekloth 1996) but is more commonly psychogenic, either in patients with conversion reactions or in anxious patients in whom the "spasm" is a manifestation of misdirected effort. The differential diagnosis is that of esotropia (Table 39.6). Miosis on gaze testing generally establishes the diagnosis but can be difficult to discern. Accomodative esotropia and latent hypottopia must be excluded by obtaining cydoplegic refraction. Patients with "psychogenic" spasm of the near reflex have associated somatic complaints and behaviotal abnormalities. Blepharoclonus on persistent lateral gaze and poor cooperation in performing motor tasks, such as smiling, opening the mouth, protruding the tongue, and the like (features of neurasthenia and asthenopia), are often found during examination (Table 39.7). Management should focus on identifying the source of the psycho pathology and may require psychiatric evaluation. Strategies such as the use of cycloplegia (homatropine eye drops) to prevent accommodative spasm, thus inhibiting the near triad, are helpful.

Table 39.6: Causes of esotropia

Congenital esotropia (also acquired, cyclic)
Duane's syndrome
Accommodative esotropia
Abducens palsy (unilateral or bilateral)
Spasm of the near reflex
Tonic convergence spasm (part of dorsal midbrain syndrome)
Pseudo-sixth cranial nerve palsy of Fisher
Acute thalamic esotropia
Posterior inrernuclear ophthalmoplegia of Lutz (pseudo-sixth)
Neuromyotonia
Divergence insufficiency
Divergence paralysis
Cyclical oculomotor palsy (spastic phase)
Nystagmus blockage syndrome
Abducens palsy with contracture of antagonist (ipsilatcral medial rectus) during recovery
Myasthenia
Medial rectus entrapment (blowout fracture)
Thyroid myopathy (rare, at presentation)
Orbital disorders (orbital varix, infiltrative lesions)
Wernicke's encephalopathy (bilateral abducens palsies)
Chiari malformation
Rippling muscle disease

Disorders of Divergence

Divergence insufficiency is characterized by sudden-onset esotropia and uncrossed horizontal diplopia at distance, in the absence of other neurologic symptoms or signs. The esotropia may be intermittent or constant, but the patients can fuse at near. The esodeviation (see Chapter 16) is greater at distance than near but is comitant in all directions. Versions and ductions are full, and saccadic velocities, if measured quantitatively, appear normal.

Table 39.7: Features of spasm of the near reflex (psychogenic)

Near tetrad
Convergence
Miosis
Accommodation (blur at distance, myopia by retinoscopy)
Extorsion (exeyclotorsion)
Neurasthenic symptoms
Rlcpharoelonus (frequent blink rate)
Poor cooperation in other motor tasks
Other behavioral changes, such as tunnel vision
May disappear with rapid saccades
Full range of eye movement
With pursuit of own hand
With one eye covered
Doll's eyes with fixation
lee-cold calorics
Normal response
liizarre bL-havior.il response
Normal optokinetic nystagmus if patient encouraged or distracted (e.g., count stripes)
Demeanor
Affective disorder
Tinted glasses or sunglasses
Excessive makeup

Fusional divergence is reduced. The origin of divergence insufficiency is unclear, but it may result from a break in fusion in a patient with a congenital esophoria, usually coming on later in life; it also occurs in patients with midline cerebellar disease. The condition is easily treated with base-out prisms for the distance correction and rarely requires extraocular muscle surgery.

Divergence paralysis, a controversial entity that may be difficult to distinguish from divergence insufficiency, usually occurs in the context of a severe head injury or other cause of raised intracranial pressure. Such patients also have horizontal diplopia at distance, but quantitatively, abducting saccades are slow. Patients with bilateral palsies of the sixth cranial nerve who recover gradually may go through a phase in which the esotropia becomes comitant with full ductions, mimicking divergence paralysis. Divergence paralysis can also occur with Fisher's syndrome, Chiari malformations, pontine tumors, and excessive sedation from drugs.

Central disruption of fusion, or post-trauma tic fusion deficiency, can occur after moderate head injury and causes intractable diplopia, despite the patient's ability to intermittently fuse and even briefly achieve stereopsis. The diplopia fluctuates and varies among crossed, uncrossed, and vertical. Versions and ductions may be full, but vergence amplitudes (see Chapter 16} arc greatly reduced. Prism therapy or surgery is ineffective, but an eye patch may provide symptomatic relief. The location of injury is presumed to be in the midbrain. Central disruption of fusion has also been associated with brainstem tumors, stroke, removal of long-standing cataracts or uncorrected aphakia, and neurosurgical procedures. This condition must be distinguished from bilateral fourth cranial nerve palsies, when diplopia is constant and associated with eyclodiplopia and excyclotropia (>12 degrees), and also from psychogenic disorders of vergence (see Disorders of Convergence, earlier in this chapter).

A congenital inability to fuse is associated with amblyopia or congenital esotropia (see Chapter 16).

The hemislidc (hemifield slip) phenomenon causes diplopia in patients with large visual field defects, particularly dense bitemporal hemianopias or, occasionally, heteronymous altitudinal defects (Borchert et al. 19%). Because of loss of overlapping areas of visual field, patients have difficulty maintaining fusion and can no longer suppress any latent ocular deviation (see Chapter 16).

Cyclical esotropia, also called *circadian, alternate-day,* or *clock-mechanism esotropia,* usually begins in childhood, although it can occur at any age; it can also follow surgery for intermittent esotropia. The cycles of orthotropia and esotropia may run 24-96 hours and parallel many other cyclical or periodic biological phenomena of obscure mechanisms. Patients with cyclical esotropia can decompensate into a constant esotropia that can be corrected surgically.

Ocular ncuromyotonia is a brief episodic myotonic contraction of one or more muscles supplied by the ocular motor nerves, most commonly the oculomotor nerve (Yee and Purvin 1998). It may occur spontaneously or be provoked by prolonged gaze in a particular direction. It usually results in esotropia of the affected eye accompanied by failure of elevation and depression of the globe. When the oculomotor nerve is affected, there may be associated signs of aberrant reinnervation (see Chapter 76). The pupil may be fixed to both light and near stimuli or become myotonic (Abulia and Eustace 1999). Ocular ncuromyotonia occurs most often after radiation therapy tor sellar region tumors; less often it is associated with compressive lesions, such as pituitary adenomas, cavernous sinus meningiomas or aneurysms, thyroid orbitopathy, and occasionally following myelography with thorium dioxide (Yee and Purvin 1998), with Paget's disease of the skull base, or neurovascular compression by a dolichoectatic basilar artery (Tilikete et al. 2000). Demyelinating lesions in the region of the third cranial nerve fascicle can also cause "paroxysmal spasm" of the muscles innervated by the oculomotor nerve (Ezra and Plant 1996) but are usually accompanied by other findings, such as eyelid retraction or paroxysmal limb dystonia (Sethi K, personal communication, 1998). Occasionally no cause can be found. Ocular ncuromyotonia may respond to carbamazepinc or other antiepilcptic drugs. It should be distinguished from superior oblique myokymia (see Chapter 16) and the spasms of cyclical oculomotor palsy.

Cyclical oculomotor palsy is characterized by paresis alternating with "cyclic" spasms of both the extra- and intraocular muscles supplied by the oculomotor nerve. It is a rare condition usually noted in the first 2 years of life,

Table 39,8; Gazc-cvokcd phenomena

1, Physiological phenomena
- Blinks
- End-point nystagmus
- Flaring of the nostrils during vertical saccades
- Mentalis contraction during horizontal saccades (personal observation)
- Oculo-auricular phenomenon: retraction of ear during lateral gaze (or convergence)
- Orbicularis oculi myokymia
- Phosphenes (more intense in patients with optic neuritis, retinal/vitreous detachment: Moore's lightning streaks)

II. Pathological sensory phenomena
- Gaze-evoked amaurosis in the eye ipsilateral to an orbital apex tumor
- Gaze-evoked tinnitus with cerebellopontine angle tumors or Following posterior lossa surgery
- Reverse-Tullio's phenomenon (gaze-evoked swooshing sound) caused by end-organ damage in a patient with Tullio's phenomenon (sound-evoked nystagmus and vertigo) (personal observation)
- SUNCT (Sudden Unilateral Conjunctival injection and Tearing) syndrome with saccades (Pareja et al. 1994)
- Tinnitus with periodic saccadic oscillations
- Vertigo

III. Pathological motor phenomena
- Convergence retraction nystagmus on attempted upgaze (dorsal midbrain syndrome)
- Facial twitching, clonic limb movements, blepharoclonus, lid nystagmus, involuntary laughter and seizures
- Gaze-evoked nystagmus (see Chapter 16)
- Neuro myotonia
- Retraction of the globe in Duane's syndrome
- Superior oblique myokymia (see Chapter 16)
- Synkinetic movements with cyclical oculomotor palsy and with aberrant reinnervation of the oculomotor nerve (see Chapter 77)

although the majority of cases are believed to be congenital and are often associated with other features of birth trauma. During the spasms, which last 10-30 seconds, the upper eyelid elevates, the globe adducts, and the pupil and ciliary muscle constrict, causing miosis and increased accommodation (Loewenfeld 1999); the paretic phase usually lasts longer. Signs of aberrant oculomotor reinnervation (see Chapter *76)* are usually present. Spasms, often heralded by twitching of the upper lid, may be precipitated by intentional accommodation or adduction. Cycles occur irregularly, vary from 1.5 to 3 minutes in duration, persist during sleep, may be suppressed by topical cholinergic agents (eserine, pilocarpine), and are abolished by topical anticholinergic agents (atropine, homatropine) or general anesthesia. The cycles usually persist throughout life, but the spasms of the extraocular muscles may abate, leaving only intermittent miosis.

Symptomatic cyclical oculomotor palsy may occur in later life in patients with underlying lesions involving the third cranial nerve, but the features and cycles are atypical. The mechanism of cyclical spasms is unclear but is well discussed elsewhere (Loewenfeld 1999).

Gaze-evoked phenomena, such as end-point nystagmus, the oculo-auricular phenomenon (Urban et al. 1993), and orbicularis oculi myokymia (Jacome 1997), are physiological, or benign; others, such as gaze evoked nystagmus or tinnitus, are pathological (Table 39.8) and may be the result of damage to the horizontal neural integrator (Lockwood er al. 2001).

Eye Movement Recording Techniques

Oculographic techniques provide clinicians and researchers with objective and quantitative means of analysis that have led to a better understanding of eye movement neurophysiology and ocular motility disorders. Quantitative oculography can measure saccadic latency, velocity, accuracy, pursuit and VOR gain, and nystagmus slow-phase velocity; it can detect unsuspected oscillations and intrusions and identify different nystagmus waveforms. Oculography is used to record both spontaneous and induced eye movements to a target, such as a projected light in front of the subject, or to vestibular and optokinetic stimuli.

Electro-oculography, also known as *electronystagmography* (Chapter 41), is a popular method of quantitative oculography but has a limited range and is unreliable for vertical eye movements because of eyelid artifact. Infrared oculography is more accurate but is also not ideal for vertical eye movements. The most quantitatively accurate technique involves the scleral search coil. Details of all the recording techniques are found in Dcll'Osso and Daroff (1999b).

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Chapter 40
Neuro-Ophthalmology: Afferent Visual System

Robert L. Tomsak

From a conceptual standpoint, it is useful to considet vision as having two components: central vision (macular vision, high acuity, color perception, light adapted) and peripheral vision (ambulatory vision, low acuity, poor color perception, dark adapted). Light is refracted by the cornea and lens and focused on the retina, which is analogous to photographic film. For the best possible vision, the object of tegard must be focused on the most sensitive part of the macular retina, called the *fovea.* Central vision and colot vision are mediated mainly by the cone photoreceptors, which ate of highest density in the foveal region. The cone system functions optimally in conditions of light adaptation. Visual acuity and cone density fall off rapidly as the distance from the fovea inctcascs. For example, the retina that is 20 degtecs eccentric to the fovea is capable only of resolving objects equal to Snellen 20/200 (6/60 metric) optotypes or larger. Rod phototeceptors are present in highest numbers approximately 20 degrees from the fovea and are more abundant than cones in the more peripheral retina; rods function best in dim illumination. The total extent of the normal peripheral visual field in each eye is approximately 60 degtces superior, 60 degrees nasal, 70-75 degrees inferior, and 100 degrees temporal (Figure 40.1; see Chapter 14). Information transduced by the retina is sent from each eye to both hemisphctes of the brain by the optic nerves, each of which contains approximately 1.2 million axons. Axons that atisc from the ganglion cells of the nasal retinas of each eye cross in the optic chiasm to the contralateral optic tract. Axons from the temporal retinas do not decussate at the chiasm. The percentages of crossed and uncrossed axons in the human optic chiasm ate approximately 53% and 47%, respectively. Because of the optical properties of the eye, the nasal retina teceives visual information from the temporal visual field, and the temporal retina teceives information from the nasal visual field (see Figure 40.1). Similarly, the retina supetior to the fovea sees the inferior visual field and vice versa. These points ate clinically impottant in evaluating visual loss {see Chapter 14).

Visual information is further sttatified in the lateral geniculate body (LGB), which is the only way station between the retinal ganglion cells and the primary visual cortex. The LGB is a portion of the thalamus with six layers. Axons from ipsilateral retinal ganglion cells synapse in layers 2, 3, and 5; conttalateral axons synapse in layers 1, 4, and 6. Layers 1 and 2 of the LGB are called *magnocellular layers;* they receive input from M retinal ganglion cells. The magnocellulat pathway is concerned mainly with movement detection, detection of low contrast, and dynamic form perception. After projecting to the ptimaty visual cortex (visual atea 1, VI, or Brodmann's area 17), information from the M pathway is distributed to V2 (part of area 18) and V5 (junction of areas 19 and 37). Layers 3-6 of the LGB are called *parvacellular* and receive input ftom retinal P cells, which are color selective and respond to high contrast. These cells project to a teas V2 and V4 (fusiform gyrus) (Zeki 1993). Superior fibers that leave the LGB go straight back to the primary visual cortex; inferior fibers loop antetiotly around the superior tempotal horn of the lateral ventricles (Meyer's loop). Because these fibers are approximately 5 cm from the tip of the temporal lobe, they are sometimes damaged during temporal lobectomy, resulting in a "pie in the sky" homonymous visual field defect.

The ptimaty visual cortex (striate cottcx, atea VI, or Brodmann's area 17) is in the occipital lobe of the btain. Macular vision is represented most posteriorly at the

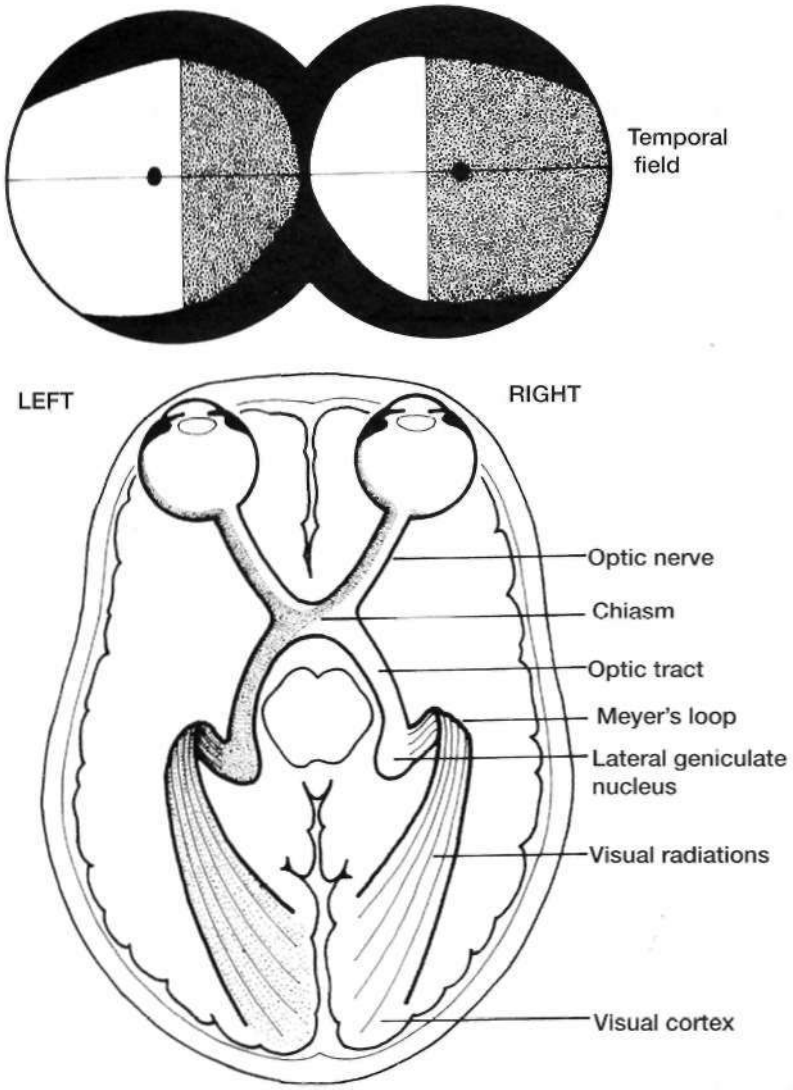


FIGURE 40.1 Visual pathways.

occipital tips. Each fovea appears to project to both occipital lobes. The peripheral visual field projects to the visual cortex that lies more anteriorly. The nonoverlapping part of the most peripheral temporal field (monocular temporal crescent) represents unpaired crossed axons from the nasal retina, which project to the most anteromedial part of the visual cortex. The primary visual cortex has interconnections with numerous visual association areas (Zeki 1993).

NEURO-OPHTHALMOLOGICAL EXAMINATION OF THE AFFERENT VISUAL SYSTEM

The neuro-ophthalmological examination makes use of ophthalmic tools and techniques but aims at neurological diagnosis. It therefore provides a bridge between neurology and ophthalmology. Many neurologists are unfamiliar with detailed ophthatmological methods, and ophthalmologists often are not facile with neurological localization.

Examination of Visual Acuity

Visual acuity describes the spatial limit of visual discrimination. Visual acuity always should be measured with each eye individually and with the best possible optical correction (i.e., using the patient's glasses); other optical means such as the pinhole device or a refraction may be needed (Clascr *1999).* The resultant response, called *best corrected* visual acuity, is the only universally interpretablc measurement of central visual function. Ideally, vision should be measured both at a standard distance (usually 20 ft, or *6* m) and also at a near distance (usually *0.33* nil- The notation 20/20 *{6/6* metric) means that the patient (numerator) is able to see the same optotypes at 20 ft as would a normal

subject (denominator). A vision of 20/60 (6/18 metric) means that the patient sees a standard optotype at 20 ft that a normal person sees at 60 ft.

A disparity between the best corrected distance and near visual acuity often indicates a specific problem. For example, the most common cause of distance acuity being better than near acuity is uncorrected presbyopia. Other conditions in which distance vision often is better than near vision include Parkinson's disease and progressive supranuclear palsy. Common causes of near acuity being better than distance acuity are myopia and congenital nystagmus. In the latter disorder, convergence needed for near vision damps the nystagmus amplitude, resulting in more consistent foveation and better binocular near acuity than distance acuity.

When measuring near vision, the reading card should be held at the specified distance of 14 in., or 0.33 m, to control for image size variation on the retina. If a nonstandard distance is used, it should be specified clearly in the medical record.

Two types of near cards are readily available; one has numbers and the other type has written text (Figure 40.2). Both are useful, but in neurological or neuro-ophthalmological practice, a near card with text measures not only visual acuity hut also reading ability. A disparity between these measurements may reveal a disturbance of cortical functions, specifically language and visual perception (see Chapter UB).

Contrast Sensitivity Testing

Contrast sensitivity testing measures the perception of lines of different width (spatial frequency) and varying degrees of

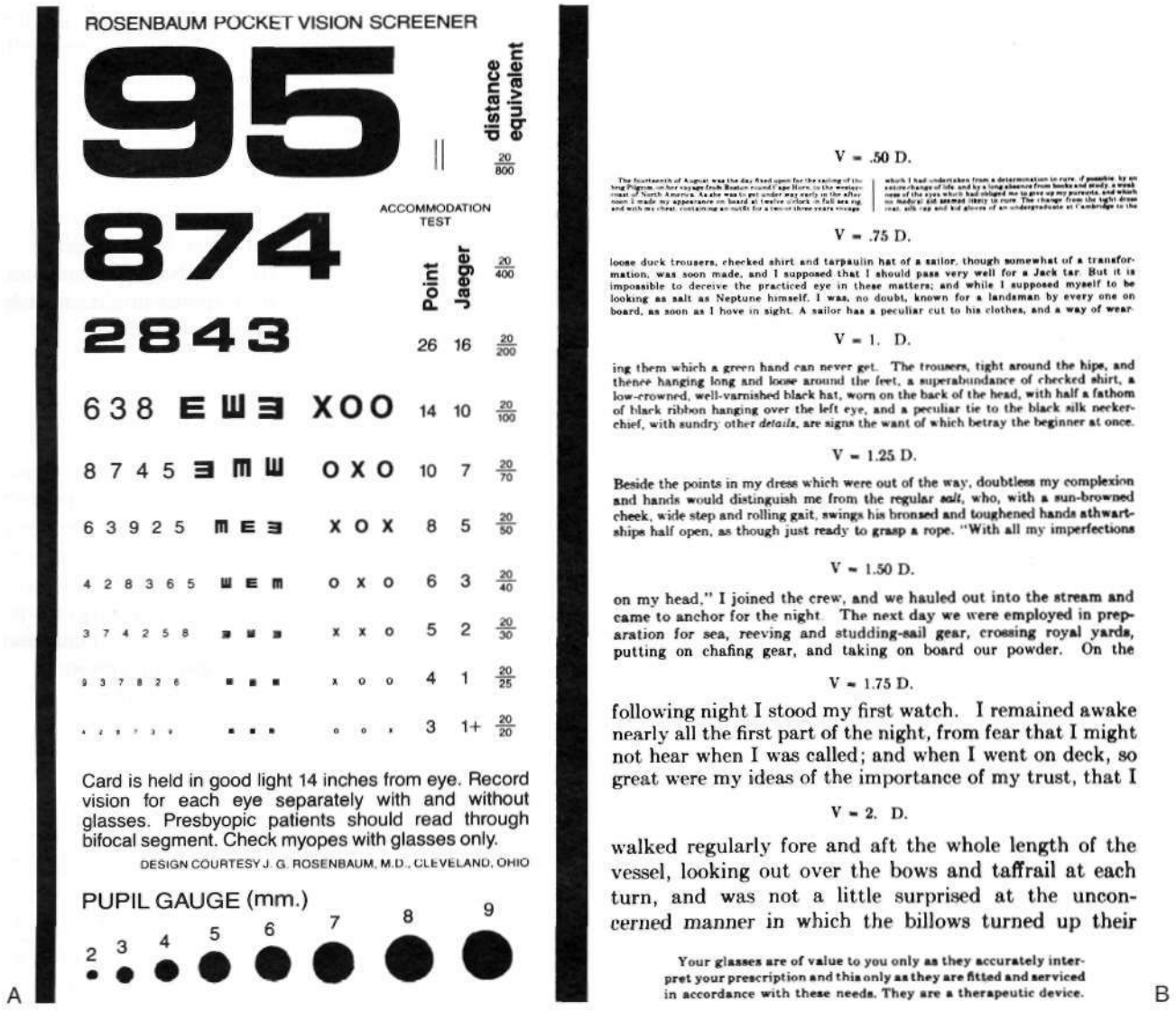


FIGURE 40.2 (A) Rosenbaum-style near vision card. (B) Near vision card with written text.

contrast. This visual function is different from visual acuity and is abnormal in numerous diseases of the eye and retrobulbar visual pathways. Measurement of contrast sensitivity in the office setting requires a special series of test plates (e.g., Atden gratings or Peli Robson chart). More complex testing is possible with computer-generated sine wave gratings.

Light Stress Test

Some disorders that affect the macula are difficult to observe with the direct ophthalmoscope. Fortunately, the light stress (or photo stress) test is an excellent method for determining whether a reduction in visual acuity is caused by an abnormality in central retinal function (Glaser 1999). The test is performed by first measuring the best corrected visual acuity with each eye. Then die eye with faulty vision is occluded and the normal eye is subjected to a bright light for 10 seconds. Immediately thereafter the patient is instructed to read the next, larger line, and the recovery period is timed. The same procedure is done with the other eye. and the results are compared. Fift; seconds is the upper limit of normal for visual recovery. In diseases that affect the macula, it is not unusual for the recovery period to take several minutes.

Color Vision Testing

Disordered color perception, especially if asymmetrical between the eyes, is a good indication of optic nerve dysfunction; symmcttical acquired color vision defects should raise the possibility of a retinal degeneration such as cone-rod dystrophy. Congenital color vision anomalies occur in approximately 8% of men and 0.5% of women. Techniques for measuring color vision range from the simple to the sophisticated. Holding a brightly colored object in front of each of the patient's eyes individually and asking for a comparison of both brightness and color intensity is a useful office and bedside technique for detecting central color defects. Also, testing with colored objects on each side of fixation often can detect a subtle hemianopia.

More formal estimates of color vision can be made with standard pseudoisochromatic color charts (Ishihara's or Hardy-Rand-Rittler) or with sorting tests such as the Farnsworth-Munsell or Sahlgren's saturation tesr.

Examination of the Pupils

Examination should include measurement of pupil size, the direct and consensual reaction to light, the accommodative reaction, and the presence or absence of an afferent pupillary defect. If anisocoria is found, ptosis should be looked for, keeping in mind the possibility of Horner's syndrome or third cranial nerve paresis. This information should be recorded in an easily understood format; for one example, see Table 40.1.

The measurement of pupil size and light reaction should be made in constant dim illumination with the patient fixating an immobile distance target. At times it is useful to measure pupil sine in the dark and also in bright ambient light. For example, anisocoria caused by oculosympathetic paresis (Horner's syndrome) often is more pronounced in the dark because the affected pupil does not dilate well. Conversely, a pupil with parasympathetic denervation (e.g., Adie's tonic pupil) often is more evident in bright light because of abnormal constriction (see Chapter 17).

When one is measuring the light reaction or looking for the afferent pupillary defect, the brightest light available should be used. The reaction to a near object is best brought out by having the subject look at his or her own finger or thumb at a distance of 15-30 cm. Using this method, one can observe a near pupillary response in a completely blind person because of proprioceptive influences.

The observation of a relative afferent pupillary defect (Gunn's pupil or Marcus Gunn's pupil) is an invaluable indication of a conduction defect in the optic nerve. Indeed, many neuro-ophtbalmologists regard this as the most important pupillary abnormality. This difference in pupillary reaction is best brought out by alternately illuminating one pupil and then the other, hence the name *swinging flashlight test.* The swinging flashlight test also can be thought of as a comparison of the direct and consensual response in the same eye. Normally, these pupillary responses are equal; in an eye with an optic nerve conduction defect the direct response is less than the consensual response.

The test for a relative afferent pupillary defect should be performed as described in Table 40.2 and shown in

Tabic 40.1: Simple method of record "::ipillary examination

	Size (mm)	*Direct light reaction*	*Comemua! reaction*	*Near response*
Right eye	4,0	+4	+2	+4
Left eye	4.0	+2	+4	+4

Note: In this example, the resting pupil size is equal in the two eyes at 4 mm. The pupillary reactions can he estimated using 1+ to *4+* scale, as shown here, or by actually recording the pupil sixe before and after the light or near response. In the example shown, the direct response is better in the right eye than in the left eye, and the reverse is true for the consensual reaction. This table illustrates a left relative afferent pupillary defect.

Tabic 40.2: Testing for the relative afferent pupillary defect

1. The patient should fixate at a distance to minimize fluctuation in pupillary size and accommodative miosis.
2. A light bright enough to cause maximum pupillary constriction should be used.
3. Each pupil should be checked individually for its direct light response, which can be graded on a scale of 1-4 (see Table 40.1).
4. The light should be moved quickly to illuminate each eye alternately every 1-2 sec (the swinging flashlight test of Levitan).
5. The initial constriction of the pupil and the presence or absence of pupillary escape should be observed.
6. Only 3 or 4 swings of the light should be made to minimize bleaching of the retina with subsequent slowing of the pupillary reaction.

Figure 40.3. There is one caveat: The swinging light test brings out an asymmetry of optic nerve conduction. Therefore if both nerves are injured to the same extent, no obvious telative afferent pupillary defect is observed. Furthermore, severe macular or retinal disease can produce Marcus Gunn's pupil, but these problems are almost always apparenr on funduscopic examination. By contrast, minimal optic nerve disease commonly yields an obvious relative afferent pupillary defect. See Chapter 17 for a more complete discussion of pupillary abnormalities.

Light Brightness Comparison

Light brightness comparison can be considered as a subjective swinging flashlight test. The subjective appreciation of light intensity often is impaited in optic nerve disease but not in macular problems. The test is done by directing a bright light into both eyes in succession, and the patient is asked to estimate the difference in subjective brightness as a percentage. For example, the examinet might ask, "If this light [normal eye illuminated] were worrh $1, in terms of light brightness or intensity, what would this one be worth [abnormal eye illuminated]?" The patient often is able to estimate the difference in perceived brightness.

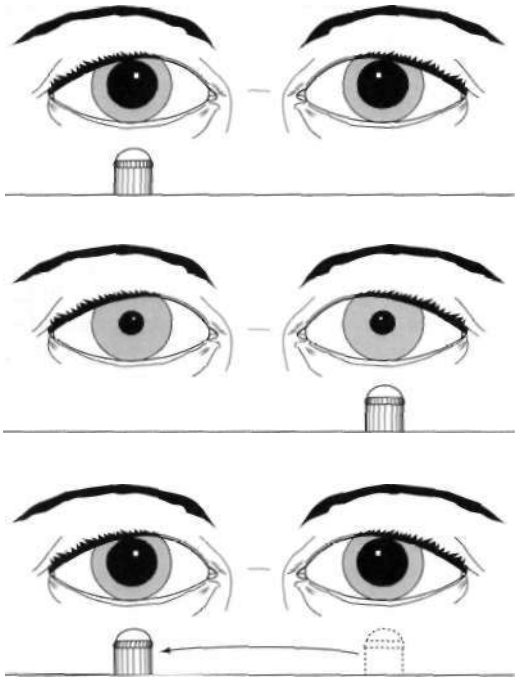


FIGURE 40.3 Right relative afferent pupillary defect (Marcus Gunn's pupil) from right optic nerve lesion. (A) Right eye illuminated. Poor direct and consensual reaction. (B) Excellent direct and consensual response. (C) Light swung from left to right with redilatation of both pupils.

Visual Field Testing

Evaluation of the visual fields is vital in everyone with unexplained visual loss. Confrontation testing should be part of the routine neurological examination. Numerous techniques are available for visual field examination, ranging from simple confrontation testing to sophisticated thteshold static perimetry. For the purposes of this discussion, simple, practical techniques adapted from the teachings of J. Lawton Smith are emphasized, and the mote complicated methods are summarized briefly.

The first assessment involves asking the patient to observe the examinet's face or another part of the environment with each eye and to report whether anything is missing or blurred; Smith called this step the "history field." For example, a patient with optic neuritis and a centtal scotoma might look at a face and report that the eyes and nose are missing. Another patient with ischemic optic neuropathy and an inferior altitudinal visual field defect might not see anything below the nose. Similarly, to a patient with a homonymous hemianopia, one half of the face would appear to be missing.

Confrontation testing should follow. Although there are many methods, a simple, thorough examination can be done by finger counting in quadrants coupled with hand comparison. The steps are as follows:

1. The physician has the patient cover one eye and fixate on the center of the examiner's face.
2. *dinger counting in the quadrants:* The physician holds up fingers sequentially in each of the four quadrants of the visual field and asks the patient to count how many are seen.
3. *Simultaneous finger counting using both hands:* If step 2 is completed normally, the physician asks the patient to count the number of fingers he or she is displaying with both hands, first in both the right and left upper quadrants of the patient's visual field, then in both the right and left lower quadrants. The patient is then asked to add the total number of fingers shown with

both hands. This stage of confrontation testing often brings out evidence of extinction, hemineglect, or problems with calculation. It also has the effect of stabilizing wandering visual fixation.

4. *Simultaneous band comparison:* Finally, both hands are held open in the right and left upper and lower quadrants, and the patient is asked to compare the quality of the images. For example, a patient with a •subtle bitemporal hemianopia might be able to pass steps 1 through 3, but when shown hands on either side of the vertical midline the patient might state that the hands in the temporal hemifields arc not as clear as the ones held in the nasal hemifields.

A major advantage to the finger counting method over kinetic methods of confrontation testing is that the potential for Riddoch's phenomenon is minimized. Riddoch's phenomenon is a dissociation between the visual perception of form and movement so that the patient can perceive only moving targets in a hemianopic visual field (Zeki and Ffytche 1998). This phenomenon occurs in homonymous hemianopias that have resulted from injuries to the occipital cortex. Therefore a hemianopia may be missed if the examiner uses only a moving target, such as wiggling fingers in the far periphery.

Confrontation methods using colored objects can be effective in detecting visual field abnormalities. Confrontation testing is useful for patients with constricted visual fields. Normally, as the distance from the examiner to the patient increases, the visual field expands, or funnels; with psychogenic visual field constriction, the field remains the same size even at longer distances, or it tunnels (Figure 40.4).

Measurement of the central 20 degrees of visual field (in each eye separately) can be done using Amsler's grid chart (Figure 40.5). The chart is held in good light at a distance of 30 cm from the eye, with the patient wearing reading glasses, if needed. The following questions are asked:

Can you sec the spot in the center of the square?
"While looking at the center, can you see the entire square, or are any sides or corners missing?
While you are looking at the center, are any small squares missing or distorted?

If any abnormal responses to these questions arc given, the examiner should ask the patient to draw the abnormal areas on the chart. This can then be kept in the patient's medical record.

Patients with a central scotoma often report that the center of the grid is missing or blurred, those with hemianopic defects say one half of the grid is missing, and those with macular disease may report that some of the lines are wavy or distorted (see Chapter 14).

Numerous other methods for examining the visual field are available (Glaser 1999) but are beyond the scope of this chapter and the expertise of most neurologists. This section provides only an overview.

Examination of the entire field of vision requires a perimeter; the tangent screen measures only the central 30 degrees of visual field at a distance of 1 m. Perimeters can be divided into those that use a moving stimulus (kinetic) and those in which individual spots in the visual field are tested statically. Most static perimeters available today are automated and driven by computerized examination strategies. Static perimeters may measure the actual visual threshold at defined points in space (threshold static perimetry) or may test these points with light of preset luminance (suprathreshold static perimetry). A commonly used kinetic machine is the Goldmann instrument; popular automated perimeters include the Octopus and Humphrey

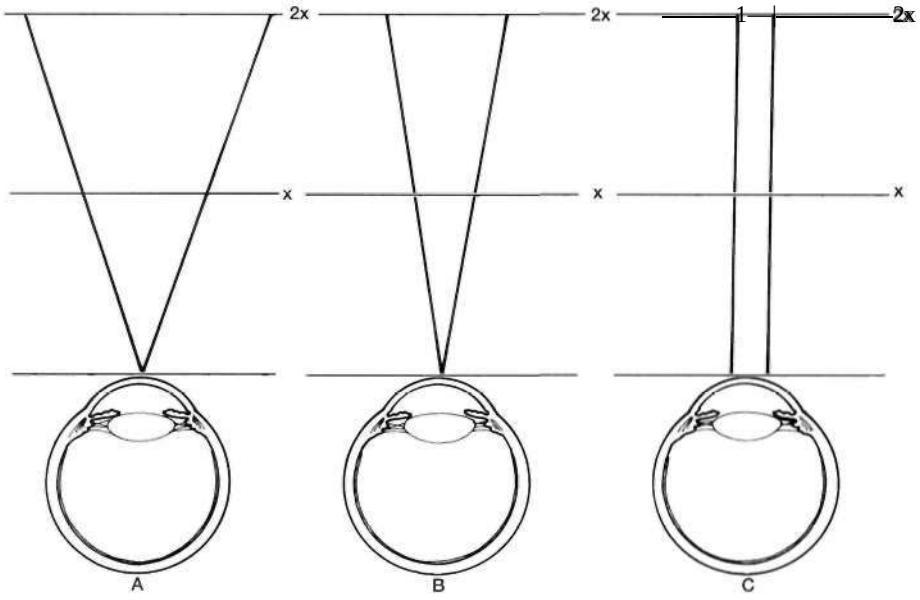


FIGURE 40.4 (A) Normal visual field enlarges with increase in testing distance; it "funnels." (B) Constricted visual field from organic disease also proportionally enlarges. (C) Constricted visual field of psychogenic origin usually docs not enlarge as testing distance increases; it "tunnels." (Data from Trobc, J. D. & Glaser, J. S. 1983, *The Visual Fields Manual: A Practical Guide to Testing and interpretation*, Triad, Gainesville, Fla., p. 135.)

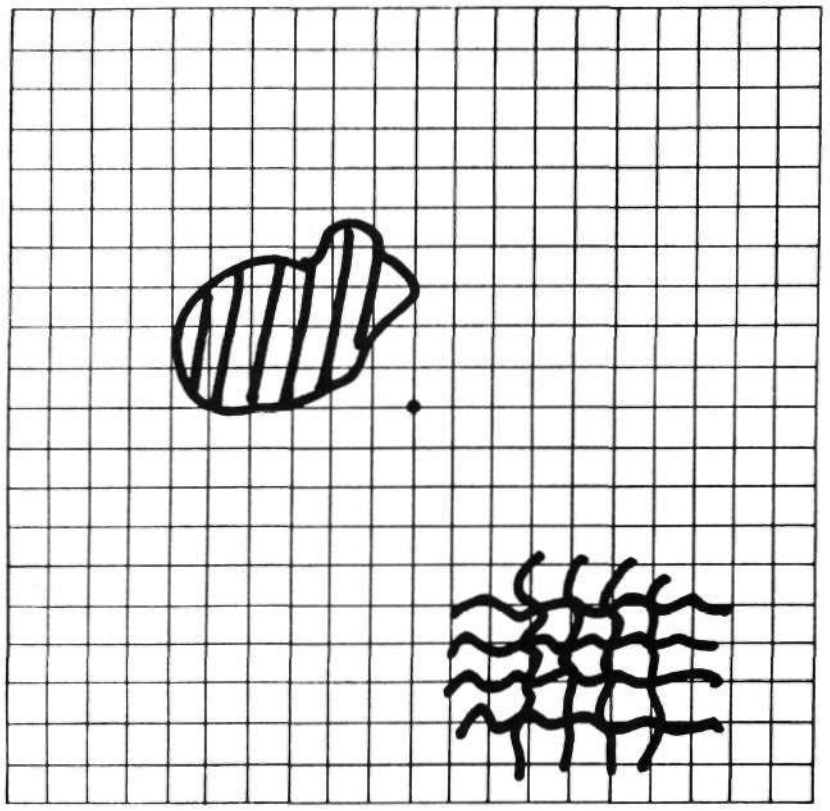


FIGURE 40.5 Amsler's grid chart. Upper left: Paracentral scotoma. Lower right: Metamorphopsia (straight lines appear wavy).

units (threshold static perimeters). On theoretical grounds, threshold static perimeters are the most sensitive and quantitative, but the examination is time consuming and tiring for the subject. Many patients with neurological disorders are unable to sit for an examination that may take as long as 45 minutes per eye and requires intense concentration and alertness. Therefore, many neuro-ophthalmologists rely on kinetic perimeters of the basic Goldmann design because of their versatility.

VISUAL FIELD ABNORMALITIES

Eight general rules for visual field interpretation are summarized in Table 40.3. Comments about six of these general rules are discussed in the following sections.

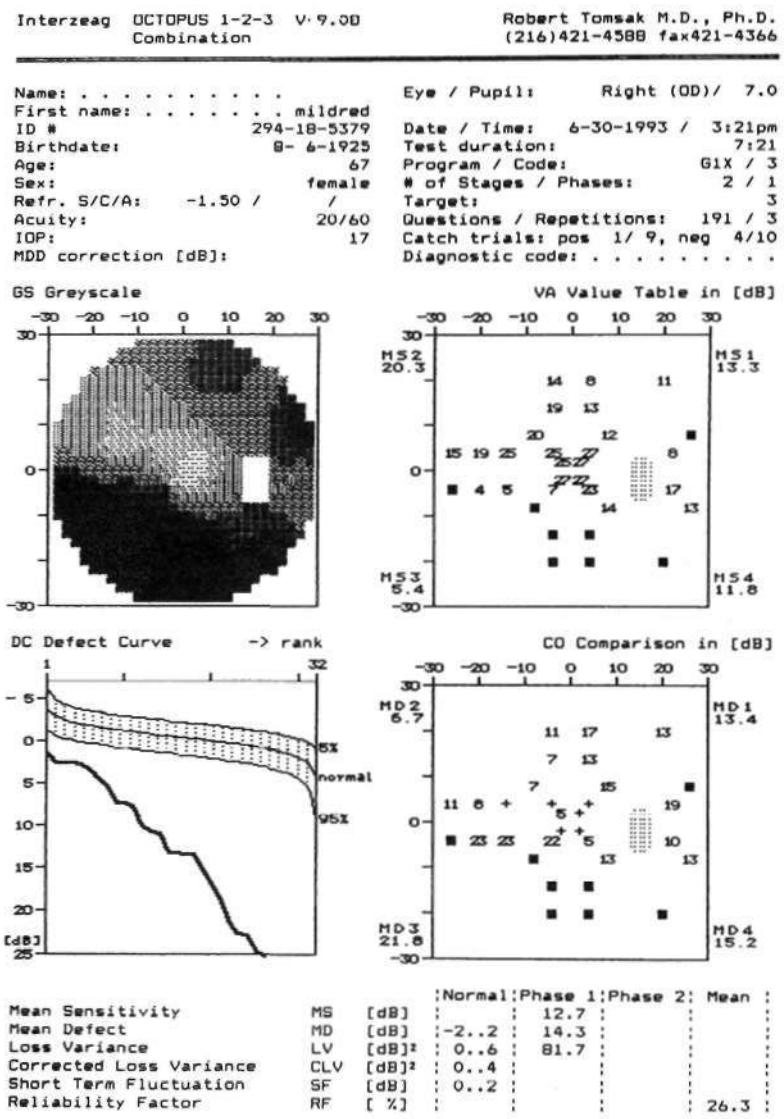
Rule 1

Optic nerve lesions produce prechiasmal visual field abnormalities that are often characteristic. Ischemic optic neuropathy usually leads to inferior altitudinal defects (Eigure 40.6A), optic neuritis usually manifests as a cecocentral scotoma (Figure 40.6B), and compressive lesions cause abnormalities in the peripheral field as well as centrally (Eigure 40.7).

A lesion involving the posterior optic nerve and anterior chiasm results in a junctional scotoma (i.e., ipsilateral cecocentral scotoma and contralateral upper temporal defect) from involvement of ipsilateral and crossing fibers from the opposite inferonasal retinal (Willbrand's anterior knee). Binasal hemianopias usually are the result of local ocular disease {Figure 40.8); these diseases include papilledema, ischemic optic neuropathy, glaucoma, optic

Tabic 40.3: General rules of visual field interpretation

1. Lesions of the retina and optic nerve produce field defects in the ipsilateral eye only, unless the lesions are bilateral.
2. True hitemporal hemianopia is caused only by a lesion at the optic chiasm.
3. Retrochiasmal lesions produce homonymous visual field defects.
4. Anterior retrochiasmal lesions produce incongruous homonymous visual field defects.
5. Posterior retrochiasmal lesions produce congruous visual held defects.
6. Temporal lobe lesions give slightly incongruous homonymous hemianopias involving the upper quadrant,
7. There is no localizing value to a complete homonymous hemianopia except that the lesion is retrochiasmal and contralateral to the visual field defect.
8. A unilatetal homonymous hemianopia does not reduce visual acuity.



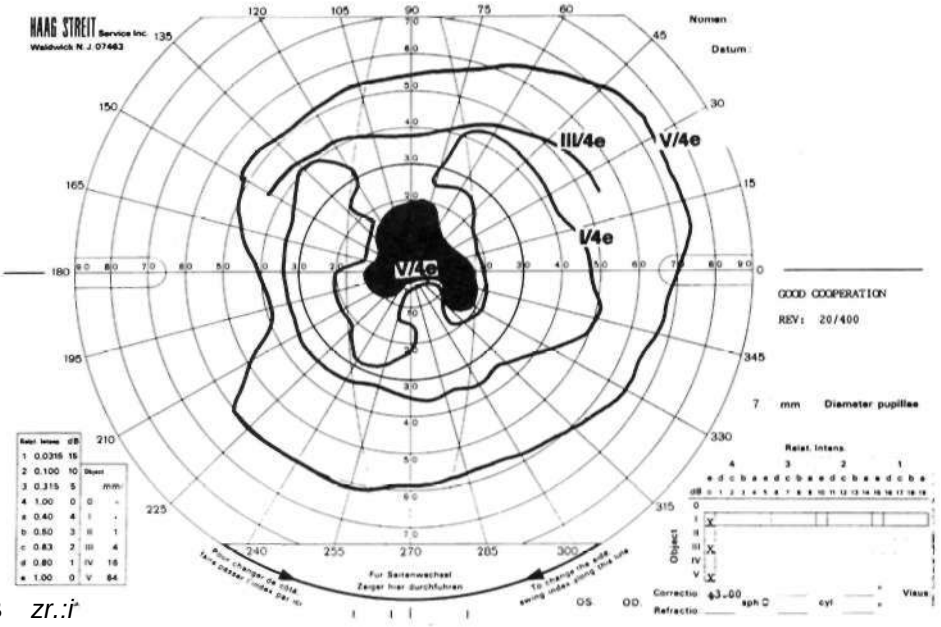


FIGURE 40.6 (A) Threshold static measurement of central 30 degrees of right visual field (Octopus 1-2-3 perimeter; G1X program). Sixty-seven-year-old woman with anterior ischemic optic neuropathy OD and inferior altitudinal visual field defect. Upper left: Gray-scale measurement; darker areas correspond to abnormal areas of visual field (displays measured and interpolated data). Area of blind spot is not investigated and therefore is reproduced as white, not black. Upper right: Mean sensitivity (MS) display in decibels. The decibel (dB) is a logarithmic relative scale to quantify differential light sensitivity (dB = 0.1 log-unit of stimulus intensity). Lower right: Mean defect (MD) display (MD = mean of the deviation of measured dB from age-matched normal values). Positive values indicate decreased sensitivity. Lower left: Cumulative defect curve (Bebie curve) arranges test locations with the least difference on the left side. This curve helps differentiate local from diffuse damage. (B) Kinetic perimetry of right visual field by Goldmann's technique.

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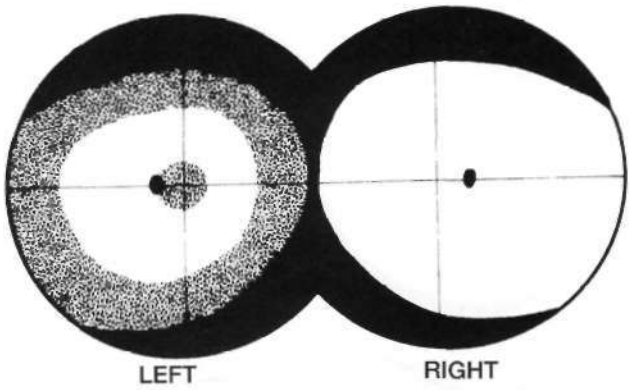

FIGURE 40.7 Contraction of left visual field with cecocentral scotoma caused by compressive optic neuropathy. Normal right visual field.

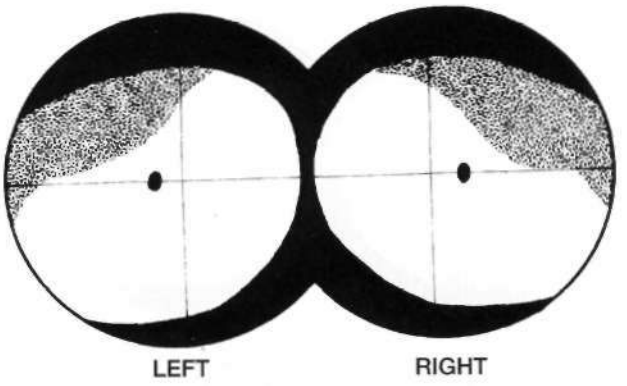

FIGURE 40.9 Pseudobitemporal hemianopia. Note that vertical midline is not respected.

nerve drusen, congenital optic nerve pits, optic nerve hypoplasia, and sectoral retinitis pigmentosa. Less often, hydrocephalus, ectatic parasellar arteries, and basal tumors cause binasal field defects. Binasal visual field defects of organic causes do not respect the vertical visual field meridian, whereas psychogenic binasal defects may.

Rule 2

True bitemporal hemianopias are the hallmark of chiasmal disease; the common causes are discussed in Chapter 14. Less commonly, ischemia, radiotherapy, and demyelination can cause chiasmal syndromes. Bitemporal defects that cross the vertical midline (pseudobitemporal hemianopias) are almost always caused by a congenital anomaly causing rotation or tilting of the optic discs (Figure 40.9) (see Chapter 15). Bilateral cecocentral scotomas can also masquerade as bitemporal field defects.

Rule 3

A homonymous visual field defect is present in the same hemifield or visual quadrant of each eye. The only exception to this rule is the monocular temporal crescent syndrome, in which only unpaired visual fibers residing in the contralateral anterior medial occipital lobe are affected.

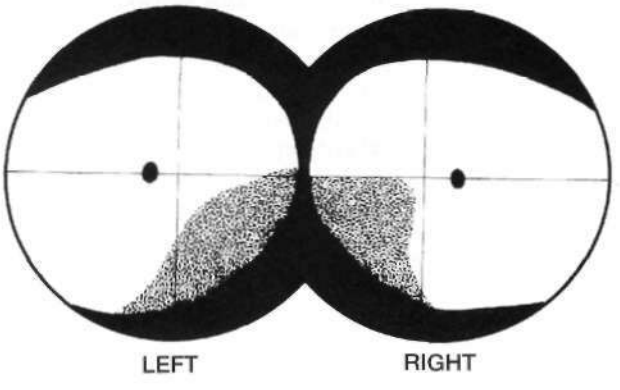

FIGURE 40.8 Binasal hemianopic visual field defects.

Rule 4

Incongruous hemianopias are seen in more anterior retrochiasmal lesions (e.g., those affecting the optic tract or temporal lobe; Figure 40.10). Optic tract hemianopias often are associated with a contralateral relative afferent pupillary defect.

Rule 5

Congruous homonymous hemianopias have patterns that are identical in each affected visual field; they usually result from occipital lobe infarcts (Figure 40.11).

Rule 8

Even a complete unilateral homonymous hemianopia does not decrease the visual acuity because the remaining macular cortex in the opposite hemisphere is still functioning. If input to both macular cortices is abnormal, however, then central acuity often is diminished, but the acuities should be equal in both eyes. If the visual acuities are unequal, there must be another explanation for the visual asymmetry.

NONORGANIC (FUNCTIONAL OR PSYCHOGENIC) VISUAL DISTURBANCES

Functional visual problems may represent up to 5% of an ophthalmologist's practice (Tomsak 1995). A variety of synonyms exist for these disorders, including *hysterical*

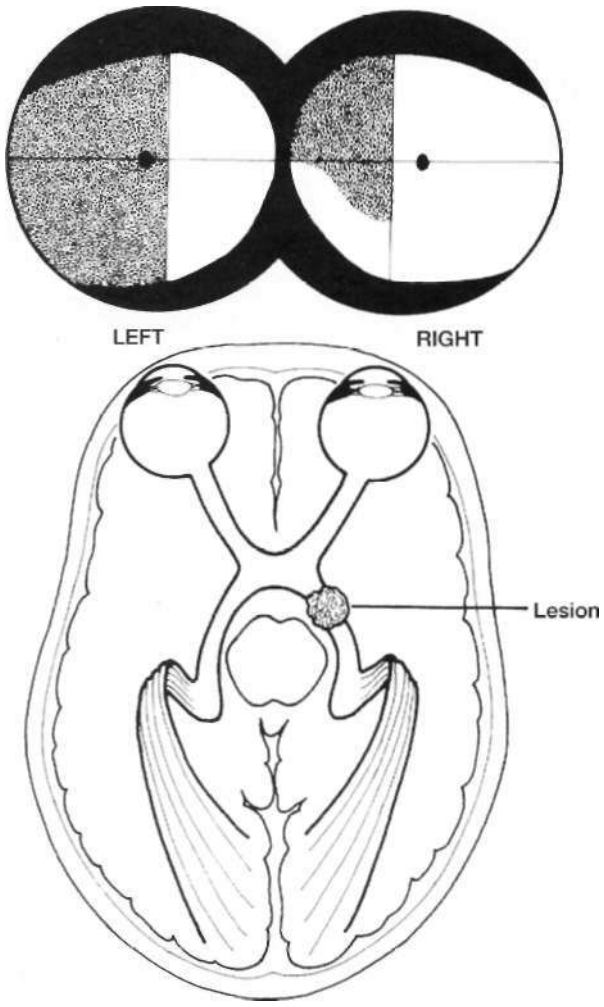

FIGURE 40.10 Incongruous left homonymous hemianopia from right optic tract lesion.

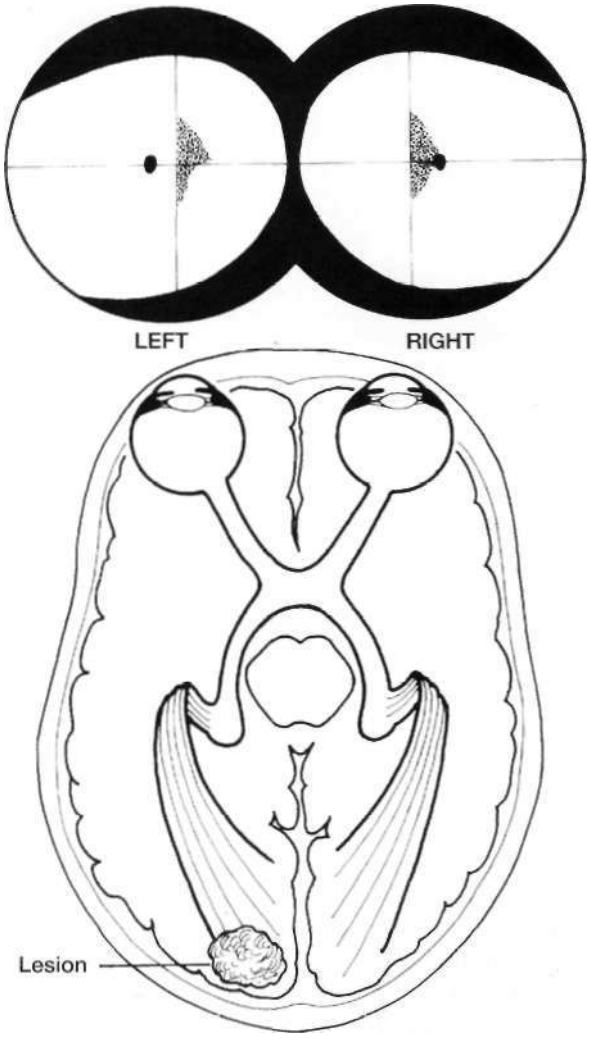

FIGURE 40.11 Congruous paracentral right homonymous hemianopia.

visual loss, psychogenic amblyopia, and *ocular conversion reaction* (Table 40.4).

Diagnostic Techniques

A careful social and family history is needed for evaluating patients with psychogenic visual disturbances, especially regarding abuse, peer pressure, and visually impaired friends and family members. Different tests are necessary for different functional visual disturbances. For example, if a person claims total blindness in one or both eyes, important tests might include examination of the pupils, optokinetic nystagmus, and the use of a large mirror held close to the face to induce eye movement via a pursuit refit[1] x. If the patient claims some vision, then it is often useful to test for disparity in distance and near acuity and for stereopsis.

Visual fields are extremely important and usually have one of four patterns: tubular contraction, spiral, star-shaped, and isopter inversion (Figure 40.12). A confrontation field done at different distances can be useful in evaluating a patient with tunnel vision. Normally the area of visual field increases with increasing distance from the object. In other words, the normal visual field funnels. Thus

Table 40,4; Some forms of functional visual disturbance

Visual acuity loss (one or both eyes)
Visual field loss (unilateral or bilateral)
Color perception abnormalities
Convergence insufficiency or accommodation insufficiency
Convergence spasm
Loss of depth perception
Diplopia
Night blindness
Photophobia
Pharmacological pupils
Voluntary nystagmus

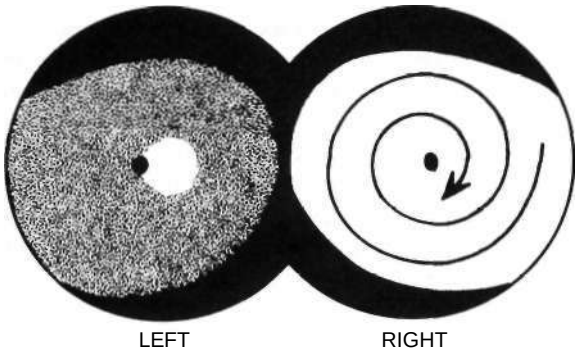

FIGURE 40.12 Two common visual field abnormalities with psychogenic vision loss. Left: Concentric (tubular) contraction. Right: Spiral pattern (seen only with kinetic visual field testing).

the visual field of a patient with an organic cause for tunnel vision should enlarge as the distance from the examiner or object increases. If the field does not expand at longer distances, the visual disturbance is not organic (see Figure 40.4). Isopter inversion means that the visual field plotted with a larger test object is smaller than the visual field plotted with a smaller test object; this also does not have an organic cause.

The use of visual evoked potentials (VEPs) to diagnose functional visual loss can be frustrating. If the VEP is normal, useful information is gained, but factitious abnormalities in the VEP are easily induced by normal subjects who fix eccentrically on the target or who converge and accommodate to blur their vision. Therefore an abnormal VEP is not always diagnostic of an organic visual disturbance.

Approximately one half of patients with functional visual disorders improve with time and reassurance (Tomsak 1995). Factors that indicate a good prognosis include youth and the presence of anxiety, whereas older age and depression are associated with a poor prognosis.

Pediatric Afferent Neuro-Ophthalmology

Examination techniques for children often differ from those for adulrs, and the reader is referred to more comprehensive discussions of the pediatric neuro-ophthalmological examination (Tomsak 1995; Brodsky, Baker, and Hamcd 1996). Many of the same diseases that affect vision in adults also affect children, but some are specific to youths or present during early growth and development (Table 40.5). Optic nerve hypoplasia, Leber's congenital amaurosis, and albinism are discussed in more detail.

Tabic 40.5: Neurological causes of vision loss in children

Albinism
Leber's congenital amaurosis
Gliomas of the optic nerves or chiasm
Craniopharyngiomas
Optic nerve hypoplasia
Other optic nerve dysplasias
Hereditary optic atrophies

Optic Nerve Hypoplasia

Optic nerve hypoplasia is a congenital and nonprogressive condition that may reflect a primary defect in differentiation of the retinal ganglion cell axons. The optic disc and scleral canal are of subnormal diameter; a peripapillary ring of pigmentation often is present, called the *double-ring sign* (see Chapter 15). The hypoplasia may be segmental, as in children born of insulin-dependent diabetic mothers.

Optic nerve hypoplasia may Iv unilateral 01 bilateral. Visual acuities may be variable in affected eyes and can be anywhere from 20/20 to light perception. Associated ocular conditions include microphthalmos, aniridia, and albinism. Astigmatism is common. Visual field defects usually are nasal or inferior altitudinal.

Patients with bilateral optic nerve hypoplasia often have strabismus, nystagmus, endocrine disturbances, and developmental delay. The common endocrine disturbances are hypothyroidism, growth hormone deficiency, diabetes insipidus, and neonatal hypoglycemia. Bilateral optic nerve hypoplasia in association with absence of the septum pelliicidum and hypopituitarism is called *septo-optic dysplasia* (de Morsier's syndrome). Optic nerve hypoplasia usually is sporadic but may be associated with fetal alcohol syndrome, marernal diabetes, or maternal anticonvulsant ingestion during pregnancy.

Leber's Congenital Amaurosis

Leber's congenital amaurosis is most broadly defined as a syndrome of bilaterally poor vision beginning in early childhood that is associated with a depressed or absent electroretinogram result. It is estimated to be the cause of 10-18% of childhood blindness. This disease is not related to Leber's hereditary optic neuropathy (see Chapters 14 and 15). Visual acuity in Leber's congenital amaurosis usually is less than 20/200 (6/60 metric). The retinal pigment epithelium has a salt-and-peppcr appearance, and rerinal vascular attenuation is sometimes marked. Optic disc swelling may be present. Pathological changes in the retina are variable and may affect all layers or just the ganglion cells. Nystagmus occurs in approximately 75% of cases, and oculomotor apraxia and other eye movement problems may be present. Approximately 30% of patients with Leber's congenital amaurosis have neurological abnormalities, which include hyperkinetic behavior, poor coordination, spastic paraparesis, psychomotor retardation, and hydrocephalus. Patients may exhibit the oculodigital phenomenon, or eye gouging, as an attempt to

produce phosphenes from mechanical stimulation of the retina. Leber's congenital amaurosis usually occurs sporadically but may be inherited in an autosomal recessive manner in approximately one third of cases.

Albinism

Albinism is a genetically determined abnormality in melanin synthesis that is associated with congenital nystagmus, foveal hypoplasia, and impaired visual acuity. Albinoidism affects tissues derived from the neural crest (iris, skin, hair) and does not have associated visual abnormalities. True albinism may affect the skin and the eyes (oculocutaneous albinism) or may affect the eyes only (ocular albinism) and be less obvious to the examiner. The ocular fundus can be totally devoid of pigment or simply have a blond appearance. The degree of visual impairment seems related to the degree of ocular pigmentation; tyrosinase-negative albinos have more marked reductions in visual acuity and more obvious nystagmus. Normal foveal development appears to be influenced by melanin in the retinal pigment epithelium in the macular area.

In albinos, about 20% of axons from temporal retinal ganglion ceils cross at the optic chiasm; this has been confirmed by VEP studies that demonstrate significant hemispheric asymmetry to monocular stimulation. Albinos lack normal stcrcopsis. Albinism also occurs in the Hermansky-Pudlak syndrome (albinism with hemorrhagic diathesis) and in the Chediak-Higashi syndrome (a complex neurodegenerative disorder associated with pyogenic episodes) (sec Chapter 66).

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Chapter 41
Neuro-Otology

B. Todd Troost and Lisa C. Arguello

Neuro-otology is a subspecialty that encompasses disorders of the peripheral and central auditory and vestibular systems. Neuro-otology is similar to neuro-ophthalmology in that it is defined by those who practice it. Most neuro-otologists have come from the field of otolaryngology, and their emphasis has been on the organ that is presumably abnormal: the ear. This resembles the early history of neuro-ophthalmology, when the emphasis was primarily on the eye; only later were central visual ocular motor connections and symptoms considered, and the field began to involve neurologists. Similarly, neuro-orology concentrated on the primary functions of the ear, vestibular and auditory, without much reference to information processing in the central nervous system or to neurological conditions that could produce dizziness, vertigo, or alterations in hearing. As outlined in Chapter 18, many neurological and systemic conditions can produce dizziness and disequilibrarion. Therefore neurologists have become increasingly involved in evaluating patients complaining of dizziness. Just as retinal disorders remain primarily the province of the ophthalmologist, so hearing disorders, which are primarily peripheral, remain largely the province of the otolaryngologist.

Because auditory complaints often accompany vestibular symptoms, it is incumbent on neurologists who treat dizzy patients to become familiar with some aspects of auditory as well as vestibular testing.

INVESTIGATIONS

Vestibular Testing

The primary vestibular rests are the electronystagmogram (KNG), rotational tests, and posturography.

Standard ENG is well described elsewhere (Baloh 1998; Bojrab and Stockwell 1994), Eye movements are recorded by means of the corneal-retinal potential by surface electrodes and are printed on strip chart recording paper or analyzed by computer. Currently, many laboratories use infrared video goggles for nystagmus testing, which can produce a pictorial record of the presence of vertical nystagmus, as distinct from eyelid artifact. Standard testing usually includes calibration, gaze testing, bithermal or simulraneous caloric testing, positional testing, and pursuit and optokinetic nystagmus. In most clinical laboratories, eye movements are recorded using only bitemporal electrodes that monitor the movements of both eyes. In more sophisticated laboratories, the movements of each eye are recorded separately. Individual recordings are necessary to determine asymmetries between the eyes, such as occur in internuclear ophthalmoplegia. During calibration, the patient is asked to look between two targets, ±10 degrees from the center of fixation. Frequent overshoots indicate ocular dysmctria, a sign of cerebellar system disorder (Chapter 16).

Most laboratories perform bithermal caloric testing (Figure 41.1A), in which each ear is irrigated separately with warm and cool stimulation produced by water or by air jets. The resulting nystagmus is analyzed manually or by computer to determine the slow phase of the induced nystagmus. Peak slow-phase velocity (SPV) resulting from the warm and cool stimulation of one ear is compared with that from the other ear. The most important finding during ENG is a significant difference in the responses. A difference of more than 20% between ears is a clear indication of hypofunction in one peripheral vestibular apparatus {provided there are no technical artifacts), and the ear with the weaker response is said to have a reduced vestibular response or unilateral weakness (canal paresis). The quality of such testing varies widely among laboratories. If possible, the neurologist should always review the primary tracings or at least have available the calculated SPVs from each ear. The absolute value of SPVs is not as important as the comparison between responses of each ear.

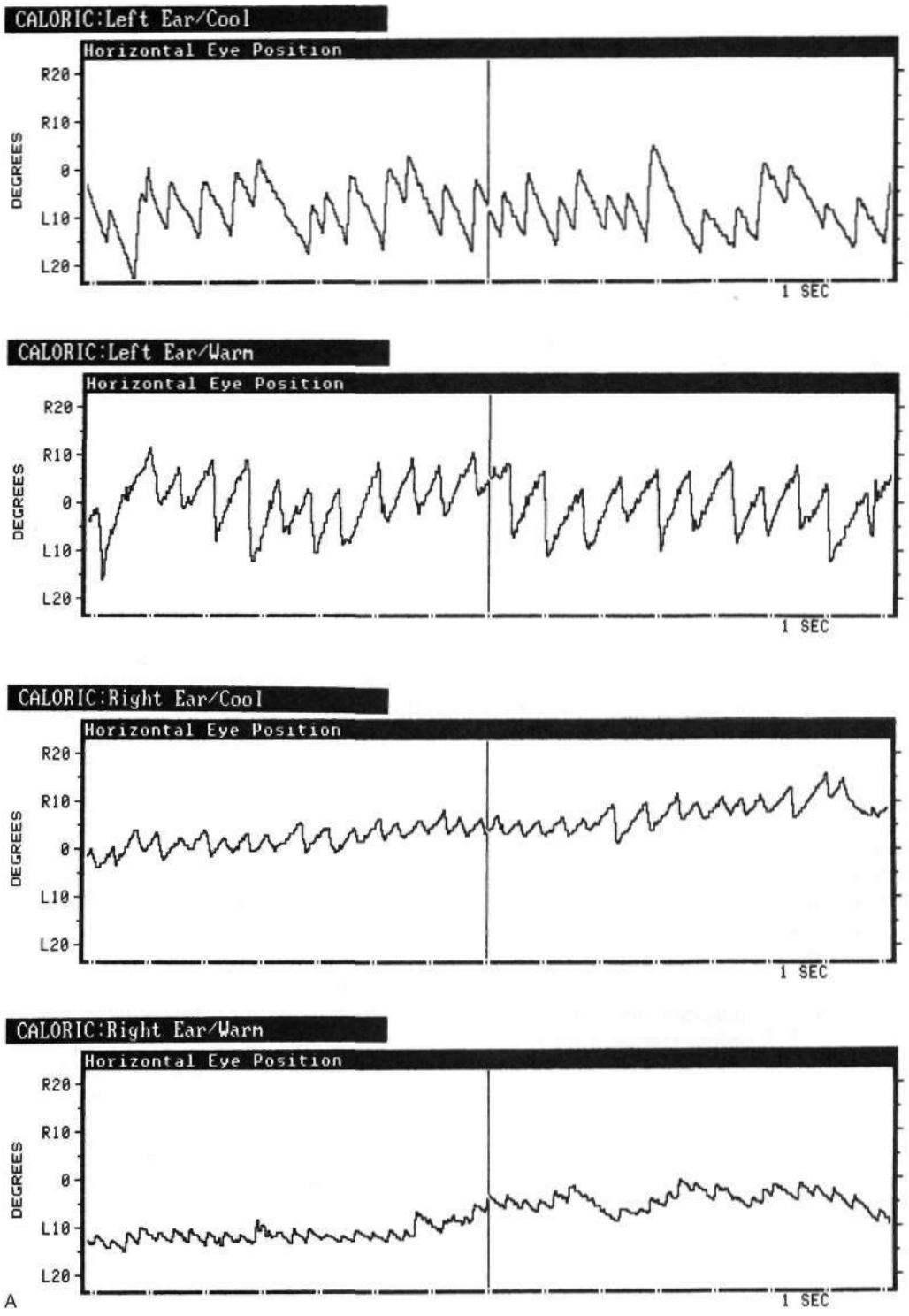


FIGURE 41.1 Computer printout of electron ystagmog ram. (A) Bithermal caloric irrigation. First panel: Responses obtained stimulating the left car with cool air (24'C). Right-beating nystagmus is provoked with a peak slow-phase velocity of 47 degrees per second. Second panel: Left-beating nystagmus provoked by stimulating the left ear with warm air (50°C). Peak slow-phase velocity is measured at 45 degrees per second- Third panel: Left-beating nystagmus induced by stimulating the right ear with cool air (15 degrees per second). Fourth panel: Right-beating nystagmus produced by stimulating the right ear with warm air (12 degrees per second). Results of caloric stimulation indicate a unilateral weakness (canal paresis) of 54% on the right side, suggesting a lesion involving the labyrinth or vestibular nerve on the right side.

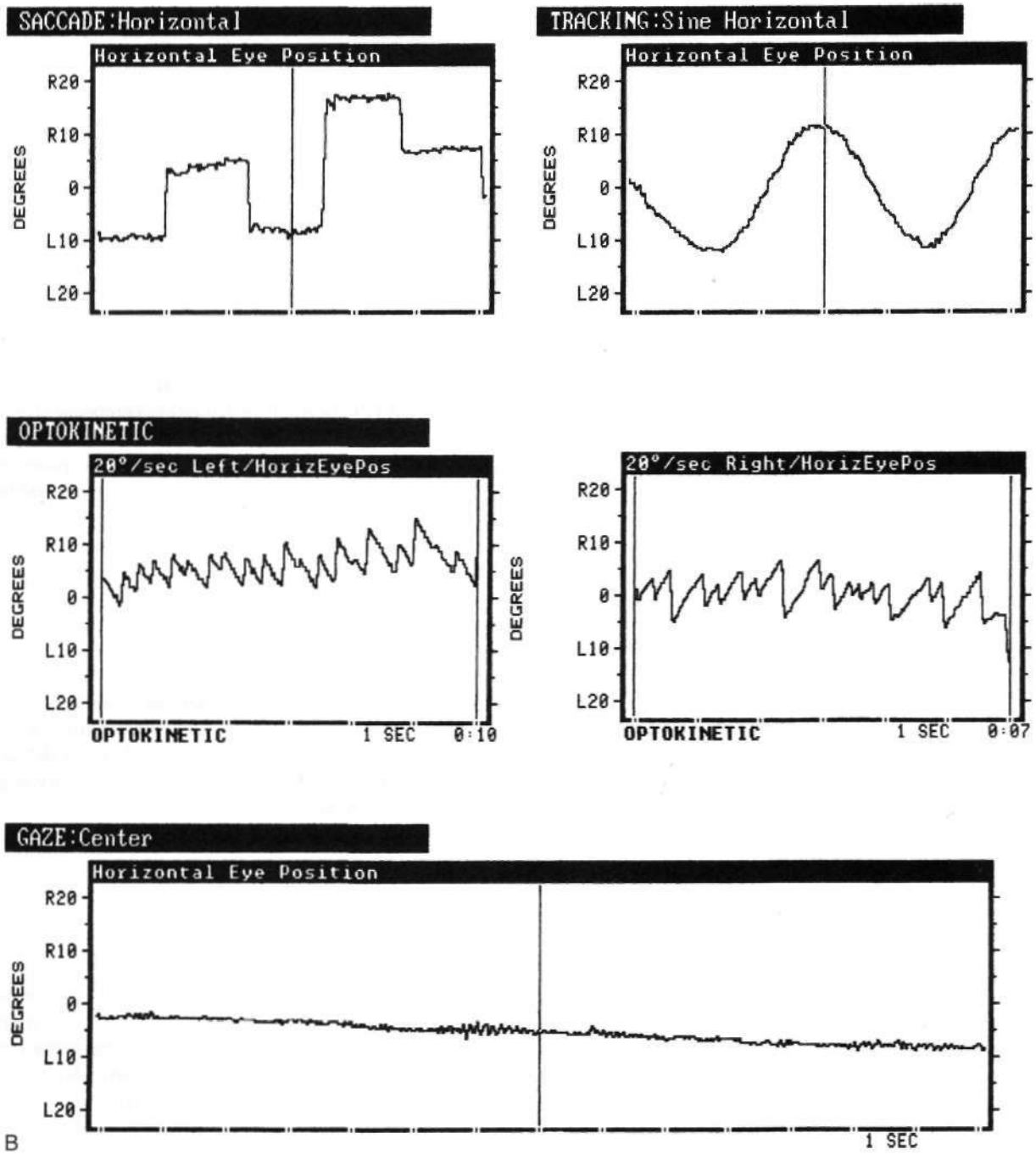


FIGURE 41.1, cont'd. (B) Ocular motor assessment. First panel, left; Saccadic eye movements showing no significant overshoot or dysmetria; normal. First panel, right: Horizontal ocular tracking, normal, without interspersed saccades. Second panel: Optokinetic responses demonstrating symmetry. Third panel: Central gaze showing no significant spontaneous nystagmus.

Another value sometimes given is directional preponderance. One sums the values of the SPV of right-beating nystagmus (cold water in the left ear and warm water in the right ear) and compares the sum with that of the SPV values of left-beating nystagmus (cold water in the right ear and warm water in the left ear). The significance of directional preponderance remains unclear and often is not calculated. Primary position nystagmus can add to or subtract from the nystagmus produced by caloric stimulation, altering the results.

The ability to suppress a caloric-induced nystagmus by visual fixation is evaluated during caloric testing. Most normal subjects can suppress the nystagmus to at least one half of its original amplitude during visual fixation. The

inability to suppress caloric-induced nystagmus usually is interpreted as indicating a central lesion, particularly cerebellar dysfunction. However, many normal people, particularly those who experience intense vestibular symptoms during testing, cannot suppress the induced nystagmus to less than 50% of the baseline value.

The ocular motor assessment consists of saccadic eye movement, gaze testing, tracking (visual pursuit), and optokinetic tests (Figure 41.IB). With the current availability of a commercial apparatus for recording and analyzing fast eye movements, ocular motor evaluation is feasible. Most saccade tests measure the speed and accuracy of saccadic eye movements at various amplitudes. The results are printed out as a velocity-amplitude relationship and compared with those of age-matched controls. Ideally, each eye should be measured individually and recorded in each horizontal direction. Vertical eye movements usually are not studied because the standard recording apparatus does not eliminate eyelid artifact and often does not give accurate vertical eye movement information.

During rotational testing in vestibular function laboratories, the patient is rotated in a chair controlled by a computer. The chair rotates slowly at different constant velocities, usually expressed in terms of frequency or cycles per second (hertz). Typical rotation speeds include 0.01 Hz, 0.02 Hz, 0.04 Hz, 0.08 Hz, and 0.16 Hz, all slow speeds. Patients are rotated in the dark with their eyes open while performing mental tasks designed to distract them from mental imagery, which can suppress eye movement. During a chair rotation to the right, the eyes move to the left and then reccnter with a fast phase. Thus the slow component (phase) is in the direction opposite the spin, and the fast component of the resultant nystagmus is in the direction of the rotation. A computer eliminates the fast components, and a slow phase is reconstructed and compared with the speed of the chair rotation. In this way, a gain (slow eye movement speed divided by chair rotation speed) at different frequencies is obtained. Measuring symmetry compares the responses of rotating in one direction with those rotating in the opposite direction.

Another measurement made during rotational testing is of the time relationship between slow eye movements and the slow movement of the chair. This difference is called the phase lag, and various phase lags are also plotted against the frequency of rotation of the chair. Therefore both gain and phase plots are produced during rotational testing. Unlike caloric testing, rotational testing (which stimulates both ears simultaneously) generally provides little clear-cut information about the site of the lesion; however, it is beneficial in quantitating bilateral weakness in a reproducible fashion. The symmetrical response of a person with a unilateral peripheral vestibular abnormality indicates vestibular compensation. Patients who become asymptomatic after peripheral vestibular abnormality can still show a phase lag, particularly at the lower rotation frequencies. An abnormal phase lag is a nonspecific marker and usually indicates some degree of vestibular peripheral abnormality. Rotational test abnormalities are quite reproducible, more so than caloric tests, and it is often difficult to determine which side is abnormal and whether any resultant abnormality is peripheral or central with rotation tests alone. Such determinations must be made using other information, such as the results of an ENG or a clinical examination.

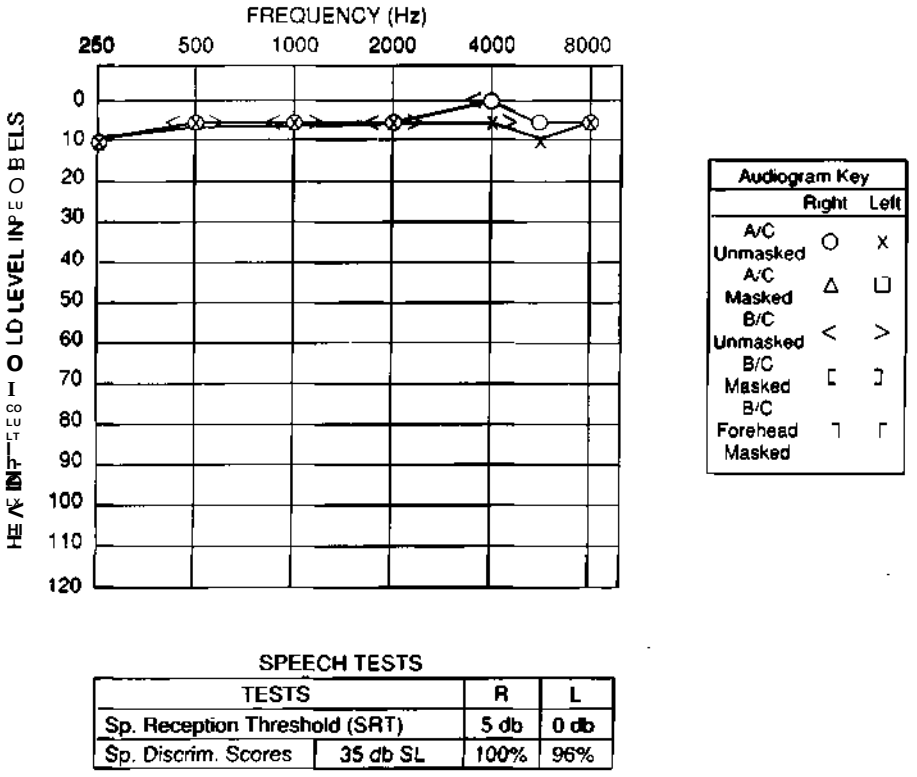
Posturography is an attempt to quantify the Romberg test (Furman 1995). Changes in body sway during Romberg testing, with the feet directly together, with eyes open and with eyes closed, are measured by means of a computer. Most of the earlier attempts to quantify the Romberg test used a static posture platform, but correlating an abnormality with different states (e.g., peripheral vestibulopathy, peripheral neuropathy, cerebellar dysfunction, and neuromuscular disorders) on the platform was largely unsuccessful. Now, a dynamic posture platform is used. The patient is surrounded by a movable visual field, and the posture platform itself may be moved. The theory is that moving the visual surround may eliminate visual cues that help maintain posture. Similarly, moving the posture platform in response to a movement of the feet also may eliminate proprioceptive cues, which assist in posture maintenance. Both visual and proprioceptive cues may be eliminated simultaneously. Theoretically, attempts to maintain posture depend solely on vestibular afferent information. The test results in all conditions are reported, and the interpretation is based on the systems that are defective. Dynamic posturography is a promising technology that is still being improved.

Audiological Testing

Audiological assessment is the basis for quantifying auditory impairment. Most neurologists rely on clinical hearing testing and may use tuning forks, as described in Chapter 19.

In defining an auditory abnormality, tuning forks are no substitute for a complete audiological battery. Audiological testing is most reliable in defining peripheral or cochlear auditory disturbances and often may provide useful information, based on subtests, to diagnose retrocochlear disease. Basic assessment and subtests may be helpful in identifying cerebellopontine angle tumor, most commonly a vestibular schwannoma. Central auditory testing for the rare central disorders of audition is more difficult and poorly understood. Detailed descriptions of audiological tests, both peripheral and central, arc provided in standard texts (Troost and Waller 1998).

The basic audiological evaluation establishes the degree and configuration of hearing loss, assesses ability to discriminate a speech signal, and provides some insight into the type of loss and possible cause. The test battery consists of pure-tone air and bone conduction thresholds,



SPEECH TESTS

TESTS		R	L
Sp. Reception Threshold (SRT)		5 db	0 db
Sp. Discrim. Scores	35 db SL	100%	96%

FIGURE 41.2 Normal audiometric results showing normal hearing sensitivity with excellent speech discrimination bilaterally. (A/C = air conduction; B/C = bone conduction.)

speech thresholds, speech discrimination testing, and immittance measures.

Pure-tone air conduction thresholds provide a measure of hearing sensitivity as a function of frequency and intensity (Figure 41.2). When a hearing loss is present, the pure-tone air conduction test indicates reduced hearing sensitivity.

Definitions

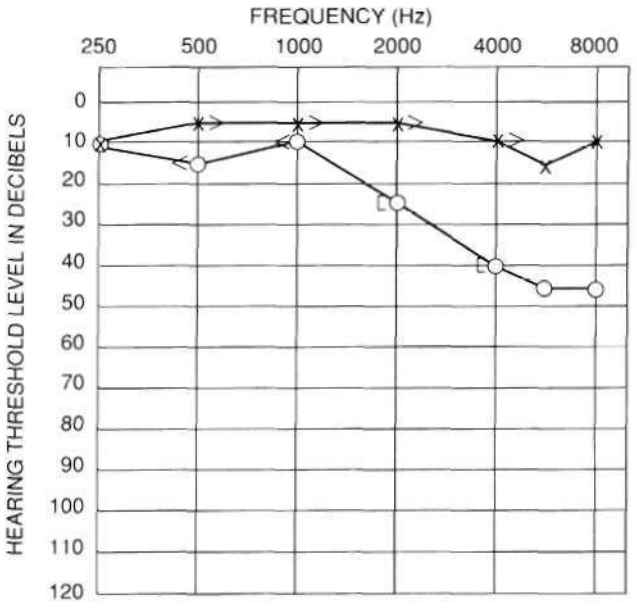
It is appropriate at this point to define some basic audiometric terms. Pure tones are defined by their frequency (pitch) and intensity (loudness). Normal hearing levels for pure tones are defined by international standards. Brief-duration pure tones at selected frequencies are presented through earphones (air conduction) or a bone conduction oscillator on the mastoid bone (bone conduction). The audiogram indicates the lowest intensity that a person can hear at a given frequency and displays the degree (in decibels) and configuration (sensitivity loss as a function of frequency) of a hearing loss. *Thresholds* can be defined as the lowest-in tensity signal that a person can detect approximately 50% of the time during a given number of presentations. The speech reception threshold (SRT) is the lowest intensity level at which the listener can identify or understand speech 50% of the time. The SRT may also be called the *spondee threshold* because spondees arc the test material. Spondee words are two-syllable words that are given equal syllable stress, such as *baseball, toothbrush, sidewalk, oatmeal, popcorn,* and *railroad.* Once the SRT is determined in this manner, the audiologist determines speech discrimination ability by presenting a list of 50 phonetically balanced words at volume levels approximately .35^*0 dB above SRT. The list is a standardized one, containing monosyllabic words of equal phonetic composition. Word recognition is scored as the percentage correct, with each correct word counting for 2% of the total. Pure-tone bone conduction thresholds are obtained when a stimulus is presented by bone conduction,

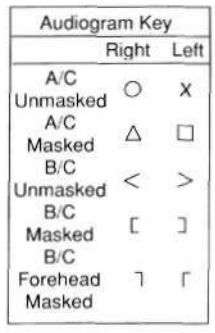
Bone conduction tests are intended to be a direct measure of inner ear sensitivity. Comparison of air and bone conduction thresholds establishes the type of hearing loss. Conductive loss results from disorders in the outer or middle ear. Sensorineural loss is associated with disorders of the cochlear and eighth cranial nerves. Mixed loss is a conductive and sensorineural loss coexisting in the same ear.

Speech Testing

Speech reception threshold testing measures the patient's ability to repeat familiar spondaic words. It provides a comparative measure for confirming pure-tone thresholds. Lack of agreement between speech thresholds and pure-tone threshold averages indicates a discrepancy and the need for additional testing or retesting to establish valid measures.

Word recognition tests measure a patient's ability to differentiate speech sounds. Discrimination ability may be





SPEECH TESTS

TESTS		R	L
Sp. Reception Threshold (SRT)		20 db	5 db
Sp. Discrim. Scores	35 db SL	84%	100%

FIGURE 41.3 Abnormal audiogram. Findings indicate normal hearing sensitivity for the left ear, with a mild to moderate high-frequency hearing loss for the right ear. The asymmetrical hearing loss, in addition to the decreased discrimination score for the right ear, indicates possible retrocochlear pathology, such as a vestibular schwannoma. (A/C = air conduction; B/C = bone conduction.)

affected in varying amounts, depending on the type, cause, configuration, and degree of hearing loss. Discrimination scores contribute to estimates of the amount of handicap to be expected from the hearing loss and to the prognosis for rehabilitation.

Figure 41.3 depicts an audiogram from a patient with a cerebellopontine angle tumor demonstrating asymmetrical hearing loss. Patients with asymmetrical heating sensitivity should undergo neuroimaging to rule out a cerebellopontine angle tumor.

Middle Ear Testing

Immittance measures assess the status of the middle ear and confirm information obtained in other tests of the battery. The basic immittance battery consists of tympanometry, static immittance, and acoustic reflex thresholds. Data from the tympanogram permit determination of the static compliance of the middle ear system. A result of "type A tympanogram" means that mobility of the tympanic membrane and middle ear structures is within normal limits (see Chapter 19).

Acoustic Reflex Testing

Acoustic reflex measures a contraction of the stapedius muscle (innervated by the seventh cranial nerve) in response to a loud sound. The afferent limb of the reflex arch is through the auditory portion of the eighth cranial nerve, and the efferent portion of the reflex arch is through the seventh cranial nerve. The stapedius muscle normally would contract bilaterally regardless of which car was stimulated, assuming normal afferent input. After contraction of the stapedius muscle, the tympanic membrane is tightened or stiffened, thereby increasing the impedance or resistance of the eardrum to acoustic energy and resulting in a slight attenuation of sound transmitted through the middle ear system. In a normal subject, the acoustic reflex occurs in response to a pure tone between 70 and 100 dB above hearing level or when a white noise stimulus is presented at 65 dB above hearing level. Patients with conductive hearing loss do not have reflexes because the lesion prevents a change in compliance with stapedius muscle contraction. With cochlear lesions, the acoustic reflex may be present at sensation levels less than 60 dB above the auditory pure-tone threshold, which is a form of abnormal loudness growth or recruitment. Cochlear hearing losses must be moderate or severe before the acoustic reflex is lost. In contrast, patients with retrocochlear or eighth cranial nerve lesions often have abnormal acoustic reflexes with normal hearing. The reflex may be absent or exhibit an elevated threshold or abnormal decay. Reflex decay is present if the amplitude of the reflex decreases to half its original size within 10 seconds of stimulation at 1000 Hz, 10 dB above reflex threshold. This abnormality occurs in approximately 80% of patients with acoustic neuromas. Observation of the pattern of acoustic reflex testing, along with hearing evaluation, permits inferences to support the presence of a cochlear, conductive, or neural lesion of the seventh or eighth cranial nerves (Table 41.1).

Tahle 41.1: Pattern of acoustic reflex measurements with unilateral lesions

	Stimulus presented			
	C	ɹ	**C**	*I*
	Reflex measured			
Type of lesion	*/*	*C*	**C**	*1*
Cochlear (<85 dBHL)	-	+	+	+
Conductive (>30 dBHL)	-	-	+	-
VIII cranial nerve	+	-	+	-
VII cranial nerve	-	+	+	-

C = contralateral to lesion; dBHL = decibels hearing loss; I = ipsilateral to lesion; + = reflex present; — = reflex absent.
Source: Adapted from Baloh, R. W. 1984, *Dizziness, Hearing Loss, and Tinnitus: The Essentials of Neurolology,* Davis, Philadelphia, pp. 59-96.

Accurate administration of the basic test battery should establish the presence and the characteristics of hearing loss. Interpretation of the battery and observation of patient behavior may indicate a need for additional testing, such as neutoimaging, hearing aid evaluation, or medical evaluation.

Evoked Potentials

Bt a in stem auditory evoked potentials ate also known as brainstem auditory evoked responses or auditory brainstem responses (ABRs) (see Chapter 36A). These physiological measutes can be used to evaluate the auditory pathways from the ear to the upper brainstem. In addition, ABR threshold testing, although not a test of hearing sensitivity, may be used to determine behavioral threshold sensitivity in infants or uncooperative patients. The most consistent and reproducible potentials are a series of five submicrovolt waves that occur within 10 milliseconds of an auditory stimulus. These potentials are recorded by averaging 1000-2000 responses from click stimuli by use of a computer system and amplifying the response (figure 41.4). The anatomical correlates of the five reliable potentials have been only roughly approximated. Wave I of the brainstem auditory evoked potential is a manifestation of the action potentials of the eighth cranial nerve and is generated in the distal portion of the nerve adjacent to the cochlea. Wave II may be generated by the eighth cranial nerve or cochlear nuclei. Wave III is thought to be generated at the level of the superior olive, and waves IV and V are generated in the rostral pons or in the midbrain near the infetior colliculus. The complex anatomy of the central auditory pathway (Troost and Waller 1998), with multiple crossing of fibers from the level of the cochlear nuclei to the inferior colliculus, makes interpretation of central disturbances in the evoked responses difficult.

The brainstem auditory evoked potential is a sensitive, noninvasive diagnostic test for diagnosing cerebellopontine angle tumors. It is used to differentiate cochlear from eighth cranial nerve hearing defects and, on some occasions, demonstrates an auditory abnormality when behavioral audiometric testing is still normal. The majority of patients with acoustic tumors have abnormal responses.

The least specific finding is the absence of all waves. This occurs in some patients with vestibular schwannoma and in some with cerebellopontine angle meningiomas. Such patients often have marked hearing deficits with poor discrimination on behavioral testing, suggesting retrocochlear disease. The absence of all waves should not occur

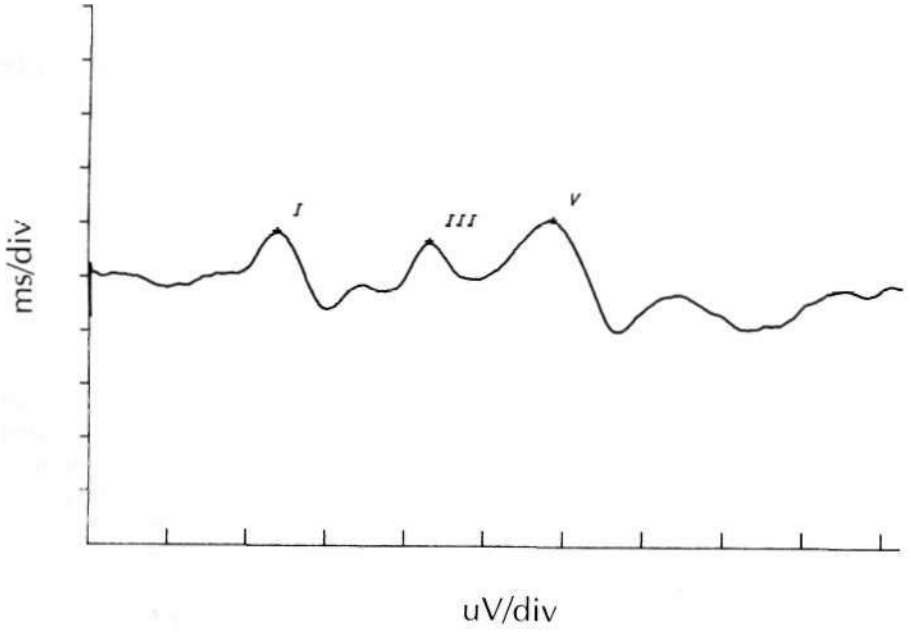


FIGURE 41.4 Brainstem auditory evoked potential in a normal adult. Responses were recorded between electrodes on the vertex and the ipsilateral mastoid. Waves I, HI, and V are labeled. (uV/div = microvolts per division; ms/div = milliseconds per division.)

unless a severe hearing loss exists. The most specific evoked potential abnormality is the presence of an increase in interwave intervals. Abnormal interwave latencies {I-III or I-V) are the most specific and sensitive abnormalities seen with cerebellopontine angle tumors. The abnormal prolongation or absence of wave V at increased click rates is also characteristic of retrocochlear disorders. Increased absolute latencies of all waves, when compared with responses from the other ear, may signify a conductive deficit.

Before ABR testing, the patient should undergo a full audiological evaluation. **The ABR** does not test hearing itself, and both conductive and sensorineural hearing losses can affect the wave latencies and amplitudes.

Other Tests

Electrocochleography is a method of recording the stimulus-related electrical potentials associated with the inner ear and auditory nerve, including the cochlear microphonic, summating potential, and compound action potential of the auditory nerve. This measure is beneficial in the differential diagnosis of certain types of sensory disorders, such as Meniere's disease. The amplitude of the summating potential and compound action potential is measured and is of primary interest in evaluating an ear for increased endolymphatic pressure.

High-resolution computed tomographic scanning provides excellent imaging of the temporal bone and assists in defining congenital abnormalities and infection. Magnetic resonance imaging has largely supplanted computed tomography for the diagnosis of cerebellopontine angle tumors. Contrast-enhanced magnetic resonance imaging and special imaging techniques have allowed diagnosis of unusual lesions, such as meningeal carcinomatosis, which may affect the cerebellopontine angle and eighth cranial nerve. It is also useful in evaluating sudden hearing loss because it may show bilateral metastatic deposits in the cerebellopontine angle or other conditions responsible for sudden bilateral hearing loss (Fitzgerald and Mark 1998),

Table 41.2: Medical therapy for vertigo

Class	*Dosage **
Antihistamines	
Meclizine	2550 mg 3 times/day
Cyclizinc	50 mg 12 times/day
Dimenhydriuate	50 mg 12 times/day
Promethazine	2550 mg/day
Anticholinergics	
Scopolamine tablets	0.45-0.50 mg 12 times/day
Scopolamine transdermal patch	1/day for 3 days
Donna tal[f]	1 three times/day
Sympathomimetics	
Ephedrine	25 mg/day
Antiemetics	
Tr imeth o benza m id e	250 mg 12 times/day PO 200-mg suppository
Promethazine	2550 mg/day
Prochlorperazine	510 mg 13 times/day PO 25-mg suppository
Tranquilizers	
Diazepam	510 mg 13 times/day
Oxazepam	1060 mg/day
Haloperidob	0.5-1.0 mg 12 times/day
Combination preparations and others (dosages as listed above)	
Scopolamine with ephedrine	
Scopolamine with promethazine	
Ephedrine with promethazine	
Diuretics	
Diet	

* Usual adult starting dosage; maintenance dosage can be increased by a factor of 2-3. The most common side effect is drowsiness.

[+]This is a combination preparation, containing a mixture of atropine alkaloids with approximately one fourth grain (15.0-16.2 mg) phenobarbital.

*Note the very low dosage when compared with usual antipsychotic treatment. Nevertheless, the patient should still be observed for dystonias.

MANAGEMENT OF PERIPHERAL VESTIBULOPATHY

Medical Treatment

Therapy is outlined for symptomatic treatment of dizziness presumed to be of peripheral origin (Table 41.2), When a definitive diagnosis, such as vestibular schwannoma, autoimmune disorder, perilymph fistula, or systemic vasculitis, has been made, therapy must be directed to the underlying disorder.

In treating a patient with dizziness, particularly one with a chronic problem who has seen numerous physicians, understanding and patience are needed to relieve anxiety and depression. One may need to reassure the patient of the absence of progression in the usual case and the natural history of most symptoms with peripheral vestibulopathy (i.e., improvement with time). Exercise therapy is especially helpful for patients with positional vertigo (Brandt, Steddin, and Daroff 1994; Furman and Cass 1999).

Although most of the drugs used for dizziness are loosely called *vestibular suppressants,* it is often unclear which agents will be effective in a given patient. The mechanism of action of these drugs is largely unknown. The primary vestibular afferent system could be suppressed directly or indirectly through the inhibitory portion of a vestibular efferent system. An important effect of some agents may be to act on other sensory systems, such as proprioceptive or visual inputs to the vestibular nuclei of the brainstem.

Hew controlled studies have investigated the response of patients with presumed peripheral vestibular dysfunction. The use of many drugs for treating such patients is based on studies of the prevention of motion sickness in normal subjects or of various regimens used by otologists to treat patients with Meniere's disease.

Antihistamines are among the most commonly used agents in treating dizziness. Few neurologists see a dizzy patient who has not already been treated with meclizine. Histamine antagonists are classified according to the responses to histamine that are prevented. Antagonists that act at receptors for histamine are classified as H] or H_2 receptor-blocking agents, or simply Hi or H_2 blockers.

Antihistamines in the Hi antagonist group are used for dizziness. Stimulation of the vestibular apparatus produces motion sickness, but the vestibular cerebellar integrative vomiting center and medullary chemorcccptivc trigger zone are involved in the process. Electrophysiological recordings in dogs show that diphenhydramine diminishes excitability of the vestibular nuclear complex to vestibular afferent activity induced by motion or electrical stimulation of the vestibular afferents. The H| blockers effective in motion sickness may act by central antagonism of acetylcholine, as does scopolamine. Promethazine, a phenothiazinc with strong acetylcholine-blocking action, is one of the most effective agents in preventing motion sickness.

Anticholinergics that block the muscarinic effect of acetylcholine often are used for motion sickness. Atropine acts centrally to stimulate the medulla and cerebrum, but the closely related alkaloid 1-hyoscine or scopolamine is more widely used. Transdermal delivery of scopolamine may prevent or mitigate the nausea and vomiting associated with motion sickness but not the dizziness. In general, transdermal scopolamine is not useful in patients with vestibulopathy. Common side effects arc blurred vision and dry mouth, in addition to occasional confusion. Some patients have significant difficulty when they try to discontinue scopolamine patches. A side effect of low-dose oral scopolamine or atropine is the transient bradycardia (4-8 beats reduction per minute) associated with the peak action of oral scopolamine at 90 minutes and diminishing thereafter.

Sympathomimetic agents may be used to treat motion sickness, particularly in combination with anticholinergics. The sole agent in this class that may have an application, in combination with other drugs, is ephedrine, but tolerance may develop after a few weeks of treatment.

Antiemetics should be used when prominent nausea is a symptom. Many of the antihistaminic and anticholinergic drugs listed here arc also used for their antiemetic actions. Prochlorperazine should be used with caution, particularly by the intramuscular route, because of the high frequency of dystonic reactions.

Tranquilizer is the general name given to drugs from different classes having central and probably peripheral effects. Such drugs include benzodiazepines, buty top hen ones, and phenothiazincs. Despite extensive publicity concerning the use and abuse of diazepam and the lack of direct evidence of an effect on the vestibular system, diazepam is still one of the most widely prescribed drugs for treating dizziness. It should not be the first choice, primarily because of the significant potential for habituation and depression and because it can actually cause dizziness. Nonetheless, it remains the first choice of many neuro-otologists and otologists. The mechanism of action of the benzodiazepines appears related to the metabolism or action of y-aminobutyric acid. Potential effects on the vestibular system are speculative. Other longer-acting benzodiazepines may be helpful in certain patients, but no study has substantiated their effectiveness. Haloperidol in small oral dosages appears to be effective in many patients with peripheral vestibular dysfunction, including those with positional vertigo, who seem to be less affected by other antidizziness medications.

Combination preparations, including agents listed in Table 41.2, often are useful, particularly the combination of ephedrine and promethazine. Some other agents and regimens used primarily to treat Meniere's disease are briefly reviewed in this section. Because in some cases an effect on blood supply to the peripheral end organ might be a factor, agents such as cyclandelate are used. Reports in the literature are contradictory, and the therapeutic value of cyclandelate has never been convincingly demonstrated for any condition.

An unusually high frequency of metabolic abnormalities, particularly hyperlipidemia, has been reported in series of patients with peripheral vestibular dysfunction, especially Meniere's disease. For this reason, dietary regimens have been prescribed as adjunct therapy. Among the most widely used medical therapy in Meniere's disease is the combination of salt restriction (1000- to 2000-mg sodium diets) and diuretic therapy. There is still uncertainty about the natural history of Meniere's disease, and it is unknown whether medical management affects the ultimate outcome for vestibular function or hearing. However, because the long-term results of surgery, such as endolymphatic shunts, are far from proven, there is still a clear role for medical management in this condition.

Exercise therapy can be beneficial in treating persistent positional vertigo (Brandt, Steddin, and Daroff 1994). Patients are first instructed about the type of exercise to be done. They are asked to move rapidly from a scared position to lying on one side. They remain in that position for 30 seconds and then return to the upright position and wait until any recrudescence of symptoms subsides, or for a minimum of 30 seconds. The patients are then instructed to move rapidly lateral to the opposite recumbent position and wait for 30 seconds and then return to the upright position, thus completing one repetition. Patients are asked to perform 20 repetitions two times a day. Most patients experience significant relief within a week, although it might take 3 months to become asymptomatic. Although

there are some recurrences, the majority of patients are permanently cured. This exercise, called *Brandt-Daroff,* has been largely replaced by more complicated maneuvers (Brandt, Steddin, and Daroff 1994) that can alleviate the problem in a single office visit. On the rare occasions when rhe exercise therapy is unsuccessful, such patients are candidates for section of the nerve from the posterior semicircular canal.

Surgical Treatment

Surgical treatment of chronic peripheral vestibular dysfunction is primarily destructive. In patients with severe Meniere's disease for whom medical therapy has been ineffective and who have severe recurrent disabling attacks, a labyrinthectomy may be performed. Unfortunately, Meniere's disease may become bilateral, eventually resulting in the need for labyrinthectomy or vestibular nerve section on the contralareral side. A medical labyrinthectomy may he performed by the use of aminoglycoside drugs, which are particularly destructive to the peripheral vestibular hair cells. Surgical or medical labyrinthectomy usually is a last resort for patients who have clearly defined, severe attacks of peripheral vestibulopathy, presumably from Meniere's disease.

Various shunting procedures have been used to treat MniieiT's disease and endolymphatic hydrops. Although some patients can benefit, long-term success with such shunting procedures to the mastoid region and to the subarachnoid space has been modest.

MANAGEMENT OF CENTRAL AND SYSTEMIC VESTIBULAR DISORDERS

Medical Treatment

The management of central vestibular disorders depends on the diagnosis. A simple separation into peripheral and central vestibular dysfuncrion is not always possible, as discussed in Chapter 18. Some patients have inadequare central compensation for a peripheral vesribular abnormality and thus remain symptomatic. In such patients, medical therapy for peripheral vestibular dysfunction may prove quite effective. When a specific diagnosis (e.g., postural hypotension secondary to diabetic peripheral neuropathy) is made, attention should be directed to treatment of the primary condition. Severe postural hypotension is notoriously difficult to manage. Although mineralocorticoids have been used, they should be prescribed cautiously to avoid congestive heart failure.

The patient who is diagnosed as having primary disease of the central nervous system, whether brainstem infarction or spinocerebellar degeneration, must be treated as would a patient without the accompanying symptoms of disequihbration. Medical therapy of vertebrobasilar insufficiency is directed at preventing new infarctions, primarily with antiplatelet agents and anticoagulation. Cerebellar dysfunction not caused by tumor may be treated symptomatically. On occasion, isoniazid might reduce ataxia. Vestibular suppressant medication can add a modicum of improvement, and agents helpful in the therapy of essential tremor, such as beta-blocking drugs or primidone, may result in symptomatic improvement.

Therapy for systemic conditions producing vertigo also depends on the diagnosis. Systemic drug therapy, as with benzodiazepines, may actually cause disequilibration. Withdrawal of all drugs, whether anticonvulsants or benzodiazepines, must be done cautiously to prevent withdrawal reactions,

Surgical Treatment

Surgical treatment is directed primarily toward removal of the tumors that can affect the peripheral or central vestibular apparatus. When disequilibration, ataxia, or dizziness is caused by a Chiari malformation (see Chapters 66 and 77), surgical decompression of the posterior fossa can produce major symptomatic relief.

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Chapter 42
Neurourology

Clare J. Fowler and Ranan DasGupta

The investigation and management of disorders of urogenital function were formerly regarded as the domain of urologists. But as neurologists and rehabilitation specialists become aware of the range of possible effective nonsurgical treatments and increasingly investigate patients' complaints of disordered urogenital function, they are taking a more active interest in uroneurology, or bladder dysfunction viewed from a neutological perspective. This chapter describes what a neurologist needs to know to manage neurogenic urogenital problems. Urodynamic, neurophysiological, and radiological investigations and available medical treatments are described.

INVESTIGATIONS

Physical Examination of Patients with Urogenital Symptoms

The findings on clinical examination are crucial to determining whether a patient has a neurological cause for a urogenital complaint. The reflexes that control the storage and phases of bladder function are transspinal, connecting the pontine micturition center to the sacral spinal cord (Figure 42.1). The examination therefore should concenttatc on the lowet limbs because the spinal segments that innervate the bladder are caudal to those that innervate the legs, and spinal cord disease that affects the innervation of the bladder almost inevitably also produces lower limb signs. Exceptions might be lesions of the low sacral cord or ainus, bur only the most caudal lesions tail to produce some overactivity in the legs and extensor plantar responses. Cauda equina lesions at SI and S2 may impair the ankle reflexes, and those at S3 may affect the intrinsic foot muscles, causing foot deformities and fasciculation of the muscles. Saddle anesthesia is a feature of cauda equina or conus lesions, but the patient is more likely to spontaneously complain of the symptom than the physician is to discover sensory loss on examination. As explained in the following sections, sacral reflex responses recorded electrophysiologically are of limited value, and when elicited clinically they are even less useful.

Examination for evidence of peripheral neuropathy is important. Peripheral neuropathy, notably diabetic, is a common cause of male erectile dysfunction (MED), and as the neuropathy progresses, abnormalities of innervation of the detrusor muscle may develop also. Clear evidence of neuropathy affecting the feet is likely to emetge before bladder innervation is involved.

When the neurological examination of the legs is completed, the patient should be asked to stand and the lumbosacral spine inspected. Congenital malformations of the spine can produce symptoms presenting in adulthood, and dimpling in the sacral region, hypertrichosis, and a nevus or sinus may prove to be relevant.

Evidence of extrapyramidal disease, cerebellar ataxia, laryngeal involvement, and postural hypotension should raise suspicion of multiple system atrophy (MSA), a condition characterized by early and severe urinary incontinence and MED.

If a patient with urogenital complaints has a normal neurological examination, detailed investigation with imaging and neurophysiology is unlikely to teveal a relevant underlying neurological disorder.

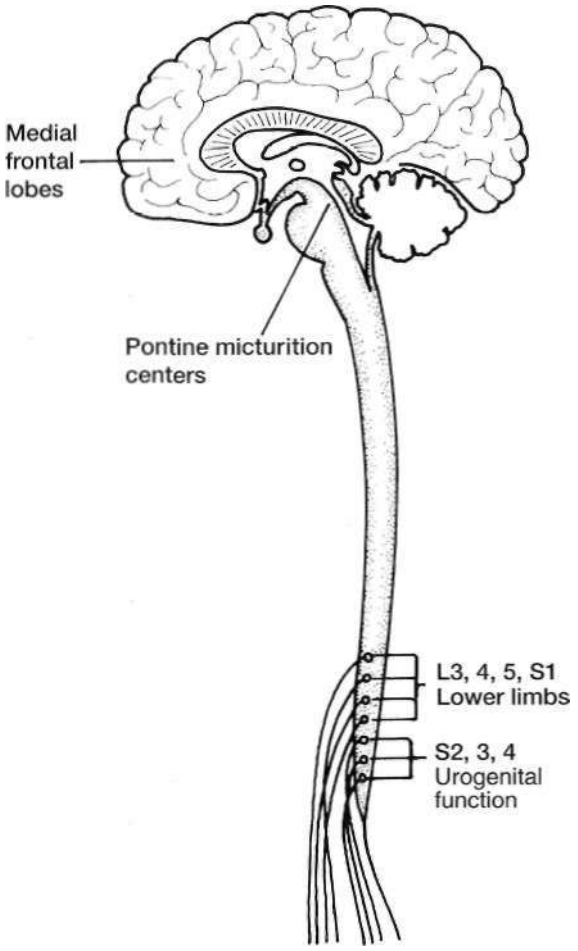


FIGURE **42.1** The peripheral innervation of the Madder and genitalia arises from the sacral spinal cord, and central control over the hladder is exercised by micturition centers in the pons and frontal lobes. It is obvious from this organization that any spinal cord lesion causing neurological symptoms and signs in the lower limb will interrupt the transspinal connections between the pons and sacral cord, also causing impaired bladder control. Likewise, it would he unusual fot spinal pathology to cause a disorder of bladder function without also producing a neurological deficit of the lower limbs unless the lesion affected only the conus.

Urological Investigations

Patients with urogenital complaints without known neurological disease should he investigated fitst by a urologist; otherwise, urological disorders such as prostatic hypertrophy, urethral strictures, interstitial cystitis, **and** bladder stones may go unrecognized. Flexible cystoscopy can be performed as a painless outpatient procedure and readily excludes intravesical disorders. By contrast, if the patient develops genitourinary symptoms as part of a progressive neurological disease, the neurologist should initially become involved in the management of those symptoms. However if the patient does not respond to fitst-line medical treatments or experiences hematuria or recurrent urinary tract infections, a urological opinion should he sought.

Urodynamic Studies

Urodynamic studies examine the function of **the** lower urinary tract. Included in this term are measurements of urine flow rate, residual volume, cystometry during filling and voiding, videocystomerry, urethral pressure profile measurements, and pelvic floor neurophysiology. The term *urodynamics* is used often incorrectly as a synonym for *cystometry.*

From the patient's point of view, tests of bladder function can be divided into the noninvasive tests and those involving a urethral catheter.

Noninvasive Bladder Investigations

The patient or a caregiver can keep a voiding diary of the approximate amount drunk, frequency of micturition, and episodes of incontinence, recorded over the course of several days. This is a useful measure of the severity of bladder complaints on which management decisions can he based.

Urinary flowmetry is a valuable noninvasive investigation, particularly when combined with an ultrasound measurement of the postmicturition residual volume. A commonly used design for a flow meter consists of a commode or urinal into which the patient passes urine as naturally as possible. In the base of the collecting system is a spinning disk; urine flow tends to slow the rotation of the disk, which a servomotor holds constant. Urine flow is derived from measurement of the power necessary ro maintain disk rotation, and the machine usually produces a graphic printout and an analysis of the time taken to reach maximal flow, the maximum and average flow rate, and the voided volume (Figure 42.2).

It is important that the patient prepares to perform the test with a comfortably full bladder, containing if possible a volume of at least 200 ml.. Privacy is essential; a spurious result might be obtained if the patient is not fully relaxed. **Published** nomograms give urine free flow rates against volume for men and women. An aging effect has been found in men over age *65* but not in women. A significant neurogenic bladder disorder is unlikely if the patient has good bladder capacity and normal urine flow rate and empties to completion, all of which may he noninvasivcly demonstrated.

Knowledge of a patient's postmicturition residual volume is critical in planning treatment of neurogenic hladder symptoms. Although this information is available from urethral catheterization after voiding, the same data can be obtained noninvasively by ultrasound. Small, simple ultra sound machines are available that require little operator training and make it easy to determine whether the

postmicturition residual volume is negligible or greater than 100 mL (Figure 42.3).

Larger, more elaborate ultrasound machines are found in radiology departments equipped for urological work, and in some instances ultrasound scanning of the upper urinary tracts has replaced intravenous urography as a means of examining the kidneys and ureters for dilatation, stones, and tumors. Interpretation of those scans takes special expertise.

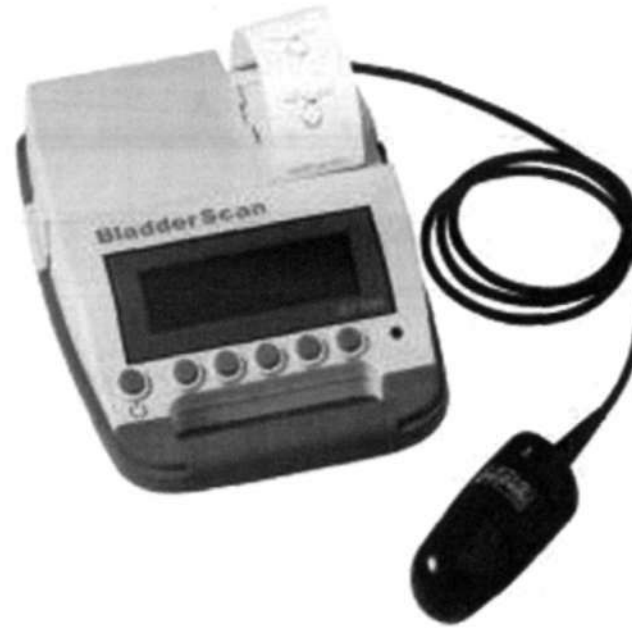


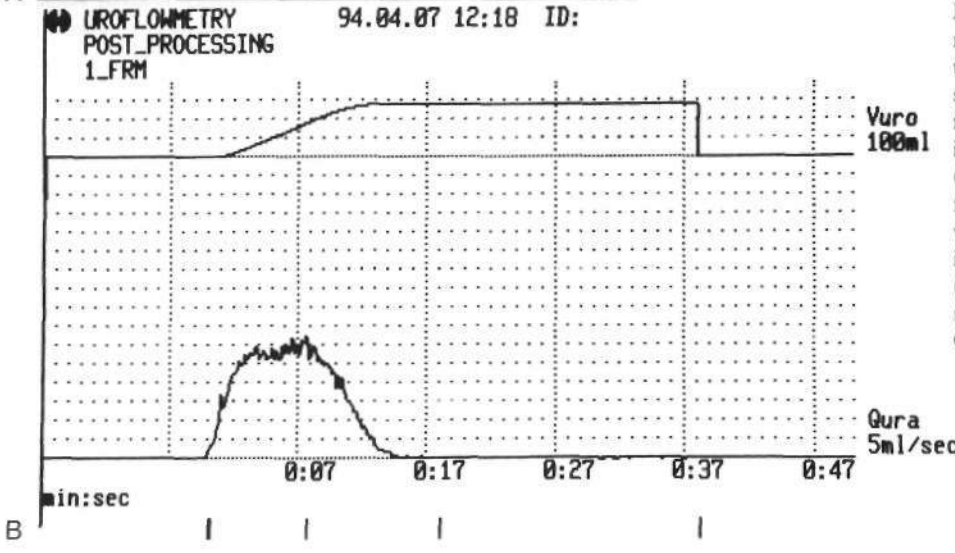
FIGURE 42.3 Postmicturition residual volume can be measured using a small, portable ultrasound machine.

Investigations Necessitating Catheterization

Cystometry, the registration of bladder pressure, can be performed during filling and voiding. The essential measurement is the intravesical pressure, but because this also reflects increases in intra-abdominal pressure, rectal pressure must be simultaneously recorded and the value subtracted from the measured intravesical pressure to calculate the true changes of detrusor pressure alone. The efficiency of the subtraction usually is checked at the beginning of cystometry by asking the subject to cough (Figure 42.4). This produces an increase in abdominal pressure and hence intravesical pressure but no increase in detrusor pressure.

Two catheters are used for these measurements. A dual-lumen (6-Fr) catheter is inserted through the urethra for filling the bladder and measuring intravesical pressure. Another fine-gauge catheter (4 Fr) is then inserted into the

A



B

FIGURE 42.2 (A) Urinary flow meter. The side of the uroflow transducer has been cut away to show the disk at the base of the funnel that rotates as urine passes into the collecting vessel. (B) Typical (normal) printout from the uroflowmeter. A total of 290 mL was voided (*upper trace*), with a maximum flow rate of 30 mL per second (*lower trace*). (Reprinted with permission from Dantec Medical A/S, Copenhagen.)

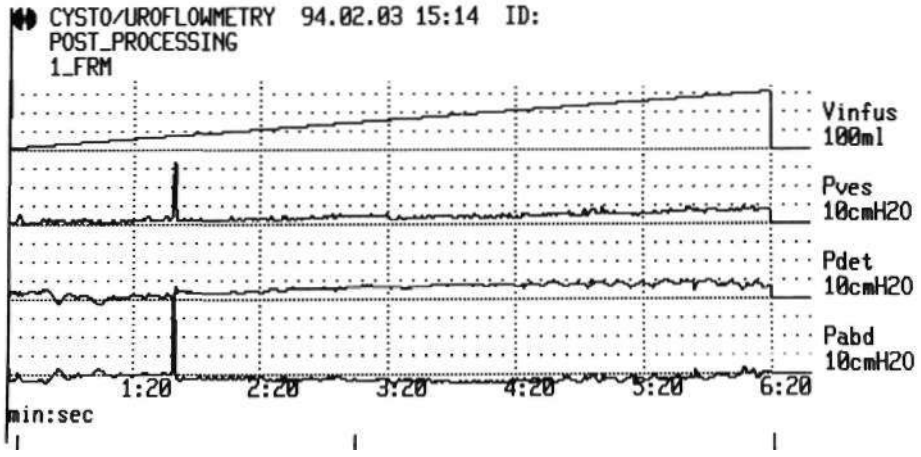


FIGURE 42.4 Cytometry during bladder filling. The bladder was lilled *(top truce)* at 50 mL per minute {Vinfus) to a total of 300 mL. Detrusor pressure fl'det'l is derived by subtracting pressure in the rectum (Pabd) from the measured intravesical pressure (Pves). At the beginning of the trace these two values can be seen to be subtracting effectively because on coughing there is an abrupt increase in intravesical pressure but no increase in detrusor pressure. Pdet did not exceed 10 cm of water, which is normal.

rectum to record intra-abdominal pressure. Once the lines arc in place and satisfactory subtraction of the two pressures demonstrated, bladder filling may commence. The rate of filling is recorded by the machine, which pumps sterile water or saline solution through the filling catheter into the bladder. The optimum rate of bladder filling has been much discussed, and there is little doubt that it affects the result, but for speed and convenience most laboratories use filling rates of 50 mL per minute. This is unphysiologically rapid but does mean that full bladder capacity usually can be reached within 7 or B minutes. First sensation of bladder filling may be reported at about 100 mL and full capacity reached between 400 and 600 mL. In healthy subjects the bladder expands to contain this amount of fluid without an increase of pressure of more than 15 cm of water (Figure 42.4). A bladder that behaves in this way is said to be stable. The main abnormality sought through cystometry in patients with incontinence is detrusor overactivity. According to the most recent definition of the International Continence Society, detrusor overactivity is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked. The disorder is called *neurogenic detrusor overactivity* when a neurological condition is recognized as being causative, and the term replaces the formerly used *detrusor byper-reflvxia, Idiopathic detrusor overactivity* is the term used when there is no defined cause, and this replaces *detrusor instability* (Abrams ct al. 2002). It should be emphasized that the urodynamic findings of neurogenic detrusor overactivity is indistinguishable from idiopathic detrusor overactivity.

When bladder filling has been completed, the filling catheter is removed, and the patienr voids into the flow meter with the intravesical and rectal pressure lines still in place. Urine flow rate depends both on detrusor pressure **and** outlet resistance. Much valuable information can be obtained about the latter by measuring detrusor pressure and urine flow. As a rough guide, the pressure for men should he less than 50 cm water and for women less than 30 cm water, with flow rates greater than 15 mL per second and 20 mL per second, respectively. With increasingly sophisticated developments in the equipment used for urodynamic studies, real-time computer analysis of rhe flow rates and pressures has become available. Much debate surrounds the question of the best mathematical formula to use in analyzing the degree of outflow obstruction; this is of particular importance in investigating suspected prostatic hypertrophy.

When cystometry is carried out using a contrast filling medium and the procedure is radlograpfiically screened, the technique is known as vidcocystomctry, which gives much additional information about the lower urinary tract. The advantages are that the bladder outline can be inspected during filling, and any reflux into the ureters is seen. A neurogenic bladder often produces characterisric changes with thickening of the bladder wall and bladder diverticula. Urologists and urogynecologists have found videocystometry useful in detecting sphincter or bladder neck incompetence in genuine stress incontinence, and the opportunity to inspect the outflow tract during voiding is of great value in patients with suspected obstruction. However, the procedure exposes the patient to irradiation and is inevitably more expensive than simple cystometry. In assessing patients with spinal cord injury, when examination of the upper tracts is critical, videourodynamic studies have an important role, but simple cystometry alone usually is adequate to demonstrate detrusor overactivity in nontraumatic neurogenic bladder disorders. A general criticism of cystometric studies is that, valuable as they are in demonstrating the underlying pathophysiology of a patient's urinary tract, the findings contribute little knowledge of the underlying cause of the disorder. *Urodynamic diagnosis* therefore is a meaningless term.

The urethral pressure profile is measured using a catheter-mounted transducer that is drawn slowly through the urethra by **a** motorized armature. The test can be performed in men or women and is called static if no

additional procedure such as coughing or straining is performed. If intravesical pressure is measured simultaneously and the patient is asked to cough repeatedly while the catheter is withdrawn, the transmission of the cough impulse in the urethra and bladder can be measured and expressed as the transmission pressure ratio, k was hoped that measurements of the urethral pressure profile and parameters derived from it would he useful in assessing genuine stress incontinence, but the overlap of measurements in controls and in women with genuine stress incontinence is such that the test is without diagnostic value in that context. However, it may be of value in assessing women with obstructed voiding, some of whom have abnormally high urethral pressures.

Neurophysiological Investigations

Various neurophysiological investigations of the pelvic floor have been developed by which the innervation of muscles that are difficult to test clinically can be assessed. These tests have been used by urologists, andrologists, urogynecologists, and colorectal surgeons. The role of clinical neurophysiological testing in assessing incontinence has recently been reviewed by an expert panel {Fowler 2002).

Electromyography

Electromyography (EMG) was first introduced as part of urodynamic studies to assess the extent of relaxation of the urethral sphincter during voiding. Interruption of the neural pathways between the pons and the sacral cord results in loss of coordination of sphincter and detrusor muscle activity, a condition known as detrusor-sphincter dyssynergia. In this disorder, instead of the sphincter relaxing to initiate and facilitate urine flow, it contracts at the same time the detrusor contracts. This may have important consequences, including incomplete bladder emptying and the potentially lethal condition of upper urinary tract dilatation, leading to renal failure. For this reason it was considered important that dyssynergic detrusor-sphincter activity be recognized. However, sphincter EMG is now rarely tecorded, for a number of reasons. First, it is often technically difficult to obtain a good-quality EMG signal from a site as inaccessible as the urethral sphincter, particularly in the hostile recording environment in which urodynamic studies are performed. The best signal is obtained using a needle recording electrode, but the discomfort from the needle itself is likely to impair normal relaxation of the pelvic floor. Surface recording electrodes have been used but rarely pick up signals well from distant muscles. Furthermore, there is doubt about the value of the information the procedure provides. Detrusor-sphincter dyssynergia is a disorder that arises as a consequence of spinal cord disease; if the patient comes to the urodynamic laboratory in a wheelchair or has even a milder degree of paraparesis, dyssynergic bladder activity can reasonably be presumed. The urologist's main concern is to establish whether it is causing upper ttact dilatation, and for this videocystometry is needed to detect ureteric reflux. Video screening allows the outlet tract to be seen, and sphincter EMG recording becomes redundant.

Although there is doubt about the value of kinesiological FMG studies recorded during urodynamics, the value of EMG studies of the pelvic floor performed as a separate neurophysiological investigation to assess innervation is more certain. EMG has been used to demonstrate changes of denervation and reinnervation in the urethral or anal sphincter or pelvic floor in several neurogenic disorders. The motor units of the pelvic floor and sphincters fire tonically, so they can be captured conveniently using a trigger and delay line and subjected to individual motor unit analysis. Well-established values exist for the normal duration and amplitude of motor units recorded from the sphincters and other pelvic floor muscles using a concentric-needle electrode, Reinnervation can be detected by abnormal prolongation of duration or increase in amplitude of motor units. Alternatively, single-fiber EMG studies can look for changes of reinnervation producing an increase in fiber density. Changes of denervation and reinnervation have been demonstrated in patients with idiopathic fecal incontinence, showing that there is a significant neurogenic component to this disorder. Denervation of the pelvic floor has been demonstrated in women with genuine stress incontinence. EMG of the pelvic floor is of particular value in demonstrating the existence and extent of denervation and reinnervation in patients suspected of having a cauda equina lesion.

Sphincter Electromyography in the Diagnosis of MSA

MSA may have protean manifestations, but urinary incontinence is often an early and troublesome complaint. In a study of 62 patients with established MSA, 56% had been seen by a urologist or gynecologist before the correct neurological diagnosis was made (Beck, Betts, and Fowler 1994). The early development of incontinence and its severity is caused by a combination of factors. It has been suggested that loss of pontine neurons causes the detrusor overactivity that occurs in the early stages of the disease. Loss of the parasympathetic innervation of the detrusor leads to poor contractility and incomplete emptying, and incontinence is compounded by sphincter weakness caused by loss of the anterior horn cells, which innervate the sphincters. These anterior horn cells lie in the sacral spinal cord in a group of cells known as Onufs nucleus. Neuropathologies! studies have shown that these anterior horn cells are selectively lost in MSA. Sphincter EMG can show changes of reinnervation in the muscles innervated by these neurons, characteristically manifest by prolongation of duration of motor units. These changes can be detected

easily, but it is important to include measurement of the late components of the potentials. Either sphincter may be studied, but the more superficial anal sphincter is most conveniently studied.

Although there has been recent debate about the value of sphincter EMG in the differential diagnosis of parkinsonism, a body of opinion maintains that a highly abnormal result in a patient with mild parkinsonism is of value in establishing a diagnosis of probable MSA (Vodusek 2001). In more advanced stages, however, EMC docs not appear to differentiate between MSA and other parkinsonian disorders. In early stages of the disease the EMG may be important not only for the neurologist but also for the utologist because inappropriate surgery can then be avoided. The response to medical management of incontinence in MSA, especially in the early stages of the disease, often is very good.

Sphincter Electromyography in Investigating Urinary Retention in Young Women

Urinary retention in young women has long been an enigma, and in standard urological texts the differential diagnosis of this condition used to be stated as either multiple sclerosis (MS) or a psychogenic disorder. Much the same is said about obstructed voiding in young women. However, upper motor neuron signs are not found in these young women, and their bladder disturbance is an isolated complaint, unaccompanied by other definite neutological features. Magnetic resonance imaging in particular, but also other laboratory investigations, can readily rule out MS ot a cauda equina lesion, and often there is no apparent neutological ot utological explanation. It has been proposed that this abnormal spontaneous activity results in an impaitment of relaxation of the urethral sphincter, which may cause urinary retention in some women and obsttucted voiding in others. Thus the EMG abnormality can be found in several bladder disorders because clinical presentation is determined by the behavior of the detrusor, not the urethral sphincter muscle. An association between the occurrence of this EMG abnormality in the urethral sphincter and polycystic ovaries was described in the original description of the syndrome {Fowler et al. 1.988).

Attempts to ttcat this primary sphincter disorder with hormonal manipulation, injections of botulinum toxin, application of trinitrate cteam, alpha blockers, and oral anticonvulsants have been largely unsuccessful. However, women with this syndrome have been found to respond particulatly well to sacral nerve stimulation using an implanted stimulator (Swinn et al. 2002) (see Sacral Nerve Stimulators later in this chapter). Although it is not difficult to understand how sacral nerve stimulation (which probably acts by stimulating pelvic afferents) mijdir suppress detrusor overactivity, the mechanism wheteby it reverses urinary retention is far from clear and is being researched.

Other Neurophysiologies Investigations of the Pelvic Floor

Other neurophysiological means of assessment rest largely on measurements of conduction velocity or latency and therefore correlate less well with function.

The bulbocavernous reflex was the first measurement of nerve conduction to be performed in the sacral region. Stimulation of the dorsal nerve of the penis or clitoris results in a reflex contraction of much of the pelvic floor musculature. The bulbocavernous reflex may be obtained by recording from the bulbocavernous muscle, although synchronous conttaction also can be recorded from the sphinctets. The latency of this reflex gives an estimate of conduction through the affcient and efferent fibers at the S2-S4 level, and a demonstrable delay may be of localizing neurological value. The limitation of this test is that, like all other reflex studies, it measures only conduction in the fastest fibers, the largest myelinated fibers. Many disorders of urogenital function and MED in particular are the result of unmyelinated fiber disease, and conduction in those fibers is not tested by this means. Furthermore, normal latency sacral reflexes may be obtained in patients with partial cauda equina lesions. Howcvct, a pathologically prolonged response in a patient suspected of having a ncutogenic disorder is valuable.

The pudenda] evoked potential may be as easily recotded as the tibial evoked potential and, remarkably, has a similar morphology and latency (Figute 42.5), despite the much shortet conduction distance involved. This similarity is thought to reflect the slower conducting affetent pathways of the potential. When it was first described it was hoped that by recording the pudendal tcsponse much could be learned about the affetent innervation of the urogenital ttact. However, in practice this has not proved to be the case. Although thete have been many reports of abnormal pudendal somatosensory evoked potentials in patients with established neurological disease and urogenital disorders, such as bladder or sexual dysfunction in MS, the diagnostic value of this test is minimal. This is because the spinal cord disease that gives tise to the urogenital disorder and delays conduction of the potential is almost always also clinically evident (Delodovici and Fowler 1995).

Electrical and magnetic stimulation have been used to measure motor conduction velocity from cortex to muscles in the pelvic floor. Magnetic stimulation also has been used to study spinal conduction between the cortex and sacral spinal cord. Stimulation of the motor cortex to produce a contraction of the pelvic floor entails a higher intensity of stimulation than that needed to produce a contraction in the lower limb, which in turn entails a higher intensity than that needed to cause uppet limb muscle contraction. This is thought to reflect the interhemispheric location of the cottical representation of the perineum. However, it is possible to obtain responses from the sphincters and pelvic floor. Prolonged conduction times in patients with

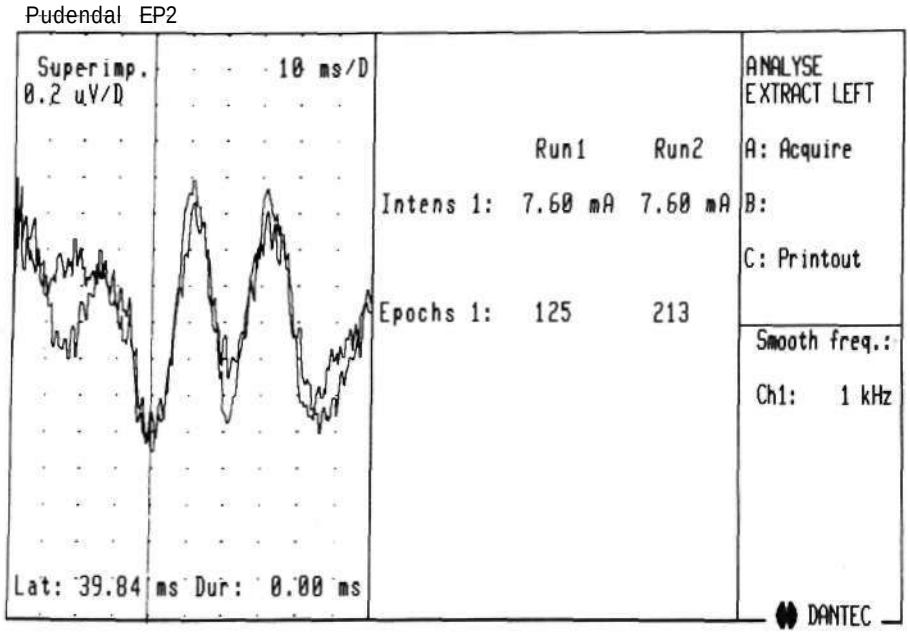


FIGURE 42.5 The pudendal somatosensory evoked potential. In this figure the cursor has been set to measure the latency of the first positive deflection, the PI or P40 shown here at 39.8 ms. Two evoked potentials have been superimposed to demonstrate the consistency of the response.

neurogenic bladder disorders have been reported, but no study showing abnormal conduction times in patients with bladder symptoms who do not have clinical evidence of spinal cord disease has been reported.

Stimulation of the spinal roots has been performed wirh magnetic stimulation and electrical stimulation. Magnetic stimulation of the sacral roots is a painless, simple means of testing sacral root conduction. It is important when making recordings in response to central nervous system stimulation to use a needle electrode to record from the sphincter muscles, to avoid volume conducted responses from the gluteal muscles. It is now thought that it is not possible to stimulate the efferent innervation of the detrusor directly by magnetic stimulation, and any rise in detrusor pressure is caused by an afferently mediated reflex contraction (Bcmehnans, Mundy, and Craggs 1999). Repetitive magnetic stimulation of the roots has been shown to transiently block detrusor hyper-reflex ic contractions in patients with spinal cord injuries.

Use of a per rectal stimulator for measuring terminal pudendal motor latency leads to the identification of abnormally slow conduction in the pudendal nerve in women with idiopathic neurogenic anorectal incontinence. Pudendal nerve stimulation proved to be valuable in establishing the pathogenesis of several pelvic floor disorders, but because motor latency is a poor reflection of axonal loss, terminal pudendal motor latency should not be used alone to assess denervation.

To assess the functionally important innervarion of the urogenital tract, some means of testing the unmyelinated and small myelinated fibers of the region is needed. Different approaches have been taken ro this problem, and some success has been achieved by measuring the sympathetic skin responses from the genital region. These potential changes can be obtained using the same technique used for recording from the foot and hand in response to electrical stimulation of the median nerve or for magnetic stimulation of the brain. In some patients with MED caused by diabetic neuropathy, the responses from the perineum cannot be recorded. However, one of the limitations of this method is that a small response cannor be considered abnormal, and only an absent response is thought to be significant. Similarities between continuously recorded sympathetic skin responses and the activity that has been called corpus cavernosal KMG are marked, and the possibility remains that this latter signal is a form of electrodermal response.

Because many neuropathies are length dependent, it has been argued that relevant abnormalities of small fiber function causing urogenital dysfunction can be detected in the feet of patients with generalized peripheral neuropathy. Testing thermal thresholds in the lower limbs therefore is of particular value in these circumstances.

Neuroimaging

The ease and clarity with which the cauda equina and conus region can be visualized by magnetic resonance imaging have made it the investigation of choice in patients suspected of having a structural lesion causing a neurogenic bladder disorder. In conditions of congenital cord malformation, rhe bony, dural, and intradural abnormalities are clearly shown on magnetic resonance imaging. Plain roentgenographic films of the region generally are nor helpful because they may show normal results with a lesion of the cauda equina, and spina bifida occulta is a common incidental finding.

Table 42.1: Medication for treatment of detrusor overactivity

Route	*Agent*	*Side effects*
Oral	Anticholinergics (e.g., oxybutynin, tolterodine, darifenacin)	Dry mouth, blurred vision, drowsiness
Oral	Tricyclic antidepressants (e.g., imipramine)	Tolerance
Oral	Desmopressin (or Desmospray intranasally)	Hyponatremia
Intravesical instillation	Vanilloids {capsaicin, rcsiniferatoxin)	Pungency
Sublingual spray	Cannabis-based medicinal extract	Dry mouth, disorientation
Intradctrusor injection	Botulinum toxin	No long-term data

MANAGEMENT OF BLADDER DISORDERS

Detrusor Overactivity

Dettusot overactivity is the major cause of incontinence in patients with neurogenic bladder disorders and is charactetized by the development of spontaneous incteases in bladder pressure that the patient is unable to suppress. These usually occur at volumes less than normal capacity so that the patient also complains of frequency. Urgency is felt as the detrusor muscle begins to contract, and if the pressure continues to increase, the patient senses impending micturition.

Anticholinergic medications are the mainstay of treatment for detrusor overactivity. Table 42.1 lists commonly used drugs.

Anticholinergics are the most widely used drugs for urgency and urge incontinence, acting specifically on muscarinic receptors. The first-line medications in this group are oxybutynin and tolterodine. The starting dosage for oxybutynin is 2.5 mg twice daily (up to a maximum of 20 mg daily in divided doses), and that for tolterodine is 2 mg twice daily; a newer once-daily formulation is now available for both medications. The main side effect is dry mouth; blurred vision, drowsiness, and constipation are less common. Darifenacin is a newer anticholinergic with greater specificity for the M3 receptor (the predominant type in the bladder). Propiverine and trospium chloride are other anticholinergic agents used in detrusor overactivity.

Positive anecdotal reports on the effect of cannabis in controlling bladder symptoms in patients with MS and identification of the cannabinyid receptor in animal and human studies have led to studies of caiinabis-based medicinal extracts in this group. An open-label study in patients with advanced MS (in whom indwelling catheterization was being considered) has shown promising results, with improvements in frequency, nocturia, and incontinence (Brady et al. 2001). The mechanism of action remains to be elucidated.

Botulinum-A toxin is a neuromuscular blocking agent that inhibits the release of acetylcholine from nerve terminals. It has been used to treat disorders of overactive muscle (including various dystonias) and has recently been introduced in the treatment of bladder overactivity by injection into the detrusor smooth muscle (Schurch et al. 2000). The effect is thought to last 6-12 months, and long-term results are eagerly awaited.

Desmopressin spray, first introduced to treat diabetes insipidus, is widely prescribed for children with nocturnal enuresis. Patients with MS and nighttime frequency also have used it. For a disabled patient and caregiver, the difficulties of the patient having to use the toilet several times a night can be significant. One or two nasal puffs of desmopressin from a mctered-dose spray administered on retiring reduces urine output for 6-8 hours and may significantly lessen nighttime urinary frequency. An oral preparation of desmopressin is now available. Daytime use seems to be free of ill effects, but the medication can be used only once in 24 hours and should not be given to oldet adults, in whom its use may precipitate congestive heart failure. Increased nighttime frequency does not seem to occur in those who have used it during the day. The serum sodium may decrease, usually to not less than 132 mmol/liter. If significant hyponatremia does occur, it usually happens within the first week or so, and the chief symptoms are general malaise, headache, and visible edema of the face and ankles. There is a rapid restitution of the sodium level once the medication is stopped.

Animal studies have shown that the lower urinary tract is richly innervated by capsaicin-sensitive afferent neurons, now known to be small sensory nerves expressing the vanilloid (VR1) receptor. In healthy animals, these afferenrs are quiescent, although they may be activated by inflammation by bacteria or chemicals, giving rise to the symptoms of cystitis. Under physiological circumstances in animals with an intact spinal cord, the detrusor reflexes are transspinal, with the afferent limb from the bladder to the spinal cord conveyed by small myelinated *AS* fibers (Figure 42,6), In chronic spinal animal models, after a period of spinal shock, a new afferent limb from the detrusor emerges as being of dominant functional importance, the afferent fibers of which are unmyelinated C fibers. In the case of the neurogenic bladder, the afferents that drive the volume-determined reflex detrusor contractions probably are sensitive to capsaicin. Capsaicin has a biphasic effect; it is initially an irritant, but if applied in sufficiently high concentration its secondary effect is as a selective neurotoxin acting on unmyelinated afferent C fibers.

Intravesical capsaicin has been used to decrease detrusor overactivity in patients with intractable incontinence caused

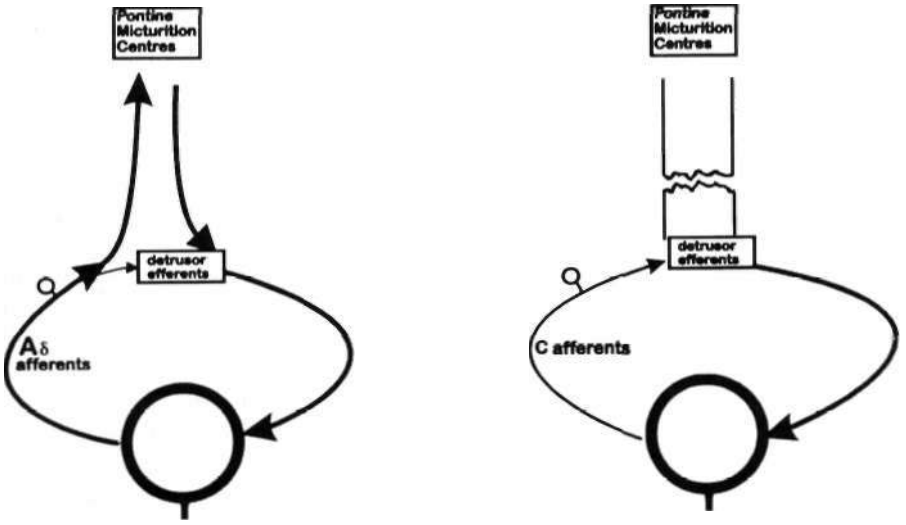


FIGURE 42.6 The route of afferent impulses from the bladder to the pontine micturition center in a patient with an intact spinal cord. (A) In health the peripheral bladder afferents are mainly A5 fibers. (B) After transection of the spinal cord a new reflex emerges at a sacral level, the afferents of which are unmyelinated capsaicin-scnsitive C fibers.

hy spinal cord disease. A 1- or 2-mmol solution of capsaicin in 30% alcohol and 70% saline was instilled into the bladder using a balloon catheter and left for 30 minutes. Some patients experienced a decrease in episodes of incontinence, and the benefit lasted up to 6 months, at which time the instillation must be repeated (Fowler et al. 1994). However, the pungency of capsaicin and its nonpharmaceutical status meant that resiniferatoxin, a much less irritating, selective neurotoxin vanilloid, was the preferred alternative. Although there have been reports of its effectiveness in treating hypersensitive bladdct disorders and detrusor overactivity of spinal origin, large-scale clinical trials were abandoned when it was found that the molecule's adsorption to plastic was affecting the efficacy of the studies. More recently, a study controlling for **this** factor demonstrated a reduction in episodes of incontinence in patients with idiopathic detrusor instability, suggesting that C-fiber overactivity has a role in the genesis of that condition (Silva et al. 2002). Unfortunately, there are currently major difficulties in obtaining supplies of pharmaceutical-grade resiniferatoxin.

Incomplete Bladder Emptying or Urinary Retention

The widespread use of intermittent catheterization has had a great effect on the management of the neurogenic bladder. Incomplete emptying can exacerbate detrusor overactivity, and an overactive bladder constantly stimulated by a residual volume responds by contracting and producing symptoms of urgency and frequency. Incomplete emptying is particularly likely to occur in patients with spinal cord disease caused by a combination of detrusor sphinctet dyssynergia occurring during attempts to void and poorly sustained detrusor contractions during the voiding phase. A generally accepted figure for significant residual volume is 100 mL. It seems that higher volumes may be usefully removed using intermittent self-catheterization.

Sterile intermittent catheterization was first introduced in the 1960s, but it was found that a clean rather than sterile technique was adequate. Used in children with spina bifida and even older adults with disotdets of bladder emptying, it has proved highly effective in many patients with MS and various other neurogenic bladder disorders.

Patients often are unaware of the extent to which they incompletely empty their bladder, and the amount of residual volume often is a surprise for both the patient and the doctor. For this reason, this parameter is the single most important measurement to be made when planning bladder management (Fowler 1996; Figure 42.7). The volume may be measured ultrasound or in-out catheterization.

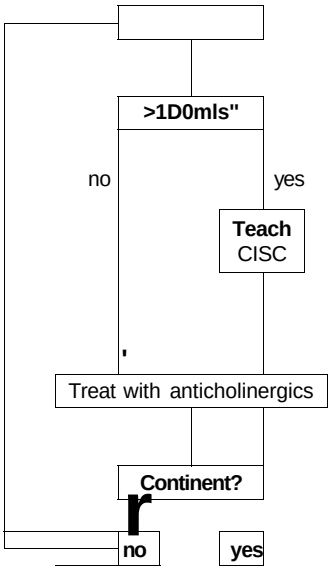


FIGURE 42.7 Algorithm showing the recommended management of neurological incontinence. (CISC = clean intermittent self-catheterization; PVR = posrvoid residual).

The advantage of the latter procedure is that it familiarizes the patient with catheterization and so makes teaching the technique of self-catheterization easier. Intermittent catheterization is best performed by the patients themselves, who should be taught by someone experienced in the method. In the United Kingdom, nurse continence advisors are particularly expert at this. A main requirement for success with this technique is patient motivation; a degree of physical disability may be overcome if the patient is sufficiently motivated. As a general rule, if patients are able to write and feed themselves they are likely to be able to perform the procedure. Sometimes tremor, impaired visual acuity, spasticity, and rigidity may make it impossible for the patient to sclf-cathcterize; in such circumstances catheterization may be performed by a partner or care assistant. Because the principle of this technique is to reduce the postmicturition residual volume, most patients are advised initially to perform the technique at least twice a day. No fixed limit exists on how often it should be performed, and it may be done throughout the day, but it should be performed regularly; the worst possible state of affairs is for the patient to do it very occasionally because this may introduce bacteria but does not have a constant beneficial effect on bladder emptying. Although bacteriuria is noted in 50% of patients doing clean intermittent self-catheterization, the incidence of symptomatic urinary tract infections is low. Transient hematuria when the patient first learns the method is common.

In spinal cord disease, a combination of intermittent self-catheterization and an oral anticholinergic deals effectively with both aspects of bladder malfunction (the intermittent catheterization for the incomplete emptying and the anticholinergic for overactivity). In a patient with a borderline significant residual volume, starting an anticholinergic may increase it (Figure 42.8). This should be suspected if the medication has a beneficial effect for several days that then disappears. Also, a patient who has marked hesitancy and difficulty in initiating micturition should wait to start an anticholinergic until intermittent catheterization is well established; otherwise, complete retention may result. This combined approach works well in patients with spinal cord disease such as MS if the patient is not too severely disabled. It is also highly effective in the earlier stages of MSA because incomplete bladder emptying is particularly likely to present a problem in rhat disorder. Intermittent self-catheterization is the main means of symptomatic relief in women with urinary retention, although a number of them find the technique unacceptable because of discomfort on withdrawing the catheter, presumably caused by the hypertrophicd muscle contracting down on the catheter.

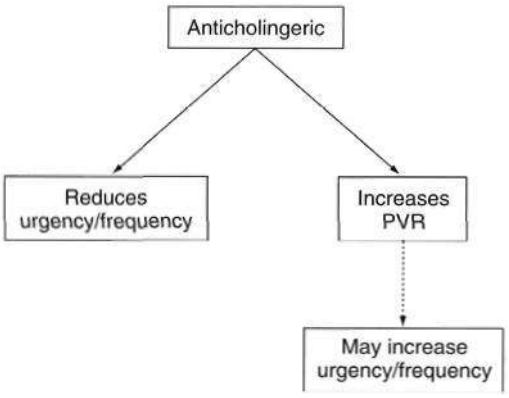


FIGURE 42.8 Although an anticholinergic is effective in lessening detrusor overactivity, it may also impair bladder emptying. The resulting increase in postmicturition residual volume (PVR) may lead to worsening symptoms of urgency and frequency.

Permanent Indwelling Catheters

Although a combination of anticholinergic medication and intermittent catheterization is the optimal management for patients with detrusor overactivity and incomplete bladder emptying, there comes a rime when the patient is no longer able to perform self-catheterization or when urge incontinence and frequency are unmanageable. In patients with spinal cord disease this may be reached when the patient is no longer ambulatory, and at this stage an indwelling catheter becomes necessary (Figure 42.9).

The most immediate simple solution is an indwelling Foley catheter, a device held in place by an inflatable balloon in the bladder proximal to the catheter opening, but the long-term ill effects of these devices are well known. One of the major problems may be urine leakage around the catheter, which occurs when strong detrusor contractions produce a rapid urine flow that cannot drain quickly enough. A common reaction is to insert a larger-caliber catheter, with the effect that the bladder closure mechanism becomes progressively stretched and destroyed. The detrusor contractions may be of sufficient intensity to extrude the 10- or 20-mL balloon from the bladder, further rupturing the bladder neck. The result may then be a totally incompetent bladder neck and urethra. Bladder stones and recurrent, resistant infections are also more likely in a bladder with an indwelling catheter.

A preferred alternative to an indwelling urethral catheter is a suprapubic catheter. This can be inserted under local anesthetic. However, the procedure should be undertaken only by a trained urologist because there is a danger that bowel overlying the bladder may he punctured, especially in patients with small, contracted bladders. Once in situ, the catheter is left on constant drainage. Because no attempt is made to close the urethra, continence depends on the suprapubic drain remaining unimpeded. If the catheter becomes blocked or kinked, the patient leaks urethrally. Although it is by no means a perfect system, a suprapubic catheter is a better long-term alternative to an indwelling urethral catheter and often is the method of choice in

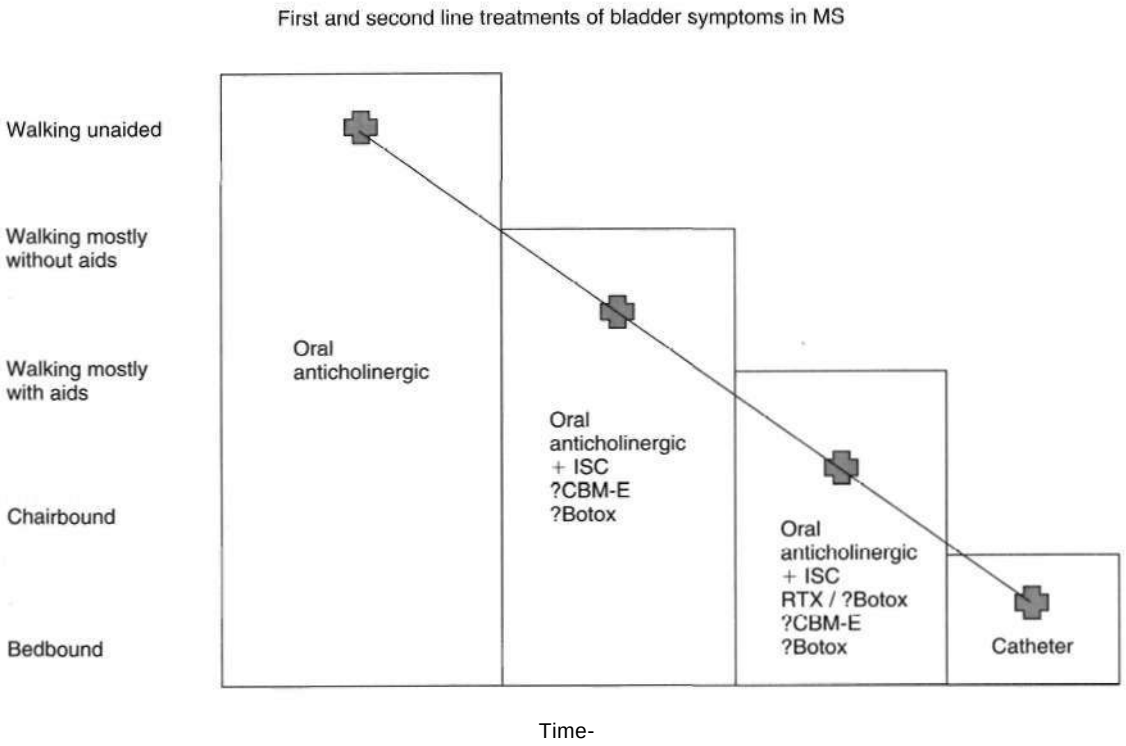


FIGURE 42.9 The bladder symptoms in multiple sclerosis become increasingly difficult to manage with progression of spinal cord disease. This diagram summarizes the various measures that may be effective at each stage. {Botox = borulinum toxin; CBM-E = cannabis-hased medicinal extract; ISC = intermittent self-catheterization; RTX = resiniferatoxin.)

managing incontinence in patients for whom other means are no longer effective.

External Device

If urge incontinence is the main problem and the bladder empties completely, some men are able to wear an external device attached around the penis. The simplest and least obtrusive is a self-sealing latex condom sheath, which can be pur on each night or kept in place for up to 3 days. More elaborate body-worn appliances are also available, but an expett must fit them. An effective external appliance for women has not been devised.

Sacral Nerve Stimulators

An extradural sacral nerve stimulator can be highly effective in lessening detrusor overactivity that is resistant to anticholinergic medication. It seems highly likely that its mechanism of action is by stimulation in the ptesacral region of the pelvic afferents, which arc known to have an inhibitory effect on the detrusor. However, it is more difficult to explain how it may have an effect in young women with urinary retention,

Implanting a stimulatot is a two-stage procedure; rhe first stage is an outpatient procedure in which the stimulating lead is inserted through an S3 foramen under local anesthesia and connected to an external stimulator for 3 days. If the patient's symptoms improve significantly during this time, as judged by measutement of residual volumes and diary-recorded voided volumes, the patient is eligible for a permanent stimulator. Formerly this was implanted under general anesthesia in a subcutaneous pocket and the stimulating lead tunneled subcutaneously back to the sacrum and the electrode implanted through the foramen, but there is now a trend to implant the definitive stimulating lead as a minimally invasive procedure with the patient awake and able to report sensations induced by the lead in different positions because a strong sensation in the central perineal region seems to be ctitical for obtaining a good clinical outcome. The stimulator is continuously active, giving a 15-Hz pulse to the sacral nerves on one side. The permanent stimulators arc expensive, and the patient may need to undergo a number of revisions, but in well-selected cases this form of treatment can gteatly improve bladder symptoms.

Nerve Root Stimulators

In patients who have suffeted a complete spinal cord transection but in whom the caudal section of the cord and its roots are intact, the implantation of a nerve root stimulatot should be considered. This device was pioneered

by **Professor** Giles Brindiey and his collaborators, and approximately 2000 have been implanted worldwide. The principle on which they work is that the stimulating electrodes are placed around the lower sacral roots {S2-S4) and activated by an external switching device. The stimulating electrodes are implanted during a neurosurgical procedure and usually are applied intrathccally to the anterior roots; the posterior roots are cut at the same time. After the implant, the stimulation parameters are adjusted so that the patient obtains the maximum benefit from the stimulator in terms of making the bladder contract for voiding, assisting defecation, or even producing a penile erection. Although the procedure is highly effective in selected cases, the additional neural deficit caused by the need for section of the dorsal roots and consequent loss of reflex erections has reduced its popularity. These stimulators are suitable only for patients with complete spinal cord lesions rather than partial cord lesions or progressive neurological disease.

Surgery

Various urological procedures can be carried out to treat incontinence, as summarized in Table 42.2. A surgical procedure to rectify a disorder causing incontinence in an otherwise fit and healthy patient often is highly successful, and even after spinal cord injury a surgical option may be the best solution for long-term bladder management. However, this does not apply to patients with progressive neurological disease causing incontinence. For example, at a time when the bladder is becoming unmanageable by a combination of intermittent catheterization and an anticholinergic, the patient with MS may just be managing to remain independent. This is not the moment to suggest major urological surgery. Few patients with progressive neurological disease affecting bladder control opt for surgery.

MANAGEMENT OF NEUROGENIC SEXUAL DYSFUNCTION

A discussion of the patient's difficulty is the first step in advising management for sexual dysfunction. An explanation of the neurological basis of sexual dysfunction, sometimes to both partners, may relieve anxieties that the problem was thought to be psychological in origin. The topic can be introduced without embarrassment during explanation of the neurological basis of any coexistent bladder symptoms. The main qualification for undertaking this type of discussion is that the doctor should feel comfortable with it and able to convey this comfort to the patient. Patients prefer to discuss intimate problems with someone they know already, and this is usually the neurologist they see regularly.

Table 42.2: Urological operations that may be performed to treat various causes of incontinence

Disorder	*Surgical procedure*
Genuine stress incontinence	Bladder neck suspension, transvaginal tape
Detrusor overactivity	Augmentation cystoplasty
Sphincter failure	Arrificlil sphincter
Intractable incontinence	Urinary diversion with stoma collection bag

Sexual Dysfunction in Women

Little is known about sexual dysfunction in women with neurological disease. Although patients rarely complained in the past, problems undoubtedly occur, and they may become more evident in the current climate of frank discussions about male sexual dysfunction. Women with spinal cord disease such as MS encounter difficulties with intercourse because of poor bladder control and lower limb spasticity, in addition to loss of sensation (Hulter and Lundberg 1995), Loss of perineal sensation is a major problem for women with cauda equina lesions and may be a persisting cause of dissatisfaction, even when adequate means of managing bladder and bowel have been established. The erotic apathy that may occur with temporal lobe epilepsy can be a serious cause of disharmony in couples,

Male Erectile Dysfunction

The treatment of MED has been transformed in recent years by the introduction of orally active erectogenic agents. The first such agent was sildenafil (Viagra). This is a phosphodiesterase inhibitor that increases nitric oxide release in the corpora cavernosa and thus induces penile erection. Clinical studies have demonstrated that the optimal dosage should be taken up to 1 hour before anticipated sexual activity. It is not an aphrodisiac, but it improves penile erection with appropriate stimulation. The medication appears to have few side effects, and those that exist relate to its vasodilator action. In some patients it produces headache, flushing, and dyspepsia. The medication has undergone extensive testing in many groups of patients with MED and has been shown to be well tolerated. Contraindications to this medication include myocardial infarction in the previous fi months, concomitant use of nitrates, and other strong cardiac risk factors. It has been shown to be effective in men with a variety of medical conditions and in particular is of benefit in diabetic-induced MED and in spinal cord-injured patients; it has been shown to be very effective in MS.

Sildenafil has been shown to be highly effective in treating erectile dysfunction in a double-blind, placebo-controlled

trial in 217 men with MS using self-administered questionnaires. In response to the question "Did the medication you took over the last 4 weeks improve your erections?" 89% of those receiving sildenafil said "y^{es}!" compared with 24% of those receiving placebo. Furthermore, the study demonstrated an improvement in quality of life after treatment (Fowler et al. 2002).

Other phosphodiesterase inhibitors such as tadalafil and vardenafil arc expected to be available soon; they differ from sildenafil in terms of speed of onset and in duration of effect. Long-term results arc awaited.

Sublingual apomorphine hydrochloride is a D1/D2 dopamine receptor agonist that acts centrally to induce penile erection. At a dosage of 2 mg, increasing to 3 mg, it has a reported faster onset than sildenafil, with nausea in 7%. Whether it works in patients with MS remains to be seen.

Although oral agents arc now established as first-line treatment for most patients, some patients will need an alternative. This may be an injection of prostaglandin El (alprostadil) directly into the penis, which acts by relaxing the smooth muscle of the cavemosal vessels. The administration of alprostadil as an intraurethral pellet, called medicated urethral system for erection (MUSE), was introduced to obviate self-injection.

For men who do not respond to vasoactive agents or who want to use alternative means of treatment, vacuum pump devices may be suggested. These induce tumescence in a rigid cylinder that is placed over the penis and from which the air is pumped by hand. A band is then placed around the base of the penis, and the cylinder is removed.

Rarely in some men, usually those with vascular disease rather than progressive neurological illness, a penile prosthesis is implanted. The implants are available either as a simple semirigid or malleable rod or a complex inflatable device.

With the advent of an effective nonsurgical therapy for erectile failure, the emphasis for investigation and treatment of MED has changed. Previously, investigations aimed at determining whether the cause of erectile failure was organic or psychosomatic. Various neurophysiological investigations were used in an attempt to identify a neurological basis, and nocturnal penile tumescence studies were considered to be the major deciding factor. However, it is now well established that nocturnal erections are preserved in men with spinal cord injury or partial spinal cord dysfunction, as occurs in MS. Furthermore, there is no single neurophysiological test that can distinguish between neurogenic and psychogenic erectile dysfunction. Assessment of the response to an intracorporeal injection of a vasoactive agent provides some information about the likely pathogenesis because men with neurogenic or psychogenic erectile difficulties respond well, whereas those with vascular disease do not. The role of the International Index of Erectile Function questionnaire in assessing MED has become well established.

Ejaculatory Failure

Ejaculatory failure commonly accompanies erectile failure of neurogenic origin in men wirh spinal cord disease, whereas in diabetics, ejaculation seems to be better preserved than erectile function. Much less can be done for ejaculatory difficulties, although it is worth trying oral yohimbine. This substance is obtained from the yohimbine tree, which grows in West Africa. It is an «$_2$-adrcnergic blocker that is said to facilitate male sexual arousal. A controlled trial of the effect of yohimbine in treating organic MED showed a small effect when compared with placebo. The recommended dosage is either a starting dose of 10 mg (increasing to 20 mg) taken approximately 2 hours before intercourse is attempted or 5 mg three times a **day** taken regularly. Its side effects include a feeling of general exciration, anxiety, nausea, and trembling hands.

Infertility caused by ejaculatory failure can be managed by means quite different from those that would be suggested for ejaculatory difficulties. Patients should be referred to a center that specializes in this problem; such centers usually arc found in association with a spinal cotd unit.

MANAGEMENT OF FECAL **INCONTINENCE**

Coordinated lower bowel function depends less on the integrity of the spinal cord than does bladder function. Consequently, fecal incontinence is much less common than urinary incontinence in neurological disease. Indeed, the first step in managing fecal incontinence is to establish the cause (see Chapter 32). It is usually evident from the history if the complaint is caused by a diatrheal state or urgency of defecation, and if so the patient should be referred to a gastroenterologist for investigation. If no cause can be found and the problem persists, symptomatic treatment with a constipating agent that reduces lower bowel motility, such as loperamide, may be helpful.

Many patients with partial spinal cord disease complain of constipation, and some of them also have occasional fecal incontinence. Constipation can be caused by either slow colonic transit or difficulties with defecation. The incontinence may result from loss of voluntary control of the pelvic floor. If this occurs, the patient should use suppositories and attempt to empty the bowel at a predictable and convenient time, thereby lessening the risk of unexpected defecation. A survey of patients with spinal cord injury found that problems with bowel function were a major physical and psychological problem and were rated only slightly less serious than the loss of mobility (Glickman and Kainm 1996).

Pelvic floor incompetence can occur in the context of a Cauda equina lesion or as a result of more selective neurological injury to the pudendal nerves. Referral to a colorectal surgeon is necessary for consideration of a sphincter repair or postanal repair. Alternatively, a

"ncosphincter" can be created using healthy nonsphincter striated muscle, such as the gracilis, transposed around the anal canal.

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Chapter 43
Neuroepidemiology

Mitchell T. Wallin and John F. Kurtzke

A useful definition of epidemiology is "the science of the natural history of diseases." This concept is based on the original roots of the word: *logos,* from *legein,* "to study"; *epi,* "[what is] on"; *demos,* "the people." In epidemiology, the unit of study is a person affected with a disorder of interest. Therefore diagnosis is the essential prerequisite. This is why Hie neurologist must be an essential pari of any inquiry into the epidemiology of neurological diseases.

After diagnosis, the most important question is the frequency of a disorder. Much of this type of information has been based on case series, that is, the scries of cases encountered by individual practitioners, clinics, or hospitals. However, whether taken as numerator alone (case series) or compared with all admissions (relative frequency), the difficulty with such data is that one has little assurance that what has been included is representative of the total population. Such case material needs to be referenced to its proper denominator, its true source: the finite population at risk.

POPULATION-BASED RATES

Ratios of cases to population, together with the period to which they refer, make up the population-based rares. Those commonly measured are the incidence rate, mortality rate, and the so-called prevalence rate. They arc ordinarily expressed in unit-population values. For example, 10 cases among a communiry of 20,000 represent a rate of 50 per 100,000 population or 0.5 per 1000.

The *incidence* or *attack rate* is the number of new cases over a defined study period divided by the population at risk. This is usually given as an annual incidence rate in cases per 100,000 population per year. The date of onset of clinical symptoms typically dictates the time of accession, although occasionally the date of first diagnosis is used.

The *(point) prevalence rate* is more properly called a *ratio,* but it refers to the number of those affected, both old and new cases, at one point in time within the community per unit of population. The *lifetime prevalence rate* refers to the proportion of persons manifesting a disorder of interest during the period of their life up to the survey date. It is typically reported per 1000 of the population at risk. If there is no change in case-fatality ratios over time and no change in annual incidence rates (and no migration), then the average annual incidence rare times the average duration of illness in years equals the point prevalence rate.

When numerator and denominator for a rate each refers to an entire community, their quotient is a crude rate, for all ages. When both terms of the ratio are delimited by age or sex, these are age-specific or sex-specific rates. Such rates for consecutive age groups, from birth to the oldest group of each sex, provide the best description of a disease within a community.

In comparing morbidity or mortality rates between two communities for an age-related disorder (such as stroke or epilepsy), there may be differences in crude rates solely because of differences in the age distributions of the denominator populations. This can be avoided by comparing only the individual age-specific rates between the two, but this rapidly becomes unwieldy. Methods exist for adjusting the crude rates for all ages to permit such comparisons. One such method involves taking community

age-specific rates and multiplying them by the proportion of a "standard" population within the same age group. The sum of all such products provides an age-adjusted (to a standard) rate, or a rate for all ages adjusted to a standard population. One common standard in the United States is its population for a given census year,

The *mortality* or *death rate* is the number of deaths in a population in a period with a particular disease as the underlying cause, such as an annual death rate per 100,000 population. The standardized mortality ratio (SMR) is the observed number of deaths in the study group of interest, divided by the expected number of deaths based on the standard population rates applied to the study group.

The great advantage of death rates is their current availability over time and geographical area for many disorders. Geographical distributions arc especially informative because most population studies available are, of necessity, spot surveys that may tell us little about areas that were not investigated. Most often, too, the numbers are larger by orders of magnitude than those that prevalence studies can provide. The principal disadvantage, and it is a major one, is the question of diagnostic accuracy. There are also problems with coding practices and demographic errors (age and residence in particular),

The code used for mortality rates is a three- or four-digir number representing a specific diagnosis in the *International Statistical Classification of Diseases, Injuries and Causes of Death* (/CD), which is revised about every 10 years. The changes in the tenth revision *[ICD-10)* were major. *ICD-10* was published in 1992 with the innovation of an alphanumeric coding scheme of one letter followed by three numbers (e.g., 163.1, cerebral infarction due to thrombosis of precerebral arteries). One drawback of the *ICD* system of classification is that several diseases are frequently subserved under the same primary code. To provide a more refined classification for individual diseases, several disciplines have published specialty-related expansions of the primary *ICD* structure. *ICD-10-NA* is the expansion of the codes relating to neurological diseases, so that virtually every known neurological disease or condition has a unique alphanumerical identifier (World Health Organization 1997; van Drimmelen-Krabbe et al. 1998). In the United States, hospitals currently use the *ICD-9* clinical modification, which may be replaced hy an update based on **the** *ICD-10.*

Space precludes attention to community survey methods, risk factors, treatment comparisons, and statistical methods—all intrinsic aspects of epidemiology. As for neuroepidemiology *per se,* the material presented here provides some highlights for a few major diseases chosen to represent the field.

CEREBROVASCULAR DISEASE

Stroke is the third leading cause of death and the most common reason for disability in Western countries (Poungvarin 1998) (see Chapter 57). Cerebrovascular disease has been variably classified, particularly in mortality data. The general usage in morbidity studies has been to subdivide stroke into (1) subarachnoid hemorrhage {SAH}, (2) intracerebral hemorrhage, and (3) cerebral infarction. Cerebral infarction is the most common type of stroke in developed countries, making up more than 70% of cases. Intracranial hemorrhages make up about 10-15% of strokes, SAH make up less than 5%, and the remainder are of undetermined etiology.

Mortality Rates

Between 1950 and 1996, U.S. stroke death rates declined by 70% overall (Centers for Disease Control and Prevention 1999). There are similar decreasing rates for other countries, including Japan, Australia, New Zealand, Canada, and all of Western Europe. Reported rates over the last four to five decades actually increased for Czechoslovakia, Yugoslavia, Bulgaria, Poland, and Hungary. The changes in stroke death rates by racial/ethnic groups in the United States between 1990 and 1998 are recorded in Table 43.1. The age-adjusted stroke death rate was higher for black non-Hispanics compared with other groups. The stroke death rates for American Indians

Table 43.1: Age-adjusted death rates (1940 U.S. standard population) per 100,000 for stroke by race and Hispanic origin 1990, 1998, and percent change form 1990 to 1998: United States

Year	*Total*	*Non-bispanic white*	*Non-hispanic black*	*Hispanic*	*American Indian or Alaska native*	*Asian or Pacific Islander*
1990*	27.5	25.1	47,8	20.7	19.1	24.7
1998	25.1	23.3	42.5	19.0	19.6	22.7
Percent change 1990 to 1998	-9.0	7.2	-11.1	-8.2	2.6	-8.1

* Age-adjusted death rates for 1990 were calculated based on population estimates for July 1, 1990. Rates published elsewhere for 1990 are based on the enumerated population on April 1, 1990, for the year in which the decennial census was taken. Rates for noncensus years are based on July 1 (mid year) populations. In order to measure changes over time, rates based on the July 1 populations are used. *Source:* Keppel, K. G., Pearcy, J. N., & Wagener, D. K. 2002, "Trends in racial and ethnic-specific rates for the health status indicators: United States, 1990-98". *CDC-Statistical Notes,* vol. 23, pp. 1-15.

or Alaska natives increased by 3%, and the rates for the other four groups declined by 7-11%.

U.S. racial and ethnic disparities in mortality by stroke type have been reported for the period 1995-1998 (Ayala et al. 2001). National Vital Statistics Death certificate data were used to calculate age-standardized rates for ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage among Hispanics, Blacks, American Indians/Alaska Natives, Asians/Pacific Islanders, and whites. For ischemic stroke, the ratio of the age standardized death rate among blacks (96 per 100,000) compared with whites was 1.30. All other groups had lower rates of ischemic stroke compared with those of whites. Death rates for intracerebral hemorrhage were highest for blacks (23 per 100,000) and Asian/Pacific Islanders (20 per 100,000), with corresponding risk ratios compared with whites of 1,70 and 1.52. Subarachnoid hemorrhage death rates were higher for all other minority groups as compared with whites.

Morbidity Rates

Like mortality rates, stroke incidence has declined rapidly over the past fifty years. In Rochester, Minnesota, stroke incidence fell by 54% from 1945-1954 and 1975-1979. Over the past two decades, however, stroke incidence rates have stabilized or slightly decreased in Western countries (Thorvaldsen et al. 1999). Average annual age-adjusted incidence rates by sex show a modest, but possibly increasing, male excess. In recent years the annual stroke incidence rate in Europe and North America has been between 100 and 300 per 100,000 population.

Rates in the United States for blacks remain higher than do those for whites. The Greater Cincinnati and Northern Kentucky Stroke Study was the first large metropolitan-based study of stroke trends among blacks (Brodenck et al. 1998). The incidence for first-ever stroke among blacks in the region was 288 per 100,000 (age- and sex-adjusted 1990 U.S. population). The incidence rate for first-ever and recurrent stroke was 411 per 100,000. The first stroke incidence rate was approximately 1.6 greater than the overall age- and sex-ad] Listed incidence rate of stroke among the white population of Rochester, Minnesota, in 1985-1989. Figure 43.1 illustrates those age-specific incidence rates in these two populations. Based on extrapolation techniques using the two study populations, there were at least 731,000 first-ever or recurrent strokes in the United States in 1996.

In Rochester, Minnesota, the age-adjusted average annual incidence rate declined from 200 per 100,000 population during 1945-1954 to 107 per 100,000 for 1975-1979. The decrease was for both sexes, for essentially all ages, and for both cerebral hemorrhage and thrombosis; it was not found for SAH, however. Brown et al. (1996) reported an extension of the Rochester data through 1989, A 13% *increase* in total stroke incidence rates was noted during the years 1985-1989 versus 1975-1979. The most prominent increases were in those 85 years or older.

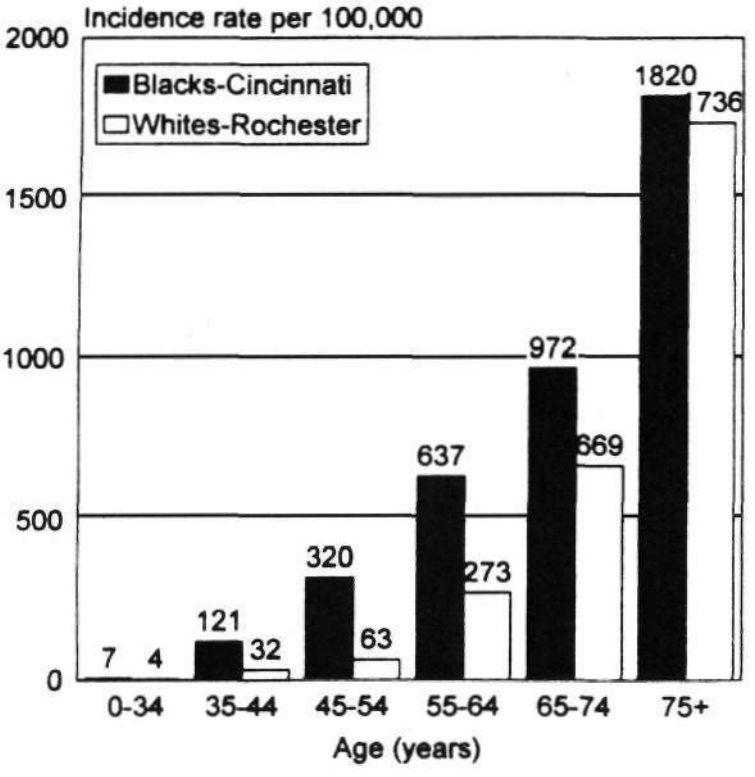

FIGURE 43.1 Age-specific incidence rates of first-ever stroke among blacks in Greater Cincinnati during the first 6 months of 1993 and among whites in Rochester, Minnesota, during 1585-1989. (Reprinted with permission from Brodcrick, J., Brott, T., & Kothari, R. 1998, "The Greater Cincinnati and Northern Kentucky Stroke Study: Preliminary first-ever and total incidence rates of stroke among blacks," *Stroke^* vol. 29, 415-421.)

Since 1975-1979, the incidence rate among women aged 85 years or older has increased 90%, with a corresponding increase of 11% for men.

The World Health Organization's Multinational Monitoring of Trends and Determinants in Cardiovascular Disease project is an ongoing study to compare incidence and mortality of stroke across multinational populations adjusted to a "world standard population" (Stegmayr et al. 1997). The highest incidence rates out of 18 countries were in men in Kuopio, Finland, and Novosibirsk, Russia (adjusted incidence rates >300 per 100,000). In women, the highest rates were in Novosibirsk. The highest rates for both sexes were more than three times higher than those in Friiili, Italy. In half the populations, the- stroke incidence rate was twice as high in men as in women. Significantly, a regression analysis showed that conventional cardiovascular risk factors (i.e., smoking and hypertension) explained only 21% of the variation of stroke incidence among the population in men and 42% among women.

Prevalence rates in the early 1980s were around 600 per 100,000 in the West and 900 per 100,000 in Asia. In the United Stares, age-, race, and sex-adjusted stroke prevalence rates increased from 1.41% in 1971-1975 to 1.87% in 1988-1994 (Muntner et al. 2002). This corresponded to an increase of 930,000 noninstitutionalized stroke survivors with increases observed in all age, race, and gender groups. With decreasing mortality trends and relatively stable stroke incidence rates during the 1980s, these data point to a decreasing stroke case fatality rate as a driver of this prevalence trend.

PRIMARY NEOPLASMS

Three large centralized databases have been created in the United States that provide descriptive epidemiologic data on primary brain tumors. These include the Central Brain Tumor Registry of the United States (CBTRUS); the Surveillance, Epidemiology and End Results (SEER) database; and the National Cancer Database (NCDB). According to the CBTRUS and SEER databases, an estimated 350,000 persons were living with a primary brain tumor diagnosis in the United States in the year 2000 (Davis et al. 2001). This translates to a prevalence rate of 131 per 100,000 persons. The lifetime risk of developing a CNS malignancy is estimated to be 0.66% for men and 0.54% for women (Ries et al. 2000). Little is known of the causes of most primary brain tumors, but their epidemiologic features may provide clues for more definitive studies.

In clinical experience, 85% of primary central nervous system (CNS) tumors are intracranial and 15% are intraspinal. For the brain, the major groupings are the gliomas (40-50%, of which about half are glioblastoma multiforme) and the meningiomas (15-20%). Pituitary adenomas plus neurilcmmomas, especially acoustic, add another 15-20%. The most common spinal cord tumors are neurofibroma and meningioma, followed by ependymoma and angioma.

Mortality Rates and Survival

In the United States between 1995 and 1999, malignant CNS tumor deaths by age showed a steep rise from very low rates in early adult life to a peak of around 20 per 100,000 by age 75, followed by a steep decline with further increasing age (Davis et al. 2001). There was a notable excess of whites over nonwhites in this group, with rates two to three times higher in the whites. There was also in all race groups an excess of male deaths.

Reported 5-year survival ratios have been about 60% for clinically diagnosed meningioma and 20% for gliomas as a group. Median survival for glioblastoma has been about 1 year after diagnosis. Taken together, median survival for benign brain tumors may be estimated at 6 years. The relative 5-year survival rate for children younger than age 15 years with brain and other nervous system tumors is now 61%, compared with 35% twenty years ago (Parker et al. 1997).

Survival for patients with metastatic brain tumors is poor. Even after whole brain radiation, median survival is about four months with 40-60% of patients dying of systemic disease (Lagcrwaard et al, 1999), Long-term survival for 740 patients with brain metastases was reviewed by Hall and colleagues (Hall et al. 2000). For all tumor types, the actuarial survival rate was 8.1% at 2 years, 4.8% at 3 years, and 2.4% at 5 years. At two years from diagnosis, ovarian carcinoma had the highest survival rate (23.9%) and small cell lung cancer the lowest (1.7%). Favorable prognostic variables for survival included a single metastatic lesion, surgical resection, and whole brain radiation.

Morbidity Rates

Average annual incidence rates for primary brain tumors in the more complete surveys have ranged mostly between 10 per 100,000 and 15 per 100,000 population, including pituitary tumor rates at 1-2 per 100,000. Primary tumors of the spinal cord arc recorded at about 1 per 100,000, and in one survey peripheral nerve tumors had a rate of 1.5 per 100,000.

From the late 1960s to the late 1980s, the incidence of primary brain neoplasms has at least doubled in the United States. The Connecticut Tumor Registry showed a dramatic increase in incidence for age groups 65-84 years, with relatively stable rates for younger cohorts. For the 65- to 69-ycar-old age group, the incidence rate increased from 18.42 per 100,000 in 1965-1969 to 28.29 per 100,000 in 1985-1988. Similar increases were seen in older age groups. There was a trend of increasing incidence for the

1890 and 1900 birth cohorts, implying a cohort effect. Whether these cohort trends are due to environmental effects or improved diagnostic capabilities is not clear.

Using the SEER database, incidence trends were computed by age group for malignant brain tumors for the years 1975-1997 (Figure 43.2). Incidence rates remained stable for those <20 years to 69 years of age during the period. There was a gradual increase in malignant tumor rates, however, for individuals older than 70 years between 1975 and 1990. During the 1990s, the rates for the oldest groups have essentially remained unchanged.

In meningioma, the age-specific rates continue to rise with age to the oldest group, and there is a female preponderance. The suspected excess in blacks was borne out in a survey in the Los Angeles County Cancer Surveillance program. Age-adjusted average annual incidence rates for meningiomas were 1.8 per f00,000 males and 2.7 per 100,000 females. Respective non-Hispanic white rates were 1.8 per 100,000 and 2.5 per 100,000; for blacks, they were 2,5 per 100,000 and 3.6 per 100,000. In Rochester, Minnesota, annual incidence rates for all cases were 4.9 per 100,000 males and 5.8 per 100,000 females for 1935-1977, but only 1.2 per 100,000 and 2.6 per 100,000 for cases diagnosed antemortem. The true rare for meningiomas, then, would seem to be around 5 per 100,000 population.

An overall estimate for malignant intracranial tumors is about 5 per 100,000 population, most of which is attributed to glioblastoma multiforme. For benign brain tumors, a reasonable figure would be 10 per 100,000; 5 per 100,000 for meningioma; and 1-2 per 100,000 each for benign gliomas, pituitary tumor, and all others.

Although some CNS tumors have a clear genetic character, fewer than 5% can be attributed to inheritance. Astrocytic gliomas may show loss of genetic information from chromosomes 9p, lOq, lip, 13q, 17p, *or* 22 (Kyritsis et al. 1993). Mutations of the *pS3* tumor-suppressor gene on the short arm of chromosome 17 are found mostly in malignant astrocytic forms and arc linked to malignant tumor transformation and progression. Many factors are implicated in human brain tumors, the vast majority of which are unsubstantiated by scientific evidence. High-dose radiation leads to an increased incidence of primary brain tumors, but the association of higher brain tumor risk with low doses of radiation is more controversial.

CONVULSIVE DISORDERS

Epilepsy is defined as recurrent seizures (i.e., two or more distinct seizure episodes) that are not the immediate result of an acute cerebral insult. The four broad categories of

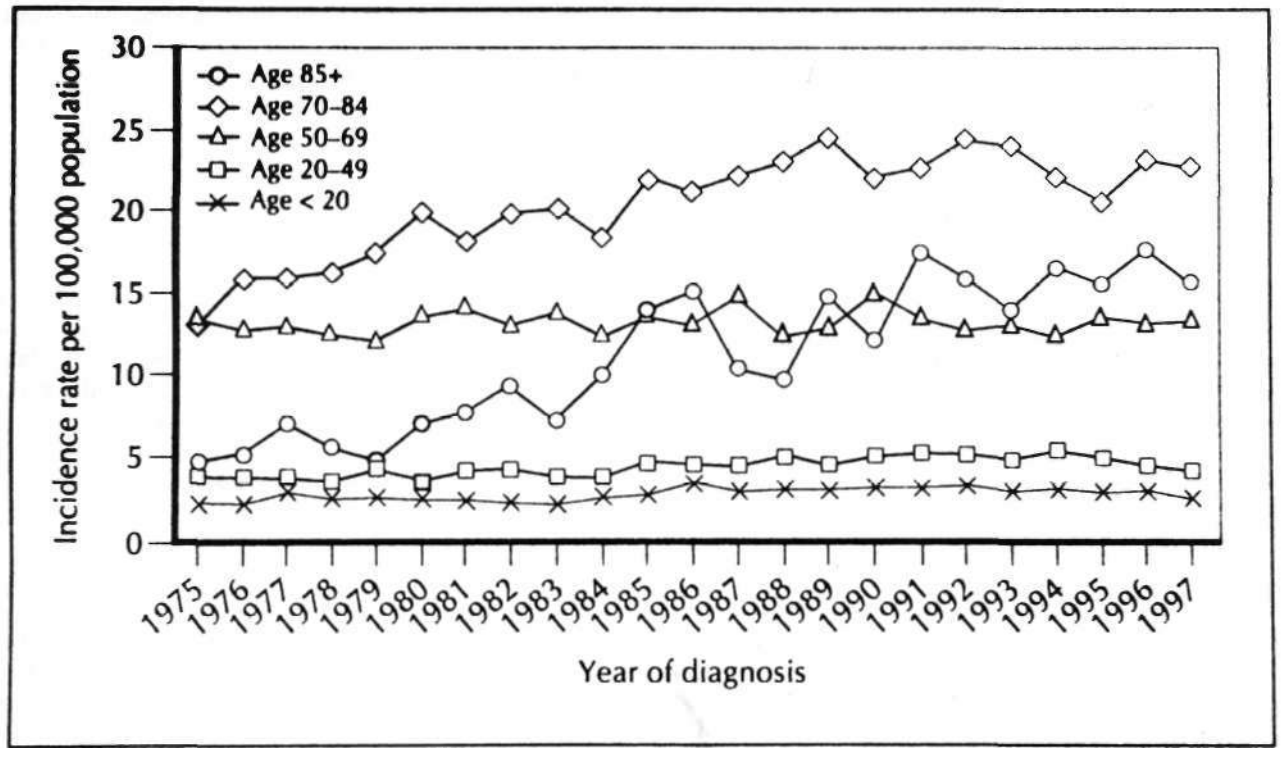

FIGURE 43.2 Trends in central nervous system malignancy incidence rates by age (years) at diagnosis: Surveillance, Epidemiology, and End Results 1975-1997. Incidence rates are age standardized to the United States 2000 standard population. Central nervous system malignancies were classified as ICD-0-2 topography codes C70.0 and C75.1-75.3 and behavior code 3. (Reprinted with permission from Gurney, J. & Kadan-Lottick, N. 2001, "Brain and other central nervous system tumors: Rates, trends, and epidemiology," *Curr Opin Oncol,* vol. 13, pp. 160-166.}

seizure disorders used in many epidemiologic studies are epilepsy, isolated seizures, febrile convulsions, and acute symptomatic seizures. Depending on the amount of clinical and electroencephalographic (EEG) information available, patients with epilepsy can then be further subclassificd by seizure type. The major types of seizures are generalized tonic-clonic (grand mal), absence (petit mal), incomplete convulsive (myoclonic), simple partial (focal), and complex partial (temporal lobe or psychomotor). Status epilepticus is defined as any seizure lasting for 30 minutes or longer or intermittent seizures lasting for longer than 30 minutes from which the patient did not regain consciousness. There are other seizure disorders that do not fulfill the standard definitions of epilepsy that require separate classification in epidemiological studies.

Mortality Rates

Several population studies have reported excess mortality rates with epilepsy compared with that expected. Nilsson etal. (1997) used the Stockholm County inpatient register to study 9601 patients hospitalized during 1980-1989 with a diagnosis of epilepsy. Fach patient was studied until death or December 31, 1992. The calculated standardized mortality ratio was 3.6, meaning that people with epilepsy were *3.6* times more likely to die during the follow-up period than were the general population. Causes of death included those related to epilepsy (e.g., brain tumor, stroke, and dementia}, complications of seizures (e.g., pneumonia and falls), and other causes. Surprisingly, motor vehicle accidents did not contribute to the decreased survival in the Stockholm epilepsy population. Rafnsson et al. (2001) showed that all-cause mortality was increased among men (SMR 2.25) but not women {SMR 0.79) in an Icelandic population-based incidence cohort of patients with unprovoked seizures. The increased male mortality was partly attributable to excess deaths from accidents ant) suicides. This pattern of a higher male mortality in an epilepsy cohort has been confirmed in other studies as well. Using a time trend analysis, O'Donoghue and Sander (1997) reported on the epilepsy mortality in a U.K. population from 1896-1965. The overall standard mortality ratio was 2.3, with little variation during the entire period. In general, these studies indicate that epilepsy is associated with a higher risk for death. Furthermore, the introduction of modem treatments for epilepsy has not appeared to affect reported mortality, but only a minority of affected subjects have epilepsy listed as a cause of death.

Age-specific mortality rates for Rochester, Minnesota, are shown in Figure 43.3. Mortality rates were similar to age-specific prevalence rates but were 1000-fold less. This finding suggests that each year 0.1% of the patients with epilepsy die of causes directly related to their epilepsy.

Status epilepticus (SE) affects 105,000 to 152,000 persons annually in the United States (DeLorenzo, Hauser, and Towne 1996). SE is a neurological emergency, and despite improvements in treatment, mortality is still high. Population-based studies have reported 30-day mortality rates of about 20%. Short-term mortality after SE is associated with the presence of an underlying acute etiology. Logroscino et al. (2002) are the first to report on the long-term mortality after an initial episode of SE. The study was a population-based retrospective cohort performed in Rochester, Minnesota, between 1965 and 1984. Forty percent of subjects who survived the initial 30 days after SE died within the next 10 years. Long term mortality was worse for patients with myoclonic status epilepticus, those presenting with SF. lasting more than 24 hours, and for those with symptomatic SE. Long term mortality rates for patients with idiopathic/cryptogenic SE was not increased. The results indicate that SE alone does not modify long-term mortality.

Morbidity Kates

Figure 43.3 shows morbidity measures for epilepsy in Rochester, Minnesota, by age group. Age-specific incidence of epilepsy was high during the first year of life, declined during childhood and adolescence, and then increased again after age 55. The cumulative incidence of epilepsy was 1.2% through age 24 and steadily increased to 4.4% through age 85 years. Age-specific prevalence increased with advancing age; nearly 1.5% of the population over 75 years had active epilepsy.

Point prevalence and average annual incidence rates for epilepsy are available from a number of community surveys. In general, the prevalence of convulsive disorders is about 3–9 per 1000 population. In Bogota, Colombia, there was a strikingly high rate, 19,5 per 1000, which included inactive seizure disorders. Prevalence rates have tended to increase in recent years in several surveys. Males and blacks do have higher rates than females and whites.

Between 1979 and 1987, prevalence for active epilepsy was 5.1 per 1000 in Vecchiano, Italy; 6.3 per 1000 in Kuopio Central Hospital District (CUD), Finland; 6.8 per 1000 in Rochester; and 8.0 per 1000 in northern Ecuador, Follow-up of a U.K. birth cohort showed a rate of 4.3 per 1000 at age 10 years,

Worldwide, neurocysticercosis is considered the most common reason for epilepsy, being twice as common in developing as in developed countries (International League Against Epilepsy 1994). Neurocysticercosis affects thousands of people in Latin America, Asia, and Africa. The disease has also been reported more frequently in industrialized countries with a high immigration rate of people from endemic countries. A collaborative network of U.S. emergency departments reported on the epidemiology of neurocysticercosis in seizure patients (Ong et al. 2002).

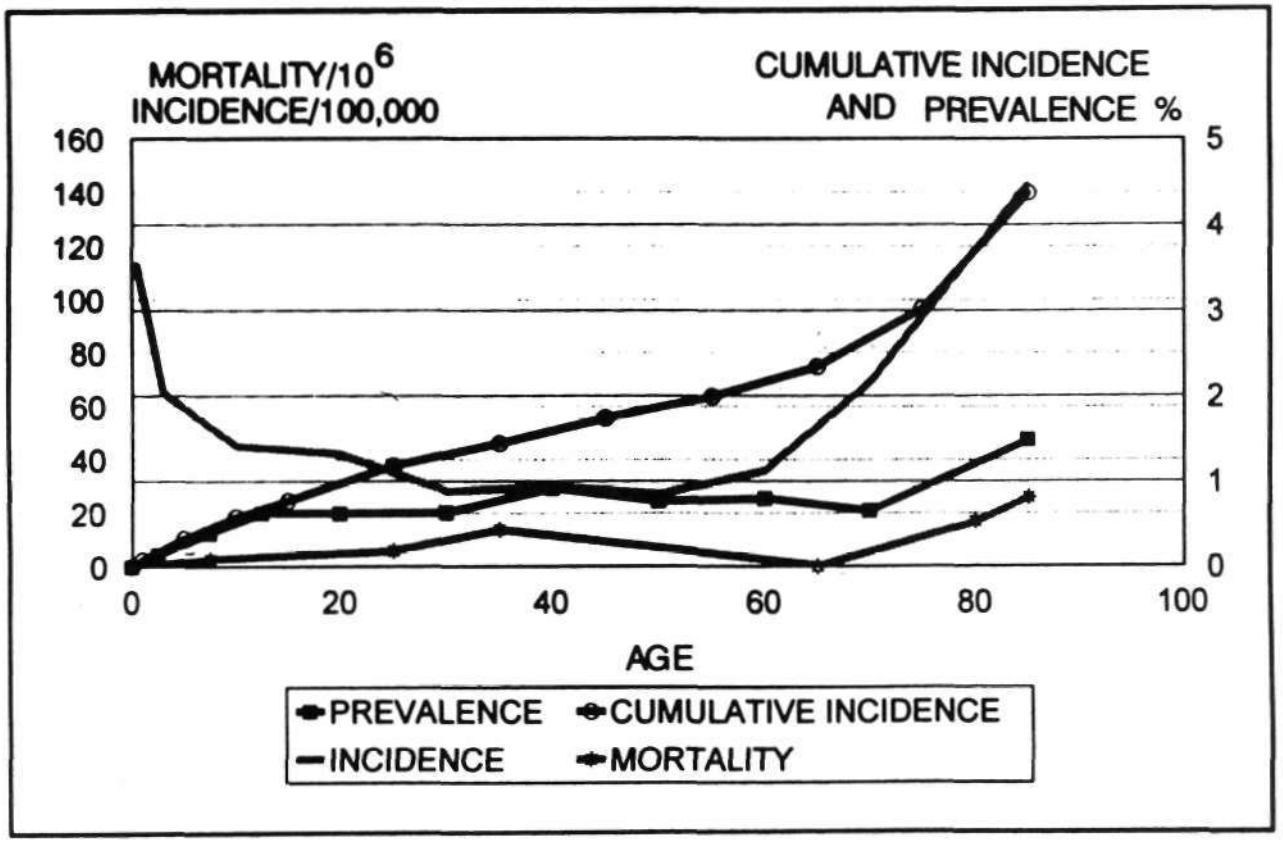

FIGURE 43.3 Measures of epilepsy (Rochester, Minnesota, 1935-1984): age-specific incidence per 100,000 person-years; cumulative incidence (percent); age-specific prevalence (percent); and age-specific mortality per 100,000 person-years. (Used with permission from Hauscr, W. A., Annegcrs, J. F., & Rocca, W. A. 1996, "Descriptive epidemiology of epilepsy: Contribution of population-based studies from Rochester, Minnesota," *Mayo Clin* fYoe, vol. 71, pp. 576-586.)

Data were collected on patients with seizures at 11 university-affiliated urban emergency departments from 1996-1998. Of the 1801 patients enrolled, 2.1% had seizures attributable to neurocysticercosis. The disease was widely distributed throughout the United States **with** highest concentration in Hispanics in the southwestern region.

Average annual incidence rates for epilepsy as of 1980 were approximarely 20-70 per 100,000 population per year. There was a slight male excess, which averaged about 1.2 to 1.0, and almost a 2 to 1 black-white ratio. Later surveys showed annual rates of 24 per 100,000 for Kuopio, Finland; 34 per 100,000 for Vastetbotten, Sweden; and 48 per 100,000 for Rochester, Minnesota. Ecuador provided an annual incidence rate of 190 per 100,000 in 1985-1986. A high frequency of epilepsy appears to exist in Central and South America, as suggested by death and prevalence rates. Elsewhere in the West, an expected range for annual incidence is approximately 30-60 per 100,000, with a reasonable general estimate of 50 per 100,000. With the concomitant prevalence rates, an average duration of active seizure disorders could then be calculated as about 13 years.

Age-specific incidence rates for epilepsy from several surveys showed a sharp decrease from maximal rates in infancy to adolescence and thereafter a slow decline for new cases throughout life. In others, rates were essentially constant after infancy or showed an irregular rise with age. In Rochester, Minnesota, however, the configuration was U-shaped, with a marked increase in incidence rates at age 75 and older (Figure 43.4). This configuration reflects generalized tonic-clonic disorders, together with absence and myoclonic seizures for the left arm of the U, and partial epilepsies for the right arm. Myoclonic seizures were the major type diagnosed during the first year of life; they were also the most common in the 1- to 4-year-old age group, but rarely occurred after 5 years of age. Absence (petit mal) seizures peaked in the 1- to 4-year-old age group and did not begin in patients older than 20. Complex partial (psychomotor) and generalized tonic clonic (grand mal) seizures both had fairly consistent incidence rates of 5-15 per 100,000 in ages 5-69 after low maxima at ages 1^1; for age 70 and older, the rates of each were sharply higher. The grand mal rates had similar configuration for both primary and secondary seizures. Simple partial (focal) seizures increased only slightly with age.

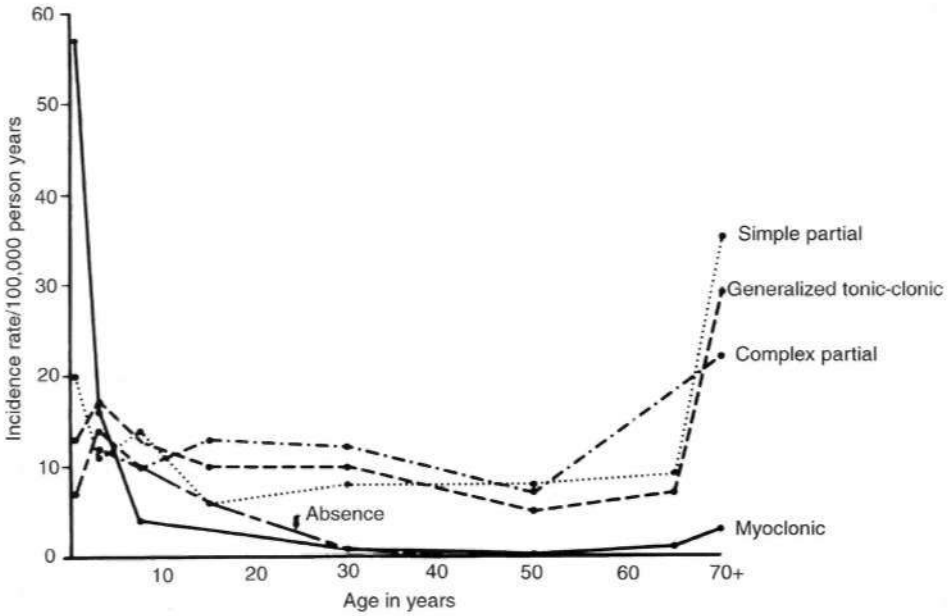

FIGURE 43.4 Epilepsy. Average annual age-specific incidence rates per 100,000 population by clinical type of seizure (absence, myoclonic, generalized, simple per complex partial). (Reprinted with permission from Kurtzke, J. F. & Kurland, L. T. 1983, "The epidemiology of neurologic disease," in *Clinical Neurology*, vol. 4, eds A. B. Baker & L. H. Baker, Harper & Row, Philadelphia.)

Febrile Seizures

The risk of a child developing febrile seizures has been about 2%, varying between 1% and 4%, in the United States and Europe. Surveys from Japan and the Mariana Islands showed rates of 7% and 11%, respectively. The Guaymi Indians of Panama had a rate of 14%. As with epilepsy in general, there was a male preponderance of 1.2 to 1 for febrile convulsions. In most studies, recurrent febrile seizures occur in about one third of the cases, and overall the risk of later epilepsy is about 2^1% for simple and 11 % for complex febrile seizures.

MULTIPLE SCLEROSIS

Mortality Rates and Survival

Over the last four decades, mortality for multiple sclerosis (MS) declined steadily in North America and Western Europe and remained stable or increased in eastern and northern Europe. As to cause of death, many patients with MS die of complications related to their disease. Koch-Henriksen and colleagues (1998) attributed more than half of all deaths in a large population cohort to MS or complications from the disease. As more patients with MS survive to older ages, however, a greater proportion of them can be expected to die of causes unrelated to MS, and thus will not be coded as dying of MS. This last point is supported by analysis of contributory causes of the death of patients with MS in Denmark and in the United States.

The estimated 25-year survival of the MS population in Rochester, Minnesota, was 76.2%, compared with 87.7% for the general U.S. white population of a similar age and gender (Wynn et al. 1990). Survival for men was less than for women. This survival figure was slightly greater than earlier estimates. The Danish National MS Registry data provided a median survival of 30 years from onset of the disease (Bronnum-Hansen, Koch-Henriksen, and Hyllested 1994). Median survival for World War II veterans from MS disease onset was 43 years (white females), 30 years (black males), and 34 years (white males) (Wallin, Page, and Kurtzke 2000).

Morbidity Rates

Prevalence rates **for** Europe and the Mediterranean basin as of 1980 arc plotted against geographical latitude in Figure 43.5. The surveys appeared to separate into two zones or clusters, one to the north with rates of 30 per 100,000 and higher, considered high frequency, and the other to the south with rates less than 30 per 100,000 but greater than 4 per 100,000 population, classified as medium frequency.

The northernmost parts of Scandinavia and the Mediterranean basin were medium-prevalence regions in 1980. More recent surveys of Italy and its islands, however, have documented prevalence rates well into the sixties, and therefore this country is now clearly within the high-frequency band (Kurtzke 1993). This appears to be a recent change because some of the earlier Italian surveys with lower rates were well done.

Boiko (1994) of Moscow University summarized a large literature on the distribution of MS in the former Soviet Union that was previously unavailable in the West. Much of northwestern Russia past Kiev and Moscow appears to be of high prevalence (greater than or equal to 30 per 100,000), surrounded to the north, east, and south

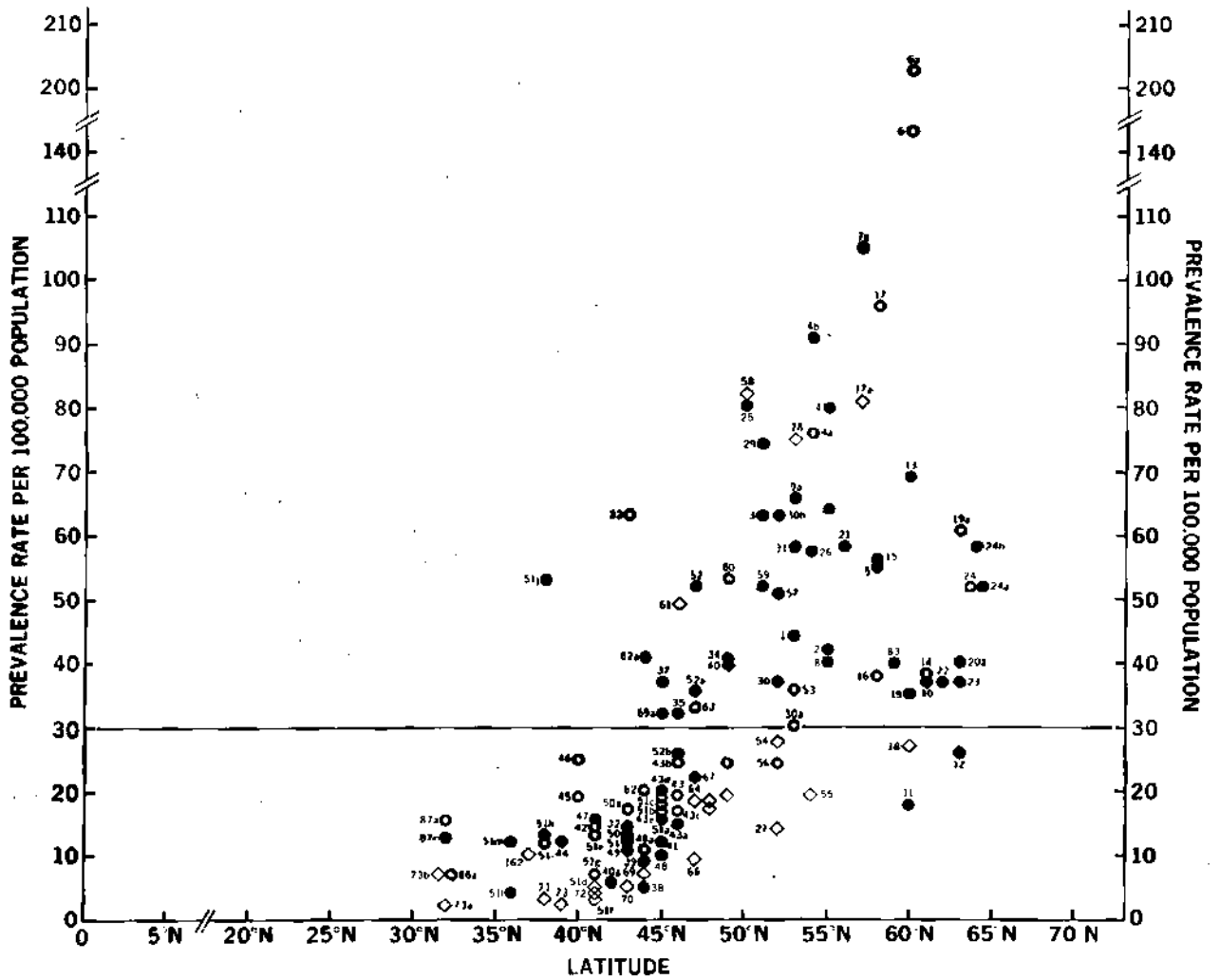

FIGURE 43.5 Multiple sclerosis (MS). Prevalence rates per 100,000 population for probable MS in Europe and the Mediterranean area as of 1980, correlated with geographical latitude. Numbers identify studies in Kutrzke {1980}. *Solid circles* represent class A (best) surveys; *open circles,* class B; *open diamonds,* class C; and *closed diamonds,* class E (MS: amyotrophic lateral sclerosis case ratios). Class C (poor) studies arc listed only if no better-quality survey was available for the specific site. (Reprinted with permission from Kurtzke, J. F. 1980, "Geographic distribution of multiple sclerosis: An update with special reference to Europe and the Mediterranean basin," *Acta Neurol Scand,* vol. 62, pp. 65-80. Copyright 1980, Munksgaard International Publishers Ltd., Copenhagen, Denmark.)

by medium-prevalence areas (5-29 per 100,000). Overall, the Ukraine and the Caucasus seemed on average to be in the medium-prevalence range. Uzbekistan, Samarkand, Turkistan, and Turkmenistan appeared to be low. In the Far East, medium prevalence once again appeared, and rates were indeed in the high range in the central and western parts of the Amur region, which abuts the Pacific Ocean above China and includes Vladivostok.

The general worldwide distribution of MS may be described within three zones of frequency or risk. The high-risk zone, with prevalence rates of .30 per 100,000 and above population, included northern and central Europe into the former Soviet Union, the northern United States, Canada, New Zealand, and southeastern Australia. These regions were bounded by areas of medium frequency, with prevalence rates between 5 and 29 per 100,000, consisting of the southern United States, possibly northern-most Norway, and probably Russia from the Ural mountains into Siberia, as well as the Ukraine. Except for Italy, now with high rates, the entire northern Mediterranean basin from Spain to Israel was of medium prevalence. In this zone, too, still fall most of Australia and perhaps Hawaii and the midportion of South America, plus whites in South Africa. Low-frequency areas, with prevalence rates below 5 per 100,000, comprised all other known areas of Asia, Africa, Alaska, Greenland, and the Caribbean region, including Mexico and probably northern South America. Recent data suggest medium rates in the North African littoral and high rates in Spain, Portugal, Israel, and Cyprus (Kurtzke 1997).

MS clearly is a place-related disorder. All the high- and medium-risk areas are found in Europe or the European colonies: Canada, the United States, Australia, New Zealand, South Africa, and probahly central and southern South America. MS likely originated in northwestern Europe and was brought to the other lands by European settlers. In Europe itself, although the disease clearly has shown geographical clustering in some countries, there is evidence even within these clusters of diffusion over time.

In the United States, white females are at greater risk than arc white males; blacks, Native Americans, and Asians all were at notably lower risk than whites. These race and sex differences persist regardless of geography.

The annual incidence rate in high-MS areas at present is about 3—5 per 100,000 population, whereas in low-risk areas it is about 1 per 1,000,000. Medium-risk areas have an incidence near 1 per 100,000. In Denmark in 1939-1945, age-specific incidence rates rose rapidly, from essentially zero in childhood to a peak at about age 27 of more than 9 per 100,000 for females and almost 7 per 100,000 for males. Beyond age 40, there was little difference between the sexes, both of whose rates declined equally to zero by age 60. Most recent evidence suggests women of all races in the United States have higher rates than males (Wallin, Page, and Kurtzke 2000a).

Family Studies

Family studies in MS have provided a means of assessing environmental factors against a set genetic background. Studies have shown that the risk for multiple family members with MS is 3—4% for primary relatives and 20-30% for monozygotic twins. This is in contrast to the general population prevalence of approximately 0.1%. The increased family frequency might be related to shared environment as opposed to shared genetic factors because close relatives would be expected to share similar environmental influences. However, further evidence that MS is under some genetic control includes the following:

1. Twin studies, most of which show an excess of concordant monozygous twins. The difference in concordance rates between monozygotic and dizygotic twins is primarily attributable to genetic factors. The maximum concordance rate for MS in monozygotic twins is about 30%. This indicates that although genes play a role in MS, the maximal effect of genes is at most 30%.
2. The association of HLA alleles and MS, and the higher frequency of HLA sharing in affected sibling pairs.
3. Population groups relatively resistant to MS in high-frequency areas (Asians and Amerindians in North America, Lapps in Scandinavia, and Gypsies in Hungary).

Genetic screening has been used more recently to identify candidate markers for MS. This approach tests families with multiple cases of MS for linkage to polymorphic markers spread through the genome. There have been five published genomic screens for linkage in MS, the Lit est Coraddii et a I. (2001). Although some chromosome markers have been suggestive of linkage, there have been no major predisposing genes found.

Migration in Multiple Sclerosis

If the risk of MS is altered by a change of environments, MS must In- an acquired, i-xos^nmis, I/IH inmniemal disease or set of diseases. In a number of studies of MS in migrants, there was a tendency for immigrants to retain much of, but not all, the risk of their birthplace if they came from high- or medium-risk areas. Evidence also surfaced that migrants from low-risk areas to high-risk areas increased their risk of MS. A large case-control series among U.S. veterans clearly demonstrated a change in risk of MS by changing residence between birth and entry into military service. Those moving south decreased their risk; those moving north increased it. This series also indicated that the time when such moves are critical is well after birth but also well before clinical onset.

As part of our studies on MS in the Faroe Islands (see Epidemics of Multiple Sclerosis, later in the chapter), we identified a group of 15 patients who had been living, for at least 3 years before onset, off the islands in high-MS-risk Denmark. These long overseas residences were limited to the 10 years or so before clinical onset. All the patients stayed off the Faroes for at least 2 years between ages 11 and 43. We concluded that residence in a high-MS-risk area by a susceptible but virgin (as to MS) population for a period of 2 years from age 11 could result in clinical MS, which would begin after a further incubation period of 6 or 7 years (Kurtzke 1993).

Kurtzke and colleagues (1998) identified North African immigrants among 7500 MS patients in a nationwide survey in France in 1986. A total of 260 had immigrated from North Africa, mostly between 1960 and 1965. Two thirds were from Algeria, where virtually its entire European population had emigrated in 1962 at the end of the Algerian war for independence. The migrants were younger at prevalence day (1986) and at onset of MS than the French-born individuals with MS. The 225 with onset more than one year after migration presumably acquired their MS in France. They provided an age-adjusted (U.S. 1960) MS prevalence rate 1.5 times that for all of France. If the latter is taken at 50 per 100,000 population, their estimated adjusted rate is 77. The other 27 migrants with presumed acquisition in North Africa had an estimated adjusted prevalence of 16.6 per 100,000, the same as expected in their native land.

There are other studies of migrants from high- to iow-nsk areas that suggest a critical age for risk retention, Those migrating at age 15 or older retained the MS risk of their birthplace, but those migrating before age 15 acquired

the lower risk of their new residence. This also indicates that young children are much less susceptihle to MS, despite their then living in high-risk areas (Northern Europe).

Two reviews highlighted some of the inherent problems with migration studies (Kurtzke 1997; Martyn and Gale 1997). Defining the population at risk, choosing appropriate denominators, and ensuring complete case ascertainment are critical. Ages at migration and follow-up are also important. Updates of migration studies that reported relatively little change in risk for MS of the initial migrants showed that the risk for MS in offspring of these immigrants has increased to the levels of the population of the host country.

Epidemics of Multiple Sclerosis

The Faroe Islands are a semi-independent unit of the Kingdom of Denmark in the North Atlantic Ocean between Iceland and Norway. As of 1998, we had found 54 native resident Faroese with onset of MS in this century. There were none before 1943, but between 1943 and 1949, 17 patients had symptom onset in this populace of less than 30,000. If, as noted, Faroese migrants required two years exposure from age 11 on to acquire MS, the same should be true for the resident Faroese, two years before 1943 being 1941. We therefore divided the entire resident series of 54 according to when they had attained age 11, by 1941 or later. The 17 with onset between 1943-1949 were then joined by four more of that age, whose onset was 1950-1961. These 21 patients constituted a type 1 point source epidemic of MS. Annual incidence rates rose steeply from 0 to over 10 per 100,000 in 1945, and then fell almost as steeply with a short tail. The other 33 patients were divided by when they too reached age 11, and in this way provided three more (type 2) epidemics of 10, 10, and 13 patients each (data as of 1991 are shown in Figure 43.6) (Kurtzke and Heltberg 2001).

We concluded that the disease was introduced into the Islands by British troops who occupied the islands for 5 years, starting in April 1940. What was likely introduced was an infection that was transmitted during the war to the Faroese population at risk, of whom the epidemic I cases of clinical MS were a part. We called this infection the *primary MS affection* (PMSA), which we defined as a single, specific, widespread, systemic but unknown infectious disease (that may be totally asymptomatic). PMSA produces clinical neurological MS (CNMS) in only a small proportion of the affected population after an incubation period averaging 6 years in virgin populations and perhaps 12 years in endemic areas. Using this hypothesis, transmissibility is limited to part or all of this systemic phase, which ends by the usual age of onset of MS symptoms.

The PMSA cases from the first cohort of Faroese transmitted the disease to the next Faroese population cohort, those who reached age 1 I in the period when the first cohort was transmissible. Included in the second Faroese cohort were the epidemic 11 cases of CNMS, and this cohort similarly transmitted PMSA to the third population cohort with its own (epidemic III) cases, and from there to the fourth cohort with epidemic IV.

Two years of exposure between age 11 and 47 are therefore required to acquire PMSA in virgin but susceptible populations. Thus PMSA appears to be a specific, but unknown, age-limited infection that can be acquired only during these hormonally active years, and one that only rarely leads to clinical MS.

HUMAN IMMUNODEFICIENCY VIRUS AND NEUROLOGICAL DISEASE

Human Immunodeficiency Virus Epidemic

Human immunodeficiency virus (HIV) infection has become a global epidemic since it was first identified in 1981 as the cause of acquired immunodeficiency syndrome (AIDS). The virus is a member of the retrovirus family and selectively infects T-helper cells (T4, $CD4^+$), causing a defect in cell-mediated immunity. It is spread through blood and bodily fluids. After acute infection, most people enter an asymptomatic period of 8-10 years before the virus manifests clinically through immune dysregulation (Harrison and McArthur 1995) (see Chapter 59).

Despite recent advances in treatment and prevention, the scope of the HIV epidemic remains daunting. An estimated 36 million persons worldwide are infected with HIV; an additional 21.8 million have died (UNAIDS 2000). The vast majority of cases occur in sub-Saharan Africa where in some regions HIV prevalence exceeds 25%. More than 14,000 new HIV infections occur daily with *53* million in the year 2000 alone.

During the first 6 months of 1996, the first reported decline in AIDS mortality occurred in the United States (CDC 1997). Compared with estimates for January-June 1995 (24,900), there was a 13% drop in AIDS deaths in January-June 1996 (22,000). This decline occurred in all racial and ethnic groups and in all regions of the United States. Sclik and colleagues (2002) argue from U.S. death certificate data that the fall in AIDS deaths after 1995 was probably due to the increasing use of highly active antiretroviral therapy (HAART). They note that the proportions of deaths of individuals with HIV that were caused by other conditions increased between 1995 and 1999.

Neurological Aspects of Human Immunodeficiency Virus Infection

HIV disease can produce a variety of effects on both the central and peripheral nervous systems (Price 1996).

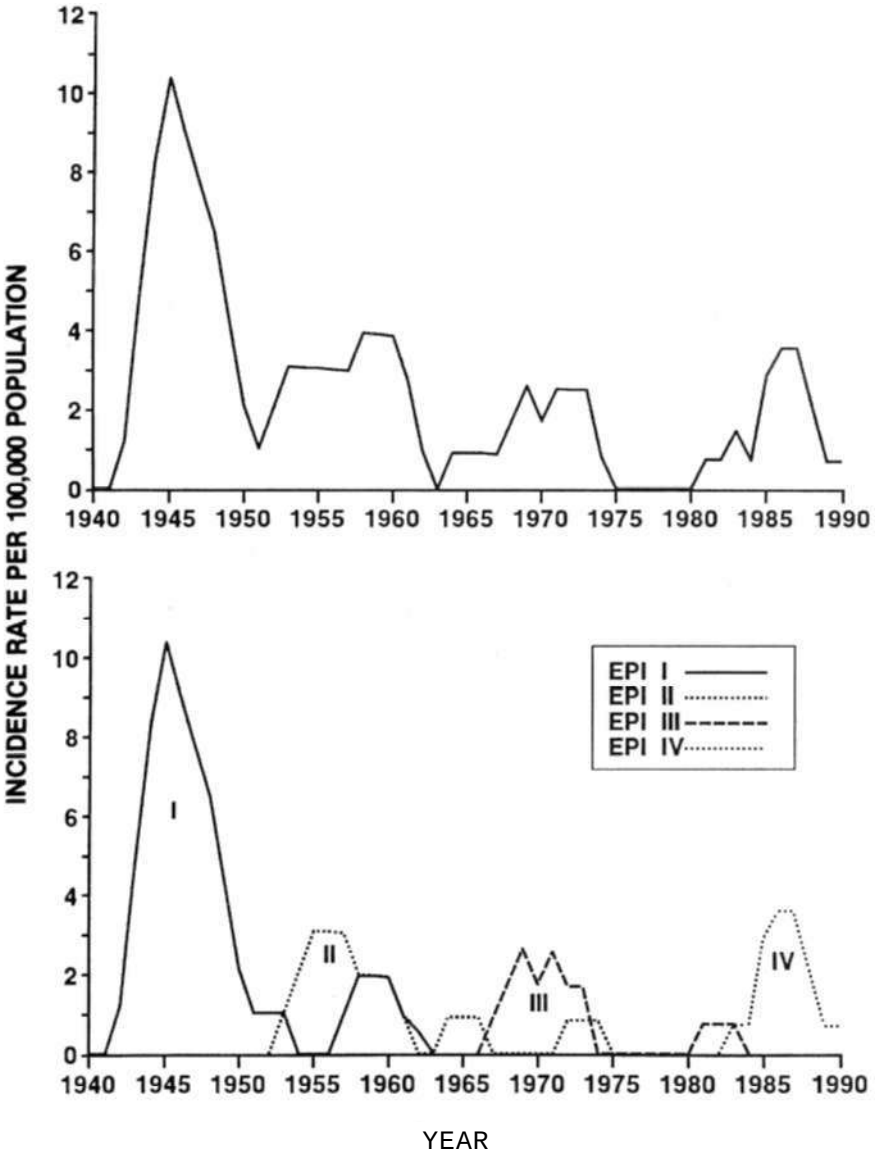

FIGURE 43.6 Multiple sclerosis in the Faroes as of 1991; annual incidence rates per 100,000 population calculated as 3-ycar centered moving averaged for four epidemics (hPI) defined by time when patients were age 11, by 1941 or later. Top: total series. Bottom: rates by epidemic. (Reprinted with permission from Kurtzke, J. F., Hyllcstcd, K., Heltberg, K., et al. 1993, "Multiple sclerosis in die Faroe Islands. 5. The occurrence of the fourth epidemic as validation of transmission," *Acta Neurol Scand*, vol. 8ii, pp. 161-173. Copyright 1993, Munksgaard International Publishers Ltd., Copenhagen, Denmark.)

A useful way of classifying these complications is to use the temporal profile of HIV infection on the immune system (Table 43.2 illustrates a simplified classification scheme). Early complications include acute aseptic meningitis, acute and chronic demyelinating polyneuropathy, and multiple mononeuropathy. These early complications are autoimmune in nature and occur at CD4 cell counts greater than 200 cells/mm . Late complications typically appear when there is a severe depression in cellular immunity with CD4 counts less than 200 cells/mm^3. Most of these disorders are opportunistic infections (cryptococcal meningitis) or a reactivation of a prior infection (toxoplasmosis and progressive multifocal lcukoenccphalopathy [PML]). HIV dementia, distal sensory polyneuropathy, and vacuolar myelopathy arc directly related to late stages of HIV infection itself. Other complications of the nervous system involve metabolic and toxic effects of treatment, including zidovudine myopathy and nucleoside neuropathy.

Tahic 43.2: Neurological complications of human immunodeficiency virus

Early complications (CD4 >200 cells/mm)*
Acute aseptic meningitis
Demyelinating polyneuropathy (acute and chronic)
Mononeuritis

Late complications ($CD4^+$<200 cells/mm^1}
Cryptococcal meningitis
Cytomegalovirus encephalitis or polyradiculopathy
Cerebral toxoplasmosis
Progressive multifocal I eu koe nee p halo pa thy
Primary central nervous system lymphoma
Human immunodeficiency virus dementia
Sensory neuropathy
Vacuolar myelopathy

Six AIDS-indicator neurological illnesses are defined by the CDC: HIV dementia, CNS cryptococcal infection, CMV infection, primary CNS lymphoma, CNS toxoplasmosis, and PML. The CDC records data on these illnesses primarily if they are the initial AIDS diagnosis. Morbidity of these illnesses in the course of HIV infection must, therefore, be studied in other populations. One such population is the Multicenter AIDS Cohort Study, which is a longitudinal study of the natural history of HIV-1 infection in homosexual and bisexual men in five U.S. cities: Baltimore, Washington, Chicago, Pittsburgh, and Los Angeles. For the years 1985-1992, there was an upward trend for all incidence rates, with the exception of HIV dementia (Bacellat ct al. 1994). After adjusting for CD4 cell counts in the cohort, however, most incidence trends remained stable. An extension of this cohort study through 1998 showed a significant decrease in incidence rates for HIV dementia, cryptococcal meningitis, and CNS lymphoma (Sacktor et al. 2001). Incidence fates dtopped most dramatically in 1996 after the introduction of HAART therapy. There was a trend for decreased incidence rates fot toxoplasmosis, and PML rates remained stable.

Brodtetal. (1997) reported on the changing incidence of AIDS-defining illnesses in the Frankfurt AIDS Cohort Study, consisting of approximately 1000 homosexual men. Major AIDS-defining illnesses decreased between 1992 and 1996 (Figure 43.7). Included in the decline were toxoplasmic encephalitis, CMV disease, PML, and AIDS encephalopathy, all of which reached incidence rates less than 5 per 100 patient-years. Treatment with combination antiretroviral therapy and with protease inhibitors increased during the study period. Undoubtedly, these new combination therapies have had a role in the declining incidence rates in this cohort.

OVERVIEW OF NEUROLOGICAL DISORDERS

What follows are the best estimates of the numerical impact of neurological diseases. The data refer primarily to whites of the Occident. For the 66 disorders listed in Tables 43.3 and 43.4, the average annual incidence rates add up to over 2500 per 100,000 population, or 2.5%. This includes eight disorders for which only one tenth of the incident cases were thought to require neurological attention: the two vertebrogenic pain syndromes, nonmigrainous headache, nonbrain head injury, alcoholism, psychosis, nonsevere mental retardation, and deafness. Total blindness numbers were taken as an estimate for the proportion of all the visually impaired patients that the neurologist should encounter. Even if all headaches, trauma, vertebrogenic pain, vision loss, deafness, and psychosis are excluded from consideration, there arc still more than 1100 new cases of neurological disease beginning each year in every 100,000 of the population, or more than one case for every 100 people.

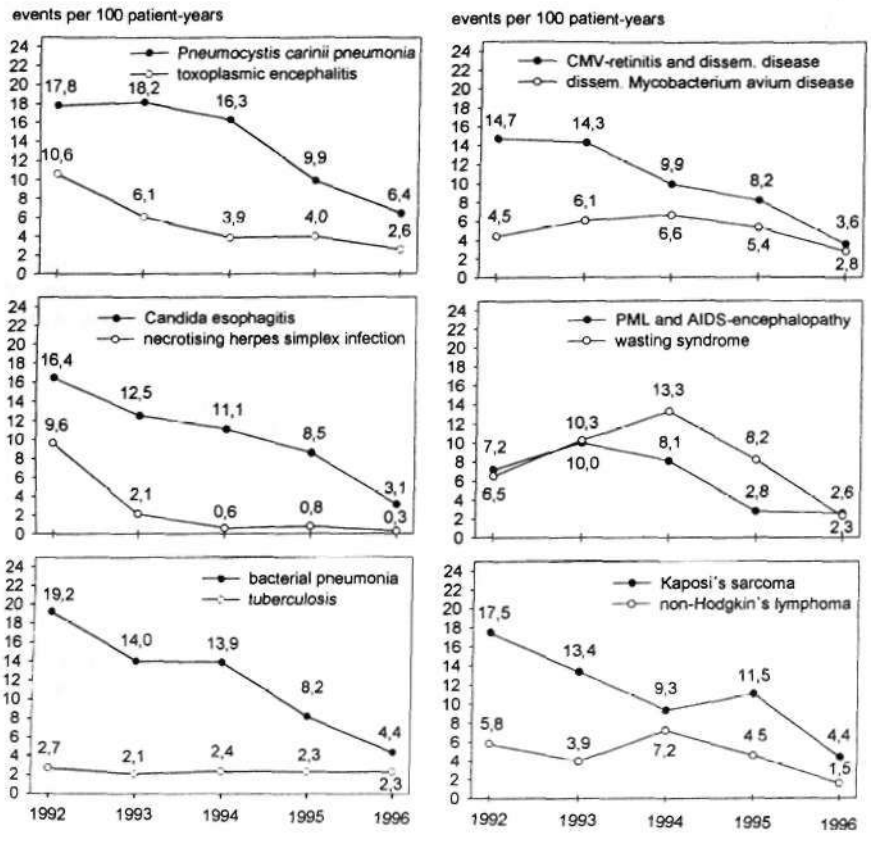

FIGURE 43.7 Annual events of acquired immunodeficiency syndrome defining diseases, calculated as events per 100 patient-years. (CMV = cytomegalovirus; PML = progressive multifocal leukoencephalopathy.) (Reprinted with permission from Brodt, H. R., Gute, P., Kamps, P. S., et al. 1997, "Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy," *AIDS,* vol. 11, pp. 1731-1738.)

Table 43.3: Neurological disorders: approximate average annual incidence rates (per 100,000 population), all ages. Most common entities

Disorder	*Rate*
Herpes zoster	400
Migraine	250
Brain trauma	200
Other severe headache	200*
Acute cerebrovascular disease	150
Other head injury	150*
Transient postconcussivc syndrome	150
Lumbosacral herniated nucleus pulposus	150
Lumbosacral pain syndrome	I S0
Neurological symptoms (with no defined disease)	75
Epilepsy	50
Febrile fits	50
Dementia	50
Meniere's disease	50
Mononeuropathies	40
Polyneuropathy	40
Transient ischemic attacks	30
Bell's palsy	25
Single seizures	20
Parkinsonism	20
Cervical pain syndrome	20*
Persistent postconcussive syndrome	20
Alcoholism	_()
Meningitides	15
Encephali tides	15
Sleep disorders*	15
Subarachnoid hemorrhage	15
Cervical herniated nucleus pulposus	15
Metastatic brain tumor	15
Peripheral nerve trauma	15
Blindness	15
Benign brain tumor	10
Deafness	10*

* Cited rates are 10% of actual rates, as proportions likely to need care by a physician competent in neurology.
+Narcolepsies and hypersomnias (with sleep apnea).
Source: Modified from Kurtzke, J. F. 1982, "The current neurologic burden of illness and injury in the United States," *Neurology,* vol. 32, pp. 1207-1214.

Table 43.4: Neurological disorders: approximate average annual incidence rates (per 100,000 population), all ages. Less common entities

Disorder	*Rate*
Cerebral palsy	9.0
Congenital malformations of central nervous system	7.0
Mental retardation, severe	6.0
Mental retardation, other	fi.0
Malignant primary brain tumor	5.0
Metastatic cord tumor	5.0
Tic douloureux	4.0
Multiple sclerosis	3.0
Optic neuritis	3,0+
Dorsolateral sclerosis	3.0
Functional psychosis	3.0*
Spinal cotd injury	3.0
Motor neuron disease	2.0
Down's syndrome	2,0
Guillain-Barre syndrome	2.0
Intracranial abscess	1.0
Benign cord tumor	1.0
Cranial nerve trauma	1.0
Acute transverse myelopathy	0.8
All muscular dystrophies	0.7
Chronic progressive myelopathy	0.5
Polymyositis	0.5
Syringomyelia	0.4
Hereditary ataxias	0.4
Huntington's disease	0.4
Myasthenia gravis	0.4
Acute disseminated encephalomyelitis	0.2
Charcot-Marie-Tooth disease	0.2
Spinal muscular atrophy	0.2
Familial spastic paraplegia	0,1
Wilson's disease	0,1
Malignant primary cord tumor	0.1
Vascular disease cord	0,1

*Cited rates are 10% of actual rates, as proportions likely to need care by a physician competent in neurology.
*Rate for high-risk areas.
Source: Modified from Kurtzke, J. F. 1982, "The current neurologic burden of illness and injury in the United States," *Neurology,* vol, 32, pp. 1207-1214; and "The Epidemiology of Neurologic Disease", *Clinical Neurology,* vol. 4, eds Baker, A. and Baker, L. H. Harper & Row, Philadelphia.

There arc arguments, however, as to what such numbers really denote in terms of the number of neurologists required. In the United States, patient care needs alone for 240 million people were estimated to require 14,000 neurologists, according to the American Neurological Association-American Academy of Neurology Joint Commission on Neurology (Bradley 2000). Other, similar estimates were 11,200 (Graduate Medical Education National Advisory Committee [GMENAC] Delphi Panel), 6200 (GMENAC Advisory Panel), and 12,600 (Committee on National Needs for Neurologists [CN3], American Academy of Neurology), The last source estimated total needs for clinical neurologists, including faculty, at 16,500 neurologists, twice the figure of the GMENAC Advisory Panel, The primnry discrepancy for patient care needs is not so much the frequency of neurological disorders but rather the differences in proportions of patients that each group thought should be seen by neurologists. Also in question is whether attention is needed acutely or throughout the course of the illness (i.e., are neurologists to be consultants or practitioners?). Furthermore, the figure for total needs for the GMENAC Advisory Panel was based on a marked undercount of current faculty neurologists.

Predictions of the numbers of neurologists in the United States have ranged widely. Using a survey conducted by the American Academy of Neurology in 1996, Holloway and colleagues (1999) calculated the density of U.S. neurologists to be 3.4 per 100,000 population (9164 neurologists/ 265,179,411 population). A survey of all residency training

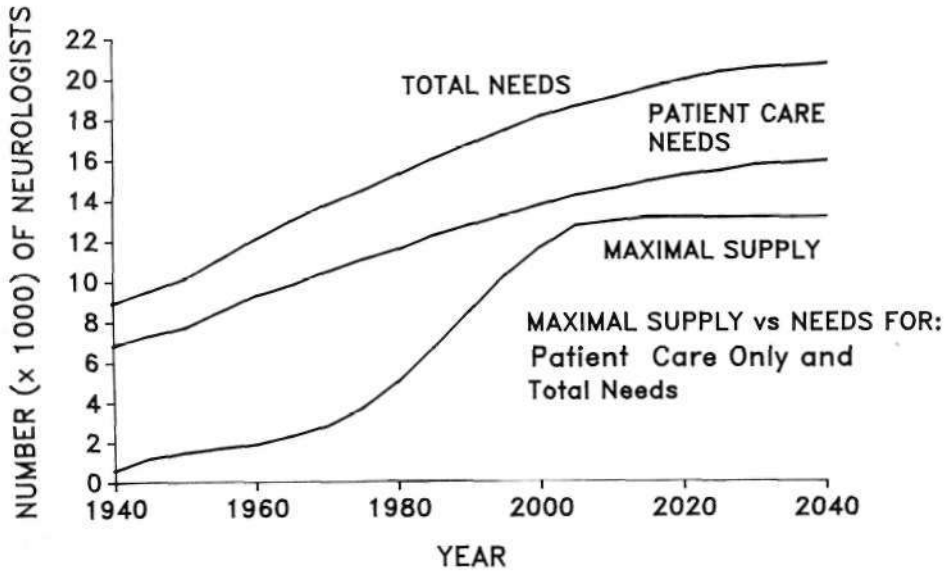

FIGURE 43.8 Neurologists in the United States, 1940-2040. Estimated maximal supply versus needs (patient care needs alone and total needs). (Reprinted with permission from Kurrzke, J. F., Murphy, F, M., & Smith, M. A. 1991, "On the production of neurologists in the United States: An update," *Neurology,* vol. 41, pp. 1-9.)

programs in 1985-1986 and recalculations by actuarial methods estimated the number of general neurologists to be 7500 for 1990, plus 1100 child neurologists, for a total of 8600. The figure for the year 2000 was 11,800 total. The number of neurologists was then predicted to plateau near the year 2020 at approximately 13,700, including 1700 child neurologists, of whom 9800 (1100 child) would be board certified. These total figures are approximately 30% (in 2010) to *35%* (in 2050) below the estimated need (Figure 43.8). Neurology is not, nor do we believe it will be, an overstocked specialty in the United States—if neurologists arc permitted to practice neurology as it has developed here.

Neurological practice, of course, varies widely among countries and even within the United States. The concept of the neurologist as a physician directly responsible for both acute and chronic care of patients with neurological diseases has only evolved over the last 25 years in the United States. But such responsibilities, as well as provisions for continuity of care, are explicit statements in the current special requirements for residency training programs in neurology and child neurology.

Regardless of the type of practice a given country deems appropriate for neurologists, the patients with neurological disease will exist. The data in Tables 43.3, 43.4, 43.5, and 43.6 therefore could well serve as a basis at least for a

Table 43.5: Neurological disorders: approximate point prevalence rates per 100,000 population, all ages. Most common entities

Disorder	*Kate*	*Disorder*	*Rate*
Migraine	2000"	Transient ischemic attacks	150
Other severe headache	1500[+]	Febrile fits	100
Brain injury	800	Persistent posteoncussive syndrome	80
Fpilcpsy	650	Herpes zoster	SO
Acute cerebrovascular disease	600	Congenital malformations of central nervous system	70
Lumbosacral pain syndrome	500[+]	Single seizures	60
Alcoholism	500[+]	Multiple sclerosis	60[5]
Sleep disorders*	300	Benign brain tumor	60
Meniere's disease	300	Cervical pain syndrome	
Lumbosacral herniated nucleus pulposus	300	Down's syndrome	50
Cerebral palsy	250	Subarachnoid hemorrhage	50
Dementia	250	Cervical herniated nucleus pulposus	50
Parkinsonism	2(H)	Transient postconcussive syndrome	50
		Spinal cord injury	50

'Cited rate is 20% of actual prevalence rate, as a proportion likely to need care by a physician competent in neurology.
'Cited rates are 10% of actual rates, as proportions likely to need care by a physician competent in neurology.
"Narcolepsies and hypersomnias (with sleep apnea).
*Rate for high-risk areas.
Source: Modified from Kurtzke, J. F. 1982. "The current neurologic burden of illness and injury in the United States," *Neurology,* vol. 32, pp. 1207-1214.

Table 43,6: Neurological disorders: approximate point prevalence rates per 100,000 population, all ages. Less common entities

Disorder	*Rale*	*Disorder*	*Rate*
Tic douloureux	40	Progressive muscular dystrophy	*6*
Neurological symptoms without defined disease	40	Malignant primary brain tumor	*5*
Mononeuroparhies	40	Metastatic cord tumor	*5*
Polyneuropathies	40	Meningitides	*5*
Dorsolateral sclerosis	30	Bell's palsy	*5*
Peripheral nerve trauma	30	Huntington's disease	5
Other head injury	30*	Charcot-xMarie-Tooth disease	5
Acute transverse myelopathy	15	Myasthenia gravis	4
Metastatic brain tumor	15	Familial spastic paraplegia	3
Chronic progressive myelopathy	10	Intracranial abscess	2
Optic neuritis	10	Cranial nerve trauma	2
Encephalitides	in	Myotonic dystrophy	2
Vascular disease spinal cord	9	Spinal muscular atrophy	2
Hereditary ataxias	8	Guillain-Barre syndrome	1
Syringomyelia	7	Wilson's disease	1
Motor neuron disease	*6*	Acute disseminated encephalomyelitis	0.6
Polymyositis	6	Dystonia musculorum deformans	0.3

*Cited rate is 10% of actual rate, as a proportion likely to need care by a physician competent in neurology.
Source: Modified from Kurtzke, J. F. 1982, "The current neurologic burden of illness and injury in the United States," *Neurology,* vol. 32, pp. 1207-1214; and "The Epidemiology of Neurologic Disease", *Clinical Neurology,* vol. 4, eds Baker, A. and Baker, L. H. Harper Sc Row, Philadelphia.

rational allocation of available resources in any country for the reaching, research, and patient care of neurological disorders.

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Chapter 44
Clinical Neurogenetics

Thomas D. Bird and Stephen J. Tapscott

To appteciate the variety and complexity of genetic influences in neurological diseases, one must first understand the basic principles of human inheritance patterns. This chapter is an introduction to the various modes of inheritance, including single gene (Mendelian), chromosomal, multifactorial, and mitochondrial. More tecent insights regarding imprinting, anticipation, and uniparental disomy ate also briefly discussed. Furthermore, thete are likely to be many patients with a neurological disorder that is the result of a combination between a genetic predisposition and an environmentally acquired insult. All these phenomena are of clinical importance and form an introduction for a more detailed analysis of the relevant molecular biology.

MENDELIAN DISORDERS

Mendelian disorders are caused by mutations in single genes. They can be autosomal dominant, autosomal recessive, or X-linked.

Autosomal Dominant Disotdcrs

The 46 chromosomes contained in the nucleus of each human cell represent 22 pairs of autosomes, one of each pair being inherited from the mother and the other from the father (Figure 44.1). The twenty-third pair contains the sex chromosomes—the Y inherited from the father and the X from the mothet. In autosomal dominant disotdcrs, a mutation occurring in a single gene on any of the 22 autosomes can ptoduce clinical symptoms or signs. The carrier of a single mutation on one chromosome is called a *heterozygote.* Each child of an affected person has a 50% risk of inheriting the mutation and potentially developing the disease. Males and females arc affected in equal proportions; the disease appears over multiple genctations, and heterozygote mothers or fathers pass the gene on with equal risk to sons or daughters (Figure 44.2 and Table 44.1).

Examples of autosomal dominant neurological disorders include neurofibromatosis, tuberous sclerosis, Huntington's disease, several forms of hereditary ataxias and hereditary neuropathies, myotonic dystrophy, juvenile myoclonic epilepsy, benign neonatal convulsions, and some forms of familial Alzheimer's disease.

Expression of a gene refers to any clinical manifestation of the mutation. This could include a seizure, mental retardation, skin lesions, an abnormal electroencephalogram (EEC), a movement disorder, dementia, or slow nerve conduction velocities, *Phenotype* refers to the observed biochemical, physiological, or clinical manifestations in an individual. *Genotype* refers to the genetic constitution of an individual, specifically the alleles ai one chromosomal locus.

Penetrance of a gene refers to the proportion of gene carriers who show any clinical expression. For example, if out of 100 known earners of a mutation there are 80 with some clinical manifestation and 20 without, the gene is said to show 80% penetrance. Penetrance is age- and

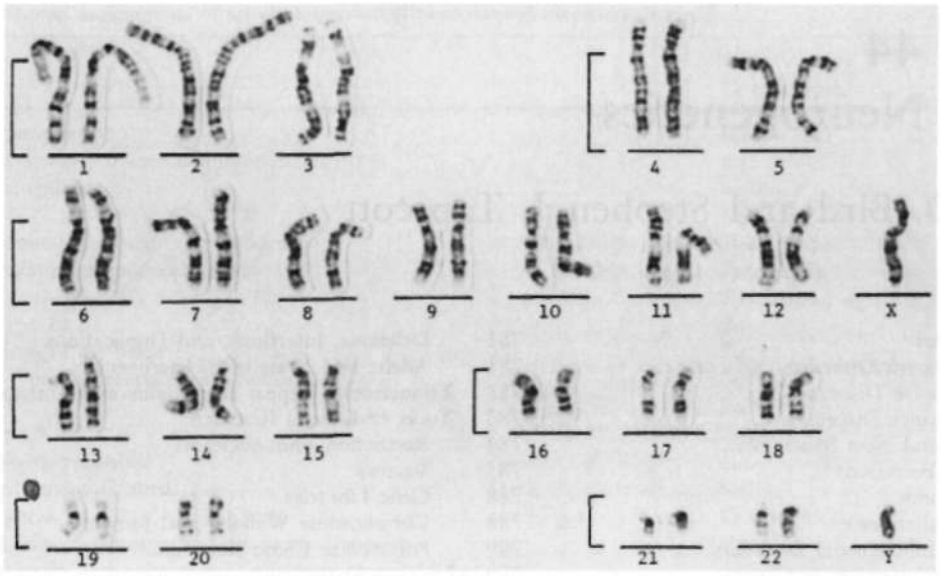


FIGURE 44.1 A normal male karyotype. The chromosomes are in the early metaphase stage of mitosis. The 22 pairs of autosomes and one pair of sex chromosomes are distinguished by their size and arm ratio and by each chromosome's unique pattern of transverse bands. The chromosomes here are stained by the Giemsa banding technique. Note that this male karyotype has one X and one Y chromosome. A normal female karyotype would have 2 Xs and no Y. (Photomicrograph courtesy I. Teshima.)

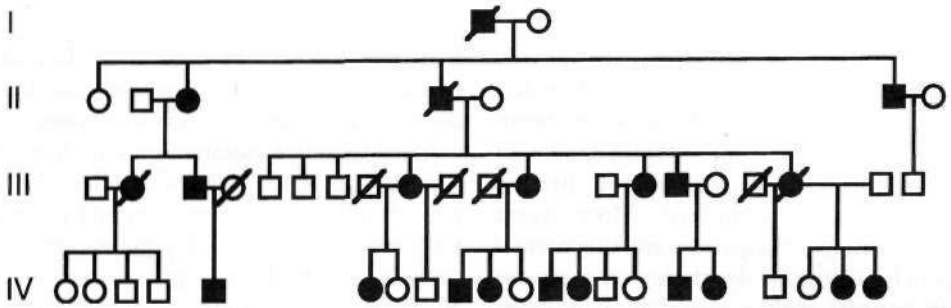


FIGURE 44.2 Pedigree demonstrating autosomal dominant inheritance in a family with Charcot-Marie-Tooth (CMT) neuropathy. Squares indicate males, and solid symbols represent persons affected with the disease. A slash through a symbol indicates a death. Note that multiple generations are involved, males and females are affected, and there is transmission from father to son (male to-male).

Table 44.1: Patterns of inheritance

Autosomal dominant	*Autosomal recessive*	*X-linked inheritance*	*Primary mitochondrial*
50% risk to each child	25% risk of homozygosity	Carrier females have: 50% risk to sons 50% risk to daughters	Transmission via females only
Males and females affected in equal proportions	Males and females affected in equal proportions	Affected males have: 0% risk to sons All daughters are carriers	All children at risk
Male-to-male transmission	Single affected generation	Males affected: Only (recessive) Worse (dominant)	Highly variable expression and severity
Multiple affected generations	Consanguinity sometimes present	Multiple affected generations	Cytoplasmic inheritance
Highly variable expression		Female transmission Affected females are mosaic	

test-dependent. That is, a gene such as Huntington's disease may show only 10% penetrance at age 20, but 90% penetrance at age 60. Also, the recorded penetrance of a gene may increase with more detailed and careful testing and examination. For example, the apparent penetrance of the tuberous sclerosis gene will increase with careful skin examination and magnetic resonance imaging (MR1) of individuals at risk. Likewise, asymptomatic carriers of a putative epilepsy gene may have only an abnormal EEG and no seizures.

Gene *carrier* was used to refer only to asymptomatic persons having a mutant allele (gene) for a recessive disorder. Nowadays, it may refer to any person having an abnormal gene, symptomatic or asymptomatic, recessive or dominant.

For some dominant mutations, the heterozygous carrier may show mild manifestations of the disease, whereas the *homozygous* carrier of a mutant gene at the same locus on a chromosome pair demonstrates much more severe clinical manifestations. An example of this is familial hypercholesterolemia, in which a heterozygous carrier may have myocardial infarction at age 48, whereas a homozygote (having inherited the mutation from each parent) may have a coronary occlusion at age 12. This phenomenon tends to blur the distinction between dominant and recessive diseases. On the other hand, for some dominant mutations such as Huntington's disease, the homozygous state is no worse than the heterozygous state. Huntington's disease therefore acts like a "true" dominant disorder.

Genetic heterogeneity refers to the phenomenon in which similar clinical phenotypes are the result of entirely different genetic mutations. For example, the Charcot-Marie-Tooth (CMT) hereditary neuropathy syndrome type 1 can be the result of different mutations in at least three different chtomosomal loci (chromosomes 1, 16, and 17) (Dejonghe et al. 1997). Likewise, there are more than 20 different dominant mutations causing hereditary ataxias. Clinical examination does not usually reveal which gene is involved.

Different forms of a gene at one locus are called *alleles.* If different mutations in the same gene each cause a clinical disorder, this is called *allelic genetic heterogeneity.* If mutations in different genes at different chromosomal loci each cause a similar disorder, it is called *nonallelic genetic heterogeneity.*

Autosomal Recessive Disorders

With autosomal recessive inheritance, the heterozygous carriers of a single mutation are usually clinically normal; rarely, they may show some clinical signs (manifesting heterozygotes). However, individuals who have inherited a mutation in the same gene from both parents (homozygotes) will show clinical manifestations of the disease. If both parents are carriers of a mutation in the same gene, then each of their children has a 25% risk for being homozygous for that gene and having the disease. Autosomal recessive disorders are usually seen in only one generation, typically among siblings (Figure 44,3; see Table 44.1), Both males and females can be affected. In small families, autosomal recessive disorders may appear as isolated or sporadic cases. Autosomal recessive disorders may sometimes appear in multiple generations of highly inbred families with consanguineous marriages. Examples of autosomal recessive neurological disorders include phenylketonuria, Tay-Sachs disease, Lafora-body myoclonic epilepsy, infantile spinal muscular atrophy, Wilson's disease, and Friedreich's ataxia.

X-Linked Inheritance Disorders

In X-linked disorders, a mutation occurs in a gene On the X chromosome. Heterozygous female carriers are usually clinically normal but occasionally have mild manifestations of the disease (manifesting carriers). In X-linked recessive

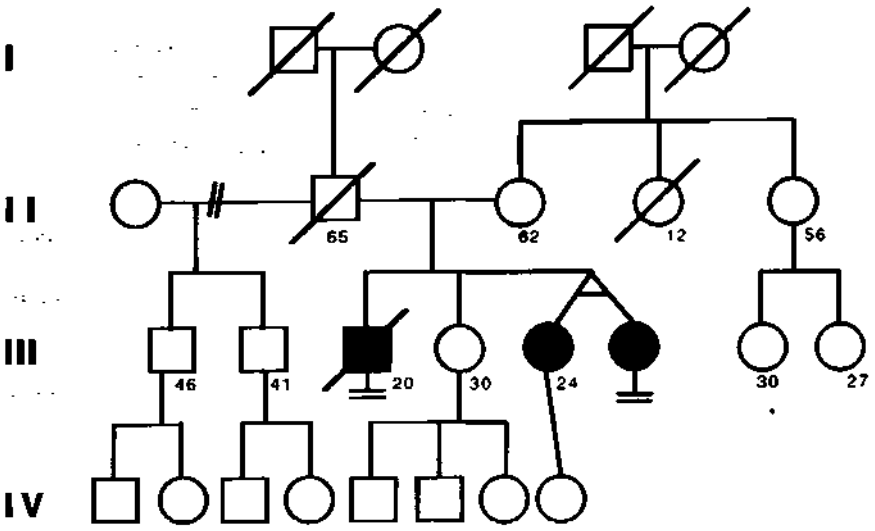


FIGURE 44.3 Pedigree demonstrating autosomal recessive inheritance in a family with Friedreich's ataxia. Three of four siblings in ^t'licnnioii *1* are aftotted (homozygous). The two affected sisters are 24-year-old identical twins. Their affected brother died at age 20. Parents are unaffected (heterozygous). Two parallel horizontal lines indicate no children.

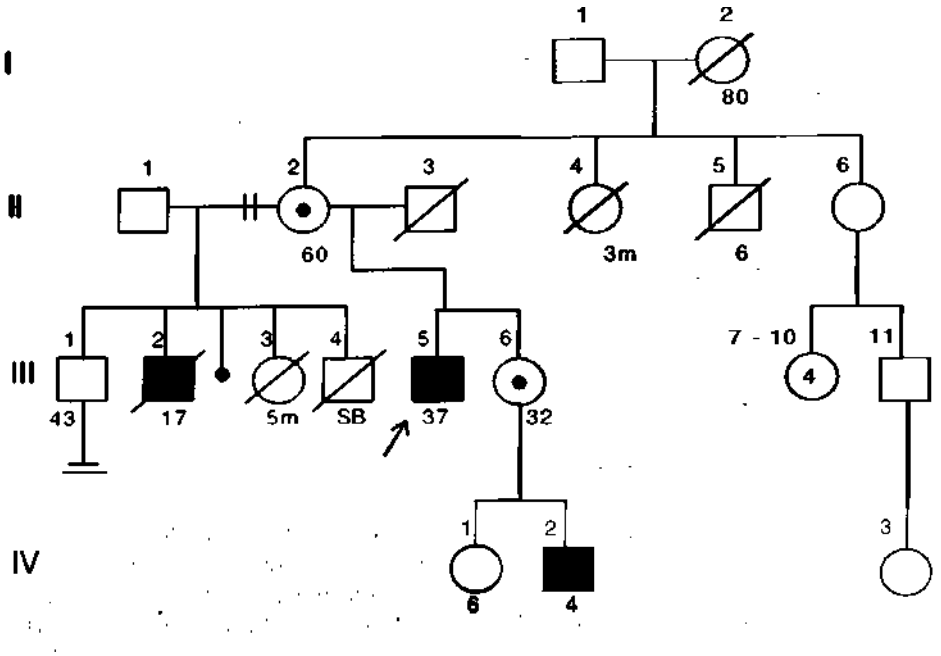


FIGURE 44.4 Pedigree with X-linked recessive inheritance in a family with Pelizaeus-Merzbacher leukodystrophy. Note that only males arc affected in two generations, and they are related by clinically normal carrier females (depicted by circle with a dot). There is no male-to-male transmission of the disease.

disorders, each son of a carrier female is at 50% risk for the disease. Each daughter of a carrier female is at 50% risk for also being a carrier. Affected males are said to be *hemizygous.* If an affected male has children, his daughters are at 100% risk for being carriers (they automatically inherit his abnormal X chromosome), and his sons do not risk inheriting the mutation (because they automatically inherit only the Y chromosome from their father). Thus X-linked recessive disease shows almost exclusively affected males in multiple generations with transmission through normal carrier females, and it never shows male-to-male transmission (Figure 44.4; see Tabic 44.1), Examples of X-linkcd recessive neurological disorders include Menkes' kinky hair syndrome, Pelizaeus-Merzbacher disease, the fragile-X mental retardation syndrome, Kennedy's spinal-bulbar muscular atrophy, Duchenne's and Becker's muscular dystrophies, and adrcnoleukodystrophy.

Heterozygous female carriers of X-linked disorders may occasionally have clinical manifestations because of the phenomenon of *random X-inactivation* (also called *lyonization).* In any given cell, only one X is active. Therefore women are *mosaic* for the X chromosome. In a few carrier females, a large proportion of their cells contain active X chromosomes bearing the mutation. Thus they may occasionally express signs of the disorder.

X-linked dominant inheritance also occasionally occurs. In this situation, heterozygous females commonly express the disease, but the condition is generally more severe in hemizygous males.

The Y chromosome contains only a few genes, such as the testis-determining factor, and no neurological disorder is related to a Y chromosome gene.

Sporadic Cases and New Mutations

A single case of an apparently genetic disease may occur in a family. Such isolated cases are often called *sporadic.* There are several different possible explanations for this phenomenon, and they may have different implications for genetic counseling. For example, the disease may not be genetic at all but actually have an environmental cause. This would represent a nongenetic *phenocopy* and, of course, would not be inherited. An example would be lead poisoning mimicking acute intermittent porphyria. Also, autosomal recessive disorders may often appear as isolated cases in small sibships, because the risks to children of carrier parents are only 25% with each pregnancy. There are recessive disorders that can look phenotypically very much like other diseases that are dominant {e.g., some hereditary neuropathies, ataxias, and movement disorders). Risks to rhe children of persons with autosomal recessive diseases are very small unless the individual happens to mate with a carrier of the same disease gene (and most such carriers are very rare in the general population).

Sporadic instances of dominant diseases may represent actual *new mutations.* The exact causes of new mutations for human diseases are generally unknown, but irradiation, toxins, and viral exposures presumably play a role. Some new mutations seem to result from the sudden expansion of unstable regions of DNA (described later). In any case, each offspring of a person with a new dominant mutation is at 50% risk for inheriting the abnormal gene, even when there are no other previously affected persons in the family.

Furthermore, a sporadic instance of a disease may represent *false paternity.* That is, the affected individual may not he aware of the fact that his or her true biological

father (and not the apparent father) carried a particular disease gene. Nevertheless, if the disorder is dominant, the children of the affected person are at 50% risk.

Finally, some carriers of dominant disease genes have only very mild clinical expression or none at all *{lack of penetrance).* Affected children of such individuals assume that neither of their parents had the disease, and the child appears to be a new isolated case. Detailed evaluation of their parents may uncover mild physical signs and explain the apparent sporadic case. Such situations are especially common with dominant disorders with highly variable expression such as CMT disease, neurofibromatosis, tuberous sclerosis, and myotonic dystrophy,

Chromosomal Aberrations

Detailed chemical banding of chromosomes has greatly improved the identification of microscopic alterations especially with prometaphase high-resolution banding (Figure 44.5). Molecular cytogenetic techniques can demonstrate DNA sequences directly on chromosome preparations so that the exact regional location of a DNA sequence on its corresponding chromosome can be determined. This is accomplished by use of biotin antibodies bound to a fluorochrome, the so-called fluorescent *in situ* hybridization (FISH) technique.

Gross aberrations of chromosomes may result in structural defects that are microscopically observable during karyotyping. Examples of such aberrations include trisomies, deletions, duplications, insertions, inversions, isochromosomes, ring chromosomes, and translocations. Because these aberrations are relatively large, they may impair many genes and result in severe clinical manifestations, such as spontaneous abortion, stillbirth, neonatal death, severe mental retardation, or multiple congenital anomalies. Neurological problems are common. Trisomy 21, or Down syndrome, is a common cause of mental retardation in which the prevalence of seizures is on the order of 5% and that is associated with Alzheimer's disease after age 40. Seizures may occur in 25-50% of patients who are trisomic for chromosomes 13, 18, or 22. A partial deletion of the short arm of chromosome 4 (Wolf-Hirschhorn syndrome, or chromosome 4p—) has a high frequency of convulsions (approximately 70%), In contrast, another short-arm deletion syndrome (cri du chat syndrome, or chromosome 5p—) is seldom associated with seizures.

Most chromosomal aberrations are sporadic and have very small recurrence risks in subsequent pregnancies (typically on the order of 1% or less). Occasionally, a chromosomal syndrome is in he rued through normal carriers of a balanced *chromosomal translocation* (e.g., Down syndrome as the result of a chromosome 14/21 Robertsonian translocation). Children of balanced-translocation carriers have a 4-15% risk of being chromosomally unbalanced and having the clinical syndrome (Figure 44.6).

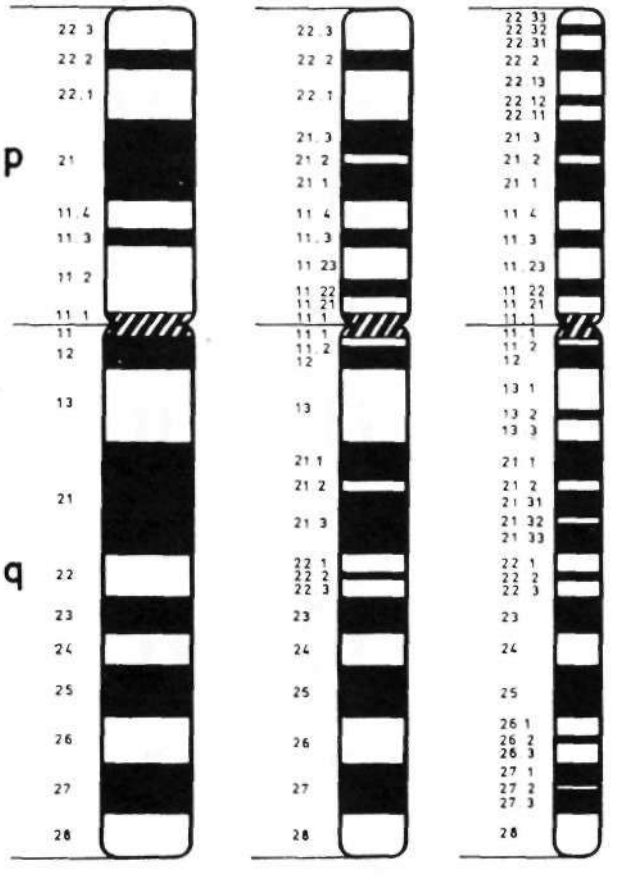


FIGURE 44.5 Schematic diagram of the X chromosome at three different stages of banding resolution showing the standard bunding partem and the system numbering chromosome hands and sub-bands. A "p" refers to the short arm and a "q" refers to the long arm of individual chromosomes. Note, for example, that band Xp21, which includes the D lichen nc/Becker muscular dystrophy gene, can be further resolved into bands Xp21.1, Xp21.2, and Xp21.3. (Reprinted with permission from Harnden, D. G. & Klinger, H. P. [eds]. 1985, *ISCN 1985: An International System for Hitman Cytogenetic Nomenclature,* Kargcr, Basel.)

Aberrations of the sex chromosomes include the following: Turner's syndrome (XO) in females associated with short stature, infertility, and visuospatial problems but not mental retardation; Klinefelter's syndrome (XXY) in males associated with infertility, hypogonadism, tall stature, and psychosocial adjustment problems; XYY syndrome in males associated with tall stature and behavioral problems; and XXX syndrome in females with mental retardation.

Some patients with very mild manifestations of a chromosomal disorder may be the result of *somatic mosaicism.* In such individuals, the chromosomal defect occurs postfertilization in the early stages of embryo development. In the full-grown individual, only a **small** proportion of cells carries the chromosomal defect. For example, a few individuals have rhe facial manifestations of Down syndrome but have normal intelligence. Careful karyotyping may show normal results in most cells,

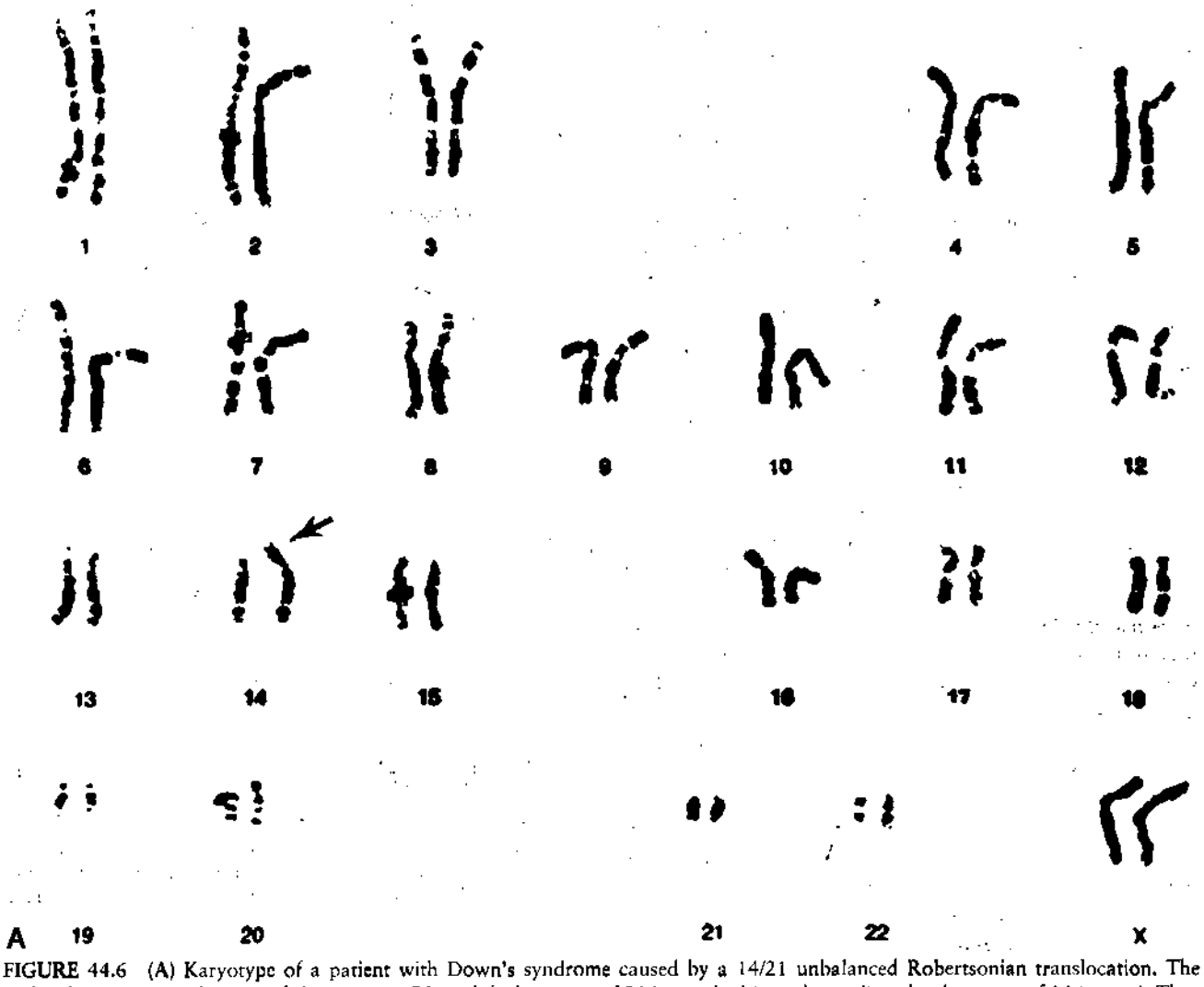


FIGURE 44.6 (A) Karyotype of a patient with Down's syndrome caused by a 14/21 unbalanced Robertsonian translocation. The patient has two normal copies of chromosome 21, and the long arm of 21 is attached (translocated) to the short arm of 14 (*arrow*). Thus there are three copies (trisomy) of 21, although the total number of chromosomes appears to be normal (46). *Continued*

although a small proportion has trisomy 21. These individuals have mosaic Down syndrome.

Some small chromosomal deletions may be submicroscopic (not visible on the usual karyotype) but produce defects in several adjacent genes. This may result in a so-called *contiguous gene deletion syndrome.* One well-documented example is a boy who had Duchennc's muscular dystrophy, retinitis pigmentosa, chronic granulomatous disease, and McLeod's syndrome. This was the result of a deletion affecting four adjacent genes on the X chromosome; the boy's X-chromosomal DNA played a major role in the discovery of the gene for Duchenne's muscular dystrophy.

Individuals with an inherited mutation at a single locus on one chromosome may acquire an additional somatic mutation at the same locus on the other chromosome of that pair, resulting in the *two-htt phenomenon.* For example, an individual who has inherited a mutation in the retinoblastoma gene on chromosome 13 may develop multiple eye tumors, because an additional acquired somatic mutation occurs at the same locus in the other member of the chromosome 13 pair in a retinal cell. This results in homozygosity for the mutation and the subsequent growth of the tumor, because the normal gene suppresses tumor growth. A similar phenomenon occurs in many astrocytomas involving the tumor suppressor gene *(pS3)* on chromosome 17p.

imprinting refers to germ line-specific modification of chromosomes and their genetic material. This results in differential expression of genetic information when inherited from the mother, as compared with inheritance from the father. The phenomenon is probably at least partially

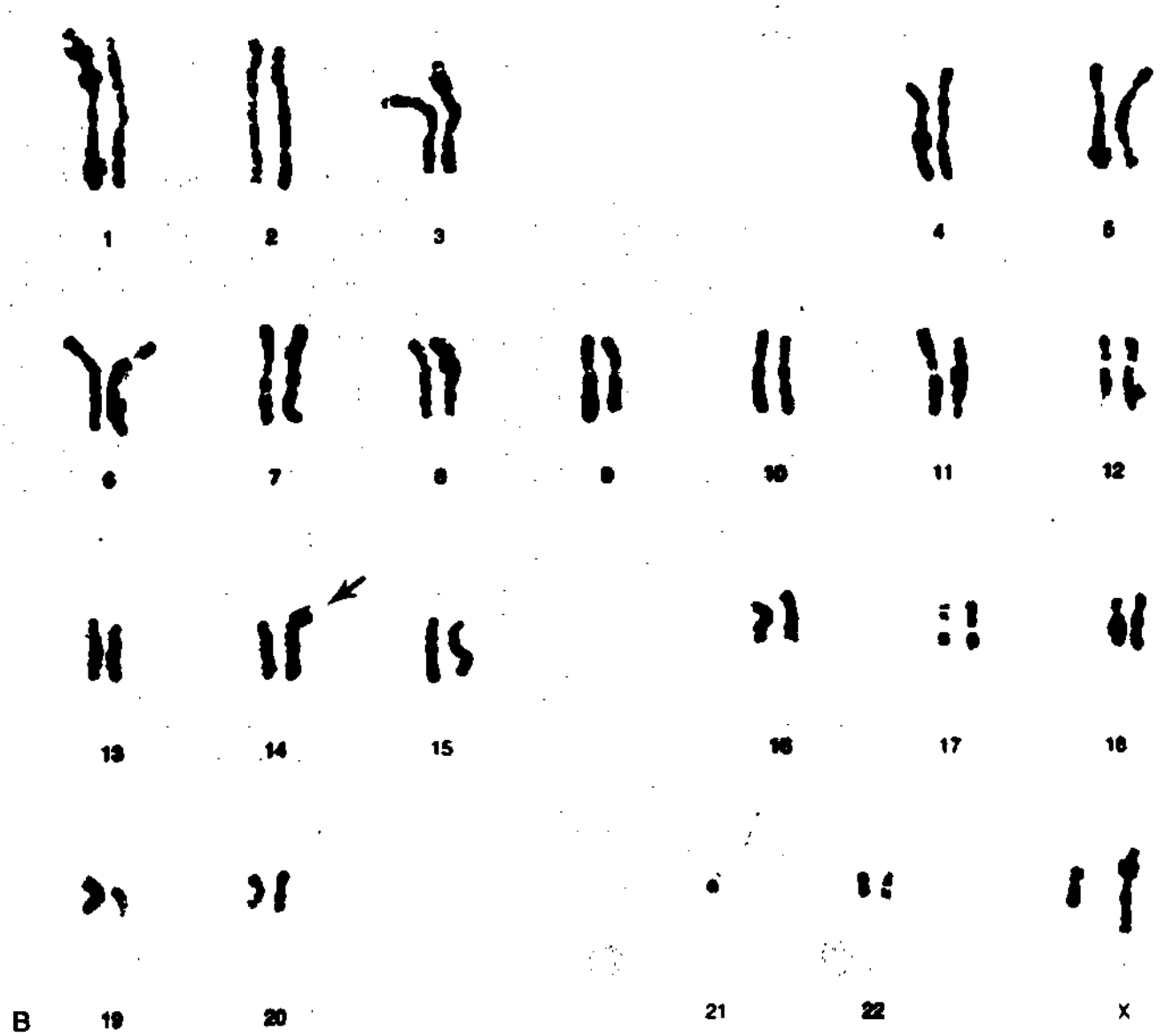


FIGURE 44.6, cont'd (B) A carrier of 14/21 translocation has the chromosome 14 with the attached 21 (*arrow*) but only one other copy of chromosome 21. Thus there is the normal total number (2) of chromosome 21, although the person appears to have only 45 chromosomes. (Courtesy K. Leppig.)

reined m differential metfiylation of DNA, which is known to inactivate some genes. An example of imprinting occuts in the unusual inheritance pattern yf the fragile-X mental retardation syndrome. In this disorder, some males with normal intelligence transmit the gene to their daughters, who may also be mentally normal but who subsequently have mentally retarded sons. The involved region of the X chromosome is altered as it passes through oogenesis in the mother. It has also been speculated that imprinting may play a role in juvenile Huntington's disease, which occurs almost exclusively in the offspring of affected fathers, and in neonatal myotonic dystrophy, which occurs almost exclusively in the offspring of affected mothers.

Angelman's syndrome and the Prader-Willi syndrome both result from a small deletion in the same site ot chromosome 15. However, it an individual inherits the deletion from a maternal chromosome 15, the result is Angelman's syndrome, whereas if the mutation is on a paternal chromosome 15, the result is Prader-Willi syndrome. This appears to be another example of imprinting. Of further interest here is that although mental retardation is common to both disorders, seizures are much more common in Angelman's syndrome, and a

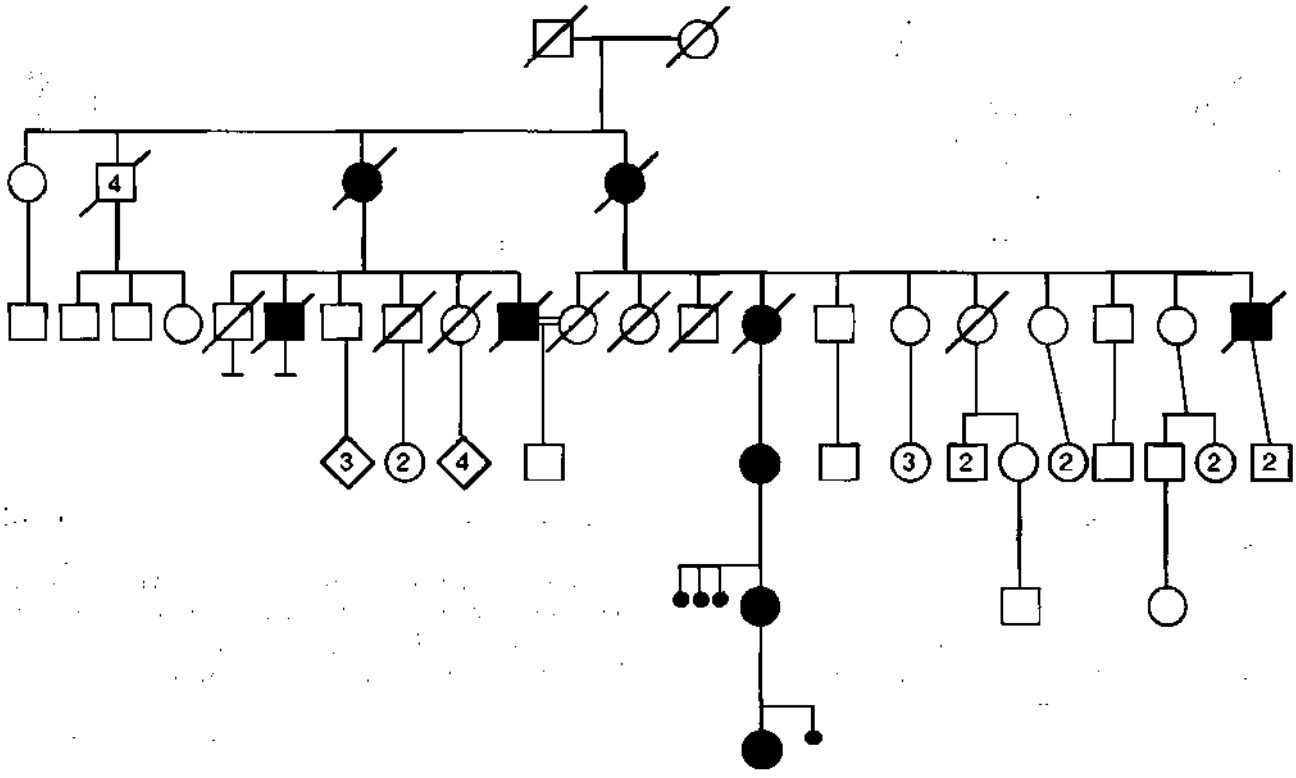
y-aminobutyric acid receptor gene maps to rhe involved region of chromosome 15.

Uniparental Disomy

As noted previously, normally within each pair of chromosomes one is inherited from the mother and the other from the father. Occasionally, however, an individual may inherit both members of a chromosomal pair from a single parent. This is called *uniparental disomy.* This occurrence has resulted in some interesting genetic phenomena. An individual who was homozygous for the autosomal recessive cystic fibrosis (CF) gene was found to have only a carrier mother (the father was demonstrated not to be a carrier of rhe CF mutation), It was further determined that the affected child had inherited both chromosome 7s (the site of the CF gene) from the heterozygous mother. This same phenomenon has also occurred in a child with autosomal recessive spinal muscular atrophy.

Mitochondrial Inheritance

In the past few years, it has become apparent that several interesting disorders are the result of mutations in mitochondrial DNA (DiMauro 1993). Mitochondrial DNA codes for 13 proteins that are involved in oxidative phosphorylation and for ribosomal and transfer RNAs. Mitochondrial DNA is inherited in the cytoplasm of a mother's egg but is not inherited from the sperm of the father. Therefore primary mitochondrial disorders are transmitted only by mothers and never by fathers *(cytoplasmic inheritance)* (Figure 44,7), Male and female children can both be affected, and the disease may appear in all children of an affected mother. The ovum contains many mitochondria, only some of which have the mutation in the mitochondrial DNA in such a primary mitoehondriopathy. Each child of an affected mother may vary in the number of mitochondria that he or she has inherited that contain the DNA mutation. Furthermore, the proportion of mutant mitochondria may vary considerably from cell to cell in any given affected individual *(heteroplasmy).* Therefore mitochondrial disorders often show extreme variability in clinical expression both within and between families. Point mutations in mitochondrial DNA tend to be inherited through females, whereas deletions of mitochondrial DNA rend ro be noninherited, sporadic events in isolated individuals. Primary mitochondrial disorders include the myoclonus epilepsy with ragged-red fibers (MFRRF) syndrome; the mitochondrial encephalomyopathy, lactic acidosis, and stroke (MELAS) syndrome; Leber's hereditary optic neuropathy (LHON); and the



EIGURE 44.7 Pedigree demonstrating mitochondrial inheritance in a family with a variant of myoclonus epilepsy with ragged-red fibers (MERRF). Note that multiple generations are involved, male and females arc both affected, but the disease is only transmitted by females. The small dots attached by vertical lines represent spontaneous abortions.

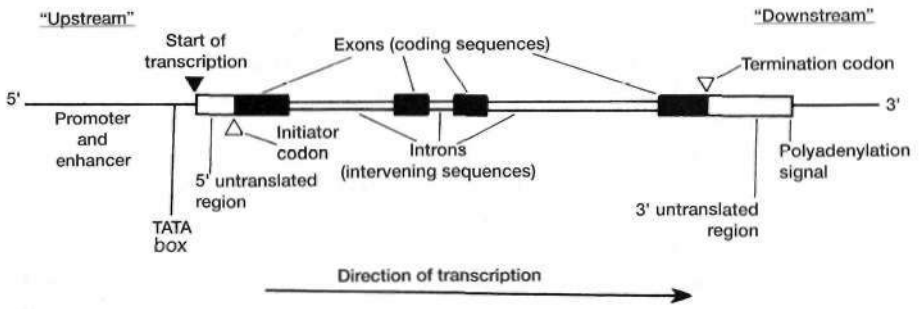


FIGURE 44.8 Hypothetical structure of a typical gene. The exons contain the three base-pair codons that are eventually translated into the amino acids of a polypeptide. The intervening sequences of introns are spliced out of the genetic code during transcription. A gene may have one or many exons. A gene may range in size from a few thousand base pairs to several million base pairs,

Kearns-Sayre syndrome (myopathy, retinopathy, cardiomyopathy).

Most of the macromolectiles of mitochondria are encoded by nuclear genes, mutations of which are inherited in a typical mendelian fashion. Mutations of the nuclear mitochondrial genes are responsible for the secondary mitochondriopathies. These disorders are actively being elucidated.

Polygenic and Multifactorial Disorders

Some syndromes are presumed to be the result of the additive effect of a small number of multiple genes. Such polygenic conditions are mostly speculative but could include some forms of mental retardation, hypertension, epilepsy, dementia, or diabetes mellitus.

Multifactorial inheritance refers to disorders that result from the combination of an inherited predisposition acting in concert with an acquired environmental insult. Some latent carriers of a single gene mutation may be unmasked by exposure to an environmental agent. Symptomatic acute intermittent porphyria following phenobarbital administration is an example. The area of pharmacogenetics will be of great importance to neurology as the genetic control of anticonvulsant and other drug metabolism becomes fully delineated. Genetically programmed rapid or slow metabolizers of anticonvulsants present major challenges to the clinical management of seizure disorders. Multiple sclerosis is suspected to be another model of multifactorial inheritance in which there is a presumed genetic immunological predisposition to some unknown environmental trigger.

Table 44.2: The human genome

3 billion base pairs (bp)
30,000–40,000 functional genes
3000–5000 known genetic disorders
1000 bp = 1 kilobase (kb)
1 million bp = 1 megabase (Mb)
1% recombination = 1 cM (centimorgan)
1 cM = 1 Mb

ORGANIZATION AND EXPRESSION OF GENES

Most genetic information inherited by each individual is coded in the nuclear chromosomal DNA, although mitochondrial DNA and maternally transmitted RNA molecules can contribute important inherited information. DNA is composed of the four bases—adenine, guanine, cytosine, and thymine—as deoxyribonucleotides. Human chromosomes contain a total of approximately 3 billion base pairs (bp) (Table 44.2). It has been estimated that the human genome codes for approximately 35,000 different genes. A gene is a region of the DNA that contains the information necessary for the appropriate expression of a specific RNA species (Figure 44,8). Regions of DNA are converted to RNA by a process called transcription. Specialized regions of the DNA, termed enhancers and promoters, regulate the initiation of RNA transcription, A complex set of proteins that composes the RNA polymerase holoenzyme is recruited to the promoter and proceeds along the DNA in a *5′* to 3' direction, producing a copy of the DNA sequence in ribonucleotides composed ol the same bases as DNA except that uracil substitutes for thymine (Figure 44.9). Most RNA is processed in the nucleus: it receives a cap on the *5′* end and a polyadenylation tail gets spliced to the 3' end. In addition, most genes have introns, regions of the RNA that arc removed in the nucleus, splicing together the regions present in the mature RNA, the exons, that get exported to the cytoplasm. Each gene can have multiple exons, and several different RNA species can be generated from a single gene by alternative exon usage or splicing, a process that is regulated both by the sequence of the RNA and by factors that interact with the RNA ui a tissue-specific manner.

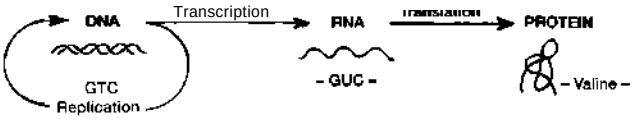


FIGURE 44.9 Schematic diagram demonstrating transcription of DNA into RNA followed by translation of the RNA to a polypeptide protein. The GTC codon in DNA is transcribed to GUC in RNA, then translated to valine in the protein. Transcription occurs in the nucleus and translation occurs in the cytoplasmic ribosomes.

The mature RNA is transported out of the nucleus to the cytoplasm as messenger RNA (mRNA). In the cytoplasm the nbosome attaches to the capped 5' end of the mRNA and translates the mRNA into a protein using a three base-pair code, the genetic code. Each three bases represents a unit of information termed a codon, either specifying an amino acid or a signal for the ribosome to terminate translation. Because there are 64 possible combinations of four bases taken three at a time and only 20 amino acids used for protein synthesis, each amino acid is represented by more than one codon. Most of the degeneracy in the codons occurs in the position of the third base. For example, valine is specified by GUN, where N represents any of the four bases; alanine is specified by GCN and glycine by GAN. As discussed later, base changes in the DNA that occur in the third position of these codons will not change the amino acid specified and will be silent mutations.

How does the ribosome know which of the three possible reading frames to translate into a protein? There are some rules that increase the probability that the ribosome will initiate transcription in a particular reading frame. First, the ribosome scans along the RNA but does not initiate protein translation until it reaches the codon for methionine, the codon ATG. RNA sequences surrounding the ATG determine the probability that protein translation will be initiated and sometimes the ribosome will pass several potential initiation codons until it reaches an ATG in the context of a favorable surrounding sequence, the Kozak consensus sequence. Once translation is initiated, sequential codons are used to determine the protein sequence until the ribosome encounters a stop codon that causes it to cease translation and dissociate from the mRNA. The codons between a methionine and a stop codon are referred to as an open reading frame **(ORE),** because it has the potential to be translated into a protein by a ribosome.

The amino acids are brought to the codon by a small, specialized RNA molecule, the transfer RNA (tRNA). Each tRNA has a region that is the complementary triplet sequence to the codon, called the anticodon. The 3' end of the tRNA is covalently linked to a specific amino acid. Therefore when the tRNA anticodon pairs with the mRNA codon, ii brings the spccilicd ammo acid into position to In- added to the nascent polypeptide chain. (For a more detailed discussion of the molecular biology of gene expression see Alberts et al. 2002.)

The estimated 30,000 to 40,000 human genes actually are responsible for a much larger number of final protein products (probably four to five times more). This multiplication effect is accomplished in several different ways. One is the variable splicing of genes described previously. A single gene may result in several different types of RNA depending on the addition or subtraction of various exons. Another mechanism is the posr-rranslarional modification of proteins, including glycosylation and/or phosphorylation, that produces a huge variety of protein variation. Proteomics, the study of this protein variability and its role in normal biology and mechanisms of disease, is a burgeoning new field of molecular research.

POLYMORPHISMS, MUTATIONS, AND EVOLUTION

During the replication of any cell, the DNA has to be faithfully copied. A complex set of proteins copies the DNA, proofreads, and corrects the copied product. The average mutation rate, the rate of incorporating the wrong nucleotide in the final DNA product, is approximately one per one billion replicated bases. Given the size of the human genome, mutations are an anticipated event with nearly all replication cycles. The population diversity generated by these low mutation rates is thought to be critical for evolution and species adaptation. Therefore the imperfection of DNA replication that sometimes gives rise to disease also supports the survival of the species.

The accumulated mutations that have occurred since the common ancestor of *Homo sapiens* are reflected as sequence differences between individuals. On average, DNA from two unrelated individuals will have one difference every 500 hundred bp, for an average total of 6,000,000 differences per genome. These single base-pair differences are called single nucleotide polymorphisms (SNPs). Although most SNPs represent silent mutations, some have profound consequences on human characteristics, such as the polymorphism in codon six of the beta-chain of hemoglobin that substitutes valine for glutamate and causes sickle cell anemia when present as a homozygous polymorphism.

The SNPs can be used as markers of a chromosomal region. Because each of a parent's paired chromosomes will have different SNPs, the SNPs donated to each child can be identified, and cross-over events can be used to map the location of a gene for a particular trait. Identifying the SNPs that segregate with a trait will identify the region of the chromosome that contains the gene conferring the trait. Historically, restriction endonucleases were used to identify a subset of SNPs. Restriction endonucleases recognize and cut DNA at small palindromic sequences, cleaving the DNA **into** smaller fragments. If an SNP occurs at an cndonuclease restriction site, then the size of the fragment will be changed. These restriction fragment length polymorphisms (RFLPs) can be used as genomic markers to **follow the** segregation of chromosomal regions within families (see discussion of linkage analysis later).

Because only SNPs that changed the sequence of a known restriction site could be used for **RFLP** analysis, only a small portion of all SNPs were informative. Recent advances in hybridization techniques, such as DNA microchip arrays, can screen for nearly any identified SNP. High-density SNP maps of the human genome are being constructed that have the promise of rapidly mapping

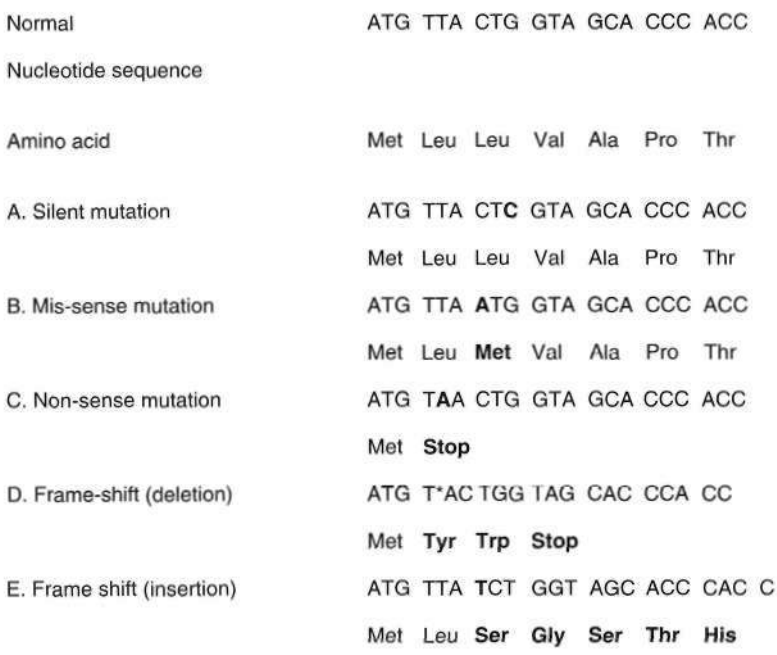


FIGURE 44.10 Types of mutations. Single base-pair changes in a coding region can cause different types of mutations. (A) Conversion of a guanine to a cytosine in the third codon is *a* silent mutation because it does not change the amino acid in the protein. (B) Conversion of the cytosine to an adenosine in the third codon is a mis-sense mutation because it results in the substitution of a methionine for a leucine in the protein. (C) Conversion of the thymine to an adenosine in the second codon is a non-sense mutation because it creates a stop codon and terminates translation of the protein. (D) and (F.) Single or double base-pair insertions or deletions are frame-shift mutations, because they change the reading frame of the mRNA, resulting in multiple mis-sense or non-sense codon changes. In (D) the second T has been deleted from the second codon leading to *a* premature stop codon. In (E) a T has been inserted at the beginning of the third codon leading to a new amino acid sequence. (Bold type face indicates a change from the reference sequence.)

an individual human genome at high resolution. The possibility of high-density genetic mapping in a large population may allow the association of particular sets of SNPs with phenotypic characteristics in the absence of generating family pedigrees.

In addition to SNPs, repeat polymorphisms have been used to map genetic traits. The genome is interspersed with simple dinucleotide, trinucleotide, and tetranucleotide repeats. During DNA replication these repetitive elements can gain or lose repeat units. The high rare of repeat instability makes these elements highly polymorphic in the population. Although most of the repeat instability is thought to be without phenotypic consequence and is mainly used to establish linkage with a disease, the expansion of some trinucleotide repeats can cause diseases, as discussed later.

Strains of mice and other laboratory animals have been inbred to minimize the number of genetic differences between individuals, whereas the human population is outbred and maintains a high degree of genetic diversity. This diversity represents the imperfect system of DNA replication and repair that regularly introduces imitations into the population. The mutations, or polymorphisms, that have accumulated during the evolution of the human species contributes to the rich diversity of the human phenotype but also to the prevalence of genetic diseases.

GENETIC MECHANISMS OF HUMAN DISEASE

Single Base-Pair Mutations

Mutations that alter a single base pair can be completely silent mutations or cause profound disease. If the mutation is in the coding region of a gene there are four possible outcomes. A silent mutation changes the base pair but does not change the amino acid specified by the codon (Figure 44.10A). In a mis-sense mutation, the codon is changed to specify a different amino acid {Figure 44.10B), possibly affecting the function of the protein. A non-sense mutation converts an amino acid codon into a stop codon, causing a premature termination of the protein polypeptide (Figure 44.1 OC). This type of mutation sometimes occurs in neurofibromatosis *(NF1)* {Figure 44.11) Finally, a frame-shift mutation either introduces or deletes base pairs, resulting in a shift in the reading frame of the ribosome (Figure 44.10D and E) and is one of the common mutations in Tay-Sachs disease (Figure 44.12).

Mutations that occur in noncoding regions are often silent but have the potential to occur in the regulatory regions of promotors or enhancers or in regions critical for appropriate RNA splicing. Mutations that occur in the genes coding for tRNA can have broad effects on protein synthesis. Neurological diseases sometimes caused by mutations in introns that result in abnormal splicing include ataxia telangiectasia, neurofibromatosis 1, and frontotemporal dementia *(FTD P-17).*

FIGURE 44.11 The substitution of a T for a C in the neurofibromatosis gene (*NF1*) results in a non-sense mutation in the coding sequence, which causes a premature termination of translation (stop codon).

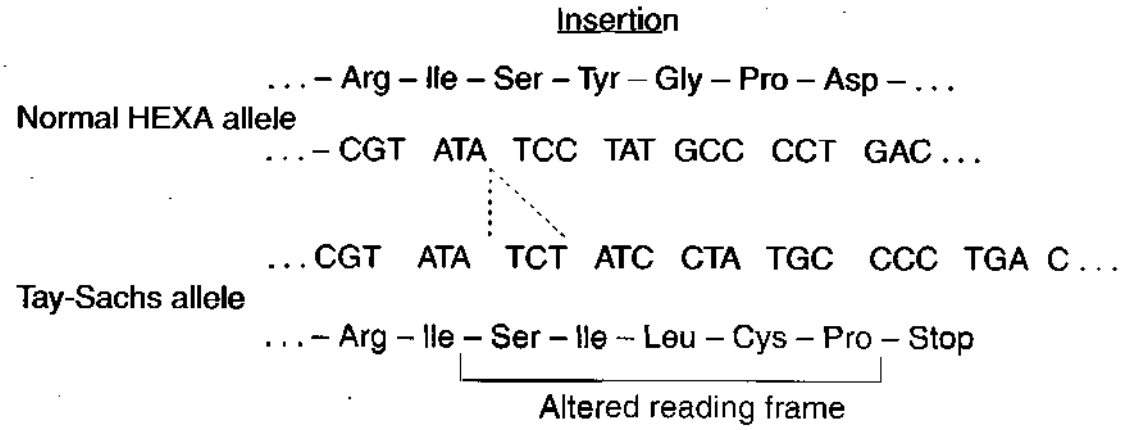


FIGURE 44.12 A four base-pair insertion in the hexosaminidase-A gene leads to a frame-shift mutation. This is the major cause of Tay-Sachs disease in Ashkenazi Jews.

Deletions, Insertions, and Duplications

Deletions and insertions of DNA can either disrupt the coding sequence of a gene or remove the gene entirely. Deletions in the dystrophin gene can cause the severe Duchcnnc's muscular dystrophy or the more mild Becker's muscular dystrophy. The dystrophin gene spans more than 2 million bp and has more than 40 exons, making it one of the largest known genes (Figure 44.13), Deletions of the gene that disrupt the reading frame result in a truncated protein that is not stable and cause the Duchenne phenotype. Internal deletions of the gene that maintain the reading frame, removing internal sections of the protein but leaving the aminotcrminal and carboxytcrminal regions intact, are often associated with the more mild Becker phenotype.

Insertions of small regions of DNA can either add new codons to a gene or change the reading frame of the portion of the gene that follows the insertion. A four base-pair insertion in the hexosaminidase-A gene causes a reading frame shift that inactivates the protein (see Figure 44,12), Carriers of a single allele are asymptomatic and homozygous individuals have Tay-Sachs disease.

Deletions and duplications of very large regions of the genome are associated with specific syndromes. In some cases it is thought that the disease is caused by the loss or addition of a copy of a specific gene. For example, a point mutation in the peripheral myelin protein-22 *(PMP-22)* gene causes a demyelinating peripheral neuropathy (CMT-lA/hereditory motor-sensory neuropathy |HMSN]-I). The most common cause of CMT-1A, however, is a duplication of a 1,5 megabasc (1.5 million bp) region of chromosome 17p that encompasses the *PMP-22* gene, Because a balanced translocation that results in a trisomy of chromosome 17p has a similar neuropathy, it is likely that the presence of an additional copy of the *PMP-22* gene causes the demyelinating neuropathy. The possibility that some aspects of myelination might be sensitive to gene dosage of *PMP-22* is supported by the observation that the deletion of the 1.5 megabase region encompassing the *PMP-22* gene results in hereditary neuropathy with liability to pressure palsies (HNPP).

Allelic and Nonallelic Heterogeneity

Figure 44.14 illustrates that several different mutations can all result in similar disease phcnotypes, in this case inherited demyelinating neuropathies. As noted previously, a duplication of 1.5 million bp of chromosome 17p that includes the *PMP-22* gene results in an autosomal dominant demyelinating neuropathy (CMT-1A). One point mutation in *PMP-22* causes a phenotypically similar dominant neuropathy, whereas a different point mutation in *PMP-22* gives rise to a recessively inherited demyelinating neuropathy. Deletion of the entire 1.5 million bp region containing the *PMP-22* gene causes the phenotypically distinct demyelinating disease HNPP. Inherited demyelinating syndromes of the CMT type are also caused by mutations of other genes. A point mutation in the P-zero (P0) myelin protein gene on chromosome 1 causes demyelinating peripheral neuropathy (CMT-1B). Finally, a mutation in ;i gap junction protein connexin32 gene on the X chromosome results in an X-linked inherited demyelinating neuropathy (CMT-X). The mutations involving *PMP-22* are examples of the allelic genetic heterogeneity of CMT-1A, whereas the group of mutations of chromosomes 1, 17, and X that cause clinically similar demyelinating inherited peripheral neuropathies are examples of the nonallelic genetic heterogeneity of the CMT syndrome.

TRINUCLEOTIDE REPEAT EXPANSIONS AND ANTICIPATION

The phenomenon of generic anticipation has been debated for many decades. The term was primarily used to describe

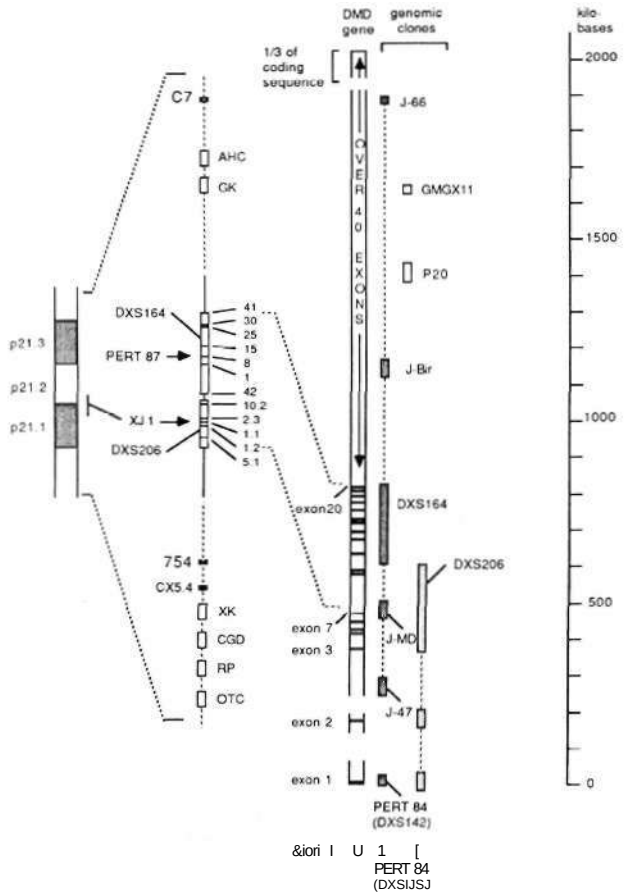


FIGURE 44.13 Schematic of the Duchenne's muscular dystrophy gene. On the left is the tegion of the X chromosome that contains the gene, showing the relation of the chromosomal region to the DXS164 and DXS206 regions, detected by the pERT and XJ1 probes, respectively. The genes for congenital adrenal hypoplasia *[AHCj*, glycerol kinase *(CK)*, the McLeod phenotype *(XK)*, chronic granulomatous disease (CGD), retinitis pigmentosa (RP), and ornithine transcarhamylase *{OTC)* are shown in their relative positions. C7 and 754 are anonymous flanking probes often used in restriction fragment length polymorphism (RFLP) analysis. On the tight is the genomic map showing the relation between the DXS164 and DXS206 regions and exons of the gene. At the time this figure was produced, exons 1 and 2 were not yet linked to one another or to DXS206 and are shown connected to DXS206 by a dashed line. Several "jump" clones *{}-&(>*, J-Bir, J-MD, J-47) found by isolation of deletion junctions with pERT K7 probes arc shown connected to the DXS164 locus. Probe pERT84 and the untelated probes GMGX11 and P20 are shown in their approximate positions. The size of the gene is about 2 Mb.

the observed increasing clinical severity of the autosomal dominant myotonic dystrophy gene over subsequent generations (Harper 2001). Typically, a father might have early-onset cataracts, his daughter mild muscle weakness and myotonia, and the daughter's child severe weakness and myotonia associated with mental retardation. This repeatedly observed clinical observation of increasing disease severity across generations has now been given a biologic foundation. Myotonic dystrophy is caused by the expansion of a trinucleotide repeat in the dystrophia myotonia protein kinase *{DMPK)* gene on chromosome 19. The general population has between 5 and 44 repeats of the CTG trinucleotide. Expansions of more than 100 repeats cause myotonic dystrophy, and very large expansions of thousands of repeats are associated with more severe forms of the disease. The size of the expansion can change from parent to offspring, and increases across generations account for the clinical phenomenon of anticipation (Figure 44.15). Recent studies have shown that the direction of the DNA replication fork may be a critical factor in repeat instability.

Several neurogenetic diseases have now been shown to be caused by unstable triplet repeats, including Kennedy's X-linked spinal-bulbar muscular atrophy, the fragilc-X mental retardation syndrome, Huntington's disease, several forms of hereditary ataxia (SCA-1, -2, -3, -6, -7, -8, -12, and Friedreich's ataxia), and a rare form of dentatorubral-pallidoluysian atrophy (DRPLA) (Zoghbi and Orr 2000). As seen in Figure 44.16, many of these diseases arc caused by the expansion of a CAG repeat in the coding region of the gene. In each case the reading frame of the CAG repeat codes for a stretch of glutamines, producing a longer polyglutamine tract in the protein product. For some of these diseases it has been shown that this polyglutamine tract results in abnormal nuclear inclusions that might contribute to the cause of the disease.

Three of these repeat diseases, however, are caused by repeat expansions in noncoding regions of the gene. In fragile-X syndrome, there is an expanded CGG repeat in the 5' untranslated region of the *FRX-1* gene. Methylation of this sequence is associated with suppressed expression of the *FRX-1* gene. Because *FRX-1* is on the X-chromosome, males have only one copy of the gene and inactivation results in the fragile-X syndrome of mental retardation. In Friedreich's ataxia, an expanded repeat is present in an intron of the frataxin gene and is thought to decrease gene expression, Friedreich's ataxia is a recessive disease and both alleles have an expansion or mutation in affected individuals. In the most common form of myotonic dystrophy the repeat expansion occurs in the 3' untranslated region of the *DMPK* gene on chromosome 19. Therefore the repeat is present in the mRNA after the stop codon and does not alter the ORF for the protein. It has been demonstrated that the repeat can decrease *DMPK* expression by interfering with RNA processing and nuclear transport. The expanded CUG repeat in the RNA appears to cause the disease. Indeed, a similar myotonic dystrophy (DM2) is caused by the expansion of a CCTG repeat in the intron of the *ZNF9* gene on chromosome 3, resulting in a CCUG repeat in the RNA.

Trinucleotide repeat expansions have formed the basis of rapid diagnostic tests for their associated diseases. Polymerase chain reaction (PCR) (see later) and Southern hybridization to genomic DNA obtained from blood samples can be used to determine the repeat size in individuals. The presence of an expansion indicates that the individual inherited the mutation that can cause the disease.

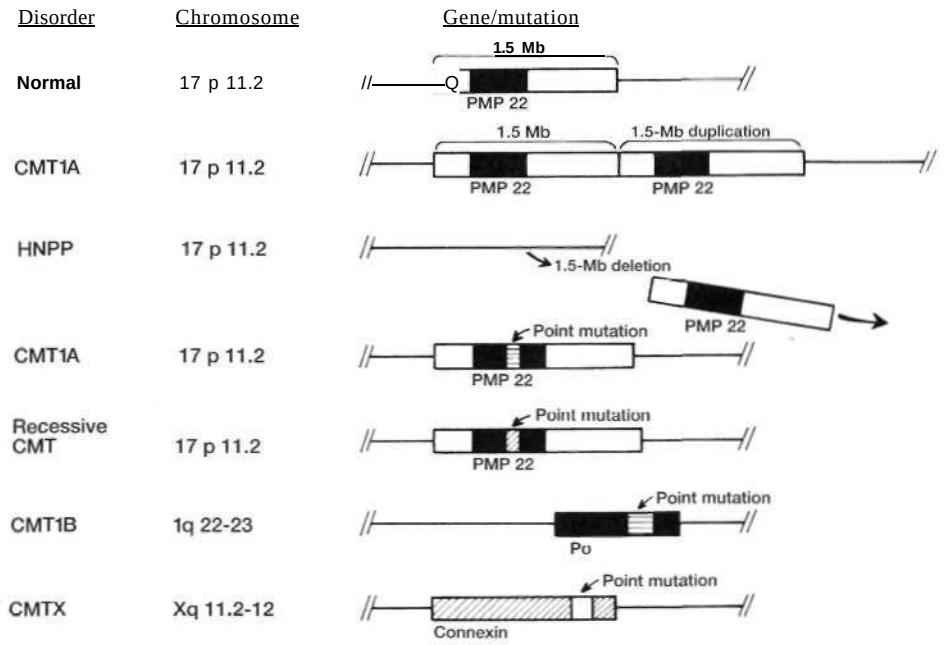


FIGURE 44.14 Several different mutations resulting in various forms of hereditary neuropathy (Charcot-Marie-Tooth [CMT]/ hereditary motor-sensory neuropathy [HMSN]) and thus examples of genetic heterogeneity. The normal sequence of DNA at chromosome 17p11.2 has a 1.5-Mb region that includes a peripheral myelin gene (*PMP-22*). A 1.5-Mb tandem duplication results in CMT-1A, and a 1.5-Mb deletion of the same region results in hereditary neuropathy with liability to pressure palsies (HNPP). Two different point mutations in the *PMP-22* gene can cause either a dominant form of CMT-1A or a recessive form of CMT. Furthermore, a point mutation in the P0 myelin protein gene at chromosome 1q22-23 results in CMT-1B, a clinical syndrome very similar to CMT-1A. Finally, a point mutation in the connexin32 gene at Xq11.2-12 results in an X-linked inherited form of neuropathy.

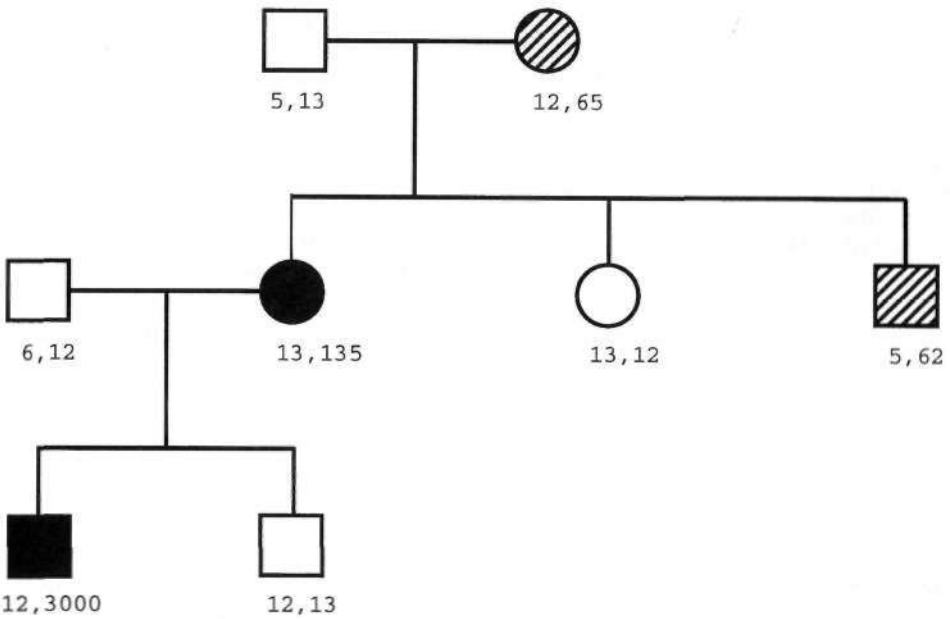


FIGURE 44.15 Clinical anticipation is partly explained by generation instability of the CTG trinucleotide repeats at the myotonic dystrophy locus. In this hypothetical family, the first-generation male has two normal-sized repeats at the myotonic dystrophy locus (the numbers under the symbol indicate the repeat size for each allele), whereas the first-generation female has one normal allele and one allele above the normal range but below the range that causes the clinical syndrome, referred to as a premutation range expansion. With transmission to the second generation, the premutation allele is unstable and is expanded to 135 repeats in a daughter that develops the clinical syndrome of myotonic dystrophy and contracted to 62 repeats in a son who remains asymptomatic. In the third generation, there is a large expansion of the repeat from 135 in the mother to 3000 in the son who is affected with a severe congenital form of myotonic dystrophy. Hatched symbols indicate abnormal size repeat but no clinical disease; filled symbols indicate clinical disease.

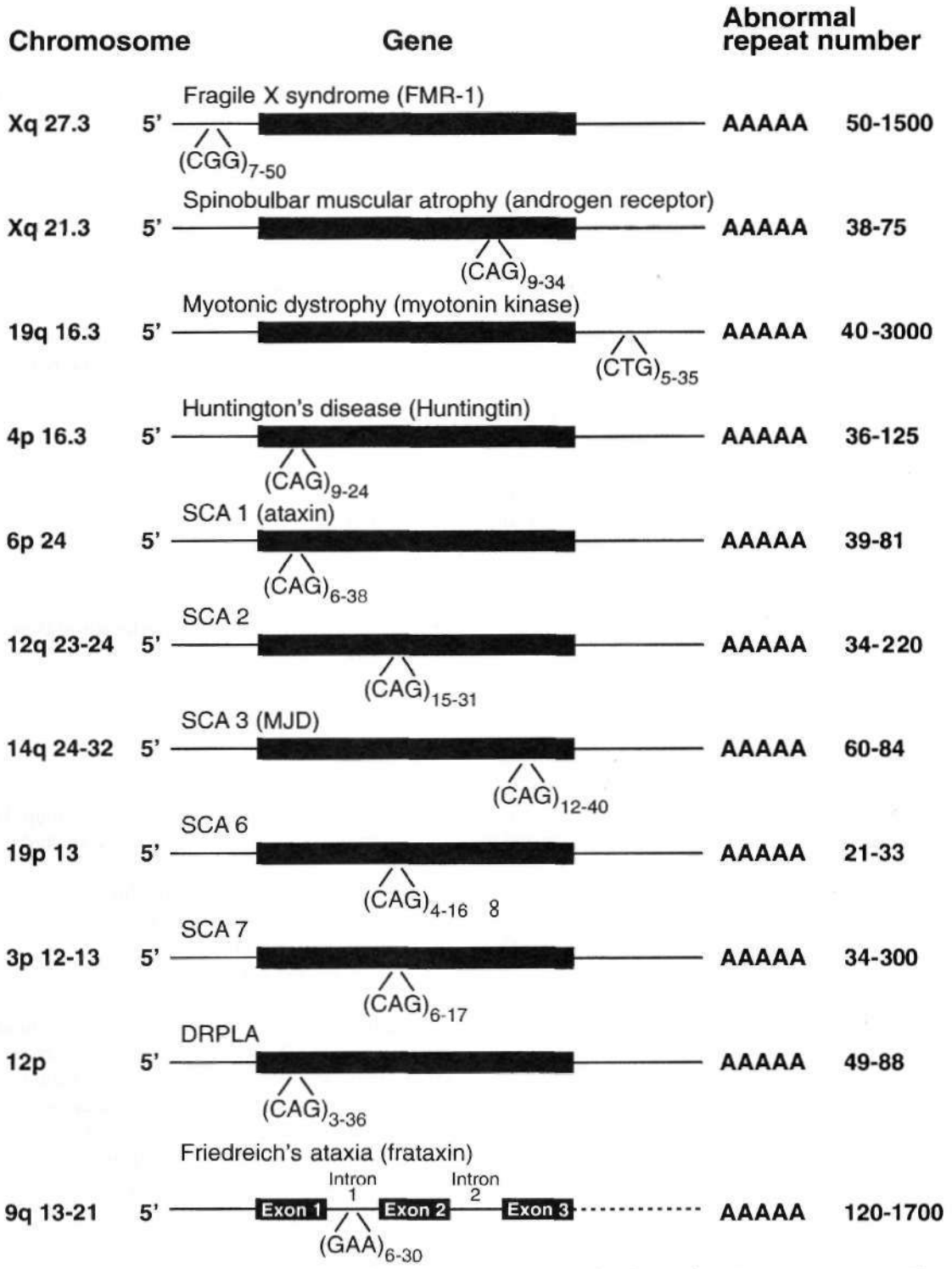


FIGURE 44.16 Eleven neurological diseases that have been shown to be associated with trinucleotide repeat expansions. The region of DNA containing each gene's protein-coding segments is indicated by the solid horizontal bar. The repeats (CGG, CAG, or GAA) may lie inside or outside these coding segments. The range of normal number of repeats found in the general population is indicated next to each repeat region. The abnormal number of repeats that may be found in affected individuals is indicated in the last column. MJD = Machado-Joseph disease.

Interpretation of the results, however, can be complex (Bird 1999). For example, having the expansion is not the same as having the symptoms of the disease. Nor does it accurately predict the age of onset or severity of disease for any individual. In many cases there is significant somatic heterogeneity of repeat length, meaning that the expansion size might be different in blood cells compared with other tissues, such as brain or muscle. Therefore although expansion length roughly correlates with disease onscr and severity when analyzing a large population, the correlation is not sufficient to accurately predict the course of the disease in any single individual. Furthermore, an individual can have an expansion that is in an intermediate range between the normal and the affected populations (e.g., 29 to 35 repeats in the *HD* gene). This ambiguity is a **difficult** issue for both patients and physicians because their association with the disease phenotype is not clear. Finally, in some of these syndromes a few patients have been described who have the clinical characteristics of the disease but do not have an expanded repeat at the disease locus. In summary, the ability to directly test for repeat size has dramatically improved our ability to identify people at risk for these inherited syndromes, but we still have much to learn about the application of this knowledge to patient care.

TOOLS **OF GENETIC** RESEARCH

Restriction Endonucleases

Certain bacterial enzymes have the ability to cleave foreign DNA into fragments, their site of action being restricted to specific sites within the molecule. This function appears to be an evolutionary development that protects the organism's own DNA from incorporating foreign DNA. Each restriction cndonuclease can recognize a specific DNA sequence *(restriction site)* several bases in length and cut a strand of foreign DNA at a particular position within that sequence. The sequences on the paired strands at which a restriction enzyme cuts arc palindromic; that is, the sequences on the two strands read the same but in opposite directions. For example, the restriction enzyme Hindlll cuts a duplex strand of DNA as follows:

1. 5'A | AGCTT3'
2. 3' TTCGA | A 5'

If the same enzyme is used to cut both the DNA of the vector and the DNA to be incorporated into it, the cut ends of the foreign and host DNA may join by complementary base pairing, thereby incorporating the foreign DNA into that of the vector. After base pairing, the ends of the strands are sealed together by the enzyme DNA ligasc (which tequires ATP),

The fragments of the DNA produced by restriction enzymes along a particular DNA segment can he used to construct a restriction map, showing the cutting sites for the various enzymes in relation to one another,

The technique used to detect specific sequences of **DNA** is Southern blotting, named after its originator. The DNA of interest is digested into short fragments by one or more restriction enzymes, and gel electrophoresis is used to separate the fragments by size. The DNA is then denatured to the single-strand form and transferred by blotting with paper towels to a more stable medium, nitrocellulose filter membrane. The pattern of DNA fragments on the gel is faithfully transferred to the filter membrane. The resulting blot can be baked to make it more permanent and can then be hybridized to a specific probe. Using autoradiography, the fragment(s) of interest can be visualized on the blot (Figure 44.17).

Because the size of each DNA fragment is determined by position of the sequence recognized by the restriction enzyme used to cleave the DNA, polymorphisms that alter a restriction site will result in a change in the size of a DNA fragment (Figure 44.17B), These RFLPs have been used in linkage analysis (see later).

By analogy to Southern blots, the transfer of RNA molecules is called Northern blotting, and the transfer of proteins is Western blotting. (Northern and Western do not derive from names of scientists,)

Vectors

Vectors arc prokaryotic organisms, or DNA molecules, into which foreign DNA can be grafted for cloning. Four types are commonly used: plasmids, phages, cosmids, and yeast artificial chromosomes (YACs).

Plasmids are small, circular duplex DNA molecules within bacteria and yeast that replicate independently of the host chromosome. The genes they carry may be of great importance for the survival of the host cell, such as genes for antibiotic resistance. The plasmids used for DNA cloning have been constructed with three essentia] features: (1) an origin of DNA replication allowing the recombinant DNA molecule to replicate in the host; (2) a marker such as a gene for antibiotic resistance that can be used to select for bacterial cells containing the plasmid; and (3) a region into which small fragments (<6-10 kb) of cloned DNA can be inserted, with the help of cleavage sites for one or more restriction enzymes.

Phage (bacteriophage) is a virus that infects bacteria. Its duplex DNA molecule may either become incorporated into the bacterial chromosome or replicate independently and produce large numbers of phage particles, which lyse the host cell and infect other bacteria in the culture. The presence of phage-infected bacteria is shown by plaques (clear areas) in the culture dish. Specialized versions of the best-known phage, phage lambda, have been developed that can carry intermediate-sized fragments (5-20 kb) of cloned insert DNA. There are also single-strand phage

cloning vectors, which have special advantages fur DNA sequencing and other experimental uses.

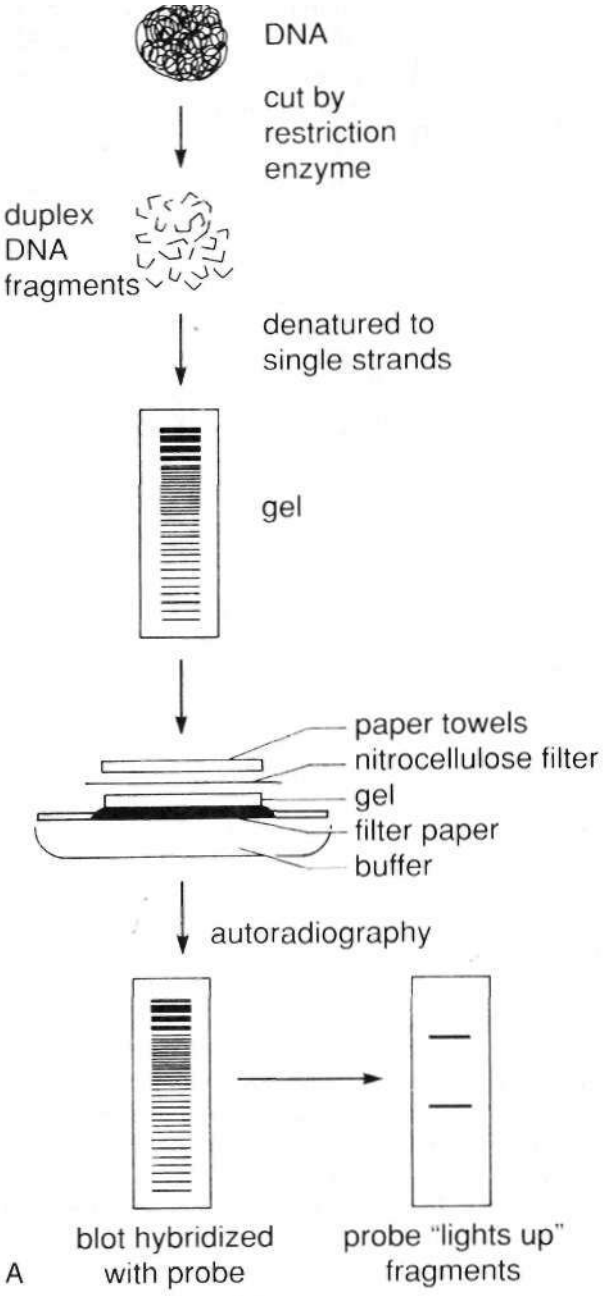
A cosmid is a construct that combines plasmid and phage features. It is composed of plasmid DNA that contains the cos site of phage lambda, which carries the sequences required to package the cloned insert DNA. Like other vectors, it also contains a replication origin and selectable markers. Cosmids have an advantage over plasmid and phage vectors because relatively long (35- to 45-kb) foreign DNA sequences can be inserted into them,

Until recently, it was not possible to clone DNA fragments of 100 kb to more than 1000 kb. With tin-advent of rare cutting-restriction endonucleases that cut at rare sites, these large ftagments can now be cloned using special yeast and bacterial vectors. The new constructs are called YACs or bacterial artificial chromosomes (BAOs).

Gene Libraries

A set of DNA fragments from a specific source that has been cloned in appropriate vectors is called a gene lihraty, indicating that it contains genetic information from its DNA source. A human gene library may be prepared from total genomic DNA or from the DNA of a single chromosome or chromosome segment. Although the experimental procedures may be complex, the principle is relatively simple. The DNA of interest and that of the vectot are cleaved by the same enzyme and allowed to reeombine. In principle, all or most of the DNA of interest will be inserted into the vector DNA. The vectors, some of which now contain the foreign DNA sequences of interest, ate inserted into bacterial hosts, allowed to multiply *in vitro* undet selective conditions, and stored for long-term availability. To access the clones that have incorporated the DNA sequences of interest, it is necessary to use a method ot selection. This process often requires the use of radioactive DNA or RNA probes that are specific for the sequence of interest and will hybtidize with them.

For many experimental purposes, *complementary DMA (cDNA) libraries* are used. Complementary DNA is prepared from mature mRNA obtained from a tissue in which the gene of interest is expressed. This is not a trivial procedure, because most tissues contain many types of mRNA transcripts, among which the specific one tran-scribed from the gene of interest may be rare. Because an mRNA transcript is a continuous RNA strand containing only the exons of the gene and lacking the introns, it is considerably shorter than the corresponding genomic DNA molecule (e.g., 14 kb of mRNA instead of about 2000 kb of DNA for the *DMD* gene). The single mRNA strand to be copied is prepared by addition of an oligo (dt) primer that hybridizes to the poly-A tract and allows reverse transcrip-tase to begin synthesis of a complementary DNA strand. The DNA strand ends in a short hairpin loop. The RNA transcript is then degraded, leaving the single DNA strand,



FICUKE 44.17 (A) The technique of Southern blotting. DNA is cut into small fragments by restriction endonucleases, separated on a gel, then transferred by blotting onto nitrocellulose membrane (see text). *Continued*

which is converted into a duplex molecule by the action of DNA polymerase 1 using the hairpin as the primer. The hairpin is degraded by the enzyme SI nuclease, leaving a duplex DNA molecule copy of the original mRNA molecule that can be inserted into an appropriate vector molecule, amplified, and stored. A LDNA library prepared from a given tissue usually contains a variety of clones representing all the different genes that are being expressed in that tissue at that developmental stage.

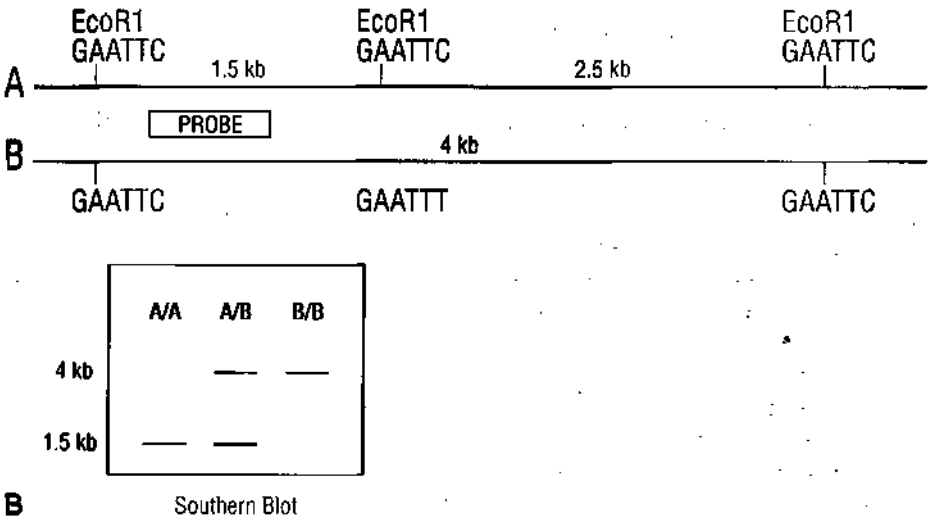


FIGURE 44.17, cont'd. (B) Restriction fragment length polymorphisms (RFLPs) can result from single nucleotide polymorphisms (SNPs) that change the recognition sequence for a restriction enzyme. The restriction enzyme EcoRl recognizes the recognition site GAATTC. Allele A has three F.coRI restriction sites in the region of the probe. When the enzyme cuts at these sites, two pieces of DNA are produced (1.5 kband 2.5 kb). Allele B has an SNP that eliminates one of the sites because GAATTC has been changed to GAA I J I. Now, with allele B the restriction enzyme only cuts in two places producing a single 4-kb length of DNA. Southern blot hybridization can be used to determine whether an individual has inherited two A alleles (A/A), two B alleles (B/B), or is heterozygous (A/B).

Chromosome Walking and Jumping

Chromosome walking is an approach used to clone relatively long stretches of the genome. The walk begins with a clone that has already been isolated. Terminal fragments of the clone are used as probes to identify adjacent overlapping clones from a genomic library. This process can be repeated to cover lengths of 100 kb or more, but the size of a single step is limited by the size of the insert of foreign DNA that can be incorporated into vectors, about 20 kb for lambda vectors and 45 kb for cosmids. The direction of the walk along the chromosome can be determined by making successive restriction maps and identifying matching regions.

Much longer distances can be covered by chromosome jumping. In this method, very long (100-200 kb) restriction fragments of genomic DNA are circularized *in vitro*, resulting in the formation of artificial junctions between sequences normally separated by long distances. These junctions are then cloned using conventional technology and radioactive probes. The clones isolated thus contain the starting sequence (the probe binding site} and a new genomic sequence 100-200 kb away. Because the sequence between the sites is not cloned by this method, one has effectively jumped from the probe site to a position 100-200 kb farther along the chromosome.

Polymerase Chain Reaction

PCR represents a powerful technique for the analysis of DNA. Basically, it is a tool for greatly amplifying tiny pieces of DNA. This includes, for example, minute samples of hair, blood, skin, sperm, or saliva. It is especially useful in the diagnosis of human genetic mutations through the analysis of small blood samples, including identification of the trinucleotide repeat expansions described previously, The theory and technology underlying PCR are beyond the scope of this chapter, PCR and its application to neurological disease are well described by Darnell (1993). PCR uses a heat-stable DNA polymerase to extend synthetic DNA primers that flank and bind to DNA sequences of interest. Samples are then heated to near 100°C to denature the DNA into single strands and cooled to reanneal newly synthesized DNA with the synthetic primers. As this cycle is repeated, newly synthesized DNA is available to anneal with primers and be extended. In this way the reaction amplifies itself (a chain reaction) with a doubling of products at each cycle. Thirty cycles can be performed in a few hours in a single tube in an automated thermal cycling machine. Thus a relatively small input yields an enormous amplification of product—ideally more than 200 copies of a single starting molecule. However, one of the problems with PCR is its great sensitivity, sometimes resulting in false results from amplification of minute amounts of contaminating DNA (Darnell 1993).

LINKAGE ANALYSIS

Genetic linkage analysis has been extensively used to map genes for human diseases to specific chromosomes. The concept is straightforward (Ott 1990), All genetic mutations occur at a single point or locus somewhere on the

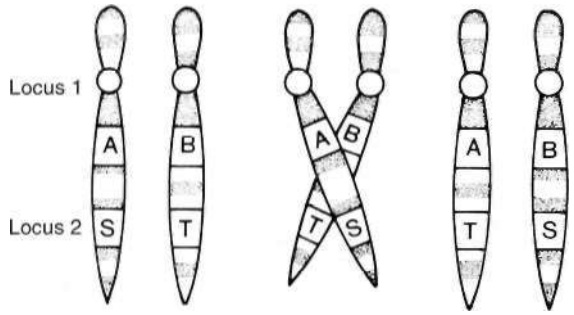


FIGURE 44.18 A crossover between the long arms of a homologous chromosome pair resulting in a recombination between the hypothetical linked genes. The gene loci at A and S arc close to each other on the saint chromosome (linked). The alleles at locus 1 are A and B. The alleles ar locus 2 are S and T. Thus this person is heterozygous at both the 1 (AB) and 2 (ST) loci. Locus 1 could represent the site of a disease gene, and locus 2 could be the site of a polymorphic DNA marker. Initially, gametes resulting from these chromosomes would be AS or BT. Following the crossover and recombination, the gametes would he AT or BS. The A allele at locus 1 would now be inherited with the S allele at locus 2.

22 human autosomes or the X chromosome. If two genes occur close to each other on the same chromosome, they are said to be linked. Note that linkage is simply a physical relationship between two loci on a chromosome and implies no pathogenetic or metabolic association between the two genes.

Crossing over of homologous chromosomes during meiosis may result in a recombination between the two loci of linked genes (Figure 44.18). The frequency with which these recombinations occut increases with increasing distance between the two genes. Therefore the frequency ol recombination events between two loci is a relative measure of the distance between them, A 1% frequency of recombination between two loci indicates 1 ccntimorgan (cM) of genetic distance between them. One centimorgan represents about 1 million DNA base pairs (1000 kb). (Note that a cM represents recombination events and is an estimate of genetic distance on a chromosome but not a true physical distance,) The total human genome contains approximately 3300 cM and at least 30,000 genes. It should be noted that recombination frequencies (crossovers) are not necessarily the same for chromosomes in males and females (generally more frequent in females for unknown reasons), not always the same for different chromosomes, and not the same for different portions of the same chromosome (recombination hot spots). The recombination frequency is expressed by the Greek letter theta (?) and has a maximum of 0.5 (one half, or 50%).

If a dominant monogenic clinical disorder is traced through a family pedigree to the inheritance of another unrelated genetic marker (such as the ABO blood group), one can determine the probability that the two genetic traits (the disorder and the marker) are linked or not linked. If all persons affected with the genetic disorder always have the same form (polymorphism) of the genetic marker and all unaffected persons have the other form of the marker, the two genetic traits are said to be segregating together. If enough individuals can be tested, the two traits can be shown to be linked or unlinked.

In order for linkage analysis of a family to be useful, the family must be informative for both the disease and the genetic marker. That is, it must be possible to distinguish between persons affected and unaffected with the disease, and there must be variability of the polymorphic states of the marker within the family. For example, the first two generations of the family in Figure 44.19 are not informative, because all the offspring in the second generation are type AB for the marker whether they have the disorder or not. However, in the third generation all the affected individuals have the AB form of the marker, and all the unaffected individuals are type AA. The pedigree contains useful genetic linkage information because there have been several informative matings in the second generation. On inspection of the pedigree, it becomes apparent that the disease seems to be segregating with the B form of the genetic marker. Linkage analysis of this family would then give us an estimate of the probability that the disorder is indeed linked to the genetic marker under study.

A statistical measure of linkage is the LOD score, which is an estimate of the probability or likelihood that two genetic traits are linked. The LOD score is the log of the odds favoring linkage versus independent assortment. A LOD score of +3.0 represents theoretical odds of 1000 to 1 (10) that two traits are linked and is generally accepted as proof of linkage, especially if the analysis has been restricted to a single family. (A LOD score of +3 actually represents a practical probability of about 95% that two genes are linked.) A true linkage relationship in a large, genetically homogeneous population of families should produce a LOD score of +4 or +5 with a highly polymorphic marker. A LOD score of —2.0 represents odds of 100 to 1 (10^2) that two traits are not linked. LOD scores falling between +3.0 and -2,0 are more or less suggestive of linkage, respectively, but not accepted as proof. LOD scores are calculated for a given recombination fraction. Two traits may be considered loosely linked with a recombination fraction of 10-20%, closely linked with a recombination fraction of about 5%, or tightly linked with a recombination fracrion of 1% or less. (These are helpful but not strict definitions.) As noted previously, the recombination fraction is related to distance along the chromosome. During linkage analysis LOD scores are computed for many possible recombination fractions. Therefore the recombination fraction with the highest positive LOD score is the best estimate of the distance between two potentially linked genes.

The usefulness of genetic linkage analysis is demonstrated in Table 44.3. The LOD scores for three different CMT families are shown for various genetic markers on chromosomes 1 and 17. Family 1520 has clearly positive LOD scores (greater than +3.0) for two markers

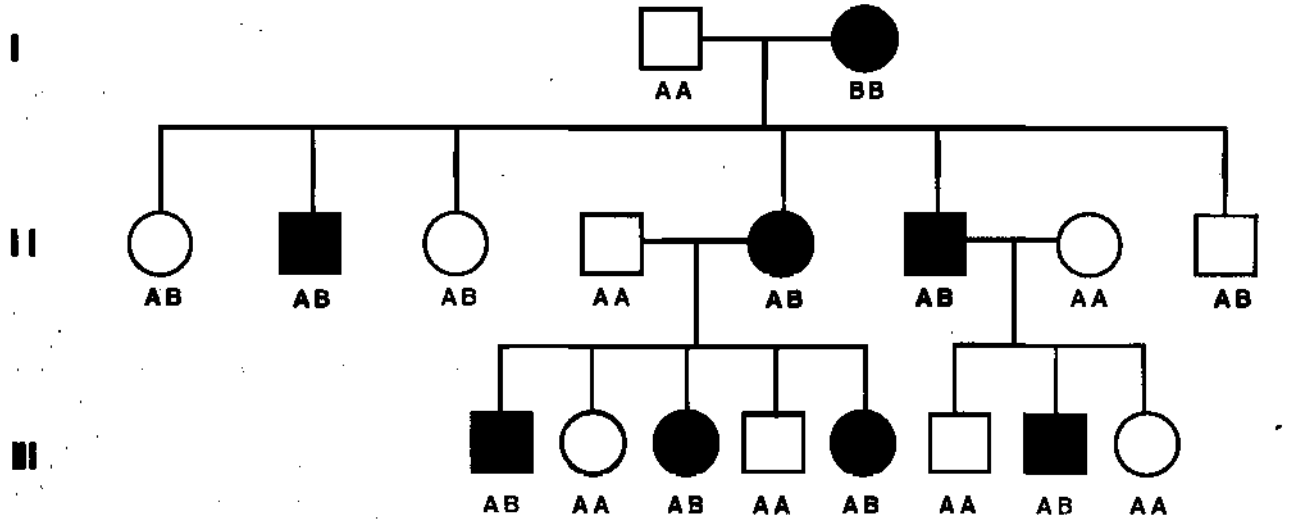


FIGURE 44.19 Autosomal dominant inheritance (uninformative mating versus informative mating.) Pedigree demonstrating the basic principle of linkage analysis. Persons affected with the disease are indicated with solid symbols. Results of genetic testing for inherited DNA markers (A and B) are indicated under each symbol. Generation 2 is uninformative, because there is no obvious association between the disease and the genetic markers. However, generation 3 makes the family analysis informative. It now can be seen that all affected individuals have inherited the B allele of the DNA marker, and none of the unaffected persons lias in lie ri red the B allele. This suggests that the disease gene resides in a chromosomal region close to the genes for the A and B genetic markers—that is, the analysis suggests linkage. If the chromosomal location of the A and B markers is known, then it is likely that the disease gene also lies on this chromosome.

on chromosome 17 and negative LOD scores for two markers on chromosome 1. The gene for hereditary neuropathy in this family must lie on the short arm of chromosome 17, and such families are designated CMT-1A. The IND family has a very significant negative LOD score with a marker on chromosome 17 (—4.10) and positive LOD scores with the chromosome 1 markers. The gene for hereditary neuropathy in the IND family must lie on the long arm of chromosome 1, and such families are designated as CMT-1B. Finally, family 1550 has significantly negative LOD scores, with all markers on both chromosomes 1 and 17. The gene for hereditary neuropathy in this family must lie elsewhere in the human genome, and such a family is tentatively designated as CMT-1C. Thus genetic linkage analysis has demonstrated genetic heterogeneity and indicated that there arc at least three distinct genetic forms of autosomal dominant GMT with separate genes on chromosomes lq, 17p, and some other location,

LOD scores from different families comparing a genetic marker and a disease may be added if one is certain that the families have the same genetic disorder (a mutation at the same locus). (The LOD scores are added because they represent logs or exponents, as noted previously.) For example, the first four families with CMT to undergo linkage analysis had a cumulative added LOD score of greater than 4-6.0 for linkage with the Duffy blood group locus on chromosome 1. This was accepted as proof of linkage of this form of autosomal dominant CMT to a marker on chromosome 1. Subsequently, numerous

Table 44.3: Comparison of linkage analysis for three Charcot-Marie-Tooth (CMT) disease families

	Family		
Marker	*#1520*	*IND*	*#1550*
A, Chromosome lq markers (LOD scores at 0.001 recombination)			
Duffy (Fy)	3.1 I	1.96	-6.67
Fey I	-8.85	5.17'	-0.97
R. Chromosome 17p markers (LOD scores at O.0S recombination)			
EW 301	3.10*	NI	-4.62
pTH 17.19	3.15*	NI	-2.3.5
8B10	NI	-4.10	NI

*l.OD score >3.0, indicating strong evidence for linkage.
NI = not informative.

families with autosomal dominant hereditary neuropathy have had negative LOD scores for the Duffy locus. This raises an important issue in genetic linkage analysis that is a common and complex problem. There are two possible explanations for these different LOD scores for families with apparently the same disease. The first is that they all do have exactly the same generic disease (mutations at the same locus). The LOD scores should all be added, and the net total score shows no linkage with Duffy. However, a second explanation is that different families with a similar clinical syndrome may represent genetic heterogeneity (mutations at different loci). Positive and negative LOD scores from the various families when added will cancel out and show no linkage, whereas linkage may be present in one or a few families and be missed during the pooling of multifamily data. Often, the issue of possible genetic heterogeneity must await the evaluation of further families and the generation of additional linkage data. Further investigation has, for example, indeed shown that a common locus for CMT resides on chromosome 17, and a less common locus for CMT is on chromosome 1.

Genetic heterogeneity can be difficult to predict from clinical or pathological information. For example, it was once thought that the so-called peripheral and central forms of neurofibromatosis might actually represent different expressions of the same genetic disease (mutation) or at least be alleles (different mutations at the same locus). However, linkage analysis has shown that the two conditions are entirely different mutations on chromosomes 17 and 22, respectively. A similar situation has occurred with hereditary polycystic kidney disease and tuberous sclerosis. That is, the same clinical syndrome (phenotype) shows genetic heterogeneity by linkage analysis. On the other hand, two forms of familial polyposis of the colon that seemed different phenotypically have proved to be mutations at the same locus. Likewise, families with early- and late-onset Huntington's disease represent mutations at the same locus on chromosome 4.

Obviously, it is safest to limit linkage analysis to single large families, eliminating the problem of genetic heterogeneity. Unfortunately, most single families are not large enough to generate statistically significant linkage data. Data from multiple families arc often pooled but must be viewed with healthy skepticism until the data are unequivocally significant or it is clearly established by other means that the families arc genetically homogeneous. For example, initial studies showing linkage of schizophrenia to chromosome 5 markers and manic depressive illness to chromosomes 11 and X have not been replicated, and the assignments remain uncertain.

Statistical tests are available that give an indication of genetic heterogeneity by comparing LOD scores from various families with similar clinical disorders. The results may range from a high probability to a very low probability of linkage.

Also, separate families with disorders produced by alleles (different mutations at the same locus) can appropriately have pooling of their linkage analysis data. For example, Becker's and Duchenne's muscular dystrophies are now known to be allelic mutations in the same gene and show the same linkage relationships to other X-chromosome markers.

It should also be obvious that correct clinical diagnosis of each and every family member is crucial in linkage analysis. Incorrecrly identified family members will produce serious errors in the analysis and can falsely bias the data toward linkage or nonlinkage. For example, with hereditary neuropathy with slow nerve conduction, clinically equivocal cases must have careful nerve conduction velocity (NCV) studies. In myotonic dystrophy, electromyography (EMG) and slit-lamp examination of the lens may be necessary in family members at risk who appear clinically unaffected by physical examination. Imprecise clinical diagnosis is partly responsible for the conflicting linkage results in studies of schizophrenia. Also, diseases with delayed onset (such as Huntington's and Alzheimer's diseases) must have age-of-onset correction factors included in the analysis.

One may also take advantage of two or more genetic markers known to reside close to each other on the same chromosome, in a statistical technique known as multipoint genetic linkage analysis. This increases the power of demonstrating linkage and may allow more refined subrcgional location of a given disorder.

If the gene controlling the expression of a marker is known to have its locus on a specific chromosome, then any genetic trait that is shown to be linked to that marker must also have its locus on the same chromosome. Thus the power of linkage analysis is the actual identification of genetic loci on specific chromosomes or even finely mapped regions of a chromosome. This can lead to advances in diagnosis and even to the discovery of the nature of mutations and the protein abnormalities underlying genetic diseases.

If there arc no previous clues to the chromosomal location of a genetic disease, then a large number of random genetic-markers covering all human chromosomes must be systematically studied to discover a linkage relationship. It is estimated that about 200 to 300 evenly spaced markers would reasonably cover the entire human genome. More than enough markers are now available. The markers must be polymorphic—that is, have several possible identifiable forms in the general population so that various combinations can be found in any given family. Theoretically, with enough genetic markers and sufficient time and effort, all monogenic disorders can be located on specific chromosomes. This task can be very tedious and time consuming. A remarkable advance has been the advent of new DNA polymorphisms that make available the hundreds and even thousands of inherited markers necessary to cover the human genome in a complete manner. The first such markers were RFLPs, which arc now complemented by a variable number of tandem repeats (VNTR) and

microsatcllitc CA repeats, which make most families informative and improve the success rate of linkage studies. The first example of an autosomal dominant linkage relationship using these new techniques was the linkage of the Huntington's disease gene in 1983 to the D4S10 (G8) RFLP marker on the distal end of the short arm of chromosome 4. The pace of chromosomal assignment of neutological diseases has subsequently greatly accelerated. There are now more than 200 disorders of the nervous system with specific chromosomal assignments (Tables 44.4 and 44.5).

POSITIONAL CLONING

Once disease genes have been given regional assignments on chromosomes by linkage analysis, the search is begun to identify the gene itself by *positional cloning* (previously [erined *reverie genetics).* I his strategy relies only on the chromosomal location of the gene. Once the gene is discovered, one can attempt to determine the protein for which it codes. This strategy is the opposite of beginning with a known protein, determining its amino acid sequence, and using that information to locate and isolate a gene. All the tools and methods described previously are brought to bear in the process of isolating a gene, including restriction endonucleases, genetic libraries, vectors including YACs, and chromosome walking and jumping. The strategy has been spectacularly successful with the identification of numerous genes for neurological disorders including Duchenne's and Becker's muscular dystrophies, myotonic dystrophy, Huntington's disease, and neurofibromatosis. Several examples of such genes and their known protein functions are shown in Table 44.6.

How is it known when a gene is found? Another way to express this question is, "How is it known if a change in a DNA sequence represents a benign polymorphism or causes a clinically significant alteration in the functions of a protein?" One method is to return to linkage analysis and demonstrate that the newly discovered change, or mutation, always segregates with the disease in the family. That is, people with the disease always have the mutation, and people without the disease never have the mutation. Obviously, penetrance and expression must be taken into consideration. Furthermore, unrelated, normal individuals in the general population never show the mutation. It is also useful to demonstrate de novo occurrence of the mutation. That is, isolated individuals with the disease carry the mutation, hut the mutation is not found in any of their siblings or either of their parents (and paternity is proved).

What follows gene identification? When a new gene is isolated, relatively little may be known about its function. The DNA and predicted amino acid sequences can be compared with those of known genes and proteins in humans and other species. Also, the amino acid sequence can be analyzed for the presence of predicted secondary-structures and specific functional motifs, such as known membrane-spanning regions. Antibodies can be raised to the gene product; then the distribution, cellular, and subcellular location of the protein can be determined.

To study the effect of overexpression or underexpression of a gene, the foreign gene can be introduced into a mouse germ-cell line to produce transgenic animals. Eggs are removed from a female mouse and fertilized with sperm in a test tube, and a recombinant plasmid carrying a new gene is microinjected into the zygote. The new gene can be placed under the control of a promotor, and high expression levels can be reached. One can then study overexpression of that particular gene in the resulting transgenic animals. Attempts have been made, for example, to overexpress the amyloid precursor protein gene in transgenic mice as a model of Alzheimer's disease.

Knockout mutants can also be created. Embryonic stem cells are used, and a portion of the mouse gene is exchanged for an altered DNA sequence—for example, one containing a pre mature-stop codon. This technology can produce heterozygotes (having one mutant and one normal allele) or homozygotes (having no functional gene product at that locus, so-called null mutants). Homozygous knockout mice may also provide an important source of cell lines that lack the gene product. Knockout mice for the P0 myelin gene have been produced, for example, to aid in understanding hereditary neuropathies.

The two major long-term goals of neurogenetic research are (1) to further our understanding of the biological and physiological functions of the human organism and (2) to create new diagnostic, therapeutic, and preventative measures for human genetic diseases.

GENETIC COUNSELING

Genetic counseling is a perfect example of the mixture of art and science inherent in the practice of medicine. It requires the communication of complex data to patients by physicians in an objective and nonjudgmental but diplomatic and compassionate fashion. The first step in genetic counseling is to establish an accurate diagnosis. This is obviously critical and must be done as carefully as possible. As in all of medicine, the accurate diagnosis of genetic diseases depends on history, physical examination, and laboratory tests. In addition, obtaining a full family pedigree is important. Information about medical disorders in other family members will provide important clues to the diagnosis in the ptoband. Also, inspection of the family pedigree will often indicate the correct inheritance pattern, be it dominant, recessive, X-linked, or mitochondrial (see Figures 44.2, 44.3, 44.4, and 44.7).

Following accurate diagnosis, the next major step in genetic counseling is educating the patient. This includes an estimate of risk to the proband and other family members

Table 44.4: Chromosomal assignments of selected autosomal neurological disorders

Disorder	*Chromosome*	*Inheritance pattern*
Zellweger syndrome type II (cerebro-hcpato-renal)	lp22-qter	AR
Dihydrolipoyl transacylase/maple syrup urine disease	lp31	AR
Schwartz-Jampel syndrome (myotonia/short stature)	Ip34-p36.1	AR
Alpha-1-fucosidasc T/fucosidosis	lp34	AR
Uroporphyrinogen decarboxylase/porphyria cutanea tarda	Ip.M	AD
Charcot-Marie-Tooth (CMT-2) 2A	lp35-36	AD
Infantile ceroid lipofuscinosis	\pM	AR
Paroxysma1 choreoarhetosis/spasticity	IP	AD
Carnitine palmitoyltransferase deficiency	lp32-12	AR
MiKi.li- phi>sphof|-uctokmasir/glyLogenosis type Vll	lcen-q32	AR
Charcot-Marie-Tooth (CMT-1B)	lq22-23	AD
Glucocerebrosidase/Gaucher's disease	Iq2l	AR
Nemaline myopathy (*a* tropomyosin)	lq21-23	Al)
Alzheimer's, familial early onset (presenilin 2)	lq31-42	AD
11\ pokalemic periodic paralysis (calcium channel)	lq.il	AD
Rippling muscle disease	Iq41	AD
Usher syndrome type 2 (deafness/ret in o pa thy)	iq	AR
Retinitis pigmentosa	iq	AR
Myoshimyopathy	2pl2-14	AR
Limb girdle muscular dystrophy (LGMD 2B)	2pl3 If,	AR
Congenital myasthenic syndromes/" slow-channel'" syndrome (SCS)	2q	AR
Familial spastic paraplegia (1)	2p21-24	Alt
Holoproscnccphaly type *1*	2p21	AD
Xeroderma pigmentosum	2q21	AR
Nemaline myopathy (nehulin)	2q21.2-q22	AR
Cerebrotcndinous xanthomatosis (sterol 27 hydroxylase)	2q33-qter	AR
Paroxysmal dystonic choreoathetosis	2q34	AD
Amyotrophic lateral sclerosis (recessive)	2q33-35	AR
SCA 15	3p	AD
Dominant ataxia with retinal dystrophy (ADCA type II; SCA7)	3pl2-p2l.l	AD
Xeroderma pigmentosa	3p25	AR
Limb girdle muscular dystrophy (LGMDIC)	3p25	AD
Rcra-galactosidasc]/GM| gangliosidosis	3pter-3p21	AR
von Hippel-Lindau disease	3p26-25	AD
Retinitis pigmentosa (rhodopsin)	3q	AD
Retinitis pigmentosa (ROM)	3q	AR
Usher syndrome type 3 (deafness/retinoparhy)	3q	AD
Essential tremor	?ql3	AD
Myotonic dystrophy 2 (DM2)	3q21	\D
Blcpharophimosis/ovarian failure	3q22-23	AD
Retinitis pigmentosa (PDE)	4pl6.3	AR
Huntington's disease	4pl6.3	AD
Hurler and Hurler-Scheie syndrome	4pl6.3	AR
Muscular dystrophy (limb-girdle, LGMD2K; *fl* sarcoglycan)	4ql2	AR
Mucolipidosis types II and III	4q21-q23	AR
Abetalipoprotcinemia (Rassen-Kornzweig)	4q24	AR
FSH muscular dystrophy	4q35-ter	AD
Dihydrofolatereductasc/dcficiency	.Sqll.2-ql3.2	AD
Infantile/juvenile spinal muscular atrophy	5q 11.2-13.3	AR
i levosiiiiiinidase !'. Sandhoffs disease	5ql3	AR
Dominant limb girdle muscular dystrophy Type 1A	5q22-34	AD
SCA 12	5u3 1	AD
CMT4C	5q23-33	AR
Muscular dystrophy (Limb-girdle, LGMD2F; *f*> sarcoglycan)	5q33-q34	AR
Hfyperekplexia (startle disease; glycine receptor)	5q	AD
Branch chain kctoacid dehydrogenase F.i/maplc syrup urine disease	6p22-p21	AR
SCA 1 (spinocerebellar ataxia)	6p24	AD
Juvenile myoclonic epilepsy	6p24	AD

Continued

Tabic 44.4: Chromosomal assignments of selected autosomal neurological disorders—cont'd

Disorder	*Chromosome*	*Inheritance pan em*
Retinitis pigmentosa (periphenn)	6p2 1	AD
Congenital muscular dystrophy (mcrosin/laminin deficient)	6q2	AR
Lafora body myoclonic epilepsy	6q24	AR
SCA 17	6q27	AD
Myopathy due to phosphoglyccrare mutasc deficiency	7pl3-pl2.3	AR
Argininosuccinatc lyase/argininosuccinicaciduria	7ptet-q22	AR
Retinitis pigmentosa	7pl5.1-pl3	AD
Retinitis pigmentosa type 10	7q	AD
Cavernous malformations of the brain	?q •	AD
Zellweger's syndrome type 1 (cerebro-hepato-renal)	7q 11.23	AR
Myotonia congenital	7q35	AD
Holoprosencephaly type 3	7p36	AR
Familial spastic paraplegia (recessive)	8q	AR
Progressive epilepsy with mental retardation	8p	AR
Retinitis pigmentosa typi .:	8pll-q21	AD
Hereditary motor and sensory neuropathy-Lorn (with deafness)	8q24	AR
Ataxia, vitamin H deficiency; alpha tocopherol transport protein defect	.So 1 5	AR
Benign neonatal seizures (EBN2; K^1 channel)	8q	AD
Charcot-Marie-Tooth (CMT-4A)	8ql3-21	AR
SCA 16	8q22-24	AD
Hereditary inclusion body myopathy, recessive	9q1	AR
Ga lactose-1-phosphate uridylrransferase/galacroscmia	9ql3	AR
Friedreich's ataxia	9ql3-21.l	AR
Hereditary sensory neuropath)' type 1	9q22.1-q22.3	AD
Walker-Warburg syndrome (WWS)	9q3l-33	AR
Fukuynma congenital dystrophy	9q31-33	AR
Familial dysautonomia	9q31-33	AR
Sequin/amylin neuropathy, Finnish type (gelsolin)	9q33	AD
Torsion dystonia (some families)	9q34	AD
Ataxia oculomotor apraxia	9q34	AR
Coproporphyrinoxidase/coproporhyria	9	AD
Xeroderma pigmentosa	9q34	AR
Tuberous sclerosis (TSC1)	9q34.1-34.2	AD
Usher Syndrome ID (deafness/retinopathy)	lOq	AR
Epilepsy, simple partial with auditory features	I0q22	AD
Ataxia, infantile onset	10q23-24	AR
G1 yco p rote i n n eu ra m i n i da se/si a 1 i dos is	10	AR
SCA 5 (spinocerebellar ataxia)	11	AD
Usher syndrome type [C (deafness/retinopathy)	Up	AR
Niemann-Pick types A and B (sphingomyelinase)	Up15	AR
Usher syndrome type IB (deafness/retinopathy; myosin VII A)	Ilql3.5	AR
Retinitis pigmentosa (ROM)	1 lql 3	AD
Tuberous sclerosis (some families)	1 lq 14-23	AD
Usher syndrome ID (deafness/retinopathy)	lOq	AR
CY1T4B	llq23	AR
Ataxia telangiectasia	Uq23	AR
Acute intermittent porphyria	1 lq23.2	AD
Apolipoprotein Al/amyloid neuropathy, Iowa type	11q23-q24	AD
McArdlc's disease (myophosphorylase)	llql3	AR
Dentato-rubro-pallido-luysian atrophy; (DRPLA)	I2p 12-ter	AD
F.pisodic ataxia/myokymia (K ' channel)	I2pl3	AD
Congenital fibrosis of the extraocular muscles	12cen	AD
Lipofuscinosis, late infantile	12q21-32	AR
Phenylalanine hydroxylase/phenylketonuria	12q22-q24.2	AD
SCA 2 (spinocerebellar ataxia)	I2q23-24.1	AD
Distal hereditary motot neuropathy type 11	12q24	AD
British dementia	13	AD
SCA8	I3q	'A D

Continued

Table 44.4: Chromosomal assignments of selected autosomal neurological disorders—cont'd

Disorder	*Chromosome*	*Inheritance pattern*
Spastic ataxia (ARSACS)	13qll	AR
Muscular dystrophy LGMD 2C	13ql2	AR
Wilson's disease	13ql4.2	AR
Retinoblastoma	13ql4.2	AD
Spastic paraplegia (SPG 3A, atlastin)	14q	AD
Distal myopathy	14qll	AD
himilial Alzheimer's (early onset; presenilin 1)	14q24.3	AD
Krabbe's leukodystrophy	14q24.3-32	AR
SCA 3 (Machado-Joseph disease)	14q24.3-32	AD
Usher syndrome type 1A (deafness/retinopathy)	14q32	AR
Familial spastic paraplegia (2)	14q	AD
Dopa-responsive dystonia	14q	AD
Protoporphyrin oxidase/variegate porphyria	14q	AD
Oculopharyngeal muscular dystrophy	14qll.2-ql3	AD
Angelman's and Prader-Willi syndromes	15q 11-12	Sporadic
SCA 1 1	15q 14-21	AD
Recessive limb girdle muscular dystrophy type 2A	15ql5-?22	AR
Hexosaminidase A/ray-Sachs disease	15q23-24	AR
Peripheral neuropathy and agenesis of the corpus callosum	15q	AR
Familial spastic paraplegia (3)	I5q	AD
Infantile convulsions/paroxysmal chorcoathetosis	16p	AD
Tuberous sclerosis (TSC2)	16pl3.3	AD
Juvenile lipofuscinosis {Batten's disease)	16pl2	AR
Bardct-Bicdl (mental retardation, retinitis pigmentosa, Polydactyly)	I6q	AR
SCA 4 (spinocerebellar ataxia)	16q24	AD
Spastic paraplegia (SPG7, paraplcgin)	16q24	AR
Giant axonal neuropathy	16q24	AR
Charcot-Marie-Tooth (CMT-1A; duplication)	17pll.2	AD
Neuropathy, recurrent, with pressure palsies (HNI'P; deletion)	17p-ll.2	AD
Retinitis pigmentosa	I7pI3.3	AD
Congenital myasthenic slow channel syndrome	I7p	AR
Canavan leukodystrophy	17pl3	AR
Miller-Dicker syndrome, lissencephaly	17p-13.3	Sporadic
Limb-girdle muscular dystrophy (LGMD2D; *a* sarcoglycan)	17ql2-q21.33	AR
Frontotemporal dementia/parkinsonism (FTDP-17)	I7q21-q22	AD
(Pompe disease) acid alpha-glucosidase/acid maltase deficiency	17q23	AR
Sjogren-Larsson syndrome (ichthyosis, spasticity, MR)	l-i	AR
Neurofibromatosis NF1	17qll,2	AD
Muscle sodium channel disorders (hyperkalemic periodic paralysis, atypical myotonia congenita, paramyotonia congenita)	17q22-24	AD
Niemann-Pick type C	I8p	AR
Familial amyloid neuropathy (transthyretin)	I8qll.2-I2.1	AD
Episodic ataxia with nystagmus	19pl3	AD
Hereditary hcmiplcgic migraine	19pl3	AD
Spinocerebellar ataxia (SCA6)	19pl3	AD
Mannosidosis	19p	AR
Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADS1L)	I9ql2	AD
SCA 13 and SCA 14	9ql3	AD
Malignant hyperthermia (ryanodine receptor)	I9ql3.1	AD
Central core myopathy (ryanodine)	19ql3.1	AD
Myotonic muscular dystrophy	19ql3.2	AD
Epilepsy with febrile seizures plus	19ql3	AD
Familial Alzheimer's (late onset; APOF.4 related)	19q	AD
Retinitis pigmentosa	I9q	AD
Cystatin C/Icelandic amyloid angiopathy	20pl 1.22-11.21	AD
PKAN (Hallervorden-Spatz)	20pl3	AR
Familial prion dementias (Creutzfeldt-Jakob, Gerstmann-Straussler diseases)	20ptcr-pl2	AD

(*'.unturned*

Table 44.4: Chromosomal assignments of selected autosomal neurological disorders—cont'd

Disorder	*Chromosome*	*inheritance pattern*
Familial benign neonatal convulsions (EBN1; K^+ channel)	20q, 13	AD
Epilepsy, nocturnal frontal lobe	20ql3.2-ql3.3	AD
Familial Alzheimer's (APP gene, early onset)	21qll-22	AD
Familial amyotrophic lateral sclerosis (some families)	21q22.1-22.2	AD
Bethlem myopathy (Collagen type VI)	21q22.3	AD
Cystathionine bcta-synthasc/homocystinuria	21q22.3	AR
Dutch hereditary cerebral hemorrhage; APP gene (codon 693)	21q21.2	AD
Myoclonic epilepsy (Unverricht-Lundborg)	21q22.3	AR
SCA 10	22qI3	AD
Neuroaxonal dystrophy	22q 13-qter	AD
Cytochrome P450 HD/debrisoquine sensitivity	22ql3.1-ql3.2	AD
Metachromatic leukodystrophy (arylsulfatasc A)	22q13.3-qter	AR
Bilateral acoustic neurofibromatosis (NF2)	22qll-13.1	AD

AD = autosomal dominant; AR = autosoma! recessive; MR = mental retardation; SCA = spinocerebellar ataxia.

for inheriting the pertinent gene. Risks always need to be put into context and perspective. For example, with each pregnancy all normal couples take a *2-A%* risk of having a child with birth defects. It is often unpredictable how any given person will react to a risk probability for inheriting a disease. Some people will find a 50% risk of no great concern, whereas others may find a 1% risk to be very disturbing. Obviously, the perceived severity or burden of the disease is of major importance. Physicians, patients, and other family members may not agree as to what constitutes a "severe" disease. In addition to risk estimates, the counselor must give a description of expected symptoms and signs, natural history of the disease, variability of expression, and long-term prognosis. Potential treatment options must also be discussed. Physicians are accustomed to considerable variability in symptoms and prognosis of various diseases, but these ambiguities can be difficult concepts for many patients.

The presymptomatic diagnosis of neurogenetic disorders is becoming more common. Huntington's disease has been a model in this regard. By DNA testing for the trinucleotide repeat expansion on chromosome 4, carriers of the HD

Table 44.S: Regional assignments of selected X-linked neurological disorders

Kallman anosmia-hypogonadism	Xp22.3	Pelizaeus-Merzbacher disease	**Xq22**
Aicardi's syndrome (MR, seizures, agenesis corpus callosum)	Xp22	Coffin-Lowry (MR, seizures, dysmorphic)	**Xq22**
CMTX2	Xp22.2	l.isseriu-phaly subcortical hand hererorypia	**Xq22.3**
Mental retardation, nonspecific (1)	Xp22	Lowe's oculocercbral renal syndrome	Xq25-q26.1
1 Hichcnne's/Becker's muscular dystrophy (dystrophin)	Xp21.2	CMTX3	Xq26
Retinitis pigementosa type 3	Xp21.1-pll.4	Lesch-Nyhan HGPRT deficiency	*Xq26*
Ornithine transcarbamylasc deficiency	Xp21.1	Iduronate 2-sulfatase/Hunter's syndrome	Xq27.3-q28
Retinitis pigmentosa type 2	Xpl 1.4-11.2	Fragile X/mental retardation	Xq27.3
Norrie's disease (retinal malformation, deafness, MR)	Xpll.4-11.3	Deutan and protan colot blindness	Xq28
Menkes' kinky hair	Xpll-qll	Adrenoleukodystropby	Xq28
Charcot-Marie-Tooth (CMTX; connexin 32)	Xql3-q21	X-linked spastic paraplegia (2)	Xq28
Ataxia/sideroblastic anemia	Xql3	Fmery-Dteifuss muscular dysttopby	Xq28
Mental retardation, nonspecific (2)	Xqll-ql2	X-linked myotubular central nuclear myopathy	Xq28
X-linked spastic paraplegia (1)	Xq13-22	X-linked hydrocephalus (aqueductal stenosis)	Xq28
Lubag dystonia parkinsonism	Xq21	Bilateral periventricular nodular heterotypia	X28
Choroidcremia	Xq21.2	Rett's syndrome	Xq28
Spinal-bulbar muscular atrophy (Kennedy's disease)	Xq2l.3-ql2		
Fabry's disease (tnhexoside storage)	Xq22		

MR = mental retardation.

Table 44,6: Neurological disease genes classified by function

Gene class	*Disease*	*Protein*	*Chromosome*
Structural gents	Duchenne's muscular dystrophy (DMD)	Dystrophin	Xp21.2
	Becker's muscular dystrophy	Dystrophin	Xp21.2
	Paramyotonia congenita	Sodium channel	17q23.1-25.3
	Hypcrkalemic periodic paralysis	Sodium channel	17q23.1-25.3
	1 lypokaleinic periodic paralysis	Calcium channel	lq31
	Myotonia congenita	Chloride channel	7q35
	Episodic ataxia/myokymia	Potassium channel	12pl3
	Epilepsy, benign neonatal (2 rypes]	Porassium channels	8q;20q
	Charcot-Marie-Tooth disease (CMT-1A)	PMP-22	17p11.2
	Hereditary neuropathy with liahiliry to pressure palsies (HNPP)	PMP-22	17pll.2
	CMT-1B	P0 myelin	tq21,2-23
	X-linkcd CMT	Cunnexin32	Xq13
	Alzheimer's disease	Amyloid precursor protein (APP)	21q21.3-22.05
	Retinitis pigmentosa	Rhodopsin	3q
	Startle disease (hyperekplexia)	Glycine receptor	5q
Tumor suppressor genes	Neurofibromatosis 2 (NF2)	Merlin	22ql 1.21-13.1
	Neurofibromatosis 1 (NF1)	Neurofibromin	17qll,2
	Retinoblastoma	*Kb*	13ql4.1-14.2
	von Hippcl-Lindau disease	Unknown	3p25
	Tuberous sclerosis TSC1	Hammertin	9q34
	I uberous sclerosis TSt *1*	Tuberin	16pl3.3
Transport protein genes	X-linked adrenoleukodystrophy	ALDP	Xq28
	Menkes' syndrome	Copper transport protein	Xql3.3
	Wilson's disease	Copper transport protein	13ql4.3
Trinucleotide expansion genes	Eragilc-X mental retardation	IMRI	Xq27,3
	Huntington's disease [HD}	Huntingtin	4q!6.3
	Myotonic dystrophy	Myosin kinase	19ql3.3
	Spinocerebellar ataxia {SCA 1)	Ataxin	6p23-24
	Spinocerebellar ataxia (SCA 2)	Unknown	12q23
	Macha do-Joseph disease (SCA 3)	Unknown	14q
	Spinocerebellar ataxia (SCA *6}*	Unknown	19pl3
	Spinocerebellar ataxia (SCA 7)	Unknown	3pl2
	Kennedy'sspina1-bu1bar muscular atrophy	Androgen receptor	Xq21.3-22
	Dentato-rubra1-pa11ido-luysian atrophy	Unknown	12
Cell protection genes	Familial amyotrophic lateral sclerosis (AI.S)	Superoxide disinutase (SODI)	21q22.1-22.2
Signaling molecules	CMT-1B	I'O myelin protein	lq21.2-23
	Miller-Dieker syndrome	G-proteins	17pl3.3
	Retinitis pigmentosa	Rhodopsin	3q
Mitochondrial genes	Leigh's disease	OXPHOS pathway	-
	MERRF	OXPHOS pathway	-
	MELAS	OXPHOS pathway	-
	Leber's optic atrophy	OXPHOS parhway	-
	Kcarns-Sayrc disease	OXPHOS pathway	-
Prion proteins	Crcutzfekk-Jakob disease	Prion protein (PrP}	20prer-pl2
	Ccrstmann-Straussler-Sheinker syndrome	PrP	2()prer-pl2
	Familial fatal insomnia	PrP	20prcr-pl2
Cell cycle genes	Retinoblastoma	Rb	13q 14.1-14.2
	von 1 lippcl 1 ind.ni JisiMsi'	Unknown	3p25
Nuclear regulatory factors	Myotonic dystrophy 2 (DM2]	ZNF9	3q21
	Rett's syndrome	MeCP2	Xq28
Potential diffuse RMA toxic effect	Myotonic dystrophy 1	DMPK	I9ql3
	Myotonic dystrophy 2 (DM2)	7.NF9	3q21

Source: Adapted, updated, and reprinted with permission from Greenstein P & Bird T.D. 1994, "Neurogenetics: triumphs and challenges," *West) Med,* vol. 161, pp. 242-245.

MELAS — mitochondrial, encephalopathy, lactic acidosis, and strokelike episodes; MERRF myoclonic epilepsy, ragged red fibers.

gene can now be fairly reliably detected, as described previously (the exception being the equivocal range of 33 to 35 repeats). This means we have the ability to discover who has inherited the gene for a severe, progressive, incurable, fatal degenerative brain disease. At the same time, we are unable to predict age of onset or severity of the disease with much accuracy. These issues raise serious problems for both the physician and the patient, including the patient's motivation for having the test, the patient's emotional reaction to the result, and potential long-term implications for employment and insurance. Detailed discussions of these medical and ethical issues are available (Bird 1999; Guidelines 1994; Hersch et al. 1994).

Finally, genetic counseling should include opportunities fot follow-up and long-term contact with the patient. The patient must be given an opportunity to ask questions. Additional testing of the patient and other family members may be necessary. Detailed genetic counseling often involves a long-term process involving months or years, and it becomes a basic thread in the fabric of good medical care.

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Chapter 45
Neuroimmunology

Tanuja Chitnis and Samia J. Khoury

The past decade has provided a rich interaction between the fields of neurology and immunology. This has given rise to new therapies for multiple sclerosis (MS) and has improved existing treatments of many other neuroimmunological diseases. A solid grasp of immunology is required to use the emerging therapies in the field of neuroimmunology. Here we provide a brief overview **of the major** components of the immune system and highlight important advances in the field of neuroimmunology.

The immune system function is to protect the organism against infectious agents and prevent reinfection by maintaining immunologic memory, to perform tumor surveillance, and to help healing and prevent damage from dying cells.

The immune system normally does not react to **self-**antigens, a state known as tolerance, except in the setting of autoimmune disease. Conversely, an active immune system is important in tumor surveillance. A critical factor in tumor survival is its ability to mask itself from immune surveillance. The normal functions of the immune system and the disorders resulting from its dysfunction arc listed in Table 45.1.

ADAPTIVE AND **INNATE IMMUNITY**

The immune system has two functional divisions: the innate immune system and the adaptive immune system. The innate immune system acts nonspecifically as the body's first line of defense against pathogens. However, this type of response, if perpetuated, would result in unwanted nonspecific damage to the host. Therefore a secondary, antigen-specific response develops and leads the attack. This is mediated by T cells and B cells, which are equipped with antigen specific receptors. The effector cells release mediators and trigger other components of the immune system to eliminate the target. Subpopulations of T and B cells develop and maintain immunological memory, which facilitates a more rapid response in the case of recurrenr infection.

The innate immune system consists of the following components:

1. Skin—The exterior surface of the body, primarily the skin, is the body's primary defense against foreign pathogens. In addition many inflammatory cells and antigen-presenting cells (APCs) line the epidermis **and** serve as the first line of defense.
2. Phagocytes—Phagocytes are cells capable of phagocytosing foreign pathogens. They include polymorphonuclear cells, monocytes, and macrophages. These cells are present in the blood, as well as in organs. They recognize cell surface receptors on a variety of microorganisms that allow them to attach nonspecifically and phagocytose pathogens, which are then killed via intracellular lysosomes.

Tabic 45.1: Normal functions and disorders of the immune system

Normal functions

Immunity against microorganisms and pathogens
Wound healing
Tumor surveillance
Disorders resulting from immune system dysfunction
Autoimmunity
Immune-mediated disorders
Bystander damage
Graft rejection

3. Natural killer (NK) cells—NK cells recognize cell surface molecules on virally infected or tumor cells. They subsequently bind to the infected cells and kill them via cell-media ted cytotoxicity.
4. Acute-phase proteins—C-reactive protein is a model acute-phase protein whose concentration increases in response to infection. C-re active protein binds to cell surface molecules on a variery of bacteria and fungi and acts as an opsonin, essentially increasing recognition of pathogens by phagocytic cells.
5. Complement system—The complement system is a cascade of scrum proteins whose overall function is to enhance and mediate inflammation. The complement system has the intrinsic ability to lyse the cell membranes of many cells including bacteria. It functions in concert with components of both the innate and adaptive immune systems and can also act as an opsonin, facilitating phagocytosis. The complement cascade can be directly activated by certain microorganisms through the alternative pathway, or it can be activated by particular antibody subtypes through the classical parhway.

The adaptive immune response consists of the following components:

1. Antibodies—Antibodies, otherwise known as immunoglobulins (Igs) are able to specifically recognize a variety of free antigens. Igs are produced by B cells and arc present on their cell surface. In addition, Igs arc secrered in large amounts in the serum. Antibodies recognize specific microbial and other antigens through their antigen-binding sires and bind phagocytes via their Fc receptors, thereby facilitating antigen removal. Some subclasses of Ig are capable of activating complement via their Fc portion, thereby lysing their targets.
2. B cells—The primary function of B cells is to produce antibody. Antigen binding to B cells stimulates proliferation and maturation of that particular B cell, with subsequent enhancement of antigen-specific antibody production. Most B cells express class II major histocompatibility complex (MHC) antigens and have the ability to function as APCs.

i. T cells—T cells or thymus-derived cells have the ability to recognize specific antigens via their T-cell receptors (TCRs). T cells may be classified into two main groups, T-helper (Th) cells expressing CD4 antigen on their cell surface and T cytotoxic (Tc) cells expressing CDS on rheir surface. CD4 T cells recognize antigen presented in association with MHC class II on the surface of APCs. CD4 T cells provide help to promote B-cell maturation and antibody production and produce factors called cytokines to enhance the innate or nonspecific immune response. CDS T cells recognize antigen in association with MHC class I antigen on the surface of most cells and play an important role in the elimination of virus-infected cells. Cytotoxic T cells are capable of damaging rarger cells via the release of degrading enzymes and cytokines. Responses in which the T cell plays a major role are termed cell-mediated immunity (CMI), T celi-macrophage interactions often lead to delayed reactions, termed delayed-type hypersensirivity (DTH).

4. Antigen-presenting cells (APCs)—APCs are required to present antigen to T cells. They are found primarily in the skin, lymph nodes, spleen, and thymus. Unlike B cells that can recognize free antigen, T cells are only capable of recognizing antigen in the context of self MHC molecules. APCs process antigen intracellularly and present antigen peptide in the groove of their MHC class II molecules. The primary APCs are macrophages, monocytes, dendritic cells, and Langerhans' cells.

PRINCIPAL COMPONENTS OF THE IMMUNE SYSTEM

Cells of the immune system arise from the pluripotent stem cells in the bone marrow and diverge into the lymphoid or myeloid lineages. The myeloid lineage primarily contains cells with phagocytic functions such as neutrophils, basophils, eosinophils, and macrophages. The lymphoid lineage consists of T cells, B cells, and NK cells.

Monocytes and Macrophages

Bone marrow-derived myeloid progenitor cells give rise to monocytes (mononuclear phagocytes of the reticuloendothelial system) that serve important immune functions. They constitute about 4% of the peripheral blood leukocytes and are morphologically identified by an abundant cytoplasm and a kidney-shaped nucleus. Their cyroplasm conrains many enzymes, which are important for killing microorganisms and processing antigens. Monocytes

differentiate into tissue-specific macrophages, including Kupffer cells of the liver, and brain microglia.

Natural Killer Cells

NK cells make up about 2.5% of peripheral blood lymphocytes and are synonymous with large granular lymphocytes because of their large intracytoplasmic azurophilic granules and high cytoplasm-to-nucleus ratio. Unlike cytotoxic CD8+ T cells, NK cells lack immunological memory and have the ability to kill a wide variety of tumor and virus-infected cells without MHC restriction (see the discussion of the function of MHC genes) or activation. NK cells lack the cell surface markers present on B cells and T cells. The biological function of the NK cell is uncertain. In view of its *in vitro* function of lysing tumor cells, it may play a role in tumor immunity (Trichincri 1989). NK1+ T cells are a subset of cells sharing characteristics of both NK cells and T cells. They express the «/f> TCR and the NK1.l receptor. These cells are significant because of their ability to secrete large amounts of interleukin-4 (IL-4) in response to TCR stimulation and may play a role in maturation of Th2 cells (see later).

T Lymphocytes

T cells originate from the thymus. Differentiation of T cells occurs in the thymus, and every T cell that leaves the thymus is conferred with a unique specificity for recognizing antigens. T cells that recognize self-antigens are generally either deleted or rendered tolerant within the thymus, a process called central tolerance.

T cells may be divided into two groups on the basis of expression of either the CD4+ or CD8+ marker, Functionally, CD4+ T cells are involved in DTH responses and also provide help for B-cell differentiation (and hence are termed helper T cells). In contrast, CD8+ T cells are involved in class I restricted lysis of antigen-specific targets (and hence are termed cytotoxic T cells). T cells with suppressor activity can express either CD4 or CD8.

T-Cell Receptors

The TCR consists of two glycosylated polypeptide chains, alpha (a) and beta (/3), of 45,000 and 40,000 dalton molecular weight, respectively. This heterodimer of an alpha and beta chain is linked by disulfide bonds. Amino acid sequences show that each chain consists of variable (V), joining (J), and constant (C) regions closely resembling Igs (Figure 45.1). There are about 10^2 TCR-variable genes, grouped by homology into a small number of families, compared with 10^3 or greater for Igs (see later). The principles governing generation of diversity in the TCR are very similar to those for Ig genes. T cells can only recognize short peptides that are associated with MHC molecules. In contrast, the Ig receptor can recognize peptides, whole proteins, nucleic acids, lipids, and small chemicals.

T cells also express a variety of nonpolymorphic antigens on their surfaces. The most abundantly expressed is CD45, comprising 10% of lymphocyte membrane proteins. CD45 exists as a number of isoforms that differ in the molecular weight of their extracellular domains as a result of RNA splicing. These isoforms can be distinguished serologically. The low molecular weight (CD45RO) isoforms define activated, or memory, T-cell populations.

B Lymphocytes

B cells are the precursors of antibody-secreting cells. The cells develop in the bone marrow and during their ontogeny acquire Ig receptors that commit them to recognizing specific antigens for the rest of their lives. B cells normally express IgM on their cell surfaces but switch to other isotypes as a consequence of T cell help, while maintaining antigen specificity (see later). Following antigenic challenge, T lymphocytes assist (help) B cells directly (cognate interaction) or indirectly by secreting helper factors (noncognate interaction), to differentiate and form mature anti body-sec ret ing plasma cells.

Immunoglobulins

Igs are glycoproteins that are the secretory product of plasma cells. Their biochemical structure and genomic organization is shown in Figure 45.1. All Ig molecules share a number of common features. Each molecule consists of two identical polypeptide light chains (kappa or lambda) linked to two identical heavy chains. The light and heavy chains arc stabilized by intrachain and interchain disulfide bonds. According to the biochemical nature of the heavy chain, Igs are divided into five main classes: IgM, IgD, IgG, IgA, and IgE. These may be further divided into subclasses depending on differences in the heavy chain.

Each heavy and light chain consists of variable and constant regions. The amino terminus is characterized by sequence variability in both the light and the heavy chain, and each variable heavy- and light-chain unit acts as the antigen-binding site (the Fab portion). The carboxy terminal of the heavy chain (also known as the Fc portion) is involved in binding to host tissue and in fixing complement. This part of the molecule is important for antibody-dependent, cell-mediated cytotoxicity by cells of the reticuloendothelial system and for complement-mediated cell lysis. Classes of Igs differ in their ability to fix complement. In humans, IgM, IgG1, and IgG3 antibodies are capable of activating the complement cascade.

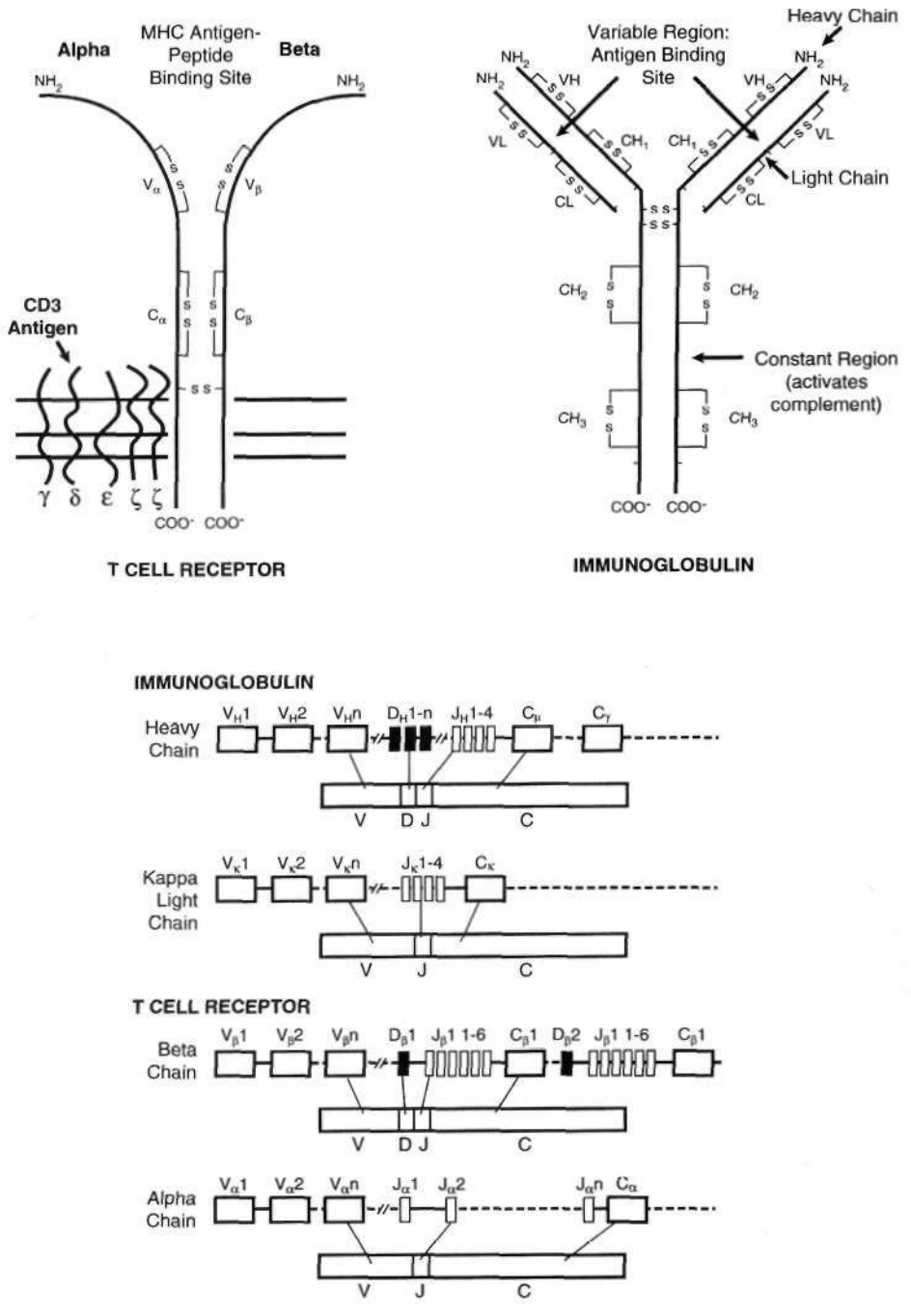

FIGURE 45.1 Molecular and **gl'llCtic** <)[•!•;)IIi/Htioil **()t tilt' Tl_v[l** receptor (TCR) and immunoglobulin (Ig) molecule. (A, B) Structural organization of the TCR and lg molecule. The TCR is a heterodimer consisting of two chains, a and b; the Ig molecule consists of two heavy and light chains. Both molecules are stabilized by interchain and intrachain disulfide bonds. Variable-region domains are located at the amino terminal, and constant-region domains are located on the carboxy terminal. The antigen binding site on the Ig molecule is located between the variable-region domains of the heavy and light chains. The variable region of the TCR recognizes foreign peptides in the context of self-major histocompatibility complex (MHC) molecules. The TCR is also associated with the CD3 antigen (consisting of g, d, e, and z-z chains) to form the TCR complex. (C) Organization of the gene families of Ig and TCR. The common feature of the four gene pools is that they contain a numbet of variable (V) gene segments that are separated from the constant (C) region genes by the joining (J) genes. In the case of the TCR b chain and the Ig heavy-chain gene, additional diversity (D) genes are present. During ontogeny, one of the V gene segments is juxtaposed to the J segment through a process of chromosomal rearrangement to form the V(D)J gene. This, along with the constant region genes, is transcribed to fotm messenger RNA and then protein.

GENETICS OF THE IMMUNE SYSTEM

Antigen Receptor Gene **Rearrangements**

During B- and T-ccll development, multiple gene rearrangements occur to form their respective antigen receptors, the Ig and the TCR. Diversity of the antigen receptors is due to diversity in theit principal components, the variable (V) gene segment and the joining (J) gene segments. One of the many V gene segments is juxtaposed by chromosomal rearrangements with one of the J segments (and when present, with the diversity [D] segment) to form the complete variable region gene, Recombinational inaccuracies at the joining sites of the V, D, and J regions further increase the diversity of the antigen receptors.

Constant (C) gene segments are present in all receptors. The V, D, J, and C gene segments along with the intervening noncoding gene segments between the J and C regions are initially transcribed into mature RNA. Through a process of RNA splicing, the noncoding gene segments are excised and the V(D)JC messenget RNA (mRNA) is

translated into protein. In addition, after binding antigen B cells undergo somatic mutations that increase the diversity and the affinity of antigen binding. This phenomenon does not occut in T cells. During isotypc switching in B cells, futthcr rearrangements lead to recombinarion of the same variable region gene with new constant region genes (see Figure 45.1).

Major Histocompatibility and Human Leukocyte Antigens

MHC gene products or the human leukocyte antigens (HI.As) serve to distinguish self from nonself. In addition, they serve the important function of presenting antigen to the appropriate cells. The MHC class I gene product contains an MHC-cncoded alpha chain, and a smaller non-MHC encoded /^-microglobulin chain. The MHC class II gene product consists of two polypeptide chains, alpha and beta, which are noncovalently linked. Both class I and class II proteins are stabilized by intrachain disulfide bonds. Class I antigens are expressed on all nucleated cells, whereas class II antigens are constitutively expressed only on dendritic cells, macrophages, and B cells and are also expressed on a variety of activated cells, including T cells, endothelial cells, and astrocytes.

In humans, class I molecules are HLA-A, B, and C, whereas the class II molecules are HLA-DP, DQ, and DR. Several alleles are recognized for each locus; thus the HLA-A locus has at least 20 alleles, and HLA-B has at least 40. The number of alleles for the D region appears to be as extensive as that for HLA-A, HLA-B, and HLA-C. In view of the extensive polymorphisms present, the chances of two unrelated individuals sharing identical HLA antigens are extremely low. The reason for the extensive diversity and the evolutionary pressure that lead to this are not fully-understood (Nepom 1991).

Class I antigens regulate the specificity of cytotoxic T cells, which are responsible for killing cells bearing viral anrigens or foreign transplantation antigens (Figure 45.2). The target cells share class I MHC genes with the cytotoxic cell. Thus the cytotoxic cell that is specific for a particular virus is capable of recognizing the antigenic determinants of the virus only in association with a particular MHC class I gene product. The function of class II MHC gene products appears to be to regulate the specificity of T-helper cells,

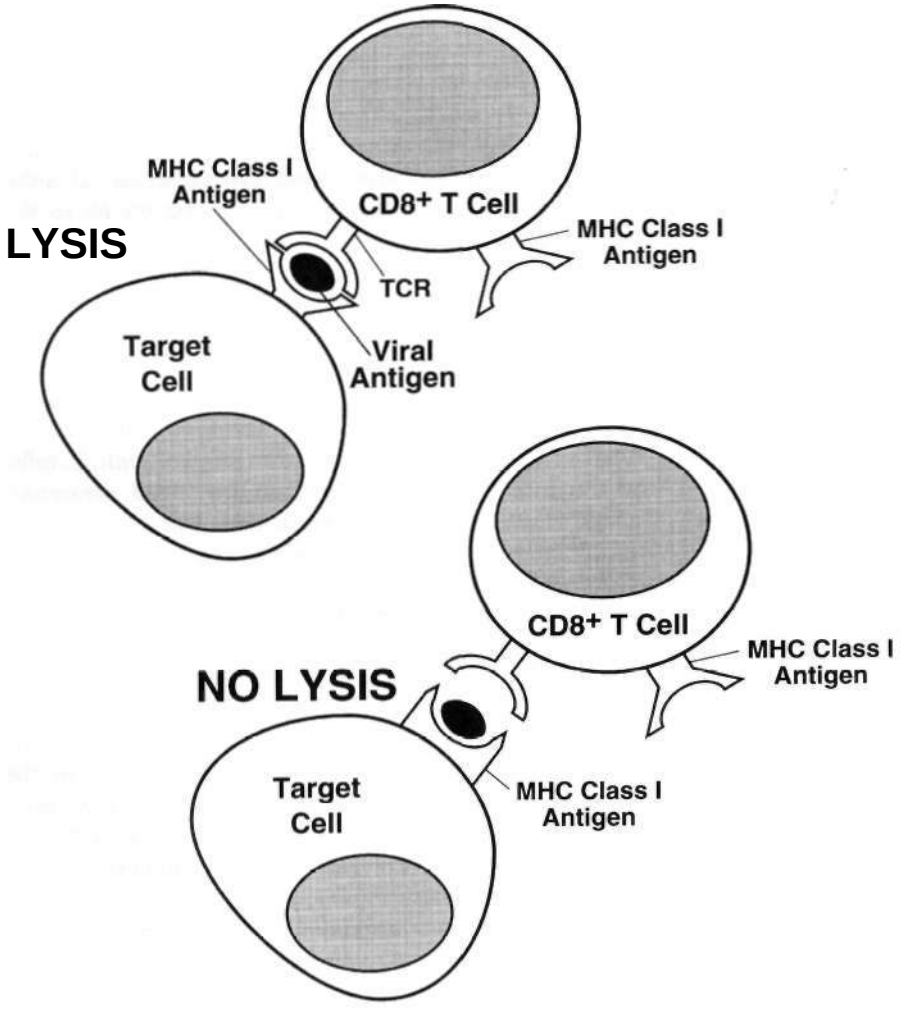

FIGURE 45.2 The phenomenon of major histocompatibility complex (MHC) restriction. For antigen-specific eytolysis of virus-infected targets to occur, T cells should be sensitized to the virus and share the same class I HLA with the target cell. In the lower part of the figure, the MHC class I antigen expressed on the CD8+ T cell is different from the MHC class 1 antigen expressed on the target cell; therefore lysis does not occur. TCR = T-cell receptor.

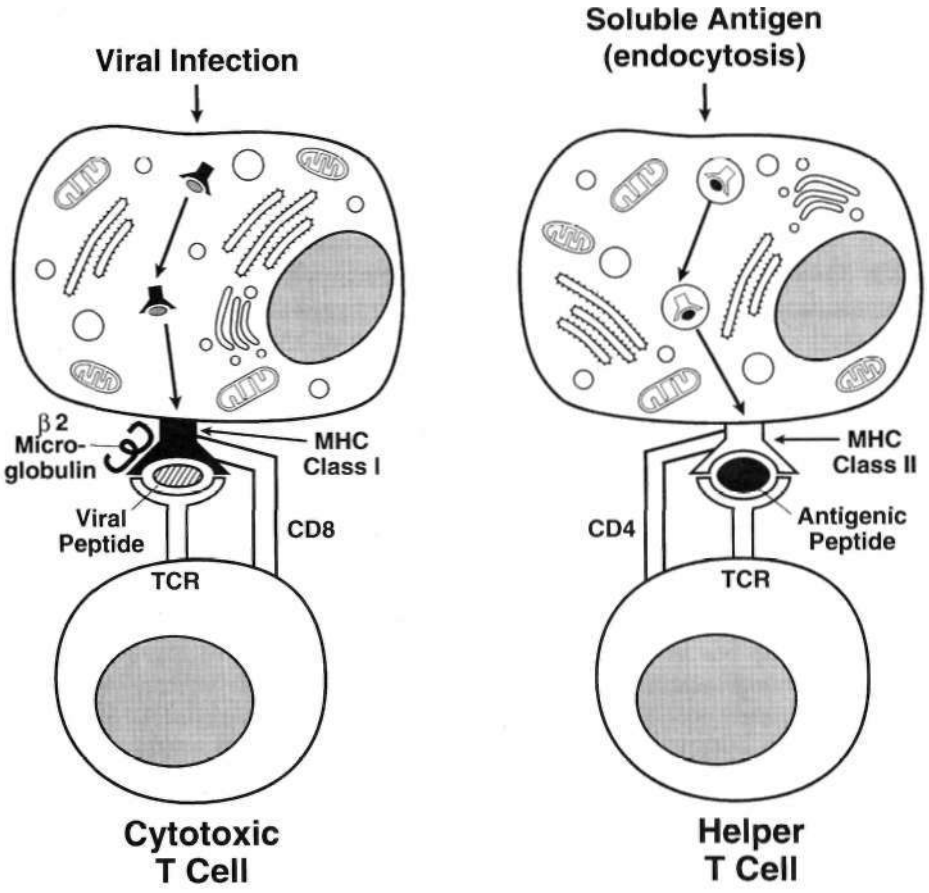

FIGURE 45.3 Antigenic recognition of cytotoxic and helper T cells. The cytotoxic T cell recognizes viral peptides associated with human leukocyte antigen-A (HLA-A), HLA-B, or HI.A-C molecules. The coreceptor for the helper T cell is the CD4 molecule. MHC = major histocompatibility complex; TCR = T-cell receptor.

which, in turn, regulate DTH and antibody response to foreign antigens. Similarly, an immunized T-cell population will recognize a foreign antigen only if it is presented on the surface of an APC that shares the same class II MHC antigen specificity as the immunized T-cell population. Thus the functional specificity of the T-cell population is restricted by the MHC molecules that they recognize. CD8+ T cells (cytotoxic) and CD4+ T cells (helper) are referred to as MHC class I and class II restricted T cells, respectively (Figure 45.3).

The analysis of the three-dimensional structure of the class I and class II molecules has confirmed the notion that these molecules are carriers of immunogenic peptides that are processed by APCs and presented on the cell surface (Figure 45.4), Both MHC class I and class II molecules share similarities in crystal structure that allow them to accept and retain immunogenic peptides in grooves, or pockets, and present them to T cells (Brown et al. 1993).

ORGANIZATION OF THE IMMUNE RESPONSE

Initiation of **the** Immune Response

Antigen Presentation

One of the crucial initial steps in the immune response is the presentation of encountered antigens to the immune system. Antigens are carried from their site of arrival in the periphery by way of lymphatics or blood vessels to the lymph nodes and spleen. There, antigens are then taken up by cells of the monocyte-macrophage lineage and by B cells, processed intracellularly, and presented not as whole molecules but as highly immunogenic peptides.

Accessory Molecules for T-Cell Activation

The interaction of MHC-peptide complex with T cells, although necessary, is insufficient for T-cell activation. Other classes of molecules are involved in T-cell antigen recognition, activation, intracellular signaling, adhesion, and trafficking of T cells to their target organs. The distinction between the functions of these classes of molecules is not absolute, and many may be involved in interactions between other cells of the immune system.

CD3, Molecules whose primary role is signaling include the CD3 molecule. The CD3 molecule is part of the TCR complex. Although the TCR interacts with the MHC-peptide complex on APCs, the signals for the subsequent enactment of T-cell activation and proliferation are delivered by the CD3 antigen. The cytoplasmic tail of the CD3 proteins contains one copy of a sequence motif important for signaling functions, called the immunoreceptor tyrosine-bascd activation motif (ITAM).

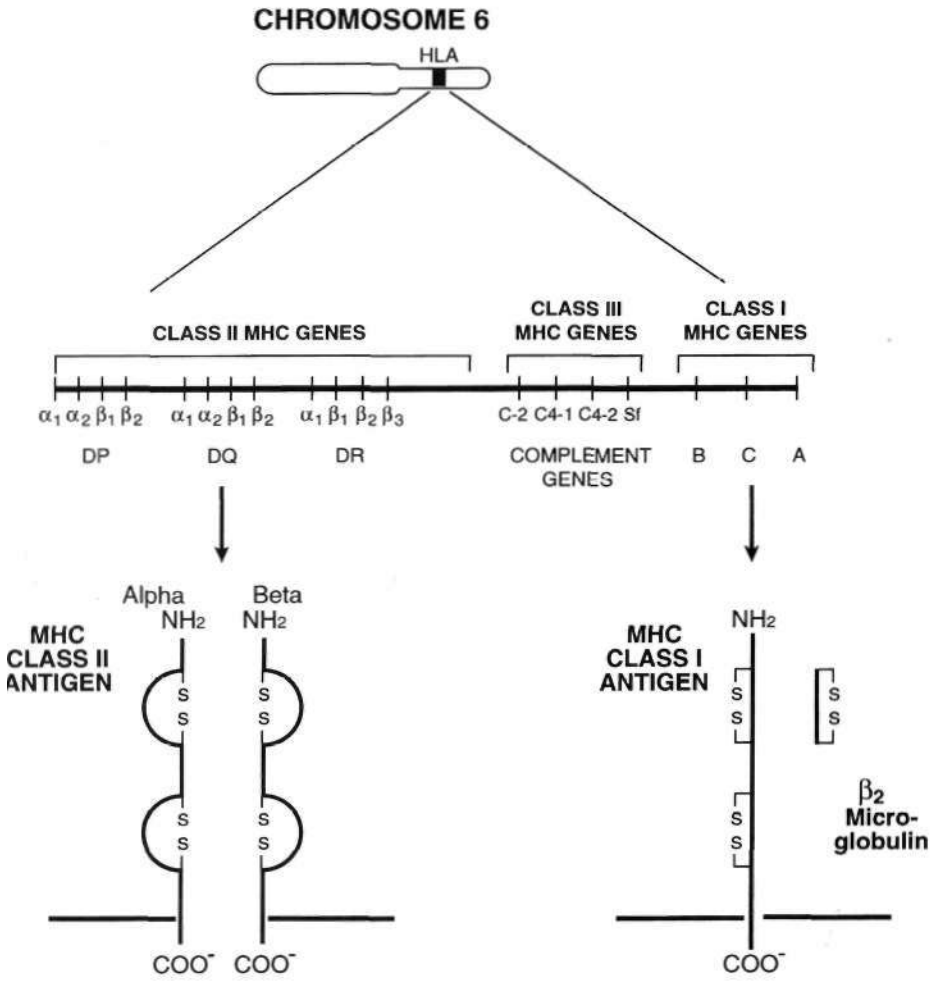

FIGURE 45.4 Schematic diagram tit [In- human leukocyte antigen (HLA) complex in humans, located on chromosome 6. The HLA class 1 gene (HLA-A, -B, and -C) codes for a single heavy-chain molecule. The /^-microglobulin is coded by genes on a different chromosome. The HLA class II genes (DR, DP, and DQ) form the a-b heterodimer. The HLA class 111 genes include those encoding for members of the complement family of proteins. MHC = major histocompatibility complex.

Phosphorylation of the ITAM initiates intracellular signaling events. In experimental situations, anti-CD3 antibodies can nonspecifically activate these intracellular signals, producing activated T cells in the absence of antigen.

CD4 and CD8. CD4 or CDS antigens are expressed on mature T cells and serve an accessory role in signaling and antigen recognition. CD4 binds to a nonpolymorphic site on the MHC class II beta chain, and CDS binds to the alpha-3 domain of the MHC class I molecule. Signals for cell division that are delivered to the nucleus are mediated by second messengers. When the receptor binds its ligand, it causes the activation of protein kinases. These kinases add phosphate groups to other proteins that ultimately signal the cell to divide. CD4, CD8, and CD3 on T cells and CD19 on B cells are examples of receptors that are linked to kinases. CD4 is the cell surface receptor for human immunodeficiency virus (HIV-1), and the fact that certain non-T cells, such as microglia and macrophages, can express low levels of CD4 may explain the propensity of the virus for the central nervous system (CNS).

Costimulatory Molecules. Other molecules required for costimulation in T-cell activation are B7-CD28; CD40-CD154; the integrin families that include vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule (ICAM-1), and leukocyte function antigen 3 (LFA-3); CD45; and CD2. The integrin family also mediates T-ccll adhesion, facilitates interaction with the APCs, mediates adhesion to nonhematopoietic cells such as endothelial cells, and guides cell traffic. Other molecules primarily involved in cell migration into tissues, are CD-44, L-selectin, and matrix metalloproteinases (MMPs) (Figure 45.5). L-Selectin facilitates the rolling of leukocytes along the surface of endothelial cells and functions as a homing receptor to target peripheral lymphoid organs. The MMPs are a family of proteinases, secreted by inflammatory cells, that digest specific components of the extracellular matrix. MMPs facilitate lymphocyte entry through basement membranes and are the principal pathway through which T-cclls enter the CNS. In addition, MMPs may cleave the membrane-bound form of tumor necrosis factor-alpha (TNF-a), facilitating the secretion of this cytokine. Chemokines

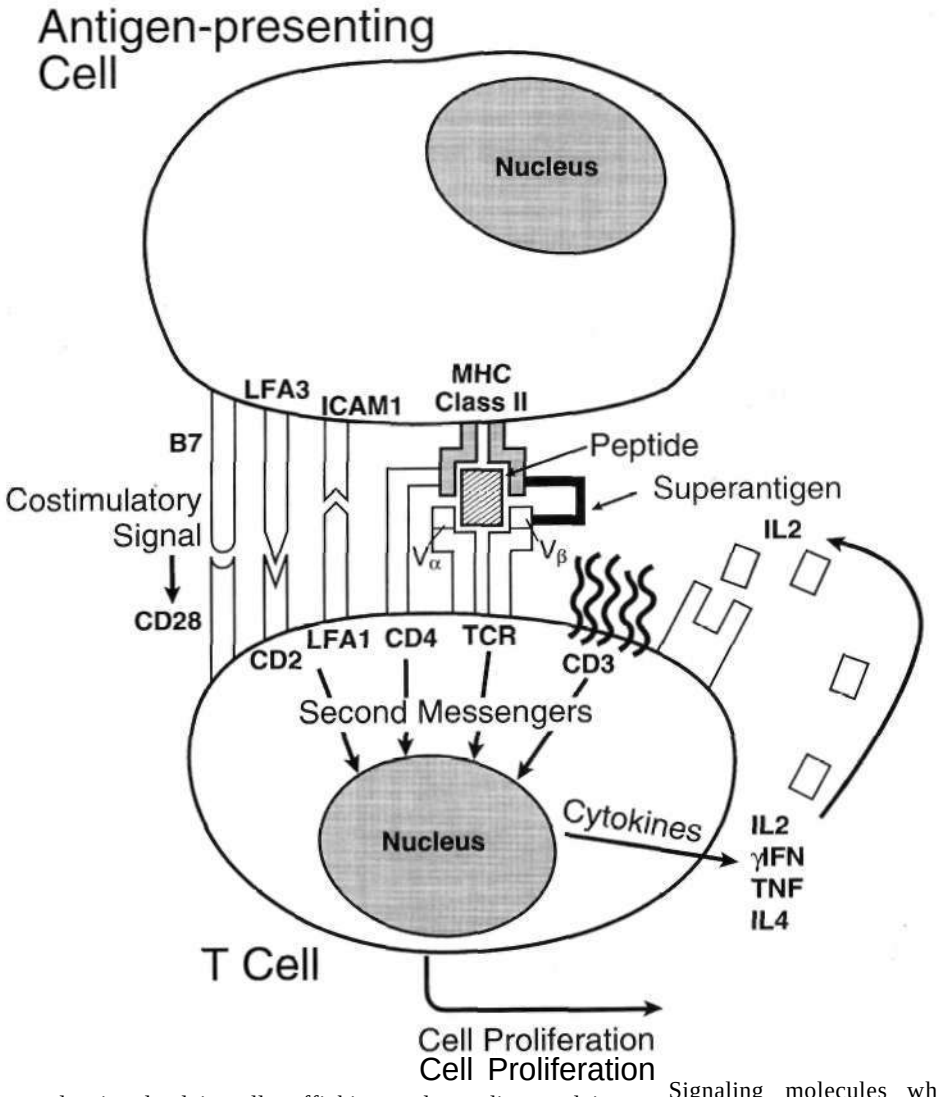

FIGURE 45.5 Antigen-driven activation of helper T cells. Proliferation of T cells requires the delivery of a number of concordant signals. Along with stimulation through the T-cell receptor-CD3 complex, the presence of appropriate costimulatory signals via CD28 antigen, adhesion molecules, leukocyte function antigen 1 (LFA1) and CD2, and the coreceptor molecule CD4 are essentia) for T-cell activation and proliferation. The membrane events ⊱t anriiteu recognition lead to acti vation of second messengers. The second messengers signal the nucleus and cell to divide and secrete cytokines. lntcrleukin-2 (IL-2) acts as an autocrine growth stimulator, thereby amplifying the response. lFN-y = interferon gamma; MHC = major histocompatibility complex; TCR = T-cell receptor; TNF = tumor necrosis factor.

Cell Proliferation

are also involved in cell trafficking and are discussed in a separate section.

The B7-CD28 interaction is one of the most extensively studied costimulatory systems. The B7 molecules arc expressed on antigen presenring cells, and their expression is induced in activated cells. There are two forms of B7, B7-1 (CD80) and B7-2 (CD86), that share some homology but have different expression kinetics. The B7 molecules interact with their ligand CD28, which is constitutively expressed on most T cells. Rinding of the CD28 molecule mediates intracytoplasmic signals that increase expression of the growth factor IL-2 and enhance expression of the anti-apoptotic molecule Bcl-x_L. An alternate ligand for B7 is CTLA-4, which is homologous to CD28 in structure, but in contrast to CD28 functions to inhibit T-cell activation. CTLA-4 is upregulated after T-cell activation and serves to downregulate the immune response.

Accessory Molecules for B-Cell Activation

Like T cells, B cells require accessory molecules that supplement signals mediated through cell-surface Igs. Signaling molecules whose functions arc likely to be analogous to CD3 are linked to Ig. Unlike T cells that may only respond to peptide antigens, B cells can respond to proteins, peptides, polysaccharides, nucleic acids, lipids, and small chemicals. B cells responding to peptide antigens are dependent on T-cell help for proliferation and differentiation, and the antigens are termed thymus-dependent (T-depcndent). Nonprotein antigens do not require T-ccll help to induce antibody production and are therefore T-inde pen dent.

The interaction between B cells and T-hclper (CD4+) cells requires expression of MHC class II by B cells and is antigen dependent. In addition, a number of other molecules mediate adhesion between T and B cells and induce signaling for B-cell activation. These include B7 expressed on B cells interacting with CD28 on T cells and CD40 on B cells interacting with CD 154 . Interaction of 1 - helper and B cells occurs in the peripheral lymphoid organs, initially in the primary follicles and later in the germinal centers of the follicle. Activation of B cells induces activation of transcription factors (c-Fos, JunB, Wl-'&B, and c-Myc), which in turn promote proliferation and Ig

secretion. Cytokines elicited from the T-helper cell induce isorype switching in B cells, producing stronger and long-lived memory responses, in contrast to weak IgM responses to T-independent antigens.

Further generation of high-affinity antibody producing B cells and memory B cells occurs in the germinal center of lymphoid follicles, through a process called affinity maturation. As the amount of available antigen lessens, B cells that do not express high-affinity receptors for antigen are eliminated by apoptosis. Some B cells lose the ability to produce Ig but survive for long periods and become memory B cells.

Regulation of the Immune Response

Cytokines

Cytokines play a major role in the regulation of the immune response. Cytokines are broadly divided into the following categories, which are not mutually exclusive: (1) growth factors: II-1, II.-2, IL-3, and IL-4 and colony-stimulating factors; (2) activation factors, such as interferons (alpha, beta, and gamma, which are also antiviral); (3) regulatory or cytotoxic factors, including IL-10, IL-12, transforming growth factor-beta (TGF-$), lymphotoxins, and tumor nectosis factor-alpha (TNF-a); and (4) chemokines that are chcmotactic inflammatory factors, such as IL-8, MIP-1K, and MIP-l/J.

Cytokines are necessary for T-celi activation and for the amplification and modulation of the immune response. A limited representation of the cytokines that participate in the immune response is shown in Table 45.2. Secretion of IL-1 by macrophages results in stimulation of T cells. This leads to synthesis of IL-2 and IL-2 receptors and finally to the clonal expansion of T cells. Only activated T cells express the IL-2 receptor; therefore the cytokine induced expansion favors antigen-activated cells only. T-cell activation causes secretion of interferon-gam ma (IFN-j/), which induces expression of MHC class I and class II molecules on many cell types including APCs. This in turn increases the T-cell response to the antigen. Secretion of IL-2 also results in activation of NK cells that mediate lysis of tumor cell targets. In addition, IL-3 is released, resulting in stimulation of hematopoietic stem cells. The signal for differentiation of B cells to form antibody-secreting cells involves clonal expansion and differentiation of virgin memory B cells, IL-4 and B-cell differentiation factors secreted by T cells induce differentiation and expansion of committed B cells to become plasma cells.

IFN-w and IFN-/J are both type I interferons. IFN-a is produced by macrophages, whereas IFN-^l is produced by fibroblasts. Both inhibit viral replication by causing cells to synthesize enzymes that interfere with viral replication. They also can inhibit the proliferation of lymphocytes by unknown mechanisms.

Although the emphasis has been on factors that cause expansion and differentiation of lymphocytes, there are cytokines that can downregulate immune responses. Thus IFN-a and IFN-^, in addition to possessing antiviral properties, can modulate antibody response by virtue of their antiproliferative properties. Similarly, TGF-/3 (a cytokine produced by T cells and macrophages) can also decrease cell proliferation. IL-10, a growth factor for B cells, inhibits the production of *lYN-y* and thus may have anti-inflammatory effects.

CD4+ T-helper cells differentiate into Th I or Th2 phenotypes, which secrete characteristic cytokines, and stimulate specific functions. Thl cells secrete IFN-j/, IL-2, and TNF-a. These cytokines exert proinflammatory functions and, in Thl-mediated diseases such as MS, promote tissue injury. IL-2, TNF-a, and IFN-y mediate activation of macrophages and induce 1)111, l'h 1 cell differentiation is driven by IL-12, a cytokine produced by monocytes and macrophages. In contrast, the Th2 cytokines IL-4, IL-5, IL-*6*, IL-10, and IL-13 promote antibody production by B cells, enhance eosinophil functions, and generally suppress CMI. Th3 cells secrete TGF-/S, which inhibits proliferation of T cells and inhibits activation of macrophages. Cytokines of the Thl type may inhibit production of Th2 cytokines and vice versa.

Chemokines

Chemokines are a recently discovered and extensively studied group of molecules that aid in leukocyte mobility and directed movement. Chemokines may be grouped into two subfamilies based on the configuration and binding of the two terminal cysteine residues. If the two residues participating in disulfide bonding are adjacent, they are termed the C-C family (e.g., MCP, MlP-la, RANTES). Those separated by one amino acid, are C-X-C family members (e.g., IL-8), where X indicates a nonconserved amino acid. An important recent discovery is that two chemokine receptors, CCR-5 and CXCR-4, can act as coreceptors for strains of HIV. Chemokines are produced by a variety of immune and nonimmune cells. Monocytes, T cells, basophils, and eosinophils express chemokiiu' receptors, and these receptor ligatid interactions are critical to the recruitment of leukocytes into specific tissues,

Termination of an Immune Response

The primary goal of the immune response is to protect the organism from infectious agents and to generare memory T- and B-cell responses that provide accelerated and high-avidity secondary responses on re-encounteting antigens. It is desirable to terminate these responses once an antigen has been cleared. In parallel, the immune system must constantly function to prevent autoimmune activation

Table 45.2: An abridged list of cytokines involved in interactions between the immune and nervous systems

Cytokine	*Cell source*	*Cells principally affected*	*Major functions*
IL-I	Most cells; macrophages, microglia	Most cells; T colls, microglia, astrocytes, macrophages	Costimulates T- and B-cell activation Induces **11.-6,** promotes IL-2 and IL-2R transcription Endogenous pyrogen, induces sleep
II.-2	T cells	T cells, NK colls, B cells	Growth stimulation
IL-3	T cells	Bone marrow precursors for all cell lineages	Growth stimulation
IL-4	T cells	B cells, T cells, macrophages	MHC II uprcgulation Isotypc switching (IgGl, IgE)
IL-6	Macrophages, endothelial cells, fibroblasts, T cells	Hepatocytes, B cells, T cells	Inflammation, costimulates T-cell activation Ml *K.* I uprcgulation, increases vascular permeability Acute phase response (Schwartzman reaction)
1L-10	Macrophages, T cells	Macrophages, T cells	Inhibition of lFN-y, TNF-o, **IL-6** production Downregulation of MHC expression (macrophages)
II.-12	Macrophages, dendritic cells	T cells, NK cells	Costimulates B-cell growth, $CD4^+$ Thl cell differentiation, IFN-y synthesis, cytolytic function
Interferon-^, interferon-^	Many cells; leukocytes, macrophages	Many cells, macrophages	Inhibits proliferation, viral replication Downregulates MHC I Inhibits cytokine production
Interferon-/	T cells, NK cells	Astrocytes, macrophages, endothelia, NK cells	MHC I and II expression Induces TNF-or production, isotype switching (IgG_{2n}) Synergizes with TNE-a for many functions
TNF-t(	Macrophages, microglia (T cells)	Most cells, including oligodendrocytes	Cytotoxic (e.g., for oligodendrocytes), lethal at high doses Upregulates MHC, promotes leukocyte extravasation Induces IL-1, IL-6, cachexia; endogenous pyrogen
Lymphotoxin (TNF-/J)	T colls	Most cells (shares receptor with TNF-a)	Cytotoxic (at short range Or through contact) Promotes extravasation
TGF-jS	Most cells; macrophages, T cells	Most colls	Pleiotropic, antiproliferative, anticytokine Promotes vascularization, healing

IFN = interferon; Ig = immunoglobulin; IL = interleukin; MHC major histocompatibility complex; NK = natural killer; TGF = tumor growth factor; TNE = tumor necrosis factor.

and maintain self-tolerance. A number of systems operate to prevent uncontrolled responses. Here we discuss the termination of individual components of the immune response. Following is a discussion of the mechanisms that maintain self-tolerance, many of which are also involved in immune-response termination.

B-cell Inhibition

In most instances, an antigen is cleared either by cells of the reticuloendothelial system or through the formation of antigen-antibody complexes. These complexes can themselves result in the inhibition of B-cell differentiation and

proliferation through binding of the Fc receptor to the CD32 (FcyRU/S) receptor on the surface of the B cell.

Immunoglobulin

The variable region of the lg and the TCR molecule represent novel proteins that can act as antigens. Antigenic variable regions are called idiotopes, and responses against such antigens are called anti-idiotypic. Niels Jerne's network hypothesis postulates that anti-idiotypic responses serve to regulate the immune response; however, the extent to which this operates is unclear.

T Cells

Termination of the T-ccll immune response is mediated by several mechanisms including anergy, deletion, and suppressor cell activity. Anergy or functional unresponsiveness occurs when there is insufficient T-cell activation. Repeated stimulation of T cells may lead to activation induced cell death through apoptosis. Cytokine-mediatcd regulation can also serve to terminate the immune response notably by secretion of Th2 and Th3 cytokines. Suppressor cells generally inhibit the immune response through secretion of cytokines, through cytotoxic mechanisms, or by modulation of the function of APCs. A combination of these mechanisms cooperate to maintain self-tolerance, particularly peripheral tolerance, and are discussed later.

SELF-TOLERANCE

An organism's ability to maintain a state of unresponsiveness to its own antigens is termed self-tolerance. Self-tolerance is maintained through three principal mechanisms: deletion, anergy, and suppression. Self-tolerance may he broadly categorized as either central or peripheral tolerance. Similar mechanisms may also be used to induce tolerance to a foreign antigen or to terminate an immune response.

Central Tolerance

Bone marrow stem cells migrate to the thymus, thereby becoming thymocytes, or T cells. In this location, T-cell VDJ germline genetic elements recombine to create *a* and *fi* chains, which in turn form the TCR. Thymocytes then undergo a process of education that involves positive and negative selection. Positive selection of thymocytes occurs in the thymus cortex when the cells are in the double negative stage, CD4— CDS—. The cortex contains dendritic and epithelial cells that present MHC antigens to the developing thymocytes. T cells with receptor having no affinity to MHC will fail to receive signals needed for maturation and will die *in situ.* Those with low affinity toward MHC survive *Mid* become single-positive thymocytes depending on their affinity toward MHC] I (CD8+) or MHC II (CD4+). In the thymus medulla, thymocytes that display a high affinity toward self-antigen are deleted by apoptosis, a process called negative selection. Most T-ceil education occurs in the thymus; however, extra-thymic sites may exist.

Peripheral Tolerance

Self-reactive lymphocytes may escape central tolerance; therefore peripheral mechanisms exist to maintain self-tolerance. This is termed peripheral tolerance. Peripheral tolerance is maintained through clonal anergy or clonal deletion. It is not clear to what extent each of these mechanisms functions in maintaining human self-tolerance; however, extensive research has been done to elucidate the mechanisms through which anergy and deletion work. In addition, self-tolerance may be maintained despite the presence of antigen-responsive lymphocytes. It is postulated that this is due to the presence of suppressor T cells or other factors, which may interfere with a successful lymphocyte response.

Anergy Due to Failure of T-cell Activation

In normal circumstances, an APC presents antigen as a peptide + MHC complex (signal one). In the absence of signal one, the T cell dies because of neglect. If signal one is presented in the absence of cosrimulaiory signals (signal two), the T cell becomes anergic. An example of this situation occurs when an antigen is presented by non-professional APCs that lack the appropriate costimulatory molecules (figure 4.S.6}. However, when a T cell gets activated, it upregulates the expression of an alternate costimulatory molecule, CTLA—4 . CTLA4 engagement by CD SO and CD86 on the surface of APCs sends a negative signal to the T cell, inhibiting cell growth and proliferation. Animals deficient for CTLA—4 expression on their T lymphocytes have an uncontrolled lymphoproliferative phenotype with auto re activity (Waterhouse et al. 1995).

Apoptosis

Apoptosis is the process in which a cell undergoes programmed cell death. As opposed to necrosis when interruption of the supply of nutrients triggers cell death, apoptosis may be triggered by various signals including withdrawal of growth factors, cytokines, exposure to corticosteroids, and repeated exposure to antigens. Mediators of apoptosis include the *Bel* family of genes, which are mostly antiapoptotic, and the *Fas* family of genes, which are proapoptotic. Activated T cells also express Fas ligand (CD95L or FasL) and Fas (CD95); ligation of Fas and FasL induces apoptosis of the T cells.

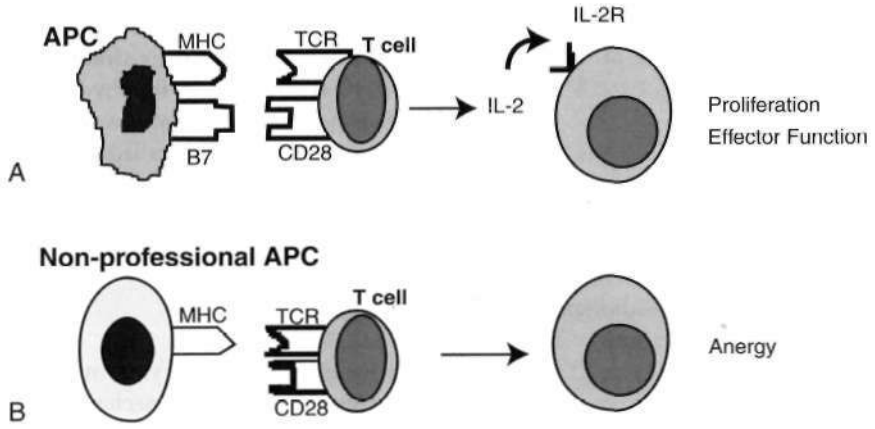

FIGURE 45.6 A two-signal model of Tcell activation. Activation of the Tcell receptor (TCR) by an antigen-major histocompatibility complex (MHC) provides signal 1, which is sufficient to induce the T cell to enter the cell cycle and begin blast transformation, which is characterized by an increase in cell size. Signal 2, the costimulatory signal, can be provided to the T cell through interaction of CD28 with molecules of the R7 family found on the surface of bone-marrow-derived antigen-presenting cells (APCs). In this instance (A), TCR signals are complemented, enabling the T cell to proliferate, produce cytokines, and develop mature effector functions. In the absence of a second signal, T-cell activation is abortive, and the cell becomes anergic {B). Signal 2 might not be delivered if the APC does not express a costimulatory ligand on its surface, perhaps because a nonprofessional APC, such as an epithelial cell, is presenting antigen (B). IL = interleukin.

Repeated stimulation with an antigen may also induce apoptosis via the Fas/FasL pathway, a process termed *activation-induced cell death* (AICD). Therefore an autoreactive T lymphocyte may encounter large doses of self-antigen in the periphery and consequently may be deleted by AICD. Mice lacking Fas or FasL develop a lupus-like syndrome (Zhou et al, 1996), and mutations in the Fas gene were associated with an autoimmune disease with lymphoproliferation in humans (Drappa et al. 1996).

IL-2 is the prototypical growth factor, inducing clonal expansion of antigen-stimulated lymphocytes. However, paradoxically, disruption of the IL-2 gene leads to accumulation of activated lymphocytes and autoimmune syndromes (Sadlack ct al. 1993). This is because IL-2 induces the transcription and surface expression of Fas ligand (FasL). Interactions of Fas with FasL lead to cell death (Figure 45.7). Therefore IL-2 plays a dual role in T-cell regulation, reflecting a possible role for cytokine concentration and timing of exposure. Othet cytokines that mediate apoptosis and cell death are TNF-o; and IFN-y. Complete absence of either of these cytokines results in deficient T-cell apoptosis, inability to terminate the immune response, and uncontrolled autoimmune disease.

Suppressor T cells

Suppressor T cells function to downregulate CD4 and CDS T cell responses. T-suppressor cells can be of the CD4+ or CD8-F subtypes. Suppressor cells have been found in several animal models of disease, and some are antigen specific. *In vitro* they can be generated under similar conditions used to generate anergic cells, and it has been postulated that they ate the same entity (Lombardi et al. 1994). Suppressor T cells may mediate supptession through the production of modulating cytokines (Th2 or TGF-/3}, via cell-cell contact and expression of negative regulatory molecules (CTLA-4), or through other mechanisms that are currently being explored. In humans, there is little evidence for antigen-specific suppressor cell responses. MS patients have been found to have fewet CD4+ CD25+ cells than normal controls, suggesting that suppressor cells may play a role in modulating this disease.

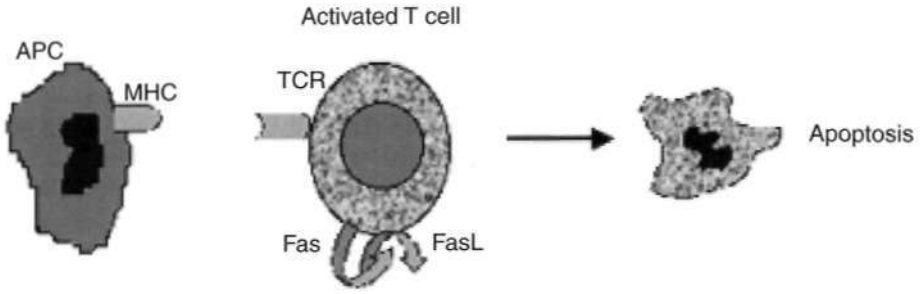

FIGURE 45.7 Activation of the T cell leads to coexpression of the death receptor Fas (f ~,*D95)* and its ligand (FasL), resulting in death of the cell and of the neighboring cells. APC = antigen-presenting cell; MHC = major histocompatibility complex; TCR = T-cell receptor.

THE IMMUNE SYSTEM AND THE CENTRAL NERVOUS SYSTEM

Immunological reactions in the CNS differ from those in the rest of the body because of its unique architecture, cellular composition, and molecular expression. The CNS has been tetmed an *immunologically privileged site* because of the relative improved survival of allografts within this region. Indeed, the same factors that play a role in immunological tolerance in the CNS play a tolc in immune-mediated diseases involving the CNS, infections of the CNS, tumor survival, and therapies.

Important factors relevant to immunological tesponscs in the CNS are as follows: (1) absence of lymphatic drainage, limiting the immunological circulation; (2) the blood-brain barrier (BBB), which limits the passage of immune cells and factors; (3) the low level of expression of MHC factors, particularly MHCII in the resident cells of the CNS; (4) the lack of potent APCs, such as dendritic or Langerhans' cells; and (5) the presence of immunosuppressive factots such as TGF-/3 (Wilbanks and Streilein 1992).

Because of the lack of a lymphatic system, antigens drain along perivascular spaces. Monocyte-derived CNS resident cells play an important role in immune surveillance in these areas. Using bone marrow chimeras, it has been demonstrated that perivascular microglia are derived from bone marrow macrophages (Hickey and Kimura 1988). Other subclasses of microglia include parenchymal microglia and monocytes of the meninges.

The BBB is composed of tight junctions between endothelial cells and a layer of astrocytic foot processes that prevent entry of inflammatory cells and other factors into the CNS. Entry of inflammatory cells across the BBB is facilitated by up regulation of adhesion molecules, [CAM-1 and VCAM-1 on endothelial cells. T cells must be activated before crossing the BBB. Entty is facilitated by expression of receptots for adhesion molecules, including alpha-4-integrin,

The CNS houses cells that arc capable of antigen-presentation under certain conditions *in vitro,* but to what extent this occurs *in vivo* remains under debate. In the CNS, endogenous expression of MHC class I and class II on APCs, such as microglia, is low and in oligodendrocytes and astrocytes it is almost undetectable. Neurons express MHC class I only when damaged and in the presence of IFN-y (Neumann et al. 1995). Expression of MHC antigens on both microglia and astrocytes are enhanced by the presence of cytokines, TNF-a, and IFN-y (Zajiceck 1992). Under inflammatory conditions, microglial cells are likely to be the principal APCs in the nervous system {Perry 1994).

Immune privilege in the CNS is influenced by the previously discussed factors. A series of studies have demonstrated that immune privilege also exists in the anterior chamber of the eye, which shares many of the characteristics of the CNS. Anterior chamber immune privilege is due in part to expression of TGF-jS in the aqueous of the eye. In the CNS, TGF-0 is produced by astrocytes and microglia and may play a role in down-regulating immune responses locally. Increased expression of Fas ligand in the CNS compared with the peripheral nervous system (PNS) may increase apoptosis of T cells, thereby downregulating the immune response (Moalem eral. 1999).

Some CNS tumors express large amounts of TGF-^S, which may play a role in protecting them from immune surveillance. CNS tumors may also express Fas or Fas ligand, again protecting them from immune surveillance.

Cells of the CNS not only respond to inflammatory stimuli but are also capable of secreting cytokines. Neural cells also secrete cytokines, often directly under the influence of lymphocytes. Microglia produce TNF-a and IL-1. Astrocytes secrete cytokines and are also influenced by IL-1 and interferons to divide and express proteins such as costimulatory molecules on their surfaces. These observations lead to the conclusion that the brain is not an immunologically sequestered organ but that it interacts, produces immunologically active factors, and is closely involved with the systemic immune response.

PUTATIVE MECHANISMS OF HUMAN AUTOIMMUNE DISEASE

Why does autoimmune disease occur? It largely results as a culmination of interactions between genetic predisposition, environmental factors, and failure of self-tolerance maintenance mechanisms. Some diseases such as MS arc termed *immune mediated,* because no definitive autoantigen has been demonstrated. Other diseases are clear cases of molecular mimicry such as Gd1b mediated axonal neuropathy, in which the self-antigen attacked by the immune system is similar to that of an environmental antigen (in this case the Penner 0:19 serotype of *Campylobacter jejuni).* Thus autoimmune diseases may be mediated by heterogeneous mechanisms, and in some cases more than one mechanism may be operating.

Autoimmune diseases may be classified as T- or B-cell mediated. Some, such as myasthenia gravis (MG), are mediated through a combination of both. In many B-cell mediated diseases, an autoantigen has been identified, to which the B cell produces autoantibodies. Examples ate MG, in which sera from patients contain antibodies to the alpha subunit of the TCR, and Lambert-Eaton syndrome in which symptoms ate caused by antibodies targeting calcium channels. In contrast to T-ce 11-media ted diseases, identification of autoantigens in antibody-mediated diseases may be easier, because B cells react to whole proteins, whereas the determinants recognized by T cells tend to be APC-proccsscd small peptides of 10-20 amino acids. Thus for T-cell-mediated diseases such as MS, inflammatory demyclinating polyneuropathy, and polymyositis (PM) there is little evidence demonstrating a causal relationship

between an autoantigen and autoimmune disease. In addition, T-cell reactivity to autoantigens does not necessarily guarantee disease, because auto re activity to some self-antigens is seen in healthy individuals. Thus the only conclusive evidence that can indicate causality between an antigen and T-cell-mediated autoimmune disease would be the reversal of the disease process by removal of the putative autoreactive T-cell repertoire. Although this has been feasible in some animal models, establishing the efficacy of such a strategy is difficult in most human T-cell-mediated diseases.

Genetic Factors

Genetics plays a role in susceptibility to autoimmune diseases. In particular, an association between certain MHC haplotypes and disease has been noted. MS is linked to the HI.A-DR2 allele, and the relative risk of having this allele in the Northern European population is 3.8. MG has been linked to HLA-DR3. However, the presence of the allele docs not guarantee disease. In general, the relative risk of developing disease among individuals who carry the antigen may be calculated by the following formula:

Number of patients carrying the HLA antigen	number of controls lacking the antigen
Number of patients lacking the HLA antigen	number of controls carrying the antigen

Association of a particular HLA haplotype with autoimmune disease may be due to the ability of a patticular MHC molecule to bind and present autoantigen to the T cell. Conversely, if an MHC molecule does not bind a particular self-antigen in the thymus, the developing T cell will not recognize that antigen as self and will escape negative selection. Therefore certain MHC haplotypes have an association with disease, whereas others protect against disease. Disease linkage tends to be with class II genes of the MHC rather than class I, suggesting a key role for T-cell autoimmunity.

Association of a particular HLA-haplotype with disease may be due to its linkage to another locus or disease susceptibility gene. Linkage disequilibrium refers to the increased chance of inheriting two alleles together because they are genetically linked as opposed to inheriting them together as separate random events.

One of the most obvious genetic factors associated with autoimmune disease is sex. Recently, much attention has been focused on the role of sex hormones in regulating the immune system. Many autoimmune diseases arc more frequent in females; systemic lupus erythematosus (SLE) is 10 times more common in women, and MS twice as common in females. Evidence from animal models has shown that females are more resistant to infections and reject foreign skin grafts sooner than their male counterparts. This is especially true during periods of high estrogen availability. Estrogen levels decrease after ovulation or during pregnancy, with a progesterone surge. The lowering of estrogen ensures immunological toletancc toward the sperm and subsequently toward the fetus. Therefore estrogen's effects on the immune system may predispose women toward autoimmune diseases. This is reflected in experimental disease models of autoimmunity. Only female (NZB X NZW)F1 mice develop the SLE-like disease, and this is abrogated by androgen treatment. Similarly, in experimental autoimmune encephalomyelitis (EAE) the experimental model fot MS, female SJL mice are more susceptible to disease induction and are protected with testosterone (Dalai et al. 1997).

Failure of self-tolerance mechanisms may lead to autoimmune disease, and this has been seen in experimental models. In particular, Fas and FasL knockout mice develop a severe systemic autoimmune disease resembling SLE. Fas or FasL abnormalities have not been identified in SLE but have been described in a rare lymphoproliferative syndrome (Drappa et al. 1996). Ir is not known to what extent failure of self-tolerance may contribute to autoimmunity.

Environmental Factors

Environmental factors may play a role in the pathogenesis of autoimmune diseases. Molecular mimicry is one of the mechanisms implicated. In this situation, an environmental antigen resembling a self-antigen elicits an immune response ro both itself and the sclf-antigcn. The environmental antigen involved in molecular mimicry may be a supcrantigen. Superantigens have the property of stimulating all T cells that express a given TCR variable gene family, regardless of their exact specificity, because of direct TCR-superantigen intctaction (Dellabona et al. 1990). They are usually of bacterial or viral origin and bind as intact molecules to MHC.

In many cases of molecular mimicry, the environmental antigen is a pathogen, and autoimmune disease follows the pathogen-caused disease. The classic example of this is strcptococcal-induced endocarditis. Neurological diseases caused by this mechanism include streptococcal-induced chorea, Gdlb axonal neuropathy, and the anti-Hu paraneoplastic syndrome. Molecular mimicry has been implicated in many neurological diseases. However, thus far, a definitive pathogen has yet to be identified in MS and chronic inflammatory demyelinating polyneuropathy. Difficulty in identifying the disease-causing pathogen may be partially due to the chtonicity of these diseases, and the original autoantigen may have already disappeared.

It is possible that once an inflammatory reaction proceeds, the tissue injury may expose other self-antigens that wete previously unrecognized by the immune system.

For unknown reasons, peripheral tolerance mechanisms may fail, and an autoimmune reaction ensues. If an autoimmune reaction spreads from one antigen to another by this mechanism, this is termed *determinant spreading* or *epitope spreading.* Epitope spreading may play a role in perpetuating immune-mediated reactions and therefore in causing chronic diseases.

DISEASES IN NEUROIMMUNOLOGY

Immune-mediated disorders occur at all levels of the nervous system. Disotdcrs of the CNS and PNS, including the peripheral nerve, neuromuscular junction, and muscle have been described. Some of these disorders are clearly autoimmune, in that a cleat autoantigen has been identified, whetcas others are immune mediated. In this section, we identify neurological immune-mediated diseases and highlight immunological features pertinent to pathogenesis and treatment. A full description of each disease may be found in the appropriate sections ot tins book.

Multiple Sclerosis

MS is a heterogeneous disease and is characterized by neurological deficits disseminated in time and space. It is a major cause of disability in the adult population in North America. Women are predominantly affected in a ratio of 2:1. The disease is chatactcrized by a varying array of neurological deficits. There are four main disease types, classified on the basis of the clinical disease course: relapsing-remitting (RR), secondaty ptogtessivc (SP), primary progressive (PP), and progressive relapsing (PR). RR disease affects *65%* of patients and is characterized by onset of neurological deficits that remit over a period of weeks to months. Aftet 15 years, most RR patients go on to have an SP form of disease, in which neurological deficits become fixed and accumulate. PP patients accumulate permanent neurological deficits from the onset of disease, whetcas patients with PR disease have a combination of progressive and stepwise deficits. Disease onset generally occurs in the early 20s for RR disease and in the mid-30s for PP disease.

MS is a complex polygenic disease. Monozygotic twins have a concordance rate of 27%, whereas dizygotic twins of the same sex display a 2.3% concotdance rate. The incidence for first-degtee relatives of MS patients is 2-5%, whereas the incidence for the general population is 0.2%, Genetic linkage studies have been performed and several regions of interest have been found, but the most robust association remains with the HLA region. There is an increased incidence of MS in patients with the HLA-DR2 (DR1501) haplotype (Chataway et al, 1998; Name-, et al. 1998; Sawcet and Goodfcllow 1998). MS temains most prevalent among people of Northern European descent. There is a lower prevalence in other populations, such as Arabic and Mediterranean people, but among those with disease there is a higher incidence of other disease-associated haplotypes such as DR4 and DR6.

Therefore genetic factors play an important role in pathogenesis; however, migration and othet studies have demonstrated that environment also plays a critical role. Epidemiological studies have shown that residence in certain geographical areas and immigration to these areas before the age of 15 increases the incidence of MS. In addition, there is a diminishing north to south gradient in MS prevalence in the Northern Hemisphere, with an opposite trend in the Southern Hemisphere.

Pathologically, MS is characterized by inflammatory infiltrates in the CNS white matter with resultant demyelination. and axonal transections (Trapp et al. 1998) producing sclerotic plaques. Inflammation is generally perivenular, and lesions typically occur in the periventricular subcortical white matter, corpus callosum, optic nerve, brainstem, cerebellum, and spinal cord. Recently, the pathology of MS lesions has been classified into four distinct subtypes with the following predominant features: (1) cellulat infilttation, (2) antibody deposition, (3) oligodendrocyte apoptosis, and (4) oligodendrocyte death without apoptosis (Lucchinetti et al. 2000). The observations to date show a single subtype of lesion in each patient raising the possibility of distinct MS disease pathogenetic types.

It is clear that the immune system plays a central role in mediating CNS damage in MS. Oligoclonal bands are commonly observed in the CNS of MS patients; however, the target of these antibodies has yet to be elucidated. CMI primarily involving T-helper cells is believed to play an important role in initiating the disease, and immunological studies have substantiated the presence of activated T cells in MS. Most of the therapies for MS also target T cells. No clear autoantigen has been described in MS, and it thetefore remains an immune-mediated disease rather than autoimmune disease. Reactivity to various myelin antigens, including myelin basic ptotein (MBP), ptoteolipid ptotein (PLP), and myelin oligodendrocyte protein (MOG) has been investigated. MBP-reactive T cells are present in notmal individuals; however, MS patients have a higher frequency of activated MBP-reactive T cells in the peripheral blood and the cerebrospinal fluid (CSF) (Zhang et al. 1994).

MS is thought to be a T-helper 1 {Thl) mediated disease. Thl cells secrete predominantly the Thl cytokine IFN-y. Increased levels of Thl cytokines have been observed in MS lesions, and a clinical trial of IFN-y worsened MS. In addition, there is increased production of EL-I2 (the ma]or inducer of Thl cytokines) by APCs in the peripheral blood of MS patients, especially those with active disease. EAE, the animal model of MS, has been helpful in dissecting the pathogenic mechanisms of the disease. Vatious EAE models have demonstrated that mice with a Thl cytokine profile are more susceptible to EAE than wild-type mice, whereas animals with a Th2 (IL-4, IL-10) cytokine ptofile are resistant to disease development. However, this is far from

being a universal finding because EAE can be induced by transfer of Th2 cells.

The immunopathogenesis of MS is thought to involve activation of myelin-specific T cells via molecular mimicry or by a superantigen presumably in the periphery. The cells then cross the BBB and get reactivated in the CNS when they ate presented with their cognate antigen. Adhesion molecules and their ligands are expressed on T cells and endothelial cells to facilitate passage through the BBB. VCAM-1 and its ligand VLA-4 are upregulatcd in T cells during chronic disease thus perpetuating inflammation, wheteas ICAM-1 and its ligand LEA-1 were upregulated in both acute and chronic lesions (Canncllа and Raine 1995). Several studies have demonstrated increases of soluble ICAM-1 in CSF and L-selectin in serum during exacerbations of disease. The invasion of activated T cells into the btain and possible reactivation within the CNS initiates a cascade of cytokines. IL-2, IFN-^, and TNF-a activate macrophages, which in turn elicit nitric oxide and TNF-a. In experimental models, myelin damage is mediated by nitric oxide lipid peroxidation, direct TNF-a damage, and complement-induced pore formation. As mentioned previously, Th2 cytokines can induce B-cell activation and antibody production that further damage myelin. F.ach of these steps in the pathogenesis may be targeted for therapeutic intervention.

A number of immune-mediated autoimmune disorders of the nervous system are available for study in laboratory animals. Besides allowing for the analysis of the immunoregulatory network, they have been critical in designing immunotherapies. Although these model systems show many similarities to the human disease, it is likely that the human and experimental diseases have different immunological substrates; therefore extrapolation to human disease should be undertaken with caution (Owens and Sriram 1995).

Two major animal models exist that mimic the clinical manifestations of MS. These arc EAE and Theiler's murine encephalomyelitis virus-induced disease (TMFV-IDD). The issue of whether cither of these diseases is identical to MS in their pathogenesis remains unresolved.

EAE is a T-cell-mediated autoimmune dcmyelinating disease of the CNS. The disease can be induced in a number of experimental laboratory animals including primates by subcutaneous injection of whole-brain homogenate or of a purified preparation of MBP, PLP, or MOG. By altering the immunization protocols and animal strains, a relapsing remitting or a chronic form of the disease may be induced.

TMEV-IDD is induced by injecting TMEV picornavirus into the cerebral hemisphere. The virus infects neurons and glial cells. In some strains of mice, the host is unable to clear the virus, resulting in encephalitis and death; in other cases, the virus is cleared completely, and the host is resistant to demyelination. In TMEV-IDD susceptible strains of mice, the virus is partially cleared, saving the host from death but inciting an immune response that results in demyelination. Thus the damage induced by the virus is due to a failute of the host to mount a fully protective response, which predisposes the pathogen to persistence, resulting in immunopathology. TMEV-IDD is a T-ccll-mediated disease; although the exact immunological mechanisms inducing demyelination remain unclear, damage may be a result of epitope spreading (Miller et al. 1997). Studies in both EAE and TMEV have contributed vastly to our understanding of MS, and these models offer a system for testing new therapeutics.

Details of available therapies in MS are discussed in Chapter 60. Here, we discuss the immunological mechanisms of currently used medications, as well as experimental therapeutic strategies,

During the past 10 years IFN-0 therapy for MS has become one of the most important advances in the treatment of this disease. It is available in three different forms—subcutaneous IFN-/J-lb (Betaseron), subcutaneous IFN-jS-la (Rebif), or intramuscular IFN-0-la (Avonex). Interferons have many properties including suppressing proliferation of viruses and T cells. The mechanisms of IFN-/3 action in MS has been attributed to several different mechanisms. Intcrferon-associated increased production of IL-10 by macrophages downregulates the number of Thl cells. IFN-/J has also been shown to decrease production of IL-12 by dendritic cells, potential CNS APCs. In addition, IFN-*fi* modulates adhesion molecule expression, primarily by facilitating the conversion of cell-associated VCAM-1 into soluble VCAM-1. These drugs also downregulate costimulatory molecule expression, thus decreasing T-ccll activation and migration to the CNS (Yong 2002).

Glatiramcr acetate (GA) also known as copolymcr-1 or Copaxone is anothet class of drug recently used in the treatment of MS. In contrast to lFN-,8, GA is a synthetic molecule that was originally designed to resemble MBP. It is composed of random repetitive sequences of the amino acids glutamic acid, lysine, alanine, and tyrosine (G-L-A-T). Its mechanism of action is unclear; however, it is thought to bind with high affinity to the MHC groove, leading to the generation of GA-spccific T cells. Several studies have suggested that GA-specific T cells are Th2 biased, and animal models have demonstrated that these cells can migrate to the CNS and ameliorate EAE disease (Aharoni 1997). Studies in patients treated with GA have also demonstrated this Th2 bias {Dnda et al. 2000) and also have shown an upregulation of these cells during the first 3 months of treatment, with a subsequent downregulation or anergy during the next 3 months. The significance of this finding is unclear. It is thought that GA mediates its effects via migration of GA-specific Th2 cells into the CNS, where they downregulate the immune response locally. It has also been demonstrated that GA-specific T cells protect from optic nerve crush injuries, possibly by production of brain-derived neurotrophic factor (BDNF) (Kipnis et al. 2000).

Altered peptide ligands (API.) resembling MBP have been used in phase I trials for MS, with little success.

Two concurrent trials were initiated using the same compound CGP77116. One showed an increased number of lesions on magnetic resonance imaging (MRI) in some patients after the initiation of treatment (Bielckova 2000). In the other trial, 9% of patients developed allergic-type reactions associated with a Th2 deviation (Kappos 2000), Both trials were stopped because of safety concerns.

Other therapies that are currently under investigation in phase I and II trials include anti-VLA4 antibody that blocks the entry of activated cells to the CNS, anti-GDI 54 antibody that blocks CD40-CD154 T cell costimulatory signal, and CTLA4Ig. The latter blocks B7-CD28 costimulatory signals on T cells and may induce T cell anergy *in vivo.*

Many therapeutic strategies that have been used in the past nonspecifically target components of the immune response. Nonspecific strategies include cyclophosphamide, mitoxantrone, and cladribine, which deplete the bone marrow including T cells. Recent work has demonstrated that cyclophosphamide rather than causing T-cell depletion may work by inducing a cytokine switch with a decrease in IL-12 and an increase in IL-4, IL-5, and TGF-/J (Comabclla etal. 1998).

The role of the immune response in the induction of axonal damage in MS is unclear; however, both bystander damage or specific mechanisms that target neurons may be the causative factors. Therefore early modulation of the immune response is critical,

Efforts have been made toward replacement of damaged oligodendrocytes with transplant grafts. In addition, because axonal damage has occurred, transplantation of neurons or their progenitors is a promising avenue of research,

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is defined as a monophasic demyelinating disease associated with vaccination or a systemic viral infection, which may affect both adults and children. It was originally described in association with rabies and smallpox vaccines, both of which were prepared with neural tissues, suggesting a parallel with EAE, the animal model of MS. These vaccines have since been modified, using non-neural human diploid cell lines. ADEM has not been associated with any vaccines that are currently administered in the United States. The parainfectious variant of ADEM has been associated with measles infection, rubella, mumps, and several other viruses.

The lesions in ADEM resemble those of MS. The CNS white matter contains perivascular inflammatory infiltrates, as well as demycliuation. The most likely mechanism by which this disease occurs is molecular mimicry. Experimental evidence has shown that T cells isolated from patients with ADEM are 10 times more likely to react with MBP than controls, likening this disease to EAE in animal models (Pohl-Koppc et al. 1998). Because of the monophasic nature of the illness, it appears that the immunological response occurs acutely, but further reaction is abrogated.

MRI demonstrates multifocal white matter lesions involving the cerebrum, brainstem, cerebellum, and spinal cord, which may or may not enhance with gadolinium, Lesions generally resolve over time. CSF is characterized by normal pressure, moderately elevated cell count (5-100/ uL), moderately elevated protein (40-100mg/dL), and normal glucose. The presence of red blood cells may indicate a diagnosis of hemorrhagic leukoencephalitis. Oligoclonal bands may very rarely be present, and these cases should be followed for the development of MS.

Acute episodes of ADEM should be treated with intravenous steroids. The usual dose is 1 g of mcthylprednisolone (Solu-Medrol) for 5 days in adults. Refractory cases have been treated with plasmapheresis or cyclophosphamide. Cases that are suspicious for MS should be followed with MRI.

Immune-Mediated Neuropathies

The immune-mediated neuropathies are a large and heterogeneous group of diseases. We shall focus on acute inflammatory demyelinating polyneuropathy {AIDP) and chronic inflammatory demyelinating polyneuropathy (GIDP), which may be defined by the time to peak disability; in the former, 4 weeks, and in the latter, 2 months. Although AIDP and GIDP share many characteristics, the question of whether one is a continuum of the other, is still under debate. AIDP or Guillain-Barrc (GBS) syndrome usually presents with symmetrical ascending weakness and may be associated with autonomic dysfunction and respiratory depression. Sensory systems may be involved and may present with paresthesias or numbness. Demycliuation and axonal damage may be involved to varying degrees. If the patient's symptoms continue to progress beyond 4 weeks, the illness is termed CIDP.

AIDP is the most common acute paralytic disease in the Western world, with a mean annual incidence of 1.8 per 100,000 persons. There is an increasing incidence with age. Mortality was generally due to respiratory failure and has now been significantly reduced with the introduction of positive pressure ventilation. Epidemics have been found, most notably, in northern China where a high incidence has been associated with C. *jejuni* infections (McKhann ct al. 1993).

AIDP or GBS is characterized pathologically by a perineuria! lymphocytic, monocytic, and macrophage infiltrate. Several autoantibodies to myelin glycolipids have been identified, including GM1, Gdla, and Gdlb, Antibody-mediated demyelination as a result of complement fixation has been identified in pathology specimens. In some cases, axonal damage is present and is believed to

be a result of bystander damage. GBS is primarily an antibody-mediated disease as evidenced by the fact that many patients improve after treatment with plasmapheresis and that serum from GBS patients causes demyelination after transfer into experimental animals and peripheral nerve cultures.

The occurrence of AIDP has been linked to many infectious diseases, including C. *jejuni*, herpes virus, *Mycoplasma pneumonia*, and many other bacterial and viral infections, as well as vaccinations. The incidence of infection has been reported to be 90% in the 30 days before occurrence of GBS, C. *jejuni* is one of the most commonly identifiable agents, and molecular mimicry and host susceptibility are believed to play a role in disease pathogenesis. Autoantibodies not present in controls have been identified in the sera of GBS patients associated with C. *jejuni*, including GM1, Gdla, Gdlb, and Gqlb (Sheikh et al. 1998).

In contrast to AIDP, in CIDP no specific autoantibodies have yet been discovered. The histopathologic;! 1 picture is similar to AIDP; however, most studies identify fewer inflammatory infiltrates. Nerve biopsy reveals mixed demyelination and axonal changes. Onion bulbs may be present indicating attempts at remyclination. There is little laboratory evidence that this disease is antibody mediated; however, paradoxically, patients do improve with plasmapheresis. There is indirect evidence that GIDP is T-cell mediated; however, this area is still under investigation.

Treatment of AIDP involves supportive care and cardiac and respiratory monitoring. Plasmapheresis or intravenous immunoglobulin (IVIG) have been used tor acute treatment of AIDP and have been shown to be equally effective in shortening the recovery time. High-dose steroids have not been found to be effective in AIDP.

In contrast to AIDP, CIDP responds well to high-dose oral steroids. Both plasmapheresis and IVIG have been used with success. Plasmapheresis is a short-term immunotherapy, which nonspecifically removes antibodies from the circulation. IVIG is an immunomodulating agent commonly used in the treatment of allergic and autoimmune diseases. Immunosuppressants such as cyclosporine A, cyclophosphamide, and azathioprine have had positive outcomes in refractory cases; however, these require further testing in controlled studies.

Autoimmune Myasthenia Gravis

MG is a disorder of the neuromuscular junction. It is an autoimmune disorder, and 80-90% of cases have detectable autoantibodies to the alpha subunit of the acetylcholine receptor (AChR). MG is characterized by fluctuating weakness and fatigability, primarily in muscles innervated by the cranial nerves, but may occur in skeletal and respiratory muscles. MG has a biphasic age distribution. Most cases occur in women ages 20^40 years, and the remainder in older patients with an equal sex distribution. Thymomas occur in 10-15% of cases; most are in the older age group. Seventy-five percent of patients will have some thymic abnormality, 85% being thymic hyperplasia. MG is often associated with other autoimmune diseases, thyroid disorders, rheumatoid arthritis (RA), pernicious anemia, and SLE. A similar syndrome termed Lambert-Eaton is associated with antibodies against the presynaptic, voltage-gated calcium channel.

Autoimmune MG is caused by the presence of anti-AChR antibodies and is a B-ce!l-medmted disease, bighty to 90% of patients have detectable autoantibodies. These are polyclonal and may be of any IgG subtype. Transfer of serum from myasthenic patients to experimental animals results in neuromuscular blockade. The mechanism by which antibody mediates neurological symptoms is controversial. Possible mechanisms include neuromuscular blockade or damage to the AChR from complement mediated damage after attachment of the IgG antibody. There is, however, poor correlation between scrum antibody titers and disease course and severity.

Although the B cell is the effector cell producing antibodies, experimental evidence has shown that autoreactive T cells are necessary for the disease to occur (Yi and Lefvert 1994), Removal of the thymus results in improvement of disease in 80-90% of myasthenic patients. The role of thymic abnormalities remains unclear, and patients wirh thymomas have antibodies to additional skeletal muscle ptotcins such as the ryanodine receptor and titin. Patients may also display symptoms of neuromyotonia.

A large body of research is targeted at understanding the reasons for the failure of T-cell and subsequent failure of B-cell tolerance in MG. Both normal and myasthenic thymus glands contain myoid cells and epithelial cells that express the AChR, T cells expressing the V beta 5.1+ TCRs are over-re pre sen ted both in the core of germinal centers and in perifollicular areas of hyperplastic thymuses, suggesting a role in the autoimmune response (Truffault et al. 1997). Failure of central or thymic tolerance may play an important role in disease pathogenesis.

Genetic factors play a role in the pathogenesis of autoimmune MG, but monozygotic twins demonstrate less than 50% concordance rate. There is a moderate association of MG with the HLA antigens B8 and DRw3 in young women. The stronger association with HLA-DQw2 remains controversial, There is an unusually high incidence of other autoimmune diseases such as SLE, RA, and thyroid diseases in first-degree relatives of myasthenic patients suggesting the presence of shared autoimmune genes.

Therapies in MG are targeted toward alleviating symptoms with acetylcholinesterase inhibitors and using strategies to abrogate the disease target the immune system. Thymectomy is recommended for patients 15-65 years old, with 80-90% remission rate (Durelli et al. 1991). The thymus plays an important role in T-cell education in the developing human; therefore prepubertal thymectomy is discouraged. A variety of anticholinesterase inhibitors

provide temporary symptomatic relief in most patients. Pyridostigmine bromide (Mestinon) and neostigmine bromide (Prostigmin) are the most commonly used agents and must be taken daily.

MG is an antibody-mediated disease, and therefore responds to therapies that nonspecifically target antibodies. Both plasmapheresis and treatment with 1VIG are used for acute MG exacerbations or in preparation **for** surgery (Gajdos et al. 1997). Because the autoantigen is known in MG, investigational therapies may target specific molecules such as the B-cell surface Ig or the TCR and deliver immunotoxins.

Immunosuppressives such as cyclosporine and azathioprine are used to augment treatment when symptoms are not adequately controlled by the previously mentioned methods, but the decision to use such agents must balance the need and the side effects. Gorticosteroids are used at various stages of treatment and have multiple effects on the immune system, including reducing AChR antibody levels.

Inflammatory Muscle Diseases

PM, dermatomyositis (DM), and inclusion body myositis (IBM) are all immune-mediated diseases of the muscle and the surrounding connective tissue. Each has its own unique clinical and immunohistological features. Both PM and DM are more common in females, whereas IBM is more common in males. DM is associated with an increased risk of cancer, and therefore a full cancer screening should be part of patient management.

PM is thought to result from a multitude of causes, including systemic autoimmune, connective tissue disorders, and viral and bacterial infections. PM is characterized histopathologically by an endomysial inflammatory infilttate containing predominantly GD8+ T cells. There is relative sparing of blood vessels. In one subtype of PM, T cells with *y$* receptors have been identified surrounding non-necrotic muscle fibers (Hohlfeld et al. 1991).

In contrast, DM is characterized by peri fascicular atrophy. There is hypoperfusion and subsequent degeneration of the muscle fibers in the periphery of the fascicle secondary to microvascular damage. Damage to capillaries resulting in microinfarcts is mediated by complement. Immunofluorescence studies have revealed immune-complex deposition within the endothelium, indicating that this is an antibody-mediated disease; therefore the disease differs from PM (Kissel et al. 1986).

Various autoantibodies directed against nuclear and cytoplasmic cell components are found in up to 30% of inflammatory myopathies. Most are nonspecific for connective tissue disease. Viruses including Goxsackie B are implicated in the pathogenesis of disease, and both PM and DM patients may have anti-Jo-1 antibodies to the viral enzyme histidyl-tRNA synthetase (Mathews and Bernstein 1983).

As with PM, IBM is mediated by CD8+ T cells. However, in contrast to PM, the muscle biopsy in IBM may also demonstrate the presence of characteristic autophagic •'rimmed" vacuoles. Amyloid deposits may be demonstrated in the muscle, similar to those seen in Alzheimer's disease, suggesting similarities in pathogenesis of these two diseases (Askanas et al. 1992).

The mainstay of treatment of PM and DM is steroids. Dosages may vary from 60-100 mg/day of prednisone, and duration is determined by clinical outcome. Alternative treatment options for the inflammatory myositis diseases include IVIG, methotrexate, azathioprine, cyclophosphamide, cyclosporine, and in extreme cases total body irradiation (Mastaglia 1998). Mortality rates vary between 15-35% and are generally due to cardiac or respiratory failure. Because there is a higher incidence ot malignancy with PM and DM, screening for breast, lung, hematological, ovary, stomach, and colon carcinoma should be performed on each patient with the diagnosis. IBM may be more resistant to steroid therapy and is often diagnosed after an assumed PM fails to respond to treatment.

THE IMMUNE RESPONSE TO INFECTIOUS DISEASES

The immune response within the CNS must carefully balance the need to eliminate the pathogen and the risk of inducing bystander damage to the delicate and vital nervous tissues. It is believed that it is for this reason the immune response in the CNS deviates from that in the rest of the body, and it remains an immune-privileged site. The result is that many pathogens are not completely eliminated and may persist to cause further symptoms. Examples of this are CNS syphilis, Lyme neuroborreliosis, herpes zoster, HIV, and *Mycobacterium tuberculosis.* Lyme *Borrelia* incites IFN-y production, with correspondingly low levels of IL-4 in the CSV, thus predisposing the CNS tissue to bystander damage.

The portal of entry and site of replication of the pathogen plays a critical role in the elimination of the infection. In the case of viral meningitis, the portal of entry is the mucosal membrane, usually the nasopharynx. This incites a strong local immune response to the proliferating organism. By the time the virus disseminates to the leptomeninges, a sufficient immune response has been mounted in the periphery to eliminate the pathogen. However, in the case of viral encephalitis, the CNS invasion is so sudden that the peripheral immune system has insufficient time to react, and the weak CNS immune response is often inadequate, resulting in a poor outcome.

TUMOR IMMUNOLOGY

The immunological response to tumors has elicited much interest in the past 10 years. This field provides

opportunities for understanding the cause and immunological features of tumors and venues for treatment.

The body uses a mechanism called tumor immunosurveillance to prevent the formation of tumors or inhibit further growth. The main effector cells are CTLs, NK cells, and TNF-a producing macrophages. Tumor-reactive antibodies have also been identified in patients but are thought to play a lesser role. It has been recognized that tumors express tumor specific antigens that may be recognized by the previously mentioned cells. However, tumor cells may escape the body's natural surveillance mechanisms resulting in cancer. Tumor cells escape surveillance mechanisms by masking or modulating antigens on their surface, downregulation of class I and II, thereby inhibiting antigen presentation, and through the expression of immunosuppressant factors.

Tumors in the CNS have similar abilities to evade the immune system, and it has been shown that some gliomas produce high levels of TGF-/3, an immunosuppressant. In addition, there may be downregulation of class II MHC; however, this is controversial. It has recently been established that gliomas may express high levels of FasL, allowing for local apoptosis of Fas-bearing cells including lymphocytes.

Therapies are being designed to exploit the body's natural tumor immunosurveillance mechanisms. One avenue of research is vaccination with killed tumor cells or tumor antigens. Another technique employs genetic engineering to transfect tumors with plasmids bearing genes for costimulatory molecules to enhance the tumor APC ability. Injection of cytokines such as IL-2 and TNF-a, which enhance lymphocyte and NK function, has been attempted with variable results. Alternately introduction of stimulated lymphokine-activated cells (LAK) holds promise.

PARANEOPLASTIC SYNDROMES

Neurological paraneoplastic disorders are defined as neurological syndromes arising in association with a cancer. These are mediated by antibodies produced by the immune system in reaction to a tumor antigen, which cross react with neural tissue. Because many autoantibodies have been identified, the pathogenesis of paraneoplastic syndromes is autoimmune. It is likely that aberrant, primitive, ot hamartoma to us antigens are expressed by the tumor cells. The anti-Hu antibody arises in association with small cell cancer of the lung and cross-reacts with neurons to produce a syndrome of encephalomyelitis and/or sensory neuropathy. Similarly, anti-Yo antibody produces cerebellar degeneration because of cross-reactivity with Purkinjc cell cytoplasm and is associated with breast and ovarian cancer. Opsoclonus-myoclonus syndrome is due to and-Ri antibody and has been associated with cancer of the ovary and breast.

There is evidence of a more active cellular infiltrate in tumors associated with paraneoplastic syndrome than those not associated with a paraneoplastic syndrome. Therefore one can postulate that the immune system is more active in these situations. Cancers associated with paraneoplastic syndromes are generally associated with a bettet outcome.

THE IMMUNOLOGY OF CNS TRANSPLANT

Recently, there have been many advances in the field of CNS transplant, with the use of fetal dopaminergic striatal cells, and now various types of genetically engineered cells. A major factor in the survival of these grafts is their immunogenicity. As stated previously, the CNS is an immune privileged site. Therefore transplant grafts in the CNS tend to have longer survival times than peripheral grafts; however, this is not absolute, and cellular infiltrates associated with rejection have been identified. The immunology of CNS transplant grafts is currently under investigation and will be a critical factor in graft survival.

CONCLUSION

The field of immunology has progressed significantly in the past 20 years. This knowledge is currently being applied to immune-mediated diseases in neurology. In this rich environment, we can expect many advances in the field of neuroimmunology including new therapies and better strategies for inducing remissions.

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Chapter 46
Neurovirology

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BACKGROUND

Neurovirology is the study of viral infections of the nervous system. Viruses are small, replicating microorganisms that are unable to multiply outside a host organism—that is, they are obligate intracellular parasites. They are classified into families based on the (1) nature of their genome; (2) site and method of replication; and (3) structural features including size, shape, symmetry, and the presence or absence of an envelope. Viruses can infect humans, other animals, and even other microorganisms such as bacteria. Some viruses may infect more than one host species, whereas others are restricted to one or just a few hosts. Similarly, viral infections may be restricted to single organs or focal areas within an organ of a host or may be widespread. Viral infections may be acute, chronic, or recurrent, and their manifestations may be altered by a variety of host factors, including age, nutritional status, and immimocompetence.

In this chapter, we begin with a description of the basic features of the major clinical syndromes associated with viral infections of the human nervous system. Next is a sequential overview of the individual steps in the pathogenesis of viral central nervous system (CNS) infection, beginning with the entry of viruses into the host and ending with a discussion of the mechanisms by which viruses injure rarget cells within the CNS and other organs. The chapter concludes with a brief review of the diagnosis and treatment of CNS viral infections. More detailed information on specific viral CNS infections can be found in Chapter 59B.

CLINICAL SYNDROMES

Meningitis

Viral meningitis is an infection of the subarachnoid space caused by a virus (Rotbart 2000) (Table 46.1). Most cases of viral meningitis are acute, benign, self-limited illnesses. Less commonly, viruses may produce recurrent or chronic meningitis. Although viral meningitis often occurs as an isolated syndrome, it also may involve the brain (meningoencephalitis), spinal cord (men in goencep halomyelitis), or nerve roots (meningoradiculitis). Viruses are the most common cause of *aseptic meningitis*, a generic term for cases of meningitis in which bacteria cannot be isolated from the cerebrospinal fluid (CSF). Using modern diagnostic techniques, it can be shown that up to 85% to *95%* of cases of acute aseptic meningitis are caused by enteroviruses (especially Echo 3-7, [l]J, 11.21, and 30 and Coxsackie A9 and Bl-5) (Rotbart 2000). The remainder are caused by arboviruses {California encephalitis virus, St. Louis encephalitis virus, Western equine encephalitis virus [WEEV], Eastern equine encephalitis virus |EEEV], West Nile virus [WNVj), herpesviruses, human immunodeficiency virus (HIV), and mumps. It is important to recognize that the same viruses that produce meningitis

Table 46.1: Synopsis of clinical syndromes caused by families of neurotropic viruses and their diagnosis and treatment

Taxonomy	*Disease*	*I .atxirat'iry*	*Treatment*
RNA viruses			
Picornaviridac		CSF PCR; brain, CSF culture	Supportive ?Pleconaril
Coxsackie	Men, my el		
Echo	Men, my el		
Polio	Men, my el		
Togaviridac		HI, CF, NA, IFA	Supporrivc
EEEV	Enc	Brain Ag or cukure, CSF IgM	
WEEV	1.ML	Brain Ag	
VEEV	Enc	CSF IgM	
Rubella	Enc		
Flaviviridae		HI, CF, NA	Supportive
SLEV	Enc, men	CSF IgM, IFA	
JEV	KIK\ men	CSF Ag, IFA	
Murray Valley	Enc	Oil lure	
West Nile virus	Enc, men, myel, PN, ON	Serum/CSF IgM, serum IgG, CSF PCR	Supportive
Reoviridac			**Supportive**
Colorado tick fever	Enc, men	RBC Ag, HI, CF, NA, IFA	
Rhabdoviridac			Supportive
Habit's	Enc, myel	Ag (skin, conjunctiva, brain), PCR brain, IFA, CF, HI, CIE, culture	Postexposute prophylaxis
Borna	?Enc/affective dsorder		
Paramyxoviridac			Supportive
Measles	Enc-SSPE	i.:si- i.n.\i	?Ribavirin
Mumps	Men* enc_s myd	CSF culture, serum IgM, IgG	
Nipah	Enc, myel	ELISA, NA, cell culture	rRibavirin
Fiendra	Enc	EI.ISA, NA, cell culture	rRibavirin
Orthomyxoviridae			Supportive
Influenza	Postin enc	Culture from other site	
Bunyaviridae			Supportive
La Crosse	Enc, men	i si .uhure. CSF [B.M, HI, CF, NA, IFA, CIE	**? Ribavirin**
Arcnaviridae			Supportive
LCMV	Men, enc	CSF, blood, urine culture, serology	
Kctroviridac			
HIV-1	Enc, men, myel, PN, myos	Blood ELISA, clinical	Combination antivirals
HTLV-I	Myel, enc	Blood ELISA, CSF IgG	]nterferon-«
I)\A viruses			
Herpesviridae			
HSV-1	Enc, men, postin	CSF PCR, brain culture	Acyclovir Famciclovir Valacyclovir
HSV-2	Men, enc	CSF PCR, brain culture	Same as HSV-1
V/.V	Gan, myel, enc, postin	(SI- Iv R, brain or lesion culture	Same as HSV-1
EBV	Enc, men, myel, postin, NT	CSF PCR, serology	Supportive
CMV	Enc, PR, myel	CSF PCR, brain or CSF culture	Ganciclovir Foscarnet Cidofovir
HHV-6	Enc, febrile seizures, ?MuLtip]e sclerosis	CSF PCR, blood culture	Ganciclovir
HHV-8	?NT, ?enc	PCR blood, serology	Supportive
Papovaviridac			Supportive
JCV	Enc	CSF PCR, brain 1SH	?Cidofovir
Aden ol\ rid ae			Supporrive

Ag = antigen; CF = complement fixation; CrE = countcrimmunoelectrophoresis; CMV = cytomegalovirus; CSF = cerebrospinal fluid; EBV = Epstein-Bart virus; EEEV = Eastern equine encephalitis virus; ELISA = enzyme-linked immunosorbent assay; Enc = encephalitis; Gan = ganglionitis; HHV-6, -8 = human herpesvirus type 6, 8; HI = hemagglutination inhibition; HIV-1 = human immunodeficiency virus type 1; HSV-1, -2 = herpes simplex virus type 1, 2; HTLV-I = human T-lymphotropic virus type i; IFA = immum)fluorescent antibody; IgG = immunoglobulin G; IgM = immunoglobulin M; ISH = *in situ* hybridization; JCV = J C vitus; JEV = Japanese encephalitis virus; LCMV = lymphocytic choriomeningitis virus; Men = meningitis; Myel = myelitis; Myos = myositis; NA = neutralizing antibody; NT = neoplastic transformation; ON = optic neuritis; PCR = polymerase chain reaction; PN = polyneuropathy; Postin = postinfectious; PR = polyradiculitis; RBC = red blood cell; SLEV = St. Louis encephalitis virus; SSPE = subacute sclerosing panencephalitis; VZV = varicella zoster virus; WEEV = western equine encephalitis virus.

also can produce encephalitis, although specific viruses differ in the frequency with which they cause the two syndromes. For example, herpes simplex virus type 1 (HSV-1) more commonly produces encephalitis than meningitis, although the converse is true for herpes simplex virus type 2 (HSV-2). Similarly, most arboviruses are more likely to produce encephalitis than meningitis, whereas most enteroviruses produce far more cases of meningitis than encephalitis.

The cardinal clinical features of viral meningitis include fever, headache, and nuchal rigidity (meningismus). Common associated symptoms include nausea, vomiting, abdominal pain, chills, and generalized malaise. These symptoms are similar to but less severe than those found with bacterial meningitis. The presence of significant alteration in mental status, focal neurological signs or symptoms, or seizures suggests that infection has involved the brain parenchyma producing encephalitis rather than remaining restricted to the subarachnoid space. Symptoms of viral meningitis develop over hours to days and rarely persist for more than a week to 10 days.

The most important diagnostic test in a case of suspected viral meningitis is examination of the CSF. Typical CSF findings include a mild to moderate lymphocytic pleocytosis, slightly elevated protein concentration, and a normal glucose concentration. Stain results for microorganisms including bacteria (Gram's stain), mycobacteria (Ziehl-Neelsen stain), and cryptococci (India ink stain) are negative, as are test results for bacterial, cryptococcal, and fungal antigens and for the presence of endotoxin. Among the common causes of acute viral meningitis, most can be specifically identified using polymerase chain reaction (PCR) of CSF.

In general, acute viral meningitis is a self-limited illness requiring only symptomatic therapy with analgesics and bed rest. Acute viral meningitis caused by HSV-1 or HSV-2 may be treated with intravenous or oral acyclovir, oral famciclovir, or oral valacyclovir, although data supporting their efficacy are largely anecdotal. Acute HIV-1 meningoencephalitis may respond to combined antirctroviral therapy with zidovudine, other reverse transcription inhibitors, and protease inhibitors. Enterovirus meningitis may respond to pleconaril.

A small number of patients have recurrent episodes of aseptic meningitis (Tedder et al. 1994}, First described by Mollarct in 1944, these episodes may recur over years and generally arc self-limired and resolve without residual sequelae. Studies using CSF PCR suggest that most cases of benign recurrent lymphocytic meningitis are caused by HSV-2.

As noted, most cases of viral meningitis resolve within 7-10 days. Some patients report mild persistent symptoms including headache or fatigue. Resolution of CSF abnormalities may lag behind clinical improvement, and a mild pleocytosis may persist for several weeks. Immunocompromised patients may develop chronic viral meningitis. The most common and extensively described example-is chronic enteroviral meningitis, often resulting from Echovirus 11, in patients with agammaglobulinemia.

Encephalitis

Viral encephalitis is a viral infection of the brain parenchyma (Whitley and Gnann 2002). Most human viral cncephalitides are acute infections. Infection may-involve the entire brain (diffuse encephalitis) or be confined predominantly to specific areas (focal encephalitis). In the United States, HSV-1 is the most common cause of acute focal sporadic encephalitis in adults, with several thousand cases occurring throughout the year. Epidemics of encephalitis in the United Stares may be caused by flaviviruses (St. Louis encephalitis virus, WNV), togaviruses (EEEV, Western encephalitis virus, and Venezuelan encephalitis virus), and bunyaviruses (California encephalitis virus and LaCrosse virus) (Nash ct al. 2001). These viruses are often designated *arboviruses*, reflecting that they are borne by arthropod vectors such as mosquitoes and ticks. Other encephalitis-producing arboviruses are common in other parts of the world, such as Japanese encephalitis virus in China and the Far East and tick-borne encephalitis in Northern and Central Europe and Scandinavia. Arbovirus cncephalitides typically have well-defined seasonal and geographical predilections reflecting the life cycle and distribution of their arthropod vectors. In the United States, infections occur predominantly during the summer months and decline precipitously in frequency after the first winter freezes reduce the number of insect vectors. Certain arboviruses have relatively limited geographical ranges (e.g., EEEV, California encephalitis virus), whereas others produce cases of encephalitis throughout the United States (e.g., St. Louis encephalitis virus). WEEV has an intermediate pattern, with human cases limited to the western two thirds of the United States. WNV produced the original human outbreak in New York City in 1999, in which 7 of the 59 patients with encephalitis or meningitis died (Nash et al. 2001), and since that time human infection has spread to many states. In 2002 there were 4156 human cases of WNV in *39* states in the United States with 284 deaths. Greatest incidences were in Illinois, Louisiana, Ohio, Mississippi, and Indiana, with human cases as far west as California (http://www.cdc.gov/ncidod/dvbid/wcstnile/index.htm).

The symptoms of acute viral encephalitis include fever, headache, and focal neurological symptoms and signs. Common neurological signs and symptoms include decreased level of consciousness, altered mentation, focal weakness, speech disturbances, and seizures. Diffuse encephalitides, such as that caused by St. Louis encephalitis virus, result in widespread neurological dysfunction. The CSF pattern in viral encephalitis is similar to that found in viral meningitis, with moderate pleocytosis, elevated

protein, and normal glucose concentrations. In severe cases of encephalitis, almost nil patients have abnormalities on neuroimaging studies. Computerized axial tomography shows areas of hypodensity, and magnetic resonance imaging (MRI) reveals areas of increased signal on T2-weighted images, resulting from tissue destruction and associated cerebral edema. Electroencephalography (EEG) may show diffuse slowing, seizures, or epileptiform discharges in multiple locations. As with viral meningitis, specific diagnosis depends on isolation of the virus, serological studies, or amplification of viral nucleic acid from CSF by PCR (Davis 2000; Redington and Tyler 2002). Specific treatment is available for encephalitis caused by HSV, varicella zoster virus (VZV), cytomegalovirus (CMV), and HIV (see therapy, later in this chapter). Treatment of encephalitis caused by viruses other than HSV is generally supportive; however, interferon-a and ribavirin are being tested in several viral enccphalitidcs. Morbidity and mortality vary with the specific virus. For example, Epstein-Barr virus (EBV) encephalitis is associated generally with a good prognosis and complete recovery, whereas EEEV is associated with substantial morbidity and mortality.

HSV-1 encephalitis in adults is the prototype of a focal viral encephalitis. Infection and associated tissue injury predominantly involve the inferior temporal and frontal brain regions and may be unilateral or bilateral. Patients often develop bizarre behavior, hallucinations, focal or generalized seizures, aphasia, and hemiparesis. Neuroimaging study results are almost invariably abnormal, although computed tomographic scans are considerably less sensitive than MRI and may be normal early after onset of infection, MRI reveals areas of increased T2 signal in the frontotcmporal regions, often with significant associated mass effect. The EEG may be the first laboratory test to show the focal nature of the lesion. EEG abnormalities can include seizures, sharp waves, and periodic latcralizcd epileptiform discharges, often localized to the frontotemporal regions. CSF is abnormal, with a lymphocytic pleocytosis of up to several hundred cells per microliter, an elevated protein, and normal glucose concentrations. Amplification of HSV DNA from CSF by PCR is extremely sensitive and specific and allows for rapid definitive diagnosis of HSV encephalitis. The PCR result may remain positive for 2-3 weeks in HSV-1 encephalitis, even in treated patients. PCR has largely supplanted other diagnostic techniques, although demonstration of HSV-specific intrathecal antibody synthesis (see diagnostic techniques, later in this chapter) or identification of **HSV** by immunocytochemistry or culrure of brain biopsy specimens remain useful in certain specific circumstances. Prompt treatment of HSV encephalitis with intravenous acyclovir (30 mg/kg/day for at least 14 days) reduces mortality from 70% in untreated patients to as little as 15% (Raschilas et al. 2002; Whitley 1997). Despite apparently optimal antiviral therapy, a significant number of treated patients are left with moderate to severe disability. Corticosteroids may be used as adjunctive therapy in patients with increased intracranial pressure and significant brain edema, although their efficacy has never been evaluated in controlled clinical trials. Poor prognostic features include delay in initiation of therapy, diminished level of consciousness, age older than 30 years, occurrence of hospital-acquired infection, and high CNS viral load.

In most viral cncephalitides, it appears that the neuron is the target cell for the viral infection. Oligodendrocytes, however, are the target of the JC virus, in which infection results in the clinical syndrome of progressive multifocal leukoencephalopathy (PML). PML is manifested usually by a subacute course of confusion, weakness, and visual disturbance. Infection occurs almost exclusively in patients with the acquired immunodeficiency syndrome (AIDS) or other forms of impaired cell-mediated immunity, MRI reveals multifocal confluent white matter lesions, often in the parietal-occipital region, and without associated mass effect. Some patients have enhancement at the margins of their lesions on gadolinium-enhanced Tl-weighted scans. The CSF is usually normal, although occasionally a mild lymphocytic pleocytosis occurs. PCR amplification of JC viral DNA from CSF is specific for PML, but of only modest sensitivity (70-80%). If the PCR result is negative, definitive diagnosis requires brain biopsy with demonstration of either JC virus antigen by immunocytochemistry or DNA by *in situ* hybridization (ISH). Typical ncuropathological features include noninflammatory demyelination associated with the presence of bizarrely shaped and enlarged multinucleated astrocytes and oligodendrocytes bearing intranuclear viral inclusions. Neurons are typically spared. Currently, no specific therapy exists for **PML,** although clinical trials of cidofovir and topoisomerase inhibitors arc currently in progress. To date, results with cidofovir have not been promising. Prognosis remains grim, with most patients dying within a few months of diagnosis. There are rare reports of stabilization of disease or even remission in patients who have recovered from their immunocompromised state. For example, initiation of antirerroviral therapy in previously untreated or inadequately treated patients with AIDS with PML may result in clinical improvement that parallels reconstitution of their immunological status.

Most viral encephalitides manifest as acute, monophasic infections. Encephalitis resulting from the emerging Nipah virus (paramyxovirus family), however, can sometimes relapse or present acutely with encephalitis up to 21 months after the original, encephalitic or asymptomatic infection. A small number of viral cncephalitides are chronic in their presentation. HIV-1 often infects the nervous system shortly after peripheral inoculation and may result in an acute, and sometimes severe, meningoencephalitis (Berger and Levy 1997; Gendelman et al. 1998). More common, however, is a more chronic infection that manifests clinically when the $CD4^+$ lymphocyte count usually is less

than 200 cells per pL. This results in a slowly progressive dementia referred to as the *AIDS-dementia complex* or the *HlV-1 -associated dementia.* Symptoms include a slowing of behavioral responses and motor function, personality changes, and withdrawal from social activities. CSF shows only a modest pleocytosis and elevation of protein, and the MRI may reveal numerous punctate or confluent lesions in the subcortical white and gray matter on T2-weighted imago. Pathological abnormalities include multinucleated giant cells, microglial nodules, myelin pallor, and neuronal loss in multiple areas. Aggressive treatment with zidovudine (formerly azidothymidine [AZT|) alone or in combination with other reverse transcriptase inhibitors and viral protease inhibitors probably has reduced the incidence and prevalence of AIDS-dementia complex over the last 10 years and may stabilize or improve neuropsychological function in those patients not previously treated with these medications (Bcrger and Levy 1997; Gcndelman et al. 1998). Some of these medicines have greater CSF penetration than others, but studies of the utility of specific treatment regimens, which take this into account, have not been attempted (Redington and Tyler 2002). Another therapeutic approach involves the use of drugs designed to inhibit HIV-induccd neuronal damage rather than directly inhibiting **viral** replication. For example, nimodipine, a voltage-dependent calcium-channel antagonist, is currently undergoing clinical trials in AIDS-dementia complex.

Rarely, measles and rubella can produce chronic CNS infection (subacute sclerosing panencephalitis and progressive rubella panencephalitis, respectively). Fewer than 20 cases of progressive rubella panencephalitis have been reported, and the incidence of subacute sclerosing panencephalitis has declined dramatically following widespread use of measles vaccine. Symptoms of subacute sclerosing panencephalitis begin with a progressive decline in cognitive function and behavioral abnormalities followed by the appearance of myoclonic jerks and corticospinal tract dysfunction. Over one half of the affected patients were initially infected with measles virus before the age of 2 years, although signs and symptoms of subacute sclerosing panencephalitis do not typically develop until between 5 and 15 years of age. CSF shows massive elevation in IgG, oligoclonal bands, and extremely high titers of measles-specific antibodies. EEC is diffusely slow early in the disease, and later reveals a pattern of high-voltage and generalized 4- to 6-Hz polyphasic sharp and slow-wave complexes followed by periods of low-voltage attenuated activity (burst suppression). Neuroimaging studies show generalized ventricular enlargement and evidence of periventricular and subcortical white matter disease. There is no effective therapy for subacute sclerosing panencephalitis, although anecdotal reports have suggested possible therapeutic benefits from isoprinosine, intraventricular interferon-or, and ribavirin. Death usually occurs within several years of onset. Progressive rubella panencephalitis develops 6-12 years after congenital or perinatal rubella infection. It is manifested by cognitive difficulties followed by progressive ataxia, dysarthria, nystagmus, weakness, and seizures. There is no effective therapy.

Myelitis

Viral myelitis is viral infection of the spinal cord. Paralytic infection caused by wild-type poliovirus has now been almost entirely eliminated from the Western hemisphere, but poliomyelitis still serves as the prototypical viral myelitis. Before mass immunization in the developed countries in the 1950s and 1960s, poliomyelitis was the most common form ol viral myelitis in the world. After the introduction of mass immunization, the incidence of paralytic polio in the United States dropped from 13.7 cases per 100,000 to 0.003 cases per 100,000. Although paralysis caused by wild-type virus no longer occurs in the United States, approximately 10-20 cases a year of paralytic polio occur in vaccinated individuals or their close contacts and have been associated with reversion to virulence of vaccine strains (vaccine-associated poliomyelitis). Neurological illness may also follow inadvertent vaccination of children or adults with unrecognized immunodeficiency. Polio has been targeted by the World Health Organization for eradication through an aggressive vaccine campaign analogous to that used for smallpox.

During polio epidemics, more than 90% of infections are asymptomatic. Approximately 4—8% of infected individuals have a minor viral illness consisting of mild fever, sore throat, gastrointestinal upset, headache, and malaise. Just 1-2% develop neurological involvement, which begins with acute viral meningitis. This is followed 2-5 days later by multifocal, asymmetrical paralysis, primarily of the extremities, reflecting the infection of the anterior horn cells of the spinal cord. Involvement usually is more severe in the legs than the arms, more proximally than distally. Paralysis may spread over 3-5 days. On examination the muscles are flaccid and weak, and reflexes are typically diminished. Approximately 10-20% of such paralytic patients may have significant bulbar involvement, with chewing, swallowing, and breathing difficulties. Encephalitis is uncommon, but may occur. A progressive postpolio syndrome, which develops decades after original paralytic infection, does not appear to be associated with reactivation of poliovirus infection.

A similar pattern of illness may occur with both nonpolio enteroviruses (notably enteroviruses 70 and 71), and viruses other than enteroviruses. A syndrome similar to that of poliomyelitis has been described in patients with WNV (MMWR, 2002a) (http://www.cdc.gov/ncidod/dvbid/westnile/index.htm).

Myelitis caused by HSV and EBV may present as an acute transverse myelitis. A similar picture may follow VZV infection (shingles), although this is more commonly associated with a local myelitis producing muscle weakness

limited to muscles belonging to myotomes in proximity to involved cutaneous dermatomes. Chronic myelitis may oecur as a result of retroviral infection (Berger and Levy 1997; Gendelman et al. 1998). In the late stages of HIV-1 infection, often in association with AIDS-dcmentia complex, patients with AIDS may develop a slowly progressive myelopathy with symptoms and signs of weakness, small- and large-fiber sensory loss, increased tone, impotence, and bowel and bladder dysfunction. The most common area affected pathologically is the thoracic spinal cord, which may show atrophy on T2-wcighted MRI. At autopsy, pathological examination of the spinal cord reveals vacuolar changes in 20-50% of HIV-infected individuals. The pathogenesis of HIV-associated vacuolar myelopathy is unknown. Antirerroviral drugs do not prevent disease progression, suggesting that myelopathy may be caused by indirect effects of HIV rather than as a result of direct virus-mediated in jury. Promising results in pilot treatment trials using [.-methionine support this hypothesis and suggest that myelopathy may be caused by interference with transmethylation mechanisms analogous to, but not identical with, those seen in B_t2 deficiency.

Infection with human T-lymphotropic virus type I (HTLV-I) is endemic in Japan and the Caribbean. In some patients it is associated with an acute T-ccll leukemia, whereas others develop a slowly progressive myelopathy referred to *as tropica! spastic paraparesis (TSP)* or *HTLV-I-associated myelopathy (HAM).* The syndrome affects males more often than females, and typically has onset before age 30. Symptoms consist primarily of upper motor neuron weakness and bladder disturbance, with variable sensory loss. Rarely, there may be encephalitis. By 10 years after symptom onset, 60-70% of individuals are unable to walk. MRI lesions are variable and can include cord swelling and enhancement in the acute stages followed by atrophy in later stages. The CSF shows mild pleocytosis, increased protein, immunoglobulin G (IgG) and IgG synthesis, and the presence of oligoclonal bands. The pathology shows myelin loss with axonal degeneration, especially in the lateral corticospinal and spinocerebellar tracts. There is chronic inflammation, with leptomeningeal and perivascular cuffing with lymphocytes, plasma cells, and histiocytes. Injury may be mediated by HTI.V-I-specific cytotoxic T cells rather than caused by direct viral injury to cells. As a result, the most effective therapies seem to involve use of immunomodulating agents, including interferon-a and corticosteroids. In general, this is a chronic, slowly progressive illness that extends over many years.

Ganglionitis

Viral ganglionitis is a viral infection of dorsal root or cranial nerve ganglia, infection with VZV is the prototype for this type of infection. Primary infection with VZV produces varicella (chickenpox). Following the acute infection, virus becomes latent in sensory ganglia. Decline in cell-mediated immunity may precipitate viral reactivation and probably accounts for the increased incidence of shingles with increasing age and in immunocompromised patients. Reactivation produces shingles, with pain, itching, and paresthesias, followed by erythematous papular skin lesions in a dermatomal pattern. The lesions develop into vesicles that then crust over. Most often, a single dermatome is involved, although disseminated shingles may occur, especially in immunocompromised patients. The areas most commonly involved are thoracic and lumbar dermatomes, the ophthalmic division of the trigeminal ganglion (zoster ophthalmicus), and the geniculate ganglion (Ramsay Hunt syndrome). Rarely, patients may present with dermatomal pain in the absence of skin lesions, so-called *zoster sine herpete.* Resolution of shingles may be complicated by the development of chronic pain in the involved dermatome (postherpetic neuralgia). The duration and severity of shingles may be reduced by antiviral drugs including acyclovir, famciclovir, and valacyclovir. Some studies suggest that prompt initiation of antiviral therapy, especially in older patients, may reduce the subsequent incidence of postherpetic neuralgia. Therapy for postherpetic neuralgia includes analgesics, corticosteroids, and other medications with efficacy in the treatment of chronic pain syndromes including anticonvulsants (e.g., carbamazepine and gabapentin) and tricyclic antidepressants (e.g., amitriptyline and imipraminc). In addition to these peripheral nerve complications, reactivation of VZV can sometimes be associated with myelitis or encephalitis/arteritis in both immunocompetent and immunocompromised patients (Gilden et al. 2000).

Polyradiculitis

Polyradiculitis may he caused by viral infection of the nerve roots and is distinguished from polyneuropathy by the predominant involvement of the nerve roots rather than the peripheral nerves. The most common example is CMV polyradiculitis in patients with AIDS (Berger and Levy 1997; Gendelman et al. 1998). A rare manifestation in patients with AIDS is an acutc-subacute multifocal polyradiculopathy affecting primarily the lumbosacral roots. Patients appear ill, with fever, pain, weakness, and variable sensory and bladder dysfunction. The symptoms and signs are progressive, often in spite of aggressive antiviral therapy with ganciclovir and foscarnet, although some individuals have shown significant improvement or resolution of symptoms,

Polyneuropathy

Viral polyneuropathy is viral infection of multiple peripheral nerves and is distinguished from polyradiculitis by the

relative sparing of the nerve roots, although the two syndromes can coexist. A significant number of patients with AIDS develop a primarily sensory, axonal polyneuropathy late in the disease (Berger and Levy 1997; Gendelman et al. 1998). This is characterized by both large- and **small-fiber** dysfunction and may be extremely painful. The cause is presumed to be HIV-1 itself, because no other opportunistic infection or other cause (e.g., vitamin deficiency, endocrine abnormality) has been identified as the cause in these patients. Rare cases are caused by vasculitis, requiring a nerve biopsy for diagnosis. An axonal polyneuropathy also has been seen in 10% of patients with WNV encephalitis or meningitis (Nashetal. 2001).

Myositis

Although symptoms of muscle pain (myalgia) commonly accompany a variety of viral infections, true viral myositis is rare. Most cases follow infection with influenza, HIV-1, or enteroviruses. Symptoms of myositis include muscle pain and weakness associated with evidence of muscle fiber injury. Common indicators of muscle fiber injury include elevations in muscle enzymes (creatine kinase, aldolase), a myopathic pattern on electromyographic studies, and evidence of muscle fiber necrosis and inflammation on muscle biopsy. A small number of patients with AIDS develop myopathy, which may be secondary ro treatment with zidovudine or to HIV-1 itself (Berger and Levy 1997; Gendelman er al. 1998). Typical features of a proximal, greater than distal muscle weakness with wasting characterize the latter, which may be painful. Muscle enzyme levels are elevated and the electromyographic result is consistent with muscle damage. This may improve with antiviral therapy.

Neoplastic Transformation

Primary CNS lymphomas are lymphomas that arise in and are restricted to the CNS, usually just the brain. Although primary CNS lymphomas account for just 3% of all brain neoplasms, their incidence is rising in both immunocompromised and immunocompetent patients. In patients with AIDS, nearly 100% of primary CNS lymphomas contain EBV DNA, and more than one half contain human herpes virus 8 (HHV-8, also known as *Kaposfs sarcoma-associated herpes virus)* DNA. In non-AIDS patients with this lymphoma, the percentages are lower, but DNA from both viruses is found. What pathogenic role these viruses play in primary CNS lymphomas is unclear, but both have been associated with other tumors, including other lymphomas. The retrovirus HTLV-I has been associated with both acute T-cell leukemia and the progressive myelopathy HAM. Interestingly, it is extremely rare for one patient to develop both these disorders. This may be caused, in part, by the fact that both are relatively rare. Another possibility is there are variations in either viral or patient characteristics, or both, which predispose individuals to develop one or the other disorder, but these features are unknown at this time.

ROLE OF THE IMMUNE SYSTEM

Age-related attenuation in virus-specific cell-mediated immune responses may play a role in facilitating reactivation of certain latent viruses. Several CNS viral infections result from the reactivation of latent virus infections acquired earlier in life. Common examples include shingles resulting from the reactivation of VZV or herpes labia lis and herpes genitalis resulting from reactivation of HSV. Some forms of reactivation occur almost exclusively in immunocompromised individuals, as exemplified by PML resulting from reactivation of JC virus.

In immunosupprcssed patients, the nature of potential viral infections of the nervous system may change dramatically. Some primary viral CNS infections are seen almost exclusively in the immunosuppresscd (e.g., CMV-induced polyradiculitis, myelitis, and ventriculitis). Immunosuppression also may exacerbate the severity of viral infections. Reactivation of zoster usually leads to the development of shingles limited to a single dermatome, but in an immunocompromised individual it may result in disseminated zoster. Although relatively unusual in patients with AIDS, HSV-1 encephalitis often lacks the typical frontotemporal distribution noted in immunocompetent patients (see previous discussion). Finally, persistent infections resulting from failure of the host's immune system to clear virus may facilitate the development of viruses resistant to antiviral therapy. This is illustrated by the increased frequency of acyclovir-resistant HSV and ganciclovir-resistant CMV isolates in individuals with AIDS.

Activation of the immune system may sometimes contribute to CNS injury. There are several immune-mediated postviral or parainfectious syndromes involving the peripheral nervous system and CNS. The hallmark of many of these syndromes is the presence of demyelination. The pathogenic mechanisms producing demyelination or other types of postviral nervous system injury are not completely understood. In some cases immune-mediated damage may involve the process of molecular mimicry. In this situation, the immune system recognizes an epitope on an infecting virus. This epitope, or one closely related to it, is shared with a protein in the nervous system, often myelin-associated. Because the CNS is relatively sequestered behind the blood-brain barrier, the immune system may not recognize antigens within the nervous system as part of self. In responding to the foreign antigen, the immune system therefore may react inappropriately against this shared epitope.

The Guillain-Barre syndrome, in which multiple peripheral nerves undergo acute demyelination, may be preceded by a viral infection. Common viral antecedents include infection with 1I1V-1, CMV, EBV, and hepatitis viruses. The mechanisms by which antecedent infections precipitate peripheral nerve demyelination are not completely understood. However, cases of Guillam-Rarrc syndrome associated with bacterial infection by *Campylobacter jejuni* may involve molecular mimicry, and an analogous situation may occur following certain viral infections.

Acute disseminated encephalomyelitis is a monophasic illness of the CNS in which demyelination follows infection with a number of viruses, including measles, varicella, rubella, influenza A, mumps, EBV, or preceding vaccination. Generally, the neurological illness follows the systemic illness by days to weeks and may occur in from 1 in 1000 to 1 in 20,000 or more cases, depending on the virus. A postinfectious illness has been described also after HSV-1 encephalitis in adults. This resembles acute disseminated encephalomyelitis and is associated with postinfectious demyelination, rather than reactivation or persistence of HSV infection. MRI scans reveal disseminated white matter disease, and viral DNA is not present in the CSF.

Other examples of postviral syndromes include Reye's syndrome, postpolio syndrome, and chronic fatigue syndrome. The pathogenesis of these syndromes is still poorly understood.

Viruses and Multiple Sclerosis

The cause and pathogenesis of multiple sclerosis (MS) remain incompletely understood, but there is general agreement that both genetical and environmental components play a role. Several lines of evidence have suggested the possibility that one or more viruses might be the environmental factor in MS. JC virus in humans and other viruses in rodents are known to produce demyelination, either by direct infection of oligodendrocytes or by indirect effects of immune overactivity or dysregulation. Viral infection or vaccination often precedes acute disseminated encephalomyelitis, which results in widespread demyelination that is similar pathologically to the acute lesion of MS. Finally, acute viral infections with influenza and other viruses may precede acute exacerbations of MS. A long list of viruses has been investigated as possible etiological agents in MS, Candidate viruses have included paramyxoviruses, corona viruses, retroviruses, and herpesviruses including HHV-6. An etiological role for these viruses in MS has been suggested based on finding elevated titers of specific viral antibodies in the CSF or serum or detection of viral DNA or antigen in the blood, CSF, or brain. In some cases, viruses have reportedly been isolated from CNS tissues of patients with MS. Routinely, further study has shown that the findings cannot be replicated or are nonspecific. The important immunological abnormalities of CSF oligoclonal bands and elevated IgG have not yet been linked to a specific viral infection. Thus although the possibility that MS is related to viral infection is tantalizing, definitive proof of such an association is still lacking,

PATHOGENESIS OF CENTRAL NERVOUS SYSTEM VIRAL INFECTIONS

Stages in Viral Pathogenesis

Viral pathogenesis is the method by which a virus produces disease in the host (Tyler and Nathanson 2001).

Entry

Vituses that infect the CNS must first enter the host, then spread from their initial site of entry to the CNS. Viruses that enter the host typically do so through the respiratory tract, gastrointestinal tract, genitoutinary tract, skin, or ocular conjunctiva. Individual neurotropic viruses use each of these pathways to infect the CNS. Fot example, infections caused by many herpesviruses and HIV may begin at the mucous membranes of the mouth or genital tract. Coxsackie, polio, cchovirus, and enteroviruses enter the host through the gastrointestinal tract following otal inoculation. Viruses transmitted by the bite of arthtopod vectors such as ticks ot mosquitoes (arboviruses) including the togavituses, flaviviruses, and bunyaviruses responsible for most epidemic outbreaks of encephalitis arc transmitted across the skin barrier to the underlying subcutaneous tissues by bite of the vector. More dramatic examples of transdermal inoculation occur when the bite of a tabid animal transmits tabies or a monkey bite transmits herpesvirus simiae into the subcutaneous tissue and muscle.

Viruses are rarely inoculated directly into the bloodstream by arthropod or animal bites but may be iatrogenically introduced ditectly into the blood following transfusion or injection (Tyler and Nathanson 2001). Ttansfusion of blood or blood products has been implicated in the pathogenesis of infection by a variety of potentially neurotropic viruses including HIV, HTl.V-I, HTLV-II, hepatitis viruses, CMV, EBV, parvoviruses (B19), and most recently WNV (MMWR, 2002b).

The respiratory tract provides a portal of entry for such potentially neurotropic viruses as the paramyxoviruses (measles, mumps), certain toga viruses (rubella), and herpesviruses (VZV). In most, but not all, of these cases entry through the respiratory tract usually occurs without initiating respiratory symptoms. Exceptions occur, as when primary varicella (chickenpox) infection is associated with varicella pneumonitis.

A final and rare portal of entry for neurotropic viruses is through the conjunctiva of the eye. Although many viruses can induce conjunctivitis, and conjunctival infection can occur as a secondary manifestation of systemic viral

infections (e.g., measles), the only neurotropic virus to enter the host via this route is enterovirus 70.

Systemic Invasion

The exact cellular pathways used hy neurotropic viruses to initiate systemic invasion following initial entry into the host are understood incompletely (Tyler and Nathanson 2001). Experimental studies following the fate of reoviruses after oral or respiratory inoculation into rodents have provided important insights into this process. Following oral inoculation into neonatal mice, reoviruses adhere to the surface of specialized epithelial cells, referred to as M (microfold) cells, that overlie submucosal collections of small intestinal lymphoid tissue (Peyer's patches). Virus can be followed as it is transported across M cells to the underlying lymphoid tissue, from which it can disseminate to the nervous system by hematogenous or neural spread (vide infra). A similar sequence of events occurs following intratracheal inoculation of reovirus into rats, M cells play a similar role in the transport of poliovirus and HIV following inirial enteric infection.

Polarized Infection

Another important evenr in facilitating systemic invasion by neurotropic viruses may be the capacity of cerrain viruses to be released preferentially from either the apical or basolateral surface of infected cells (polarized infection). In the case of epithelial cells located at mucosal surfaces, apical release of virus favors local spread of infection, whereas basolateral release allows viral access ro submucosal tissues. A number of neurotropic viruses including HIV, poliovirus, and pseudorabies virus are capahle of polarized infection. In the case of both HIV and pseudorabies virus, it appears that viral envelope glycoproteins are inserted preferentially into one side of the cellular membrane and that this site determines the subsequent direction of viral release in polarized epithelial cells. Information that determines the direction of membrane sorting of the envelope glycoproteins is contained in their amino acid sequence (sorting signal).

Spread

Once a neurotropic virus has entered the host, it must then spread to reach the CNS {Tyler and Nathanson 2001). The two predominant pathways for viral spread to the CNS are through the bloodstream and through nerves. As noted, under special circumstances viruses may be inoculared directly into the bloodstream, generating a *passive viremia,* This is distinct from the *active viremia* that is generated following viral replication. Passive viremia is typically brief (<24 hours) and of low titer. Experimental studies with bunyaviruses in mice suggest that less than 0.1% of virus present in a subcutaneous inoculum enters the bloodstream as a passive viremia. In the case of passive viremia, the likelihood that a virus will successfully reach the CNS depends predominantly on the magnitude of the inoculum and the adequacy of host defenses. Factors that impair the capacity of the reticuloendothelial system to clear circulating virus may facilitate CNS invasion.

Viremia

Active viremia may occur in two phases (Tyler and Nathanson 2001). In the initial phase (primary viremia) virus enters the bloodstream after replicating in cells near the site of initial entry. The types of cells depend on both the nature of the infecting virus and the site of entry and may include epithelial cells, lymphoid cells, dendritic cells such as macrophages and Langerhans' cells, adipose, or muscle cells. Primary viremias are typically of brief duration and low titer. They serve to disseminate virus to a variety of organs and tissues where subsequent replication allows for the generation of a more sustained and higher titer viremia (secondary viremia). Typical sites of secondary viral replication in the host include spleen, liver, bone marrow, and endorhelial cells. In contradistinction to passive viremia, the secondary phase of active viremia typically lasts far longer (several days to a week) and are typically several orders of magnitude higher in titer.

Viremia is a dynamic process, the net result of which reflects the continuing introduction of virus into the bloodstream and its subsequent clearance by a variety of host defense mechanisms (Tyler and Nathanson 2001). The duration of time a virus particle spends in the host circulation has been called its *transit time.* Early studies suggest that for most viruses, transit times are between 1 and 60 minutes. The appearance of circulating neutralizing virus specific antibody coincides with, and in most circumstances appears to be responsible for, the abrupt termination of most active viremias. In the presence of antibody, viral transit times arc dramatically reduced. Conversely, inhibirion of host reticuloendothelial phagocytosis can markedly increase viral transit rime.

Viruses that enter the bloodstream may travel free in the plasma, in association with cells, or in both states (Tyler and Nathanson 2001). Most picornaviruses, as exemplified by poliovirus, and most togaviruses travel free in the plasma. Many neurotropic viruses are cell-associated or circulate in both cell-free and cell-associated states. This group includes HIV, the herpesviruses (HSV, VZV, CMV, EBV), measles, mumps, and rubella. Cell-associated virus is associated most commonly with circulating lymphocytes and monocytes and may show striking cell-type specificity, For example, cell-associated HIV is found almost exclusively in $CD4^+$ circulating T lymphocytes and monocytes. Monocyte infection also occurs with CMV, measles, and certain flaviviruses and rogaviruses including dengue and rubella. HTLV-I and HHV-6 and HHV-7 can either acutely

or persistently infect T lymphocytes. Conversely, EBV preferentially replicates in circulating B lymphocytes. The arbovirus, Colorado tick fever virus, provides an unusual example of virus associated with erythrocytes. Colorado tick fever virus initially infects erythroid precursor cells in the bone marrow (as these cells mature they are released into the circulation, carrying virus with them). Although some viruses have been found in association with circulating neutrophils or platelets, the importance of this association remains to be established.

In many cases only a small percentage of potentially susceptible circulating cells actually harbor infectious virus; however, this can vary dramatically with the particular virus and state of disease in the host. The frequency of cell infection has been studied extensively in HIV-positive humans. There is a general correlation between the severity of disease and the proportion of infected cells. For example, only 0.2-10.0% of $CD4^1$ T lymphocytes of asymptomatic HIV-positive individuals are HIV infected. This percentage can increase to as high as 60% in individuals with advanced AIDS, The percentage of cells that harbor HIV genome, as detected by ISH or *in situ* PCR appears to be significantly higher than the percentage of cells from which infectious virus can be isolated.

As noted, active plasma vircmia is typically terminated by the appearance of virus-specific antibody (Tyler and Nathanson 2001). Phagocytic cells in reticuloendothelial organs such as the liver or spleen clear virus-antibody complexes from the circulation. In many cases the binding of the Fc portion of the antiviral antibody molecule to specific receptors on the surface of macrophages and other phagocytic cells facilitates this process. Under certain circumstances viral-antibody complexes may retain infectivity and Fc receptor-mediated binding may actually provide a route of entry that allows viral infection of target cells. This process is referred to as *antibody-mediated enhancement* and has been shown to play an important role in the pathogenesis of Dengue virus infection. At times the host may fail to mount an antibody response to a circulating virus. Examples of such host tolerance can occur following congenital infection with lymphocytic choriomeningitis virus or when immunosuppression prevents the host from producing antibody.

Central Nervous System Invasion and the Blood-Brain Barrier

The mechanism by which circulating viruses exit the bloodstream to invade target tissues is still poorly understood (Tyler and Nathanson 2001). This problem is particularly complex in the CNS where the existence of the blood-brain barrier adds an additional anatomical dimension not present in other organs. The anatomical substrate for the blood-brain barrier includes high-resistance tight junctions {zona occludens) between brain capillary endothelial cells. The capillary endothelial cells are separated from brain parenchyma by a dense basement membrane. The basement membrane is covered on its parenchymal-facing surface by a complex network of processes derived from CNS astrocytes. The blood-brain barrier should be considered a selectively permeable barrier. Many small molecules (<30 kD} can cross freely, as can lipophilic compounds. A variety of transport systems also allow for facilitated transport of substances including D-glucose, essential neutral amino acids, and certain circulating peptides including insulin.

Any process that disrupts the integrity of the blood-brain barrier can facilitate viral invasion of the CNS. Experiment.! I ly, this is illustrated by the enhanced CNS invasion of certain neurotropic viruses that follows pretreatment of animals with vasoactive amines or carbon monoxide.

It has long been suggested that bloodborne viruses may invade the CNS at specific anatomical sites (loci minoris resistante) in which the capillary endothelial cells are not joined by tight junctions (fenestrated capillary endothelium), the basement membrane is sparse, and astrocyte foot processes are scant or absent (Tyler and Nathanson 2001). These areas include the choroid plexus, circumvcntricular organs (area postrema, median eminence, subfornical and subcommissural organs), and the posterior pituitary. Under experimental condirions several bloodborne neurotropic viruses including mumps, rat parvovirus, and both Western and Eastern encephalitis viruses can be shown to initiate CNS infection through the choroid plexus. This route of infection is likely to occur in many types of viral infection in which hydrocephalus is a prominent feature. The infection and subsequent sloughing of ependymal cells obstruct the flow of CSF and contributes to subsequent induction of obstructive hydrocephalus. Infection of the stroma of the choroid plexus is followed by infection of choroid plexus epithelial cells and subsequent entry of virus into the ventricular CSF. Virus then spreads from the ventricular CSF to infect the ependymal cells lining the ventricles and the subependymal tissues.

Some viruses can directly infect cerebral capillary endothelial cells and can spread from these cells into the surrounding brain tissue (Tyler and Nathanson 2001). Among the neurotropic viruses that have been visualized inside cerebral endothelial cells by electron microscopy or shown to be capable of growing in endothelial cells are picornaviruses, such as poliovirus and Theiler's virus, togaviruses, bunyaviruses, reoviruses, CMV, and several retroviruses including HIV.

Another potential mechanism of viral CNS infection has been evocatively referred to as the *Trojan horse* model (Tyler and Nathanson 2001), In this model viruses infect and are transported within circulating cells, which subsequently enter the CNS via diapedesis, bringing virus with them. This model was described originally for lentivirus infection but is likely to be of more generalized importance. Indirect support for this model as

a mechanism of CNS invasion following HIV infection comes from the fact that most HIV strains isolated from CNS tissue are macrophage tropic, and most HIV-infected cells within the CNS are of microglial-macrophage lineage.

In addition to monocytes and macrophages, several additional types of cells including neutrophils and lymphocytes are capable of crossing the blood-brain barrier by diapedesis. The molecular mechanisms involved in this process are beginning to be unraveled and include the interaction between specific cellular receptors and molecules on endothelial cell surfaces including leukocyte function antigens, intercellular adhesion molecules (ICAMs), vascular cell adhesion molecules (VCAMs), and intcgrins. Chemokines, such as macrophage inhibitory protein-la and monocyte chemoattractaiit protein secreted by macrophages may serve as chemotactic factors enhancing lymphocyte or monocyte migration into CNS tissue. Macrophages may also secrete nitric oxide and other free radicals that can react to form neurotoxic molecules or enzymes (e.g., gelatinase B) that degrade matrix proteins and thereby facilitate cellular penetration of the subendothclial basement membrane.

Specific receptors have been identified for many of the inducible adhesion molecules including ICAM-1, which binds to lymphocyte function-associated antigen (LFA-1) on lymphocytes and macrophage-1 antigen on monocytes, and VCAM-1, which binds to very late activation antigen-4 (VLA-4). In some models of CNS infection or inflammatory disease (e.g., experimental allergic encephalomyelitis) antibodies directed against ICAM-1, VCAM-1, or their respective receptors (LFA-1, VLA-4) can be shown to inhibit binding of lymphocytes to brain capillary endothelium and the subsequent diapedesis of lymphocytes into brain parenchyma. Infection with viruses including measles and HIV can alter the expression of LFA-1, CD11/CD18 integrins, ICAM-1, VCAMs, and other similar molecules, thereby facilitating egress and extravascular dissemination of lymphocytes and related cells from the circulation into brain tissue.

Neural Spread

Another major pathway of spread for neurotropic viruses from the site of entry to the CNS is through nerves (neural spread) (Tyler and Nathanson 2001). Viruses capable of spreading through nerves include HSV, rabies, poliovirus, reovirus, pseudorabies, coronaviruses, and Borna disease virus. Experimental studies have established certain basic features of neural spread that seem to be common to a large number of neurotropic viruses. Although replication in non-neural rissue (e.g., muscle cells for rabies) typically precedes viral entry into nerves, ir is not essential. This was elegantly demonstrated in studies by Bodian and colleagues with polioviruses in monkeys. In these animals, immersion of the distal stump of the sciatic nerve in a solution of poliovirus was sufficient to induce paralytic poliomyelitis. Although some viruses, such as HSV, are capable of infecting perineural cells including Schwann cells, the physiologically important route of neural spread is through axoplasmic transport within neurons. The axoplasmic transport of viruses has been demonstrated repeatedly by ultrastructural visualization of virions or viral nucleocapsids within the axons of neurons. The process has been studied also using cultured neurons in which the neural cell body and its processes are isolated from each other in a specially designed multichamber tissue culture system. The effects of initiating infection at the cell soma or via the distal end of axons can then be investigated.

Examples exist in which neurally spreading viruses travel within axons of motor, sensory, or autonomic neurons, suggesting that all types of neural cells can participate in this process. Depending on the initial site of infection and the particular virus, neural spread may involve either the anterograde or retrograde systems of transport. Studies of the kinetics of viral spread and the effects of pharmacological inhibitors indicate that neural spread occurs predominantly and perhaps exclusively via the microtubule-associated system of fast axonal transport. Some viruses, including reoviruses, can be shown to bind directly to microtubules, although it appears likely that transport is mediated by virus contained within microtubule-associated vesicles rather than by the direct interaction of virions with the mierotubular transport system,

All neurally spreading viruses also appear to be capable of transncuronal spread. Conceivably, this spread may occur at either synaptic or nonsynaptic sites. However, studies in which viruses such as HSV, coronavirus, or pseudorabies virus have been used as neuroanatomical tracers suggest that transncuronal transport occurs within particular pathways and that viruses do not promiscuously jump from one nerve fiber to an anatomically unrelated fiber system that lies in contiguity or proximity. This suggests that trans-synaptic transport may be more functionally important than nonsynaptic transport. Neurons, like epithelial cells, are polarized cells. The typical neuron has a cell body with short dendritic processes and a long axon. Selective entry and subsequent release of viral particles from distinct parts of the cell may facilitate trans-synaptic spread of virus. There is evidence, on at least some types of neurons, that the cell receptors for certain viruses, including HSV and rabies, may be concentrated near synaptic terminals. Similarly, in certain experimental models of infection, rabies virions accumulate in muscle cells near the neuromuscular junction.

Viruses that are capable of spreading to the CNS through nerves escape the inhibitory effects of the blood-brain barrier. Many nerve cells, including the motor neurons of the spinal cord, the sensory neurons within dorsal root ganglia, and olfactory neurons have processes that extend outside the blood-brain barrier, A virus, such as rabies, that enters motor neuron axons in the periphery (e.g., at the neuromuscular junction) is transported retrograde directly

into the CNS. Experimentally, it can be shown that certain neurotropic viruses including reovirus, poliovirus, pseudorabies virus, and swine hemagglutinating encephalomyelitis virus, which can enter the host through the intestine, infect neurons in the myenteric plexus and are then transported to the CNS via the vagal nerve to reach the dorsal motor nucleus of the vagus in the medulla.

It is important to recognize that hematogenous and neural spread need not be mutually exclusive processes. Some viruses use different pathways of spread at different stages in their life cycle. For example, VZV spreads via the bloodstream to the skin to produce the characteristic rash of chickenpox. Virus then spreads centripetally through the axons of sensory nerves to reach their cell bodies in dorsal root ganglia. Reactivation of varicella from dorsal root ganglions results in centrifugal spread of virus from the cell bodies of sensory neurons to specific skin dermatomes to produce zoster. In some cases, different strains of the same virus use different pathways to spread to the CNS. For example, after inttamuscular inoculation into mice reovirus serotype 1 Lang (TIL) spreads predominantly via the bloodstream to reach the spinal cord, whereas reovirus serotype 3 Dearing (T3D) spreads via nerves.

The penetration of a neurotropic virus into the CNS depends on its pathway of spread (Tyler and Nathanson 2001). As noted, neutally spreading viruses such as rabies, HSV, and VZV can enter the peripheral axons of either motor neurons or the peripheral processes of bipolar sensory neurons. Once inside these cells, virions or virion nucleocapsids are transported into the CNS via axoplasmic transport. The rods of olfactory receptor cells, a special class of sensory neurons, also lie outside the CNS within the epithelium of the nasal mucosa. Many neurotropic viruses including HSV, coronaviruses, poliovirus, vesicular stomatitis virus, and certain togaviruses can be shown to infect olfactory neurons under experimental conditions. From these neurons, virus can then spread sequentially to the olfactory bulb and enterorhinal cortex. Although experimental studies have demonstrated repeatedly that olfactory spread is a feasible pathway for viral invasion of the CNS, it has been difficult to definitely demonstrate that this pathway is of importance for the pathogenesis of naturally occurring human CNS infection. However, there are isolated cases of herpes simplex encephalitis and rabies infection following massive aerosol exposure in which the neuropathological features are consistent with this method of CNS infection.

Neurotropism

Once a virus has invaded the CNS, the clinical features of illness depend on the regions of the CNS that are infected and subsequently injured by the virus. The capacity of a virus to infect specific populations of cells is referred to as *tropism,* and when infection involves cells within the CNS, as *neurotropism.* When a virus specifically infects neurons within the CNS it is occasionally referred to as *neuronotropic.*

Tropism is the end result of a complex and multifactorial interaction between an infecting virus and a host (Tyler and Nathanson 2001). Factors that can influence tropism include (1) epidemiological factors including the age, sex, immune status, and genetical composition of the host; (2) the site of entry and pathway of spread of a virus within the host; (3) the interaction between the virion cell attachment protein and target cell receptors on host cells; and (4) viral proteins that enhance transcription of viral proteins in a cell- or tissue-specific manner.

Viral Receptors

One of the most dramatic and productive areas of viral research has been the identification of host cell receptors fot a large number of viruses (Tyler and Nathanson 2001). Examples of receptors for neurotropic viruses are shown in Table 46.2.

In some cases the assignment of a specific host cell receptor remains controversial. It has also become clear that many viruses are capable of using more than one cellular receptor and in some cases more than one pathway to enter cells {e.g., direct membrane penetration and receptor-mediated endocytosis). Different strains of the same virus may also use different host cell receptors. For many viruses, as exemplified by the herpesviruses, the interaction with host cell receptors is a complex process that involves the interaction of multiple virion surface proteins with the target cell (Tyler and Nathanson 2001). Similarly, for viruses such as HIV, additional cell surface proteins serve as coreceptor molecules that can dramatically influence the success with which the virion binds to its primary receptor (Berger and Levy 1997; Gcndelman et al. 1998). The first of the HIV coreceptor molecules identified was fusin (CXCR-4), a G-p rote in-like transmembrane protein, which functions as a coreceptor for T-lymphocyte tropic viral strains. Subsequently, a variety of molecules were found to serve as coreceptors for macrophage-tropic HIV strains including the /3-chcmokine receptors for macrophage inhibitory protein-la, macrophage inhibitory protein-lb, and RANTES (CCR3, CCR5). HIV also illustrates the fact that a single virus can use different receptors to infect distinct classes of cells. For example, although CD4 and the coreceptor molecules CXCR4, CCR3, and CCR5 arc key determinants of microglial infection, galactosylceramide or related glycolipids appear to be the critical receptor for HIV on colonic and cervical epithelial cells and certain types of cultured neuroblastoma cells.

Viral Effects on Target Celts

The interaction between a virus and a target cell can have a variety of outcomes (Tyler and Nathanson 2001). Some

Table 46.2: l-'.x:jniples DI neurotropic viruses and their host cell receptors

Family	*Example*	*Receptor*
Arenaviridae	LCMV	ot-Dystroglycan
Coronaviridae	MHV	Carcinoembryonic antigen family
Hcrpcsviridae	EBV	CD21 (CR2 receptor)
	HSV	Heparan sulfate
		HVEM
		PVR-1
	Pseudorabies	Heparan sulfate
		PVR-1
	CMV	Heparan sulfate
		^-Microglobulin
Myxoviridae	Influenza	Sialic acid residues
	Measles	CD46
		Moesin
Parvoviridae	Parvovirus B19	Erythrocyte P antigen
Picomaviridae	Coxsackievirus	Decay accelerating factor (CD55)
		Vitronectin receptor
		Inregrin a_v^j
	Kchovirus	Jntegrin VLA-2 (a_2/j,)
	Polio virus	IgGsuperfamily (PVR)
Reoviridae	Reovirus T3D	Sialic acid residues
		JAM
Retroviridae	HIV	CD4
		Chcmokinc receptors (CXCR5, CCR4)
		Galactosylceramide
Rhabdoviridac	Rabies	Acetylcholine receptor
		NCAM
		NGF-R
		Gangliosides
		Phospholipids [phosphatidyl serine)
Togaviridae	Sindbis	Lam in in receptor

CMV = cytomegalovirus; EBV = Epstein-Barr virus; HIV = human immunodeficiency virus; HSV = herpes simplex virus; JAM = Junctional adhesion molecule, MHV = mouse hepatitis virus; NCAM = neural cell adhesion molecule, NGF-R = nerve growth factor receptor, PVR = poliovirus receptor related protein; VLA-2 = very late activation antigen-2.

viruses are capable of becoming latent in neurons. In this situation, infected neurons contain viral genomes, either integrated into their DNA or episomally. Latently infected cells may display little or no obvious alteration in morphology or function. Viral latency in neuronal cells has been extensively studied for HSV, although the molecular mechanisms underlying the establishment, maintenance, and reactivation from latency are still only incompletely understood. Much research has involved attempts to identify viral genes, transcripts, or proteins expressed during latency (e.g., latency-associated transcripts) and the interplay between these factors and host cell proteins including trophic factors (e.g., nerve growth factor) and signal transduction proteins.

In some cases, infection of neuronal cells can result in perturbation of differentiated cellular functions without striking alterations in cellular morphology. For example, viral infection results in diminished production of growth hormone by infected, but morphologically normal, pituitary cells. The resulting growth hormone deficiency accounts for a dramatic Hunting syndrome in infected mice. Another example is inhibition of production of various ncurotransmittcr-rclated proteins, including tyrosine hydroxylase, choline acetyltransferase, and acetylcholinesterase, in virus-infected cells.

Virus infection can also lead to cell death. There are two major forms of cell death: necrosis and apoptosis, Apoptotic cell death is characterized by shrinkage and cytoplasmic membrane blebbing (zeiosis) associated with compacting, margination, and fragmenrarion of nuclear chromatin. In many cases the chromatin fragmentation occurs predominantly where nucleosomes are bound to DNA. This internucleosomal cleavage resulrs in the generation of DNA fragments that arc mulriplcs of 180—200 nucleotide base pairs in length. This oligonucleosomal ladder of DNA fragments can be visualized by isolating DNA from apoptotic cells and clcctrophorcsing it on agarose gels followed by rhe use of DNA sraining dyes (e.g., ethidium bromide). Their characteristic ultrastructural or morphological changes and demonstration of DNA fragmentation typically identify apoptotic cells in tissues. One method of demonstrating this fragmentation in cells involves terminal deoxytidyl nick end-labeling, which makes use of the fact that apoptotic DNA fragmentation produces large numbers of DNA ends containing 3'OH groups. A biotinylated or otherwise labeled nucleotide is added to these free ends using terminal deoxynucleotidyl transferase. The labeled nucleoride is then identified immunocy toe hemic ally or by immunofluorescence. It is important to recognize that terminal deoxytidyl nick end-labeling staining alone is not pathognomonic for apoptosis and that accurate identification of apoptotic cells requires demonstration of both the characteristic morphological changes and associated evidence of DNA fragmentation.

In contradistinction to apoptotic cell death, necrotic cell death is characterized by early failure of cytoplasmic membrane integrity. The resulting release of intracellular proteins, including a variety of enzymes, typically induces a prominent inflammatory response. DNA fragmentation occurs in necrotic cells, but the fragments are of a wide variety of sizes, and fragmentation does not occur predominantly at internucleosomal points.

Many neuronotropic viruses have been shown to induce apoptosis in cultured cells including neurons. Examples of neurotropic viruses capable of inducing apoptosis in cell culture include bunyaviruses (LaCrosse), herpesviruses (VZV), picornaviruses (poliovirus, Thcilcr's virus), reoviruses (T.3D), retroviruses (HIV-1, HTLV-I), rhabdoviruses (rabies virus), and togaviruses (Sindbis), Several of these viruses, including LaCrosse, Theiler's virus, reovirus,

HIV-1, and Sindbis, have been shown also to produce apoptosis in vivo. In many cases an excellent correlation exists between the distribution of viral infectivity as demonstrated by immunocytochemistry to localize viral antigens or ISH to localize viral nucleic acid, apoptotic cells, and neuropathological injury,

The viral and cellular mechanisms responsible for induction of apoptosis are still incompletely understood. For some viruses experimental studies have identified specific viral genes or proteins that may be important in induction of apoptosis including the <r1 protein of reoviruses, gpl20 of HIV, and E2 glycoprotein of Sindbis. The mechanism by which these viruses trigger apoptosis is gradually becoming better understood. In some cases viral infection may result in activation of proteases involved in apoptotic cascades, as exemplified by calpain activation during reovirus infection of cultured cells. In other cases apoptosis may be triggered by virus-induced alterations in intracellular calcium concentration, a mechanism suggested for HIV gpI20-induced neuronal cell death. Infection of cells with viruses including reovirus, Sindbis, and HTLV-I may perturb signal transduction pathways that lead to the activation of transcription factors that in turn induce gene activation resulting in apoptosis. This pathway has been elegantly elucidated for HTLV-I. HTLV-I *tax* protein interacts with and activates the cellular kinase MEKK1. Activated MEKK1 phosphorylates and thereby activates the I/cB kinase. kB kinase phosphorylates LrB. kB is complexed with NF»rB in the cytoplasm. **The** cytoplasmic NF^B-kB complex is inactive. However, once kB is phosphorylated by kB kinase it is rapidly ubiquitinated and degraded. NF/fB is then free to translocate to the nucleus, where it functions as a transcriptional activator. The results of NFKB-dependent transactivation may be either proapoptotic or antiapoptotic depending on the nature of the inducing stimulus and the cell type. In many viral systems the end effect of NFVB activation seems to be proapoptotic as inhibition of its activation inhibits virus-induced apoptosis.

DIAGNOSTIC TECHNIQUES

The diagnosis of CNS viral infections has evolved in parallel with the increasing sophistication in research techniques. In the seventeenth and eighteenth centuries, the classification of CNS diseases was based predominantly on their cardinal symptoms. Most cases of what would today be recognized as viral encephalitis or meningitis were simply considered brain fevers. In a similar vein, rabies virus infection was typically included under the descriptive term "hydrophobia," and many cases of viral myelitis were lumped together under designations such as "debility of the lower extremities."

In the nineteenth century, improved methods for the fixation and staining of tissues and enhancement in the quality of microscopical optics ushered in a golden era for pathology in general, and neuropathology in particular. Neurological diseases, including those caused by viruses, were now characterized and classified according to the regions of the CNS involved and the nature of the pathological injury. Improved nosology of neurological disease reflected the new emphasis on neuropathology, as exemplified in Charcot's classic descriptions of poliomyelitis, the name reflecting the predominant involvement of the gray matter of the spinal cord and the associated inflammation.

The nineteenth century also saw the first attempts to systematically examine how specific pathogens produced disease. In the area of ncurovirology this was strikingly demonstrated in Pasteur's studies of rabies virus. Pasteur carefully elucidated rabies' mode of infection, route of spread, and localization within nervous tissue. Pasteur's work can be said to have inaugurated the scientific study of both microbial pathogenesis in general and the pathogenesis of viral CNS infections in particular.

Early studies of the pathogenesis of CNS viral infection were limited by their almost exclusive dependence on visualizing pathological alterations in tissue as a marker for viral infection. In some cases this was facilitated by the presence of specific markers of viral infection such as the cytoplasmic Negri and Lyssa body inclusions in rabies and the Cowdry type A intranuclear inclusions seen in herpesvirus infections. The availability of electron microscopy allowed viral particles to be identified in both biopsy and autopsy tissues derived from patients with CNS viral infections. However, electron microscopy was too cumbersome to permit routine quantification of the number of viral parricles or the sequential tracking of the development and spread of virus infection.

The advent in the 1950s of tissue culture systems to cultivate viruses allowed for easier and more precise quantification of the amount of virus present in particular tissues. Another significant advance was the ability ro localize viral antigens in tissue using immunocytochemica! methods. This began following Coons's description in the late 1940s of techniques to couple antibodies with fluorescent molecules and the use of these antibodies to localize antigens in tissues. This technique was not applied to the study of CNS viral infection in any comprehensive manner until the 1960s when R. T. Johnson used fluorescein-conjugated antiviral antibodies to study the spread of HSV and Sindbis virus to the CNS.

In the modern era, immu no flu orescent techniques have been supplemented by immunocytochemical techniques in which antibodies arc linked, either directly or indirectly via avidin-biotin or similar coupling reactions, to enzymes such as horseradish peroxidase, alkaline phosphatase, or glucose oxidase. Antigen-antibody binding is then detected by use of a criminogenic substrate. The availability of monoclonal antibodies directed against specific epitopes on individual viral proteins has further extended the range of immunocytochemical studies.

Techniques to identify the presence of viral nucleic acid, including genomic RNA or DNA, and messenger RNAs has added another valuable ser of tools ro studying the localization and pathogenesis of CNS viral infections. Initially, these studies involved the localization of labeled probes complementary to viral mRNA or gene sequences, a technique known as ISH. PCR has also added an invaluable diagnostic tool (see later in this section).

A variety of clinical features should raise the possibility of CNS viral infection. These include fever, meningismus, altered or depressed consciousness, and focal neurological signs. Sometimes the specific clinical scenario combined with results from CSF analysis, neuroimaging srudies, and EEG may allow a presumptive diagnosis of a viral CNS infection. For example, in an immunocompetent adult patient in the United States who presents during the winter with acute onset of fever, depressed consciousness, and seizures, HSV-I encephalitis is an important diagnostic consideration. A number of reviews of the role of laboratory investigation in the diagnosis and management of HSV encephalitis have now appeared. If the CSF profile, neuroimaging studies, and EEG are consistent with this diagnosis, then empirical antiviral therapy with acyclovir should be instituted promptly. However, a significant number of patients with clinical and laboratory features indistinguishable from HSV-1 encephalitis have other treatable viral and nonviral diseases. Because all currently available antiviral drugs are efficacious only against particular viruses, it becomes critical to develop fast, sensitive, and specific techniques for viral diagnosis.

Before the application of molecular biological techniques to vira! diagnosis, identification of viral infections depended on culture, serology, and antigen detection (see Table 46.1). Viruses can be cultured from body fluids including CSF (many viruses), blood or blood cells (herpesviruses, retroviruses), urine (CMV), feces (poliovirus, echovirus), nasopharyngeal washings (enteroviruses, mumps, adenovirus, influenza viruses), or tissues such as skin lesions (HSV-1 and -2, VZV) or brain (many viruses). Systems used for isolation of virus include a variety of cultured cell lines, chick embryo chorioallantoic membranes, and direct inoculation into neonatal mice. The sensitivity of these methods varies widely and depends on the particular virus and the specimen being tested. In general, viral isolation is slow, inefficient, and expensive.

Several immunological tests are available to identify acute viral infection of the nervous system. Most commonly used tests arc designed to quantify levels of virus-specific antibodies. For many viral infections, demonstration of a fourfold or greater increase in virus-specific antibody titers between acute and convalescent sera is diagnostic of acute infection. Demonstration of virus-specific antibody in a single scrum specimen is generally not adequate to diagnose an acute viral infection, because it may merely indicate past exposure. The presence of virus-specific IgM in serum or CSF is usually indicative of recent infection, because IgM antibody rarely persists for more than a few months. Detection of intrathecal virus-specific antibody production is a useful diagnostic test for many CNS viral infections. However, increases in virus-specific antibody in the CSF may result from breakdown of the blood-brain barrier or from polyclonal immune activation as occurs in certain diseases including systemic lupus erythematosus and MS. Correcting for leakage of protein across the blood-brain barrier using the CSF to serum albumin ratio may enhance the specificity of intrathecal antibody tests. Showing that intrathecal antibody responses arc limited to a particular virus, rather than part of a more general phenomenon, also enhances the specificity of antibody testing. When antibody production resulrs from activation of a few discrete B-cell clones within the CNS compartment, oligoclonal bands may be detected in CSF. Oligoclonal bands are not specific for viral infection and occur in a wide variety of immunological neurological diseases. Virus-specific antibody responses are rarely detectable until 2 or 3 weeks after onset of illness, and hence an increase in such a titer between acute and convalescent sera is required for diagnosis. As a result, serological tests arc rarely useful in acute diagnosis and management of viral infections.

Diagnosis of specific viral infections can be made also by identification of viral antigens in tissues or body fluids including CSF. The most commonly employed techniques use radiolabeled or enzyme-linked antibodies in immunosorbent assays. Viral antigens in tissues or cells can be identified using enzyme-linked or fluorescent-labeled virus-specific antibodies. In general, detection of viral antigens provides rapid, sensitive, and specific diagnosis, but the techniques are suitable for only a limited number of viral infections. The major limitation of the technique is the requirement that virus-infected tissue be available for study. In the case of viral CNS infections, this often requires brain biopsy, because antigen is only rarely detectable in CSF.

The application of molecular biological techniques to the diagnosis of viral CNS infections has revolutionized diagnosis. The most useful techniques are designed to identify viral nucleic acid in body fluids or tissue specimens. For analysis of intact tissues, ISH with radiolabeled or enzyme-labeled (especially horseradish peroxidase and digoxigenin) viral nucleic acid probes allows for reasonably rapid viral identification. This technique also has been adapted for use with small populations of cells, as might be available from body fluids such as saliva or urine. The major advantages of this technique are its great specificity and its capacity to detect even a few copies of the viral nucleic acid. ISH is useful also in identifying individual infected cells in tissue specimens.

After extracting cellular and genomic DNA or RNA from a tissue, two basic techniques, immunoblotring and PCR, can be used to determine whether viral nucleic acid is present in the sample. The older techniques, Southern hybridization for DNA and Northern hybridization for RNA, involve the same hybridization techniques described

previously for ISH, except the target nucleic acid has been extracted from the infected tissue, digested with restriction end on ue leases, run on a gel, and transferred and fixed to a membrane. The advantages of these techniques are the same as for ISH, and they are technically simpler. Their only disadvantage is the inability to identify which cells in a population are infected, but this has little effect on the clinical management of the patient.

The major revolution in diagnostic virology has been the rapid development of PCR {DcBiasi and Tyler 1999). By using known nucleotide sequences 20 bases or longer as primers, PCR allows for amplification of tiny quantities of whole genes or just fragments of genes of interest. In its simplest form, this is performed as liquid PCR, with a single set of primers, using exttacted DNA or RNA samples. Aliquots of the amplified nucleic acid arc run on a gel containing ethidium bromide and visualized under ultra-violet light. This is a highly specific and sensitive technique, which is able to identify a small number of copies of viral nucleic acid among thousands ot cells. Technical and methodological advances have allowed for even greater sensitivity and specificity, so that single copies of genes can often be identified in samples of nucleic acid derived from large numbers of cells. These advances include the addition of a hybridization step after running the sample on a gel; the use of nested PCR, in which a PCR reaction is first done with an outer set of primers, and then a small aliquot of this fitst teaction is subjected to a second round of PCR using an inner set of primers that are contained within the first amplified gene prod net; and *in situ* PCR, in which PCR is done on intact tissues and followed by ISH. In clinical laboratory practice nearly all PCR tests involve liquid PCR of target nucleic acid extracted from body fluids or tissues. For viral meningoencephalitis, PCR of CSF or other body fluids is the study of choice. Reptoduciblc protocols exist for HSV-1 and -2, CMV, EBV, VZV, HHV-6, HIV-1, and enteroviruses.

Sensitivity of PCR varies according to the tissue or body fluid from which the nucleic acid is derived and the viral genes assayed. For example, from patients with AIDS with biopsy-proven PML, JC virus can be amplified from 100% of brain samples, 89% of peripheral blood lymphocytes, and 79% of CSF samples. By contrast, sensitivity of HSV PCR from CSF of patients with biopsy-proven HSV-1 encephalitis is extremely high and exceeds 95%. There have been reports of false-negative HSV PCRs obtained during the first 72 hours of infection (Weil et al. 2002). The incidence of positive PCRs also declines with time following infection and associated therapy. Only "~20% of CSF PCRs remain positive after day 14 of illness.

In asymptomatic immunocompetent individuals the CSF does not contain amplifiablc viral nucleic acid. The finding in the appropriate clinical setting of viral nucleic acid in CSF by PCR is virtually diagnostic of viral CNS infection. Extensive experience suggests that false-positive CSF PCR results arc extremely rare when the test is performed by a reliable laboratory according to generally accepted techniques designed to minimize the risk of inadvertent contamination. The value of a negative CSF PCR test result in excluding a specific viral infection varies with the specific virus and the clinical setting.

PCR has been used also to amplify viral nucleic acid directly from brain tissue. The sensitivity and specificity of brain tissue PCR have not yet been established. Initial studies suggest that PCR may amplify viral nucleic acid from the brain tissue of asymptomatic individuals without known or neuropathologically evident neurological disease. The frequency of positive brain tissue PCR results depends on the specific virus, the PCR techniques, and the region of the brain being examined. The high incidence of positive brain tissue PCR results in apparently normal individuals means that extreme caution should be exercised in interpreting positive brain tissue PCR results as evidence for acute viral infection. Positive brain tissue PCR results have been used also to suggest a viral cause for a diverse group of neurological disorders including Rasmussen's syndrome, MS, epilepsy, and Alzheimer's disease. These associations should be considered suspect until more information about brain tissue PCR becomes available.

THERAPY

Therapy for viral infections of the nervous system can be categorized as preventive, supportive, or antiviral (Rcding-ton and Tyler 2002). The simplest preventive therapies are designed to eliminate or greatly reduce the likelihood of inoculation with potential infectious agents. This can include public health measures such as mosquito or tick eradication programs and improvement of sewage systems and aggressive eradication of insects and mammals infected with tabics or arboviruses; blood transfusion screening programs to avoid transmission of HIV-1, hepatitis B and C, HTLV-I, and other infections via blood products; and education programs, such as the promotion of safe sex programs to limit the risk of transmission of sexually transmitted diseases, or efforts to increase the number of homes with screened windows and doors in areas with arbovirus epidemics. Changes in personal behavior, such as elimination of unsafe sexual practices (to avoid contact with, e.g., HIV-1) or changing of work schedules (to avoid exposure at high-risk times to arboviruses) also may be extremely important. Postexposure practices such as removal of ticks or proper wound care (e.g., in rabies permitting bleeding and washing with inactivating soap and water) also may reduce the risk of viral transmission in some cases.

The other significant approach to prevention is immu-noprophylaxis with vaccines. Traditionally, vaccines have been divided into *live attenuated vaccines,* producing infection with and immune response to nonvirulcnt strains of virus, and immunization with *inactivated, non-replicating virus vaccines.* Recombinant DNA technology

has produced vaccines that stimulate immune responses directed against single viral antigens or subunits of antigens. The antiviral vaccines routinely administered in the United States during early childhood, including those to mumps, measles, varicella, polio, and rubella viruses, all are live, attenuated vaccines, which may retain a certain amount of pathogenicity or may revert to a more neurovirulcnt form. This may pose a relatively higher risk of the use of these vaccines in immunocompromised patients, who may not cleat the infection properly. In the United States, the relative risk of paralytic complications of oral polio vaccine is increased markedly in the immunocompromised patient population. The vaccine to Japanese encephalitis virus, used extensively in Japan, China, and other areas of the Far East, is inactivated. The inactivated rabies vaccine is used both for preexposure prophylaxis in individuals at relatively high risk of bites from rabid animals and in combination with human rabies immune glohulin for postexposure prophylaxis.

Supportive and Symptomatic Therapy

After onset of viral infections of rhe nervous system, supportive care can be very helpful. For the common viral meningitides and encephalitides, this may include bed rest, analgesics, anticonvulsants, and antipyretics. Aggressive management of pneumonia and other bacterial infections, hypotension, dysautonomia, and elevated intracranial pressure may be crucial in more severe infections such as rabies or EEEV. Judicious use of high-dose glucocorticoids in the first several (.lays ot HSV-1 encephalitis therapy, when there is a great deal of cerebral edema and the risk of herniation is high, may be useful, although this has not been properly studied. After resolution of the acute neurological illness, rehabilitative services may be a necessary and important part of the patient's return to his or her usual activities.

For postinfectious neurological illnesses, modulation or alteration of the immune system may have positive results. In Guillain-Barrc syndrome, both plasmapheresis and administration of intravenous immunoglobulin have been shown to significantly reduce morbidity. In acute disseminated encephalomyelitis and related postinfectious demyelinating disorders, high doses of intravenous glucocorticoids typically arc used, although their efficacy has never been established.

The era of antiviral drug use in nervous system infections was ushered in with the landmark studies of Whitley and colleagues, who looked first at adenosine arabiuoside and subsequently acyclovir in the treatment of HSV-1 encephalitis. Their studies showed a clear, significant effect of acyclovir in reducing mortality, especially if given early in the course of the illness, and morbidity. Subsequently, acyclovir has been shown effective against VZV, also a member of the alpha-herpesvirus subfamily.

All of the antiviral therapies developed to date interrupt one or more crucial steps in the life cycle of the replicating virus. Acyclovir inhibits the HSV-encoded DNA polymerase. The active metabolite is acyclovir triphosphate. The initial phosphorylation of acyclovir occurs much more efficiently in virus-infected cells, because it requires a virus-encoded enzyme (thymidine kinase). This selective phosphorylation, and the fact that acyclovir triphosphate is a much more potent inhibitor of HSV DNA polymerase than human DNA polymerase, accounts for acyclovir's specificity of action. Acyclovir is not effective as an antiviral agent against viruses that lack a DNA polymerase (e.g., RNA viruses) or against DNA viruses without a virus-encoded thymidine kinase (e.g., CMV). The newer antiviral drugs famciclovir and valacyclovir have similar mechanisms of action and specificity as acyclovir. The primary advantage of these agents is their enhanced bioavailability after oral administration and their longer half-life that permits less frequent dosing intervals.

Ganciclovir has a similar mechanism of action to acyclovir. Its major advantage is its efficacy against CMV infection. CMV lacks a virus-encoded thymidine kinase, but ganciclovir, unlike acyclovir, is phosphorylated in CMV-infected cells by another virally encoded kinase. Cidofovir is a newer antiviral nucleoside analogue that like ganciclovir does not depend for its activity on the presence of a virus-encoded thymidine kinase. It is efficacious against CMV and has been used with success in treating CMV retinopathy and CNS infections. The drug has a prolonged iiitiML-ellular half-lite that permits once-daily dosing. Complications of intravenous therapy include nephrotoxicity and bone marrow suppression.

Another antiviral drug, foscarnet, is also effective against CMV. Foscarnet is an inorganic pyrophosphate analogue that differs in its mechanism of action from the nucleoside analogues (e.g., acyclovir, ganciclovir). Unlike the nucleoside analogues, foscarnet is not metabolized inside infected cells, but like the nucleosides it also acts to inhibit viral DNA polymerase. The utility of foscarnet is limited by its toxicity, nonetheless it remains useful in the treatment of infections caused by CMV and acyclovir-resistant strains of HSV.

A number of antiviral drugs have been developed to combat HIV-1 infection (Bcrgcr and Eevy 1997; Gendelman et al. 1998). The first generation of antirctrovirai drugs were inhibitors of reverse transcriptase, the viral enzyme necessary for production of the DNA form of the virus. Zidovudine, and subsequently dideoxyinosinc and didcoxycytidine, have been shown to delay the progression of AIDS-demcntia complex. Newer antiretroviral drugs include a number of protease inhibitors. These drugs work by inhibiting an enzyme required for the processing of viral proteins. Therapeutic regimens using complex combinations of several different protease inhibitors have

had a dramatic effect on the progression of HIV infection, and in the incidence of many HIV-related opportunistic infections. It remains to be seen whether these effects will be sustained. Studies of the efficacy of protease inhibitors on the neurological complications of HIV infection arc limited, but one study has shown that multidrug therapy including protease inhibitors can reduce HIV-1 viral load in the CSF.

Although azidothymidine appears to have efficacy *in vitro* against HTLV-I, it has not been clinically successful in the treatment of HAM. This may reflect the fact that neuronal injury in HAM may result from immunological attack by virus-specific cytotoxic T cells, rather than as a result of direct viral infection. Consistent with this model of pathogenesis is the suggestion that treatment with immunomodulatory agents including corticosteroids and interferon-a may be beneficial in HAM.

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Chapter 47
Neuroendocrinology

Paul E. Cooper

Homeostasis—the maintenance of the constancy of the internal milieu—requires, in all but the simplest of organisms, communication among cells and organs that are widely separated. This communication is achieved through the coordinated interaction of the nervous, endocrine, and immune systems. It is the study of this coordinated interaction that is the field of neuroendocrinology,

NONENDOCRINE HYPOTHALAMUS

Neuropeptides, Neurotransmitters, and Neurohormones

The term *neurotransmitter* is applied traditionally to a substance released by one neuron to act on an adjacent neuron in a stimulatory or inhibitory fashion. The effect is usually rapid, brief, and confined to a small area of the neuron surface. In contrast, a *hormone* is a substance that is released into the bloodstream and travels to a distant site to act over seconds, minutes, or hours to produce its effect over a large area of the cell. *Neuropeptides* can act in cither fashion. For example, the neuropeptide vasopressin, produced by the neurons of the supraoptic and paraventricular nuclei, is released into the bloodstream and has a hormonal action on the collecting ducts in the kidney. In the central nervous system, vasopressin acts as a neurotransmitter. Similarly, the neuropeptide substance P acts as a neurotransmitter in primary sensory neurons that convey pain signals and as a neurohormone in the hypothalamus.

The influence of neuropeptides on the brain can be divided into two broad categories: organizational and activational. Organizational effects occur during neuronal differentiation, growth, and development and bring about permanent, structural changes in the organization oi the brain that affect its function. An example is the structural and organizational changes brought about in the brain by prenatal exposure to testosterone. Activational effects are those that change pre-established patterns of neuronal activity, such as an increased rate of neuronal firing caused by exposure of a neuron to substance P. Numerous neuropeptides are found in the brain, and research has shown these compounds to have a variety of effects on neuronal function (Table 47.1).

Neuropeptides and the Immune System

Stress, acting through the hypothalamic-pituitary-adrenal axis, modulates the function of the immune system. Certain peptides and their receptors, once thought to be unique to either the immune or neuroendocrine system, are actually found in both.

Cytokines (interleukin [IL]-I, -2, -4, and -6, and tumor necrosis factor [TNF]) arc synthesized by glial cells in the central nervous system in response to cell

Table 47.1: Neuropeptides found in the brain and their effects on brain function*

Neuropeptide	*Central nervous system function*
Hypothalamic peptides modulating pituitary function	
Corticotropin (ACTH)-relea sing hormone	Regulation of ACTH secretion
	Integration of behavioral and biochemical responses to stress
Vasopressin	Learning and memory facilitation
	Memory processes
Oxytocin	Induction of maternal and M-viial behaviors
Growth hormone-releasing hormone	Regulation of growth-hormone secretion
Growth hormone release inhibiting hormone (somatostatin)	Regulation of growth-hormone secretion
Ghrelin	Regulation of growth-hormone secretion
	Regulation of feeding
Thyrotropin-releasing hormone	Regulation of thyroid-stimulating hormone secretion
	May he involved in depression
	Enhances neuromuscular function
Gonadotropin-reIcasing hormone (luteinizing hormone-releasing hormone)	Regulates gonadotropin secretion
	Sexual receptivity
Prolactin-releasing peptide	Stimulates prolactin secretion
Neurotensin	Endogenous neuroleptic
	Regulates mesolimbie, mesocortical, and nigrostriatal dopamine neurons
	Thermoregulation
	Analgesia
Neuropeptide V	Satiety and drinking
	Sexual behavior
	Locomotion
	Memory
Pituitary peptides	
Prolactin	
Growth hormone	
Thyroid-stimulating hormone	
Follicle-stimulating hormone	
Luteinizing hormone	
Proopiomelanocortin	
ACTH	
ACTH-like intermediate lobe peptides	
^-Endorphin	Analgesic mechanisms
	Feeding
	Thermoregulation
	Learning and memory
/i-Lipotropic hormone	
Melanocyte-stimulating hormone *(a* and *y)*	
Oxytocin	
Vasopressin	
Neurophysins	
Brain-gastrointestinal tract peptides	
Vasoactive intestinal polypeptide	Cerebral blood flow
Somatostatin	
Insulin	Feeding behavior
	Hunger
Glucagon	
Pancreatic polypeptide	
Gastrin	
Cholecystokinin	Feeding behavior
	Satiety
	Modulates dopamine neuron activity
Tachykinins (e.g., substance P)	Substance P colocalizcs with serotonin and is involved in nociception

Continued

Tabic 47.1, cont'd. Neuropeptides found in die brain and their effects on brain function*

Neuropeptide	*Central nervous system function*
Secretin	
Thyrotropin-releasing hormone	
Bombesin	Thermoregulation
	Appetite
Orcxins (hypocretin)	Gastric and GI motility and secretion
	Pancreatic hormone release
	Regulation of energy homeostasis
Growth factors	
Insulin-like growth factors I and II	
Nerve growth factors	Axonal plasticity
Opioid family	
Endorphins	
Enkephalins (Met-, Leu-)	Analgesic mechanisms
	Feeding
	Temperature control
	Learning and memory
	Cardiovascular control
Dynorphins	
Kytorphin	
Neuropeptides modulating immune function	
ACTH	
Endorphins	
Interferons	
Neuro leu kins	
Thymosin	
Thymopeptin	
Other neuropeptides	
Atrial natriuretic factors	
Bradykinins	Cerebral blood flow
	Migraine
Angiotensin	Hypertension
	Thirst
Synapsins	
Calcitonin gene-re I a ted peptide	
Calcitonin	
Sleep peptides	Regulation of sleep cycles
Orexins (hypocretin)	SleepAvake regulation
	Narcolepsy
	cniTgv homeostasis
Carnosine	
Precursor peptides	
P ro-op iomela n ocort i n	
Proenkephalins (A and B)	
Calcitonin gene product	
Vasoactive intestinal polypeptide gene product	
Pro-glucagon	
Pro insulin	

"This is only a partial list of all of the neuropeptides that have been found in the brain and not all of the putative functions have been listed. Gl = gastrointestinal.

Snurci-. Modified with permission from Doraiswamy, P. M., Krishnan, K. R., Nemeroff, C. B. 1992, "Hormonal effects on brain function" in *Neuroendocrinology. Concepts in Neurosurgery*, vol. 5, eds D. L. Barrow & W. Selman, Williams & Wilkins, Haiti more.

injury, 1L-1, through its ability to stimulate the synthesis of nerve growth factor, may he an important promoter of the repair of neuron damage. Cytokines also appear **to play a** role in the hypothalamus to activate the hypothalamk-pituitary-adrenal axis in response to inflammation elsewhere in the body and to inhibit the pituitary-thyroid and pituitary-gonadal axes in response to systemic disease.

Several other hormones and neuropeptides **have** modulatory effects on immune function (Table 47.2).

Tabic 47.2: Immunoregu latory effects of several hormones and peptides

Hormone or peptide	*Immune function affected*
Inhibitory	
Glucocorticoids	Lymphokine synthesis, inflammation
Corticotropin (ACTH)	Macrophage activation, synthesis of immunoglobulin G (IgG) and y-intcrfcron
Chorionic gonadotropin	Activity of T cells and natural killer cells
a-Endorphin	IgG synthesis, T-cell proliferation
Somatostatin	T-cell proliferation, inflammatory cascade
Vasoactive intestinal peptide	T-cell proliferation and migration in Peyer's patches
or-Mel a n oeyte-sri m u I ati ng hormone	Fever, prostaglandin synthesis, secretion of intcrleukin-2
Stimulatory	
Estrogens	Lymphocyte proliferation and secretion
Growth hormone	Thymic growth, lymphocyte reactivity
Prolactin	Thymic growth, lymphocyte proliferation
Thyrotropin	IgG synthesis
^-Endorphin	Activity of T, R, and natural killer cells
Substance P	Proliferation of T cells and macrophages, inflammatory cascade
ACTH-releasing hormone	Lymphocyte and monocyte proliferation and activation

Source: Reprinted with permission from Rcichlin, S. 1993, "Neuroendocrine-immune interactions," N *Engl j Med,* vol. 329, pp. 1246-1253.

Similarly, immunocompetent cells contain hormones and neuropeptides that may affect neuroendocrine and brain cells (Table 47.3). Despite speculation about the ability of the psyche to influence immunological function and therefore disease outcome, there is no conclusive evidence to date to suggest that this is clinically significant (Reichlin 1993).

Temperature Regulation

The hypothalamus plays a key role in ensuring that body temperature is maintained within narrow limits by balancing the heat gained from metabolic activity and the environment with the heat lost to the environment. A theoretical schema of the mechanisms of hypothalamic temperature regulation is depicted in Figure 47.1. Although numerous neurotransmitters and peptides alter body temperature, their physiological roles remain unclear.

Hypothalamic injury can cause disordered temperature regulation. One potentially serious consequence is the hyperthermia that may occur when the preoptic anterior hypothalamic area is damaged or irritated by ischemia, subarachnoid hemorrhage, trauma, or surgery. In some patients, the marked impairment of heat loss mechanisms and the resulting hyperthermia may be fatal. In those individuals who survive, temperature control returns to normal over a period of days to weeks; chronic hyperthermia of hypothalamic origin is uncommon. It may occur when there is ongoing inability to dissipate heat adequately or when there is difficulty sensing temperature elevations. Chronic hypothalamic hyperthermia does not

Table 47.3: Hormones and neuropeptides found in immunocompetent cells

HaniHitie	*Source*	*Comments*
Corticotropin	B lymphocytes	Stimulated by corticotropin-re I easing hormone; inhibited by Cortisol
Growth hormone	T lymphocytes	Stimulated by growth hormone
Thyrotropin	T cells	Stimulated by thyrotropin-relcasiiig hormone; inhibited by somatostatin
Prolactin	Mononuclear cells	
Chorionic gonadotropin	T cells	
Enkephalins	B lymphocytes	
Vasoactive intestinal peptide	Mononuclear leukocytes, mast cells	
Somatostatin	Mononuclear leukocytes, mast cells, polymorphonuclear leukocytes	
Vasopressin	Thymus	
Oxytocin	Thymus	
Neurophysin	Thymus	

Source: Reprinted with permission from Reichlin, S. 1993, "Neuroendocrine-immune interactions," N *Engl j Med,* vol. 329, pp. 1246-1253.

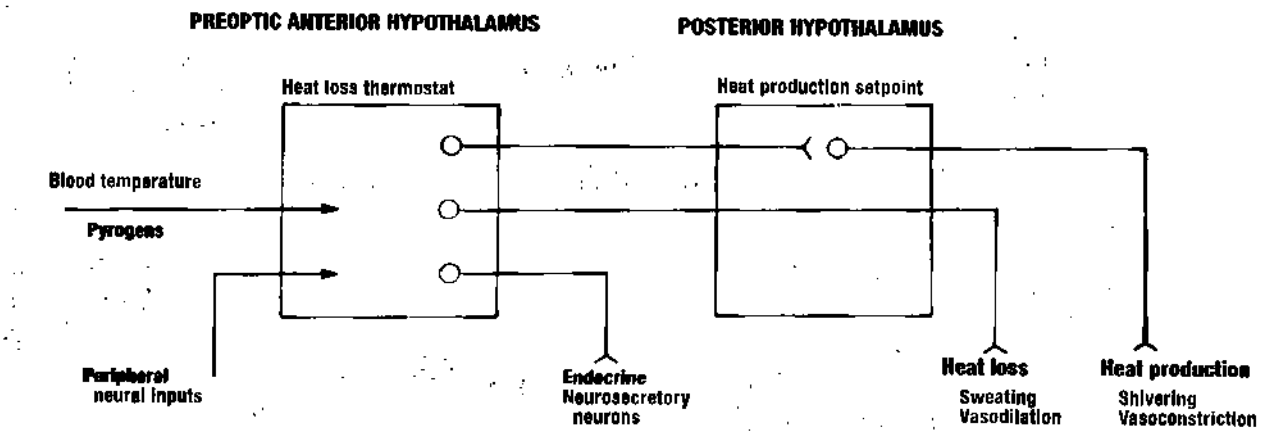


FIGURE 47.1 Schematic representation of hypothalamic temperature-regulation mechanisms. The preoptic anterior hypothalamus functions as a thermostat and contains mechanisms for regulation of heat loss. The posterior hypothalamus integrates heat-production mechanisms. Lesions of the preoptic anterior hypothalamus result in hyperthermia; lesions of the posterior hypothalamus cause hypothermia or poikilothermia. (Reprinted with permission from Cooper, P. E. & Martin, J. B. 1983, "Neuroendocrine disease," in *The Clinical Netimsciences,* ed R. N. Rosciiherg, Churchill Livingstone, New York)

respond to salicylates and other antipyretics because it is not prostaglandin-mediated. Both acute and chronic hypothermia can be caused by hypothalamic injury, the most common causes being head trauma, infarction, and demyelination. Also in the differential diagnosis one should consider severe hypothyroidism, Wernicke's disease, and drug effect. Some patients with no apparent hypothalamic structural abnormalities may have episodes of recurrent hypothermia. The cause of this syndrome is unclear although the response of some patients to anticonvulsant agents, and of others to clonidine or cyproheptadine, suggests a possible neurotransmitter abnormality. Agenesis of the corpus callosum, in association with episodic hyperhidrosis and hypothermia (Shapiro's syndrome), is caused in some individuals by an abnormally low hypothalamic set point. These symptoms may respond to clonidine (an α_2-adrenergic agonist). A similar condition associated with hyperthermia (so-called reverse Shapiro's syndrome) has been found to respond with normalization of temperature to low-dose L-dopa and hypothermia with higher doses (Hirayama et al. 1994). Large lesions in the posterior hypothalamus may impair both heat production by altering the set point and heat loss by damaging the outflow from the preoptic anterior hypothalamic area. This results in poikilothermia, a condition in which body temperature varies with the environmental temperature.

Fever

The body's inflammatory cells (primarily monocytes) release cytokines in response to infection and inflammation. These cytokines act on the hypothalamus to cause fever. IL-1 circulates from areas of inflammation to the hypothalamus, where it acts to induce phospholipases that release arachidonic acids from plasma membranes. This results in an increase in prostaglandin E, which in turn increases the body temperature set point. The body then uses its normal physiological mechanisms of vasoconstriction, vasodilation, sweating, and shivering to maintain this new set point. TNF, another cytokine, acts directly on the hypothalamus to raise the set point and stimulates the production of IL-1. Bacterial endotoxin is a potent stimulator of macrophages, the major source of production and release of TNF. IL-6 and ^-interferon are two other cytokines that act directly on the hypothalamus to raise the set point. It is probably through interfering with prostaglandins that drugs such as acetylsalicylic acid and acetaminophen are useful in treating fever.

A complex interaction occurs among the cytokines. IL-1 stimulates its own production, as do elevated levels of y-interferon. IL-4 suppresses the production of IL-1, TNF, and IL-6. IL-1 production is inhibited also by glucocorticoids and prostaglandin E.

In otherwise healthy individuals, extreme elevations of body temperature (as high as 41.1^{U}C [106°F]) sometimes can be toletated without serious effects. However, hyperthermia associated with prolonged exertion, heatstroke, malignant hyperthermia, neuroleptic malignant syndrome, hyperthyroidism, phcochromocytoma crisis, and some drugs may have serious and even fatal consequences (Simon 1993). Exertional hyperthermia occurs with prolonged physical activity, particularly in hot, humid weather. It may decrease athletic performance and cause muscle cramps or heat exhaustion. When severe, it may result in heatstroke, a syndrome characterized by hyperthermia, hypotension, tachycardia, hyperventilation, and decreased consciousness. Malignant hyperthermia, a syndrome associated most often with the use of various general anesthetic agents, is caused by a disorder of muscle that involves an excessive release of calcium from sarcoplasmic reticulum that stimulates severe muscle contraction (see Chapters 70 and 85). The neuroleptic malignant syndrome is characterized by diffuse muscular rigidity,

akinesia, and fever accompanied by a decreased consciousness level and evidence of autonomic dysfunction: labile blood pressure, tachyarrhythmias, excessive sweating, and incontinence. The neuroleptic malignant syndrome is associated with taking major tranquilizers, with rapid withdrawing from dopaminergic agents, and less commonly with administration of tricyclic antidepressants. It appears to result from an alteration of temperature control mechanisms in the hypothalamus. As part of treatment, withdrawal of the patient from all neuroleptics is mandatory. In addition to general supportive measures, the use of bromocriptine (5 mg orally or nasogastrically four times daily) or dantrolene (2-3 mg/kg daily intravenously to a maximum of 10 mg/kg per day) may hasten recovery.

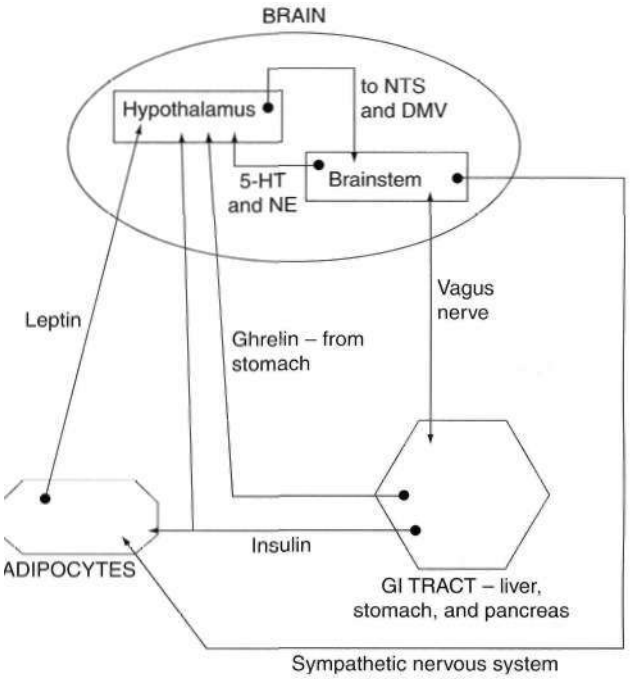
Appetite

Given free access to food and water, most animals maintain their body weight within narrow limits. If there is a change in the intake of energy (a change in the size or number of individual meals that is not balanced by an equal and opposite change in energy LLSC), then the animal experiences a change in weight. One possible model of nutrient balance is depicted in Figure 47.2. There are four components to energy balance: (1) the afferent system, (2) the central nervous system processing unit, (3) the efferent system, and (4) the absorption of food from the gut and its metabolism in the liver. Disorders at any point in these systems may lead to weight loss or weight gain.

In response to a meal or to starving, hormonal and neural signals are generated in the periphery. Some are short-term, and others are long-term. Some relate to satiety, others relate to feeding behavior, and still others relate to "thinness and fatness." Ghrelin, a stimulator of growth hormone (GH) release, is released from the stomach in the fasting state. Ghrelin activates neuropeptide Y and agouti-relatcd protein in the hypothalamus that leads to increased feeding and deposition of energy into body fat. Peripheral insulin seems to mediate a satiety signal in the ventromedial! hypothalamus. Leptin is the other component of the afferent system (see later),

Destruction of the ventromedian hypothalamus, both in animals and in humans, leads to obesity. Lesions in the paraventricular nucleus have a similar effect. Overeating (hyperphagia) is only one of the mechanisms producing hypothalamic obesity. Hypothalamic lesions also can cause weight loss. Lesions in the dorsomedial nucleus lead to **a** reduction in body weight and fat stores, as do lesions in the lateral hypothalamus. Studies in the decerebrate rat suggest that oral motor and meal-size responses are dependent on centers in the caudal brainstem on which the hypothalamus has only a modulatory effect (Grill and Kaplan 2002).

Meal size and food intake are influenced by many different stimuli. Sensory cues such as the sight, aroma, and taste of food arc major factors in dietary obesity. A decrease in blood glucose or a decrease in the oxidation of fatty acids in the liver stimulates the act of eating. Stomach distention gives rise to neural and hormonal signals that reduce food intake. Gastrointestinal (GI) peptides such as cholecystokinin, **bombesin, and** glucagon inhibit feeding by their actions on the autonomic nervous system, particularly the vagal nucleus. Increased fatty acid oxidation leads to higher levels of 3-h yd roxy bury rate that act on the hypothalamus to reduce food intake. Interference with any of these sensing systems in the central nervous system can lead to obesity. Neuropeptide Y infused into the ventral



E1GURE 47.2 Sympathetic Nervous System. In the regulation of energy balance, the brain is the central processing unit. It receives afferent neuronal signals from the vagus nerve, via the brainstem and hormonal signals—ghrelin (from the stomach), insulin (from the pancreas), and leptin (from adipocytes). The brainstem also has input to the hypothalamus via norepinephrine (from the locus ccrulcus) and serotonin (5-OH-tryptamine) (from the raphe nuclei). These afferent signals are interpreted both in the brainstem (in the nucleus of the tractus solitarius) and in the hypothalamus (in the ventral medial nucleus). The ventral medial nucleus of the hypothalamus communicates with the lateral hypothalamic area (I.HA) and the paraventricular nucleus (PVN) by means of pro-opiomelanoeortin-cocaine/ampheta mine-regulated transcript (POMC-CART) an anorexigenic peptide (the release of which is stimulated by insulin and leptin) and by neuropeptide Y/agouti-related protein (NPY/AGRP) an orexigenic peptide (the release of which is stimulated by ghrelin and inhibited by leptin and insulin). Output from the LHA and PVN is either via the sympathetic nervous system—which leads to energy expenditure through physical activity, activation of ^-adrenergic receptors and uncoupling proteins in the adipocyte to cause energy release through lipolysis. Output via the vagus nerve leads to increased insulin secretion, which causes adipogenesis and energy storage. For a more complete explanation of this control of energy balance the interested reader is directed to I.ustig 2001.

medial nucleus of the hypothalamus induces obesity, perhaps by inhibiting sympathetic drive and stimulating insulin release. Although this may explain obesity with hypothalamic lesions, obesity related to eating highly palatable food is probably not related to central changes in neuropeptide Y,

In animals, the *ob, db,* and *fa* genes play a role in the ability of adipose tissue to regulate feeding through a circulating factor. The product of the *ob* gene, leptin, is a peptide that when administered peripherally to the genetically obese *(ob/ob)* mouse—an animal that is deficient in leptin—reduces its intake of food, with a resulting decrease in body weight The role ot leptin in appetite regulation is complex. Leptin does not reverse the obesity seen in *db/db* mice and in obese humans. In these situations, serum leptin concentrations are higher than in subjects of normal weight, suggesting an insensitivity to endogenous leptin production.

When melanocyte-stimulating hormone (alpha-MSH) binds to its receptor in the hypothalamus it causes satiety. Up to 5% of obese children have been found to have an abnormality of the alpha-MSH receptor—MC_4R as a cause of their obesity (Lustig 2001).

The orexins (hypocretins) are neuropeptides that play a role in energy balance and arousal. Narcolepsy is caused by failure of orexin-mediated signaling. They are found in the hypothalamus where they regulate sleep-wake cycles and in the GI tract where they excite secretomotor neurons and modulate gastric and intestinal motility and secretion.

Anorexia nervosa and bulimia nervosa are clinical eating disorders seen primarily in young women and girls. Anorexia nervosa is characterized by reduced caloric intake and increased physical activity associated with weight loss, a distorted body image, and a fear of gaining weight. Bulimia nervosa is characterised by episodic gorging, followed by self-induced vomiting, laxative and diuretic abuse, dieting, and exercise to reduce weight. For many years, these syndromes were considered to be purely psychiatric. However, the finding of reduced serotonin levels in the cerebrospinal fluid (CSF) of patients with bulimia nervosa, the low CSF levels of norepinephrine in patients with anorexia nervosa, and the enhanced secretion of cholecystokinin in patients with anorexia nervosa suggest that neurotransmitter or neuropeptide abnormalities could be responsible for at least part of the clinical picture in these patients. Furthermore, patients with anorexia nervosa seem to have an increased total daily energy expenditure because of their increased physical activity. Whether these are causes or effects of the condition remains to be determined.

Emotion and Libido

Fxperimental and clinical data support the hypothesis that interaction of the frontal and temporal lobes and the limbic system is necessary for normal emotional function. Lesion and stimulation experiments in the cat have shown that rage reactions can be provoked from the hypothalamus. In the human, electrical stimulation of the septal region produces feelings of pleasure or sexual gratification, whereas lesions of the caudal hypothalamus or manipulation of this area during surgery may cause attacks of rage. The amygdala, with its rich input from polyscnsory areas and limbic-associated areas and its output to the hypothalamus, and other subcortical areas are important structures through which the external environment can influence and cause emotional responses.

Libido, like other feelings, requires the participation of both hypothalamic and extrahypothalamic sites. In most instances of hypothalamic disease, loss of libido is caused by impaired release of gonadotropin-releasing hormone (GnRH) and a subsequent decrease in testicular testosterone in men. In women, libido is related more to adrenal androgens. These levels may be low in women with cotticottopin (ACTH) deficiency and secondary adrenal insufficiency. Hypersexuality associated with hypothalamic disease is rare and may occur with or without a subjective increase in libido.

There is a gradually expanding understanding of the human hypothalamus in relation to normal development, sexual differentiation, aging, and some degenerative neurological disorders (Swaab et al. 1993). The sexually dimorphic nucleus, or intermediate nucleus, of the preoptic area is twice the volume in male subjects as it is in female subjects. The size does not differ between homosexual and heterosexual men. Although the shape of the suprachiasmatic nucleus differs in male and female subjects, the vasopressin cell number and volume are similar in men and women. Homosexual men seem to have a larger suprachiasmatic nucleus, containing twice as many cells as heterosexual men (Swaab et al. 1993). The significance of this observation is, at present, uncettain.

Biological Rhythms

Most endocrine rhythms are circadian—that is, a complete cycle takes approximately 24 hours. Although longer and shorter cycles do occur, the circadian rhythms have been studied most extensively. In many animals, light plays an important role in regulating circadian rhythms. Nerve fibers project from the optic chiasm to the suprachiasmatic and arcuate nuclei of the hypothalamus. The hypothalamus is responsible for the hormonal rhythms, such as Cortisol and GH secretion and the behavioral rhythms such as sleep-wake cycles and estrous activity. Although patients with hypothalamic disease often have disturbances in their biological rhythms, these are usually of less clinical importance than the other problems caused by such lesions.

Hyporhalamic-Pituitary Unit Functional Anatomy

In humans, discernible hypothalamic-pituitary tissue begins to develop during week 5 of embryonic life. Rathke's pouch, a diverticulum of the buccal cavity, forms and expands dorsally to contact and invest the diverticulum, which develops from the floor of the third ventricle. By week 11, the buccal tissue has lost its connection with the foregut and has flattened to form the primitive anterior pituitary, whereas the neural tissue from the floor of the third ventricle is forming the posterior pituitary. Residual Rathke's pouch tissue is postulated to give rise to the craniopharyngiomas, which can occur in this region. Rarely, ectopic functional pituitary tissue in the oropharynx can cause signs and symptoms of hyperpituitarism.

The hypothalamus, despite its small size, is the region of brain with the highest concentrations of neurotransmitters and neuropeptides. Beginning with the pioneering work of Ernst and Berta Scharrer and Geoffrey Harris in the 1940s, the hypothalamus lias been assigned a central role in the regulation of anterior pituitary function. In addition to the identified hypophysiotropic hormones (Table 47.4), other peptides with putative regulatory functions are found in high concentration in the hypothalamus, including neurotensin, substance P, cholccystokinin, neuropeptide Y, vasoactive intestinal polypeptide, and the opioid peptides. The hypothalamus is also rich in acetylcholine, norepinephrine, dopamine, serotonin, histamine, and y-aminobutyric acid. In many neurons, these neurotransmitters colocalize with peptides, although this colocalization and presumptive corelease have uncertain physiological significance. A common presentation of patients with nonfunctioning pituitary or parapituitary tumors is symptoms produced by compression of neural structures adjacent to the pituitary gland. Understanding these symptoms requires knowledge of the anatomy of the region (Figure 47.3).

Tumor erosion of the floor of the sella turcica may lead to CSF rhinorrhea. Conversely, sinusitis or sphenoid sinus mucocele can invade the sella and cause anterior pituitary dysfunction. Expansion of pituitary tumors into the cavernous sinus can produce a variety of upper cranial nerve palsies. This is especially common with the sudden expansion of pituitary tumors that occurs in pituitary apoplexy. Carotid aneurysms or ectatic carotid arteries in the cavernous sinus may expand medially and mimic pituitary adenomas by enlarging the sella and causing anterior pituitary hypofunction.

The dura overlying the sella is sensitive to pain and, when stretched by expanding pituitary tumors, gives rise to headache referred to rhe vertex and retro-orbitally. In certain individuals, especially if intracranial pressure is elevated, the dura may herniate in the reverse direction into the sella, where with time continued pulsation of the CSF leads to remodeling and expansion of the sella. This produces the radiological finding of the empty sella syndrome, another cause of which is lymphocytic hypophysitis. The pituitary gland becomes a thin ribbon of tissue along the walls of the expanded sella, and the sella consists mostly of CSF. Rarely is there evidence of pituitary function impairment in such patients.

Expansion of pituitary tumors out of the sella tends to lead to compression of the anterior and inferior crossing fibers of the optic chiasm (see Chapters 14 and 40). These fibers subserve vision in the superior temporal quadrants. Therefore pituitary adenomas typically cause bitemporal superior quadrantanopias. Lesions such as craniopharyngiomas that impinge on the posterior and superior optic chiasm tend to present with bitemporal inferior quadrantanopias. Despite these rules, the variability of the positioning of the optic chiasm and the tendency for tumors to be asymmetrical in their growth result in a wide variety of field defects being caused by parasellar lesions.

Blood Supply

The pituitary's major source of blood is via the superior and inferior hypophyseal arteries (Figure 47.4). The posterior pituitary gland is supplied principally by the inferior hypophyseal arteries and is drained by the inferior hypophyseal veins. The superior hypophyseal artery forms a primary capillary plexus in the median eminence of the hypothalamus. From here, the blood flows into the long hypophyseal portal veins, which carry it to the anterior

Tahlc 47.4: Hypothalamic peptides controlling anterior pituitary hormone release

Pituitary hormone	*Hypothalamic factor*
Growth hormone	Growth hormone-releasing hormone
	Growth hormone release inhibiting hormone (somatostatin)
Prolactin	ProJactin-rcleasing factor
	Pnihctiii rvli':iv: inhibiting faemr: dopamine *and* JKHMIIIV (In- precursor of gonadotropin-releasing hormone
Thyrotropin	Thyrotropin-releasing hormone
	Thyrotropin release inhibiting factor: somatostatin can do this, but it is uncertain if it docs so physiologically
Proopiomelanocortin is cleaved to form corticotropin	Corticotropin-releasing hormone
Luteinizing hormone and follicle-stimulating hormone	Gonadotropin-releasing hormone

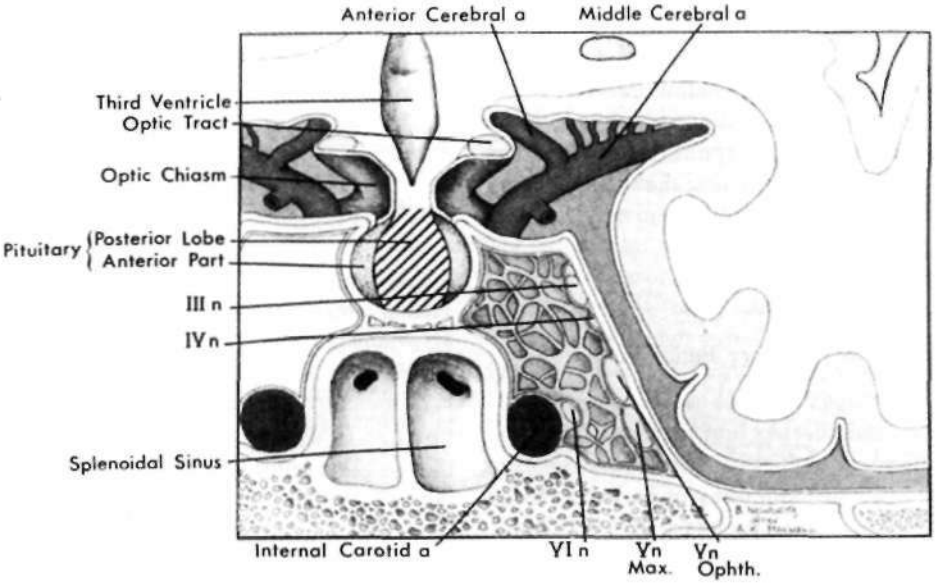


FIGURE 47.3 Diagrammatic representation of the anatomical relations of the pituitary fossa and cavernous sinus. The lateral wall of the sella turcica is formed by the cavernous sinus. The sinus contains the carotid artery, two branches of the fifth cranial nerve (ophthalmic and maxillary), third nerve (oculomotor), fourth nerve (trochlear), and sixth nerve (abducens). The optic chiasm and optic tract are located superior and lateral, respectively, to the pituitary. (Reprinted with permission from Martin, J. B., Reichlin, S., &c Brown, G. M. 1977, *Clinical Neuroendocrinotogy,* Davis, Philadelphia. Drawing by B. Newberg.)

pituitary. Although some of the blood from the anterior pituitary drains into the cavernous sinus, some drains into the posterior pituitary, and some returns to the median eminence via the long portal veins, which are capable of bidirectional blood flow. This vascular anatomy provides a potential mechanism for the important feedback loops that ate necessary for regulation of hypothalamic-pimitary function.

ANTERIOR PITUITARY

Hypothalamic Control of Anterior Pituitary Secretion

The hypothalamus produces hypophysiotrophic substances that control the secretion of anterior pituitary hormones. Five neuropeptides and one neurotransmitter (dopamine) are known to be important physiological regulators of

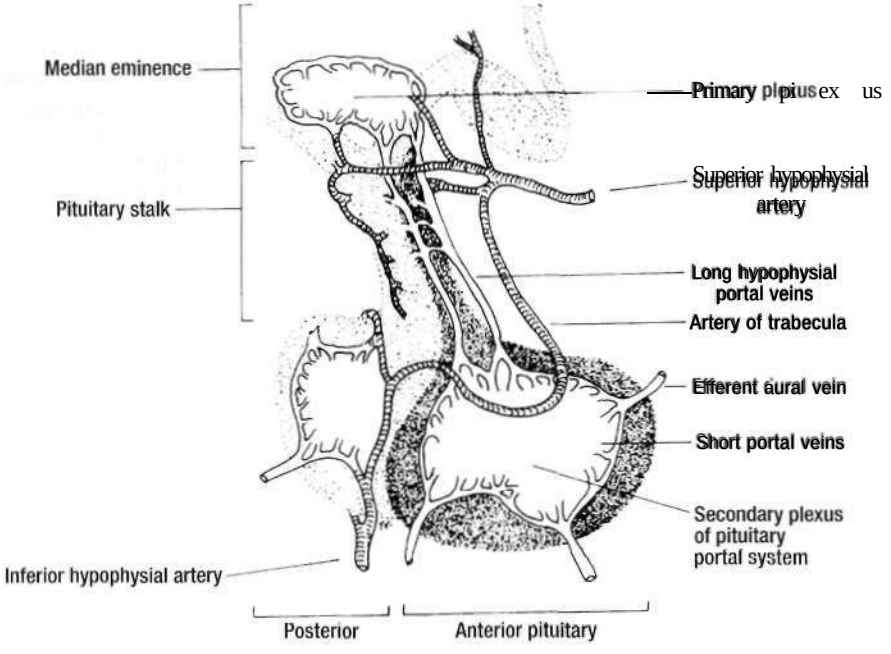


FIGURE 47.4 The blood supply of the median eminence and pituitary gland. {Reprinted with permission from Marrin, J. B. &C Cooper, P. E. 1983, "Neuroendocrine disease,"[1] in *The Clinical h!enrosciences,* ed R. N. Rosenberg, Churchill Livingstone, New York)

pituitary function {see Table 47.4). In addition, several neurotransmitters affect pituitary hormone release, although their physiological role remains uncertain. The pri-cursor moliviili' for (riiKI i, in addition to containing the sequence for GnRH, contains a peptide that is a potent inhibitor of prolactin release, suggesting that hypothalamic control of pituitary secretion may be even more compli-cated than previously thought.

Abnormalities of Anterior Pituitary Function

Hypofunction

The causes of pituitary insufficiency are summarized in Table 47.5. In general, the symptoms of hypopituitarism (Table 47,6) are those of the secondary failure of end-organ function. Because the symptoms usually develop slowly and some autonomous end-organ function remains, the symptoms are often less severe than those that occur with primary end-organ disease. The term *Simtnonds' disease* is applied to panhypopituitarism. When this develops postpartum following an episode of pituitary infarction, it is called *Sheeban's syndrome.*

Intrauterine growth is independent of GH. Therefore although GH-dcficient children are of normal size at birth, they fail to grow. Somatic growth in the human is mediated by at least two factors: insulin-like growth factor I (IGF-I) and insulin-like growth factor II (IGF-II). IGF-I production in the liver is GH-dependent, whereas IGF-II is relatively insensitive to GH. True GH deficiency is rare. It may present in an isolated fashion or as part of general pituitary failure. Apparent GH deficiency may result from an isolated deficiency of GH-releasing hormone or a lack of GH receptors in the liver leading to failure of IGF-I production (Laron dwarf). GH is a contra-insulin hormone, and, in children especially, its deficiency may be associated with episodes of fasting hypoglycemia. A detailed discus-sion of growth is beyond the scope of this chapter. The interested reader is referred to the review by Rosenfield (19%).

Tabic 47.S: Causes of pituitary insufficiency

- Pituitary aplasia
  - Complete
  - Mono hormonal
- Trauma
  - Head injury
  - Surgery
  - Radiotherapy
  - Compression by cysts or tumors
- Pituitary apoplexy
- Pituitary infarction
- Hypophysitis
  - Infection
  - Granulomatous disease
  - Autoimmune disease
- Hypothalamic failure

Pituitary insufficiency in the child may present as delayed or absent puberty. Onset of puberty depends, to some extent, on achievement of a critical body mass. Thus, anything that delays growth, such as GH deficiency or hypothyroidism, delays puberty. If breasts or sexual hair have not started to develop in girls by age 14, or if testicular enlargement and sexual hair have not occurred in boys by age 15, then puberty should be considered delayed. Luteinizing hormone (LH) or follicle-stimulating hormone (FSH) deficiency may occur as part of generalized pituitary failure or as a result of high prolactin levels or of GnRH deficiency.

One cause of hypopituitarism is *pituitary apoplexy,* a term that should be reserved for infarction of, or

Table 47.6: Clinical syndromes of anterior pituitary dysfunction

Hormone	*Excess secretion*	*Deficient secretion*
Growth hormone	In children: gigantism	In children: growth failure and tendency to hypoglycemia
	In adults: acromegaly	
Prolactin	In children: delayed puberty	
	In adults:	
	Women: amenorrhea, galactorrhea, and infertility	In adult women: inability to breast-feed and possible infertility
	Men: impotence, infertility, and (rarely) galactorrhea	
Luteinizing hormone and follicle-stimulating hormone	In children: precocious puberty	In children: delayed puberty
	In adults: infertility, hypogonadism, polycystic ovary syndrome	In adults: amenorrhea, infertility, impotence
Thyrotropin	Hyperthyroidism	Hypothyroidism
	Hyperprolactinemia	
Pro-opiomelanocortin	Cushmg's disease, Nelson's syndrome	Hypoadrenalism—glucocorticoids affected more severely than mineralocorticoids

hemorrhage into, the pituitary gland or a pituitary adenoma that is of sufficient severity to produce signs of compression of parasellar structures or evidence of meningeal irritation. The sudden expansion of the pituitary gland may lead to chiasmal compression or cranial nerve palsies. Rupture of the necrotic gland into the CSF may lead to a picture that is indistinguishable clinically from subarachnoid hemorrhage caused by rupture of a berry aneurysm or arteriovenous malformation. Hypotension, aggravated by pre-existing ACTH deficiency, may further complicate the picture. The diagnosis can usually be made readily by computed tomographic (CT) scanning or magnetic resonance imaging (MRI). Treatment includes general supportive measures, corticosteroid replacement, and, if necessary, surgical decompression.

Hyperfunction

Precocious Puberty. Development nf secondary sexual characteristics before age *$* in girls and age *9* in boys is considered abnormal. Approximately one fifth of girls and one half of boys develop precocious puberty because of neurological lesions. A variety of tumors have been associated with the development of precocious puberty including hamartoma; teratoma; ependymoma; optic nerve glioma; glioma; and neurofibroma, either alone or as part of von Recklinghausen's syndrome. Tumors are most commonly located in the posterior hypothalamus, pineal gland, or median eminence, or they put pressure on the floor of the third ventricle. The cause of precocious puberty under these circumstances has not been clearly delineated. However, some of these tumors may be an ectopic source of GnRH or of human chorionic gonadotropin, a placental peptide with LH- and FSH-like activity.

In the investigation of precocious puberty, LH and FSH levels should be measured as well as human chorionic gonadotropin. A CT scan or MRI of the head is mandatory. If LH and FSH levels are in the adult range and the head scan result is negative, it is most likely that the precocious puberty is idiopathic. High human chorionic gonadotropin levels suggest ectopic production. If LH and FSH levels are low, then adrenal, ovarian or testicular, or exogenous causes must be sought.

Chronic administration of long-acting analogues of GnRH is followed by an initial stimulation of LH and FSH secretion and then complete inhibition. This effect on LH and FSH release can be used to prevent progression of hypothalamic precocious puberty.

Hyperprolactinemia. Probably the most common abnormality of pituitary function encountered by the neuroendocrinologist is hyperprolactinemia. The causes of hyperprolactinemia are summarized in Table 47.7. Prolactin levels in excess of 200 ng/mL (normal, *<25* ng/mL) are almost always caused by excessive production of the hormone by a pituitary adenoma. In premenopausal

Tabic 47.7: Causes of hyperprolactinemia

- Drugs
  - Dopamine receptor blockers
    - Phenothiazines such as chl or promazine
    - Buryrophenones such as haloperidol
    - M e toe lopr amide
  - Reser pine
  - u<-Mctliyldopa
  - Monoamine oxidase inhibitors
  - Tricyclic antidepressants (unusual, probably idiosyncratic)
  - Benzodiazepines (unusual, probably idiosyncratic)
  - Verapamil
  - Cocaine
  - Fluoxetine
  - Amoxapine
- f lonnoilL-s
  - Estrogens
  - Thyrotropin-releasing hormone (as can occur in primary hypothyroidism)
- Pituitary tumor
  - Prolactin-sec re ting adenoma
  - Interference of flow of dopamine down the* pituitary stalk by a large pituitary or parapituitary tumor
- Chest wall stimulation
  - Chronic skin disease (e.g., severe acne)
  - Tumors of chest wall
- Chronic renal failure
- Cirrhosis
- Ectopic production
- Hypothalamic disease
- Pseudocyesis
- Idiopathic

women, the development of amenorrhea secondary to direct inhibition of LH and FSH by prolactin leads to early investigation and diagnosis of tumors at the microadenoma (<10 mm in diameter) stage. In men, the insidious onset of impotence and reduced libido usually means that these tumors arc found iate, often only after they have produced signs and symptoms of optic nerve compression. Galactorrhea is a common accompaniment of elevated prolactin in women and a rare finding in men.

Serum prolactin levels increase after generalized tonic-clonic seizures and complex partial seizures but show no change after virtually all cases of psychogenic, absence, or simple partial seizures or complex partial seizures of frontal lobe origin. Following a seizure, prolactin levels peak at 15-20 minutes, then decrease to baseline levels within 60 minutes. The increase should be at least two times baseline. Caution should be exercised in interpreting early-morning prolactin levels, because there is a normal 50-100% increase in prolactin just before waking. Furthermore, prolactin elevations are far from specific for epilepsy, and there may be some tendency for the elevation to attenuate in patients with frequent seizures.

Because prolactin secretion is under strong inhibitory control by the hypothalamus, anything that interferes with the free flow of blood down the pituitary portal veins can reduce tin[1] exposure ol the pituitary m the dopamine

released by the hypothalamus. This results in raised peripheral blood prolactin levels. In patients with this condition, prolactin levels usually range from 50-150 ng/mL (normal, <25 ng/mL). Such elevations can be seen, for example, in patients with granulomatous disease involving the pituitary stalk; however, the most common situation in which this occurs is in patients in whom the pituitary stalk is kinked by a pituitary adenoma. In such circumstances, this may lead to the erroneous assumption that the pituitary adenoma is secreting prolactin, and long-term therapy with bromocriptine might be undertaken. I have seen such patients whose prolactin levels became normal but whose tumors continued to grow. The mistake with these patients is to assume that a macroadenoma would result in a moderately elevated prolactin level, when in reality microprolactinomas usually produce prolactin levels in excess of 200 ng/ml. and macroadenomas would be expected to have much higher levels, often in excess of 1000 ng/mL.

Patients treated with neuroleptic medications also may have elevated prolactin levels, and occasionally the elevation is enough to cause galactorrhea or amenorrhea. In such patients, it may be uncertain whether symptoms are secondary to drug-induced hyperprolactinemia or a microadenoma. My practice is to perform an MRI scan of the pituitary to look for a tumor and to perform dynamic pituitary testing with thyrotropin-releasing hormone and metoclopramide. In most individuals, drug-induced hyperprolactinemia responds normally to stimulation with these agents. The treatment of drug-induced hyperprolactinemia is difficult. In many instances, the drug cannot be stopped, and often there is a concern about using drugs such as bromocriptine because of their potential to block the beneficial effects of the patient's neuroleptics and because of their ability to cause hallucinations or frank psychosis. Such patients may benefit from the use of atypical antipsychotics with reduced or absent action at dopamine receptors {at normal therapeutic doses}.

Gigantism and Acromegaly. Excessive amounts of circulating GH before closure of the epiphyses leads to gigantism. If the epiphyses have closed, then only tissue still capable of responding to GH grows, leading to the clinical syndrome of acromegaly. The clinical features of acromegaly arc summarized in Table 47.8, Of particular note to the neurologist and neurosurgeon is the frequent complaint of headache and symptoms related to the carpal tunnel syndrome. It is not uncommon to find patients with acromegaly who have had carpal tunnel releases performed 3-5 years before diagnosis of their disease.

Most cases of gigantism and acromegaly are caused by excess GH production by a pituitary adenoma. However, rare cases of ectopic GH production have been described, and excessive GH-releasing hormone production by pancreatic rumors can cause acromegaly. Excess production ol GH-releasing hormone by the hypothalamus could theoretically cause an identical clinical syndrome.

Table 47.8: Common clinical signs and symptoms of acromegaly

Headache, felt at the vertex and behind the eyes
Impaired glucose tolerance and diabetes mellitus
t iil.ry.riiifiit of hands and feet
Enlargement of the jaw, with increased spacing between the teeth and malocclusion
Hypertension
Menstrual irregularities or soft tissue growrh
Thick skin
Doughlike feel to palm (e.g., during handshake)
Carpal tumid syndrome
Arthralgia and osteoarthritis
Proximal muscle weakness
Hypcrhidrosis

Cushing's Disease and Nelson's Syndrome. The term *Cushing's syndrome* refers to the clinical picture caused by exposure to excessive corticostetoids, either endogenous or exogenous. If this picture is caused by excessive production of ACTH from the pituitary, it is referred to as *Cushing's disease.* Its common clinical features are listed in Table 47.9. The syndrome of hyperpigmentation and local compression of parapituitary structures that occurs in approximately 10% of patients with Cushing's disease who have been treated with bilateral adrenalectomy is called *Nelson's syndrome.*

For years now, the dexamethasone suppression test has been pivotal in the diagnosis of Cushing's disease. Normal patients, given 0.5 mg of dexamethasone every *6* hours for eight doses, during the second 24 hours of administration, show a suppression of Cortisol production, as reflected by reduced urinary levels of 17-ketogenic stetoids or urinary free Cortisol, Patients with Cushing's disease usually show a similar suppression only when the dose of dexamethasone is increased to 2 mg every 6 hours for eight doses. Also, in Cushing's disease, ACTH levels are in the normal range or moderately elevated. Failure to suppress on high-dose dexamethasone and unmeasurable ACTH levels is seen with primary adrenal problems such as adenoma or carcinoma. Ectopic ACTH production is usually unsuppressible, and the ACTH levels are much higher than those

Table 47.9: Common clinical features of Cushing's disease

Truncal obesity: Arms and legs tend to be thin; excess fat deposition in preauricular and supraclavicular fat pads
Hypertension
Impaired glucose tolerance and diabetes mellitus
Menstrual irregularities or amenorrhea
Excessive hair growth
Acne
Proximal myopathy
Abdominal striae (purplish)
Osteoporosis
Thin skin with excessive bruising

seen in typical pituitary Cushing's disease, although there are many exceptions to these rules. First, the dexamcthasone test itself can be perturbed by a variety of influences and give false results. Second, there are well-documented cases of ectopic ACTH production and primary adrenal problems that produce dcxamethasone suppression test results compatible with a diagnosis of pituitary ACTH production. Intermittent excess ACTH production can give rise to false-normal results in patients who actually have Cushing's disease.

Even when all test results point to a pituitary source for the excessive ACTH production, care must still be taken in diagnosing someone with Cushing's disease. Patients may or may not have an abnormality of the sella on CT or MRI. Intermediate lobe cysts or clefts may mimic the appearance of adenoma on CT or MRI. In such cases, simultaneous sampling from the petrosal sinuses bilaterally and the inferior vena cava can help localize the excessive ACTH production.

The pituitary glands of some patients with biochemical Cushing's disease do not show adenoma formation but show evidence of hyperplasia of the cells that secrete ACTH, Although this picture can be caused by the ectopic production of corticotropin-releasing hormone, the hypothalamic peptide that stimulates the release of ACTH, or an excessive release of corticotropin-releasing hormone from the hypothalamus, this happens in less than 0.3% of patients with Cushing's disease who have pituitary surgery.

Excessive Secretion of Thyroid-Stimulating Hormone. Elevated levels of thyroid-stimulating hormone (TSH) are seen most commonly with primary hypothyroidism. The resulting pituitary hypertrophy can infrequently be of sufficient magnitude to cause visual field defects. Hyperthyroidism caused by excessive TSH secretion is a rare (accounting for <1% of all pituitary tumors) but well-recognized entity, and these tumors arc readily visible on CT scans.

Pituitary resistance to thyroid hormone may produce also a clinical picture of hyperthyroidism with high-normal or mildly elevated TSH levels. Unlike the case of TSH-secreting tumors, which arc relatively autonomous, the TSH levels in patients with pituitary resistance usually respond well to stimulation with thyrotropin-rclcasing hormone or to suppression with dexamethasone or dopamine.

Gonadotropin-Sec re ting Tumors. Many pituitary tumors, formerly classified as nonfunctioning, arc actually gonadotropin- or gonadotropin subunit-producing tumors. The usual presentation is a macroadenoma in an elderly man; however, they occur in individuals of all ages and both sexes, with a male preponderance.

Many of these tumors secrete only ESH, and only rarely do they secrete LH alone. Some may secrete both LH and FSH, and others secrete biologically inactive gonadotropin subunits: a-subunit, LH-^J subunit, or *¥$H-0* subunit. Most clinical radioimmunoassays used to measure LH and FSH require the *a-* and ^J-subunits to be associated before they register in the assay. This means that subunit secretion is not detected. FSH levels usually are elevated in patients with FSH-sccreting tumors, and testosterone or estradiol levels are almost always low. In patients with LH-secreting tumors, LH levels are usually elevated and estradiol or testosterone levels may be high. Despite high sex steroid levels, these patients are often clinically hypogonadal. Patients with tumors that secrete both LH and FSH usually have normal or high sex stctoid levels, but again, they are clinically hypogonadal. Because subunits are biologically inactive, subunit-sccrcting tumors do not interfere directly with hormonal function, although through pressure effects on the pituitary, they can cause hypopituitarism.

Long-standing primary hypogonadism may cause pituitary enlargement secondary to gonadotroph hyperplasia. Rarely, this may lead to gonadotroph tumor development. Most of the time, the pituitaty enlargement is asymptomatic and regresses in response to sex steroid replacement.

Pituitary Tumors and Pituitary Hyperplasia

Pituitary tumors account for approximately 15% of all intracranial tumors. Although most are benign, they can be locally invasive. Only rarely is true malignancy evidenced by metastases. The old classification of pituitary adenomas into chromophobe, acidophil, and basophil has been supplanted by a more functional classification based on immunological and electron microscopic examinations (Table 47.10). Hyperplasia of various cellular elements of the pituitary is relatively rare and is usually seen in cases of ectopic hypothalamic-releasing hormone production.

G proteins are a family of proteins, comprising *a-*, *fi-*, and y-subunits, that bind to guanine nucleotides. Their role in pituitary tumor genesis has been reviewed by Spada et al. (1993). There are several classes of G proteins. Gs proteins are activators of adenylyl cyclase. Gi proteins are

Table 47,10: Classification of pituitary adenomas

Tumor	*Percent*
Growth hormone cell adenoma	14.0
Prolactin cell adenoma	27.2
Growth hormone-prolactin cell adenoma	8.4
Corticotroph cell adenoma	8.1
Thyrotroph tell adenoma	1.0
Gonadotroph cell adenoma	6.4
Clinically nonfunctioning adenoma	31.2
Plurihormonal adenoma	3.7

Source: Modified with permission from Thapar, K., Kovacs, K., Muller, P. J. 1995, "Clinical-pathological correlations of pituitary tumours," *Clin Endocrinol Metab*, vol. 9, pp. 243-270.

substrates for pertussis toxin and may inhibit adenylyl cyclase. Gq proteins are mediators of phospholipase C activation. The functions of GI2 and GI.-5 proteins arc, at the moment, unknown. The a-subunit of the Gs protein contains the guanosine triphosphate (GTP) binding site. After the Gs protein binds to GTP, there is release of the beta/gamma-dimer and the active w-GTP complex. The intrinsic GTPase activity of the a-subunit hydrolyzes ff-GTP to a-guanosine diphosphate to end the activity.

A variety of mutations involving single amino acid substitutions in the portion of the *Gs* gene that codes the Gs or-subunit have been identified in nearly 40% of GH-secreting tumors. These mutations inhibit the breakdown of the ff-subunit and thereby mimic the effect of specific growth factors, which lead to increased adenylate cyclase activity and elevated intracellular cyclic adenosine monophosphate levels. Somatostatin inhibits both GH and cyclic adenosine monophosphate production, and this may be the mechanism by which it shrinks GH-secreting pituitary tumors.

The *ras* proteins, a family of at least three protooucogenes, arc structurally similar to G proteins. Like the G proteins, *ras* proteins affect cell differentiation and proliferation. *Ras* mutations arc found commonly in thyroid tumors but are uncommon in other endocrine neoplasms. A *rat* mutation has been found in a particularly invasive prolactinoma.

Transforming growth factor-or is found on normal human adenohypophyseal cells and on tumors. It is capable of altering the production of GH and causing cell proliferation. GH-secreting tumors also express epidermal growth factor, as do some other human pituitary adenomas. Aggressive G! l-secrcting tumors have excessive numbers ot transforming growth factor-** and epidermal growth factor receptors (Ezzat 1997).

Although the observations on G proteins seem to support the hypothesis that pituitary adenomas are of primary pituitary origin, it is still possible that alterations in G-protein function could be triggered initially by abnormal hypothalamic or peripheral stimulation. In support of this latter hypothesis, transgenic mice that overexpress GH-releasing hormone (GHRH) develop pituitary tumors; however, humans with continuous overstimulation of the pituitary by ectopic GHRH production do nor seem to develop pituitary adenomas. Estradiol has mitogenic action of pituitary prolactin-secreting cells. Although prolactin-secreting tumors are the most common human pituitary tumors, their cause is uncertain. Estradiol exposure may lead to prolactinoma formation through the action of transforming growth factor beta (TGF-^J).

Other Tumors

Gliomas, meningiomas, chordomas, teratomas, and dermoid and epidermoid tumors can all occur in the region of the sella turcica and may mimic the local compressive effects of primary pituitary tumors. The pituitary gland is the site of metastatic deposits in 4% of cancer patients. Usually these metastases are asymptomatic; when symptoms do occur, however, they are most often related to disturbance of posterior pituitary function,

Craniopharyngiomas are only one third as common as pituitary tumors. They are thought to arise from residual resrs of Rathke's pouch tissue. Most commonly found in a suprasellar location, they also occur anywhere along the pituitary-hypothalamic axis, including within the sella. Craniopharyngiomas can appear at any age; however, approximately one third of the cases arise before age IS. Because these tumors produce no hormones, patients present with signs of local compression, especially of the visual system, or with hypothalamic dysfunction such as growth failure or diabetes insipidus (DI). In children, almost one half show evidence of growth failure. Three fourths of these patients, adults and children, have visual symptoms.

Hypophysitis

Hypophysitis from infection or granulomatous disease such as sarcoidosis can result in hypopituitarism. Lymphocytic hypophysitis, a sterile inflammation of the pituitary of probable autoimmune origin, is seen almost exclusively in women, particularly in pregnancy. Usually it causes hypopituitarism, although it can cause hvpiTpml.icnnemia and may be a cause of the empty sella syndrome.

POSTERIOR PITUITARY

Physiology

Vasopressin

Vasopressin or antidiuretic hormone (ADH), an essential hormone in fluid and electrolyte homeostasis, is synthesized in the magnocellular neurons of the supraoptic and paraventricular nuclei as a large precursor molecule, which is cleaved enzymatically to yield vasopressin and neurophysin. The function of this latter peptide is unknown.

Four vasopressin-containing pathways have been recognized in the brain: (1) liypothalamoneurohypophysial, (2) paraventricular nucleus to the zona incerta of the median eminence, (3) paraventricular nucleus to the limbic system (amygdala), and (4) paraventricular nucleus to the brainstem and spinal cord. The best characterized of these is the hypophyscal-portal pathway. Virtually all of the neurons from the supraoptic nuclei contribute to this pathway, whereas only a portion of paraventricular nuclei terminate in the posterior pituitary. Some of the vasopressin-containing fibers from the paraventricular nuclei appear to be more

involved in ACTH regulation than in fluid balance. Vasopressin-containing fibers also project widely outside the hypothalamus, where there is evidence to suggest they may participate in memory.

Oxytocin

Oxytocin, like vasopressin, is synthesized in magnocellular neurons of the supraoptic and paraventricular nuclei as a large precursor molecule, which is cleaved into oxytocin and a specific ncurophysin. Many of the physiological stimuli of vasopressin also result in oxytocin release, and, although in suprapbysiological doses oxytocin does have ADH-like properties, its physiological role in these circumstances remains obscure. The only specific stimulus that causes the release of oxytocin but not vasopressin is suckling. Oxytocin's role in normal lactation and parturition in the human remains to be defined clearly.

Thirst and Drinking

Certain cells of the anterior hypothalamus are sensitive to changes in the osmolality of the blood bathing them and respond by signaling the cells of the supraoptic and paraventricular nuclei to alter their secretion of vasopressin. These cells arc most sensitive to osmotic substances that do not freely diffuse into cells, such as sodium, sucrose, and mannitol. Substances such as urea produce less osmotic stimulation because they diffuse freely. Glucose, in addition to diffusing freely, actually inhibits ADH release. These cells respond not only to increased osmolality and hence dehydration but also to hypotension with marked increases in ADH secretion.

Water homeostasis cannot be maintained by antidiuresis alone but also requires thirst and the drinking behavior induced by it. A drinking center is thought to be located near the feeding center in the lateral hypothalamus. Angiotensin may play an important role in stimulating drinking in humans and animals.

Sodium Homeostasis and Atrial Natriuretic Peptide

Sodium homeostasis is extremely important for normal functioning of the organism. Most of the regulation of body sodium takes place in the kidney. Sodium reabsorption is under the control of the renin-angiotcnsin-aldosterone system. Under normal physiological circumstances, aldosterone, the principal mincralocorticoid produced by the adrenal gland, is affected in only a minor way by ACTH.

The human heart has been shown to synthesize and secrete atrial natriuretic peptide, which has diuretic, natriuretic (increased urinary sodium excretion), and vasorelaxant properties. In addition to atrial natriuretic peptide, the brain contains brain natriuretic peptide and C-type natriuretic peptide. Because of the pattern of their distribution in the brain, these substances may have important roles in the central control of the cardiovascular system. The natriuretic peptides seem to act as natural antagonists to the central actions of angiotensin II.

Diabetes Insipidus

DI is a clinical syndrome characterized by sevete thirst, polydipsia, and polyuria. Central DI must be distinguished from nephrogenic DI (an inability of the kidney to respond to ADH) and from compulsive water drinking. Distinguishing these entities is normally done using a water deprivation test. A urine osmolality of greater than 750 mmol/L following water deprivation excludes the diagnosis of DI. Centra] DI is characterized by an increase in osmolality to greater than 750 mmol/L following desamino-D-arginine-vasopressin (DDAVP). In nephrogenic DI, there is little change in osmolality after DDAVP. The polyuria induced by chronic compulsive water drinking may produce a renal tubular concentrating defect because of medullary washout—that is, the loss of sodium and other solutes from around the loops of Hcnlc. This can make it difficult to differentiate partial DI of central or renal cause from polydipsia. Treatment with DDAVP and gradual fluid restriction can be used to reverse the medullary washout and hence increase the sensitivity of the test.

The water deprivation test must be strictly supervised by a physician familiar with the technique. Severe and potentially fatal dehydration can occur rapidly in patients with complete DI. Similarly, patients with compulsive water drinking given DDAVP can drink themselves into hyponatremic coma.

Etiology

Approximately one third of patients with central DI have no demonstrable disease of the hypothalamic-postenor pituitary unit. The remaining patients have damage to the supraoptic-hypophyseal-portal pathway from trauma, surgery, tumors, inflammatory lesions (which may be granulomatous or infectious), or vascular lesions. In patients with polyuria, the urine should be examined to ensure that there is not a solute diuresis, as with hyperglycemia, or that a type of nephrogenic DI has not been induced by hypokalemia, hypercalcemia, or lithium carbonate therapy. The investigation of DI is well summarized by Baylis (1995).

Management

Patients with DI excrete mainly water, and therefore water alone is the mainstay of their management. Patients who are alert and have intact thirst mechanisms should be given free access to water. Only if urine output exceeds 7 L per day is treatment necessary. In most circumstances, DDAVP given as a nasal solution is the treatment of choice.

To avoid water intoxication, it is preferable to under-replace these patients and allow them to modulate their water balance by drinking.

The unconscious patient can present a problem in management. When calculating such a patient's fluid needs, one should be aware that the urine in DI is electrolyte poor. Thus the electrolyte requirements of such a patient are little different from those of other patients. The bulk of the urinary replacement should be given as 5% dextrose in water. The administration of 5% dextrose in 0.2 NaCl or solutions with even higher salt concentrations present a high solute load to the kidney and tend to exacerbate the polyuria.

Syndrome of Inappropriate Antidiuretic Hormone Secretion

Etiology and Pathophysiology

The syndrome of inappropriate ADH secretion (SIADH) is characterized by low serum sodium, high urine sodium, and urine relatively or absolutely hyperosmolar to serum. Before making the diagnosis, the physician must exclude all of the following: (1) dehydration, (2) edema-forming states such as congestive cardiac failure, (3) primary renal disease, (4) adrenal or thyroid insufficiency, and (5) use of medication that causes salt-loss in urine (e.g., diuretics).

The initial clue to the diagnosis of SIADH is the low scrum sodium. Measured scrum osmolality must also be low to exclude the artifactual hyponatremia that occurs with hypcrlipidemia and hypcrproteinemia, in which the sodium concentration in the plasma water is actually normal. The urine osmolality in SIADH is not always above the serum osmolality, but the urine is less than maximally dilute, which excludes the dilutional hyponatremia of water intoxication. Causes of SIADH are listed in Table 47.1 1.

Table 47.11: Causes of the syndrome of inappropriate antidiuretic hormone secretion

- Disorders of the nervous system
  - Tumor
  - Trauma
  - Surgery
  - Metabolic encephalopathy
  - Infections (meningitis, encephalitis)
  - Vascular (e.g., stroke)
  - Subdural hematoma
  - Hydrocephalus
  - Guillain-Barrc syndrome
  - Acute intermittent porphyria
- Drugs
  - Carbamazepine
  - Chlor promazine
  - Chlorpropamide
  - Cis-platinum
  - Clofibrate
  - Cyclophosphamide
  - Oxytocin
  - Thiazide diuretics
  - Vasopressin
  - Vinblastine
  - Vincrisrine
  - Tricyclic antidepressants
  - Selective serotonin reuptake inhibitors (SSRIs)
- Disorders of the chest
  - Pneumonia
  - Tuberculosis
  - Cystic fibrosis
  - Pneumothorax
  - Empyema
  - Asthma
- Endocrine causes
  - Hypoad renal ism
  - Hypothyroidism
- Ectopic production of antidiuretic hormone
- Carcinoma: lung, gastrointestinal tracr, and genitourinary tract (especially kidney)
  - Mesothelioma
  - Lymphoma and leukemia
  - Thymoma
  - Sarcoma
- Idiopathic

Clinical Features

The clinical features of SIADH are nonspecific and are related to the hypo-osmolality of the body fluids. The more rapidly this develops, the more symptomatic is the patient. Serum sodium less than 115 mmol/L is almost always associated with confusion or obtundation, and seizures can occur. With milder hyponatremia, the symptoms may be nonspecific, including fatigue, general malaise, loss of appetite, and some clouding of consciousness.

Treatment

For asymptomatic or mildly symptomatic SIADH-induced hyponatremia, the mainstay of treatment is restriction of fluid. Intake should be reduced to insensible losses (approximately 800 mL per day). Obtundation by itself does not necessitate more aggressive treatment of hyponatremia. However, in patients with severe hyponatremia complicated by seizures, a more rapid partial correction can be undertaken. Diuresis is induced with furosemide (1 mg/kg intravenously), and urinary losses are replaced with 3% sodium chloride at a rate of 0.1 mL per kg per minute, to which appropriate amounts of potassium are added (to counter urinary losses). There is considerable controversy over the rate at which serum sodium can be raised safely. Ayus and Arieff (1993) suggest that active correction be by no more than 20-25 mmol/L during the first 48 hours, to a level no higher than 130 mmol/L. They suggest that the rate

of treatment is not important. Patients must he monitored carefully to avoid acute elevation to hypcrnatremic or even normonatremic levels, and to avoid a change of more than 25 mmol/L in 48 hours, which seems to be dangerous and can cause central pontine myelinolysis. Prolonged fluid restriction is often poorly tolerated by patients, who may quickly become noncompliant. In cases in which the underlying cause of the SIADH cannot be eliminated or corrected, the drug demeclocycline, a tetracycline, in a dose of 300-600 mg twice a day, induces a temporary nephrogenic DI and alleviates the necessity for fluid restriction.

Cerebral Salt Wasting

Some patients with hyponatremia do not have SIADH secretion with resultant retention of renal free water. Instead they have an inappropriate natriuresis. Hyponatremia, accompanied by renal sodium loss and volume depletion, occurs in patients with primary cerebral tumors, carcinomatous meningitis, subarachnoid hemorrhage, and head trauma and following intracranial surgery and pituitary surgery. Unlike patients with SIADl 1. these patients respond to vigorous sodium and water replacement, and their condition is actually worsened by fluid restriction. This inappropriate natriuresis that accompanies intracranial disease (so-called cerebral salt wasting) may be caused either by a natriuretic hormone such as atrial natriuretic peptide or by an alteration of the neural input to the kidney.

It is critical to distinguish between these patients and those with SIADH, because the treatment for SIADH worsens the hyponatremia of cerebral salt wasting. Differentiation is best done by a careful assessment of volume status, using the clinical and laboratory examination to detect signs of volume depletion. If there is uncertainty about the diagnosis, the patient should have fluids restricted. Then, if the natriuresis persists in the face of volume restriction, the syndrome of cerebral salt wasting should be suspected and appropriate therapy instituted.

APPROACH TO THE PATIENT WITH HYPOTHALAMIC-PITUITARY DYSFUNCTION

History and Physical Examination

Patients with suspected hypothalamic or pituitary disorders should be questioned specifically about dysfunction of the nonendocrine aspects of the hypothalamus, including appetite, body temperature, sleep-wake cycles, emotion, libido, and autonomic nervous system function. Such symptoms may point to a hypothalamic rather than a pituitary location. A careful functional inquiry should also cover clinical aspects of the hyperfunction and hypofunction of each of the anterior and posterior pituitary hormones,

Because of the proximity of the optic nerves to the hypothalamic-pituitary unit, a careful examination of the visual fields is essential (see Chapters 14 and 40).

Assessment by Imaging Studies

MR] has replaced CT scanning as the investigation of choice in the diagnosis of pituitary and parapituitary lesions. Stadnik ct al. {1 994) indicate that the use of MRI with gadolinium contrast is associated with a detection rate of 82-94%. When using two-dimensional techniques, it is important to obtain thin (1-2 mm) coronal slices of the sella to achieve the best results. Cerebral angiography is rarely required, because large cerebral aneurysms mimicking pituitary adenomas are readily picked up by MRI. Angiography is reserved primarily to demonstrate the blood supply of suspected meningiomas.

Endocrinological Investigation

Not every patient with hypothalamic-pituitary disease requires a full battery of pituitary tests. In general, one attempts to determine the extent of pituitary functional damage, if any, and—in patients in whom blood levels of hormones are elevated or if there is a clinical suspicion of excessive hormonal secretion—to determine if the hormones in question respond normally to physiological suppressors and stimulators.

No single endocrine rest can provide all the answers about pituitary function. Conclusions are based on a synthesis of evidence gained from clinical examination, endocrine tests, and MRI. Endocrine testing is used to determine the residual pituitary function following surgery or radiotherapy. The return of biochemical markers of abnormal pituitary sectetion or their failure to resolve is used to gauge the success of surgery and to aid in differentiating scar tissue from tumor recurrence on postoperative MRI scans. Table 47.12 summarizes pituitary tests and their use.

Treatment of Pituitary Tumors

Medical

Prolactinoma. Hyperprolactinemia of whatever cause often can be suppressed by the dopamine agonist bromocriptine, but such suppression is not diagnostic of a prolactinoma. Bromocriptine (2.5-7.5 mg per day in divided doses) usually normalizes serum prolactin. Maximum shrinkage of tumors occurs within 6 months

Table 47.12: Common tests of pituitary function

Test	*Comments*
Insulin hypoglycemia (regular insulin 0.1 U/kg body weight IV, fasting)	Adequate hypoglycemia is associated with a rise in growth hormone, ACTH, and prolactin. It is probably the most physiological stressor of the hypothalamic-pituitary-adrenal axis. The test should not be used in patients with epilepsy or unstable angina.
Gonadorropin-releasing hormone (2 ug/kg IV to a maximum of 100 ng)	Stimulates LH and FSH release directly at the pituitary. May be used to test LH and FSH reserve. Cannot reliably distinguish between pituitary and long-standing hypothalamic problem.
Thyrotropin-releasing hormone (7 pg/kg IV to a maximum of 400 ug)	Stimulates thyroid-stimulating hormone and prolactin pituitary. Failure of prolactin to respond to thyrotropin-stimulating hormone is very suggestive of autonomous secretion by an adenoma but exceptions do occur.
Meryrapone test (750 mg q4h for 6 doses; collect 24-hr urines the day before, day of, and day after the test)	Meryraponc blocks the production of Cortisol in the adrenal gland. This results in increased ACTH secretion. It is an alternative to insulin hypoglycemia as a test of the hypothalamic-pituitary-adrenal axis
L-Dopa (500 mg po)	L-Dopa can be used to stimulate growth hormone release (probably by increasing growth hormone-releasing hormone). It is a less potent stimulus than insulin-induced hypoglycemia but can be used as an alternative.

ACTH = corticotropin; FSH = follicle-stimulating hormone; LH liMi'iin/iii!', hormone.

and often within 6-8 weeks. Experience indicates that bromocriptine is safe to use to restore fertility. Once pregnancy occurs, the bromocriptine can be stopped with little risk of expansion of the prolactinoma during the remainder of the pregnancy and the immediate postpartum period. Bromocriptine appears to cause growth of fibrous tissue in prolactinomas. In a few patients, this may allow bromocriptine to be withdrawn without prolactin levels rebounding. This fibrous tissue may make such tumors more difficult to remove surgically and result in lower rates of surgical success. Cabergolinc, a newer dopamine agonist appears to be equally effective but better tolerated and can be taken once or twice a week instead of daily.

Cushing's Disease. The results of long-term medical therapy of Cushing's disease have been disappointing. Cyproheptadine temporarily lowers ACTH levels in some patients; however, it is rarely effective for long and is commonly associated with somnolence and increased appetite. Drugs such as mctyrapone and ketoconazole, which block corticosteroid synthesis, can be used to lower Cortisol levels and improve patients' clinical status before surgery. Ketoconazole can be used to control Cortisol levels over the long-term, but patients must be monitored closely for side effects. Recently, mifepristone (RU 486), in high dose, has been shown to provide good control of Cushing's disease that was refractory to other medications.

Acromegaly. Until the development of a long-acting somatostatin analogue (octreotide), the outcome of medical therapy for acromegaly, like that for Cushing's disease, was disappointing. Bromocriptine, in doses of 20-60 mg per day, could reduce GH levels and cause tumor shrinkage, hut it seldom normalized GH levels. Octreotide can normalize GH levels when given by subcutaneous injection every 8 hours. This route of administration is the main drawback to its clinical use, but eventually it may be possible to give it as an intranasal preparation similar to DDAVP. The analogue can be combined with bromocriptine if necessary to achieve maximal suppression and tumor shrinkage.

Thyroid-Stimulating Hormone-Secreting and Gonadotropin-Secreting Tumors. Most patients with these types of tumors are treated surgically, sometimes followed by radiotherapy. TSH-secreting tumors respond to octreotide with *a* decrease in hormone production; however, there is little if any tumor shrinkage. Early reports suggest that octreotide can reduce levels of or-subunit secretion in gonadotropin-secreting tumors, as can bromocriptine. Although some tumor shrinkage may occur with bromocriptine, it is unclear whether long-term octreotide use will have the same effect,

Surgical

In a medically fit patient with an accessible lesion, surgery is the treatment of choice for all nonsecretory pituitary and parapituitary lesions. For secretory tumors, surgery offers the possibility of rapid and complete cute. It is the preferred treatment when serious compression of parapituitary structures occurs. Surgical cure rates have been reported to be more than 80% in cases of microadenoma, although these rates may well be lower when strict endocrine criteria

for cure are applied and when patients are followed for 15 years. In the hands of an experienced neurosurgeon, pituitary surgery has low morbidity and mortality.

Radiotherapy

Conventional radiotherapy is used primarily as an adjunct to surgery and medical therapy, most commonly in the treatment of acromegaly, although octreotide may reduce its use. It is also used frequently in surgical failures in cases of Cushing's disease. It is rarely used in treating microprolactinoma in North America, although it is used in larger tumors. Recurrence of nonsecrcting adenomas after partial removal is effectively prevented by radiotherapy. The major problems with conventional radiotherapy are the long delay in the onset of its effect (often I $ months), its tendency to incomplete efficacy in secretory tumors, and the high frequency of eventual development of panhypopituitarism.

Proton beam therapy permits a dose of radiation to be given at the pituitary gland that is 20-25 times greater than with conventional radiotherapy techniques. At the same time, radiation doses to other brain areas are limited. Unfortunately, because this technique requires the use of a cyclotron to produce protons, it is available in only a few centers. The reported results compare favorably with those of transsphenoidal surgery. Similar results can probably be obtained using the gamma knife. Because of the sensitivity of the optic nerves and chiasm to high doses of radiation, visual field defects and suprasellar extension of tumor arc relative contraindications to the use of these techniques.

Treatment of Hypopituitarism

Vasopressin, ACTH, and TSH are the pituitary hormones critical to an individual's health and well-being. The management of vasopressin deficiency has been discussed already. ACTH deficiency is managed by glucocorticoid replacement; mineralocorticoid supplementation is seldom necessary. Most patients require 5 mg of prednisone (or 25 mg of cortisone acetate) each morning, and some require an additional 2.5 mg of prednisone in the evening. With the development of mild intercurrent illness the dose of prednisone should be doubled. Corticosteroid replacement in the glucocorticoid-dcficicnt patient with serious illness or undergoing surgery consists of hydrocortisone sodium succinate, 10 mg per hour intravenously, around the clock. As the patient recovers, the dose is slowly tapered to maintenance levels.

TSH deficiency is managed by j.-thyroxine replacement. Suppression of elevated TSH cannot be relied on to determine the adequacy of replacement in patients with pituitary-hypothalamic disease. Resolution of the clinical signs and symptoms of hypothyroidism is the important goal. In patients adequately replaced (i.e., with triiodothyronine [T}] levels in the upper one half of the therapeutic range), thyroxine (T_4) levels arc often at or above the upper limit of normal.

Gonadotropin deficiency is usually managed by administration of testosterone or estrogen. This, however, does not restore fertility. In patients for whom fertility is sought, a reproductive endocrinologist consultation and administration of various substitution therapies for LH and FSH may allow induction of fertility.

GH deficiency in children is treated by the administration of synthetic GH. CH-dcficient adults currently do not receive GH replacement. There is gathering evidence **that** muscle strength, wound healing, and lean body mass are all improved by treating these individuals with synthetic CH. Unfortunately, these studies have been short term, and the dose of GH required for long-term replacement is unknown. Because of the potentially deleterious effects of excessive levels of GH, studies are under way to determine appropriate replacement doses. There is no therapy available for prolactin deficiency.

NEUROSECRETION SYNDROMES

Apudomas

The term *APUD* is applied to cells that are capable of Amine Precursor Uptake and Decarboxylation. These cells are distributed throughout the body and arc capable of synthesizing biogenic amines or polypeptide hormones. APUD cells are found in the pituitary gland, adrenal gland, peripheral autonomic ganglia, lung, GI tract, pancreas, gonads, and thymus. Tumors arising from APUD cells are referred to as *apudomas.* As a class of tumors they generally produce symptoms through the secretion of biogenic amines (norepinephrine, epinephrine, dopamine, serotonin) or hormones. Of the apudomas, insulinomas, gastrinomas, vasoactive intestinal polypeptide-secreting tumors, medullary carcinomas of the thyroid, pheochromocytomas, and carcinoid tumors can all present as clinical emergencies. Of these, only pheochromocytomas and carcinoid tumors are discussed here.

Pbeocbramacytoma

Pheochromocytomas are rare tumors that arise most commonly (85-90% of the time) from the catecholaminc-producing cells of the adrenal medulla; they can also arise from extra-adrenal chromaffin tissue in the cervical and thoracic regions and in the abdomen. The majority of these tumors occur spontaneously; however, they can be part of other syndromes such as multiple endocrine neoplasia type II and **lib,** von Hippel-Lindau disease, neurofibromatosis, ataxia-telangiectasia, tuberous sclerosis, and Sturgc-Wcbcr syndrome.

Pheochromocytomas predominantly secrete norepinephrine, epinephrine, and some dopamine. These compounds

are responsible for the most common symptoms **of** pheochromocytoma: throbbing headache, sweating, palpitations, pallor, nausea, vomiting, and tremor. Pheochromocytomas arc also capable *o* secreting other neuropeptides that can be responsible for different clinical symptoms {Fonseca and Bouloux 1993). Pheochromocytoma should be suspected in patients with progressive or malignant hypertension; hypertension of early onset without family history; hypertension resistant to conventional therapy; paradoxical worsening of hypertension in response to treatment with beta blockers; and a history of pressor response provoked by anesthesia, labor or delivery, or angiography. I screen for pheochromocytoma by collecting two 24-hour urine specimens and having them analyzed **for** vanillylmandelic acid, norepinephrine, epinephrine, and metanephrines. These collections should be done at a time the patient is symptomatic because periodic hormone secretion does occur and levels may at times be normal. The completeness of the 24-hour collection should be confirmed by an analysis of urinary creatinine.

Tumor localization can usually be achieved by CT scanning of the adrenals. If a wider search is necessary, MRI scanning may be more helpful. ^{m}I-MIBG (meta-iodobenzyl guanidine), an iodinatcd guanethidine derivative, is taken up by chromaffin tissue and can be helpful in the localization of nonadrcnal tumors and metastases. Some centers have been using " 'indium-labeled pentetreotide, an analogue of somatostatin, to localue somatostatin receptors on these tumors. Soma tost a tin-receptor scanning and positron emission tomographic scanning with hydroxyephedrine remain experimental.

Patients with pheochromocytoma should be managed in centers with previous experience of the treatment of this type of tumor. Suitable preoperarive preparation is necessary to prevent hypertensive or hypotensive crisis during surgery. For benign tumors, complete surgical removal is the treatment of choice. Malignant tumors may be palliated with a variety ol treatments.

Carcinoid Tumors

Carcinoid tumors arise from entetochromaffin cells in the GI tract, pancreas, or lungs and only rarely from the thymus or gonads. When carcinoid tumors release biogenic amines directly inro the systemic circulation, bypassing the liver, the carcinoid syndrome results. This is characterized by episodes of flushing, often with accompanying diarrhea or asthma. Later in the syndrome there is fibrosis of the endomyocardium. Carcinoid tumors may be a source of ectopic ACTH, corticotropin-releasing hormone, or GHRH secretion.

The diagnosis is made by finding elevated urinary 5-hydroxyindolacetic acid levels. As in pheochromocytoma, carcinoids also secrere peprides (e.g., kallikrein, substance P, neurotensin} and other amines (e.g., histamine, dopamine), and some of these substances may be responsible for the flushing that occurs in the syndrome,

Surgery is the treatment of choice; however, by the time the tumors become symptomatic they are often incurable because of the metastases. Serotonin antagonists may be used to treat some of the symptoms, and octreotide may successfully manage carcinoid crisis.

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Chapter 48
Management of Neurological Disease

Walter G. Bradley, Robert B. Daroff, Gerald M. Fenichel, and Joseph Jankovic

Wc discussed how an experienced neurologist uses the history of the patient's illness, the neurological examination, and investigations to diagnose neurological disease in Chapters 1 and 35. In this chaptet, wc present some general principles guiding the management of neurological disease. Chapters 49-54 cover individual areas of neurological management, such as pain management, neuropharmacology, intensive cate, neurosurgery, and neurological rehabilitation. Details about the management of individual neurological diseases are presented in Chapters 55-85. In addition many aspects of management are common to all neurological disorders and are discussed in this chapter.

PRINCIPLES OF NEUROLOGICAL MANAGEMENT

As in all medical disciplines, many neurological diseases are "incurable." However, this does not mean that there is nothing that can be done to help the patient. The help that can be provided short of curing the disease ranges from treating the symptoms to providing support for the patient and family and end of life cate (Table 48.1). Medical personnel are so committed to the scientific undctstanding of diseases and their treatment that there is a natural tendency to feel guilty when confronted with a patient with an incurable disease. The number of neurological diseases that are curable or can be arrested is constantly expanding as a result of research. However, a physician who is fixated on the need to cure disease may simply concentrate on making the diagnosis, and give no thought to its management. Such a physician will tell the patient that it is an incurable disease, so there is no point in coining back for further appointments ("diagnose and *adias").* This attitude is not only an abrogation of the physician's responsibility to care for the patient, hut it also leaves the patient without the many modalities of assistance that can be ptovided even to patients with incutable disease. The neurologist who is interested in treating the patient will review with the patient and the family all the issues listed in Table 48.1. It is often necessary to spend more time with the patient with an incurable disease than with one for whom effective treatment is available. In addition to providing all the practical help available, the compassionate neurologist should shatc the gtief and provide consolation; both ate essential aspects of patient management.

GOALS OF TREATMENT

In defining the goals of treatment it is important to separate neurological impairment, disability, and handicap. *Neurological impairment* (the presence of abnormal neurological signs) allows a diagnosis to be made, Impairment may cause *disability,* which in turn produces a *handicap.* The patient does not care about the abnormal neurological signs, but wants correction of the disability and relief from the handicap. For instance, a stroke causes a hemiplegia, which is the impairment. The hemiplegia causes difficulty in walking, which is the disability. The difficulty in walking may make it impossible for the patient to leave the house, which is the handicap. It may not be possible to correct the undct lying stroke or the hemiparesis, but symptomatic treatment, such as providing physical therapy, a walker, and a wheelchair, can help alleviate the handicap. The improvement in functional state of a stroke patient resulting from neurological rehabilitation is gratifying when compared with the state of untreated patients.

Amyotrophic lateral sclerosis (ALS) is perhaps the disease that epitomizes the role of symptomatic cate (Miller et al. 1999, 2002). Patients with ALS often report

Table 48.1: Help a physician can provide to patients with any disease

Curative treatment
Cure of the disease
Arrest of the disease
Symptomatic treatment
Arresting an attack
Slowing the rate of progression of the disease
Relief of symptoms
Circumventing the effects of the disease
Treatment of secondary effects of the disease
Psychological
Soeial
Family
Definition of the prognosis
Genetic counseling
End of life care

being told by their doctor that they have ALS; that they are likely to die within 3 years; and that because nothing can be done for them they should go home, put their affairs in order, and prepare to die. A doctor who dispenses such advice is not only uncaring, but also leaves the patient without hope and the symptomatic treatment that can help the patient circumvent the disabilities and handicaps that attend the disease. The psychological support of a caring neurologist who is familiar with the disease can be of great help to the patient and the family. There is an increasing number of lay organizations and support groups that provide information and services. Patients will often have found these by searching the internet, but the physician should keep available the addresses and phone numbers of the key organizations to give to patients.

Symptomatic treatment depends on the nature of the disease. It can consist of arresting an attack in a disease such as multiple sclerosis; circumventing the effects of the disease, such as with antispasticity medications; or end of life care for a patient approaching death. The latter is sometimes called palliative care, but in fact every treatment short of cure, even in the early stages of a disease, is palliative.

Arresting an Attack

Many neurological diseases cause episodic attacks. These include strokes, migraine, multiple sclerosis, epilepsy, and periodic paralysis, and in some of these diseases treatment may halt the attacks. Although it does not cure the underlying disease, aborting the attacks is of great help to the patient. Triptan-class drugs generally arrest a migraine, and valproate, a beta blocker, or a calcium channel blocker will reduce the frequency of the attacks (see Chapter 75). Status epilepticus can usually be arrested by intravenous phenytoin, diazepam, or barbiturate, and the frequency of epileptic attacks can he reduced by anticonvulsant drugs (see Chapter 73). Intravenous and intra-arrerial thrombolytics may terminate an otherwise disastrous "brain attack" (stroke) (see Chapter 57A).

Slowing Disease Progression

There are many examples of treatments that slow the progress of neurological disease. A malignant cerebral glioma is almost universally fatal, but high-dose corticosteroids, neurosurgical debulking, and radiotherapy may slow tumor growth and lengthen survival (see Chapters 5SSE and 581*). The /3-interferons and glatiramer may reduce relapses and slow the progress of multiple sclerosis (see Chapter *60).* Liver transplantation in familial amyloid polyneuropathy may slow or arrest disease progression (see Chapter 82). Riluzole may slow the progress of ALS (see Chapter 80).

Relieving Symptoms

Symptomatic treatment is available for many neurological diseases. Relief of pain, although not curative, is the most important duty of the physician and can be accomplished in many ways (see Chapter 50). Baclofen and tizanidine can reduce spasticity, particularly in spinal cord disease, without affecting the disorder causing it. Injections of hotulinum toxin provide marked relief for several months in patients with dystonia, spasticity, and other disorders manifested by abnormal muscle contractions. High-dose corticosteroid therapy reduces the edema surrounding a brain tumor, temporarily relieving headache and neurological deficits without necessarily affecting tumor growth. In Parkinson's disease, dopaminergic drugs partly or completely relieve symptoms for a period without affecting the progressive degeneration of substantia nigra neurons (see Chapter 77), The physician-patient relationship and the placebo response arc both important tools used by the experienced neurologist in helping to relieve a patient's symptoms.

Circumventing Functional Disability

Neurological diseases like Alzheimer's disease, Parkinson's disease, and ALS have a course that is usually continuously progressive. Others, like stroke and spinal cord injury, have an acute onset and the damage occurs before the neurologist first sees the patient. Although some recovery is expected, substantial functional deficits often persist. In both situations, there are many ways to circumvent the functional disability and the resultant handicap.

Neurological rehabilitation is the discipline that concentrates on restoration of function (see Chapter 54). Physical and occupational therapy help the patient to strengthen weak muscles, to retrain the nervous system to compensate

for lost function, to increase mobility, and to reduce spasticity. Some believe that cognitive or behavioral therapy may similarly re-educate undamaged cortical areas to compensate for the effects of brain injury and stroke. Orthopedic procedures can be beneficial for rehabilitation; transfer of the tibialis posterior tendon to the dorsum of the foot can correct a footdrop in appropriate cases. Surgical release of Achilles tendon and iliotibial contractures in boys with Duchenne's muscular dystrophy can delay the loss of ability to walk by 2 years or more.

Aids and appliances, such as ankle-foot orthoses to prevent footdrop, canes, walkers, and wheelchairs, can increase mobility and limit handicap. Changes to the home and work environment, such as a ramp or stair lift, widening of doors to allow wheelchair access, rails for the bath and toilet, or replacement of the bath with a shower and shower chair, can be of great help to the patient. Only the ingenuity of clinicians and biomechanical engineers, the availability of technology, and the cost limit the scope of such appliances. Cochlear implants are already in clinical use for those born deaf. Computer-controlled motorized body and lower-limb braces may allow paraplegic patients to walk,

The range of options available to help a patient with a severe, chronic neurological disease can be illustrated by reference to ALS (Miller et al. 1999, 2002). In the early stages, the patient may simply need enlarged handles on pens, tools, and utensils to compensate for a weak hand grip or a cane to help with walking. Later, the patient may need a wheelchair and home adaptation. Speech therapy, a communication board, or a computer with specialized software can help when speech is severely impaired. Weight loss and choking from dysphagia may necessitate a percutaneous gastrostomy. An incentive spirometer and an artificial cough machine can protect respiratory function (see Respiratory Failure, later in this chapter). If the patient decides not to use a ventilator, end of life and hospice care are needed.

Management of disabilities in patients with progressive neurological diseases may tax the neurologist's knowledge and ingenuity, but the beneficial effect of symptomatic therapy on patients and families makes the effort worthwhile and demonstrates that no neurological disease is **untreatable.**

PRINCIPLES OF SYMPTOM MANAGEMENT

Treatment of Common Neurological Symptoms

A number of symptoms, such as pain, weakness, dysphagia, and respiratory failure, are common to many different neurological diseases. General principles governing the management of these symptoms are outlined below and more fully discussed in Chapters 49, 50, 51, and 54. Specific treatment for individual diseases is discussed in the relevant chapters in Volume II of this book.

Pain

The first step in pain management is to diagnose the source of the pain and assess the prognosis of the disease {see Chapter 50), Consider, for example, a patient with incapacitating pain in one leg from carcinoma infiltrating the lumbosacral plexus on one side. This patient's life expectancy is measured in months, and progressive plexus damage will produce leg paralysis. Destructive surgery (see below) and narcotics are justified in this situation. Tachyphylaxis for narcotics can occur, and the oral dose of narcotics required to control pain may rise rapidly in patients who live for several months. This does not appear to occur with morphine administered by an intrathecal or epidural spinal catheter using a subcutaneous infusion pump. Surgical interruption of pain pathways is considered the final choice to relieve pain from carcinomatous infiltration of the lumbosacral plexus. These procedures include surgical or chemical posterior rhizotomy, contralateral anterolateral spinothalamic tractotomy in the midthoracic region, or stereotactic contralateral thalamotomy,

Narcotics should not be used for patients with nonmalignant chronic pain syndromes, such as painful polyneuropathies or low back pain, because of the risk of producing drug dependency. Biofeedback, hypnosis, and acupuncture may help some patients control the pain. Antidepressant drugs benefit many chronic pain syndromes by blocking the neurochemical transmitter mechanisms of central nervous pain pathways, as well as treating depression. This is a point that needs to be explained to the **patient.** Sometimes a single drug may he effective, but frequently a combination of a selective serotonin reuptake inhibitor (SSRI), such as sertraline, and a tricyclic, such as amitriptylinc, is better,

Sensory Loss, Paresthesias, and Burning Pain

Occasionally, sensory loss produces an intolerable positive sensation termed *anesthesia dolorosa,* which may respond to a combination of a tricyclic with either carbamazepine or an SSRI. Paresthesias generally result from damage to the large diameter myelinated axons in the peripheral nerves or posterior columns of the spinal cord. Two thirds of patients with painful paresthesias and electric shock-like pains can obtain relief with carbamazepine, and a smaller proportion with phenytoin. Burning sensations from small fiber peripheral neuropathies arc often helped by a tricyclic or SSRI, or a combination of the two. Gabapentin in high doses (up to 4,8 g/day) can benefit burning and to a lesser extent other pains.

Weakness

The management of weakness, considered more fully in Chapter 54, is a major component of neurological rehabilitation. The choice of treatment depends on the

extent, severity, and prognosis of the patient's weakness. For example, weakness of dorsiflexion of the ankle due to Charcor-Marie-Toorh disease may be treated with a triple arthrodesis of the foot. Such a procedure, however, would not be appropriate to overcome the footdrop caused by a more rapidly progressive condition, such as ALS. For such patients, an ankle-foot orthosis would be best. Most neuromuscular conditions are benefited by exercise, although fatigue limits the amount that can be tolerated. Myasthenia gravis, however, is worsened by exercise. Weakness due to upper motor neuron disease can be helped by physical and occupational therapy to promote the use of alternative neuronal pathways. Medications such as baclofen and tizanidine reduce spasticity and may improve function in upper motor neuron disorders.

Ataxia

Ataxia can result from cerebellar dysfunction or sensory deafferentation. If the disease causing the ataxia cannot be reversed, occasionally treatment with trihexyphenidyl or a benzodiazepine can decrease the degree of ataxia. A weighted cuff placed on an ataxic limb may lessen incoordination; the added inertia reduces the excursion of the limb during movement. Gait ataxia is best managed by the use of walking aids, such as a cane, walker, or wheelchair. The gait of elderly patients, whose loss of postural reflexes causes retropulsion and falls, is improved if the center of gravity is displaced forward by increasing the height of the heels on the shoes and lowering the walker so that the patient must stoop forward.

Slowness of Movement or Abnormal Involuntary Movements

Along with rest tremor and rigidity, slowness of movement (bradykinesia) is one of the clinical hallmarks of Parkinson's disease and other parkinsonian disorders. Bradykinesia usually responds to dopaminergic therapy. Conversely, excessive involuntary movements, such as chorea and stereotypies, typically improve with drugs that deplete dopamine. Postural tremors (e.g., essential tremor) often improve with beta blockers and primidone. Botulinum toxin injections are considered the treatment of choice for most focal dystonias. Stereotactic surgery, particularly high frequency deep brain stimulation, is an emerging therapeutic strategy in patients with severe movement disorders that continue to be troublesome or disabling despite optimal medical therapy (Jankovic 2001).

Aphasia and Dysarthria

The treatment of language disorders is, in principle, very similar to that of limb weakness. Speech therapy can improve aphasia by retraining the nonspeech areas of the brain to compensate for the effects of damaged speech centers. If the lesion is limited, some aspects of language function may be preserved and so provide an immediate mechanism for communication. For instance, an aphasic patient may be able to communicate through writing. With speech therapy, dysarthric patients can learn to slow their delivery and emphasize words, thus improving the clarity of speech. Treatment with baclofen may improve the spastic dysarthria of upper motor neuron disorders.

Respiratory Failure

Respiratory failure can develop in several neurological diseases (Table 48.2} (sec also Chapter 51). Patients with chronic neuromuscular diseases often complain of respiratory distress when they are close to pulmonary failure. Patients with a weak diaphragm experience dyspnea when lying supine because the abdominal contents prolapse into the chest, thereby lowering the patient's vital capacity and tidal volume. A neurologist or pulmonary specialisr who is relatively inexperienced in neurological problems affecting respiration may underestimate the warning signs of potentially fatal respiratory failure. This is particularly true in myasthenia gravis and Guillain-Barrc syndrome. Blood gas measuremenrs do not change until late in the development of respiratory failure in chronic neuromuscular diseases. By the time hypoxia and hypercapnia develop in the blood, the patient may be bordering on acute respiratory collapse. Reduced vital capacity, patient distress, and a good knowledge of the disease are better ways of judging impending respiratory failure. A patient with Duchenne's muscular dystrophy and a vital capacity of 600 mL may survive for several years without dyspnea. A patient with myasthenia gravis who has a vital capacity of 1200 mL but is anxious, sweating, and complaining of dyspnea is at serious risk of developing total respiratory paralysis. With borderline respiratory function, sleep or sedation may produce carbon dioxide retention and narcosis, respiratory suppression, and death.

Ethical Considerations in the Treatment of Respiratory Failure. Respiratory failure, once invariably fatal, is now commonly treated by noninvasive positive pressure

Tahle 48.2: Types of neurological disease associated with respiratory failure

Acute neurological disease
Brainstem damage
High cervical cord injury
Subacute or chronic neurological disease
Bulbar palsy with airway compromise
Motor neuron degenerations, such as amyotrophic lateral sclerosis
Neuropathies, such as Guillain-Barre syndrome
Neuromuscular junction diseases, such as myasthenia gravis
Muscle diseases, such as muscular dystrophy

ventilation in the early stages, and by intubation and positive pressure ventilation in the terminal stages. The treatment of chronic progressive respiratory failure in neuromuscular diseases like ALS and muscular dystrophy is very challenging (Jones, Darras, and DeVivo 2003}. However, cultural differences in expectations in different countries must be recognized. For example, in Japan it is the established practice to provide the patient with ALS with a tracheostomy and positive pressure ventilation when signs of respiratory failure appear. In Western countries, most consider that life on a ventilator is far from ideal, and quality-of-lifc issues must he discussed by the neurologist with the patient and family before intubation (Bernat 2002; Miller etal. 1999,2002).

Ideally, decisions about life support measures should be made long before the patient is in acute respiratory distress, because it is more difficult to make these decisions when death is imminent. Patients and families require considerable counseling by the neurologist and pulmonary specialist. Parients may benefit from speaking to others who have experienced the situation. Many patients cannot make a definitive decision about life-support measures and so defer the decision until the emergency occurs.

In these matters, the decision of a competent patient, or of the health care surrogate (in the case of an incompetent patient, or one with whom communication is impossible) holds primacy. For instance, a 40-year-old patient with ALS may request respiratory support to see a child graduate or marry, even though there is no likelihood of recovery. The physician may be able to accommodate this request. However, a request to continue ventilator support for a 90-year-old patient with terminal cancer and a severe brainstem stroke is not considered rational, and the physician will try to convey the hopelessness of the situation, and the patient's unnecessary suffering, to the next of kin. Those who decide against ventilator support should provide a living will or terminal care document to their physician and next of kin and legally grant to a designated person (the health care surrogate} the power of attorney to make medical management decisions for them if they become incompetent. Even if patients have prepared a living will, they will be taken by emergency services to a hospital emergency department and be intubated unless proper arrangements arc in place for end of life care at home, usually through hospice services (Miller et al. 2002).

For those who decide to request ventilator support, health insurance and economic matters must be considered. Although the availability of insurance to cover the cost of ventilator care is paramount in the United States, in Japan the government pays for the costs of 24-hour home ventilatory care for all ALS patients.

Patients with a tracheostomy may still be able to talk using a valved tracheosromy tube or a partially inflated cuff, but many lose bulbar functions and need to use communication devices, such as computers, typewriters, or letter boards. Many of the conditions listed in Table 48.2 also cause limb paralysis, which further impairs the patient's quality of life. Quality of life usually becomes an issue when ventilator dependency becomes permanent. In many patients the prognosis becomes clear within a relatively shorr time, as with stroke and coma. Because the patient is unconscious, the next of kin must decide, with the advice of the doctor, whether to continue ventilator support. If the family requests that respiratory support be discontinued, it is standard medical practice in most parts of the world to do so (Bernat 2002). The legal and ethical issues arc more complex with an awake and competent patient who requests that the ventilator be switched off. Although the legal systems in many parts of the world accept that such requests fall under the right of the patient to refuse medical treatment, involvement of a hospital ethics committee is strongly recommended (Bernat 2002).

Managing Terminal Respiratory Failure. If the patient opts for life-support measures, an elective tracheostomy and intermittent positive pressure ventilation should be offered at the first signs of terminal respiratory failure. Patients who have respiratory insufficiency, whether or not they decide to opt for tracheostomy, can often be helped for a prolonged period by noninvasive positive pressure ventilation through a nose mask or nasal "pillows." Patients who decide against respiratory support should be counseled *not to go to the hospital in a crisis* because they will inevitably be intubated. They should be referred to home hospice services, and when terminal respiratory distress appears, home treatment with oxygen, morphine, and sedation will be provided, despite the risk that this may hasten death. Neurologists should learn to manage chronic respiratory failure due to neurological disease. Although neurologists must work collaboratively with the intensive care specialist and hospice doctors, rhey should assume an active role in management decisions.

Memory Impairment and Dementia

Alzheimer's disease is the most common cause of progressive impairment of memory and dementia, and only symptomatic care is possible, which includes anticholinesterase inhibitors. Some causes of progressive demenria are curable (see Chapter 72), and their recognition is important. Even if no specific curative treatment is available, the experienced neurologists can provide essential advice to the family of a patient with a condition like Alzheimer's disease on how to anticipate problems and minimize them. This includes helping the patient to make shopping lists and checklists of things to do before leaving the kitchen or the house and before going to bed. For a period, these measures can prevent the patient from leaving the house unlocked or a pot boiling on the stove. Inevitably, the patient will have difficulty managing a checkbook, and a family member should take over money management before financial disaster occurs. The patient will eventually need either a

live-in companion or to move in with a family member or into a nursing home. Much of the neurologist's efforts are directed toward helping the patient and family to circumvent problems and adjust to expected changes. Family members need access to books and publications by foundations and support groups, such as the Alzheimer's Disease Association.

Treatment of Secondary Effects of Neurological Disease

Predictable reactions occur in a patient who is given the diagnosis of a chronic neurological disease. These reactions progress at variable rates through the stages of anger, denial, "why me?", depression, and eventually acceptance, often with oscillation among these phases. The neurologist must provide support through this process of adjustment, sometimes with the assistance of a mental health professional.

The impact of the disease on the family must also be considered. The family members caring for a patient with Alzheimer's disease often say that it is like looking after a young child but with much more stress. The family of a boy with Duchenne's muscular dystrophy experiences both mental and physical stress because the child will eventually lose the ability to walk and must be lifted in and out of chairs, bed, and bath (Jones, Darras, and DeVivo 2003). Mechanical lifting devices can help, but they are slow and clumsy. Often, a home needs alterations to allow one-level living and wheelchair access. Someone needs to get up several times a night to turn the patient in bed. Lack of sleep and increasing daytime care strain the family dynamics. Other children may be neglected and emotionally deprived; marital disharmony is common. The physician may need to refer the family for counseling or put them in touch with a family support group. The school aurhorities need information and encouragement for the child to continue in mainstream schooling. As the young man with Duchenne's muscular dystrophy reaches maturity, he may consider college or employment, and the neurologist can provide information to assist the relevant authorities.

The neurologist caring for a patient with a progressive neurological disease plays an important role for both the patient and the family. Help from many other professionals is often required, but the neurologist must anchor the management team.

EXPLAINING THE PROGNOSIS

Establishing the diagnosis is necessary to define the prognosis for the patient and the family. The physician should ascertain what the patient and family want to know, and provide answers at a rate they can accept. Some patients fear that they will die or become a "vegetable" within a few months and are greatly relieved to learn that they have several years of useful life ahead. Patients may wish to make financial arrangements or accelerate unfulfilled plans if the prognosis is poor. Patients may not always wish to be told the prognosis, but relatives generally want to know. The neurologist should always present the prognosis with some caveats, because the diagnosis may be wrong or the disease may not follow the expected course. Patients should always be given some hope; even ALS can arrest or remit (Tucker er al. 1991)! A useful way to cushion bad advice is to say that the patient needs to *hope for the best but plan for the worst.*

PALLIATION AND CARE OF THE TERMINALLY ILL PATIENT

Palliative care starts from the earliest stage that the patient is seen by the physician. Pain, depression, and anxiety are the three major symptoms that require palliation. The treatment of pain is considered in Chapter 50. Psychological reactions are treated with a range of pharmacological agents, including benzodiazepines for anxiety, neuroleptics for psychotic symptoms, and an ever-increasing list of medications for depression. However, the psychological support for the patient and family provided by the doctor is usually more important than pharmacological therapy. The experienced neurologist provides help to the patient and family by drawing on lessons learned from treating many similar patients. Even though the disease and its effects cannot be arrested, the neurologist can ease the burden. When possible, the neurologisr should discuss each new phase of the disease with the patient and family *before* it occurs. No patient likes to hear of impending deterioration, but if the neurologist clarifies the importance of anticipation, the patient is reassured that the doctor is ready ro deal with change, when and if it occurs.

GENETIC COUNSELING

Approximately 1 in 10 neurological conditions is inherited. The rapid advances in molecular genetics require that the neurologist keep abreast of the many diseases that can be diagnosed by genetic testing (see Chapter 44). A parent with a neurological disease commonly fears that the disease will pass to the children. Hence if a disease has no hereditary component the couple should be reassured. If the disease has a hereditary tendency, the risk to offspring must be discussed. For instance, the chance of multiple sclerosis occurring in the offspring of a patient with multiple sclerosis is higher than that in the general population, but it is still only about 3%.

However, in Huntington's disease the risk that each offspring will inherit the disease is 50%; at-risk individuals may choose not to have children because of this. Such couples can be advised about alternatives, including

adoption; artificial insemination hy donor, when the husband is at risk; and surrogate gamete in vitro fertilization when the wife is at risk. An individual carrying a mutant gene who wishes to have a child can use the technique of embryo genotesting. After in vitro fertilization with the parents' ova and sperm, the embryo is allowed to grow to the four or eight cell stage. A single cell is then removed for DNA testing; embryos bearing two normal huntingtin genes are accepted for implantation. Cost and availability of services limit the use of this procedure.

The neurologist should provide the patient and spouse with the available information about the mode of inheritance of the disease and, where relevant, the possibilities for prenatal and preclinical diagnosis. A couple's attitude to therapeutic termination of pregnancy should be part of the discussion. When a disease has an autosomal recessive mode of inheritance and the gene frequency in the population is low, the children of an affected parent are at very little risk unless the patient marries a close relative. If the gene frequency in the general population is known, the risk of having an affected child can be quantified.

Each pregnancy of a parent with a fully penetrant autosomal dominant disorder has a 50% risk of resulting in an offspring bearing the mutant gene. If the proband is apparently a sporadic case, a risk approaching 50% must still be given because many apparently sporadic cases are in fact due to dominantly inherited mutations in which the proband was the product of undisclosed parentage, new mutations, and unrecognized mild disease in other family members.

In response to genetic counseling, some patients may make what the neurologist considers to be an irrational decision about having children. Some patients consider 50% quite good odds even when considering the risk of having a child with Huntington's chorea. On the other hand, some patients may decide against having children because of odds of 1 in 100. In both circumstances, physicians should offer advice, and can even say what decision they would make in the same circumstances, but must emphasize that the ultimate decision rests with the couple.

The result of genetic testing can reveal that an asymptomatic individual will almost certainly develop the disorder. Asymptomatic individuals who carry the mutation for the disease can be identified by the use of testing for the mutant gene. Huntington's disease and myotonic dystrophy ate two such examples. Because Huntington's disease currently is nor treatable and Huntington's patients have a high suicide rate, the neurologist should be aware of the risks that accompany disclosure. The services of a qualified genetic counselor is very helpful for managing these problems. Before testing is begun, the genetic counselor will review thoroughly the hypothetical possibilities and the potential responses with the patient and spouse. Though most people think they want to know their generic status, after considering the implications, many conclude that a positive gene test would be too difficult to tolerate and hence forego screening.

CONCLUSION

In this chapter, we have presented a general outline of the principles involved in managing patients with neurological disease. When taken together with Chapters 49-54, dealing with specific aspects of neurological management, and with Chapters 55-85, dealing with the individual diseases, there can be no doubt that the neurologist is more than just a diagnostician. Although the diagnosis is essential, the neurologist's proper focus is on the treatment and management of the patient and the disease.

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Chapter 49
Principles of Neuropharmacology and Therapeutics

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Molecular genetic techniques are gradually revealing how changes in ligand (or neurotransmitter) gated receptors and voltage-gated ion channels in different parts of the neuraxis produce neurological disease. These genetic advances have helped focus the development of new drug therapies. This chapter reviews some of the basic knowledge concerning neurotransmitter systems, their receptors, and their implicated diseases. This chapter attempts to synthesize a small picture of a vast, complex, interactive, molecular world.

NEUROTRANSMITTERS, NEUROMODULATORS, AND RECEPTORS

The ability to purify, sequence, and clone functional receptors and neurotransmitter transporters proves the existence of discrete, selective macromolecules that regulate neurotransmission **in different** parts of the nervous system. Neurotransmitters include amino acids (e.g., y-aminobutyric acid [GABA] and glutamate) and biogenic amines (e.g., serotonin and norepinephrine [NE]), Polypeptides processed from larger precursor peptides serve dual roles as neurotransmitters and neuromodulators. A combination of biochemical techniques and cloning of receptors with variable subunit composition have revealed the structural and functional features of various receptor types (Figure 49.1).

Ligand-gatcd receptors are broadly of two types: *inotropic* and *metabotropic.* Some neurotransmitters bind to both inotropic and metabotropic receptors. For example, glutamate activates three different excitatory inotropic receptors and nine different metabotropic receptors (mGluRs). The mGluRs can be divided into three groups: One is excitatory by virtue of G protein coupling to phospholipid hydrolysis and intracellular calcium release. The other two are negatively coupled to adenylate cyclase. The result of their activation is to decrease activity dependent on cyclic adenosine monophosphate (cAMP) and reduce neurotransmitter release (autoreceptor function). In the short run, the control of neuronal activity is within normal limits by modulating excitatory and inhibitory events simultaneously. Many steps can go awry in the interlocking cascades resulting in pathological processes. These steps serve as points of molecular diagnosis and targets for pharmacological intervention. In the end, genetic regulation determines the subunit **composition, turnover** rate, and number of receptors in the membrane under extant conditions.

Guanosine triphosphare (GTP)-binding proteins (G proteins) couple several receptors to intracellular signaling systems. This links neuronal excitability to energy metabolism and second messenger systems. Normally, neuronal

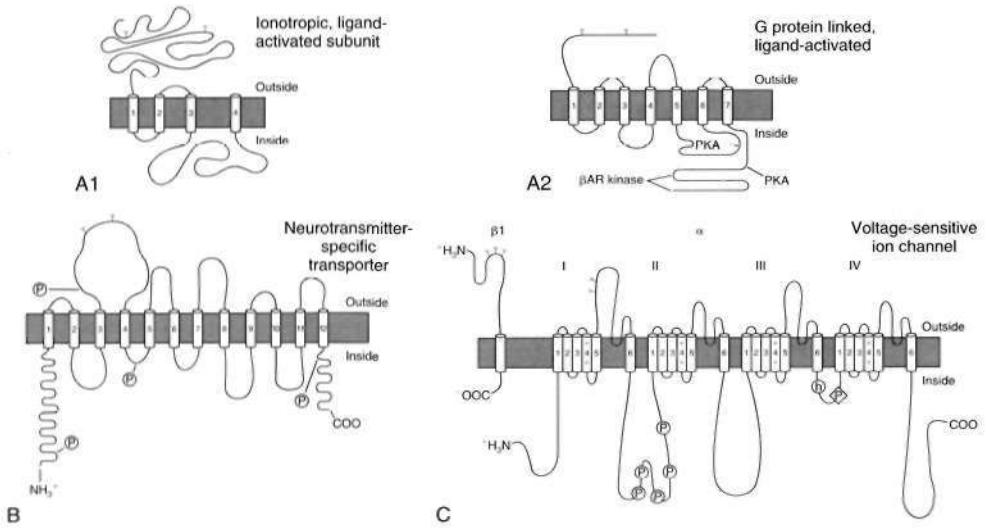

FIGURE 49.1 Molecular structure of Iigand-activated receptors, neurotransmitter transpottets, and voltage-sensitive ion channels. (Al) Ionotropic, tigand-activated receptor structure. A single subunit consisting of an amino and carboxy peptide sequence, font transmembrane segments, and connecting loops is shown. Assembly of approximately five suhunits is thought to be necessary ro construct ligand-gatcd ion-conducting channels. (A2) Some receptors of known neurotransmitters arc coupled to intracellular second-messenger systems indirectly by interaction with C! proteins. G protein-linked receptors arc thought ro have extracellular amino sequences, each followed by seven covalently linked transmembrane domains and an intracellular carboxy terminal of variable length. Kadi transmembrane domain is covalcntly linked by a loop of amino acid residues. The intracellular loop connecting the fifth and sixth ttansmembrane domains is thought to modulate interaction with G proteins, along with the tarhnw icrTiim.il sequence. function of the *(I* adrenergic receptor depicted here K modulated In phosphorylation at different sites by /(-adrenergic receptor kinase (/iAR kinase) or protein kinase A (PKA). (B) The termination of the action of amine neutotransmitters depends on specific transporters, which reduce synaptic concentrations of a neurotransmitter by re-uptake. Transporter proteins have 12 membrane-spanning regions, and both the amino and carboxy regions arc thought to be intracellular. A long extracellular loop connecting rhe third and fourth transmembrane domains is thought to contain the recognition sequence for a specific neurotransmitter, thereby conferring specificity on the transporter system. (C) Voltage-sensitive ion channels arc sequences of 1800-2100 amino acids. They are essentially multiple suhunits that are covalcntly linked. The example shown is the structure of rhe voltage-sensitive sodium channel. The fourth transmembrane domain in each of the four suhunits is positively charged and is likely to be the voltage-sensitive gare. When folded on itself, the four su bun its line a central cavity such that rhe fourth transmembrane domain in each of the suhunits is in a position to open or close the channel depending on its conformational state. Voltage changes and binding of various alkaloids may alter the opening and closure of the channel. The intracellular loop berween the third and fourth subunits contains a sequence that is thought to be responsible for spontaneous inactivation of the sodium channel. The intra cellular loop con nee ring the first and second subunits has multiple sites for modulation by phosphory la ting systems. The amino and carboxy terminals are both thought to be intracellular. Accessory subunits *(ft* is shown) can modulate the kinetics and, possibly, the drug-binding characteristics of the channel. Accessory subunits have been described for hoth the sodium and calcium channels that have been cloned to date. These figures show putative structures based on sequences of purified receptors, Transporters, and ion channels, h = sequence required for spontaneous inactivation of the channel; P = phosphorylation site; Y = glycosylation site; — = anionic loi for retrodotoxin binding; + = cationic sites on voltage-sensing transmembrane segment, (Al Redrawn with permission from Macdonald, R. L. & Olsen, R. W. 1*994*, "GA6A_A receptor channels," *Annu Rev Ncurosci,* **vol.** 17, pp. 569-602; A2 redrawn with permission from Liggett, S. B. & Raymond, J, R, 1991, "Pharmacology and Molecular Biology of Adrenergic Receprors," *Bailiiere's Clin Endocrinol Metab,* vol. 7, pp. 279-306; B redrawn with permission from Frazer, A. *6c* Hensler, *J.* G. 1994, in *Basic Neurochetnistry,* 5 ed, G.J. Siegel, B. W. Agranoff, R. W, Albers, etal., Raven, New York; C redrawn with permission from Carterall, W. A. 1992, "Cellular and molecular biology of voltage-gated sodium channels," *Pharmacol Rev,* vol. 72, pp. S15-S48.)

activity does not exceed the capacity of its neuronal support. Conditions in **which energy metabolism** is inadequate to support the degree of activity (e.g., sustained depolarization resulting from leakage of excitatory amino acids and potassium) may result in reversible or irreversible dysfunction (excitotoxicity and neuronal death). The genetic regulation of transmitter release and receptors under normal and pathological circumstances is the subject of intense investigation,

Ligand-Gated Receptors

Inotropic receptors consist of channel-forming polypeptide subunits (Figure 49.1A1). Neurotransmitters of drugs that modulate these receptors facilitate or inhibit opening or closing of a central channel that allows passage of specific ions. The binding of agonists to inotropic receptors causes conformational changes of channel components. These changes alter ionic conductance and modify intracellular processes rhar require specific ions. The synthesis and identification of selective agonists and antagonists has facilitated understanding many receptors.

G Proteins

The binding of ligands to mctabotropic receptors activates GTP-binding proteins (G proteins) that modulate intracellular second-messenger systems. Any of several G proteins

may couple different receptor subtypes to specific signaling systems. When G proteins couple mctabotropic receptors directly to ion channels, their function appears to be inotropic. The established sequences for nearly 100 G protein-co u pled receptors seem to share several characteristics. They are all monomeric proteins with seven transmembrane domains, each consisting of 20 to 30 hydrophobic amino acids (Figure 49.1A2). The amino terminus, pockets formed by the transmembrane domain, and three extracellular polypeptide loops confer ligand-binding characteristics and membrane interactions. Intracellular polypeptide loops, especially the third loop, and the carboxyl terminus interact with G proteins and through them with other second-messenger sysrems.

G protein coupled receptors can be grouped based on conserved nucleotide sequences. A superfamily of traditional neurotransmitter receptors includes G protein binding receptors for adenosine, acetylcholine (ACh) (muscarinic type), NE, dopamine, serotonin, eannabinoids, and tachykinins. A second family of G protein binding receptors, with little homology in amino acid sequences to the first superfamily, localizes to the brain, endocrine systems, kidneys, and gastrointestinal tract, it includes receptors for peptides (e.g., secretin, calcitonin, parathormone, and vasoactive intestinal peptide) and neurohormones (e.g., glucagon, corticotropin, and growth hormone releasing factor).

G proteins are trimers consisting of alpha (of) (39-52 kD), beta *(0)* (35-36 kD), and gamma *(y)* (-500 kD) subunits. G proteins possess inherent GTPase activity. The result of binding a neurotransmitter or exogenous ligand to a specific receptor is the binding of the «-subunit of the G protein to the transmembrane receptor. In this configuration, GTP displaces guanosine diphosphate (GDP) from the a-subunit; then the *fi*- and y-subunits dissociate from the «-subunit, and the GTP binding K-subunit is liberated from the receptor. The activated or-subunit then regulates ion channels directly or activates the first enzyme in various enzyme cascades that modulate intracellular second messengers. These enzymes include adenylyl cyclase, phospholipase C, phospholipase A2, and phosphodiesterases. The activation of these enzymes is coupled to hydrolysis of GTP to GDP on the a-subunit and reassociation of the *fi*- and y-subunits with the a-subunit.

Mutations of G proteins alter function and cause disease. A series of mutations in G proteins are associated with pseudohypoparathyroidism, and a mutation in the gene for GTPase activation protein (GAP) is associated with neurofibromatosis type 1. Affected individuals show the abnormal GAP protein in neurons, Schwann cells, and oligodendrocytes. The ras family of small G proteins is implicated in the pathogenesis of human colorectal adenocarcinoma. This emphasizes the regulatory role of the ras family in growth and differentiation. Proto-oncogenes is the name used for genes encoding ras proteins. Some psychoactive drugs (antidepressants, lithium, opiates, cocaine, and alcohol) alter levels of G protein subunits. These changes may participate in both the therapeutic and addictive effects of psychoactive drugs.

y-Aminobutyric Acid

GABA is ubiquitous in the nervous system and regarded widely as the principal inhibitory neurotransmitter of the brain. Although this is true in the peripheral nervous system and central nervous system (GNS) of mature individuals, GABA may be excitatory during embryogenesis. During development, chloride ions flow outward instead of inward on channel opening, resulting from a less negative reversal potential for chloride ions. With maturation, the receptor composition may stay the same, but chloride permeability of the membrane declines abruptly and inward flow of chloride ions occurs through open channels in the center of GABA receptors.

Chemistry and Distribution

Glutamic acid dehydrogenase (GAD) synthesizes GABA from glutamare in the terminals of GABAergic neurons in the CNS. GABA transaminase (GABA-T), the principal degradarory enzyme, is present in mitochondria of GABA-synthesizing neurons and neurons bearing GABA reeeptors. The distribution of GABA-T is throughout the body, allowing rapid metabolism of exogenous GABA outside the nervous system. GABA-T reversibly deaminatcs GABA to succinic semialdehyde at the same time that *a*-ketoglutarate is aminated to form glutamate. This process occurs in synaptosomes and glia, and it may be important postsynaptically. Succinic semialdehyde dehydrogenase, aloni; with GAD and GABA-T, tonus the GABA *shunt,* which links amino acid and carbohydrate metabolism. The percentage of GABA in the total neuronal pool that contributes to neurotransmitter function is unknown.

GABA released from vesicles on depolarization of nerve terminals diffuses from the point of release and binds to postsynaptic receptors to produce fast inhibition. GABA also binds to presynaptic autoreceprors that modulate release of the transmitter. Enhancement of GABAergic inhibition is a major strategy for treatment and discovery of new drugs for disorders of neuronal hyperexcitability. The termination of GABA action is primarily by reuptake into neurons and glia by specific transporter molecules (Figure 49.IB) that are targets of pharmacotherapeutic agents and genetic alteration in disease.

GABA Receptors

$GABA_A$, GAB AH, and $GABA_C$ are rhe three classes of receptors known to bind GABA. $GABA_C$ receprors are in the retina. Binding of GABA opens chloride-selective channels in the center of the inotropic $GABA_A$ and GABAc receptors, resulting in a rapid influx of negatively

charged chloride ions through the postsynaptic membrane. The net increase of intraneuronai negativity results in so-called fast inhibitory postsynaptic potentials (IPSPs), except in the developing brain when the resting potential is negative to the chloride reversal potential. $GABA_{(1}$ receptors are metabotropic receptors that share extensive homology with metabotropic ghitamate receptors. The mediation of a long-lasting hyperpolarization or slow IPSP is by postsynaptic GABAn receptors linked directly by a G protein to a potassium channel. GABAD receptors are also present on the presynaptic membrane, where they serve as a ti to recep tors to inhibit or reduce the release of neurotransmitter GABA.

The *$GABA_A$ receptor* is a channel-forming aggregate of several different subunits, that is, a hetero-oligomer or hi'tiTonuT, Fifteen subtypes of five different subunits have been cloned from the mammalian brain. Mathematically, more than I SO,000 unique pentamers could be assembled from this number of subunits and provide an astounding range of receptor heterogeneity, with respect to both structure and pharmacology (Figure 49.2). Relatively few GABAA, however receptor complexes have been demonstrated in vivo, however.

$CABA_B$ receptors are distributed widely throughout the cerebral cortex, brainstem, and spinal cord. Binding of GABA or baclofen and its analogues to GABA^ receptors inhibit neurons directly by G protein-mediated opening of a potassium channel that produces a slowly peaking hyperpolarization, and indirectly by G protein-mediated enzymatic pathways that block calcium currents involved in neurotransmitter release (GABAn auto receptors) and membrane potential oscillations.

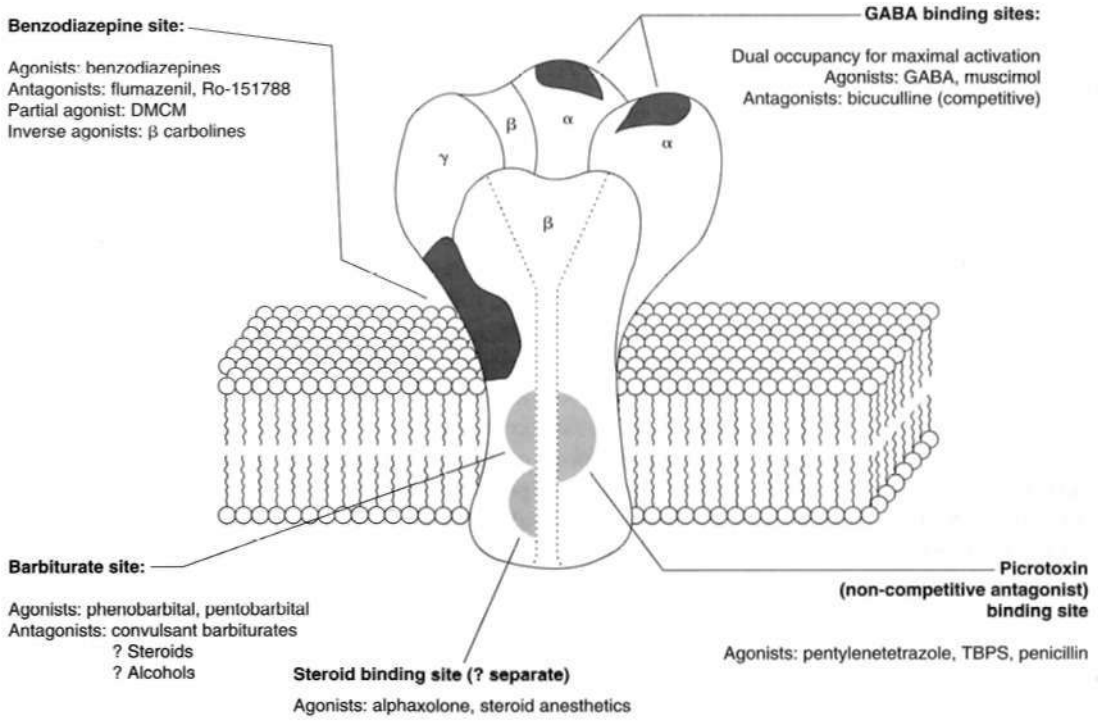

FIGURE 49.2 Pharmacology of the y-amino butyric acid subtype A ($GABA_A$) receptor. The $GABA_A$ receptor is thought to be an assembly of five subunits, probably of two to three distinct types per receptor. Affinity for GABA is modulated by a variable combination of or-, *fS*-, *y*-, and <S-subunits. The y-subunits are essential for benzodiazepine binding, but the binding site is probably a pocket between *y*- and /i-subunits near the membrane surface. In fully developed cells, binding of one or two GABA molecules leads to conformational changes, which opens a central pore and allows entry of chloride ion down its concentration gradient. The entry of anions into the intracellular milieu leads to hyperpolarization and decreased excitability. Multiple allosteric modulatory sites have been defined pharmacologically, including those for benzodiazepines, barbiturates, steroids (including anesthetics), and alcohols. Agonist binding to various modulatory sites generally increases the chloride conductance and enhances hyperpolarization. Antagonists and convulsant barbiturates decrease chloride conductance and hyperpolarization. These actions may promote seizures or anxiety. The pharmacology of the benzodiazepinc-binding site has been characterized best. Agonists and antagonists have been identified. The partial agonist methyl f>,7-dimethoxy-4-erhyl-beta-carboune-3-carboxylate (DMGM) enhances chloride conductance when it is present alone, but it diminishes the augmenting effect of benzodiazepines. The binding of ^-carbolines to the benzodiazepine site results in decreased chloride conductance due to a different conformational change. Barbiturates are thought to bind at a separate allosteric modulatory site. Allosteric modulators, such as phenobarbital and pentobarbital, augment the chloride conductance gated by GABA binding. Convulsive barbiturates also bind to this site. Steroids and alcohols may bind to the same site. Alternatively, steroids may bind to a separate allosteric site in or near the channel. Agonists at this site include alphaxalone and steroid anesthetics, A separate allosteric site in the channel is thought to bind the convulsant picrotoxin noncompetitive^. Binding of pierotoxin and other convulsants, such as pentylcnctctrazolc, penicillin, and r-burylbicycliiphosphoriirliionarc (TBPS), results in reduction of the chloride conductance activated by GABA. Endogenous substances, such as taurine and a putative naturally occurring benzodiazepine antagonist, arc also thought to alter the chloride conductance. The phosphorylation of intracellular loops of the different subunits is also thought to modulate receptor sensitivity anil availability.

Clinical Role of GABA Receptors

AJlosteric modulators of GABAA receptors are often used in the treatment of the epilepsies particularly generalized tonic-clonic and generalized absence status cpilepticus. In the course of experimental status epilepticus, $GABA_A$ receptors become less sensitive to benzodiazepines, thereby producing GABA-resistanr status epilepticus. This reveals how dynamic regulation of receptors can be. Barbiturates and benzodiazepines are believed to act at different sites ro increase GABA-activated inhibitory chloride current. Among the newer antiepileptic drugs, felbatol and topiramate augment chloride current allosterically at lion benzodiazepine sires. Vigabatnn, by Nocking GAISA-T and tiagabine, by blocking GABA reuptake by its transporter, elevate interstitial GABA concentrations. Tiagabine is an analogue of the GABA reuptake blocker, nipecotic acid. Benzodiazepines are often used alone or in combination to treat situational anxiety, panic attacks, other affective disorders, spasticity, and insomnia {Table 49.1}.

Baclofen is a prototypical spasmolytic agent (see Tabic 49.1). Activation of $GABA_R$ receptors facilitates kindling in animal models of epilepsy, modulates hippocampal long-term potentiation, underlies slow-wave sleep (stages III—IV), causes muscle relaxation, and has antinociceptive effects. Seizures may result from indirectly disinhibiting crucial limbic circuits or by activation of oscillatory membrane potentials due to marked hyperpolarization. $GABA_B$ receptor activation also facilitates generalized absence seizures in animal models, and GABAu antagonists are anticonvulsant in animal models. Some GABAu antagonists block the T-ca!cium current thought to underlie bursting behavior in the thalamus. The so-called date rape drug, y-hydroxybutyrate (GHB, also a drug of abuse), is a $GABA_B$ receptor agonist. GABAB antagonists may serve as an antidote. The sequence of a cloned $GABA_B$ receptor has extensive similarity to the metabotropic glutamate receptor and is negatively coupled to adenylate cyclase.

Genetic anomalies affecting GABA receptors have been associated with clinical disorders. Mutation of the *yl* subunit of GABAA receptors has been linked to the syndrome of childhood absence epilepsy with febrile seizures (GEFS+; Table 49.2). A specific human GABA,, receptor gene *(hR1b)* with inwardly rectifying potassium channels (Kir3 type) maps near a susceptibility locus for idiopathic generalized epilepsy on chromosome 6p21.3. This provides a candidate gene for some forms of inherited epilepsy.

Glycine

Glycine receptors are members of the ligand-gated ion channel superfamily group 1 that also includes $GABA_A$, serotonin $5\text{-}HT_3$, and nicotinic cholinergic receptors. Glycine receptors are cblonde-conducting inotropes bur blockade by strychnine makes their ionophores different from those of $GABA_A$ receptors. Glycine is also a co-agonist at excitatory N-methyl-D-aspartatc (NMDA)-type glutamate receptors. The involvement of glycine in cellular metabolism has complicated assessment of its role as a neurotransmitter. Glycine is a classic inhibitory neurotransmitter of the spinal cord and brainstem. It is the neurotransmitter of Renshaw cells; these interneurons modulate excitation of spinal motoneurons by recurrent inhibition. !t also is important as the neurotransmitter of reciprocally inhibited interneurons involved in stretch reflexes, allowing antagonist muscles to relax while agonists contract. This is important for motor coordination. Widespread distribution of glycinergic synapses indicates a more complex role. Glycine-iinmunoreacrivc somata and fibers have been described in the cochlear nucleus, the superior olivary complex, cranial nerve nuclei, the area postrema, deep cerebellar nuclei, the cerebellar cortex, and the retina. Interestingly, where immunorcactive cell bodies are absent, stained fibers appear. Examples are the periaqueductal gray, mesencephalic reticular formation,

Tabic 49.1: Role of GABA in Disease States

Disoriirr	*Fa tkophysiology*	*Treatment*
1. Epilepsy	Seizures oil withdrawal of BDZs	Restote BDZs, GABA augmenting AEDs
	Seizures with pyridoxine deficiency (cofactor for CAD and GABA-T) due to decreased GABA	Administer pyridoxine
		Antiabsence AEDs
	GABA metabolite, j'-hydroxybutyrate causes absence-like seizures GABAu activation facilitates absence seizures	GABAu antagonists, antiabsence AEDs
		Vigabatrin enhances midbrain GABA
	Midbrain "gate" for secondary generalization of seizures	Barbiturates; AEDs with other mechanisms
	GABAA receptors become BDZ resistant during experimental status epilepticus	GABA-enhancing drugs; AEDs with other mechanisms
	GA1SA,\ antagonists (e.g., bicucullme, picrotoxin) produce seizures in experimental models	No known preventative or restorative Rx
	Fewer GABAergic neurons in human focal epilepsies	Estrogen antagonists; GABA augmenting AEDs
	Proconvulsant effect of estrogen due to GABA antagonism	
2. Anxiety states	Excessive excitation presumed to underlie panic, situational anxiety, and other mood disorders	m>A

AED = antiepileptic drug; BDZ = benzodiazepine; GABA = K-aminobutyric acid; GAD = glutamic acid dehydrogenase; Rx = treatment.

Table 49.2: Examples of clinical disorders (human unless noted) puratively associated with mutations of ligand-gated receptors

	Gene, channel component affected	*Disorder(s)*	*Comments*
GABA	GABRG2 affect ins- iiaiimia-2 Milium!	Childhood absence epilepsy plus (GEFS+)	Linkage disequilibrium detected in French, but not Chinese, families
Glycine	1. GLRA1 affecting alpha-1 subunit 2, Glycine cleavage enzyme genes P (85%), T (15%), H (rare)	1. Hyperekplexia 2. Nonketotic hyperglycinemia (glycine encephalopathy)	1. Uncouples ligand binding from opening of chloride channel 2, Inadequate mitochondrial metabolism of glycine
Glutamate	1. Mutant *huntingtin* expressed in cell line 2. Expression of exon 1 of human Huntington's disease gene in transgenic mice 3. Polymorphism linked to kainate receptor 4. mGluRS knockout mice 5. GluRl AMPA receptor subunit knockout mice *6.* Receptor subtype mRNA for GluR3 low, GiuR4 high	1. Enhanced NMDA-mediated excitotoxicity 2. Increased NMDAR1 and decreased NMDAR2 currents and proteins 3. Huntington's disease 4. Reduced nonvisual learning 5. Impaired spatial learning *6. mnd* mouse model of motor neuron disorders and ceroid lipofuscinosis	1. Product of Huntington's disease gene interacted « itll NMDA receptors to enhance vulnerability 2. *HD* gene modulates NMDA receptor expression 3. Accounts for variable age of onset of Huntington's disease in patients 4. Metabotropic glutamate receptors play a role in learning 5. AMPA receptors play a role in learning *6.* AMPA receptor changes contribute to phenorype
Acetylcholine	*CHRA4* gene for nicotinic cholinergic receptor <*4	Autosomal dominant nocturnal frontal lobe epilepsy	First epilepsy mutation discovered
Serotonin	1. *HTR1B* gene polymorphism, especially G861C 2. HTR2A polymorphism 3. 5-HT2C receptor knockout mice 4. 5-HT transporter knockout mice 5. S-HT transporter polymorphism	1. Alcoholism, suicide attempts in personality disorders, low weight in bulimics 2. Hallucinosis and psychosis; clozapine responsiveness; ?schizophrenia 3. Audiogenic seizures, obesity, wakefulness 4. Reduction of aggressive behaviors 5. Bipolar disorder?, depression?	1. Multiple functional consequences of linkage disequilibrium *2.* Fffects of polymorphism unexpected from family-based association studies 3. Suggests anticonvulsant effect of serotonin mediated by 5-HT2C receptors; other modulatory effects 4. Role of S-HT in aggression and passivity, mediated hi 5-HT1A/B receptors 5. Candidate susceptibility gene
Dopamine	I. DRD2 receptor gene polymorphisms 2. Transcription factor Nur-related receptor 1 mutations 3. Mutations in tyrosine hydroxylase gene (rare limiting for dopamine and norepinephrine) 4. Dopamine transporter gene polymorphism	1. Implicated in Tourette's, PTSD, affective disorders, schizophrenia, Parkinson's disease 2. Different mutations in schizophrenia, bipolar disorder, and ?Parkinson's disease 3. ? Relationship with bipolar disorder 4. Bipolar disorder	1. Modulates susceptibility and phenotype 2. Dysfunction of this retinoid receptor results in decreased mesencephalic dopaminergic neurogenesis 3. Could account for characteristic ncurotransmitterabnormalities 4. Replicated indicator of genetic predisposition
Norepinephrine	1. Dopamine-/*-hydroxylase gene polymorphisms 2. Norepinephrine transponer (NET) gene mutation	1. Orthostatic hypotension, bradycardia and ptosis 2. Orthostatic hypotension, tachy-cardia, cerebral hypoperfusion	1. Undetectable levels of norepinephrine and epinephrine 2. Marked reduction of NET activity
G protein	*ct* Subunit gene 18P11.2 mutation	Bipolar disorderf?)	Lithium prevents G protein activation by interaction with of subunit

AMPA = a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; GABA — y-aminobutyric acid; NMDA = N-merhyl-n-asparcatc; PTSD = post-traumatic stress disorder.

the pretectal region, intralaminar nuclei of the thalamus, and the anterior and posterior hypothalamus (including preoptic areas). This suggests that those areas receive projections from unknown sources. Physiological effects of glycine in some of these regions are strychnine sensitive. In rats, cortical glycinergic fibers are sparsely distributed. Glycinergic inhibitory potentials were discovered in cerebellar intcmcurons, olfactory bulb neurons, and hippocampal CA3 neurons with electrophysiological techniques. In these regions, glycine modulates motor rhythms, reflexes, and sensory processing. Glycine provides recurrent and surround inhibition that enhances the fidelity of pathway activation by preventing lateral dispersal of inpurs to crucial circuits.

The function of non-NMDA related glycine receptors changes during development. They are excitatory in early stages because the chloride equilibrium potential is set at a less negative potential than the resting potential. At a specific stage, expression of a chloride transporter lowers the intracellular chloride concentration making the chloride equilibrium porential more negative than the resting potential. Thereafter, glycine receptor activation becomes inhibitory under most conditions.

Throughout the neuraxis, glycine acts as a co-agonist at NMDA receptors. Its role is excitatory. Evidence indicates that some NMDA receptors lack voltage-dependent magnesium block (see later) and are activated by glycine not glutamate. Because patches of glycine receptors are near postsynaptic glutamate receptors, glycine is positioned to modulate both inhibition and excitation simultaneously. Extremes of either activity are ptevented. As more is learned of how alterations in glycinergic neurotransmission contribute to disease, pharmacological therapeutics related to glycine will increase.

Chemistry and Distribution

Glycine, the structutally simplest amino acid, is a nonessential amino acid. It comprises up to *5%* of dietary protein and is distributed to all tissues of the body. It is readily transported across the blood-brain barrier and is probably transported into neurons. Glycine is synthesized, even in brain, from glucose and pyruvate and/or serine. The immediate precursor is serine, with which it is reversibly interconvertible. The rate-limiting enzyme in the synthesis of glycine is serine hydroxymethyl transferase, which requires tetrahydrofolate, pyridoxal phosphate, and manganese ions as cofactors. Ubiquity of this reaction prevents it from localizing glycinergic neurons. Glycine is an important one-carbon donor in the synthesis of peptides, proteins (including creatine), nucleotides, nucleic acids and glutathione. For metabolism, glycine binds to pyridoxal phosphate and is cleaved to form 5,10-methylene-tetrahydrofolate and ammonia. These products integrate glycine metabolism into multiple aspects of amino acid and protein processing,

The origin and partitioning of the neurotransmitter pool of glycine are unclear. Glycine is released from presynaptic vesicles. In some locations, it is coreleased with GABA, suggesting that the vesicular inhibitory amino acid transporter in presynaptic terminals of GABAergic and glycinergic neurons is not selective. This and the demonstration of selective transporter molecules on glia suggest a neuromodulator role of glycine.

Glycine Receptors

Glycine receptors are pentamers. The second transmembrane domains (TM2) of the alpha subunits are alpha-helices that form the pore. Four different alpha subunits (al-4), two with splice-variants, and one modulatory *fi* subunit have been identified. Adult glycine receptors are thought to include three *a* (predominantly c*l) and two *fi* subunits. In developing animals, «2 subunits predominate. Functional and pharmacological properties of various receptors differ. The diversity of constructs allows for regional, and perhaps pathological, variation in receptor expression.

Glycine binds near the membrane on the extracellular N-terminus of a subunits consisting of four transmembrane domains and connecting loops (see Figure 49.1 Al). Outward movement of the TM2 domain opens the channel. Dcscnsitization is slow compared with other receptors, but mutations in the intracellular loop between TM1 and TM2 enhance desensitization. The endogenous substances, taurine and ^-alanine, bind with lower affinity. Strychnine binds to two regions of the extracellular N terminus and blocks channel activation. Binding of low concentrations of zinc, released from vesicles with the transmitter, to the N-terminus enhances glycine-activated current. High concentrations (>10 micromolar) of zinc decrease the current. Phosphorylation and glycosylation of the large intracellular loop between TM3 and TM4 modulate channel function. Conflicting effects of phosphorylations mediated by protein kinases A and C and calcium-dependent calmodulin kinase 2 have been demonstrated under different experimental conditions and in a variety of cell types. The contradictory findings have not been completely explained. The receptors are anchored in rhe membrane by gephyrin. Turnover involves ubiquitination (attachment of ubiquirin), internalization, and degradation.

The pharmacology of glycine receptors is not as well worked out as that of GABA receptors. Alcohols and volatile .inesthetics increase glycine-activated currents. 1 lie pain neurotransmitter, substance P (SP), potentiates glycine activation. The GABA receptor antagonist picrotoxin blocks glycine receptors as well. It binds to *a* subunits at an undetermined site that does not affect strychnine binding. Both mean open time and frequency of channels openings are decreased. This suggests that that picrotoxin alters coupling between agonist binding and channel activation, rather than by producing a competitive block. Some l.-type calcium channel blockers (verapamil and some dihydropyridines) block glycine receptors while others (nitrendipine and nicardipine) increase glycine-activated current. Some opioids and dextromethorphan inhibit glycine-mediated inhibition, a potentially proconvulsant effect. The neuroprotective agent riluzole enhances glycine receptor desensitization. Effects of neurosteroids depend on the subunit composition of the glycine receptors.

This mixed bag of effects may contribute to variable efficacy and adverse effects of the clinically used drugs but docs not steer the development of compounds that selectively and predictably target glycine receptors. However, several tropeincs that were first shown to block 5-HT3 receptors, including tropisetron and bemesetron,

have been found to enhance glycine receptor activity at low concentrations. Glycine and tropeines together inhibit strychnine binding. The tropeincs arc highly potent and do not displace zinc, propofol, or ethanol. Therefore they seem to recognize a novel binding site and may prove useful for clinical drug development. The anticonvulsant, chlormethiazole, potentiates glycine.

Clinical Role of Glycine Receptors

Mutations affecting genes encoding glycine receptor subunits produce disorders of motor function in mice, cattle, horses, and man. These mutations reduce glycinergic inhibition in several ways. Three autosomal recessive disorders in mice are manifested by tremor, muscle rigidity, myoclonic jerks, and exaggerated startle responses. Hyperekplexia is a congenital startle syndrome of humans with similar findings. Several mutations can produce the human phenotype (Table 49.2}. Clonazepam, a GABA receptor agonist, is considered the drug of choice for treating the abnormal movements. Clonazepam is thought to augment GABA-ergic inhibition and compensates for deficits in glycinergic inhibition. High doses with attendant adverse effects are required for benefit. This could also reflect recruitment of additional mechanisms of action of clonazepam, namely glycine receptor activation, at high concentrations. Specific glycine receptor agonists or allosteric modulators undoubtedly would be useful.

Mutations of genes that encode mitochondrial glycine cleavage enzymes cause nonketotic hyperglycinemia (glycine encephalopathy; see Table 49.2).

Glutamate and Aspartate

Chemistry and Distribution

Glutamate and aspartate are nonessential dicarboxylic amino acids. They excite mammalian cerebral cortical neurons. Glutamate is the most common amino acid in the nervous system and is the principal excitatory neurotransmitter in the brain. Other glutamate functions are to modulate ammonia metabolism, to form proteins, and to serve as a precursor to Krebs cycle intermediates and GABA. Exclusively aspartate-driven pathways have not been isolated or identified. Glutamate and aspartate are chemically interconvertible, and both are agonists with different affinities at glutamate receptors (GluRs). Excitatory amino acid analogues and release of endogenous stores of glutamate in pathological settings cause neuronal damage. This process is called *excitotoxicity.*

Glutamate and aspartate are synthesized within central neurons and glia from carbohydrates involved in the tricarboxylic acid cycle. The mitochondrial enzyme, aspartate transaminase, interconverts glutamate and aspartate and is involved in the production of transmitter-related pools of both amino acids. Glia contain glutamine synthetase, which converts glutamate to glutamine. Glutamine is subsequently transferred to neurons, where it is deaminatcd to glutamate by glutaminase. This glial inactivation and the specific uptake systems for glutamate reduce interstitial glutamate levels to terminate the neurotransmitter action and prevent excitotoxic damage.

Glutamate concentrations are highest in the temporal lobe, basal ganglia, cerebellum, and neocortex. Gluramatergic pathways descend from the brainstem to the spinal cord, where segmental glutamarergic interneurons are also present. Some primary afferent pathways are glutamatergic.

Glutamate Receptors

The two main classes of glutamate receptors (GluRs) are ionotropic and metabotropic. The basis for identification of three ionotropic GluR subclasses B is their affinity for the synthetic analogs: NMDA, «-amino-3-hydroxy-5-merhyl-isoxazole-4-propionic acid (AMPA), and kainic acid (KA; kainate). All three compounds produce seizures and brain injury when administered systemically or into the cerebral ventricles of animals. The NMDA and AMPA receptor subtypes have received attention, because they are implicated in the pathogenesis of seizures, stroke, and neurodegenerative diseases and because highly selective antagonists are available. A family of metabotropic receptors has functions related to phosphorylation of ionotropic receptors and release of intracellular calcium.

Ionotropic glutamate receptors contain ligand-gated ion channels and are important in rapid excitatory neurotransmission in the CNS. Ionotropic receptor subunits are single polypeptide sequences that fold into a tertiary structure. The subunits aggregate to form receptor-channel complexes. Based on the size of ion channels needed to conduct both monovalent and divalent cations, it is assumed that glutamate channels in the brain are pentamers composed of at least two different types of subunits.

NMDA Receptors. Subunits of cloned NMDA receptors form ion channels with many pharmacological properties of native NMDA receptors. Using *in situ* hybridization techniques, the differential distribution of NMDA receptor subunits varies among several regions of the adult brain and at different stages of development. For example, mRNA for NMDA-R1 subunits exists in virtually all neurons, whereas the expression of isoforms of NMDA-R2 is variable throughout the nervous system. These findings suggest that brain NMDA receptors are heteromcric and that functional diversity is a result of combination of NMDA-Ri subunits with various types of NMDA-R2 subunits. Therefore drugs can be designed to target specific brain regions, possibly even in unique pathological conditions. The intracellular carboxy-tenninal region of rhe NMDA-R2 subunit is large, more than 400 amino acid residues compared with the usual 50 to 100 residues

found in AMPA/kainate receptors. Protein kinase C can phosphorylate this region as a means of regulating synaptic efficacy and plasticity, as in the case of long-term potentiation.

AMPA Receptors. GluR subunits 1 to 4 can assemble into recombinant receptors with high (nanomolar) or low (micromolar) affinity for KA. Mixing and matching receptor subunits alters channel kinetics and confers unique properties. For example, channels containing GluR-1 and GluR-3 subunits are permeable to calcium, whereas inclusion of GluR-2 subunits results in low permeability to calcium. Highly calcium-permeable AMPA receptors are more abundant during development in some regions of the brain. Different subunits localize to different human chromosomes: GluR-1 to chromosome 5, GluR-2 to chromosome 4, GluR-3 to the X chromosome, and GluR-4 to chromosome 11. Excitotoxicity is a pathogenetic mechanism in neurodegenerative disorders. Chromosome 4 contains genes encoding GluR-2 and huntingtin, a gene product involved in Huntington's disease. Mutations or editing of various subunits may be important in the pathogenesis of acute disorders of the nervous system, including epilepsy and stroke, and inherited disorders of the nervous system.

Kainate Receptors, Recombinant receptors with a high affinity for kainate can be formed from subunits GluR-5, -6, and -7 and sequences from another family, KA-1 and -2. Chromosome 21 contains the gene coding for GluR-5 subunits in humans. Some cases of familial amyotrophic lateral sclerosis (ALS) also localize to chromosome 21, This is a coincidence, because GluR-5 are expressed only in some neurons in the dorsal horn where they may function in pain transmission, and the chromosome 21-linked cases of familial ALS are due to mutations of the *SOD'l* gene.

Metabotropic Receptors

The metabotropic glutamatc receptor (mGluR) family consists of nine receptors with uniquely conserved regions in the transmembrane domains. These receptors have little homology with the neurotransmitter superfamily or the hormone receptors. The glutamatergic mGluRs are much larger than other G protein linked receptors. Modulation of receptor activity occurs by glycosylations at the extracellular N-terminus and by phosphorylation at multiple threonine and serine residues of the intracellular C-terminus. In addition, phosphorylation of the loop between transmembrane domains 3 and 4 may modulate interaction with G proteins. Association of the metabotropic receptors with different G proteins and effector systems can then produce a variety of responses by modulating ionotropic receptors and intracellular biochemical processes. Both ionotropic and metabotropic receptors are in the same region of the postsynaptic membrane and are probably coactivated.

Retinal glutamate pre fere nri ally activates (+) -2-amino-4-phosphonobutyric acid (1-AP4), a metabotropic receptor in bipolar cells, resulting in G protein dependent activation of phosphodiesterase. This opens a sodium channel by decreasing the concentration of cyclic nucleotides. L-AP4 receptors may also be present presynaptically in the brain. Several metabotropic receptors are activated by (+) -trans-l-aminocyclopentane-l,3-dicarboxylic acid (ACPD). The G proteins, in turn, activate phospholipase C that releases two intracellular second messengers, diacylglyccrol (DAG) and inositol triphosphate (IP3), from membrane lipids. Activation of protein kinase C by DAG phosphorylates GluRs. For example, phosphorylation of the NMDA receptor relieves voltage-dependent magnesium block and augments calcium influx through activated channels, IP3 releases calcium from intracellular stores such as the endoplasmic reticulum. This step may lead to production of nitric oxide, which has mixed presynpatic and postsynaptic actions. It may decrease NMDA receptor activity by binding to the redox site. Excessive activation of these so-called Group I mctabotropes (mGluR| and mGluRj) contributes to excitotoxicity. Different metabotropic receptors (Groups II and III) alter cAMP levels and may be neuroprotective.

The regulation of glutamate receptors includes interlocking mechanisms that facilitate excitability, such as long-term potentiation and synchrony, without cell injury. Increased intracellular calcium contributes to long-term potentiation, an experimental model of synaptic plasticity. In the hippocampus, the production of long-term potentiation is by brief high-frequency tetanic stimulation of Schacffer collaterals. Stimulation enhances excitatory postsynaptic potentials (EPSPs) in CA1 neurons. An early, or induction, phase lasts about 30 seconds and requires activation of NMDA receptors. A prolonged maintenance phase may last hours, and it depends on phosphorylation of receptors. The result is increased synaptic efficacy, which may be important in learning and memory. Long-term potentiation is facilitated by specific agonists of metabotropic GluRs and is prevented by highly selective antagonists and blockade of protein kinase C (e.g., by staurosporine). Injection of staurosporine also reduces hippocampal injury produced by brain ischemia in rodents. This suggests that antagonists of multiple steps in the calcium-releasing enzyme cascade activated by metabotropic GluRs may be neuroprotective.

Postsynaptic metabotropic receptor activation in hippocampal pyramidal neurons also closes voltage-dependent potassium (M-typej and calcium-dependent potassium channels. These effects prolong repetitive firing of action potentials. Activation of presynaptic metabotropic receptors reduces the release of glutamatc, probably by blockade of ion channels that admit the calcium needed for excitation-release coupling. The result is a filtering effect that reduces the efficacy of low-intensity stimulation and amplifies (postsynaptically) inputs strong enough to bypass

the reduction of neurotransmitter release. This bias on the signal-to-noise ratio is a proposed mechanism of controlling attentiveness.

Activation of presynaptic mctabotropic glutamate receptors also reduces IPSPs, presumably by reducing GABA release. This reduction of inhibition combined with the postsynaptic excitatory effects of metabotropic receptor activation may be proconvulsant. Injection of ACPD into the hippocampus results in the development of limbic seizures and damage that simulates the injury produced by kindling cpileptogenesis,

The cause of contralateral turning behavior induced by ACPD injection into the striatum may be enhanced dopamine release, because haloperidol and dopamine depletion blocks the effect. This suggests .1 role for metabotropic GluRs in motor system dysfunction and a possible therapeutic role for metabotropic receptor antagonists. Activation of metabotropic receptors in the brainstem excites barorcf lex-like responses, suggesting a further role in cardiovascular tcgulation.

Pharmacology of Glutamate Receptors

Ionotropic glutamate receptors have several known agonists and antagonists (Figure 49.3). Activation of NMDA receptors requires binding of agonists at two sites. The principal site is the NMDA or glutamate-binding site. The most important endogenous agonist is glutamate, although other endogenous agonists (e.g., aspartate and quinolinate) may bind at the same site. Phosphonate derivatives (e.g., AP-5 and AP-7; CPP and CPP-ene) are among the many synthesized high-affinity competitive antagonists for glutamate binding to this site. The second essential site binds glycine. Neurotransmitter glycine mediates IPSPs in the spinal cord, but glycine is present in sufficient quantities in interstitial fluid to serve a permissive or co-agonist function at NMDA receptors. The channel within the NMDA receptor cannot open when glycine is removed completely under experimental conditions. This makes the glycine site a strategic target for designer antagonists, such as 7-chlorokynurenic acid.

One of the most important controls on the ionic conductance through the NMDA receptor channel is voltage-sensitive block by magnesium. Hippocampal pyramidal neurons, for example, require 10 mV to remove the magnesium block. This effectively raises the threshold for opening NMDA receptor channels. It also means that modulation of firing rates by AMPA-receptor-mediated neurotransmission can occur at smaller depolarizations without activation of the NMDA channels. The fact that phencyclidine, initially developed as an anesthetic but now an illegal hallucinogen ("angel dust"}, is an NMDA channel blocker suggests that NMDA channel blockade is psychotogenic. However, phencyclidine has other actions, and some clinically used NMDA channel blockers produce no significant adverse behavioral effects. Another dissociative anesthetic in clinical use, ketamine, is also an NMDA channel blocker with psychotogenic effects. Drugs that block the channel, including the prototype MK-801 and the cough suppressant dextromethorphan have potential therapeutic value for diverse neurological conditions.

A separate site that modulates the gating of the channel binds polyamines, such as spermine and spermidine, which neurons synthesize. Different concentration-dependent effects have been observed. Another site, called the REDOX site, binds nitric oxide, a volatile gaseous by-product of cell metabolism,

Endogenous zinc reduces NMDA-acrivated current. Zinc is present in high concentrations in the hippocampus and released with some neurotransmitters in the nervous system. Hydrogen ions also modulate the ionic conductance. The conductance is maximal at slightly alkaline pH and reduces with increasing acidity. This may prove to be an important safeguard. During hypoxic-ischemic injury, progressive acidification resulting from glycolytic metabolism may turn off the NMDA receptor channels and limit the transmembrane influx of calcium that underlies excitotoxic cell death.

AMPA receptors are less understood. These ion channels are opened with slight depolarization and do not demonstrate voltage-dependent magnesium block. AMPA channels admit sodium (entering) and potassium ions (exiting), but calcium-conducting AMPA receptors (without GluR-2 subunits) are presenr in the cerebellum and in other locations at certain times in development {see previous discussion). Highly selective quinoxazolidmedione antagonists, such as CNQX and DNQX, have been synthesized. Activation of AMPA receptor channels may depolarize the neuron sufficiently to remove voltage-dependent magnesium block and activate NMDA channels. AMPA and NMDA channels are coactivated and are present on the same parts of neurons; these two receptor channels, each with diverse modulators, can he envisioned as acting in concert.

Kainate channels are the least understood of glutamate receptors. Experiments with selective antagonists should help to understand their properties better. The anticonvulsant drug, topiramate, reduces kainate-gated but not NMDA-gated activity. The molecular mechanism of this effect appears to be indirect by altering phosphorylation of kainate channels.

Metabotropic receptors are best activated by L-glutamate. No known agents in clinical use block metabotropic receptors significantly. Several ATP-dependent protein kinases normally are activated by the metabotropic GluR. Because a series of enzymes is involved in this cascade, it stands to reason that selective antagonists at each enzyme step could be developed as therapeutic agents to control glutamatergic hyperactivity. It is also conceivable that mixtures of antagonists of inotropic and metabotropic GluRs might ultimately be used to limit or prevent neuronal damage induced by prolonged srarus epileptieus or stroke.

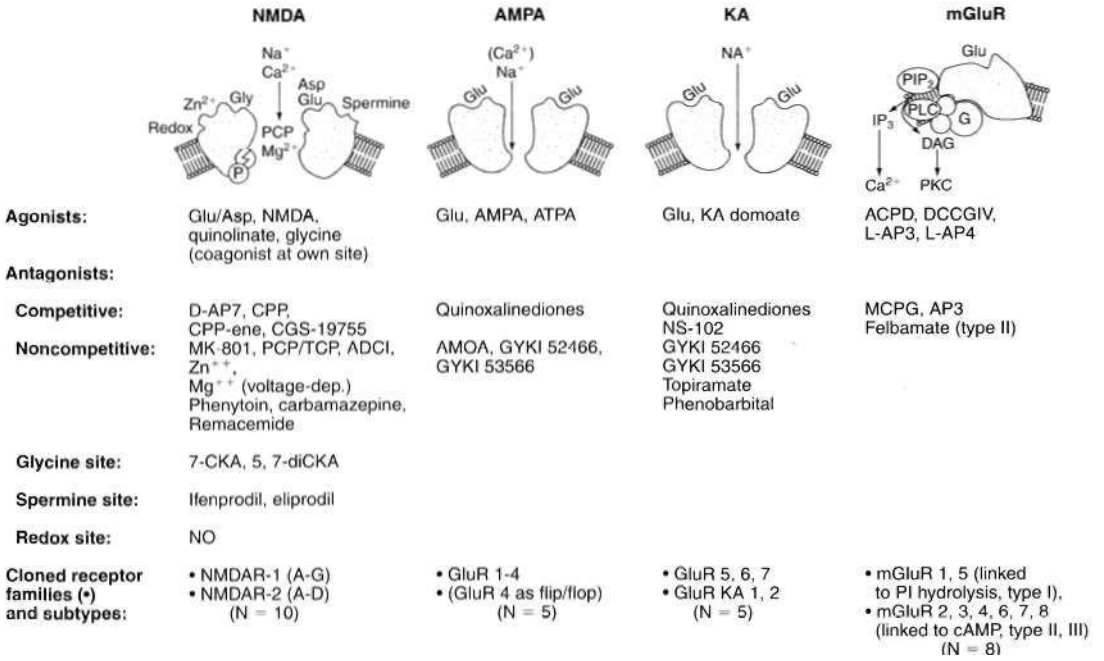

FIGURE 49.3 Pharmacology of gluramare receptors (GluRs). The GluR family includes three ionotropic receptors that recognize the exogenous ligands N-methyl-o-aspartatc (NMDA), u'-amino-3-hydroxy-.')-methylisoxazole-4-propionic acid (AMPA), and kainatc. A family of metabotropic receptors is also activated by glutamatc. These receptors are linked to phosphoinositidc hydrolysis and cyclic adenosine monophosphate (cAMP) production. Release of synaptic glutamate is thought to activate all the receptor subtypes within diffusion range. This results in mixed postsynaptic effects, depending on the profile of receptor types. Aspartate and quinolinic acid are naturally occurring agonists that activate a mixed cationic conductance (sodium and calcium enter, and potassium exits) through the NMDA type of ionotropic receptors. Glycine is a coagonist, but it is insufficient to activate the ionic conductance alone. The binding of zinc (Zn^{2+}) to a separate site tends to decrease the ionic conductance through the channel. A polyamine site binds agonists, which increase the conductance at low concentrations and inhibit the conductance at high concentrations. The channel itself has a voltage-sensitive binding site for magnesium (Mg^{+}). Until sufficient depolarization leads to dissociation of magnesium from its binding site, the conductance is blocked or low. Noncompetitive agonists, such as MK-801 and PCP, bind in the channel. Activation of the mctabotropic GluR (mGluR) may ultimately activate nitric oxide synthetase and result in the production of nitric oxide, which feeds back negatively by binding to the redox site on the NMDA receptor and results in a decreased entry of calcium and sodium. Two gene families, NMDAR-1 and NMDAR-2, have been cloned. These two families contain multiple receptor isoforms. AMPA and kainate receptor subtypes are also ionotropic but are less well characterized because of the limited availability, until recently, of antagonists. Competitive and noncompetitive antagonists have been discovered, however, and they are listed above. The AMPA family consists of five gene products, CiluR 1-4. Alternate splicing results in flip and flop conformcrs of the GluR 4 isoform. Kainate receptors contain subunits of two gene families. GluR 5, 6, and 7 constitute one family, and GluR KA-1 and *-2* constitute the second family. Some AMPA channels are activated less potently by kainate. Metabotropic receptors are linked through G proteins to phospholipase C and phosphoinositidc metabolism. The mGluRs 1 and 5 result in increased diacylglycerol (DAG) and inositol triphosphate (IP3). IP.i serves as a second messenger to release calcium from intracellular stores, and DAG activates protein kinase C. These actions may result in phosphorylation of the NMDA channel, an action that removes the voltage-sensitive magnesium block. Phosphorylation of calcium calmodulin and activation of nitric oxide synthetase results in synthesis of the ephemeral second messenger nitric oxide, which can modify both presynaptic and postsynaptic function. Other metabotropic receptors, including mGluRs 2, 3, 4, 6, and 7, arc linked to cAMP production and regulation of metabolic processes.

Clinical Role of Glutamate Receptors

The normal role of the neurotransmitter glutamate is to generate fast EPSPs that contain two components. The production of one component is by activation of **AMPA** and/or kainate receptors through a hroad range of mcmlir.nic potentials. The production of the other is by activation of NMDA receptors with increased calcium entry after sufficient depolarization removes voltage-dependent magnesium block. The factors determining the duration of these EPSPs are the amount and pattern of neurotransmitter release, the rate of reuptake of glutamate, and activity-dependent modulation of the response by coactivation of metabotropic receptors. Long-term potentiation may be involved in learning and memory. The marked prolongation of the EPSPs during long-term potentiation probably results from phosphorylation of inotropic receptors postsynaptically following activation of mGluRs.

Glutamateric hyperexcitability may underlie neuronal damage in diverse neurological diseases. Olney observed that injection of excitatory amino acids produced seizures and brain damage in rodents and introduced the concept of neuronal excitotoxicity. In vitro techniques and animal models have studied the concept. The administration of anticholinergic medications helped abbreviate seizures in an animal model of status epilepticus produced by excitatory amino acids. This suggests that enhancement of excitotoxicity follows entrainment of other excitatory systems after

the amino acid trigger. The spectrum of neurological disorders mediated by exeitotoxic injury includes epilepsy, stroke, and neurodegenerative disorders {Table 49.3). The development and evaluation of neuroprotective drugs have become a prioriry of the ncuroscience community (basic and clinical) and of' the pharmaceutical industry.

The involvement of glutamate in pain illustrates the potential for transforming physiologically regulated glutamatergic excitability into neuronal injury. NMDA receptor activation is involved in normal pain perception and in chronic pain states. The persistence of pain may require remodeling of nociceptive circuits in a way similar to that involved in kindling cpileptogenesis. Kindling is an experimental method of producing seizures in animals that, like long-term potentiation, depends on patterned stimulation. This laboratory model provides insight into cpileptogenesis and the mechanisms of action of antiepilcptic drugs. Even though kindling is unproved in humans, clinical epilepsy entails synaptic remodeling and giutamatergic hypcrexcitability as found in the kindling model of epilepsy. The amygdala and hippocampus kindle more readily than the neocortex. Even a single after-discharge produces structural changes in the hippocampus. Neurons in the dentate hylus die, and the dendritic processes of dentate granule cells sprout and spread to distances of up to 1 cm. The result is that an input that normally excites a discrete band of hippocampal neurons now produces hypersynchrony that can spread from the kindled focus and trigger seizures,

Tabic 49.3: Role of glutamate and other excitatory amino adds in clinical disorders and experimental models of neurological disease

Disorder/model	*Path ophysiology*	*Treatment*
1. Kindling cpileptogenesis	New NMDA component of the EPSP Loss of dentate granule cells and sprouting result in hypersynchrony	AEDs (e.g., MK-801) slow but do not prevent kindling acquisition Many AEDs prevent fully kindled seizures.
2. Epilepsy	Histological changes resemble kindling	Some AEDs block glutamate receptor subtypes: CBZ, FBM, REM vs. NMDA; I'l II'.. 'I'l'M v-. KA
3. Stroke	Hypoxic/ischemic injury leads to glutamate release and exciroroxicity	NMDA and AMPA antagonists (experimental) Na blocking AEDs (PHT, MK-801)
4. Nen rod egen era five disorders, e.g., Parkinson's disease, ALS	Delayed (apoptotic or programmed) death of neurons in specific brain regions	No methods to prevent progression
V AIDS dementia	Quinolinic acid (endogenous NMDA agonist amino acid} elevated in CSE	Mcmantine (experimental)
(.. XfoiKii.il glycine cncephalopath)	Genetic deficit of glycine cleavage enzyme results in elevated levels of NMDA co-agonist glycine	Dextromethorphan; tacrine (weak open channel blocker); other NMDA antagonists (?: rcmacemide, fclbamate, memantine)
7. Psychosis	Psychotogenic effects of competitive (CPP-ene) and noncompetitive (PCP) NMDA antagonists	Detoxification
8. Pain	Role in hypersensitivity and wind-up pain under investigation Glutamate microinjection into midbrain produces pain behaviors (experimental)	• NMDA antagonists (experimental)
9. Headache	Monosodium glutamate (MSG) produces migrainous headache (Chinese restaurant syndrome)	Abstinence from MSG Glutamate antagonists (hypothetical)
111. Alcoholism	Ethanol blocks NMDA receptors	Abstinence from cthanol
11. Dietary intoxication	BOAA in chick peas causes neurolathyrism Role of I1MAA in cyad flowers in Guamaman park in son ism/ALS/ dementia complex Exeitotoxic mechanisms	Avoidance of plant toxins in diet
12. Memory	LTP (experimental model) involves ionotropic and metabotropic NMDA receptors Antagonists could cause cognitive deficits	Discontinue offending drugs

AED = antiepileptic drug; ALS = amyotrophic lateral sclerosis; AMPA = a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; CSF = cerebrospinal fluid; EPSP = excitatory postsynaptic potential; LTP = long-term potentiation.

A new NMDA receptor component of excitatory synaptic potentials also underlies kindling. Kindling is permanent. No established method exists for unkindling. Strategies for preventing excitotoxic injury underlying kindling are under investigation. Drugs that augment (rABAergic inhibition, such as benzodiazepines or vigabatrin, and NMDA-channel blockers such as MK-801 slow the development of kindling.

In some cases, investigational compounds that seemed ideal in animal testing have been ineffective or proconvulsant in clinical trials. One competitive NMDA-antagonist, D-CPP-ene, appeared very effective and had little toxicity in animals. However, half of the eight patients in the phase II clinical trial experienced increased seizure frequency or status epilepticus, and all withdrew because of side effects, many of them cognitive. To explain this discrepancy between efficacy in animal models and patients, Loscher and colleagues have suggested that epileptic tissue may respond differently to drugs than normal tissue induced to express electrical and behavioral seizures. Anecdotes about the noncompetitive channel blocker MK-801 included psychotomimetic effects. MK-801 failed in clinical trials for other reasons, purportedly because of poor oral bioavailability and tachyphylaxis despite repeatedly increased doses.

What is the impact of such findings on the development of glutamate antagonists for clinical use? Eelbatol is an example of a noncompetitive NMDA-glutamate antagonist that did not produce untoward behavioral effects in most patients, yet potently decreased seizures. It has a relatively low affinity for its binding site. On the other hand, MK-801 and CPP-ene are very potent compounds with high affinities for their binding sites. These examples show that potent drugs with high selectivity may have side effects that limit clinical utility,

Mutations in genes encoding glutamate receptor subunits alter learning and memory and contribute to motor neuron disease in experimental models (see Table 49.2}. Mutations associated with Huntington's disease alter subunit composition of NMDA receptors and polymorphism in the kainatc receptor gene may contribute to variable age of onset of Huntington's disease (sec Table *49.2).*

ACETYLCHOLINE

The nicotinic receptor was the first to be purified, sequenced, and cloned. Over the past two decades, the structures of several nicotinic and muscarinic receptors, and of choline transporters and the synthetic enzyme, choline acetyl transferase (CAT), have been deduced using biochemical and molecular techniques.

Chemistry and Distribution

ACh is a monoamine neurotransmitter that rotates around bonds in its alkyl spine. The *cis* conformation is the predominant species in solution, but the *trans* conformation is the one that binds to muscarinic receptors. Therefore ACh binding to its receptor requires adaptive torsional changes within rhe molecule, presumably induced by electrostatic interactions with the receptor. The formation of ACh from choline and acetyl coenzyme A (Co-A) is catalyzed by CAT, and its hydrolysis is catalyzed by acetylcholinesterase (AChE). Histochemical localization of CAT allows detection of neurons capable of synthesizing ACh. CAT is synthesized in neuronal somata and transported down ixons to the nerve terminals. It is present in synaptosomes in two states: soluble in cytoplasm and bound to the outer membrane of the transmitter storage vesicles. Neurotransmitter synthesis takes place in the terminals. Neurons do not synthesize choline *de novo.* A high-affinity transporter recycles choline released by enzymatic degradarion of ACh by AChE or released into the interstitial space by the breakdown of phosphatidylcholine. The rate-limiting step in ACh synthesis may be the transport of acetyl Co-A out of mitochondria.

Neurons have two uptake systems for choline: a low-affinity and a high-affinity system. The high-affinity transporter gene has been cloned. However, hemicholinium, a potent inhibitor of neuronal choline uptake, does not block sodium-dependent choline uptake by the high-affinity transporter. This finding could indicate that functional components of the cloned transporter system are missing or malfunctioning. Alternatively, another system may be involved in vivo.

ACh is present in the cytoplasm and in vesicles in nerve terminals. Neurophysiological and neurochemical studies suggest the existence of two functional pools of ACh, one that is readily available for release and one held in reserve. How these pools relate to the location of ACh is uncertain. Newly synthesized ACh is the first released. An ATPase pumps hydrogen ions into the vesicles causing internal acidification and a positive charge. A highly specific transporter in rhe vesicle wall then exchanges ACh for hydrogen ions (countertransport) to maintain electroneutrality and the osmotic balance within the vesicle. Vesamicol blocks noncompetitively the uptake of ACh into vesicles. The release of newly synthesized radioactively labeled ACh is blocked without affecting ACh synthesis, the influx of calcium into nerve terminals, or high-affinity choline uptake. This provides strong evidence that cholinergic terminals release vesicular ACh. The readily available pool may be composed of vesicles close to the subsynaptic membrane and therefore more readily released by exocytosis. Vesicles more distant from the terminal membrane then represent the reserve pool.

Slow release of ACh occurs continuously, presumably because of spontaneous fusion of vesicles to the presynaptic membrane. The constant trickle of ACh produces miniature endplatc potentials that are detectable at rest. Depolarization of the axon terminal by the arrival of action potentials augments transmitter release. The amount

released depends on the duration of depolarization and rate of firing, the depolarization-induced influx of calcium through specific prc-synaptic calcium channels, and the ratio of extracellular calcium to magnesium. Each vesicle contains several thousand molecules of ACh, which are usually bound to ATP or a proteoglycan within the vesicles. Exocytosis releases all of these components after fusion of the vesicle to the inner side of the synaptic membrane. Calcium-ACh translocation of cytoplasmic ACh may contribute to depolarization induced release.

The released ACh diffuses across the synaptic space, where it binds to pathway-specific ACh recepcots in the central and peripheral nervous system and at the neuromuscular junction and exerts its physiological effects. The effect of ACh is terminated by dissociation from the postsynaptic receptors, hydrolysis by AChE, and reuptake of the released choline into the terminals. The exocytosis of neurotransmitter, membrane recycling, and reuptake of choline must be tightly coupled to avoid significant changes in the surface area of the synapse. Cycling of the vesicular membrane may be the rate-limiting step for both release and reuptake.

Cholinesterases are widely distributed in the body. The liver produces nonspecific or butyryl cholinesterase that circulates in the plasma and is present in the CNS. A specific AChE is associated with cholinergic innervation and localizes ;it synapses. The structure and the transcriptional and posttranscriptional regulation of AChE production are established. A soluble globular form of AChE and a so-called asymmetric form exist. The latter has a collagenous tail for membrane-binding in synaptic areas. AChE inhibition can occur by several mechanisms: (1) binding of dtugs such as edrophonium to the active site of the enzyme to prevent access of substrate; (2) binding of reversible inhibitors such as gallamine and propidium to peripheral binding sites on the enzyme; and (3) the combination of carbamyl groups of drugs, such as physostigmine and neostigmine, with the active site serine group. Anticholinesterase compounds can cause clinical symptoms in humans; these include insecticides, drugs used to treat myasthenia gravis, and those developed for use as chemical warfare agents.

Figure 49.4 outlines the pharmacology of ACh receptors.

Acetylcholine Receptors

Nicotinic and muscarinic receptors are distributed widely in the nervous system. Nicotinic receptors are present at the mammalian muscle endplate and sympathetic ganglion neurons. Centrally, nicotinic responses occur in the cerebral cortex, hippocampus, thalamus, neostriatum, and interpeduncular nucleus. The optic tectum seems to rely primarily on nicotinic muscarinic activity, as does the negative feedback of the Renshaw cell on motor neurons of the spinal cord,

Muscarinic receptors with a high affinity for pirenzepine, a high-affinity antagonist of M1 receptors, are abundant in the hippocampus and cerebral cortex. The cerebellum and brainstem contain neurons bearing receptors with low affinity for pirenzepine. Outside the CNS, muscarinic receptors are present on tissues innervated by parasympathetic postganglionic neurons. Some sympathetic responses, especially sweating and piloercction, depend on postganglionic sympathetic fibers that secrete ACh onto tissues with muscarinic receptors.

Muscle Nicotinic Receptors

The nicotinic ACh receptor was isolated and purified first, because of its abundance in *Torpedo* clcctroplax. The receptors arc so plentiful that they form virtually a crystalline array and are readily studied with electron microscopy. The receptor is a pentamer formed of different types of subunits: two a-subunits and one each of the *f}-*, *y-*, and *8-* subunits (Karlin 1993). Several receptor types are present in embryonic muscle and extrajunctionally in denervated adult muscle. Differences in subunit combinations account for subtle differences in conductance through these receptor subtypes. The pentameric structure surrounds a central cavity or channel that opens to a diameter of about *6.5* A when agonists bind to each of the c-subunits. Occupation of both sites is necessary for receptor activation. Sites within the channel bind noncompetitive inhibitors such as local anesthetics. The sequence of the different subunits includes a long extracellular amino end of approximately 200 amino acid residues followed by four membrane-spanning regions connected by intracellular and extracellular peptide loops. A short car boxy-terminal end follows. The subunits of *Torpedo* electroplax nicotinic ACh receptors have 495 to 5I2 amino acid residues each. Each of the membrane-spanning regions has 19 to 27 amino acid residues. The long cytoplasmic loop between the third and fourth membrane-spanning regions is about 150 residues long. This type of structure is typical of inotropic ncurotransmitter-gate receptors. Because of the hydrophobic! ty of the membrane-spa lining regions, it seems likely that the organization of the residues is in *a* helical or 0-pleated sheet formations. The different subunits have about 30-40% identity of their amino acid residues. The agonist-binding site is included in the extracellular amino terminal segment, and mutations in this portion of the a-subunits cause changes in the binding of ACh,

Lophotoxin, a diterpenoid plant toxin, competitively blocks the binding of ACh at residues 190 to 192 of the a-subunit. Serine residues in the *fi-* and y-subunits and in the second membrane-spanning region bind the noncompetitive inhibitors chlorpromazine and tetraphenylphosphonium. tr-Toxins from snake venom, including «-bungaiotoxin, bind to extensive regions of the *a-* subunit. Hcxamcthonium and decamethonium produce a voltage-dependent block of recombinant neuromuscular

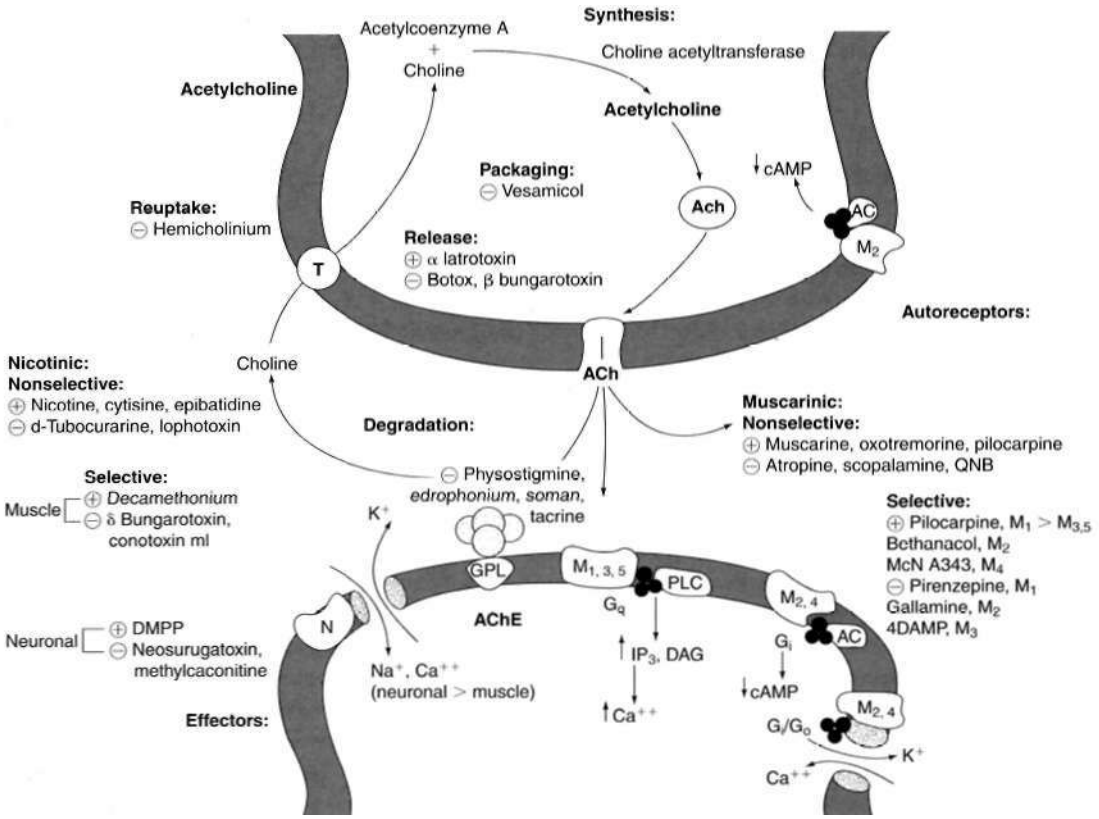

FIGURE 49.4 I'harniacologyofccntralacctylcholincfAt^hJreceptors.Therearenoclinicallyusediiihihirorsof AChsyntliesis.Thepackagingof ACh into presynaptic vesicles can be reduced experimentally hy vesamicol. Release of ACh is enhanced hy or-latrotoxin and inhibited by botulinum toxin (Botox) and /J-bungarotoxm. Release is also modulated hy presynaptic autoreceptors. The G protein-linked M> muscarinic receptor decreases cyclic adenosine monophosphate (cAMP) production presynaptically and indirectly decreases neurotransmitter release, presumably by decreasing activation by phosphorylation of calcium-dependent calmodulin. Released ACh diffuses across the synaptic cleft and activates both nicotinic and muscarinic receptors in the CNS. Nicotinic receptors are ionotropic, and activation results in admission of sodium and exit of potassium through the channel. Muscarinic receptors are metahotropic. Muscarinic M_h M_5, and M_5 receptors are linked by Gq to phospholipase C. Activation of these receptors results in increased intracellular calcium due to the production of inositol Triphosphate (IP.i) as the intracellular second messenger. Muscarinic M_z and M_4 are linked to adenylyl cyclase hy the inhibitory G protein Gj. The result is decreased intracellular cAMP, Some postsynaptic M; and M^ receptors arc linked by G proteins directly to ion channels, which allow entry of calcium and exit of potassium. The action of ACh at its postsynaptic receptors is terminated principally by degradation. Acetylcholinesterase (AChE) in the postsynaptic membrane results in the release of choline, which is rescqucstcrcd by a specific transporter (T) in the presynaptic membrane and is then resynthesized into ACh for subsequent release. Agonists (+) and antagonists (-) have been identified for many of these specific receptors and processes,

nicotinic-cholinergic receptors suggesting that they enter the channel. Other toxins bind at different sites. Neosurugatoxin selectively blocks ganglionic nicotinic receptors, and lophotoxin blocks ganglionic and neuromuscular nicotinic receptors. The marine cr-conotoxins, G1A and M1, potently block neuromuscular transmission but not ganglionic nicotinic activity. This differential binding suggesrs that the ganglionic nicotinic receptors differ in subunit composition from the neuromuscular receptor.

Neuronal Nicotinic Receptors

Neuronal nicotinic receptors are inotropic receptors. Ten or more receptor subunit genes have been cloned. Functional ACh-gated channels arc expressed in frog oocytes injected with mRNAs for *a*- and ,6-receptor subunits in combination or when cell lines are transfected with cDNAs for both *u*- and /I receptor subunits.

Central nicotinic neuronal receptors have been mapped using *in situ* hybridization methods. The «2-subunit is widely distributed. Different brain regions contain variable electrophysiological and pharmacological properties of receptors containing a2-subunits in combination with several other subunits.

Neuronal Muscarinic Receptors

Muscarinic receptors are metahotropic receptors. Five receptors belonging to the family of G protein-associated receptors have been isolated. Agonists bind in a deep

pocket formed by the seven transmembrane regions. Variations in the long third intracellular loop result not only in differences in the binding to G proteins, but also in the effects of antagonists, as shown by site-directed mutagenesis. This technique introduces mutations of one or a few amino acids that alter receptor function. Selectivity of antagonists for cloned receptors parallels pharmacologically defined receptor activity in naturally occurring, intact systems. For example, pirenzepine selectively blocks both cloned and naturally occurring Ml receptors and AFDX-116 preferentially blocks M2 receptors.

Muscarinic receptor types M1, M3, and M5 couple to members of the Gq family of G proteins. In turn, the G protein activated by ligand binding to the receptor activates phospholipase C. This results in phospholipid hydrolysis that liberates two intracellular second messengers, IP3 and diacylglyccrol (DAG). Each of these intracellular second messengers has unique effects, as described previously. The IP3 releases intracellular calcium stores and can be involved in cascades of cellular injury. DAG activates protein kinase C, which phosphorylates several receptors and alters their conductance states. Receptors of the M2 and M4 type couple to the a-subunit of the inhibitory Gi protein that inhibits adenylyl cyclase and reduces intracellular cAMP levels. Alternatively, these two receptors can couple to certain ion channels directly by either of the GTP-binding proteins, Gi or Go. Muscarinic receptor subtypes are differentially distributed in the brain. The hippocampus is virtually devoid of the M2-type receptor, but the other four types are expressed to varying degrees, with Ml having the densest expression. ACh induces a pirenzepine-insensitive hyperpolarization in the thalamus where the M2 receptor is significantly expressed. The hyperpolarization appears to result directly from increased potassium conductance secondary to receptor activation coupled to Gi. Thus physiologically and pharmacologically defined regional effects of ACh parallel expression of genes for various subtypes of muscarinic receptors.

A consideration of long-term regulation of receptor numbers is an important property of muscarinic receptors for designing drugs to treat neurological disorders. Prolonged exposure to ACh or other agonists causes downregulation of muscarinic receptors. The Alzheimer's disease treatment agent, tetrahydroaminoacridine, raises brain ACh levels by weakly inhibiting AChE. Reports of mixed efficacy could in part be due to downregulation of receptors, which opposes the effect of chronically increased ACh levels. Protein kinase activation can mimic the effects of prolonged exposure to agonists. Presumably, phosphorylation reduces affinity of the receptor for agonists, and dephosphorylation, by unknown phosphorylases, results in resensitization or availability of the receptors. Phosphorylation-dcpendent desensitization may be a common mode of regulation of G protein-coupled receptors. Control of this process could provide therapeutic agents designed to modulate receptor numbers in specific brain regions.

Acetylcholine Receptors in Disease States

The treatment of several clinical disorders uses cholinergic agents (Table 49.4). A number of important clinical disorders involve muscarinic cholinergic neurotransmission. Reduction of cholinergic neurons and capacity to synthesize ACh occurs with normal aging. However, premature degeneration of cholinergic neurons occurs in Alzheimer's disease. Excitotoxic injury to cholinergic neurons plays a role in Parkinson's and Huntington's diseases. Experimental models also implicate ACh in the pathophysiology of human epilepsy. Reduced ACh synthesis occurs in some inherited disorders of mitochondrial enzymes and thiamine-dependent pyruvate dehydrogenase (the enzyme that catalyzes the oxidation of pyruvate to acetyl Co-A). Affected patients have mental retardation, spasticity, ataxia, and dystonia. The symptom diversity emphasizes the multiple functions subserved by cholinergic neurotransmission. Medications that block muscarinic receptors are used to treat vertigo, motion sickness, and diarrhea. ACh triggers the pontogeniculooccipital (PGO) spikes at the onset of rapid eye movement (REM) sleep and anticholinergic medications have sleep-inducing properties. Smoking is an example of addiction resulting from habitual use of nicotine. Myasthenia gravis is an important clinical problem involving nicotinic receptors. Intoxications with pesticides, nerve agents, and bacterial toxins (e.g., botulinum toxin) affect cholinergic receptors centrally and peripherally. No discussion of cholinergic mechanisms would be complete without mentioning the mydriatic effect of belladonna *(Atropa belladonna),* once used as a cosmetic and later as a poison.

A mutation in the gene encoding the c4 nicotinic cholinergic receptor has been associated with autosomal dominant nocturnal frontal lobe epilepsy {see Table 49.2). Ongoing genetic research is examining the role of polymorphisms in AChR-associated genes in susceptibility to Alzheimer's disease

DOPAMINE

The role of dopamine in neurological disease initially received attention in 1957 with the demonstration that reserpine depletes the brain and heart of NE and dopamine. Dihydroxyphcnylalaninc (DOPA), a precursor of catecholamine synthesis, restores dopamine levels and reverses the sedative action of reserpine. During the 1960s, the formaldehyde fluorescence technique allowed the visualization of monoamines, including dopamine. Reports of low dopamine concentrations in the basal ganglia of patients with Parkinson's disease led to the discovery that increasing doses of L-dopa relieved the symptoms of parkinsonism. Optimizing dopaminergic neurotransmission remains central to the treatment of Parkinson's disease (see Chapter 78).

Table 49.4: Acetylcholine in disease states

Disorder	*Pathophysiology*	*Trail men t*
Nicotinic receptors		
1. Smoking	Habituation, associated behaviors	Slow taper and discontinuation
2. Myasthenia gravis	Antibodies against postsynaptic receptors at neuromuscular junction	AChE inhibitors + muscarinic antagonists
3. Myasthenic syndrome	Antibodies against presynaptic calcium channels reduce A eh release	Guanidine; amino pyridines sensitize netve terminals to Ca^{2+}; AChE' inhibitors
4. Botulism	Ingested toxin decreases Ach release	Guanidine or aminopyridiues; pyridostigmine; antitoxin
i. Snake bite (krait)	c-Bungarotoxin decreases Ach release; /f-Rungarotoxin blocks NAChR	Antivenin; good luck
6'. Pain	ACh released by acupuncture in adrenergic locus ceruleus and serotonergic dorsal raphe	Nicotine (old war movies); nicotinic agonists(dimethylphenylpiperazine)
Muscarinic receptors		
1. Aging	Decreased CAT and AChE accompany cognitive decline	No known preventative treatment
2. Alzheimer's disease	Excessive and premature loss of cholinergic neurons (n. basalts of Meynert)	Tacrine and doncpezil slow course
.5. Parkinson's disease	Excessive cholinergic activity in basal ganglia with loss of dopaminergic innervation	Muscarinic antagonists (trihexyphenidyl); tricyclic antidepressants
4. Huntington's disease	Decreased (. .AT in striatum	Muscarinic antagonist for some abnormal movements
5. Epilepsy	Seizures produced in animals by pilocarpine Seizures in man/anitnals by nerve agents (AChE inhibitors)	Anticonvulsants; benzodiazepines; memantine
6. AChE inhibitor intoxication	Nerve agents and pesticides produce-deadly seizures	Muscarinic anticholinergics; anticonvulsants
7. Pain	Spinal cord (posterior horn) and midbrain circuits involved in pain neu retransmission; Acupuncture releases ACh and opioids	Tricyclic antidepressants; acupuncture
8, Sleep	ACh triggers PGO spike at onset of REM Insomnia and narcolepsy increase REM	Antimuscarinic tricyclic aillidcpres^inK
9. Mitochondropathies	Decreased ACh synthesis (decreased acetyl Co-A synthesis due to low activity of thiamine-dependent pyruvate dehydrogenase and other enzymes)	No effective treatment
10. Vertigo/motion and space sickness	Vestibular ± vestibulocerebellar dysfunction	Antihistamines (meclizine}, tricyclic antidepressants, and phenorhiazines with anticholinergic action Antimuscarimcs (scopolamine + dcxedrine)

ACh = acetylcholine; AChE = acetylcholinesterase; CAT = choline acetyl transferase; REM = rapid eye movement.

Chemistry, Pharmacology, and Distribution

The catecholamines' (dopamine, NE, and epinephrine) synthesis from L-tyrosine is by a cascade of enzymes. Immiino-eytochemical and *in situ* hybridization techniques have allowed these enzymes to be purified to homogeneity, cloned, and localized in the CNS. Phenylalanine forms tyrosine, which is actively transported across the blood-brain barrier. The enzyme phenylalanine hydroxylase catalyzes the conversion. Deficiency of this enzyme is responsible for the classic form of phenylketonuria (see Chapter 71). Tyrosine hydroxylase catalyzes an alternate pathway in the synthesis of tyrosine from phenylalanine. Tyrosine hydroxylase is a cytoplasmic mixed-function oxidase that requires retra-hydrobiopterin and oxygen as cofactots.

Tyrosine hydroxylase catalyzes the conversion of L-tyrosine to L-dopa, and dopa decarboxylase, a pyridoxal phosphate-dependent enzyme (also known as aromatic acid decarboxylase), converts [,-dopa to dopamine. This lattet reaction is the target of oral precursor treatment with L-dopa in the treatment of Parkinson's disease. Dopa decarboxylase is present in the cytoplasm of catecholaminergic and serotonergic nerve terminals; this enzymatic step is intermediate in the synthesis of the other monoamines.

Dopamine is transported into storage vesicles for later release as a neurotransmitter. Amine transporters similar to drug resistance transporters of bacteria have been cloned; they characteristically have twelve transmembrane domains. The uptake of monoamines into storage vesicles is ATP-depcndent and linked to a proton pump. In the vesicles, the catechols form complexes with ATP and acidic proteins called chromogranins. Monoamine oxidase (MAO) deaminates free dopamine inside nerve terminals, Drugs that interfere with vesicular storage, such as

amphetamines or reserpinc, displace dopamine into the cytoplasm, where it is inactivated. Catechol-o-methyl transferase (COMT) breaks down dopamine that has diffused into the extracellular space.

The basal ganglia contain about 80% of total brain dopamine. Dopaminergic neurons in the ventral tegmental tract send fiber bundles to the nucleus acumbens (the mesolimbic tract) and to the cerebral cortex (the mcsocor-t:;,)l h.iiui\' . I I:HT-, also I'MLTIII from [IK- arcuate nucleus ro the median eminence. The mesolimbic projection ascends in the medial forebrain bundle. The further distribution of these fibers is to telencephalic structures including the olfactory bulb, olfactory nucleus and tubercle, lateral septal nucleus, stria terminalis, and parts of the hippocampus and amygdala. This branch also innervates the mesial frontal, anterior cingulatc, pyriform, and entorhinal cortices. The mesocortical projections terminate predominantly in the frontal (especially prefrontal) neocortex. Scattered groups of dopaminergic neurons are also present in the retina and spinal cord,

Dopamine Receptors

Dl and D2 arc the two families of dopamine receptors. Their different effects on adenylate cyclase originally separated these two families. DJ receptor activation augmented enzyme activity and D2 receptor activation decreases activity. Both families are linked to G proteins and have the predicted structure of seven transmembrane domains. The major difference between the two families of dopamine receptors is the sequence of the third intracyto-plasmic loop, which governs G protein binding.

The Dl family consists of two receptors, Dl and D5, which couple to the <y-siibunit of the stimulatory G protein, Gs. Gs activates adenylate cyclase directly and increases cAMP production from ATP. The mRNA for Dl is located primarily in the caudate, putamen, nucleus accumbens, and olfactory tubercle. The mRNA for D5 is primarily located in the hippocampus and hypothalamus.

The D2 family consists of four receptors (D2S, D2L, D3, and D4) linked to inhibitory G protein, or Gi. Activation of the receptors decreases the concentration of cAMP, The D2 receptor exists in two forms that arise from alternative splicing. They are expressed predominantly in the caudate, nucleus accumbens, putamen, and olfactory tubercle. The D3 receptors are highly expressed in the striatum and in the limbic areas. The D4 receptor is present in the frontal cortex, midbrain, amygdala, and medulla and to a lesser extent, basal ganglia, D3 and D4 receptors share a high affinity for atypical neuroleptics Such as clozapine. Atypical neuroleptics produce fewer extrapyramidal side effects than typical phenothiazine or butyrophenone neuroleptics that block D2 receptors. The relative antipsychotic efficacy of the atypical compound may be due to antagonism of the D3, D4, and D5 types of receptors in limbic structures and the cortex, whereas blockade of D2 receptors in the striatum may cause parkinsonian symptoms. This raises the hope that chronic-use of neuroleptics and antipsychotics need not result in tardive dyskinesia.

Pharmacology

Many aspects of dopaminergic neurotransmission are modifiable for clinical therapeutic advantage (Figure 49.5). Dopamine is released when nerve terminals are depolarized by the arrival of action potentials that open voltage-dependent calcium channels. The entry of calcium promotes the fusion of vesicles with the synaptic membrane and the release of soluble contents of the granules. Several classes of drugs alter the amount of catecholamines that are released, Reserpinc profoundly depletes dopamine and NE by initially augmenting their release, then irreversibly inhibiting their reuptake into storage vesicles. Both reserpine and guanethidine effectively reduce packaging. The depletion of catecholamines in animals is used as a model of parkinsonism,

Catecholamine transporters are not specific; they also transport tryptamine, tyramine, and amphetamines. Tyramine and amphetamines displace the catecholamines from their storage vesicles and cause depiction of the terminal and leakage of catecholamines from the nerve terminals. The initial result is an indirect increase of dopamine- and NE-mediated neurotransmission, but depletion may follow if drug exposure is chronic. The action of dopamine is terminated by reuptake or enzymatic degradation. An energy-dependent sodium exchanger mediates the uptake process. Blockers of Na-K-ATPase (e.g., cardiac glycosides), tricyclic antidepressants, cocaine, and amphetamines inhibit the sodium exchanger.

Enzymatic degradation is mediated by MAO and COMT. The two isoenzymes of MAO are types A and B. Type A is potently blocked experimentally by clorgyline and preferentially cataholizes 1ME and serotonin; type B is blocked by selegiline (deprcnyl). Type B is located prominently in serotonergic neurons and astrocytes and preferentially deaminates dopamine. Selegiline is metabolized to amphetamine and mcthamphetamine, which may increase alertness and mood elevation in addition to its effects on the movement disorder of Parkinson's disease. The COMT antagonist tolcapone (Ro 40-7592) received Eood and Drug Administration (FDA) approval for the treatment of Parkinson's disease,

Several selective agonists and antagonists, specific for subtypes of dopamine receptors, have been synthesized for investigation. Clinically used ergot derivatives include bromocriptine and pcrgolide. Bromocriptine is a more potent agonist at D2 than Dl and ff-adrencrgic receptors. It has weak antiparkinsonian action alone but has synergistic effects with endogenous dopamine. It is not usually

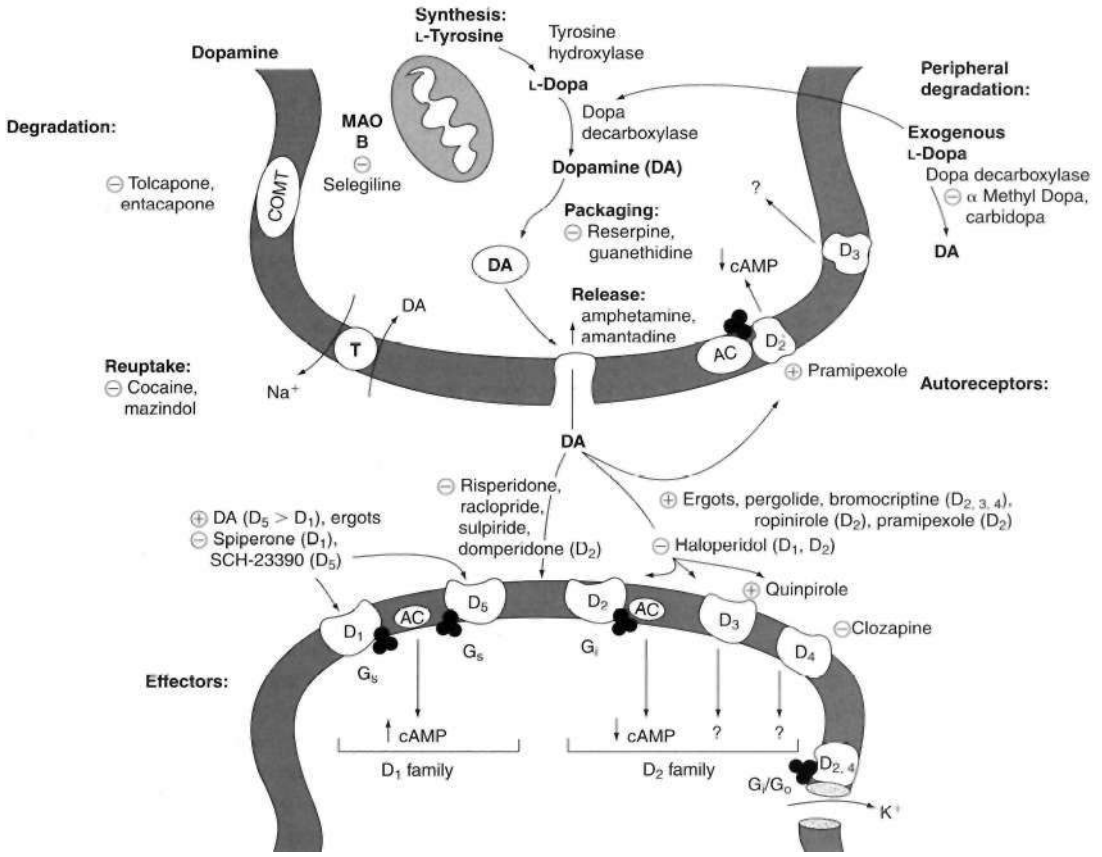

FIGURE 49.5 Pharmacology of dopamine neurotransmission. AC = adeny] cyclase; cAMP = cyclic adenosine monophosphate; COMT catechol O-mcrhyl transferase; MAO = monoamine oxidase; T = transporter (selective for a particular neurotransmitter).

considered an allosteric modulator but acts like one by enhancing the apparent affinity of the receptor or prolonging the binding of dopamine. In contrast, pergoiide is a D2 agonist at low doses and a mixed D2 and Dl antagonist at higher doses. Its presynaptic D2 effect is to decrease dopamine release postsynaptically. It has dopamine-like action and inhibits firing by binding to D2 receptors. Lisuride is a potent D2 agonist with lesser affinity for Dl and serotonin receptors. Side effects typical of antiparkinsonian medications (nightmares, hallucinations, and psychosis) limit its usefulness.

Non-ergot agonists are being developed to circumvent adverse psychiatric effects. The use of the agonist, a pi.) morphine, is limited by its peripheral dopaminergic effects, but it decreases "off-hours" in Parkinson's disease patients when it is administered subcutaneously. Intranasal and sublingual forms have been used safely. The FDA has approved highly potent and selective D2 agonists (ropinirole and pramipexole). Autoreceptors have much higher affinity for agonists than do postsynaptic receptors. Selective auto receptor (presynaptic D2 receptor) antagonists arc also under investigation. Hopefully, the combination of agents may allow normalization of dopaminergic activity without creating dystonia and dyskinesia.

The mechanism of action of amantadine is not established. It slightly improves the symptoms of Parkinson's disease and is best used as an adjunctive agent. Its efficacy decreases over a period of months, but discontinuation may cause worsening of symptoms suggesting partial desensitization. It probably has multiple weak actions that enhance dopamine release. This may be accomplished by displacing dopamine from vesicular storage and blocking reuptake. Other possible mechanisms of action are presynaptic D2 antagonism or allostcric enhancement of dopamine receptor activation. Non-dopaminergic mechanisms of actions of amantadine and memantine include antimuscarinic and NMDA channel-blocking actions. Memantine is also a weak sodium channel blocker with anticonvulsant efficacy in the maximal electroshock model. Selegiline selectively blocks MAO-B and augments dopamine concenttations in the brain.

Clinical Role of Dopamine

Both deficiency and excess of dopamine result in clinical disorders (Table 49.5*)*. Parkinson's disease is the prototypical deficiency state. Gynecomastia occuts when dopaminergic inhibition of prolactin release is removed

Table 49.5: Clinical role of dopamine

Disorder	*Pathophysiology*	*Treatment*
I. Parkinson's disease	Degeneration of dopaminergic neurons	Precursor: l.-dopa Prevent breakdown: MAO-B (selegiline) or COMT (tolcapone) block Receptor agonists: D2 selective (ropinirole, pramipexole); mixed (bromocriptine, pergolide, lisuride)
2. Psychosis	Excessive activity in dopaminergic pathways Increased expression of D2 receptors (human brain post mortem)	Receptor antagonists: D3,4 selective (clozapine); mixed (haloperidol; Thorazine)
3. Epilepsy	Facilitari'S kindling in experimental models Neuroleptics lower seizure threshold	None known Discontintic neuroleptics
Gynecomastia	Removal of dopamine inhibition of prolactin release	Bromocriptine
Spasticity	Dorsal horn circuitry	l.-dopa
Tardive dyskinesia (TD)	Prolonged use of neuroleptics (D2 antagonists) Clozapine/olanzapine {D3,4 antagonists) do not produce TD	Minimize duration of neuroleptic use when possible Use clozapine/olanzapine instead of D2 antagonists

COMT = Catechol-o-methyl transferase; MAO = monoamine oxidase.

pharmacologically (e.g., by antipsychotic medications) or by tumors affecting connections of the hypothalamus to the pituitary. The fatigability in patients with multiple sclerosis can be treated with dopaminomimetic drugs.

Mutations in dopamine receptor, tyrosine hydroxylase, and dopamine transporter genes have been implicated in increasing predisposition to movement disorders and schizophrenia (see Table 49.2). Also, mutations in transcription factors may predispose to movement disorders by decreasing the number of dopaminergic neurons produced during neurogenesis (see Table 49.2). The identification of candidate genes for various movement disorders is still in progress.

NOREPINEPHRINE AND EPINEPHRINE

NE and epinephrine were among the first CNS neurotransmitters characterized and visualized with fluorescence techniques. Disturbances of adrenergic neurotransmission occur in the Shy-Drager syndrome (multiple system atrophy) and probably in depression; yet our understanding of these two catecholamines is incomplete. They serve important roles in the regulation of blood volume and blood-pressure control. NE is also important in sleep-wake cycles and epileptogenesis.

Chemistry and Distribution

The adtencfgic neurons of the locus ceruleus, pons, and medulla project to virtually every area of the brain and spinal cord. These neurons contain tyrosine hydroxylase and dopa decarboxylase, to make dopamine. They also contain dopamine /(-hydroxylase (like tyrosine hydroxylase, a mixed-function oxidase), which catalyzes the conversion of dopamine to NE. This enzyme requires copper as a cofactor, and chelators such as diethyldithiocarbamate produce inhibition. Dopamine /J-hydroxylase is bound to the inner membrane of synaptic vesicles and released with NE in a tetrameric glycoprotein.

A small number of neurons in the medulla contain phenylethanolamine-N-methyl transferase (PNMT), an enzyme rh.it converts NE to epinephrine with S-adenosyl methionine as a methyl donor. These neurons project to the thalamus, brainstem, and spinal cord. The concentration of cpincphrinc-sccrcting terminals in the paraventricular nucleus suggests a role in the secretion of oxytocin and vasopressin. This, coupled with the dense innervation in the region of the dorsal motor nucleus of the vagus and nucleus solitarius, suggests a role in regulating cardiovascular and respiratory reflexes. A thitd projection synapses on the sympathetic intermedioventral nucleus of the spinal cord. Physiological experiments demonstrate a vasopressor area in the rostral medulla corresponding to the epinephrine-contaimng cell group. In addition, PNMT is overcxprcsscd in spontaneously hypertensive rats.

Circulating adrenocorticotropic hormone (ACTH) links the hypothalamie-pituitary axis to adrenal secretion of epinephrine. Corticosteroids, released from the adrenal cortex, regulate the synthesis of cpincphrine-synthesizing chromaffin cells in the adrenal medulla. This circuit integrates and controls salt and water metabolism, blood volume, and blood pressure. Central epinephrine pathways appear to contribute to these vitally important functions.

Norepinephrine and Epinephrine Receptors

NT, and epinephrine act at *a*- and /i-receptors in the brain and periphery. Four receptors are present in the brain: ccl-, *a2-*, *01-*, and 02-receptors, *jil*-Adrenergic receptors are predominantly in the heart and cerebral cortex, whereas

^2-receptors are principally found in the lung and cerebellum.

The known types of adrenergic receptors are members of the G protein superfamily. As such, they are believed to have seven transmembranc-spanning hydrophobic regions of 20 to 25 amino acids each, a long C terminal hydrophilic section that contains sites for phosphorylation, a shorter extracellular N terminal end that contains glycosylated residues, and a long third intracellular loop that interacts with G proteins. Sequence homology among /Jl- and *fll*-receptors is about 71%, The sequence diffctcnccs probably account for differences in agonist preference (/31-receptors equally prefer epinephrine and NE as agonists and practolol as an antagonist; ^2-receptors prefer epinephrine over NE, and terbutaline or salbutamol as an agonist). The catecholamine binding site is thought to be a pocket formed by the helical transmembrane regions. Agonist binding to both *fil*- and *02*- receptors activates the stimulatory protein Gs to increase cellular cAMP concentrations. Activation of jS-rcceptors results in coactivation of *fi*-adrenergic receptor kinase (BARK). This kinase phosphorylates the C terminus of the ^-receptor and ^-arrestin complexes with the receptor to decrease its affinity for Gs. Phosphorylation is a prominent mechanism of receptor desensitization. Other transcriptional, post-transcriptional, and post-translational regulations control the number of receptors.

Two families of a-adrenergic receptors are identified that are also G protein linked. The *otl*- and «2-receptor families have approximately 40% sequence homology with the *fil*-receptor. The o/1-group of receptors are linked by Gs to phospholipase C. Activation of phospholipasc C generates IP3 and DAG from membrane phospholipids. The [P3 triggers release of intracellular calcium, and DAG activates protein kinase C, which is then available for phosphorylation of membrane proteins. The of2-family is coupled to the inhibitory protein G; to decrease the cellular cAMP concentration.

Physiology and Pharmacology of Central Adrenergic Receptors

Several pharmacological agents allow clinical manipulation of adrenergic mechanisms at multiple levels {Figure 49.6). NE increases firing in hippocampal pyramidal neurons by blocking the slow after-hyperpolaming potential that follows a depolarizing burst. The principal current underlying this potential is a calcium-activated potassium current

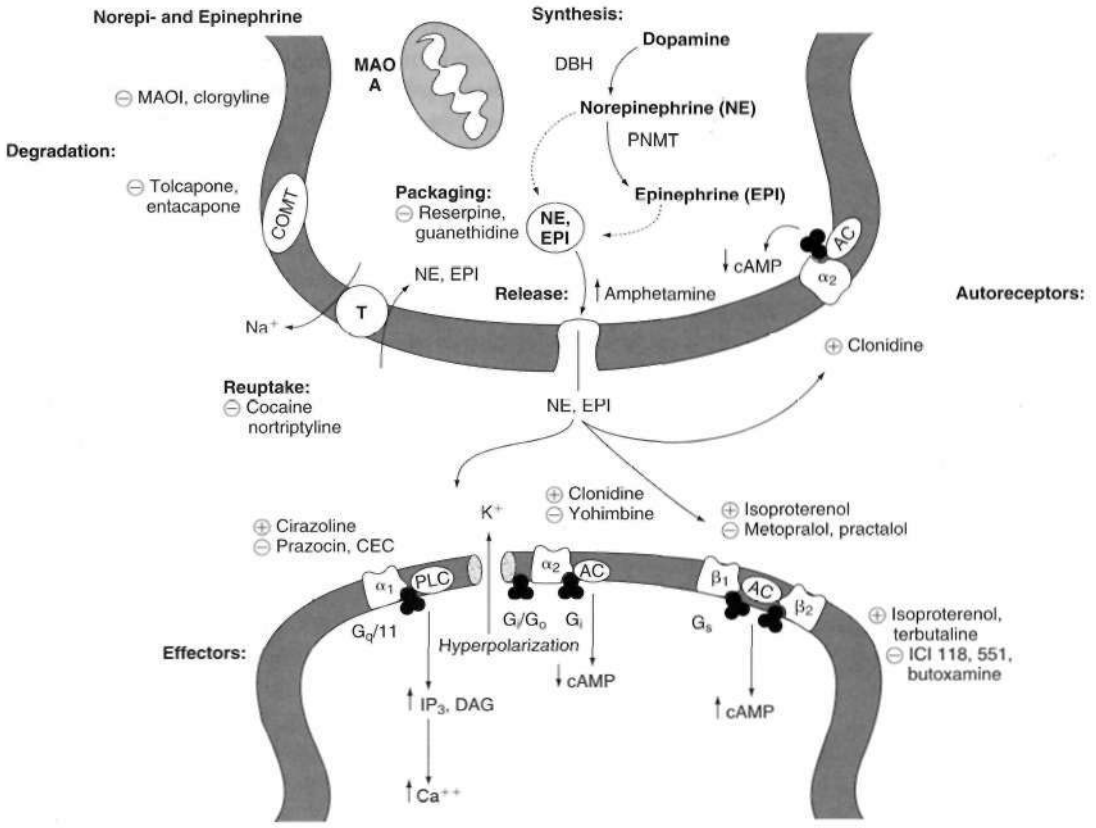

FIGURE 49.6 Pharmacology of catecholamine neurotransmission. AC = adenyl cyclase; cAMP = cyclic adenosine monophosphate; CEC = chlorocdiyk'lonidine; i)BH dopamine beta hydroxylase; ICI = manufacturer's abbreviation MAO = monoamine oxidase; MAOI = monoamine oxidase inhibitor; PLC = phospholipase C; PNMT = phcnylethaiiolaminc N-methyltransferase; T = transporter (selective for a particular neurotransmitter).

that is activated hy membrane depolarization. This effect of NE is blocked by *ji*\-selective antagonists but not by *fi2*-selective compounds or antagonists at ar-receptors, Isoproterenol is the most potent agonist in this regard, followed by epinephrine and NE; phenylephrine (al-agonist) and clonidine («2-agonist) are ineffective. NE also blocks afterhype rpolarization s in thalamic and preganglionic sympathetic neurons, although the receptor type has not been determined. In sympathetic neurons, NE abbreviates and decreases the amplitude of calcium spikes. Importantly, the action of NE is mimicked by cAMP analogues and forskolin, an activator of adenylate cyclase, and by blocking phosphodiesterase activity with methyl xanthines. The effect of NE is decreased by blocking adenylate cyclase. In addition, ^-receptor activation and cAMP analogues enhance calcium currents in dentate granule cells, similarly to the ^-adrenergic effect on the heart.

Excitatory effects of NE in various parts of the CNS and in sympathetic ganglion neurons result from al-receprors activation. This activity depends primarily on blockade of a resting potassium conductance. As a result, neurons depolarize, and firing rates increase. Inhibitory effects of NE result from or2-receptor activation, which increases potassium conductance. This hypcrpolarises the neuron and decreases its firing rates. NE acting at *oil* -receptors also blocks calcium current, an effect prevented by pertussis toxin, suggesting the involvement of a GTP-binding protein. Both of these inhibitory mechanisms may account for the auto receptor function of «2-receprors, which decrease neurotransmitter release.

Clinical Role of Adrenergic Receptors

Adrenergic innervation is involved in regulation of the cardiovascular system behavior and appetite. The Shy-Drager syndrome results from degeneration of adrenergic neurons. Depression involves adrenergic deficiency, whereas excessive adrenergic activity contributes to mania and intoxication with nonmedicinal drugs, such as cocaine. The inhibitory influence of *al*-agents (clonidine, tizanidine) is useful for treating spasticity and may have adjunctive utility for treating pain, epilepsy, and possibly sleep disorders. Table 49.6 summarizes these applications. Clinical dysautonomic disorders have been linked to mutations and/or polymorphisms in genes encoding dopamine-s-hydroxylase and the NE transporter (see Table 49.2).

SEROTONIN

In the mid-nineteenth century, a potent vasoconstrictive substance was identified in the serum of clotted blood and named vasotonin. It was almost 100 years later that 5-hydroxytryptaminc (serotonin) was isolated and synthesized. More than 95% of the body's serotonin is srorcd in platelets and the gastroinrestinal tract, and only 5% is in the brain. However, serotonin is distributed in brain regions that could affect behavior, especially the hypothalamus and the limbic system. It meets all criteria for being a neurotransmitter.

Chemistry and Distribution

The indole amino acid tryptophan is the precursor of serotonin. Tryptophan is derived from dietary protein and is transported with other neutral amino acids (including leucine, phenylalanine, and methionine) by the L-amino acid transport mechanism into the brain. Interestingly, gabapcntin, an antiepileptic drug, has an amino acid-like structure and is transported by this energy-dependent active transport mechanism. Tryptophan is metabolized to 5-hydroxytryptophan in serotonergic neurons through the action of tryptophan hydroxylase, a pteridine-recjuiring enzyme. Complementary DNAs that encode tryptophan hydroxylase have been cloned and sequenced. The enzyme contains 444 amino acids corresponding to a molecular weight of about 51 kD and is 50% homologous with tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis.

Next, 5-hydroxytryptophan is converted to serotonin through the action of L-aromatic amino acid decarboxylase. This enzyme is also present in catecholaminergic neurons, where it converts dopa to dopamine. The decarboxylase has also been sequenced. It contains 480 amino acids and has a molecular weight of 54 kD. *In situ* hybridization of its mRNA shows that the decarboxylase is present in serotonergic cells of the dorsal raphe and dopaminergic neurons in the midbrain. Raising the dietary intake of both tryptophan and 5-hydroxytryptophan increases brain serotonin levels, a strategy used in the treatment of postanoxic myoclonus with some success. Since the removal of commercial preparations of L-tryptophan from the market in 1992 because of a contaminant that caused the eosinophilia-myalgia syndrome, brewer's yeast has become an important source of L-tryptophan.

Hydroxylation of tryptophan by tryptophan hydroxylase is the rate-limiting step. Tyrosine hydroxylase is irreversibly inhibited by parachlorophenylalaninc (PCPA), which causes a long-lasting reduction of serotonin levels. PCPA is used often in experimental models designed to study the effects of brain serotonin depletion.

Fluorescence techniques localize nine groups of serotonergic neurons in the brainstem, primarily in the raphe nuclei. Serotonin-containing nerve terminals are widely distributed throughout the forebrain. Projections from the dorsal raphe, median raphe, and a pontomesencephalic cell group ascend through the dorsal paraventricular and ventral tegmental radiations to join the medial forebrain bundle, where they ascend with dopaminergic fibers. Axons of neurons in the caudal pons and

Tabic 49.6: Role of norepinephrine (NE) and epinephrine in disease states

Disorder	*Pathophysiology*	*Treatment*
1. Depression	Adrenergic deficiency state Overexpression of <*2- and /^-receptors in human autopsy specimens	Reuptake blockers (protri pry line) Chronic antidepressant therapy decreases a 2-auto receptors Electroconvulsive therapy requires intact adrenergic neurotransmission
2. Mania	Excessive adrenergic activity NE" release by drugs (cocaine)	Detoxification
i. Pain	Analgesic action	*al* -agonists (clonidine)
4, Epilepsy	NE slows kindling in experimental models; depletion facilitates	*al* -agonists (clonidine; tizanidine)
5, Shy-Dragcr syndrome	Degeneration of adrenergic neurons	None known
6, Spasticity	Loss of upper motor neuron input	<*2-agonists (tizanidine)
7, Appetite suppression	Increased *al*-receptors in ventromedial hypothalamus and clonidine use produce weight gain	Amphetamines; 0f2-antagonists (yohimbine)

medulla project within the brainstem and down the spinal cord.

Neurons in the median raphe innervate limbic structures such as the hippocampus and septum, whereas neurons in the dorsal raphe are the principal innervation of the striatum and substantia nigra. Both neural groups send projections widely throughout the neocortex. Toxic amphetamine derivatives, such as 3,4-mcthylene dioxymethamphetamine (known in the illegal drug trade as "ecstasy") or p-chloroamphetamine, preferentially destroy dorsal raphe neurons more than median raphe neurons.

The synthesis of serotonin, like other monoamine neurotransmitters, is linked to neuronal activity. Invasion of the nerve terminal by action potentials firing at high frequency increases intraterminal calcium, the activation of calcium-dependent phosphorylating enzymes (e.g., calmodulin), and phosphorylation of tryptophan hydroxylase.

Serotonin is taken up into storage vesicles in nerve terminals by a specific transporter. In the vesicles, serotonin is bound to a specific binding protein without ATP. Rcscrpine and tetrabenazine inhibit the transporter and deplete the vesicles of serotonin. These agents also deplete catechol-containing vesicles. The transmitter-containing vesicles are released by exocytosis after depolarization of the terminals and entry of calcium.

Serotonergic terminals are associated with specialized postsynaptic regions in many parts of the brain, but they lack postsynaptic specializations in some areas where varicosities seem to run en passant. This is especially true of the dorsal raphe projections to the basal ganglia, where the release of serotonin is diffusely into the interspace, much as the release of neurotransmitters into the interspace of the heart. This type of telease allows a diffuse modulatory effect rather than the specific influence dictated by point-to-point synaptic contacts. Released serotonin diffuses to presynaptic (autoreceptors) and postsynaptic receptors, and a specific presynaptic reuptake system terminates its effects. The transporter is present on serotonergic neurons and glial cells. About 50% sequence homology exists between this and the transporters for catecholamines. Different systems express different functional recombinant transporters. Antidepressant drugs, such as the serotonin selective uptake blockers fluoxetine and sertraline, inhibit the cloned transporter.

The other mechanism for termination of serotonin action iscatabolism by MAO. Serotonergic neurons contain predominantly MAO-B, although MAO-A prefers serotonin as a substrate. The presence of MAO-B may prevent serotonergic neurons from accumulating catecholamines.

Serotonin Receptors

Seven subtypes of serotonin receptors have been identified in the brain. All seven were subsequently cloned, sequenced, and characterized. 5-HTl, 5-HT2, and 5-HT4 subtypes are coupled to G proteins and modulate one or more second messenger systems. The 5-HT3 subtype is a ligand-gated ion channel. Physiological roles of the other types is less well understood. Pharmacology of cloned receptors correlates well with that determined by receptor binding techniques (Figure 49.7}.

The 5-HTl family consists of four receptor subtypes, 1A to ID. In the hippocampus and raphe nuclei, 5-HT1A receptors open potassium channels and cause hyperpolarization by a G protein-coupled interaction. 5-HT1A receptors both increase and decrease cAMP formation by G protein-coupled effects on adenylyl cyclase. Buspirone, a novel anxiolytic compound, is a partial agonist at 5-HT1A receptors. The exertion of its effect may be by the hyperpolarizing action of serotonin on these receptors. Excitation by serotonin could result from blockade of a resting or leak potassium conductance, or from the calcium-dependent potassium conductance underlying the slow after-hyperpolarization.

5-HT1B and 5-HT1D receptors inhibit adenylate cyclase and decrease cAMP. The densest expression of these receptor subtypes is in the substantia nigra. 5-HT1C receptors and 5-HT2 receptors stimulate the production of IP3 through a phospholipasc C-linked pathway. 5-HT2 receptors also close potassium channels through a G protein-coupled mechanism that results in a slow depolarization.

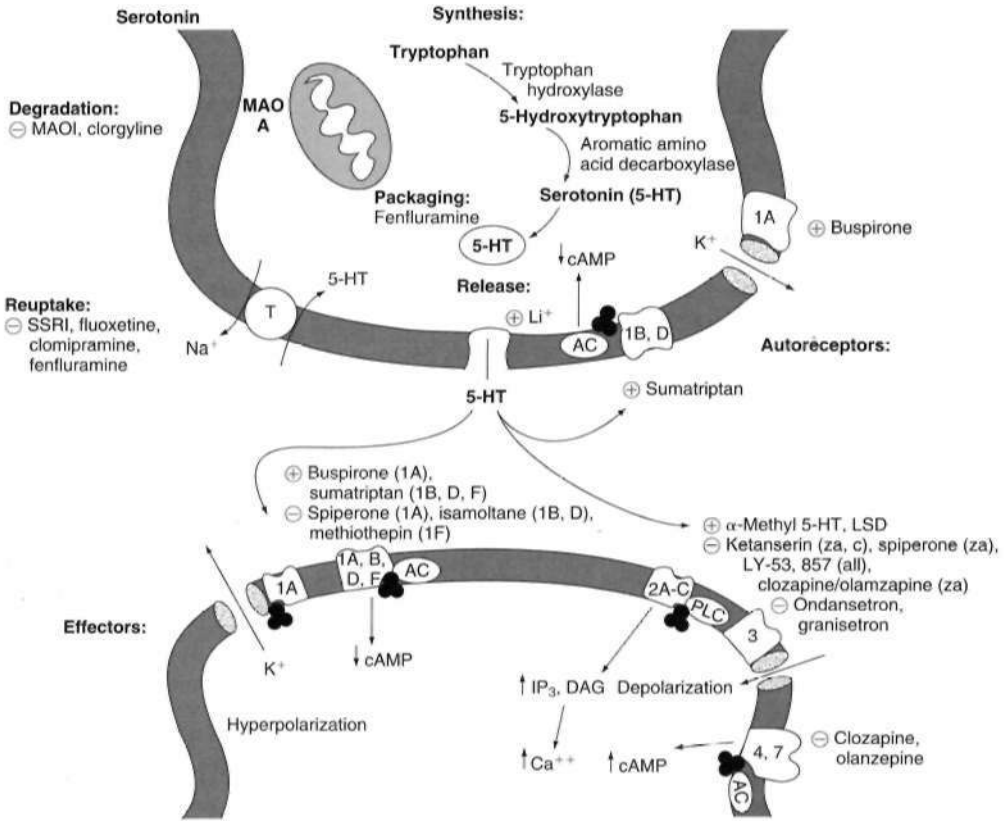

FIGURE 49.7 Pharmacology of serotonin neurotransmission. AC = adenyl cyclase; cAMP = cyclic adenosine monophosphate; DAG = diacylgrycerol; LSD = lysergic acid diethylamide; LY = Lilly Pharmaceuticals; MAO = monoamine oxidase; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitors; T = transporter (selective for a particular neurotransmitter).

5-HT1B and **5-HT1D** receptors probably subserve the autoreceptor function of presynaptic serotonergic receptors; both are highly expressed in the basal ganglia. These subtypes may be involved in the pathophysiology of some movement disorders.

5-HT1C receptors, which are enriched in choroid plexus epithelial cells, may regulate the composition and volume of cerebrospinal fluid **(CSF).** Effects on mood and behavior may be mediated through 5-HT1C receptors in limbic structures. Expression of 5HT1C receptors in the basal ganglia suggests a possible role in motor behavior as well. A fifth subtype (5-HT1P) is found in the gastrointestinal tract and produces a slow depolarization of some myenteric plexus neurons.

5-HT2 receptors are highly expressed in various regions, including the cortex, limbic system, and basal ganglia. In the cortex, they are thought to he postsynaptic receptors on intrinsic neurons, because disruption of projection paths docs not influence the receptor density, as determined hy radioligand techniques.

The 5-HT3 receptor docs not belong to the G protein superfamily but is a ligand-gated ion channel. The depolarization caused by activation of this channel produces a fast excitatory potential. The 5-HT3 receptor subtype is most abundant in peripheral ganglia and nerves and in the substantia gelatinosa of the dorsal horn of the spinal cord. This suggests a role in the modulation of pain neurotransmission (see Chapter 52). 5-HT3 receptor antagonists, such as ondansetron and granisetron, are antiemetic. This effect corresponds to a high density of 5-HT3 receptors in the area postrema, the site of the chemoreccptor trigger zone.

The 5-HT4 receptor is coupled to adenylate cyclase and is associated with inhibition of potassium current in collicular neurons and the hippocampus. Receptor activation presumably increases cAVll', which then activates protein kinase A. The resultant phosphorylation inhibits the channel. The absence of selective antagonists makes it difficult to study the function of 5-HT4 receptors. Additional cloned serotonin receptors include 5-HT5A **and** -B, 5-HT6, and 5-HT7. These receptors are called "orphans" because their function remains unclear.

Long-term regulation of the serotonin receptors varies with receptor type and circumstances. As expected, 5-HT1 receptors downregulate when chronically exposed to mianserin, a receptor antagonist. Contrary to expectation, destruction of serotonergic neurons does not change 5-HT2 receptor density. However, 5-HT2 receptors downregulate and desensitize as expected after administration of hallucinogenic agonists, chronic administration of inhibitors of serotonin uptake, or chronic exposure to 5-HT2 receptor antagonists.

Clinical Role of Serotonin Receptors

Serotonin is an essential modulator of inhibition in the CNS and is involved in a wide variety of important functions and clinical disorders (Table 49.7). It has a prominent role in behavior disorders. It normally functions to promote sleep and is a precursor for the synthesis of melatonin, a regulator of circadian rhythms. Deficiency of serotonin underlies depression and its related sleep disorder. Psychotogenic drugs, such as lysergic acid diethylamide (LSD), bind to 5-HT2 receptors. This serves as a prototype for the pathophysiology of psychosis. Reduction of 51 IT-1 and -2 receptors and neuronal loss in the dorsal raphe in Alzheimer's disease may underlie behavioral changes in that degenerative disorder. The 5HT-1A partial agonist, Buspirone, is useful in the treatment of alcoholism. The role of serotonin in epilepsy is multi faceted. Depletion facilitates kindling epileptogcnesis and prevents the anticonvulsant effect of carbamazepine in the genetically epilepsy prone rats. Blockade of 5HT-2 receptors prevents the anti-convulsant effect of serotonin and tryptophan in experi-mental models. These findings suggest that serotonin may be an endogenous anticonvulsant. Some antidepressants lower seizure threshold, whereas others may be anti-convulsant, perhaps because of multiple mechanisms of action. Serotonin depletion decreases efficacy of opiate-induced analgesia and intrathecal administration of serotonin can produce analgesia by activating 5HT-1 receptors. The activation of 5HT-1D receptors by suma-triptan and its analogues are a standard for migraine therapy. The 5HT-3 agonist, ondansetron, and its analogs are antiemetic. Serotonin 5HT-1C receptors are plentiful in the choroid plexus and antagonists, including ondanse-tron, may help to decrease hydrocephaly. Anoxic injury to

Tabic 49.7 Role i>t sororonLn in disease states

Condition	*Patbophysio logy*	*I ictturrll!*
1. Sleep/insomnia	Role in normal sleep onset Precursor of melatonin, a regulator of circadian rhythms also under sympathetic influence and decreased in depressed patients Modulates release of ACTH (high Cortisols and insomnia in depressed patients)	Not required; tryptophan (precursor of 5HT) may improve sleep or induce sleep onset SHT/NE uptake blockers (tricyclic antidepressants} 5HT uptake blockers (sertraline, Prozac)
2. Depression	5HT deficiency state	5HT uptake blockers (sertraline, Prozac, TCAs) Electroconvulsive therapy (ECT) enhances 5HT neurotransmission
3. Schizophrenia	Precise mechanism unknown Psychotogenic effect of 5HT2 receptor-active drugs (LSD, partial agonist) suggests role	5 HT2 antagonists (clozapine)
4. Alcoholism	Reduced or depleted (by acute ingestion) 5HT Agonist chlorphcnylpipcrazine enhances craving	5HT1A partial agonist (buspirone)
.S. Pain	SHT depletion reduces efficacy of stimulation- and morphine-induced analgesia Intrathecal .SHT antinociceptive effect antagonized by presynaptic and postsynaptic 5HT1 (Post: 5HT1A, spiperone; Pre: 5HT1C, mianserin), but not 5HT2 or -3, antagonists	.SHT reuptake blockers (SSRIs and TCAs)
6, Migraine	Increased free plasma 5HT precedes headache	• 5HT1D agonists (sumatriptan) abort headache • TCAs effective prophylactically
7. Alzheimer's disease	• Reduction of 5HT1 and 5HT2 receptors plus neuronal loss in dorsal raphe	• 5HT manipulation docs not slow progression
8. Epilepsy	5HT depletion facilitates kindling and prevents anticonvulsant effect of carbamazepine in genetically epilepsy-prone rats 5HT2 antagonist (ketanserin) blocks anticonvulsant effect of .SHT/5-hydroxy-tryptophan Some antidepressants lower seizure threshold, mechanism(s) unclear	• Carbamazepine increases dialyzable .SHT that sub-sequently enhances GABA release • 5HT1A agonist (80H-DPAT) activates hyperpo I arizing potassium current • No systematic trials of 5HT-activc drugs in humans
9. Kinesis	Overactivity of trigger zone in floor of fourth ventricle at obex	5HT3 agonists (ondansetron)
10. Myoclonus	Anoxic injury to 5HT neurons in dorsal raphe produces Lance-Adams syndrome	Precursor (tryptophan) may help
11. CSE synthesis	SHT1C receptors plentiful in choroid plexus; possible role in hydrocephaly and pseudotumor cerebri	Potential benefit from 5HT1C antagonists (ondansetron)

A CTH = a drenocorticotrop ic hormone; CS F = cere bros pina I fluid; LSD = lysergic acid diethyl a m i de; SS R1 = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Tahle 49.K: Colocalization of principal ("classical") and peptide transmitters

Neurotransmitter	*Peptides*	*Location*
Acetylcholine	CGRP ENK, GAL, SP, **VIP**	Cerebral cortex, brainstem, spinal cord
Dopamine	CCK, NT	Hypothalamus, mesencephalon
Norepinephrine	ENK, NPY	Locus ccrulcus, medulla
Serotonin	SP±TRH, CCK, ENK, GAL	Medulla, area postrema, spinal cord
GABA	CCK. LNK, GAL, ENK, NPY, SST	Cortex, amygdala, basal ganglia, brainstem, spinal cord
Glu tarn ate	CCK, CRH, DYN, ENK, SP	Cortex, amygdala, hippocampus

CCK = cholccystokinin; CGRP = calcitonin gcnc-rclatcd peptide; CRH = corticotropin-re lea sing hormone; DYN = dynorphin; ENK = enkephalin; GAISA = f-aminoburyric acid; GAL = galanin; NPY = neuropeptide Y; NT = neurotensin; SP = substance P; SST = somatostatin; TRH = thyrotropin-relcasing hormone; VIP = vasoactive intestinal peptide.

the dorsal raphe results in myoclonus (Lance-Adams syndrome). Treatment with the serotonin precursor tryptophan may be beneficial for some, although some commercial preparations caused allergic reactions.

Mutations and polymorphisms of serotonin receptor genes are implicated in susceptibility to alcoholism, psychoses, and other behavioral disorders (see Table 49.2). Mice without 5-HT2C receptors are hyperalert and have audiogenic seizures. The serotonin transporter gene is under consideration as a candidate gene for bipolar disorder and polymorphism of this gene may predict susceptibility to depression.

PEPTIDES

The role of peptide hormones, such as oxytocin and vasopressin, in pituitary and visceral function indicated the importance of peptides initially. The principal role of peptides as neurotransmitters was discovered first in coelencerates, then in vertebrates. The role of some neuropeptides as cotransmitters and modulators of excitability in vertebrates is of interest in the present discussion for several reasons. First, neuropeptides co-localize with conventional neurotransmitters (Tabic 49.8). Depending on the pattern of firing, peptides may be released in temporal sequence after the conventional transmitters. In turn, the peptides modulate release and postsynaptic efficacy of the principal transmitter. Second, overexpression and underexpression of various peptides have been implicated in a broad array of clinical disorders (Table 49.9). Elucidation of how dysfunction of peptidergic neurotransmission and neuromodulation occurs is a stimulus for the development of novel treatment agents that are antagonists or agonists at peptide receptors. Third, identification of mutations in genes for peptides or peptide receptors is providing insight into pathogenesis of clinical disorders, susceptibility to diseases and adverse effects of drugs, and novel avenues for the development of therapeutic agents (Table 49.10).

Neuropeptides are sequences of 10 to 50 amino acids that are enzymatically cleaved from larger precursor peptides 90 to 500 amino acids in length. Alternate splicing of RNA transcripts results in multiple mRNAs and increases the variety of products of peptide and peptide receptor genes. Synthesis of peptide transmitters and modulators differs from the synthesis of conventional transmitters that takes place locally in nerve endings. After intranuclear transcription, translation of peptide mRNAs takes place in the neuronal somata on ribosomes on the endoplasmic reticulum. Further processing in the Golgi apparatus leads to production of large dense core

Tabic 49.9: Involvement of peptide neuromodulators/neurotransmitters in clinical disorders

	CCK	*CGRP*	*CRh*	GAL	NPY	*Opioids*	*SP*	*SST*	*TRH*	*VIP*
Epilepsy	/		/	/	/	/		/	/	
Anxiety states	/		/	/	/	/	/	/	/	
Bipolar		/	/		y		/	/		
Schizophrenia		/			/					
Depression				/		/	/	/	/	
Substance abuse					/	/				
Suicide					/					
Pain	/	/		/	/	/	v'	/		•
Alzheimer's				/						
Parkinson's	/	/								/
Hating behavior					/	/				
Learning and memory				/	/	/			/	
Reproductive function				/						/
Sleep and its disorders					/		•f			

CCK = cholecystokinin; CGRP = calcitonin gene-related peptide; CRH = corticotropin-relcasing hormone; GAL = galanin; NPY = neuropeptide Y; SP = substance P; SST = somatostatin; TRH = thyrotropin-relcasing hormone; **VIP** = vasoactive intestinal peptide.

Table 49.10: Mutations of peptide receptor genes in relation to disorders in humans and experimental animals

Peptide/receptor	*Mu tation/a Iteration*	*Disorder*	*Comments*
Calcitonin gene-related peptide (CGRP)	*CALCA* gene polymorphisms	One associated with bipolar and unipolar depression, bur nor schizophrenia or Parkinson's disease	Supports role in affective disorder
Cholecysrokinin (CCK)	Four polymorphic sires in CCK gene	One associated with susceptibility to hallucinosis in Parkinson's patients raking i.-dopa	Subtle change suggesting susceptibility to adverse drug effects
Corticotropin releasing hormone (CRH)	1. Human ptomoter gene polymorphism 2. Increased CRF mRNA post kindling in rats 3. CRH overexpression in transgenic mice 4. CRH receptor type 1 knockout 5. CRH receptor type 2 knockout	1. Rheumatoid arthritis susceptibility marker 2. Promotion of experimental epileptogenesis I. Increased anxiety-related activity, impaired learning 4. Reduced anxiety-related activity, impaired spatial memory 5. Increased anxiety-related activity	1. Supports regulatory role in inflammation and immune events 2. CRH induces seizures and promotes epileptogenesis 3-5. Supports role of CRHR1 in anxiogenesis and memory/ learning impairment, and anxiolytic role of CRHR2. Impaired learning supports role of CRH in dementia
Galanin (GAL)	1. Inactivating mutation of GALR1 receptor gene in mice 2a,b. GAL overexpression in Transgenic mice	1. Spontaneous seizures, low levels of insulin-like growth factor 2a. Impaired learning and memory, reduced number of choline acetyl transferase imrmmoreactivc neurons, reduced susceptibility to seizures 2b. Reduces anxiety in mice in response to stress induced by noradrenergic challenge	1. Endogenous anticonvulsant effecr and neuroendocrine regulatory role 2a. Possible relation to Alzheimer's disease is **under** intense study 2b. Suggests potential for developing novel anxiolytic compounds
Neuropeptide Y (NPY)	la. NPY overexpression in transgenic mice 1b. NPY knockout mice 2. Reduced expression of mRNA for NPY in post mortem frontal cortex 3. Reduced mRNA for NPYl and Y2 receptors in postmortem prefrontal cortex	la. Reduced incidence of seizures in response to i.c.v. kainic acid and slowing of kindling epileprogenesis lb. Increased lethality of kainate-induccd seizures 2. Association with bipolar disorder 3. Association of decreased Yl with aging and Y2 with suicide as cause of dca[h	la,b. Importance as endogenous anticonvulsant suggests potential for developing novel anticonvulsant drugs 2. Supports role in affective disorders 3. Different receptor subtypes have different behavioral effects
Opioids	1. ii and *S* opioid receptor polymorphisms 2. Polymorphism in prodynorphin gene in temporal lobe surgery specimens	1. Weak association with addiction to opiates and alcohol 2. L-homozygotes had higher risk of secondarily tonie-clonic seizures and status epilepticus	I. Suggest basis tor genetic susceptibility to addiction 2. Suggests anticpilcprogenic and anticonvulsant role of dynorphin
Somatostatin (SST)	1. Human SSTR5 receptor gene polymorphism 2. SST knockout mice	1. Region includes genes associated with adult polycystic kidney disease **(PKD1)** and tuberous sclerosis (TSC2) 2. Increased severity of kainate-induccd seizures	1. Possible factor in neuropilakomatoses and developmental errors 2. Endogenous anticonvulsant

i.c.v = infracerebro ventricular,

vesicles {LDCVs) that move by axonal transport to nerve terminals before secretion. Release at synaptic terminals depends on firing frequency and duration of depolarization. Low-frequency firing results in sufficient Ca^{2+}* entry to effect release of conventional neurotransmitters from small synaptic vesicles. High-frequency sustained firing engages release of peptides from LDCVs. After release, peptides bind to specific presynaptic and postsynaptic receptors to modulate neurotransmitter release and postsynaptic efficacy. The effects of peptides are slower in

onset but more sustained. For example, NE and neuropeptide Y (NPY) may be present in sympathetic nerve endings on blood vessels. Release of NE is rapid, but rapid desensitization occurs. The slower release of NPY leads to more sustained vasoconstriction. Most neuropeptide receptors are G protein-coupled receptors with seven transmembrane domains (sec Figure 49.1A2). Peptide binding sites are present on loops near the outer membrane surface and on the extracellular N-terminal sequence. Receptor activation is mediated by intracellular signal transduction processes that depend on the type of G protein involved. Termination of synaptic events depends on diffusion and proteolysis of peptides, because there are no pep tide-selective transporters for reuptake and recycling. Diffusion results in stimulation of receptors on distant cells. One last important characteristic is that expression of peptides and their receptors is extremely plastic. It can be altered within a few hours of stimulation in a number of ways.

Calcitonin Gene-Related Peptide

Calcitonin gene-related peptide *a* (CGRPa) consists of 37 amino acids. CGRPa is produced by alternate splicing of transcripts of the calcitonin gene. The G protein-linked component of CGRPa is associated with a modulatory subunit RAMP 1 that enhances affinity for CGRP. After removal of the first seven amino acids, CGRP8-37 is an antagonist. A homologue, CGRP/S, is encoded by a different gene that does not contain an exon for calcitonin. CGRP (a > *0)* binds to two receptors, CGRP1 and CGRP2, that are coupled to G_s and stimulate cAMP production. CGRPa is manufactured by nociceptive dorsal root ganglion neurons that synapse in lamina I of the dorsal horn in particular and by ventral horn motor neurons as well. The rise in dorsal horn receptors after rhizotomy is a sign of denervation hypersensitivity, indicating the role of CGRP as a proalgesic neurotransmitter of primary afferent nociceptors. Levels of CGRP increased in some patients with reflex sympathetic dystrophy. Seizures in experimental models induce elevations of CGRP (in frontal lobes>striatum>hippocampus>amygdala). Severe hypoxic-ischemic injury to newborn rats also induced increases of CGRP in cerebral cortex, basal ganglia, and hippocampus. The blood of patients with vasospasm has elevated levels of CGRP. Nonpcptidc antagonists have been synthesized with the aim of developing novel therapies for neuropathic pain, migraine, and possibly seizures.

Cholecystokinin

Cholecystokinin (CCK) consists of 37 amino acids. It is produced from the polypeptide preprocholecystokinin, which contains 115 amino acids. Fragments of 4 to 56 residues are found in the brain. Most abundant and potent is a suifurated octapeptide (CCK-8S). Two receptors for CCK-8S (CCK_A and CCK_B) have been cloned from the brain of humans and animals. They arc coupled to Gq/11 and activate phospholipase C to produce diacyl glycerol and inositol triphosphate. These induce release of calcium from intracellular stores. Peripheral administration of CCK activates c-fos expression in brain indirectly via vagal afferents. This exemplifies how systemic elevations of CCK from the gut can trigger centrally mediated effects.

CCK is implicated in the mechanism of anxiety. Intravenous CCK triggers panic in patients with panic disorder. Effects of agonists and antagonists depend on the experimental paradigm, but CCK_{fi} agonists induce anxiety-like behaviors in animal models.

Results of several experimental paradigms in animals indicate enhanced learning and memory after CCK administration, However, in postmortem brain specimens of Alzheimer's disease patients and in those of matched controls, CCK peptides concentrations do not differ, or CCK is relatively reduced (not as severely as somatostatin). In an animal model, CCK-8S may have protected cholinergic neurons from degeneration after lesions of the basal forebrain. This finding is of uncertain clinical significance. Administration of the CCK-like peptide ceruletide to schizophrenic patients had no cognitive or antipsychotic effects but caused mild sedation. Ceruletide may improve some electrophysiological indicators of cognitive function or attention in young, but not elderly, healthy subjects. The CCK tetrapeptide fragment may affect memory adversely. A computer search yielded no published data from placebo-controlled clinical trials that support the idea that CCK enhances human learning or memory.

A small percentage of dorsal root ganglion neurons express mRNA for CCK. Axotomy markedly increases CCK expression in these neurons. This may play a role in neuropathic pain. Experimental findings suggest that CCK antagonizes pain-relieving effects of morphine. Thus giving CCK receptor (especially CCKu) antagonists with narcotics is an option for treatment of refractory pain.

Kindled seizures and status epilepticus raise CCK levels in cerebral cortex and parts of the hippocampus in experimental models. The suifurated fragment CCK-8S had anticonvulsant effects against picrotoxin- and electroshock-induced seizures. Rats with genetically determined audiogenic seizures had low brain CCK levels and CCK-8S prevented seizures. This suggests another molecular mechanism of action, perhaps by preventing increases of intracellular calcium by NMDA or other glutamate receptors. In the same rats, transfer of an exogenous CCK gene with viral vectors also prevented seizures. Ceruletide, a CCK-8S-like peptide, slowed kindling acquisition. Such findings suggest possible

anticonvulsant and anticpilcptogenic actions of CCK or synthetic analogues.

Corticotropin-Releasmg Hormone

Corticotropin-releasing hormone (CRH) or corricotropin-relcasing factor (CRF) is a 41 amino acid polypeptide. This peptide is involved in behavioral, endocrine, immune, and autonomic responses to stress. Two receptors that increase cAMP by interactions with G_s mediate these functions. The primary localization of CRF1 is to the cerebral and cerebellar cortices. Antagonists to CRF1 receptors are under development for the treatment of anxiety and depression. They have also reduced stroke-induced damage and inflammatory pain. CRF2 receptors exist in three splice variants that are differentially distributed. So far, no selective antagonists exist. The paraventricular and ventromedial hypothalamus and the septum contain *CRVloi* receptors. Involvement of these receptors could account for eating disorders. CRF2^ receptors are located in brain arterioles and in the choroid plexus. These could be involved in migraine and vasospasm. The localization ot *(.'.RYly* rt-ceptors is the amygdala where u could he involved in the several functions subserved by this critical area. Among these are the structures that links sensory inputs to emotion. In addition, CRF2 receptors inhibit angjogenesis and CRF2 deficient animals are hypertensive.

CRH is localized with, and enhances, the excitatory effect of glutamate under conditions of sustained firing. This contributes to hyperexcilability as seen in epilepsy. For example, CRH is involved in neurotoxicity and proconvul-sant effects of kainic acid and creates severe seizures in the developing brain. From the physiological standpoint, the release of CRH occurs under conditions akin to post-tetanic potentiation (PTP). Both sodium and calcium influx through voltage-sensitive channels at nerve terminals are important for PTP. Both ionic currents are targets for antiepileptic drugs, but CRH enhanced excitability opposes drug efficacy. Thus the development of CRH antagonists may offer improvement in control of age-dependent seizures.

Galanin

Galanin (GAL) has 30 amino acid residues in humans and 29 in other species. It is derived from prcprogalanin, a gene product with a 7 to 9 residue signaling sequence, followed by the 29- or 30-residue galanin sequence, and then a terminal 60-residue galanin message-associated peptide of unknown significance. The elongated sequences were isolated from the adrenal gland, gut, and urinary tract, for example. Estrogens regulate galanin niRNA transcription and increased expression occurs in the pituitary during pregnancy. Thyroid hormones, ACTH and GAL, are also inter-regulated. Galanin mRNA expression is increased up to 100-fold in sensory neurons and in neurons of the dorsal horn after axotomy.

Galanin is a potent inhibitor of hormone release including insulin, but it increases growth hormone release. In this role, it is a neuroendocrine regulator. Inhibition results from blockade of I.- and N-rype voltage-sensitive calcium channels, activation of ATP-sensitive hyperpolarizing potassium current, antagonism of ACh-stimulated phospholipase C activity, and reduction of cAMP. GALRl and GALR3 receptors mediate these actions. The expression of GALRl is in the hypothalamus, where it regulates the release of hormonal factors; in the spinal cord, where it dampens nociceptive barrages from the periphery; and, in the hippocampus, where it acts as an endogenous anticonvulsant. GALR2 receptors are in the hypothalamus, where they may stimulate growth hormone release, and in dorsal root ganglion neurons, where they may serve as autoreceptors to facilitate transmitter release. The excitatory effects of these receptors are mediated by activation of phospholipase C mediated by $G_{t|/|}$]. This leads to generation of diacylglyccrol and IP3, with the subsequent release of intracellular calcium.

Galanin colocalizes with ACh in some neurons and is released by sustained high-frequency firing. Galanin exerts a negative modulatory effect by reducing ACh release through presynaptic autoreceptors coupled to hyperpolarizing potassium current. Postynaptically, GAL opposes mus-carinic activation of phospholipase C. This relationship exemplifies how GAL might counter muscarinic over-stimulation. In the case of Alzheimer's disease, GAL could worsen cognitive deficits associated with loss of cholinergic neurons. As plaques increase, however, GAL immunoreac-tivity declines, either as a sign that lost neurons contained both ACh and GAL, or in compensation for changing activity levels. Effects on nociception further demonstrate the dual nature of GAL activity. Stimulation of GAL1 receptors in the dorsal horn is antinociceptive, whereas stimulation of GAL2 receptors on dorsal root ganglion neurons is pro nociceptive by facilitating release of pain-relared neurotransmitters such as glutamate and CGRP. Colocalization with NE provides an example in which GAL may contribute to depression. At low firing frequencies, adrenergic neurons of the locus ceruleus excite dopaminer-gic neurons of the ventral tegmental area. At high frequencies, corelease of GAL inhibits dopaminergic neu-rons. Direct injection of GAL into the ventral tegmental area induces symptoms in an animal model of depression. In this model, excessive GAL-mediated inhibition produced the disorder. On the other hand, anxiolytic effects result from instilling GAL into the lateral ventricle in animal models, suggesting that the effects of GAL-mediated inhibition depend on the area in which it occurs. Microinjection of GAL into the dentate hilus prevented the development of self-sustaining status epilcpticus in an animal model. This provides a rationale for developing GAL1 receptor agonists for the treatment of epilepsy.

Neuropeptide Y

NPY is a 36-residue polypeptide derived from preproneuropeptide Y. Its production requires the action of a signal peptidase, which removes a signaling sequence, and a prohormone convertase. The latter is an endopeptidase that removes the C-terminal flanking region during processing in the large dense-core vesicles. Six known receptors for NPY exist. Five (Yl, 2, 4, 5, 6) have been cloned and are coupled negatively to adenylate cyclase by G;. A proposed sixth receptor, Y3, explains differential binding of NPY and the pancreatic peptide YY. NPY, a potent vasoconstrictor, is abundant in brain and implicated in epilepsy, depression, anxiety, memory and cognition, and obesity. Increasing evidence exists that different receptor subtypes mediate each of the actions of NPY, in large part resulting from the development of knockout (lacking specific receptors) and transgenic (ove rex pressing a peptide or receptor) mouse models.

Concentrations of NPY and prepro-NPY levels rise after seizures induced by kainic acid, electroshock, or kindling. Inhibitory Y2 receptor expression increases in the hippocampus within six hours after seizure activity. NPY is coexpressed in a subset of GABA interneurons. Such findings in experimental animal models and in human specimens from epilepsy surgery suggest increased inhibitory neurotransmission involving NPY, and probably GABA, after seizures. Microinjection of NPY into the hippocampus prevents or ameliorates seizures after kainate administration and self-sustaining status epilepticus induced by perforant pathway stimulation *in vivo.* In NPY knockout mice, the lethality of kainate-induced seizures is greater than in wild type. In transgenic mice overexpressing NPY, seizures are more difficult to induce. Electrophysiological evidence comparing tissues from wild type and knockout mice suggests that Y5 receptors are necessary for the anticonvulsant effect. Other studies have suggested a role for Yl and Y2 receptors. A subset of neurons expresses both NPY and NE. Dopamine *fi*-h ydr ox yl as e-deficient mice are more sensitive to seizure-producing stimuli than NPY-deficient mice. This suggests that NE is a more potent endogenous anticonvulsant neurotransmitter than NPY.

Low levels of NPY in spinal fluid have been associated with major clinical depression and anxiety is often a comorbid feature of depression. Reduction of experimental anxiety by NPY in animal models depends on Yl receptors. Yl receptors are also important in sedation triggered by sleep-regulating areas of the posterior hypothalamus, as shown with knockout mice.

Some reports suggest that NPY effects memory retention and short-term memory in several experimental animal paradigms. Involvement in clinical dementias is unclear.

NPY colocalizes with NE in sympathetic neurons and inhibits release of NE, probably by a presynaptic autoreceptor mechanism. Nociceptive dorsal root ganglion neurons express Yl receptors and experimental inflammatory pain increases Yl receptors in ORG neurons and in cells of laminae I and II of the spinal cord. Modulation of NPY receptors may be a novel route for the development of anti-hyperalgesic drugs.

Opioid Peptides

Several classes of opioid peptides exist: methionine- and leucine-enkephalins derived from proenkephalin; dynorphins A and B and «-neoendorphin derived from prodynorphin; ^-endorphins derived from proopiomelanocortin; and, the most recently described, endomorphins 1 and 2 of uncertain gene origin. The distribution of three principal receptors, *5, K,* and ji, is different throughout the neuraxis. The peptides have different orders of preference for these receptors (enkephalins bind to *&>fi^K* receptors, dynorphins bind to *K>fi* and *S* receptors, and endorphins prefer *fj.* and *5* over *K* receptors). Endomorphins arc potent endogenous /* receptor agonists. The receptors are all negatively coupled to adenylate cyclase by G;, activate inwardly rectifying potassium current (hyperpolarizing) coupled to $G^{\wedge}_{0}$ and close N-calcium channels coupled to G_n. On balance, these mechanisms provide presynaptic inhibition of transmitter release by afferent neurons and inhibition of dorsal horn neurons mediated by postsynaptic receptors.

Opioid peptides have a documented role in pain and its control, seizures, drug abuse, psychiatric illnesses, locomotion, pregnancy, exercise, immune responsiveness, cardiovascular function, respiration, thermoregulation, and gastrointestinal activity. Administration of receptor agonists for the relief of pain and their adverse effects are well known. Comments on their role in pain and epilepsy serve to illustrate, the importance of the endogenous systems.

Opiatergic pathways descend from the midbrain to the superficial laminae of the dorsal horn, particularly to laminae I and II. *ji*- and ^-receptors are especially present in lamina II. Although the distribution of delta receptors is throughout the dorsal horn, their main concentration is in laminae I and II. These receptors, especially ^-receptors, are targets of pain modulation by exogenous opiates. Furthermore, their strategic dispositions indicate that multiple endogenous opioid peptides are projected to regions of the dorsal horn in which the first synapse along nociceptive pathways occurs. They decrease the responsiveness of dorsal horn neurons to incoming nociceptive volleys by affecting cAMP levels, blocking of calcium channels, and opening of potassium channels. Conceivably this system has phasic activation. In acute settings central propagation of afferent nociceptive volleys along spinothalamic pathways activates midbrain neurons (in the periaqueductal gray and pontine reticular formation). These neurons then project back to the active spinal levels and inhibit dorsal horn neurons. Synaptic delay

indicates that this system is reactive, not preemptive. It is more likely to prevenr persistent hyperexcirabiliry resulting from activation by afferent neurons; this is the situation in normal pain sensation. Sustained afferent volleys and depletion of the descending systems by sustained activity over time could contribute to chronic pain, a pain that is abnormal because it does not turn off.

Less well recognized is the fact that dorsal rhizotomy results in a loss of 50% or more of the total binding of opioid peptides in the dorsal horn. This indicates that primary afferent (dorsal root ganglion) neurons express receptors for opioid peptides, including endomorphins. Thus they express the means of controlling their own excitability. Disorders that reduce expression of these presynapric inhibitory receptors are more likely to contribute to chronic pain. Dorsal root ganglion neurons change the types of sodium channels they express in response to injury. These signs of plasticity indicate how primary afferents respond to pathological changes by genetic alterations.

Opiares have mixed effecrs on seizures. Proconvulsant effects of *n* opiates occur occasionally in clinical situations. High dosages of exogenous and possibly glucuronidared metabolites may explain some cases, whereas withdrawal explains others. u.- and <S-agonists enhanced hippocampal excitability and/or caused seizures in animal models. Morphine dependence enhances kindling acquisition and susceptibility to chemoconvulsant-induced seizures by interactions with GABA and NMDA systems. Seizures release opioid peptides. Naloxone reverses the protective effect of *fi*- and K-agents against chcmoconvulsant- and hypoxia-induced seizures. The same mechanisms of action that reduce nociception are operant in limbic structures involved in experimental seizure production.

Changes in opioid receptor systems occur after seizures and ischemia. Both conditions kill neurons. Kappa receprors increase in the hippocampus after chemically induced seizures and chronic alcohol administration. Opiate antagonists (e.g., naloxone) and ^-receptor agonists are neuroprotective after cerebral ischemia and in vitro conditions promoting hypcrexcitabiliry. Delta receptor agonists reduce loss of substantia nigra neurons after exposure to the toxin 6-hydroxy-dopamine and protect dopaminergic nerve rerminal from destruction by amphetamines, suggesting potent neuroprotective effects.

Substance P

SP is a member of the tachykinin family, discovered because of their ability to enhance smooth muscle contractility and salivation. The tachykinins are translated splice variants of inRNA transcribed from the prcprotachykinin gene. SP is an 11-residue polypeptide derived from three precursor peptides that result from the alternative mRNA splicing. SP is an agonist of NK-1 receptors that are involved in pain (e.g., fibromyalgia), migraine, affective disorders, and emesis. Autopsy specimens from depressed patients show decreased NK-1 receptors, a sign of downregulation resulting from excessive SP-relatcd activity. Experimenral antagonists of NK-1 receptors are antidepressant in animal models of depression. Three types of tachykinin receptors are differentially distributed in the CNS. Binding of agonists leads to rapid internalization and degradarion of receptors. Peptide and nonpeptide NK-1 receptor antagonists are useful tools for pharmacological research. Nonpeptide antagonists are under development and/or in clinical trials in all these areas.

SP is a pain neurotransmirter and excites dorsal horn neurons bearing synapses of nociceptive dorsal root ganglion neurons. SP-activated NK-1 receptors are concentrated in laminae I (65% of lamina I neurons bear NK-1 receptors) and H of the dorsal horn where primary nociceptors synapse. Dorsal rhizotomy leads to supersensitivity ro SP and increased expression of NK-1 receptors. Many dorsal root ganglion neurons express the peptide and the recepror. NK-2 and NK-3 receptors are found on dorsal horn neurons not afferenr fibers. NK-3 receptors increase in models of inflammation. Some evidence exists that SP modulates excitability of ventral horn neurons, and SP binding decreases dramatically with motor neuron loss in ALS models.

SP also enhances glutamate release in the hippocampus. This may explain its role in iniriation of status epilepticus triggered by dentate stimulation. Expression of preprotachykinin mRNA and SP arc increased after seizures, suggesting a role for SP in epileptogenesis. More than 50% of GABAergic neurons and more than 90% of NE-containing neurons of the locus ceruleus also contain SP. Some brainstem serotonin neurons also contain SP. These neurotransmitters play a role in disorders of mood and epilepsy.

Somaro statin

Somatostatin (SST) is a 14 amino acid peptide derived from rhe 92-residue product of the prcprosomatosratin gene. SST, a cyclic pepride, and its 28-residue cousin were first discovered in extracts of the hypothalamus. The name *somatostatin* was used because the extracts inhibited growrh hormone secretion. Hormonal functions of SST include growth regulation, inhibition of tumor growth, and modulation of endocrine and exocrine hormone release. Somarosratin has neurotransmitter and ncuromodularory functions in pain, epilepsy, sleep, cognition, and locomotion. Depolarizarion releases somatostatin from neurons. It colocalizes in some neurons with GABA. l'ive receptors (SSTl to 5) have been cloned that have differential distribution in the nervous system. Of these, SSTl and SST2 arc most studied for CNS effects. All five are negarively coupled to adenylate cyclase by Gi, although

there probably are splice variants coupled to phospholipid metabolism and excitation, e.g., SSTR2B. Electrophysiological evidence indicates G-dependent activation by SST-14 of hyperpolarizing potassium current (M type) and inhibition of voltage-dependent I.-type calcium current as mechanisms underlying inhibitory effects such as decreased glutamate release. SST-14 and -28 block potassium current and open i.-calcium channels. These excitatory effects probably involve increasing phospholipase C activity and intracellular calcium release. Correlation of these actions with receptor subtypes is incomplete. Somatostatin agonists reduce glutamate-activated but not GABA-activated currents by presynaptic inhibition employing SSTR1 receptors. SSTR2 receptors mediate reduction in depolarizing responses to applied glutamate. Some evidence exists of enhancement of responses of hippocampal neurons to ACh by SST.

Dorsal root ganglion neurons in laminae I and II of the dorsal horn contain SST receptors. SST in the superficial dorsal horn decreases with the induction of inflammatory arthritis in an animal model. Administration of SST into joint fluid reduces inflammatory pain of osteoarthritis and rheumatoid arthritis, probably by activating SSTR2 receptors on nociceptive afferents. Epidural or systemic administration of SST or a synthetic analogue, octreotide, relieves postoperative pain, opiate-resistant bone pain, and cancer pain. Thus interest is developing in producing SST analogues for use in the treatment of pain.

High-frequency neuronal activity releases SST. Seizures in experimental animal models enhance SST mRNA expression, whereas experimental status epileptic us decrease it through excitotoxic injury and loss of SST-containing neurons. SST-containing neurons also are fewer in temporal lobe specimens of patients with chronic medication-resistant epilepsy. Infusion of SST analogues blocked electrographic changes induced by excitatory amino acids. SST also has antiepileptogenic effects as injection of SST antibodies into the hippocampus facilitates kindling. Such observations have stimulated interest in development of SST analogues for the treatment of epilepsy.

Additional findings indicate a role of SST in other disorders. SST receptors change in some neurodegenerative diseases, such as Alzheimer's and Huntington's disease. Patients with mania, depression, and schizophrenia have altered CSF concentrations of SST. A few patients with panic attacks have benefited from SST administration. Clarification of the role of SST in these disorders is likely ro stimulate development of therapeutic analogues further.

Thyrotropin-Releasing Hormone

Thyrotropin-releasing hormone (TRH) is a tnpepride product of the preprothyrotropin releasing hormone gene. Two receptors have been cloned, TRHRl and TRHR2. The expression ot TRIIKI is extensive in limine structures. whereas the primary distribution of TRHR2 is in sensory areas. Intracellular calcium is rapidly mobilized by TRH binding to both receptors, which arc coupled to G_{tl}/n and activate phospholipase C. The calcium reduces inwardly rectifying potassium current allowing faster firing of action potentials. This action does not explain all of the actions of TRH. TR] 1 also reduces transcription of potassium channel genes and decreases the total cellular number of potassium channels. TRH probably reduces fast GABAergic IPSPs by a presynaptic mechanism. Furthermore, TRH increased the NMDA component of glutamate EPSPs. These effects should be excitatory. On the other hand, TRH inhibits voltage-gate calcium channels, activates calcium-dependent potassium channels, and has anticonvulsant effects that may depend on blockade of glutamate-stimulated uptake of calcium. These effects are inhibitory. Receptor specificity of these actions is not established, and it is difficult to conceive of a single unifying molecular mechanism for all of these actions. Recovery from traumatic brain and spinal cord injury in animal models was increased by TRH administration, indicating neuroprotective efficacy. In part, this may he due to elevations of kynurenine, a metabolite of tryptophan and a precursor of the NMDA antagonist kynurenic acid.

The basis of TRH use for depression is anecdotal observations. The proposed mechanism is inhibition of hyperactive glutamatergic neurons in frontal and subcortical limbic neurons. Such inhibition is the proposed mechanism of action of electroshock therapy, which also may increase TRH levels. TRH and the endogenous TRH-like tripeptide EEP produced antidepressant-like effects in an animal model of depression. EEP does not bind to TRH receptors and is processed from a different prohormone. Lithium modulates TRH and EEP levels in different brain regions and lithium withdrawal leads to marked elevations of both peptides. This suggests a role for TRH and TRH-like peptides in the antidepressant mechanisms of lithium. TRH also produces arousal in narcotized animals. The analeptic effect, without significant mood-stabilizing effects, has been documented in bipolar and schizophrenic patients.

Treatment of refractory epilepsy with TRH further illustrates the potential of using anticonvulsant neuropeptides as add-on therapy. Several small clinical trials demonstrated efficacy of TRH in the treatment of infantile spasms, Lennox-Gastaut syndrome, myoclonic seizures, and partial seizures with or without secondary generalization. No published placebo-controlled studies exist. Patients with infantile spasms, Lennox-Gastaut syndrome, and acquired immunodeficiency syndrome {AIDS) dementia have low CSF concentrations of kynurenic acid. TRH-induced elevation of kynurenic acid may be therapeutic in these illnesses. Interactions may occur with the pituitary - adrenocortical axis, especially ACTH, a known beneficial agent for infantile spasms. Evidence of anticonvulsant

effects of TRH in animal models supports the clinical data. TRH concentrations initially fall, perhaps resulting from ictal depletion, and then rise after kindled and clcctroshock-induccd seizures. EEP concentrations also rise. Prepro-rhyrotropin mRNA and receptor expression changes also increase after chemically and electrically induced seizures, perhaps representing compensatory or neuroprotective changes, lntrahippocampal TRH shortened after-discharge duration without major alterations of seizure stage in kindled animals. The chronic administration of a TRH analogue suppresses seizures and prolongs life in spontaneously epileptic rats.

Neuroprotective effects of TRH in vivo and in vitro suggest a possible role in preventing or ameliorating chronic pain by minimizing dorsal horn remodeling. A computer search failed to detect published studies of therapeutic trials of TRH for pain. Preclinical and small clinical studies of TRH for spinal cord injury have been promising, but no large clinical trials have been undertaken.

Vasoactive Intestinal Polypeptide

Vasoactive intestinal polypeptide (VIP) is a 28 amino acid polypeptide produced by a single VIP gene. Different genes encode the two receptors, VIP1 and VIP2. G_s positively couple both receptors to adenylate cyclase and raises cellular cAMP levels. VIPf receptors are concentrated in the hippocampus, olfactory bulb, and cortex. VIP2 receptors are highly expressed in the hippocampus, thalamus, and hypothalamus (especially the suprachiasmatic nucleus, which is involved in circadian rhythms}. Pineal content of VIP triples at night and, with NE, stimulates production and release of melatonin by stimulation of VIP1 receptors. Substituting aromatic amino acids at position 22 enhances the potency of agonists at VIP2 receptors and this leads to smooth muscle relaxing actions (bronchodilation, vasodilation). A third receptor activated primarily by pituitary adenylate cyclase-activating peptide (PACAP; a 38-residue peptide) also responds to VIP less potently. This receptor has five splice variants connected to cAMP and phospholipid metabolism. Its distribution overlaps that of the VIP receptors.

VIP plays important roles in neuronal development and survival. A VIP antagonist produced severe microcephaly in the mouse fetus. It protects against neuronal injury produced in vitro by glutamate, nitric oxide, nerve growth factor deficiency, HIV glycoprotein 120, and /j-amyloid in a mouse model of Alzheimer's disease. The mechanisms of these neuroprotective effects may include antagonism of nitric oxide toxicity by free radical scavenging, activation of cAMP response element-binding protein (CREB) that activates the antiapoptotic pro to-oncogene Bcl2, and inhibition of apoptosis-related caspases. It also has anti-inflammatory effects through inhibition of cytokine synthesis and regulation of inflammatory cells.

Highlighting the potential therapeutic importance of VIP in Alzheimer's disease is protection against /J-amyloid in vitro and in apolipoprotein E knockout mice. This has stimulated the development of lipophilic analogues of VIP that can cross the blood-brain barrier after oral administration. Low concentrations of VIP also protected against injury of cultured neurons by dopamine oxidation produces, suggesting a place for VIP agonist therapy in the treatment of Parkinson's disease. Unexplored is the potential for VIP-mediated neuroprotection to prevent remodeling of hippocampal circuits involved in kindling epileptogenesis and dorsal horn remodeling that produces allodynia.

VOLTAGE-GATED ION CHANNELS

The effects of neurotransmitters on membrane potentials contribute to patterns of action-potential firing and modulate neurotransmitter release by central neurons. G protein-mediated interactions with calcium or potassium channels mediate the actions of some neurotransmitters, such as ACh or serotonin. As the membrane potentials change under the influence of these neurotransmitter-gated ion channels, the likelihood of opening voltage-sensitive ion channels increases during EPSPs and decreases during IPSPs. EPSPs of sufficient amplitude to bring the membrane potential to threshold trigger action potentials. The upstroke of the action potential depends principally on the entry of sodium ions through voltage-activated sodium channels. In some instances, the influx of calcium through voltage-activated calcium channels contributes to the rising phase of the action potential. Conduction of sodium-dependent action potentials is along axons and causes depolarization of nerve terminals, triggering neurotransmitter release. Only calcium-dependent action potentials are identified in dendrites of central neurons. These action potentials probably serve to ensure the transmission of excitatory potentials on the distal dendrite to the soma and axon hillock where potentials sum to modulate axonal firing rates. Action-potential firing over the soma and down the axon couples the electrical output of the neuron to its biochemical machinery for the maintenance of the membrane potential and modulation of neurotransmitter release.

Largely, voltage-dependent calcium and potassium currents determine action-potential duration. Action-potential duration limits the maximal rate of firing. Calcium and potassium also generate after-potentials that modulate firing frequency and determine patterns of firing. Hyperpolarizing after-potentials slow firing, and depolarizing after-potentials increase firing.

Voltage changes in the nerve terminal modulate release of neurotransmitter. Action potential-induced depolarization of the terminals stimulates entry of calcium through voltage-dependent channels. The resultant slow depolarizing wave facilitates fusion of neurotransmitter-containing

vesicles with the releasing zone of the terminal and subsequent exocytosis of the neurotransmitter.

Activation of voltage-dependent chloride channels affords rapid entry of chloride ions, which increases the rate of action potential repolarization. The contribution of chloride ions to early repolarization is particularly evident in the action potentials of cardiac Purkinje fibers and skeletal muscle fibers.

Information encoded in the pattern and frequency of action potential firing is critical for the projection of activiry from one brain region to another along selectively activated pathways subserving specific functions. Myelination of central and some peripheral nerve fibers increases the fidelity and security of action potential firing and conduction over long distances. The brain operates in the millisecond timeframe. Brief (l-2msec) action potentials, high-velocity propagation along short myelinated fibers, and neurotransmission requiring less than a millisecond confer this property. Mutations associated with each of the voltage-sensitive ion channels have been associated with clinical disorders (Table 49.11). Discussion of these mutations is in Chapter 69.

Sodium Cliannels

Sodium Channel Structure

Voltage-gated sodium channels are glycosylated proteins with a molecular weight in the range of 230-270 kD. Channels from both sources consist of 1800 to 2000 amino acid a-subunits. The a-subunit seems to contain sequences conferring most of the known electrophysiological and pharmacological properties of these channels. Cloning techniques identified multiple isoforms of a-subunits. Functional diversity is less apparent and determined primarily by pharmacological and elecrrophysiological Techniques. In the rat brain, however, auxiliary $1- and j82-subunits exist with molecular weights ranging from 33,000-36,000 kD. These contain approximately 200 amino acid sequences that are not covalently bound to the £i-subunit. The /3-subunit of skeletal muscle is slightly larger but has properties similar to those of the brain ^-subunits. The j3-subunits probably modulate the rate of sodium channel inactivation (spontaneous closure) and possibly the voltage-dependence of activation of the channels.

Molecular pharmacology has identified sequences in the sodium channel that account for various functional features (see Figure 49.1C). Sequencing of the or-subunit suggests that both the amino and car boxy sequences are intracellular. The core sequence consisrs of four domains of six hydrophobic transmembrane sequences. Their connection is by intracellular and extracellular peptide loops. These domains are roughly analogous to subunits of neurotransmitter-gated receptors, but their linkage is covalent. They surround a central channel that allows passage of sodium and other ions of similar size on opening. The extracellular loop connecting the fifth and sixth transmembrane sequences of each domain is longer than the other extracellular loops. In the first domain, this loop is glycosylated. Intracellular loops connecting the sixth transmembrane segment of the first domain to the first transmembrane segment of the second domain is very long and contains many sites for modulation by phosphorylation. The intracellular loop connecting the third and fourth domains is relatively short. This loop seems to be responsible for the inactivation characteristics of the sodium channel. Phosphorylation of this loop by protein kinase C slows inactivation of the channel and links channel phosphorylation to activation of G proteins coupled to the cascade-activating protein kinase C. Binding of tctrodotoxin, isolated from the ovaries of the puffer fish of the genus *Tetradon*, depends on negatively charged residues in the extracellular loop linking the fifth and sixth transmembrane segments of each domain. The fourth transmembrane segments of each domain contain positively charged amino acid residues, which probably constitute the voltage sensor. Fither in response to electrical stimulation or ncurotransmitter-mediated changes in ionic conductance, voltage changes electrophorese these charged residues. The latter results in conformational changes in these segments and in relationship to other transmembrane segments in each domain of the sodium channel. The result is transitory opening of the sodium channel, with sodium entry until the kinetically slower inactivation process occurs.

Channel Function and Pharmacology

Flectrophysiological refinements from patch-clamp experiments and the molecular characterization of the channel have led to a well-focused picture of how sodium channels behave, singly and in concert. Sodium influx through voltage-sensitive channels generares the upstroke of action potentials recorded from axons and somata of central neurons. In the Hodgkin and Huxley model, channels may be in the resting, activated (conducting), or inactive configuration. With depolarization, available resting channels open quickly and nearly synchronously, and they admit sodium ions flowing inward along their concentration gradient. If this influx generates enough current, it triggers the action potential. The channels inactivate spontaneously as slower conformational changes close the inner mouths of the channels. Gradual repriming, or recovery from the inactive to the resting conformation, occurs after repolarization. The interval between spikes is largely determined by the number of available channels contributing to the next action potential. This confers rate-dependence. **The** transmembrane voltage confers voltage-dependence. At high frequencies (>150 Hz), the rate of cycling may not be fast enough for sufficient channels to rcprimc. The result is that sodium current \-^3 and maximal rate of rise of action

Tabic 49.11: Clinical disorders associated with mutations of voltage-sensitive ion channels (channeloparhics}

	Gene, *channel component affected*	*Disorder(s)*	*Comments*
Sodium channels			
	SCN1A, SCN4A, and *SCNSA* genes for different ot-subunits	Generalised epilepsy and febrile seizures plus Hyperkalemie and hypokalemic periodic paralysis Paramyotonia congenita Mi oronic conditions Long QT syndrome	Mutations involve different ff-subunits with a variety of substitutions and deletions
	SCN1B gene for 0-suminit	Generalized epilepsy and febrile seizures plus	
Calcium channels			
	Multiple CACN genes for or-subunits	Kpisodit ataxia type *1* (P/Q channels) Spinocerebellar ataxia type 6 (P/Q channels) Hypokalemic periodic paralysis (L channels) Familial hemiplegic migraine (P/Q channels) Malignant hyperthermia susceptibility (L channel) Incomplete X-linked congenital stationary night blindness (L channel)	Various mutations ol same or different types of a-subunits associated with different disorders
	CACNA2D1 gene for ^-suhunit	Malignant hyperthermia susceptibility Murine generalized spike-wave absence	
	CACNAB4 for 04-subunit	Idiopathic generalized epilepsy Murine generalized spike-wave absence	
	RYRl for ryanodine receptor	Malignant hyperthermia syndrome *+1*— central core disease Central core disease	
Potassium channels			
	KCN1A gene affecting Kv	Episodic ataxia -Im-partial epilepsy Isaac's syndrome (neuro myotonia)	Reduced Kv prolongs action porention dtiration and sodium current leading to hyperexcitability
	KCM2) gene affecting Kir2.1 of-subunit	Anderson's syndrome (defects of bone development, periodic paralysis and cardiac arrhythmia)	Mutation results in loss of stabilization of resting potential by G-protein activated inward rectifier
	KCNQ2 and *KCNQ3* genes	Familial benign neonatal convulsions	Reduce inhibitory M current
	Kcnal	Murine tonic-clonic seizures	Reduced Ca^{2}"*-sensitive potassium current causes loss of inhibitory after-hype rpolari/ations
Chloride channels			
	Cl.CNl	Myotonia congenita, autosomal dominant Myotonia congenita, autosomal recessive	F.ach disorder is associated with a variery of differenr substitutions and intron mutations

potentials (V_{ma}J decrease at fast rates. Although kinetic parameters vary, all voltage-sensitive ion channels must go through a similar operational cycle. Kinetic models of drug interaction with different aspects of sodium channel function have had an important impact on antiepileptic and antiarrhythmic drug development.

Several standard antiepileptic medications bind to sodium channels. 'This results in accumulation of sodium channels in the inactivated state, prolongation of refractoriness, and failure of some action potentials. At concentrations that correspond to therapeutic free-plasma levels, phenytoin, carbamazepine, and valproic acid limit sustained

high-frequency repetitive firing (SRF) of sodium-dependent action potentials involved in the spread of ictal activity. Some of the new antiepilcptic medications may also block sodium channels. Progressive reduction of V_{max} before action potential failure suggests an effect on sodium channels, although potassium and calcium currents could he involved. This effect on sodium channels parallels the ability of these compounds to protect against tonic hind-limb extension in the maximal elcctroshock model in animals. It may also contribute to clinical efficacy against partial seizures with or without secondary tonic-clonic generalization. Other compounds, including local anesthetics, verapamil, and tricyclic antidepressants, act at voltage-sensitive sodium channels hut are not useful clinically as anticpilcptics.

The effect of standard anticonvulsant drugs on sodium channels has several important characteristics. First, its effect is concentration-dependent, as expected from the clinical definition of therapeutic range. Second, the effect is voltage-dependent. At very negative transmembrane potentials, drugs bind to a small percentage of sodium channels with some reduction of sodium current or action potential rate of rise (tonic block). With depolarization, such as occurs at the ictal transition, drug binding becomes more likely and blockade accrues more quickly. Third, the effect on sodium channels is use-dependent, requiring multiple activations of sodium currents or firings of action potentials to become maximal. It is also frequency-dependent. Fast rates and less-negative membrane potentials enhance the blocks, which occur at the depolarizing shift signaling the ictal transition. Channels to which drug is bound are effectively unavailable to contribute the next action potential. Firing at slower rates is possible despite the continuing presence of the drug. Therefore anticonvulsant drugs with this action modulate rather than block sodium channel function.

How does this relate to clinical anticonvulsant effects? Ideally, concentration-dependence *in vitro* should predict the therapeutic range. Limitation of SRF by phenytoin, for example, occurs at concentrations equivalent to therapeutic free-plasma (i.e., not bound to plasma proteins) levels. Brain-tissue levels increase with time. Slow accumulation in brain may account for gradual improvement in efficacy on a constant dose of an anticonvulsant drug. Alternatively, an active metabolite may accumulate and add to the efficacy of the parent compound. For example, carbamazepine epoxide and the trans-2-en metabolite of valproic acid both limit high-frequency firing and accumulate in the brain and CSF. High-frequency action potentials fire along projection pathways from a chemically induced cortical focus. This firing pattern underlies the spread of abnormal activity from the seizure focus. Extrapolating from the cellular data, limitation of high-frequency action potential firing should prevent seizure spread. However, brief bursts of fast firing or firing sustained at slower rates are not blocked. This could explain refractoriness of some seizures to sodium channel-blocking medications.

Voltage-dependence may explain why ambulatory patients tolerate sodium channel blocking antiepilcptic medications chronically, with minimal dysfunction. Intcrictally, the patient may function almost as if the drug were **not** present. However, when abnormal focal activity commences with prolonged depolarization, drug action becomes more effective and limits high-frequency firing responsible for the spread of seizures. Frequency-dependence allows the use of drugs as anticonvulsants. Excessive sodium channels blockade may occur because of a high concentration of one drug or pharmacodynamic interaction between two sodium channel blockers. Sedation, reduced motor speed, and impaired cognition result. In the extreme, compounds that bind tightly and extensively to sodium channels, such as tetrodotoxin, are lethal. Therefore the same cellular action may be relevant to both therapeutic efficacy and toxicity.

Nociceptive fibers of peripheral nerve have tetrodotoxin-resistant sodium channels. Lidocaine blocks these more severely than the classic tetrodotoxin-sensitive, kinetically fast sodium channel of the CNS and mechanoceptive fibers. This exemplifies the functional diversity of sodium channels.

Point mutations in the gene on human chromosome 17q encoding the skeletal muscle sodium channel are the basis for some human channelopathies. These include hyperkalemic periodic paralysis and paramyotonia congenita. These disorders result in muscle paralysis and myotonia resulting from disorders of sodium channel inactivation. Some families with paramyotonia congenita have point mutations leading to a single amino acid change in the voltage-sensing fourth transmembrane sequence.

Calcium Channels

Pharmacological and electrophysiological characteristics of four distinct calcium channels are established, T, L, N, and P are the assigned names. The L and N types have been cloned. This suggests that greater molecular diversity exists than has been discovered functionally. Calcium channels are evolutionary descendants of, and share 50% homology with, sodium channels, primarily in the transmembrane regions. This structural similarity may account for the fact that some classes of compounds, such as hydantoins and calcium-entry blockers, bind to both sodium channels and calcium channels. Significant differences in the intracellular linkers between transmembrane domains are likely to account for the unique regulation and function of calcium channels. A long intracellular carboxy terminus of the L channel contains a sequence to which calcium must bind before dihydropyridines such as nifedipine or nimodipine can produce their pharmacological block. The intracellular loop connecting the second and third transmembrane domain of L-type channels in muscle T-tubules may be the voltage sensor signaling calcium release from sarcoplasmic reticulum in muscle. This loop differs in neuronal L-type

channels. By analogy to the sodium channel, the fourth transmembrane sequence of each domain contains multiple positively charged lysine and argmine residues, which appear to confer voltage sensitivity on channel opening.

The operating cycle of calcium channels is similar to that of the sodium channel and involves changing from resting to conducting and inactivated conformations. Frequency or use-dependence of blockade by certain drugs is crucial for calcium channels as well as sodium channels. A good example is use-dependent block of L channels by dihydropyridines. This feature confers activity-dependence on the effect of the drug and suggests the drug may be present with minimal effects at low activity levels.

Physiology and Pharmacology of Calcium Channels

Slight depolarization from rest may activate low-threshold T-type channels, which open briefly and inactivate relatively quickly. These channels probably underlie oscillatory behavior, which confers burst firing properties on neurons. As the membrane depolarizes sufficiently, the high-threshold types of calcium channels, namely L, N, and P, open. The opening of P-type channels is implicated in the production of dendritic calcium spikes, which propagate to the soma. Here, depolarization to threshold results in firing of sodium-dependent action potentials over the somatic membrane and axon hillock. Although sodium-dependent action potential firing accounts for propagation along axons, neurotransmitter release depends on the admission of calcium into the terminals through voltage-dependent calcium channels. Neurotransmitter release depends at least on N-type channel activation and probably also on activation of P-type channels. The peptide f3-conotoxin isolated from predatory cone snails selectively blocks the N-type channels. S-agatoxin, isolated from spider venom, blocks the P-type channels. Under some conditions, dihydropyridine-sensitivc L-type channels may be involved in transmitter release. However, transmission in most experimental paradigms is unaffected by dihydropyridines. In the experimental paradigm known as post-tetanic potentiation, a nerve is stimulated at high frequency. Following the tetanus, a single stimulus produces a markedly enhanced postsynaptic excitatory response. Fnhanced neurotransmitter release is responsible for the phenomenon, because of calcium accumulation in nerve terminals with repetitive activation. Phenytoin, which blocks both sodium channels and L-type calcium channels, inhibits post-tetanic potentiation.

Oscillatory activity appears to be important in both normal and abnormal activity of thalamic neurons. Low voltage-activated T-typc calcium channels appear to underlie this activity. Ethosuximide and dimethadionc, drugs used for absence epilepsy, block T-typc current at therapeutically relevant concentrations, but phenytoin and carbamazepinc do not. This difference may explain in part, the different efficacy of antiepileptic drugs. The broad-spectrum antiepileptic drug, valproic acid, blocks the T-type current only slightly at high concentrations in dorsal root ganglion neurons, but not in thalamic or human neocortical neurons. Ethosuximide does not block T-currcnt in human cortical neurons, suggesting regional and species differences in the pharmacology of this type of current.

Abnormalities of calcium channel operation underlie at least two disorders of muscle. In the Lambert-Faton myasthenic syndrome, plasma contains antibodies against synaptic voltage-sensitive calcium channels (see Chapter 84), F^xci tat ion -con traction coupling in skeletal muscle involves propagation of sodium action potentials along the sarcolemma, which excites voltage-sensitive calcium channels at the T-tubular triad. These are probably dihydropyridine-sensitive L-type channels. Calcium reuptake occurs through a second type of calcium channel, which ryanodine blocks. This is probably identical to the calcium channel activated by IP3 and subject to modulation by activation of phospholipase C. A point mutation in this channel is associated with malignant hyperthermia in swine and in some humans. The result of the mutation is that sarcoplasmic calcium concentrations remain elevated causing the myofibrillary lattice to remain contracted, Life-threatening heat production, rigidity, and muscle breakdown result.

Potassium Channels

Potassium channels share some structural features with other voltage-sensitive ion channels, including four subunit domains each with six transmembrane sequences. However, unlike sodium and calcium channels, the summits arc not covalcntly linked, and the polarity of the potassium channels is different. Potassium channel subunits are the most numerous and diverse of all voltage-sensitive ion channels. When the channels are opened, potassium ions move outward from the neuronal cytoplasm where the potassium concentration is high (approximately 140 mmol/1.) to the extracellular space where the potassium concentration is low (less than 5 mmol/L). Cloning of multiple potassium channels from a variety of species, especially *Drosophila,* has confirmed much of the behavior of the delayed rectifier channels responsible for action potential repolarization described by Hodgkin and Huxley. Other potassium channels responsible for oscillations in membrane potential and clamping of the membrane potential toward the resting level have also been characterized electrophysiologically and pharmacologically. Also, unlike sodium and calcium channels, the inactivation particle of the potassium channel is located at the end of the intracellular amino terminus and swings into the channel opened by voltage changes like a hall on the end oi a rope. Mutations in the pore-forming principal subunit of K channels are associated with benign neonatal familial convulsions.

The delayed rectifier channel, or K^R, initiates repolarization of the action potential. It turns on quickly with depolarization although not as quickly as the sodium current and is maximally active as the sodium current becomes inactivated. Persistence of potassium current after inactivation of the sodium current results in a hypcrpolarizing after-potential, which inactivates quickly and allows maximal firing rates in the range of several hundred per second. Mutation in K^R channels, so-called channelopathies, are associated with myokymia, episodic ataxia, and cardiac arrhythmias {long QT syndrome).

Depolarization, especially when it is prolonged in response to steady synaptic excitation, also activates the so-called A-current. This outward current hyperpolarizes the neuron and delays the onset of firing after a voltage change by driving the membrane potential away from threshold, back toward the resting potential. As the current inactivates, the membrane potential depolarizes to threshold, and firing commences.

A third potassium current, the M-current (IM)J is activated by depolarization. Activation of the IM opposes the tendency toward threshold and repetitive firing. A unique feature of this current is that it is not inactivating, and it causes depolarization to drift toward the resting potential. Neurotransmitters that block I_M, such as ACh or muscarine after which the I_M is named, promote increased firing frequencies. Normal excitation by multiple biogenic amine neurotransmitters involves blockade of KIR channels and calcium-dependent potassium conductances. M-current is carried by inwardly rectifying (KIR) channels connected by G proteins to the neurotransmitter receptors. Mutations in $K[_K$ channels can cause ataxia in mice. Mutations in ATP-sensitive $K_{[R}$ channels can result in salt-wasting (Bartton's syndrome). Modulation of these conductances may be important in the pathophysiology and control of epilepsy and in normal processes such as sleep,

Two calcium-dependent potassium channels contribute repolarizmg outward currents (IkCaj that are activated by depolarization. A kinetically fast I«Ca is activated with the delayed rectifier. A rise in intracellular free calcium resulting from transmembrane influx or release from intracellular stores is essential for activation of this current. A kinetically slower \&*Ca*, I^HP; contributes a slow component to the after-hyperpolarization. Tctraethylammonium blocks fast I_KCa more potently than it blocks IAHP. Other antagonists, such as apamin (extracted from the venom of the honeybee), charybdotoxin (a peptide toxin in scorpion venom), curare, and barium act preferentially on I A W

Hippocampal pyramidal neurons have all of these outward potassium channels. The overlap of function is insurance against sustained depolarization. In addition, these neurons have an inward potassium current (1Q) activated by hyperpolarization that causes the membrane potential to drift back toward the resting potential. This particular current probahly prevents reduction of spiking capacity by excessive hyperpolarization.

As important as potassium channel activity is in determining firing patterns and frequency, relatively little is known about the effects of medications on potassium channels. Perhaps the best example of modulation of potassium channels to control neurological disease is the use of aminopyridines and guanidine to treat the myasthenic syndrome and in some cases myasthenia gravis. Two aminopyridines, 4-aminopyridine and 3,4-diaminopyridine, have been used clinically. They are presumed to act by blocking potassium channels in nerve terminals to can si[1] depolarization, entry of calcium, and enhanced neurotransmitter release. Guanidine, which probably sensitizes nerve terminals to calcium in a similar manner, has been used in the treatment of these disorders and botulism. The availability of therapeutic agents to modulate potassium channel activity might be very useful in the treatment of epilepsy.

Chloride Channels

Multiple chloride channels are being discovered by cloning techniques. Nonetheless, our understanding of the role ⊳t voltage-dependent chloride channels in the brain **lags** behind that of the cationic channels already described. Chloride ions are involved in regulation of cell volume and must move to maintain charge neutrality when cations enter. Without electroneutrality, osmotic shifts would occur, and neurons would swell or shrink, depending on activity levels. The balance is accomplished through a leak channel. Neurons have a relatively low resting conductance to chloride. However, the chloride conductance in fast-twitch muscle at rest is high. In addition to the high leak conductance to chloride, a voltage-activated chloride channel or current contributes to sharp repolarization of action potentials in skeletal muscles. Experimentally, blockade of this current by aromatic monocarboxylic acids or zinc results in repetitive firing of action potentials in addition to a very slow repolarizing phase. This situation is mimicked in myotonic goats and in humans with myotonia congenita, an autosomal dominant disease with a mutation on chromosome 7q in the region of the skeletal muscle chloride-channel gene. With increased understanding of voltage-sensitive chloride channels, the development of therapeutic agents that activate chloride channels and repolarize muscle may be possible.

Cystic fibrosis is also associated with abnormal pulmonary chloride channels, resulting from single-gene mutation on the long arm of human chromosome 7q. Gene therapy for this illness is in the pioneering stages.

PRINCIPLES OF THERAPEUTICS

The art of administering medications is a complex product of the therapeutic alliance between a patient and the

physician and the availability of safe and effective medications. Ethical pharmaceutical companies coordinate the need for new medications with internal programs for identifying and testing candidate compounds at their own expense. Discovery programs are usually directed toward finding novel medications for a particular condition. Compounds are chosen based on efficacy and lack of significant toxicity in appropriate animal models. Compounds that emerge from these targeted programs were categorized by the use for which they were discovered historically. However, recognition of multiple uses after approval has resulted in a tendency toward testing for multiple uses during the preapproval phase of testing. Proof of efficacy and safety is the basis of regulatory approval. This establishes the claims that can be supported in the package insert. Meeting these criteria for multiple applications affords the company maximal exclusivity under patent protection after approval. Once a compound is identified, human clinical trials are designed in collaboration with regulatory agencies—the FDA in the United States. Ethical considerations are important in determining who should be admitted to the studies. This often results in the inclusion of adults with conditions refractory to available alternatives. The paramount concern for safety has resulted in the exclusion of children and women of child-bearing potential from many studies. As a result, guidelines for the use of many new medications are limited and drugs become used in these populations after approval despite the lack of specific indications. Many FDA-approved medications are prescribed for "off-label" uses. Some physicians adhere rigorously to approved uses, whereas others use familiar medications for alternative uses. This can have medicolegal implications.

Study designs result from collaboration between regulatory agencies and companies. In the United States, approval for marketing requires by law that the investigational compound is safe and superior to anorher treatment (usually a placebo or a low dose of a drug). This requires statistically significant outcomes. Recent changes in FDA regulations have made evaluation of devices more like that of pharmaceuticals. Clinical trials for regulatory review are conducted in three phases. Phase I studies determine pharmacokinetics of drugs, parameters for devices, and methodologies for procedures. Freedom from acute toxicity can also be assessed. Dose ranging during phase II studies provides the first information about efficacy and continues assessment of the safety of the compound. Based on these pilot studies, doses are chosen for the rigorous company-sponsored studies of phase III studies. Inclusion of subjects in such studies is always voluntary. Informed consent is an absolute entry criterion and study subjects may leave the trials at any time and for any reason. Approval of the study-protocol by rhe institutional review board for safety of human subjects at each participating institution is also required. Investigators may be at university medical centers or in private practice.

Study design is important in obtaining interpretable data. Inappropriate designs or choice of doses may result in an uninformative study. Inclusion and exclusion criteria ensure inclusion of subjects with accurate diagnoses. These criteria are important for selecting as homogeneous a study population as possible so that interindividual variation does not prevent an interpretable outcome. Sample size is predetermined by statistical power analysis so that sufficient data can be obtained to arrive at valid conclusions. Several hundred patients may be included in a placebo-controlled study. Study protocols include escape criteria for removal of patients from the study at the discretion of the investigators because of concerns about safety and noncompliance. Multicenter, double-blind, placebo-controlled trials are common, but details of the design are tailored to test the features under study. A baseline period allows determination of the frequency and severity of symptoms while the patient takes a constant amount of conventional medication before beginning the investigational compound. Well-defined clinical endpoints or outcome measures are predetermined so that appropriate assessments of efficacy and adverse events (side effects and systemic toxicities) can be obtained at repeated intervals throughout the blinded period and open-label extensions. The duration of the blinded observation period may be only a few months. This and the sample size limit the ability to assess long-term safety. For example, toxicities with an incidence of I in 2000-5000 may not be observed in the course of the preapproval studies. In the case of felbatol, aplastic anemia in this range of incidence was not detected until more than 100,000 individuals had been exposed to the drug. Assessments by the study subject and investigator of impact of the novel treatment on quality of life are often included. The investigator and the company are accountable for all participants and their safety and for quality control of data relating to efficacy and treatment-emergent adverse effects. Because these studies typically require rigid assignments to placebo or active medication and to a specific dose and titration schedule, practical knowledge of how to use the medication after approval may be lacking. Postapproval (phase IV) studies are sometimes conducted to extend knowledge of safety, tolerability, and efficacy. Phase IV studies may be open-label studies to learn how to optimize use of the new medication on an individual basis. Postmarketing surveillance is not regulated by law in the United States. It depends, in large part, on the reporting of adverse event to the company and FDA by treating physicians.

The treating physician must diagnose a condition correctly, select the most effective remedy, and teach the patient how to self-administer the medicine. Responsibility does not end with a prescription. Physician-patient contact must occur at intervals to confirm the diagnostic impression, determine the efficacy of treatment, and assess dose-related and idiosyncratic adverse reactions. The patient must be motivated to rake medications

as prescribed, often several times a day. Compliance depends on confidence in the physician, understanding of the disease process, a sense that the medicine is beneficial and tolerable, and a dosage regimen that is consistent with the individual's lifestyle. These factors comprise what can be called acceptability of the medication to the patient.

Desirable Properties of Medications

Anticonvulsant drugs exemplify what is good, bad, and acceptable in the development and use of pharmaceuticals. Their properties are reviewed in the framework of pharmacokinetic and pharmacodynamic principles that enter into the bedside decision-ma king process.

1. The selected medication must be appropriate for the disease. In the example of anticonvulsants, this means making a correct seizure diagnosis and selecting a medication with a clinical spectrum of efficacy that includes the specific seizure type. Some anticonvulsants are effective against partial seizures with or without secondary generalization; others are effective against primary generalized seizures such as generalized absence; and a few, such as valproate, have a broad spectrum of activity against partial seizures and both primary and secondary generalized seizures.
2. Knowledge of the therapeutic index and mechanism of action simplify drug selection. The therapeutic index is a ratio of the toxic dose to a measure of a therapeutically relevant dose. In practice, it equates to the ratio of the blood concentration at which limiting side effects appear, usually the top of the therapeutic range, to a minimally effective dose, the bottom of the therapeutic range. Potency may not be the most desirable property of anticonvulsants, and a drug with greater potency may have a lower therapeutic index. To some degree potency is a trade-off against therapeutic index. A drug with a very large therapeutic index may actually encompass several therapeutic ranges, which can be tailored to the severity of the seizure disorder.
3. A broad spectrum of clinical efficacy seems a desirable characteristic in anticonvulsant drugs. However, broad spectrum implies multiple mechanisms of action, some of which may actually contribute to toxicity in a given seizure disorder or individual. A reductionist corollary of this reasoning is that a compound requires the least number of actions to treat effectively a specific disorder should be used.

Preparations

Several factors determine if a compound is user-friendly for the patient and the physician. Ease of use ensures compliance but not efficacy. The following factors contribute to case of use:

1. Dosage forms that allow graduated dosing throughout the therapeutic range of the medication
2. Easy-to-swallow capsules or rablets and a liquid preparation for children, the aged, and the debilitated
3. Once- or twice-a-day dosing to avoid taking medicine at school or work
4. Parenteral preparations for unconscious patients and for emergency situations such as status epilepticus

Bioavailability

Bioavailability is the amount of a dose that enters the body. In practice, it is determined as the peak plasma level after oral ingestion divided by the peak after intravenous administration. Currently used anticonvulsant drugs are freely available after oral ingestion. Bioavailability of some compounds is dose-related and may decrease with increasing dosages. Nonetheless, blood levels rise, although less than expected, with dose increments. This implies that above a certain practical limit, further dosage increments will not raise the plasma level sufficiently to justify the cost of the higher dose. Bioavailability may be limited by an uptake mechanism. Optimal dosing requires knowledge of compounds that interfere with or augment uptake and the effects of food.

Titration Rate

Ideally, a therapeutic concentration should be present in the blood and brain as soon as possible after starting a new drug. In practice, this means that a loading dose can be given or that the titration rate should be fast. Loading doses can be given in urgent situations, such as frequent seizures with physical harm to the patient or status epilepticus.

A loading dose is a large dose, usually administered intravenously or by mouth that brings the plasma level into a therapeutically effective range after one or a few administrations. Loading doses cannot be given with many drugs because of limiting adverse effects or because parenteral preparations arc noi available-.

The titration rate is the speed at which dose increments can be made, and it is an inverse function of the elimination, or half-life, of the medication. A steady state should be reached before conclusions are drawn about the results of a dose increase and a decision about further increments is made. Steady state is reached in five half-lives after initiation of therapy or a dose increment. Further increments before achieving steady state may result in overdose, increased adverse effects, and even more seizures. Multiple doses smooth the oscillations in blood level between doses. The maximum tolerable daily dose may be increased by dividing the dose further. Thus

toxic effects encountered by giving a 1-g dose twice daily may be eliminated by giving the same drug 600 mg four times daily. Seizure control may improve at the higher dose.

Distribution

Drug distribution is commonly discussed in terms of volume of distribution and binding to plasma proteins. The volume of distribution is a virtual number; it can be computed as the amount of drug injected into the body divided by the plasma concentration. This value, in liters, is the fluid volume necessary to dilute the total amount of drug injected to the concentration found in plasma. It is affected by the degree of binding to plasma protein, hydrophobicity of the compound (its partition coefficient in fat), regional blood flow, and other physical factors. The volume of distribution is often reported as the computed volume divided by body weight in kilograms. A low volume of distribution of about 0.15 L/kg suggests distribution only within the vascular compartment, which consists of about 5,5 L total blood volume and 3 L of plasma in a normal 70-kg man. A value of 0.15 to 0.50 L/kg suggests distribution throughout extracellular fluid, which is about 12 L in the average man. Values of 0.5 to 0.6 L/kg indicate that the drug is distributed throughout total body water. Assuming no regional selectivity, total body water is a volume of about 42 L in a 70-kg man. Values in excess of 0.6 L/kg suggest that the drug is concentrated other than in body water at concentrations higher than those found in the **plasma.** This would be particularly true for highly lipophilic compounds, such as phenytoin, and compounds that are actively accumulated in the CNS, such as gabapentin.

Lipophilic compounds are bound significantly to plasma proteins (e.g., albumin). This may be a site for competition with other lipophilic compounds. Use of water-soluble compounds (e.g., gabapentin) avoids the potential for such interactions among drugs,

Biotransformation

The body metabolizes drugs to rid itself of them, as it would many harmful exogenous chemicals. In the case of highly lipid-soluble drugs such as phenytoin, carbamazepine, and valproic acid metabolism in the liver results in multiple metabolites, some of which are sufficiently water-soluble to be excreted efficiently by the kidney. To accomplish this, the liver uses four fundamental types of reactions: oxidation, reduction, hydrolysis, and conjugation. The first three reactions produce hydroxy!, carboxylic acid, and amine groups, which are polar. This is phase I of enzymatic catalysis in the liver. This step generally results in reduced activity of the metabolites, However, active metabolites are produced from caibamazepine and valproic acid (carbamazepine epoxide and *tratts-2-en* valproic acid). The active metabolites are subsequently modified to more water-soluble compounds for elimination.

In phase II, the polar groups are coupled to endogenous compounds such as glucuronic or acetic acid or inorganic sulfate to produce water-soluble conjugates. Most conjugates are inactive and are excreted in the urine or bile. We generally think of these reactions as taking place in the liver, but microsomal and cytosohc enzymes in other organs, including the brain, may actually metabolize drugs to some extent.

Ultimately, biotransformation accomplishes two tasks inactivation of exogenous chemical substances and their modification for elimination. The capacity of the body to transform drugs determines, m large part, the interval between subsequent doses required to sustain a therapeutic level. The standard antiepileptic medications are metabolized to varying degrees; gabapentin and vigatrim are not metabolized at all.

Pbarmacogen etics

Pharmacogenetics is the study of variations in rates and patterns of drug metabolism. Awareness of such variations is crucial in optimizing therapy for the individual patient. Phenytoin provides one of the best and earliest examples of pharmacogenetic variation. Variation of parahydroxylation of phenytoin results in variable nonlinearity of the relationship between oral dose and steady-state plasma concentrations of phenytoin. This is manifest as the well-known zero-order kinetic curve. The phenytoin blood level rises linearly, up to **a** break point above which a slight dose change causes a very large increase in plasma phenytoin concentration. The break point varies from individual to individual and with age. The elderly-experience this effect at lower doses than children. The break point represents saturation of the liver's capacity to metabolize phenytoin to the parahydroxy derivative. To a large extent, this phenomenon was responsible for the invention of therapeutic blood-level monitoring and for the evolution of models based on Mic ha el is -Me men kinetics to pharmacokinetically optimize dosing in individuals taking phenytoin.

The half-life of phenytoin is longer in slow hydroxylators, who achieve higher concentrations at lower doses than patients who are fast hydroxylators. Slow hydroxylation is an autosomal recessive trait that appears in about 1 in 500 individuals. In practice, unfortunately, these individuals are identified only empirically.

Predisposition to hepatotoxicity resulting from phenytoin is probably inherited as a genetic polymorphism, Patients with elevated liver enzymes during phenytoin therapy proved to be slow acetylators. Isoniazid is a noncompetitive inhibitor of phenytoin hydroxylation. Inhibiting phenytoin metabolism may result in toxic drug levels and hepatic injury resulting from effects on other liver en/ymes,

Drug Interactions. Interactions resulting from effects of concomitant medications on the metabolism of standard antiepileptic medications are among the most frequent problems complicating drug therapy of epilepsy. Addition of a second medication may increase, decrease, or not affect the plasma concentration of the first anticpilcptic medication. Phenytoin and carbamazepine induce hepatic microsomal enzymes of the P-450 system, which augment the metabolism of other antiepilepties and decrease their levels. These metabolic interactions may reduce efficacy of oral contraceptives by enhancing metabolism. Valproic acid, on the other hand, inhibits metabolism of other antiepilepties and may cause significant elevations in their concentration. Gabapentin and vigabatrin are not metabolized and do not alter metabolism of other antiepileptic drugs or oral contraceptives. Blood levels of these two amino acids are not affected by addition of other drugs. Use of medications without drug-drug interactions at the level of metabolism is desirable, bur optimal ust- of standard antiepilepties requires knowledge of these interactions and the art of miiiimi/,ing their consequences.

Physiological Variation

Several factors influence the rate of drug metabolism. Phenobarbital levels have been reported to be higher in males than in females, suggesting slower metabolism in the males. Whether this is due to induction of liver enzymes by female sex hormones or other factors is unclear. The rate of drug oxidation is higher in elderly men than women. Pregnancy introduces several variables. These include changes in steroidal hormones, a rise in body temperature, alteration in volume of distribution and reduced drug binding to plasma proteins, increased blood flow and rate of delivery of drug to the liver, and drug metabolism by the placenta.

Circadian variation in metabolic rates and gastric emptying may significantly alter drug disposition. Plasma-free fractions of phenytoin and valproate have been shown to vary throughout the day and in response to urinary pH changes, suggesting that the ionized fraction of drugs such as phenytoin may change and affect blood levels no matter how slightly. Awareness of these factors is increasing as studies of chronopharmacokinctics evolve.

Developmental factors also affect metabolic rates. Newborns generally have slower phase I reactions than adults, but the rate increases to a peak over several years and may exceed the adult metabolic capacity in older children. One of the best examples of this is difficulty of sustaining a significant blood level of phenytoin in children who often require very large doses. In general children in the range of 1-6 years of age require larger doses on a milligram per kilogram basis than adults to achieve therapeutic levels of phenytoin, carbamazepine, ethosuximide, and valproic acid. The effect of developmental factors on metabolism of novel antiepileptic medications has not yet been reported. Among the elderly, phase I reactions are much slower than in early adulthood. On the other hand, conjugation reactions arc not significantly different.

Elimination

Drug elimination is really a two-step process of biotransformation and excretion from the hody. One of the most important parameters guiding dosage adjustment and dosage intervals is the elimination half-life. After oral or intravenous administration, the plasma level of a drug rises to a maximum, then begins to fall. A curve describing plasma concentration against time after administration can be described by one or more exponential components. The elimination half-life is approximated by assessing the time required for the blood level to fall to 50% of the peak blood level. Clinically, this is very useful in determining the time to reach a steady state. In multiple dosing situations typically encountered in the treatment of epilepsy, the drug concentration in plasma (and at its receptor sites) will rise in a stepwise manner with successive doses after initiation or a change in dose. This process will continue until drug elimination matches drug delivery. This situation defines the steady state. A practical rule of thumb is that five half-lives are required to achieve a steady state after drug initiation or a dose change. Changing doses before achieving the steady state obfuscates evaluation of the effect of a dose change; hence the dictum that time should be allowed for steady state to be achieved before contemplating an additional dose change. Dosing intervals are greater for drugs with longer half-lives.

Half-life may vary with chronic dosing. This is particularly true of carbamazepine, which undergoes the process known as autoinduction of metabolism. After an initial steady state is achieved during the first week of therapy, the half-life may be as long as 24 hours. However, after an average of 1-2 months, hepatic enzyme metabolizing capacity increases, and the plasma level falls despite a constant medication regimen. Autoinduction of other standard antiepileptic medications is not significant.

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Chapter 50
Principles of Pain Management

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NOCICEPTION

The management of pain requires a complete understanding of the afferent pathways that serve nociception. The localizing value of sensory deficits caused by disorders of the petipheral nerves and spinothalamic tracts has been appreciated for more than a century. Primary involvement of these tracts in conveying pain signals has been a fundamental element in the understanding of pain for over 100 years. In the last 30 years a more detailed and dynamic model of nociception has emerged. This model incorporates (1) knowledge of the descending pathways that modulate pain transmission, (2) biochemical information about the neurotransmitters involved in the pain pathways, and (3) new insights into the pathological mechanisms that underlie changes in the nervous system in relation to injury or chronic stimulation that alters the function of nociceptive systems. This model also incorporates information about the interaction of primary nociceptive systems with othet neural systems (limbic, hypothalamic, and other systems) that gives rise to aspects of pain experience that are not primarily sensory. Better understanding and use of currently available pain control methods and the development of new treatments for pain are emerging as the model of neural mechanisms subserving pain evolves.

Receptors and Primary Afferents

Nociceptors are formed by the peripheral ramification of certain finely myelinated and unmyelinated afferent axons. Their morphology is relatively simple. The most common nociceptive receptors are bare nerve endings. Nociceptors are subcategorized by tissue distribution, tcsponse to various types of potentially noxious stimuli, threshold of response, and changes in activity in response to prior stimulation (e.g., sensitization). Nociceptors are found in skin, intramuscular connective tissue, blood vessels, periosteum, and most thoracic and abdominal viscera.

The afferent fibers that convey nociceptive information are small myelinated fibers with conduction velocities of 5-30 m per second (A fibers) and unmyelinated axons with conduction velocities of 0.5-2.0 m per second (C fibers). Nociceptive fibers account for 10% of the myelinated and 90% of the unmyelinated fibers in cutaneous nerves. Visceral afferent fibers at any spinal level represent a smaller percentage of the total afferent fibers and contain a higher proportion of unmyelinated fibers than do cutaneous afferent fibers.

Cutaneous nociceptors include (1) high-threshold mechanical nociceptors (HTMs) associated with small myelinated axons (A fibers), (2) myelinated mechanothermal nociceptors (MTs) {A fibers), and (3) polymodal nociceptors associated with unmyelinated axons (C fibers). HTMs respond only to intense mechanical stimuli, and their thresholds are many times higher than those of non-nociccptive mechanoreceptors. Stimulation of single afferent A nociceptive fibers causes a sharp, well-localized pain sensation. The intensity of the perceived pain is roughly proportional to the frequency of discharge. The threshold and rate of response of HTMs and MTs can be altered by thermal injury. These sensitizing effects may be involved in the development of hyperpathia. Polymodal nociceptors respond to mechanical, chemical, and thermal stimuli. Stimulation of nociceptive C fibers is associated with a dull, burning, or aching quality that is less well localized than A fiber stimulation. Unlike HTMs, repeated stimulation and thetmal stimuli do not produce sensitization of polymodal nociceptors, but local inflammatory responses to tissue injury do lead to sensitization.

The deep somatic nociceptors associated with muscle, tendons, fascia, jomts, and periosteum are largely free nerve endings with A and C fibers. The extensive plexus of fibers investing the periosteum and joints gives hone the lowest pain threshold of the deep tissues. The effects of sensitizing stimuli and the distribution of central terminals from deep somatic afferents differ considerably from cutaneous afferents. These differences result in the aching rather than sharp nature of deep somatic pain and in its less well-defined localization.

Visceral pain contributes greatly to the symptomatology of many medical and surgical disorders. Unfortunately, the physiology and pathophysiology of visceral nociception are less well studied than that of somatic nociception. Many viscera] afferents are involved in reflex autonomic regulation and do not serve a sensory function. The lack of sensation other than pain, perceived on stimulation of many viscera, is an important distinction between visceral and somatic, particularly cutaneous, sensation. When compared with skin, the intestine is remarkably insensitive to direct tissue damage, such as cutting or burning. Visceral nociceptive stimulation generally produces a poorly localized aching or spasmodic, cramping pain. The terminals of the visceral afferents in the spinal cord tend to be more widely distributed than are cutaneous afferent terminals, which contributes to the poorly localized character of the pain. Visceral pain often is accompanied by perception of pain arising in somatic structures that share the same spinal level of innervation. This phenomenon, known as *referred pain*, results from the convergence of nociceptive fibers from different structures onto the same population of cells in the dorsal horn.

Visceral nociceptors are free nerve endings without obvious architectural specialization. The majority are related to unmyelinated C fibers. Lightly myelinated fibers also contribute to the population of nociceptive visceral afferents, but the proportion of nociceptive A fibers is lower than in cutaneous nerves. The visceral nociceptive afferents are divided into two general categories, based on their characteristics of activation. HTMs in many viscera function specifically as nociceptors and respond to distention or changes in intraluminal pressure. In addition, low-threshold receptors respond in a graded fashion, in proportion to stimulus intensities ranging from innocuous to noxious, contribute to nociceptive input at high levels of stimulation. Both types of nociceptive afferents are present in some organs {e.g., esophagus). Thus unlike cutaneous nociception, which predominantly results from the stimulation of fibers specifically nociceptive in nature, visceral nociception combines intensity-coded input from low-threshold receptors along with activation of specific nociceptors. The distinction between liber specificity and pattern or intensity coding of visceral nociceptive input is detailed by Cervero (1994).

Some visceral nociceptive afferents are also sensitive to chemical stimulation, for example, by bradykinin, and other physiological stimuli, such as hypoxia. **These** afferents demonstrate sensitization, particularly in the setting of mucosal inflammation. Through presumably centrally mediated mechanisms, cutaneous hypalgesia can occur in conjunction with visceral nociceptive input. The phenomenon may be analogous to referred pain.

Most of the visceral afferent nociceptive fibers travel via the sympathetic nerves into the thoracic spinal cord. They enter through both the dorsal and ventral roots and have a broader pattern of termination than somatic afferents. The visceral affercnts traveling in the vagus nerve convey some nociceptive information, including sensations of tightness in the chest and gastric distention. However, most afferent vagal fibers are regulatory and not primarily sensory or nociceptive. The afferent fibers in the lumbosacral parasympathetic nerves do convey important nociceptive information from the bladder and other pelvic viscera.

Alterations in primary sensory afferents result from peripheral nerve injury, inflammation, and other pathological processes. Such changes may affect nociception acutely and alter the perception of chronic pain. Changes in membrane cation channels (i.e., vanilloid receptors) and the subsequent alterations in the intracellular second messengers active in peripheral endings of nociceptive afferents are thought to underlie the sensitization following thermal, chemical, and inflammatory activation (Bolay and Moskowitz 2002), These peripheral sensitization phenomena are probably transient.

Alterations in the proximal elements of nociceptive and non-nociceptive afferents also contribute to changes in pain perception that may become chronic. Changes in voltage-gated sodium channels that arc relatively specific to C fibers occur with injury or inflammation. Changes that occur in non-nociceptive afferents, such as A-beta fibers, are also interesting. These fibers normally convey information about non-noxious mechanical stimuli. Following injury, neurotransmitter production may change and substance P is released. New synaptic connections may form within the superficial laminae of the dorsal horn. These alterations may explain the pain induced by non-nociceptive stimuli (e.g., allodynia),

Dorsal **Horn and Central Projections**

Tin.' central projections ot the primary nociceptive afferents, whose cell bodies are located in the dorsal root ganglia, are directed through the dorsal roots to the most superficial of Rexed's laminae (I and II) and to some of the deep laminae (V) of the dorsal horn over a vertical distance of one or two vertebral levels. The A fibers conveying input from HTMs and MTs terminate primarily in laminae I and V; C fibers terminate in lamina II. Visceral afferents included in the sympathetic nerves also terminate in laminae I and V, sometimes overlapping with somatic affercnts, and also terminate more widely in the lower laminae (VI, VII, and X),

The viscerosomatic convergence of nociceptive afferents is important in the genesis of referred pain. These terminals use multiple neurotransmitters, including excitatory amino acids and neuropeptides, particularly substance P. Postsynaptic modulation may result from substance P's long-term modulating effects. In addition, both presynaptic and postsynaptic events may be modified by supraspinal input involving monoamines and opioid neuropeptides.

The postsynaptic neurons in the dorsal horn include cells that respond only to noxious stimuli (e.g., nociceptive specific neurons) and others, *wide dynamic range neurons* that respond to both nociceptive and non-nociceptive sensory stimuli. These neurons project as a largely decussated pathway that projects in the contralateral antctolateral portion of the spinal cord comprising the principal spinothalamic tract. This tract is somatotypically organized with sacral elements situated posterolateral^ and cervical elements more anteromedially. included in this tract are fibers that project to the periaqueductal gray (spinoreticular pathway) and brainstem nuclei. These fibers, along with projections to the central or laminar nuclei of the thalamus, make up the paleospinothalamic tract. In humans, most of the spinothalamic tract projects to the ventral posterolateral nucleus of the thalamus as the neospinothalamic tract. The cortical projections of the paleospinothalamic tract are widespread, whereas the cortical projections of the neospinothalamic tract are directed to the primary sensory cortex.

The integration of nociceptive input to the thalamus shares some similarities with those at the spinal level. The phylogenically distinct components of the spinothalamic tract probably convey qualitatively different information. The paleospinothalamic pathway serves arousal and the emotive or affective component of pain; the neospinothalamic component conveys discriminative and localizing information. Like dorsal horn neurons, thalamic neurons are activated as either nociception-specific or as polymodal wide dynamic range neurons. In addition, the convergence of somatic and visceral input at the thalamic level adds another possible source for referred pain,

The development of functional neuroimaging techniques, such as positron emission tomographic (PET) scanning and functional magnetic resonance imaging, has provided new information about the anatomy of central nociceptive processing. Methods that demonstrate regional activation based on changes in cerebral blood flow indicate that multiple areas are activated in conjunction with the perception of pain. Particularly interesting is the activation of the anterior cingulate gyrus, which may mediate attentional and affective aspects of pain perception. Primary and secondary somatosensory cortex, thalamus, periaqueductal gray, supplemental motor, inferior prefrontal, and insular cortex are also activated (ladarola et al. 1998). These regions provide the networks that subserve the various neural components (sensory-perceptual, behavioral, modulating) that comprise the complex experience of pain. Understanding the integration and chemical regulation of these components remains challenging (Jones 1998).

Central Modulation of Nociception

Afferent nociceptive input is modulated by peripheral mechanisms, such as sensitization of nociceptors by thermal or chemical stimuli. Central mechanisms that modulate nociceptive input also exist. At the spinal level, both local neuronal circuits and descending pathways originating in the brainstem modulate nociceptive transmission through the dorsal horn and the spinothalamic projections. This modulating effect is generally inhibitory and produces analgesia via endogenous opioid and aminergic systems. Studies of systems that facilitate nociceptive input are ongoing.

Intrasegmental and intersegmental projections arising from cells located in Rexed's laminae I and II (e.g., substantia gelatinosa) modulate both presynaptic and postsynaptic elements of primary nociceptive afferent terminals in laminae I, II, and V. These local circuits also serve to integrate nociceptive and other sensory inputs. Suppression of nociceptive transmission in the dorsal horn by non-nociceptive afferent stimulation was the hasis for the development of circuitry models referred to as the *gate control theory* of pain transmission. This model has influenced studies of nociceptive mechanisms for the last 30 years. Although the specific dorsal horn circuits originally hypothesized in gate control theory were never identified, the phenomenon of modulation of nociceptive input by peripheral and descending central influences remains a fundamental topic of study in the understanding of nociception.

Endogenous opioids serve as principal neurotransmitters in the local circuitry of the dorsal horn. Opioid receptors (mu- and kappa-receptors; see the section on endogenous opioids and opioid receptors later in this chapter) are found on both presynaptic and postsynaptic elements of primary nociceptive afferents in the substantia gelatinosa, which also contains a high density of enkcphalinergic terminals. These interneuron synapses are an important site of action for systemically administered opioid analgesics.

Descending influences on spinal nociceptive transmission were first demonstrated by producing analgesia sufficient to perform laparotomies on rats after electrical stimulation of the periaqueductal gray. Similar effects have been produced by local iontophoretic application of opioid analgesics on regions of the brainstem. The best established of the descending nociceptive modulating systems derives from cells in the midhrain periaqueductal gray that project to the nucleus raphe magnus (NRM) in the medulla. The NRM in turn projects to neurons in Rexed's laminae I, II, and V of the dorsal horn. Analgesia induced by stimulation of cither the midbrain or medullary region is sensitive to opioid antagonists (e.g., naloxone), and specific opioid receptors

exist at both sites. The descending pathway from the NRM travels through the dorsal lateral column of the spinal cord medial to the corticospinal tracts. Sectioning these tracts blocks the analgesic effect of stimulation of the periaqueductal gray or NRM. Electrophysiological studies indicate that stimulation of these descending pathways inhibits activity in wide dynamic range dorsal horn neurons that contribute to the spinothalamic tract. The fibers originating in the medullary nuclei, particularly the NRM, use serotonin as a principal neurotransmitter. Norepinephrine is the principal neurotransmitter of fibers from other medullary nuclei, such as the nucleus reticularis gigantocellularis, and from more rostral components of the monoaminergic system. These pathways specifically inhibit nociceptive input without affecting other somatic or visceral sensory input. They represent the principal supraspinal sites for the analgesic effects of endogenous and exogenous opiate action.

Activity in wide dynamic range neurons and nociceptive neurons of the dorsal horn are altered differently by supraspinal input. Chronic changes in the control of transmission through these paths, either by inhibition or facilitation, may contribute to the development of some chronic pain states (Millan 2002).

Transitory analgesia also can be produced by stimulating the somatosensory cortex and certain periventricular nuclei in the hypothalamus. This effect is mediated by direct fibers included in the corticospinal tracts that terminate in the dorsal horn and by polysynaptic pathways that may use the reticulospinal and raphe spinal pathways described earlier. The analgesic effect resulting from electrical stimulation at these supratentorial sites is less consistent than that achieved by stimulation of the periaqueductal gray.

Endogenous Opioids and Opioid Receptors

Two major neuroscience breakthroughs since the 1970s are (1} the identification of specific neuronal receptors that mediate the effects of opiates and (2) the identification of endogenous peptides that act as ligands for these receptors. In recent years, the number of opioid-rclatcd peptides has increased with the identification of endomorphins, nociceptin, and nocistatin. New types of opioid receptors have also been identified. Modulation of the endogenous opioid systems in the setting of inflammation, neurological disorders, and chronic pain has added greatly to insights and treatments in curtcnt pain therapy (Przewlocki and Przewlocka 2001).

Three families of endogenous opioid neuropeptides have been identified: enkephalins, dynorphins, and endorphins. Each family derives from a distinct gene, yet all active opioid species have in common the amino terminal sequence Tyr-Gly-Gly-Phe. In each family, the active peptides arise from the cleavage of a larger precursor protein. The two opioid precursors most closely associated with brainstem and spinal nociceptive transmission are pro-enkephalin A, the precursor of met- and leu-enkephalin, and pro-enkcphalin B (prodynorphin), the precursor of dynorphin. These precursors are concentrated heavily in those regions of the periaqueductal gray, medullary nuclei, and dorsal horn involved primarily with nociception. The principal member of the endorphin family of opioid peptides is /J-cndorphin, which is derived from pro-opiomelanocortin and is relatively restricted to the hypothalamus and pituitary. It is also the parent precursor of melanocyte-stimulating hormone, adrenocorticotropic hormone, and other peptides.

In the late 1990s, the *endomorphins,* peptides with mu-recepror agonist properties and a distinct terminal amino acid structure, were identified. Endomorphins I and 2 are found in brain regions that arc important in pain signaling, Endomorphin 2 colocalizes with substance P in some of the primary nociceptive afferents in the dorsal horn and appears to have an inhibitory effect on nociceptive transmission. Other peptides with analgesic properties, such as nociceptin, have also been found.

Opioid receptors, initially identified by the specific binding of ligands, such as morphine, are subcategorized by differing ligand affinities. The major subcategories are the mu-, kappa-, and delta-receptors. Each of the receptor subtypes has been cloned and sequenced. The receptors are membrane-spanning proteins that appear to be coupled by G proteins to adenyl cyclase, using cyclic adenosine monophosphate as the second messenger. They probably act by regulating K^+ and Ca^+ channels. Pharmacological evidence, based on ligand binding specificities, suggests that additional opioid receptor subtypes exist, but cloning data has not supported that view.

The mu-receptor, so named because of its high affinity for morphine, is present in the periaqueductal gray and dorsal horn. The analgesic potency of opiate compounds correlates well with the agonist-binding affinity to the mu-receptor. Genetically engineered mice lacking the mu opiate receptor demonstrate no analgesic effect from morphine. In addition, these mice fail to manifest behavioral evidence of physical dependence or naloxone-induced withdrawal symptoms after chronic morphine treatment. Thus mu-receptor expression is necessary and sufficient to explain all the pharmacological actions of motphine. Kappa-receptors also are distributed in the spinal and brainstem regions that are important in the modulation of nociception. These distributions clearly overlap those of the enkephalins and dynorphins.

Other receptors with sequence similarities to the opioid receptor have been identified. The orphan opioid-like receptor (ORE 1) was found, and an endogenous ligand nociceptin has also been discovered. This receptor is found in many brain regions including the dorsal horn of the spinal cord. Nociceptin is also widespread but heavily concentrated in the superficial laminae of the dorsal horn.

The endomorphins and nociccptin have analgesic actions when administered intrathecally in animals. However, in some experimental situations nociceptin and dynorphins can facilitate nociceptive transmission.

As in other neurotransmitter systems, changes in the level of activity within nociception-rclated pathways and other influences such as inflammation lead to alterations that modify the pathways both acutely and chronically (Przewlocki and Przewlocka 2001}, Systemic inflammation increases the nociceptive effect of endogenous opiates. These changes include an increase in potency of mu-receptor agonists probably because of changes in the mu receptor. The loss of afferent neurons resulting from peripheral nerve injury may decrease the presence of opioid receptors in the dorsal horn. This is suggested as an explanation for the relatively reduced efficacy of opiates against neuropathic as compared with somatic pain,

Chronic pain states may reflect long-term changes in the endogenous opioid systems. For example, increased levels of dynorphin in the spinal cord following segmental nerve injury result in a decrease in the analgesic efficacy of morphine (Malan ct a!. 2000). This may contribute acutely to hyperalgesia through N-methyl-D-aspartate (NMDA) receptor-related mechanisms because the effect can be prevented by NMDA receptor antagonists. Persistent effects attributed to NMDA-mcdiated excitatory neurotoxicity may then contribute to the development of chronic neuropathic pain.

The termination of opioid receptor activation depends on peptidases with active sites located on the extracellular surface of the cell membrane that cleave the peptides into inactive fragments. The so-called enkephalinascs may serve as a target for a new class of analgesics.

PAIN MECHANISMS

Nociceptive Pain

Nociceptive pain is a response to tissue injury that produces activation of nociceptors. The acute pain caused by tissue injury usually is divided into somatic and visceral pain, based iin their differences in character. Somatic pain is more clearly localized and described as sharp or dull, Visceral pain is less well localized and has a crampy, spasmodic, or aching character. Visceral and deep somatic pain more commonly arc associated with referred pain than is cutaneous pain.

Chronic nociceptive pain is usually similar in character to acute pain arising in the same area, but with time, the consequences of the modulation of nociceptive transmission and the affective components of pain become more important in the character of the pain syndrome. Depression, sleep disorders, and the sequelae of disuse (e.g., muscle atrophy and limited joint mobility} contribute to the disability of chronic pain disorders.

Although nociceptive pain usually arises from localized tissue injury, the distribution of perceived pain does not always directly identify the source of pain—that is, tissue injury occurring at one site may be felt as arising from another (referred pain}. The best known example is the association of left arm pain with angina. Other common examples arc listed in Table 50.1. In addition to the convergence of visceral and somatic input at the spinal level, other possible mechanisms of tefcrred pain include innervation of two structures by different branches of the same nociceptive afferent fiber and changes in the receptive field of thalamic neurons.

Neuropathic and Deafferentation Pain

Pain is an important consequence of direct injury to peripheral nerves; common examples are nerve and nerve root compression syndromes, acute and chronic pain after nerve transection, neuritis in association with infectious and inflammatory lesions (e.g., herpes zoster), and diffuse polyneuropathies.

Neuropathic pain often has several different qualities that are experienced concurrently. One common form is sharp, lancinating pains that are brief but very intense, or shocklike, and well localized. Typically, the pain radiates

Tahle 50.1: Common referred pain syndromes

Pain location	*Segmental distribution*	*Causes*
Frontal or vertex headache	Trigeminal nerve	Traction, inflammation, or other lesions involving the supra tentorial meninges
Ear pain	Glossopharyngeal and vagus nerves	Tumor, abscess, or inflammatory lesion in the oropharynx or hypopharynx
Right shoulder pain	Plireiiie IHTO (C.5-C5)	Cholecystitis or diaphragmatic irritation
Left chest/arm pain	T1-T4	Cardiac ischemia
Left upper abdominal wall pain	T8	Gastric diseases
Middle and lower abdominal wall pain	T10-T11	Small intestine and colon disorders
Testicle/inguinal region pain	T12-L2	Renal or perirenal abscess or tumor
Knee pain	L3-L4	Pelvic, acetabular, and femoral head disorders

in a pattern that suggests a dermatomal or peripheral nerve distrihution. In trigeminal neuralgia (see Chapter 75) or postherpetic neuralgia, a trigger zone exists such that stimulation applied to a specific area elicits intense, shock-like pains. A superimposed burning pain is common, and sensory stimulation of the affected region often exacerbates the burning pain far out of proportion to the intensity of the stimulus. A slight breeze or movement of a sheet over the skin is often sufficient to produce exquisite pain in patients with painful neuropathies. A variety of mechanisms are involved in pain accompanying nerve disease, and multiple mechanisms may be operating simultaneously in any given patient. These mechanisms include: (1) activation of normal nociceptors contained in a nerve (e.g., ncrvi nervorum), (2) spontaneous discharges in injured nociceptor afferents, (3) induced discharges in injured nociceptor afferents, (4) deafferentation with subsequent changes in dorsal horn or central nociceptive transmission leading to central pain generation, pj activation ot sensitized mechanoreceprors by efferent sympathetic activity (sympathetically maintained pain}, and (6) specific ion channel changes in primary afferents. The last of these, upregulation of voltage-gated sodium channels specific to sensory neurons following injury, raises the suggestion that chronic pain states may be a channelopathy (Waxman et al. 1999}. Alterations in the descending inhibitory and facilitatory modulation of nociceptive transmission are also important in the genesis of chronic pain syndromes, including those of neuropathic origin.

Histological evidence supports the presence of nociceptors in the perineural and epineural tissues investing peripheral nerves, the ncrvi nervorum; therefore nerve injury can cause nociceptive pain in the sense described in the section on nociceptive pain, earlier in this chapter. This likely contributes to pain resulting from nerve root compression and peripheral nerve entrapment.

Neuropathic pain can result from abnormal discharges in injured or regenerating sensory afferents. Injured nerve fibers sometimes develop spontaneous discharges, and afferent impulses may be evoked by electrical activity in surrounding axons (ephaptic transmission) in injured nerves both acutely and later, during axonal regeneration or neuroma formation.

The nature of some nerve disorders is to selectively affect small-caliber afferent fibers; examples are neuropathies associated with diabetes and amyloidosis (see Chapter 82). This selective effect generates abnormal activity in nociceptor afferents, resulting in neuropathic pain. More commonly, the damage to the afferent fibers is not selective, Abnormal activity in non-nociccptivc tactile afferent fibers also may take on a painful quality that is distinct from or superimposed on the pain produced by nociceptor afferent activity. Synaptic plasticity in the dorsal horn and changes in neurotransmitter production by injured non-nociceptor afferents contribute to this phenomenon (Boiay and Moskowitz 2002). In these situations, pain is produced by activity generated in the peripheral nervous system. However, the failure of peripheral nerve blockade by nerve transection or local anesthetic infiltration to relieve chronic neuropathic pain syndromes indicates that the pain related to peripheral nerve injury or disease also has a central nervous system (CNS) component.

The mechanisms of central pain generation are becoming better understood through studies elucidating the anatomical and synaptic plasticity, biochemical alterations in neurotransmitter systems, and changes in neural systems that modulate nociceptive transmission. Sensitization of dorsal horn cells may result from high frequency stimulation by nociceptive afferents, a phenomenon described as "wind up." Wide dynamic range neurons become sensitized in this manner such that repeated activation triggers a progressively stronger response. Some of the biochemical mechanisms important in this process include the activation of NMDA receptors resulting in prolonged depolarizarion of the postsynaptic membrane. Under pathological conditions the process may become persistent. Intense afferent activity may also lead to release of excitatory amino acid neurotransmitters with resultant loss of local neurons resulting from neurotoxic effects. Sprouting of afferent terminals may also contribute to chronic sequelae.

Chronic pain syndromes resulting from peripheral nerve injuries and from CNS disorders rhat involve the sensory pathways probably share mechanistic central changes. The distribution and character of pain associated with central lesions differ somewhat from those of peripheral lesions. However, central pain is usually more diffuse and less well defined in distribution. It is also less likely to be lancinating in quality or associated with a trigger zone. Similarities of central and peripheral induced pain are as follows: (1) both are usually distributed in a region of impaired tactile perception, (2) tactile input takes on a painful quality (hyperpathia) out of proportion to the intensity of stimulus applied, and (3) the pain often has a highly emotive burning quality.

The clinical and conceptual overlap between central and peripheral neuropathic pain syndromes has led many investigators to lump both types of pain syndromes under the category of deafferentation pain. Tricyclic antidepressants and anticonvulsant drugs can relieve both types of deafferentation pain.

In addition to nociceptive and deafferentation mechanisms, efferent peripheral nervous system activity may contribute to chronic neuropathic pain syndromes. Abnormal activation of adjacent peripheral axons by electrical coupling (ephapses) is seen in animal models, but its contribution to pain generation in humans is difficult to estimate. A second postulated efferent mechanism of neuropathic pain is that of *sympathetically maintained pain.*

Efferent sympathetic activity, or overactivity, may be generated in the CNS or as a reflex response to peripheral stimuli. Electrical stimulation of efferent sympathetic fibers

in cats induces spontaneous discharges in non-nociceptive cutaneous mechanorcceptors with subsequent activation of neurons of wide dynamic range in the dorsal horn. This is a proposed mechanism by which efferent sympathetic activity sustains chronic pain subsequent to pain originally induced by trauma. This proposal complemented several clinical observations regarding chronic pain syndromes with neuropathic features, including the related conditions formerly known as *causalgia* and *reflex sympathetic dystrophy* (RSD), However, the importance of sympathetic activity in these pain syndromes has been questioned (Max and Gilron 1999). These disorders illustrate the evolving nature of the understanding of neuropathic pain mechanisms and the limitations that persist in the treatment of neuropathic pain.

Complex Regional Pain Syndromes

In the 1870s, Weir Mitchell characterized a syndrome of severe progressive distal limb pain with swelling, changes in color and temperature, atrophy, and loss of use. It was based on his observation of soldiers whose wounds had resulted in major nerve injuries. He termed the condition *causalgia.* A process with very similar clinical features that often follows minor trauma in the absence of major nerve trunk injury has been termed RSD, RSD is much more frequent than causalgia, especially in civilian practice. Numerous labels have been applied over the years. In recent years, a substantial change in the understanding of these disorders has occurred, and the nomenclature has been revised to avoid terminology that implies specific postulated mechanisms of pain production. The currently used terms are (1) complex regional pain syndrome (CRPS) type I (formerly RSD) and (2) CRPS type II (formerly causalgia).

Although no accepted standard exists for the diagnosis of these syndromes, the clinical criteria for the diagnosis of CPRS type I have been refined. In 1994 the International Association for the Study of Pain (IASP) proposed the following diagnostic criteria: (1) the presence of and initiating noxious event or cause of immobilization, (2) continuing pain, allodyma, or hyperalgesia with which the pain is disproportionate to any inciting event, (3) evidence at some time of edema, changes in blood flow, or abnormal pscudomotor activity in the region of pain, and (4) the absence of conditions that would otherwise account for the degree of pain and dysfunction (Reinders et al. 2002; van de Beek et al. 2002). The critctia are vague in many respects, and even with attempts to define more rigorous criteria for research purposes it remains uncertain that the criteria define a uniform population of patients (Harden et al. 1999). In addition, despite attempts at defining diagnostic criteria, the recent literature continues to show wide variation in their application (van de Beek et al. 2002).

These syndromes are three rimes more common in women than in men, and most patients are in early- to mid-adulthood. The primary feature of these syndromes is pain, usually in the distal part of a limb, with the hand being more frequently involved than the foot. The pain generally has neuropathic qualities (burning, allodynia, and hyperalgesia) that with time spread proximally to involve areas that are not identifiable as the distribution of a single peripheral nerve or dermatome. This tendency to spread is one of the most characteristic features of the syndrome and gave rise to the descriptive term *spreading neuralgia.* In cases associated with major nerve injury {CRPS type II), the pain begins within days and is severe from the start. In the more common CRPS type I, weeks or months may elapse between the inciting injury and the development of pain, which tends to progress more gradually. The pain is characteristically worsened by activity and by placing the affected limb in a dependent position. CRPS type I is estimated to occur after 7% or more of Colles' fractures, 1-2% of other fractures, and 2-5% of minor peripheral nerve injuries. It may also occur after myocardial infarction. No identifiable precipitant is found in up to 25% of cases. Rarely, a similar syndrome may affect cranial or axial structures.

In addition to neuropathic pain, other characteristics include the presence of edema; changes in skin temperature; hyperhidrosis; and trophic changes in the skin, muscles, and bone. These features led to the impression that abnormal sympathetic function was fundamental to the development of the syndrome, including the pain. The observation that regional sympathetic blockade, either by pharmacological or surgical means, produced dramatic pain relief for most patients added greatly to this mechanistic interpretation. Mam experts felt that a favorable response to regional sympathetic blockade established the diagnosis as RSD. The observation that efferent sympathetic activity can activate nociceptive cells of wule dynamic range in the dorsal horn by stimulating polymodal sensory affcrcnts provided a mechanistic explanation {e.g., sympathetically maintained pain) that unified the diverse features of this syndrome.

Although the explanation is conceptually appealing, further research and clinical experience has indicated that the understanding of these neuropathic pain syndromes is far from complete. Attempts to show that sympathetic activation worsens pain produced by capsaicin-induced C fiber activation in normal humans have been negative (Baron et al. 1999; Max and Gilron 1999). Furthermore, microneurography has not demonstrated excessive sympathetic output in most CRPS patients. Several place bo - controlled studies have shown that regional sympathetic blockade is not superior to placebo treatment. Furthermore, regional sympathetic blockade may affect visceral afferent nociceptive fibers associated with vascular or other visceral elements, and its efficacy may not be entirely a

reflection of sympathetic efferent modulation. It is likely that a small percentage of CPRS patients may have sympathetically maintained pain, but current evidence suggests that the pain is usually independent of sympathetic activity. This evolution in the mechanistic understanding of these syndromes has led to revisions in nomenclature in an attempt to remove mechanistic inferences such as *reflex* and *sympathetic* from the names,

These disorders are often chronic and result in disabling changes in the affected limb. Thus in a descriptive sense, the term *dystrophy* provides a useful concept for the chronic aspects of the CRPSs. The skin tends to become taut and glossy, with loss of subcutaneous fat and trophic changes in the nails. Demineralization of bone, typically in the hand, can be identified radiographically. Decreased range of motion, muscle atrophy, and weakness are common. Unusual hand postures develop in half of patients. Some of these are contractures, but many represent dystonia and, like other neurological symptoms, they tend to be progressive. Progressive sensory loss, including anesthesia dolorosa and progressive hyperalgesia, may occur. **These** motor and sensory phenomena are an indication of the remarkable CNS changes that contribute to the development of the CRPSs. However, some patients experience a self-limited process without the development of chronic dystrophic features,

The natural evolution of CPRSs continues to be debated. The traditional descriprion is a progressive disorder with three stages: acute, dystrophic, and atrophic. However, a self-limited form is also thought to occur. A prospective trial to examine the natural history of early CPRS of the hand, with treatment limited to limb elevation and analgesic and anti-inflammatory medications, suggested that pain and swelling resolved much faster than vasomotor instability and trophic changes (Zyluk 1998). At 6 months, pain and swelling persisted in less than one third of patients, whereas persistent discoloration, trophic changes, and temperature changes were present in 50%. At 13 months, only 15% had pain and swelling, whereas 30% showed persistent discoloration and trophic and temperature changes. Approximately 85% obtained full finger flexion at 13 months. Overall, 70% of patients had a good result, defined as pain free with full finger flexion. However, nearly two thirds of patients had a grip strength ratio (affected vs. normal hand) of less than 50% indicating that, despite symptomatic improvement, the likelihood of long-term functional impairment was high.

The treatment of the CRPSs is often only partially successful. Recent models of neuropathic pain that suggest an analogy with the kindling-like changes of repeated seizures add to the rationale for aggressive early treatment. A trial of regional sympathetic blockade is still recommended as part of the early management by many practitioners, usually with the inclusion of placebo trials. The dichotomy of opinion about the efficacy of regional sympathetic blockade is apparent when one considers that only a few years ago, response to this procedure was considered fundamental to the diagnosis. The literature contains many citations in which complete pain relief was obtained in more than 80% of patients. The long-term efficacy of sympathectomy for chronic neuropathic pain is relatively poor, with less than one third of patients achieving sustained relief.

Physical therapy and analgesics including nonsteroidal anti-inflammatory drugs (NSAIDs) and agents fot neuropathic pain such as gabapentin are **also** common in the early management of CRPS. Although opioid analgesics are often considered less effective for chronic neuropathic pain, they add substantially to pain control for some patients. For chronic neuropathic pain of high intensity and for other late complications, such as dystonia and contracture, other specialized methods may be used.

The efficacy of implanted spinal cord stimulators for chronic neuropathic pain syndromes has been demonstrated. A randomized, controlled trial of spinal cord stimulation for CRPS I suggests a decrease in intensity of pain for patients in whom standard thctapics including physical therapy, sympathetic blockade, transcutaneous electrical nerve stimulation (TENS), and analgesics were ineffective (Kemler et al. 2000). Spinal cord stimulation is accomplished by means of an implanted electrode in the epidural space near the spinal level associated with the most intense dysesthesia. After a trial with an external generator, the electrode is connected to a subcutaneous pulse generator situated in the anterior abdominal wall. Compared with physical therapy alone, electrical stimulation resulted in considerable improvement in pain at 6 months with an average reduction of 2.4 cm on a 10-cm visual analogue pain scale. Unfortunately, concurrent analgesic use and changes in analgesic use were nor reported. The complication rate approached 25%, largely related to electrode placement, but most were easily managed. Despite improvements in pain control and global rating of benefit, no improvement in functional status was observed.

Contracture and dystonia also contribute to the pain and disability of CRPS I. Intrathecal baclofen markedly reduce dystonia and improve function in the affected limb of patients with multifocal or generalized dystonia from CRPS I (van Hilten et al. 2002). Some patients improved dramatically, regaining normal hand function or ability to walk. Myoclonic jerks and muscle spasms may also improve.

Botulinum toxin is another approach to dystonia treatment in CRPS. In a small study of four patients with dystonic clenched fist, including one with bilateral involvement, all patients experienced pain improvement. One obtained complete finger extension with functional improvement and a second experienced postural improvemenr with repeated botulinum toxin injections (Cordivari etal. 2001).

Idiopathic and Psychogenic Pain

Pain that occurs without a definable cause of nociceptor activation or any mechanism of neuropathic generation often is categorized as idiopathic or psychogenic. The terms, however, are not synonymous; not all apparently idiopathic pain problems prove to be psychogenic. Still, with rigorous evaluation and ample follow-up observation, many patients with chronic pain lacking a defined cause have psychological factors that promote or sustain the pain problem. This is a heterogeneous group, both in terms of the nature of the pain complaint and the nature of the psychological processes involved.

For many people, recurring pain complaints are related to the stresses and anxieties of work, family relations, and other aspects of daily life. Tension headaches and fibromyalgia syndromes commonly fall into this category. The supposition that emotional tension, fatigue, and other factors produce nociceptive somatic pain secondary to muscle contraction is simplistic. Psychogenic factors are suspected when such complaints become a major focus of concern or disability far out of proportion to any evidence of nociceptive stimuli.

Identifying specific psychological or psychiatric problems that promote and sustain pain problems is important in determining therapeutic strategies **(Eisendrath** 1995). Patients with anxiety disorders and those with obsessive or other personality traits associated with somatization must be identified so that appropriate therapy can be undertaken. Conversion disorders also present ftequently with pain complaints, particularly headache. Chronic analgesic thetapy is of little benefit and, in some cases, may worsen the pain problem.

Unexplained pain is not a common presenting complaint of a ma]or psychiatric disorder. Occasionally, somatic delusions that include pain occur as part of depression and resolve with antidepressant therapy. Headache is the most frequent pain complaint in patients with depression. Conversely, depression is relatively common among chronic pain patients, and the severity of pain from minor injuries or other lesions is often magnified. Using stringent criteria, major depression is present in about 5-10% of chronic pain patients. The frequency may reach 50% or more when evidence of mild affective disorders is included. Among patients with schizophrenia, somatic delusions and hallucinations that primarily involve pain arc relatively rare. Chronic headache is the most common pain complaint in these patients.

Malingering is feigning illness, such as a chronic pain syndrome, for the purpose of obtaining an obvious, often tangible, secondary gain. Malingering patients are dramatically and demonstratively incapacitated by their symptoms. They tend to be uncooperative during examinations and noncompliant in therapeutic efforts. Frank malingering is relatively uncommon; for example, less than 5% of patients with chtonic back pain are thought to be malingerers. However, many patients embellish minor deficits, and many coincidentally receive secondary gains for being ill. Thus in physician surveys, the frequency of reported malingerers in chronic pain clinics varies greatly. As a poorly defined and uncommon entity, malingering should be considered a diagnosis of exclusion in chronic pain patients. The psychological factors that contribute to the chronic pain problems described previously should be identified as potential avenues of therapy.

The pathophysiological basis of psychogenic pain remains speculative, and multiple mechanisms are probably involved. The fact that nociceptive pain is so strongly influenced by anxiety and other psychological factors suggests that the overlap between centtal pain mechanisms and emotive mechanisms, particularly in regard to the opioid and aminergic systems, is important in the production of psychogenic pain.

APPROACH TO THE PATIENT WITH PAIN

This chapter and most discussions of pain management focus on symptomatic control of pain by pharmacological, surgical, and other means. Successful pain management always is based on a clear understanding of the pain's cause. This requires a history of the nature of the pain, a full accounting of medical history, and a physical examination that often includes a detailed neurological assessment. On this basis, a pain complaint can be characterized as nociceptive (somatic or visceral), neuropathic, psychogenic, or including a combination of these features. This characterization directs the subsequent evaluation of the patient and guides the choice of therapy.

Acute Pain

History

When characterizing a new pain complaint, the most useful features arc location, character, mode of onset, factors that aggravate and relieve pain, and concurrent features (e.g., fever, dyspnea, and nausea). The complaint that "pain radiates" may be a valuable indicator of referred or neuropathic pain. From these elements of the history, a working differential diagnosis usually can be formulated and then further evaluated by physical examination and laboratory studies.

Even during the initial interview, an assessment must be made of the relationship between the pain's severity and the patient's emotional response and attributed disability. This assessment is difficult because the experience of pain is intensely subjective and highly variable among people. It is easy to dismiss a pain complaint as minor if the patient is not wincing or grimacing or to consider the patient histrionic if the complaint is accompanied by dramatic

crying, writhing, or posturing. The physician is wise to accept the patient's report of pain severity unless overwhelming evidence to the contrary exists.

Prior medical problems often explain current pain syndromes; for example, diabetes may be associated with limb pain as the result of ischemia or peripheral neuropathy. A history of cancer suggests vertebral or epidural metastasis as the cause of progressive back pain. A remote history of trauma, neuritis, sciatica, or shingles, elicited only after careful inquiry, may be the basis for neuropathic pain syndromes. Depression and psychological factors that may contribute to the pain syndrome also must be explored.

Physical Examination

The initial examination is directed mainly by the stated location of pain. The physician searches for evidence of local inflammation to help locate the source of pain: tenderness; warmth; swelling; limited joint mobility; and signs of pleural, peritoneal, or meningeal irritation. Observations of subtle changes in posture (e.g., slight hip flexion in patients with pelvic abscess) are often helpful. Maneuvers that elicit or relieve pain should be duplicated. These include direct pressure, coughing or sneezing, joint flexion, straight-leg raising, reverse straight-leg raising, and nerve percussion (Tinel's sign).

Establishing the cause of a pain complaint often provides a mechanistic explanation of somatic or visceral nociceptive pain, neuropathic pain, or some combination of the three. An understanding of cause and mechanism allows the best opportunity to develop a rational treatment plan. The symptomatic relief of a new pain complaint when the cause is not clearly identified is a common pitfall that may lead to permanent tissue damage. For example, most patients with neurological symptoms resulting from spinal epidural metastasis have experienced back pain that was not fully evaluated for weeks or months. This is not to recommend withholding symptomatic therapy for severe pain while waiting for results of diagnostic tests but rather to perform an investigation that is thorough enough to establish a specific cause. When a specific cause (i.e., infection, fracture, tumor) of a new pain complaint is not established and the diagnosis of a benign or self-limited problem is entertained by exclusion, the management plan must include reassessment.

Even with rigorous investigation, however, the pathophysiological basis of many pain complaints cannot be defined. Most people experience transitory aching in muscles or joints and occasionally brief lancinating or sharp pains without a previous history of injury or other explanation. The self-limited and generally mild nature of a pain, identifies it as part of the normal repertoire of sensations. Such complaints can become self-perpetuating, as in analgesic-rebound headache, for which regular use of mild analgesics prolongs rather than terminates headache. The coexistence of unexplained pain complaints along with a history of bona fide medical illness (e.g., a history of diabetes or cancer) is common. It may be difficult to determine whether the pain is causally related to the preexisting illness. Often, this problem can be solved only with patience, repeated examinations, and clinical insight into whether or not the nature of the pain is appropriate in the context of the underlying illness. Attributing a new pain complaint to a psychiatric disorder requires the rigorous exclusion of other causes.

Chronic Pain

Pain that lasts months or longer without a defined cause and is of sufficient severity to interfere with normal daily activities is a relatively common and often difficult problem. Chronic, incapacitating pain may follow relatively minor trauma or even occur without prior trauma, as seen in patients with CRPS or RSD. Several CNS disorders can produce chronic pain syndromes that pose difficult diagnostic problems (e.g., multiple sclerosis, thalamic tumors, or infarcts). Most chronic pain patients do not have a definable disturbance that remains unidentified after prolonged observation. Psychological factors appear to predominate in many of these patients, and a pharmacological approach to management is rarely useful when used alone. Treatment in clinics that specialize in a multidisciplinary approach to pain control, including pharmacological, behavioral, and psychological management, is more likely to be successful.

Pharmacological Approaches to Pain Management

A systematic pharmacological approach to pain management has been espoused for cancer patients, a group with a high frequency of both acute and chronic pain syndromes, This escalating analgesic approach, advocated by the World Health Organization, is most applicable to the patient with a defined lesion producing persistent somatic nociceptive pain but also provides a rational approach to the treatment of many pain problems. The main points of this approach are (1) the titration of analgesics in relation to severity of pain, (2) the superiority of regularly scheduled dosing over "as-needed" dosing for persistent pain, and (3) the use of adjuvant medications whose actions are not primarily analgesic to improve the efficacy of the principal analgesics.

NSAIDs are used first. If pain control is not achieved, a low-potency opiate, adjuvant agents (e.g., tricyclics), or both are added. If pain persists, more potent opiate analgesics are used while continuing adjuvant agents. Alternate routes of analgesic administration {i.e., intravenous, epidural) and surgical approaches are reserved for specialized situations in which pain control cannot be achieved or maintained with the first steps of the approach.

Placebo Therapy and Pain Relief

The placebo effect contributes to the therapeutic benefit derived from many types of pain treatment. In general, 15-30% of patients enrolled in placebo-controlled trials respond to placebo, irrespective of the nature of the pain. The response rates in psychogenic and nociceptive pain are the same; therefore a placebo response is not a diagnostic test for psychogenic pain or malingering. Even relatively severe pain states, such as CRPSs, may improve substantially with placebo treatment. The efficacy of placebo is sufficiently reproducible that pain control studies often are thought to have a flawed study design if the frequency of response to placebo is less than 10%.

The mechanism of placebo action is probably central modulation of nociceptive input and alterations in other CNS functions, such as those associated with arousal and anxiety. Despite its efficacy, placebo therapy is often foregone because it appears deceptive and, more appropriately, because many analgesic drugs are more efficacious. Establishing the efficacy of certain treatments (e.g., a peripheral nerve or sympathetic blockade) in a given patient, however, requires the use of some placebo trials, in addition, placebo-controlled studies remain the standard for testing both pharmacological and nonpharmacological methods of pain control.

Nonopioid Analgesics

Nonopioid analgesics include acetaminophen and NSAIDs (e.g., salicylates, propionic acids [e.g., ibuprofen, naproxen sodium], and acetic acids [e.g., indomethacin, sulindac, and ketorolac)) (Table 50.2). As a group, these agents are indicated for mild-to-moderate nociceptive pain and arc particularly useful in the treatment of pain originating in bone and joints. They are generally less useful in the management of neuropathic pain syndromes. In addition to their analgesic action, NSAIDs arc anti-inflammatory and antipyretic. The predominant mechanism of action is probably inhibition of prostaglandin synthesis at the site of tissue injury, thus directly decreasing nociceptor stimulation. Although these agents have CNS effects (particularly antipyretic), it is unclear how much they contribute to the analgesic action, NSAIDs may be useful in combination with opiates for more severe pain. Unlike opioid use, NSAID use is not associated with tolerance or physical dependence. Also unlike opioids, progressive increments of NSAIDs beyond a certain dosage often fail to provide improved pain control (i.e., there is a "ceiling effect" to the analgesia produced by NSAIDs).

Acetaminophen has a 2- to 4-hour duration of action. A relative lack of gastrointestinal (GI) toxicity has led to its widespread use as an over-the-counter analgesic and antipyretic. Acetaminophen is a much less potent inhibitor of peripheral prostaglandin synthesis than aspirin or other NSAIDs and lacks clinically significant anti-inflammatory and antiplatelet effects. The mechanism of analgesia is not established but may be predominantly a CNS action. Formulations combining acetaminophen with mild opiates, such as codeine or oxycodone, have become widely used. Dose escalation with these formulations is limited by the risk of hepatic toxicity associated with the chronic use of acetaminophen in amounrs greater than 3-4 g per day. Severe and sometimes fatal hepatotoxicity may result from ingestion of more than 200 mg/kg at once.

Aspirin remains one of the most commonly used pain medications. The duration of action is generally 2-4 hours, although the plasma half-life increases significantly (threc- to fivefold) with increasing dosage. Despite the relatively common occurrence of nausea and GI irritation, many people tolerate chronic administration of *2-A* g per day, and it remains an important drug in the treatment of chronic inflammatory disorders, such as rheumatoid arthritis. Antiplatelet effects, resulting from irreversible inhibition of platelet cyclo-oxygcnasc, limit its use in patients with coagulopathies or thrombocytopenias, which often include cancer patients receiving chemotherapy. Choline magnesium trisalicylate, acetaminophen, and selective COX-2 inhibitors are notable for their lack of antiplatelet activity. The anticoagulant action of warfarin is accentuated by aspirin at high doses and by some of the other NSAIDs because of interference with plasma-protein binding and decreased metabolism. Other dose-dependent aspirin toxicities are tinnitus, vomiting, encephalopathy, and acidosis. Idiosyncratic reactions, notably acute asthma or anaphylaxis and Reye's syndrome, are the most serious adverse reactions but are relatively uncommon.

The propionic acid NSAIDs, ibuprofen and naproxen, are being used increasingly as short-term or as-needed analgesics for mild-to-moderate nociceptive pain; both are available in the United States without prescription. Ibuprofen has a relatively short half-life of 3-4 hours, whereas the longer half-life of naproxen (12 hours) makes it advantageous for persistent or chronic pain. GI toxicity is the main adverse effect limiting their use, although propionic acids are generally better tolerated than other NSAIDs. Ten percent to 15% of people taking ibuprofen discontinue the drug because of GI intolerance. Antiplatelet actions occur, but unlike aspirin the cyclo-oxygcnasc inhibition is reversible. The interaction of propionic acids with warfarin is usually insignificant. Uncommon adverse effects arc renal toxicity and aseptic meningitis.

The acetic acid NSAIDs, including indomethacin and sulindac, have been available longer than propionic acid NSAIDs. The half-life of indomethacin is variable, ranging from 2 to 11 hours. Sulindac is a prodrug whose major active metabolites have a half-life of 18 hours. The primary use of these NSAIDs is to treat chronic arthritis, such as rheumatoid arthritis and osteoarthritis. Acetic acid NSAIDs have a higher incidence of adverse effects than other NSAIDs; 20% of patients discontinue indomethacin because of toxicity. The main toxic effects are

Tabic 50.2: Selected nonopioid analgesics

Class	*Dnifi*	*Half-life (in hrs)*	*Dose range*	*Major toxicities*
Paraminophenol derivative	Acetaminophen	3	650-1000 mg q4-6h	Hcpatotoxicity with high doses
Salicylates (carboxylic acids)	Aspirin	0.5	650-1000 mg q4-6h	GI, including dyspepsia, gastritis, ulceration Increased bleeding time CNS toxicity at high doses Hypersensitivity reaction (may occur with all NSAIDs)
	Diflunisal (Dolobid)	13	500-750 mg ql2h	No antiplatelet effects GI toxicity less common than aspirin
	Choline magnesium trisal icy late (Trilisate)	215	1000-1500 mg q8-12h	No antiplatelet effects
Nonselective COX-1 and COX-2 inhibitors				
Propionic acids	Ibuprofcn (Motrin)		400-1000 mg q6-8h	GI toxicity, may be less common than with acetic acid NSAIDs Renal toxicity, particularly in combination with diuretics May aggravate hypertension CNS toxicities include dizziness, headache, drowsiness, fatigue
	roxen (Naprosyn)	14	250-500 mg ql2h	Similar to ibuprofen
Acetic acids	imethacin (Indocin)	45	25-50 mg q8-12h	GI toxicity CNS toxicity, particularly headache Renal toxicity, particularly with triamterene May produce hyperkalemia
	Sulindac (Clinoril)	**14**	150-200 mg ql2h	GI and CNS effects are less common than with indomethacin; may have less renal toxicity
	Ketorolac (Toradol)	**47**	15-30 mg IM or 10mgPOq6h	GI toxicity; for short-term therapy only
Enolic acid	Piroxicam (Feldene)	57	20-10 mg da ily	GI toxicity
Fenamic acid	Mefenamic acid (Meclomen)	2	100-250 mg q6-8h	For short-term use only; GI toxicity and diarrhea
COX-2 inhibitors				
	Celecoxib (Celebrex)	11	100-200 mg RID	No antiplatelet effects; possibly fewer GI side effects than nonselective COX-1 and COX-2 inhibitors
	Rofecoxib (Vioxx)	17	12.5-25 mg daily	No antiplatelet effects; possibly fewer GI side effects than nonselective COX-1 ,md COX-2 inhibitors
	Valdecoxib (Bextra)	8	10-20 mg daily	No antiplatelet effects; possibly fewer GI side effects than nonselective COX-1 and COX-2 inhibitors

CNS = central nervous system; GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs.

GI discomfort, frontal headache, drowsiness, and dizziness, A third acetic acid NSAID is ketorolac, which can be administered orally or parenterally and has a half-life of 5-6 hours. It is one of the most potent NSAIDs, with an analgesic effect similar to morphine. It is not recommended for chronic therapy because of the risk of gastric ulceration.

Several other NSAIDs are available for analgesic and anti-inflammatory purposes. Piroxicam has an analgesic potency similar to aspirin but can be taken once daily

because it has a relatively long half-life and enterohepatic recirculation. The first dose of piroxicam and other long-duration NSAIDs may be double the recommended maintenance dose to increase the rate of onset of analgesia.

Selective COX-2 inhibitors have become an important addition to the NSAIDs in recent years. These are potent anti-inflammatory agents that also exert analgesic and antipyretic actions. They have relatively long half-lives and can be dosed once or twice daily. Osteoarthritis and rheumatoid arthritis are the principal pain indications. The toxicity profile is in many ways similar to that of nonselective COX-1 and COX-2 inhibiting NSAIDs with some important exceptions. Toxicity data indicates a smaller risk of gastric ulcers, although with prolonged therapy and at higher doses the differences in incidence may not be as great, and GI complaints remain an important part of their toxicity profile. The selective COX-2 inhibitors do not impair platelet aggregation.

The initial choice of an NSAID is based on the type of pain, the drug's toxicity profile in relation to the patient's underlying medical condition, the patient's prior experience with NSAIDs, and drug cost. For minor or self-limited somatic pain, the first choice should be a short-acting agent with a low likelihood of side effects, usually ibuprofen. For persistent or chronic pain, an agent with a longer half-life, such as naproxen, sulindac, or piroxicam, may be chosen to reduce the dosing frequency.

For many patients with chronic pain, serial trials of different agents are needed to determine the most effective NSAID. A 2-week trial is required to properly assess the response to a given dose. If pain control is inadequate and significant toxicity has not occurred, dose escalation is appropriate. The limiting dosage is determined by drug toxicity and the ceiling effect in regard to analgesia; for most NSAIDs, little additional analgesic effect is achieved by further escalation at the high end of the dose range (see Table 50.2). If one NSAID fails to relieve pain at a reasonable dose or is poorly tolerated, it should be replaced by another NSAID from a different chemical class. Failure to benefit from one NSAID does not predict the response to others. Therefore a working knowledge of one or two drugs from each class of NSAIDs is important.

Opioid Analgesics

Opioid analgesics differ from NSAIDs in their mechanism of action, pharmacological features of the analgesia produced, and toxicity profiles. These differences have led to the common approach of simultaneous administration of opioid and nonopioid analgesics, often in a combined formulation.

Opioids are divided into the mild and strong analgesics, based on their relative potency (Table 50.3). This distinction is somewhat arbitrary, and potency *per $e* is not a good indicator of efficacy. Codeine is the prototype of the mild opioid analgesics. The duration of action (2—4 hours} is similar to that of aspirin and acetaminophen. It is used for acute or persistent pain of moderate severity, generally when NSAIDs alone have proved ineffective or are contraindicated. Codeine works better for nociceptive than neuropathic pain. The impression that neuropathic and deafferentation pains are not responsive to opioids is incorrect; opioids are an important option for patients with refractory neuropathic pain syndromes. Nausea is one of the more common and limiting side effects of codeine. If it occurs, switching to a different opioid may relieve the problem. Autonomic side effects, particularly constipation, are sufficiently common that they should be anticipated by prescribing stool softeners. Dysphoria is another common side effect. Oxycodone, propoxyphene, and meperidine are other mild opioid analgesics. Meperidine is particularly likely to cause dysphoria or less commonly to cause myoclonus, encephalopathy, and seizures. These toxic effects result from metabolites that accumulate with repeated dosing. Meperidine therefore should be avoided in patients requiring chronic treatment.

Morphine and hydromorphone are the prototypes of high-potency opioid analgesics. Morphine has a relatively rapid onset, especially when administered pa renters lly and a short duration of action, about 2-4 hours. A sustained-release oral preparation (MS Contin) with a duration of action of 8-12 hours is useful for patients who require chronic therapy. High-potency opioids, like mild opioids, may cause nausea, constipation, and dysphoria. Sedation and respiratory depression also may occur. Tolerance (tachyphylaxis) to the side effects develops over 1-2 weeks. Tolerance also develops to the analgesic effects of opioids, but this is not always clinically significant, lor example, many patients with metastatic cancer who achieve good pain relief with opioids can be maintained on stable doses over prolonged periods. In these patients, recurrence of pain, particularly when rapid, is more commonly caused by tumor progression than by the loss of analgesic efficacy because of tolerance.

Chronic opioid use is associated with physical dependence, in which a typical pattern of symptoms develop after rapid withdrawal, including irritability, chills, salivation, diaphoresis, and abdominal discomfort with nausea and vomiting. The time course and severity are a function of the opioid's potency and half-life. The onset of withdrawal symptoms is approximately 6-12 hours after stopping treatment with morphine, as opposed to 36—48 hours for methadone. To avoid acute withdrawal symptoms and exacerbating pain symptoms, care must be taken in discontinuing opiates or switching from one opiate to another. The use of opioids with mixed agonist-antagonist properties, such as pentazocine, may precipitate withdrawal or lead to deteriorating pain control when substituted for a potent mu-receptor agonist, such as morphine. Similarly, the use of naloxone, a potent mu-rcccptor antagonist used to treat serious CNS toxicity, must be undertaken very

Table 50.3: Commonly used opioid analgesics

	Drug	*Half-life*	*Dose equianalgesk to morphine 10 mg IM*		*Typical dasage*	*Comments*
			IM	PO		
Mild						
	Codeine	3 hrs	120	200	30-60 mg PO q4-6h	Often coadministered with acetaminophen Nausea, constipation, and dysphoria common
	Oxycodone (+ acetaminophen = Percocet) (+ aspirin = Percodan)	2-3 hrs		30	5 mg PO q4-6h	Often useful when codeine is not well tolerated
	I [ydrocodoiie (+acetaminophen = Lortab or Vicodin)	4 hrs		30	2.5-7.5 mg PO q4-6h	Same as oxycodone
	Propoxyphene (Darvon)	6-12 hrs		150-200	65 mg PO q4h	Active metabolite (norpropoxyphene) with long half-life (30-36 hrs)
	Meperidine (Demerol)	2 hrs	75	300	50-100 mg IM	Encephalopathy, myoclonus, and seizures due to metabolite (normeperidine) limit chronic use Contra indicated in patients taking monoamine oxidase inhibitors
Strong						
	Morphine	2-3 hrs	10	30-60	2-10 mg IM/IV 30-60 mg POq4h	With chronic use the IM:PO ratio falls from 1:6 to 1:3 Available in slow release preparation (MS Contin)
	Hydromorphone (Dilaudid)	2-3 hrs	1.5	7,5	1-4 mg POq4h	Good choice for chronic therapy due to high potency and short half-life
	Pentazocine (Talwin)	2-3 hrs	60	180	50-100 mg PO q4h	Mixed agonist-antagonist Ceiling effect for analgesia May precipitate withdrawal in opioid-dependent patients Encephalopathy with dose escalation
	Methadone (Dolophine)	15-30 hrs	10	20	10-20 mg PO q4-8h	Duration of analgesia is highly variable, often only 4-K hrs Long half-life leads to drug accumulation and prolonged CNS toxicity
	Lcvorphanol (Levo-Dromoran)	12-16 hrs	2 mg IM	4 mg PO	2-4 mg PO q4h	Like methadone
	Fentanyl transdermal (Dnragesic)	3-12 hrs when given IV	*	*	25-100 ug/hr transdermal patch every 3 days	CNS toxicities like morphine Slow onser with peak concentration at 24-72 hrs Reservoir effect leads to prolonged toxicity Slow titration

CNS = central nervous system.
*Dosc equivalence is not well defined, but the ratio of fentanyl (transdermal) to parenteral morphine is approximately 1:30.

judiciously for chronic pain patients. Only respiratory depression should be treated with naloxone, and the required dosage is only one tenth of that used for an acute overdose.

The development of psychological dependence, or addictive behaviors, such as craving, drug seeking, and other maladaptive behaviors, is a concern for patients and physicians alike with regard to chronic opioid therapy. These concerns are heightened by the great impact of drug abuse in modern society, but they also may interfere with the delivery of effective and appropriate pain treatment. In cancer patients, for example, fear of developing dependence has contributed to the undertrcarment of pain syndromes. The actual risk of developing psychological dependence has been addressed in two types of studies. Studies of **drug** addicts in the first half of this century indicated that up to

10% of addicts first received narcotics for medical purposes. More recent studies analyzing the rate of development of psychological dependence in large populations of medical patients receiving narcotics indicate that the risk is less than 1 %. For the purpose of defining the rate of an adverse outcome, the more recent studies arc more informative. These results also support the current view that physical dependence and psychological dependence are distinct phenomena. Advances in the understanding of addiction including the neural and biochemical basis of reward systems in the brain suggest that genetic factors are important in the likelihood of developing addiction (Lingford-Hughes and Nutt 2003). Dopaminergic and glutaminergic actions in the nucleus accumbens are important in the development of addiction. Polymorphic variations in the endogenous opioids and opioid receptors are common, but their role in addiction remains unclear (Mayer and Holt 2001}. The risk of addiction is increased in patients with depression and personality disorders as a relatively common comorbidity. For these reasons the risk of addiction may be higher in patients with psychogenic pain syndromes as opposed to those with nociceptive or neuropathic pain. A prior history of drug abuse or other addictions also influences the risk of developing psychological dependence to prescribed medications. In practice, the principal adverse effects of chronic opiate therapy are dysphoria, nausea, autonomic effects, and the risk of withdrawal symptoms; however, prescribing practices and patient acceptance remain heavily influenced by the potential for psychological dependence and abuse.

As with NSAIDs, the initial choice of an opioid analgesic is empirical, based on the nature and severity of the pain, the potential side effects, and the individual's medication history. In most cases, a short-acting opioid is the initial choice. The most common regimen is to start with a mild-potency opioid analgesic, either codeine, hydrocodone or oxycodone, often combined with acetaminophen, on a 4- to 6-hour dosing schedule. For persistent and chronic pain symptoms, regularly scheduled (i.e., around-the-clock) dosing with supplemental dosing for breakthrough pain is more effective than as-needed dosing. The dose is escalated until pain is controlled or toxicities occur. Using short-acting opioids, titration can be achieved in hours to days, unlike using NSAIDs, which may require weeks. Incremental dosing changes of less than 25% seldom produce significantly improved pain control for patients on chronic opioid therapy. During initial titration, however, larger increments often produce nausea, dysphoria, or sedation. Unlike the NSAIDs, opioid analgesics do not have a ceiling effect, and patients with chronic pain taking opioid analgesics who are tolerant to the sedative and respiratory depressant effects occasionally require grams of morphine per day to maintain good pain control.

Rapid titration of opioids for severe pain is best achieved with parenteral administration. Inability to tolerate oral medications is another reason to use parenteral opioids. Repeated intravenous boluses may be used, although continuous intravenous infusion has certain advantages in terms of efficacy, toxicity (i.e., lack bolus effects), and ease of administration. A short-acting agent, such as morphine or hydromorphone, is preferable for parenteral thctapy. Aside from trauma and surgery, the need for parenteral opioids usually arises in patients with long-standing pain syndromes, such as metastatic bone lesions, who have been using oral opioids. Determining the correct parenteral dosage requires a change in dosage to compensate for differences in potency between drugs and for the difference in oral versus parenteral efficacy (see Table 50.3).

If a continuous intravenous infusion is chosen, the total opioid dose of the prior 24 hours is converted to the milligram equivalent of parenteral morphine, which, divided over 24 hours, becomes the basal hourly rate. A loading dose approximately equivalent to 1 hour's dose (up to 30 mg of morphine) is given as a bolus. If parenteral therapy involves switching from one opioid to another in a patient whose pain is well controlled, the newly calculated dose should be decreased by 25-50% because the efficacy and cross-tolerance between opioids are incomplete. If pain control has been poor, only a 25% reduction is made. In addition to a basal rate, as-needed doses for persistent or breakthrough pain should be administered, often accomplished by a patient-controlled delivery pump. In this way, rapid titration can be achieved by recalculating the hourly basal rate, based on the combined basal and as-needed requirements. For rapid titration, a bolus is given each time the basal rate is increased.

The need for rapid intravenous titration of opioids often arises in patients with advanced cancer. In this group and in all patients with chronic pain syndromes that become rapidly worse, symptomatic relief must be achieved concurrently with attempts to define the exact reasons that pain control is being lost. Treatment of the underlying process, such as a bone or epidural metastasis or abscess, remains one of the most important aspects of pain management. The judicious use of radiotherapy for painful metastases often reduces the need for analgesics.

The approach to the patient requiring moderate- to high-dose chronic opioid therapy has evolved considerably. Frequent doses of short-acting agents become impractical at high doses because of the large amounts of medication needed. Switching to a long-acting opioid, such as methadone, is an effective approach for some patients, although methadone's analgesic effect is often much shorter than its pharmacological half-life. In addition, titration must be done slowly to avoid excessive steady-state levels that cause prolonged sedation and other adverse reactions. Newer approaches are based on the use of short-acting agents formulated for relatively slow or prolonged release.

MS Contin, the sustained-release oral preparation of morphine, provides relatively stable serum levels of morphine that can be supplemented with standard oral morphine on an as-needed basis for breakthrough pain.

Titration, with initial dosing based on the milligram equivalent of morphine taken in the prior 24 hours, is relatively easy to accomplish, A slow release oxycodone preparation, Oxycontin, can he used similarly.

Transdermal fcntanyl is another approach to continuous, chronic opioid therapy. Fcntanyl is an extremely porent synthetic opioid agonist with a very short half-life when administered intravenously. The transdermal system delivers doses ranging from 25 to 100 pg per hour for 2-3 days through the development of a subcutaneous reservoir at the site of the transdermal patch. The continuous release provides the long duration of analgesia. Because of the reservoir effect, however, the attainment of effective analgesia is delayed 24—48 hours, titration must be performed over several days, and the management of adverse effects is complicated by the persistence of active blood levels for 2 or more days after the transdermal patch has been removed. As with MS Contin, most patients on fcntanyl require a short-acting opioid, such as morphine or hydromorphonc, for breakthrough pain.

With increasing opioid dosage, the adverse autonomic and CNS effects become dose limiting for many patients. This is particularly true of patients with CNS metastasis or those who are concurrently taking orher sedative-depressant medications. Several approaches are available for patients with poor pain control in the setting of significant opioid toxicity. One approach is to switch to an equally potent analgesic dose of a different opioid, recalling that cross-tolerance is incomplere and effective analgesia may be obtained with a modest decrease in the equivalent dose of a different opioid. In addition, optimizing the use of nonopioid analgesics and other adjuvanr medications may allow a decrease in opioid requirements. The addition ot methylphenidate (Ritalin) is another way of reducing drowsiness when that symptom limits dose escalation with chronic opioid treatment. If drowsiness or other opioid toxicities remain unacceptable, pain control is poor, or both, regional administration of opioids via intrathecal or epidural catheters and neurosurgical approaches to pain control should be considered.

Both epidural and intrathecal administration of morphine provide relatively high concentrations of opioids in the cerebrospinal fluid, producing analgesia by direct action on opiate receptors in the spinal cord. The amount of opioid reaching systemic circulation is usually considerably decreased. These approaches generally are limited to patients with pelvic or lower extremity pain. Side effects include pruritus, urinary retention, nausea, and vomiting. Respiratory depression and other CNS side effects (e.g., sedation, confusion) may occur. Factors that predispose patients to adverse reactions are advanced age, the use of water-soluble opioids (e.g., morphine), high intrathecal doses, the concurrent systemic administration of opioids or anesthetics, and lack of opioid tolerance. Unlike the administration of local anesthetics, epidural opioids rarely cause transitory weakness.

Adjuvant Medications Useful in Pain Management

Opioids and NSAIDs often are used together because their mechanisms of action are different and complementary, and their side-effect profiles do not overlap. The opioid requirements are reduced, as is the likelihood of clinically significant opioid tolerance or dependence. Several other drugs with primary actions that are not analgesic have been used to improve pain control, including anticonvulsants, tricyclic antidepressants, benzodiazepines, stimulants, corticosteroids, topical capsaicin, and anesthetics.

Anticonvulsants

Phenytoin, carbamazepine, gabapentin, and occasionally valproate are used to treat neuropathic pain syndromes, including focal (e.g., postherpetic neuralgia or trigeminal neuralgia) and diffuse neuropathies (e.g., diabetic neuropathy) (Backonja 2002; Kingery 1997). Controlled trials have demonstrated that gabapentin is superior to placebo and equivalent in efficacy to amitriptyline (Backonja et al. 1998; Morello et al. 1999; Rowbotham et al. 1998). Lancinating pains, presumably arising from abnormal neuronal discharge, respond best. Anticonvulsants are also useful for central deaf fere ntation pain syndromes. The dose required to achieve pain control is not necessarily the same as that required to produce therapeutic levels for anticonvulsant purposes, and gradual titration, usually over weeks, is required. Responses are difficult to predict, and serial trials often arc required in attempts to find an effective agent for these pain syndromes.

Tricyclic Antidepressants

Amitriptyline and several other tricyclic antidepressants improve pain control when used with other analgesics for nociceptive pain and when used alone for neuropathic pain syndromes. The analgesic effect is independent of the presence of depression or any effect on mood. Blockade of serotonin and norepinephrine reuptake is probably the mechanism by which analgesia is produced; however, rhe analgesic activity of newer and more selective serotonin reuptake inhibitors (e.g., fluoxetine) is not established. The commonly used tricyclic compounds all have considerable anticholinergic activity, and some of the common toxic effects, such as constipation, overlap with the autonomic side effects related to opioid analgesics.

Benzodiazepines and Baclofen

Diazepam and baclofen are useful in managing spasticity, which occasionally is accompanied by muscle pain. Baclofen is also beneficial in some patients with trigeminal neuralgia that is refractory to other drugs and may be beneficial for other neuropathic pain syndromes. For most patients, however, benzodiazepines add lirrle or no benefit

fot analgesic purposes but, rather, add significantly to the problems of sedation and dysphoria. Avoidance of CNS depressants is an important part of minimizing opioid toxicity.

Stimulants

Convctscly, the judicious use of stimulants can improve pain control and reduce opioid toxicities. For example, dextroamphetamine and methylphcnidatc enhance morphine-induced analgesia and reduce the sedation associated with opioid treatment. Caffeine also improves analgesia and reduces sedation from opioids.

Corticosteroids

Corticosteroids contribute substantially to pain control caused by (1) inflammatory lesions of bone, joints, muscle, or blood vessels; (2) nerve root or spinal cord compression, particularly in relation to epidural mass lesions; and (3) headaches from cerebral edema, elevated intracranial pressure, and meningeal irritation. Corticostctoids are the primary treatment lor some inflammatory conditions, such as temporal arteritis. Their use as an adjunct for pain control generally is limited to short-term treatment because of the niaiiv side effects associated with chronic therapy. Rheumatic pain complaints may follow cessation of corticosteroids.

Capsaicin

Topical capsaicin produces depletion of substance P from primary nociceptor afferents and provides satisfactory pain relief in more than 30% of patients with posthctpctic neuralgia for whom other medical treatments were unsuccessful. Unfortunately, initiation of treatment often causes severe burning pain that may prevent continuation of treatment.

Others

Several other drugs are used infrequently for refractory pain syndromes, usually neuropathic and deafferentation syndromes. These include anesthetic and antiarrhythmic agents, such as mexiletine; neuroleptics, such as flupbenazine, and a-adrenergic agents, such as clonidinc.

Nonpharmacological Approaches to Pain Management

Ablative Procedures

Regional Nerve Blockade. Nerve blocks with local anesthetics, such as lidocaine, commonly are used to manage transitory, severe, localized pain. Epidural blockade for obstetric and gynecological procedures is the most common application of a regional nerve block. Other uses are to treat postoperative incisional pain and delayed operative pain that may occur after thoracotomy. Epidural blockade is particularly useful when pain is localized to one or two dermatomal segments on the trunk. Localized neuropathic pain, such as with acute herpes zoster or traumatic neuroma, also can he controlled with nerve blocks.

Phenol can be injected to produce permanent neurolysis in patients with cancer who are expected to survive less than 1 year and in patients with intractable and severe pain who obtain significant relief with temporary nerve blockade. Burning, dysesthetic pain from deafferentation (anesthesia dolorosa) often develops months after neurolysis and may he more troublesome than the original pain complaint. The list' of temporary blockade and neurolysis is limited by their nonselective effect on all nerve fibers. Blockade of nerves to the limbs and sacral segments usually is avoided because sensory and motor deficits accompany analgesia.

Sympathetic blockade is an important component in the treatment of causalgia and related disorders. It usually is accomplished by serial blocks with local anesthetics and occasionally by neurolytic blockade. Pain relief may last long beyond the anesthetic agent's duration of action. Stellate ganglion blockade is performed for arm pain; celiac plexus blockade, for upper abdominal pain, such as that occurring with pancreatic cancer; and the lumbar sympathetic ganglia blockade, for pelvic, rectal, and leg pain. Fluoroscopic or computed tomographic guidance often is required for accurate injection placement.

Peripheral Surgical Approaches. The use of peripheral nerve and dorsal nerve root transection generally is confined to patients with well-localized or truly segmental truncal pain syndromes that have responded to nerve blockade. As with neurolysis, the late occurrence of painful dysesthesia is common and limits enthusiasm for this approach. Sympathetic ganglionectomy occasionally is performed in patients with causalgia and related syndromes who benefit transiently from sympathetic blockade.

Central Surgical Approaches. The most common central ablative surgical procedure for pain management is an anterolateral spinal cordotomy, producing transection of the latetal spinothalamic tract. As with other surgical procedures for pain management, strict criteria for patient selection—including failure of appropriate pharmacological means—must be established. Patients whose life expectancy is 12 months or longer generally are not appropriate because the analgesic benefit declines with time, and painful dysesthesia is a late complication. Thus the procedure is largely limited to patients with cancer. The best candidates are patients with unilateral somatic, nociceptive pain in one leg or the trunk. Visceral and neuropathic or deafferentation pain syndromes are not effectively controlled. Bilateral thoracic cordotomies sometimes are performed for midline lower abdominal, pelvic, or bilateral leg pain, but urinary and fecal incontinence are frequent complications. Initial

pain control is achieved in about 80% but lost in half after 6-12 months. Painful dysesthesia develops in 20% or more by 1 year. Corticospinal tract deficits are uncommon. In rare patients on very high doses of narcotics, the acute abolition of pain by surgical means or nerve blockade is accompanied by acute respiratory failure, which may be caused by an acute change in opioid tolerance and can be reversed with naloxone. Bilateral cervical cordotomies are associated with apnea resulting from the interruption of fibers subserving ventilation in about 5% of patients.

Other targets for ablative pain control procedures include the periaqueductal gray, trigeminal nucleus, thalamus, primary sensory cortex, frontal lobes, and portions of the limbic system such as the cingulate gyrus. Although few comparative data are available, no pain control procedure appears to be superior to cordotomy for pain syndromes originating below the cervical level. Analgesia tends to be transitory, and late dysesthesia is common to all procedures involving the spinothalamic tract, the thalamus, and its primary sensory projections. Destructive lesions in the cingulate gyrus interfere with the emotional experience associated with chronic pain without producing analgesia.

Another procedure used primarily to treat pain from disseminated bone metastases of hormonally sensitive cancers (i.e., breast and prostatic carcinoma) is pituitary ablation, which usually is performed by alcohol instillation via a transsphenoidal approach.

Modulating Procedures

The concept that nociceptive input can be reduced by peripheral stimulation is fundamental to the gate theory of pain transmission. In practice, this is accomplished most often by electrical stimulation using TENS. Placebo effect contributes substantially to the analgesic efficacy of TENS, although some studies of acute pain syndromes, such as postoperative pain, indicate benefit greater than obtained with sham stimulation. TENS also is used for chronic pain syndromes, particularly neuropathic pain, although studies have provided mixed results. Although some controlled studies demonstrate benefit, a randomized comparison between TENS and exercise for chronic lumbosacral pain demonstrated no difference between TENS treatment and placebo. The combination of percutaneous electrical stimulation using acupuncture-like needles for electrodes (PENS) was compared in a randomized trial with TENS, simple exercises, and a sham procedure for patients with chronic low back pain. PENS was associated with a reduction in analgesic usage, improved physical activity, and improved sense of well-being (Ghoname et al. 1999). Additional controlled trials arc needed to define the role ot these methods in acute and chronic pain management; however, it is clear that some patients obtain substantial improvement from these nonpharmacological approaches.

Stimulation of dorsal root fibers and the dorsal columns using epidural electrodes has been performed for 20 years. Clear indications arc debated but generally include (1) poor efficacy of standard medical therapy; (2) an identified cause for the pain syndrome, usually with a neuropathic component and without a primary central cause of deafferentation; and (3) a dermatomal distribution of pain that can be effectively included in a region of stimulation-induced paresthesias. Areas that are difficult to cover include the C2 vertebra; posterior axial structures, including the neck and lumbosacral spine; and the perineum. An array of electrodes, usually on a single wire, is inserted in the dorsal epidural space cither by laminectomy or percutaneously in the low- or midthoracic region. A trial period of 4-7 days of stimulation is performed to assess pain relief. If benefit is observed, the electrodes are permanently implanted.

Most series are dominated by patients with chronic lumbosacral pain after laminectomy, the so-called failed back syndrome, which is often attributed to arachnoiditis. Next most common are patients with other neuropathic pain syndromes, such as neuropathies. Fifty percent to 70% of patients show initial improvement. Long-term pain relief occurs in 40%, however, and many continue to require some analgesic medication. Mechanical problems, such as electrode breakage, have been a common cause of failure. Although these results appear hopeful, given the chronic, refractory nature of the pain syndromes addressed, prospective studies with carefully focused indications and rigorous follow-up assessment are required. One such study, a controlled trial of epidural stimulation and physical therapy versus physical therapy alone for patients with CRPS, did demonstrate a substantial reduction in pain intensity with epidural stimulation. However, no improvement in functional status was observed (Kemler et al. 2000).

Stimulation of the periaqueductal gray and primary nuclei of termination of the spinothalamic and trigeminothalamic pathways (i.e., ventral posterolateral and ventral posteromedial nuclei, respectively) has been employed for chronic neuropathic pain syndromes, including many with deafferentation components. Tic douloureux, postherpetic neuralgia involving the face, pain after cerebral infarction, postcordotomy pain, and brachial plexus avulsion have been approached in this way. As with spinal cord stimulation of the patients who have a good initial response, only about 50% report long-term benefit. Other areas used for pain control by neurostimutation include the motor cortex and the septal area. Lacking well-defined indications and controlled trials with rigorous assessment of outcome, central neurostimulation for chronic pain is an optional treatment for those whom medical therapy does not help.

CONCLUSION

Pain, the most common of all medical complaints, is becoming increasingly well understood. It is a complex

group of neurophysiologies! processes that may arise from (1) the normal response of the nervous system to tissue injury; (2) pathological alterations in neural activity in nociceptive, sensory, and other pathways; or (3) no identifiable pathology. In practice, treatmenr is based on defining the mechanisms by which the pain symptom is generated. A relatively high likelihood of therapeutic success is achieved in the case of nociceptive pain, but only a modest rate of success is obtained in the treatment of neuropathic and idiopathic pain syndromes. The understanding of pain mechanisms, both in terms of basic science and as clinical phenomena, remains incomplete. Nonetheless, this mechanistic approach is central to formulating a rational therapeutic strategy. Treatment applied without an understanding of the mechanisms involved has a high likelihood of failure, unnecessary toxicity, and potential for irreversible tissue injury.

The goal of pain management is complete pain relief. Too often, pain relief is not pursued aggressively, so that the symptom can he used as an indicator of disease activity (e.g., in patients with cancer). In comparison with the array of other clinical, laboratory, and radiographic measures of disease activity available for neoplastic, infectious, and inflammatory diseases, progressive pain as an isolated symptom is generally a moderately sensitive and modestly to moderately specific indicator of disease activity. Thus using pain as an indicator should be considered secondary to relief of the symptom, assuming that the cause of the pain is understood. The most significant factor limiting complete relief of nociceptive and neuropathic pain is analgesic toxicity. Much of pain management beyond knowledge of basic analgesic pharmacology centers on this issue.

Another reason to treat both acute and chronic pain aggressively is that for some patients intense or recurring pain leads to chronic changes in the nervous system. It is likely that these changes contribute to the development of some chronic pain syndromes. Similarities between pain and epilepsy in this regard have been pointed out recently. Some of rhe neurophysiological and neurochemical changes that underlie epilepsy are operative in the genesis of chronic neuropathic pain disorders including kindling-related phenomena, inherited and acquired membrane ion channel abnormalities, and excitatory amino acid-related neuronal injury (Post 2002).

Pain management has improved significantly as the result of systematic education programs for medical students, house officers, fellows, physicians, and other health care providers about pain assessment and the basic principles of analgesic therapy (see recommendations of the American Pain Society Quality of Care Committee 1995). However, pain management training in neurology residencies tends to be very limited, and a large majority of practicing neurologists report being inadequately trained in this area (Galer et al. 1999).

Advances in pain management also have been fueled by important basic neuroscience developments, such as the elucidation of the endogenous opioid systems, and increasingly sophisticated clinical analysis of pain syndromes. Clinical necessity will continue to fuel the development of better ways to treat patients with pain.

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Chapter 51
Principles of Neurointensive Care

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A neurointensivist is a physician with special training in caring for critically ill patients. There are child neurologists with this specialization for children and adult neurologists who care for adolescent, adult, and geriatric neurology and neurosurgery patients. This chapter concentrates on the adult population. Such patients require specialized intensive nursing and medical care in modern specialized Neurosciences Critical Care Units (NSUs). The creation of NSUs stemmed from the realization that neurocritically ill patients have special and different needs, which can only be met by a team of physicians and nurses acutely aware of the interactions between systemic and central nervous system (CNS) alterations.

Neurologists and neurosurgeons have been involved in providing critical care since the beginning of the twentieth century. During the polio epidemics neurologists became the primary caregivers for affected patients, including critical care administration. However, the advent of massive vaccination campaigns and eventual eradication of poliomyelitis in developed countries led to a decline in clinical ncuroscicntists' participation in critical care delivery. This was followed by the birth of general critical care units in the 1960s to care for patients with acute and complex respiratory and cardiovascular issues. These units were mostly direcred by physicians with internal medicine training. A notable and important exception was Dr. David Jackson, a neurologist at the University Hospitals of Cleveland (Case Western Reserve University), who took an active part in and eventually became the director of a general medical intensive care unit in the 1970s. He can certainly be credited with being the first practitioner to have demonstrated that clinical neuroscientists can effectively care for critically ill patients. However, the resurgence of NSUs proper can be traced to the beginning of the 1980s when a few NSUs were set up at major academic centers in the United States. These units were directed by physicians, who were double-boarded in neurology and internal medicine. By the mid 1980s and early 1990s neurosurgical techniques and neuromoniroring devices had furrher advanced allowing for better management of complex neurocritically ill patients.

The establishment of NSUs brought along the need for a critical care subspecialty made up of intensivists from different medical and surgical backgrounds who had a keen interest in affecting the neurological outcome of patients. This subspecialty has been called *neuracritical care* or *critical care neurology and neurosurgery,* and the specialist is a *neurointensivist.* The role of the neuroinrensivist primarily involves caring for and the management of cririeally ill neurological and neurosurgical patients and discussing their clinical condition and prognosis with family members. They also actively participate in the teaching and training of medical and nursing staff, consult in other critical care areas to prognosticate on neurological outcome and to determine brain death, and participate in institutional critical care committees to develop and monitor policies pertaining to neurocritical care.

This chapter discusses the basic principles of neurocritical care as it is delivered in the United States. We will present general principles of NSU organization, neuromoniroring, and general management of neurocritically ill patients. It concludes with descriptions of the most common neurological conditions, emphasizing management in the NSU. Because of the complexity of the topic, a detailed presentation of netirocririeal care is beyond rhe scope of this chapter.

ORGANIZATION OF A NEUROSCIENCES CRITICAL CARE UNIT

NSU care is expensive and resources are scarce. Therefore appropriate selection of patients is important. In general, patients admitted to the NSU should include those that are likely to benefit from this level of care. This implies that those patients who are not sick enough to warrant critical care or who have catastrophic conditions that result in impending death may not be good candidates for admission to NSU. The Society of Critical Care Medicine has provided guidelines for admission criteria to an ICU (Task Force of the American College of Critical Care Medicine 1999). However, we should emphasize that no definite data are available to validate the utility of such criteria. Therefore neurointensivists should create policies and mission statements specific to each hospital and level of expertise available.

In general, we have determined at the University Hospitals of Cleveland at Case Western Reserve University that patients admitted to NSUs, regardless of the underlying pathology, should fall into one or more of the following broad categories:

1. Being at risk of serious event as a result of the disease process
2. Requiring highly specialized and concentrated nursing and medical care
3. Requiring specific and unique interventions or techniques not appropriate or not available for use on the other in-patient divisions

Table 51.1 presents a summary of admission criteria as they are currently maintained in our NSU.

Upon arrival at the NSU patients are treated and monitored for any signs of either medical or neurological instability. Once such signs arc deemed stable, patients are usually discharged from the NSU to a less intensive environment for continued care (see Table 51.1). A clear and detailed plan of such continued care must be outlined and discussed with the primary neurological or neurosurgical teams to minimize the number of further complications and readmissions.

The other important aspects are the environment and physical appearance of the NSU. The Society of Critical Care Medicine has put forth recommendations for ICU design that should also be observed when planning an NSU (Task force on Guidelines Society ot Critical ("are Medicine 1988; American College of Critical Care Medicine 1999). These arc suminarized in Tabic 51.2, A physician NSU director is required. The director ideally should be a neurointensivist who will be heavily involved in the care of patients, the administrative aspects of the NSU, and development and implementation of educational activities for both medical and nursing staff. Other neurointensivists can also participate in the overall organization of the NSU under the guidance of the director. A nurse manager should be appointed to help with management of the delivery of the highest-quality care possible. This nurse manager should have both RN and MSN degrees and have the ability to foster cooperation and participate in all administrative and academic activities in the NSU. The best care is provided when an atmosphere of cooperation and camaraderie is achieved by all participating health care providers.

Table 51.1: Summary of NSU admission and discharge criteria as they are enforced in our institution

Admission criteria
Acute respiratory failure
Hemodynamic instability
Hypertensive crisis
Massive gastrointestinal bleeding
Drug overdose
Metabolic emergencies (severe hyperkalemia; hypercalcemia; acute hyponatremia; addisonian crisis; diabetic ketoacidosis; or hyperosmolar states)
Coma of any etiology in need of intensive care
Status epileptic us
Cranio-spinal post-operative patient, including endovascular procedures
Untreated cranio-spinal mass effect
Acute ischemic stroke undergoing thrombolysis
Intracranial hemorrhage
Acute, treatable, or diagnostically uncertain unstable neuromuscular disease
Critical, reversible cerebral ischemia
Severe traumatic head and spinal cord injury
Need for external ventricular drainage or neutornonitoring that can only be provided in the NSU
Discharge criteria
Respiratory stability[7]
Hemodynamic stability
Neurologic system and signs are without unexpected change
Nursing needs that can be met in less intensive environment
Terminal illnesses in whom NSU care has been deemed inappropriate

NEUROLOGICAL AND SYSTEMIC MONITORING

The most important and simplest form of monitoring in the NSU is the serial neurological examination, which can be performed by nursing staff and physicians. Despite its importance, a carefully performed neurological exam in neurocritical care has limitations. These include limitation of neurological assessment by pharmacological interventions (e.g., neuromuscular blockade, propofol or midazolam sedation, or barbiturate coma); difficulty with recognizing certain pathological conditions (e.g., nonconvulsive status epilepticus, vasospasm, early increased intracranial prcs sure |ICP| or cerebral reactive hyperemia); interobserver variability (i.e., the neurological exam is quite operator-dependent); qualitative rather than quantitative assessment (e.g., an impression of elevated 1CP may be accurate yet it

Table 51.2: Guidelines for NSU design and organization

Physical appearance
Floor plan should be designed by a multidisciplinary team (NSU director, RN manager, architects, administrators, and engineers)
Patient bed area should have ample space and provide a supportive environment
Patient bed area should provide for direct or indirect visualization of patients to facilitate detection of patients' status
Necessary equipment to support the needs of the patients and the NSU medical and nursing personnel should be available and meet regulatory requirements
All physiological continuous monitoring should be available (display of waveforms and digital values for cardiac, arterial, venous, intracardiac, and intracranial pressures and respiratory monitoring)
Computer applications should be available for data input, retrieval, and analysis
Isolation rooms should be installed
Work areas and storage of critical care data and supplies should easily accessible to the staff
Separate clean and dirty utility rooms with separate access doors should be available
A staff lounge with toilet facilities should be provided
A nourishment preparation area should be provided
A conference room should be available
A visitor's lounge should be provided near the NSU
Transportation of patients to and From the unit should be easily-carried out
Physician on-call room should be next to the NSU
Neurocritical Care Personnel
A physician NSU direcror
Other neurointensivists
A nurse manager
Other nursing staff with special training in neurocritical care
Twenty-four hour in-house coverage by medical staff
Physician subspecia lists available for consults
Rcspitatory therapists at all times
Pharmacy services at all tunes
Other personnel: unit clerks, physical and occupational therapists, pastoral care specialists, social workers, dietary specialists, and biomedical en gin nee rs
A clinical laboratory available 24-hours a day with tapid transport systems

cannot quantify the severity of the elevation); and finally the tendency to recognize problems after they have occurred rather than foreseeing them. Different monitoring techniques are currently used to complement the neurological examination in the neurocritically ill patient. These include systemic and brain monitoring methods. The latter methods are capable of providing information regarding whole or regional brain functions, as is discussed later. Despite the availability of multiple monitoring modalities, there is not enough literature to support the use of one over the others. In fact, the current trend is for neurointensivists to use so-called "multi-modality neuromonitoring," which involves combining several systemic and brain monitoring techniques in the hope of achieving the best possible neurological outcome (Kirkpatrick, Czosnyka, and Pickard *1996;* Andrews 2000; Alvarez del Castillo 2001).

Nonbrain Monitoring

Systemic or nonbrain monitoring comprises continuous or intermittent measurement of arterial blood pressure (ABP), core body temperature (T), and arterial blood oxygenation iZimmerman and Dcllinger 1996; Cnuliano et al. 2000: Fallis 2000). Continuous ABP monitoring is preferred and is easily accomplished by the insertion of an indwelling cannula into a medium caliber artery, which allows for a visual display of arterial waveforms. Such continuous monitoring is very important to ensure proper ABP management in the NSU. The most common examples of benefits include avoiding lowering ABP, which may exacerbate ischemic injury in patients with acute ischemic stroke; controlling excessive elevations of ABP, which may lead to hematoma expansion in patients with intracranial hemorrhage (ICH) or may increase the risk of ICH following thrombolysis for acute ischemic stroke; guiding induced hypertension in patients with vasospasm after subarachnoid hemorrhage (SAH) and in those with critical vascular stenosis; helping to control ABP in patients at risk for autonomic instability (e.g., G-uillain-Barre syndrome [GBS]) and septic shock (e.g., bacterial septicemia or meningitis); and maintaining adequate cerebral perfusion pressure (CPP) in patients with elevated ICP.

The main purpose of T monitoring in the NSU is twofold: detection of hyperthermia in patients with systemic or brain infections, and maintenance of normothermia or hypothermia to protect the brain from further insult (Busto and Ginsberg 1998). The most accurate way to measure T is via recordings from a pulmonary artery catheter (PAC) thermistor. However, this method is invasive and can only be carried out in those patients with specific indications for PAC insertion. More practical approaches include oral and tympanic methods. **The** former appears to be more reliable, less subjected to operator variability, and may be useful even in patients with endotracheal tube placement. Bladder and rectal probes correlate well with PAC thermistor readings. Their main drawback is that there is a lag between T change detection by PAC thermistor and bladder probe, which may delay interventions.

Continuous arterial blood gas determination has undergone significant refinement in the past few years. Newer intra-arterial fiberoptic catheters are capable of providing reliable measurements of pH, PaOz, Paco2. This allows for early detection of abnormalities and prompt recognition and intervention.

Brain Monitoring

Brain monitoring techniques have been developed and refined over the past twenty years to include a variety of methods that are available for use in the NSU. These techniques are divided into two main categories: whole- and

regional-brain monitoring. Whole-brain monitoring techniques measure ICP, electrical potentials, and venous oxygen saturation. Regional-brain monitoring focuses on cerebral blood flow (CBK), cerebral blood flow velocities (CBFV), brain tissue metabolism, and oxygenation.

Whole-Brain Monitoring

Intracranial Pressure Monitoring. The Monro-Kellie Doctrine, one of the most basic principles of intracranial physiology, states that as a result of the rigid skull the intracranial space represents a fixed volume, and that an increase in the volume of any of its three constituent compartments (brain, CSF, blood) must be met by a corresponding decrease in the volume of other compartments or ICP will rise. This is clinically relevant in brain matter herniation from an expanding lesion and in the use of hyperventilation to reduce the volume of the blood compartment in elevated ICP states. Normal mean ICP is less than 10 mm Hg, and levels exceeding 15 mm Hg are generally considered abnormally elevated. However, it has been suggested that levels greater than 20 mm Hg for at least 2 minutes be used as a treatment threshold. CPP is telatcd to ICP and to mean arterial pressure (MAP) by the equation: CPP—MAP — ICP. Thus assuming a relatively constant MAP, an elevation of ICP will be paralleled by a reduction of CPP. It has also been argued that the main purpose of ICP monitoring is maintenance of normal CPP {normal >70 mm Hg), because the lattet may be more telatcd to secondary ischemic injury (Rosner 1993).

ICP is pulsatile and has systolic and diastolic components (Lang and Chestnut 1994). In addition to the value of mean ICP, these components also need to be evaluated carefully. The normal ICP waveform consists of a 3-pcakcd wave (Figure 51.1). PI, the first and generally the tallest peak, is also known as the percussion wave and corresponds to the transmitted systolic blood ptcssure. P2 (the tidal wave) and P3 (the dictotic wave) are normally smaller peaks, and the notch between them corresponds to the dicrotic notch of the arterial waveform. As ICP increases, P2 and P3 rise to the level of and then surpass PI, and ultimately with continued elevation of ICP the waveform loses distinct peaks and assumes a triangular morphology. During pathologic states of sustained elevations of ICP, the so-called "plateau wave (or A-wave) of Lundberg" can be observed. This A-wave has a plateau motphology that reflects a sudden dramatic sustained elevation in ICP to levels of 50-100 mm Hg. Plateau waves indicate critically low intracranial compliance, such that vety minor variations in intracranial volume result in marked changes in ICP.

Since the 1950s several ICP monitoring devices have been marketed. These include intraventricular, epidural, subarachnoid, and inttaparenchymal fiberoptic catheters

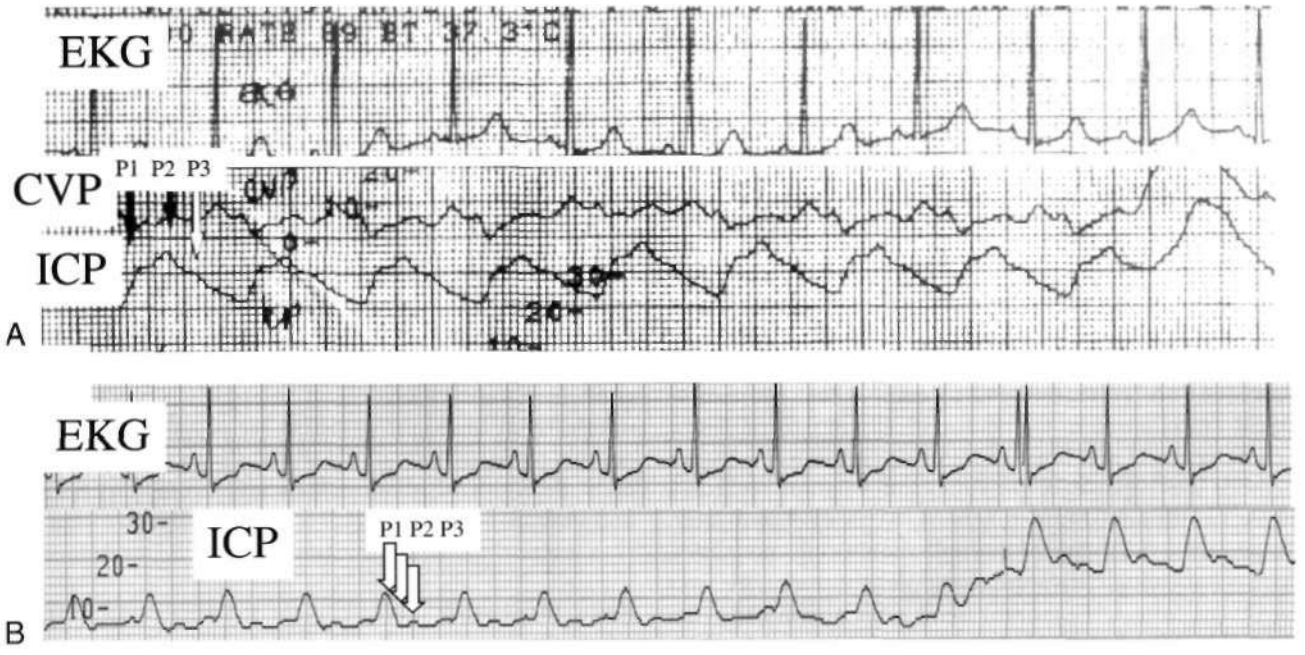

FIGURE 51.1 (A) A composite tracing of systemic and cerebral hemodynamic waveforms shows the electrocardiogram (ECG), central venous pressure (CVP), arterial blood pressure, ."id intracranial pressure (ICP). The PI, P2, and P3 waves of the ICP are outlined. P2 is equal to or higher than PI in this patient with an elevated ICP of 22 mm Hg. (B) Normal ICP with PI higher than P2, which is buried in the downslope of PI.

("Recommendations for intracranial pressure monitoring technology" 2000). A thorough review of these devices is beyond the scope of this chapter. However, in general the intraventricular cathetets remain the gold standard but are associated with the highest rate of infectious and mechanical complications. The most common indications for ICP monitoring in patienrs after traumatic head injury include patients in coma (Glasgow Coma Score [GCS| of 8 or less) with an abnormal head computed tomography (CT) findings; patients in coma with a normal head CT findings but at least two other risk factors for elevated ICP (age older than 40, abnormal posturing to pain, systolic blood pressure [BP] under 90 mmHg); and other head-injured patients at the physician's discretion (American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care 2000). In general, NSU patients with hemispheric processes associated with midline shift and depressed consciousness should also be considered for ICP monitoring,

Jugular Bulb Oximetry, Jugular bulb oximetry measures the oxygen saturation of venous return from the brain (normal >50%) (Feldman and Robertson 1997; Robertson et al. 1989; Cruz ct al. 1991). The fundamental goal of jugular venous oxygen saturation ($Sjv0_2$) monitoring is to provide a continuous index of the changing balance between cerebral oxygen delivery and cerebral oxygen consumption or metabolic requirement. Simultaneous determination of SjvOi using the jugular bulb catheter and arterial oxygen saturation (Sao_2) allows for the calculation of the intracranial arteriovenous oxygen difference (AVDO2) (normal 24^42%). From this parameter cerebral o\yju'ii con si 1111 prion :.ilso ruicn'cd to as cerebral metabolic rate) can be calculated as the product of $AVD0_2$ and CBE. The cerebral oxygen extraction rate (0_2ER) can then be derived as the ratio of cerebral oxygen consumption to cerebral oxygen delivery.

Indications for $Sjv0_2$ monitoring in the NSU have included head injury particularly but also include SAH, cere lira 1 infarction, and perioperative monitoring for various intracranial procedures. Advantages of the jugular bulb catheter as a monitoring modality include the practicality of continuous bedside monitoring, the capability to confirm the oximeter by drawing blood through the catheter, and the numerous physiological parameters that can be derived from the $Sjv0_2$ to arrive at a picture of cerebral oxygen balance. Disadvantages of the catheter include its susceptibility to artifacts of positioning and its invasiveness (Latronico et al. 2000).

Electrophysiological Monitoring: Electroencephalography and Evoked Potentials. The use of electroencephalography (EEG) in the NSU setting has dramatically affected patient care. This section discusses its salient applications relevant to the care of the neurocritically ill patient. Readers are referred to an excellent review by Jordan (1995) delineating the use of EEG as a monitoring tool. The utilization of continuous EFG monitoring is based on four major neurobiological rationales: (1) its close relationship to cerebral metabolic rate; (2) its sensitivity in detecting hypoxic-ischemic neuronal dysfunction at an early stage; (3) its obvious primacy as a monitor of seizure activity; and (4) its value in cerebral localization. Thus continuous EEG has been advocated as another routine tool for all NSU patients.

Despite the fact that the technical aspects of EEG application in the NSU do not differ greatly from the standard outpatient EEG, some factors arc relatively unique to the NSU setting. The main differences are the abundance of artifact sources (ventilators, intravenous pumps, dialysis pumps, other electrical machinery, suctioning) and the inability of the patient to cooperate secondary to various degrees of encephalopathy.

The most common indication for EEG monitoring includes generalized convulsive status epilepticus (GCSE) because the clinical ascertainment of ongoing seizure activity is often obliterated by the administration of various sedatives and analgesics in the NSU. Once such ongoing seizures arc found, the EEG becomes essential for monitoring the effects of further aggressive management, including the administration of barbiturates or general anesthetics to achieve a burst-suppression pattern. Detection of nonconvulsive seizures and nonconvulsive status epilepticus (NGSE) is equally important and can only be accomplished by EEG monitoring (Young, Jordan, and Doig 1996). Continuous EEG monitoring has revealed nonconvulsive seizures in *35%* of NSU patients in one study with a 76% incidence of NCSE. Other applications of continuous EEG monitoring, especially in patients in coma, include confirmation of metabolic encephalopathy, psychogenic unresponsiveness, locked-in state, and brain death (Diringer 1992; Synek 1988; Wijdicks 1995).

Evoked potentials have a more restricted role in the NSU (Moulton, Brown, and Konasiewicz 1998). The median nerve somatosensory evoked potential (SEP) has been mostly used. The technical details are discussed in Chapter 36A. Bilateral absence of the N20-P22 response has been associated with poor prognosis in coma in several studies, generally indicating outcome no better than a persistent vegetative state. SEPs, like EEG, have also been proposed as a confirmatory test to support a clinical diagnosis of brain death, again based on bilateral absence of the N20-P22 response.

Regional'/Focal-Brain Monitoring

Transcranial Dopplcr Ultrasonography, Transcranial Doppler ulttasouography (TCD) is a noninvasive technique to evaluate the mean cerebral blood flow velocity (MCBFV) in the large intracranial arteries. TCD can easily be done at the bedside (Manno 1997). TCD takes advantage of the principles of ultrasound and Doppler shift to image

erythrocyte flow in the basal cerebral arteries. This allows the operator to determine the presence or absence, velocity (systolic, diastolic, and mean), and direction of blood flow. The graphic waveform depicted on the screen will indicate depth of insonation, MCBFV, angle of insonation, and the so-called "pulsatility index" (PI). The latter is calculated as peak velocity minus end diastolic velociry divided by mean velocity and represents downstream resistance such as that found during ICP elevations. Another commonly followed parameter is the ratio of middle cerebral artery (MCA) to extracranial internal carotid artery (ICA) MCBFV (hemispheric index or Lindegaard's ratio), which is used to distinguish vasospasm (ratio >3) from hyperemia (ratio <3).

Three approaches are routinely used to in son ate the cerebral vessels: transtemporal, transorbital, and suboccipital. The transtemporal approach is used to insonate the proximal segments of the MCA and the anterior cerebral artery (ACA), the ACA/MCA bifurcation, the posterior cerebral artery (PCA) and a portion of the carotid siphon. The main constraint with this approach is that in about 10% of patients, particularly elderly females, it is difficult to insonate any of the cerebral vessels due to skull thickness. The transorbital approach iusonates the ophthalmic artery and most of the carotid siphon. The suboccipital approach insonatcs the vertebrobasilar system,

The major indications for TCD in the NSU are determination of vessel patency (absence or presence of MCBFV); identification of focal vessel stenosis (elevated MCBFV); cerebral vasospasm monitoring after SAH (MCBFV>120 cm/sec, Lindegaard's ratio >3, and MCBFV increments >50 cm per second within a 24-hour period) (Suarez et al. 2002); verification of cerebral hyperemia after traumatic brain injury (elevated MCBFV with Lindegaard's ratio <3); and confirmation of the clinical diagnosis of brain death (severely diminished MCBFV, absent diastolic flow, reverberating flow, and severely elevated PI) (Hassler, Steinmetz, and Gawlowski 1988).

Near-Infrared Spectroscopy (Cerebral Oximetry). Although the technology is not yet in widespread use, near-infrared spectroscopy (NIRS) potentially fills a significant void in the NSU by providing a noninvasive means of monitoring cerebral oxygen availability (Jobsis 1977; Lewis et al. 1996). NIRS is based on the ability of incident light of 700-1000 nra wavelength to pass through tissues into all components of the vascular tree, indicating by its absorption characteristics trends in the oxygenation state of hemoglobin. This provides a noninvasive picture of the adequacy of tissue oxygenation.

NIRS has been used for cerebral oximetry in head injury, epilepsy, cerebral venous thrombosis undergoing endovascular thrombolysis, and ischemic stroke. However, the reliability of NIRS has also been called into question because normal readings have been obtained over areas of hemispheric infarction. In addition to this, NIRS is sensitivity to extraneous light, susceptible to motion artifacts and signal drift. Moreover, there are frequently problems obtaining a signal through intracranial hematomas or through blood in the CSF, and it usually monitors focal regions. The main advantages of NIRS are that it is noninvasive, safe, can be performed at the bedside, and has the potential to be used as a trend monitor, particularly when used in conjunction with other monitoring modalities.

Regional Cerebral Blood Flow Techniques. Thtee methods have been introduced into clinical practice to measure regional cerebral blood flow (rCBF): Xenon-133 (Xel33) scans, laser Doppler flowmetry (LDF) (Haberl, Villringer, and Dirnagl 1993), and thermal diffusion flowmetry (TDF) (Carter 1996; Martin and Doberstcin 1994). Of the three, Xel33 scan is the most commonly used (Anderson 1996). Xel33 is a radioisotope that, after administration by various routes, is briefly taken up by the brain but docs not undergo metabolism. It is then cleared by the venous system and exhaled with a 90% first-pass clearance from the body. Using multiple stationary scintillation detectors, the cerebral uptake and elimination of Xel33 can be measured and expressed as a two-dimensional rCBF map with emphasis on cortical CBF. Xel33 has been used extensively to determine rCBF in severe head injury and SAH and has been employed intraoperatively during carotid endarterectomy and during carotid occlusion for cerebral aneurysms. The main advantages of the Xel33 method are its long track record as a reliable, reproducible gauge of rCBF; its minimally invasive nature and rapid clearance; and its portability, permitting bedside use in the NSU.

Microdialysis. The basic concept of microdialysis involves the insertion of a fine catheter into the brain parenchyma, followed by perfusion of the catheter with a physiological solution such as Ringer's solution, thereby facilitating the exchange of molecules between the perfusate and the extracellular fluid (ECF) across a dialysis membrane located within the catheter tip. The dialysate is sterilcly sampled at hourly or other regular intervals in vials, which arc placed in a microdialysis analyzer at the bedside. In this manner the clinician may monitor semi-on-line pH, lactate and pyruvate, glucose, glycerol, glutamate, urea, and potentially other soluble molecules of interest (Nilsson et al. 1999; Vespa et al. 1998; Landolt, Langemann, and Alessandti 1996). Changes in lactate and the lactate/pyruvate ratio have been used as indices of cerebral ischemia, as has elevations in the concentrations of excitotoxic amino acid glutamate. Rises in glycerol are believed most likely to reflect phospholipid breakdown as a result of cell membrane damage. Because of this, cerebral microdialysis has been employed in the NSU to monitor for cerebral vasospasm and delayed cerebral ischemia in SAH, to identify indicators of secondary brain injury after severe brain trauma, and to

follow ECF glutamate concentration peri-ictally in patients with epilepsy,

Controversy exists regarding some aspects of microdialytic analysis, such as whether lactate alone or the lactate/pyruvate ratio is a better indicator of early cerebral ischemia, and the technology is not yet in widespread clinical use. Other problems are the invasiveness of the procedure and the inability to foresee what areas of the brain should be sampled,

Tissue Monitoring. Another recently introduced invasive cerebral monitor is the implantable microsensor catheter for the measurement of brain Po_2, Pco_2, pH, and temperature (van den Brink ct al, 2000). As with many other monitoring technologies described here, the tissue Po_2 probe has been applied most extensively in the head injury population (normal >15 mm Hg), As a means of detecting cerebral ischemia in this setting, it has compared favorably to SjvOi and may aid in prognostication. The main risks associated with tins technique are those encountered with other invasive monitors (i.e., ICH and infection).

GENERAL MANAGEMENT OF NEUROCRITICALLY ILL PATIENTS

Care of the critically ill neurological and neurosurgical patient encompasses knowledge and awareness of the general medical management in the context of CNS pathology. The balance between the two presents a real challenge to the neurointensivist and creares a real dilemma when caring for and treating such patients. This section discusses several approaches to managing each of the body systems, bearing in mind the underlying severe neurological and neurosurgical diseases with special attention to the ICP and ischemic penumbra. The main goals of treatment of NSU patients are amelioration of primary insults and prevention or correction of secondary insults (e.g., seizures, cerebral edema, fever, and elevated ICP) to guarantee the best possible outcome.

Basic Critical Care Approach

The standard of care in the NSU, like in any other ICU, begins with securing the airway and establishing adequate breathing and circulation ("ABC"). Caution must be used when evaluating the ABC, Neurointensivists should pay particular attention to the possible complications associated with endotracheal intubation (ETI) in the NSU population to prevent increasing neurological problems. Two important elements need to be considered when handling the airway: cervical spine stability and ICP. Neck extension and flexion may aggravate an already existing cervical spine injury. In such cases, nasotracheal intubation with fiberoptic techniques may be preferred over orotracheal route. An equally important issue is that many of the NSU patients present with space-occupying brain lesions, which may trigger subsequent reflex elevation in the ICP during ETI, Administration of adequate sedatives and neuromuscular blockade agenrs in addition to lidocaine {either intravenously or orotracheally) may help in blunting such increases in ICP. This may he best achieved by the so-called "rapid sequence intubation" (RSI) (Talucci, Shaikh, and Schwab 1998). RSI consists of preoxygenation followed by administration of a short-acting sedative agent, such as etomidate at a dose of 0.1-0.3 mg/kg, and a nondepolarizing neuromuscular blocking agent, such as vecuronium at a dose of 0.1 mg/kg, in addition ro applying cricoid pressure (Sellick's maneuver) to prevent aspiration when consciousness is lost. To blunt the cough reflex during ETI, lidocaine (1-1.5 mg/kg) is administered 1-2 minutes prior to laryngoscopy (Helfman et al, 1991). Hyperkalemia and worsening of the underlying weakness may occur after administering depolarizing paralyric agents, particularly in those patients with renal impairment or focal neurological weakness of 3-90 day duration. Continuous cardiac monitoring and determination of potassium serum concenttation are routinely checked after such agents are given,

Once the ABC has been stabilized, patients are closely followed and neuroprotective measures are instituted (Table 51.3). MAP should be maintained at 100-120 mmHg in ischemic brain and spinal cord injury to maintain a CPP around 70 mmHg (Rosner, Rosner, and Johnson 1995), Other measures include maintaining at all times in NSU patients a T below 37,0-37.5^{J}C, a serum glucose concenrration between 80 and 120 mg/dL, and adequate hydration (Rodorf et al. 2000).

Another important aspect of care in NSU is the neurointeusivist-family relationship. Emphasis should be placed on early institution of direct contact between the treating physician and the patient's family. Identifying a spokesperson and all legally authorized nexr of kin is crucial and will allow for a more effective decision-making process. This is particularly important when end-of-life decisions and organ donation need to be addressed. Withdrawal of care in patients who have suffered catastrophic brain injuries can be difficult to approach. The establishment of good rapport between families and sensitive and well-trained health care personnel will accomplish a rate of up to 96.5% family satisfaction (Mayer and Kossoff 1999).

Respiratory Care in the NSU

One of the major reasons for the development of critical care units was the institution of acute respiratory care. Such care includes mechanical ventilation, aggressive suctioning, chest therapy, and maintenance of airway patency. Currently, mulriple indications exist for critically ill

Table 513: Basic considerations in NSU

Respiratory and airway protection	Perform rapid sequence orotracheal intubation
	Nasotracheal intubation in head and spinal trauma
	Eromidate 0,3 mg/kg followed by Jidocaine 1-2 mg/kg IV, 2 minutes prior to intubation
Cardiovascular	Maintain euvolemia in cases of increased ICP
	Maintain hypervolemia in cases of ischemic brain injury and SAH
	Use isotonic and occasionally hypertonic solutions
	Keep MAP 100-120 mm Hg
Renal	Maintain: Magnesium >2,0 mg/dL
	Calcium >8.5 mg/dL
	Phosphorus >2.5 mg/dL
	Potassium >4.0 meg/L
Pain/sedation	Morphine sulfate 2-4 mg IV/IM q 4 hr
	Codeine ."50-60 mg IM q 6 hr
	Midazolam 0.1 mg/kg in divided IV doses for sedation
	Clonidine 0,1 mg orally bid or tid
	Ativan 1-2 mg IV/IM/PO qid
	Olanzapine 5—10 mg orally bid
Neuroprotective measures	Keep glucose 80-120 mg/dL (use insulin drip if needed)
	Keep core body temperature <37.5°C
	Institute early nutrition

neurological and neurosurgical patients to be admitted to the NSU for respiratory care (Table 51.4). This section discusses basic principles of respiratory and ventilatory care, spanning indications for endotracheal intubation, weaning process, cxrubation, and chronic ventilatory care,

Indications for Mechanical Ventilation: A Life-Sustaining Treatment

When patients are admitted in respiratory distress they need a fast and safe assessment. Mechanical ventilation should be instituted in those patients meeting certain criteria, as outlined in Table 51.5 (Banner et al. 1997). Acute respiratory failure (ARF) implies that the respiratory system has failed to meet the patient's oxygenation, ventilation, or metabolic requirements. ARF has been classified into types I and II. Type I is the so-called "hypoxemic ARF" and is defined by a Pao_2 <60 mm Hg. This is commonly seen in patients with lung parenchyma processes such as pneumonia, pulmonary embolism, or acute respiratory distress syndrome (ARDS). Type II is the so-called "hypercapnic ARF" with or without hypoxemia and is defined by a $Paco_2$ >50 mm Hg. This type is usually seen in those patients with neuromuscular disorders such as myasthenia gravis and GBS. In many occasions neuro-intensivists are faced with patients who have both types I and II ARF (Gujjar et al. 1998).

Airway integrity depends on the patient's level of consciousness (LOG) and lower brainstem reflexes (gag, swallow, and cough). When one of these factors is affected, patients are at greater risk of upper airway obstruction or aspiration pneumonia. The threshold LOC is usually given by a GCS <8. Breathing patterns can be easily evaluated by observing thoracic and abdominal breathing movements. Paradoxical movements of the abdomen and rib cage, increased respiratory rate, and use of accessory muscles of ventilation arc an indication that the patient is iti impending respiratory failure secondary to weak respiratory muscles,

Table S1.4: Most common indications for admission to the NSU of critically ill neurological and neurosurgical patients with respiratory problems

Factor	*Underlying process*
Muscle weakness	Neuromuscular disease (MG, GBS, polymyositis)
	Cervical spine injury
	Critical care myopathy and polyneuropathy
Poor oxygenation with abnormal work of breathing	Aspiration pneumonia, lung collapse, pulmonary edema, ARDS, COPD, neuromuscular disease, upper airway obstruction
Inability to protect airway	Dysphagia, brainstem disorders, Glasgow Coma Scale <8, poor cough
Decreased respiratory drive	Medications (opioids, sedatives), brain or brainstem insults (traumatic brain injury, stroke, intracranial hemorrhage, brain tumors), central hypoventilation (Ondine's cutse)

ARDS = ; COPD = chronic obstructive pulmonary disease.

Table 51.5: Common indications for institution of mechanical ventilation in the NSU

Evaluate promptly and solve the problem

Glasgow Coma Scale score <8
Forced vital capacity (FVC) <15 ml./kg
Negative inspiratory force (NIF) <20 cm H,>0
Positive inspiratory force (PIF) <40 cm H_20
Respiratory rate >35/min
Pao_2 <fiO iinm Hg
$Pac:o_2$ >60 mm Hg
Cardiovascular shock
Upper airway obstruction not corrected by noninvasive methods
\piH\l

Bedside spirometry measurements are very useful for assessing respiratory muscle strength: forced vital capacity {F'VC, normal >60 mL/kg), negative inspiratory force (NIF, normal >70 cm H_20), and positive expiratory force (PEF, normal >100 cm H2O). Inadequate oxygenation can be diagnosed by obtaining arterial blood gas samples or noninvasive pulse oximetry (Sao_2). The former can also offer information regarding $C0_2$ retention. A chest roentgenogram (CXRay) may help elucidate the underlying disease such as pneumonia, atelectasis, or pneumothorax. In the presence of an unremarkable CXRay and hypoxemia, pulmonary embolism must be ruled out or treated.

Once the need for mechanical ventilation has been established, we usually proceed with rapid sequence intubation as described previously. Typical initial ventilatory settings used in the NSU are outlined in Table 51.6. The patient should be maintained with sedation (short-acting agents such as propofol or midazolam) and, if needed, neuromuscular blockade. As soon as the patient is intubated, treating physicians must start improving and treating the underlying condition that led to respiratory distress to ensure a quick and smooth weaning and ex tu bat ion.

Classes of Available Ventilators and Modes of Ventilation

Mechanical ventilators produce positive pressures at the airway opening, which can be cycled by volume, time, and flow. During volume cycling, the ventilator delivers a breath until a preselected volume has been delivered. These ventilators can potentially deliver a predetermined volume regardless of the airway pressure required to deliver it. Therefore to avoid excessive inhalation, a pressure relief valve is introduced. During time cycling, inspiration lasts for a preset interval and is therefore time-dependent. Exhalation begins at a preset time regardless of the volume delivered. During flow cycling, inspiration is terminated when a predetermined decrement of flow is achieved. With this type of cycling, patients exert more control over inspiratory and expiratory efforts.

Table 51.6: Initial ventilator settings for a typical patient requiring mechanical ventilation in the NSU

Start with this and then titrate down as soon as feasible

Mode: assist-control (AC)
Inspired fraction of oxygen ($FiC>_2$): 100%
Respiratory rate: 12-18/min
Tidal volume (Vt): 7-10 cc/kg
Positive end-expiratoty pressure (PEEP): 5 cm H,0

The four most common modes of ventilation used in the NSU are assist-control mode ventilation (ACMV), synchronized intermittent mandatory mode ventilation (SIMV), pressure support ventilation (PSV), and inverse ratio ventilation (IRV) (Shelledy, Ran, and Thomas-Goodfellow 1995; Stcnberg and Sahebjami 1994). In ACMV, a preset tidal volume (Vt) is given every time an inspiratory effort is sensed as a fall in the pressure at the airway opening, and a backup rate is set to avoid hypoventilation in patients with decreased respiratory drive or chemical paralysis. In SIMV, the ventilator delivers breaths that are triggered by the patient's inspiratory effort up to a preset rate. If the number of inspiratory efforts exceeds the preset rate, all the excess breaths will be unassisted. In this mode a backup rate is also given, and in order to exercise the patient, the rate of machine-delivered breaths or Vt is progressively decreased. In PSV, patients receive a preset pressure triggered by an inspiratory effort. Once the inspiratory flow falls below a certain threshold, the breath is terminated. Vt depends on lung compliance, chest wall compliance, status of respiratory muscles, and airway resistance. This mode can be used in isolation or as adjunct to SIMV or ACMV. To exercise the patient, the amount of pressure supplied is gradually reduced. In IRV, the inspiratory/expiratory ratio (I:E) is set at >1. The major application is in those critically ill neurological patients who have acute lung injury or ARDS and have failed to improve oxygenation with positive end expiratory pressure (PEEP). Because IRV is very uncomfortable for patients, they should be heavily sedated and paralyzed. Last, PEEP and continuous positive airway pressure (CPAP) are also often used. They are not separate modes of ventilation but are used together with other modes to improve arterial oxygenation. The benefits of PEEP may result from its ability to improve residual functional capacity, thus increasing lung compliance. Usual PEEP levels are 5-10 cm H_20, which may be increased by 2.5-5 cm H_20 to achieve the desired oxygenation, Disadvantages include risk of barotrauma, hypotension, and elevated ICP due to decreased cerebral venous return. However, clinical experience has shown that PEEP levels of 5-15 do not affect ICP or CPP in critically ill neurological patients (McGuire et al. 1997).

Once the patient has been intubated and a mode of ventilation chosen, it is important to monitor and assess

several parameters: ventilation and oxygenation, lung and chest wall mechanics, intrinsic PEEP, and muscle strength. Ventilation and oxygenation are followed through continuous Sa02 and end-tidal $C0_2$ recordings or intermittent arterial blood gas sampling. Lung and chest wall mechanics are integrated in the equation for dynamic compliance calculation, which is given by dividing Vt by peak inspiratory airway pressure minus PEEP ($Qv_n = Vt/(P,,i_{at}$ — PEEP), Auto PEEP is usually present in those patients with airway obstruction, with rapid respiratory rates, or with IRV. It refers to dynamic hyperinflation of the lungs when Vt is given before complete exhalation. Auto PEEP can be measured at the bedside by pausing the ventilator at the end of expiration and closing the expiratory circuit flow. Finally, muscle strength monitoring is usually accomplished by following FVC and NIF. These measurements provide information about respiratory muscle strength but not endurance.

Medical Management of Ventilated Patients

Medical management of critically ill neurological and neurosurgical patients who require mechanical ventilation concentrates on five points: chest physiotherapy, nutrition support, correction of electrolyte imbalance, gastrointestinal prophylaxis, and treatment of concurrent hospital-acquired infections. Although further data from controlled randomized studies are needed to provide more scientific validation, chest physiotherapeutics techniques have been used for the past 30 years and are widely accepted. These include manual hyperinflation, gravity-assisted drainage, and chest wall vibrations to improve airway secretion clearance (Denehy 1999; Langerderfer 1998). In patients with atelectasis or mucus plugging, aggressive chest physiotherapy should always be instituted before other procedures are performed (i.e., bronchoscopy). Nutrition support, whether enteral or parenteral, should be initiated as soon as feasible (Taylor et al. 1999). The enteral route is preferred and is discussed in a later section. There is scientific evidence that early feeding may be associated with enhanced neurological recovery in critically ill patients with intracranial lesions. In addition, from the ventilatory viewpoint, malnourished patients have weaker respiratory muscles and are therefore more difficult to wean (Moxham 1984}. Electrolyte imbalance, including hypomagnesemia and hypophosphatemia, may also be associated with prolonged need for artificial ventilation, especially in patients with other factors that may adversely affect weaning,

Prophylaxis against stress ulcers and aspiration pneumonia has always been recommended in mechanically ventilated patients (Markowicz et al. 2000). Our current recommendation is to administer ranitidine to all ventilated patients in the NSU except those with thrombocytopenia or renal failure who are treated with sucralfate (Cook et al. 1998; Cook etal. 1999).

Weaning Patients from Mechanical Ventilation

There are several issues that need to be resolved before starting a weaning trial in mechanically ventilated neurological and neurosurgical patients:

1. Resolution of the cause of respiratory failure
2. Presence of good oxygenation (Pao_2 >60 mm Hg with $Fi0_2$ <50% and PEEP <5 cm H_20)
3. Ability of patient to protect airway (normal bulbar function)
4. Establishment of adequate respiratory drive
5. Adequately strong respiratory muscles (vital capacity [VC] >15mL/kg)
6. Identification of adequate cough reflex
7. Maintenance of a minute ventilation <15 L/min
8. Rapid shallow breathing index (RSBI) <105 breaths per minute (see later discussion)
9. Secretion suctioning frequency less than every 2-3 hours
10. Hemodynamic stability and normal electrolytes

A number of individual parameters have been suggested as predictors of successful weaning, but most of them have limited predictive power in critically ill patients: NIF >-30 cm H_20, VC >10 mL/kg, minute volume <10 L/min (Sahn and Lkshminarayan 1973), and the airway occlusion pressure measured at 0.1 second of an inspiratory effort against an occluded airway (Po.i) <—2 cm H_20 (index of respiratory drive) (Whitelaw and Derennc 1993). Because respiratory failure is a multifactorial condition, indices including several parameters are probably more reliable at predicting successful weaning. The most commonly used one is the RSBI (Yang and Tobin 1991). RSBI appears to be the best predictor of all the indices published thus far and can be derived from the following equation:

$$RSBI = //Vt$$

where /is the respiratory rate and Vt the tidal volume.

This index has to be obtained while patients arc off ventilatory support. RSBI values <105 arc predictive of successful weaning. Once patients meet these criteria, a weaning trial is started, It is important to realize that there is no such thing as an ideal weaning method (Brochard et al. 1994; Esteban et al. 1995). The most accepted method of weaning consists of a gradual reduction of support using PSV, SIMV, a combination of both, or spontaneous breathing trials (SBT). Some authors found that PSV was better than SIMV or SBT, whereas others have reported better results with SBT, These differences may be related to differences in patient population.

Whatever weaning method is chosen, it should be executed early in the day, the patient should have received a good rest the night before, tube feedings should be held at least 4 hours before the trial, and treating physicians should be ready to reintubate if the patient fails extubation.

Chronic Ventilatory Care

The majority of patients placed on mechanical ventilation are extubated within 7 days. However, about 4-16% require prolonged ventilatory support (>15 days). Neurological patients represent a large proportion of these patients. After 14 days of intubation, the risk of rracheolaryngeal injury increases (Koh et al. 1997). It is generally accepted that such patients should undergo tracheostomy. In patients with neurological and neurosurgical diseases, the risk of extubation failure is high because of upper airway obstruction and tenacious secretions; thus early tracheostomy (sooner than 14 days) in this patient population has been advocated. Once patients have undergone tracheostomy, they can be classified into two groups: those who require mechanical ventilation for airway protection and those with parenchymal lung disease or dysfunction. The former will be able to come off the ventilator shortly after tracheostomy is performed, whereas the latter group may need to be cared for in a long-term ventilatory rehabilitation unit (Gluck 1996).

Cardiovascular Care in **the** NSU

Cardiac diseases are common comorbidities in patients with neurological illness and may present concomitantly or occasionally may precede the neurological insult. Acute neurological and neurosurgical insults may lead to different types of cardiac manifestations that pose a challenge to ncurointensivists {Rolak and Rokey 1999; Sakr, Ghosn, and Vincent 2002; Prieto, Eisenberg, and Thakur 2001; Ay, Arsava, and Saribas 2002; Lang, Borner, and Figulla 2000). Such cardiac manifestations may include acute coronary syndrome, cardiac arrhythmia, and fluid overload.

Acute Coronary Syndrome

When patients present after an acute brain injury {e.g., acute ischemic or hemorrhagic stroke or SAH or even large space occupying lesion) and develop elevated cardiac enzymes, it may be difficult to ascertain whether these cardiac abnormalities are primary or secondary. Acute coronary syndrome (ACS) in particular represents a significant challenge since cardiac enzymes can be elevated in patients with acute vascular and nonvascular disease such as status epilepticus in the NSU. In one study the elevation of serum creatinine kinase was not found to be cardiac in origin in ischemic stroke patients, whereas the troponin T elevation was more sensitive in detecting myocardial ischemia and damage (Ay, Arsava, and Saribas 2002; Lang, Borner, and Figulla 2000). The main mechanism is myocytolysis secondary to autonomic system overdrive leading to nonischemic ACS. Another possible mechanism is rupture of a coronary artery plaque following the acute ischemic stroke or neurological injury and subsequent myocardial ischemia. The EEG findings **may** vary from symmetrically inverted T waves to ST segment elevation.

When patients are found to have elevated troponin serum concentrations with or without acute electrocardiogram (ECC) changes, rhey should be considered as having ACS and appropriate treatment should be initiated. The management of these patients usually includes standard medications including antiplatelet agents, beta blockers, and nitroglycerin. An echocardiogram should be obtained to evaluate ventricular function. In general, medication dosages are usually adjusted to maintain adequate CPP while decreasing cardiac demands. MAP of or above 90 mm Hg is preferred. Angiotensin-convcrting enzyme inhibitors and beta blockers may be given at a lower than standard dose. Anticoagulation or intravenous GHb/IIla inhibitors should be avoided within the first week after large stroke or neurosurgical procedure and in cases of ICH for up to 2 weeks. Of course, thrombolyric therapy for ACS may not be administered, but interventional petcutancous angioplasty tteatment can be considered, Pain control with nitroglycerin intravenously or morphine may be given with prevention of excessive sedation. Fluid therapy guided by invasive cardiovascular techniques may be required since dehydrating neurologically damaged patients may be deleterious to brain function.

Cardiac Arrhythmia

Abnormalities in cardiac rhythm may occur after ischemic and hemorrhagic stroke, as well as in other diseases encountered in the NSU including GBS and status epilepticus. Different types of cardiac abnormalities may be seen and approach to treatment may vary according to the underlying rhythm subtypes. Atrial fibrillation with rapid ventricular response is better converted after transesophageal echocardiography has demonstrated absence of intracavitary clots and after it has been determined that the patient can be anticoagulated (Hebbar 2002). Medical or electrical conversion may be accomplished in the context of acute neurological injury, and the latter should not be an absolute contraindication. Sinus rhythm is preferred if possible since this will increase the cardiac output and ultimately CPP. If the patient cannot be converted and the heart rate still requires control, less hypotensive agents such as digitalis are preferred as the first drug of choice. Other drugs may be used, including beta blockers and calcium channel blockers.

The use of vasoactive drugs in the NSU may lead to worsening of the underlying rhythm and may induce cardiac arrhythmias. The vasopressors that are commonly used to manage patients with SAH may be problematic in elderly individuals with sensitive rhythm and underlying cardiovascular morbidities. Caution should be used when administering such medications.

Congestive Heart failure

Fluid overload and pulmonary edema are common in the NSU setting, where patients are routinely overloaded with intravenous fluid to maintain CBF and CPP as a standard therapy for certain conditions (e.g., vasospasm prophylaxis after SAH and hypervolemic therapy after acute ischemic stroke for penumbra salvaging}. In elderly neurocritical care patients with concomitant cardiac dysfunction the risk of congestive heart failure and pulmonary edema may be high. Up to 80% of patients with SAH experience varying degrees of severity of pulmonary edema (Vespa etal. 1994). The standard of care is to obtain a comprehensive cardiac evaluation with plain chest radiograph, echocardiography, and ECG at baseline and to monitor hypervolemic, hypertensive, and hcmodilutional therapy accordingly. If the cardiac function is compromised at baseline the fluid management may be tenuous and central venous catheters, including Swan-Ganz catheter, may be needed to guide this therapy.

Pulmonary capillary leak and pulmonary edema may occur secondary to massive brain insult (known as neurogenic pulmonary edema) in patients with brain mass, stroke, or SAH and hydrocephalus with sudden rise in ICP (Gluecker et al. 1999). The mainstay of treatment is to provide adequate and gentle diuresis and short periods of PEEP. Other therapeutic strategies may include albumin combined with diuretic therapy and agents to augment the cardiac output such as dobutamine or amrinone (Knudsen, Jensen, and Petersen 1991).

Gastrointestinal and Nutritional Management in the NSU

Gastrointestinal Abnormalities

Severe stress in the NSU population may frequently be accompanied by secondary deleterious effect on the gastrointestinal (GI) system. Common CI complications encountered in the NSU and their management are summarized in Table 51.7. Secondary CI manifestations that are related to acute neurological injury include gastric and colonic ulcers, bleeding, and ileus. The gastric stress ulcer may be related to sudden ICP elevations with GI ulceration and bleeding caused by catecholamine surge. The bleeding can be in the upper or lower tract and can be accompanied by hypovolemic-hypotensive shock, which may subsequently lead to a vicious cycle of cerebral ischemia and further increase in ICP with subsequent increase in the GI bleeding. This may be seen in the advanced stages of increased ICP and before death or cerebral herniation. Treatment involves emergency control of the ICP and immediate whole blood transfusion and volume resuscitation. Except for this extreme situation, the GI complications from acute ischemic stroke are usually mild and may be related to the concomitant use of medications (Wijdicks et al. 1994). GI prophylaxis in NSU patients is recommended with sucralfate or ranitidine, particularly in ventilated patients (Holland 2001).

Tabic 51.7: Gastrointestinal manifestations and management in NSU

GI manifestations	*Approach*
GI bleeding	Stop anticoagulation
	Administer protamine sulfate 1 mg/100 units of heparin or fresh frozen plasma for warfarin reversal
	Volume and blood resuscitation
	Gastric protection
	Look for underlying etiology
Ileus	Replete potassium
	Replete magnesium
	Bowel rest
	Decompression
	Discontinue offending agents
Diarrhea	Discontinue potential medications
	Fluid management
	Metronidazole if *Clostridium difficile* suspected

Elevated liver enzymes and hepatic encephalopathy secondary to the frequent use of hepatically metabolized anticonvulsants or antibiotics are common in the NSU. Valproic acid may be associated with elevation of the serum ammonia concentration with encephalopathy and occasional pancreatitis (Holland 2001). EEG can be useful to assess for hepatic encephalopathy versus asymptomatic elevation of the liver enzymes. Discontinuation of the offending agent and supportive care with lactulose and neomycin is the mainstay of treatment.

Gastrointestinal ischemia and angina can occur and should be considered in cases of hypotension in NSU patients who already suffer from increased tendency to thrombosis and clotting. Occlusive and nonocclusive types of mesenteric ischemia can be encountered in the NSU, although the former is more common than the latter. This is a medical and surgical emergency, which presents with a painful abdomen without sufficient corresponding physical signs on examination, the so-called "benign abdomen." This classical presentation may not be evident in the NSU, and it should be suspected in patients with recalcitrant sepsis who also have elevated serum lactate concentration. Diagnosis can be established with abdominal CT scanning, Immediate medical and possibly surgical evaluation is life saving (Greenwald 2001).

Another significant GI manifestation that is commonly encountered is intestinal ileus (Liolios, Oropcllo, and Benjamin 1999). Paralytic ileus may occur in a variety of neurological conditions and in the postoperative period in neurosurgical patients. GBS requiring NSU care is commonly if not universally complicated by some degree of abdominal distension and GI obstruction secondary to ileus. Treatment usually involves supportive care with intravenous fluid and electrolyte repletion while avoiding

oral feeding and removing any offending agents such as sedatives or analgesics that could worsen the intestinal dilatation. Decompressive nasogastric tube and rectal tube may be tried before surgical decompression in those who do not improve with suppottivc medical therapy.

An additional GI complication wotth mentioning that is commonly encountered in the NSU is diarrhea. Diarrhea can be related to the underlying neurological disease or may be secondary to the critical care management. Drugs used in the NSU known to induce diarrhea are mainly antibiotics and gastric protection medications. Enteral feeding is another common cause and should be stopped if all othct causes are excluded. Infectious etiologies such as *Clostridium difficile* (C. *diff)* and *vancomycin-resistant enterococci* (VRE) arc also common, particularly after long-term use of broad-spectrum antibiotics (30^10% may be associated with C. *diff).* Treatment of *C. diff* consists of discontinuation of the offending agents and administering metronidazole or vancomycin by entetal route (Liolios, Oropello, and Benjamin 1999).

Nutritional Requirements

Nutritional support is essential in patients with neutologi-;,;il insults. Daily requirements vary according in the underlying disease, the patient's ideal body weight adjusted formula, and the Harris Benedict equation used to calculate the daily calorie needs. This equation is often used to estimate Resting Energy Expenditure (REE):

$$\text{Male (kcal/day)} = 66.473 + (13.7516 \times W) + (5.0033 \times H) - (6.755 \times A)$$

$$\text{Female (kcal/day)} = 655.0955 + (9.5634 \times W) + (1.8496 \times H) - (4.6756 \times A)$$

For both equations, *W* is body weight in kilogtams, H is height in ccntimctets, and *A* is age in years. This may be operationally translated into approximately 25-30 kcal/kg/day. Nutritional requirement may be adjusted to the particulat disease and nutritional status indicatots. For instance, sepsis may require increased nutritional support by 30%, wheteas high caloric feeding should be avoided in GBS and myasthenia gravis. Nutritional support adequacy may be assessed using prealbumin {half-life of 2-3 days) rather than albumin (half-life of 20 days). Insulin growth factot-I is another promising nutritional assessment parameter (half-life of 24 hours) but it is not commonly used in clinical practice (Schears and Dcurschman 1997). Regarding the tomes of nutrition administration, enteral feeding is preferred whenever possible. Oral feeding in the NSU may not be feasible because of the patient's mental status and risk of aspiration with impaired swallowing mechanism. Feeding tubes should be placed in the distal stomach or first part of the duodenum to avoid the risk of aspiration. The risk of aspiration may be higher in those patients with gastroparesis; gastric motility agents may be added as necessary. The right timing to start feeding and nutritional support is not defined for neurological diseases, but early feeding is usually recommended based on preliminary evidence from head-trauma and surgical post-operative studies associating it with bettet outcomes (Schears and Deutschman 1997).

Renal and Electrolytes

Patients with acute neurological insult may have a concomitant underlying renal dysfunction. Primary renal diseases that may worsen while patients are in the NSU include acute or chronic renal failure secondary to renal hypoperfusion from the use of vasoactive drugs or antibiotics and urinary tract infection caused by indwelling catheters. The latter may also be a leading cause of fever, and antibiotics should be initiated appropriately.

Urinary retention may be seen after spinal neurosurgical procedures and can be managed with frequent intermittent catheterization. Uremia may supervene while the patient is in the intensive care unit; this should be considered in the differential diagnosis of delirium in the NSU. Furthermore, patients in the NSU for acute neurological emergency who arc receiving hemodialysis (HDj should have no heparin in their dialysis lines if ICH or a large cerebral infarct is ptesent. Blood pressure changes during HD should be attended to, and fluid balance at the end of the dialysis session should also be monitored closely. Drugs that may intetferc with renal function should be used with great caution to avoid nephrotoxicity. Whenever possible renal dose adjustment of anticonvulsants and antibiotics in those with renal dysfunction should be made and free unbound drug concentrations should be monitoted.

Electrolyte imbalance, including hyponatremia, may be encountered in the neurocritical care setting. Hyponattcmia can be caused by the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) or cerebral salt wasting syndrome (CSWS). The formet can be seen in patients with SAH, massive stroke, GBS, IGH, and after pituitary adenoma resection. Stress, pain, and anxiety may also lead to incteased secretions of ADH. SIADH is usually managed with fluid restriction. CSWS may also lead to hyponatremia with normal-to-decreased total body volume and in the presence of nattiurcsis may require fluid therapy rather than restriction. Symptomatic acute hyponatremia may tequitc more aggressive therapy with hypertonic saline, but the latter should be avoided in patients with chronic hyponatremia because of the major risk of producing central pontine myelinolysis.

Hypernatremia can be secondary to diabetes insipidus (DI), which may occur with SAH, increased 1CP, cerebral edema, or following pituitary adenoma resection. Increase in the urine output to more than 250-300 cc/hour for 2 consecutive hours with low specific gtavity (less than 1.010) may be an early indication of DI. Setum and urine

osmolality and electrolytes should be monitored every 6 hours and results used to guide further therapy. Initial management in patients who are awake with intact thirst mechanism is merely by replacement with oral fluid in a volume equal to the urine output plus 20%. If patients are obtunded this can be supplemented with intravenous hypotonic solutions according to the calculated total body water deficit (TBWD). This is usually calculated using the following equation:

$$\text{TBWD in liters} = 0.6 \times \text{usual body weight in kg} \times \frac{\text{serum sodium} - 140\ \text{mEq/L}}{140\ \text{mEq/L}}$$

Shorter acting vasopressin may be given early on in doses "I 2-5 units 1\! nr SQ every 4 hours if the urine volume is more than 300 cc/hour for 2 consecutive hours. The advantage is that if DI is transient, the vasopressin effect is not long acting and will not carry over. Desmopressin or 1-desamino-D-arginine vasopressin (dDAVP) is preferred over vasopressin because of its longer duration of action. The dDAVP may be administered to patients with persistent hypernatremia not responding to fluid therapy or requiring constant short acting vasopressin therapy. An initial dose of 2.5-10 j.ig may be given intranasal!)' at bedtime or two times daily. Alternatively, 0.5-4 ug may be given intravenously, subcutaneously, or intramuscularly every 8-10 hours (Diringer 2001).

Hematological System

Several important hematological diseases that may be seen in NSU populations are worth mentioning. Patients are often paralyzed and fulfill all the criteria of Virchow's triad and are thus prone to thrombotic events. The incidence of deep venous thrombosis (DVT) in patients with stroke and neurosurgical patients may vary. In patients who have experienced acute stroke, the incidence of DVT may range between 11% and 17%, and pulmonary embolism (PE) may range between 3% and 39% (Hillbom ct al. 2002). In neurosurgical postoperative patients and in general critical care patients it may range between 22% and 80%, depending on the underlying disease (Attia et al. 2001; Warbel, Lewicki, and Lupica *1999).* NSU patients with a DVT may nor have leg pain and swelling. This diagnosis is mainly encountered either in routine screening or in the context of fever workup. Clinical findings in a case of PE can also be obscured by the patient's inability ro complain of shortness of breath. However, any difficulty in breathing should be taken very seriously. An arterial blood gas with high alveolar-arterial gradient should raise a red flag, and the diagnostic studies for PE should be obtained.

The main screening test for DVT is the noninvasive bedside vascular ultrasound; venography is rarely required. In cases of PE, spiral computed chest tomography, ventilation-perfusion scan, or pulmonary arteriography may be obtained to establish the diagnosis. Current data do not support increased risk of bleeding in the use of cither enoxaparin 40 mg daily or un fractions ted heparin 5000 units subcutaneously thrice daily in NSU patients for DVT and PE prophylaxis (Hillbom et al. 2002; Attia et al. 2001). Both animal and human studies have shown the safety of heparin or warfarin administration if started after 7 days from the time of craniotomy surgery. Thus the use of those agents for therapeutic management of DVT or PE can be recommended 1 week after neurosurgical procedures. Unfortunately, similar data are not available for ICH or large ischemic strokes. For patients with a high risk of developing bleeding complications from anticoagulation, a Greenfield filter should be placed in the inferior vena cava or rarely a thrombectomy can be performed.

Any patient with evidence of cerebral or systemic bleeding while on anticoagulation therapy needs prompt evaluation. Reversal of warfarin may be needed emergently because of possible life-threatening complications. The use of vitamin K a r a dose of 10 mg intravenously slowly every 8-12 hours for three doses may be required. If more urgent reversal is necessary, fresh frozen plasma (FFP) or prothrombin complex concentrate should be administered. The latter has been shown to be more effective than FFP and vitamin K at reversing the effect of warfarin (Cartmill et al. 2000). In cases where heparin has been given, protamine sulfate (1 mg/100 units of heparin) should be administered immediately after stopping the infusion.

SPECIFIC CLINICAL CONDITIONS

We will review important issues in the critical care of patients with certain neurological diseases whose course may sometimes involve acute phases requiring the need for *neitro-*critical care, I'll esc diseases include a cure ischemic stroke, cerebral edema, intracranial hypertension, ICH, SAH, myasthenia gravis crisis, GBS, and status epilepticus. These diseases are reviewed in general elsewhere in this text, but the purpose here is to emphasize the aspects of their neurocritical care. Other neurological diseases, such as congenital myopathies, spinal muscular atrophy, muscular dystrophies, and amyotrophic lateral sclerosis, may require intensive care. However, generally the problems patients with these diseases face which would require critical care fall within the spectrum of generalized intensive care. It is the need for specialized neurocritical care that chiefly concerns us here.

Acute Ischemic Stroke

There are several reasons for instituting intensive care of the acute ischemic stroke patient. These are both neurological and non-neurological. The neurological reasons depend on

whether the patient has received thrombolytic therapy. If a stroke patient is treated with thrombolytic therapy, the patient is at risk for hemorrhage into the infarct or even in noninfarcted areas of the brain (or even elsewhere in the body}. Such patients need careful monitoring with special attention to their neurological status. Should they in tact suffer intracranial bleeding, the risk of expansion of the hematoma and cerebral edema necessitate aggressive management of hematocrit and any coagulopathy and constant monitoring of blood pressure. Even without thrombolytic therapy, large infarcts such as a massive middle cerebral infarct (which generally produces profound neurological deficits and suggestive changes on head CT scans, as desctibed below) generally warrant close monitoring because of the high frequency of cardiac and pulmonary problems, as well as the high mortality associated with their tcsulting cerebral edema and consequent possible herniation. Other stroke-re la ted conditions that deserve neurocritical care management include crescendo transient ischemic attacks (because of the risk of impending ischemic stroke), progressive neurological decline in the setting of an acute ischemic stroke (for the purpose of induced hypertensive therapy), arterial dissection (hypervolemic and hypertensive therapy are necessary}, postendovascular procedure (because of the significant risk of embolization and reocclusion), and cerebral vasospasm following subarachnoid hemorrhage (sec later discussion). In addition, stroke victims can require intensive care for non-neurological reasons such as respiratory failure and subsequent mechanical ventilation, vasopressor administration for hypotension, therapy for critical hypertension, cardiac disease such as myocardial ischemia or arrhythmias, management of systemic bleeding complications due to thtombolytic therapy, or management of pulmonary complications {e.g., pulmonary edema).

The management of an acute ischemic stroke must begin with both clinical stabilization of the patient and an evaluation for thrombolytic therapy. If the patient presents within six hours of symptom onset, there is the possibility of administering a thrombolytic agent either intravenously (within first 3 hours) (National Institute of Neurological Disorders and Stroke 1995) or intra-arterially (from *3-6* hours) (Suarez et al. 1999). These patients arc evaluated with the National Institutes of Health Stroke Scale (NIHSS). The NIHSS scores the stroke severity through assessment of consciousness, visual fields, sensorimotor systems, and speech and language. The maximal score is 42 and represents the most devastating of strokes. Current guidelines qualify patients with an NIHSS score >4 as potential thrombolytic candidates. Patients with NIHSS scotes >18 have the worst clinical outcomes. In addition to the use of the NIHSS, imaging techniques such as CT, MR1, angiography, and TCD can assist in the evaluation of acute stroke patients. With the advent of rapid MRI technology, imaging can even help with the triage of acute stroke patients for treatment (Sunshine et al. 1999}.

However, before there can be any discussion of treating a patient, the stroke victim must be clinically stabilized. This brings us back to the "ABCs" of basic life support. For patients whose airway is at risk, who arc in respiratory distress, or whose GCS score is less than eight, immediate intubation and mechanical ventilation arc necessary. Acute stroke patients with evidence of Cushing's triad {systemic hypertension, bradycardia, and respiratory disturbances) raise the suspicion of elevated ICP and therefore require immediate intubation. Controlled hyperventilation for management of elevated ICP can then be performed {see later discussion). Rapid sequence intubation, the generally preferred method, is described previously (Peterson et al. 1998). Following intubation, optimization of patient comfort and the need to avoid elevations in intracranial pressure (caused by vasodilation as a result of abnormal cerebrovascular compliance that occurs in cerebral tissue damage) warrant sedation with short-acting agents such as propofol or midazolam.

If the patient is acutely hypotensive at presentation, aggressive fluid replacement must be initiated. Because of the need to avoid dextrose or hypotonic solutions that can worsen cerebral edema, 0.9% saline fluid is routinely used. Should vasopressors be necessary, phenylephrine is used because it is an *a*\ agonist, and cerebral vessels tend to have a very small population of al agonists. Dopamine is often used when bradycardia is present. Animal studies and clinical evidence suggest the benefit of increasing CPP through the ischemic penumbra that surrounds the core ischemic brain tissue. As a result it is recommended to aggressively hydrate all ischemic stroke patients (with due consideration for other factors such as heart failure). This is thought to increase the CPP by increasing total intravascular volume or truly increasing cerebrovascular ABP. Some clinicians try to achieve a systolic blood pressure between 140 and 180 mm Hg in acute ischemic stroke patients. Although it may not be necessary to induce hypertension in clinically stable patients, for patients with known stenoses of the cerebral arteries (both intracranial and extracranial vessels, such as the carotid and vertebral arteries), it has been shown to be safe and effective to do so.

Note also needs to be made about control of elevated ABP. Auto regulation following ischemic sttoke usually produces elevated ABP. This is in fact the inherent compensatory mechanism of the brain to maintain adequate CBF. It also forms part of the basis for the theory behind the efficacy of induced hypertension to improve clinical outcome in stroke by increasing CBF to the ischemic penumbra. But m the setting of the need to administer thrombolytic therapy, systemic hypertension can be dangerous. This is due to the increase in incidence of post-thrombolysis ICH seen with elevated ABP. Likewise, even in the absence of the use of thrombolytics, extremely elevated ABP can alone be a risk factor for hemorrhagic conversion of an infarct. Guidelines for the management of

elevated ABP in the setting of acute ischemic stroke have been established (Adams et al. 1996):

1. For diastolic blood pressure >140 mm Hg on two readings 5 minutes apart, administer IV infusion of sodium nitroprusside (0.5-10 jjg/kg/min) and titrate until diastolic blood pressure goes down by 20%.
2. For systolic blood pressure >230 mm Hg and/or diastolic blood pressure of 121-140 mm Hg, administer IV infusion of labetalol (10 mg delivered over 1-2 minutes; repeat this bolus or double the dose of labetalol successively every 10 minutes up to a total dose of 150 mg). If labetalol is still not effective, administer sodium nitroprusside.
3. For systolic blood pressure of 180-230 mm Hg and/or diastolic blood pressure of 105-120 mm Hg, administer IV infusion of labetalol as in (2), up to 150 mg total dosage.
4. After initial control of the elevated ABP, labetalol can be administered every 4-8 hours. For patients with asthma, bronchial hyper-re activity, heart failure, or severe cardiac conduction defects, labetalol is not the drug of choice, and other agents are indicated.

In addition to close monitoring of ABP, blood glucose must also be monitored closely. At a minimum blood glucose should be checked every six hours for all acute ischemic stroke patients, even nondiabetic ones. For serum concentration above 150 mg/dL serum glucose should be lowered, since hyperglycemia is known to exacerbate focal neurological deficits (Weir ct al. 1997}. T needs to be taken frequently and maintained at less than 37.5 C. F.levated T has also been associated with poor outcomes in acute stroke patients.

If a patient who has received thrombolytic therapy for an acute stroke is suspected to have bled, the hematocrit, hemoglobin, PTT, PT/INR, platelet count, and fibrinogen must be determined. Transfusion of blood products may be necessary. Because patients receiving thrombolytic therapy should be admitted to an NSU in the immediate post-thrombolysis phase, recommendations by the American Heart Association for management of bleeding are reviewed here:

1. Thrombolytic therapy should not be used unless there are readily available facilities to handle bleeding complications.
2. Until head CT scanning is available for a patient who experiences new or worsened neurological deficits, ICH must be suspected as the likely cause of deterioration of clinical status. In this case—as in all cases of suspected thrombolysis-associated bleeding—the infusion of the thrombolytic agent or any anti-coagulant therapy must be stopped, I lead CT scanning is obviously emergently necessary.
3. Surgical consultation should be considered.

For large ICH, any coagulopathy will have to be corrected. Cerebellar hematomas and large (>60 cc) lobar hemorrhages that have mass effect require emergent drainage.

Either in the case of ICH or simply because of large ischemic strokes (for example, complete MCA occlusion with poor collateral flow [has causing infarction of the complete MCA territory) or for other reasons, there can be so much cerebral edema that significant mass effect and elevation of ICP can occur. In these cases an intensive care environment, if the patient is not already in one, is critically important. Management of this condition is reviewed in the following section.

Cerebral Edema and Elevated Intracranial Pressure

Through a complex mechanism relating to multiple membrane proteins and transporters involved in the formation of the blood-brain barrier (BBB) and to several autacoids and proinflammatory proteins, under certain pathological conditions this barrier can break down. Once BBB is permeable there can be a net influx of water and solutes to the interstitium and intracellular spaces, thereby causing cerebral edema. Some of the conditions that can cause this are primary cerebral injuries such as ischemic infarcts, ICH, and traumatic brain injury. Cerebral edema can be worsened by such secondary factors in brain injuries as hypotension, hypoxemia, and seizures. Once an affected area of the brain is edematous, the potential for mass effect arises, because the intracranial volume is essentially fixed by the rigidity of the skull. In the setting of mass effect, ICP can rise and raise the grim prospect for the development of herniation syndromes. This is the profound danger of cerebral edema and explains the need for close monitoring of patients with the potential for cerebral edema who show neurological worsening or of parients with significant cerebral edema even without evidence of neurological worsening. An example of the latter is large lobar ischemic strokes that can develop cerebral edema up to 96 hours after the initial infarct.

The normal mean ICP is in the range of 5-10 mm Hg, Levels above 15 mm Hg are considered absolutely abnormal (see the previous discussion). Once ICP is elevated, it is considered an emergency and may require emergent treatment to lower it.

Management of elevated ICP involves both medical and surgical maneuvers (Suarez 1999). The first step (assuming the cervical spine is stable for flexion) is to place the patient's head and upper trunk at 30"; in many cases this is effective in reducing ICP (Frank 1993). Medical treatment then begins with evaluating the need for intubation. If the airway is unstable, if there is respiratory distress, or if the GCS is less than 8, the patient needs emergent intubation. However, elevated ICP alone can necessitate intubation to perform one of the primary means of treatment, which is controlled hyperventilation (HV). This means increasing

the respiratory rate of the intubated patient to blow off more $C0_2$. The goal Pa«>2 is between 28 and 33 mm Hg. Lowering the $Paco_2$ beyond this range carries a risk of inducing cerebral ischemia and therefore must be avoided. Hyperventilation is the fastest method of medical management for elevated ICP, and its effect lasts for several hours. Once the target Pact); has been achieved, recommended practice is to slowly decrease the ventilatory rate to allow the Paco2 to rise at about a rate of 2 mm Hg per hour up to the normal range. This will allow the treating physician to use hyperventilation later on, should it be necessary in a given patient.

The next step is to administer hyperosmolar solutions, most commonly mannitol. Generally mannitol is given as a bolus over 10-15 minutes at a dose of 0.5-2.0 g/kg. A phenomenon known as "rebound" cerebral edema has been described in the setting of continuous mannitol infusions, and thus continuous infusion is not advised. Serum osmolarity must be measured, usually every six hours, to adjust the requisite dose of mannitol to keep osmolarity above normal (usually 300-320 mOsm/L). If an intraventricular catheter is already in place, this can be used to draw off CSF to directly lower ICP.

When these methods fail to lower ICP, barbiturate coma is the next step. The commonly recommended technique is to induce coma with high-dose pentobarbital as a 40 mg/kg IV bolus followed by a continuous infusion at a dose of 1-2 mg/kg per hour. The coma should be maintained for 24-48 hours *after* achieving control of the elevated ICP. Several factors, especially the adverse effects of the treatment, must be kept in mind while using this therapy. These are summarized in Table 51.8. As with stroke patients, part of the neurocritical care of patients with elevated ICP is maintaining normothermia and normoglycemia, avoiding increased intrathoracic pressures, and monitoring closely for, as well as taking prophylactic measures against, seizures (including giving phenytoin). One of the alternative or adjunctive experimental therapies to barbiturate coma that is showing promise is hypertonic saline administration (Qureshi and Suarez 2000; Suarez et al. 1998). Other experimental therapies, such as induced hypothermia and the use of neuroprotective agents, are on the horizon.

Table 51.8: Protocol of care of patients treated with pentobarbital coma

Intubation/mechanical ventilation
Peripheral arterial line
Pulmonary artery catheter placement (Swan-Ganz catheter) to measure central venous, pulmonary capillary wedge pressure, and cardiac output
Aggressive IV hydration for a goal wedge pressure of 12-18 mm Hg
Use of vasopressors (phenylephrine, norepinephrine, or dopamine) to keep CPP >70 mm Hg
Normothermia: 35.5-37.5"C
Pulmonary toilet
DVT/GI prophylaxis
Adequate nutrition: ideally through enteral route; parenteral route if this is not possible
Avoid hypotonic solutions
Maintain normoglycemia: 100-150 mg/dl,
Monitor leukocyte count on peripheral blood smear (CBC) closely; pan culture and possible empiric antibiotics to be started at first sign of significant elevation
Bedside I'.I'C monitoring tor bursi suppression partem
Jugular bulb catheter for monitoring (and treatment) of cerebral venous oxygen saturation

Surgical management obviously involves treatment of surgically relevant lesions. Therefore tumors need to be resected or dcbulked, hematomas may need to be evacuated, and brain abscesses may need to be aspirated and drained. There are experimental surgical techniques of performing bifrontal craniectomy for head trauma to reduce ICP and performing hemicranicctomy for large cerebral infarcts (Schwab et al. 1998).

Subarachnoid Hemorrhage

Virtually all patients with SAH will need to be initially managed in an NSU setting because of the complications associated with this potentially devastating condition (Van Gijn and Rinkel 2001). The goal of management in the acute phase of SAH is to prevent rebleeding and the sequelae from the initial hemorrhage, such as vasospasm and consequent cerebral ischemia. As a result of autoregulation, as well as other systemic factors, hypertension in the immediate post-hemorrhage phase can be profound. Extreme hypertension must be treated in this phase to reduce the risk of rebleeding. While some argument exists as to what constitutes the level at which to treat elevated ABP, the recommendation is to keep systolic blood pressure below 160 mm Hg. Even mundane measures such as maintaining a quiet environment with few distractions can keep ABP low. Artificially lowering ABP should not cause problems with respect to vasospasm-induced ischemia because available evidence indicates this process does not take place until at least postbleed day 3. Patients will need continuous ABP monitoring, usually with an arterial blood pressure transducer. Once cerebral aneurysms are secured, aggressive fluid hydration with normal saline solution (often at twice maintenance rates) can help to prevent vasospasm and cerebral salt wasting.

Symptomatic cerebral vasospasm usually occurs between 4 and 14 days after SAH and manifests itself acutely as focal or diffuse neurological symptoms. Should vasospasm occur, hydration with intravenous normal saline is part of recommended hyperdynamic therapy or, as it is colloquially called, "triple H" therapy, for hypervolemia, hypertension, and Aemodilution (Egge et al. 2001). While demonstrated efficacy in controlled trials is currently lacking, the American Heart Association docs recommend use of aggressive hydration with crystalloid such as normal saline or 5% albumin to elevate central venous pressure

(Mayberg et al. 1994). The technique of induced hypertension is essentially the same as noted above for acute ischemic stroke, with the use of phenylephrine and possibly dopamine or other pressor agents.

Some of the other complications, which may complicate management of SAH in the neurocritical care setting, are hydrocephalus, hyponatremia, and seizures. Hyponatremia can be caused by increased levels of atrial natriuretic factor (ANF) or by SIADH. Distinguishing between the two causes can be difficult but is important because restricting fluid for SIADH mitigates the therapeutic effect of hypervolemia and precludes aggressive fluid hydration. While a full discussion of this issue is not possible here, it should be noted that measuring the patient's volume status (i.e., weight, fluid balance, central venous pressure, and pulmonary capillary wedge pressure) can be critical to distinguishing between these two causes. These measurements are low in cerebral salt wasting (due to diminished intravascular volume), but normal or elevated in SIADH. Thus placement of a central venous catheter may be necessary.

Communicating hydrocephalus (HCP) can present acutely (within 1 week) or subacutely (a few weeks) after SAH. Clinical presentation of these patients is usually diffuse brain dysfunction secondary to elevated ICP. HCP is usually treated with intraventricular catheters; some patients may require permanent ventticuloperitoneal shunts. Clinical seizures are seen in about 26% of SAH patients. Such patients should be managed as described in the following section.

Spontaneous Intracranial Hemorrhage

Our purpose here, as in the other sections, is to simply note issues in neurocritical care of patients with ICH. Most important is the fact that the risk of neurological deterioration and cardiovascular instability in patients with ICH achieves its highest level during the first 24 hours after the bleed {Qureshi et al. 2001). For this reason many experts recommend admitting such patients to an NSU setting for at least 24 hours after the onset of ICH (Broderick et al. 1999). However, such a decision is often based on the fact that around 30% of patients with supratentorial ICH and nearly all patients with brainstem or cerebellar ICH have impaired consciousness, require intubation, and thus require admission to an NSU. Once m the NSU, monitoring of various clinical parameters just as for acute ischemic stroke will apply to patients with ICH *except* for the issue of aggressive hydration and induced hypertension. Much controversy surrounds the question of whether elevated ABP causes expansion of the hematoma. Current guidelines from the American Heart Association recommend that patients with a mean ABP >130 mm Hg be treated with IV antihypertensive agents (but keeping CPP above 70 mm Hg) for 3 days. After this, oral hypotensive agents can be given as long as the patient is clinically stable. Other issues of neurocritical care that may come up for a patient with ICH are mass effect from the hematoma and surrounding cerebral edema resulting in elevated ICP. The principles of management are the same as described previously. In addition, some cases ol K I 1 involve intraventricular blood, which can predispose the patient to hydrocephalus.

Myasthenia Gravis Crisis

A myasthenia gravis crisis (MGC) is defined as myasthenia gravis (MG) weakness severe enough to require mechanical ventilation (Mayer 1997). In 74% of patients in whom MGC occurred, it did so within the first two years after disease onset, and MGC can occur in up to 20% of all patients with MG (Thomas et al. 1997). A number of factors have been identified as precipitants of MGC (Table 51.9), although up to 30-40% of patients with MGC do not have clearly identifiable predisposing factors. It is important to do as much as possible to identify these precipitants, because a fundamental principle of managing the MGC is to remove them. Because of the involvement of the oropharyngeal and respiratory muscles, as the weakness of these muscles progresses, the FVC declines, which allows atelectasis to develop and then lead to respiratory failure. As described in Chapter 84, serial monitoring of hospitalized MG pun cuts must he performed with close attention to physical examination evidence of respiratory distress, as well as ABG and bedside rests of respiratory function (namely, NIF and VC). It must be remembered that the ABG, NIF, and VC can become abnormal only very late in the progression towards MGC. Also, while a maximal NIF or VC may be apparently adequate in a one-time test, fatigue may reduce respiratory function to below a critical level shortly thereafter,

Rapid-sequence orotracheal intubation, as described previously, is preferred. Recommended ventilator settings are small tidal volumes at 7-8 cc/kg with more rapid respiratory rates at 12-16 breaths per minute. In addition, atelectasis can be avoided with intermittent sighs of 1.5 x tidal volume at a frequency of 3-4 times per hour.

Tahlc 51.9: Precipitants of myasthenia gravis crisis

Infections:
Most commonly upper and lower respiratory tract
Medications:
Corticosteroids
Antibiotics: aminoglycosides, ciprofloxacin, clindamycin
Antiarrhythmics: procainamide, propranolol, timolol
Neuropsychiatric drugs: phenytoin, trimethadione, lithium
Stress:
Recent surgery
Trauma
Botulinum toxin administration
Thymoma

Several conditions should be met to make a decision about readiness for extubation. The ability of the patient to withstand procedures producing respiratory or bulbar muscular fatigue is crucial. Proper care of the MGC in the NSU setting also involves attention to adequate nutritional support, maintenance of adequate hydration, careful attention to electrolytes, aggressive pulmonary toilet, and DVT and GI prophylaxis. Acute treatment of neuromuscular failure from MG includes plasma exchange or intravenous immunoglobulin and corticosteroid therapy {Qureshi et al. 1999),

Guillain-Barre Syndrome

As with patients with MG, those with GBS will need neurocritical care most commonly for difficulty with respiration, although other critical conditions such as cardiac arrhythmias, sepsis, and pulmonary embolus can complicate their hospital course and require admission to an NSU {Ropper 1992). For this reason, when patients with GBS are admitted to nonintensive care settings within the hospital, special attention must be given to pulmonary toilet (e.g., incentive spirometry and chest percussion), GI and DVT prophylaxis, hydration, adequate nutrition, and frequent neurological examinations to avoid complications and rapidly identify patients who are clinically decompensating. Inspiratory and expiratory weakness together with bulbar weakness, if present, forms the basis of the significant risk that patients with GBS have for respiratory failure, either directly because of the weakness or because of aspiration and pneumonia. It is precisely this risk that necessitates the frequent neurological monitoring, including measurement of NIF and FVC. Should FVC fall to 20 cc/kg or less, the patient needs to be transferred or admitted ditectly to the NSU. FVC less than or equal to 15 cc/kg necessitates intubation and mechanical ventilation. Corresponding levels exist for NIF, but because of effort dependence they are less reliable. Fatigue is as much of a factor in GBS as it is in MG. A study on vital capacity in GBS showed that a decrease of 50% in the vital capacity over 48 hours predicted the need for mechanical ventilation (Chevrolet and Deleamont 1991). Other clinical clues predicting a need for mechanical ventilation include severe bulbar weakness, tachycardia, tachypnea, staccato speech, inability to count from 1 to 20 in a single breath, use of accessory muscles for breathing, and paradoxical breathing. Hypoxemia and respiratory acidosis seen on ABG tend to be late findings. Should intubation be necessary, as with other neurological conditions, rapid-sequence intubation and avoidance of depolarizing agents are recommended. In addition, the risk of aspiration is significant in patients with GBS. Therefore extreme vigilance must be maintained for the earliest evidence of pneumonia to promptly initiate antibiotic therapy.

It has been well documented that patients with GBS may have autonomic dysfunction and even failure, in addition to muscle weakness. Thus in addition to respiratory reasons for neurocritical care, there can sometimes be cardiac reasons. Some of the reported cardiovascular abnormalities include ECG changes, bradycardia, labile ABP (both extreme hypotension and hypertension, brady-rachycardias, and even fatal arrhythmias). Therefore careful attention must be paid to an admission ECG and any evidence of cardiac rhythm changes or other evidence of autonomic dysfunction (such as orthostatic hypotension, pupillary abnormalities, sweating abnormalities, and gastrointestinal dysfunction). Depending on the clinical scenario, cardiac monitoring may be appropriate. In such settings vasoactive medications must be used with caution.

Status Epilepticus

With as many as an estimated 250,000 cases of status epilepticus (SE) in the United States annually and with a mortality as much as SO,000 annually, it is no wonder that it desetves aggressive neurocritical care (Fountain 2000). Currently SE is defined as either two consecutive seizures within five minutes without intervening recovery of consciousness or a prolonged seizure (with or without impaired consciousness) for 30 or more minutes (Lowenstein and Alldredge 1998). The patient in SE needs to be acutely stabilized. This involves attending to some of the same factors as in acute ischemic stroke: establishing airway patency, maintaining adequate breathing, and determining the need for intubation; delivering oxygen, providing intravenous hydration, and ensuring cardiovascular stability; and controlling the seizures.

We provide the following recommended protocol:

1. Lorazepam should be administered at 0.1-0.2 mg/kg IV at a rate of 2 mg per minute.
2. If seizures continue, if the etiology is known but not corrected, or a cause for the seizure activity is not known, the patient should be loaded with phenytoin 20 mg/kg IV at a rate of 50 mg per minute or fosphenytoin 20 mg/kg IV at a rate of 150 mg per minute. If IV access cannot be obtained, fosphenytoin can be administered intramuscularly. For patients allergic to phenytoin, valproic acid can be loaded at 20-25 mg/kg IV at a rate of 50-100 mg per minute.
3. For repeated seizures, additional lorazepam may be given (at above dose) or additional phenytoin or fosphenytoin can be administered at 10 mg/kg IV at a rate of 50 mg per minute.
4. Should seizures continue after this, the next step is essentially some kind of induced coma using one of the following agents:

    - Midazolam IV 0.2-0.3 mg/kg loading dose, with maintenance dose of 0.1-2 mg/kg per hour
    - Propofol IV 50-250 gg/kg per minute

Either of these agents requires that the patient be intubated and have central venous access, continuous cardiovascular monitoring, and continuous EEC monitoring for the purpose of titrating these medications to achieve a burst-suppression pattern. The medication must be continued for at least 12 hours after initiation of therapy. Other choices include phenobarbital 20 mg/kg IV at a rate of 50-75 mg/min and valproic acid as described previously.

As with the other conditions discussed, the neurocritical care of SE patients involves attention to proper pulmonary toilet, cardiac monitoring, electrolyte balance, GI and DVT prophylaxis, and adequate nutrition. Fxccpt in cases in which the specific cause of the seizures is unquestionably known. n is ;iKn r-c-ciiMiMiended to give thiamine 1 0(1 mg IV upon presentation and daily to cover for seizures in chronic alcoholics, while various etiologies are being explored.

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Chapter 52
Principles of Neurosurgery

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The practice of neurosurgery is founded in neurology, and a solid understanding of neurological diseases is fundamental to good clinical neurosurgical practice. Likewise, neurology cannot be practiced well without a basic knowledge of the surgical implications of neurological diseases. Most of the specific pathological entities that constitute the bulk of neurosurgical practice (e.g., head and spinal cord injury, brain tumors, aneurysms and arteriovenous malformations [AVMs], degenerative and neoplastic spinal disorders, central nervous system infections, peripheral nerve problems, and pain) are covered in detail in specific chapters elsewhere in this book. Therefore in this chapter, we concentrate on three particular aspects of current neurosurgical practice. The first section deals with some neurosurgical emergencies that can occur in patients who are generally cared for by neurologists. The second section deals with some specific neurosurgical considerations that arise frequently in patients cared for by neurologists. Finally, in the third section, we discuss briefly some recent technological developments that have had a significant impact on neurosurgical practice and that are of interest to neurologists.

NEUROSURGICAL EMERGENCIES IN THE NEUROLOGY PATIENT

Acute Hydrocephalus

Hydrocephalus is usually a relatively chronic problem, but it can result in very dramatic acute symptomatology in a number of clinical settings. An awake patient can rapidly become drowsy, sometimes preceded by agitation, and progress rapidly to stupor and coma with small, poorly-reactive pupils. The importance of considering acute hydrocephalus in this setting is that the condition can often be reversed by one of the simplest neurosurgical maneuvers, an emergency ventriculostomy. Any neurosurgeon can perform a ventriculostomy in a matter of minutes with simple equipment kept available in a sterile tray specifically designed for this purpose in almost all hospitals in which neurosurgery is practiced. Most frequently, a frontal "twist drill" trephination is performed through a small incision in the frontal region (11 cm behind the nasion and 3 cm lateral to the midline), and the anterior horn of the lateral ventricle is cannulated with a small ventricular catheter connected to external drainage. There

arc a number of specific instances in which this maneuver can be life saving,

Herniation after a lumbar puncture is indeed a rare event. Before computed tomographic (CT) scanners were available, this was seen more often when patients with large supra ten to rial or posterior fossa masses underwent lumbar puncture. However, there are still occasional instances of patients with conditions that are not diagnosed by an initial CT scan, which can result in herniation after a lumbar puncture, such as in patients with acute bacterial meningitis and in patients with basal meningitis due to either tuberculosis or sarcoidosis. A simple ventriculostomy can immediately reverse this situation.

Patients who have had a subarachnoid hemorrhage (SAH), usually from a ruptured aneurysm, can deteriorate abruptly and rapidly lapse into coma, usually as a result of rerupture of the aneurysm cither into the parenchyma of the brain or into the ventricles causing acute hydrocephalus. In these patients, we recommend an emergency ventriculostomy even before a CT scan is performed. We have seen several patients wake up within a few minutes of a ventriculostomy when the problem was intraventricular hemorrhage and acute hydrocephalus. Obviously, the patient with a massive intracerebral hemorrhage would not be helped by this maneuver, but even then nothing is lost except the time taken to do the ventriculostomy. Acute hydrocephalus from intraventricular hemorrhage can also be suspected as the cause of abrupt coma in patients known to have an AVM or a cavernous angioma in the periventricular region.

Patients with a lesion m the region of the anterior third ventricle and the foramen of Monro can deteriorate acutely, and in these instances, acute hydrocephalus musr be suspected. This is a common cause of sudden death in patients with colloid cysts of the third ventricle (Figure 52,1). These patients often have a history of abrupt headaches related to posture or to coughing or performing a Valsalva maneuver that produce an abrupt increase in intracranial pressures. An emergency ventriculostomy can be life saving in these cases.

Patients who have an in-dwelling shunt for hydrocephalus can deteriorate acutely as a result of shunt malfunction. Again, when this occurs and the patient has lapsed into coma, the first step should be a "shunt tap"; by placing a small needle in the shunt reservoir, cerebrospinal fluid (CSF) can be freely extracted if the obstruction is disral. If this fails, usually because the obstruction is proximal, an emergency ventriculostomy is indicated even before the CT scan is obtained.

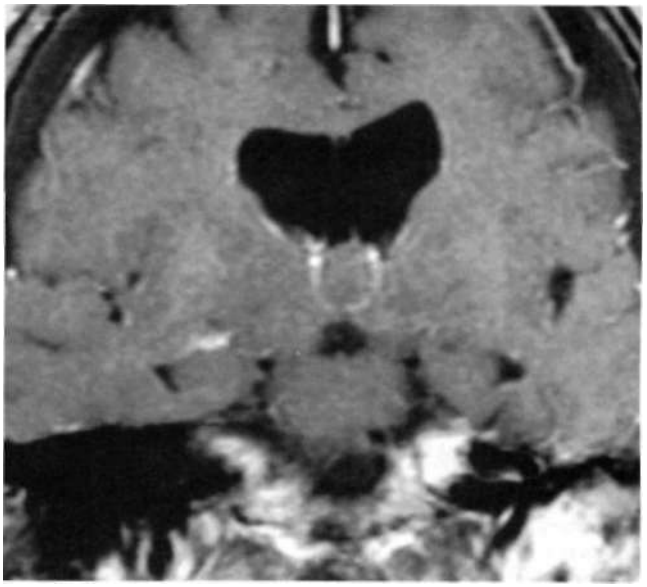

FIGURE 52.1 Colloid cyst of the third ventricle. Note the severe hydrocephalus caused by this small colloid cyst, which is blocking hoth foramina of Monro. The lesion was removed by a microsurgical transcallosal approach without neurological complications,

Cerebellar Hemorrhage and Infarction

Most patients with cerebellar infarction and many patients with cerebellar hemorrhage will be initially under the care of a neurologist. The diagnosis of either entity can almost invariably be made on clinical grounds alone and can be confirmed by a CT scan or magnetic resonance imaging (AlRIj. rhc neurologist must recognize when neurosurgical intervention, which is frequently life saving and function restoring for these patients, is indicated. For this reason, it is convenient ro classify the clinical stages seen in both of these conditions as follows: an initial "cerebellar" stage in which the only clinical deficits detected are referable to the cerebellum; an intermediate stage in which in addition to cerebellar signs, there are signs and symptoms referable to hydrocephalus; and the final stage of brainstem compression. We firmly believe that neurosurgical intervention is indicated when the earliest signs and symptoms of hydrocephalus develop. At this stage, the patient may be treated with a ventriculostomy alone; however, this carries the danger of upward herniation, which is seen frequently after the lateral ventricles are decompressed if the large posterior fossa mass is not dealt with. We prefer to use ventriculostomy cither to gain time to perform a definitive surgical decompression of the posterior fossa or to go directly to the operating room for surgical decompression without a preliminary ventriculostomy. Once definite signs of brainstem compression develop, emergency surgical decompression is mandatory if the patient's life and function are to be saved.

The patient with cerebellar hemorrhage usually presents with the classic history of a headache of relatively abrupt onset frequently accompanied by nausea and vomiting. Very commonly, the patient or his or her family members

will give a history of inability to walk due to instability that develops soon after the headache. When examined, these patients have striking truncal ataxia and often cannot even sit on the examining table to be examined; they can practically never walk. In addition, they frequently have nystagmus and signs of cerebellar appendicular ataxia. When the patient is wide awake and the hemorrhage is not too large (usually <3 cm in diameter by CT scan), surgery can be delayed and the patient can be observed in an intensive care setting. Drowsiness or agitation followed by drowsiness signals the onset of hydrocephalus and calls for surgical intervention. Surgery, in particular a paramedian suboccipital craniotomy with removal of the hematoma, is crucial at the earliest signs of brainstem compression such as an ipsilateral sixth nerve palsy that rapidly advances to a complete ipsilateral gaze palsy accompanied by a peripheral facial weakness on the same side.

With cerebellar infarction, the syndrome tends to progress more slowly than with cerebellar hemorrhage, and very often, the patient can be managed conservatively with careful neurological observation, preferably in an intensive care unit. As opposed to the case of cerebellar hemorrhage, headache may not be prominent at the onset in patients with cerebellar infarction; complaints of dizziness and difficulty walking may be the only signs of cerebellar dysfunction. It is important to remember that because symptomatic cerebellar infarction is most commonly due to occlusion of the vertebral artery at the origin of the posterior inferior cerebellar artery (PICA), a lateral medullary infarct may coexist. The signs and symptoms of intrinsic lateral medullary damage, of course, do not call for surgical intervention. It is therefore essential to differentiate brainstem infarction from brainstem compression resulting from the mass effect of the edema or hemorrhagic transformation of the infarct. The detailed clinical signs and MRI can differentiate the two conditions. The recommended surgical procedure is a bilateral suboccipital craniotomy extending through the foramen magnum. Because the infarction is most commonly in the territory of the PICA, the tonsil is often involved and herniates through the foramen magnum, which needs to be decompressed to relieve brainstem compression. Because the progression of cerebellar swelling is usually much slower with cerebellar infarction than with hemorrhage, it is possible to temporize with a ventriculostomy in patients who have signs and symptoms of hydrocephalus (confirmed by CT scan) but who do not have signs of direct brainstem compression. The syndrome often will gradually resolve without the need for suboccipital decompression in these patients (Camarata and Heros 1996).

The prognosis for good functional recovery is excellent in patients with cerebellar hemorrhage and infarction who had a timely suboccipital decompression before they lapsed into coma. Even comatose patients can make an excellent functional recovery provided that the decompression is performed expeditiously soon after the onset of coma. These patients often require a prolonged period of rehabilitation, sometimes with a tracheostomy and a gastrostomy, but eventually they improve and their intellectual function remains intact.

Intracerebral Hemorrhage

Intracerebral hemorrhage as a clinical entity is covered in detail in Chapter 57B. Here, we only refer to the fact that this entity may be a neurosurgical emergency. This is particularly true when any intracerebral hemorrhage breaks into the ventricle and results in acute obstructive hydrocephalus. As discussed earlier in this chapter, the situation can be significantly palliated with a unilateral or bilateral ventriculostomy if the ventricles are filled with blood. There is considerable evidence that in some circumstances, emergency surgical evacuation of intracerebral hematomas can not only be life saving but also function sparing. Much of the evidence comes from large, but uncontrolled, scries from Japan, where these patients arc often managed in neurosurgical units and considered true surgical emergencies.

Current practice in the United States is to treat patients with supratentorial intracerebral hemorrhage conservatively with maximal medical therapy for increased intracranial pressure (e.g., mannitol and hyperventilation). If they show significant neurological deterioration to the point of herniation, evacuation of the hemorrhage can be life saving, but frequently these patients are left devastated. The important question, which can only lie answered by a randomized controlled trial, is whether early intervention (during the first 6 hours aftet the hemorrhage) may be beneficial in terms of preserving or rcstotiug neurological function. There is clear experimental evidence that secondary changes occur over the first several hours as a result of direct local pressure, ischemia, focal vasospasm, and perhaps release of noxious substances from the clot (Mendelow 1991). These secondary changes in the experimental setting can be prevented by early evacuation of the clot.

For the more accessible lobar subcortical and putaminal hemorrhages, refined microsurgical techniques have been introduced to remove rhc clot with minimal trauma to the brain and with a better chance of achieving thorough hemosrasis. There are also surgical means of evacuating hematomas in less accessible locations like the thalamus that are relatively less invasive rhan direct surgical intervention. These techniques include a device that acts as an Archimides screw to aspirate the clot, the use of a nucleotome type of device to emulsify and then aspirate the clot, the stereotactic injection of lytic agents to liquefy the clot and then aspirate it, and the use of the endoscope to directly visualize and suction the clot. It is now more likely that the proper randomized study to answer the question of whether early surgery is beneficial will be conducted

because patients are seeking medical care sooner as a result of public education campaigns that emphasize the importance of treating stroke as an emergency (i.e., Brain Attack) (Camarata, Heros, and Latchaw 1994). A recent study, however, indicates that postoperative reblccding may be a problem in very early surgical evacuation (Morgenstern etal. 2001).

At the present time, because of lacking specific practice standards or guidelines, individual patient-specific treatment plans are developed. The ovetall medical health of the patient, age, and other issues of quality of life play an important role in the final decision. Emergency operations are often performed on patients who have a significant neurological deficit, who are seen soon after the onset of the symptoms, and who have a relatively accessible hematoma. Patients who were tteated conservatively initially, but who have failed maximal medical therapy and are showing signs of herniation, may also be good surgical candidates. In these patients, the operation is undertaken as a life-saving measure, with little hope of significant functional recovery. We are more conservative with thalamic hemorrhages and will operate only rarely as a life-saving procedure. In elderly patients in whom amyloid angiopathy may be suspected as the cause of hemorrhage (because of evidence of previous hemorrhages, subcortical location, and history of dementia), a conservative approach is advised, because operating on these patients can lead to catastrophe due to poor hemostasis resulting from the friability of the cerebral vasculature.

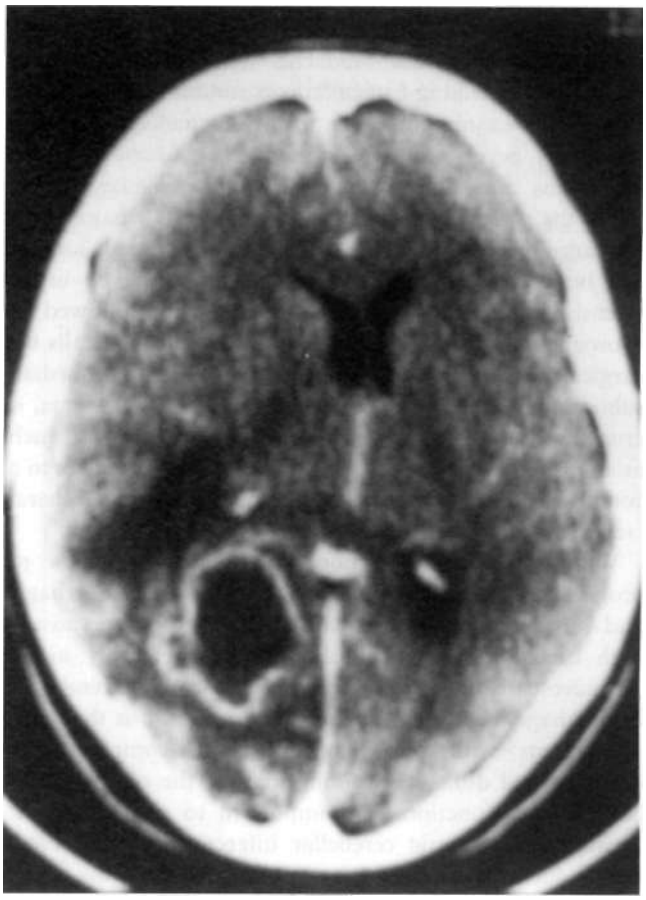

FIGURE 52.2 Brain abscess. Note the location of this abscess just behind the atrium of the ventricle. If not drained urgently, this lesion couki rupture into the ventricles wirh resulting ventriculitis, which could be fatal.

Intracranial Tumors

In general, intracranial tumors usually present as a neurosurgical emergency only if there is an acute hemorrhage into the tumor with abrupt deterioration. With intrinsic brain tumors, this is statistically most likely to occur with astrocytomas because they are so much more common; however, oligodendrogliomas and ependymomas have a relatively greater propensity for hemorthagc. Of the metastatic tumors, melanoma, hypernephroma, choriocarcinoma, and thyroid carcinoma are particularly prone to hemorrhage.

Some patients with intrinsic brain tumors and occasionally with meningiomas can develop rather massive cerebral edema to the point at which deterioration occurs abruptly. Although generally we try to manage most of these patients with corticosteroids, the neurological deterioration may be abrupt and severe enough to require immediate surgical decompression.

Brain Abscess

A brain abscess may present with acute neurological deterioration resulting from rupture of the abscess into the ventricular system. A brain abscess is suspected in a patient with signs of sepsis in whom the CT or MRI scan shows a parenchymal lesion that is "ring enhancing" (Figure 52.2). Such patients with either a relatively inaccessible brain abscess or multiple brain abscesses are primarily treated medically with antibiotics, usually after aspiration for cultures of at least one of the abscesses. Acute deterioration in these cases is suggestive of intraventricular rupture, particularly if one of the lesions is in the periventricular region. These situations call for immediate surgical drainage of the abscess and ventricular lavage, leaving a catheter for continuous drainage and intraventricular antibiotic injection.

Pituitary Abscess

A rare condition that often calls for emergency neurosurgical intervention is a pituitary abscess. These patients frequently have a history of meningitis, sinusitis, or rhinorrhea. Chronic headaches and signs and symptoms

of pituitary insufficiency are not uncommon. The presentation is usually acute with a sudden exacerbation of symptoms including visual loss, extraocular nerve dysfunction, and disturbance in the level of consciousness. When such a presentation is accompanied by signs of sepsis, a pituitary abscess must be suspected and ruled out. An emergency transsphenoidal debridement, accompanied by systemic administration of antibiotics and appropriate hormonal replacement therapy (including a large loading dose of corticosteroids) is indicated. We use dexamethasone at 10 mg intravenously, immediately followed by 4 mg every 6 hours. Others prefer hydrocortisone at a dose of 200-300 mg intravenously three to four times daily.

Pituitary Apoplexy

Patients with cither a known pituitary tumor or more commonly without such a history may present with an apoplectic attack that includes sudden severe headache, decreased vision, diplopia, and later drowsiness and coma. In these instances, pituitary apoplexy must be suspecred, particularly if the initial CT or MRI scan indicates an enlarged sella or a pituitary tumor. The apoplectic nature of the attack is usually due to infarction, hemorrhage, or hemorrhagic infarction within a pre-existing pituitary adenoma. Not uncommonly, the course is more subacute lasting several days and with less dramatic symptomatology. On examination, the patient may show photophobia and meningismus, bitemporal hemianopia and/or decreased visual acuity in either or both eyes, and deficits of extraocular motion, most commonly a partial or complete third nerve palsy unilaterally or bilarerally.

Pituitary apoplexy represents a medical and surgical emergency. These patients must be treated immediately with intravenous corticosteroids in the doses indicated earlier. A transsphenoidal operarion to remove as much of the tumor and/or hemorrhage as possible, and to decompress the optic apparatus, is mandatory and urgent. The results are excellent if the operation is performed promptly.

Spinal Cord Compression

Acute paraparesis or quadriparesis rapidly progressing to complete paralysis is a common situation in neurological practice. Although the diagnosis of acute demyelinating transverse myelitis is frequently entertained, this diagnosis is untenable without an imaging study thar rules out spinal cord compression. Such a syndrome of acute myelopathy can have a number of causes that require emergent neurosurgical decompression. Most commonly, the problem is due to merastatic tumors, though in this case, unless there has been hemorrhage within the tumor, the progression is usually over days and weeks rather than minutes or hours.

Nevertheless, sometimes the patient does not seek neurological consultation until unable to walk. If the progression has been rapid, emergency decompression or emergency irradiation is indicated depending on the clinical setting. Glucocorticosteroids are usually administered emergently in these instances. Surgery is the preferable recommendation in cases in which the primary tumor is known to be radioresistant, such as a hypernephroma. Lymphomas are very radiosensitive and radiation therapy is usually the preferred modality. When the pathological diagnosis of the tumor is not known, it must be established by open surgery or a percutaneous biopsy.

More dramaric causes of acute spinal cord compression are hematomas, which can be subdural, epidural, or intramedullary, and abscesses, which are mostly epidural but can also be subdural. Both conditions usually call for emergency surgical intervention. An epidural or subdural spinal hematoma can develop spontaneously, but more often, it develops in the setting of anticoagulation, blood dyscrasias, or trauma. Wc have seen a few cases develop after spinal puncture was unadvisedly performed in patients who were anticoagulated. An abscess should be suspected in any patient with a subacute paraplegia who has a history of recent sepsis or who is predisposed to infection either because of diabetes or immunodeficiency. An epidural abscess can also develop in a patient without any predisposing history, and in this instance, the primary event commonly is discitis (infection of the intervertebral disc). The results of emergency surgical decompression both in hematomas and in abscesses arc excellent provided thar the patient undergoes operation quickly after the onset of the symptoms of myelopathy. Even paraplegic patients can recover if operated on within the first few hours after the onset of paraplegia.

Acute spinal cord compression can also develop from compression fractures or fracture dislocations that can occur as a result of relatively minor trauma in patients with severe osteoporosis, metastatic bone disease, rheumatoid arthritis, or ankylosing spondylitis.

Of special consideration is acute cauda equina compression, which often requires emergency neurosurgical decompression. The causes of acute compression of the cauda equina are similar to those of spinal cord compression, However, when the cause is a neoplasm, the evolution of symptoms tends to be considerably slower and less dramatic. Subdural and epidural hematomas and abscesses can affect the cauda equina acutely, and because the potential for recovery of function is better for the cauda equina than for rhe spinal cord, even with a profound deficit, there is reason to perform decompression as rapidly as possible because of the correlation between delay in decompression and extent of recovery. This is particularly true when there is loss of bladder and bowel control; in these cases, full bowel and bladder function rarely returns if decompression is delayed more than a few hours after loss of function. The same is true when compression of the

cauda equina is caused by an acute disc extrusion. Although this can occur at any lumbar level, it is seen most commonly between the fourth and fifth lumbar vertebrae and most of these patients show a complete block to CSF flow at myelography, CT scanning, or MRI scanning. A common mistake is to attribute acute urinary retention in a patient with acute low back pain to the effect of the narcotics that these patients often require to control their acute pain. We teach our residents that acute urinary retention in a patient with a suspected ruptured disc calls for emergency neuroradiological investigation and emergency surgery if a large disc herniation causing cauda equina compression is found. In fact, even the acute development of a foordrop, which is a common and significant disabling neurological deficit, calls for at least urgent (within 24 hours) if not emergent investigation and possible surgery because again the probability of full recovery is related to the rapidity of decompression.

NEUROSURGICAL CONSIDERATIONS IN COMMON NEUROLOGICAL DISORDERS

Subarachnoid Hemorrhage

Patients with SAH may be initially cared for by the neurologist. Although these patients are frequently transferred at some point to a neurosurgical service, **the** neurologist must be aware of some surgical considerations (sec also Chapter 57C).

Timing of Angiography and Surgery

The mainstay of the initial diagnosis of SAH is the CT scan. The results of the CT scan may dicrate immediate neurosurgical intervention, for example, if there is acute hydrocephalus or a large intracerebral hematoma. The scan will also frequently suggest the site of the aneurysm, and the amount of blood is an excellent predictor of the likelihood of vasospasm. The likelihood of a patient developing vasospasm and the specific arteries involved in the spasm are closely correlated with the thickness and location of the clot seen in an early (within 48 hours) CT scan in the basal subarachnoid spaces. Intracerebral and/or intraventricular blood does not appear to correlate with vasospasm, although it does adversely influence the outcome.

Timing of angiography is the next aspect to be considered. Generally, unless the patient is in very bad neurological and medical condition, we recommend proceeding with angiography immediately, regardless of whether early surgery or cndovascular treatment is entertained. Early angiography has the advantage of establishing the diagnosis and the presence or absence of an aneurysm or an AVM and is helpful in establishing the plan of treatment. If endovascular treatment is chosen, sometimes it can be performed in the same angiographic session without need for recatheterization (see Chapter 37C). In addition, early angiography is extremely helpful in establishing the site of bleeding, which is important even if early surgery is not planned because the patient may suffer recurrent hemorrhage. This may result in the need for immediate surgical intervention, particularly if the subsequent hemorrhage is intracerebral. In such instances, there may be no time for angiography and the surgeon must intervene to evacuate the hematoma without delay. It is most helpful in these instances to know the details of the aneurysm. There is a recent tendency to substitute CT angiography for catheter arteriography (see Chapter 37B). This is particularly helpful in patients in bad neurological condition in whom emergency surgery can be planned using a CT angiogram demonstrating the aneurysm rather than catheter angiography.

To guide the timing of surgery, a number of grading systems of the patient's neurological condition and, particularly, level of consciousness have been developed. Generally, grade I and II patients are awake and oriented and in good neurological condition, whereas grade IV and V patients are stuporous or comatose and in very bad condition or are agonal. Grade III patients are awake but confused or drowsy and usually have a mild to moderate neurological deficit. Most neurosurgeons currently advocate early surgery or endovascular occlusion in most cases of ruptured aneurysm when the patient is in relatively good condition, that is, awake with or without a cranial nerve palsy, and either intact neurologically or with only a mild neurological deficit (grades I, II, and "good" grade III patients). The exception is in cases in which the aneurysm presents a major technical challenge such as with giant aneurysms in which open surgery is difficult and endovascular therapy is not likely to succeed. These patients may need to be treated with complicated clipping techniques, **which** may require temporary arterial occlusion or bypass grafting and arterial sacrifice. In these cases, brain relaxation is necessary for optimal exposure, and it may be preferable to wait until the increased intracranial pressure and hyperemia secondary to the initial hemorrhage subside. From the practical point of view, this means 12 or 14 days, and it may be longer in patients whose course is complicated by vasospasm. In patients in poor neurological condition (stupor, coma, and/or a major neurological deficit—grades IV and V), we personally prefer to use endovascular occlusion early or, if this is not feasible, to wait until the hemodynamic effects of the initial hemorrhage and the intracranial hypertension subside before entertaining open surgery. Clearly, having the aneurysm either clipped or completely obliterated by endovascular coiling eliminates the risk of early recurrent hemorrhage and allows the treatment of vasospasm with hypervolemia and hypertension, which augments the risk of rehemorrhage when the aneurysm is unsecured.

Hydrocephalus

Hydrocephalus frequently complicates SAH. Hydrocephalus after SAH is divided into three relatively different clinical syndromes (Heros 1989). The first is *acute, obstructive hydrocephalus,* which is discovered by CT scan in a patient who is in bad condition after the initial SAH. This calls for an emergency ventriculostomy (see Acute Hydrocephalus, earlier in this chapter). The second syndrome is *subacute hydrocephalus,* which characteristically develops after the first few days and results in increased headache and a gradually declining sensorium. We tend to be conservative with these patients and temporize with measures such as mannitol infusion and corticosteroid treatment, which may carry the patient through this stage without the need for a permanent shunting procedure. When the decrease in consciousness is severe, a ventriculostomy is necessary. We prefer to avoid this procedure in the awake patient, particularly if the aneurysm has not been secured, because there have been instances in which rcblecding has been induced by either ventricular drainage or a spinal tap withdrawing a substantial amount of spinal fluid. Some of these patients will eventually need a permanent shunt, but if this can be delayed until the CSF is completely clear, the chances of a successful shunt increase significantly. The third syndrome is *delayed hydrocephalus,* which presents as the syndrome of normal-pressure hydrocephalus. The typical setting is the patient who has recovered or is recovering gradually from an SAH, has had the aneurysm clipped or coiled, and then either fails to continue to improve or starts to deteriorate. The classic triad of symptoms, namely impairment of cognition, difficulty with gait, and incontinence, is frequently seen in these patients. In this clinical setting, when the CT scan shows that the ventricles arc larger than they were initially, we proceed with a shunting procedure without any other tests. These patients respond very well to shunting.

Vasospasm

Although there is no effective way of preventing vasospasm, calcium-channel blockers have proven effective in ameliorating its ischemic consequences, so most neurosurgeons currently use them from the onset in patients with SAH, The mainstay of the treatment of vasospasm remains the induction of hypervolemia, usually with colloids that result secondarily in hemodilution and the artificial induction of hypertension. We use hypervolemia prophylactically from the onset in those patients in whom the initial CT scan suggests a high likelihood of the future development of vasospasm. We also tallow ilu'se patients with daily transcranial Doppler examinations, which show increased flow velocities in arteries exhibiting vasospasm. At the earliest onset of ischemic symptoms presumably related to vasospasm, we perform a CT scan to rule out hydrocephalus and check the blood studies to make sure that abnormalities like hyponatremia and hyperglycemia are not the cause of the deterioration. If vasospasm is left as the probable cause, we proceed with vigorous medical treatment, raising the arterial pressure as necessary to reverse the neurological deficit, sometimes to 190-200 mm Hg systolic. If the patient does not respond promptly with resolution of the ischemic symptoms, an angiogram for possible angioplasty (sometimes preceded by intra-arterial papaverine injection) is obtained (Figure 52.3). It has been our impression, supported by recent anecdotal reports, that such treatment is most beneficial when instituted during the first hours after the onset of the symptoms. For this reason, we consider the treatment of vasospasm a relative emergency.

Y.ndovascular vs. Direct Surgical Treatment of Intracranial Aneurysm

At the present time, there is no definitive answer as to whether endovascular or direct surgical treatment of an intracranial aneurysm is better. Our experience and review of the current literature indicate that endovascular aneurysmal obliteration, when possible, is an acceptable alternative to surgical clipping in terms of preventing early rehemorrhage (Figure 52.4). This form of treatment is generally feasible in patients with nongiant aneurysms whose aneurysmal configuration is "favorable" (narrow neck compared to the width of the dome). Of course, generally these aneurysms are also favorable for surgical intervention. However, some aneurysms, because of their location, are relatively more difficult to treat surgically. In these instances, the early morbidity of endovascular treatment may be less than the surgical morbidity; aneurysms at the top of the basilar artery are a good example of this situation. A recently completed randomized international study conducted at a number of centers in Europe, Australia, and Canada has confirmed that the early morbidity of open surgery is slightly greater than that of endovascular coiling in patients who were felt to have aneurysms that could be treated either surgically or cndovascularly (International Subarachnoid Aneurysm Trial 2002). In this important study, 9278 patients were eligible for randomization. The neurovascular team at each institution felt that in the majority, one or the other form of treatment was preferable, and in those patients who were not randomized, surgery was chosen more often than endovascular therapy. In 2143 patients, the neurovascular team could not he sure which treatment was preferable, so they were randomized. In this group, endovascular therapy showed an absolute risk reduction of 6.9% in terms of likelihood of a had outcome at 1 year. This is an important difference that was significant statistically. However, rebleeding was more common after coiling than after clipping (2,6% after coiling vs. 0.9% after clipping), and if that differential rare of rebleeding continues, it will not take

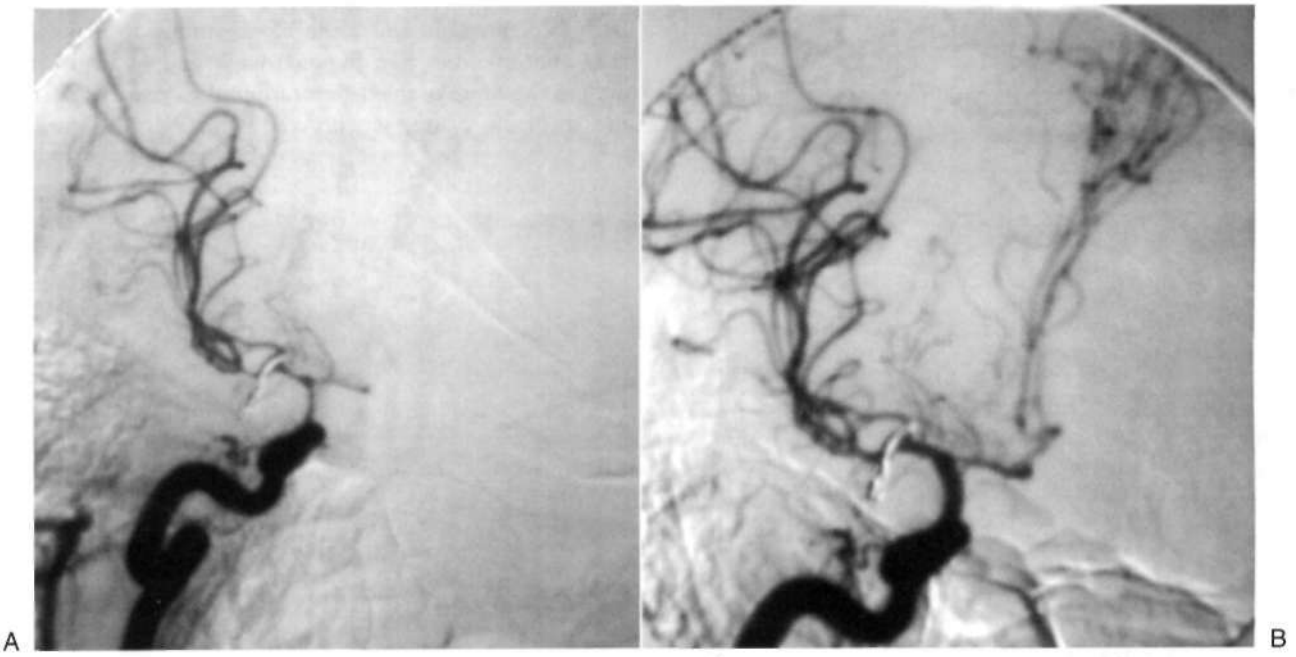

FIGURE 52.3 Vasospasm treated by endovascular balloon angioplasty. (A) Note the severe vasospasm present in the supraclinoid internal carotid artery and in the early segments of the middle cerebral and the anterior cerebral arteries. The partem had a subarachnoid hemorrhage *6* days before from a middle cerebral aneurysm rhat was successfully clipped the day after the hemorrhage. (B) Note the significant restoration to normal caliber of the previously spastic vessels by the endovascular angioplastic procedure. The anterior cerebral arteries, which practically did not fill before rhe angioplasty, now fill relatively well.

many years for the early advantages of coiling to be overcome. The ongoing follow-up study of these patients may give us a more definitive answer about which form of treatment is preferable for aneurysms amenable to borh forms of treatment. However, this study addressed only the group of parients who were felt ro be equally amenable to borh forms of treatment; because they were the minority of the patients evaluated, the results of rhe study cannot be generalized to all patients with aneurysms. Additionally, the study addressed only patients with SAH, and its results should not be extrapolated to patients with unruptured aneurysms.

Unfortunately, endovascular coiling is usually unsuccessful in most giant aneurysms or in aneurysms wirh very broad necks, or in fusiform or dissecting aneurysms. These are, of course, the aneurysms with which we also have the most surgical difficulty'. In these patients, we frequently have to consider other surgical alternatives such as proximal arrerial occlusion or rrapping (occlusion proximal and distal to the aneurysm) with or without a bypass graft, aneurysmorrhaphy (opening and decompressing the aneurysm under temporary trapping), or clipping under cardiac standstill using cardiopulmonary bypass {Figure 52.5).

In our institution, we continue to recommend microsurgical clipping for most accessible aneurysms of the anterior circulation and the vertebral artery when the patient is in relatively good neurological condition. Basilar aneurysms are considered on an individual basis, and currently most are treated by endovascular means. In patients in poor neurological grade, even if the aneurysm is surgically accessible, we prefer to at least attempt endovascular treatment initially. We then proceed to surgery, usually ar a later stage, if the endovascular trearment fails. For most patients with giant or dissecting aneurysms, or aneurysms with a very broad base, surgery remains the preferred option.

Vascular Malformations

Distinct pathological types of vascular malformations usually present as different clinical syndromes. In addition, it has become increasingly apparent that these different pathological entities are not always pure, and sometimes transitional forms and coexistence of different types of malformations are present. Because these patients are frequently cared for by the neurologist, it is pertinent to presenr rhe neurosurgical the rape uric perspective.

The first classic type of malformation, the *capillary telangiectasis,* is generally of no clinical significance and is seen only at autopsy. The second type of vascular malformation is the *venous angioma* (Figure 52.6). It seems clear that most of these lesions are clinically silent. However, occasionally there can be seizures that can be localized to the area of the venous angioma and, rarely, a hemorrhage. In the latter case, it is not uncommon to have

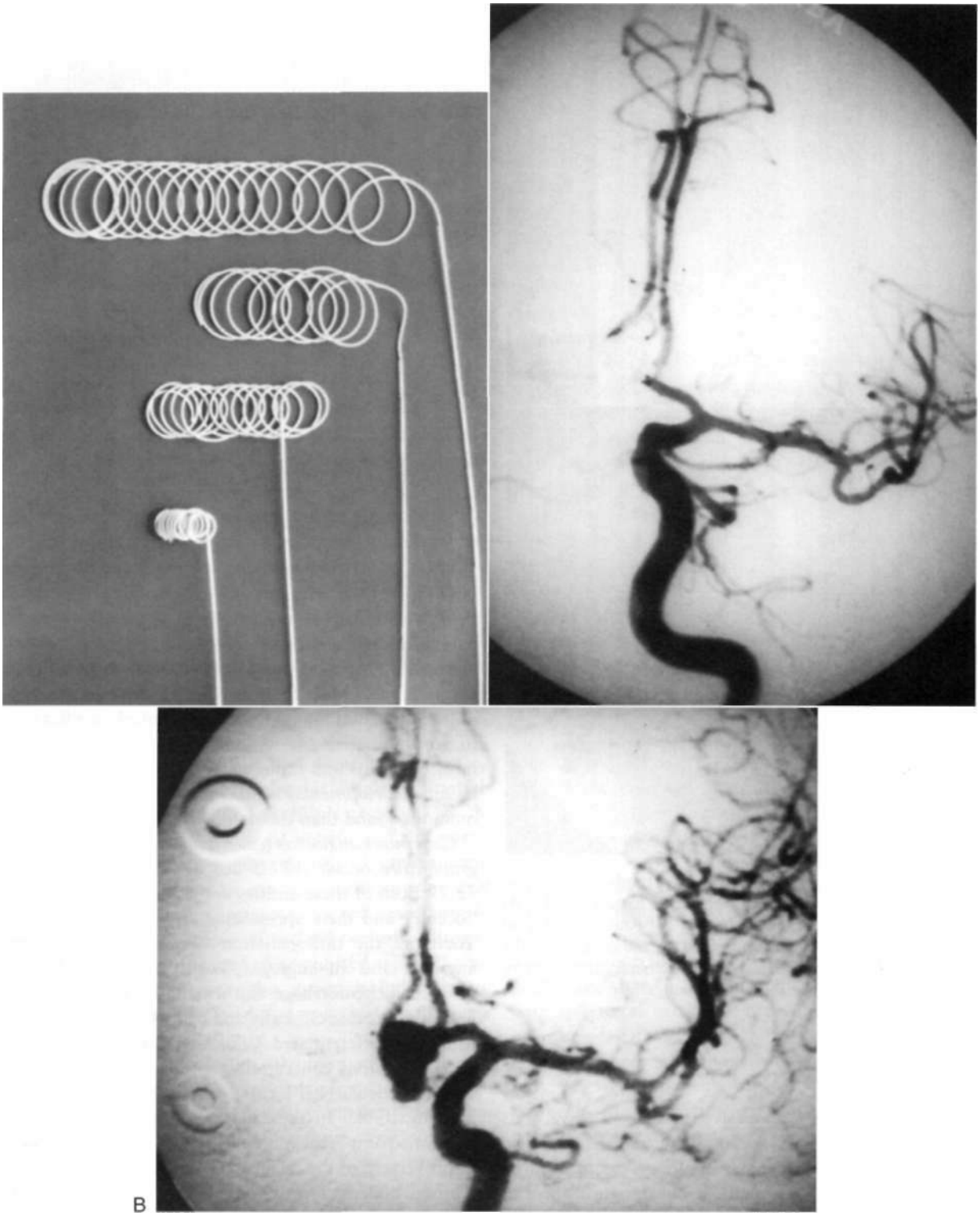

FIGURE 52.4 Endovasculat coil occlusion of aneurysms. (A) Detachable Guglielmi coils, which come in different sizes and can be detached by electrolysis from the carrier catheter once they are placed inside the aneurysm. (B) Ruptured anterior communicating artery aneurysm in a patient who had a poor neurological grade. Because of the grade, the decision was made to coil this aneurysm rather than clip it microsurgically. (C) Result after endovascniar coiling. Note that there is no filling of the aneurysm, which was Totally occluded by coiling.

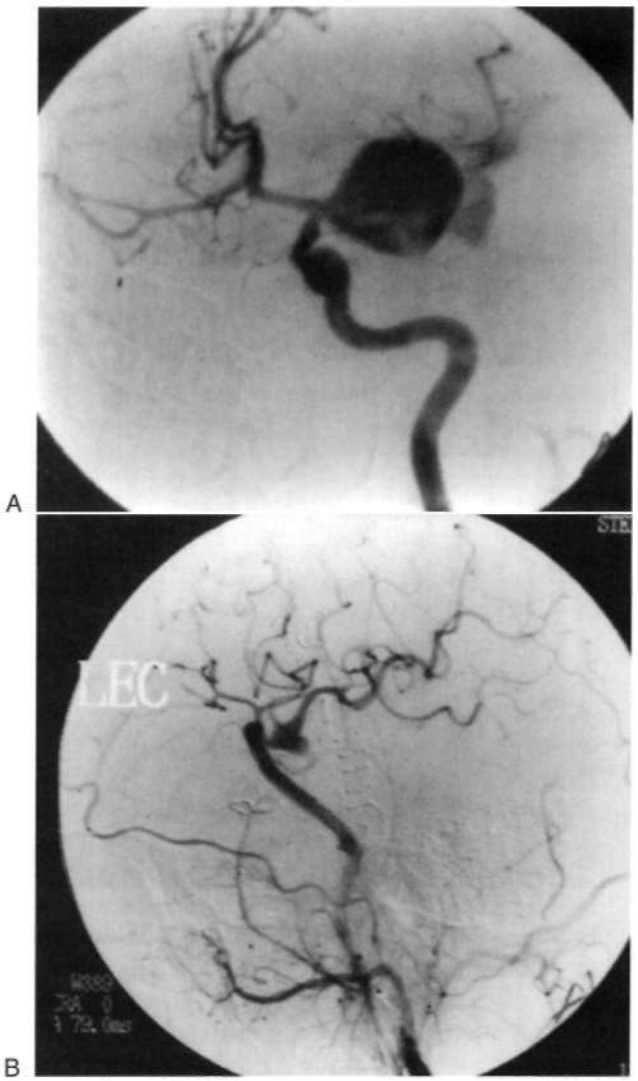

FIGURE 52.5 Unclippable giant middle cerebral aneurysm treated by middle cerebral occlusion after bypass graft. (A) Preoperative appearance of the aneurysm. (B) After occlusion of the middle cerebral artery just proximal to the aneurysm, the saphenous vein bypass graft between the external carotid artery and a distal division of the middle cerebral artery now fills the entire middle cerebral territory.

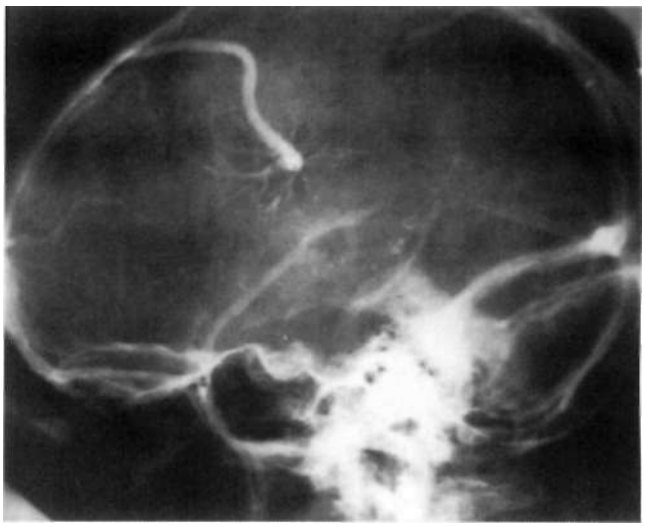

FIGURE 52.6 Venous angioma. Note the characteristic caput medusa appearance of small radial veins draining into a large venous channel. These lesions fill angiographically in the late venous phase, and they usually drain the normal brain, which makes their excision dangerous.

the lesion results in seizures, it is preferable to tteat the patient medically without surgery. When these patients are referred for surgical opinion, we prefer to reassure them and to tell them that they have not a pathological entity but a developmental anomaly of little clinical significance and to go about their life without restrictions. To this effect, most clinicians and radiologists are beginning to call these lesions *developmental venous anomalies,* which has a less ominous sound than the name *venous angioma.*

Cavernous angiomas (cavernomas) and *cryptic* or *angiographically occult AVMs* are a different matter (Figure 52.7). Both of these entities are generally angiographically "occult" and their appearance on MRI can be idenrical. Therefore the differentiation herween a true cavernous angioma and an angiographically occult AVM that has resulted in hemorrhage can usually be made only pathologically, because clinically and by MRI these lesions cannot usually be differentiated. Clinically, angiographically occult vascular lesions can certainly result in seizures, which at times, particularly if located in the medial tempotal lobe, are intractable. In these patients, resection of the lesion ("lesionectomy") most often results in resolution ot marked improvement of the seizures. Generally, we do not perform a formal epilepsy type of resection with electrophysiological recordings in these patients. In patients who present with well-controlled seizures without evidence of overt hemorrhage, a case for continuing medical treatment without sutgety can be made. However, surgical removal is very likely to result in a cure and eventual cessation of the need fot anticpilcptic medication. Because many of these lesions are located in accessible surgical regions and the surgery can be performed with little risk of morbidity, we gcnetally

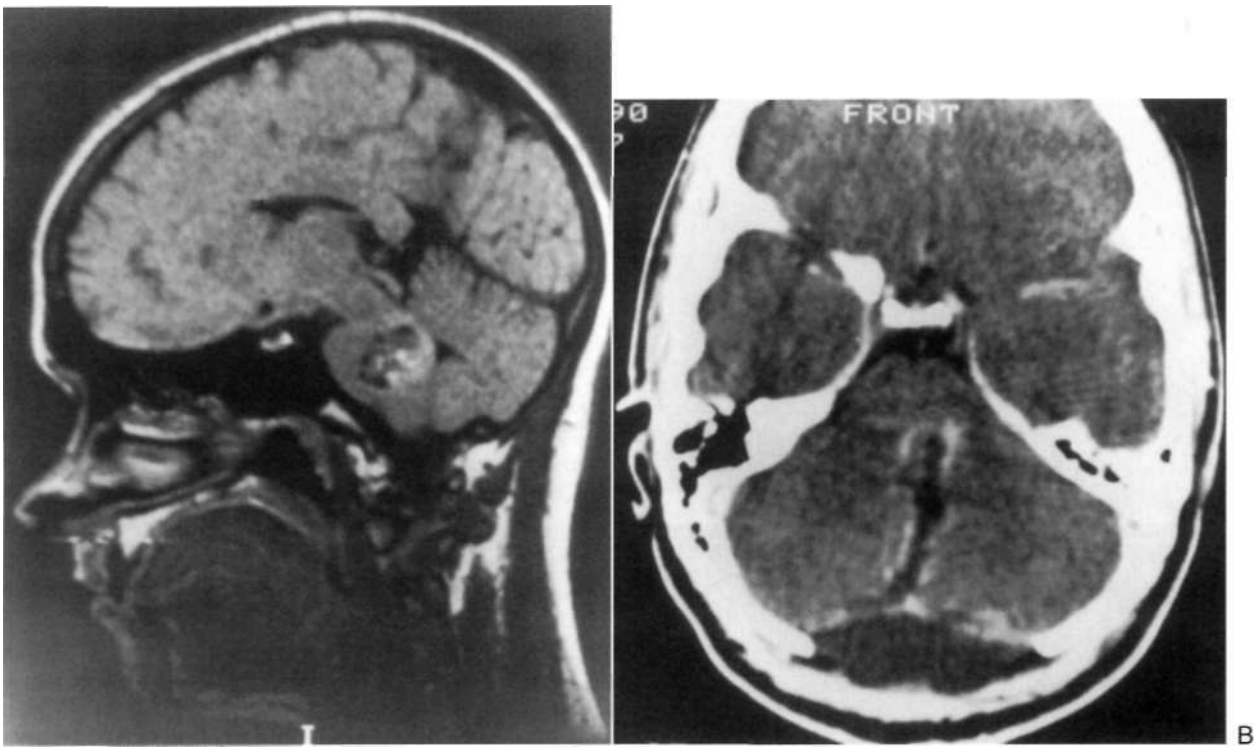

FIGURE 52.7 Cavernous angioma of the pons. (A) Note the typical appearance of the lesion in the pons, which happens to be a common location for cavernous angiomas. Because this patient had several episodes of neurological deterioration in the past related to small hemorrhages within the lesion, the decision was made tn excise the lesion surgically, (B) Postoperative computed tomographic scan showing complete removal of the lesion. There is some blood in the surgical bed and along the surgical track through the inferior vermis of the cerebellum.

advise surgery for these patients. Even in lesions in the motor and speech atea, particularly if the lesion is relatively superficial, surgery can be performed with very little risk of morbidity.

The issue is more complicated when the lesion is asymptomatic and detected on an MRI obtained for other reasons. In these cases, we tend to he conservative and **follow** the patient with pctiodic MRIs and advise surgery only if symptoms develop ot if the lesion shows significant growth, usually by focal hemorrhage, on MRI follow-up. When a lesion has resulted in a clinically overt hemorrhage, we generally recommend surgical excision for most supra-tcntorial and cerebellar lesions. Even deeply located mal formations can be accessed with traditional or framelcss stereotaxis through a trajectory that spares critical functional ateas. Once the surgeon reaches the lesion, it can usually be temoved without producing additional neurological damage,

Lesions of the brainstem are more difficult to resolve. Cavernomas are particularly common in the pons, and once they become symptomatic, almost always from the mass effect of a new hemorrhage, they tend to progress with tepeated intralesional hemorrhages and thus progressive growth of the mass. We recommend surgery in these patients if the lesion teaches a surgically approachable surface (floor of the fourth ventricle, lateral surface of the pons or medulla, anterolateral surface of the pons ot mesencephalon, or quadrigcminal plate) and the lesion can be accessed without ttavetsing normal brain. In deeper lesions that do not come to the surface, we recommend surgery only when the patient has become significantly and progtessively impaired from repeated hemorrhages. Unfortunately, radiosurgery appears to be ineffective for these lesions, although in some uncontrolled series, there is a suggestion of a slight improvement in the natural history in reference to future hemorrhage. However, the risk of significant morbidity from radiosurgery of lesions within the brainstem is high. Therefore most neurosurgeons do not recommend radiosurgery for angiographically occult malformations,

A better understanding of the natural history of these lesions is necessary to solidify indications for treatment. The available evidence indicates that lesions found incidentally have a very low (<1% per year) risk of future hemorrhage. This risk increases significantly, at least for the first few yeats after a hemorrhage, particularly in those lesions located in the brainstem. Nevertheless, our understanding of the long-term natural hisrory is still deficient because these lesions became diagnosable only after the MRI became widely available as a diagnostic tool.

The final and most important type of vascular malformation is the *true AVM* (Hcros 1995; Figure 52.8).

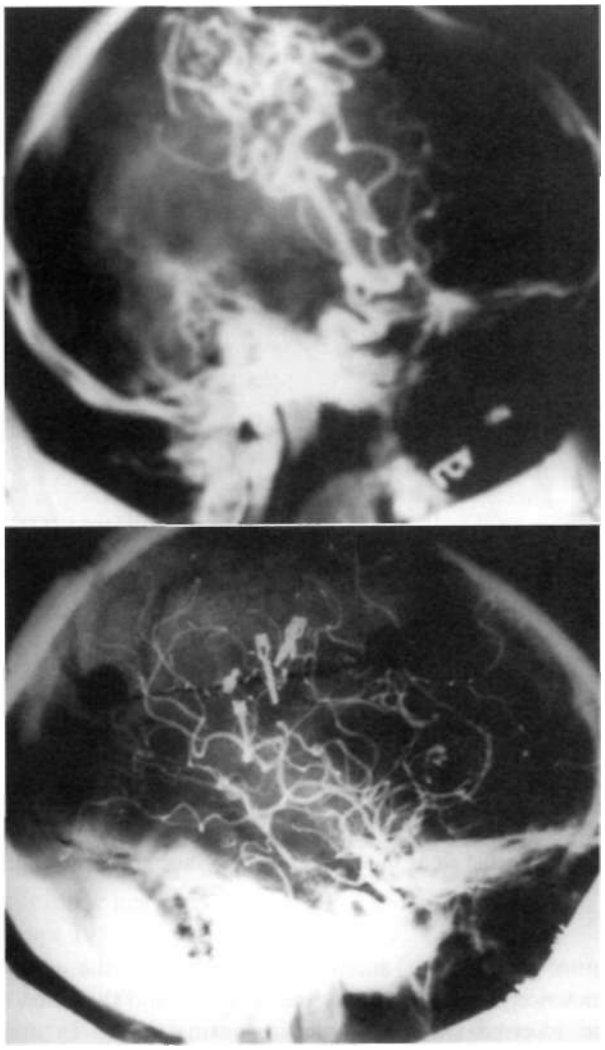

FIGURE 52.8 Arteriovenous malformation of the rolandic region. (A) Note the rapid filling of the lesion with poor filling of the rest of the middle cerebral territory. This patient was suffering from a progressive neurological deficit that we attributed to "stealing" of blood into the malformation from the surrounding brain. For this reason, we decided to recommend excision, despite that the patient would likely be at least temporarily worse after surgery. (B) Postoperative arteriogram showing complete removal of the lesion. The patient's pre-existing hemiparesis worsened significantly, but 6 months later, he was better than preoperatively. Note that after excision of the lesion, the middle cerebral vessels have returned to a more normal caliber and the rest of the middle cerebral territory fills well.

These lesions are well visualized angiographically. Their natural history is much better understood and they appear to have a risk of hemorrhage of approximately 3-4% per year regardless of whether they have bled previously. The risk of another hemorrhage after a hemorrhage increases slightly for the first 6 months {about 6%), but after that it settles to an identical rate of rebleeding as that in lesions that have never bled (3-4% per year). Each hemorrhage carries an average of 10% mortality and an additional 30% significant neurological morbidity. Therefore the natural history of a patient with an AVM of the brain is probably worse than that of a patient with an unruptured intracranial aneurysm. It is true that aneurysmal intracranial hemorrhage is much more dangerous than a hemorrhage from an AVM, because about half of patients with aneurysmal hemorrhage die. However, because the incidence of hemorrhage from an unruptured aneurysm is probably less than 1% per year and that of an AVM is 3-4% per year, calculations show that the prognosis is slightly worse for the patient with an unruptured AVM than for a patient with an unruptured aneurysm.

The therapeutic alternatives for a patient with an AVM include conservative observation, with medical treatment of seizures if necessary; surgical excision; embolization with or without subsequent surgical excision; and radiosurgery, which may be preceded by embolization in some cases. This is a complicated topic, and borderline cases are the subject of significant controversy. Currently, most experienced neurosurgeons advise surgical excision for patients who are relatively young and healthy and who harbor a surgically accessible AVM, which can be removed with relatively low surgical morbidity. What constitutes a surgically accessible AVM varies with the experience of the surgeon. Many classification schemes have been developed to help predict the surgical risk, In general, AVMs that are less than 6 cm in diameter and that are not located in an eloquent region of the brain (motor-sensory region, speech areas, basal ganglia, thalamus, and brainstem) can be removed with a surgical morbidity of less than 5% and negligible surgical mortality (<1%). For small lesions (generally <3^4 cm in diameter) located deeply in eloquent supratcntorial regions, we recommend radiosurgery. The appropriate treatment for patients with small AVMs of the brainstem is unclear; they respond to radiosurgery, but the morbidity from brainstem radiation necrosis is quite significant. Radiosurgery is recommended if they have had a major hemorrhage or if they have recurrent symptomatology from repeated small hemorrhages. For large AVMs located in critical areas of the brain, there is no good treatment. The surgical morbidity is extremely high in these patients and they generally do not respond to radiosurgery. Embolization is only palliative and embolization that does not eliminate the malformation completely appears not to improve the natural history in terms of future hemorrhage and may even significantly increase the chances of future hemorrhage from the AVM (Kwon et al. 2000). Embolization can cure some of the smaller accessible malformations, but these are the malformations that generally can he removed surgically with negligible morbidity. We do use embolization on larger lesions or on very high flow lesions to facilitate surgical removal, and there are some instances in which palliative embolization can be helpful (progressive neurological deficit from "steal," intractable headaches from very large meningeal feeders that can be obliterated by embolization, presence of

intranidal fistulas and aneurysms that probably carry higher risk of bleeding, etc.). Radiosurgery has been recommended over surgical excision of small accessible AVMs on the basis of cost. However, radiosurgical treatment is effective in only 70-80% of patients with small AVMs. In those in which it is eventually effective, it takes 1-3 years for the effect of tadiosurgery to be complete, so patients remain at risk of hemorrhage during this time. A long-term cost analysis indicates that in the long run, when the cost of predicted futute hemorrhages is taken into account, sutgical excision is the most cost effective form of treatment for these patients with surgically accessible small or medium-sized AVMs (Nussbaum, Heros, and Camarata 1994).

Brain Tumors

Brain tumors are covered in Chapter 58. Here, we review the neurosurgical approach to some specific brain tumors.

Gliomas

Pilocytic astrocytomas arc relatively well-demarcated tumors that can usually be removed completely and in general have a very good prognosis after total or subtotal surgical excision. The same can be said of the low-grade astrocytomas of the cerebellar hemisphere in children. These tumors generally do not require postoperative radiation therapy. Low-grade well-differentiated fibrillary astrocytomas generally arc not well demarcated and cannot be removed completely, particularly when they involve or are close to critical areas of the brain. Some techniques that are discussed such as intraoperative cortical mapping, frameless stereotaxis, and image-guided sutgety can help achieve a more thorough removal of these tumors. However, they are basically infiltrating tumors, and although the issue is still controversial, we generally recommend postsurgical radiation therapy unless the surgeon is satisfied with the completeness of the surgical removal. Many experts, however, prefer a policy of following these patients with periodic MRIs and using radiation therapy only when the tumor shows clinical and/or radiographic signs of progression. In the case of high-grade gliomas, it is still not clear that the extent of surgical removal affects the natural history, although there is considerable anecdotal evidence supporting the concept that when achievable without increasing morbidity, aggressive surgical removal improves overall prognosis. In addition, aggressive debulking may improve symptoms of mass effect and increased intracranial pressure and may allow the patient to tolerate radiation therapy, which might otherwise have exacerbated the symptoms.

Radiotherapy continues to be the most important adjuvant therapy for patients with malignant gliomas. Chemotherapy improves the prognosis slightly, but generally at the expense of some morbidity. We tend to recommend chemotherapy in younger patients with good functional status, especially in patients with anaplastic astrocytomas, mixed oligoastrocytomas, and oligodendrogliomas, where the evidence for the benefit of chemotherapy is more convincing. Additionally, we always consider chemotherapy as an option at the time of recurrence. Recently, intratumoral chemothciapy with implantation of carmustine-impregnated biodegradable wafers (Gliadel), whenever a good resection can be accomplished with low surgical morbidity, has become available as an option. Radiosurgery may be considered as a boost to conventional fractionated radiotherapy as initial therapy or in cases of recurrence. Young patients with unifocal, well-circumscribed tumors, who are in good neurological condition, tend to benefit the most from adjuvant radiosurgery,

Pituitary Tumors

Pituitary macroadenomas are most frequently nonsecreting and present with visual disturbances. Transsphenoidal resection can usually alleviate the visual symptomatology but is rarely curative in these cases. However, the benefit of postoperative irradiation has to be weighed against the side effects of radiation, including the late development of radiation-induced tumors, hypothalamic dysfunction, radiation encephalopathy, and visual deterioration. Fot these reasons, radiosurgery is increasingly being considered as a secondary treatment for these tumors. Simple observation with periodic MRIs is an option in many patients, particularly when they are older. Prolactinomas are now treated primarily medically with dopamine agonists, such as bromoctiptine, except in patients who are planning to become pregnanr soon, in which case ttanssphenoidal resection is usually recommended. Surgery is still the procedure of choice when the patient becomes refractory or intolerant to bromocriptine treatment or when rapid visual deterioration occurs, often as a result of pituitary apoplexy, (see Pituitary Apoplexy, earlier in this chapter}. Functional (secreting) tumors that result in acromegaly or Cushing's disease are still primarily treated surgically, with a high rate of success. However, the endocrinological definition of cure or control for these tumors has become increasingly strict, and radiosurgery is being considered an option in those patients who do not appear to have been completely cured by surgery,

Craniopharyngioma

Whether conservative surgery followed by radiation therapy, or radical surgery in an attempt to remove all the tumor, should be the preferred treatment for craniopharyngiomas is still unclear. Most surgeons nowadays will attempt a complete surgical removal if at the time of surgery this appears possible without inducing morbidity from hypothalamic or optic damage (Figure 52.9). With this principle in mind, a total microsurgical removal is

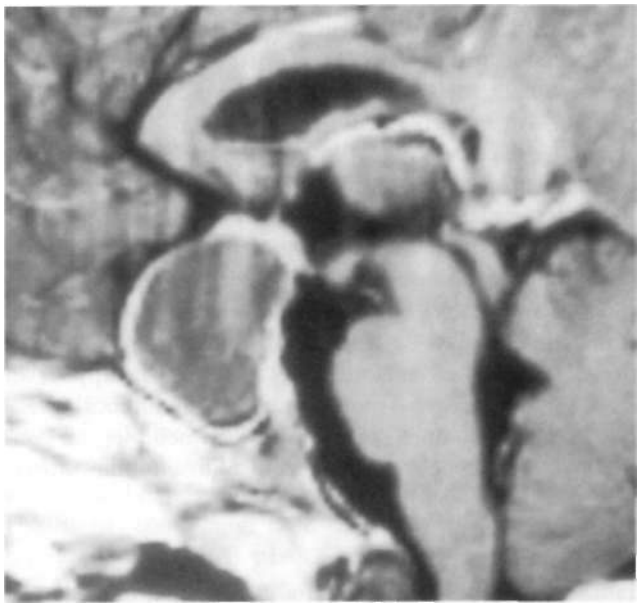

FIGURE 52.9 Craniopharyngioma. This is a rather typical appearance for a cystic craniopharyngioma. The lesion was removed completely by a microsurgical bifrontal interhemispheric approach.

possible in many patients, both children and adults, with craniopharyngiomas, and in these cases radiation therapy is not indicated. However, continuing observation with periodic MRIs is essential because even tumors that appear to have been totally removed can recur many years later. Most neurosurgeons will not attempt complete removal when the capsule of the tumor appears to be densely adherent to the hypothalamus, optic nerve, or important vascular structures and will prefer to leave some residual tumor rather than risk serious morbidity. In these instances, if the amount of residual tumor is relatively small, observation with periodic MRIs is appropriate. If a significant amount of tumor is left behind, radiation therapy is recommended for most patients unless they are elderly or very young. The radiation can be in the form of radiosutgery if the tumor is well localized. If there is a recurrence and the patient has not undergone radiation therapy, radiation should be considered as opposed to surgery unless there is progressive visual dysfunction. In that case, surgical decompression followed by radiation is appropriate. In cases of a relatively pure cystic recurrence, stereotactic aspiration with or without installation of radioactive material into the cyst can be entertained as an alternative to direct surgical decompression, followed by conventional fractionated radiation or radiosurgery.

Pineal Region Tumors

In an increasing number of patients, small asymptomatic tumors of the pineal region are being detected by MRI. Many of these patients have a typical pineal cyst. Unfortunately, this appearance can be confusing, because even though the bulk of the lesion may be cystic, there is usually some enhancement on the wall, which raises the question of a true neoplasm. In general, if the cyst is asymptomatic and relatively small (up to approximately 1 cm in diameter), we prefer to observe the patient with periodic MRIs to rule out growth, which would indicate a cystic pineal neoplasm as opposed to a true pineal cyst.

There has been an effort to make a definitive diagnosis of pineal region tumors by MRI and treat some of these tumors blindly with radiation therapy based on an MRI appearance suggestive of a pineal gcrminoma. Radiation therapy is clearly very effective for these tumors, and because these tumors are so prevalent in Japan, many-Japanese neurosurgeons use radiation as a therapeutic diagnostic test. In othet words, they will radiate the tumor, but if there is no prompt response to radiation demonstrated by significant shrinkage of the tumor, they will proceed with a biopsy. In the United States, the relative prevalence of germinomas is considerably lower than in Japan, and many other tumors of the pineal region may resemble a pineal germinoma, but they arc best tteated by total or subtotal surgical resection depending on the findings at surgery (Figure 52.10). In addition, even in malignant tumors that cannot be removed completely, establishing a pathological diagnosis by biopsy can be very helpful in terms of guiding treatment. This will vary significantly, not only in terms of the dose of radiotherapy but also in terms of whether chemotherapy may be

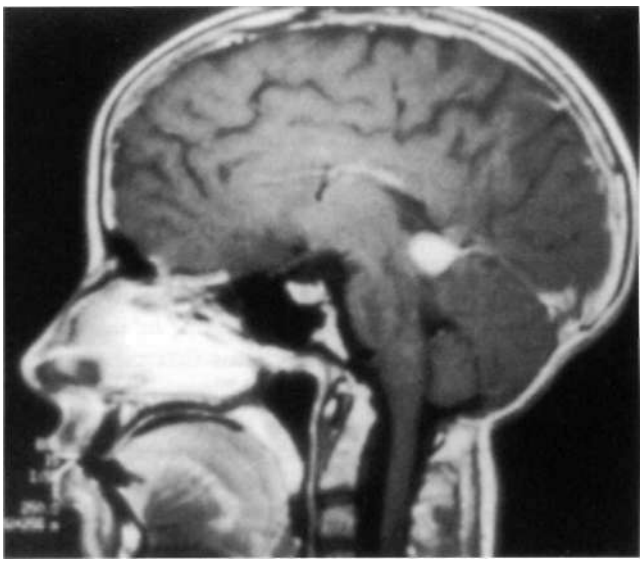

FIGURE 52.10 Pineal region tumor. This small lesion was removed completely by a microsurgical supraeerehcllar infrarcntorial approach. Pathologically, the lesion was a pinealoma, and because of the completeness of the surgical removal, the patient had no other treatment. Twelve years later, she is still intact neurologically, and the lesion has not recurred.

appropriate. For this reason, we recommend establishing a pathological diagnosis by surgical biopsy in most of these patients. There is controversy, however, over whether a stereotactic biopsy or a direct open surgical biopsy is preferable. Almost every large series of stereotactic tumor biopsy indicates that the morbidity of the procedure in the pineal region is higher than when such biopsies are performed for tumors elsewhere. This is undoubtedly related to the complicated venous anatomy in this region, which can lead to postoperative hemorrhage. For this reason, we prefer open surgical biopsy, most often by the infra tentorial supracerebellar route, in most of these patients. An open procedure has the advantage of allowing surgical resection during the same operation if such is indicated from a combination of the frozen section diagnosis and the appearance of the tumor at surgery. In our experience, about half of these patients have benefited substantially from surgical resection. These have been primarily patients with pineocytomas, meningiomas, low-grade exophytic astrocytomas of the pulvinar region, and benign teratomas. In the other half of the patients (with malignant tumors such as pineal germinomas, pineoblastomas, endodermal sinus tumors, and malignant teratomas), the surgical biopsy has been able to guide subsequent therapy. Only in cases in which the typical MRI appearance is accompanied by strong markers in the CSF of a choriocarcinoma *{fi* chain of human chorionic gonadotropin) or endodermal sinus tumor («-fetoprotein) would we entertain radiation therapy without surgical biopsy. Malignant teratomas and undifferentiated germ cell tumors can have elevation of both markers, but because the treatment of these tumors may differ, we prefer open biopsy when both markers are elevated. This may be accompanied by significant surgical dcbulking, particularly in the case of teratomas.

Acoustic Neurinomas

Schwannomas of the vestibular nerve are increasingly being diagnosed at a very early stage when they are still intracanalicular in location or have only a small intracranial extension, mainly because of decreased hearing and the availability of MRI. In these patients, radiosurgery has become an important therapeutic alternative to surgery. It appears clear that radiosurgery can achieve tumor control (i.e., no growth or shrinkage) in the majority of these patients, at least for a few years. This is an attractive option in older patients. Radiosurgery carries some risk of morbidity and many of these patients eventually do lose their hearing after radiosurgery, but at the present time, it is not clear whether facial function is better spared by careful microsurgical excision or by radiosurgery. Because the results of surgery have been very satisfactory in terms of permanent cure and preservation of facial function and hearing in patients with small tumors, we favor this option in relatively younger patients and consider radiosurgery or observation in the elderly. Patients with larger schwannomas of the cerebellopontine angle, who frequently present with brainstem symptomatology, continue to require surgical excision. Nowadays this can be achieved very safely in terms of neurological morbidity and with a high rate of success in terms of sparing facial function. Hearing, if present preoperatively, can be saved only infrequently in patients with larger tumors. In older patients or in younger patients who are adamant about having intact facial function postoperatively, it has become more common to perform a subtotal resection, leaving some tumor adherent to the facial nerve that can be either observed with periodic MRIs or treated with radiosurgery depending on the age of the patient.

Meningiomas and Other Tumors of the Base of the Skull

Benign tumors of the base of the skull have become more amenable to relatively complete surgical excision using skull base approaches (see Skull Base Techniques, later in this chapter) (Figure 52.11). These operations are typically performed by the neurosurgeon in collaboration with either a neuro-otologist or a head and neck surgeon. The same is true for more aggressive tumors of the base of the skull, such as esthesioneuroblastomas, chondrosarcomas,

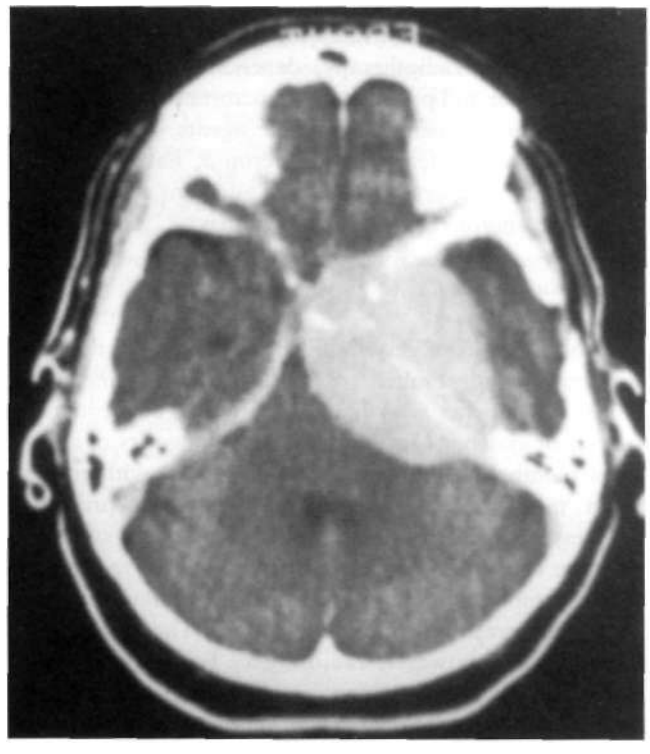

FIGURE 52.11 Large petroclival meningioma. Lesions such as these can be removed at least radically and sometimes completely with relatively little morbidity using skull base techniques. This particular lesion was removed subtotally through a cranio-orbitozygomatk approach. A small remnant of tumor was left in the cavernous sinus because the patient was in her late 60s.

chordomas, and low-grade carcinomas. The latter tumors can rarely, it ever, he cured, hut surgery can otter very significant palliation with acceptable morbidity. Most meningiomas can be cured by surgical excision, but whether some of the invasive meningiomas, particularly those that invade the cavernous sinus, can really be eradicated completely is under controversy. More radical operations are increasingly achieving total tumor excision both by intraoperative inspection and by immediate postoperative CT or MRI scanning. However, such radical resections are most commonly accompanied by significant morbidity, particularly when the tumor invades the cavernous sinus or involves the carotid, middle cerebral or basilar arteries, and their branches. Long-term follow-up studies are necessary to know whether such radical operations and their resultant morbidity are justified by a significant improvement in longevity and tumor-free survival.

We prefer to allow a small amount of residual meningioma to remain in the cavernous sinus ot around the carotid artery and optic nerve or basilar artery when removal of this could be predicted to carry a significant surgical morbidity. This is particularly true in older patients, in which case, we do nothing but observe the tesidual tumor by periodic MRI. In younger patients, we tend to be more aggressive, and if it appears impossible to remove all the tumor without substantial morbidity, we consider postoperative irradiation, either by radiosurgery or fractionated radiotherapy, depending on size of the residual tumor and proximity of structures such as the optic nerve. Various chemotherapeutic agents, such as hydroxyurea, tamoxifen, and interferon-^, have been used with variable degrees of success as adjuvant treatment for aggressive and/or recurrent meningiomas.

Metastatic Tumors

The role of neurosurgery in metastatic disease of the brain was traditionally limited to excision of single metastatic lesions in patients who had a relatively good prognosis from their systemic cancer (an expected longevity of at least a few months). Additionally, in selected cases with multiple brain metastases, a large lesion that was producing progressive symptomatology or threatening life, such as is the case of a large cerebellar metastasis, was removed to relieve symptoms or to provide time for radiation therapy or chemotherapy to control the disease. These indications are still valid; however, radiosurgery has become a very attractive way of treating small asymptomatic brain metastases. This treatment carries very little early morbidity and can be used for several metastatic lesions, which may be treated in one or more sessions. The number of metastatic lesions that can be treated safely by radiosurgery has not been established, but most radiosurgical units arc reluctant to treat patients with more than four or five metastatic lesions, Some tumors are not sensitive to radiation, and when this is the case, particularly in the case of a single lesion that continues to grow after radiosurgery, surgical excision continues to be an important consideration. Whether to neat these patients with whole-brain radiation in addition to radiosurgery is still controversial, although there has been a tendency to move away from whole-brain irradiation.

Ischemic Ccrcbrovasculat Disease

Ischemic cerebrovascular disease is covered in detail in Chapter 57A. Here, we review a few points of relevance to cerebrovascular disease from a neurosurgical perspective.

Arterial dissections, both extracranial and inrracranial, are being increasingly recognized as a cause of stroke, particulatly in younger individuals. Dissection of the cervical portion of the carotid artery can occut both spontaneously and after neck trauma (Figure 52.12). It often presents with severe retromandibular pain, and on

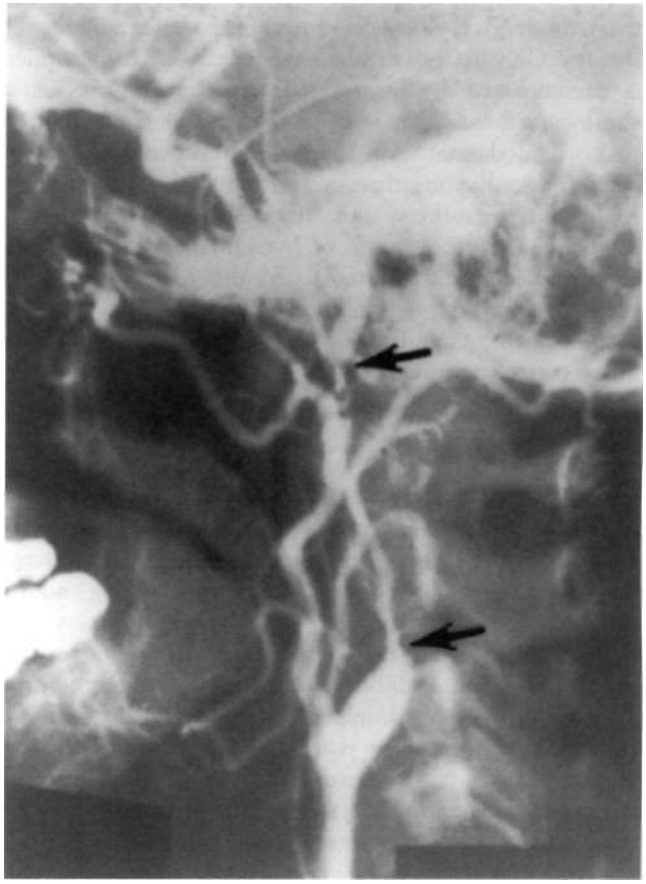

FIGURE 52.12 Dissection of the cervical portion of the internal carotid artery. Notice the typical appearance of the long, narrow segment (string sign), which begins approximately 1.5 cm distal to the bifurcation *(lower arrow)* and ends abruptly at the entrance of the internal cimrid into the hiise of the skull *[higher arrow).*

examination, it is common to detect an ipsilateral partial Horner's syndrome from involvement of rhe high cervical pericarotid sympathetic plexus. Typically, the dissection states 1-3 cm above the bifurcation and terminates abruptly where the internal carotid artery enters the base of the skull. The patient may have transient ischemic attacks (TIAs), a fixed stroke, or a fluctuating neurological deficit. Surgical intervention is rarely necessary because these patients respond well to anticoagulant treatment. Frequently the dissection heals and the artery returns to a fairly normal appearance after a few weeks. Persistent symptoms after coagulation may call for surgical intervention to directly repair the dissection, which is difficult, or to perform an extracranial to intracranial bypass graft, which at least anecdotally has been effective in some of these cases. More recently, angioplasty with stenting has become the preferred option.

Extracranial vertebral dissection presents with high cervical pain, sometimes radiating to the occipital region, as well as posterior circulation TIAs, or stroke. Again, vertebral dissection can occur spontaneously, but most commonly is due to trauma, which can be dramatic (cervical fractures and dislocation) or relatively subtle (abrupt turning of the neck, chiropractic manipulation, or simple hyperextension of the neck such as for shaving under the chin). Again, anticoagulation is the mainstay of treatment for extracranial vertebral dissection when there is ischemic symptomatology. The results are very good unless the patient has already had a major stroke.

Intracranial arterial dissections are more serious. They can result in ischemic symptoms usually from occlusion of small branches, or they can result in SAH, which can be devastating and recur frequently if untreated. The treatment is more complicated because of the risk of hemorrhage; however, when ischemic symptoms are predominant and there has been no evidence of hemorrhage, anticoagulation should still be considered.

Patients with TIAs arc most commonly seen initially by their primary care physicians, and then they may or may not be referred to a neurologist. It is important to keep in mind the difference between a patient who has had multiple TIAs over a period of months or years and the patient who has had the first TLA ever. In the former situation, the workup can be more relaxed, although still these patients should be investigated expediently. In the latter situation, however, it is important to act with urgency. After a first TIA, there appears to be an approximate 30-35% risk of a stroke in that arterial distribution over the next 3-5 years. However, most of that risk occurs during the first month and particularly during the first few days after the TIA, Important therapeutic considerations include anticoagulation and carotid endarterectomy. Other situations that require urgent evaluation are crescendo TIAs and major TIAs, where the patient develops a profound neurological deficit, usually involving the face, arm, and leg on one side with or without aphasia.

Carotid endarterectomy is an operation with winch many neurosurgeons have considerable experience. The indications have become much better defined over the last several years. At the present time, based on the results of the several excellent multi-institutional randomised studies that have addressed the issue of effectiveness of carotid endarterectomy, we recommend this operation to symptomatic patients (TIAs or a mild completed stroke) who have more than 70% stenosis of the ipsilateral carotid artery and who are in reasonably good condition in terms of medical comorbidity. In the group of patients with moderate stenosis (50-70%), we would consider endarterectomy only when the patient is relatively healthy in terms of medical comorbidity, particularly that of significant coronary disease, and when the estimated neurological morbidity of the procedure is estimated to be low. For asymptomatic patients, we consider endarrerectomy only when the stenosis is relatively severe, generally more than 75-80%, and when we can be relatively confident that the surgery can be performed wirh minimal morbidity (relatively young patient in relatively good health and no adverse risk factors, such as a very high bifurcation, contralateral occlusion, or intracranial stenosis, demonstrated by angiography). It is important for the neurologist to remember, however, that the indications for carotid endarterectomy vary not only according to the patient, but also according to the experience of the surgeon and the institution where the carotid endarterectomy is to be performed. Most experienced neurosurgeons and vascular surgeons who have a particular interest in carotid endarterectomy can perform the operation with an average combined mortality and serious morbidity of less than 5% (Table 52.1). In all the recent randomized studies that have established the general indications for carotid endarterectomy, the surgical morbidity was within this low range because the surgeons and the institutions invited to participate had considerable experience with the operation. These results may not be generally applicable, and each physician needs to consider this in terms of his or her own indications for endarterectomy. The role of angioplasty and stenting is gradually being defined. Presently, we consider this procedure in patients who are felt to be at high risk for carotid endarrerectomy, such as elderly patients with serious medical comorbidities, patients who have restenosed their artery after an endarterectomy, patients with angiographic risk factors such .is a very high bifurcation with a plaque extending to the base of the skull, patients with radiation-induced stenosis, and some patients with poor collateral circulation such as a contralateral carotid occlusion.

Moyamoya disease is an entity that has become more frequently recognized in the United States as an etiology for TIAs and stroke in children, adolescents, and young adults, and for intracerebral hemorrhage in older adult patients (Figure 52.13). This disease, which was first described in Japan, is much more common in the oriental races, but it

Table 52.1: Complications" of elective carotid endirterectomy

Indications for surgery	No. *of cases*	*Major stroke*	*Minor stroke*	*Other**	*Death*
Transient ischemic attacks	707	*6*	*5*	14	4
Stroke	108	3	3	3	3
Asymptomatic	172	1	1	2	0
TOTAL	987	10 (1%)	9 (0.9%)	19(1.9%)	7 (0.7%)

Note: These numbers include only elective operations. During this time, several endarterectomies were performed emergently for completed stroke; these results are nor included here.

"These are early complications that became evident or occurred during the immediate postoperative period.

[f]AII operations were performed by the senior author or under his direcr supervision from 1980 through 1995 at either the Massachusetts General Hospital or the University of Minnesota Hospital,

'Includes neck hematomas that required reoperation, nonfatal myocardial infarctions, and cranial nerve palsies that almost always resolved in time.

'Includes episodes of transient visual loss.

does occur with some frequency sporadically in any race. We mention this entity here because neurosurgical revascularization of the ischemic territories is a very effective way of ameliorating the symptoms and preventing stroke and hemorrhage in the future. Revascularization can be achieved in a number of different ways, such as with a direct anastomosis from the superficial temporal artery to a middle cerebral artery branch, direct apposition without anastomosis of the superficial temporal artery to the surface of the brain, or apposition of the temporalis muscle to the surface of the brain. All of these procedures can result in dramatic revascularization, as demonstrated angiographically, after a few months. Our results with approximately 25 such patients have been very rewarding.

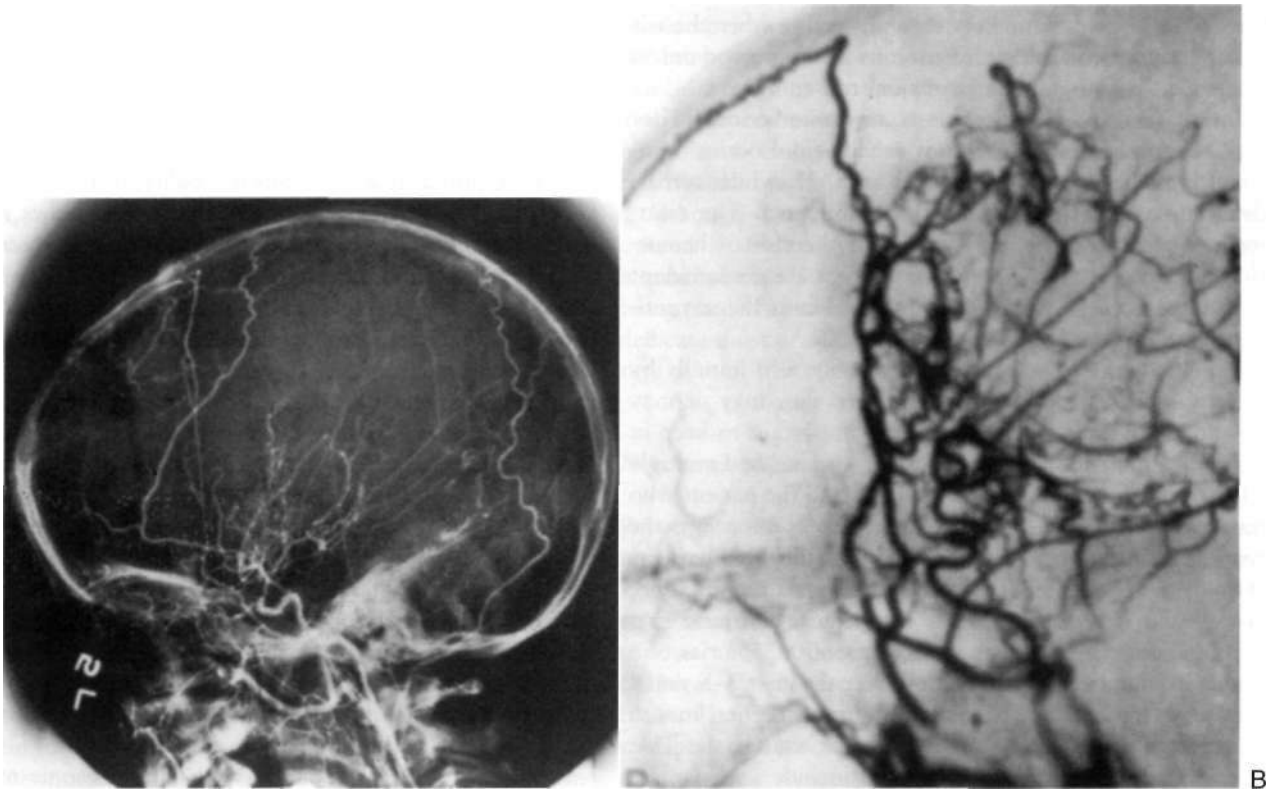

FIGURE 52.13 Moyamoya disease. (A) Note the virtual occlusion of the supraclinoid segment of the internal carotid artery and the origin of the middle cerebral artery with the moderately prominent conglomerate of small anastomotic vessels that attempt to teconstruct the middle cerebral artery distally. (B) Because the patient had recurrent ischemic symptoms, she was treated with an arterial myosynangiosis, which simply means laying the temporalis muscle, kept in continuity with its vascular supply, directly over the brain. Note the significant revascularization of the middle cerebral territory by external carotid collateral just 3 months after the operation.

Dementia

The diagnosis and management of dementia are almost always in the hands of the neurologist. Many forms of dementia are treatahle and the neurologist makes every effort to rule our such entities. One cause of dementia that deserves consideration from a neurosurgical perspective is normal-pressure hydrocephalus.

The diagnosis and the indications for CSF shunting in patients suspected of having normal-pressure hydrocephalus remain controversial (Epstein and Fried 1995). However, many patients who were incapacitated by a progressive gait difficulty, dementia, and urinary incontinence of variable severity have returned to a significantly improved functional status after placement of a CSF shunt. It is also clear that many other patients who have received a shunt with this diagnosis have not been helped. Therefore many tests have been devised to establish firmly this diagnosis and rule out the much more common diagnoses of Alzheimer's disease and multi-infarct disease. Unfortunately, no single test has been proven to be consistently reliable. The tests have been generally of two types. The first group includes rests thai attempt to measure physiologically or radiologically an impairment in CSF reabsorption. The other group includes tests that are functional and aim at testing clinically, in a variety of ways, the effects of withdrawing a significant amount of CSF.

In general, we have followed the advice of Dr. C. Miller Fisher to be guided primarily by the clinical syndrome. Patients who tespond well to shunting tend to have a history of gait difficulty that precedes and is out of proportion to the degree of dementia. These patients may have variable degrees of difficulty with sphincter control. In this clinical setting, when the CT scan or the MRI shows significant hydrocephalus, which is out of proportion to the degree of atrophy, we proceed with shunting without any further testing. We rarely consider shunting in patients who are markedly demented and who have developed some gait difficulty late in the course of their disease; such patients will almost always show atrophy out of proportion to the hydrocephalus on their CT scan, and they rarely, if ever, respond to shunting. This leaves a sizable group of patients in whom the situation is less clearly defined: (1) The gait disturbance and the dementia may have started more or less at the same time and may he of about the same severity, and the CT scan may show both significant atrophy and hydrocephalus, (2) the dementia may have preceded the gait difficulty, but the CT scan demonstrates significant hydrocephalus and only a modest degree of atrophy, or (3) there is a good clinical syndrome of gait disturbance with very little dementia, but the CT scan shows significant atrophy and only slight hydrocephalus. In these borderline cases, additional tests are indicated.

The simplest and perhaps most reliable way of testing for impaired reabsorption is still the conventional radioisotopic cisternogram. When we sec the typical pattern of retention of radioactivity in the ventricles for up to 48 hours and preferably for 72 hours, we are encouraged to proceed with shunting. On the other hand, if the test is negative with disappearance of the radioisotope from the ventricles within 24 hours, we do not recommend a shunt. When the results of the cisternogram are less clear-cut (some retention of radioactivity in the ventricles at 24 hours and disappearance at 48 hours), we proceed with a functional test of CSF withdrawal and clinical examination for improvement. If improvement is clearly documented, we proceed with shunting.

A shunting procedure is not without some risk of morbidity, particularly in patients with atrophy secondary to Alzheimer's disease, who could develop problems from overdrainage such as subdural hematomas and persistent headaches. Therefore every effort should be made to select patients carefully for surgery; when in doubt, we prefer to accept the relatively small morbidity of a shunt and proceed with this operation rather than risk leaving a patient untreated who could have been helped by a relatively-simple operation. Presently, we prefer to use programmable valves for all patients with norma I-pressure hydrocephalus. These valves can be regulated from the outside to drain at a set pressure without the need for an open surgical revision, as was necessary in the past. Thus if the patients fail to improve and the postoperative CT scan shows that the ventricles have not decreased in size, the pressure of the valve can be lowered very simply at an office visit. Likewise, if the patient complains of headaches and dizziness upon standing and the CT shows that the ventricles are now too small and/or there arc subdural hygromas on CT scan, the pressure can be raised.

Pseudotumor Cerebri

Pseudotumor cerebri is managed primarily medically. Surgical management should be reserved for the rare patient in whom maximal medical treatment of intracranial hypertension has failed. Persistent disabling headaches or progressive visual loss from papilledema in spite of maximal medical therapy mandates surgical intervention. The obvious procedure to relieve intracranial pressure is CSF shunting. This addresses the primary problem, and if successful, the papilledema should subside. However, these patients often have small ventricles, and it is difficult to insert and maintain a ventricular shunt. For this reason, lumboperitoneal shunting is usually considered in these patients. Although these patients are often obese and a lumboperitoneal shunt presents some technical difficulty, this treatment is needed at times. When the problem is primarily visual loss and the headaches can be controlled satisfactorily with analgesics, the optic nerve sheath fenestration procedure is considered, although studies have questioned the effectiveness of this procedure. In the very rare parient in whom these two procedures fail to

control the symptomatology, a subtemporal decompression may he required. This procedure was initially advocated by Dandy in the 1930s and it is still used occasionally, although we personally have no experience with it.

Pain

The neurosurgeon used to play a very prominent role in the treatment of chronic pain. This was because pharmacotherapy of pain was not as well developed, and ablative procedures, such as cordotomies, rhizotomies, midline myelotomies, and even medullary tractotomies, had a proven record of effectiveness, albeit at the price of significant surgical morbidity. Gradually, with improved pharmacological treatment of pain, and with the increased interest in this area of other specialties such as anesthesiology and physical medicine and rehabilitation, the neurosurgeon, and to some degree the neurologist, has lost interest in the treatment of chronic pain. Yet pain is a prominent and frequently the prevalent symptom in a large number of patients treated both by neurologists and by neurosurgeons. It is important then to keep in mind that there are still very valuable surgical options for patients incapacitated by chronic pain. Clearly, with sufficient amounts of narcotics, all pain can be controlled. However, this is not generally a satisfactory option for patients with chronic pain from nonmalignant disease who may have normal longevity. It may not be the preferred option even for patients with malignant pain, although for the latter group of patients, newer opioid preparations prolong pain amelioration with fewer effects on the sensorium and cognition than the traditional narcotics.

Spinothalamic cordotomy is still an attractive option for patients with pain due to malignant disease, particularly when that pain is unilateral. The early morbidity of a unilateral cordotomy in the thoracic or cervical area is relatively small. The problem with cordotomy is that the effect tends to fade with time and patients tend to develop late dysesthesias, which can become very painful and disabling over the years. Patients with cancer, however, often have a limited life expectancy and these late problems are less of a consideration. Therefore cordotomy is still a good option in patients who may not tolerate systemic natcotics and who are in good enough condition to withstand the stress of a relatively short surgical procedure. When the pain is bilateral, cordotomy becomes a less attractive option because the morbidity of bilateral cordotomies is significantly higher, particularly the risk of urinary incontinence.

Midline myelotomy, which aims at interrupting the segmental crossing pain fibers, is a particularly attractive option for patients with bilateral lower extremity and pelvic pain such as seen frequently with gastrointestinal, urological, and gynecological malignancies. This procedure carries some immediate morbidity, usually paresthesias from damage to the posterior columns, but these early paresthesias tend to subside, and when the pain is restricted to the lumhosactal region and lower extremities, the results are very good in terms of sparing strength and bladder function and controlling pain satisfactorily (Sourek 1997).

Dorsal rhizotomy for truncal pain, particularly in the chest wall, is still a useful procedure to consider in patients with malignant pain. A prerequisite is the ability to relieve the pain with appropriate nerve blocks, and the surgeon should always aim at dencrvating several segments above and below those indicated by the nerve blocks because of sensory overlap, the tendency for the analgesic area to shrink with time, and the likelihood of local spread of the disease. An open neurosurgical procedure can he done, but it is now usually done by a percutaneous radiofrcquency technique.

Intrathecal injection of morphine hy a number of the available implantable systems may be an alternative to the more invasive ablative surgical procedures for many patients. This form of treatment has obvious appeal, but many patients either do not respond to it or become tolerant to the drug, so very large doses are required to maintain pain control. Nevertheless, a large number of patients with cancer can be managed satisfactorily with these intrathecal systems.

Pain resulting from head and neck malignancies is a particularly difficult problem to treat. In these patients, the syndrome is often complicated by anxiety secondary to difficulties swallowing and breathing. If anxiety is a predominant component, bilateral cingulotomy, which can be performed stereo tactically with minimal morbidity, should be given setious considctation. In truly intractable patients, cortical or deep brain stimulation (DBS) by means of implanted electtodes can be considered, but these procedures are performed only at a few selected centers.

Intractable chronic pain from injuries or nonmalignant disease is a much more difficult problem to treat. Obviously, chronic narcotic administration is not an attractive option in these patients. Intrathecal morphine administration by implantable pump systems almost always fails eventually. Ablative procedures are not a good choice except fot rate instances. For example, dorsal rhizotomies are still a satisfactory procedure for chest wall pain after thoracotomy. Occasionally, rhizotomies have also tesulted in significant pain relief in cases of intractable radiculopathy after failed intervertebral disc surgery. More recently, dorsal root entry zone lesions, made either by open surgery or percutaneously, have shown some promise in the control of chronic pain caused by problems such as cervical root avulsions, postparaplegic pain, postherpetic neuralgia, and phantom limb pain. Relief has been reported in 50-70% of patients with these different chronic pain syndromes, and the procedure carries relatively little morbidity.

Electrical stimulation of peripheral nerves and spinal cord has been in and out of favor for the last several years.

There is no question that a number of patients can be palliated with percutaneous electrical stimulation, but in general, this treatment is only partially effective and the effect is temporary. For more chronic pain, neuroaugmentive procedures, which essentially consist of chronic stimulation by implanted electrodes, have become very attractive because they are nonablative and reversible. These procedures are particularly effective for treatment of neuroinjury (denervation) types of pain. When such pain is from peripheral dcafferentation, spinal cord stimulation with electrodes placed directly over the posterior column has been effective in well-selected patients. The more difficult central type of pain produced by spinal cord or brain **injury,** which is usually due to a stroke in the thalamus, can be treated by central stimulation, usually in the periaqueductal or periventricular gray matter. These targets have been well defined by stereotactic methodology. However, these procedures are difficult, expensive, and available at only a few centers.

Finally, hypophysectomy, which can be performed by open transsphenoidal microsurgical approach or much more frequently by the percutaneous technique using radiofrequency or absolute alcohol injection, is very effective for pain control in patients with intractable pain from metastatic disease to the bone due to hormonally dependent cancer (breast and prostate). This procedure may also be effective in a smaller percentage of patients with nonhormonally dependent cancers; however, in these cases, the effect is usually very transient. Thus the neurosurgeon still plays a role in the treatment of chronic intractable pain whether it is due to malignancy, injury, or a chronic nonmalignant disease process.

Trigeminal Neuralgia

Most patients with trigeminal neuralgia are initially treated by a neurologist. Carbamazepine and diphenylhydantoin continue to be the most effective medications to control this condition. However, patients sometimes do not tolerate these medications or the pain becomes refractory to them. With the introduction of newer drugs such as gabapentin and other antiseizure medications that have been shown to be somewhat effective in the treatment of trigeminal neuralgia, there is a tendency to continue to treat these patients indefinitely with a variety of medications, typically with inadequate control of this devastating type of pain.

Neurosurgical procedures are often very effective and frequently lead to complete disappearance of the pain in patients with typical trigeminal neuralgia. There are two types of neurosurgical procedures for the treatment of this condition. In relatively young patients, who are in good general condition and have no contraindication to general anesthesia, we generally recommend, as the first surgical line of treatment, a Jannetta microsurgical decompression operation designed to relieve the vascular compression of the trigeminal nerve at its entrance into the brainstem, which appears to be the cause of the condition in most patients with idiopathic trigeminal neuralgia (Jannetta 1996). In relatively healthy patients, this operation carries only a very minimal risk of serious neurological morbidity, The procedure is contraindicared in patients with known causes of trigeminal neuralgia such as multiple sclerosis and in patients who are elderly or who have systemic diseases that would increase the risk of general anesthesia. For the latter group of patients, which is probably the majority because this is a disease that affects mostly older people, a variety of destrucrive procedures are often effective. The most commonly used is a radiofrequency lesion, which is done percutaneously through the cheek, in the gasserian ganglion. A less effective way of achieving the same result is with an injection of glycerin into Meckel's cave. A **more** recently introduced method of producing some damage to the nerve is with a percutaneous introduction of an inflatable balloon, which can then be used to compress the trigeminal root. Radiosurgery has also been used with some success to damage the gasserian ganglion; however, its effect is delayed and frequently these patients are too incapacitated by their pain to wait several months for relief.

The destructive percutaneous procedures have the advantage of being much better tolerated and not requiring open surgery with general anesthesia. They also have the advantage that they can be repeated if the pain recurs. The disadvantage is that in general, these procedures achieve pain control only at the expense of significant hypalgesia, which, in some cases, is quite disagreeable to the patient. In addition, sometimes the lesions cannot be well controlled and the patient may develop complete analgesia with loss of the corneal reflex and subsequent visual complications from keratitis when the first division is affected. There is also the potential risk of *anesthesia dolorosa,* which is more intolerable than the pain of trigeminal neuralgia. In addition, particularly when the initial degree of hypalgesia achieved is only mild, the recurrence rate is very high with a significant initial failure rate. A last resort fur some ol these patients is open partial section of the trigeminal root, which can be accomplished by the subtemporal or suboccipital route. Open rhizotomy is rarely necessary these days, **although** historically it was the mainstay of the treatment of trigeminal neuralgia.

In brief, a neurosurgeon with an interest in the treatment of this condition should be consulted for any patient who fails to achieve acceptable pain relief without toxicity from the medications.

Hemifacial Spasm

Hemifacial spasm usually occurs as an isolated condition rather than as a manifestation of a more generalized dystonia, as is often the case with spasmodic torticollis.

These patients now can achieve significant palliation with periodic injections of botulinum toxin, a technique that has been mastered by many neurologists. The relief from these injections is temporary, lasting an average of 3-4 months, at which time they can be repeated. The long-term effects of chronic treatment with botulinum toxin remain unknown and many of these patients gradually develop some degree of facial weakness.

Most neurosurgeons have accepted the theory first postulated by Gardner and latet championed by Jannetta that in most patients, hemifacial spasm is caused by compression of the facial nerve by a vascular loop as it exits the brainstem, as most cases of trigeminal neuralgia are caused by compression of the trigeminal nerve by a vascular loop at the root entry zone in the brainstem. Therefore the decompressive procedure popularized by Jannetta, which consists of displacing the vascular loop from the facial nerve and holding it in a new position by a variety of means, has become very popular and has proven very successful in the treatment of this condition. More than 90% of the patients achieve either good control or complete resolution of their hemifacial spasm and the relief appears to be long lasting and usually permanent. The morbidity of the procedure in relatively young patients in good genctal condition is minimal. This operation is very attractive for patients with hemifacial spasm because destructive procedures that result in decreased facial function are intolerable to most patients (Jannetta 1996).

Spinal Arteriovenous Malformations

Though relatively rare, spinal AVM should be considered in the differential diagnosis of a number of neurological disorders that affect the spinal cord. Although these lesions have sometimes been subdivided into multiple types depending on their anatomical characteristics, it is sufficient to group them into three main types. The most common is the spinal dutal fistula, which is the most difficult to diagnose clinically and therefore can be confused with a number of neurological problems. The second type is the true AVM of the spinal cord, which can be strictly intramedullary or can extensively involve the spinal cord, the meninges, and even the vertebral bodies. These lesions occur at all ages and throughout the spinal cord. They can present either with acute myelopathy from intramedullary hemorrhage or with symptoms similar to those seen in the spinal dural fistulas from arterialization of the venous plexus that drains the spina! cord. Rarely, they present with spinal SAH, which may spread intracranially and simulate aneurysmal SAH. However, on close questioning, the pain in these patients almost always starts in the spinal area, and frequently they have a history of transient paraparesis or leg numbness at the onset. Therefore unless this history is obtained, there is no need to work up a patient with a typical history of intracranial aneurysmal SAH for a spinal AVM, The third group includes a variety of intradural, pcrimcdullary direct arteriovenous fistulas, which can either lead to very similar symptomatology as the spinal dural fistulas from venous hypertension or present with hemorrhage. The latter is often due to rupture of a venous aneurysm, which results from the high-pressure artcrialization of the perimedullary veins (Heros 1995).

Spinal dural fistulas occur in relation to the dural sleeve of one of the lower thoracic or lumbar roots. Less commonly, these lesions can also occur in the upper thoracic and cervical region. Typically, symptoms appear during mid and late adulthood and for this reason are thought to be acqmred legions, rather than congenital lesions. They arc more common in men than women. These lesions become symptomatic when they drain directly into the perimedullary coronal venous plexus, which normally drains the spinal cord (Figure 52.14), They rarely, if ever, result in hemorrhage and almost always become symptomatic as a result of pain and myelopathy. The pain may be radicular in nature, constant in the low back, or intermittent and frequently has a pattern suggestive of neurogenic claudication, where the pain occurs with ambulation and is relieved by rest. This is particularly pertinent because these lesions tend to occur in the same age-group as that in which lumbar spondylosis and neurogenic claudication are common. Therefore they must be entertained in the differential diagnosis of these conditions.

The myelopathy tesults from arterialization of the normal venous drainage of the spinal cord with secondaty venous hypertension. The patient may develop a progressive motor-sensory disturbance that can progress either steadily or sometimes with remissions and exacerbations that mimic multiple sclerosis. Sphincter disturbance eventually occurs, and, if untreated, the patients are usually wheelchair bound within 5 years from the onset of the leg weakness. The serious natural histoty of this disorder must be kept in mind, particularly in view of the fact that its surgical or endovascular treatment is relatively straightforward and almost always successful, provided that the neurological deficit is not profound or prolonged by the time of treatment.

In the past, diagnosis was made with a myelogram to demonstrate the dilated veins on the dorsal aspect of the spinal cotd (this tequired a complete lumbothoracic myelogram turning the patient in the supine position), Presently, the diagnosis can be made by cithct thin-cut CT myelography after injection of intrathecal contrast material or by spinal MRI. The latter can be problematic because unless it is done with special attention, the dilated veins in the surface of the spinal cord can be missed. Frequently, all that can be seen is an area of increased signal on T2-weighted images. Whenever such finding is seen without swelling of the spinal cord, this diagnosis must be suspected and confirmed by MRI with special technique. We use

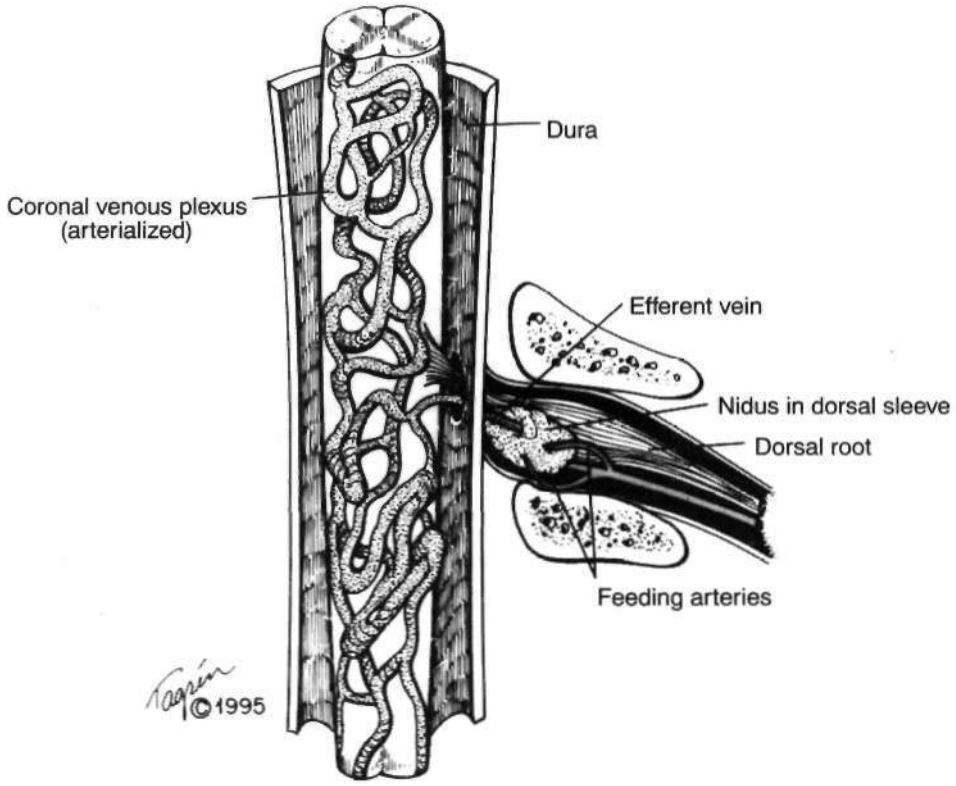

FIGURE 52.14 Schematic lvpri'smrmion ot .1 spinal Jural fistula. The actual fistula is located typically in the dural covering of one of the lower thoracic or lumbar nerve roots. The arterialized veins draining the fistula connect with the corona! venous plexus that normally drains the spinal cord. This venous plexus then becomes arterialized, thus increasing venous pressure and producing a venous hypertensive myelopathy. (Reprinted with permission from Heros, R. C. 1995, "Spinal arteriovenous malformations," in *Surgical Management of Neurovascular Disease*, eds R. C. Ojemann, C. S. Ogilvy, R. M. Crowd!, & R. C. Heros, Williams & Wilkins, Baltimore.)

standard T'l- and T2-weighted sagittal spin-echo images and T2-weighted axial gradient-echo images, as well as postcontrast three-dimensional MRI and Tl-weighted sagittal and axial images. With this technique, we have been able to reliably identify the fistula and its exact location (Bowcn ct a!. 1995). When there is no experience with these techniques and a spinal AVM is strongly suspected clinically, a spinal angiogram must be performed. This technique also requires considerable expertise and carries significant morbidity, and patients should not be indiscriminately subjected to it unless a spinal AVM is strongly suspected from the MRf or CT myelography study.

The treatment of dural venous fistulas consists either of eliminating the arteriovenous fistula completely or interrupting the arterialized venous communications (generally there is only one arterialized vein, although occasionally there arc two or three) from the fistula to the perimedullary coronal venous plexus of the spinal cord. This can be accomplished endovascularly in centers with the appropriate expertise. The procedure is difficult, and in less than very experienced hands, the morbidity of spinal angiography and endovascular therapy is quite significant. Unless the embolic material completely occludes the fistula and the beginning of the arterialized vein, recurrence is the rule. Nevertheless, in experienced hands, this is a very attractive option, particularly for older patients in whom surgery would carry a significant anesthetic risk, in most patients, we favor open surgical treatment, which consists of a small laminectomy with interruption of the arterialized vein usually with coagulation of the dural fistula in cases in which the fistula is located around a nerve root that can be sacrificed without consequences {e.g., the lower thoracic region). The results of treatment arc excellent and frequently dramatic with reversal of even very advanced paraparesis, particularly in cases in which the deterioration has been relatively acute and the treatment is undertaken early (Heros 1995).

It is important for the neurologist to include spinal AVMs in the differential diagnosis of any patient who presents with signs and symptoms of myelopathy, whether abrupt, slowly progressive, or with a pattern of remissions and exacerbations. In addition, whenever a patient in whom the diagnosis of lumbar spondylosis is entertained (frequently because of the pain pattern of neurogenic claudication), a spinal AVM should be considered. This is especially the case if there are signs of myelopathy, which obviously cannot be attributed to lumbar spondylosis, or if there is significant leg weakness or sphincteric disturbances, which are seen only very late in cases of lumbar spondylosis. We personally have operated on several patients with spinal AVMs who had been diagnosed as having multiple sclerosis. Several other patients have been operated on once or even twice before for lumbar spondylosis before the spinal AVM was eventually diagnosed and treated surgically.

Spasticity

Neurologists frequently treat patients in whom spasticity is either the predominant symptom or where it at least contributes significantly to the overall functional impairment of the patient. In children, this is most commonly due to cerebral palsy. **In adults,** stroke, multiple sclerosis, and myelopathy from spinal cord injury or other spinal cord diseases account for most of the patients in whom spasticity is an important problem. The first step in treating spasticity is pharmacological, and oral baclofen is the most common medication used. Frequently, however, the dose has to be increased to the point of intolerable drowsiness or other side effects. Other medicines such as ti/anidine, diazepam, and dantrolene may be used, but they may cause drowsiness or reduction in strength. At this stage, intrathecal administration of baclofen, usually by an implanted pump, can be very useful. When this fails, other more invasive ablative neurosurgical procedures may be considered. Dorsal rhizotomies are very effective in the treatment of spasticity. However, the side effects of complete dorsal rhizotomy are significant, and therefore more selective procedures have been developed. An open approach with intraoperative neurophysiologies! stimulation to select the dorsal rootlets involved in spasticity has been very effective, particularly in childten with cetebral palsy {Peacock and Standt 1991). Other, more invasive procedures such as a central myelotomy to interrupt the reflex arc and intrathecal phenol injections can be considered in the paraplegic patient who is severely incapacitated by spasticity. Intrathecal phenol causes loss of sensory input from the skin with the risk of decubitus ulcers and hence is rarely used other than for patients with terminal cancer.

Cervical Spondylosis

The neurosurgeon, who often operates on patients with cervical spondylosis for signs and symptoms of myelopathy and/or radiculopathy, must be intimately familiar with the nonsurgical differential diagnosis of cervical myelopathy, which includes motor system disease, subacute combined degeneration from vitamin B_{12} deficiency, demyelinating disease, tabes dorsalis, human T-lymphotropic virus type 1 (HTLV-l)-associated myelopathy and a number of other disorders. It is equally important for the neurologist to be aware that cervical spondylosis can result not only in neck pain and radicular symptoms, but also in myelopathy that may be painless and mimic these other diseases. When detected early, the myelopathy from cervical spondylosis can be either reversed completely or improved significantly with surgical correction. Even in the late stages, the patient's disease can be at least stabilized with surgery.

The early surgical treatment of cervical spondylotic myelopathy consisted of a posterior decompressive laminectomy or laminoplasty, which are still the best operations for many of these patients. However, we have become much more aware of the fact that cervical myelopathy is frequently a result of not just direct compression of the spinal cord, but also abnormal movement, Therefore depending on a careful study of each patient, other operations designed to decompress the cord anteriorly and/or posteriorly and then to fuse the spine when necessary have resulted in a considerable improvement in the treatment of these patients.

The neurosurgeon must know that the diagnosis of motor system disease must be entertained in patients with cervical spondylosis with significant myelopathy but with no sensory deficits. It is extremely unusual for cervical spondylosis to result in significant motor myelopathy without at least subtle decrease in sensation in the lower extremities. Conversely, the diagnosis of motor system disease becomes suspect when significant sensory abnormalities exist, and in these instances, cervical spondylosis is usually the culprit. The diagnosis of subacute combined degeneration is often entertained in these patients. This disease, however, is frequently preceded or accompanied by a significant peripheral neuropathy, which is not present in patients with cervical spondylosis unless they have an intercurrent disease.

Two other uncommon syndromes in the patient with cervical spondylosis can confuse the neurologist and the neurosurgeon. The first is the presence of signs and symptoms in the hands suggestive of lower motor neuron involvement in patients with upper cervical compression from spondylosis. It is not uncommon to see patients with significant compression of the spinal cord at C2-C3 or C3-C4 who despite lack of compression of the spinal cord or the nerve roots at the lower cervical levels complain of clumsiness and weakness of the hands. Most of these patients have the numb, clumsy hand syndrome, with severe loss of joint position sense. Rarely, they may have weakness of intrinsic hand muscles and some evidence of atrophy. This is similar to the well-established clinical observation ol symptoms and signs that simulate lower motor neuron disease in the lower cervical cord with tumors at the foramen magnum and other processes that produce upper cervical cord compression. The hypothesis to explain this problem proposes that impairment of ascending venous drainage produces venous infarction in the lower cervical cord. The second, and probably related problem, is the fact that patients with cervical spondylotic myelopathy without imaging evidence of motor nerve root compression can have symptoms and signs suggestive of a motor radiculopathy. The most reasonable explanation for this is that there is damage to the anterior horn cells. Recognition of this problem is important because if this problem is not recognized, patients can be subjected to unnecessary foraminotomies to decompress nerve roots, which may lead to spinal instability and the need for fusion.

In brief, cervical spondylosis is extremely common in the older population and frequently leads to myelopathic signs and symptoms that can mimic other diseases. Because surgical treatment is very effective, this diagnosis should be entertained in all patients in the middle or older age-group who present with signs and symptoms of cervical myelopathy and/or radiculopathy.

Brain Biopsy

Fortunately, with the introduction of many new diagnostic techniques, it is rare to have to perform brain biopsy for neurological diagnoses. However, there is still a well-defined role for this procedure, and it can usually be carried out with minimal or no morbidity.

Infections

Brain biopsy is still used by some clinicians before the institution of antiviral therapy when the diagnosis of herpes simplex encephalitis is suspected. However, the clinical and radiographic picture nowadays is usually specific enough to lead to a therapeutic trial of antiviral drugs before considering a biopsy, particularly in view of the fact that these patients often have significant brain swelling and the morbidity of the biopsy may be significant. Certain fungal and bacterial infections such as mucormycosis, aspergillosis, and nocardiosis often require a brain biopsy for diagnosis. The definitive diagnosis of some slow viral diseases such as Creutzfeldt-Jakob disease (CJD) requires a brain biopsy, which must be done with extreme caution according to a specially developed protocol. Presently, because of the risks to medical and paramedical personnel and to future patients (at risk because of insufficient sterilization of surgical equipment), many centers avoid brain biopsy and depend on clinical diagnosis in patients with clinically typical CJD.

The indications for biopsy in patients with acquired immunodeficiency syndrome are decreasing as MRl and radioisotope studies have become more capable of differentiating tumors (lymphomas) from infection (usually toxoplasmosis) or progressive multifocal leukoencephalopathy (PML). When the appearance is consistent with toxoplasmosis, we prefer to treat these patients empirically for about 2 weeks and proceed with the biopsy only if they do not respond to medical treatment. If the appearance is consistent with either lymphoma or toxoplasmosis, we obtain a single-photon emission computed tomography (SPECT) study; if positive, we assume that the diagnosis is lymphoma, but we usually confirm this with a biopsy before the initiation of radiation therapy. If the SPECT study is negative, we treat the patient empirically for toxoplasmosis. MRl is usually specific enough in the diagnosis of PML to make biopsy rarely necessary.

Vascitlttides

Brain biopsy is still necessary for the definitive diagnosis ol some vasculitides, such as granulomatous or isolated angitis.

Pediatric Neurodegenerative Diseases

Brain biopsy remains important in the diagnosis of some of these rare disorders including Canavan's disease and Alexander's disease.

Neoplastic Disorders

Brain (or rather meningeal) biopsy may be necessary in some cases of primary meningeal carcinomatosis, lymphomatosis, and gliomatosis, in which there is no obvious primary site and no definitive diagnosis has been obtained through spinal fluid cytology.

Dementia

Most causes of dementia can be diagnosed or at least strongly suspected clinically. In atypical cases, a brain biopsy is indicated to rule out treatable conditions such as Whipple's disease or a vasculitis.

Seizures and Epilepsy

Abnormal synchrony of neurons underlies seizure activity. Trauma, brain tumors, infection, metabolic disturbances, or abnormal cerebral development can cause irritation and/or abnormal neuronal firing patterns and rhythms. When seizures become intractable to medications, neurosurgical methods can assist in seizure control. Since the pioneering work of Wilder Pcnfield, many surgical advances have been made, adding to safety and efficacy. Today, seizure cure or increased patient manageability can be achieved with surgery. Medial temporal and selected extratemporal resections can result in 70-80% of patients becoming seizure free (Spencer 1996). Cortical mapping techniques allow the surgeon to localize and preserve brain areas that generate language and movement. Patients with widespread electroencephalographic (KEG) abnormalities or multiple foci may benefit from techniques such as multiple subpial resections, callosotomy and vagal nerve stimulation. Newer techniques such as subthalamic nucleus stimulation, gene insertion, and cell transplantation are under investigation.

Patients with intractable seizures are screened for surgery with scalp or sphenoidal EEG and video monitoring, MRl, SPECT scans, neuropsychological testing, and occasionally depth electrodes. Surgery is usually performed if these diagnostic tests can pinpoint the seizure focus and it is in a predictably safe surgical area.

Seizure surgery has become safer and more effective because of improved diagnostic methods, such as high-field and functional MRI, improved SPECT scans, and MR1 Spectroscopy. Surgical planning software stations and neuronavigational systems display images of the patient's brain and predicted seizure foci on a screen near the operative field. Preoperative functional MRI data for motor, language, and EEG can be included on the navigation screen,

A modern multidisciplinary approach to epilepsy is recommended. Neurologists, neurosurgeons, psychologists, and social workers working together can result in the best possible patient management

Movement Disorders and Parkinson's Disease

For six decades neurologists and neurosurgeons have collaborated to treat movement disorders associated with Parkinson's disease, essential tremor, multiple sclerosis, Huntington's disease, trauma, vascular conditions, and infection. When associated symptoms become intractable to medical therapy, modern neurosurgical techniques can help bring dramatic and long-standing relief. The earliest indication of this opportunity came from the recognition that motor improvement occurred in some patients with Parkinson's disease and tremor after focal strokes in the basal ganglia. Russell Meyers and others used these observations to design lesions of subcortical motor areas. Before the discovery of L-dopa, thousands of patients were treated successfully by stereoencephalotomy (thalamotomy). Lesioning the brain came back into vogue in the early 1990s with the advent of better stereotactic methods and the realization that L-dopa's beneficial effects were not curative and did not prevent progression of illness, Radio frequency lesioning of the internal segment of the globus pallidus (pallidotomy) has proven effective in relieving many of the cardinal symptoms of Parkinson's disease and selected dystonias. Essential tremor can be treated by lesioning the ventral intermediate motor thalamus (Vim's thalamotomy) or even the dentate nucleus of the cerebellum (dentatectomy).

Brain lesions can also be made using radiosurgical techniques (X-knife, gamma knife, proton beam). This technique is not recommended in most centers because it requires a high dose of focal radiation and does not allow for real-time neurophysiological localization and assessment of the patient during the procedure. Lesion accuracy, size, and potential delayed complications from radiation necrosis are concerns.

Coincident with the revival of brain lesioning, DBS has been shown to mimic the effects of lesioning with minimal damage to brain circuitry. A quadrapolar electrode is placed stereotactically into the nucleus of interest. The electrode is connected to a pulse generator implanted in an infraclavicular subcutaneous pocket. Stimulation parameters can be modified in an office setting.

Bilateral high-frequency stimulation of the subthalamic nucleus or internal segment of the globus pallidus is currently the treatment of choice for patients with Parkinson's disease, who have advanced disease with troublesome "on-off" motor fluctuations, dyskinesias, dystonias, or tremor. Patients are chosen for surgery after careful neurological and neuropsychological screening. In some patients with Parkinson's disease, the "off time" can be reduced more than 70%. With DBS, many patients' medications may be reduced. DBS is also the favored surgical treatment for essential tremor and selected dystonias. Bilateral thalamotomies can carry a significant risk of causing permanent aphasia, although the effect is reversible with DBS. Studies are in progress to determine the value of DBS in epilepsy, pain, obsessive-compulsive disorders, and depression. As the rhythms and oscillations in the brain are better understood, improved modalities of stimulation are being developed.

Advances in localization have allowed greater safety and efficacy in functional neurosurgical procedures. Brain targets of interest are acquired using planning software platforms that use anatomical atlases and the fusion of the patient's MRI and CT images. Target coordinates are translated to a stereotactic frame. Procedures are performed under mild sedation. Microelectrode recording and microstimulation is used to identify characteristic neuronal firing patterns, receptive fields, and nuclear boundaries. Intraoperative neurological examinations record beneficial and negative effects of brain lesioning or stimulation. Frameless stereotactic techniques are being developed for these functional neurosurgical procedures.

RECENT NEUROSURGICAL DEVELOPMENTS

Finally, in this section, we mention briefly some recent neurosurgical developments that have had a significant impact on neurosurgical practice or will do so.

Microsurgery

The operating microscope was introduced to neurosurgical practice about three decades ago, so it is not a recent development. However, the impact of the microscope in neurosurgery has been so significant and recent mechanical improvements in the mobility of the microscope have made it such that the microscope itself can almost float with the eyes of the surgeon as he moves within the surgical field to obtain the best possible angle of vision. The safety of operating on lesions such as aneurysms, AVMs, spinal cord tumors, tumors of the base of the skull, and intraventricular tumors has been improved remarkably. The average

morbidity of operating in some of these conditions has been reduced by half or more since the introduction of the microscope.

Skull Base Techniques

The skull base used to be like an iron curtain dividing the surgical fields of the neurosurgeon, the head and neck surgeon, the orbital surgeon, and the neuro-otologist. Over the last 10 or 15 years, neurosurgeons have learned, frequently from their colleagues in these other specialties, the techniques of removing bone safely along the base of the skull to gain access to deeply situated lesions with minimal brain retraction, better visualization, and greater safety. These techniques include the basal bifrontal craniotomy, sometimes with removal of the orbital rim and the nasion, the basal frontotemporal craniotomy with removal of the orbitozygomatic bone, the combined subtemporal-suboccipital and presigmoid craniotomy with posterior petrosectomy, and the far lateral suboccipital transcondylar approach. Using these surgical approaches and frequently working with colleagues in head and neck surgery, otolaryngology, neuro-otology, and ophthalmology, we are able to perform combined procedures that allow us to perform at least grossly complete total removals of benign tumors that were once considered inoperable. In addition, significant palliation and even cure of many tumors of low-grade malignancy can be accomplished with these techniques, and the approach to other lesions such as difficult and giant aneurysms and lesions of the brainstem has been made feasible and relatively safer,

Endoscopy

Neurosurgeons have been relatively late in adopting endoscopic techniques. However, with newly designed rigid and flexible endoscopes, the neurosurgeon can visualize, through smaller incisions, structures and pathology where the access by direct vision is much more difficult and dangerous. Endoscopes are ideal for intraventricular surgery, but they have also been incorporated in general microsurgical practice to look behind and around areas that are not directly in the field of vision of the surgeon. Also a number of traditional neurosurgical procedures, such as thoracic discectomies and transsphenoidal pituitary operations, can be performed less invasively with the use of the endoscope.

Intraoperative Angiography

Modern refinements in digital subtraction angiography have made its use in the operating room practical. This has been aided by the introduction of operating room tables and head support systems that are radiolucent and therefore allow angiograms in whatever plane and angle is best suited for the particular situation at hand. We routinely use intraoperative angiography in the surgery of AVMs to confirm complete removal before closing the wound. We also use this technique routinely in patients with giant or large, complex aneurysms to confirm the visually observed results of clipping. Other surgeons use the technique routinely for the surgery of all aneurysms. Not uncommonly, the intraoperative angiogram leads to repositioning of the clip to prevent a potentially catastrophic complication. Another application of this technique is to check patency of a bypass graft during surgery,

Neurophysiological Monitoring

Significant advances in neurophysiological monitoring have decreased the risk of many neurosurgical procedures, Spinal cord surgery, for example, is now routinely done with some form of neurophysiological monitoring involving not only sensory evoked potentials, but also motor transmission by transcranial cortical stimulation. Almost every cranial nerve can now be monitored, making surgery in or around the brainstem considerably safer. Somatosensory evoked potentials, central conduction time, and direct cortical measurements of blood flow have introduced greater safety to intracranial surgery involving temporary or permanent occlusion of major cerebral arteries. Carotid surgery has been made safer by intraoperative monitoring with EEG, somatosensory evoked potentials, and transcranial Doppler studies,

Frameless Stereotaxis

A number of new sophisticated systems of surgical navigation that incorporate stereotactic concepts and arc based on digital images (MRI or CT) that can be incorporated into a dedicated computer system have been developed. These new systems of surgical navigation consist of a method of registering images, an intraoperative localization device, a computer video display of the images, and some method of real-time intraoperative feedback. These techniques have led to the design of smaller craniotomies and very accurate intraoperative localization of deeply located lesions through minimally invasive brain trajectories. They have been particularly-useful for the surgery of deep brain tumors, skull base tumors, brain cavernomas, and for certain types of spinal instrumentation such as pedicle screw fixation. An extension of these techniques is the development of surgical robotic devices, which undoubtedly will find an important place in the neurosurgeon's armamentarium within the near future.

Real-Time Image-Guided Surgery

Systems have been devised to perform actual neurosurgical operations, either stereotactically or by open craniotomy, directly in a CT scanner or an MRI machine. Magnetic resonance^compatible instruments have been developed for this purpose. These devices were designed specifically for use in the operating room and though cumbersome and expensive have provided the neurosurgeon with real-time surgical feedback. The eventual role of these imaging devices in the operating room is still uncertain but promises to be significant.

Radiosurgery

The concept of radiosurgery and the first dedicated radiosurgical unit (the gamma knife) was developed by a neurosurgeon, Professor Lars Leksell. Since then, neurosurgeons have been almost uniformly involved in the delivery of radiosurgery, which is based on neurosurgical stereotactic techniques. Radiosurgery has become an extremely important surgical technique in the primary or adjunctive treatment of many vascular and neoplastic lesions. In addition, from its inception, radiosurgery has been used to make discrete lesions in the brain and lately in cranial nerves (such as the trigeminal nerve for treatment of trigeminal neuralgia) as part of the armamentarium available for functional neurosurgery.

Radiosurgery is clearly the treatment of choice for small (usually <3 cm in diameter) AVMs located deeply in the brain, in critical areas where open surgery would carry an unacceptably high morbidity. It is also an acceptable alternative for patients with small accessible AVMs, who would carry an inordinately high surgical risk because of age or associated medical comorbidities. Unfortunately, cavernous angiomas respond poorly if at all to radiosurgery, and the treatment of these lesions, which are often in critical locations such as the brainstem, has carried unacceptably high morbidity.

Radiosurgery has also found an important role in the treatment of some surgically inaccessible but well-demarcated benign tumors such as meningiomas in the cavernous sinus or in other regions where perhaps the bulk of the tumor can be removed surgically, but a small remnant must be left to avoid serious neurological morbidity. It appears that with small acoustic neuromas, radiosurgery tends to control the disease; many of the tumors cithct shrink or remain static in size at least for a few years. Unfortunately, there is not enough long-term follow-up information on either meningiomas or acoustic neuromas as to the permanent effectiveness of radiosurgery. This treatment is very attractive in elderly or medically debilitated patients when the tumor can be encompassed within the radiosurgical field.

Earlier in this chapter, we mentioned the fact that small metastases in the brain can be treated quite effectively with tadiosurgcry, particularly when there is a single metastasis or only a few discrete lesions. The role of radiosurgery in the treatment of primary malignant brain tumors has not been adequately defined because most of these tumors are infiltrating. However, there may be a significant role for this modality in treating focal recurrence after conventional fractionated irradiation or as an initial adjunct to conventional radiotherapy.

Endovascular Surgery

Endovascular surgery is covered in Chapter 53, and we have discussed its role in the treatment of aneurysms earlier in this chapter. The role of endovascular techniques in the adjunctive treatment of AVMs and some very vascular tumors (preoperative embolization to decrease blood supply) is well defined. In addition, it is becoming clear that in certain instances, endovascular techniques are becoming an acceptable alternative to surgery as primary treatment. Such is the case with small AVMs and fistulas that can be obliterated completely with embolization, and with some intracranial aneurysms that have a particularly favorable anatomy for this technique. Endovascular embolization has already become the preferred form of treatment for most intracranial and spinal dural fistulas, including carotid cavernous fistulas. Many vein of Galen aneurysms and other complicated arteriovenous anomalies of newborns and children can be treated successfully with endovascular techniques.

Although presently most endovascular surgeons are trained in radiology and neuroradiology, an increasing number of neurosurgeons and neurologists have been or are being rrained as endovascular surgeons and are planning to dedicate most or all their time to performing endovascular surgery.

Neurotran splantation

Reconstruction and protection of neural tissue are the ultimate goals of therapy in neurodegenerative disease. Transplants of embryonic fetal tissue into the brain of patients with Parkinson's disease or in its animal models can survive and produce dopamine and effect mechanical, chemical, and electrical connections with the host brain. The disease process does not appear to affect the transplanted cells. Several human studies using embryonic mesencephalic tissue have shown some positive effects on the disease (Freed et al. 2001; Mendez et al. 2002) and postmortem studies have shown dopamine cell survival and graft-host integration. Similarly, xenografts of porcine cells have also shown positive effects in some patients and integration into host brain (Schumacher et al. 2000).

Transplantation of neurotrophins and genetically modified cells has shown potential in animal models of Parkinson's disease and other neurodegenerative diseases. Transfection of glial-derived neurotrophic factor genes via a lentiviral vector into the Parkinson's disease primate model have demonstrated dopamine cell protection (Kordowcr ct al. 2000). Fibroblasts genetically modified to produce nerve growth factor have been shown to protect against excitotoxic destruction of neurons (Schumacher etal. 1991).

Highly specialized embryonic stem cells have demonstrated the capability in animal models to repair and reconstruct the degenerated nigrostriatal system {Isacson et al. 2001). The methodology for generating functional dopamine progenitor cells for transplantation has advanced to the stage that human stem cell transplantation studies are under consideration. The limitation of stem cell technology is the ability to generate a purified neuronal cell line while suppressing other germ cell layers and/or tumor formation. This technology might allow transplantation of specific cells into the brain to effect repair and replacement without the need for immunosuppression.

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Chapter 53
Principles of Endovascular Therapy

Ajay K. Wakhloo and Johnny S. Sandhu

Endovascular therapy (EVT) is one of the leading emerging neurological fields for the treatment of stroke, aneurysms, arteriovenous malformations (AVMs), brain tumors, and other such conditions. Over the past 20 years, it has evolved from a minimally invasive, alternative therapeutic approach to cerebrovascular diseases to a highly specialized field in its own right. EVT is now the primary approach for an increasing number of vascular diseases, with patients benefitting from better outcomes and shorter hospital stays.

The integration of new technologies, including neuroimaging and bioengineering, is likely to expand treatment indications. Significant advances in imaging technology (such as high-resolution angiography, flat-panel detectors, three-dimensional [3D] angiography, road-mapping capability, intravascular ultrasound, and interventional magnetic resonance imaging [MRIJ} are providing safer image guidance. Increased resources for biotechnology have resulted in the development of new materials and alloys using nanotechnology and micro-clcctromechanical systems (micromachinery).

Unlike the "extravascular" approach (open surgery) that involves an external approach to the outer layer of the vascular system (generally the adventitia), "endovascular" treatment focuses on the endothelium, which represents the largest receptor surface in the body that involves the coagulative system, platelets, vasodilatation processes (e.g., nitric oxide [NO]), vasoconstriction (e.g., endothclin-1), and biological responses to implanted materials. The endothelium is also sensitive to changes in blood composition and flow, including direction, velocity, and pressure. The next generation of endovascular therapies will involve the further development of newer materials, anticoagulation and antiplatelet agents, thrombolytics, growth inhibitors and promotors, and antiproliferative agents, as EVT moves from "microplumbing" to the delivery of growth factors and gene therapy.

Currently, the endovascular treatment of neurovascular diseases has two approaches: to close or devascularize (e.g., aneurysm obliteration or AVM embolization); and to open or revascularize (e.g., vascular stenting, thrombectomy, thrombolysis, and angioplasty). The key to a successful endovascular intervention is to understand basic vascular anatomy, pathology, classification of the pathology, materials, and imaging tools. In this chapter, we present the acute and elective endovascular treatment of selected disorders,

GENERAL CONSIDERATIONS

Before an intervention, one generally must perform angiograms of the posterior and anterior circulation, selective injection of external carotid arteries, and 3D angiograms (if needed). Angiograms help the interventionist to define the lesion and its architecture, classify the disease entity, and outline potential collaterals and dangerous anastomoses, as well as to plan the EVT, including device selection. Computed tomography (CT) and magnetic-resonance angiography (MRA), especially with contrast, are gradually replacing catheter angiographic diagnostic workup, although detailed information still requires digital subtraction angiography.

The femoral artery approach is the most common site of access for cerebral or spinal diagnostic angiography and intervention. When an intervention is planned together with diagnostic angiography, a large femoral artery sheath is placed to introduce a variety of specialized catheters and devices, which arc threaded into the area of interest using a coaxial technique under fluoroscopic guidance and often

road mapping. This involves obtaining an image of die vascular tree that is frozen and serves as a background map. Under real-time fluoroscopy, it is then possible to navigate the catheters, wires, and bioimplants, using the "road map" to the area of interest.

With newer devices, an intervention can also be done via direct access through the carotid artery or if deemed necessary through the brachial or radial artery (Fessler et al. 2000). Microcathcters can either be navigated safely over microwires or flow guided into most of the important vascular segments of the central nervous system (CNS). Development of high-resolution angiography, road-mappmg techniques, and iso-osmolar nonionic contrast materials has helped minimize complications of diagnostic neuroangiography, such as minor or major stroke, which in experienced hands should be less than 0.5%.

The most commonly used embolic agents include polyvinyl alcohol (PVA) particles of different sizes (PVA = 50-1000 urn), Gelfoam, collagen fibers, dehydrated (96%) ethanol, platinum (fibered) coils, polymer-coated coils, acrylatc, cellulose acetate, and detachable balloons.

Some important essentials for a safe embolization can be summarized as follows:

- Thorough understanding of normal cerebrovascular anatomy and pathology.
- Exclusion of dangerous anastomoses between the external carotid artery and vertebrobasilar system and the internal and ophthalmic arteries. Dangerous anastomoses can be visible during initial neurovascular imaging or can appear during embolization. If necessary, a provocative test can be undertaken with injection of amobarbital (Amytal) or lidocaine into the extracranial arterial branches.
- Understanding of the characteristics of biomaterial including catheters, wires, and bioimplants used, as well as available alternative options.
- Experience in the use of thrombolytics, anticoagulants, and antiplatelet agents,
- The use of supcrselcctivc catheterization, especially if liquid embolic agents are used. Protection of normal vessels may require their temporary occlusion with nondetachable balloons or Gelfoam. If permanent occlusion is desired, this may be achieved by the use of detachable balloons, coils, or acrylates.
- Embolization should be performed under fluoroscopic control. Gentle and controlled injection of embolic agents is necessary to avoid reflux into normal tissues.
- Frequent use of road mapping is required for safe catheterization.
- Treatment of arterial vasospasm induced by instrumentation is undertaken with lidocaine, papaverine, nitroglycerin, or mannitol.
- Prophylactic use of high-dose corticosteroids can avoid expanding mass effects resulting from tumor ischemia or necrosis.
- Frequent monitoring of neurological status during embolization.
- Patients should receive generous treatment with analgesics.
- Whenever feasible, conscious sedation should be used, rather than general anesthesia. However, general anesthesia should be used for embolization of AVMs, for aneurysms, complex vascular disease, children, and in extremely restless or uncooperative patients.

TUMOR EMBOLIZATION

Transarterial Embolization and Direct Tumor Puncture

Devascularization of extracranial head and neck or intracranial tumors can be performed preop era lively to reduce intraoperative blood loss, to facilitate surgical resection, and to reduce the time of surgery (Siniluoto et al. 1993). In selected patients who are not suitable for surgery, tumor embolization may be palliative to reduce tumor size and control tumor growth (Koike et al. 1990; Wakhloo et al. 1993). It has been suggested that preoperative embolization may reduce tumor recurrence after surgery, although this remains debated (Dean et al. 1994),

The tumors most commonly subjected to preoperative embolization are meningioma, glomus tumors, juvenile nasal angiofibroma, hemangioblastoma, sarcoma, and (renal) metastases (Richter and Schachenmayer 1983; Teasdale et al. 1984; Manelfe, Lasjaunias, and Ruscalleda 1986; Eskridge et al. 1996; Scholtz et al. 2001). Embolization is particularly valuable in skull base meningiomas (Jungreis 1991; Manelfe, Lasjaunias, and Ruscalleda 1986; Wakhloo et al. 1993).

In hemangioblastomas, preoperative embolization is extremely helpful, especially if the deeper parts of the tumor and the piaI arteries supplying the tumor can be approached. However, less than 50% tumor devascularization has proven not to reduce operative complications or morbidity (Takeuchi et al. 2001). Embolization is also a safe and effective method of controlling refractory epistaxis in patients irradiated for nasopharyngeal carcinoma (Mok etal. 1999).

The basic principles of tumor embolizations involve a complete assessment of tumor-supplying arteries and delineation of normal vascular structures including the venous drainage, a transarterial super selective catheterization of relevant arteries, followed by fluoroscopic-con trolled infusion of embolic agents. The most commonly used materials arc PVA, Gelfoam, acrylates, dehydrated ethanol, and fibrin glue (Manelfe, lasjaunias, and Ruscalleda 1986; Lonser, Heiss, and Oldfield 1998; Probst et al. 1999; Valavanis and Christoforidis 2000; Bendszus et al. 2000). The size of the embolic material must be tailored to the diameter of the supplying arteries to achieve a deep penetration of the embolic material into the tumor nidus for successful tumor

ischemia (Wakhloo et al. 1993). If supers elective catheterization is not feasible, for example, in tumor-supplying branches originating directly from the internal carotid or the vertebral artery, temporary occlusion of the internal carotid artery (ICA) distal to the feeders can he achieved when infusing particles or ethanol with a microcatheter that is positioned as close to the feeders as possible (Jungreis 1991; Wakhloo et al. 1993) (Figure 53.1).

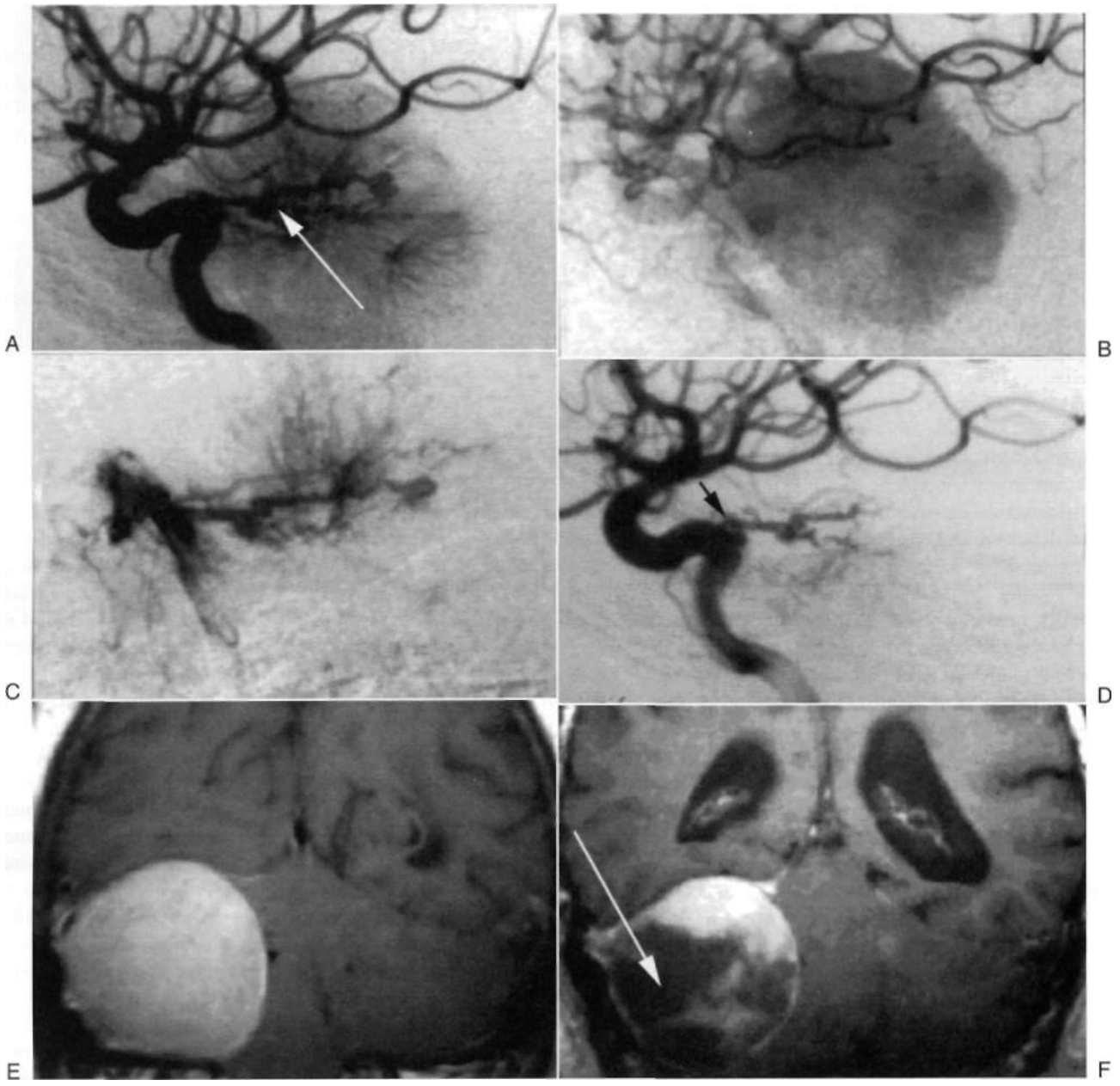

FIGURE 53.1 (A) internal carotid artery angiogram (ICA) (lateral projection) shows a hypervascular tumor at the skull base supplied via dilatated meningeal branches of the meningohypophyscaJ trunk (Bernasconi and Casanari). The centrifugal radial tumor vessel architecture is typical for a meningioma. (B) Homogenous tumor contrast enhancement with delayed washout is seen in the late arterial phase. The inferior portion of the meningioma is supplied through dural branches of the external carotid artery. (C) Supetselective catheterization of the men ingo hypophyseal artery and centrifugal polyvinyl alcohol (PVA) particle embolization. The control angiogram shows partially embolizcd tumor vessels with major central feeders perfused; dural and tumor enhancement at the clival region. (D) Postemholization ICA angiogram shows nearly complete devascularization with a patent meningohypophyscal trunk. (E) Contrast-enhanced coronal Tl-weighted magnetic resonance imaging (MRI) scan shows a large posterior fossa meningioma with attachment to the tent and mass effect on the brainstem. The extra-axial tumor shows homogenous enhancement and increased contrast uptake of the adjacent dura. Dilatated peritumor draining veins are visible. (F) MRI scan after embolization. Large areas of devascularization represent necrotic tissue. The remaining enhancing tissue is supplied via pial branches of the posterior circulation.

Postembolization gadolinium-enhanced MRI is an excellent imaging tool to evaluate the efficacy of embolization (Grand etal. 1993; Wakhloo et al. 1993). On MRI, marked tumor size reduction and a decrease in contrast uptake are associated with magnetic resonance spectroscopic (MRS) signs of a transient lactate peak, followed by a large aliphatic signal consistent with tumor necrosis. The necrosis as shown by proton spectroscopy is complete within 4 days (Jucngling, Wakhloo, and Hcnnig 1993; Bendszus et al. 2000).

As maximal tumor softening is seen, the optimal interval between embolization and surgery in 'meningiomas is proposed to be between 7 and 9 days. This facilitates a safer and easier tumor resection (Kai et al. 2002).

Attention must be paid to potential dangerous anastomoses between branches of the external carotid, internal carotid, and vertebral arteries, which may be present before embolization, adjacent to or within the tumor, or may open during embolization as a result of changes in vascular impedance (Casasco et al. 1999; Turner, Trobe, and Deveikis 2002). Facial palsy after preoperative embolization of glomus tumors has been described but is a rare complication (Marangos and Schumacher 1999). If an inappropriate particle size is chosen or embolization is performed from a proximal catheter position, lower cranial nerve deficits may be seen because of ischemia of vasa nervorum. Risk of embolization-induced increased endocrine activity of paragangliomas has been described but generally does not occur (Milewski, Eimannsberger, and Pflughaupt 1993).

Recently, a successful percutaneous or transnasal intratumoral injection of N-butylcyanoacrylate or ethanol has been described (Casasco et al. 1994). It may also be used in combination with transarterial embolization. It is a safe and effective method in the management of hypervascular neoplasms of the head and neck (Chaloupka et al. 1999).

Chemoinfusion with Blood-Brain Barrier Disruption

Primary treatment of brain tumors with neuroendovascular approaches has attempted to overcome the blood-brain barrier (BBB) by disrupting the BBB with the delivery of c he moth era pen tic agents. The tight junctions of microvessel endothelium have been a long-standing obstacle to delivering chemotherapeutic agents through the systemic circulation. Doses necessary to cross the BBB have typically been highly toxic to the rest of the body. Rapoport et al. (1970, 1972, 1976) first theorized the possibility of transiently opening the BBB with intra-artenal (IA) infusion'; of hyperosmotic agents. Mannitol was found to cause osmotic disruption with shrinkage of the endothelium and subsequent "opening" or "separation" of tight junctions. Neuwelt et al. (1979) first used osmotic disruption to subsequently deliver chemotherapy for brain tumors in a phase I trial in 1979. Since then, other agents such as vasoactive compounds have been studied to augment the local delivery of chemorherapy to brain tumors with varying degrees of success. These include leukotrienes, histamine, serotonin, interferon-^, hradykinin, and bradykinin analogues (RMP-7), A multicenter trial treated 221 adult patients with IA chemotherapy with or without BBB disruption. Patients had tumors that included primary CNS lymphoma (PCNSL), primitive neuroectodermal tumors (PNETs), germ cell tumors, cancer metastasis to the brain, or low- or high-grade gliomas. A total of 40 (75%) of 53 patients with PCNSL achieved complete response (CR). All patients with PNET, metastatic disease, or germ cell tumor achieved stable disease (SD) or better. Of the 57 evaluated patients with glioblastoma multiforme, 45 (79%) achieved SD or better. The study concluded that IA chemotherapy with or without osmotic opening of the BBB is feasible across multiple centers, with a low incidence of catheter-related complications (Doolittle et al. 2000).

ISCHEMIC STROKE

Prevention

Stroke remains a significant public health problem in the United States as the third leading cause of death and the number one cause of neurological disability {Weir 1987, 2002; Wolf and D'Agostino 1998). The American Heart Association (AHA) estimates that there are more than 4.6 million stroke survivors in this country, and more than 150,000 deaths annually are attributed to stroke {Wolf and D'Agostino 1998; AHA 2001). Recent studies estimate an incidence of 700,000 to 750,000 new strokes per year, with 83% of these secondary to ischemic events {Broderick et al. 1998; Rosamond et al. 1999; Williams et al. 1999). The most common etiology is the occlusion of an intracranial blood vessel that supplies a critical brain territory. Acute ischemic stroke results in death within 30 days for 7.6% of victims (Rosamond et al. 1999; AHA 2001).

The most effective treatment is prevention because of the nature of stroke and the difficulty in immediately identifying symptoms. Treatment is often delayed beyond the point of saving the ischemic penumbra—the salvageable area of brain tissue. Therefore prevention, especially in high-risk populations, may be an effective method in reducing the morbidity and mortality of stroke. Patient education, antiplatelet therapy and anticoagulation, carotid endarterectomy (CEA) and stenting, and intracranial stenting whenever indicated are all preventive medical measures that can be applied.

Carotid Artery Stenting

Large studies have estimated that 0.5% of people between the ages of 60 and 70 years and 10% of people older than 80 years have carotid artery stenosis. Atherosclerotic

occlusive disease of the carotid artery has been estimated to be responsible for 20-30% of all strokes (Timsit et al. 1992).

Age, race, gender, genetics, and family history are nonmodifiable factors that play a role in the development of carotid artery disease. Older age, African American and Hispanic descent, male gender, and a positive family history are all positive risk factors. Modifiable risk factors include the following: smoking, hyper)ipidemia, sedentary lifestyle, incteascd body mass index, oral contraceptive use, alcohol and substance abuse, diabetes mellitus, hypertension, prior transient ischemic attack (TIA) or stroke, elevated homocysteine levels, elevated anticardiolipin antibodies, presence of a carotid bruit, cardiac disease, increased fibrinogen, and low serum folate (Biller and Love 2000).

Indications for Treatment. Approximately half of the patients considered for endovascular treatment present with a symptomatic cerebrovascular event, cither a completed stroke or a single or multiple TIAs. The TIA syndrome resulting from ICA stenosis generally consists of ipsilateral amaurosis fugax, contralateral sensory or motor dysfunction, aphasia (if affecting the dominant hemisphere), contralateral homonymous hemianopia, or combinations thereof. Ocular symptoms are sudden, brief, and painless and last 1-5 minutes, rarely more than 30 minutes. Primary care physicians may also refer patients after auscultation of a carotid bruit, although this is not a very sensitive sign. Atherosclerotic occlusive disease is the most common etiology of carotid artery stenosis. However, stenoses can be caused by fibromuscular dysplasia, arterial dissection, arteritis (especially Takayasu's arteritis), which may produce stenoses of the great vessels and the intracranial circulation or neurofibromatosis. Long-standing hypertension may result in marked tortuosity of the proximal great vessels and intracranial small-vessel arteriopathy. Less common causes of carotid occlusive disease include tumor encasement, radiation-induced stenosis, and trauma. Revascularization in this group is indicated to improve hcmodynamic-related neurological symptoms secondary to high-grade stenosis.

Plaque Characteristics. Clinical observations and histopathological studies of the carotid plaque suggest that two different diseases of the carotid artery bifurcation can be distinguished: the "asymptomatic" and the "symptomatic" carotid plaque.

Carotid plaques can be distinguished as either homogenous or heterogenous. Diffuse intimal thickening or growth of the intima occurs through the migration of medial smooth muscle cells into the subendothelial space through the fenestrations of the internal elastic lamina, associated with increasing amounts of elastic fibers, collagen, and glycosaminoglycans. Homogenous plaques are stable and rarely show evidence of ulceration or hemorrhage. Homogenous plaques undergo the deposition of fat and fibrous tissue. Conversely, heterogenous plaques are unstable and contain lipid-laden macrophages, monocytes, leukocytes, necrotic debris, cholesterol crystals, and calcification. Plaques may harden with calcium, lipid, and cholesterol accumulations.

Several studies of plaque characteristics have revealed a correlation between the histological features of a plaque and its susceptibility to cause thromboembolic events. These findings have been mostly related to ultrasound findings. Plaques that are more likely to be related to stroke have a low echogenicity on ultrasound. This is because lipid and hemorrhage weakly reflect ultrasound, that is, show echoluccncy. These plaques are soft and friable. Irregularities of the surface (plaque ulceration) have been shown to be a risk factor for thromboembolic events. Ulcerated plaques arc often covered by soft, gelatinous clots that contain platelets, fibrin, white blood cells, and red blood cells. Heterogenous plaques have been shown to be an independent risk factor for stroke regardless of the degree of stenosis.

The cholesterol-rich, slightly raised fatty streak becomes a fibrous plaque. The complicated plaque may undergo rupture, intraplaque hemorrhage, extensive necrosis, calcification, and subsequent thrombosis. Infiltration of the fibrous cap of the plaque by foam cells may also contribute to the rupture. Symptomatic plaque shows a significantly higher incidence of rupture (74%) as compared with asymptomatic plaque (32%) (Carr et al. 1989; Bassiouny et al. 1997). Although there is no difference in the amount of necrotic core in the symptomatic versus the asymptomatic plaque (26% vs. 22%) or calcification (6% vs. 7%), a significantly higher number of macrophages are found in the symptomatic plaque (1114 vs. 385), indicative of the inflammatory nature of the disease.

Surgical and Endovascular Treatment. The North American Symptomatic Carotid Endartcrcctomy Trial (North American Symptomatic Carotid Endarterectomy Trial Collaborators 1991) was a randomized study that determined that CEA reduced the risk of stroke in patients with ipsilateral carotid stenosis and a recent cerebrovascular event. Patients treated with a high dose of aspirin over 24 months had a risk of ipsilateral stroke of 26%, whereas only 9% of the patients undergoing CEA presented with stroke in the same time period. Thus CEA became the standard of care for carotid disease with high-grade stenosis (70-99%). The periprocedural major stroke and death risk was 5.5% and 0.6%, respectively. Other surgical complications included cranial nerve injury, wound hematoma, and myocardial infarct, for a total periprocedural complication of *26%.* However, surgical high-risk patients were excluded from the study (Table 53.1).

The annual stroke event rate for asymptomatic patients with hemodynamically significant carotid artery stenosis ranges from 2-5% (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study 1995). The

Table 53,T; Patients excluded from die North American Symptomatic Carotid Endartercctomy Trial

1. Mentally incompetent or unwilling to give informed consent
2. Inadequate angiographic visualization of both carotid arteries and their intracranial branches
3. Intracranial lesion that was more severe than the surgically accessible lesion
4. Organ failure of the kidney, liver, or lung, or cancer judged likely to cause death within 5 years
5. Cerebral infarction on either side that deprived the patient of all useful function in the affected territory
6. Symptoms that could be attributed to nonatherosclerotic disease
7. Cardiac valvular or rhythm disorder likely to be associated with cardiocmbolic symptoms
8. Previously undergone an ipsilateral carotid endarterectomy
9. Older than 79 years
10. Experienced angina or myocardial infarction in the previous 6 months
11. Progressing neurological signs
12. Conrralarcral carotid endarterectomy within 4 months
1.1. Underwent a major surgical procedure within 30 days

5-year stroke and death risk for an asymptomatic high-grade carotid stenosis with medical treatment was found to be 11%, whereas the surgical arm had a stroke risk of 5.1% (Executive Committee for the Asymptomaric Carotid Atherosclerosis Study 1995). The Asymptomatic Carotid Artery Stenosis (ACAS) trial found that CEA was justified in asymptomatic men with 60% or greater stenosis only if the perioperative morbidity and mortality rate of the procedure is less than 3%. The acceptable perioperative morbidity/mortality rate for symptomatic patients was 6%. Although the findings were not as clear for women, women also experienced a reduction in stroke risk with CEA.

Restenosis is not uncommon after CEA. Studies have reported an incidence of anywhere from 1.5% in symptomatic to 19% in asymptomatic patients (Healy et al. 1998). Furthermore, reoperation is often more difficult for restenosis after CEA, with higher rates of local and neuro logical complications.

The initial carotid stenting trials focused on patients who were not good candidates for CEA and continued to have TIAs on optimal medical therapy (Lanzino et al. 1999; Mericle et al. 1999; Lopes et al. 2002). Also, patients who fall into the following categories were considered for carotid artery angioplasty/stenting: lesions that were anatomically inaccessible to surgery, lesions with CEA restenosis, high-risk patients with severe comorbidities, radiation-induced stenosis, medically refractory patients, cases with arterial dissection and tumor-encased carotid arteries, and patients older than 80 years. Multiple current trials showed reduced peri procedural morbidity and mortality of endovascular treatment versus surgery if distal cerebral protection is used during carotid stenting I'CS). A randomized trial of stenting versus CEA in surgical high-risk paricnts showed that at 30-day postprocedure, stroke, myocardial infarction, and death were encountered in 12.6% in the surgical arm (N = 151) and only 7.8% in the stentcd group that used a cerebral protection device (N = 156) (Yadav 2002). The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) (CAVATAS Investigators 2001) was a randomized trial that sought to compare endovascular treatment with conventional carotid surgery. The multicenter trial in Europe, Australia, and Canada randomly selected 504 patients with carotid stenosis. Patients with stenosis of the common carotid artery, carotid bifurcation, or ICA that needed treatment were included only if both endovascular and surgical treatments were suitable. The CEA group had 253 patients, and the endovascular group had 251. Stenting was used in 55 patients (26%), and angioplasty alone was used in 158 patients (74%). The mean stenosis in the surgical group was 86.4%, and the 30-day stroke and death rate was *5.9%.* In the endovascular group, the mean stenosis was 85.1% and the 30-day stroke and death risk was 6.4%, No cerebral protection was used (Figure 53.2).

The Carotid Revascularization Endarterectomy Versus Stent Trial (CREST) is currently enrolling patients for a multicenter clinical trial to compare the efficacy of CEA and carotid angioplasty/stenting in symptomatic patients with stenosis of 50% or more. As of mid-2001, 47 centers had been selected (Hobson 2002). This study is evaluating whether carotid stenting, the new technology, is more or less efficacious than open surgery, the current standard treatment.

The latest update on the global carotid stent registry includes almost 11,000 stented patients with more than 12,000 carotid arteries stented (Wholey et al. 1998). Data show that the technical success with stenting was more than 98%. The minor and major stroke risk and mortality in the symptomatic group without the use of a distal cerebral protection device was almost 7%, whereas the use of a distal cerebral protecrion device reduced the risk to 3.25%. In the asymptomatic group, the minor and major stroke risk and mortality associated with carorid artery stenting was *4.7H"A,* but could be reduced significantly to 2.53% by using a distal cerebral protection device. The rate of restenosis (>50%) at 48 months was 5.5%. Other studies with follow-up of 1 year and less have reported in-stent restenosis rates after carotid angioplasty and stenting between 3.5% and 8.0% (Chakhtoura, Hobson, and Goldstein 2001). Stenting of vessels has been shown to overcome previously high rates of restenosis with angioplasty alone.

Cerebral protection devices are based either on balloon or on filter technology. The basic idea is to prevent embolic stroke during stenting. The cerebral protection device is placed distal to stenosis; once stenting is accomplished, the device is removed through a guiding catheter. Despite the use of a cerebral protection device, approximately 2-3% of symptomatic and asymptomatic patients suffer minor and major srroke. Generally, this is related to embolic debris

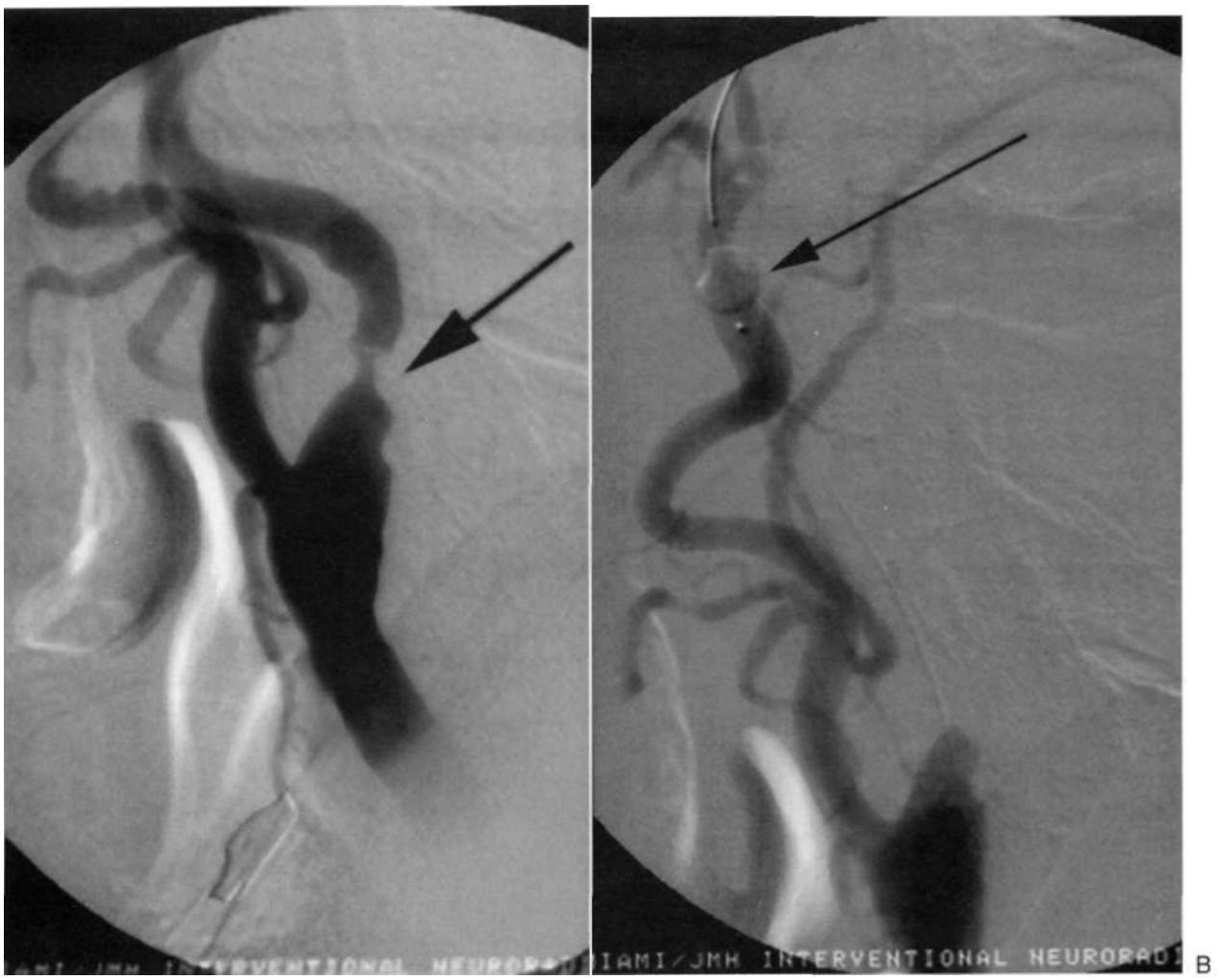

FIGURE 53,2 (A) Common carotid artery angiogram in lateral projection shows an ulcerated plaque and high-grade stenosis of the internal carotid artery (ICA) *[arrow).* (B) A balloon has been inflated within the ICA distal to the stenosis in preparation for stenting. The balloon serves as a cerebral protection device *{arrow).*

Continued

small enough to pass through the pores of the filter (<100 jam) or generated postprocedurally at the stented segment.

Other common complications of carotid stenting/ angioplasty include bradycardia and hypotension that can be prevented by applying slow inflation and lower pressures during percutaneous transluminal angioplasty (PTA) (Wakhloo et al., unpublished data).

Atropine (0.6-1.0 mg intravenously [IV]) and dopamine are rarely necessary to treat these complications yet are options if the need arises. Generally, vasospasm during catheterization, PTA, or stenting does not require any treatment because of its spontaneous resolution, although infrequently papaverine, mannitol, or sodium nitroprusside (Nipnde) may he used. Arterial dissection during catheter manipulation, PTA, or stenting may require extensive stenting to avoid vessel occlusion. After stenting, patients arc kept for 24 hours in a critical care or step-down unit before discharge. Special attention should be paid to hypotension and hypertension, renal function, the access site, and new neurological symptoms, including headaches, which can be related to hyperperfusion of the previously relatively ischemic distal vascular territory or cerebral hemorrhage. Patients should ambulate the next day and resume normal activities. Clinical follow-ups are recommended at 1 month, 3 months, *6* months, and 1 year, Patients should be carefully monitored for groin hematoma, fever, and neurological symptoms (e.g., amaurosis fugax, headaches, aphasia, and sensory or motor impairment). Doppler ultrasound to monitor restenosis is recommended at 6 months and 1 year.

Patients are put on clopidogrcl bisulfate (Plavix) at 75 mg per day orally and aspirin at 325 mg per day orally for 6" weeks after stenting. After 6 weeks, patients are instructed to take only aspirin at 81 mg per day orally for life,

In conclusion, carotid stenting with cerebral protection is safer than carotid surgery in symptomatic patients and in

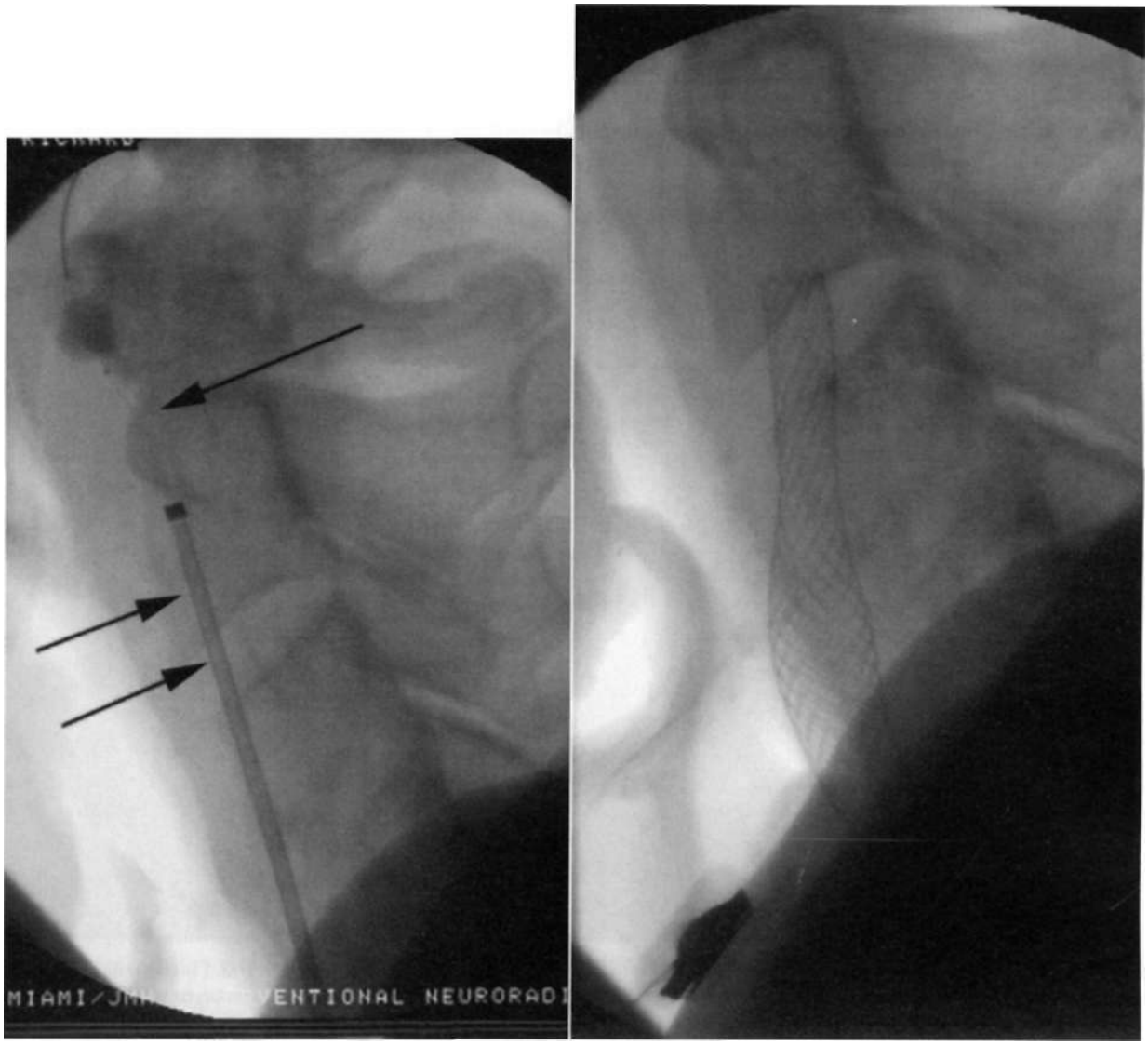

FIGURE 53.2, cont'd. (C) The stent delivery system (double arrows) is placed over the balloon wire *(arrow)* and positioned over the plaque while the balloon remains inflated. (D) Placement of a self-expanding stent. Before the delivery system is removed and the balloon is deflated, 50-60 mL of hlood is aspirated through the guide catheter to remove the potentially accumulated emboli. (E) Control angiography shows stent placement and complete revascularization of the ICA. *Continued*

surgical high-risk symptomatic and asymptomatic patients. Surgical high-risk patients can be classified into those with anatomical factors that increase the risk of surgery and those with medical conditions that increase the risk of surgery (Tables 53.2 and 53.3). The exclusion criteria for stenting are listed in Table 53.4. In asymptomatic patients, stenting using a cerebral protection device is still associated with slightly higher morbidity than carotid surgery but may be used in selected patients.

Stenting in the United States remains an investigational procedure, but approval from the Food and Drug Administration (FDA) is expected in 2003. Carotid artery stenting will most likely grow safer, with fewer complications, as biomedical technology advances with new materials and devices that overcome current limitations. These include dedicated carotid stenting equipment with low-profile stent delivery systems and a variety of stent designs, better access sheaths, special balloons, and wires. MRI will also play a major role in the characterization of plaques, and more sophisticated interventional MRI will overcome current spatial and temporal resolution limitations. Various cerebral protective devices are being optimized to decrease the incidence of embolic events. Drug-coated stents will also play a role in carotid stent development.

Intracranial Stenting

Intracranial arterial stenosis plays a major role in cerebral ischemic disease and accounts for approximately 50,000-70,000 strokes per year (Chimowitz et al. 1995).

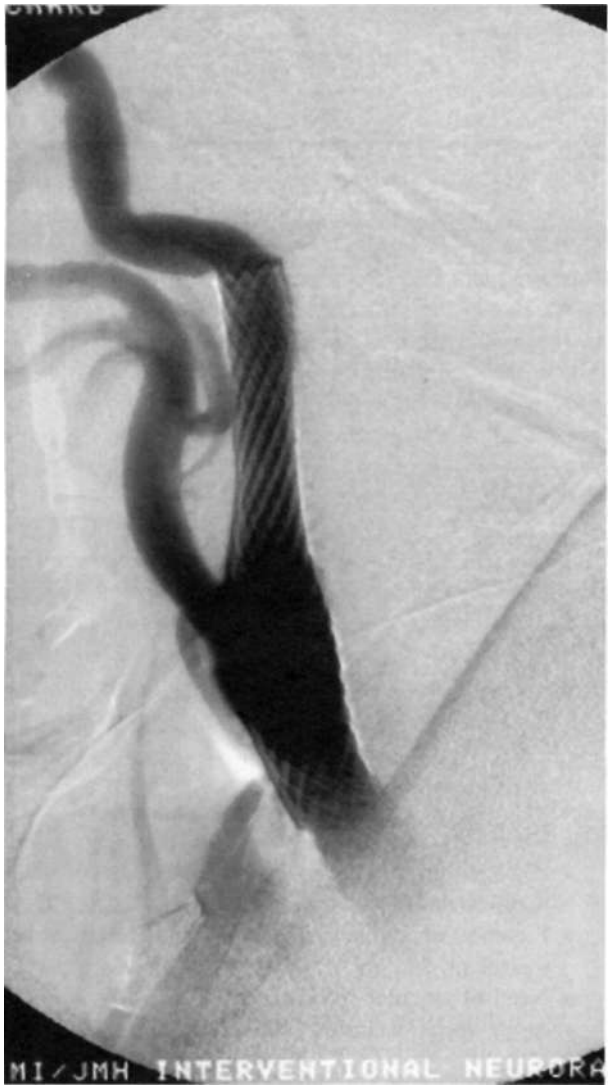

FIGURE 5 3.2, cont'd, (E) Control angiography shows stent placement and complete revascularization of the ICA.

The clinical impact of intracranial atherosclerosis is not yet fully understood, but reports have revealed that anywhere from 5-29% of all ischemic strokes are attributable to this disease (Hass et al. 1 968; Craig et al. 1982; Marzewski et al. 1982; Bogousslavsky and Regli 1983; Wechsler et al. 1986; Gorelick 1993; Chimowitz et al. 1995; Sacco et ai. 1995; Wityk et al. 1996; Akins et al. 1998; Connors and Wojak 1999; Thijs and Albets 2000; Lylyk et al. 2002). Previous studies have also reported an incidence of intracranial stenosis in 5-23% of all angiograms performed on stroke patients (Hass et al. 1968; Borozan et al. 1984; Keagy et al. 1986). Stenosis greater than 50% is considered hemodynamically and clinically significant.

Most patients with intracranial stenosis present with a stroke without the typical warnings of TIAs. The prognosis is even more ominous for patients with certain intracranial stenotic lesions, with mortality rates of 50% fot patients with an intracranial ICA stenosis (Matzewski et al. 1982). The distribution of intracranial stenosis is as follows: ICA 49%, middle cerebral artery (MCA) 20%, posterior cerebral artery (PCA) 11%, vertebrobasilar circulation (VB) 11%, and anterior cerebral artery (ACA) 9% (Akins etal. 1998).

Stroke associated with a stenosis of the MCA has been reported to occur at a rate of 8% per year (Bogousslavsky et al. 1986; EC/IC Bypass Study Group 1985). Other studies have reported an annual stroke rate of 4-12% per year for the anterior circulation and 2.5-15% per year for rhe posterior circulation (Craig et al. 1982; Marzewski et al. 1982; Botozan 1984; EC/IC Bypass Study Group 1985; Bogousslavsky et al. 1986; Wechsler et al. 1986; Thijs and Albers 2000).

Previous treatment modalities for inttactanial stenosis have been limited. The Watfarin Aspirin Symptomatic Intracranial Disease (WASID) study suggested that patients with vertebral, basilat, and posterior cerebral or posterior inferior cerebellar artery stenosis who were treated medically had annual stroke rates of 7.8%, 10.7%, and

Tabic 53.2: Anatomical high-risk population for surgery

Surgically inaccessible lesion above C2 or below the clavicle
Previous head or neck radiation therapy
Previous surgery [hat included the area of stenosis/repair
Previous ipsilateral neck dissection for cancer surgery
Spinal immobility of the neck resulting from cervical disorders
Restenosis after previous or unsuccessful carotid endarterectomy
Presence of recurrent laryngeal nerve palsy
Presence of tracheotomy
Contralateral total occlusion of the carotid artery
Tandem lesions (e.g., internal carotid artery stenosis at its origin and at the siphon)

Table 533: Medical high-risk population for surgery-

Congestive heart failure (New York Heart Association classification III/IV)
Unstable angina (Canadian Cardiovascular Society classification III/IV)
Pre-coronary artery bypass graft or valve-replacement procedure
Chronic obstructive pulinonarj disease :forced etpirarorv volume <30%)
Left ventricular ejection fraction <30%
Age older than 79 years
Recent myocardial infarction
Two or more coronary arteries with more than 70% stenosis

Table 53.4: Exclusion criteria for carotid artery stenting

Patients with bleeding disofdeis that preclude antiplatelet medication
Allergy to antiplatelet medication
Positive blood cultures/sepsis
[riiiiiimotompromised stare
Recent history of intracranial hemorrhage
Acute large middle cerebral artery stroke (<4-6-week-old infatct) fresh clot within the stenosis

6.0%, respectively (Chimowitz et al. 1995). The stroke rates in patients with carotid siphon or MCA stenosis who were medically treated were 8% and 10% (EC/IC Bypass Study Group 1985; Bogousslavsky et al. 1986). This indicates the need for more effective primary treatment of intracranial atherosclerosis. In the initial WASID study that recruited 151 patients, over a follow-up period of less than 2 years, the rates of stroke were 10.4 per 100 patient-years for those taking aspirin and 3.6 per 100 patient-years for those taking warfarin (Chimowitz et al. 1995). The National Institutes of Health is currently funding a larger study with more than 800 patients.

Extracranial-intracranial (EC-IC) bypass surgery that uses the superficial temporal artery to MCA anastomosis was once thought to offer an alternative treatment for patients with intracranial atherosclerosis. However, the EC/IC Bypass Study revealed that surgery did not reduce the risk of stroke compared with medical therapy (aspirin) (EC/IC Bypass Study Group 1985).

Atherosclerosis is the most common cause of intracranial arterial stenoses. Other etiologies of intracranial stenoses and occlusions include arteritis, radiation changes, drug abuse (methamphetamine and cocaine), vasospasm following subarachnoid hemorrhage (SAH), arterial dissection, sickle cell disease, neurofibromatosis, Menkes' kinky hair syndrome, idiopathic progressive arteriopathy of childhood, and metabolic disorders (e.g., homocystinuria). High-grade stenosis or occlusion of the supraclinoid ICA and Ml and Al segments may result in a pseudoangiomarous angiographic appearance of multiple lenticulostriate, thalamoperforating, choroidal, and leptomeningeal collateral vessels providing collateral flow to M2 and A2 branches. The term *moyatnaya* (Japanese for *puff of smoke)* syndrome is applied to this angiographic pattern.

PTA for intracranial stenosis was first attempted in the early 1980s (Sundt et al. 1980) but was later abandoned because of complications that included dissection, recoil, vasospasm, platelet aggregation, and acute occlusion. These high rates of morbidity and mortality continued until the mid-1990s (Higashida et al. 1993; Takis et al. 1997). Stenting and angioplasty have been limited by stroke from distal embolization, arterial dissection, arterial rupture (Purdy et al. 1990; Clark et al. 1995; Al-Mubarak et al. 1998), and acute vessel occlusion secondary to platelet aggregation (Clark et al. 1995; Takis et al. 1997).

Analogous to the development in occlusive disease of the extracranial carotid artery, primary stenting may replace angioplasty for the treatment of intracranial arterial stenosis. The downfall of angioplasty has been the lack of appropriate devices (Mori et al. 2000}. Recent advances in biotechnology, imaging, coagulativc and platelet pharmacotherapy, and catheter technology have addressed previous limitations of treating intracranial stenosis. Many cases of successful angioplasty have been reported (Honda et al. 1994; Clark et al. 1995; Connors and Wojak 1999; Marks ct al. 1999}.

Low-profile, more flexible, and highly trackable stents are capable of reaching and treating small distal tortuous arterial segments (Clark et al. 1995; Feldman et al. 1996; Callahan and Berger 1997; Al-Mubarak et al. 1998; Kellogg et al. 1998; Horowitz et al. 1999; Lanzino et al, 1999; Malek et al. 1999; Morris et al. 1999; Mori et al. 2000; Phatouros et al. 2000; Koenigsberg et al. 2000; Gomez and Orr 2001; Lylyk et al. 2002). Results have suggested its safety and efficacy.

We have our own experience in 30 patients with intracranial stenting (N = 25) and angioplasty (N = 5). The procedure-related major and minor complications were 6%, with no deaths (Wakhloo et al. 2003). Out of 13 patients studied angiographically approximately 12 months after the procedure, we have seen in-stent stenosis in one patient only.

Indications. Patients who are selected for intracranial stenting and angioplasty are generally refractory to optimal medical management. Inclusion criteria are as follows:

- Patients with greater than 50% stenosis of a major intracranial vessel (minimum vessel diameter of 2.5 mm)
- Previous stroke
- TIA
- Neurological symptoms referable to the target lesion
- High-grade stenosis or total occlusion of another major artery
- Presence of symptoms during the 6 months before treatment
- Need of vascular reconstruction
- Acute vessel occlusion or dissection after PTA

Common exclusion criteria are as follows;

- Severe neurological deficit from stroke
- Chronic total occlusion
- History of intracranial hemorrhage, hemorrhagic stroke, major stroke, or any stroke with mass effect within 6 weeks of procedure

The FDA has not approved any of the existing stents for use in the intracranial vascular system. Several stents are being investigated in feasibility studies for the treatment of intracranial aneurysms and intracranial atherosclerotic occlusive disease.

The technical success with intracranial stent ing/angioplasty is high. Connors and Wojak (1999) reported greater than 90% successful revascularization with PTA. The restenosis rate at 6 months was less than 10% in 44 patients and approximately 30% after 24-36 months. The complication rate of dissection, stroke, TIA, and other like conditions was between 10% and 15% (Connors and Wojak 1999).

In another scries of 10 patients with 12 intracranial stenotic lesions, the use of flexible balloon-expandable

coronary stents was attempted. Ten lesions in eight patients were treated; navigation difficulties prevented treatment of the other two. The mean pretreatment stenosis was 80% and decreased to 7% immediately after stenting. Three months later, the average stenosis was 19%. There were no reports of TIA, stroke, or orher morbidity or mortality during the mean follow-up period of 11 months (Mori et al. 2000).

In a series of patients with symptomatic intracranial stenosis or dissection, I.ylyk ct al. {2002) stented 34 lesions with a mean stenosis of 75%. The average stenosis was 30% after treatment. The peri procedural morbidity was 12%, and one patient died from hemorrhagic transformation of the stroke after reperfusion (Lylyk et al. 2002).

In summary, intracranial stenting provides a basis for treating the diseased arterial segment through stabilization of the local flow dynamics and biomechanics of the vascular wall. It serves as a matrix for new endothelial growth. Current medical treatment of atherosclerotic disease might prevent TIA or stroke but does not have significant reparative capability for the diseased vascular segments (Figure 53.3).

Further refinement of intracranial stents may be drug-eluting stents, covered stents, and stents with a lower profile and higher flexibility. Currently used neurostents are MRI compatible; therefore iteming docs not preclude an MRI investigation of the brain or even possibly an intraluminal evaluation of the stented arterial segment. The obliteration of perforators is a commonly perceived limitation of intracranial stenting. However, the fate of the "jailed" side branches depends on the fraction of the ostium surface area that is covered by the stent struts. In canine and rabbit models, these branches remain patent if less than 50% of the ostial diameter is covered by the stent (Wakhloo et al. 1995; Masuo et al. 2002). Recently, a report on a wide-necked persistent trigeminal artery aneurysm treated with stent-assisted coiling, wherein the trigeminal artery was "jailed," showed that the trigeminal

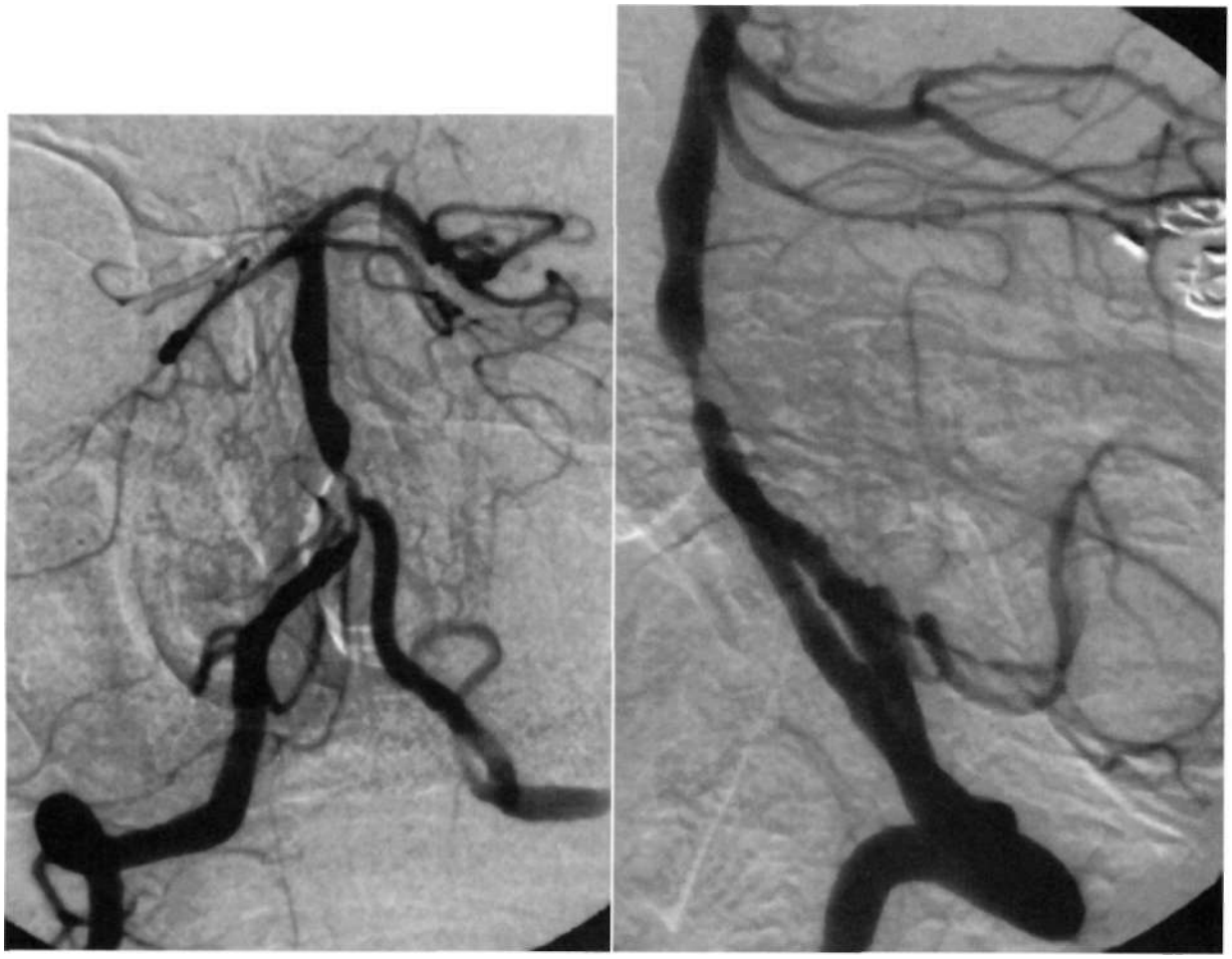

FIGURE 53.3 A 68-year-old man with dysarthria, diplopia, and nausea refractory to maximal medical therapy with Coumadin, Plavix, and aspirin. (A, B) Angiograms in the anteroposterior and lateral projections of the posterior circulation show vertebrobasilar stenosis. The plaque extends from both distal vertebral arteries to the mid basilar trunk. *Continued*

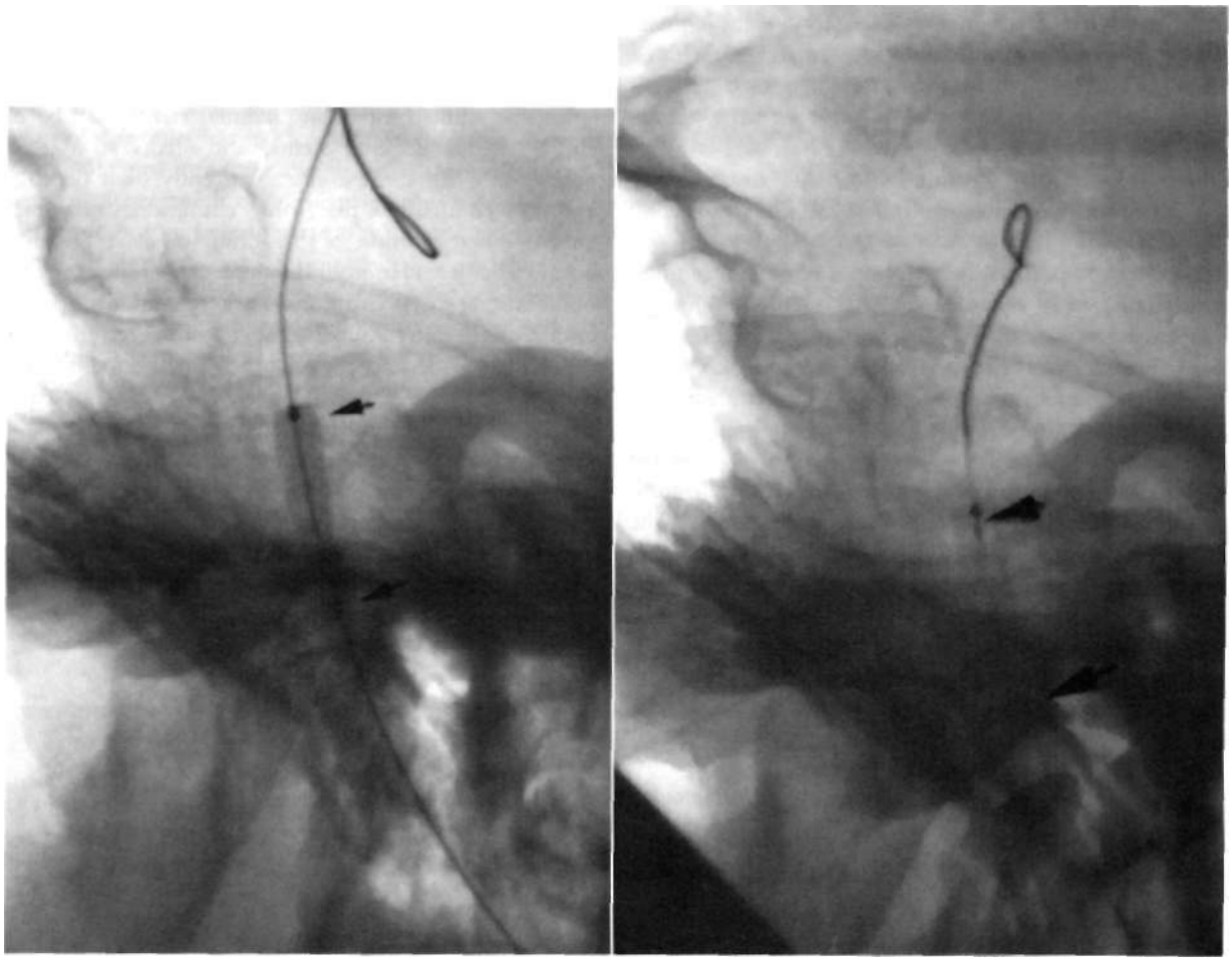

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FIGURE 53.3, cont'd. (C, Dj Deployment of a balloon-expandable stent (lateral view, *arrows).*

Continued

artery remained patent after 2 years, with no evidence of embolic stroke in its vascular distribution (Mohammed, Sandhu, and Wakhloo. 2002). Moreover, there have been multiple cases of the endovascular treatment of basilar trunk aneurysms and stenoses using stents {Horowitz et al. 1999; Lanzino et al. 1999) with favorable outcomes.

Acute Treatment

The development of several treatment options for acute stroke has changed the historical perception that stroke was untreatablc into the realization that stroke is a medical emergency with potential treatments. The time-sensitive window of opportunity for the treatment of stroke is due to the characteristics of the ischemic penumbra. Neuronal function is affected in two stages during ischemia. Neuronal electrical function is lost when the blood flow falls below a critical threshold of approximately 20 ml. of blood per 100 g of brain tissue per minute (normal = 50 mL of blood per 100 g of brain tissue per minute). At this level, brain tissue is thought to be revivablc, with the potential to reverse ischemic damage. However, irreversible damage occurs when blood flow falls below 10 mL of blood per 100 g of brain tissue per minute. Inefficient anaerobic metabolism of glucose commences, which rapidly leads to lactic acidosis and failure of the normal energy-dependent cellular ion homeostasis. Potassium leaves the cell, and sodium and water enter the cell and lead to cytotoxic edema. Calcium also entets the cell and sets a cascade of molecular events into motion that eventually leads to neuronal death, hence the urgency to treat the patient with acute stroke.

The treatment goals of acute thromboembolic stroke are to diagnose early, initiate rapid thrombolysis and treatment, restore normal cerebral blood flow (CBF), prevent iatrogenic hemorrhagic events, and thus to preserve human life and function. We discuss neurointerventional procedures for acute stroke that consist of IA administration of thrombolytics, mechanical thrombectomy, hypothermic devices, and future potential therapies.

Thrombolysis

Thrombolytic therapy has been proposed as a potential stroke therapy for many years. The first randomised trial was conducted in 1963 but was inconclusive.

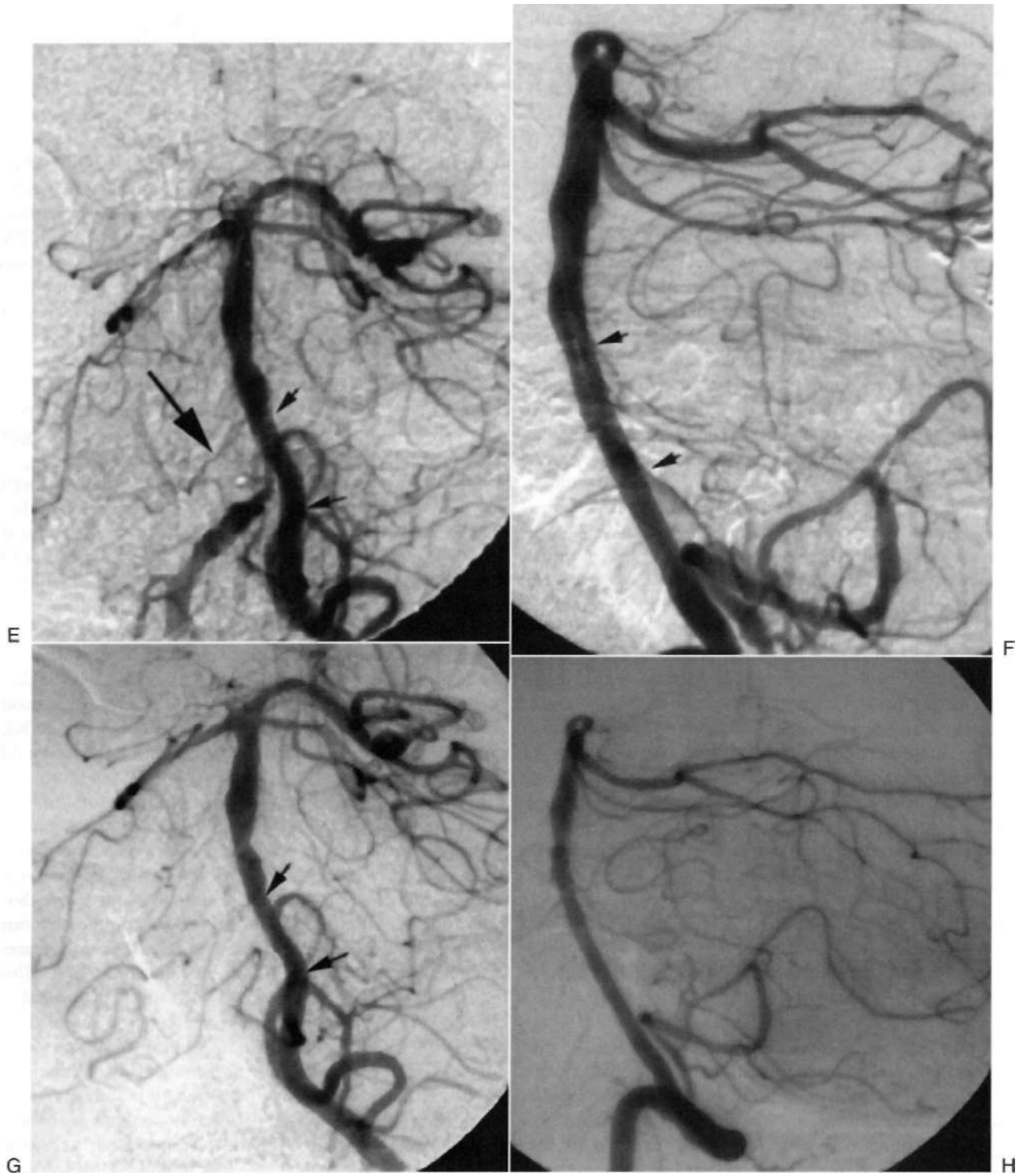

FIGURE 53.3, cont'd. (E, F) Control angiography after stent placement reveals improved flow of contrast in the left vertebral artery and basilar arteries. Note that the right anterior inferior cerebellar artery *{arrow)* remains parent after being "jailed" by the struts of the stent. The right distal vertebtal artery was not treated. (G, H) No evidence of in-stent stenosis seen on the 14-monrh follow-up angiography.

Six randomized studies were conducted from then until 1992 but were again inconclusive because of small numbers of patients, wide range of symptoms, and diversity of medications used (tissue plasminogen activator [t-PA], urokinase, streptokinase, fibrinolysin). In 1993, the PDA approved the use of IV t-PA, which is currently the only FDA approved therapy for stroke. Zcumer, Hacke, and Ringelstcin (1983) first proposed IA thrombolysis in 1983.

Neuroprotection. Hyperacute treatment has mainly focused on thrombolysis. However, neuroprotective agents have been shown to be effective in animal models. Agents considered include calcium-channel antagonists, N-methyl-D-aspartate (NMDA) antagonists, AMPA antagonists, y-aminobutyric agonists, lubeluzole, statins, antibodies to adhesion molecules, inhibitors of cytokines, and free radical scavengers (Fisher and Schacbitz 2000). However, they have not been shown to be effective in clinical trials. These trials have had problems of insufficient statistical power, excessive time delay in starting therapy (>2 hours}, inadequate dosing, and poor patient selection. Unfortunately, animal models have not correlated well with clinical realities, and neuroprotective agents have not been effective because of the very limited time window to block the calcium influx cascade. Nevertheless, promise remains for neuroprotection. Citicoline is a choline precursor that forms phosphatidylcholine, an important neuronal membrane lipid. Meta-analyses have revealed its potential use in small human trials. (Saver and Wiltcrdink 2002; Warach, Harnett, and the Citicoline 010 and 018 Investigators 2002). Another study has determined the feasibility of emergency paramedics administering magnesium in the field to combat delay in using neuroprotection (Saver et al. 2002). Hypothermia can also be applied as a form of neuroprotection, and many new devices have been developed specifically for this purpose.

Intravenous and Intra-Arterial Thrombolysis. A brief overview of the basic concepts of thrombolysis should precede the discussion of thrombolytic therapy. A balance of the coagulation and fibrinolytic systems is maintained through several mechanisms that may be altered in the treatment of acute stroke. Thrombus formation and thrombolysis are on opposite ends of the spectrum. This homeostasis maintains a balance in between thrombosis and hemorrhage. Fibrin and plasmin play key roles in this balance. Thrombin is also important to link platelet aggregation and coagulation and intrinsic and extrinsic pathways. It is sensitive to outside factors such as flow and is used in feedback control of fibrinolysis. Fibrinogen is cleaved into fibrin in the presence of thrombin.

Plasmin is key to thrombus dissolution. It acts on fibrinogen and fibrin in plasma, works on reactive surfaces (thrombi and cells), and mediates the proteolytic cleavage of matrix ligands. Plasminogen is converted into plasmin through the presence of t-PA, which is an endogenous plasminogen activator that is secreted from endothelium and other cells. It has fibrin and thrombus specificity'. Recombinant t-PA (rt-PA) is used as an exogenous source that has increased clot specificity and involves different mechanisms of action. It also affects platelet function and aggregation. There are novel forms of rt-PA with genetic-alterations to its half-life, specificity, and lower binding to plasminogen activator inhibitors. Genetically engineered rt-PA has advanced the treatment of stroke with pharma-cotherapy. Genetically altered derivatives of native t-PA include tenecteplase, which has three amino acid substitutions that have increased resistance to plasminogen activator inhibitor-1 (PAI-1). Tenecteplase has increased fibrin binding and decreased plasma clearance. It binds to fibrin and converts plasminogen to plasmin (Keyt et al. 1994). Other promising agents include *Dcsmodus rotundus* salivary plasminogen activators (DSPAs) from the vampire bat saliva that is selective for fibrin-bound plasminogen (Figure 53.4).

Platelet glycoprotein Ilb/IIla receptor blockers have been used in acute myocardial infarction. Preliminary studies have revealed a potential to increase the 3-hour treatment window in acute stroke using Ilb/IIla receptor blockers to block platelet aggregation (Bogousslavsky et al. 2001). Twenty-four patients were treated with combined IV lib/Ilia receptor blocker (cptifibatide) and IA t-PA. Patients were compared with historical controls treated with IA t-PA alone. The combined treatment patients had higher recanalization rates (58% vs. 31%) and better good outcome rates (Rankin Scale score 0-2, 38% vs. 27%), with no increase in hemorrhagic complications (McDonald et al. 2002).

The FDA approved thrombolytic treatment for stroke in 1996 after the IV t-PA trial sponsored by the National Institutes for Neurological Disorders and Stroke (NINDS) was published in 1995. The NINDS trial using IV t-PA was a multicenter, randomized, double-blinded, placebo-controlled study of 624 patients. Patients enrolled had an acute ischemic stroke, with clearly defined time of onset and measurable deficit on National Institutes of Health Stroke Scale (NIHSS) (Table 53.5). All patients had a baseline CT with no evidence of intracerebral hemorrhage (ICH). IV t-PA was given within 3 hours at a dose of 0.9 mg/kg. Treated patients were 30% more likely to have little or no neurological disability (3, 6, and 12 months). Treated patients were less likely to be severely disabled or to have died when compared with the placebo group at 1-ycar follow-up.

The Prolyse in Acute Cerebral Thromboembolism (PROACT I) was a double-blinded, placebo-controlled, centralized, randomized trial of IA thrombolysis in patients within 6 hours of onset of symptoms suggestive of MCA occlusion. It was the first trial to compare the safety, recanalization frequency, and clinical efficacy of direct IA infusion of recombinant prourokinase (rpro-UK) with placebo (del Zoppo et al. 1998). Forty patients were treated

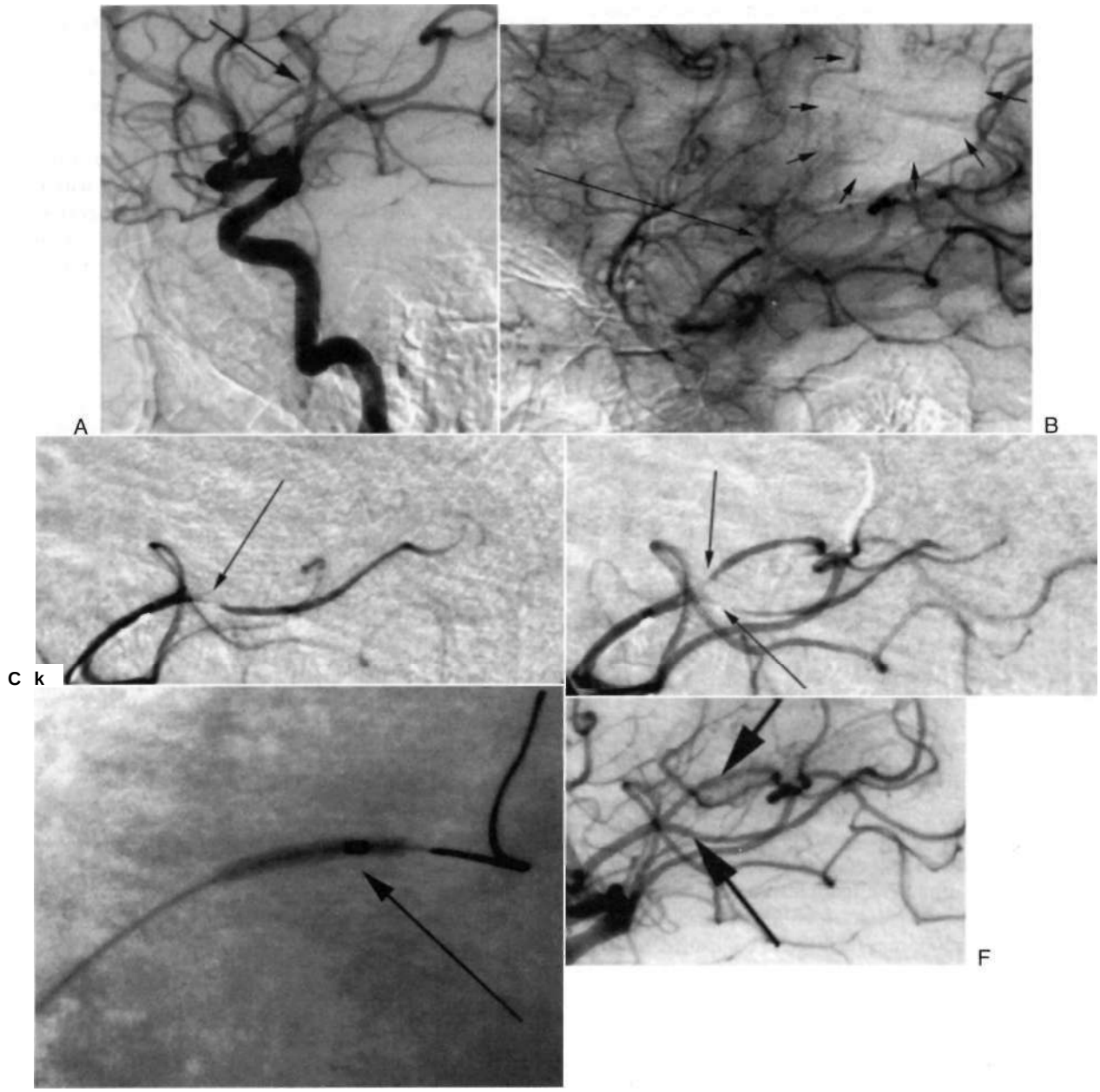

FIGURE 53.4 (A) An acute left angular artery thromboembolic occlusion *{arrow)* in a patient with a National Institutes of Health (NIH) Stroke Scale score of 12 was treated with intra-artcrial tissue plasminogen activator (t-PA). (B) Late arterial phase shows a large area of hypoperfusion *{arrows).* (C, D) Partial recanalization of superior and inferior divisions after a bolus of inrra-arterial local 5 mg of t-PA and an infusion of 10 mg over 1 hour. (E) Mechanical revascularization with a 1.5-mm balloon catheter of upper and lower branches. (F) Immediate recanalization of the entire angular artery occurred after percutaneous transluminal angioplasty. The patient improved neurologically within a few hours and had an NIH Stroke Scale score of less than 5.

with rpro-UK (« = 26) or placebo *(n* = 14) at a mean of *5.5* hours after the onset of symptoms. Recanalization was significantly associated with rpro-UK. Hemorrhagic transformation that caused neurological deterioration was no different between the two groups at 24 hours and 90 days.

The PROACT II study was undertaken to determine the clinical efficacy and safety of IA rpro-UK therapy in patients with acute stroke less than 6 hours in duration caused by MCA occlusion. PROACT II was a multiccntcr, randomized, and controlled, open-label clinical trial with blinded follow-up. Patients received either *9* mg of IA rpro-UK with heparin *{n* = 121) or heparin alone (w = 59). In the primary outcome analysis, 40% of treated patients and 25% of control patients had a modified Rankin Scale score of 2 or less at 90 days *[p* = .04), The pro-UK group had a mortality rate of 25%, and the control group had a mortality rate of 27%. The recanalization rate in the

Table S3.5: National Institutes of Health Stroke Stale. Points are accumulated for seventy of impairment. Higher scores correlate with more severe sttoke

Neurological examination	*Score*
1A. Level of consciousness (alett to coma)	0-3
IB. Month/age (both right to none tight)	0-2
1C. Commands eyes open/closed	0-2
2. Best gaze	0-2
3. Visual	0-3
4. Facial palsy	0-3
.5/6. Best motor arm/leg (right/left)	0-4
7. Limb ataxia	0-2
8. Sensory	0-2
9. Best language	0-3
10. Dysarthria	0-2
11. Neglect	0-2
Scoring	
Normal/neat-normal examination	0-1
Minot stroke	1-4
Moderate stroke	5-15
Moderate/severe stroke	15-20
Severe stroke	>20

pro-UK group was *66%* and only 18% in the control group *(p* < 0.001). Intracranial hemorrhage at 24 hours was observed in 10% of the pro-UK group and only 2% of the control patients *(/>* = .06). The investigators concluded that IA rpro-UK significantly improved clinical outcomes at 90 days, despite increased frequency of early symptomatic intracranial hemorrhage (Furlan et al. 1999).

The Emergency Managemenr of Stroke (EMS) Bridging Trial was a pilot study that suggested combined IV and IA therapies are feasible and safe and lead to higher rates of recanalization. The feasibility, safety, and efficacy of combined IV rt-PA and IA rt-PA were evaluated in this multicenter, randomized, placebo-controlled, double-blinded trial (Lcwandowski et al. 1999}. Thirty-five patients were enrolled, with eighteen in the IV/IA group and seventeen in the placebo/IA group. Outcomes were measured by the Barthel Index, NIHSS, and modified Rankin Scale. There were no significant differences in outcomes between the two groups at 7 days, 10 days, and 3 months. Recanalization was better in the IV/IA group with statistical significance. It was determined that IV/IA rt-PA was feasible to use and had better recanalization rates. However, the combined therapy did not reveal improved clinical outcomes. There was not a statistically significant difference in the rate of symptomatic ICH between the two groups.

In a study to determine the safety and efficacy of local IA thrombolysis with urokinase, Arnold et al. (2002) followed 100 consecutive patients with stroke caused by MCA occlusion. They found that the median NIHSS was 14 on admission. Excellent or good outcomes, a modified Rankin Scale score of 2 or less, were found in 59% of patients with an Ml or M2 occlusion and 95% of patients with an M3 or M4 occlusion. Fifty-six percent of patients had a recanalization score (Thrombolysis in Myocardial Infarction [TIMI1 score) of 2, and twenty percent had a score of 3 (complete recanalization). They concluded that local IA thrombolysis with urokinase can be safe and efficacious (Arnold et al. 2002).

As the randomized NINDS trial showed the beneficial effect of IV given t-PA in patients who present within the 3-hour time window for treatment, in most centers IA thrombolysis is frequently reserved for patients presenting with symptoms 3-6 hours after the onset of the ictus. For the IA use of thrombolytics, a superselectivc positioning of a microcathetcr adjacent to the clot is recommended. The endovascular approach allows fibrinolytic agents to be infused ptoximally, disrally, and within clots in main cerebral arteries. A higher local concentration of fibrinolytic agents is achieved, thus reducing systemic exposure to thrombolytics. In addition, a mechanical disruption of the clot with the microwirc and catheter can be accomplished. The collateral blood supply and the vascular system distal to the occluded atca can be visualized simultaneously, and a sense for the degree of recanalization gained (Saver 2001). IA thrombolysis has provided better early recanalization rates (60-80%) than IV therapy (20-60%) (del Zoppo 1997; Jahan et al. 1999; Saver 2001). Recanalization is graded according to the TIMI grade (T1M1 Study Group 1985). Grade 0 no recanalization; grade 1 minimal recanalization; grade 2 partial recanalization; and grade 3 complete recanalization. Modified Rankin Scale scores, Barthel indices, and NIHSS may all be used to assess patient outcomes over follow-up periods. Inclusion and exclusion criteria for IA thrombolysis are listed in Tables 53.6 and 53.7.

Conventional IV or IA chemical thrombolysis is time consuming, with a significant risk of hemorrhagic transformation of ischemic strokes.

Mechanical thrombolysis may afford more rapid and complete relief of cerebral ischemia, with decreased hemorrhagic transformation. Devices for revascularization in acute stroke have the potential risks of producing showers of distal emboli, vessel perforation, and damage to vessel walls with secondary platelet aggregation. Other strategies that may play a larger role in the future include various devices to remove clots, such as laser energy,

Table 53.6: Acute stroke intra-arterial thrombolysis inclusion criteria

Clinical diagnosis of ischemic stroke
Computed tomographic exclusion of hemorrhagic stroke
Four-vessel angiography that reveals vessel occlusion that correlates to clinical stroke
Significant long-term neurological deficit can be expected without treatment
lime from symptoms to intervention is less than 6 hours
No contraindications {laboratory findings) against the use of thrombolytics

Tabic 53.7: Acute stroke mtra-arterial thrombolysis exclusion criteria

Mild symptoms (deficits that are quickly resolving)
Sustained hypertension of > 180/100 mm Hg
Hemorrhage on computed tomography or magnetic resonance imaging
Known vascular malformation or tumor
Recent history of stroke, trauma, or surgery

ultrasound, photo acoustic laser energy, rheolytic thrombectomy, clot retticvers (including snarclikc devices, excision and aspiration), and suction thrombectomy.

Cathetet-hascd methodologies include hypothermia for neuroprotection, with heat exchangers placed in the inferior vena cava and systems that provide controlled induction, maintenance, and reversal of hypothermia. Other devices provide increased cerebral perfusion with intra-aortic balloons, hyperoxygenated perfusion using fluorocarbon and othct major oxygen carriers. Functional recovery of stroke includes rehabilitation with physical, occupational, and speech therapy. Stem cell research is ongoing with human bone matrow stem cell gtafting and neuronal growth hormones to replace neuronal loss.

It is apparent the histotical perspective on the treatment of acute sttoke has dramatically changed over the last decade and will continue to expand with neuroendovascular technologies. National analysis was reported by Nilasena and coworkers (Nilasena et al. 2002) from the National Stroke Project of the U.S. Centers for Medicare and Medicaid Service. They analyzed 14,295 inpatient Medicare medical records from a national sample of patients with acute stroke who were treated between April 1998 and March 1999. Fibrinolytic therapy was employed in only 1,7% of patients. In a study of Cleveland hospitals, only 1.8% of patients received IV t-PA (Kat/an et al. 2000). Furthermore, the 5-year recurrence rate for stroke has been reported anywhere from 24-42% (Sacco et al. 1982, 1994; Petty et al. 1998; Stapf and Mohr 2002). The etiology of the stroke must be addressed to minimize the risk of an additional stroke.

Vasospasm

Vasospasm associated with SAH accounts for major morbidity and mortality in approximately 20% of patients who initially survive an aneurysm rupture. It is considered one of the most preventable types of ischemic brain injury by prevention care and newer interventional techniques. It typically presents within 3-14 days after the initial hemorrhage and is usually greatest in severity at 7 days posthemorrhage. It can result in extensive cerebral and brainstem infarction and death. The etiology of cetebral vasospasm is directly related to the rupture of an aneurysm and hemosiderin products. However, a cascade of events results in a decrease in CBF. The events are likely related to the disturbed balance between vasoconstriction (mediated by endorhclin-1) and vasodilatation (mediated by NO), but have not been clearly elucidated. Compensatory mechanisms of autoregulation, collateral flow, and increased oxygen extraction eventually become exhausted and ischemic neurological damage ensues. The potential end result of prolonged vasospasm is cerebral infarction. Smooth muscle cells in the arterial wall undergo sustained contraction between 4 and 14 days (peak 7 days) after the initial hemorrhagic event. Subsequently, collagen is deposited in the adventiria and there is thickening of the intima, which may last for several weeks (Chan et al. 1995). Cerebral vasospasm has been reported to occur in 60-80% of all patients with SAH. Almost 30% of patients are thought to have symptomatic manifestations (Heros, Zervas, and Varsos 1983; Kassell et al. 1985, 1990; Srinivasan et al. 2002).

Patients with vasospasm may present with symptoms, and transcranial Doppler studies may reliably determine vasospasm at the patient's bedside in a noninvasive fashion, Conventional angiography is the gold standard for determining vasospasm. Several other studies have been proposed to evaluate regional CBF that include single-photon emission CT (SPECT), positron emission tomography (PET), xenon CT scan, and radioactive xenon clearance.

Prevention of vasospasm is attempted through maintaining normovolemia, normothermia, and normal oxygenarion. Volume contraction can predispose patients to vasospasm; hence, careful monitoring of fluid status is paramount.

Prophylactically, an oral calcium-channel blocker, nimodipiue, is given for 21 days following SAH to prevent vasospasm (Allen et al. 1983; Pickard et al. 1989). Other preventive modalities being investigated include thrombolytic therapy via intracisternal injections, aspiration and irrigation at time of craniotomy, intraoperative sodium chloride lavage, and early ventriculostomy to control intracranial pressure (Newton, Krawczyk, and Lavine 2002).

When patients become symptomatic and vasospasm is suspected as the culprit, hypertensive, hypervolemic, and /jemodilution (triple H) therapy is most commonly administered, However, symptoms may coincide with rebleeding or hemorrhage and should be distinguished with head CT. The role of endovascular approaches to the treatment of vasospasm becomes foremost in the case of failure of conventional therapies. In patients at risk for pulmonary edema, myocardial infarction, or other medical risk factors preventing triple-H therapy, endovascular techniques including mechanical and/or pharmacological treatment options should be initiated.

Mechanical Therapies. Balloon angioplasty has been shown to be effective in the treatment of vasospasm secondary to SAH. Zubkov, Nikiforov, and Shustin

(1984) first described this technique in 1984, As with other treatment options in the endovascular field, advances in balloon, catheter, microcatheter, and imaging technologies have expanded the application, efficacy, and safety of this technique over the course of the last several years **(Figure** 53.5).

Before treatment, a CT scan should be obtained to rule out hemorrhage or large infarct that could potentially be enhanced through repcrfusion. Intracranial pressure and arterial blood pressure are monitored throughout the procedure. Balloon angioplasty is performed with a low-pressure (2 atm), soft, compliant silicon microballoon. Angioplasty has been shown to have long-lasting effects, possibly due to stretched and torn collagen fibers (Yamamoro, Smith, and Klag 1992), rupture of the internal elastic lamina, and stretched smooth muscle fibers (Chan et al. 1995; Srinivasan et al. 2002). Many investigators have reported improved clinical outcomes after mechanical angioplasty for vasospasm (Higashida et al. 1989; Newell et al. 1989; Eskridge et al. 1990; McDougall et al. 1997; Maybcrg 1998). Transluminal balloon angioplasty has been shown to improve neurological outcomes in 60-70% of treated patients (Eskridge et al. 1998; Rosenwasser et al. 1999). Furthermore, complete vessel revascularization is

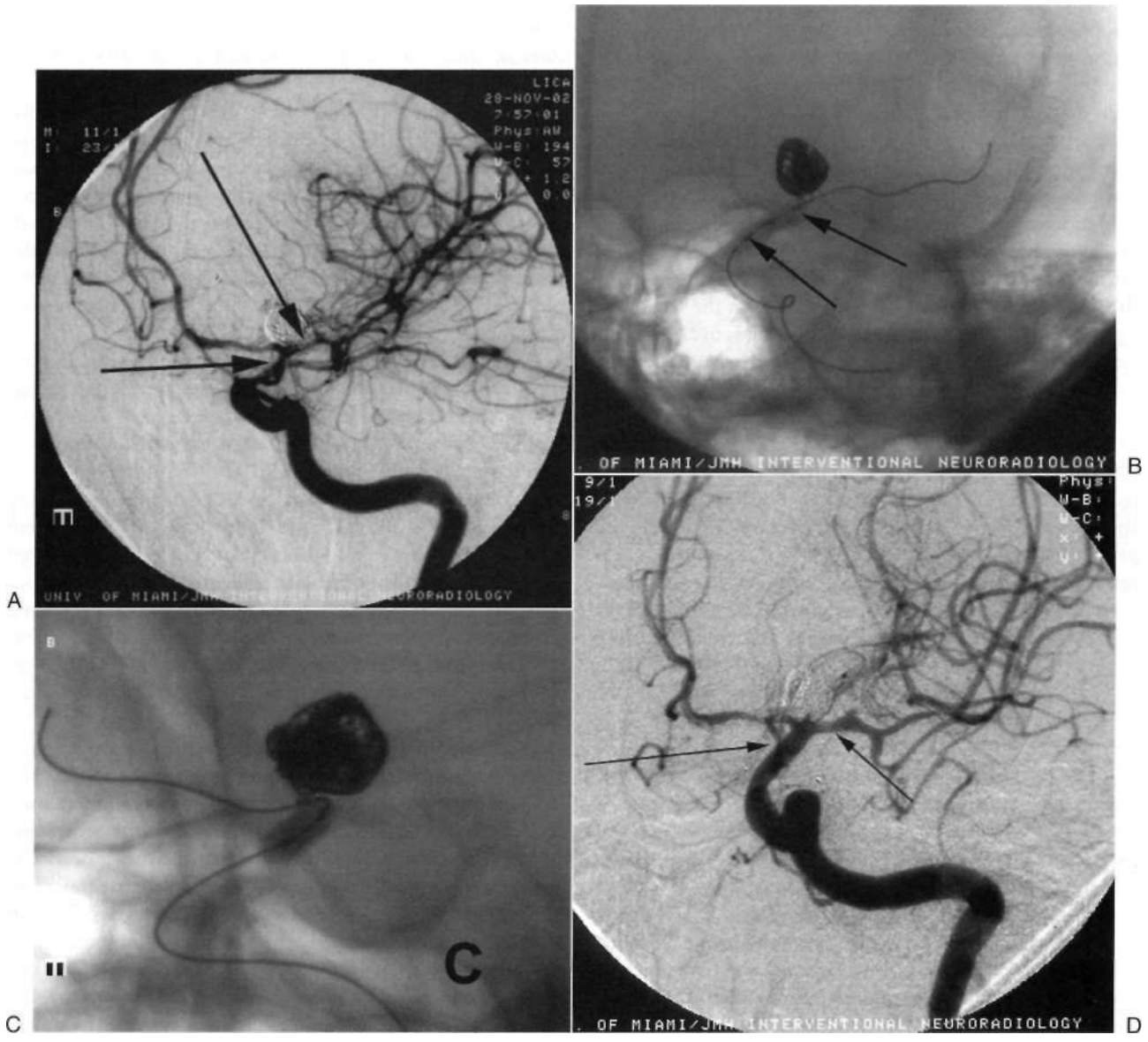

FIGURE 53.5 (A) Right hemiparcsis and aphasia associated with moderate to severe vasospasm of the CI and C2 segments of the internal carotid artery (ICA), and the Ml segment of the middle cerebral artery (MCA), and Al segment of the anterior ccrchral artery after coiling of a ruptured ICA terminus aneurysm *{arrows). {Arrows* in [A| reveal the extent of spasm. Note the decreased caliber of the ICA.) (B, C) Balloon angioplasty of the distal ICA and the Ml segment *(arrows).* (D) Improved distal perfusion after angioplasty of the ICA and Ml *{arrows).*

seen in virtually all cases and imaging studies, such as SPEC! and transcranial Doppler, correlate with clinical improvement (Mayberg 1998).

Currently, however, angioplasty can address only larger proximal vessels (>1.5 mm in diameter). Improved microcirculation is seen due to removal of the proximal increased impedance, with subsequent increased perfusion pressure. The potential complications of angioplasty include vessel rupture, dissection, or occlusion, as well as ICH, which is extremely rare in experienced centers and if appropriate material is used (American Society of Interventional and Therapeutic Neuroradiology 2001; Newton et al. 2002). Hypetplasia with subsequent narrowing of the artery is not seen.

Vasospasm of the smallet caliber distal vessels is not amenable to angioplasty. However, the most commonly used pharmacotherapy has been the use of IA papaverine. Papaverine is a phosphodiesterase inhibitot that causes smooth muscle telation possibly through decreasing the level of intracellular calcium (Mathis, Jensen, and Dion 1997; Milburn et al. 1998; Srinivasan et al. 2002).

Superselective injections of 100-300 mg of papaverine (3% solution) ovet 30-60 minutes may be delivered close to the target vessel. Its effect has been observed only transiently, which requires repeated injections. Infusions should be avoided below the ophthalmic artery to avoid pupillary dilatation, which may be misconsttued as evidence of neurological decompensation. Other side effects of papaverine include seizure, respiratory depression (if the infusion is given below the posterior inferior cerebellar artery), and increased intracranial pressure. Therefore intracranial pressure and arterial blood pressure should be monitored during its administration.

HEMORRHAGIC STROKE

Aneurysms

Intracranial Aneurysms

Studies have shown overall prevalence rates of intracranial aneurysms that vaty from 0.2-9.9%. The mean of 5% would correlate to nearly 15,000,000 Americans with an intracranial aneurysm. Approximately 10 of every 100,000 aneurysms will rupture per year, which equates to nearly 30,000 cases in the United States per year. The vast majority of aneurysms do not rupture, thereby presenting the need to classify patients into two gtoups: those with ruptured inttacranial aneurysms and those with unruptured intracranial aneurysms. The clinical management of these patient groups is evolving with the advent of ncuro-endovascular therapeutics.

Unruptured Intracranial Aneurysm. Patients with unruptured intracranial aneurysms far outnumber those with ruptured aneurysms. Most patients have a single unruptured aneurysm that is identified incidentally during the workup of conditions such as headache, cerebrovascular ischemic event, cranial nerve deficits, convulsive disorder, ill-defined spells, aneurysm mass effect, subdural hemorrhage or ICH, brain tumor, and neurological degenerative disease. The diagnosis of an unruptuted inttactanial aneurysm is made after suggestive findings on CT (40%) and MRI (37%) (International Study of Unruptured Intracranial Aneurysms Investigators 1998). The various types of imaging modalities and their utility in detecting aneurysms are listed in Table 53.8.

Juvela, Porras, and Poussa (2000) followed the natural history of intracranial aneurysms for an average of nearly 20 years in 142 patients with 181 unruptured aneurysms. The average annual incidence rate of ruptute was 1.3%, and the relative risk of rupture increased with the size of aneurysms. Smoking, size of aneutysm, and patient age were the most important risk factors for rupture. The International Study of Unruptured Intracranial Aneurysm (LSUIA) investigarots provided the most comprehensive study on the natural history of unruptured aneurysms. They reported a retrospective study of 1449 patients with 1937 aneurysms. Patients without a history of SAH (group 1, « = 727) were separated from those with a histoty of SAH from a separate aneurysm (group 2, *n* — 722), In group 1, the study revealed a cumulative tate of rupture of 0.05% per year for aneurysms that were less than 10 mm in diameter at the time of diagnosis. The tate was 20 times higher for aneurysms greater than 10 mm in diameter {nearly 1% per year). The rate of rupture in group 1 was 6% for the first year for giant aneurysms (>25 mm). Size and location of aneurysms were predictive factots of future rupture in group 1. Posterior circulation aneurysms were more likely to rupture independent of size.

Group 2 included patients with a history of SAH who had the ruptured aneurysm properly treated and a second nonruptured aneurysm. The rupture rate for the untreated

Table S3.8: Diagnostic studies for detection of intracranial aneurysms

CT examinations with slice thicknesses of 5-10 mm; however, small aneurysms may not be visible even with IV contrast (Hsiang et al. 1396; Bederson et al. 2000)
CT angiography shows aneurysm sizes as small as 2 mm with sensitivity of 77% and specificity of 87%
CT angiography for size >3 mm has specificity of 97% and 100%, respectively (Hope et al. 1996)
MRl/MRA: Good for screening with sensitivity of 69-93%, particularly for aneurysms >3 mm (Korogi et al. 1996)
Intra-arte Ha I angiography: Gold standard, but risks include complication rate of about 5%, neurological event of about 1%, and permanent neurological deficit of about 0.5% (Rinneetal. 1993; Ronkainen et al. 1998)

CT = computed tomography; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging.

aneurysm was 11-fold higher at 0.5% per year for aneurysms less than 10 mm in diameter than for similar aneurysms in patients who had not suffered an SAH. The rupture rate was less than 1% per year for aneurysms greater than 10 mm in diameter in both groups. Surprisingly, the size was not an independent risk factor for group 2 aneurysms. The location of the aneurysm and the age of patients were independent factors for rupture; specifically, basilar tip aneurysms provided a 5.1 relative risk and older age was ,i 1 .3 1 relative risk for rupture. Since the publication of this report, Wiebers et al. (unpublished data) have prospectively studied a larger cohort and the critical aneurysm size has now been redefined as 6 mm. This confirms the earlier observation made by McCormick and Acosta-Rua (1970) that 5-mm aneurysm size seems to be critical for an increased risk of rupture,

Indications for the treatment of unruptured intracranial aneurysms are listed in Table 53.9 (Bederson, Awad, and Wicbcrs 2000, revised by authors).

Surgical Treatment. Surgical outcomes were prospectively studied in the ISUIA report; 972 patients underwent intracranial surgery in group 1, and 198 patients in group 2, The overall morbidity and mortality rate at 1 month for patients in group 1 was 17,5%. At 1 year, the overall rate was 15.7%, with only 15.6% of patients at their baseline neurological status. Furthermore, 3,8% of patients died from surgical-related complications.

Mortality rates of direct surgical treatment of unruptured intracranial aneurysms have been reported as low as 0% and as high as 7%. Morbidity rates have been reported as low as 4% and as high as 15.3%. Unfortunately, various studies have established different criteria for morbidity and even mortality, depending on the time period of follow-up. The ISUIA study has been recognized as the most comprehensive study on this issue (International Study of Unruptured Intracranial Aneurysms Investigators 1998). Specific risk factors for poor surgical outcomes have been grouped into the following categories and subcategories: patient characteristics (age, symptoms, and medical condition), aneurysm characteristics (size, location, and morphology), and other factors (hospital and surgical team experience).

Endovascular Treatment of Unruptured Intracranial Aneurysms. Preliminary results of endovascularly treated unruptured intracranial aneurysms have revealed lower morbidity and mortality rates when compared with surgery. However, the rates of incomplete aneurysm obliteration and re-canalization arc current challenges tin this field. More than 120,000 aneurysms have been treated with the Guglielmi detachable coil (GDC) system. In a case series of 42 unruptured aneurysms that were treated with an endovascular approach, Wanke et al. (2002) found a morbidity rate of 4.8% and a mortality rate of 0%, with a follow-up range of *6-S3* months. Murayama et al. (1999) reported a morbidity rate of 4.3% in 109 treated patients. In a blinded review of patients with aneurysms that were deemed amenable to both coiling and clipping, 68 patients were treated with surgery and 62 were treated with endovascular coil embolization. The rates of complications were 34% in the surgical arm and 8% in the endovascular arm (Johnston et al. 2000). A retrospective study of patients with unruptured intracranial aneurysms in California reported the outcomes of surgically treated patients versus endovascularly treated patients. Adverse outcomes were more common in patients treated with surgery (25%, *n = 1699)* than in those with EVT (10%, *n* = 370). Remarkably, a testimony to improved procedures and materials, the frequency of adverse outcomes declined with statistical significance from 1991 to 1998, whereas the surgical adverse outcomes did not decline. Deaths occurred in 3.5% of surgeries and 0.5% of endovascular treatments (Johnston et al. 2001) (Figure *55.6).*

A cohort study of patients with unruptured intracranial aneurysms from 1994 to 1997 were evaluated and found to have significantly more adverse outcomes with surgery (18.5%, *n* = 2357) versus EVT (10.6%, *n* = 255). Adverse outcomes were defined as death or transfer to a rehabilitation hospital or nursing home at the time of discharge. The results were not altered after adjustments were made for age, sex, race, transfer admissions, emergency room admissions, and year of treatment (Johnston et al, 1999).

In the infancy of endovascular neuroradiology, it was widely believed that only posterior circulation aneurysms were amenable to coiling. It was also thought that aneurysms with mass effect would suffer great effects from the mass of platinum coils. However, the last 10 years have brought exponential growth in the field in terms of biotechnology, materials, and the understanding of fluid flow. A call has been made for a randomized controlled trial for unruptured intracranial aneurysms with surgical

Table 5.1.9: Indications for the treatment and management of unruptured aneurysms

1. Treatment of small intra caver nous internal carotid artery aneurysms generally is not indicated. Treatment of large symptomatic ones should be individualized based on patient age, severity, and progression, in addition to alternatives.
2. Symptomatic intradural aneurysms of all sizes should he-considered for treatment, with large or giant carrying higher risks for surgery.
.). Cdtxisiiiij; aneurysms nf all sizes in patients with subarachnoid hemorrhage from a separate aneurysm warrant treatment. Aneurysms at the basilar tip have high risk of rupture. Patient age, medical condition, and neurological status and relative risks should he considered.
4. Young patients with aneurysms approaching .5-6 mm should receive special consideration. Also, unique characteristics include aneurysms with daughter sacs, hemodynamic features (high-flow impingement zone, for example, internal carotid artery terminus aneurysm); familial considerations deserve special treatment consideration,
5. Asymptomatic aneurysms >5 mm should be strongly considered for treatment.

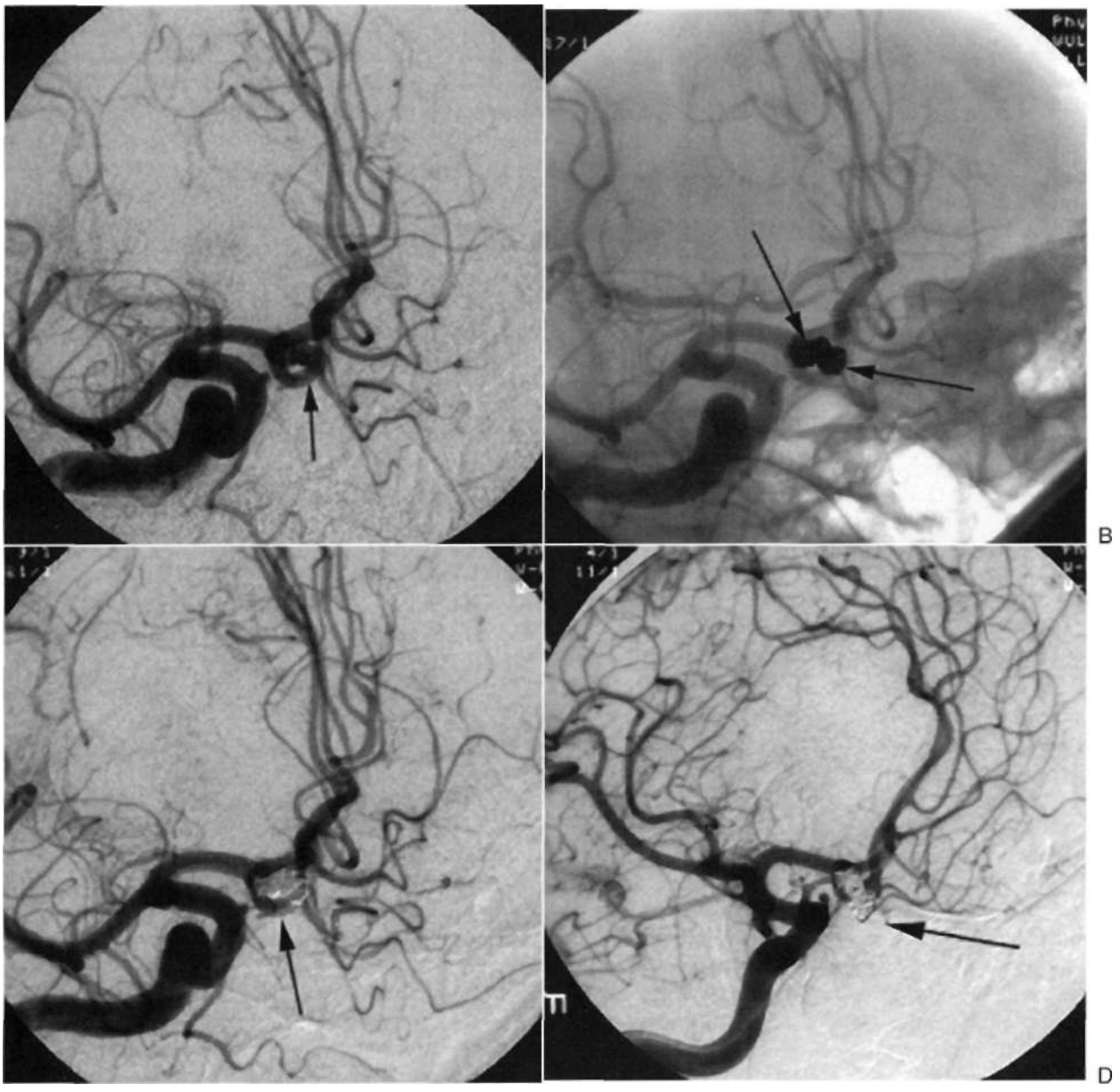

FIGURE 53.6 (A) Twice-ruptured .5-mm bilobed anterior communicating artery aneurysm in a 51 -year-old man who presented with a Hunt and Hess grade of 1. (B, C) Coiling of the aneurysm with complete obliteration *[arrows).* (D) The aneurysm remains completely occluded on 6-month follow-up angiography.

clipping, endovascular coiling, or medical management Oohnston et al. 1999, 2001; Broderick 2000).

The American Society of Interventional and Therapeutic Neuroradiology has, for management purposes, categorized aneurysms as either ruptured or unruptured. This classification can be further expanded to indicate endovascular treatment for therapeutic purposes, including treatment with parent vessel sparing or parent vessel occlusion (Tables 53.10, 53.11, and 53.12). The indications for endovascular treatment of aneurysms follow general guidelines based on aneurysm morphology, medical stability of the patient, and the risks of endovascular procedure versus clipping. The overall goal is to prevent aneurysm rupture or rebleed, or to stabilize or decrease the symptoms of mass effect caused by large or giant aneurysms. Successful outcomes are dependent on the degree of aneurysm exclusion from the overall circulation. Degree of exclusion

Table 53.10: Indications for endovascular treatment in unruptured aneurysm

Poor surgical candidate due to medical risk factors
High surgical clipping risk due to location or size
Failed clipping attempt
Patient/family refusal of open surgery
Multiple aneurysms that would require several craniotomies

Table 53.11: Indications for endovascular treatment with parent vessel sparing in ruptured aneurysm

Poor surgical candidate due to medical risk factors
Poor clinical grade
High surgical clipping risk due ro location or size
Failed clipping attempt
Significant vasospasm in vascular distribution removed from aneurysm location

by coiling will be based on the anatomy of the circulation (access and tortuosity leading to aneurysm), aneurysm morphology (specifically neck size), and collateral circulation. Aneurysms with a small neck (<4 mm) and small dome (<10 mm) have the highest potential success rate.

The onset of new more conforming coils with bioactivity, hydraulic detachment, hydrocoils, balloon and stent assistance, and experience have led to the exponential growth in this field, which has caused a major decrease in the recanali/ation rates to an overall less than 10%. Post-GDC bleeding of large aneurysms has been reported (based on a literature review of 48 studies over 7 years) to occur in 4% of cases and 33% of giant aneurysm cases. Brilstra et al. (1999) found a low permanent complication rate (3.7%) of both ruptured and unruptured aneurysms.

A case-controlled randomized prospective trial is required to determine whether open surgery or endovascular treatment results in better outcomes in unruptured intracranial aneurysms. However, the International Subarachnoid Aneurysm Trial (ISAT) has clearly defined the better clinical outcome to be after endovascular treatment of ruptured cerebral aneurysms at 1 year (Molyneux et al. 2002).

Ruptured Intracranial Aneurysm. The ruptured intracranial aneurysm is one of the most devastating events for patients with hemorrhagic stroke today. Nearly 30,000 Americans suffer annually from ,SAH associated with a ruptured aneurysm. Anywhere between 5% and 15% of all strokes can be attributed to SAH from a ruptured aneurysm. The most staggering statistic is that the 30-day aneurysmal SAH mortality rate is 45%, Half of the survivors will suffer from irreversible brain damage (Graves 1990; AHA 2001) (Figure 53.7).

The ISAT has provided a randomized, controlled trial of surgical clipping versus endovascular coiling of ruptured intracranial aneurysms (Molyneux et al. 2002). The multicenter trial enrolled 2143 patients with aneurysms who were deemed suitable for either treatment modality.

Table 53.12: Indications for endovascular treatment with parent vessel occlusion (ruptured or unruptured)

Fusiform ain'mysm
Pseudoaneurysm secondary to trauma, infection, neoplasm, or dissection
Some large or giant aneurysms

Random assignment included 1070 patients for clipping and 1073 patients for coiling. Most of the aneurysms (>50%) were less than 6 mm in diameter. Most of the aneurysms were located in the ACA (50.5%), followed by the ICA (mostly a posterior communicating artery aneurysm). Only a small number of aneurysms were located in the posterior circulation (2.7%), which is considered the most amenable for endovascular treatment. Most of the patients were in excellent condition before the intervention. Clinical outcomes were assessed based on modified Rankin Scale scores at 2 months and 1 year. Recruitment into the trial was stopped by the steering committee after an interim analysis per protocol revealed survival free of disability that was significantly better with endovascular coiling. In the surgical arm, 31.1% of patients were significantly restricted, partly or fully dependent, or dead (modified Rankin Scale score of 3-6} at 1 year (N = 758), compared to 23.5% in the endovascular arm (N = 770). The absolute risk reduction was 7.6% (relative risk reduction 24.3%, p = .00082). With more patients being evaluated at 1 year, the absolute risk reduction in endovascular treatment is becoming more obvious. The annual risk of rebleed of endovascularly treated aneurysms at 1 year was 0.12%, slightly higher than in the surgical arm because of incomplete endovascular aneurysm obliteration and the use of thrombolytics during the intervention.

Endovascular treatment of aneurysms is a genuine alternative to surgery for ruptured and unruptured anterior and posterior circulation aneurysms. The key component for a successful and permanent aneurysm occlusion and for a reduction in the rebleed risk is the initial complete aneurysm obliteration, I'eriprocedural morbidity and mortality for endovascular treatment are superior to surgery. Currently, a follow-up angiography (or a contrast-enhanced MRA in selected patients) is recommended at 3-6 months, and 1 and 3 years to rule out a reopening of the aneurysm resulting from coil compaction. The initial results with bioactive coils and other biologically active implants are promising and should further reduce the risk of aneurysm regrowth or recanalization, further reducing the rebleed rate.

Arteriovenous Malformations

AVMs are almost exclusively congenital; a few casts oJ familial occurrence have been described. The prevalence of AVMs is in the range of 1.4-4,3%, and most of them are located supratentorially (90%). Spontaneous thrombosis occurs in about 2-3% of patients. Symptoms typically present before the age of 40 years; AVMs arc uncommon in children. Sixty-five percent of patients present with intracranial hemorrhage, which can be intracerebral, subarachnoid, intraventricular, or a combination thereof. A new-onset seizure may be the presenting reason for hospitalization in about 15-35% of patients. Fifteen percent

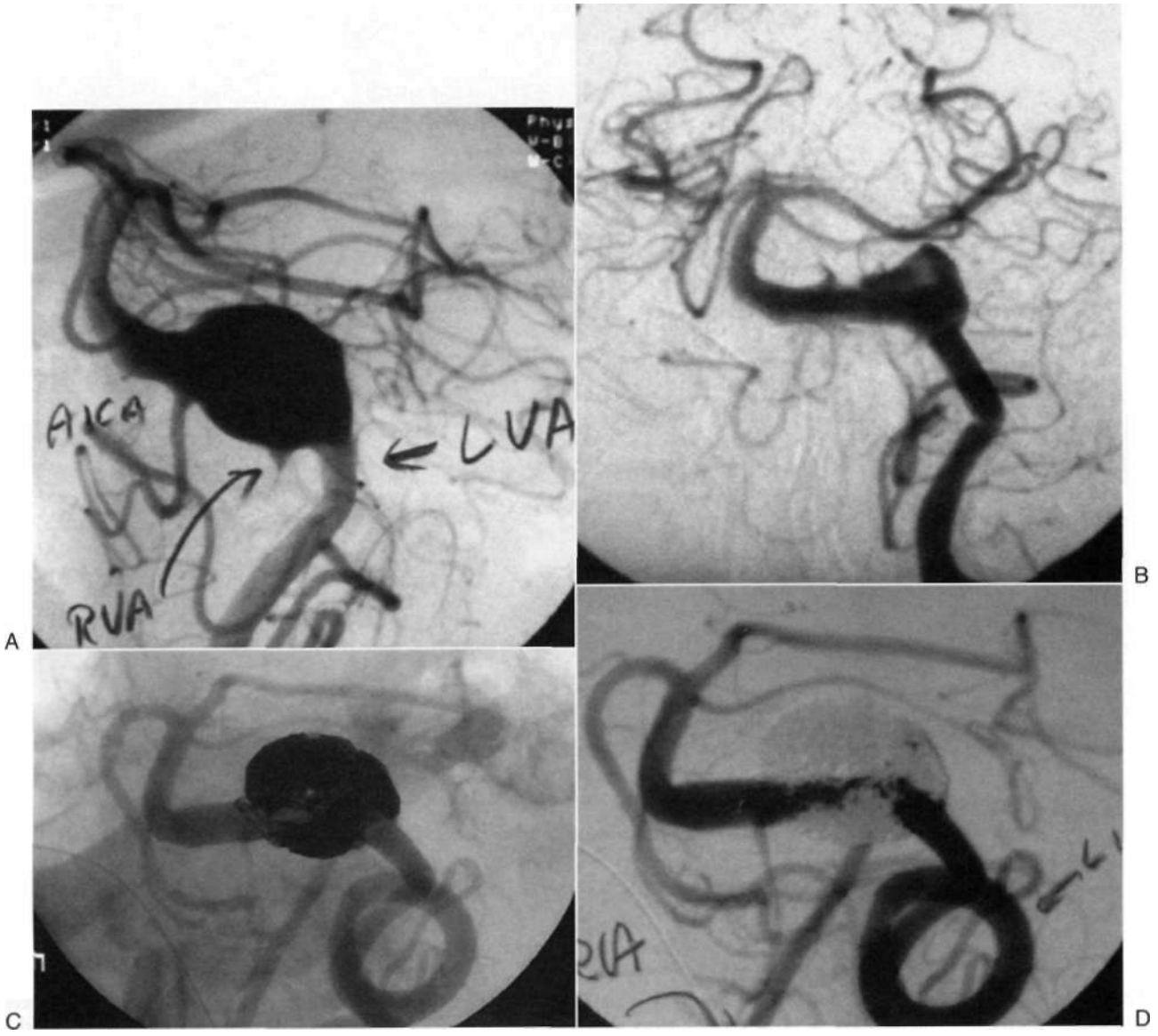

FIGURE 53.7 (A) Fusiform aneurysm of the vertebrobasilar junction. (B) Four-week follow-up angiography after placement of three overlapping noncovered stents *(arrows)* shows partial closure of the aneurysm. (C, D) Coiling of the aneurysm through the stent struts *(arrows).*

Continued

of patients complain of headaches. The annual hemorrhage risk has been described as 2-3%. ICH occurs in 60-65% of the cases, ICH combined with intraventricular hemorrhage in about 26%, pure intraventricular hemorrhage in about 8%, and pure SAH in 4%, The mortality for the first hemorthage is 29%, and the long-term disability is approximately 23%. After the first bleed, there is a 1-year recurrence risk of 6%, which then drops back to 2-3% in the following ycats. Thirty-four percent of patients have a risk of recurrent hemorrhage with 13% mottality {Graf, Perret, and Tomer 1983; Crawford et al. 1986; Brown etal. 1988; Ondra et al. 1990; Hartmann et al. 1998).

Radiographic features predictive of hemorrhage arc size, location, deep versus cortical venous drainage, impaired venous drainage, the nature of arterial feeders, and the presence of intranidal aneutysms. Approximately 3.7-17.0% of AVMs are associated with aneurysms. Aneurysms can be located distant and unrelated to the AVM, within the AVM feeding artery, in the AVM pedicle, or in the AVM nidus. Endovascular treatment also has a role in an AVM-associated aneutysm if it represents the site of rupture (Figure 53.8).

Treatment options include surgery, presurgical embolization, and radiosurgery, a combination of embolization and radiosurgery, and embolization alone. Endovascular embolization with liquid embolic agents such as dehydrated ethanol or M-butyl-2-cyanoacrylate has shown a cure rate with embolization alone in about 40% of Sperzer-Martin

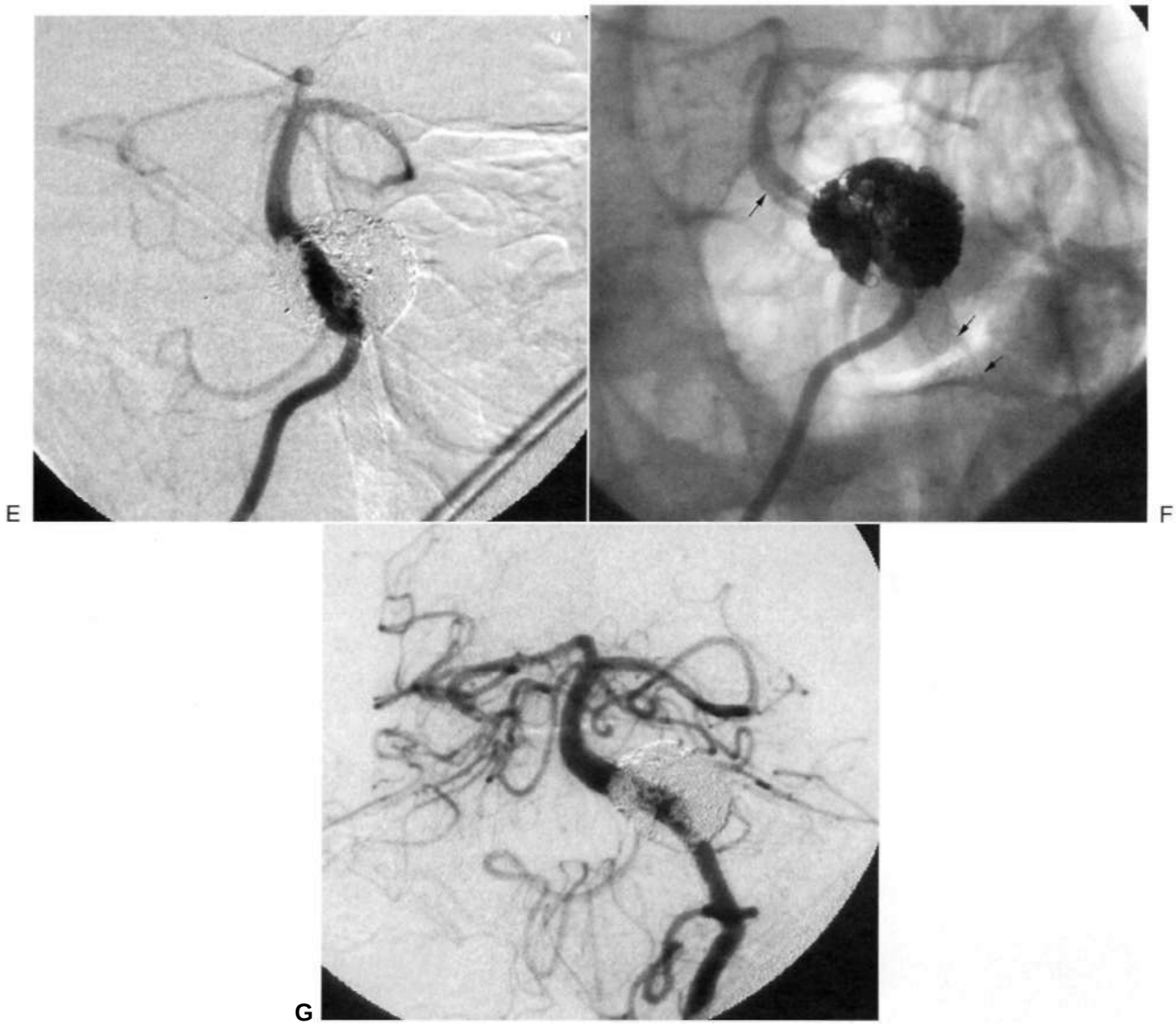

FIGURE 53.7, cont'd. (E, F) No filling of the aneurysm at 8-month follow-up angiography. Flow from the right vertebral artery enters the basilar artery through the stent struts. (G) The left vertebral artery supplies the basilar artery. The patient was asymptomatic after the procedure.

grade 1 AVMs, 30% of grade 2, and 10% of grade 3 AVMs smaller than 3 cm (Wikholm, Lundqvist, and Svendsen 1996; Debrun et al. 1997; Willinsky et al. 1999). In AVMs larger than 3 cm, cure with endovascular treatment is generally not possible, although embolization can downgrade the AVM before surgery or radiosurgery. Embolization has morbidity with a permanent neurological deficit of 6-8% and a mortality of 1-2% (Frizzel and Hsher 1995; Wikholm, Lundqvist, and Svendsen 1996; Debrun et al. 1997).

Successful endovascular treatment of an associated aneurysm that may be the source of AVM hemorrhage can decrease the risk of rebleed for 2-3 years, until radiosurgery is fully effective. In addition, reduction of flow can decrease venous congestion and occasionally reduce the frequency of seizures and other neurological symptoms. The Spetzler and Martin grading system was developed for surgical treatment strategies and is not useful for determining appropriate types of endovascular treatment. Certain aspects of the grading system such as deep venous drainage may negatively categorize an AVM into a higher grade in the Spetzlcr and Martin system but are helpful for endovascular treatment (Figure 53.9).

Recent improvements in endovascular techniques such as microwircs, flow-guided microcatheters, and liquid embolic agents have increased the cure rate to 40%. Longer follow-up studies are promising and show no recanalization or regrowth after complete embolization of AVM with acrylates (Lasjaunias et al. 1986, 1988; Wikholm, Lundqvist, and Svendsen 2001). Radiation therapy or surgery should be considered only if complete obliteration of an AVM cannot be accomplished.

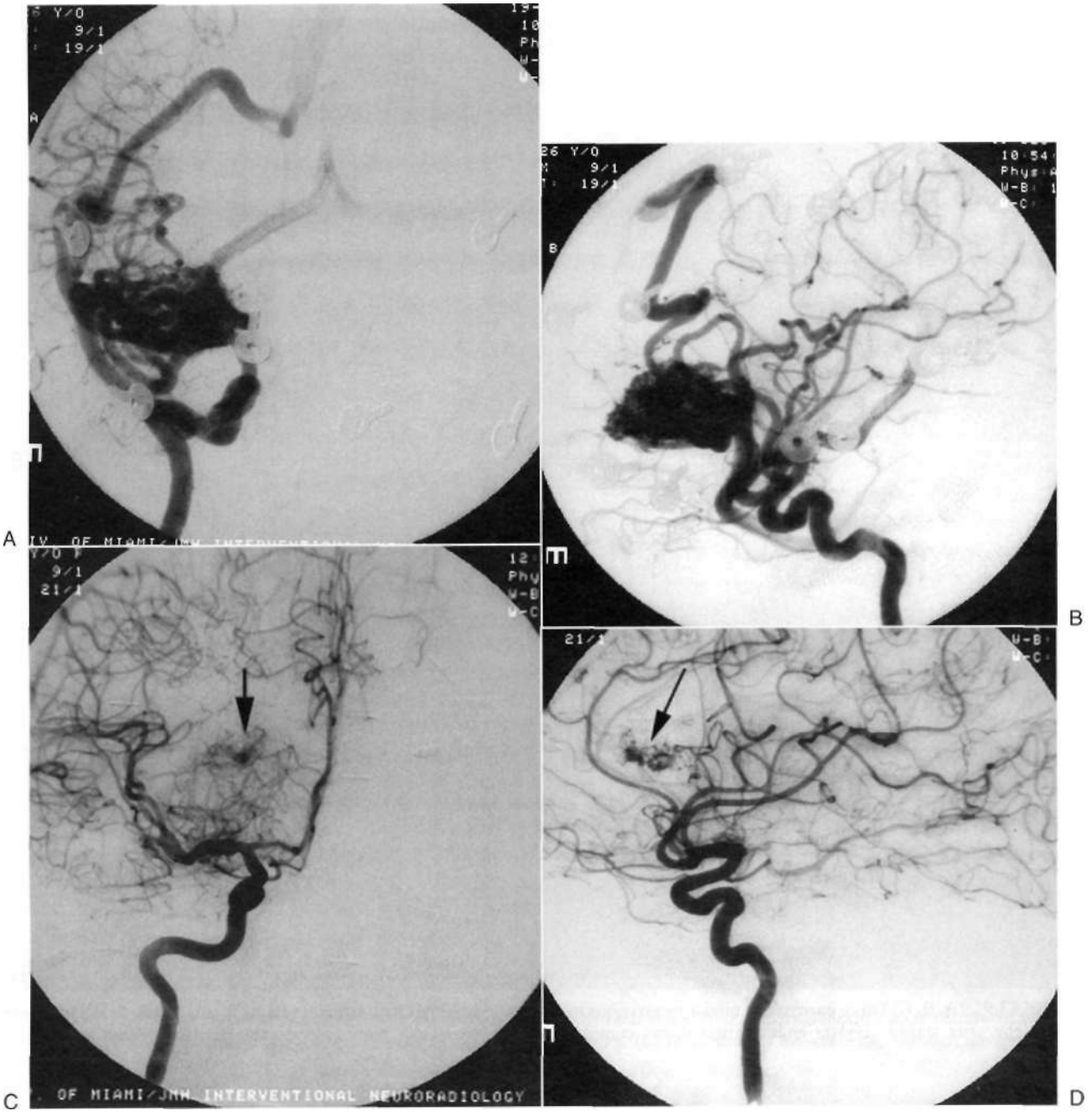

FIGURE 53.8 (A, B) Anteroposterior and lateral views of a right frontal arteriovenous malformation (AVM). (C, D) Control angiography after partial acrylatc embolization of the malformation. The remaining deep parts of the AVM *(arrows)* were treated with gamma-knife radiation.

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Carotid Cavernous Fistula

Carotid cavernous fistulas (CCFs) are the abnormal connections between the carotid artery and the cavernous sinus. CCFs make up 10-15% of all intracranial arterial venous malformations. Fistulas arc generally categorized based on the following factors: direct or indirect (dural), spontaneous or traumatic, high or low flow, and anatomy (internal carotid or external carotid ot both). Most fistulas are of the direct type, Barrow type A, which are characterized by direct flow from the cavernous segment of the ICA to the venous circulation. These are most commonly associated with trauma. The remaining fistulas are indirect or dural fistulas classified into Barrow types B through D. These are shunts between the meningeal branches of the ICA and the cavernous sinus (type B), meningeal branches of the external carotid artery (type C),

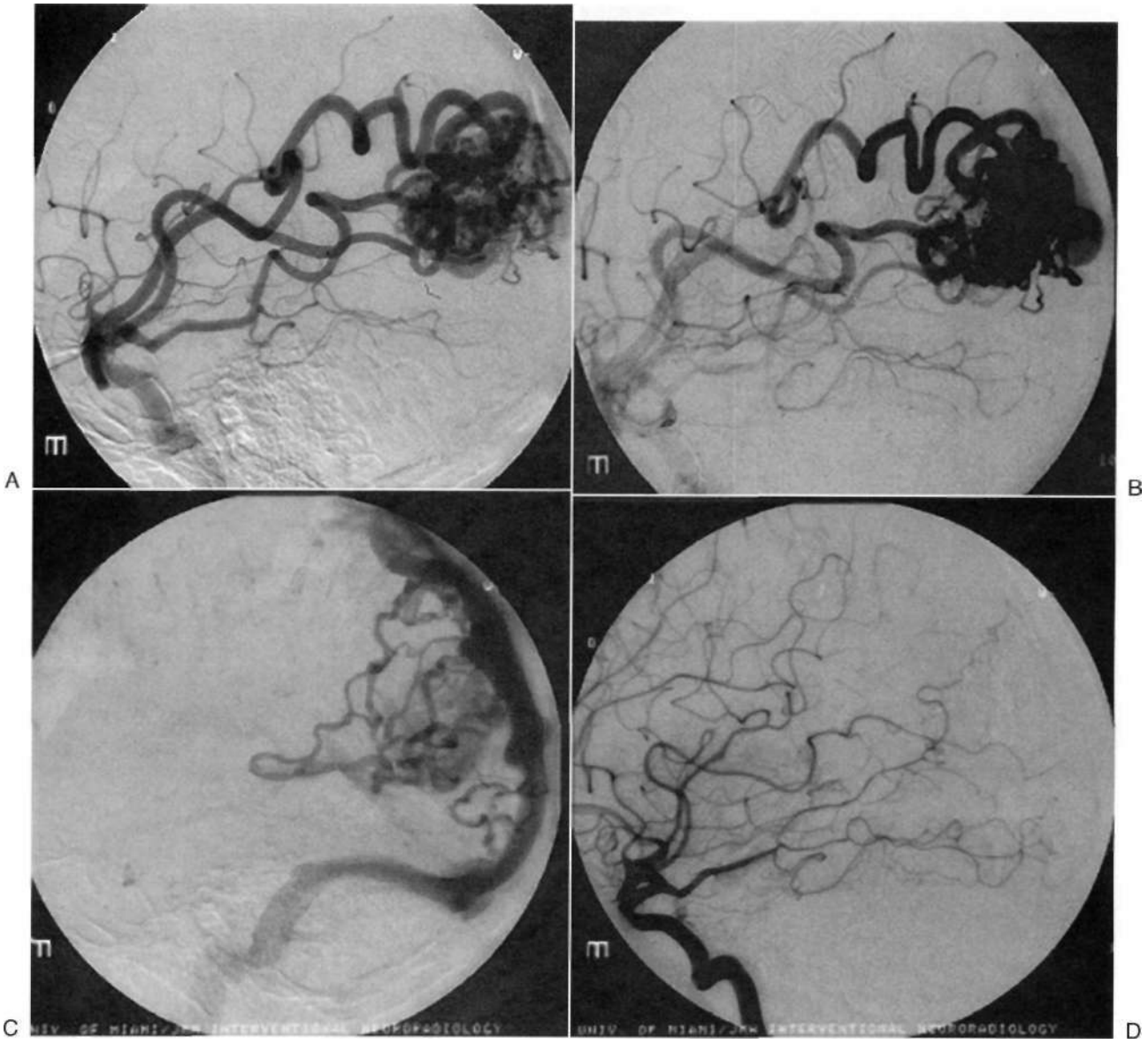

FIGURE 53.9 (A, B, C) Large parietooccipital arteriovenous malformation (AVM) with cortical venous drainage. (D, E, F) Follow-up angiography after staged acrylate embolization shows complete AVM obliteration. Note angiographic artifact created by acrylate *[arrows).* *Continued*

or the meningeal branches of both the internal and the external carotid artery (typeD) (Barrow et al. 19H5) (Figure 53.10).

Previous treatments included closure of the fistula with flow-guided balloons. Although balloons would successfully occlude the fistula and preserve carotid artery patency, several complications, albeit transitory, occurred such as worsened orbital congestions and ocular motor nerve paresis (Hedges 1999). Curative embolization of type A CCF involves the obliteration of the arteriovenous fistula, generally accomplished by using platinum fibered coils or dctachable balloons. In indirect CCFs, embolization of the cavernous sinus is generally required. This can be accomplished using a transvenous approach and obliteration of the affected part of the cavernous sinus with cither fibered coils or acrylates. The obliteration of the cavernous sinus is generally very well tolerated in patients with CCF. The ocular symptoms generally resolve within a few weeks.

Venous Occlusive Disease

Stenoses may occur within major dural sinuses, causing varying degrees of cerebral venous obstruction. These stenoses may be associated with chronic headache syndromes. Dural sinus and cerebral vein thrombosis may be associated with hypercoagulable conditions (including pregnancy and malignant disease), infection (e.g., mastoi-

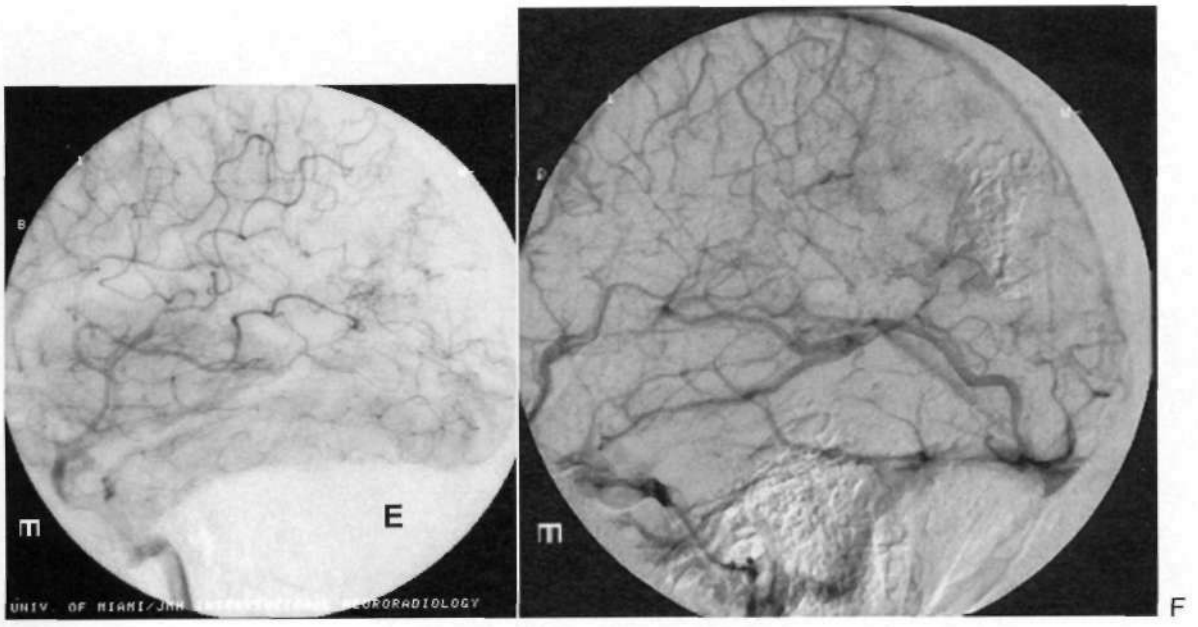

FIGURE 53.9, cont'd.

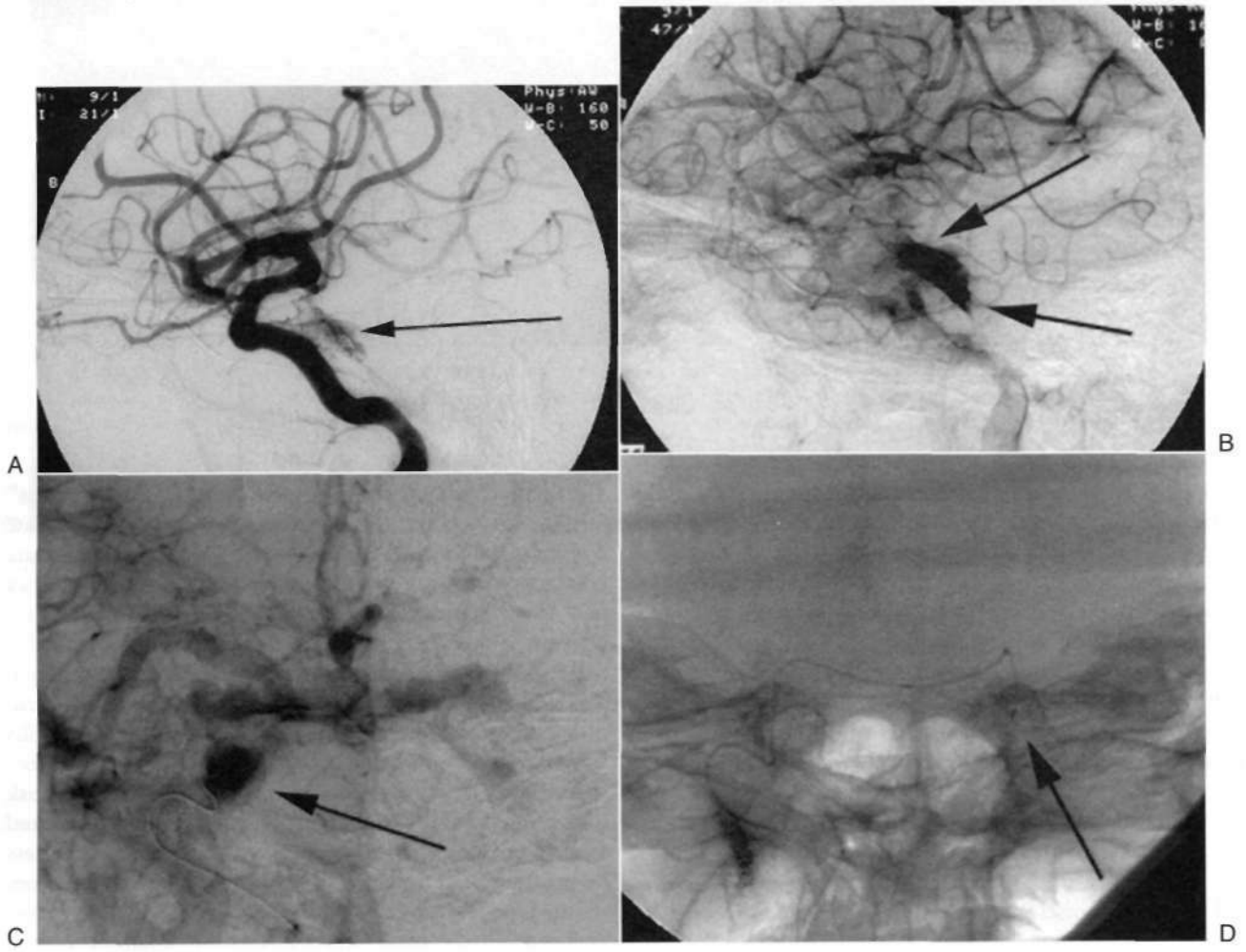

FIGURE 53.10 (A, B) Bilateral Barrow type D carotid indirect cavernous fistulas. Early (A) and late (B) arterial phase shows tiny dural blood supply with early filling of the cavernous sinus (*arrows*). (C) Magnified frontal view shows filling of the entire cavernous sinus. (D) Transvenous access and placement of a microcatheter into the left cavernous segment through the right inferior petrous sinus and the intracavernous segment (*arrow*).

Continued

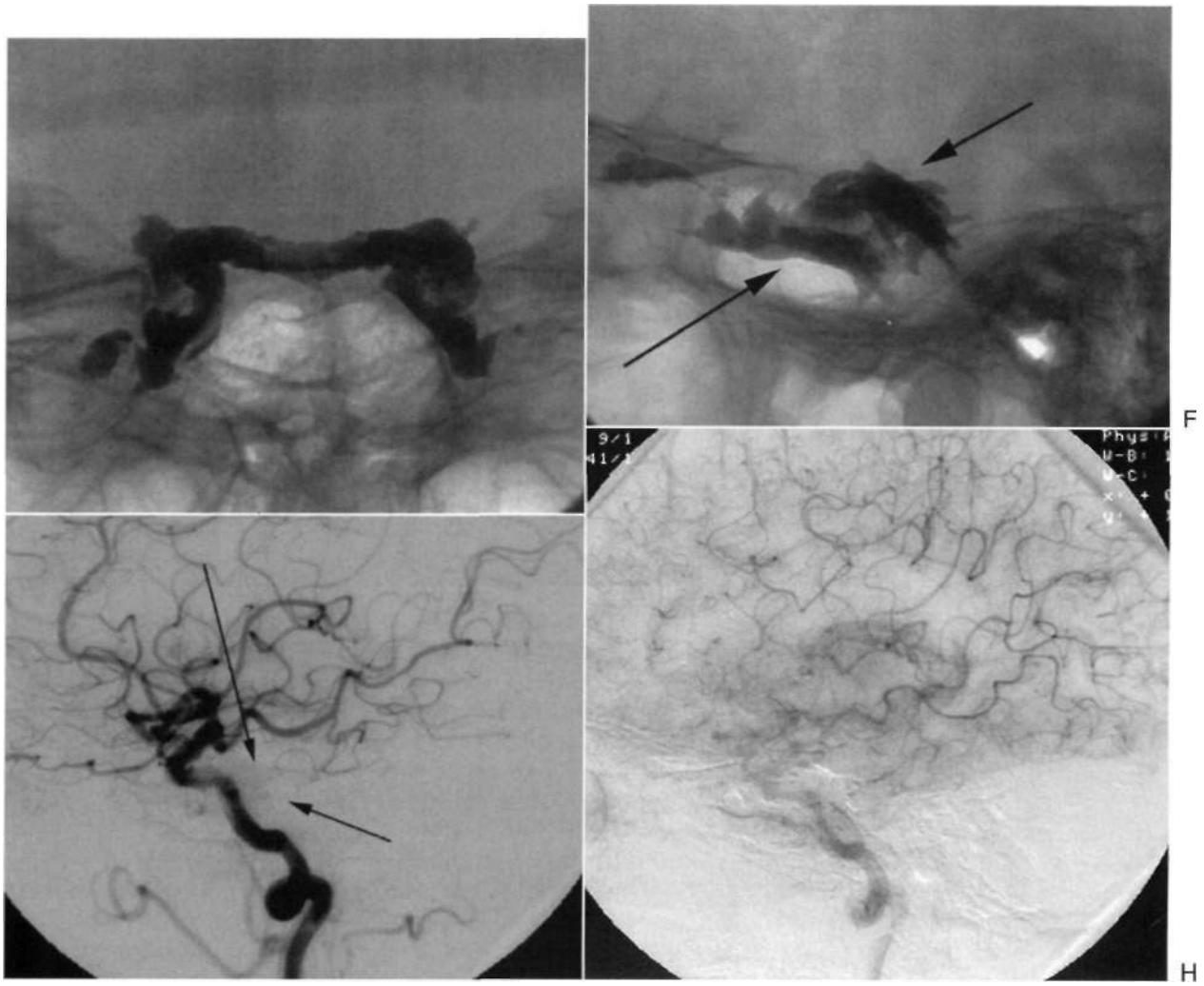

FIGURE 53.10, cont'd. (E, F) Acrylate cast in frontal and lateral views of the entire cavernous sinus for curative treatment of the carotid cavernous fistulas (CCF). *Arrows* indicate the location of the internal carotid artery. (G, H) Final angiographic images show a completely obliterated bilateral CCF. *Arrows* indicate the a cry I ate-caste d cavernous segment that was previously filled and is now obliterated.

ditis), or dehydration. Occlusive thrombophlebitis of a dura] sinus can result as a complication of mastoiditis or as a result of intracranial spread from a facial infection, transmitted by draining veins of the face into the cavernous sinus. The dural sinuses also may be invaded and occluded by tumyrs, especially meningiomas.

Increased intracranial pressure and venous infarctions (with or without intracranial hemorrhage) can result. If initiated early enough after onset, local thrombolysis using urokinase or percutaneous endovascular thrombectomy has shown some success in the management of sinus and cerebral vein thrombosis,

OTHER

The petrous ICA may cake an aberrant course through the middle ear cleft, rather than through the petrous temporal bone. In that case, it may cause pulsatile tinnitus and a blue tympanic membrane. Biopsy of the "mass" behind the tympanic membrane may injure the ICA or create a pseudoaneurysm. Aneurysms of the petrous ICA are uncommon and are usually traumatic or congenital. They may be a source of intracranial embolization and thus warrant either occlusion of the ICA with detachable balloons or endovascular bypass using a vascular (covered) stent. Similar approaches are used in treating deceleration or penetrating injuries that result in arteriovenous fistulas between the ICA and the internal jugular vein.

Aneurysms of the cavernous ICA present a lower risk than those present in the supraclinoid region (subarachnoid space) because rupture into the cavernous sinus is far less devastating than intracranial hemorrhage, although it does result in a direct carotid-cavernous fistula. Very large aneurysms may cause mass effects on adjacent cranial nerves. Symptomatic inoperable fusiform aneurysms of the cavernous and supraclinoid ICA may be treated by occlusion of the parent ICA using detachable balloons.

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Chapter 54
Principles and Practices of Neurological Rehabilitation

Bruce H. Dobkin

Neurological rehabilitation extends its assessments and ptaetices into every aspect of the cate of patients with acute and chronic disabilities, regardless of the location of a lesion or its cause. Conducting patient rehabilitation becomes a high priority for the physician who wants to provide more than diagnostic setvices and short-tetm care. To best assist patients, the clinician must determine what tasks patients can and cannot perform, determine what skills are most important for them to tegain, apply skill learning principles based on an understanding of neuro-plasticiry mechanisms, work with allied health professionals to lessen disabilities, and anticipate and manage neuro-medical and psychosocial complications of immobility, loss of motot control, cognitive impairment, and functional dependence (Dobkin 2003).

GOALS AND STRUCTURE OF REHABILITATION

Rehabilitation can be defined as an educational process that aims to reduce disability and improve functional independence and quality of life. An alternative definition, perhaps a little more dynamic, describes rehabilitation as an active process of change by which a petson who has become disabled acquires and uses the knowledge and skills necessary for optimal physical, psychological, and social function. It is important to remember that neurological impairment (the presence of abnormal neurological signs) is the basis of the diagnosis. Impairment may in turn cause disability. These definitions inttoduce a number of concepts that will be dealt with more fully later in this chapter, but they underscore the fact that rehabilitation is an active educational and learning ptocess and that patient in-volvement is crucial.

Aims

Rehabilitation aims to improve functional and cognitive skills such as walking and language, reduce disability in petsonal care and other daily activities, prevent and manage com plications such as aspiration, contractures, pressure sores, and depression, lessen the burden of care needed by disabled people, and enhance health-related quality of life by maximizing functional independence and participation in home and community putsuits.

Disabled people and their families and caregivers should be intrinsically involved in the rehabilitation process. Therapies can be carried out only by or with disabled people, not at them.

Rehabilitation includes the following aims:

- Promote physical, psychological, and social adaptation to disability.
- Facilitate independence in daily self-care and community activities.
- Prevent secondary health complications.
- Encourage self-management.

To achieve these aims, the process differs from the usual medical model of care by including personnel from multiple disciplines, goal-directed assessments and interventions, outcome evaluation, and organization of community services to meet the patient's needs.

Personnel

A team approach to inpatient and outpatient care is necessary to manage the diverse problems faced by disabled patients and their families (Figure 54.1), In a mulridisciplinary model, each member with specialty training treats particular disabilities. In an interdisciplinary model, roles blend. An interdisciplinary approach orients toward problem-solving to improve functional outcomes rather than being bound by guild-oriented disciplines. For example, training procedures for motor and cognitive learning or behavioral modification are reinforced by all members of an interdisciplinary group, using agreed-upon strategies. Moreover, an interdisciplinary structure sets its goals with a view toward dealing with a patient's disabilities and returning him or her to a usual role in daily life activities. These interaction styles are not mutually exclusive, Most teams move between the two models when they formally meet to discuss the patient's progress and to adjust goals and treatments.

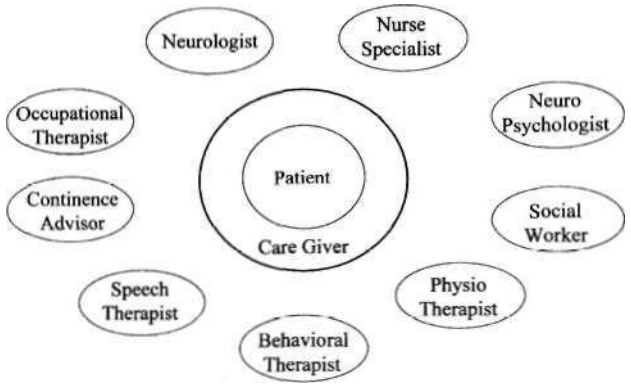

FIGURE 54.1 The mulridiscipJinary team centered around patient and caregiver.

The care milieu created by the team of therapists, nurses, social workers, neuropsychologists, and physicians, with its emphasis on lessening disability, is one of rehabilitation's most powerful tools. The team approach to neurological rehabilitation has come under remarkably little scrutiny, however. Studies of inpatient stroke rehabilitation support the approach primarily as an efficient way to organize services for patients with functional disabilities. For otbet neurological diseases, almost no well-designed trials about how to provide a system of care exist.

Physicians

An understanding of the underlying disorder, including the mechanisms of disability, potential outcomes, and natural history of the disease being managed, is critical in planning the rehabilitation program, particularly for chronic and progressive neurological disorders. This expertise may be provided by the growing number of neurologists with expertise in neurorehabilitation, who can bring principles from their growing storehouse of knowledge to bear on recovery, and by rehabilitation physicians or physiatrists, who also have broad experience in musculoskeletal, orthopedic, and cardiopulmonary rehabilitation issues. Podiatrists and other physicians, including orthopedists, urologists, psychiatrists, plastic surgeons, and neurosurgeons, often are consulted during rehabilitation and long-term management of disabled patients.

The clinician superimposes the contributions of neurological, musculoskeletal, cardiopulmonary, and other impairments on a map of the patient's functional abilities and disabilities. For example, docs spasticity or palpably tender musculoligamentous tissue cause pain or limit movement? Does a medication or episodic orthostatic hypotension lessen attention span and endurance for exercise? Rehabilitation physicians tend to be the facilitators of the team, especially in an inpatient service. Here, the physician leads a weekly team conference that reviews the patient's progress in reaching the functional goals that will permit a discharge to the home. To do this well, the physician must help build the team's infrastructure and understand the practices of its disciplines. With a backgtound in general medicine, neuromedicine, neuroscience, mechanisms of plasticity, and scientific experimentation, rehabilitation physicians should serve as clinician-scientists. The physician can encourage therapists to weigh, formulate, and test strategics. Drawing on current literature and collaborating with basic and clinical researchers, the neurological rehabilitation specialist assesses and develops interventions (Dobkin 2003).

Physicians should explain to both patient and primary care doctor the indications for medications, measures for secondary prevention of complications, management of risk factors for recurrence or exacerbation of the disease, and the type and duration of rehabilitative interventions. During outpatient care, physicians must develop their

counseling skills in matters such as exercise and specific directions about home practice for motor and cognitive retraining. The clinician reviews the details of how the patient is practicing to improve walking, the functional use of an affected upper extremity, language and memory skills, and socialization. Education should he offered about how task-specific practice may alter the brain's representations of these activities and improve the patient's abilities, even years after the initial neurological illness. For patients with chronic diseases that progress, practice is perhaps even more important because it may spur gradual neural reorganization to maintain function.

Rehabilitation Nursing

Traditionally, the nursing role has been one of providing care and support during a phase of illness and doing for others the things they would normally do for themselves. Nurses have particular expertise in bowel and bladder management and have developed the post of continence advisor, particularly for teaching chronic intermittent self-catheter ization (CISC). They are also the acknowledged experts on skin care and pressure sore management. In an inpatient unit, nurses are in constant contact with the patient undergoing rehabilitation. The nurse's extended contact with patients allows him or her to address the issue of carryover of skills from physical and occupational therapy sessions to other areas fundamental for discharge into the community. Each activity is integrated with others; for instance, continence management through CISC may require improvements in upper limb coordination, trunk control, mobility, lower limb tone, medications to optimi/.e bladder and sphincter control, and strategies to facilitate learning. Similarly, the therapy schedule depends on the success of these management strategies. Nurses have also become involved in the management of individual chronic diseases, including multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Parkinson's disease, especially attending to gaps in services needed by patients. A nurse practitioner can be a great asset to the physician and team in a busy inpatient service, especially in a university hospital, where patients tend have complex medical illnesses and needs. The Association of Rehabilitation Nurses has excellent resources for continuing education (www.rehabnurse.org).

Physical Therapist

Physical therapists or physiotherapists (PTs) contribute especially to the rehabilitation of bed mobility, transfers to a chair or toilet, stance, and ambulation. Their assessments emphasize measures of voluntary movement, sensory appreciation, range of motion, strength, balance, fatigability, bed and wheelchair mobility, and gait. The clinician's goals for neurological rehabilitation aim toward compensatory strategies for carrying out activities of daily living (ADLs), such as the use of a wheelchair, as well as interventions to lessen specific impairments when time allows. PTs play a primary role in managing musculoskeletal and radicular pain, contractures, spasticity, and deconditioning.

Two broad categories of exercise programs, therapeutic exercise and the so-called neurophysiological and neurodevelopmental approaches, have received the most attention in the past (Table 54.1). Newer concepts related to neuroplasticiry, motor control, and motor skill learning arc merging with these approaches. Traditional exercise programs emphasize repetitive passive and active joint-by-joint exercises and resistance exercises in anatomical planes to optimize strength and range of motion. The approach aims to prevent the complications of immobilization, such as contractures, muscle atrophy, and spasticity.

Exercise and Compensatory Functional Training. Most therapy programs emphasize education about impairments and disabilities, compensatory techniques for ADLs and mobility, and repetitive passive and active exercises to build from less complex to more functional movements. In the therapeutic exercise approach to stroke, spinal cord injury (SCI), and other upper motor neuron (UMN) diseases, residual motor skills in affected and unaffected extremities are used to compensate for impairments. The acquisition of self-care and mobility skills may take precedence over the quality of movement as long as patients are safe. Upper and lower extremity orthotics and assistive devices tend to be used early to promote functional compensation. Therapists also use breathing and general conditioning exercises and energy conservation techniques, particularly to reduce the energy cost of a pathological gait.

Conditioning and Strengthening. Light resistance exercises across UMN diseases and diseases of the motor unit, from the postpolio syndrome and ALS to myasthenia gravis and some of the muscular dystrophics, are generally safe and effective in improving strength and, sometimes,

Table 54.1: Practices in physical therapy

Therapeutic exercise and re-education
Resistance exercises
Ncurofaciliration techniques
Proprioceptive neuromuscular facilitation
Bo bath
Others
Motor control approaches
Motor skill learning
Task-oriented practice
Forced use
Massed practice
Biofeedback
Musculoskeletal manipulation techniques
Orthotics [e.g., ankle-foot orthosis) and assistive devices (e.g., quadcane)

function. Strength can be increased without an increase in spasticity in patients with U\t\ diseases ami without evidence of muscle injury in those with neuromuscular diseases. Concern about falls, disabihty, and muscle atrophy in older adults has led to many studies that show that a strengthening program can benefit any sedentary person. Resistance training can lead to an increase in strength before any muscle hypertrophy occurs, probably by augmenting the amount of supraspinal input that is brought into the task. Thus strengthening can be considered a form of motor learning. Isometric resistance exercises probably arc the safest approach for weak patients and can be performed without equipment. For example, flexing the elbow of one arm about 60 degrees and pressing down on that forearm with the palm of the other arm to reach an equilibrium of tension in each arm will enhance strength in the shoulder girdle, elbow flexors and extensors, and forearm groups.

Medications that act on the neuromuscular junction, such as pyridostigmine, those that work on muscle, such as 02 adrenergic agonists, those that work on demyelinatcd axons, such as the aminopyridines, and hormones such as androgens and human growth factor that limit disuse-atrophy may come into clinical use along with specific retraining programs.

Fitness training is valuable in LIMN, extrapyramidal, and motor unit diseases. Treadmill walking can be used as an aerobic workout for the older adult with hemiparetie stroke. After a complete SCI, cardiovascular conditioning can be limited by the use of only the upper body's small muscle mass, by pooling of blood in the leg muscles that reduces cardiac preloading, and by impaired cardiovascular reflexes. Functional electrical stimulation (FES) of the lower extremities during cycle ergometry can improve both peripheral muscular and central cardiovascular fitness. FES exercise in sets of 5 to 15 repetitions against an increasing load resistance of 1 to 15 kg over 12 weeks will increase muscle bulk, improve strength, and reduce fatigability for the FES activity. Although psychological and other physiological benefits have been attributed to FES in paraplegic subjects, long-term home programs require much motivation.

Neurophysiological Schools. Many schools of physical therapy have developed approaches that focus on enhancing the movement of paretic limbs affected by UMN lesions. They use sensory stimuli and reflexes to facilitate or inhibit tone and single- and whole-limb muscle movements in and out of mass actions called synergies. Most try to sequence therapy in a progression reminiscent of the neurodevclopmental evolution from reflexive to more complex movements. They emphasize normal postural alignment before any movement. Some techniques permit mass movement patterns early in treatment; others inhibit spastic, overflow, synergistic movements. Mobility activities might proceed in a developmental pattern from rolling onto the side with arm and leg flexion on the same side, followed by extension of the neck and legs while prone, then lying prone while supported by the elbows, and then doing static and weight-shifting movements while crawling on all four extremities. These mat activities are followed by sitting, standing, and finally walking. This progression is used most often in children with cerebral palsy, but some therapists also apply it to stroke and traumatic brain injury (TBI) rehabilitation. Different schools vary in their attempts to activate or minimize reflexive movements and in their use of training functional movements in ordinary activities. These schools have underused strengthening exercises.

The schools' use of reflexive movements, vibration to stimulate a muscle contraction, and cutaneous stimulation to facilitate a voluntary contraction is reasonable from a physiological point of view, but any carryover of responses into functional or volitional movement is uncertain. When these approaches have been compared for patients with stroke and cerebral palsy, as noted earlier, no real differences in outcomes related to gains in ADLs have been shown. However, these approaches teach movement, not specific ADLs, so perhaps the outcome measures have been inappropriate. More importantly, studies in neuroplasticity suggest that therapy structured around learning new sensorimotor relationships in the wake of altered motor control will be more effective than methods that aim to foster a developmental sequence. Over the past 10 years, practitioners have shown more flexibility in their approach to neurorchabilitation and have incorporated more recent concepts of motor learning and neuroplasticity.

Neurodcvclopmental techniques attempt to reproduce the developmental sequence shown by infants as they evolve motor control. Practitioners believe that normal movement requires normal postural responses, that abnormal motor behaviors are compensatory and that the quality of motor experiences helps train patients for normal movement. The Bobath approach is a particularly popular neurophysiological technique. It aims to facilitate normal movement and desired automatic reactions and to restore postural control while inhibiting abnormal rone and reflex activity using specific motor patterns. Bobath therapists avoid provoking mass flexor shoulder, elbow, and wrist synergies of the arm and extensor knee and plantarflexor ankle synergistic movements of the leg. Coordination of patterns of muscle group activity is viewed as more important than the actions of individual muscles. A typical exercise routine may work on stance and trunk control with a large ball and careful hand placement by the therapist to evoke movements out of synergy (Figure 54.2). These methods were originally developed for children with cerebral palsy but have been adapted for stroke and other neurological disorders.

Motor Learning Approaches. Over the past 10 years, several trends have emerged. The bases for motor control

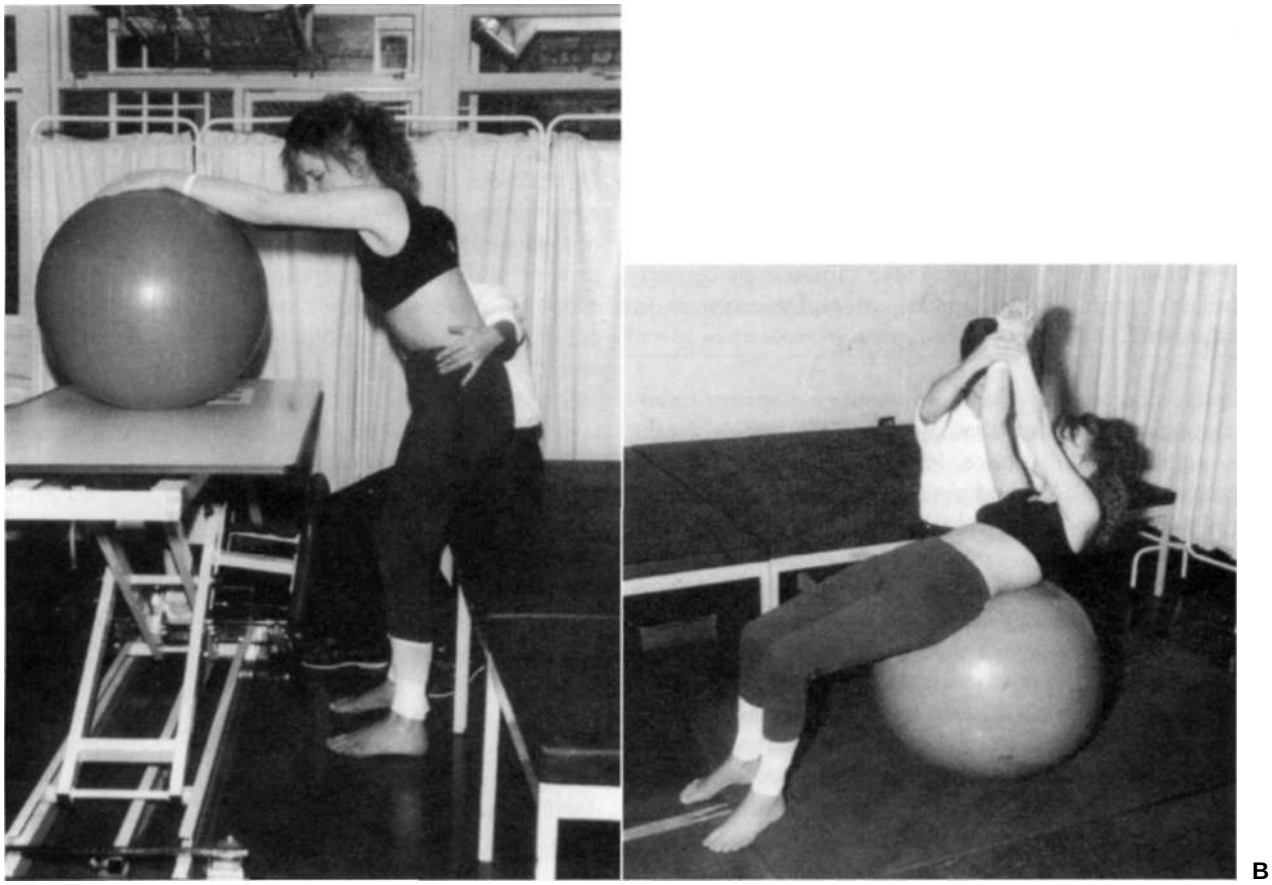

FIGURE 54.2 Gymnastic ball used to facilitate (A) standing and postural adjustments for standing up and (B) flexion and extension of the trunk and reaching.

have become key concepts for understanding normal movement and analyzing motor dysfunction. The motor control approach may incorporate techniques to eliminate unnecessary muscle activity, feedback of information about performance and practice, and task-specific or task-oriented therapies that promote practice with optimal reinforcement. In rehabilitation settings, little attention has been paid to whether training procedures—not what is taught but how it is taught—optimize gains in cognitive skills, motor functions, and self-care and community activities. The essence of therapy for any disability, as for acquiring any novel motor skill, is practice. However, a practice session can have a powerful but only temporary effect. A positive effect on performance during a training session may not lead to long-term learning. The goal of practice should be a permanent effect. Studies of interventions should include a dose-response curve to establish how much practice is needed to achieve a retraining goal. In 24 subjects with chronic stroke, random practice of functional activities using the hemiparetic left or right arm for reaching and grasping items led to better retention over time than blocked practice. Despite the contextual interference of intermixing other tasks such as pointing and touching during learning in the random practice group, both groups acquired their learning in the same number of trials. Thus random practice did not impede the rate of gains and still increased retention. Motor learning that prevents simple massed practice may be impeded in patients with striatal lesions that interfere with procedural memory and in mentally retarded subjects, but in most studies learning proceeds after a unilateral stroke and leads to adaptations in motor networks.

Task-Orientcd Practice. Motor learning emphasizes visual, verbal, and other sensory feedback to achieve task-specific movements, in contrast to neurophysiological techniques that rely on cutaneous, ptoprioccptive, and other sensory stimuli to elicit facilitation and inhibition of movement patterns. Constraint-induced movement therapy for the upper extremity and body weight-supported treadmill training for walking, discussed later, are among the task-oriented approaches to regaining movement. Mental practice, electromyography (EMG) and other forms of biofeedback (BFB), EMG-triggcrcd clecttical stimulation of a muscle group, and virtual reality training are potential therapeutic tools.

Studies of the efficacy of particular schools of therapy have not revealed differences between approaches.

These studies, primarily in patients with stroke, used outcome measures that emphasize independence in ADLs and not an outcome directly related to the primary focus of the specific technique of physiotherapy, which is motor performance and patterns of movement. Studies of efficacy should concentrate on the best well-defined practice for an important goal, such as reaching, grasping items, and walking that may, in theory, be modulated by the intervention. Most therapists take an eclectic experimentalist's approach, not unlike what physicians do in daily practice.

Adaptive Equipment. Canes and walkers improve stability through a lever arm that can share the body's weight between the leg and device, keep the pelvis level during stance on the weak leg, and generate a moment to assist the hip abductors and reduce loading on the knee. Devices must be fitted properly. For example, handgrips should be at a height that allows about 20-30 degrees of elbow flexion. The cane should swing forward with the involved limb and bear most weight during stance on that leg.

Light and very light wheelchairs must be fitted with at least a dozen characteristics in mind (Table 54.2). Severe spasticity, poor head or trunk control, the amount of upper extremity function, and the type of work and sports engaged in necessitate additional modifications. Motorized wheelchairs can be maneuvered by joystick switches and chin or sip-and-puff mouth controls. The high cost of custom-designed wheelchairs means that therapists, vendors, patients, and families need to work together to obtain what is most apptoptiate.

Tabic 54.2: Wheel ch a i r ch a ra c tenstics

- Frame
  - Material
  - Weight
  - Foldablc structure
- Seat
  - Height, width, depth, angle
  - Sling or cushioned, inserts
  - Cushion (foam, air, fluid, gel, gel-foam)
- Back
  - Height, fixed or reclining, headrest
  - Flexible, custom molded; foam or gel inserts
- Armrests
  - Height (fixed or adjustable)
  - Fixed, removable, swing-away
  - Arm troughs, clear plastic lap board, power controls
- Leg and footrcst
  - Height, adjustment from edge of seat, knee flexion angle
  - Fixed, removable, swing-away; straps
- Rear wheels
  - Materials (alloys, plastic)
  - Tires (width, tread; pneumatic or solid)
  - Camber for speed and turning radius
  - Handrims
- Front casters
- Brakes (locking, backsliding)
- Anti-tip bars
- Power supply, control system

Occupational Therapist

Occupational therapists (OTs) facilitate the practical management of disability. The philosophical foundation of occupational therapy is that purposeful activity helps prevent and remediate dysfunction and elicits maximum adaptation. These goal-oriented tasks are meant to be culturally meaningful and important to the needs of clients and their families. Activities include daily life and work skills, exercise, recreation, and crafts. Occupational therapy is also concerned with improving the patient's interaction with the environment and maximizing the patient's role in society in terms of relationships, occupation, and personal standing. The OT implements a program to enable patients to leatn or relcarn specific activities, develop new or compensatory skills, adapt their behavior to what is feasible, make adjustments to increase the accessibility of their environment, and perform leisure activities.

A ptogram may include the use of appliances (Table 54.3) to improve independence, ranging from simple devices (e.g., a thickened gtip to better grasp cutlery or

Table S4.3: Adaptive aids for daily living

- Feeding
  - Utensil: thickened handle, cuff holder
  - Dish: food guard, suction holder
  - Cup: no-spill covers, holders
- Bathing
  - Shower scat, transfer bench
  - Washing: mit, long-handled scrub brush
  - Safety: grab bars
- Dressing
  - Velcro closures for shoes, pants
  - Button hook, zipper pull
  - Low clothes rods in closet
  - Long-handled comb or brush
- Toileting
  - Safety rails, raised seat, commode
- Mobility
  - Prefabricated ramp
  - Powered stair lift
  - Wheelchair, standing wheelchair
  - Transfer devices and ceiling-mounted track lifts
  - Automobile and van: lifrs; hand controls
- Communication
  - Cellular phone, hand-held Internet device
- Computer workstation
  - Environmental controls
  - Communication: printing; voice synthesis
  - Interface adaptations: keyboard, mieroswitch, voice activation
- Miscellaneous
  - One-handed jar opener
  - Doorknob extension for better grip
  - Book holder; page turner (electronic or by a mouth stick)
  - Holder for one-handed cutting
  - Long-reach jaw grabbers

a pen) to complex ones (e.g., use of an environmental control unit). Hemicuff and Bobath slings are used to reduce shoulder subluxation and prevent pain (Figure 54.3), A balanced forearm orthosis supports the upper arm and allows a modest activation at the shoulder or elbow to swing the arm over a table, which may be especially effective for the patient with a C5 level SCI. Figures 54.4 and 54.5 show standing devices that allow subjects to do some tasks upright while they load joints to lessen the likelihood of developing contractures in hypertonic legs.

For patients with stroke and brain injury, OTs work closely with the neuropsychologist to address visuospatial inattention, memory loss, apraxia, difficulties in problem solving, and the skills needed to return these patients to school or employment. Many OTs manage dysphagia and interpret modified barium swallow (MBS) studies.

Task-oriented and motor learning strategies have gained attention in formal occupational therapy research. Using this approach, the OT presents activities in a way that elicits the retention and transfer of particular skills for use in a functional setting. For example, in one study, limb kinematics improved in normal and hemiparetic subjects when training included purposeful goals with objects of interest. Thus practice in object-related tasks, rather than simple repetition of reaching and grasping items that bear no significance to a person, may provide more concrete sensory information and offer rewards that motivate performance.

Speech and Cognitive Therapist

Speech and language therapists are trained in all aspects of communication, including phonetics and linguistics, audiology, and developmental psychology, and provide expertise in the investigation and management of

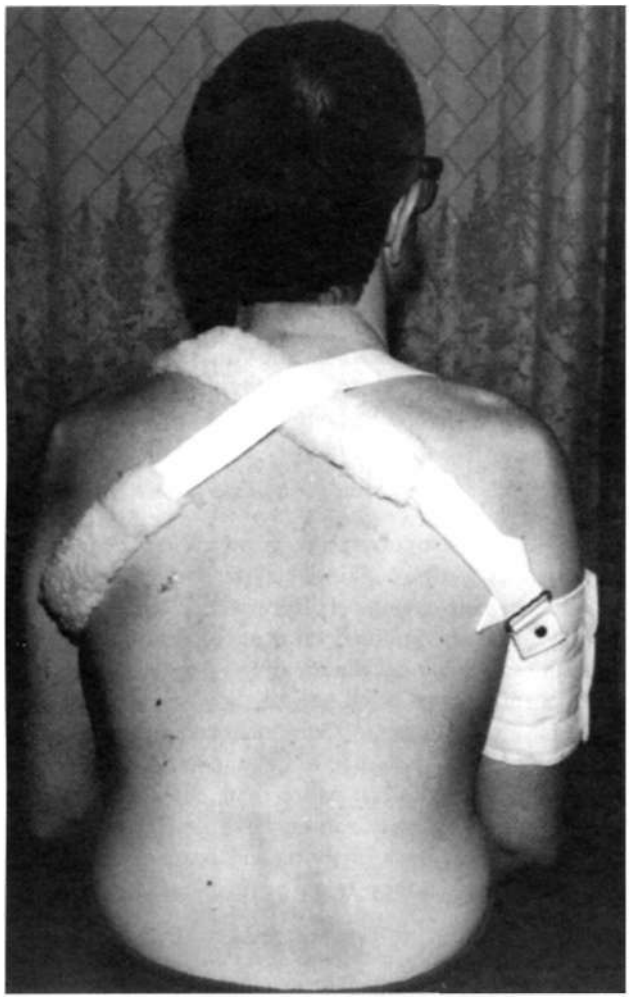

FIGURE 54.3 A cuff support to prevent pain and lessen the subluxation of die glcnohumeral shoulder joint in a patient with left hemiplegia sifter stroke.

FIGURE 54.4 This fabricated ankle-foot orthosis is designed for ankle and knee control of a hemiparetie patient who has minimal hypcrtonicity. A wider lateral flange and Velcro straps across the trout ot tin- ankle would provide greater ankle control,

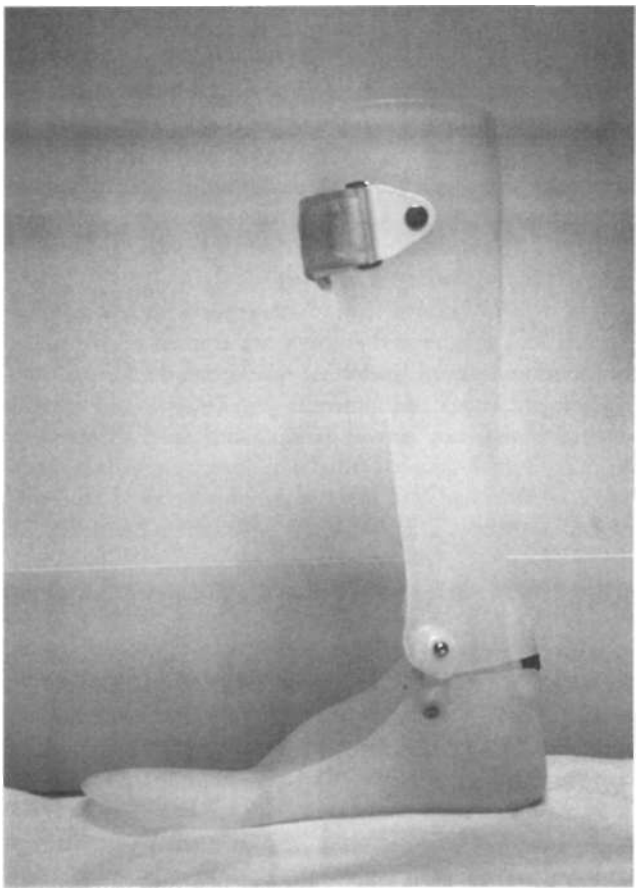

FIGURE 54.5 This thermoplastic orthotic includes a hinged ankle with a stop to allow about 5 degrees of dorsiflexion when the subject goes from sitting to standing and in portions of the srimce prme.

dysphagia. The therapists treat primarily patients with dysarthria and aphasia.

Therapies to improve the patient's speech intelligibility, volume, and fluidity include exercises of affected structures. For example, patients may be trained to slow their articulation, use shorter sentences, maximize breath support, extend jaw motion, and purposefully place the tongue or exaggerate articulatory movements. Therapists advise patients, relatives, and staff and recommend appropriate communication aids when necessary. They also provide assessment and guidance for those with swallowing difficulties; assessment includes the MBS with videofluoroscopy.

Treatment for aphasia is based on the clinical evaluation of the patient's cognitive and linguistic assets and deficits. The thetapy plan is fine-tuned by standardized language and neuropsychological tests, knowledge of the cortical and subcortical structures damaged, and the ongoing response to specific therapies. Speech therapists attempt to circumvent, deblock, or help the patient compensate for defective language behaviors. Stimulation-facilitation approaches are the most common (Table 54.4). Interventions for specific syndromes are applied as appropriate, For example, melodic intonation therapy is a

Table 54.4: Stimulation-facilitation approaches for aphasia therapy

Gestural expression and pointing
Word to picture matching
Yes-no response reliability
Oral-motor imitation
Phoneme, then word repetition
Verbal cueing for words and sentence completion
Contextual cueing
Phonemic and semantic word retrieval strategies
Priming for responses
Auditory processing at the phrase, then sentence level
Word-, phrase-, then sentence-level reading
Melodic stimulation
Graphic tasks: tracing, copying, word completions
Calculations
Pragmatic linguistic and nonlinguistic conversational skills
Psychosocial supports

Source: Adapted with permission from Dob kin, B. 2003, *The Clinical Science of Neurologic Rehabilitation,* Oxford University Press, New York.

well-defined treatment for Broca's aphasia, in which patients have sparse or stereotyped speech and good auditory comprehension. Therapists and patients melodically intone multisyllabic words and commonly used short phrases while the therapist taps the patient's left hand to mark each syllable, Words are spoken with an exaggerated prosody that includes high and low pitches at short and longer durations. Gradually, the continuous voicing and rapping arc withdrawn. A positron-emission tomography **(PET)** study showed that the technique induces a systematic change in how the acoustic features of spoken and perceived speech are engaged by the brain after a left hemispheric stroke. Views on the value of speech therapy for aphasia vary. Most randomized controlled trials demonstrate a significant benefit.

Recreational Therapist

These therapists involve patients on an inpatient unit in group games, crafts, cooking, playing with pets, and other activities to help them socialize, practice skills, and enjoy the physical and emotional value of recreation despite new disabilities. In addition, the recreational therapist joins with the PTs and OTs to teach patients how to reintegrate into the home and community. Outpatient recreational activities carried out in a wheelchair or one-handed also foster socialization and fitness. More than 200 local, national, and international organizations have developed rules and equipment for at least 75 sports and recrearional activities that take into account a range of functional abilities.

Psychologist

Neuropsychologists with skills in clinical psychology help to define and manage cognitive impairments and mood and behavioral disorders. Detailed psychometric testing is

fundamental to establishing a rehabilitation program for a patient with cognitive impairment. The neuropsychologist often takes the lead in the management of sevetc brain injury resulting from trauma ot sttoke and plays an important tolc in counseling patients, caregivers, and staff. When working with patients after TBI, the neuropsychologist establishes operant conditioning patadigms or a token economy to reinforce appropriate social interactions and learning. The neuropsychologist also develops relaxation techniques for anxiety states and behavioral approaches for chronic pain management.

Social Worker

Social workers deal with the psychosocial aspects of disability and provide counseling and often brief psychotherapy. Their concerns extend to the ability of the patient and family to cope with disability in and out of the hospital. They play a key role in apprising the rehabilitation team about family issues, supports needed by the disabled patient, and appropriate care providers in the community. The close interactions of social workcts and patients or caregivers often provide great insighi into the dynamics of family involvement and the adequacy of resources. They act as a liaison to a wide range of agencies and to case managers from insurance companies. Smooth discharge planning from an inpatient service usually includes their assistance.

Ortbotist

Expertise in the manufacture, selection, and application of orthotic devices is another key component of a rehabilitation service. The PT or OT works with an otthotist to select external devices that apply or remove forces to ot from the body in a controlled manner. Although many orthotic devices are mass-produced, the expertise of a trained orthotist is often invaluable in choosing and constructing orthoses and supervising theit fitting and adjustment. Orthoses include ankle and ankle-knee braces, hand and shoulder splints, spinal braces, collars, and corsets. Materials are most often a type of plastic, but leathet and metals may be used, depending on mechanical needs. The effects of pressure, shear forces, and heat retention with sweating must also be considered to protect the skin.

With shortened inpatient stays, ankle-foot orthoses (AFOs) that fit inside a shoe tend to be used eatly to achieve ambulation in patients with a central or peripheral lesion. Observation of gait usually is enough to determine the need for a trial with an AFO. Indications include inadequate dorsiflexion for initial heel contact or for toe clearance during midswing, excessive hip-hiking during swing, media I-lateral subtalar instability during stance, tibial instability during stance, uncontrolled foot placement caused by sensory loss, and an operative heel cotd lengthening. If the knee of the hemiplegic buckles during stance, angling the AFO in slight plantatflcxion will extend the knee catlicr. Dorsiflcxing the AFO by 5 degrees can decrease knee hyperextension and help prevent the snapping back that causes instability and pain in midstance. Ankle inversion may necessitate greater rigidity and longer anterior foot trim. Figure 54.4 shows a thermoplastic AFO that fits in a shoe to limit plantar flexion and rotation and help control the knee. Orthoses may be static, such as a rest splint worn at night, or dynamic with joints that may be lockable or free moving. Figure 54.5 shows a thermoplastic AFO with a hinged joint that allows some flexibility when a patient goes to stand, and some give at heel strike to start the stance phase of the gait cycle. Toe clawing can be managed with a metatarsal pad that spreads the toes. The ankle can be articulated with a stop that permits greater flexion during stance. The brace can also be spring loaded for dorsiflexion of a drop foot in eatly stance.

A metal double-upright brace can offer greater rigidity for mediolateral instability and allows more versatility in adjustments for the amount of plantar and dorsiflexion but can be more expensive, too heavy, and cosmetically unappealing to the hemiplegic patient. Metal bracing systems are used more often by select subjects with pataplcgia from spinal injuries and in those with polio. Lightweight plastic knee-ankle-foot orthoses (KAFOs) with locking metal knee joints can also assist patients with profound polyneuropathy, muscular dystrophy, meningomyelocele, or SCI. Reciprocal gait orthoses (RGOs) with wire cables that link flexion of one hip to extension of the opposite hip are available for paraplegics. Short-distance ambulation for exercise can also be aided in the patient with SCI by vatiations on a KAFO and other devices. Bracing in people with SCI has been combined with FES to improve stepping and decrease its energy cost.

The thoracolumbar support shown in Figure 54.6 was molded to the patient to lessen neck motion after a high thoracic vertebral injury and surgical stabilization. Static orthoses allow no motion of the primary joint. Solid wrist-hand orthoses usually are set between neutral and 30 degrees of extension. Dynamic orthoses use elastic, wire or powered levers that compensate for weakness or an imbalance in strength and allow some controlled movement, Figure 54.7 shows the paretic left hand of a patient with a C6 SCI holding a card with the aid of a thumb opposition splint. The weaker right hand needs wrist extension to mechanically oppose the thumb to the second and third digits. Such custom-made devices can be produced with lightweight metals and plastics.

Process of Rehabilitation

Assessment

The quality of cate is only as good as the assessment on which it is based, particularly in relation to the complex difficulties encountered by patients with neurological

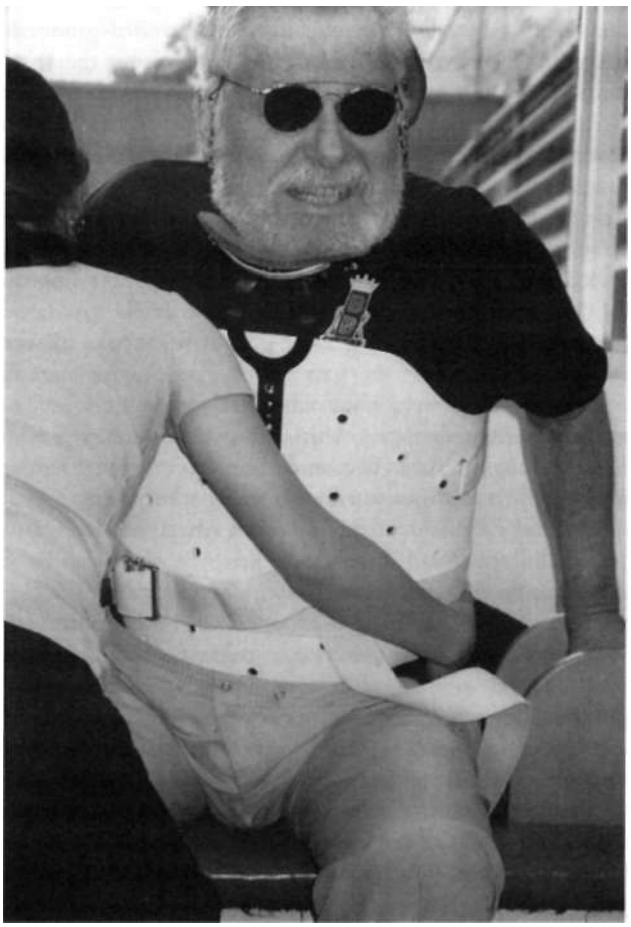

FIGURE 54.6 Tins thoracolumbar support orthotic was molded to the patient's chest to limit upper thoracic vertebral motion after a high spinal cord injury and surgical fusion. The chin brace and stiffness of the jacket limit early progress in mobility tasks for transfers. The riser grips he holds make it easier to practice pushing down into the mat to raise his buttocks.

disability. Accurate assessment means getting to the bottom of the mechanisms behind problems that affect patient functioning. It is the only sound basis for care plans, individual treatment, and effective advice. Assessment incorporates analysis, synthesis, and evaluation. Neurorehabilitation assessment involves identifying the most productive focus for interventions and the most appropriate setting in which they can be achieved and predicting anticipated outcomes and time frames. Assessment in neurorehabilitation may also be described as formative, that is, an ongoing process to target and develop appropriate interventions. In this respect the rehabilitation process is unusual in that assessment and treatment are an integral process: Assessmenr initiates a treatment program that i[1]- continually revised in li^ht ot successive assessments.

duiit Selling

An expert assessment should provide sufficient information to allow a reasonably accurate prediction of the potential

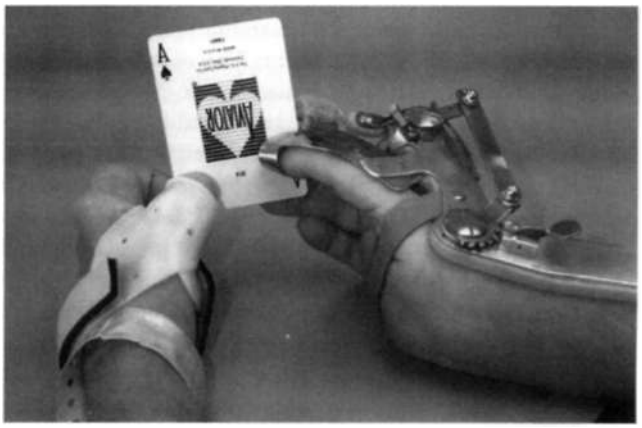

FIGURE 54.7 This card-playing patient with a C6 spinal cord injury uses a molded thumb opposition splint to pinch better with the right hand and a lightweight metal tenodesis orthotic that pinches the thumb to the next two fingers when he dorsiflexes his wrist.

outcome for the patient after a course of rehabilitation. Both short-term and long-term goals take into account the amount of likely neurological recovery and the amount of residual disability. The long-term goal must be broken down into logical, measurable steps that move steadily toward the final outcome. Goal-setting serves as an encouragement ro the patient as the short term goals are achieved, as a way to monitor rehabilitation, and as a way to identify newly emerging problems. Short-term goals must be relevant and motivating, express explicitly what is to be accomplished, and be functional, attainable, realistic, and measurable. They should be discussed with the patient and agreed upon.

Evaluation: What to Measure in Neurological Rehabilitation

In the past decade there has been a major increase in inrerest in outcome measurement as a method of demonstrating the effectiveness of an intervention, an essential prerequisite for evidence-based clinical decision making. What is especially important to measure, and how are these measures taken?

Measures

What to measure depends on the clinical setting and must be based on the anticipated effect of the intervention. Crude, quantitative clinical endpoints such as mortality and survival duration may be important in evaluating early interventions in acute spina! cord or brain injury and stroke but would tell little about disability and quality of life of survivors. For progressive neurological disorders such as Parkinson's disease or MS, qualitative measures are far more valuable for testing interventions than mortality rates.

To provide a comprehensive assessment of the impact of disease, outcomes may be considered at four levels:

- Pathophysiological parameters of disease such as magnetic resonance imaging, PET, and transcranial magnetic stimulation
- Crude clinical endpoints such as relapse rate in MS, seizure frequency in epilepsy, and mortality in stroke
- Relevant aspects of health status, such as disability
- Health-related quality of life

Each of these levels addresses distinct aspects of the disease process. The relationships between them are complex, The first two levels entail physician-oriented outcomes, whereas those at the third and fourth levels are more accurately called patient-based outcomes, although only the fourth incorporates the patient's perspective. Rehabilitation is especially interested in measures of the impact of disease, which is contained within the World Health Organization (WHO) International Classification of Impairments, Disabilities and Handicap. As shown in Table 54.5, the focus is on the consequences of the disease or health condition rathet than the disease alone (i.e., a classification of disablements and functioning). A classification available on the WHO Web site (www.who.int/icidh/) examines activities that disabled people can and cannot do and indicates whether people actually perform these activities. The dimensions of the WHO classification also include personal and environmental factors that affect functioning. The emphasis on activities, participation, and contextual factors interacting with impairments and disabilities may influence the design of new measurement tools.

Two types of measures exist for each of these domains: measures that arc specific to a given disease and generic ones that may, with caution, be applied across a range of diseases (sec Table 54.5). The former may be more sensitive in detecting changes particular to the effects of an individual disease, whereas the latter may allow comparisons across different diseases and serve as an off-the-shelf tool. Examples of generic measures of disability include the 10-item Barthel Index (BI), which can be totaled to a maximum score of 20 or 100 (Table 54,6), and the 18-item Functional Independence Measute (FIM), which includes a modestly responsive cognitive component for a total of 126 points (Tables 54.7 and 54.8). The FIM is used more often in America than in Europe or Asia. Although it has been applied to many neurological diseases, more than a few investigators have questioned this applicability. The FIM and BI and two other scales (Tables 54.9 and 54.10) are commonly used in clinical trials. They correlate closely with each other. In many respects, they reflect the burden of care needed by patients. These and most scales have floor or ceiling effects, dubious meaning when applied to a

Table 54.5; World Health Organization system of classification

		Exemplar outcome measures	
Term	*Definition*	*General*	*Disease specific*
Impairment	Clinical signs or symptoms resulting from nervous system damage	British Medical Council Scale of Muscle Strength ASIA Neurological Classification for SCI Glasgow Coma Score Wechslcr Adult Intelligence Scale Boston Diagnostic Aphasia Examination Ashworth Scale of Spasticity Timed tasks (walking 10 m; hand function, e.g., Nine Hole Peg Test)	Fugl-Meyer Assessment of Physical Performance Scale (stroke) National Institutes of Health Stroke Scale MS Functional Composite Scale Expanded Disability Status Scale (MS)
Disability or activity	Limitations on activities of daily living from neurological impairment	Barthel Index Functional Independence Measure Beck Depression Inventory	Guy's Neurological Disability Scale (MS) Frcnchay Activities Index (stroke) Stroke Impact Scale Glasgow Outcome Scale (TBI) Disability Rating Scale (TBI) United Parkinson's Disease Rating Scale Quadriplegia Index of Function
Handicap or participation	Social and environmental consequences from impairment and disability	London Handicap Scale	Environmental Status Scale (MS) Craig Handicap Assessment and Reporting Technique (SCI)
Health-related quality of life	The satisfaction that patients have with health-related dimensions of life, as judged by the patient	Short Form-36 Nottingham Health Profile Sickness Impact Profile	MSQoL-54

ASIA = American Spinal Injury Association (see Chapter 56); MS = multiple sclerosis; SCI = spinal cord injury; TBI = traumatic brain injury.

Table 54.6: The Barthel Index

	Help	*Independent*
1. Feeding (if food needs to be cut up = help)	5	10
2. Moving from wheelchair to bed and return (includes sitting up in bed)	5-10	15
3. Personal toilet (wash face, comb hair, shave, clean teeth)	0	5
4. Getting on and off toilet (handling clothes, wipe, flush)	5	10
5. Bathing self	0	5
6. Walking on level surface (or, if unable to walk, propel wheelchair)	10	15
(*scorc only if unable to walk)	0*	5*
7. Ascend and descend stairs	5	10
8. Dressing (include tying shoes, fastening fasteners)	5	10
9. Controlling bowels	5	10
10. Controlling bladder	5	10

disease for which no validity and reliability data have been obtained, and variable sensitivity to change, especially when used during outpatient care. Useful measures with an assessment of their applicability for neurological rehabilitation can be found (Dobkin 2003).

How to Measure

Irrespective of what is to be measured, two essential issues must be addressed if the data are to be clinically meaningful. The outcome measure must be clinically useful and scientifically sound.

Clinical Usefulness. Factors that determine whether an instrument can be successfully incorporated into clinical practice and is appropriate to the study sample are the method of administration, appropriateness, user acceptability, and score distributions. The most widely used methods of administration are patient completion (Medical Outcome Study 36 Item Shore Form [SF-36] Survey;

Table 54.7: Functional Independence Measure (FIM)

Items
Self-care
- Eating
- Grooming
- Bathing
- Dressing upper body
- Dressing lower body
- Toileting

Sphincter control
- Bladder management
- Bowel management

Mobility and transfers
- Bed-to-chair and wheelchait-to-chait transfer
- Toilet transfer
- Tub and shower transfer

Locomotion
- Walking or wheelchair use
- Climbing staits

Communication
- Comprehension
- Expression

Social cognition
- Social interaction
- Problem solving
- Memory

Burden of Care Rating
7 = Complete independence (timely, safely)
6 = Modified independence (device)
5 = Supervision
4 = Minimal assistance (subject = 75% +)
3 = Moderate assistance (subject = 50% +)
2 = Maximal assistance (subject = 25% +)
1 = Total assistance (subject = 0% +)

Table 54.8: Description of functional independence measure levels of function

Independent
Another person is not needed for the activity (no helper).
7. Complete independence: All tasks desctibed as making up the activity typically are performed safely without modification, assistive devices, or aids and within a reasonable time.
6. Modified independence: The activity involves one or more of the following: an assistive device is needed, more than a reasonable time is needed, or there are safety (risk) considerations.

Dependent
Another person is needed for supervision or physical assistance for the activity to be performed, or it is not performed (requires helper).

Modified Dependence: The patient expends half (50%) or more of the effort. The levels of assistance needed are the following:
5. Supervision or setup: The patient needs no more help than standby assistance, cueing, or coaxing, without physical contact, or the helper sets up needed items or applies orthoses.
4. Minimal contact assistance: With physical contact, the patient needs no more help than touching and expends 75% or more of the effort.
3. Moderate assistance: The patient needs no more help than touching or expends half (50%) or more {up to 75%) of the effort.

Complete Dependence: The patient expends less than 50% of the effort. Maximal or total assistance is needed, or the activity is not performed. The levels of assistance needed are the following:
2. Maximal assistance: The patient expends less than 50% of the effort but at least 25%.
1. Total assistance: The patient expends less than 2.5% of the effort.

Table 54.9: Glasgow outcome scale

Score	*Outcome*
1	Death
2	Vegetative: unresponsive and speechless
3	Severe disability: dependent on others for all or part of care or supervision because of mental or physical disability
4	Moderate disability: disabled but independent in activities of daily living and community
5	Good recovery: resumption of normal life; may have minor neurological or psychological deficits

Ware et al. 1993), interview rating {standard neuropsychological testing), behavioral observation (BI), examination rating (Ashworth Scale), and raring by team consensus by trained observers (FIM). The method of administration has important implications for the design of clinical studies and for cost.

Appropriareness of a measurement tool takes into account the anticipated effect of the intervention and of the patient population, including factors such as disease type and severity. Considering the area of neurorchabilitation, it may be anticipated that intervention will result in change in disability and health-related quality of life, and have an impact on mood, emotional well-being, coping skills, and self-efficacy. Each of these outcomes may need to be measured because they may change independently of each other; that is, a rehabilitation intervention may have a different effect on disability than on general well-being or affect mobility but not disabilities related to functional use of the upper extremities.

User acceptability is equally important. If an instrument is to be clinically useful and acceptable so it can be incorporated into daily practices, it must be brief, user friendly, practical to administer, and cost-effective. Unwieldy, time-consuming, or re source-heavy instruments have limited use in clinical practice.

Finally, if an instrument is to be a useful measure of an attribute such as disability, it must adequately represent the true distribution of that attribute in the study, must discriminate between individuals in the study sample, and must detect change in the attribute being measured. These issues can be addressed by examining the score distribution in the sample of interest, that is the range of scores, mean score and standard deviation, and floor and ceiling effects. Ideally, the range of the sample should approximate the possible range of the scale, and the mean score should be near the midpoint of the possible scale range. Floor and ceiling effects are calculated as the percentage of subjects scoring the minimum and maximum possible scores, respectively, and should not exceed 15%. Higher deviations may compromise the sensitivity of an instrument to detect change in the attribute being measured.

Table 54.10: The Rankin Disability Scale

Score	*Disability*
1	No disability
2	Slight disability: unable to carry out some previous activities but looks after own affairs without assistance
3	Moderate disability: needs some help but walks without assistance
4	Moderately severe disability: unable to walk and do bodily care without help
5	Severe disability: bedridden, incontinent; constant nursing care needed

Scientific Soundness. Clinical usefulness docs not guarantee scientific soundness in terms of rigorous measurement. The outcome measure must contain three essential and intimately related scientific properties: reliability, validity, and responsiveness. A reliable measure produces results that are accurare, consistent, stable over time, and reproducible. The purpose of reliability testing is to determine the extent to which random measurement error is present. Random error includes all chance factors of produced variations on repeated measurement. The potential sources of random error include errors in the measure itself, the person doing the measuring, and the person being measured. Measures have four types of reliability: internal consistency, test-retest, interrater and intraratcr reliability, and parallel test forms. Reliability is also necessary for an instrument to be valid.

Validity concerns the relationship between the concept being measured and the instrument being used to assess that concept. It is broadly defined as the extent to which the instrument measures the concept it purports or is intended to measure. Three rypes of evidence support validity: content related, criterion related, and construct related.

Responsiveness is the ability of an instrument to measure clinically important change and change over time. It is essential in evaluating the relative benefits of differing interventions. Sensitivity to change is particularly important when treatments are associated with small but significant differences that may be undetected by insensitive measures. Responsiveness often is reported in the form of an effect size that is most commonly defined as the mean change score divided by the standard deviation of the baseline score.

Measures and Designs for Clinical Trials

Rehabilitation interventions have been slow to conform to scientifically designed clinical trials. Although general rehabilitation has been the subject of trials in patients with stroke, MS, aphasia, and other diseases and disabilities, trials are especially needed to assess a particular intervention for subjects with a particular set of disabilities **that** are the target of the well-defined intervention. Physical interventions arc far more difficult to provide in a

reproducible fashion than drug therapies. Outcome measures are also less easy to develop and apply when the primary outcome is levels of disability or of a specific disability rather then outcomes such as mortality, morbidity, survival time, or subjects who survive without disability, which are typical measures of drug and surgical studies. Ongoing multicenter randomized trials of locomotor training with body weight support for acute SCI and of constraint-induced movement therapy for patients with subacute stroke will help determine the feasibility of complicated but defined physical treatment strategies provided by many therapists. A variety of designs for rehabilitation studies have been summarized (Dobkin 2003).

General Organization for Neurorehahilitation

Rehabilitation is a complex, multifaceted entity in that it attempts to address a wide range of needs across diverse conditions and involves multiple disciplines that must interact effectively if the outcome is to be optimal. Such complexity requires a clearly articulated structure supported by appropriate documentation.

The development of a comprehensive, shared system of documentation that reflects the process of the rehabilitation unit's activity from initial assessment to discharge can provide clear evidence of unit practice and reflect its underlying philosophy about patient care and team work. From this commonly agreed baseline, proposed innovations can be analyzed in terms of their relative value and how they may affect other aspects of unit activity. If the documentation is regularly reviewed and accurately reflects current practice, new staff from all disciplines can quickly orient themselves to the agreed system without relying on subjective interpretations of routine. A comprehensive system of unit documentation may include integrated care pathways or the latest version of inpatient rehabilitation payment created for Medicare in the United States. An integrated pathway details the expected interventions occurring during a given episode of clinical care. Departures from the expected pathway are documented, coded, and analyzed after an agreed number of patients have been through the pathway. This identifies areas in the service that need improvement. In addition to documenting the process of care, rehabilitation pathways incorporate the long-term and short-term goals that form rhe basis of most rehabiliration programs. This audit can have a reciprocal role in describing, guiding, and promoting effective unit practice.

Service Provision

The way in which services are organized depends to some extent on the disease being managed. The most fundamental differentiation is between acute events such as brain and spinal cord trauma and stroke, mostly static conditions in which disability might increase with aging and overuse of muscles and joints such as cerebral **palsy** and polio, and progressive disorders such as MS and Parkinson's disease. Service provision should also be driven by the acknowledged philosophy underlying rehabilitation: to optimize home and community activities and return the patient to the community as soon as possible. The speed with which this is done depends as much on the services available in the community as on the severity of the disability and the capacity of the family and caregivers to look after the patient. Some tension arises between inpatient services, in which all the necessary ingredients may be gathered under one roof, and community services, which may be less centralized but support patients in their own environment. More important is the smooth interface between these two settings,

Inpatient Rehabilitation Unit. The most efficient rehabilitation setting is an inpatient unit designed and staffed specifically for this purpose. The value of such dedicated units was first appreciated in the acute management of SCI by Sir laid wig Guttman after World War II and has been applied to other diseases such as polio after epidemics. The benefits of acute units in stroke management have been convincingly demonstrated. Patients treated in stroke units are significantly less likely to die than those cared for on ordinary wards. Death, institutionalization, and dependency are all significantly less common in stroke unit patients, in part because of a reduction in secondary complications of stroke and a milieu dedicated to managing disability. Parly functionally oriented therapies by an organized team tend to get patients independent enough to return home sooner than sporadic therapy that does not articulate specific attainable goals for mobility, self-care, and family training. These benefits persist for up to 5 years after discharge and improve quality of life (Jorgensen et al. 2000).

Several studies of TBI suggest the benefit of coordinated care starting during the inpatient stay. Investigators randomly assigned 120 active-duty military personnel who suffered moderate TBI to a standardized, inpatient milieu-based cognitive rehabilitation program or to a home program with weekly phone support from a nurse and mental and physical exercises carried out on their own for about 30 minutes a day (Salazar et al. 2000). The inpatient program used both a didactic cognitive and functional experiential approaches. Treatment lasted 8 weeks. Outcomes did not differ 1 year later in standard cognitive tests, social adaptation, mood, behavior, or fitness for military duty. More than 90% returned to work. Aggression increased in both groups, suggesting the need for ongoing support.

The role of inpatient rehabilitation units in managing progressive conditions such as MS and Parkinson's disease is much less well defined, although some evidence suggests

a benefit in progressive MS. Inpatient care may also return patients home at a higher level of functioning after implantation of a deep brain stimulator for Parkinson's disease or after an exacerbation of walking disability caused by a hip fracture in a patient with a chronic hemiparesis.

Community Setting. Although community-based rehabilitation is often mentioned and appears to have a number of advantages from the perspective of the disabled patient, few studies have addressed its efficacy. This may relate at least in part to the methodological difficulties in defining the training team's level of expertise, the patient's level of disability, and the frequency, duration, and type of therapy. One large randomized trial compared rehabilitation at home after an average 12-day inpatient stay with another week of inpatient care followed by hospital-based outpatient treatment. Patients who lived alone were independent in transfers when they left the hospital, or they needed to be assisted by a caregiver. Similar outcomes 12 months after a stroke were achieved at lower cost because of less use of hospital beds by the early discharge group. An intention-to-treat randomized trial with 250 subjects showed that rehabilitation in an inpatient unit after a brief stay in an acute stroke unit or general medical ward produced better outcomes in moderate to severely disabled patients (BI score <50) compared with rehabilitation treatment in the community. No differences in quality of life were found, and levels of activity outside the home were not measured. Smaller trials confirm similar positive outcomes at 3-6 months for home compared with various forms of outpatient care, with the home group having fewer in-hospital days and greater gains in instrumental ADLs.

A day treatment program for about 100 patients who were unable to work 1-2 years after TBI provided a range of interventions during group therapy for a mean of 190 days. The investigators found a significant reduction in physical disability, increased self-awareness and emotional self-regulation, and more effective participation in interpersonal activities. One year after completion, 72% lived independently and 57% were employed.

A brief stint of outpatient therapy for a well-defined goal, such as to improve transfers in a patient who declines from MS or to make walking safe again after an illness that causes dcconditioning in a patient with chronic hemiparesis, is an invaluable means for patients to maintain their highest level of independence. A few therapy sessions a week for a few weeks plus a home program accomplishes this limited task-specific goal and relieves caregivers of new burdens. For example, a bout of therapy for aerobic conditioning and muscle strengthening lessened disability in patients with chronic stroke. A randomized trial entered 110 patients with mostly chronic TBI to an outreach program in rhe community or to provision of written material about resources for patients and families (Powell ct al. 2002). The outreach group met about twice a week for a mean of 27 weeks. The outreach group made modest but significant gains in scores on the BI and a brain injury outcome measure 2 years after the start of this late intervention,

Organization of Services

The most efficient structure for rehabilitation services in many countries includes a two-tiered system of service delivery. Regional specialists can manage complex and profound disabilities, and local community services provide neurological disability teams from local hospitals or directly in the community. Regional neurological rehabilitation centers provide experts familiar with the management of complex and severe disabilities, act as a focus for education, training, and research, and should be linked to university teaching centers. Such centers can offer care for patients with high SCIs and severe traumatic brain injuries, manage specialized orthopedic and plastic surgery procedures, and provide wheelchair and special seating needs, custom orthotics and prosthetics, rehabilitation engineering, functional electrical stimulation devices for walking and upper extremity movement, neuroprostheses, communication aids and environmental controllers for quadriparetic patients, and driving assessments.

Most disability services can be provided locally, which is likely to be both cost efficient and effective. Services provided by a multidisciplinary neurological disability team based in a local hospital can develop community outreach into clinical centers and homes. Resources arc often not adequate for this approach, and in some situations serious consideration should be given to the community-based rehabilitation model developed by the WHO, which allows communities to develop their own support mechanisms for disabled people, often with locally trained workers supervised by qualified staff providing basic rehabilitation treatment and advice. Tclerchabilitation services may prove especially useful in supporting patients who live far from available services or are too disabled to leave the home.

Service for Chronic and Progressive Neurological Disorders

Rehabilitation services for patients with chronic or slowly progressive neurological disorders ofren are inadequate. Services must anticipate and manage exacerbations and worsening disability, support self-management, and keep the patient in the community, reducing the need for hospital or nursing home admissions. Services must meet a broad range of needs that change over time. Patients after stroke may develop a painful joint or hip fracture that causes walking skills to decline. A bout of locomotor retraining can reverse this disability. Patients with MS have increasing disability and handicap over three or four decades with

little effect on longevity. For patients with muscle disorders, peripheral neuropathies, motor neuron disease, and Parkinson's disease, close surveillance can anticipate and reduce the burden of these diseases through specific goal-oriented therapies, caregiver training, and assistive devices.

BIOLOGICAL BASES FOR REHABILITATIVE INTERVENTIONS

The potential to enhance neurological recovery by manipulating the biological adaptability of the brain and spinal cord has become relevant to clinical practice. Basic ncuroscience studies suggest that physical and pharmacological interventions, along with natural biological reactions to injury, could inhibit or enhance the restoration of motor and cognitive functions. Table 54.11 outlines some of the potential mechanisms that contribute to changes in impairments and disabilities. These arc not discrete mechanisms. They overlap and many depend on each other over varying intervals of time. In addition, biological therapeutic-approaches such as tissue implants may enhance these mechanisms when applied to human studies of recovery in the near future. These potential mechanisms, drawn mostly from in vitro and in vivo experiments with invertebrates and vertebrates, are the subject of much ongoing investigation. Although care must be taken in extrapolating from animal studies of recovery to their implications for human interventions , at least a few of these potential mechanisms suggest strategies that the rehabilitation team can use to improve outcomes.

Table 54.11: Mechanisms that may support recovery of function

Net work Plasticity
Recovery of neuronal excitability
Resolve cell and axon ionic dysequilibrium and conduction block
Resolve edema, resorb blood products
Reverse diaschisis
Increased activity in neurons adjacent to injured ones and in partially spared pathways
Representational adaptations in neuronal assemblies
Expansion of representational maps
Recruitment of cells not ordinarily involved in an activity
Recruitment of parallel and subcomponent pathways
Altered activity in distributed cortical and subcortical networks
Activation of pattern generators (e.g., for stepping)
Recruitment of networks not ordinarily involved in an activity
Modulation of excitability by neurotransmitters
Use of alternative behavioral strategies
Neuronal Plasticity
Altered efficacy of synaptic activity
Activity-dependent unmasking of previously ineffective synapses
Learning tied to activity-de pendent changes (e.g., long-term potentiation, long-term depression) in synaptic strength in perilnjury and remote regions
Increased neuronal responsiveness from denervation hypersensitivity
Delayed decline in number of neurons (e.g., from apoptosis)
Change in number or variety of receptors
Change in neurotransmitter release and uptake
Regeneration and sprouting from injured and uninjured axons and dendrites
Signaling gene expression for cell viability, growth, and remodeling proteins
Modulation by neurotrophic factors
Actions of chemoattractants and inhibitors in the milieu
Remyelination
Transsynaptic degeneration
Actions of neurotransmitters and neuromodulators on cell functions
Neurogenesis

Source: Adapted with permission from Dobkin, B. 2003, *The Clinical Science of Neurologic Rehabilitation,* Oxford University Press, New York.

Recovery of Neuronal Excitability

Reversal of toxic-metabolic insults to neurons, axons, and glia plays an early role in recovery of function. Recovery of impairments could be delayed until intracellular and extracellular edema, acidosis, and ion fluxes resolve and until protein synthesis restarts, the mass and toxic effects of blood from a hemorrhage lessen, and other cellular functions return to normal. Some of the gains in the first days to few weeks after TBI, SCI, and stroke seem related to these mechanisms. Acute medical interventions to spare the penumbra of hypometabolic tissue on the edge of an infarction have been a mainstay of approaches to neuroprotection in stroke. The extent of the recovery of penumbra! tissue has been correlated with recovery of hmcrion in patients after stroke. The surviving penumbra may be a substrate for long-term potentiation (LTP) and synaptogenesis, which predisposes it to activity-dependent learning and reorganization.

Remote effects of an injury, caused by a lack of transsynaptic activity along a neural pathway after one of its links has been damaged or by loss of modulation by noradrenergic, serotonergic, dopaminergic, or cholinergic neurotransmission, could also transiently limit recovery. This transsynaptic functional deactivation, called diaschisis, has been demonstrated in autoradiography and PET studies. After a thalamic infarct, for example, hypometabolism of frontoparietal cortex that had received input from this complex is often found, as is hypometaholism of the dorsolateral frontal cortex after a stroke in the caudate and anterior limb of the internal capsule. Although resolution of remote functional deactivation has been suggested as a mechanism of motor recovery in animal studies, human studies with functional imaging have not clearly revealed a relationship between the degree of impairment of recovery and regions of anatomically remote hypometabolism.

Activity in Partially Spared Pathways

Partial sparing of neuronal clusters, as in peri-infarct tissue, or in tracts such as the posterior limb of the internal capsule, probably would permit a lessening ot impairment and disability over days ro a few months after injury. Many experimental studies reveal that as little as 20% sparing can provide the minimal residual structure necessary for near-normal functioning. For example, symptoms of Parkinson's disease evolve after about 75% of dopamine-containing neurons have died, and locomotor function decompensates when 95% are lost. In a classic human study, Bucy relieved hemiballismus by incising a portion of the cerebral peduncle. Within 24 hours, the patient's flaccid hemiplegia began to improve. By 7 months, the patient plateaued with a very mild hemiparesis, independent gait, and the ability to hop on the contralateral leg. At autopsy only 17% of the axons in the medullary pyramid persisted, and an estimated 90% of precentral giant cells of Betz suffered retrograde degeneration.

Partial wallerian degeneration of the corticospinal tract can sometimes be seen on magnetic resonance imaging after stroke (Figure 54.8). By computed tomography, sparing of more than 60% of the cerebral peduncle, including the medial portion, predicts the recovery of a precision grip and, to a lesser degree, the force of the grip (Figure 54.8A). Greater sparing of the primary motor cortex (Ml) and less wallerian degeneration are associated with better hand function in studies that involved functional neuroimaging (Feydy et al. 2002). The typical hemiplegic posture of elbow, wrist, and finger flexion followed 60% shrinkage, which roughly corresponds to a loss of 88% of the descending fibers. Better motor and functional outcomes have also been associated with sparing of metabolic activity in the thalamic and basal ganglia-frontal network and with sparing of the basal ganglia ipsilateral to the stroke. About 20% sparing of the ventral or ventrolateral funiculi after SCI permits fair motor function, and *$5%* sparing of the dorsal funiculus allows appreciation of dorsal column sensory inputs.

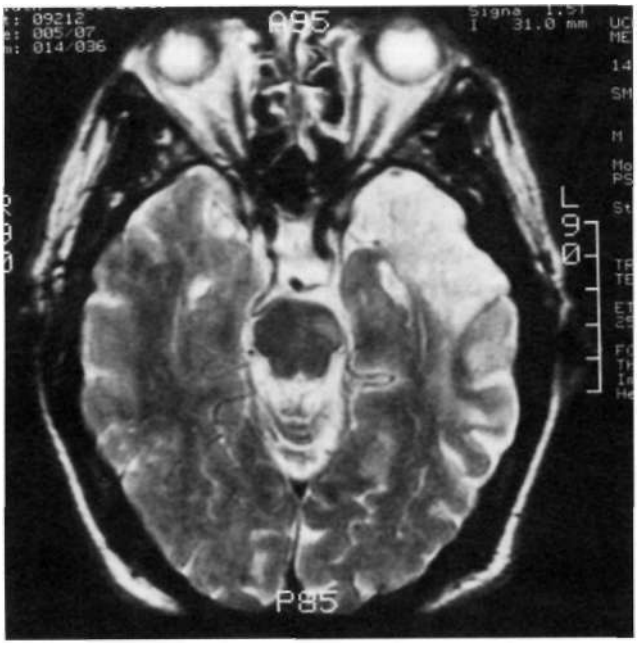

FIGURE 54.8 Magnetic resonance imaging 6 months after a left hemisphere stroke reveals atrophy of the ipsilateral cerebral peduncle of about 40% compared with its homologous peduncle on the right and wallerian degeneration of the basis pontis involving a moderate amount of the corticospinal tract. After an initial hemiparesis, the patient was able to oppose his thumb to all fingers, use the hand in activities of daily living, and walk 50 feet in 14 seconds (normal) with minimal gait deviations. The imaging is consistent with enough pathway sparing to have allowed retraining of residual sensorimotor pathways for this functional gain.

The recovery of vision after an occipital stroke may depend on spared parts of the vision-associated areas of the cortex. Patients who recover from a hemianopsia tend to activate bilateral extrastriatal cortex during hemifield stimulation to the affected occipital lobe. Involvement of primary and extrastriatal cortex leaves a persistent field loss.

Residual neurons and axons of an injured tract may need rehabilitative training to help drive activity-dependent plasticity and permit success in carrying out tasks. When the number of corticospinal fibers that synapse with spinal motor pools is too small to generate adequate excitatory postsynaptic potentials, a descending volley will not excite the spinal neurons. Recovery of an adequate excitatory postsynaptic potential might follow practice that strengthens synaptic efficacy. Other contributors to spared pathway functioning brought on by relearning and associated adaptations include changes in ion channels, increased strength of output from undamaged cortical and brainstem neurons that also descend onto spinal neurons, dendritic sprouting, and uprcgulation of the number of motor neuron and interneuron excitatory receptors. In addition, the ipsilateral motor cortex, via the uncrossed ventral corticospinal tract, has often been invoked as a pathway that might provide some of this input and compensate for a contralateral cerebral injury. The fibers of the ventral tract synapse especially with motoneurons for axial and limb girdle muscles. Functional neuroimaging studies that involve training of the upper extremity, the leg for walking, and language after aphasia suggest that better gains are associated with greater contralateral cortical activation rather than with ipsilateral homologous regional activity.

Alternative Behavioral Strategies

Many functional activities can be accomplished without the use of an affected extremity. Behavioral adaptation and compensation often allow greater independence in ADLs

despite persistent impairments. Motor functions can appear to have fully recovered when in fact residual neural activity is supporting behavioral plasticity. For example, after a unilateral pyramidal lesion in the rodent or monkey, reaching for a pellet of food gradually improves and at first glance may appear to have recovered fully. A closer analysis of the movement reveals better control of the proximal than the distal limb. The animal reaches with a grasp, brings the pellet to its mouth without the normal supination of the hand and forearm, turns its head to chase after the food, and cannot easily release its grip. The hand-to-mouth movement pattern of the hemiparetic patient is similar to the lesioned animal's strategy. Functional ambulation often improves, in part, by compensatory gait deviations and with assistive devices. For example, most patients in rehabilitation who had a full middle cerebral artery distribution infarction cannot ambulate 150 feet independently by 6 months after stroke, but more than 75% can with assistance as defined by the BI. Behavioral plasticity itself has a neural substrate that includes training-induced cortical representational reorganization and increased efficiency of residual pathways.

Rehabilitation efforts often train patients to substitute for a lost motor function or to use compensatory movements to accomplish the movement. Alternative strategies, rather than real restitution, arc emphasized. With behavioral compensation, patients learn techniques to adapt ro their new sensory, motor, and cognitive impairments. 1 lowever, substitution may prevent the activity-dependent nervous system reorganization that is needed to encourage greater recovery of a specific impairment.

Distributed Networks

A distributed system is a collection of processing units (i.e., dynamic neuronal assemblies with similar functional properties and anatomic connections), that are spatially separate and exchange messages. Hierarchical, parallel, and quasiserial linking operations arc made with the afferent and efferent systems of the brain (Table 54,12). The nodes in such systems cooperate to manage the diverse information necessary for the rapid and highly flexible control of, for example, cognition and multijoint movements. These circuits lend themselves to an understanding of the neuroplasticity that might contribute to spontaneous and training-induced recovery of function.

Tahlc 54.12: Characteristics of distributed systems

Signal flow follows a number of pathways.
Action may be initiated at any of the modal loci in a system.
Local lesions in a system may degrade but not completely eliminate a function.
Dynamic reorganization may be more important than modification of structural connections.
In a reentrant system, nodes are open to externally and internally generated signals.

The executive motor system has been the subject of recovery-related studies. The primate primary motor cortex (Ml) has separate clusters of output neurons that can facilitate the activity of a single spinal motoneuron. Also, a single cortical motor neuron can project to the spinal motoneurons for several muscles, even those that might act across a joint. In addition, neurons in overlapping Ml territories are activated to produce movements of different body parts. This overlapping organization contributes to the control of the complex muscle synergies for voluntary movement of the arm and leg within the ordinary work-space of the body (Graziano et al. 2002). Multiple representations also have been demonstrated in non-primary motor regions. They are found in the premotor cortex of Brodmann's area (BA) 6, the supplementary motor area and immediately rostral to it, and in BA 23 and BA 24 by the cingulate sulcus. These motor regions have interrelated and overlapping functions with direct and indirect anatomical connections. Each area has an independent set of inputs from adjacent and remote regions, and most have parallel but separate outputs to the brain-stem and spinal cord. The effective unit of operation in such a distributed system is not a particular neuron and its axon but groups of cells with similar functional properties and anatomical connections,

The capacity of motor-related cortices to redistribute their function is apparent from PET and functional magnetic resonance imaging (fMRI) studies that have looked at subjects with recovered hand function after a stroke. For example, after a striatocapsular infarction in patients who recovered finger tapping and hand squeezing, bilateral rather than just contralateral activation of cortical motor neurons was found, along with greater involvement of motor areas that would not ordinarily be visibly activated for that task. Other regions related to selective attention and intention also show increases in blood flow and metabolism, which suggests that they must play a larger role when the substrates for a movement reorganize. Regions that are activated in normal subjects when greater force is exerted, such as insular, premotor, and anterior opercular cortex, may also be activated during movement of a hemiparetic limb (Dettmers et al. 1997), in parallel with the increased effort needed to move that some patients describe.

Parallel, segregated circuits process different variables for movement throughout their integrated pathways, as in the striatum, thalamus, and cerebellum. One study showed that the stimulus parameters in sensory cortex for producing LTP in the motor cortex were within the range of discharges of neurons in the sensory cortex when they respond to peripheral stimulation. The authors proposed that repeated practice of a particular movement increases the excitability of a selected group of terminals in the ventrolateral thalamus so that its untrained, diffuse input

becomes able, with training, to excite selected cortical efferent zones without further input from the sensory cortex. This helps explain how loop circuits form between the motor cortex and periphery, via the sensory cortex and thalamus. They hypothesized that circuits are initially diffuse, leading to excessive muscle contractions during a new movement, but become more specific as LTP is induced by practice. They also showed that repetitive activity of the pyramidal tract neurons in response to sensory input can produce LTP in spinal interneurons.

The cerebellum receives and modulates locomotor cycle-related signals. The neocerebellum monitors the outcome of every movement and optimizes movements using proprioceptive feedback. Given the great computational interest the cerebellum has in the details of afferent information from joints and muscles, rehabilitation therapies for walking and upper extremity actions should aim to provide this key motor center with the sensory feedback that the spinal cord and cerebellum recognize as typical of normal walking and reaching-related inputs. The motor functions that the cerebellar inputs and outputs attend to, such as timing and error correction for accuracy as the hand approaches an object, are especially important for patients to practice when a lesion undermines motor control. Thus individual channels can control separate functional units of motor cortex, and in turn each is independent in its control of subcortical motor nuclei. After an injury, the balance of activities of these networks is reset. Although these systems are not likely to be highly redundant, they may provide a partially reiterative capacity for some sparing or compensation after a sensorimotor network injury. The intact parallel systems from cortical and subcortical areas may partially compensate or substitute for nonfunctional ones when their activity is enhanced by specific cognitive and motor rehabilitative retraining. For example, if the premotor cortex were damaged, compromising visually cued movements, the patient might be taught to use an internally cued strategy mediated especially by the spared supplementary motor area.

The brainstem and spinal cord also contain important subcomponents of distributed motor functions. For example, they contain their own intrinsic networks tor aspects of locomotion. The descending message for the initiation of locomotion seems to be carried by reticulospinal pathways from dorsal areas of the midbrain and pons that synapse with lumbar spinal neurons. Although cortical and peripheral sensory input is essential for normal locomotion under disparate environmental conditions, the timing of synergist and antagonist muscle activity for stepping appears to be primarily the task of a self-oscillating lumbar interneuronal network. Even an isolated section of lumbar spinal cord in mammals can produce cyclical outputs that rhythmically flex and extend a joint. This locomotor circuit is called a central pattern generator and especially depends on glutamate and glycine for alternating excitation and inhibition.

After a complete lower thoracic spinal cord transection, adult cats and other mammals can be trained on a treadmill so that their paralyzed hindlimbs fully support their weight, to rhythmically step, and to increase their walking speed toward what a normal cat can do. Additional studies on adult spinal transected cats that were trained only to stand and then encouraged to step on a moving treadmill showed that postural support alone was detrimental to subsequent locomotion. Thus the details of basic locomotor movements can be carried out by subcomponent nodes of the more complex neural networks for stepping. Evidence of spinal cord learning during step training and by modulation of the H-reflex has been shown in patients with SCI. This activity-dependent plasticity has potential value in rehabilitation. Studies of patients with spinal injury and stroke have used body weight support and treadmill training to take advantage of residual descending controls and spinal mechanisms for stepping (Dobkin 1999).

Chemical and electrical microstimulation in the ventral gray matter of the spinal cord elicits a convergence of the leg from different starting positions to a single position in the body's workspace. In each volume of spinal cord studied, a discrete set of synergistic limb muscle contractions directs the limb toward an equilibrium point across a range of muscle forces. These modules of separable force fields have been called spmal primitives by Bizzi and colleagues (Bizzi et al. 2000). This intrinsic organizarion, combined with central pattern generators, may simplify the work of the supraspinal controllers for common movements such as the synergies that compose stepping. Given the synergies elicited by Ml and premoror cortical microstimulation (Graziano ct al. 2002), it seems likely that a modest amount of residual descending input to the cord from motor areas may be able to trigger spinal synergies for reaching and stepping movements. In addition, segmental sensory inputs to the spinal cord arc likely to be critical modulators of a spinal locomotor control system.

Studies with spinal transected cats and patients with a clinically complete SCI suggest that important sensory inputs associated with stepping include the rate and degtce of hip extension, the level of weight bearing, the timing of hip extension and unloading of the leg at the end of stance for the transition to swing, the increase in loading of the stance leg at onset of swing of the opposite leg, the intensity of practice, and treadmill speed (Dobkin 1999). Normal human walking with the entire ensemble of sensory inputs and descending inputs present may be less dependent on hip position and stance-to-swing group 1 afferent activity. However, proprioceptive feedback related to movement, especially from the lengthening antagonist muscle, is an important signal for the step cycle. Sensory inputs have task-specific effects as well. The same sensory input from the foot that increases hip and knee flexion if applied during the swing phase of the gait cycle increases activation of the extensor muscles if applied during the stance phase.

Therefore to retrain a patient to walk, strategies should be directed to incorporating optimal step-related sensory inputs.

Although we have emphasized aspects of motor recovery, both distributed and hierarchical organization and plasticity are jusr as evident for higher cortical functions. Cognitive domains appear to be mapped at multiple sites that arc highly connected with feedback connections. PET and fMRI studies have begun to reveal changes in the organization ot these interactions tor particular tasks after a cerebral injury. Cognitive rehabilitation strategics have been developed based on the notion that recovery might be mediated by tapping into the locali/.able and distributed grids ot connectivity that are intact.

Cortical and Subcortical Representational Adaptations

Cortical motor and sensory neurons are not permanently fixed in the way in which they subserve their limb functions. In the adult and developing animal and in humans, these representations are distributed, dynamic, .\m\ capable ot much physiological ..\m\ perhaps structural reorganization. Many lines of animal research suggest that compensation after a central or peripheral injury can result from a functional shift to neighboring neurons. As noted earlier, the neurons of the ischemic penumbra of an acute cerebral infarction may play an important role in functional gains. Very early overuse of these neurons was shown to cause greater injury in rat models of stroke and trauma. Such overuse is unlikely in human subjects, however. Indeed, early practice appears important. A primate model of a less than 1-rara injury to the hand area of Ml found that perilesional representations for the digits decreased when the monkey failed to practice using the hand to scoop pellets out of a narrow well. Neighboring representations for the digits, wrist, and forearm increased with practice. Thus cortical representational changes are especially likely to arise during training paradigms that involve learning and the acquisition of specific skills. This plasticity probably arises from the unmasking of previously silent synapses and increases in synaptic efficacy in thalamocortical and intracortical circuits. Over weeks and months, it might arise from sprouting of dendrites over short distances. In animal studies of recovcty of forclimb function, only 12 hours of a specific therapy for the affected limb leads to behavioral gains and cortical representational changes. In human subjects after stroke, representational plasticity for the ankle movers can be shown after intensive practice in step training in patients with chtonic hemiparesis, similar to the evolution of changes observed with massed practice in patients with upper extremity paresis.

The combination of mutable neuronal assemblies that represent movements and sensation and multiple representational maps in a parallel, distributed system offers the opportunity for exploration by those involved in rehabilitation. Behaviorally relevant tasks that arc shaped by an optimal schedule of practice and feedback on neural networks might increase functional gains. The optimal duration and intensity of training are uncettain for human rehabilitation strategies, but greater intensity of practice seems to enhance subsequent performance (Kwakkel et al. 1999; Sullivan et al. 2002}. Unfortunately, most patients get only a few months of formal inpatient and outpatient retraining of modest intensity that is spread across many tasks.

Biological Interventions

The molecular processes that are induced by activity in neurons, axons, and dendrites are under intense investigation, both during normal learning and after an injury. Morphological changes such as axonal regeneration over short distances, dendritic arborization, and synaptogenesis have been observed after a brain injury or SCI. When inputs from one pathway to the dendritic tree of a neuron are lost, intact axons can sprout and form synapses on denervated receptors. The net effect of this change in the weight ol inputs could have a positive or a detrimental effect on neural function. Can such changes be manipulated? Basic neuroscience studies of biological approaches offer some exciting approaches to complement ncurorehabilitation strategies.

Regeneration of injured axons in the central nervous system occurs over very short distances. It depends in part on molecules on the surface of cells and in the extracellular matrix. Tissue culture and vertebrate models have shown that substances in the extracellular matrix and on the surface of oligodendrocytes inhibit elongation of the axonal gtowth cone. Antibodies and receptor blockers have been made to these substances, including to the inhibitor Nogo, leading to growth of axons in the rat after a partial spinal and brain injuries, When they are combined with a growth factor, such as neurotrophin-3, axonal growth further improves. Neurotrophic factors have been used to protect neurons from apoptosis and to signal neuronal machinery to make the substances necessary for neurite outgrowth. Cultured Schwann cells, transplanted olfactory ensheathing cells, embryonic tissue implants, neurotrophic factors delivered by implanted, engineered fibroblasts, and peripheral nerve bridge implants, with a combination of other biological manipulations, have also met with some success in permitting several populations of axons to regenerate across or around a rodent SCI. Bone marrow stromal cells have been injected into the blood after experimental stroke and seem to produce a trophic factor or other support for enhancing plasticity. Cottical and subcortical transplants of stem cells, engineered cells, human embryonal cells that take on the characteristics of local neurons, and progenitor cells for neurons and glia have also been introduced into the brain to promote recovery in animal models.

Physical activity alone can regulate the expression of neurotrophic factors in the cortex and spinal cord and induce neurogenesis, especially in the hippocampus and spinal cord.

Reported cell transplant experiments in humans include numerous interventions for Parkinson's disease that have so far been unsuccessful, safety studies of implantation of a human cell line after chronic subcortical stroke, and embryonic tissue placed in the syrinx of patients with chronic SCI. Several safety studies have failed, including the use of porcine cells. Studies with neuronal and oligodendroglial progenitors arc promising but face many difficulties. A review of biological interventions for rehabilitation and the applicability of animal models to human translational tesearch suggests that clinicians will need to put models into perspective and participate with basic neuroscientists in combining training and transplant technologies (Dobkin2003).

Pharmacological Interventions

Drugs that affect neurotransmission, intracellular second messenger signaling, excitation and inhibition, and the cascades associated with long-term potentiation and long-term depression are candidates to enhance learning and the reacquisition of skills after a brain injury or SCI. At least five neurotransmitter projections have modulating effects on wide regions of the cortex and spinal cord. A lesion may transsynaptically interrupt this neurotransmitter output to cortex and cord, limiting the drive to uninjured regions and producing behavioral deficits. For example, dextroamphetamine augments specific cognitive processes by increasing the signal-to-noise ratio; cholinergic projections serve as a gate for behaviorally relevant sensory information. Animal studies have provided preliminary evidence that a vatiety of pharmacological agents may facilitate or inhibit the rate or degree of recovery of sensorimotor function and walking after a cerebral injury. After being given dextroamphetamine, both rats and cats that underwent a unilateral or bilateral ablation of the sensorimotor or frontal cortex exhibited an accelerated rate of recovery, though not necessarily greater gains than the controls, in the ability to walk across a beam. This endured well pasr the single or intermittent dosing schedule of the drug. Amphetamine and other drugs to be discussed have shown promise in small human trials. Thus specific training paradigms combined with agents might enhance gains. Functional imaging studies with transcranial magnetic stimulation (Boroojerdi et al. 2001) and fMRI may aid in rhe selection of drugs to combine with rehabilitation.

Some drugs have more clear-cut mechanisms of action, For example, the conduction of action potentials along demyelinated axons may be increased by pharmacological agents such as 4-aminopyndine, which block potassium channels and improve impulse conduction. This approach has met with some success in MS treatment. In some patients with motor neuron disease and Guillain-Barre syndrome, anticholinesterase-inhibiting medications, acting on neuromuscular junctions with altered structure and function, have reduced fatigability and improved strength in a modest way.

Drug studies in humans pose confounding problems. The type, location, extent, and age of the lesion and the specific drug, its dosage, time of initiation, duration of use, and adverse effects and the accompanying physical or cognitive therapy that might add to a drug's effect must be determined. What is clear is that clinicians should select medications with special care in the months after a cerebral injury and monitor for effects that seem to impede recovery.

NEUROMEDICAL PROBLEMS DURING REHABILITATION

Neurological and systemic complications often interfere with inpatient and outpatient rehabilitation. With shorter acute hospital and inpatient rehabilitation stays, physicians, nurses, and therapists must anticipate and treat medical problems. Some will arise from new neurological impairments and immobility; others are comorbid conditions that might have caused the acute illness. In addition, patients and caregivers must be trained in the errors of omission and commission and in the risk factors for recurrence of, say, a stroke that leads to late morbidity.

As noted, some but not all studies suggest that specialized stroke, SCI, and TBI hospital programs appear to lead to better early outcomes than does treatment on general medical units. Differences in morbidity, mortality, and length of hospital stay have been associated with more organized services. For example, protocols that use prophylactic subcutaneous heparin, hold oral intake until completion of a screening test for safety of swallowing, limit indwelling bladder catheters to those in coma, and assess posrvoid residuals by ulrrasound to avoid unnecessary intermittent catheterizations can reduce medical complications.

Frequency of Complications

Complications in Patients with Stroke

Medical complications often interfere with a patient's ability to participate in therapy (Table 54.13). About 4 medical and 0.6 neurological complications per patient occur during an average course of inpatient rehabilitation. About one third of patients have a urinary tract infection, urinary retention, musculoskeletal pain, or depression. Up to 20% fall, develop a rash, or need continuous management of blood pressure, hydration, nutrition, ot glucose levels. About 10% develop a transient toxic-metabolic

Table 54.13: General frequency of inpatient stroke rehabilitation neuromedical complications

Complication	*Percentage of patients*
Urinary tract infection	40
Musculoskeletal pain	*M)*
Depression	30
Urine retention	2^
hills	25
Fungal rash	20
Hypertension	20
Hypotension	15
Incipient pressure sores	15
Hypoglycemia or hyperglycemia	15
Azotemia	15
Toxic-metabolicencephalopathy	10
Pneumonia	10
Arrhythmia	10
Congestive heart failure	5
Angina	5
Thrombophlebitis	5
Allergic reaction	5
Gastrointestinal bleeding	5
Pulmonary embolus	<5
Myocardial infarction	<5
Decubitus ulcer	<5
Recurrent stroke	<5
Seizure	<5

Source: Adapted with permission from Dobkin, B. 2003, *The Clinical Science of Neurologic Rehabilitation,* Oxford University Press, New York.

encephalopathy, pneumonia, cardiac arrhythmias, pressure sores, or thrombophlebitis. Up to 5% have a pulmonary embolus, seizures, gastrointestinal bleeding, heart failure, or other systemic complications. Where feasible, prophylactic measures for these potential problems are essential. Because many patients arc transferred from the acute hospital to a rehabilitation unit less than 10 days after a stroke, neuromedical complications may he higher at some centers and include the side effects of starting new medications during the acute stay and recurrent stroke. Across rehabilitation centers, 5-15% of patients must be transferred back to an acute hospital setting.

Complications in Patients with SCI

Medical complications of a somewhat different nature are common in the acute and chronic phases after SCI. In this younger group, chronic comorbid systemic medical problems are less common than in patients with stroke. However, prior substance abuse and emotional and behavioral disorders can complicate therapy. In the first 6 weeks aftet SCI, operative procedures affect what can be done in rehabilitation. About one half of patients get a spinal fusion and internal fixation. Acute spinal care also entails the use of externa) stabilization techniques, such as halo vest and Philadelphia collar for cervical injuries and a thermoplastic, custom molded brace for thoracolumbar

Table 54.14: Medical complications within 6 weeks of acute spinal cord Injury

Complication	*Percentage of patients*
Urinary tract infection	46
Pneumonia	2S
Decubitus ulcer	IS
Paralytic ileus	9
Arrhythmia	*6*
Sepsis	6
Thrombophlebitis	5
\\ omul inflation	4
Gastrointestinal hemorrhage	3
Pulmonary embolus	3
Congestive failure	1

fixation (see Figure 54.6). These devices limit head and trunk mobility, which makes self-care tasks that involve balance, management of the lower extremities, and CISC; more difficult. Lower extremity fractures, especially of the femur, occur in about 5% of patients with acute SCI, which could further limit mobility and increase the risk of deep vein thrombosis (DVT) and skin breakdown, 'fable 54.14 lists the complications found during a prospective clinical trial of methylprcdnisolone for acute SCI in 487 patients,

Early morbidity is greater with cervical and upper thoracic injuries and with complete lesions than with lower or incomplete lesions. Ventilatory dysfunction, aspiration, dysautonomia with upright hypotension or paroxysmal hypertension, a neurogenic bowel with impactions, a neurogenic bladder with retention and infections, a catabolic state, and gastric atony are especially likely to complicate early inpatient rehabilitation. Hypercalcuria or hypercalcemia related to immobilization may also necessitate therapy. Central and musculoskeletal pain and grief reactions warrant immediate attention,

Complications in Patients with TBI

Systemic and neurological complications are common after serious **TBI,** The older patient carries more systemic comorbidity, whereas the younger patient may have alcohol or drug abuse as a comorbidity. In addition to other bodily injuries and any of the complications that can accompany stroke and SCI, physicians must monitor for pituitary-hypothalamic dysfunction with endocrinopathies and disorders of homeostasis, salt-wasting and inappropriate secretion of antidiuretic hormone, cerebral hygromas, hydrocephalus, and the persistent vegetative state, Ventticular enlargement develops in .30-70% of patients with severe TBI. Most have hydrocephalus ex vacuo, which is passive enlargement of the ventricles from the loss of gray and white matter. In the patient with enlarging ventricles who reaches an early plateau or declines in mobility and cognition, symptomatic normal- or high-pressure hydrocephalus must be considered.

Table 54.15: Glasgow outcome scale classification for recovery of consciousness and function in adults in a persistent vegetative state (PVS) beyond 1 month

Outcome	*3 Months (%)*	6 *Months (%)*	*12 Months (%}*
Traumatic Brain Injury			
Death	15	24	r,
PVS	52	30	15
Conscious	33	46	52
Seven' disability	—	—	2S
Moderate disability	—	—	17
Good recovery	—	—	7
Nontraumatic Brain Injury			
Death	24	40	53
PVS	65	45	32
Conscious	11	15	15
Severe disability	—	—	11
Moderate disability	—	—	3
Good recovery	—	—	1

Patients who are in a persistent vegetative state often ate evaluated by the rehabilitation team for prognostication and for a trial of stimulation. After TBI, the prognosis is not quite as grim as aftct hypoxic-ischemic coma unless hypotension accompanied the TBI. Table 54.15 shows the outcomes during the first year after brain injury determined by a 1994 study of the Multi-Society Task Force on Petsistent Vegetative State.

Management of Ncuromedical Problems

Dysphagia

Neurogenic dysphagia is the potential cause of a pulmonary infection in any patient with stroke, TBI, motor neuron disease, MS, advanced Parkinson's disease, cervico-medullary disorders such as a syrinx, Guillain-Barre syndrome, myasthenia gravis, and most neuromuscular diseases. Indeed, swallowing disorders affect 10% of acutely hospitalized older adults and 30% of nursing home dwellers. Even transient dysphagia can lead to malnutrition, dehydration, aspiration pneumonia, and airway obstruction with asphyxiation. It increases the patient's risk of death and institutionalization.

The natural history of recovery from dysphagia after sttokc and TBI is good. For example, a Brirish study diagnosed dysphagia in 30% of 357 conscious patients within 48 hours of a unilateral hemispheric stroke; the patients wete rated as being impaired if swallowing was delayed or they coughed on 10 mL of watet. Lethargy, gaze paresis, and sensory inattention were present more often than in those who swallowed normally. By 1 week, 16% had dysphagia. At 1 month only 2% and at *6* months only 0.4% of survivors were still impaired.

Symptoms and signs that suggest a tisk of aspiration include lethargy, coughing or a hoarse and gurgly voice after feeding, slow eating or drinking (less than 10 mL per second of watet ftom a cup), dysphonia, and poor oropharyngeal movement. The limitations of bedside indicators have led to the use of the MBS with video-fluoroscopy as the method of choice to rule out silent aspiration. The telationship between small amounts of aspiration by MBS and clinical complications is moot, however, and requires clinical judgment. The MBS also visualizes the effects of dietary texture and compensatory techniques. In attentive sttoke rehabilitation inpatients, coughing or a wet-hoarse quality of the voice within 1 minute of continuously swallowing 90 mL of watet from a cup had a sensitivity of 80% and specificity of 54% for aspiration detected by an MBS study. The bedside test had a sensitivity of 88% and specificity of 44% fot large amounts of aspiration that may be clinically more significant.

Dysphagia management must be addressed through all phases of recovery from stroke and TBI and duting the progression of diseases such as Parkinson's, ALS, and myasthenia gtavis (see Chapter 13). Lesions in the pathways for swallowing interfere with the oral, oral preparatory, and reflex or pharyngeal phases of deglutition. The initial emphasis for care is placed on protecting the airway and maintaining adequate alimentation and hydration, using a nasopharyngeal feeding tube if necessary. Oral pooling of secretions and drooling that predispose to aspiration can be managed with a low, titrated dosage of an anticholinergic drug such as glycopyrrolate. Good oral hygiene and management of tooth caries by oral rinsing with chlorhcxidinc gluconate and stannous fluoride can lessen the likelihood of bacterial infection being carried into the lungs by otal secretions. Therapeutic efforts focus on the use of stimulation and compensatory approaches designed to reduce the swallowing impairment or to minimize the functional disability resulting from that impairment (Table 54.16). For example, postural adjustments may be made based on the MBS. A chin tuck narrows the airway opening, tilting the head to the stronger

Tabic 54.16: General therapies for dysphagia

Compensation	*Sensorimotor exercises*	*Direct interventions*
Head positioning	Oral sensory stimulation (thermal, vibration)	Palatal prosthesis
Chin tuck	Resistance and placement exercises of tongue and jaw	Surgery
Head rotation to weak pharyngeal side	Chewing, oral manipulation of bolus	Cricopharyngeal myotomy
Softer food	Laryngeal adduction	Epiglottopexy
Thicker liquids	Biofeedback	
Lower intake volume		
Slower intake pace		
Compensatory maneuvers		
Double swallow		
Supraglottic swallow		
Laryngeal elevation		

side of the pharynx directs a bolus away from the weak side, and head rotation inward the weak pharyngeal muscle channels a bolus toward the stronger side. Modification of diet texture includes thickened or gelled liquids that are less likely to be aspirated than thin liquids. Purees and formable solids such as applesauce or mashed potatoes usually are safer than foods requiring chewing and oral manipulation. Pharyngeal stimulation by the therapist may help drive representational plasticity for these muscles on the unaffected side of the brain after stroke to improve swallowing.

Gastrostomy, whether percutaneous endoscopic gastrostomy or a tube inserted radiologically, may not lessen the risk of reflux aspiration any more than a nasopharyngeal feeding tube for patients with persisting aphagia. A percutaneous endoscopic gasttostomy can be complicated b\ gastric pci'loration, peritonitis, hematoma, fistula formation with the lung, stomal infection, cellulitis, and bleeding at the insertion site. Jejunostomy may lessen the risk oi reflux Inn increase the risk ot the dumping s\ ndrome. Rarely, esophagosromy or pharyngostomy is better suited for the patient with neurological dysfunction and prior gastrointestinal disease or surgery. Clinical trials related to the efficacy of types of tube feedings and other interventions for dysphagia are monitored by the Cochrane Review (www.updatc-softwarc.com/cochranc.htm). Dysphagia therapies provided by the family under the guidance of a therapist may be as efficacious as hands-on therapy by a professional. With outpatient care, patients and family members assume greater responsibility for integrating and adapting recommended procedures to suit their individual needs and priorities.

Skin Ulcers,

Education in skin management during rehabilitation provides an important opportunity for preventing later morbidity and mortality. Ischemia of the skin and underlying tissues occurs particularly in weight-bearing areas adjacent to bony prominences. The American Model Systems data for patients admitted within 24 hours of traumatic SCI showed that 4% subsequently developed pressure sores and 13% of these were graded as severe. They occurred over the sacrum, heel, scapula, foot, and greater trochanter of the hip. Lower-grade skin lesions developed over the genitals. Sores related to sitting arc most often located over the ischial tuberosiries, where tissue pressure can exceed 300 mm Hg on an unpadded scat. A 2-inch-thick foam pad decreases the local pressure to 150 mm Hg. Even with the use of cushions designed to distribute weight-bearing skin surfaces, pressures in the sitting position are far above the 11- to 33-mm Hg pressures in the capillaries and venules. Raising the head of the bed by only a few inches especially increases shearing forces over the sacrum.

A standard classification for degrees of integument breakdown, prophylactic measures, and wound care is available from the Agency for Health Care Policy and Research in Washington, D.C. Rubor, induration, and blistering arc signs that precede a break in the skin. Pressure relief is the best approach, performed every half hour after a complete SCI and every 2 to 3 hours in patients with intact sensation after stroke or other disabling injuries. Patients must develop a skin care program based on their general health, nutrition, continence, the toughness of their skin, the most used positions, type of wheelchair seat, presence of old skin scars, and other factors.

DVT and Pulmonary Embolus

In controlled trials of prophylaxis, DVT has been found in 20-75% of untreated patients within 2 weeks of stroke; 5-20% suffered a pulmonary embolus (PE), which was fatal in about 10%. Intermittent calf compression for the paretic leg, intermittent low-dose heparin given as 5000 units every 8 or 12 hours, and low-molecular-wcighr heparinoid are far more effective than no intervention ot the use of antiembolism hose alone. Across several studies, anticoagulants have reduced DVT by a factor of 2- to 7-fold and PE by about 2- to 4-fold. If a DVT is diagnosed, patients usually can restart activities out of bed after 2 days of intravenous heparin.

For those with spinal cord or head injury complicated by bone fractures, the incidence of DVT and PE is particularly high. After an SCI without a fracture, the risk of DVT,

detected by a radiolabeled fibrinogen scan, impedance plethysmography, or Dopplcr blood flow, appears greatest in the first 12 weeks, especially in combination with paraplegia and flaccidity. Symptomatic thrombophlebitis and PF. are less common. In one study, thromboembolism was detected in 31% of plegic patients, who were randomized to 5000 units of subcutaneous heparin twice a day within 72 hours of injury. It was found in only 7% of those whose activated partial thromboplastin time was prolonged to one and a half times control values by dosage adjustment every 12 houts. Over 7 weeks of anticoagulation, bleeding complications were greater in the adjusted-dosage gtoup, especially at trauma sites. Most patients with uncomplicated SCI continue anticoagulation until discharge from inpatient rehabilitation.

Contractures

Across studies, about 15% of patients with SCI admitted for rehabilitation and 80% admitted after moderate to severe TBI lost more than 15% of the normal range of motion of at least one joint. Hemiparetic patients with stroke fall between these extremes. Contractures are found especially in the lower extremities in neuromuscular diseases, affecting at least 70% of outpatients with Duchenne's muscular dystrophy. They can limit functional use of a limb and impair hygiene, mobility, and self-care. Serious contractures can cause pressure sores, pain, and, especially in youngsters, emotional distress when odd postures distort their body. After an acute UMN lesion, proper positioning "I the arm in abduction and hand in extension and of the leg in hip abduction with knee flexed and ankle in neutral position can protect the affected extremities. Serial casting and surgeries are occasionally necessary for contractures that interfere with skin care or functional use of a limb.

Ectopic bone formation may cause functional impairment in up to 20% of patients with SCI below their neurological level, usually in the first 4 months after injury. Those with a complete lesion, pressure sores, spasticity, and age greater than 30 years may be at gtcatest risk. After TBI, heterotopic ossification (HO) especially tends to affect the proximal joints of comatose patients. During rehabilitation of less responsive and cognitively impaired or aphasic patients, pain caused by undetected musculoskeletal injury and HO can add greatly to agitation and limit participation. HO develops when multipotential connective tissue cells transform into chondroblasts and osteoblasts, presumably under the influence of locally induced growth factors. The hips, knees, and shoulders are most often affected. Swelling, erythema, and decreasing range of motion are among the first clinical signs. A three-phase technetium-99m-labelcd methylene-diphosphonate bone scan reveals focal uptake befote radiographic visualization of bone. Early treatment with disodium etidronate suppresses mineralization of the osteoid. Range-of-motion exercises, aspirin, nonsteroidal anti-inflammatory drugs, and a wedge resection of mature heterotopic bone can decrease pain and immobility.

Seizures

A seizure may complicate inpatient care, and new antiepileptic drugs given for prophylaxis (Haltiner et al. 1999) may affect patients' ability to attend to instructions. Seizures occur in 5-8% of patients within 24 hours to 2 weeks of an ischemic stroke. The risk of epilepsy after TBI varies with the severity of injury and time after onset of injury. In a population study of more than 2700 patients with mostly nonpenetrating TBI, 2% had a seizure in the first 2 weeks after injury. Those with brain contusions, hematomas, or 24 hours of unconsciousness or amnesia had a 7% 1-year and 11.5% 5-year risk of seizures. Within the fitst 2 weeks in these sevctc cases, children under age 15 had a rate of 30% compared with 10% in adults. After a moderate injury, defined as a skull fracture or 30 minutes to 24 hours of unconsciousness or amnesia, 0.7% at 1 year and 1.6% at 5 years had a seizure. The risk after a mild injury with briefer unconsciousness or amnesia was 0.1-0.6%, the same as for the general population. With a 25% rate of fitst seizures regardless of anticonvulsant prophylaxis beyond the first week after serious brain injury, it does not seem productive to continue anticonvulsant therapy beyond the firsr 2 weeks after a serious TBI, especially because an anticonvulsant medication can increase cognitive impairment.

Dysautonomia

Bedrest, dehydtation, cardiac and antihypertensive medications, antidepressants, and autonomic reflex dysfunction from diabetes mcllitus contribute to postural hypotension in the patient with stroke and TBI. The supine and standing blood pressure should be checked as mobilization proceeds during rehabilitation. Autonomic reflexes may fail in patients with SCI levels above T6. Symptomatic postural hypotension is common in the first weeks after injury and may persist in quadriplegic patients.

Initial therapies include gradual reconditioning of postural reflexes on a tilt table, sleeping in a reverse Trendelenburg position, full leg hose, and an abdominal binder. In the inpatient setting, fluid loading with saline or albumin may aid the effort to compensate for venous pooling, decreased cardiac output, and impaired vasoconstriction and venoeonstriction from interruption of sympathetic outflow. Fludrocortisone increases the intravascular volume and peripheral vascular resistance. The dosage can be pushed gradually to 1 mg per day. Salt tablets should be added to the diet. Hypokalemia and edema with pressure sores can complicate use of mineral ocorricoids. While the patient is upright, ephedrine 25 to 100 mg up to every 3 hours, ergotamine 2 mg up to several

times daily, or midodrine up to 10 mg 3 times a day can be rried.

Episodic autonomic hyper-reflexia related to uninhibited sympathetic outflow may affect 50-90% of SCI patients with high-level SCI, usually beginning several months after injury. It is instigated by visceral and joint pain, HO, pressure sores, bowel and bladder distention, fecal impaction, urinary infection and cystitis, ingrown toenails, pregnancy and labor, venous thrombosis, late development of a syrinx, and tight clothing, a patticular supine position, or oropharyngeal suctioning, which can also cause bradyarrhythmias, and sometimes it has no evident cause, Hypertension, headache, diaphoresis, anxiety, reflexive bradycardia, nasal congestion, flushing above and pallor below the SCI level, extensor spasms, and piloerection can result. The instigating agent must be removed. Acute therapies include upright positioning, search for an unemptied bladder or rectum using lidoeaine on a catheter or finger when probing, and treatment of a blood pressure that exceeds 180/100 mm Hg. A beta blocker such as labetalol, a short-acting calcium channel blocker, vasodilators such as hydralazine and nitroprusside, and occasionally phenoxybenzamine, prazosin, clonidine, or nitroglycerine usually lower the pressure safely. Some quadriplegic patients have very labile responses to antihypertensive drugs and suddenly become hypotensive with these treatments. For frequent bouts (it hypertension, maintenance therapy includes lowdosages of any of these oral agents but with dosage adjustments based on the finding of supine hypertension compared to sitting hypotension. For paroxysmal bradycardia, propantheline or a pacemaker may be needed. Scopolamine and propantheline can prevent bouts of sweating.

Bowel and Bladder Dysfunction

Urinary incontinence occurs in up to 60% of patients in the first week after a stroke but tends to improve without a specific medical treatment. This must be considered in the context of an incidence of urinary dribbling and involuntary emptying of about 30% in the healthy, noninstitutionalized population over age 65. Across studies, about 18% of those who were incontinent at 6 weeks aftet a stroke are still so at 1 yeat. By the end of inpatient rehabilitation, the incidence is about 10% in patients with a motor-only stroke and about 30% with large hemispheric strokes,

After SCI, the bladder detrusor reflex may not return for 6 weeks to 12 months. In the absence of spontaneous bladder emptying, intetmittent catheterization is done on a schedule that prevents the accumulation of more than 400 niL. Patients should measure their output from time to time and develop a voiding schedule that takes into account variations in fluid intake and the use of alcohol and caffeine. Catheters can be washed, stored in a plastic bag, and reused. If sensorimotor impairments persist, nearly all patients with an SCI lesion that spares the S2-S4 micturition center develop dyssynergia between the detrusor and the external sphincter. These uncoordinated contractions lead to incontinence and intermittent outlet obstruction.

Urodynamic studies and an intravenous pyelogram are indicated as a baseline and to assist in therapy (see Chaptet 42). Obstruction can cause recurrent infections, urosepsis, vesicourethral reflux, urolithiasis, and hydronephrosis. The person with SCI should learn his or her signs of bladder fullness, such as sweating, changes in temperature, increased spasticity, and an increase in heart rate. Some palpate the area of the bladder to determine fullness. Once awareness of fullness develops, the person can aid in initiating or completing micturition by tapping over the bladder, rubbing the skin over the pubis or on the innet thighs, pressing on the abdominal wall (Crede's maneuver), and hearing down or coughing. These maneuvers are particularly helpful in those with a lower motor neuron bladder with an open sphincter. Most patients also **learn** the signs of an early bladder infection and work out a system with their physician to obtain antibiotics immediately.

Pharmacological treatment can be understood in relation to problems in bladder filling, storage, and bladder-emptying (Table 54.17). Urodynamic studies often aid in the choice of drug trial. The goals are continence and regular emptying that occurs without high intravesicular pressure and with less than 100 mL of residual volume after voiding. If this is not achieved, there are several alternatives to the use of an indwelling catheter on a long-term basis. To prevent inadequate emptying at low pressure at the price of external sphincterotomy and resultant incontinence,

Tabic 54.17: Pharmacological manipulation of bladder dysfunction

Medication	*Indications*	*Mechanism of action*
Bcthaneehol 25 mg bid—50 mg qid	Facilitate emptying	Increase detrusor contraction
Prazosin 1 mg bid—2 mg tid or Tamsuiosin 0.4 mg qd	Decrease outlet obstruction Prostatic hypertrophy	AI pli a-blockade of external sphincter to decrease tone
Hyoseyamine 0.125 mg hs-0.25 mg tid, Oxybutynin 2.5 mg hs-5 mg qid, or Detrol 2 mg qd	Urge incontinence Frequency	Relax detrusor, increase internal sphincter tone
Imipramine 25-100 mg hs	Urge incontinence Enuresis	Increase internal sphincter tone, decrease detrusor contractions

long-term CISC can be used in combination with anticholinergic medications to paralyze detrusor function. This procedure has become increasingly accepted as an effective alternative in the management of low intravesicular pressure. An external collecting device can also be used to ensure dryness. The patient must be trained to adjust fluid intake and the timing of catheterization to meet the flexible needs of community living. The absence of an effective external collecting device for female patients makes it necessary to continue long-term intermittent catheterization if there is paralysis of detrusor function. A waterproof undergarment may be worn between catheterizations to avoid embarrassment. The difficulties of this regimen cause many women to choose constant indwelling catheter drainage despite its drawbacks. Augmentation enterocystoplasty, reservoirs, conduits, and electrical stimulation techniques are less often needed. The VOCARE Bladder System (NeuroControl, Ohio) for patients with upper motor neuron SCI allows patients to stimulate sacral nerves that have been implanted with electrodes to empty the bladder and bowel.

The optimal management of spina bifida in children includes self-catheterization. Through cartoons and drawings, children must be taught how to prevent germs from growing in the bladder. Intermittent self-catheterization of the bladder usually can begin by age 5 years or by the time the child starts school.

Bowel evacuation can be brought under control in the majority of cases of SCI or other causes of myelopathy or cauda equina injury. The goals include continence, the prevention of impaction and discomfort caused by inadequate elimination, prevention of rectal bleeding, and a reasonable amount of time for bowel care. Some people with SCI can identify a signal of rectal distension, such as sweating or an increase in spasticity. It is particularly useful to establish a fixed time, usually after a meal, for evacuation. Once a pattern has been established with stimulatory suppositories, patients often get by with dilatation of the anal sphincter, either digitally or by a glycerin suppository. Those who cannot develop enough intra-abdominal pressure to void may need manual evacuation several times a week.

Central Pain

A major source of disability can be pain from a thalamoparietal stroke or SCI. One of the most common patient complaints a year or more after SCI is burning pain at and below the level of the lesion. Approximately half gauge their symptoms as moderate or severe. Some patients only need assurance that the pain does not represent a serious complication or a warning signal of another stroke. Others need to help the physician set goals about moderating the severity, frequency, duration, and time of day of the pain. Tricyclic and selective serotonin reuptake inhibitor antidepressants, carbamazepinc, clonidine, gabapentin, benzodiazepines, and baclofen are among the drugs that diminish dysesthetic or lancinating pain in some patients. Intrathecal baclofen and morphine can be efficacious when oral approaches fail {see Chapter 50).

Sleep Disorders

During rehabilitation, insomnia, sleep apnea, and excessive daytime sleepiness can interfere with attention, learning, and carryover. Stimulants, alcohol, medications, pain, anxiety, depression, and chronically poor sleep habits contribute. Central and obstructive sleep apneas have been associated with a higher risk of stroke. Pharyngeal muscle weakness and impaired neural control during sleep of the nasopharyngeal and pharyngolaryngeal muscles caused by a stroke or TBI contribute to the risk of obstructive apnea. Up to one third of stroke inpatients may have a sleep disorder. Polysomnography is indicated when the rehabilitation team observes a hypersomnolent, confused, and snoring or apneic patient. One study found an average of 52 sleep-disordered breathing events per hour in selected subjects within 1 year of stroke. The number of oxygen desaturation events and the oximetry measures during sleep-disordered breathing correlated with poorer functional recovery scores at 1 and 12 months after stroke. It is especially important to address the possibility of apnea with outpatients with :iu> type ol neurological disease, especially stroke, TBI, thoracic SCI, and myasthenia gravis.

Spasticity

Mechanisms. The most important UMN problems that cause disability are the decrement in motor control associated with dyssynergic patterns of muscle activation and the coactivation of agonist and antagonist groups during movements, as well as paresis, slow movements, loss of dexterity, and fatigability. During rehabilitation, the signs that tend to be treated include the flexor posture of the arm and extensor posture of the leg, sometimes with dystonia, rigidity, and contractures; and exaggerated cutaneous and autonomic reflexes with involuntary flexor and extensor spasms.

Hypertonicity can also be the consequence of interactions between central and peripheral factors. The mechanical resistance to a passive change in a joint angle arises from the elastic and viscous properties of muscle, tendon, and connective tissue and from reflexively mediated stiffness. Some investigators have proposed that secondary changes in spastic muscle, such as an increase in connective tissue and loss of muscle fibers or change in their properties, explain at least some of the increased stiffness in patients. Hyperexcilability of motoneurons probably plays a larger role. A number of ill-defined mechanisms could alter membrane properties and morphologically and physiologically reorganize spinal circuits, leading to hypertonicity. A variety of neurotransmitters act within these

Table 54.18: Clinical measures of spasticity

Ash worth Scale	
1	No increase in tone
2	Slight increase, producing a catch when joint is moved in flexion or extension
3	More marked increase in tone hut easily flexed
4	Considerable increase; passive movement difficult
5	Affected part rigid in flexion or extension
Spasm Score	
0	No spasms
1	Mild spasms induced by stimulation
2	Spasms less than 1/hr
3	Spasms more than 1/hr
4	Spasms more than 10/hr

systems, although their net effects are uncertain. Thus drug interventions produce hard-to-predict changes in tone and spasms.

Assessments. For routine assessments and for clinical trials of a uti spasticity interventions, a mini her of measures of hypcrtonicity have been used. The Ashworth Scale (Table 54.18) has had good interrater reliability in studies of stroke, SCI, and MS. The relationship between this score and disability is not so evident. A clenched, plegic hand may lead to disability if pain ot maceration of the palm develops, but a treatment that changes the Ashworth score from 4 to 3, and certainly from 3 to a lower score, is unlikely to offer any benefit. Other measurement techniques require instrumentation (Dobkin 2003).

Treatment of Spasticity

Therapists usually can manage pathologically increased tone in patients with hemiplegia by aiming to maintain notmal length of the muscle and soft tissue across a joint and helping patients to avoid abnormal flexor and extensor patterns at rest and during movement. Spasticity should be treated more aggressively when it interferes with nursing care and perineal hygiene or contributes to contractures and pressure sores. Treatment is often needed for patients with myelopathies, who endure painful spasms or involuntary flexor or extensor trunk and leg movements during transfers and after minor cutaneous stimulation. After SCI, spasticity is more prominent with incomplete than complete motor and sensory impairments, especially with cervical and upper thoracic lesions. It can be useful to lessen spasticity when ir appears to restrain voluntary upper or lower limb movements by co-contraction of agonist and antagonist groups. Hypertonicity has potential value. For example, spasms can dceteasc muscle atrophy and bone dcmineralization and increase venous return. An extensor thrust can provide the rigidity needed for weight-bearing stance. Learning to induce an extensor spasm can assist bed transfers in patients with a myelopathy. Determining how and when hypertonicity interferes with a patient's activities is the most useful way to determine whether an intervention is needed. Bouts of clonus and flexor and extensor spasms during ambulation, driving, wheelchair push-up pressure releases, transfers, self-care activities, bed mobility, sleep, and sexual activities can be counted over the course of a day or week. Any intervention should aim to greatly lessen recurrences.

Nociception can exacerbate hypcrtonicity and trigger flexor and extensor spasms and dystonic postures. A painful shoulder can cause the hemiplegic arm to flex at the elbow and wrist. Even an ordinarily innocuous stimulus, such as tight clothing or sunburn, can abruptly increase tone, much as it can cause autonomic dysreflexia in the patient with a cervicothoracic SCI. Treatable pain stimuli include bowel and bladder distention, urinary tract infection, epididymitis, joint pain especially on range of motion, unrecognized fractures, pressure sores, ingrown toenails, and deep venous thrombosis. Resistance exercises, though generally useful during rehabilitation, can increase flexor or extensor tone, especially if the exercise brings out associated movements.

An overall approach to the management of pathological hypertonicity and spasms includes reversing any noxious stimulus, using physical interventions before adding drug trials, and reserving more invasive techniques such as nerve blocks and orthopedic or neurosurgical procedures to a few recalcitrant situations.

Physical Modalities. Slow stretching movements and daily passive range-of-motion exercises reduce motion-sensitive symptoms of spasticity. Static stretching with splints and serial casting can reduce stretch reflex activity and contractures. Muscle cooling, tendon vibration, pressure exerted over a tight muscle belly, postural adjustments, loading a limb by weight-bearing on an extended arm or, for paraplegics, standing in a support frame (Figure 54.9), and EMG BFB can complement a stretching program. Electrical stimulation of motor and sensory nerves, muscles, and dermatomes by a variety of paradigms may reduce tone at the ankle and knee and in the forearm and finger flexors. A single session of stimulation usually decreases resistance and clonus for a few hours.

Pharmacotherapy. Conttolled trials of antispasticity agents have varied widely in the target symptoms managed and the outcome assessments used. Usually, only a particular neurological disease is considered. Functional gains related to locomotion and upper limb use for any UMN disease often are marginal. However, a medication that prevents disabling spasms may improve quality of life. Table 54.19 lists useful first- and second-line drugs.

After a SCI, about 25% of patients arc discharged with an antispasticity agent, and half use medication by 1 year. Patients with American Spinal Injury Society (ASIA) gtades A and D (see Chapter 56C, Table 56C.2) are less likely to have been treated than those with grades B and C. Baclofen, tizanidine, and clonidine are especially useful in reducing

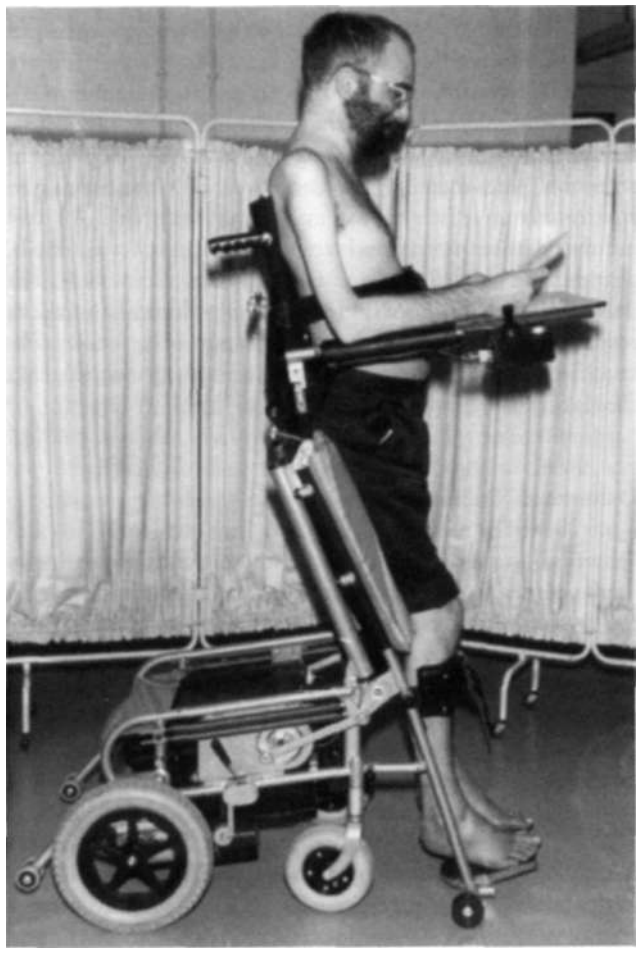

FIGURE 54.9 A patient with quadnplegia from a spinal cord injury uses a standing wheelchair to try to reduce ankle and knee contractures and overall muscle tone. Subjects who can use their upper extremities may use a wheelchair like this to perform tasks while upright, such as washing dishes.

clonus and extensor spasms caused by myelopathy. The latter two drugs are *a-2* agonists that inhibit the excitatory influences of peripheral sensory inputs on motoneurons. Medications with short-lasting effects such as tizanidine may be especially useful in limiting spasms during sleep or brief activities, such as ttansferring from wheelchair to bed. For refractory spasms and pain, intrathecal baclofen given by an implanted, programmable pump infusion has generally replaced a surgical myelotomy, intrathecal morphine, and electrical spinal stimulation. It has also replaced selective dorsal rhizotomy, except in some children with spastic diplegia from cerebral palsy. Dantrolene tends to be most useful in managing hypertoniaty of the upper extremity after stroke and TBI. Less than 0.5% of users develop hepatotoxicity after several months of intake.

Baclofen, dantrolene, and the benzodiazepines can cause muscular weakness and difficulty with weight-bearing. Children with cerebral palsy and patients with hemiplegic stroke often need their by perron icity to ambulate on a

Tabic 54.19: Dosages of medications for symptomatic spasticity

Drug	*Dosage*
First-Line Use	
Diazepam	2 mg bid—15 mg qid
Dantrolene	25 mg bid—100 mg qid
Baclofen	5 mg bid-40 mg qid
Clonidine	**0.05 mg qd-**0.2 mg tid
Ti/.anidine	2 mg bid—8 tug qiu
Gabapentin	400 mg tid-900 mg qid
Occasionally Useful Additions	
Intrathecal baclofen	50-150 pg rrial dosages
L-dopa or carbidopa	25 or 100 mg bid, respectively
Phcnytoin	Serum concentration 10-20 ng/dl.
Phenobarbital	Serum concentration 10-30 ug/dL
Threonine	500 mg-2.5 m tid
Cyprobepradine	4 mg bid—H mg qid
Chlorpromazinc	10 mg qd-50 mg tid
Mannol	2.5 mg qd-tid

paretic leg. L-dopa may be of value in these patients and in selected adults after stroke or SCI. These drugs can also cause sedation, confusion, hypotension, bowel and bladder dysfunction, and other central and systemic side effects. Great care must be taken when using them in the patient who has a pseudobulbar palsy and is at risk for aspiration. Whenever a drug appears to be useful, it is worth tapering the dosage down from time to time so that the patient can help reassess continued benefits.

Chemical Blocks. Chemical agents, such as phenol, have been injected into the lumbar theca, nerve, motor point, or muscle to lessen inappropriate muscle co-contraction, spasms, and dystonic postures. Because motor point blocks can partially spare voluntary movement and could reduce reciprocal inhibition when given to an antagonist muscle, they could improve some aspects of motor control. Intramuscular infiltrative injections of 50% cthanol or botulinum toxin reduce features of spasticity for about 3 months.

Botulinum injections have seemed most efficacious for the wrist and finger flexors and plantar flexors of the ankle. Interpretation of the results of clinical trials using botulinum toxin requires attention to how well the outcome measure reflects clinical effectiveness for an important problem. Is a change in ease of passive range of motion, as in the Ashworth Scale, as meaningful as an increase in functional use of the limb? A few trials in children with cerebral palsy and spastic diplegia reveal modest *0%* increases in walking speed after injections. The great majority of studies report a 1 - or 2-point decrease in the Ashworth Scale score and support this finding by offering a global physician score that, in reality, probably reflects a perception of a decrease in tone around one or more joints. A randomized trial compared injection of type A toxin into forearm muscles with vehicle injection in patients after stroke who scored 3 or more for the wrist and

2 or more for the fingers (Brashear et al. 2002). A statistically significant decrease in the Ashworth score occurred at 6 and 12 weeks (e.g., a change from 0.1 in controls to 0.8 in the finger flexors of the treated group). Significant changes were also found in the Disability Assessment Scale, which was said to reflect functional disability. This disability is only a subjective measure of change in hand hygiene, pain, positioning, and dressing that does not require use of the hand. It would be easy to misinterpret the data as revealing better functional use of the hand after botulinum toxin injection, but the real meaning is that with the wrist and finger flexors loosened, the hand was easier to keep open passively. Trials of botulinum toxin that are sponsored by the industry have not included a conttol intervention that uses rehabilitative passive or active range-of-motion or treatments for pain that may decrease tone. Also, these studies have not tried to maintain the effect of greater passive ranging by adding physical therapy after an injection to try to prolong benefit.

Surgical Interventions. A variety of surgical procedures, including tendon lengthening, tenotomy, and tendon transfer, can correct deformities induced by spasticity and improve function. A gait analysis with EMG helps determine which procedure might aid mobility. Physical therapy must follow any surgery. Tenotomy of the hip adductors and iliopsoas and tendon lengthening of the hamstrings, Achilles, and toe or finger and wrist flexors are among the more common interventions. Lower-extremity surgeries are performed most often in children with cerebral palsy, although the data are difficult to interpret in terms of meaningful clinical gains. Achilles tenotomies for Duchenne's muscular dystrophy and a variety of foot surgeries, including triple arthrodesis, for Gharcot-Marie-Tooth disease may be beneficial.

Posterior rhizotomy has been carried out especially in children with spastic diplegia. Selective division of posterior nerve rootlets of the second lumbar to second sacral level is based on intraoperative EMG responses of lower extremity muscles to posterior nerve rootlet stimulation. Youngsters with the most dramatic functional improvements are bright, ambulatory patients with spastic diplegia who have minimal fixed contractures and good strength. Some clinicians argue that such patients would do well with any intensive therapy. Indeed, controlled trials suggest that the intervention is no better than routine physical therapy in terms of functional walking (McLaughlin et al. 2002).

THERAPIES FOR IMPAIRMENTS AND **DISABILITIES**

Therapeutic exercise and the neurodevelopmcnral approaches have traditionally received the most attention from PTs and OTs. Newer approaches, developed from concepts related to neuroplasticity, motor control, and motor learning, arc merging with these. Success in retraining during rehabilitation, regardless of the primary approach, requires attention to many confounding variables. These include the characteristics of a task; how learning is reinforced; the patient's mood, motivation, attention, and memory for carryover of what is taught; environmental distractions; and family support. All can influence how motor and cognitive programs are built, shaped, and refined as the patient acquires a new skill. The daily practices of most individual neurological therapists reveal an eclectic, problem-oriented approach, A few well-specified approaches to therapy are being assessed in clinical trials.

Locomotor Training

Observation of rhe gait cycle for temporal asymmetries of the legs and kinematics at the hip, knee, and ankle during the stance and swing phases reveals deviations that the clinician can identify and use to help train patients (Dobkin 2003). Table 54.20 lists the easiest ones to look for as the patient walks on a flat surface. The timing of loading the stance leg and flexing the swing leg from its 10 degrees of extension is one of the important sensory inputs to the spinal cord for initiating the swing phase of gait.

The notion of task-oriented training has led to small trials of treadmill training and related walking activities in patients with hemiplegic stroke. The specificity of the training improves the speed of walking, leg strength, and fitness and may reduce the energy cost of walking. The addition of partial body weight support to treadmill training (BWSTT) has shown promise in patients with stroke and SGI and in patients with Parkinson's disease and cerebral palsy. Subjects wear a mountain climbing harness that is attached to an overhead lift. The amount of weight borne by the lower extremities is adjusted to optimize the stance and swing phases of gait. One or more therapists

Table 54.20: Easily observed components of the gait cycle-

Stance Phase	
Pelvis	Lateral and horizontal shift to the stance leg
Hip	Extension to about II)
Knee	Slight flexion upon loading
	Extension at midstance
	Flexion at foot pushoff
Ankle	Dorsiflexion to 10" at heel contact
	Dorsiflexion as the lower leg moves over the foot
	Plantarflexion to 20 with a propulsive rocker motion of the foot for pushoff
Swing Phase	
Pelvis	Drop at toe off, then forward rotation
Hip	Flexion to 20° to "shorten" the leg
Knee	Flexion to 65° to "shorten" the leg, then extension just before heel contact
Ankle	Dorsiflexion to 10^{s} for heel strike

may manually assist the lower extremities and pelvis during step training to optimize the step pattern.

In theory, BWSTT allows the spinal cord and supraspinal locomotor regions to experience sensory inputs that are more like ordinary stepping than the atypical locomotor inputs created by compensatory gait deviations and difficulty with loading a paretic limb (Dobkin 1999). More normal proprioceptive and cutaneous input may improve the timing and increase the activation of residual descending locomotor outputs on the motor pools. In patients with complete SCI, FMG activity appears to he derived from the neural circuitry of the lumbosacral motor pools that recognize the sensory inputs provided by BWSTT, Sensory inputs related to the level of loading and to treadmill speed have been shown to modulate the EMG output during BWSTT in which the legs arc fully assisted during the step cycle. Most important, BWSTT allows massed practice with many repetitions guided by the cues of the therapist. This approach should enhance motor re lea ruing.

In patients with stroke, single case studies and small clinical trials also suggest that BWSTT can increase the likelihood of achieving more independent ambulation and at greater speeds than by conventional therapy (Dobkin 1999). Gait symmetry clearly improves during treadmill step training. A Canadian randomized trial compared BWSTT with treadmill training without support during inpatient rehabilitation starting an average of 70 days after a stroke in 100 patients who could flex the affected hip. Average treadmill speeds did not exceed 1 mph. The trial showed a significantly greater overground speed in those managed with BWSTT (34 cm per second compared with 25 cm per second). Patient selection, duration of support before full weight bearing is allowed at faster treadmill speeds, practice paradigms, and the associated use of orthotics must In: better defined. Aims of this task-specific intervention include greater independence in walking and attaining walking speeds that permit home and community ambulation. The threshold velocity for home ambulation is 40 cm per second (45 cm per second equals 1 mph). Therapy ought to aim for faster walking speeds and for more energy-efficient traveling distances to permit unlimited community activities. Commtinin ambulation requires a walking velocity of 60 to 80 cm per second, or more than 1.5 mph. Therefore task-oriented training on a treadmill must exceed 1.5 mph. Note that typical disability measures such as the FIM and BI assess only the level of independence to walk 150 feet at any velocity. BWSTT did not improve overall locomotor-related outcomes in several randomized inpatient trials. The great range in time of onset of stroke to entry, slow treadmill training speeds for the BWSTT group, variations in the duration of therapy across patients, and lack of an intention-to-treat analysis make these trials less valuable. Training at treadmill speeds of about 2 mph lead to faster overground walking speeds than training at slower speeds, regardless of the initial overground walking velocity of a patient with stroke (Sullivan et al. 2002).

BWSTT is also being combined with functional neuromuscular stimulation (FNS) with surface or implanted electrodes for patients will) chronic stroke. The results to date show modest improvements in walking speed and kinematics within subjects, but the design of clinical trials with the combined approach seems premature, given that the optimal use of BWSTT has not yet been demonstrated. Robotic devices may prove useful in assisting patients and taking the physical burden of step training off therapists. Multiccntcr trials of BWSTT are in progress for acute SCI (Dobkin 1999) and stroke using faster treadmill training speeds and better-defined training strategics than in previous trials.

Temporal features of the gait cycle in patients with stroke and Parkinson's disease have been enhanced by bicycling and by rhythmic auditory stimulation that seems to entrain stepping.

Constraint-Induced Movement Therapy

This strategy calls for forced use of the affected upper extremity and gradual shaping of a variety of functional movements to overcome what is theorized as learned nonuse of the paretic limb. Learned nonuse might derive from unsuccessful early attempts to use the affected limb after a stroke. The primary intervention uses a variety of techniques that prevent the use of the unaffected arm by-placing it in a sling or glove and having the patient practice skills and ADLs with the affected arm. The first rendition of this approach for the upper extremity has been promoted by Taub ct al. (1999) with a course of 6-7 hours of massed practice with the affected arm and the restraint for 2 weeks. In these patients with chronic stroke who could dorsiflex the wrist at least 10 degrees and extend the fingers of the paretic arm, about half of the improvement in daily use was evident within the first several days of restraint of the unaffected arm combined with therapy, which suggests that a latent capability had succumbed to learned nonuse. Gains in the amount of hand use are accompanied by cortical reorganization of the hand region, consistent with the effects of practice. Other investigators have been working to eliminate the restraint and decrease the intensity of practice with a therapist. One acute trial of the approach showed positive results (Dromerick et al. 2000), and a multiccnter trial called EXCITE for patients who are 3-9 months post-stroke is in progress. The most important aspect of this approach is massed practice. Styles of practice, such as the use of shaping and reinforcement schedules and the most cost-effective practice intensity, are works in progress.

The notion of constraint with therapy has been invoked for a few treatments for walking and aphasia because the underlying style of therapy aims for massed practice of

specified activities and attempts to optimize responses and limit patient errors (Pulvermuller et al. 2001). The practice paradigm seems more important than concerns about restricting the use of an unaffected arm, leg, or language response.

Instrumented Biofeedback

BFB includes a variety of instrumented techniques that try to make the treated subject aware of physiological information that can be used to better train an activity. Electromyographic BFB to improve upper and lower extremity muscle activity, decrease co-contraction of muscles, and increase functional movements has been used across many upper and lower moroneuron diseases. Its efficacy usually is modest at best. Across controlled trials of ambulation after stroke, electromyographic BFB seems most useful as a way to increase **ankle** dorsiflexion. EMG-triggcred neuromuscular stimulation initiated by a voluntary movement such as slight wrist extension of a paretic hand has led to functional gains for hand grip in some studies. BFB can improve performance during training but not necessarily when visual or auditory guidance is stopped.

Acupuncture

A variety of acupuncture methods are widely used in China and Korea after stroke. Reports from these countries are impossible to interpret in terms of efficacy. Several small Western trials that treated subjects who had moderate hand paresis after a pure motor stroke showed gains in speed of hand manipulation or ADLs with the intervention. Better-controlled trials have not shown clear benefit (Johansson et al. 2001). A review of nine Western controlled trials with *53$* patients, carried out by investigators from a department of complementary medicine in Britain, concluded that no compelling evidence shows acupuncture to be effective for stroke rehabilitation. Despite 12 positive randomized trials reported in the Chinese literature, the results of very well-designed clinical trials do not support the use of acupuncture as a general intervention during stroke rehabilitation. Studies focused on particular types of dysfunction have yet to be carried out in a well-designed fashion.

Robotics

In addition to robotic trainers to assist stepping ptactice, unilateral and bimanual practice with the upper extremities may be enhanced with robotic and mechanical assistive devices. Devices aim to allow subjects to ptactice movements to increase motor control and functional use of the arm with only intermittent therapist oversight. The MIT-MANUS manipulates a patient's pareric elbow and shoulder much as a therapist might provide hand-over-hand therapy for reaching in a plane over a Moror. Power and control at the shoulder and elbow improve with robotic training, consistent with the greater intensity of practice using those muscle groups. A device that allows movement in multiple planes and incorporates the hand may be of greater value for training.

Functional Neuromuscular Stimulation

FNS systems can provide a hand grasp and release in C5 and C6 quadriplegics (Peckham et al. 2001). The commercially available FrecHand (NeuroConrrol, Ohio) ncuroprosthesis uses electrodes implanted in muscles of the opposite shoulder to control an external device that allows patients to complete upper limb grasp, pinch, and release tasks. The device has been less successful in reaching potential users than one might have expected. The first commercial surface electrode-driven device for grasping is the Handmastcr (NESS Ltd. Ra'anana, Israel), which has found some use in quadriplegic patients with at least *CS* intact and in hemipJcgic patients with poor hand function, FJectrodcs attached to a molded forearm orthosis that teaches across rhe wrist stimulate the wrist and finger flexors and extensors in synchrony. The external conttol unit operates from a button managed by the patient for the level of output that allows grasp, holding, or release.

FNS sysrems have been used more often to aid standing and ambulation. Used alone or combined with an RGO or with other assistive and bracing devices, these systems can allow walking as an exercise and in some instances permit stepping for distances involved in movement indoots. However, a lengthy strengthening and fitness program must precede the use of these devices. The only commercial device to assist stepping, the Patastep System (Sigmetics, Inc.}, uses six surface electrodes to stimulate the gait cycle as subjects hold onto a rolling walker. Stimulation of the quadriceps muscles and pushoff with the arms permits standing up. Constant stimulation maintains standing. A step button on the walker stops quadriceps firing as one leg srarts its swing phase and activates a triple flexion response by peroneal nerve stimulation. The patient releases the button after the hip flexes and switches on the quadriceps stimulator for stance. The other leg is then stimulated to aid swing. Other patients with a complete UMN SCI may exercise with a bicycle ergometer called the ERGYS (Therapeutic Technologies, Inc., Tampa, Florida), which uses bilateral surface electrodes over the quadriceps, hamstrings, and gluteal muscles to sequentially activate leg forces on the pedals. As muscle strength increases, contractions are made against greater ergometer resistance, and muscle bulk builds.

Neural Prostheses

Direct electrical stimulation of the brain and spinal cord and the use of neural signals to control brain-computer interfaces have become increasingly feasible.

Spinal cord stimulators placed over the dorsal spinal cord in the epidural space reduce some types of central pain and hypertonicity after SCI. Stimulation of the upper lumbar cord has also produced rhythmic leg movements in subjects with complete SCI. Stimulation with four dorsally placed lumbar electrodes reportedly improved the gait pattern of a patient with spastic quadriparcsis. Walking speed and endurance increased beyond what had been accomplished with BWSTT alone. Electrode microarrays are in experimental stages for direct spinal cord stimulation, perhaps of spinal primitive modules described earlier, Nerve cuffs placed around a portion of a peripheral nerve provide a permanent electrochemical interface to selectively initiate or record electrical signals or modulate the nerve's responses. Their initial experimental use has been for ankle dorsiflexor stimulation during walking.

Some estimates suggest that up to 2 million Americans may currently be without any voluntary control due to ALS, a locked-in syndrome after stroke or trauma, MS, cerebral palsy, or muscular dystrophy. A direct brain-computer interface can be configured to substitute for neural control of muscles. Many of the technical challenges have been addressed or clever solutions are in the making to take command signals derived from brain electrical activity to control a neuroprosthesis or robotic device (Wolpaw et al. 2002). Signals are acquired from field potentials over the surface of the scalp, dura, or subdural regions or from the spike potentials of small clusters of neurons picked up by microelcctrode arrays from motor cortex or cognitive planning regions. Selected signals are digitized and processed by algorithms to extract specific features, such as the amplitude of an evoked potential or of a specific rhythm from sensorimotor cortex, or the firing rate of cortical spikes. A translation algorithm takes the particular electrophysiological features chosen to give simple commands to a device, such as a word processor or keyboard, a Web site, or an upper extremity neuroprosthesis.

Pharmacological Adjuncts

Neurotransmitters and neuromodulators given in pharmacological dosages may augment the activation of a network during a specific task, but determining the dose-response ratio that has positive effects and no adverse effects takes much study. Human clinical trials have been small, and most investigators screen 10-50 subjects to meet entry criteria. Several trials of dextroamphetamine, methyl-phenidate, and i.-threodopa have revealed motor gains when combined with motor therapies, but others have not; a trial with l.-dopa revealed modest gains in motor function (Scheidtmann et al. 2001). A promising approach is to use functional imaging to help detect changes in response to a drug and other therapy (Boroojerdi et al. 2001).

THERAPIES FOR COGNITIVE AND BEHAVIORAL DISABILITIES

Overview of Cognitive Therapy

Cognitive and behavioral disorders are common with a recent stroke or TBI and in MS, Parkinson's disease, and degenerative diseases. Table 54.21 lists some of the cognitive impairments dealt with by the rehabilitation team. These can seriously impede gains in mobility, ADLs, and community reintegration. Prospective studies of patients with an acute stroke reveal that 15-35% have greater memory impairments 3 months to 1 year after onset than age-matched controls. Cognitive dysfunction is

Table 54.21: Cognitive impairments managed during rehabilitation

- Language
  - Aphasia
  - Affective expression
- Attention
  - Alertness
  - Speed of mental processing
  - Awareness of disability and impairment
  - Focused attention on a single stimulus
  - Sustained attention to a task
  - Selective attention during distraction
  - Divided or alternating attention between tasks
- Memory
  - Retrograde, antegrade
  - Immediate, delayed, cued, and recognition recall
- Learning
  - Visual, verbal, and procedural or skill
- Perception
  - Visual
  - Auditory
  - Visuospatial
- Executive
  - Planning
  - Initiation
  - Organization skills
  - Maintaining goal or intention
  - Conceptual reasoning
  - Hypothesis testing and ability to shift responses
  - Self'appraisal
  - Self-monitoring
- Intelligence
  - Verbal
  - IVrforuiiiTiLV
  - Problem solving
  - Abstract reasoning

especially common after TBI. Greater severity and duration of impairments are associated with a lower Glasgow Coma Score on acute admission and longer duration of post-traumatic amnesia. Up to one half of patients with an SCI have cognitive impairments from an associated TBI that may not be obvious early in their care.

The amount and rate of recovery of neuropsychological functions vary with the sophistication of the measures used; type and severity of impairment; type, severity, and distribution of lesions; time since onset; and age at onset and follow-up. More subtle factors such as the interactions of diseases, associated sensorimotor and cognitive impairments, and premorbid intellect and education can affect the efficacy of a particular therapeutic approach and the natural history of gains. Comparisons between interventions often are confounded by the intensity and duration of treatment, lack of specification of the treatment methods, personal infractions between the therapist and patient, and success of the family's ability to reinforce desired behaviors.

General management approaches include training in particular functional adaptive skills, behavioral modification, and remediation of specific cognitive processes (Cicerone et al. 2000). In the adaptive approach, therapy tries to circumvent the effects of cognitive impairments on targeted daily activities. Repetition, cues that are both internal and environmental, and cognitive assistive devices are used for training. Learning to do a particular task usually does not generalize to other tasks that are not closely telatcd. Behavioral modification techniques are most often used in acute and transitional living settings for patients with TBI. Rewards are given for accomplishing a task or reducing antisocial actions. In the cognitive remediation approach, the subcomponents or hierarchical organization of a given cognitive skill are addressed. Tbe strategy assumes that at least some of the parallel and hierarchical neural networks for cognitive processes are understood. More often, the techniques used emphasize interventions meant to boost intact domains to help compensate for more impaired ones. Few studies show the benefit of a particular approach or combination of approaches over another interventional style for most cognitive impairments. Techniques usually merge as the team experiments with interventions that address the most deleterious problems. Indeed, outpatients *wkh* a TBI are the most likely group to need multimodal programs that stress ttaining in task-specific skills by remediative techniques, awareness about impairments and limitations, and skills needed for independent living and work,

Aphasia

The incidence of language disorders has varied across studies of patients with stroke and TBI. In a British health districr of 250,000 people, new cases of aphasia numbered 202 yearly. By one month after stroke, 165 survivors were potential candidates for speech therapy, A prospective, community-based Danish study of acute stroke found that 38% of 881 patients were aphasic on admission, with 20% of the admissions rated as severe on the Scandinavian Stroke Score. Nearly one half of the severe aphasics died soon after onset, and one half of the mild aphasics recovered by 1 week. Only 18% of community survivors were srill aphasic at the time of their rehabilitation hospital discharge. Up to 28% received early speech therapy as needed. Patients were retested for 6 months. Ninety-five percent with a mild aphasia reached their best level of recovery at 2 weeks, those with a moderate aphasia peaked at 6 weeks, and patients with severe aphasia reached best language function within 10 weeks. Only 8% of the severe aphasics fully recovered by 6 months on the scoring system used. The best predictor of recovery was less severe aphasia close to the time of the stroke.

Treatments

Treatments for aphasia average 45-60 minutes, arc provided up to three times a week in most studies, and rarely exceed this number in community practices. The family tries to continue what therapists recommend at home.

Twenty percent to 50% of aphasic patients have partial features of rhe rraditional aphasia subtypes (see Chapter 12). For rehabilitation therapy, the broadly defined features used to classify patients often do not address in enough detail tbe underlying disturbances of language, so they may not be optimal for directing treatment. A neuro-linguistic assessment of aphasia aims to specify the types of representations or units of language, such as simple words, word formation, sentences, and discourse that arc abnormally processed during speech, auditory comprehension, reading, and writing. For each unit, the therapist ascertains how the disturbance affects linguistic forms such as phonemes, syntactic structures, and semantic meanings.

Speech therapists most often attempt to find ways to circumvent, deblock, or help the patient compensate for defective language function by using a great variety of stimulation-facilitation techniques (see Table 54.4). These include visual and verbal cueing techniques, such as picture matching and sentence completion tasks, along with frequent repetition and positive reinforcement as the patient approaches the desired responses. Initial treatments also use tasks that relate to self-care, the immediate environment, and emotionally positive experiences. To prevent withdrawal and isolation, ir is especially important to quickly find a way to obtain reliable verbal or gestural "yes-no" responses. Behavioral techniques, particularly for patients with TBI, can be used to improve skills in maintaining eye contact, initiating and staying on a topic, turn-taking

during conversation, adapting to listener needs, and using speech to warn, assert, request, acknowledge, or comment.

Beyond the stimulation-facilitation approach to therapy, a variety of theoretical models for therapy have been proposed, such as the modality, linguistic, processing, functional communication, and minor hemisphere mediation models. Therapy techniques have been designed for specific aphasia syndromes and neurolinguistic impairments as well. Examples of a few of the available specific-approaches for particular problems follow.

The efficacy of melodic intonation thcrapv (MIT) has been especially good. In MIT, therapists and patients meiodically intone multisyllabic words and commonly use short phrases while the therapist taps the patient's left hand to mark each syllable. Gradually, the continuous voicing and tapping are withdrawn. MIT works best in Broca's aphasics with sparse or stereotyped nonsense speech and good auditory comprehension. If a single sound, word, or phrase overwhelms any other attempted output, the Voluntary Control of Involuntary Utterance Program can help the patient gain control over perseverative intrusions.

The agrammatism of Broca's aphasia has been treated with the Helm Elicited Language Program for Syntax Stimulation, which tries to build increasingly more difficult syntactic constructions. The therapist uses a standard series of drawings of common activities and provides a brief verbal description that ends with a question. The question contains a target sentence. As the patient's responses with target words improve, the patient is asked to complete the story without having heard the target sentence. Some patients with minimal or stereotyped output and impaired comprehension have improved with multiple input phoneme therapy. This 22-step hierarchical program huilds from an analysis of phonemes produced spontaneously by the patient to attempts at eliciting a target phoneme, followed by blends of consonants, then multisyllabic words, and eventually simple sentences. Some mute or nonfluent aphasics can acquire a limited but useful repertoire of gestures using, for example, American Sign Language.

Comprehension in global and Wernicke's aphasics has been managed with the Sentence Level Auditory Comprehension Program. It trains patients to discriminate consonant-vowel-consonant words that are the same or differ by only one phoneme (e.g. "bill, pill, fill"). They then try to associate the word sounds with the written word and later try to identify the target word embedded in a sentence. For global aphasics, nonverbal communication using pantomime has decreased limb apraxia and improved auditory comprehension through a technique called Visual Action Therapy. The technique called Promoting Aphasics' Communicative Effectiveness emphasizes the ideas that need to be conveyed in face-to-face interactions rather than linguistic accuracy. It aims to develop any modality that can be used to transmit a message, including hand and facial gestures and drawing. The handbook and program called Supported Conversation for Aphasic Adults (Pictographic Communications Resources, Aphasia Centre, North York, Ontario, Canada) was designed for the nonaphasic conversation partner to facilitate interaction with global and nonfluent people. Electronic devices that provide delayed auditory feedback by about 200 milliseconds after the aphasic person makes each phoneme can be tried to improve awareness of paraphasic errors and intelligibility.

Pharmacological Adjuncts

A few studies suggest that intensive therapy combined with a drug that enhances vigilance or learning may **benefit** patients who have adequate language comprehension. Piracetam, a derivative of y-aminobutyric acid but with no GABA activity, may facilitate cholinergic and aminergic neurorransmission. A randomized, placebo-controlled trial included 50 moderately aphasic patients who had a stroke a mean of 10 months before starting the 6-week intervention of 10 hours of speech therapy weekly. The drug-treated group had a significantly better total score on the Aachen Aphasia Test, alrhough the clinical impact is not clear. In a randomized trial of 24 patients, use of piracetam was also associated with some language subtest gains and higher cerebral blood flow in left hemisphere language regions during a word repetition task. Other cholinergic agents have improved naming in patients with moderately severe Wernicke's aphasia or dysnomia, especially by reducing perseveration. Amphetamine and dopaminergic agents have improved aspects of language in several small studies but not all. Short-term trials of such agents can be carried out with parallel therapy and standardized tests in individual patients.

Outcomes

A metaanalysis was performed on *55* trials of speech therapy in aphasics with a stroke. Significant effects were found for treated patients at all stages of recovery, with the greatest outcome found when therapy was started in the acute stage. Treatments of more than 2 hours per week gave greater gains than lesser amounts of therapy. Severe aphasics showed large gams when treated by a speech-language pathologist. An inadequate number of studies were found to allow demonstration of any difference in treatment effects for differing types of aphasia. The Cochrane Library's systematic review of group trials in stroke (http://update-software.com/cochrane.htm) concludes that speech and language therapy for aphasic people after stroke has not been shown to be clearly effective or ineffective in a randomized clinical trial. Still, even a delayed pulse of a specific language therapy often improves a goal-directed aspect of aphasic communication in individual patients.

Memory Disturbances

Memory disturbances can have a profoundly negative influence on compensation and new learning in the patient undergoing neurorehabilitation. An inpatient team depends on teaching that can he encoded and retrieved. When sustained attention is impaired, even motor and functional gains may be affected.

Frequency of Memory Disturbance Across Diseases

The frequency and risk factors for memory toss and dementia caused by one or more strokes have become increasingly appreciated. The prevalence of memory disturbance in population- and community-based studies is nine times greater in the first year after a stroke than in an age-controlled group and twice as great each subsequent year. Other studies find a risk of about 20% 3 months after a stroke. The frequency of dementia rises with increasing age and varies with the definition used. Even a mild aphasia may affect verbal memory and can interfere with verbal learning during rehabilitation.

Memory impairments after TBI have been related to the time between injury and assessment, to the nature of the memory task, and to the severity of the injury. Tasks that require divided attention are especially useful to tease out executive dysfunction caused by a TBI. Natural history studies have reported varying outcomes. For example, in a group of 102 patients with TBI (ages 10-60 years) who were hospitalized for any period of unconsciousness, for post-trauma tic amnesia (PTA) of more than 1 hour, or for evidence of cerebral trauma, at 1 month the TBI group performed significantly worse on the Wcchsler Memory Scale and the Selective Reminding Test than a control group. Those who could not follow a command for the longest times beyond 24 hours after injury scored below the controls on more subtests of the Wechsler Memory Scale. Tests of orientation and short-term memory were inferior in their ability to reveal memory deficits compared with tests that required storage of new information for later use. At 1 year, patients performed better than they had at 1 month after onset.

Treatments

Most rehabilitative efforts to improve attention and to encode new information or recognize and retrieve memories are used for people with TBI. Previous exposure to verbal and especially to nonverbal information, with cues and prompts, can allow many amnestic patients after TBI to recall that information, a phenomenon called priming. Priming does not require semantic processing for encoding. It is specific to the properties of the input and relies on perceptual representations stored by modaliry-speeific memory subsystems, such as those that process word forms and visual objects. Tests of recognition memory are especially sensitive methods for detecting residual memory in patients with severe amnesia. This implicit memory neocortical mechanism can even support the rapid acquisition of novel verbal and nonverbal material. It is independent of the hippocampal and diencephalic structures that relate to amnesia. Priming seems especially useful during rehabilitation to enhance procedural memory for skill acquisition.

Cognitive remediation of amnestic disorders aims to train paricnts in using the subcomponent processes that underlie declarative and nondcelarative memory. Therapists can then take a restorative or compensatory approach to affect particular memory skills for functionally important activities, For example, therapists may address attentional impairments that could interfere with memory training by strategies for improving focused, sustained, selective, alternating, and then divided attention. Impairments in encoding and recall of information are then addressed. This approach uses associative and external cues that arc meant to prompt an action after increasingly longer intervals. It also uses aids such as memory notebooks.

Some patients with TBI underestimate their memory and emotional impairments, even as they acknowledge physical and other cognitive problems. Without insight or concern, they deny having the impairment and withdraw or become angry with attempts at rehabilitation. The rehabilitation team must provide the counseling and insight therapy needed to overcome this.

After a moderate to severe TBI, repetitive driils can have little impact on general recall or on memory outside of the training session. External aids such as a calendar and appointment diary and internal strategies such as rehearsal and visual imagery help most patients. The devices listed in Table 54.22 are helpful if patients can be cued to use them.

Computers have been used extensively in cognitive remediation and skill training. Although software programs abound for working on reaction times, aspects of attention, language, problem solving, and other cognitive tasks, almost no data demonstrate the efficacy of this approach. Some patients have learned tasks such as data entry, database management, and word processing by taking advantage oi preserved cognitive abilities, including [In-ability to respond to partial cues and acquire procedural information, even in the presence of a marked amnestic syndrome. This knowledge often does not generalize to even modest changes in the tasks. Through procedural memory, verbal and visual mnemonic strategies have been used to teach subjects a computer graphics program. Cooking and vocational tasks were taught with an interactive guidance system that cued each subtask to build up to the desired task.

Pharmacological Adjuncts

Studies of single subjects and small groups suggest that the drugs in Table 54.2.3 may benefit some patients with

Table 54.22: Aids and strategies for memory impairment

External
- Reminders by others
- Tape recorder
- Note written on hand

Time reminders
- Alarm clock or phone call
- Personal organizer or diary
- Calendar or wall planner
- Orientation board

Place reminders
- Labels
- Codes (colors, symbols)

Person reminders
- Name tags
- Clothes that offer a cue

Organizers
- Lists
- Personal organizer or diary-
- Numbered series of reminders
- Items grouped for use
- Radio pager
- Handheld computer

[menial
- Mental retracing of events
- Visual imagery
- Alphabet searching
- Associations to what is already recalled
- Rehearsal
- Eirst-letter mnemonics
- Chunking or grouping of items

amnestic and attentional impairments. TBI may lead to damage in a particular neurotransmitter system, such as cholinergic neurons. Presynaptic cholinctgic neurotransmission was abnormal in a human postmortem study of TBI. Therefore rehabilitation trials of cholinergic enhancing drugs such as donepezil and cytidme diphosphocholine

Table 54.23: Possibly useful medications for attentional and memory impairments

Cholinergic agonists
- Physostigmine
- Tacrine
- Donepezil
- Merrifonate
- Cytidine diphosphocholine
- Choline and lecithin precursors

Catecholamine agonists
- Dextroamphetamine
- Methylphenidate
- i.-dopa
- Amantadine
- Bromocriptine and other dopamine receptor agonists
- Desipraminc

Nootropics
- Pramiraceram
- Piracetam

Neuropeptides
- Vasopressin and analogues

seem warranted. Replacement therapies fotr other neurotransmittets, such as bromocriptine and noradrenergic agents, have a few human case studies to commend them. The divetsity of lesions after TBI (e.g., diffuse axonal injury, dorsolateral prefrontal cortex, hippocampus) necessitates an empiric, often individualized approach to pharmacotherapy.

Outcomes

Although memory-related processes are found to improve over the first 3 months after a stroke, reports on the natural history of ongoing cognitive sequelae suggest that both inpatient and outpatient rehabilitation efforts must pay ongoing attention to the need for compensatory aids and other strategies for these patients. After mild TBI, memoty usually recovers by 3 months. This varies with the test used to measure severity, the time from injury to testing, and the comparison group. The most impaired patients 1 year after a serious TBI are initially unable to follow a command finmore than a day and have post-traumatic amnesia for more than 14 days and a Glasgow Coma Score of 8 or less. One year after a severe closed head injury, patients followed in the Traumatic Coma Data Bank had greater impairments in vetbal and visual memoty and in other neurobehaviors, such as naming to confrontation and block construction, compared with normal controls. Selective rather than global cognitive impairments were likely at 1 year. Memory was disproportionately impaired compared with overall intellectual functioning in 15% of the moderately injuted and 30% of the severely injured patients. After moderate to severe TBI, children plateau in recovery by 1 year after onset, with little change in the next 2 years, and do not catch up to their peers in tetms of memoty, problem-solving ability, and academic performance. Late changes do evolve in some. In a long-term outcome study of mostly young adults, Wilson and colleagues reassessed 26 patients who had a TBI causing 1 hour to 24 weeks of coma, followed by rehabilitation. Five to 10 years later, 58% wete unchanged, 31% performed better, and 11% did worse on the Rivermead Behavioral Memory Test and Wechsler Memory Scale. Many needed to tcly on memory aids.

Hem i-In attention

Hennattentional disorders can arise from any node in the cottical-limbic-reticLilar network, which directs attention and integrates the localization and identification of a stimulus and its importance to the person. Unilateral neglect arises from injuries of the posterior parietal cortex; the ptefrontal cortex, which encompasses the frontal eye fields; and the cingulare gyrus. These regions include representations for sensation, for motor activities such as visual scanning and limb explotation, and for motivational televance, respectively. Subcortical areas such

as the thalamus, striatum, and superior colliculus coordinate the distribution of attention. Atrophy of frontal white matter and the diencephalon contributes to persistent anosognosia. The anterior and posterior extent of a lesion may also produce impairments in attentional and intentional processes that contribute to neglect. Therefore the most severe and subtle hcmiattentional disorders can be expected in focal stroke and more diffuse TBI.

Frequency of Hetni-lnattention Across Diseases

Community-based studies of stroke survivors detect visual neglect in 10-30% of patients. The neglect is modestly associated with poorer ADL scores and slower recovery, although severe neglect is rare beyond 6 months. Visual neglect is greater in right than left hemisphete strokes. Right-sided inattention, when looked for, has been detected in 15—40% of nonaphasic patients with acute left cerebral infarcts, although it is clinically most prominent after right brain injury. Patients with anosognosia, visual neglect, tactile extinction, motor inipersistence, or auditory neglect have the lowest BI scores at 1 year, even after the data are adjusted for initial ADL scores and for poststroke rehabilitation.

Recovery across reports has been most rapid in the first 2 weeks, regardless of the side of stroke, and has plateaued at 3 months, when most patients have little visual neglect. Severe visual neglect and anosognosia in the first week tend to predict some level of persistent impairment at 6 months. Many patients have more subtle and lingering impairments that depend on the test used to detect them. ¥*OT* example, early after a right hemisphere stroke, a group of patients showed a strong and consistent rightward attentional bias in addition to an inability to reorient their attention leftward. Twelve months later, the attentional bias continued, but they could fully reorient to left hemispacc when performing line bisection and cancellation tasks.

Treatments

The initial choice of an intervention may depend on the proposed mechanism of unilateral neglect or hemispatial inattention. For example, the patient can be treated for an underaroused right hemisphere that has difficulty processing sensory inputs. After a right brain injury, a powerful bias of the left hemisphere for attention to contralateral space could lead to an imbalance and necessitate a way to lessen the bias. A selective inability to disengage from inputs from ipsilatcral space might need to be addressed. Other strategies might have to be developed if the mental representation of contralesional space has been degraded or if a unilateral impairment m the activation of motor programs delays or prevents the intention to move to the contralesional side. If the initial theory-based intervention is not successful, then others should be tried. Table 54.24 lists some of the traditional and clever ways rehabilitationists have tried to manage hemi-inattcntion. For example, prisms have been used to transform sensorimotor coordinates, and passive prosthetics can be worn during tabletop activities. A 10-degree prism that shifts objects to the right in a patient with left hemi-inattention causes the patient to reach to the left when the glasses are removed. After adaptation to wearing the prism for 5 minutes, the patient's internal visual and proprioceptive map apparently realigns in the direction opposite to the optical deviation. The aftereffects of the prism may include significant improvement in drawing objects and performing cancellation tasks in left hemispace and in ADLs for days or more (Frassinetti et al. 2002). Noradrenergic and dopaminergic stimulants including methylphenidate and bromocriptine are especially worth trying in recalcitrant cases.

Tabic 54.24: Interventions for hemi-inartention

Multisensory visual and sensory cues, then fading cues
Verbal elaboration ot visual analysis
Environmental adaptations (bed position, red ribbon at left book margin)
Computer training
Video feedback
Monocular and binocular patches
Prisms
Left limb movement in left hemispacc
Head and trunk midline rotation
Vestibular caloric stimulation
Contralesional cervical nerve stimulation
Reduction of hemianopic defects
Pharmacotherapy

Source: Adapted with permission from Dobkin, B. 2003, *The Clinical Science of Neurologic Rehabilitation*, Oxford University Press, New York.

Behavioral Disorders

A great variety of behavioral changes can follow any hypoxic-ischemic injury or TBI. Alterations in personality have been reported in up to 75% of patients 1-15 years after a TBI and tend not to improve beyond 2 years after onset. Table 54.25 lists some of the more common changes. Agitated motor and verbal behaviors, though not easy to define or treat after TBI, are found in more than 10% and restlessness in 35% of patients during acute inpatient rehabilitation. As cognition improves, agitation declines, but directed and nondirected aggressive, impulsive behavior may evolve. Persistent aggression and emotional dyscontrol suggest premorbid mood and behavioral disorders.

Interventions include a medical assessment for exacerbating problems such as pain and drug-induced confusion, behavioral modification with positive and consistently applied reinforcements, a structured milieu, individual and group psychotherapy, and medication {Table 54.26).

Table 54.25: Potential changes in behavior and personality after traumatic brain injury and cerebral hypoxia

Disinhibition
[mpulsivity
Aggressiveness
Irritability
Lability
Euphoria
Paranoia
Lack of self-criticism and insight
Irresponsibility and childishness
Egoocntricity
Selfishness
Sexual inappropriateness
Self-abuse
Poor personal habits
Apathy, indifference
Indecision
Lack of initiation
Blunted emotional responses
Poor self-worth
Passive dependent)

Hypoarousal sometimes improves with stimulants such as methylphenidate and amphetamine or with dopamine agonists. Aggressive behavior sometimes is decreased dopaminergic or noradrenergic receptor blockade. Beta blockers can decrease irritability. A randomized trial of propranolol with a dosage escalation to 420 mg a day showed a reduction in the intensity of agitation, but not the frequency of episodes, compared with placebo. Hypomaiiic behavior may respond to lithium. Anticonvulsants such as carhamazepine sometimes prevent outbursts related to episodic dyscontrol.

Affective Disorders

Incidence

Depression is very common after a stroke. The community-based Framingham Study diagnosed depression in 47% of 6-month stroke survivors, with no difference found in the incidence between those with left- and right-sided lesions, and in 25% of age- and sex-matched controls. In a population-based cohort of Swedish stroke patients whose mean age was 73 years, the prevalence of maior depression was 25% at hospital discharge, 30% at 3 months after sttoke, 16% at 1 year, 19% at 2 years, and 29% at 3 years. In this and many other studies, a left anterior infarct, dysphasia, and living alone contributed to the prediction of depression upon discharge. At 3 months, greater dependence in ADLs and relative social isolation were associated with depression. Few social contacts at 1 and 2 years contributed.

Anxiety is another stroke-related affective disotder. Although less often studied, a generalized anxiety disorder was present in 28% of recent stroke victims and was associated with greater social isolation and greater dependence in ADLs. Apathy was found in about one quarter of patients within 10 days of a stroke, associated with greater cognitive impairment, poorer ADLs, and some cases of major but not minor depression.

Depressed people with an SCI report spending more time in bed and fewer days out of the house and receiving more personal care assistance than better-adjusted patients with SCI at 2-7 years after injury. Suicide rates may be 2-4 times that of the general population within 5 years of SCI. Anxiety and depression can also arise from a post-traumatic stress disorder associated with the event that led to the SCI.

Of patients with TBI, 25-60% ate diagnosed with depression. Left anterior injuries, as in unilateral stroke, are associated with an early, ttansient depression. However, other focal and diffuse injuries make it difficult to relate mood disorders to specific diseases. Late-onset depression has been associated with premorbid psychiatric history and lower psychosocial function. Poor social adjustment can cause long-term depression and anxiety.

[able 54.26: Drut; interventions for aggressive behavior, restlessness, and episodic dyscontrol

Anticonvulsants (carhamazepine, valproate, gabapentin)
Beta blockers (e.g., propanolol)
Lithium
Antidepressants (e.g., amitriptyline, fluoxetine)
Stimulants (e.g., methylphenidate, pemoline)
Neuroleptics (e.g., risperidone)
Benzodiazepines (e.g., clonazepam)
Clonidine
Calcium channel blockers

Treatment

Clinicians should manage mood disorders aggressively, especially when progress in rehabilitation falls short of expectations. In general, patients with depression respond to all classes of antidepressant medications and can be managed with the judicious care in dosing that is usually taken with an older adult. For example, by 6 weeks after starting fluoxetine or citalopram, two thitds of depressed subjects after a stroke recover, compared with about 15% given placebo. The same medications can help alleviate pseudobulbar emotional incontinence with its involuntary weeping, grimacing, and laughing. Close clinical monitoring for adverse reactions to the antidepressants is important during inpatient and outpatient rehabilitation. These include sedation, insomnia, anticholinergic effects on bowel, bladder, and salivation, orthostatic hypotension, cardiac arrhythmias, anxiety, extrapyramidal symptoms, and a serotonin svndrome.

FUNCTIONAL OUTCOMES **WITH REHABILITATION**

The most important outcomes for the rehabilitation team include the degree of independence in ADLs and community living. Thus functional measures that reflect the burden of care needed and the quality of life achieved by people with neurological disabilities are used in outcome studies more often than measures of change in sensorimotor and cognitive impairments. The scores on the FIM at admission for inpatient rehabilitation and at discharge offer an interesting snapshot of a large number of patients with stroke, **TBI,** and SCI from American institutions that participate in the Uniform Data System for Medical Rehabilitation. Over the past 10 years, the time from onset of neurological illness to transfer for rehabilitation has dropped about 25%, and the length of stay in rehabilitation has followed a similar course in the United States.

Table 54.27: Typical uniform data system for medical rehabilitation data for first stroke admissions, 2000

	Admission	*Discharge*
Mean Subs cores		
Self-care	3.5	5.2
Sphincter	3.7	5.4
Mobility	3.0	5.0
Locomotion	2.1	4.3
Communication	4.2	5.2
Social cognition	3.5	4.6
Total Functional Independence Measure score	62	86
Age (yr)	70	
Onset (days)	12	
Stay (days)		20
Discharge (%)		
Community	76	76
Long-term care	15	14
Acute care	7	6

Stroke

A metaanalysis of 36 trials carried out before 1992 showed that the average patient who received a program of focused stroke rehabilitation or a particular procedure performed better than about *65%* of the patients in the comparison group. Larger treatment effect sizes were associated with earlier timing of the intervention and younger age. This trend has continued over the past 10 years. Specific interventions for a well-defined functional disability, such as for improving functional use of an affected hand, walking, strength of a muscle group, balance, speech intelligibility, or community activities, show a moderate benefit.

Rehabilitation studies of patients with stroke generally show that 50% of 6-month survivors have no motor impairment, 70-80% can walk 150 feet alone, and 50-70% are independent in ADLs using the BI. These gains in subjects with the best outcomes do not imply that they can walk efficiently in the community. However, most studies suggest that 50-75% of survivors do not return to their prestroke level of activities in the community. Table 54.27 shows admission and discharge data about ADLs measured by the 7-part FIM, compiled from publications from the Uniform Data System.

Ambulation

A community-based population study in Copenhagen prospectively followed 800 acute stroke survivors. On admission, 51% were unable to walk, 12% walked with assistance, and 37% were independent. In the same facility, all who needed rehabilitation received services for an average total stay of 35 ± 41 days. At discharge, 22% could not walk, 14% walked with human assistance, and 64% of survivors walked independently by BI criteria. Recovery of ambulation correlated directly with leg strength. About 80% of those who were initially non-walkers reached their best walking function within 6 weeks, and 95% achieved this within 11 weeks. If patients walked with assistance at stroke onset, 80% reached their best function within 3 weeks and 95% within 5 weeks. With rehabilitation, 34% of the survivors who had been dependent and 60% of those who initially needed assistance achieved independent walking for at least 150 feet.

Life table analysis of patients from different impairment groups reveals a somewhat different pattern of gains. During their rehabilitation, 90% of patients with a pure motor (M) deficit become independent in walking 150 feet by week 14 after stroke onset, but only 35% of those with motor and proprioceptive (SM) loss by week 24, and 3% of those with motor, sensory, and hemianopic deficits (SMH) by week 30. The probability of walking more than 150 feet with assistance increases to 100% with M impairment by week 14. It increases to 90% in those with SM loss by week 26 and with SMH deficits by 28 weeks. At 1 month and 6 months after stroke for all survivors, 50% and 85%, respectively, of M subjects recover walking, 48% and 72% of SM subjects recover, and 16% and 38% of SMH subjects walk without human assistance (Patel et al. 2000).

Although many patients become independent in gait, sttoke patients who needed rehabilitation most often have self-selected walking speeds that peak in *3-6* months at one third to one half of normal for age. Speed is a good reflection of the overall gait pattern and, as noted earlier, reflects capabilities for walking in the home and community.

Self-Care Skills

In the Copenhagen Stroke Study, ADLs measured by the **BI** were assessed weekly in the hospital and at 6 months.

Twenty percent of survivors had a severe disability and 8% a moderate disability after a mean hospital stay of 37 days. Functional recovery peaked by 13 weeks after stroke onset in *95%.* The highest BI score was reached within 13 weeks by those with moderate impairments and within 20 weeks in those with severe impairments by the Scandinavian Stroke Scale. A Bl score greater than 60 is associated with a home discharge. Using the impairment grouping schema, the cumulative probability of reaching a BI score greater than 60 and greater than 90 at 6 months after stroke is 95% and 70%, respectively, for M subjects, 85% and 62% for SM subjects, and 52% and 35% for SMH patients (Patel et al. 2000). Similarly, about *65%* of inpatients during rehabilitation achieve a BI score greater than *95* by 15 weeks if they have only M deficits and by 26 weeks with SM loss. Only 10% score that high with SMH deficits after 18 to 30 weeks. However, 100% achieve a score greater than 60 by 14 weeks with M loss only, 75% by 23 weeks with SM deficits, and 60% by 29 weeks with SMH loss.

For patients admitted for stroke rehabilitation, the admission BI or FIM score predicts later burden of care. The FIM score on admission positively correlates with discharge FIM and negatively correlates with length of stay, except in patients under age 50. The largest FIM change over time occurs in patients with admission FIM scores of 40 to 80. Patients with admission scores grearer than 80 and age less than *55* years routinely return home. A score of less than 40 and age greater than 65 leads to a nursing home discharge for 60%.

Spinal Cord Injury

The Uniform Data System database shows that the average age of patients with traumatic SCI is 43 years old. The mean rime from onset to admission for rehabilitation is 22 days, and length of stay is about 33 days. The FIM score increases from about 63 to 89. ASIA A (sensorimotor complete) and B (sensory present) subjects from trauma become ASIA C (less than useful motor return) in only about 10% of patients during inpatient rehabilitation after a cervical or thoracic SCI. These patients tend to regain some sensorimotor function one level below the initial level of impairment. Gains may be a bit better for these ASIA-lcvcl patients with conus and cauda equina injuries. A clinical trial of CM, ganglioside found the following changes in 760 patients between 72 hours after a traumatic SCI of the cervical or thoracic cord and 26 weeks. About 80% of patients with a central cord injury were able to walk at least 25 feet. Only 4% of ASIA A patients at onset recovered any ability to walk, whereas 40% of ASIA B subjects regained this function. At least 70% of ASIA C subjects recovered unlimited walking. ASIA A patients almost never recovered normal bowel and bladder function. Overall, about 15% of subjects recovered these functions.

Self-care skills depend especially on the level and completeness of an SCI. For patients with complete lesions at C4 or above, ventilatory support and assistive devices are needed along with physical help. With C5 intact, self-feeding is achieved with devices such as a balanced forearm orthosis and wrist splints with attachments for utensils. Patients use a power wheelchair by a hand control. With C6 intact, wrist extension allows the thumb and fingers to oppose without or, better, with a tenodesis orthosis. Upper extremity dressing, self-carheterization, manual wheelchair propulsion, and sliding board transfers are feasible. With C7 intact, these activities are performed more efficiently, and use of a suppository for the bowel program is feasible. With C8 intact, long finger flexion permits most ADLs to lie accomplished from a wheelchair.

The strength of the lower extremities determines the amount of work that must be performed by the upper extremities for support, which in turn determines the energy cost and feasibility of ambulation. A study using the ASIA Motor Score found rhat 20 of 23 incomplete tetraplcgics who had an ASIA lower extremity motor score of 10 or more (the maximum normal score is 50 for five muscle groups of each leg on a 5-poinr scale of strength) at 1 month after injury became community ambulators with crutches and orthoses by 1 year. They subsequently achieved nearly effortless community ambulation if the lower extremity motor score improved to at least 30. In comparison, scores of 20 or less were associated with limited ambulation at slower average velocities, highct heart rates, greater energy expenditure, and greater peak axial loads on assistive devices. Paraparetic community ambulators usually need to have pelvic control with at least movement against gravity in the hip flexors and at one knee extensor so that they need no more than one KAFO for a reciprocal gait pattern.

Patients need encouragement and resources to be able to return to work or school. Those with education beyond high school are far more likely to return to work and stay employed. Aging with SCI poses problems for many. One fourth of patients who sustained their injuries 20 or more years ago evolve a greater need for physical assistance over the years, especially for help with transfers. They report shoulder pain, fatigue, weakness, weight gain, and a decline in the quality of life more often than patients who do not need more assistance. Clinical surveillance is needed to anticipate when a pulse of therapy for an increasing impairment or disability or a change in assistive devices or wheelchair is needed.

Traumatic Brain Injury

In general, after moderate to severe TBI, self-care and mobility improve from admission to inpatient rehabilitation to discharge, and gains are maintained or continue to increase for about 6 months. About 50% return to work at

6 months. Socialization and leisure activities generally do not return to premorbid levels. Table 54.28 shows some of the characteristics of injury and rehabilitation in a well-defined group of American patients that did not include children.

In a group of 24i consecutive admissions to a rehabilitation unit, a significant inverse relationship was found between the Glasgow Coma Score and the duration of coma, along with a strong positive relationship between the duration of coma and post-traumatic amnesia (PTA). Of 119 patients with diffuse axonal injury, no one in a coma for more than 2 weeks or with PTA for more than 12 weeks had a good recovery by the Glasgow Outcome Score at 1 year after injury. Two thirds of the small subgroup with coma for more than 2 weeks improved to moderate disability when the coma lasted 2-4 weeks. Only one third achieved this level if in coma for more than 4 weeks. Eighty percent of patients with PTA for less than *1* weeks had a good recovery, and half with PTA lasting 2-8 weeks were moderately disabled 1 year after admission. At another inpatient facility, patients who had a Glasgow Coma Score of 3-7 within 24 hours of onset had lower admission and discharge FIM scores for motor and cognitive function duting their rehabilitation. In many communities, about 10% of patients return to former jobs, and fewer than 30% are employed 2 years after severe TBI.

Parkinson's Disease

Perhaps even more than with other chronic and progressive neurological diseases, with Parkinson's disease an exercise prescription can help patients maintain range of motion, flexibility, proximal strength, mobility, and fitness. Parkinsonian patients can reduce their symptoms and improve their function with focused physical and occupational rehabilitation therapies. Speech therapy improves prosody, breath support for speaking, and intelligibility. Patients have been trained to increase the speed of a skilled movement such as buttoning, although with more practice than normal controls need. Also, twice-a-weck practice for 3 months in whole body movements such as sitting, kneeling, standing up, and throwing, along with problem-solving for these activities, improves the speed of movements needed for mobility in moderately disabled Parkinsonian patients. A randomized crossover study compared regular activity with 1 hour of repetitive stretching, endurance, balance, gait, and fine motor exer cises in moderately disabled patients. Exercises were performed three times a week for 4 weeks with a progressive increase in the number of repetitions. The total United Parkinson's Disease Rating Scale score and the ADL and motor subscores, particularly the bradykinesia and rigidity components, significantly improved with exercise. Without an ongoing formal exercise program, these gains were lost 6 months later.

Multiple Sclerosis

Evaluating the impact of rehabilitation in MS presents difficulties because it is a chronic condition continuing over many decades that is variable, unpredictable, and subject to spontaneous improvement during the first 15 years in many patients. A study of patients with rclapsing-and-remitting MS at onset found that the median time to reach a score of 4, 6, and 7 on the Kurtzke Disability Status Scale was 11, 23, and 33 years, respectively. The scores represent a change from limited walking up to 500 m (EDSS 4), to walking with unilateral support no more than 100 m

Table 54.28: Traumatic Brain Injury Model Systems Project, 1989-2000 (2553 cases)

Variable	*Onset*	*Rehabilitation discharge*	1 *Year after injury*
Mean age, years	36		
% Male	75		
% Vehicle-re) a ted	52		
% Alcohol-related	41		
% Employed	*59*		24
% Living ar home	97		85
% Loss of consciousness	94		
% Post-traumatic amnesia	98		
>30 days	34		
8-29 days	34		
1-7 days	8		
Mean lowest Glasgow Coma Score	7		
Duration of coma, days	3.8		
Acute hospiral stay, days	22		
Rehab inpatient stay, days		32	
Total Functional Independence Measure score	*56*	97	115
Disability Rating Scale	12.6	6	2.9

Source: Traumatic Brain Injury National Data Center (www.thims.org).

without rest (EDSS 5), to walking no more than 10 m while holding objects for support (EDSS 6). Patients with progressive disease from onset declined at 0, 7, and 13 years, respectively. Thus plenty of opportunities arise for rehabilitative interventions for specific disabilities.

Quasi-experimental studies suggest a benefit from inpatient rehabilitation in MS. For example, in a srratified, randomized, wait list, controlled study involving 66 patients with progressive MS, the treatment group underwent a mean of 25 days of multidisciplinary inpatient rehabilitation. At *6* weeks, the neurological status in both groups remained the same. The treated group showed significantly lower levels of disability than the control group. Despite a decline in neurological status over the following year, the group maintained its gains in disability for *6* months and in quality of life for 10 months. A randomized trial compared 3 weeks of inpatient rehabilitation with a home exercise program in 50 patients. No change in impairment was seen in either group. However, the rehabilitation arm showed a benefit in disability in the FIM motor domain for self-care and locomotion (which could include wheelchair use), which persisted for 15 weeks. Improvement in quality of life (SF-36) in the mental composite score was also present for 9 weeks. These results emphasize the importance of continuity of care between the rehabilitation environment and the community and social service sectors, if the needs of the person with MS or with other chronic neurological diseases are to be met effectively over the longer term.

The effect of an extended outpatient rehabilitation program on symptom frequency, fatigue, and functional status was studied in 46 patients with progressive MS. The 26 patients in the nonrandomized treatment arm received rehabilitation day services for 5 hours, 1 day per week. Although this program did not have any effect on functional status, significant benefits were seen in both in a reduction of symptom frequency at 1-year follow-up and in the incidence of fatigue compared with that of a wait-listed group. Although not yet studied by a scientific design, a day program may include general physical fitness exercises, practice in ADLs, group recreation, gardening, and local travel that help maintain or build self-care and community skills, along with psychosocial supports for clients and caregivers.

Other Diseases

Critical illness polyneuropathy and myopathy from sepsis and organ transplantation have become a common cause of diffuse weakness, deconditioning, and disability that necessitates inpatient rehabilitation. Exercise management is similar to that of patients with Guillain-Barre syndrome. Nearly all patients with critical illness-induced weakness improve their strength from movement only against gravity at admission to offering resistance in proximal muscles within 3 weeks of the inpatient stay. As soon as feasible, these patients need to enter a milieu that encourages them to assist themselves, stay out of bed, and do light resistance exercises throughout the day. Patients are encouraged to work their arms and legs against the resistance of a stretchablc rubber Theraband for 10 repetitions in various planes every hour, even when resting in bed, or to do isometric exercise with a family member. The average length of stay needed to achieve the ability to stand up and walk 50 feet or more with an assistive device is about 18 days. Light resistance and conditioning exercises ought to be part of any maintenance program for people with diseases of the motor unit as well, along with instruction from therapists if greater disability evolves.

SUMMARY

The essence of neurological rehabilitation is the ability to recognize and solve problems in everyday he a 1th-related activities faced by patients and their caregivers. Rehabilitation efforts attend to the details of the physical and cognitive impairments and disabilities of patients and their desire to participate more independently. The clinician must survey the patient's needs and anticipate complications by promoting prophylactic measures. Physical and cognitive interventions, supplemented by psychosocial supports and drug trials, aim to extend the quality of life of disabled patients. The design and institution of clinical trials for theory-based interventions have progressed more in the past 5 years than at any time in the past 50 years. These trials will lead to a solid base of therapies for specific needs. The success of incorporating biological interventions for neural repair and pharmacological memory-enhancing molecules into clinical practice will depend heavily on clinicians' ability to offer well-defined treatments that foster activity-dependent plasticity during the retraining of important skills.

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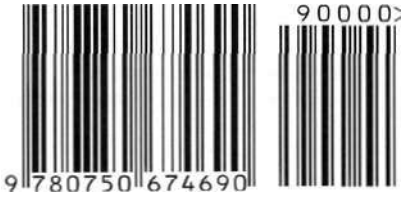

Volume II

Neurology in Clinical Practice

The Neurological Disorders

Fourth Edition

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Chapter 55
Neurological Complications of Systemic Disease

A. IN ADULTS

Michael J. Aminoff

This chapter discusses neurological complications of systemic disease in adults. Chapter 55B discusses the same subject in children. Some disorders are discussed in both chapters but with a different emphasis.

CARDIAC; DISORDERS AND THE NERVOUS SYSTEM

Neurological complications arc an important cause of morbidity in patients with cardiac disease. Cardiogenic

emboli may result from cardiac disease or its surgical treatment, and cardiac dysfunction can cause global cerebral hypoperfusion leading to syncope, stroke, or death, depending on the severity and duration of cerebral ischemia.

Cardiogenic Embolism

Cardiogenic emboli are most prevalent in patients with mitral stenosis and atrial fibrillation, intramural thrombi, prosthetic cardiac valves, atrial myxoma, infective endocarditis, sick sinus syndrome, and atrial fibrillation. Other causes include recent myocardial infarct, left atrial thrombus or turbulence, mitral valve prolapse, mitral annulus calcification, atrial fluttct, hypokinetic left ventricular segments, and congestive cardiac failure. Emboli from congenita) heart disease are discussed in Chapter 55B. The possibility of cardiac emboli must be considered in young people with either valvular heart disease or mitral valve prolapse.

Echocardiography is an important investigative procedure when cardiogenic emboli arc suspected. Transesophageal echocardiography is preferable to the transthoracic approach in the evaluation of suspected atrial disease, such as myxoma or thrombus, and to demonstrate a patent foramen ovale, but transthoracic echocardiography is an important method of visualizing the ventricular apex, mitrai or aortic valvular disease, and left ventricular thrombus.

Transesophageal echocardiography is an appropriate method to investigate people younger than 45 years with suspected cardiogenic emboii who may need anticoagulation or surgery and older people without signs of cardiac-disease, but transthoracic echocardiography is generally adequate when clinical evidence of cardiac disease is present.

Emboli are more likely when atrial fibrillation is associated with valvular heart disease. The incidence of stroke among patients with atrial fibrillation is increased 17-fold or 5-fold, respectively, depending on the presence or absence of rheumatic heart disease. Atrial fibrillation, in the absence ol cardiovascular disease or other predisposing illness, has a considerably lower risk of neurological complications. The neurological prognosis of paroxysmal atrial fibrillation is not established, but the risk of embolism is probably less than with chronic atrial fibrillation.

The benefit of anticoagulation in reducing the risk of stroke in people with atrial fibrillation is established. A consensus has developed that long-term oral warfarin therapy for atrial fibrillation unless there were specific contraindications or the atrial fibrillation was an isolated finding in people younger than 60 years without other evidence of cardiovascular disease. Aspirin (325 mg per day) is recommended when warfarin is contraindicated. Warfarin is usually started at least 3 weeks before elective cardioversion in people with atrial fibrillation of more than 2 days' duration and continued until normal rhythm has been maintained for 4 weeks.

Myocardial infarcts, especially apical, anterolateral, or large infarcts, have a risk of embolic stroke. Most occur within a week, but the risk persists for approximately 2 months. Therefore patients not on thrombolytic therapy arc heparinized after myocardial infarction and then treated for 3 months with warfarin if they have an increased risk of embolism. The groups with increased risk are those with congestive heart failure, previous emboli, evidence of a mural thrombus, left ventricular dysfunction, or atrial fibrillation.

Emboli are an important cause of death in people with rheumatic valvular disease. The risk of embolism is increased in the presence of atrial fibrillation, intra-attial thrombus, ot a histoty of emboli, and long-term warfarin treatment is recommended. Aspirin (160-325 mg per day) is added for recurrent systemic emboli despite adequate warfarin therapy.

Mitral valve prolapse is a common anomaly, especially among young women, and its relationship to cerebral emboli is now recognized. The risk of emboli is relatively small, and long-term warfarin therapy is recommended only tor people who have had previous embolic phenomena or are in atrial fibrillation. Eong-term aspirin therapy (325-975 mg per day) is recommended for people with mitral valve prolapse and transient cerebral ischemic attacks of uncertain nature.

Among patients with a history of cardiogenic emboli, recurrent stroke is more likely in those with cardiac valve disease and congestive heart failure. Nevertheless, the main cause of death in such patients is from the heart disease rather than neurological complications. The conversion of a cerebral infarct into a hemorrhage is a concern when patients with stroke from cardiogenic emboli are anticoagulatcd. The concern is especially justified in patients with large infarcts or when imaging studies suggest pre-existing hemorrhagic transformation. It is good practice to delay anticoagulation therapy after a small infarct for at least 24 hours, and then to initiate u only if computed tomographj shows no evidence of major hemorrhagic transformation. Anticoagulation is best delayed for 7 days after large infarcts. Atrial fibrillation is associated with an increased mortality during the acute phase of a stroke and in the subsequent year.

Syncope

Transitory global cerebral ischemia secondary to cardiac-arrhythmia causes syncope, sometimes preceded by non-specific premonitory symptoms such as visual disturbances, paresthesias, and lightheadedness (Sotcriades et al. 2002). Syncope is usually associated with loss of muscle tone, but prolonged ischemia causes tonic posturing and irregular jerking movements that are easily mistaken for seizures

(Adams-Stokes attacks). The syncopal patient is pale, and postictal confusion is either absent or short lived, usually lasting for less than 30 seconds. Obstructed outflow from aortic stenosis or left atrial tumor or thrombus is one cardiac cause of syncope; other causes are arrhythmias, especially from ventricular tachycardia or fibrillation, chronic sinoatrial disorder or sick sinus syndrome, and paroxysmal tachycardia. Additional causes of syncope are central and peripheral dysautonomias, postural hypotension, and endocrine and metabolic disorders. Vasovagal syncope, the most common variety, and the prolonged QT-interval syndrome are discussed in Chapter 55B.

Cardiac Arrest

Brain function is critically dependent on the cerebral circulation. The brain receives approximately 15% of the total cardiac output. Ventricular fibrillation or asystole causes circulatory failure that depending on its duration can cause irreversible anoxic-ischemic brain damage. The prognosis generally depends on age, the duration of the arrest before cardiopulmonary resuscitation is started, and the interval before starting defibriHating procedures. The prognosis is better when circulatory arrest is caused by ventricular fibrillation rather than asystole.

The pathophysiology of neurological damage caused by transitory interruption of cerebral blood flow is unclear. Suspected mechanisms are the accumulation of intracellular calcium, increased extracellular concentrations of glutamate and aspartate, and increased concentrations of free radicals.

In the mature brain, gray marter is generally more sensitive to ischemia than white matter, and the cerebral cortex is more sensitive than the brainstem. The premature brain has the reverse pattern of sensitivity (see Chapter 86). Cerebral or spinal regions lying between the territories supplied by the major arteries (watershed areas} are especially vulnerable to ischemic injury.

The severity of neurological complications of circulatory arrest correlarcs with the duration of the arrest. Brief (<5 minute) arrests cause temporary loss of consciousness and impaired cognitive function. Recovery may be followed by a demyelinating encephalopathy 7-10 days later, characterized by increasing cerebral dysfunction with cognitive disturbances and pyramidal or extrapyramidal abnormalities that may lead to a fatal outcome. Thus some patients regain consciousness after several hours and then develop progressive neurological deficits affecting cognitive and cortical function: intellectual decline, seizures, visual agnosia, cortical blindness, amnestic syndromes, and personality changes. Less common residua are rhe lockcd-in syndrome, parkinsonism or other extrapyramidal syndromes, abnormal ocular movements, bilateral brachial paresis, or action myoclonus. Spinal cord dysfuncrion is unusual and usually involves the watershed region at T5: Flaccid paraplegia with sensory loss, areflexia, and sphincter dysfunction are the immediate findings.

Prolonged cardiac arrest causes widespread and irreversible brain damage characterized by prolonged coma or a persistent vegetative state. Prolonged coma and loss of brainstem reflexes indicate a poor prognosis for survival or useful recovery. Absence of the pupillary response to light is perhaps the most useful clinical guide to prognosis; its absence even on initial examination indicates a poor prognosis for useful recovery (see Chapter 5 for further discussion).

Complications of Cardiac Catheterization and Surgery

Comments pertinent to children are provided in Chapter 55B. Cardiac catheterization causes cerebral emboli in fewer than 1% of cases; for unexplained reasons, these more often involve the posterior than the anterior circulation. The frequency of cerebral emboli following percutaneous transluminal coronary angioplasty is generally also less than 1% and may involve either the carotid or the vertebral circulation. However, the risk of stroke is greater in patients with acute myocardial infarction treated by angioplasty.

Encephalopathy, seizures, and cerebral infarction after cardiac surgery are usually caused by hypoxia or emboli. Postoperative psychoses or encephalopathies may be caused by metabolic disturbances, medication, infection, or multiorgan failure. Intracranial infection should be suspected when behavioral disturbances develop several weeks postoperatively in patients receiving immunosuppressive agents. Postoperative seizures are usually caused by focal or generalized cerebral ischemia, electrolyte or metabolic disturbances, or multiorgan failure. Intracranial hemorrhage is a rare complication of cardiopulmonary bypass. It is usually attributed to diminished platelet adhesiveness and reduced coagulation factors. Cognitive changes after cardiac bypass surgery are detectable in 53% of patients at discharge and 42% after 5 years. Patients without cognitive decline initially maintained their cognitive function at 5 years (Newman et al. 2001). Some patients with early cognitive deficits had initial improvement and later decline for uncertain reasons. Thus early cognitive changes cannot be assumed to be purely temporary.

Compression or traction injuries to the brachial plexus, especially the lower trunk, and phrenic and recurrent laryngeal nerves may occur during cardiac surgery.

Other common early complications of cardiac transplantation are organ rejection with consequent cardiac failure and side effects of immunosuppressive drugs. Cerebral air embolism may require hyperbaric oxygen therapy combined with aggressive resuscitation (Hinkle et al. 2001). Infections (meningitis, meningoencephalitis, or cerebral abscess) secondary to immunosuppressive therapy are the most important late complications. The infecting organisms include *Aspergillus, Toxoplasma, Cryptococcus, Candida,*

Nocardia, and viruses. The risk of lymphoma and reticulum cell sarcoma is increased also in patients on long-term immunosuppressive agents. Primary central nervous system (CNS) lymphoma may be impossible to distinguish clinically or radiologically from infection (see Chapter 5&).

Stroke occurs in approximately 5% of patients undergoing coronary artery bypass surgery. The risk is increasing because of the tendency to opetatc on older patients with more severe vascular disease or to undertake complicated, combined procedures such as bypass surgery plus valve replacement (Nussmeier 2002); other risk factors include proximal aortic atherosclerosis, hypertension, diabetes, and female gender. The mechanism is eithet embolic or less commonly a watershed infarction from hypoperfusion. A history of previous stroke also increases the risk, but a carotid bruit or radiological evidence of atherosclerotic disease of the carotid artery does not, and carotid endarterccctomy before the cardiac surgery is not justified.

A few patients who fail to recover consciousness after surgery despite the absence ol any identified metabolic cause have probably suttered diffuse cerebral ischemia or hypoxia. Hemispheric or multifocal infarction (Figure 55A. 1) is responsible in some cases. In evaluating patients with postoperative neurological deficits, diffusion-weighted magnetic resonance imaging (MRI) is more sensitive to ischemic change than computed tomography (CT) and most often reveals multiple embolic infarcts (Wityk et al. 2001).

Neurological Complications of Medication

The infectious and neoplastic complications of immunosuppressive agents are discussed in the previous section. The othct adverse events associated with corticosteroids are behavioral disturbances, psychoses, proximal weakness with type II muscle fiber atrophy, postural tremor, cataracts, and osteoporotic fractures. Benign intracranial hypertension may occur during treatment with or on withdrawal of corticosteroids. Neurological complications of cyclosporinc include tremor, seizures, focal deficits, paresthesias, encephalopathy, and ataxia.

Among antiarrhythmic agents, amiodarone causes tremor, sensorimotor peripheral neuropathy, myopathy, ataxia, optic neuropathy, and pseudotumor cerebri. Procainamide may unmask latent myasthenia gravis or precipitate a lupus-like syndrome with secondary vascular

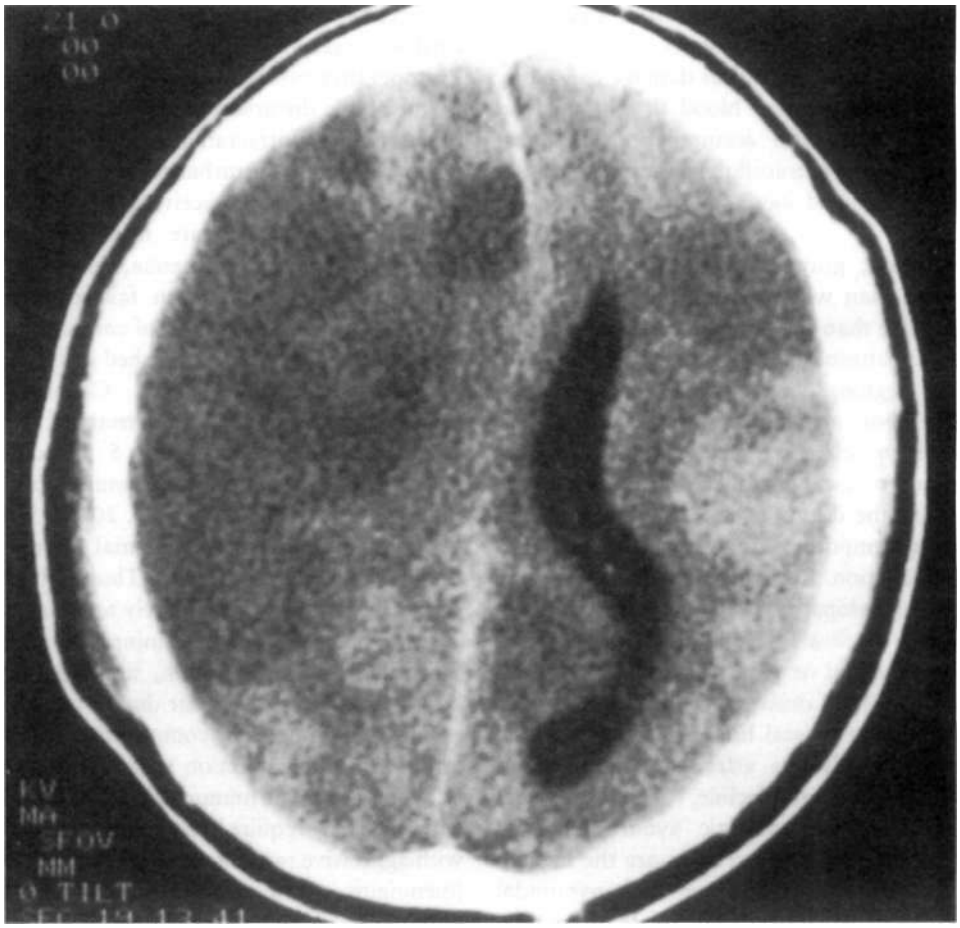

FIGURE 5SA.1 A noncontrasr computed tomographic scan performed to evaluate persistent coma 2 days after coronary artery bypass graft. Multiple bilateral ischemic lesions can be seen.

occlusive complications that are probably associated with lupus anticoagulant and antiphospholipid antibodies. Quinidine has neurological side effects similar to those of procainamide and causes headache, tinnitus, and syncope.

Lidocaine and related agents may cause seizures, tremor, paresthesias, and confusional states. Calcium-channel-blocking agents occasionally cause encephalopathy. Beta blockers are associated with mental changes, paresthesias, **and** disturbances of neuromuscular transmission, and digoxin and thiazide diuretics with an encephalopathy and disturbances of color vision.

Infective Endocarditis

The incidence of infective endocarditis has been increasing because of intravenous substance abuse and the increasing use of prosthetic cardiac valves. The overall incidence of neurological complications of infective endocarditis is approximately 25-35% but varies with the infecting organism. Such complications are the first sign or major complaint in 25-50% of instances and are associated with a significantly higher mortality. Neurological manifestations arc especially common in patients with mitral valve abnormalities and consist of embolic or hemorrhagic stroke and infections such as meningitis or brain abscess.

Cerebral mycotic aneurysms (Figure 55A.2) are recognized complications of infective endocarditis and may result in intracranial hemorrhage. They generally develop at the point of bifurcation of peripheral arteries and have a more distal location than congenital berry aneurysms. The pathogenesis of mycotic aneurysms is unclear. The most likely cause is impaction of infected material in the vasa vasorum, with resulting destruction of the wall of an artery. Intraluminal occlusion of the vessel by infected material, wiih subsequent aneurysmal formation, is less likely but has been documented in some cases. Mycotic aneurysms may be clinically silent and sometimes resolve with antibiotic therapy. They are less common but occur earlier in acute than in subacute bacterial endocarditis. Their natural history is poorly defined.

Intracranial hemorrhage is caused also by septic arteritis that destroys the vessel wall without causing aneurysm and by hemorrhagic transformation of cerebral infarcts. Arteriography is needed in patients with intracranial hemorrhage to distinguish mycotic aneurysm from septic arteritis.

Intracranial bleeding from a ruptured mycotic aneurysm can be the initial feature of an underlying cardiac disorder or may occur during the management of previously recognized infective endocarditis. Four-vessel arteriography is indicated in every patient with infective endocarditis who develops focal neurological deficits or has a subarachnoid hemorrhage. Arteriography should be performed before starting anticoagulation therapy in infective endocarditis unless an appropriate course of antibiotics has been completed without the development of neurological symptoms.

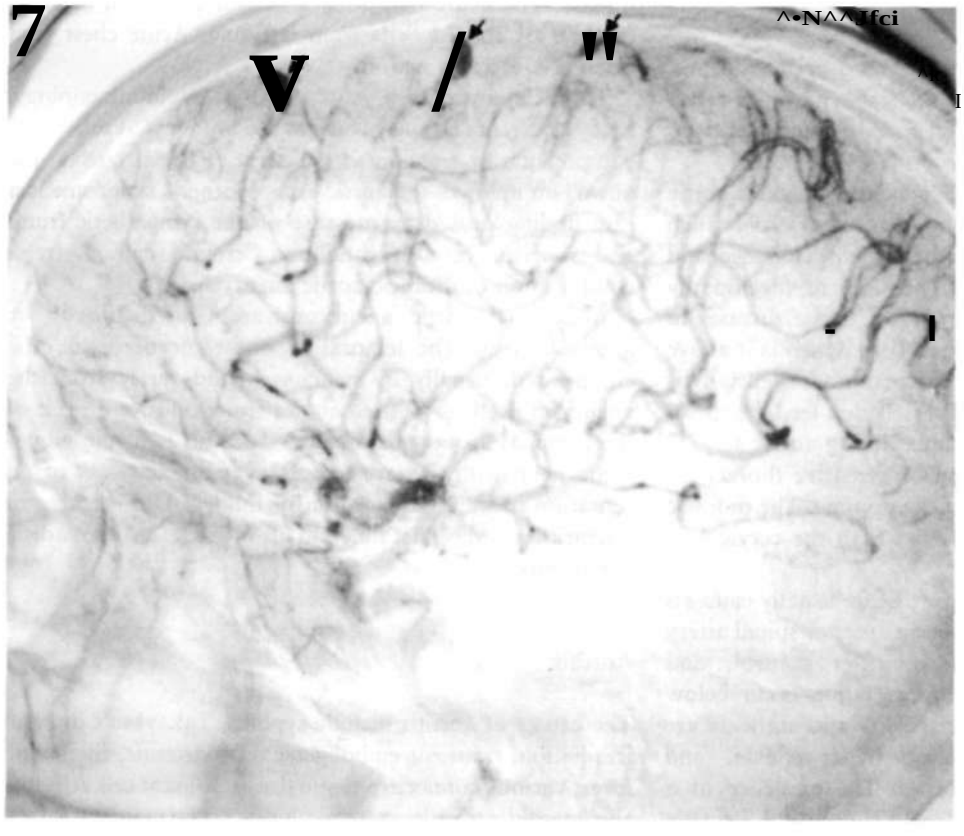

FIGURE 55A.2 Carotid angiogram, lateral view with subtraction, in a 48-year-old man with multiple peripheral mycotic aneurysms (*arrows*) verified at autopsy.

Embolization of infected material causes cerebral microabscesses and meningitis. Multiple septic emboli may cause meningoencephalitis or a diffuse encephalopathy that is characterized by a confusmnal state, headache, meningismus, and a cerebrospinal fluid (CSF) profile suggesting an aseptic process. The basis of these symptoms is probably multifactorial: infection, vascular occlusion, metabolic abnormalities, and mycotic aneurysms.

Antibiotic therapy to resolve the cardiac infection is the mainstay of treatment and is important in preventing neurological complications (Heiro et al. 2000). Neurological abnormalities usually resolve. Imaging studies are indicated in patients with progressive or persistent neurological deficits or an abnormal CSF. Arteriography is needed when MRI suggests mycotic aneurysm. Whether mycotic aneurysms require surgical resection or should be treated with antibiotics alone is unclear. Resection is recommended when cardiac valve replacement is planned, to reduce the risk of rupture from anticoagulants used during cardiopulmonary bypass. Anticoagulants are usually withheld from patients with infective endocarditis and cerebral embolism because of the risk of rupture of an unrecognized mycotic aneurysm. Moreover, control of the underlying infection with antibiotics reduces the risk of further embolism sufficiently to make anticoagulation unnecessary. Anticoagulation also may increase the risk of hemorrhagic transformation of embolic infarcts.

DISEASES OF THE AORTA

The aorta supplies blood to the CNS and peripheral nervous system (PNS). Several neurological syndromes result from aortic disease, depending on the site and severity of obstruction.

Spinal cord ischemia may result from congenital aortic abnormalities such as coarctation, acquired disorders such as aortic aneurysm or occlusive atherosclerotic disease, and aortic surgery or aortography. The level of myelopathy depends to some extent on the site of aortic disease. In general, aortic pathology that causes cord ischemia is above the origin of the renal arteries; obstruction more distally is less likely to affect the segmental vessels that feed the spinal cord. Risk factors for cord ischemia during aortic surgery include the presence of dissection or extensive thoracoabdominal disease, and a long cross-ciamp time. The thoracic cord is more susceptible to ischemia than the cervical or lumbosacral regions.

Spinal cord ischemia from aortic disease usually causes a complete transverse myelopathy or an anterior spinal artery syndrome. Weakness, loss of sphincter control, and impaired pain and temperature appreciation occur below the level of myelopathy. Initial flaccidity and areflexia are eventually replaced by spasticity, hyᵣper-ref!exia, and bilateral extensor plantar responses. The exisrence of a true posterior spinal artery syndrome is doubtful, because the posterior spinal arteries have multiple feeding vessels along their length. Occasional reports of a clinical disorder resembling progressive spinal muscular atrophy have been attributed to cord ischemia from aortic disease affecting the anterior horn cells especially.

Neurogenic claudication may be caused by ischemia of the nerve roots or cauda equina (as by a protruded lumbar disc in spinal stenosis), by intermittent cord ischemia from spinal vascular malformations, or by aortic disease. Pain, weakness, or a sensory disturbance develops in one or both legs while walking or in relation to certain postures. Symptoms are relieved by rest or change of posture. Neurogenic claudication must be distinguished from the intermittent claudication of peripheral vascular disease, because their treatments are different.

Disease of the aortic arch or its main branches also may lead to transient cerebral ischemic attacks or strokes. The risk of embolization from the aortic arch has been grossly underestimated until recently, especially in patients older than 60 years. Transesophageal echocardiography is an important means of evaluating the aortic arch.

Aortic Aneurysms

In Marfan's syndrome, there is an unusually high incidence of dissecting aneurysm ot (he ascending aorta that is associated with a dilated aortic root, but dissecting aortic aneurysms also occur in the absence of connective tissue disease. The neurological features usually consist of acute cerebral or cord deficirs from ischemia. Acute chest pain often is associated with it.

Thoracic aortic aneurysms suggest a syphilitic etiology. Left recurrent laryngeal nerve palsy may result from compression or traction of the nerve, especially when the aneurysm involves the aortic arch. Horner's syndrome is a rare finding caused by pressure on the sympathetic trunk and superior cervical ganglion. Cerebral emboli are a complication of thoracic aortic aneurysms.

Abdominal aortic aneurysms are caused usually by atherosclerosis. The femoral or obturator nerve may be compressed, usually by hematoma and rarely from the aneurysm itself, or injured at surgery. Occlusive disease of the terminal aorta sometimes leads to an ischemic monomelic neuropathy, characrerized by pain and loss of all sensation in the distal portion of the leg. Disturbances of micturition and sexual function also may result from aortic aneurysms.

Aortitis

The causes of aortitis include syphilis, Takayasu's disease, irradiation, transient emboligenic aortoarteritis, rheumatic fever, various connective tissue diseases (giant cell arteritis, rheumatoid arthritis, systemic lupus erythematosus [SLE],

scleroderma), ankylosing spondylitis, and Reirer's syndrome. Neurological complications occur when arteries are involved rhar perfuse neural tissues or in relarion to secondary aortic pathology such as an aneurysm.

Takayasu's disease is primarily a disease of young women. Nonspecific symptoms are fever, weight loss, myalgias, and arthralgia. Obstruction of major vessels of the aortic arch causes loss of pulses in the neck and arms, hypertension, and aortic tcgurgitation. Less common symptoms are headache, seizures, transient cerebral ischemic attacks, and stroke. Corticosteroids are the treatment of choice.

Transient emboligenic aortoarreritis is an inflammatory process affecting the aorta and other central elastic arteries, bur not the more peripheral vessels. It is a cause of stroke or transient ischemic attacks in young people.

Coarctation of the Aorta

Congenital coarctarion of the aorta is a narrowing of the thoracic aorta just after the origin of the left subclavian artery. Acquired coarctation may follow irradiation during infancy; the narrowing is in the irradiated region. A narrowed segment that is atypically located for congcniral coarctation and unrelated to prior irradiation should suggest Takayasu's disease.

Headache occurs in more than 25% of parients with coarctation. Subarachnoid hemorrhage may occur when an associared cerebral aneurysm ruptures, and episodic loss of consciousness of uncertain basis is reported also. Spinal cord dysfunction occurs when rhe lower part of the cord, supplied by vessels arising from the aorra beyond the narrowed Moment, becomes ischemic. Neurogenic inter mittent claudication may result from the stealing of blood from the cord by retrograde flow through the anterior spinal artery, a part of the collateral circulation bypassing the narrowed segment. Marked enlargement of collateral vessels wirhin rhe spinal canal may compress rhe cervicothoracic cord and cause myelopathy. Enlargement of the anterior spinal artety or one of its feeders may lead to aneurysmal distention and rupture, resulting in spinal subarachnoid hemorrhage. Treatment is by correction of the underlying coarctation.

Subclavian Steal Syndrome

Occlusion of either the innominate or the left subclavian artery before the origin of the vertebral artery reverses the direction of blood flow in the vertebral artery on the affected side. This often causes no symptoms but may cause ischemia in the posterior cerebral circulation. Neurological fearures are weakness, vertigo, visual complaints, and syncope. The pulse is typically diminished or absent in the affected arm, and sysrolic pressure is reduced usually by at least 20 mm Hg compared with the opposite arm. Reconsrrucrive surgery is sometimes helpful but is unnecessaty in most patients.

Complications of Aortic Surgery

Spinal cord infarction remains the most serious neurological complication of aortic surgery. CSF drainage and distal aortic perfusion may be important adjuncts to corrective surgery for thoracic and thoracoabdominal aortic aneurysms, reducing significantly the incidence of paraplegia and paraparesis (Estrera et al. 2001). Other complicarions are neuropathy, radiculopathy, postsympathectomy neuralgia when rhe sympathetic chain is surgically divided, and disrurbances of penile erection or ejaculation when the superior hypogastric plexus is divided surgically (Dougherty andCalligaro 2001).

CONNECTIVE TISSUE DISEASES AND VASCUL1TIDES

Neurological complications may be ditect consequences of connective tissue diseases, secondary to other organ involvement, or secondary to treatment. The adverse effects of corticosteroids and immunosuppressive agents were discussed earlier. Connective tissue disorders are characterized by an autoimmune inflammatory response, especially nccrorizing vasculiris. The mechanism of vasculitis is uncertain but may involve the deposition of immune complexes in vessel walls or cell-mediated immunity and release of lymphokines; autoantibodies also may be important in some instances. The common direct CNS manifestations of connective tissue diseases are cognitive or behavioral changes and focal neurological deficits. Peripheral neuropathies also occur and may take the form of a vasculitic neuropathy, distal axonal polyneuropathy, compression neuropathy, sensory neuronopathy, trigeminal sensory neuropathy, acute or chronic demyelinating polyneuropathy, or plexopathy.

Vasculitic neuropathy is caused by nerve infarction from occlusion of the vasa nervorum. It is a mononeuropathy multiplex that becomes increasingly confluent as more nerves are affecred until it resembles a disral symmetrical polyneuropathy. Nerves tend to be affected in watershed regions that lie between different vascular tctritorics, such as the mid thigh or mid upper arm.

Polyarteritis Nodosa, Churg-Strauss Syndrome, **and** Overlap Syndrome

Peripheral neuropathy occurs in up to 60% of patients with polyarreritis nodosa, Churg-Strauss syndrome, or overlap syndrome. It is usually a painful mononeuropathy multiplex that at least in polyarteritis often develops during the first year. As more nerves are affected, the deficits become

more confluent and come to resemble a polyneuropathy. A few patients exhibit only patchy hypesthetic areas; others develop a secondary polyneuropathy, for instance, from renal failure, a plcxopathy, radiculopathy, or cauda equina syndrome. Electrophysiological studies and nerve histology are often abnormal even when there is no clinical evidence of peripheral nerve involvement.

CNS involvement usually occurs later in the course than peripheral involvement. Common features are headache, which sometimes indicates aseptic meningitis, and behavioral disturbances such as cognitive decline, acute confusion, and affective or psychotic disorders. The electroencephalogram (EEG) is sometimes diffusely slow, but neuroimaging studies are generally normal. Focal CNS deficits are uncommon, are typically sudden in onset, and may be caused by infarction (Figure 55A.3) or hemorrhage. Angiography may not show the underlying vasculitis. Ischemic or compressive myelopathies from extradural hematomas are rare complications.

The 6-month survival rare of patients with untreated polyarteritis nodosa is only 35%. Prompt diagnosis and treatment arc critical. Weight loss, fever, cutaneous abnormalities, and arthralgias are common, and there may he hypertension and renal, cardiac, pulmonary, or gastrointestinal involvement. Laboratory studies show multiorgan involvement and immunological abnormalities. Common abnormalities are an increased erythrocyte sedimentation rate (ESR), anemia, and a peripheral leukocytosis. Hepatitis E surface antigen, hypocomplementemia, and uremia each occur in at least 20% of cases. Nerve or muscle biopsy often shows the necrotizing vasculitis, and angiography shows segmental narrowing or aneurysmal distention, especially in the renal, mesenteric, or hepatic vessels. Treatment is with corticosteroids, sometimes combined with cyclophosphamide.

Giant Cell Arteritis

i Icadache is the most common initial complaint of patients with giant cell arteritis, some of whom also complain of masticatory claudication. The temporal and other scalp arteries are often eryrhematous, tender, and nodular. A more serious initial symptom is acute transitory or permanent blindness, affecting one or both eyes, caused by ischemic optic neuropathy. Other CNS complications are rare, but neuropsychiatric disturbances, srrokes, diplopia, or seizures are occasionally the presenting feature. Peripheral neuropathies occur in up to 15% of patients, half of which are generalized.

One half of all patients have an elevated ESR, and polymyalgia rheumatica is often associated. High-dose corticosteroid treatment should be started once the diagnosis is suspected, without waiting to perform a temporal anew biopsy; any delay increases the risk of vision loss. Treatment is monitored by the clinical response and the ESR, but corticosteroid dose should be increased if clinical signs of disease activity occur, regardless of test results (Turbin and Kupersmith 1999). The dose of corticosteroids is gradually tapered with time, but treatment is usually required for 18-24 months.

Wegener's Granulomatosis

Neurological involvement occurs in up to 50% of patients with Wegener's granulomatosis. Peripheral involvement is manifest usually by a mononeuropathy multiplex or, less often, a symmetrical polyneuropathy. The brain may be affected directly by vasculitis or by extension of granulomas from the upper respiratory tract; the associated clinical syndromes are basal meningitis, temporal lobe dysfunction, crania] neuropathies, cerebral infarction, or venous sinus obstruction.

In one study of 109 patients with neurological complications, 53 had a peripheral neuropathy. The neuropathy consisted of mononeuropathy multiplex in 42, symmetrical polyneuropathy in 6, and unclassified involvement in 5 (Nishino et al. 1993). Cranial neuropathy was found in 21 patients (usually second, sixth, and seventh nerve involvement); 8 had multiple cranial neuropathies. Other neurological features were external ophthalmoplegia from orbital pseudotumor in 16, cerebrovascular events in 13, seizures (from metabolic, septic, or other complications, or from vasculitis) in 10, cerebritis in 5, and miscellaneous abnormalities in 25.

Isolated Angiitis of the Nervous System

Isolated angiitis (granulomatous angiitis) of the CNS is discussed in Chapter 57G, and that of the PNS is discussed in Chapter 82.

Rheumatoid Arthritis

Rheumatoid arthritis is the most common of the connective tissue diseases. Juvenile rheumatoid arthritis is discussed in Chapter 55B. Systemic vasculitis occurs in up to 25% of adult patients, but the CNS is rarely affecred. Pathological involvement of the cervical spine (Figure 55A.4), or atlantoaxial dislocation, may cause a myelopathy, headaches, or hydrocephalus or lead to brainsrem and cranial nerve deficits from compression or vertebral artery involvement. Special care is needed when hypcrcxtending the neck, as during endotracheal intubation, in patients with rheumatoid arthritis. Surgical fixation of subluxation is usually unnecessary unless displacement is marked or an associated myelopathy is severe or progressive.

Peripheral nerve involvement is common in rheumatoid arthritis. A distal sensory or sensorimotor polyneuropathy is

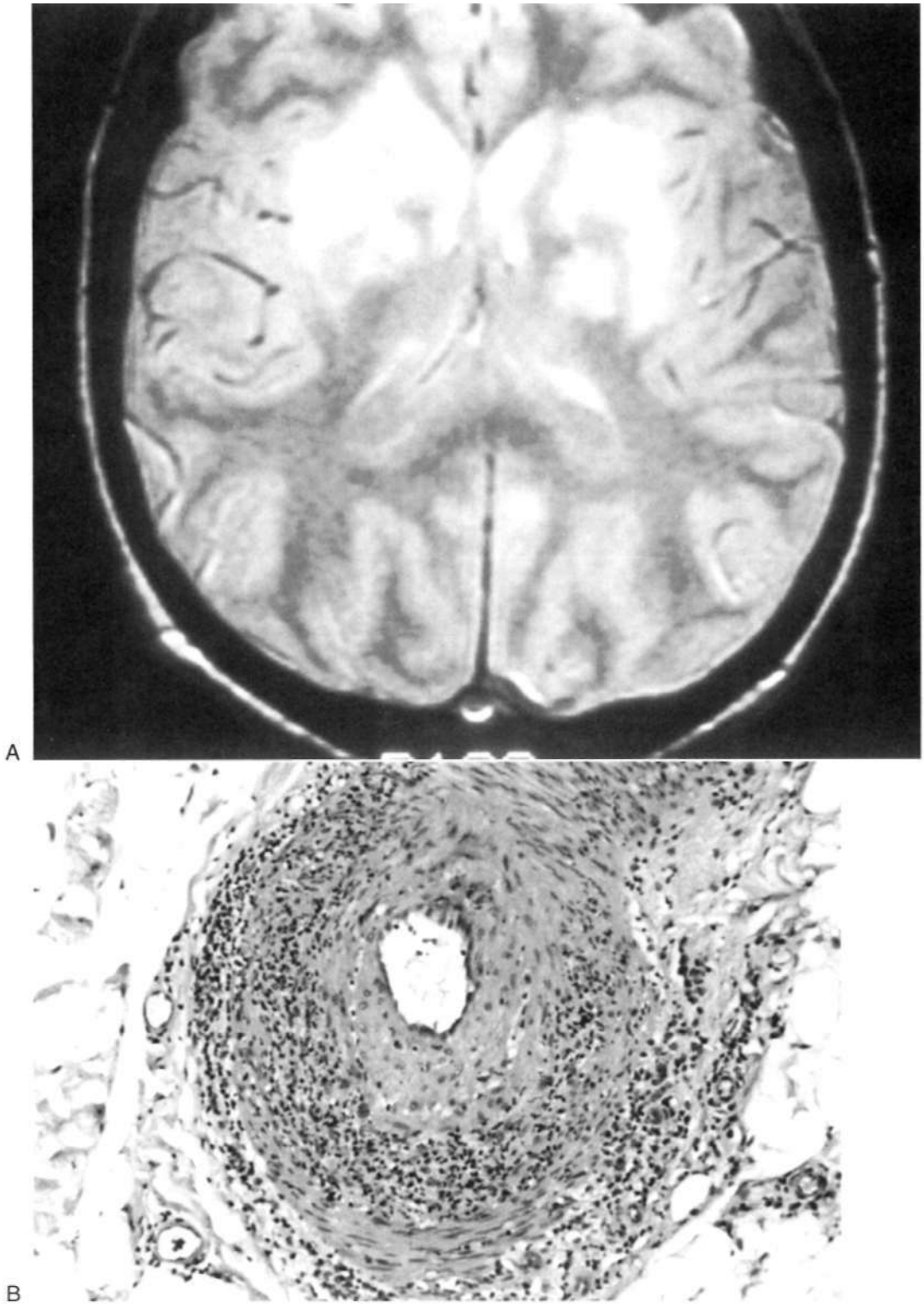

FIGURE 55A.3 (A) Proton-density-weighted magnetic resonance imaging scan showing patchy high signal in the basal ganglia bilaterally. (B) Microscopic section of a biopsied blood vessel showing marked thickening and inflammatory infiltrates indicative of a vasculitis in this patient with polyarteritis nodosa (hematoxylin and eosin, x 120).

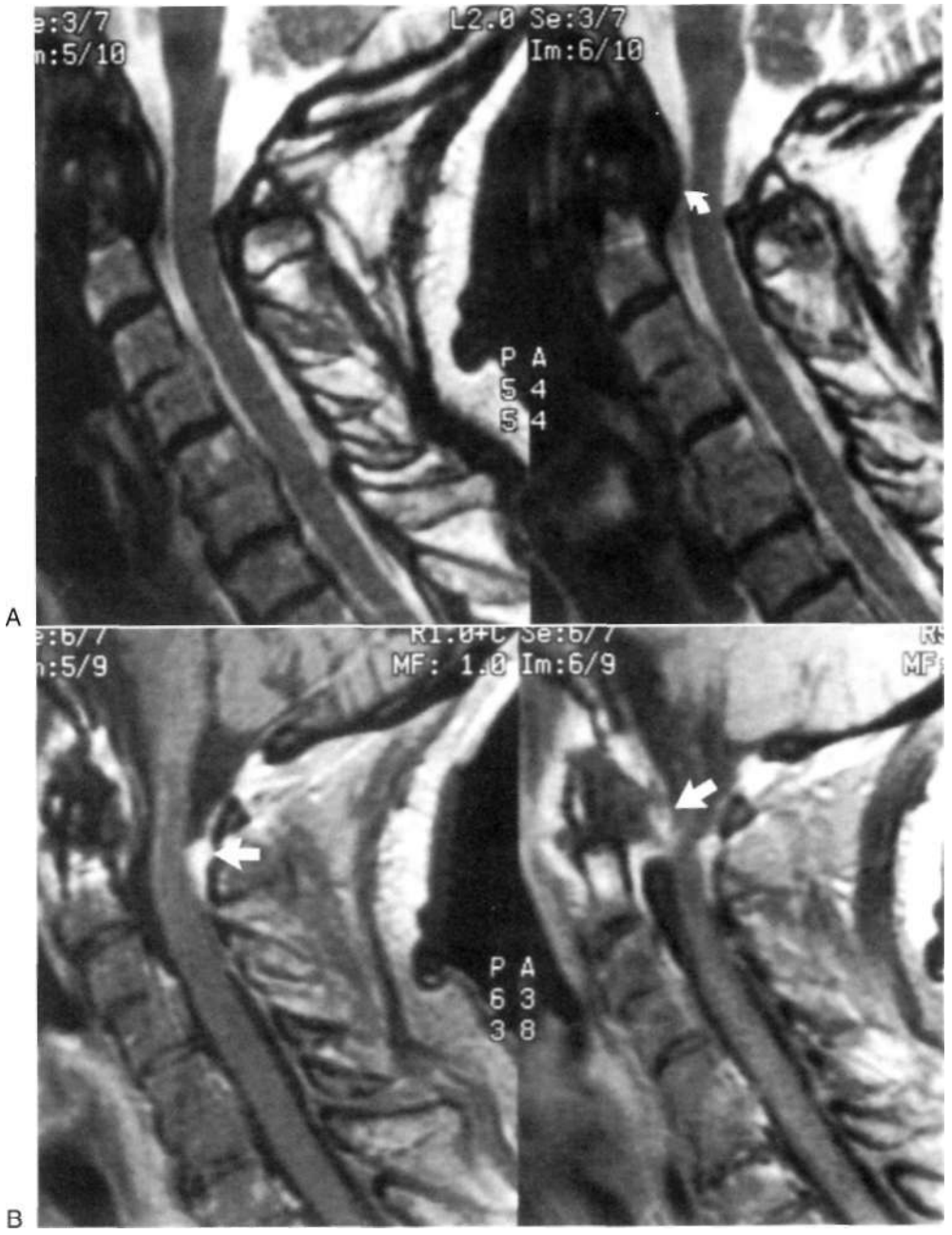

FIGURE 5SA.4 Two contiguous sagittal magnetic resonance images of the craniocervical region in a patient with rheumatoid arthritis. (A) T2-weighted and (B) Tl-weighted gadolinium-en ha need images. Arrows show pannus formation at CI, causing narrowing of the subarachnoid space and a suggestion of posterior displacement of the upper cervical cord.

common; clinical or electrophysiological evidence of sensory dysfunction is found in up to 75% of patients. Mononeuropathy multiplex and entrapment or compression neuropathies are also common. Compression injuries occur to the median nerve in the carpal tunnel, medial plantar nerve in the tarsal tunnel, ulnar nerve in the cubital tunnel or canal of Guyon, and peroneal nerve at the fibular head.

Several antitheumatic agents have adverse effects on the neuromuscular system. Gold treatment causes petipheral neuropathy in up to 1% of cases. Its onset is rapid and the evolution of weakness and the CSF profile may suggest Guillain-Barre syndrome. Chloroquine can cause neuropathy, myopathy, or both, and D-pcnicillamine causes disturbances of taste, an inflammatory myopathy, and a reversible form of myasthenia gravis.

Systemic Lupus Erythematosus

As many as 75% of patients with SLE have neutological involvement at some point during their course, often during the firsr year. Neurological complications may lead to a

fatal outcome. The mechanism of CNS involvement is unknown. Neither the presence of antineuronal and anti-astrocytic antibodies nor the deposition of antibody in the choroid plexus correlates with CNS involvement.

The most common neurological manifestations are episodic affective or psychotic disorders that may be difficult to distinguish from corticostcrokl-iiidiiL-cd mental changes. Cognitive dysfunction is often temporary. Multiple sclerosis is sometimes simulated. Treatment is empirical, depending on presentation and the probable underlying pathophysiology. Disturbances of consciousness sometimes occur, especially in patients with systemic infections. Focal neurological deficits may result from strokes, the pathogenesis of which in SLE includes cardiac valvular disease, thrombosis associated with antiphospho-lipid antibodies, and cerebral vasculitis. Anticoagulant or fibrinolytic therapy may prevent stroke recurrence. Dyskinesias, especially chorea, occur in some patients with SLE, but underlying structural pathology of the basal ganglia cannot be detected usually; chorea is associated with the presence of antiphospholipid anti-bodies. The occurrence of generalized or partial seizures is probably caused by microinfarcts, metabolic disturbances, and systemic infections (see Chapter 55B for additional information on the pediatric aspects of SLE).

PNS involvement occurs less often and is characterized usually by a distal sensory or sensorimotor polyneuropathy (Roscnhaum 2001). Other forms of neuropathy include an acute or chronic demyelinating polyneuropathy that resembles Guillain-Barre syndrome, single or multiple mononeuropathies, and optic neuropathy. Corticosteroids, immunosuppressive agents, and plasmapheresis are bene-ficial when neuropathy is caused by necrotizing vasculitis but are of less certain value in other circumstances.

Sjogren's Syndrome

Sjogren's syndrome may be a primary disorder or secondary to other connective tissue diseases. The main features are xerostomia and xerophthalmia. Women are more often affected than men. Definite diagnosis requires a positive result of the rose bengal dye test for keratocon-junctivitis, evidence of diminished salivary gland flow, abnormalities on biopsy of a minor salivary gland, and an abnormal test result for rheumatoid factor or antinuclcar antibody. Neurological complications are not common but include psychiatric disturbances, late-onset migrainous episodes, aseptic meningitis, meningoencephalitis, focal neurological deficits, and, in rare instances, an acute or chrome myelopathy. Cranial MRI may show hyperintense, small subcortical lesions. Polyneuropathy is the most common peripheral manifestation, bur mononeuropathy multiplex may occur also. Sensory ncuronopathy is unusual but is more characteristic of Sjogren's syndrome than other connective tissue diseases (Roscnbaum 2001).

Progressive Systemic Sclerosis

Progressive systemic sclerosis (i.e., scleroderma) was believed to affect the nervous system only rarely, but Avcrbueh-Heller, Steincr, and Abramsky in 1992 suggested there is neurological involvement in as many as 40% of patients. The PNS is usually affected: Distal sensorimotor polyneuropathy, entrapment mononeuropathy, trigeminal neuropathy, myopathy, or myositis may occur.

Behcet's Disease

Behcet's disease, of unknown etiology, is defined by the combination of uveitis and oral and genital ulcers. Aseptic-meningitis or meningoencephalitis occurs in 20% of cases. Focal or multifocal deficits also may occur and are caused by ischemic disease of the brain or spinal cord, related to small venous inflammatory disease. In other instances, cerebral venous sinus thrombosis occurs (Siva and Fresko 2000). The CSF commonly shows a mild pieocytosis, and the protein concentration may be increased. Peripheral nerve involvement is rare and takes the form of polyneu-ropathy or mononeuropathy multiplex, Treatment is with corticosteroids. Cerebral venous sinus thrombosis is treated with heparin (see Chapter 57A).

Relapsing Polychondritis

Relapsing polychondritis is an infrequently diagnosed inflammatory condition of cartilage such as that of the nose, ears, trachea, and joints. Episodes of ear or nose inflammation typically last 1-4 weeks, then either resolve completely or leave deformities because of cartilage destruction. Both genders are affected equally, with peak age at incidence between 30 and 60 years. Eye inflam-mation, especially episcleritis or conjunctivitis, may be associated with the attacks. Systemic vasculitis or features of other connective tissue disorders may develop. The diagnosis requires a typical clinical picture of chondritis. The ESR is elevated usually. Although autoimmunity against type II collagen may play a role in pathogenesis, only one half of patients have serological evidence of anti-type II collagen antibodies,

Auditory or vestibular dysfunction occurs in nearly one half of patients. The mechanism is usually otic rather than eighth nerve inflammation. Other cranial neuropathies, such as optic or facial neuropathy, may be associated. Headache, when it occurs, is more often caused by extracranial chondritis than intracranial inflammation. Aseptic meningitis, which may be recurrent, and vasculitic meningoencephalitis are sometimes associated.

Corticosteroids arc the traditional treatment, and other inflammatory or immunosuppressive drugs have been tried in some cases. The efficacy of treatment is difficult to assess

because of the remitting and relapsing pattern of the disease.

RESPIRATORY DISEASES

Ventilation requires the integrity of the CNS and PNS to support its coordinated motor activity. Diseases of the forcbrain, brainstem, and spinal cord cause abnormal ventilatory patterns or ventilatory arrest, and diseases of the motor unit cause hypoventilation and ventilatory failure. This section is concerned with the neurological consequences of respiratory abnormalities rather than the neurological causes of ventilatory disturbances.

Hypoxia

The neurological manifestations of hypoxia depend on its rate of onset, duration, and severity. Hypoxia may be complicated by acid-base imbalance and leads to other hematological and biochemical changes that affect cerebral function. The precise mechanisms responsible for the neurological abnormalities discussed here are therefore complex.

Encephalopathies caused by chronic pulmonary insufficiency are characterized by headache, disorientation, confusion, and depressed cognitive function. Postural tremor, myoclonus, asterixis, and brisk tendon reflexes are found commonly on examination, and papilledema is present sometimes. These features are caused not only by cerebral hypoxia but also by hypercapnia, which leads to cerebral vasodilatation, increased CSE pressure, and altered pH of the CSF.

Sleep apnea syndromes cause chronic nocturnal hypoxia and become symptomatic as excessive daytime sleepiness. Many affected patients are obese, plethoric, and snore heavily. Treatment is summarized in Chapter 74.

High-altitude sickness is characterized by headache, lassitude, anorexia, nausea, difficulty in concentration, and disturbances of sleep. Symptoms begin within hours or days of ascending higher than 10,000 feet. At even higher altitudes, consciousness may be disturbed; coma occurs in severe cases and may lead to a fatal outcome. Cerebral edema of uncertain cause is the major underlying feature that causes papilledema, retinal hemorrhages, cranial neuropathies, focal or multifocal motor and sensory deficits, and behavioral disturbances. Corticosteroids avert or relieve the syndrome.

Hypercapnia

Ventilatory impairment causes hypercapnia and hypoxemia, and the neurological manifestations of each are difficult to distinguish.

Hypocapnia

The hypocapnia that results from hyperventilation causes cerebral vasoconstriction, a shift of the oxyhemoglobin dissociation curve so that peripheral availability of oxygen is reduced, and an alteration in the ionic balance of calcium. The clinical features arc lightheadedness, paresthesias, visual disturbances, headache, unsteadiness, tremor, nausea, palpitations, muscle cramps, carpopedal spasms, and loss of consciousness.

Hyperventilation occurs in hepatic and diabetic coma, with certain brainstem lesions, with various cardiopulmonary diseases, with certain drugs causing acidosis, and on an iatrogenic basis. Episodic hyperventilation often occurs without any identifiable systemic disease.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

\"e urn logical complications may occur when infection and trauma have induced a systemic inflammatory response affecting the microcirculation to multiple organs. For example, patients with sepsis and multiorgan (including respiratory) failure sometimes develop an axonal neuropathy that only comes to attention when attempts arc made to withdraw ventilatory support. The neuropathy, which is called *critical illness neuropathy,* improves only slowly as the critical illness subsides.

Corticosteroids and neuromuscular blocking drugs may induce a myopathy, especially in patients with obstructive airway diseases. Its highest prevalence is among asthmatics who require ventilatory support in addition to corticosteroids and who have also received the neuromuscular blocking agent vecuronium. It sometimes occurs in patients who have received either corticosteroids or neuromuscular blockers, but not both. Muscle biopsy may show muscle fibers with specific loss of myosin (thick filaments).

A diffuse encephalopathy is a complication of sepsis and is most likely in patients with respiratory distress syndrome. Its pathogenesis is probably multifactorial and may relate to reduced cerebral blood flow, cerebral edema, disruption of the blood-brain barrier, direct cerebral infection, toxins produced by infecting organisms, metabolic abnormalities, and the effects of medication (Papadopoulos et al. 2000). The encephalopathy tends to fluctuate in severity, is often worse at night, and is associated with marked abnormalities of the EEC Treatment is of the underlying sepsis; no specific treatment exists for the encephalopathy.

SARCOIDOSIS

Sarcoidosis is a disorder of unknown cause with multiorgan involvement and many different clinical presentations. It is more common in blacks than in whites and in women than

in men. The disease is often discovered incidentally on routine chest roentgenography. The prevalence of neurological involvement in any series varies with case selection and diagnostic criteria but may be as high as 5%. The nervous system may be involved directly by the disease or secondary to opportunistic infections associated with abnormalities of the immune system. Only direct involvement (Figure 55A.5) is considered in this section.

Cranial neuropathies from chronic basal meningitis are the most common neurological manifestations of sarcoidosis. The facial nerve is affected most often, sometimes bilaterally. The optic nerve may be swollen or atrophied. Increased intracranial pressure from a space-occupying lesion, meningeal involvement, or obstructive hydrocephalus may cause papilledema. Visual changes are caused also by direct involvement of the optic nerves or their meningeal covering, or by uveitis. Unilateral or bilateral recurrent laryngeal, trigeminal, or auditory nerve involvement is also common, and multiple cranial neuropathies may occur.

Disturbances of the hypothalamic region are associated with diabetes insipidus, abnormalities in thermoregulation, amenorrhea, impotence, hypoglycemia, disturbances of sleep, obesity, personality changes, and evidence of hypopituitarism.

Other neurological features depend on intracranial or intraspinal meningeal or parenchymal involvement. Diffuse meningoencephalitis causes cognitive abnormalities or affective disorders. An enlarging granuloma may mimic a cerebral tumor and lead to seizures and focal neurological deficits.

Peripheral nerve involvement may take the form of a symmetrical polyneuropathy or an asymmetrical mononeuropathy multiplex. This may result from polyradicular involvement by extension of meningeal sarcoidosis or from direct involvement of the nerves by sarcoid granulomas. Muscle granulomas may cause clinical features of a myopathy and are found commonly in clinically unaffected muscles.

Neurosarcoidosis often remits spontaneously, but progressive neurological disease occurs in approximately 30% of cases. The diagnosis of neurosarcoidosis is difficult in the absence of systemic disease, especially cutaneous or pulmonary involvement. Histological confirmation often requires biopsy of seemingly unaffected tissue (e.g., muscle or conjunctiva) if other lesions are not accessible. Neither the tuberculin skin test nor the blood concentration of angiotensin-converting enzyme is definitive in establishing the diagnosis. Corticosteroid treatment is recommended generally, but its long-term value is not established. The

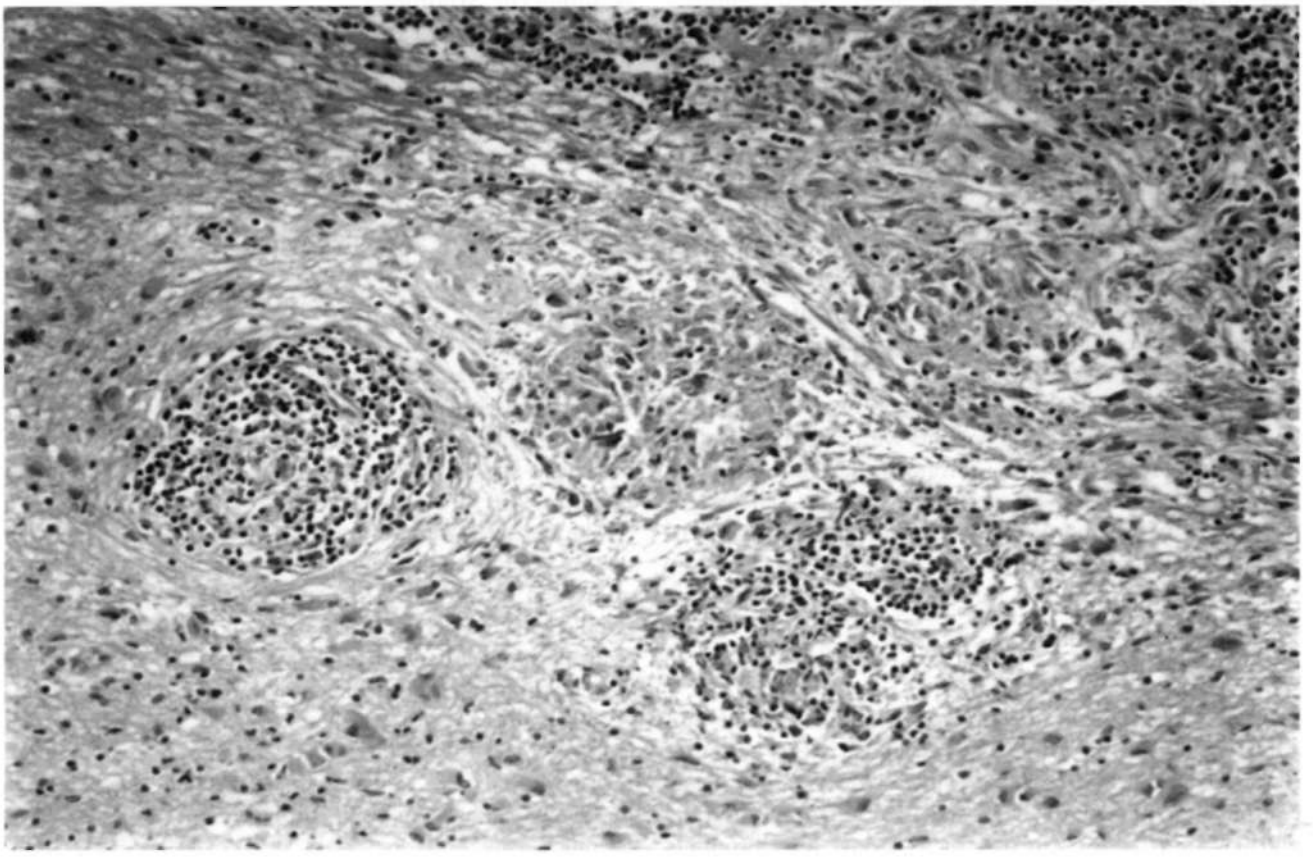

FIGURE 5SA.5 Photomicrograph showing sharply delimited granulomas without necrosis in hypothalamus of a patient with sarcoidosis (hematoxylin and eosin, x40).

initial dose of prednisone is 60 mg per day, and the dose is adjusted depending on clinical response. Irradiation of a focal lesion or cyclosporine is beneficial in some cases. Useful surgical measures arc the excision of focal, enlarging granulomas and the placement of a shunt to relieve hydrocephalus.

HEMATOLOGICAL DISORDERS WITH ANEMIA

Anemia often causes nonspecific behavioral symptoms such as lassitude, lightheadedness, inattentiveness, irritability, headache, and unsteadiness. Iron-deficiency anemia is associated with pica, restless legs syndrome, and benign intracranial hypertension, and with an increased risk of stroke or transient cerebral ischemic attacks because of thrombocytosis. Severe anemia may rarely cause focal neurological deficits in patients with pre-existing cerebral atherosclerotic disease. Pancytopenia may cause hemorrhagic CNS complications.

Megaloblastic Anemia

Vitamin B_{12} deficiency causes myelopathy, encephalopathy, optic neuropathy, peripheral neuropathy, or some combination of these disorders. The neurological complications do not necessarily correlate with the presence or severity of associated megaloblastic anemia. Folic acid masks the anemia without preventing the neurological complications. Nitrous oxide anesthesia may unmask a subclinical cobalamin deficiency (Marie et a). 2000), The food supply in the United States was fortified with folic acid beginning in 1994 to prevent spina bifida, so anemia is no longer a marker of vitamin Bi_2 deficiency.

The Schilling test is an important means of diagnosing the most common cause of vitamin B12 deficiency, impaired absorption from deficiency of intrinsic factor. Vitamin B12 is absorbed exclusively by the terminal ileum, and deficiency may occur also in patients with urinary intestinal diversion. Treatment with intramuscular injections of vitamin Bi_2 reverses the neurological disorder. The extent of residua correlates with the severity and duration of symptoms before treatment.

Sickle Cell Disease

Sickle cell disease causes vasculopathy of both large and small vessels as a result of a genetic point mutation (Prengler et al. 2002). Sickled cells adhere to the vascular endothelium, and a cascade of activated inflammatory cells and clotting factors leads to a nidus for thrombus formation. Sickling is aggravated by hypoxia, infection, inflammation, dehydration, and acidosis.

The most common neurological complication of sickle cell disease is stroke, which occurs more often in children than in adults. Other complications are convulsions, intracranial (usually subarachnoid) hemorrhage, behavioral disturbances, and alteration in consciousness. The cause of intracranial hemorrhage cannot always be determined despite detailed investigation, but some cases are caused by rupture of an aneurysm that may be surgically accessible. Blindness sometimes results from proliferarive retinopathy; retinal detachment or infarction also occurs. Spinal cord infarction is rare.

Thalassemias

Extramedullar hematopoiesis occurs in the liver, spleen, and lymph nodes of patients with severe forms of /^-thalassemia, but it may also occur in the spinal epidutal space and cause a compressive myelopathy. Treatment includes local irradiation, surgical decompression, corticosteroids, and repeated blood transfusions. Bone marrow hypertrophy also causes facial deformity, nerve root compression, and auditory impairment. Surgical decompression or radiation therapy is beneficial in some cases.

Acanthocytic Syndromes

Acanthocytes, or spiny red cells, are associated with abcralipoproteiiiemia [sec Chapter 68), neuroacanthocytosis (see Chapter 77), and McLeod's syndrome (see Chapter 85),

PROLIFERATIVE HEMATOLOGICAL DISORDERS

Leukemias

The neurological complications of leukemia are caused by leukemic infiltration of the nervous system, hemorrhage, infection, electrolyte disturbances, hyperviscosity, and complications of treatment. Localized leukemic deposits are more likely to affect the brain than the spinal cord; peripheral nerve involvement is rare.

The clinical features of meningeal leukemia are headache, nausea and vomiting, somnolence, irritability, convulsions, and coma. Obstructive or communicating hydrocephalus, papilledema, and meningismus may be associated. Cranial neuropathies and spinal radiculopathies are common, and their multifocal distribution should always suggest meningeal leukemia. Examination of the CSF shows abnormal leukemic cells, especially if cytospin techniques arc used, but a normal CSF result does not exclude the diagnosis of meningeal leukemia. Treatment is with intrathecal chemotherapy.

Intracerebral hemorrhage is more common than subarachnoid or subdural hemorrhage. It is associated with

platelet counts less than 20,000 cells/uL. The hemorrhage is often multifocal and varies in severity from microscopic to fatal. Spinal subdural or subarachnoid hemorrhage is less common than intracranial bleeding but is a potentially serious complication of lumbar puncture, sometimes requiring surgical decompression.

The hyperviscosity syndrome occurs when resistance to blood flow is increased markedly, so that transit through the microcirculatory system is impaired. It is characterized by headache, somnolence, impaired consciousness, stroke or transient cerebral ischemia, and visual disturbances. Venous sinus thrombosis, nonbacterial thrombotic endocarditis, and disseminated intravascular coagulation (DIC), discussed later in this chapter, may occur also. The most common cause of this syndrome is an increase in the concentration of -circulating gamma globulins, which is discussed in the following section.

Infection is a common complication of chemotherapy or corticosteroid therapy. The use of broad-spectrum antibiotics often encourages infection by unusual organisms. Progressive multifocal leukoencephalopathy is an uncommon complication of leukemia (see Chapter 60}.

Plasma Cell Dyscrasias

Plasma cell dyscrasias are classified on the basis of the protein synthesized. They may be complicated by para neoplastic syndromes {sec Chapter *58)* and by an increased susceptibility to infections that may involve the C\'S.

Myelomatosis

Multiple myeloma, the most common plasma cell dyscrasia, is associated with a monoclonal immunoglobulin G (IgG) or immunoglobulin A (IgA) paraprotein in the serum or urine. The clinical features are pain, fracture, and destruction of bone. Tumor infiltration of the vertebrae causes compression of the spinal cord or nerve roots. Back pain is conspicuous, radicular pain is common, and cord or root dysfunction may be present. Treatment by local irradiation and high-dose corticosteroids prevents or minimizes residual neurological deficits, but urgent decompressive surgery is required if the diagnosis is uncertain. Cranial involvement is less common than spinal involvement. Cranial neuropathies, especially of nerves II, V, VI, VII, and VIII, may occur. A reversible optic neuropathy of uncertain etiology, but probably not caused by infiltration, has been described.

Increased intracranial pressure does not necessarily indicate intracranial infiltration: Pseudotumor cerebri sometimes occurs without evidence of intracranial myeloma or hyperviscosity syndromes.

Peripheral neuropathy is a well-recognized complication of myeloma. A symmetrical axonal sensory or sensorimotor polyneuropathy occurs as a complication of the circulating immunoglobulin, and a predominantly motor neuropathy resembling chronic inflammatory demyelinating polyradiculoneuropathy may occur with osteosclerotic myeloma. Treatment with cytotoxic agents and plasmapheresis sometimes slows or reverses the neuropathy, as may irradiation of bony lesions. Tumor infiltration of nerves leads to an asymmetrical neuropathy that has the features of mononeuropathy multiplex. Amyloidosis is sometimes associated with myeloma and causes a neuro pathy characterized by dysautonomia, marked loss of pain and temperature appreciation, and weakness.

The POEMS syndrome consists of polyneuropathy, organomegaly, endoermoparhy, M protein, and skin changes in patients with plasma cell dyscrasia. It is most often associated with osteosclerotic myeloma but also occurs with osteolytic myeloma accompanied by only minor sclerotic changes and in patients without myeloma. Osteosclerotic myeloma usually is considered a variant of solitary or early multiple myeloma but may be a distinct entity. The neuropathy is a distal, sensorimotor polyneuropathy with both axonal degeneration and segmental demyelination. Other clinical features are papilledema; lymphadenopathy; hepatosplenomegaly; impotence; gynecomastia; amenorrhea; glucose intolerance; peripheral edema; ascites; pleural effusions; and cutaneous pigmentation, thickening, and hypertrichosis. Corticosteroids, cyclophosphamide, and irradiation of solitary osteosclerotic lesions may be beneficial.

Other neurological manifestations are caused by infections related to immunodeficiency, hypercalcemia, uremia, and hyperviscosity. The hyperviscosity syndrome is characterized by headache, visual disturbances, and encephalopathy. Hemorrhages, exudates, and venous engorgement are seen on funduscopic examination.

Waldenstrom's Macraglobulinemia

Waldenstrom's macroglobulinemia is a plasma cell dyscrasia associated with IgM gammopathy. Neurological complications are common. A progressive sensorimotor polyneuropathy is attributed to binding of monoclonal immunoglobulin *M* (IgM) to peripheral nerves or results from lymphocytic infiltration of the nerves. Other neurological complications relate to hyperviscosity or a bleeding tendency resulting from platelet abnormalities. Presentation is with a diffuse encephalopathy or focal neurological deficits. Common manifestations are fatigue, lassitude, lethargy, confusion, altered consciousness, and seizures. Visual, auditory, and vestibular disturbances also occur.

Neurological examination shows pyramidal, cerebellar, or brainstem abnormalities, and funduscopic examination may reveal papillitis, venous engorgement, hemorrhages, and exudates. Plasmapheresis relieves symptoms caused by hyperviscosity and helps the peripheral neuropathy in some cases.

Monoclonal Gammopathy of Undetermined Significance

Many patients with a monoclonal gammopathy have no evidence of serious underlying pathology, but some eventually develop a malignant plasma cell dyscrasia. Chronic inflammatory demyelinating polyradiculoneuropathy is the characteristic polyneuropathy associated with monoclonal gammopathy of undetermined significance. IgM autoanribodies that react with myelin-associated glycoproteins or with other target antigens may be present in the blood. Short-term treatment with intermittent cyclophosphamide and prednisone may provide long-term benefit.

Amyloidosis

Amyloidosis may occur as a familial disorder with dominant inheritance. Portuguese, Japanese, Swedish, and other varieties are described. The main neurological complication is a small-fiber sensory neuropathy, with marked impairment of pain and temperature appreciation and lesser involvement of other sensory modalities (see Chapter 82). An associated dysautonomia is conspicuous. Weakness develops later.

Nonfamilial amyloidosis is divided into primary and secondary varieties. Primary amyloidosis occurs in the absence of other disorders (except multiple myeloma), whereas secondary amyloidosis occurs in association with such disorders as chronic infection. Peripheral neuropathy is a common feature of primary but not secondary amyloidosis. It is characterized by a progressive sensory or sensorimotor polyneuropathy with autonomic involvement or by carpal tunnel syndrome. Cranial neuropathy is uncommon; cranial nerves III, V, and VII are most often affected. Cardiovascular and renal dysfunction are common, and other organ systems also may be involved. The diagnosis is suggested by the clinical findings and the presence, in most cases, of a monoclonal protein in the serum. No effective treatment is available. Death usually results from systemic complications.

Accumulation of /$_2$-microglobulin-associated amyloid in patients undergoing long-term hemodialysis may cause carpal tunnel syndrome, a cervical myelopathy, or a cauda equina syndrome. Surgical decompression may be helpful in such circumstances.

Cryoglobulinemia

Cryoglobulins are proteins that precipitate in the cold and dissolve when heated. They are classified as monoclonal IgM, IgG, IgA, or light chains (type 1), mixed but with one monoclonal immunoglobulin (type 2), and polyclonal, without any monoclonal protein (type 3).

Primary cryoglobulinemia occurs in the absence of other disease. Secondary cryoglobulinemia occurs in association with disorders such as myelomatosis or macroglobulinemia with monoclonal protein production or disorders with polyclonal protein production, such as vasculitis or chronic inflammatory disease. Cryoglobulinemia is associated with transient cerebral ischemic attacks, strokes, and a peripheral neuropathy that is probably ischemic in origin. The extent to which neurological complications arc caused by the cryoglobulinemia, as opposed to the accompanying vasculitis, is unclear. Treatment with corticosteroids, plasmapheresis, or both may be beneficial.

Lymphoma

Neurological complications of lymphoma can be caused by direct spread of tumor, compression of the nervous system by extrinsic tumor, or paraneoplastic syndromes (see Chapter 58). They may also result from irradiation or chemotherapy, thrombocytopenic hemorrhage, or opportunistic infections. Primary CNS lymphoma is a known complication of immunosuppression and occurs most often in patients with acquired immunodeficiency syndrome (see Chapter 58) and less frequently in transplant recipients.

Polycythemia

The thrombotic and hemorrhagic complications of polycythemia often affect the nervous system. Occlusion of small or large arteries or venous channels may cause cerebral infarcts that arc sometimes recurrent and fatal. This thrombotic tendency has been attributed to increased blood viscosity, thrombocytosis, and possibly chronic disseminated intravascular clotting. Intracranial hemorrhage is caused by abnormalities of clot retraction, thromboplastin generation, and platelet function. Spinal cord infarction is rare. Patients with polycythemia often complain of headache, poor concentration, unsteadiness, tinnitus, blurred vision, dysesthesias, and other nonspecific symptoms. The basis of such symptoms is unclear, but disturbances in the retinal circulation may account for the visual complaints. Pseudotumor cerebri and chorea may occur with polycythemia. Chorea reverses when the underlying hematological disorder is treated.

HEMORRHAGIC DISEASES

Hemophilia

Intracranial hemorrhage is a major cause of death in patients with hemophilia. Hemorrhages may be epidural, subdural, subarachnoid, or intracerebral and may occur spontaneously or following trivial head injury. Neurological symptoms may not develop for several days after injury. The severity of bleeding generally correlates with the severity of coagulopathy. Spinal subdural or epidural

hemorrhage may occur but is uncommon; the clinical features are back or neck pain and a progressive painful paraparesis or quadriparesis. Surgical decompression is necessary to preserve neurological function, and the deficient factor VIII must he provided as well.

Peripheral neuropathies secondary to compression of individual nerves by intramuscular or retroperitoneal hematomas are a common complication. Urgent operative decompression may be needed to preserve function,

Seizures may result from brain injury caused by previous intracranial hemorrhage. Their control with anticonvulsant agents helps prevent further bleeding.

Other Hemorrhagic Disorders

Other coagulopathies have a lower frequency of neurological complications than hemophilia, hut these are similar to those already described.

Disseminated intravascular Coagulation

DIG is characterized by thrombotic occlusion of small vessels and concomitant hemorrhagic complications because clotting factors (including fibrinogen and factors V and VIII) and platelets ate consumed in the thrombotic process. DIC occurs in association with primary brain disease, diseases of other organs, septicemia, immune-mediated disorders, diabetic ketoacidosis, neoplastic disease, and obstetrical complications. Several organs may be affected, but the brain is commonly involved. The underlying cause, rate of onset, and severity of DIC influence the clinical features, as do the organs affected and the predominance of thrombosis or hemorrhage.

Neurological features fluctuate in severity. Encephalopathy is common and varies in severity from a mild confusional state to coma. Comatose patients may recover completely, and continuing support is therefore indicated. The prothrombin time is usually prolonged, the serum level of fibrin-degradation products is increased, and thrombocytopenia may be present. The serum fibrinogen concentration is sometimes normal. Neuroimaging shows multifocal cerebral hematomas and infarctions. Treatment is directed at the underlying cause of DIC. Heparin may limit thrombotic complications but can worsen hemorrhagic complications; its value is uncertain. The same can be said of antiplatelet agents and antithrombin concentrates.

Thrombocytopenia

Thrombocytopenia, which is caused by reduced production or increased breakdown of platelets, may lead to hemorrhage. Intracerebral hemorrhage is usually from capillaries and is characterized first by clinically silent petechial hemorrhages and later by symptomatic hematomas. Spinal or peripheral nerve involvement by hemorrhage is uncommon. Platelet transfusions arrest further bleeding. Corticosteroids may be beneficial when platelet function is abnormal; splenectomy is sometimes indicated.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura is a disorder of uncertain cause, possibly immune mediated, that often has a fatal outcome. It is sometimes associated with the use of certain medications, especially quinine (Kojouri, Vesely, and George 2001). The clinical features are thrombocytopenic purpura, hemolytic anemia, fever, neurological abnormalities, and renal disease. The neurological features may include headache, mental changes, altered states of consciousness, seizures, and focal deficits. Treatment options are plasma exchange or infusion, splenectomy, and administration of corticosteroids ot antiplatelet agents. Rapid administration of platelets may lead to a fatal outcome and must be avoided.

Iatrogenic Hemorrhagic Disorders

Patients treated with heparin or warfarin may develop intracranial or spinal hemorrhage. The bleeding may be parenchymal, subarachnoid, subdural, or extradural. It can occur spontaneously or after injury and cause the acute or subacute onset of a neurological deficit. Treatment includes reversal of the coagulopathy, definition of the pathology by neuroimaging studies, and urgent decompressive surgery if necessary. Intramuscular hemorrhage may cause a plexopathy or peripheral neuropathy that requires urgent decompression.

Antiphospholipid Antibody Syndromes

Antiphospholipid antibodies (the lupus anticoagulant and anticardiolipin antibodies) are detectable in several disorders, but especially in SLE, Sneddon's syndrome (Figure 55A.6), and other connective tissue disorders (Cervcra et al. 2002). They are found also in patients taking certain medications, with some infections and obstetrical complications, and as an incidental finding in healthy people. The presence of antiphospholipid antibodies increases the risk of thrombotic disease. Cerebral ischemia is caused by either arterial or venous occlusion. Visual abnormalities include amautosis fugax and ischemic optic neuropathy or retinopathy. The occurrence of migraine-like headaches may be fortuitous. An acute ischemic encephalopathy, characterized by confusion, obtundation, quadriparesis, and bilateral pyramidal signs, may occur. Dementia, chorea, transient global amnesia, transverse myelopathy, Guillain-Barrc syndrome, and seizures have been described. Multiple

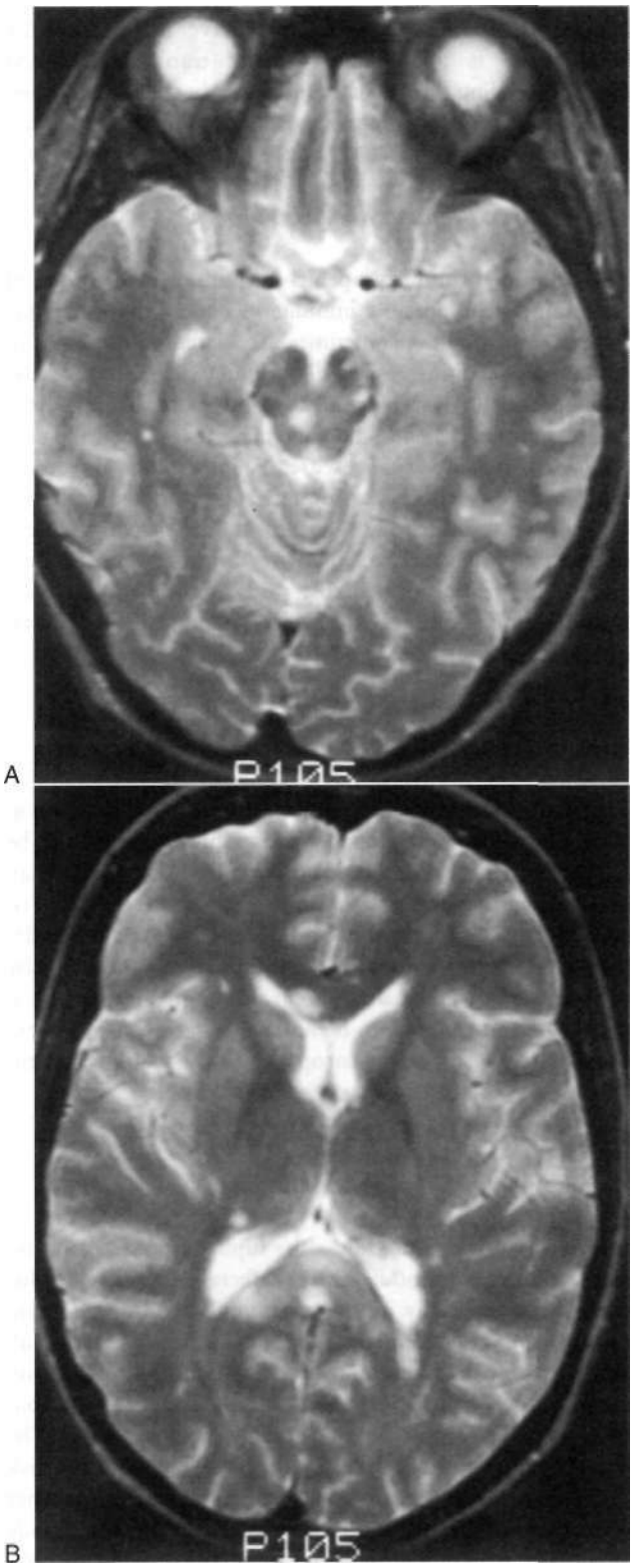

FIGURE S5A.6 A 27-year-old woman with Sneddon's syndrome (livedo reticularis and cerebrovascular disease). T2-weighted magnetic resonance imaging scan showing multiple foci of high-signal intensity in the mesencephalon (A) and in the corpus callosum and periventricular white matter (B).

sclerosis may be simulated clinically and on MRI (Cuadrado et al. 2000).

The pathogenesis of the thrombotic tendency is not established. The presence of antiphospholipid antibodies does not require immunosuppression. Cerebral thrombosis is managed in the same way as that from other causes.

LIVER DISEASE

Patients with acute hepatic failure often develop severe cerebral edema (Figure 55A.7). Several other neurological manifestations occur with chronic hepatic disorders.

Portal Systemic Encephalopathy

Chronic liver disease causes a portal systemic encephalopathy, characterized by an abnormal mental status (see Chapter 62). Points to emphasize here are that the encephalopathy may have an insidious onset, delaying its clinical recognition and treatment; a flapping tremor (asterixis) may be the only other neurological sign; and

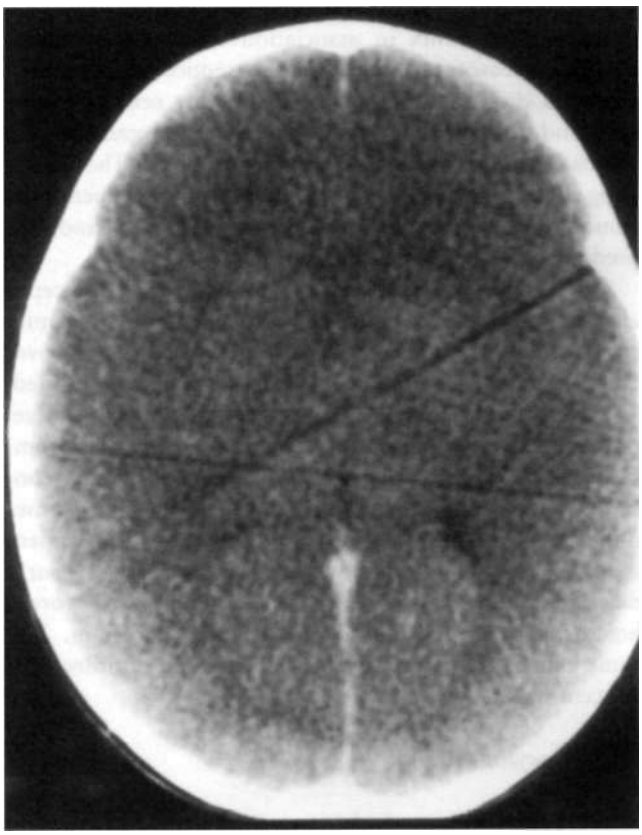

FIGURE 5SA.7 A 15-year-old girl with fulminant viral hepatitis. Computed tomographic scan without contrast shows severe diffuse cerebral edema. (The two diagonal dark bands represent artifact from an intracranial pressure monitor.)

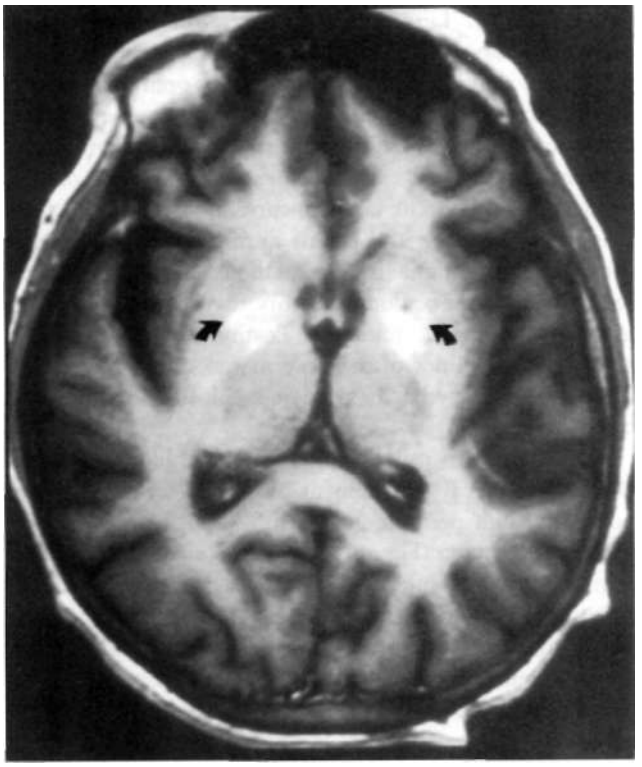

FIGURE 55A.8 Patient with chronic liver disease related to ethanol abuse. Tl-weighted magnetic resonance imaging scan, without contrast, shows bright signal in the region of the globus pallidus bilaterally *{arrows),* T2-weighted images (not shown) were normal,

liver function test results, other than the fasting arterial ammonia concentration, do not always correlate with the severity of the clinical disturbance. Focal neurological signs may be present but have no prognostic significance (Cadranel et al. 2001). EEG abnormalities also correlate with the severity of encephalopathy. MRI may show abnormal signal intensities in the basal ganglia on Tl-weighted images (Figure 55A.8). The mechanism of the encephalopathy is unknown. Treatment is discussed in Chapter 62.

Chronic Non-Wilsonian Hepatocerebral Degeneration

Some patients with chronic liver disease develop a permanent neurological deficit, even in the absence of prior portal systemic encephalopathy. The neurological features are similar to those of Wilson's disease (see Chapter 68): Intention tremor, ataxia, dysarthria, and choreoathetosis are common. As with portal systemic encephalopathy, the severity of the neurological disorder correlates best with the fasting arterial ammonia level. Neuroimaging studies may be abnormal. Specific treatment is not available.

Liver Transplantation

The neurological consequences of liver transplantation are similar to those of other organ transplants. The earliest postoperative disturbances are caused by organ rejection {with worsening hepatic encephalopathy), cerebral anoxia, cerebrovascular disease, or the side effects of immunosuppressant drugs, especially cyclosporine. Seizures are common. They result from metabolic disturbances, cerebrovascular disease, CNS infections, or adverse effects of treatment. Coagulopathies are also a complication and may cause fatal cerebral hemorrhage. Late complications are usually caused by infections or malignancies affecting the nervous system.

Pancreatic Encephalopathy

Whether acute pancreatitis is associated with a transitory encephalopathy is not established. The symptoms are nonspecific and similar to those of other metabolic encephalopathies, which must be excluded.

Gastrointestinal Diseases

Nutritional deficiency is the usual cause of neurological complications from gastrointestinal disorders (see Chapter 63). Several different dietary components are simultaneously deficient, and a single responsible nutrient is rarely defined.

Gastric Surgery

Neurological complications occur in 10—15% of patients after gastric resection. Because of the loss of gastric intrinsic factor, impaired vitamin BJ2 absorption may be responsible in part for neuropathy or myelopathy (Chaudhry, Umapathi, and Ravicb 2002). However, postgastrectomy neuropathy does not usually respond to vitamin $B|_2$ replacement alone. The myopathy that sometimes occurs is probably caused by vitamin D deficiency.

Gastric plication has been associated with encephalopathy, myelopathy, polyneuropathy, Wernicke's syndrome, and a nutritional amblyopia, but the precise nutritional deficiencies responsible remain to be established.

Smalt Bowel Disease

Neuropathy and myelopathy are associated with the malabsorption syndromes caused by small bowel disease, biliary atresia, or blind loop syndrome, or with previous extensive gastrointestinal resection. The findings may include pigmentary retinal degeneration, external ophthalmoplegia, dysarthria, peripheral neuropathy, and

pyramidal and cerebral signs in the limbs. Ataxia may be an especially conspicuous feature, so the neurological disorder resembles a spinocerebellar degeneration with an associated polyneuropathy. The syndrome is caused by vitamin E deficiency and responds to supplementation.

Chronic gluten enteropathy may cause a progressive and sometimes fatal CNS disorder in whieh there is some combination of encephalopathy, myelopathy, and cerebellar disturbance. Peripheral neuropathy is sometimes associated. An axonal neuropathy also occurs alone and without a measurable vitamin deficiency; restriction of dietary gluten leads to gradual resolution of neuropathic symptoms.

Whipple's Disease

Whipple's disease is a multiple system disorder that is believed to he caused by infection with the bacillus *Tropberyma wbtppeltt.* It is characterized clinically by steatorrhea, abdominal pain, weight loss, arthritis, lymphadenopathy, and a variety of systemic complaints. Neurological involvement is rare hut may occur in the absence of gastrointestinal symptoms. The most common neurological feature is dementia (Manzel, Tranel, and Cooper 2000). Less common are seizures, myoclonus, cerebellar ataxia, clouding of consciousness, visual disturbances, papilledema, supranuclear ophthalmoplegia, myelopathy, and hypothalamic dysfunction. A characteristic movement disorder, oculomasticatory myorhythmia, is peculiar to Whipple's disease; pcndular vergenee oscillations of the eyes occur with concurrent contractions of the masticatory muscles and persist during sleep. Oeulofacial-skeletal myorhythmia is also pathognomonic when present; it resembles oculomasticatory myorhythmia hut also involves nonfacial muscles. Postmortem examination shows abnormalities of the gray matter of the hypothalamus, cingulate gyrus, basal ganglia, insular cortex, and cerebellum.

The diagnosis is usually made by jejunal biopsy. Patients with neurological involvement also show cells that stain positively with periodic acid-Schiff stain in the CSF and brain parenchyma (Figure 55A.9}. Polymerase chain reaction analysis of intestinal tissue is sometimes helpful. Treatment is with antibiotic drugs such as trimethoprim-sulfamethoxazole, penicillin, tetracycline, or erythromycin, which should be prescribed in patients with a compatible clinical syndrome even when the jejunal biopsy result is negative.

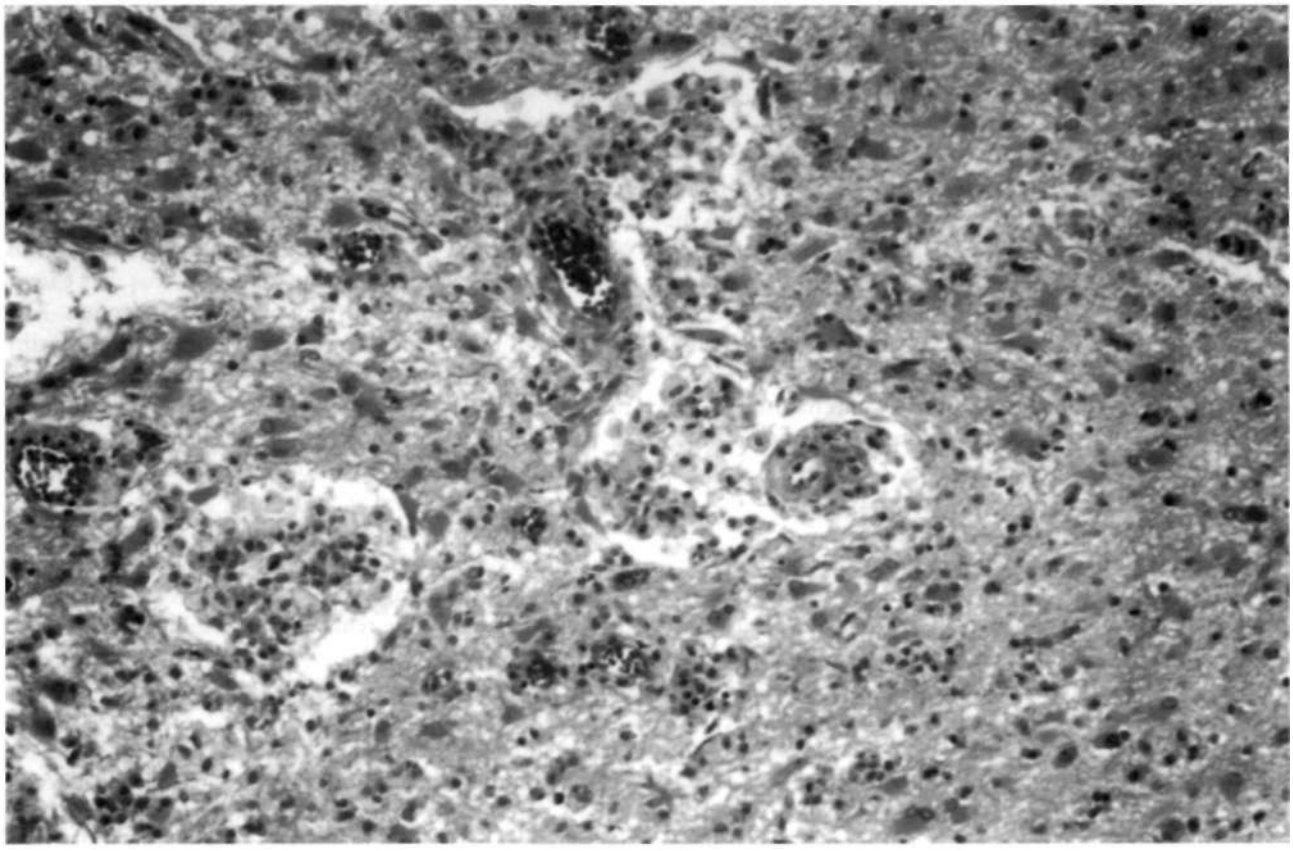

FIGURE 55A.9 Photomicrograph showing macrophages in brain tissue and around blood vessels, with prominent astrogliosis in involved brain, in a patient with Whipple's disease (hematoxylin and cosm, x40).

RENAL FAILURE

Renal failure is associated with sevetal neurological manifestations. Uremic encephalopathy is discussed in Chapter 62. Its clinical features resemble other metabolic encephalopathies, and its severity docs not correlate well with any single laboratory abnormality. The mechanism of encephalopathy is not established but has been attributed to the accumulation of toxic organic acids in the CNS or to direct toxic effects on the CNS of parathyroid hormone.

A length-dependent, symmetrical, sensorimotor polyneuropathy is a common complication of uremia. It usually worsens over several months but may progress more rapidly until the patient is profoundly disabled. Dysesthesias, muscle cramps, and restless legs are common early features. The neuropathy may stabilize or improve with long-tetm dialysis. Renal transplantation produces progressive improvement over the following year or longer, and complete recovery is possible. The neuropathy has been attributed to the accumulation of metabolites that have a molecular weight of 500-2000 daltons, but its precise pathogenesis is not established.

Autonomic dysfunction leads to postural hypotension, sudomotor abnormalities, impotence, and gastrointestinal disturbances. Dysautonomia may be important in the development of hypotension during hemodialysis, but other factors, such as volume depletion, are undoubtedly involved as well,

Uremic optic neuropathy causes a rapidly progressive vision loss that responds to hemodialysis and corticosteroid treatment. Isolated peripheral mononeuropathies occur in uremic patients from compression or entrapment, or from intramuscular hemorrhage. Hyperkalemia is sometimes responsible for a flaccid quadriparesis that responds to electrolyte correction. Treatment of uremic patients with aminoglycoside antibiotics can lead to cochlear, vestibular, or neuromuscular junction disturbances, and a myopathy sometimes results from electrolyte disturbances or corticosteroid treatment.

Neurological Complications of Dialysis

Hemodialysis requires an arteriovenous shunt in the forearm that sometimes causes a carpal tunnel syndrome attributed either to ischemia and venous congestion or to *fiz*-microglobulin amyloidosis.

The dialysis disequilibrium syndrome is probably caused by shifts of water into the brain. It is characterized by headache, irritability, agitation, somnolence, seizures, muscle cramps, and nausea during or after hemodialysis or peritoneal dialysis. Less common features are exophthalmos, increased intraocular pressure, increased intracranial pressure, and papilledema.

Patients undergoing dialysis for longer than 1 year may develop a fatal encephalopathy called *dialysis dementia*, Hesitancy of speech, leading to speech arrest, is a characteristic early feature. Intellectual function declines with time, and delusions, hallucinations, seizures, myoclonic jerking, asterixis, gait disturbances, and other neurological abnormalities ultimately develop. Death usually occurs within 6-12 months of onset of symptoms. The cause of dialysis dementia is uncertain, but aluminum intoxication was suggested by increased cerebral concentrations of aluminum at postmortem examination. Dialysis dementia has become less common since aluminum was removed from dialysates (Rob, Niederstadt, and Reusche 2001). Treatment with deferoxamine, a chelating agent that binds aluminum, is often prescribed for patients with dialysis dementia, but the optimum duration of treatment is unclear. Deferoxamine may actually exacerbate or pre cipiratc encephalopathy in patients with very high serum aluminum concentrations, and it also causes visual and auditory disturbances.

Another cause of encephalopathy in patients undergoing dialysis is Wernicke's disease. Thiamine, a water-soluble vitamin, is removed by dialysis and must be replaced by thiamine supplementation.

Neurological Complications of Renal Transplantation

The placement of the transplanted kidney close to the inguinal ligament increases the risk of retraction injury or hematoma formation around the femoral nerve. The result can be a postoperative femoral neuropathy that often resolves completely. Dysfunction of the ipsi lateral lateral femoral cutaneous nerve also may be caused by retraction or hematoma. The neurological complications associated with long-term immunosuppressive treatment are the same as those for other organ transplants.

ELECTROLYTE DISTURBANCES

Sodium

Serum osmolarity is primarily determined by the serum sodium concentration. Rapid changes in serum sodium concentration cause CNS dysfunction by altering the osmotic equilibrium between the brain and body fluids. The typical clinical features are disturbances of cognition and arousal that can progress to coma. Myoclonus, asterixis, and tremulousness are common. Seizures, when they occur, are often refractory to anticonvulsant medications until the underlying metabolic disturbance is corrected. Local symptoms (such as a hemiparesis) may occur during hyponatremia without any demonstrable structural basis but may indicate a prior or subclinical focal abnormality that is aggravated by the metabolic disturbance.

Focal abnormalities associated with hypernatremia often reflect intracerebral or subdural hemorrhage. The

hemorrhage is caused by brain shrinkage from osmotic forces, with secondary tearing of blood vessels, Hypernatremia, a common consequence of dehydration, may occur in patients receiving inadequate parenteral fluid replacement. It also occurs with diabetes insipidus, pathological involvement of the hypothalamic thirst center by tumor, and excessive salt intake.

Hyponatremia, defined as a serum sodium concentration less than 132 mKq/liter, is associated with hypo-osmolarity, except in patients with hypcrlipidcmia or hyperglycemia. It occurs in several pathological states: excessive salt loss from the kidney or gastrointestinal tract, impaired water excretion, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), adrenocortical insufficiency, and iatrogenic water intoxication.

Hyponatremia in patients with acute brain syndromes, such as subarachnoid hemorrhage, is often attributed to SIADH. In fact, hyponatremia in this circumstance is more likely ro he caused by salt wasting than SIADH, and patients have a reduced plasma volume, rather than a normal or increased plasma volume as expected with SIADH. In such cases, fluid restriction further exacerbates the hypovolemia and may cause cerebral ischemia.

The rapid correction of hyponatremia may cause central pontine myclinolysis, a disorder initially associated with alcoholism or malnutrition but now more often iatrogenic in origin. Neurological diiriKii.uion from central pontine myeliuolysis may obscure or follow the resolution of hyponatremic encephalopathy. Severe cases are characterized by a spastic or flaccid quadriparesis, pseudobulbar palsy, and decreased states of consciousness. In some patients, the clinical features arc minimal compared with the abnormalities seen on MRI. Central pontine myelinolysis is prevented when hyponatremia is corrected at a rate of less than 12 mKq/liter per day.

Potassium

The difference in the concentration of intracellular and extracellular potassium creates the resting membrane potential of nerve and muscle cells. Disturbances of serum potassium concentrations adversely affect cardiac and neuromuscular function. The hereditary periodic paralyses are discussed in Chapter 85.

Hyperkalemia usually causes cardiac arrhythmia before disturbing neurological function. The arrhythmia is sometimes associated with rapidly progressive flaccid paralysis and depressed tendon reflexes. Weakness may **last** for several hours, may be preceded by burning paresthesias, and is sometimes accompanied by mental changes. Treatment is determined by the underlying cause, severity of the hyperkalemia, and electrocardiographic findings.

Hypokalemia usually causes neuromuscular disturbances rather than encephalopathy. Mild hypokalemia causes myalgia, fatigability, and proximal weakness that spares the bulbar muscles. Severe hypokalemia causes rbabdomyolysis and myoglobinuria, and hypokalemic alkalosis causes tetany. All symptoms remit when normokalemia is re-established.

Calcium

Hypercalcemia is associated with metastatic disease, myeloma, paraneoplastic syndromes, primary or secondary hyperparathyroidism, vitamin D intoxication, and milk-alkali syndrome. Its main CNS complication is an encephalopathy, characterized by altered state of consciousness, apathy or agitation, depression or mania, headache, and in rare instances seizures that may be a result of vascular occlusive complications. In the PNS, there is muscle weakness and fatigability, especially in patients with hyperparathyroidism, who may develop myopathy.

Hypocalcemia may follow thyroid or parathyroid surgery and is a recognized feature of hypoparathyroidism, malabsorption syndromes, vitamin D deficiency, and acute pancreatitis. Tetany is the main symptom of hypo-calcemia. Perioral and distal limb paresthesias arc the initial feature and are followed by muscle cramps, a feeling of muscle spasms, and then actual spasm of the hands and feet.

CNS complications of hypocalcemia are focal or generalized seizures and an encephalopathy characterized by hallucinations, delusions, psychosis, altered states of consciousness, and cognitive impairment. The seizures respond poorly to anticonvulsant drugs but stop when hypocalcemia is corrected. Other CNS complications of hypocalcemia are parkinsonism or chorea that responds to correction of the calcium abnormality, increased intracranial pressure (in patients with hypoparathyroidism), and myelopathy.

Magnesium

Intracellular magnesium is involved in the activation of several enzymatic reactions, and extracellular magnesium is important in synaptic transmission.

Hypomagnesemia is caused by reduced intake or absorption of magnesium or by excessive loss from diuretics, kidney disorders such as renal tubular acidosis, and diabetic acidosis. Serum concentrations do not reflect accurately the severity of magnesium depletion, because magnesium is predominantly an intracellular ion.

The neurological complications of hypomagnesemia are similar to those of hypocalcemia, and the two often coexist. The possibility of concurrent hypomagnesemia must be considered when managing hypocalcemia, especially when parenteral calcium supplementation fails to provide the expected response. Complaints of weakness in patients with hypomagnesemia may be caused by magnesium deficiency

alone or with other electrolyte abnormalities. Hypomagnesemia is treated with magnesium sulfate given orally, unless there is an absorptive defect, when it is given intramuscularly or intravenously.

Hypermagnesemia is caused by excessive intake or impaired excretion of magnesium. The usual cause is renal failure. Clinical features are drowsiness and diminished responsiveness, confusion, and depressed or absent tendon reflexes. Other features are hypotension, respiratory depression, and weakness from impaired neuromuscular transmission. Severe hypermagnesemia causes coma and may be fatal.

PITUITARY DISEASE

Pituitary Adenomas

The initial features of pro lac tin-see re ting pituitary adenomas are amenorrhea and galactorrhea in women and impotence in men. However, the diagnosis of prolactinoma is often not considered until patients develop symptoms of increased intracranial pressure originating in the scllar region. The treatment choices are transsphenoidal surgery or dopaminergic agonists such as bromocriptine. Radiation therapy is used when these choices are either unhelpful or not feasible. Tension pneumocranium is a rare complication of transsphenoidal surgery: Impaired mental status, seizures, and headaches, sometimes associated with systemic hypertension and bradycardia, occur in the early postoperative period and necessitate surgical drainage of the pneumocranium (Sawka et al. *1999),*

Growth hormone-secreting pituitary tumors cause acromegaly; gigantism occurs in children, and enlargement of the jaw, extremities, and skull in adults. Approximately 50% of patients have a myopathy, which improves over many months when the underlying hormonal disorder is treated. Carpal tunnel syndrome in patients with acromegaly is from hypertrophy of the transverse carpal ligament. Symptoms usually resolve 2-3 months after Surgical excision of the pituitary tumor, but electrophysiological abnormalities may persist for longer. Patients with acromegaly also may develop a mild, usually subclinical, polyneuropathy.

Cushing's Disease and Syndrome

Cushing's disease is caused by excessive secretion of adrenocorticotropic hormone from the pituitary gland. The clinical features are truncal obesity, hypertension, acne, hirsutism, osteoporosis, diabetes mellitus, and menstrual irregularities. Mental changes are common and include anxiety, agitation, insomnia, depression, euphoria, mania, and psychoses. Proximal muscle weakness and wasting are common, especially in the legs. Muscle biopsy shows type II fiber atrophy, a characteristic feature of muscle in patients treated with corticosteroids (see Chapter 85); electromyography is generally normal. The constellation of clinical features that constitutes Cushing's syndrome is seen also as a paraneoplastic syndrome, in association with adrenal adenomas, and after long-term corticosteroid treatment.

An enlarging pituitary adenoma may cause a visual field defect {Figure 55A.10). Treatment of Cushing's disease by bilateral adrenalectomy sometimes leads to rapid expansion of the underlying pituitary adenoma (Nelson's syndrome), with compression of other cranial nerves, especially cranial nerve III. Intracranial hypertension is a recognized complication of Cushing's syndrome and occurs particularly after the pituitary adenoma is resected,

Hypopituitarism

Hypopituitarism results from diseases of the pituitary gland or hypothalamus. The neurological features depend on the severity of secretory impairment and on the hormones affected. Common features arc apathy and intellectual decline, which are often difficult to attribute to a single hormone deficiency because several are affected concurrently.

Diabetes Insipidus

Diabetes insipidus, the inability to conserve water, results from disorders of the hypothalamus or pituitary gland or from **interruption** of the neurohypophyseal tract. Transitory diabetes insipidus is often a complication of head injury or intracranial surgery and may occur without explanation in previously well patients. Nephrogenic diabetes insipidus is caused by impaired renal responsiveness to vasopressin, which is synthesized in the hypothalamus and transported to the posterior pituitary gland. The main neurological feature is an encephalopathy that varies in severity from irritability to somnolence and ultimately to coma. Hypotension and hyperthermia also occur. Treatment is with vasopressin or a long-acting vasopressin analogue.

THYROID DISEASE

Hyperthyroidism

The features of hyperthyroidism are anxiety, restlessness, irritability, emotional lability, impaired concentration, headaches, and insomnia. Elderly patients may become depressed and lethargic, a condition designated *apathetic hyperthyroidism.* An enhanced physiological tremor and generalized hyper-rcflexia are common. Hyperthyroidism itself may cause seizures or may trigger a pre-existing

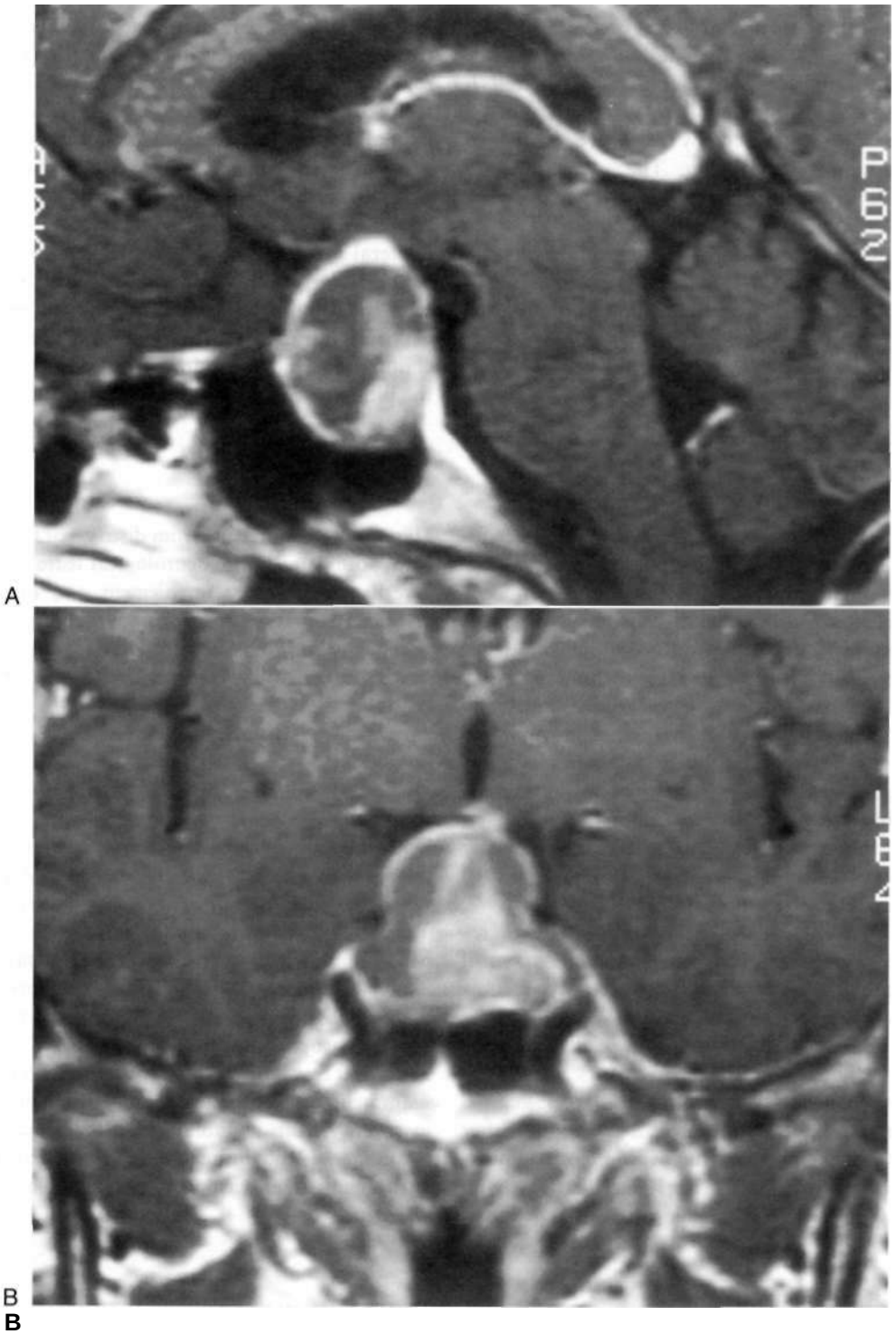

FIGURE 5SA.10 Tl-weighted gadolinium-enhanced magnetic resonance imaging. (A) Sagittal view. (B) Coronal view, A heterogeneously enhancing mass arises out of the sella turcica and extends up to involve the region of the optic chiasm. Surgery confirmed a pituitary adenoma.

seizure disorder. Chorea and paroxysmal choreoathetosis also have been described,

Thyrotoxic crisis is characterized by confusion and agitation leading to coma. Fever, cardiac arrhythmias, diarrhea and vomiting, and other systemic disturbances are associated. Treatment consists of hydration and cooling, beta-blocking drugs, corticosteroids, and in some cases plasmapheresis.

Dysthyroid orbitopathy (ophthalmic Graves' disease), characterized by exophthalmos and ophthalmoplegia, is common. Orbital edema and infiltration by inflammatory cells lead to orbital fullness, conjunctival edema and

hyperemia, proptosis, and some limitation of ocular movements. Eyelid retraction may be caused by sympathetic overactivity affecting Miillcr's muscle in the upper lids and fibrosis of the levator muscle. The occasional occurrence of optic neuropathy is related to infiltration of the optic nerve, crowding of the orbital apex, and enlargement of the extraocular muscles. Dysthyroidorbitopathy may occur in patients without a history of thyroid disease or clinical signs of hyperthyroidism. Treatment options include corticosteroids, radiation therapy, and orbital decompression.

Compression of the recurrent laryngeal nerve or cervical sympathetic fibers by an enlarged thyroid gland, commonly neoplastic, may lead to vocal cord paralysis or Horner's syndrome, respectively.

Several neuromuscular disorders are associated with hyperthyroidism. Most common is a proximal myopathy accompanied by fasciculations. Its mechanism is unknown, but the severity of myopathy does not correlate with the severity of thyroid abnormality. Scrum creatine kinase levels are generally normal. Improvement occurs with treatment of the underlying thyroid disorder. Hyperthyroidism and myasthenia gravis often coexist. Both are immune-mediated disorders (see Chapter 84). Treatment of one disorder, however, does not have any predictable effect on the other.

Thyrotoxic periodic paralysis is similar to familial hypokalemic period paralysis (see Chapter 85). It is particularly seen in Asians, and the hyperthyroidism may be clinically silent. Episodes of weakness occur after activity or after meals with high-carbohydrate content. Potassium administration treats the acute attacks, and correction of the thyroid disorder cures the periodic paralysis as well.

A sensorimotor polyneuropathy has been reported in hyperthyroidism, but the association may be fortuitous.

Hypothyroidism

Mental changes are common in hypothyroidism. Apathy, somnolence, and impaired concentration are typical *And* arc often attributed to depression. Confusion, delirium, and psychosis (myxedema madness) may occur also and improve with treatment of the underlying thyroid disorder. In severe hypothyroidism, decreased states of consciousness are associated with hypotension, hypothermia, respiratory failure, hypoglycemia, and other metabolic derangements; untreated, the disorder progresses to coma and sometimes death.

Other features of hypothyroidism are an increased incidence of seizures, truncal ataxia caused by a cerebellar degeneration, hearing loss, and cranial neuropathies. Hoarseness of the voice is caused by structural changes m the vocal cords, rather than neurological disease. The neurological complications of hypothyroidism usually recover with thyroid replacement, especially if the deficiency is not long standing.

The PNS is often involved in hypothyroidism. Most common is a proximal myopathy accompanied by myalgia and muscle stiffness. The affected muscles may be enlarged (Hoffmann's syndrome) and have my oedema (transient local mounding when a muscle is percussed).

Carpal tunnel syndrome occurs in as many as 30% of patients and usually responds to correction of the thyroid disorder. Less common is a sensory or sensorimotor neuropathy; both segmental demyelination and axonal degeneration have been implicated. There may be slow relaxation of tendon reflexes. Myasthenia gravis is associated also but occurs less commonly than in hyperthyroidism.

Hashimoto's Thyroiditis

Hashimoto's thyroiditis has been associated with myasthenia gravis and less clearly with giant cell arteritis and vasculitic peripheral neuropathy. In addition, a relapsing encephalopathy may occur in association with Hashimoto's thyroiditis and high titers of antithyroid antibodies. Clinical presentation is with confusion, altered conscious level, and sei/.ures. Tremulousness and myoclonus may be conspicuous, and strokelike episodes of deterioration are common. The EEC is diffusely abnormal, the CSE protein concentration is increased without any associated pleocytosis, and neuroimaging studies are normal except for patchy abnormal uptake on isotope brain scan. Treatment is with corticosteroids. The long-term prognosis is good.

PARATHYROID DISEASE

Hyperparathyroidism

Neurological manifestations of hyperparathyroidism are common. They are essentially those of hypercalcemia (see Calcium, earlier in this chapter). A mild proximal myopathy may occur also and improves with surgical treatment of the parathyroid disorder. A picture like that of amyotrophic lateral sclerosis has also been described.

Hypoparathyroidism

I lypoparathyroidism commonly follows thyroidectomy or has an idiopathic basis. Pseudohypoparathyroidism is caused by peripheral resistance to the effects of parathyroid hormone rather than to any deficiency of hormone secretion. The neurological manifestations of these disorders relate primarily to the effects of hypocalcemia on the nervous system. Intracranial calcification is common in patients with hypoparathyroidism and occurs especially in the basal ganglia; it is usually asymptomatic. Benign intracranial hypertension also may be associated with

hypoparathyroidism and is reversed by correction of the underlying metabolic disorder.

ADRENAL GLANDS

Pheochromocytoma

Pheochromocytoma is associated with neurofibromatosis and von Hippel-Lindau disease (see Chapter 71). The initial features of pheochromocytoma are paroxysmal symptoms of excessive catecholamine secretion; headache, hyperhidrosis, palpitations, cardiac arrhythmias, tremulousness, and anxiety. Most patients have hypertension, and seizures occur in approximately 5%. Malignant pheochromocytomas are rare, and metastatic tumors may respond to radiation therapy.

Addison's Disease

Adrenal failure results from diseases of the pituitary or adrenal gland or from adrenal suppression by long-term use of exogenous corticosteroids. The major features are generalized weakness, fatigability, lassitude, depression, headache, weight loss, anorexia, and hyperpigmentation of the skin. Increased intracranial pressure may be present. Adrenal failure is a feature of X-linked adrenomyeloleukodystrophy.

Diabetes Mellitus

Peripheral Nervous System

In developed countries, diabetes is the most common cause of polyneuropathy (see Chapter 82). The mechanism of neuropathy is not established but may be either metabolic or vascular.

Diabetic polyneuropathy has both axonal degeneration and demyelination. It may be asymptomatic; the diagnosis is suggested by depressed tendon reflexes and impaired vibratory sense in the legs. When the neuropathy becomes symptomatic, the feet are affected more than the hands. The initial symptoms are pain, paresthesias, or numbness. Profound weight loss sometimes precedes the development of an acute painful neuropathy. Progressive neuropathy is characterized by distal sensory loss and weakness in the limbs and arreflexia. Severe impairment of pain and temperature appreciation occurs occasionally and results in distal ulceration and arthropathy (acrodystrophic neuropathy).

Autonomic neuropathy is an important feature of diabetes mellitus. The clinical features range from lack of symptoms to a syndrome that includes postural hypotension, abnormal cardiovascular and thermoregulatory control, and impotence. Pupillary abnormalities, gastroparesis, and diarrhea from intestinal dysmotility may occur also, and responses to hypoglycemia may be blunted.

Diabetic polyradiculoneuropathy is characterized by pain and asymmetrical limb weakness, usually involving the thighs and often accompanied by weight loss. A diabetic plexopathy or polyradiculopathy, rather than a femoral neuropathy, probably accounts for most cases of diabetic amyotrophy (Dyck and Windebank 2002). Symptoms are rapidly progressive but stabilize after a few weeks; gradual but often incomplete recovery occurs over the following months or years.

The typical syndrome of diabetic thoracoabdominal polyradiculopathy consists of nonradicular truncal pain that may initially suggest intra-abdominal or intrathoracic pathology requiring surgical exploration. Sensory loss and weakness are mild.

Diabetic mononeuropathy multiplex has a vascular basis. Simple mononeuropathies are also common in diabetics. Entrapment neuropathies, especially carpal tunnel syndrome, occur with an increased incidence. Cranial neuropathies, usually isolated involvement of nerves III, IV, and VI, cause a painful extraocular palsy. Diabetes-induced palsies of cranial nerve IN are generally distinguished from compressive lesions by sparing of the pupillary reflex. Cranial nerve VII may also be affected, causing unilateral facial weakness. Specific treatment for diabetic neuropathy is not available, but it is important to ensure that the diabetes itself is well controlled.

Central Nervous System

Stroke is more common in diabetics than in the general population, because of an increased incidence of hypertension and atherosclerosis. Diabetes increases stroke severity and mortality and predisposes to deep subcortical infarcts.

Diabetic ketoacidosis, an important cause of morbidity and mortality, may be the presenting feature of previously unrecognized diabetes. Severe hyperglycemia and a metabolic acidosis cause an osmotic diuresis that dehydrates the patient. Clinical presentation includes an altered state of consciousness that progresses to coma. Focal or lateralizing signs are absent usually unless the patient has underlying brain disease. The pathogenesis of diabetic coma is poorly understood and probably multifactorial. Serum hyperosmolality and acidosis are probably important contributing factors. Postmortem examination in some patients with severe diabetic ketoacidosis shows evidence of DIG, which may contribute to the altered level of consciousness. Potential contributory factors are other metabolic derangements, infection, vascular occlusive phenomena, and cerebral edema.

Nonketotic hypetosmolat coma may be precipitated in diabetic patients by an acute medical complication, such as

a myocardial infarction. Affected patients are typically elderly with mild disease. Hyperglycemia and hypcrosmolality occur without significant ketosis. Progressive obtundation is the principal feature, but seizures and focal deficits may develop. Treatment includes fluid, potassium, and phosphate replacement as necessary and correction of hyperglycemia.

Hypoglycemia

Hypoglycemia can cause an acute metabolic encephalopathy, with initial features of tremuloiisncss, anxiety, confusion, stupor, or coma, depending on the level of hypoglycemia. Later features are brainstem dysfunction and transitory focal neurological deficits that resemble strokes but either resolve or alternate from side to side. Seizures are sometimes the only manifestation of hypoglycemia. Administration of glucose reverses the symptoms. Severe hypoglycemic cerebral injury causes MR1 abnormalities localized to the basal ganglia, cetebral cortex, substantia nigta, and hippocampus, suggesting a patticular vulnerability of these areas (Fujioka et al. 1997). Neuromuscular syndromes resembling *a* peripheral sensorimotor polyneuropathy or lower motor neuron degeneration have been described in patients with insulinomas or who receive excessive insulin for therapeutic purposes.

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Chapter 55
Neurological Complications of Systemic Disease

B. IN CHILDREN

Bruce O. Berg

The clinical features of many neurological complications of systemic diseases are somewhat different in children than adults depending on the child's age and stage of development. This section of the chapter considers those differences.

CARDIAC DISORDERS AND **THE** NERVOUS SYSTEM

Congenital Heatr Disease

The possible neurological complications of congenital heart disease (CHD) in childten include cerebral hypoxia, neurological abnormalities sccoiuUm to the cardiac anomaly, associated cerebral malformations, and complications of diagnostic and therapeutic interventions. The incidence of CHD is about 1% of live births but would probably be highet if adequate data wete available on stillbirths and abortions. It seems likely that the cause of CHD is an intetaction of genetic and environmental factors. Chronic hypoxia, polycythemia, cerebrovascular accidents, and brain abscesses were the main causes of the neurological disorders associated with CHD. Howevet, the advenr of modem diagnostic and therapeutic techniques have resulted in earlier surgery with reduced mortality and increased survival. Both the sutgety and the longer sutvival have resulted in a greater variety of neurological disturbances.

Patients with acyanotic CHD have left-to-tight shunts. The main anomalies are atrial septal defects, ventricular septal defects, and patent ductus arteriosus. These children are not usually at risk for neurological complications from emboli or bacterial abscess, because blood flow traverses the pulmonary vascular bed, which protects the brain from blood-borne injury. Under some circumstances, a reversal of shunt flow occurs that can result in cerebral emboli. Congenita] stenosis of the great vessels does not cause cyanosis and tarely contributes to thrombi fotmation with subsequent cetebtal and peripheral emboli (see the discussion of bacterial endocarditis, later in this section). This gtoup of malformations includes aortic stenosis, pulmonary stenosis, and coarctation of the aorta. Aortic stenosis is occasionally responsible for decreased cardiac output with secondary

cardiac arrhythmia, cerebral hypoxia, and seizures. Pulmonary stenosis rarely causes neurological complications. Coarctation of the aorta, however, may be associated with cerebral aneurysms and accounts for about one fourth of all cerebral aneurysms in children.

In contrast, the cardiac anomalies that characterize cyanotic CHD facilitate blood flow to the heart and brain without first traversing the pulmonary vascular bed. These can ultimately result in the direct transport of a nidus of peripheral infection to the brain, resulting in cerebritis, brain abscess, or stroke. This group includes tetralogy of Fallot, transposition of the great vessels, truncus arteriosus, tricuspid atresia, and complete anomalous pulmonary venous return.

Hrain abscesses had been common in children with CI II) older than 2 years. Improved diagnostic techniques that allow the early identification and repair of complex congenital heart lesions have greatly diminished their incidence. Children with inoperable cyanotic congenital heart lesions remain at risk for stroke from cerebral emboli (Carlin and Chanmugam 2002). After excluding the neurological complications of cardiac surgery, interventional diagnostic studies, and therapeutic measures, the remaining neurological morbidity of CHD is infection and cerebral dysgenesis. Early diagnosis and treatment, as well as vigorous prophylactic treatment for bacterial infections and dental surgery, have greatly reduced the risk of bacterial endocarditis and hrain abscesses (Tak et al. 2002). The neurological disorders resulting from septic emboli secondary to bacterial endocarditis include meningitis, brain abscess, stroke, and seizures. Systemic emboli occur in 50% of children with bacterial endocarditis and represent as many as *65%* of all emboli to the brain.

The clinical features of cerebral embolization are sudden alteration of consciousness, dysphasia and/or aphasia, seizures, and hemiparesis. The diagnosis of bacterial endocarditis relies on determining and documenting sepsis by multiple repeated blood cultures. Transthoracic echocardiography is used to demonstrate cardiac vegetations and magnetic resonance imaging (MRl) to show cerebral ischemia. Antibiotics are the mainstay of treatment.

Most children with CHD have normal intellectual development; however, the incidence of developmental delay is increased in children with cyanotic CHD, particularly when surgical repair is delayed until late childhood. The potential reasons for developmental delay include brain malformations, chronic hypoxia, cerebral infarction, and seizure disorders. Patients with congenital heart defects arc at greater risk for prenatal and perinatal cerebral injury. Van Houten, Rothman, and Be jar (1996) reviewed cranial ultrasound scans of 49 full-term infants with CHD and compared them with 42 healthy full-term control infants. Infants with congenital heart defects have a higher incidence of cranial ultrasound abnormalities than control infants (0.6% vs. 14%; $p < ,0001$). The most common sonographic findings are cerebral atrophy and linear eehodensities in the basal ganglia and thalamus, particularly in those infants with coarctation of the aorta or ventricular septal defect. The incidence of intraventricular hemorrhage was greater in infants with acyanotic CHD than in those with cyanotic CHD. In some autopsy studies of CHD, the incidence of cerebral dysgenesis is about 30% and some cardiac anomalies carry a greater risk than others.

In a review of 41 infants with hypoplastic left heart syndrome, Glauser et al. (1990) found that 29% of infants had either a major or a minor malformation of the central nervous system (CNS). Microcephaly occurred in 27%, an immature cortical mantle in 21%, and the remainder had a variety of other malformations including one case of holoprosencephaly. The phenotype of some chromosomal abnormalities includes both cardiac and nervous system malformations. Down syndrome (trisomy 21) is characterized by developmental delay and congenital heart defects, particularly endocardial cushion defects. Trisomy 13 with ventricular septal defect and other organ anomalies including holoprosencephaly and varying degrees of incomplete division of the cerebral hemispheres and basal ganglia occur in about 80% of cases. Patients with trisomy 18 have renal anomalies, ventricular septal defect, redundant cardiac valve leaflets, agenesis of the corpus callosum, Chiari malformation, Dandy-Walker syndrome, and heterotopias. Williams syndrome is characterized by developmental delay, supravalvular aortic stenosis, and sometimes other aortic lesions. The genetic defect is a deletion at 7q11.23, the locus for clastin. The phenotypical spectrum associated wirh deletions in the region of 22ql 1, Di George and velocardiofacial syndromes, includes a variety of cardiac abnormalities, unusual fades, cleft palate, varying degrees of hypoplasia of the thymus and parathyroid glands, and hypocalcemia.

Acquired Heart Disease

Neurological complications are associated with several acquired cardiac disorders of childhood including cardiomyopathy, arrhythmias, and hypertension. Cardiomyopathies can be idiopathic or result from myocarditis. In every case, the ventricles are abnormally dilatated and unable to function properly. The chronically dilatated heart, lacking normal pulsatile activity, causes the stasis of intraventricular blood, which results in thrombi formation and dispersion of emboli. Decreased ventricular output may cause reduced coronary blood flow, arrhythmia, and syncope.

Ventricular arrhythmia can occur in CHD before surgical manipulation but is more likely to occur during or after surgical manipulation at the time of heart surgery or in the postoperative period (Walsh 2002). The result of embolization to the cerebrovascular system is stroke.

The main neurological complication of hypertension in children is hypertensive encephalopathy. It is an uncommon occurrence in children. The most common presenting

symptoms arc seizures, headache, and cortical blindness, Hypertension is associated with neurofibromatosis type 1 and von Hippei-Lindau syndrome, because of the associated pheochromocytoma, in children with Guillain-Barre syndrome with autonomic nervous system involvement, and in bronchopulmonary dysplasia,

Neurological Complications of Diagnostic and Surgical Intervention

The techniques of cardiac catheterization have improved during the last several decades, but nonetheless, the introduction of catheters, balloons, or other devices into the vascular system has an inherent risk of causing injury to the endothelial lining of the vessel in question. Although the incidence of neurological complications associated with cardiac catheterization is low, the main risk is the possibility of thrombus formation and the subsequent dispersion of emboli to the brain and other organs.

Improved cardiac surgical techniques allow the successful repair of complex congenital heart at an earlier age; this has increased survival but also increased morbidity. In the early postoperative period, the occurrence of seizures varies from 5-25%. The use of electroencephalographic monitoring may reveal that the incidence is even higher. In the evaluation of seizures in the postoperative cardiac surgery period, cerebral dysgenesis and metabolic abnormalities such as hypoglycemia, hypomagnesemia, and hypocalcemia are important considerations. The causes of most postoperative seizures remain undefined but are presumed secondary to hypoxic-ischemic events and possibly the untoward events related to repcrfusion. Prospective studies have suggested a correlation between recurring postoperative seizures and neurodevclopmcntal delay. Previous reports have suggested that 20% of children with CHD had evidence of cerebrovascular disease. Such reports were at a time that the major cause of stroke in children was CHD, The incidence varied from 25-30% of cases. The modern diagnosis and surgical repair of complex congenital lesions has lowered the incidence of stroke, but an increased risk still exists because the mechanics of cardiopulmonary bypass increases the likelihood of cerebrovascular occlusion and emboli. The risk of stroke remains increased during the postoperative period because of altered intravascular endothelial surfaces and because prosthetic devices facilitate thrombus formation and embolization by decreasing blood flow. This increased risk of stroke necessitates the use of postoperative anticoagulation.

Reports of choreoathetosis following hypothermic heart surgery first appeared in I960. Since that time, other less common movement disorders have been recognized including oculogyric crises and parkinsonism. Movement disorders occur in 1% or fewer children following such surgery. The typical course is an uncomplicated postoperative period lasting about 7 days. The child then seems confused and irritable. The onset of abnormal movements of the head, neck, limbs, or trunk follows, which are present when awake and disappear during sleep. The abnormal movements persist for several weeks to months. The underlying mechanism of the movement disorder is not understood.

Neuroimaging studies have been nonspecific, although single-photon emission computed tomography (CT) has suggested defects of cortical and subcortical perfusion. The dyskinesias are recalcitrant to treatment. Reducing external stimulation and careful administration of sedation improves the sleep cycle,

Cardiac Transplantation

Hcatt transplantation is becoming an important procedure for children with profound and irreversible cardiomyopathy, for CHD, and for end-stage heart failure (Marelli et al. 2002}. Improved use of immunosuppressive agents has increased survival, but their long-term use facilitates opportunistic infection, and the drugs are themselves a source of neurological complications. The entire period of immunosuppression, from before to after surgery, is a time of risk. Other neurological complications continue to occur including hypoxic-ischemic episodes, stroke, drug neurotoxicity, and psychosis. The possibility of infection, the long-term effects of rejection, and the drugs used to treat these complications are important factors in morbidity and mortality. Hypertension and renal disease are usually present and coronary artery disease and lymphoproliferative disease arc major causes of dearh.

CONNECTIVE TISSUE DISEASES AND VASCULITIDES

Polyarteritis Nodosa

Systemic necrotizing vasculitis of small and medium-sized vessels characterizes polyarteritis nodosa (PN). PN occurs more often in adults than in children, but adolescents can be affected. An infantile form has been described, which is probably the same or similar to Kawasaki disease. Clinical manifestations include fatigue, anorexia, weight loss, malar skm rash, myalgia, and arthritis. Renal disease, often associated with hypertension, can occur any time during the course of the disease.

A specific diagnostic test is not available, but an elevated sedimentation rate, positive C-reactive protein and complement levels, and a positive antineutrophil cytoplasmic antibody (ANCA) each suppott the diagnosis.

Several neurological complications are associated. Headache occurs as part of aseptic meningitis. Neuroimaging studies performed at the time of the headache are usually normal. Symptoms of CNS involvement occur early in the course of disease and include behavioral changes,

disturbances of cognition, and seizures that can progress to status epilepticus. Ocular involvement is manifest by decreased visual acuity, loss of visual fields, and sco to ma ta from proliferative retinitis and retinal hemorrhage. Sudden hemiplegia is characteristic of stroke. Neuroimaging studies such as MRI and magnetic resonance angiography (MRA) are required but cerebral angiography may be required to specifically demonstrate the vascular lesion(s) for the diagnosis of angitis. Among children with diffuse myalgia and elevated blood creatine kinase concentrations, about 50% show typical electromyographic (EMG) findings of myopathy. Mononeuritis multiplex is characteristic of PN and may have a remitting and relapsing course. The clinical picture begins to resemble a polyneuropathy as an increasing number of nerves are affected. Young children with PN-associatcd neuropathy arc unable to describe symptoms of paresthesias or numbness and may not respond to the examiner's questions.

Angiography can show segmental narrowing of vessels, particularly in the renal, mesenteric, and hepatic vessels. Muscle or nerve biopsy reveals a necrotizing vasculitis. In addition to general supportive care, corticosteroids are administered and in some cases in combination with cyclophosphamide.

Takayasu's Arteritis

Takayasu's arteritis, sometimes known as "the pulseless disease," is a rare arteritis involving the aorta and its branches. Females are affected more often than males, and in children, the abdominal aorta and its branches are more often affected than the aortic arch. Clinical features before the "pulseless" phase include fever, anorexia, weight loss, myalgia, and arthralgia. Aortic arch involvement can result in aortic insufficiency or aneurysm. Dyspnea, claudication, and loss of radial pulses are the main features of aortic arch involvement. The presenting features of involvement of the abdominal aorta are abdominal mass and discomfort, congestive heart failure, hypertension, and symptoms and signs of an acute abdomen.

Neurological complications of Takayasu's arteritis are uncommon but can include transitory visual loss, vertigo, and syncope. Other features are recurring headache, seizures, and hemiplegia. Treatment consists of administration of corticosteroids, immunosuppressive agents, or both in combination. Surgical graft procedures and angioplasty are beneficial in selected cases.

Churg-Strauss Syndrome

Churg-Strauss syndrome (CSS) is an allergic angiitis characterized by peripheral neuropathy, asthma, fever, eosinophilia, heart failure, and pulmonary disease. The American College of Rheumatology has outlined the criteria for diagnosis. Four of the following six conditions must be met: asthma, eosinophilia more than 10%, mononeuropathy or polyneuropathy, nonfixed pulmonary infiltrates on radiograph, paranasal sinus abnormalities, and blood vessel biopsy with extravascular eosinophilia. Fibrinoid necrosis of the media of small arteries and veins characterizes the vascular histopathology.

Neurological manifestations of CSS in children are limited almost entirely to the peripheral nerves secondary to involvement of the vasa nervorum. Adult patients have behavioral disturbances, intracranial hemorrhage, seizures, and cranial neuropathies. Treatment of CSS, as in other vasculitides, includes corticosteroids and immunosuppressive agents.

Juvenile Rheumatoid Arthritis

The characteristics of juvenile rheumatoid arthritis (JRA) is chronic inflammation of one or more joints in patients younger than 16 years in whom other causes for the arthritis are excluded. All of the different features of JRA are attributable to complex autoimmune disease. No identifiable infectious agent causes JRA.

About 10% of children with JRA have a systemic form. The clinical manifestations of systemic JRA are difficult to manage effectively. Affected children usually have recurrent fevers, a faint evanescent skin rash, irritability, malaise, and anorexia. Some complain of severe joint pain and myalgia even before the appearance of joint involvement. Pericarditis and myocarditis are common and can be life threatening. Laboratory studies (in systemic JRA) show anemia and thrombocytosis. Children with systemic JRA are typically seronegative for rheumatoid factor (RF) and antinuclear antibodies (ANAs). An acute encephalopathy may be associated. Those affected can have abnormal liver function, hyperammonemia, and increased intracranial pressure, Flectroencephalographic studies are abnormal with or without the presence of clinical seizures.

Other types of JRA include pauciarticular form in which one or several joints are affected and a polyarticular form in which five or more joints are involved (Al-Matar et al. 2002). More females than males are affected, and female bias is greatest in the polyarticular form. Iridocyclitis is a complication of JRA, especially the pauciarticular form, which may occur at any time in the course. Periodic ophthalmologica) examinations are recommended. Focal neurological findings are uncommon and can be secondary to soft tissue involvement. Occasional sensorimotor polyneuropathies occur but less commonly than in adults. Scrum creatine kinase concentrations are elevated in one third of children with JRA, but proximal weakness or histological evidence of myositis is uncommon. Rare immune-mediated abnormalities of the neuromuscular system include inflammatory neuropathy, myositis, and myasthenia gravis.

Decreased mobility of the neck, secondary to fusion of the cervical vertebrae, can occur in both the systemic or polyarticular forms of JRA. Torticollis may be the presenting feature. Cervical myelopathy from atlantoaxial dislocation is a rare event in children.

The management of JRA is usually with aspirin or nonsteroidal anti-inflammatory agents. Some require corticosteroids, intravenous immunoglobulin (IVIG), immunosuppressive agents, or parenteral gold salts. Physical and occupational therapy lessen the discomfort of joint or muscle stiffness and may prevent the development of peripheral nerve entrapment syndromes.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an immune-mediated multisystem disorder. Onset is at all ages, and multiple organ symptoms are involved, particularly the kidneys. The fcmale-to-male gender bias is 8:1. General clinical features include fever, weight loss, malar rash, arthritis, and musculoskeletal symptoms. No single diagnostic test is confirmatory, but almost all patients show a positive immunofluorescent ANA test result.

The incidence of neurological complications varies from 20-40%, and half of these are neuropsychiatric symptoms: cognitive and behavioral disorders and psychosis. Depression and anxiety are common and often occur early in the course. Confusion, disorientation, memory loss, and even dementia characterize impaired cognition. Headache and seizures, partial and secondarily generalized, occur and are usually self-limited. These manifestations may he directly attributable to the disease or may be secondary to hypertensive encephalopathy, electrolyte disturbances, or corticosteroid treatment. Focal neurological abnormalities may involve the cranial nerves or the limbs. Cerebral thromboses secondary to vasculitis or more often immunccornpntind deposition is causative. Specific features include visual loss, optic neuritis, ophthalmoplegia, pseudotumor cerebri, facial palsy, deafness, vertigo, vocal cord paralysis, ataxia, and transverse myeloparhy. Chorea and other dyskinesias occur in about 4% of affected children. Peripheral nerve involvement occurs in 5%, characterized by numbness and distal weakness, either as mononeuritis multiplex or as an acute dcmycliuating polyneuropathy similar to the Guillain-Barre syndrome. Management includes corticosteroids, IVIG, immunosuppressive agents, and plasmapheresis.

Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD), a disorder of unknown etiology, is similar to other syndromes of small-vessel vasculitis such as SLE, scleroderma, dermatomyositis, and Sjogren's syndrome. Few children show involvement of larger vessels. Children wirh MCTD have autoantibodies to a nuclear rihonuclear protein (anti-RNI[1]), which is present in rihonuclear labile-cxtractable nuclear antigen. Fever, lymphadenopathy, and hepatosplenomegaly characterize the disorder. Poly arthritis is a common feature, as well as skin rash, myositis, and cardiomyopathy.

Neurological complications include proximal muscle weakness associated with increased scrum creatine kinase concentration, and histological findings of myositis, headache, aseptic meningitis with increased cerebrospinal fluid (CSF) protein concentrations, occlusion of the internal carotid artery, and intracerebral hemorrhage. Treatment consists of the administration of hydroxychloroquine for the management of the skin rash and nonsteroidal anti-inflammatory agents for symptoms of joint involvement. The efficacy of corticosteroids has not been established.

Wegener's Granulomatosis

Wegner's granulomatosis is a rare vasculitis of unknown origin characterized by necrotizing granulomatosis affecting small arteries and veins. The onset is usually in adult life but may begin in infancy. The major findings are rhinorrhea, nasal mucosal ulceration, sinusitis, pulmonary disease (cough and hemoptysis), and glomerulonephritis. Fever, malaise, and anorexia are associated. In a comparative study of clinical features in children and adults, subglottic stenosis occurred five times more often in children than adults, and nasal septal deformities were twice as common. One third of children have arthritis, skin ulcerations, conjunctivitis, corneal ulceration, exophthalmos, and micnigraiiiilomatous hepatitis. Increased ANCA titers are present in most cases. Neurological manifestations include mononeuritis, multiplex or polyneuropathy, cranial nerve palsies, optic nerve granuloma, and orbital pseudotumor. Management is by administration of corticosteroids and cyclophosphamide. Long-term therapy with cyclophosphamide and azathioprine is beneficial.

licheet[1]s Disease

Uveitis and oral and genital ulcers characterize Behcet's disease. It is rare in children. The current diagnostic criteria, as determined by the International Group for Behcet disease, include recurrent aphthous stomatitis and two of the following: recurrent genital ulcers, uveitis or retinal vasculitis, erythema nodosum or pustules, or abnormal reaction to allergens. Meningoencephalitis, dementia or psychosis, ischemic lesions of the brainstem or spinal cord, and thrombosis of the dural sinus or intracranial veins are the neurological complications. Mononeuritis multiplex or poKiiL-uropath} are rare. The CSF protein concentration

may be elevated. Treatment is generally supportive, but corticosteroids and immunosuppressive agents are recommended.

Cogan's Syndrome

Cogan's syndrome is a chronic vasculitis of unknown etiology that rarely affects children. Photophobia, interstitial keratitis, and vestibular acoustic symptoms (tinnitus and hearing impairment) are characteristic. Systemic manifestations may include lymphadenopathy, splenomegaly, and musculoskeletal complaints. A systemic vasculitis, when present, may involve the aorta and result in aortitis and aortic insufficiency. The coronary and renal arteries may be involved. Corticosteroids have a short-term benefit; immunosuppressive agents may also be effective.

Sjogren's Syndrome

Sjogren's syndrome is a chronic disorder characterized by recurrent lymphocytic inflammation of the salivary glands, xerostomia, and keratoconjunctivitis sicca. The primary form is rare in childhood; the secondary form is a complication of SLK, JKA, MCTD, or dermaromyositis, The disease mainly affects females.

The main features are a nonspecific anemia, leukopenia, and hypergammaglobulinemia. Several autoantibodies are positive including ANA, anti-SSA, and rheumatoid factor. Lymphoid infiltration of the minor salivary glands of the lower lip is characteristic of Sjogren's syndrome. Neurological complications are limited and may include optic neuritis, aseptic meningitis, and cerebrovascular occlusion. MRI studies show regions of increased signal intensity on T2-weighted images in the internal capsule and periventricular white matter. Treatment is generally supportive, but corticosteroids and immunosuppressive agents arc used in life-threatening circumstances.

RESPIRATORY DISEASES

Periodic Breathing and Apnea

Periodic breathing is a pause in respiration that persists 3 seconds or more, followed by a normal respiratory pattern for 20 seconds, and then repeats at least three more times. This pattern is common in the premature infant. Supplemental oxygen is required if arterial oxygen saturation is significantly decreased or the infant becomes bradycardia Neurological sequelae do not occur unless hypoxemia is significant and prolonged.

Apnea, the cessation of respiration and flow of air for more than 20 seconds, can be secondary to airway obstruction, lack of respiratory effort (central apnea), or both. The most common type of apnea is that which occurs in the premature infant of about 35 weeks beginning during the first several days of life and then decreasing in frequency and severity over the succeeding months. All potential causes of recurring apnea should be excluded utilizing interventional diagnostic and therapeutic measures. Episodes of apnea are seldom associated with gastroesophageal reflux.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia is a chronic progressive lung disorder that affects infants who had hyaline membrane disease and were mechanically ventilated while receiving high-oxygen concentration. The pathogenesis is not clearly established. Neurological complications include impaired vision, hypotonia, delayed development, particularly fine and gross motor performance, postural control, and balance. The acquisition of speech and language are impaired and articulation is impaired.

Chronic hypoventilation may cause brainstem gliosis. A movement disorder affecting the head, neck, trunk, limbs, and oral-buccal-Ungual musculature can develop during the second or third postnatal month. Episodes of respiratory failure exacerbate the movement, and sleep reduces them. Feeding is difficult because of the oral movements. Although the management of ventilation and nutrition of infants has improved during the last several decades, the mortality of bronchopulmonary dysplasia remains high. Fifteen percent do not survive the first year. Symptoms gradually resolve in those who survive.

Cystic Fibrosis

As in other chronic pulmonary disorders, neurological features of cystic fibrosis arc secondary to chronic hypoxia and retention of carbon dioxide. Lethargy, and sometimes coma, results as pulmonary function declines. Chiari type I malformation is more common in children with cystic fibrosis than the general population. Symptoms and signs are reversed with the improvement of hypoxia.

SARCOIDOSIS

Sarcoidosis is a systemic disease of unknown etiology characterized by small noncaseating epithelial granulomas affecting multiple organs. When the nervous system is involved the disorder is called *neurosarcoidosis.* Children of African heritage arc affected more commonly than those of European heritage, and females more often than males. Childhood sarcoidosis is rare, comprising about 6% of cases. In children younger than 4 years, the features are a painless arthropathy with intact range of motion,

uveitis, and cutaneous lesions. Older children have a clinical course similar to that of adults with pulmonary involvement, fever, lymphadenopathy, and weight loss. Given the vagaries of clinical identification and reporting, the prevalence of nervous system involvement in adults may be as high as 5% and as high as *9%* in children (see Chapter 55A).

HEMATOLOGICAL DISORDERS

Congenital Aplastic Anemia (Fanconi's syndrome)

Fanconi's syndrome, inherited as an autosomal recessive trait, is genetically heterogeneous. At least eight genes have been identified. Three fourths of affected children have congenital anomalies. The pathophysiology is disordered proliferation and differentiation of hematopoietic stem cells. A single cytopenia progresses to pancytopenia. The typical characteristics are microcephaly, short stature, abnormal thumbs and radii, hyperpigmented and hypopigmented spots, and structural renal anomalies. The congenital aplastic anemia can occur in children who have no other physical abnormalities usually associated with the disorder.

Hemolytic Disease of the Newborn (Kernicterus)

Hemolytic disease was once the most common perinatal hematological disorder of infancy. The incidence has significantly declined by the administration of anti D antibody (Rho U) immune globulin to mothers within 2 hours. It is an alloimmune hemolytic anemia of the fetus secondary to the transplacental passage of mother's anti-Rh antibody. The worst result is erythroblastosis fetalis and in many cases kernicterus in survivors. Until the last decade, kernicterus was uncommon, but for unclear reasons, the frequency is now increasing.

Over 2 to 7 days, the jaundiced infant developing kernicterus is initially drowsy, does not feed well, often has a high-pitched cry, and loses transitory neonatal reflexes. Muscle tone increases gradually resulting in opisthotonus and on occasion extensor spasms. During the next several months, the infant becomes hypotonic, and in the ensuing years, the full scope of neurological abnormalities become apparent. These include gaze palsies, particularly impaired upward gaze, high-frequency hearing loss or other auditory impairments, athetosis, dystonia, and developmental delay.

The cerebral areas most affected by the bilirubin encephalopathy are the basal ganglia, especially the globus pallidus and subthalamic nucleus, the cerebellar vermis, and dentate nuclei. Other affected sites include the hippocampi and some cranial nerve nuclei, especially the oculomotor and acoustic vestibular nerves.

Aside from prevention, treatment is supportive, using physical and occupational therapy, as well as potential orthopedic procedures.

Sickle Cell Disease

Sickle cell disease occurs as the result of structurally altered hemoglobin molecule in which a neutral amino acid is substituted for one that is acidic, altering the physical properties of the molecule. The most common forms of sickle cell disease include sickle cell anemia, sickle ^-thalassemia, and sickle hemoglobin C. Sickle cell anemia occurs in about 1 per 600 newborn African Americans in the United States; sickle hemoglobin C in 1 per 800, and sickle ^-thalassemia in 1 per 1700. Clinical manifestations can affect most organ systems but involvement of the CNS can be life threatening. The occurrence of neurological complications are higher in the homozygous form SS or in sickle ^-thalassemia and occurs less often in sickle hemoglobin C.

Acute and chronic neurological complications exist. Emergency diagnostic and therapeutic measures are needed in episodes of acute neurological dysfunction. Children with sickle cell disease are unusually susceptible to infections with *Streptococcus pneumoniae, Haemophilus influenzae,* and *Mycoplasma pneumoniae.* CNS infection can provoke stroke, the most common neurological complication of sickle cell disease. The symptoms of stroke may be headache, seizures, hemiparesis, or speech and language dysfunction. Abnormalities of the spinal cord and peripheral nerves also occur. The initial symptoms may be transitory but require immediate diagnostic and therapeutic attention to prevent permanent sequelae. Chronic symptoms of silent stroke can be manifested by recurring headache, seizures, abnormalities of speech and language, and learning disabilities.

Children with sickle cell disease are at high risk for stroke syndromes from cerebral infarction and may develop disorders of higher cortical function from neurologically silent small cerebral infarcts. The baseline prevalence of silent infarcts was 21.8% among 266 children, ages 6 through 19 years, in the Cooperative Study of Sickle Cell Disease. Most lesions occurred in girls before the age of *6* years, whereas boys remained at risk until the age of 10 years.

Transcranial Doppler ultrasonography is a useful screening technique to demonstrate vascular narrowing. Neuroimaging studies arc useful, but the use of prophylactic partial exchange transfusions should be considered before performing any procedure that requires infusion of hypertonic contrast material. Cerebral angiography is contraindicated because of the risk of provoking vascular occlusion. Partial exchange transfusions may be beneficial in terminating an occlusive crisis in children who had a clinical stroke and evidence of cerebral infarcts on neuroimaging studies. Sufficient packed red cells is given to reduce the hemoglobin S to no more than 30-35%.

Higher levels are associated with a significant risk of recurrent stroke.

Hemophilia

Hemophilia is a genetic disorder of deficient or abnormal coagulation proteins. The main clinical feature is frequent and excessive bleeding. The most common type is deficiency of factor VIII, accounting for about 75% of patients. The incidence is 1 in 7500 live male births. About half have increased bleeding at circumcision, but it is not until the child becomes active at about age 2 years that easy bleeding becomes apparent, usually affecting the ankles, knees, or elbows. Intracranial bleeding occurs without obvious preceding head trauma. Hemorrhage affecting the CNS, gastrointestinal'tract, or retroperitoneal space can be life threatening. In one Swedish study of 117 children with moderate or severe hemophilia type A or B, 13 were delivered by cesarean section and the remainder were delivered vaginally. Subgaleal bleeding was the most common hemorrhagic complication of those delivered vaginally and most of these were associated with vacuum extraction. Their conclusion was that the risk of vaginal deliveries of hemophiliac patients was small, but the use of vacuum extraction should be avoided. Symptoms or signs of intracranial bleeding may not be immediately apparent. Therefore all hemophilic children who sustain trauma or show features of CNS disturbance should undergo head CT to delineate the location and extent of intracranial bleeding. In one report, four of seven hemophilic patients who suffered eight episodes of intracranial bleeding died despite replacement of factor VIII. The authors strenuously suggest that administration of factor VIII is often therapeutically insufficient and that surgical intervention is required if the CNS disturbance does not resolve within hours.

Neonatal Polycythemia

Neonatal polycythemia, defined as a hematocrit of more than 65%, occurs in 5% of newborns during the first several days postpartum. The hyperviscosity may cause vascular injury to the brain and kidneys. Reducing the hematocrit prevents and may reverse venous thrombosis. Even renal vein thrombosis is usually lessened or cleared within the first weeks. No long-term studies are available of newborns, who have had renal involvement from polycythemia. In one follow-up controlled study of 111 consecutive newborns with neonatal polycythemia and hyperviscosity, a higher incidence of motor and neurological abnormalities (38% vs. 11%) was observed at 1-3 years among infants with neonatal hyperviscosity. Moreover, concurrent hypoglycemia increased the risk of poor neurological outcome in hyperviscous infants to *55%.* Of *76* infants with neonatal polycythemia and hyperviscosity, I I bad spastic diplegia, 5 were hypotonic, and hemiparesis, athetosis, and nonfebrile seizure disorder were observed in each of 3 children. In the control group, two patients were abnormal. One patient had spastic diplegia and a second was hypotonic. Other studies have reported that intracranial hemorrhage can occur.

Thrombocytopenic Purpura

Thrombocytopenic purpura is an autoimmune disorder that can have its onset from early childhood to adulthood. Males and females arc equally affected. It presents as an acute illness with bleeding into the skin, which occurs cither spontaneously or following minor trauma. The bleeds can vary from pctcchiae to large eechymoses. Purpuric lesions are particularly seen in pressure areas such as around the neck or in areas of tight-fitting clothing.

Neurological complications affect fewer than 10% of affected children. Intracranial bleeding is unusual, but headache, behavioral and learning disorders, speech abnormalities, hemiparesis, and disorders of movement are described in the chronic form of the disease. Though acute in onset, the course is usually self-limited but can relapse at the time of an acute infection. Mononcuropathy and polyneuropathy can be associated.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (IIP) is a familial microangiopathic disorder characterized by hemolytic anemia and thrombocytopenia with platelet aggregation of the microvasculature and adjacent arterioles distributed throughout the brain. Larger cerebral vessels art' rarely affected. Hemolytic-uremic syndrome, a related disorder is acute and self-limited and affects only children, whereas TTP affects adults, is chronic, and can be relapsing.

Clinical findings include fever, abdominal pain, and arthralgia. Neurological findings include headache, disorientation, visual abnormalities, and sometimes disorders of speech and language. Plasma exchange is generally effective for management.

Hemorrhagic Disease of the Newborn

Hemorrhagic disease of the newborn is caused by vitamin K deficiency and is usually apparent within the first days postpartum, although it may occur as late as several months of age. It usually occurs in infants fed only breast milk and who have not received supplementary vitamin K in the nursery. The initial features are intracranial or gastrointestinal hemorrhage. Mothers who receive anticpilcptic drugs, especially phenytoin, are more likely to have infants with hemorrhagic disease.

Neurological complications are secondary to hemorrhage into the subarachnoid space or cerebral parenchyma. The clinical features may include cortical blindness, hemiparesis, ataxia, and disorders of movement.

GASTROINTESTINAL DISEASES

Hepatic Encephalopathy

The syndrome of hepatic encephalopathy is characterized by behavioral and neurological abnormalities that occur secondary to acute or chronic liver disease. The pathogenesis is unknown, but substances that have not been cleared by the liver cause CNS intoxication. The onset of encephalopathy can be acute, subacute, or chronic (Tessier, Villeneuve, and Villeneuve 2002}. With acute liver failure, hepatic encephalopathy becomes apparent within *8* weeks. The hepatic encephalopathy associated with subacute or chronic liver diseases can be episodic and less severe. The clinical features include changes of behavior, impaired attention span, and lack of concern regarding personal hygiene and appearance. Abnormal motor findings include change of muscle tone and posture, paratonia, asterixis, and hyperactive tendon reflexes. The clinical findings are summarized in Table 55B.1.

Symptoms are subtle during the first stage of hepatic encephalopathy and can go unnoticed. As the process continues, mental status declines and asterixis may be present. In the third stage, the patient may become lethargic or somnolent, and incontinence and seizures may be present. In stage 4, response to painful stimuli is decreased and decerebrate or decorticate posturing can occur. Despite severe liver disease, jaundice, hepatomegaly, ascites, or edema may not be clinically apparent. Laboratoty documentation of livet disease is not difficult in patients with an acute fulminating hepatic failure. However, the diagnosis is more difficult to establish when hepatic involvement is milder. Elevated plasma ammonia concentrations ate helpful to confirm the diagnosis, but normal concentrations are not exclusionary and CSF ammonia concentrations do not correlate with disease severity. CSF glutamine concentrations correlate with the scvetity of hepatic encephalopathy and ate the most sensitive laboratory test. The EEG findings are abnormal but nonspecific. Triphasic slow waves, often attributed to hepatic encephalopathy, are also seen m encephalopathy of othet causes.

Table S5B.1: Signs and symptoms of hepatic encephalopathy

Stage	*Mental status/behavior*	*Motor/reflexes*
	Anxiety/confusion Irritability/agitation Impaired attention Altered sleep patterns Depression	Fine postural tremor Impaired coordination
	Lethargy Behavioral/ personality changes Disorientation/ poor recall	Asterixis Dysarthria Primitive reflexes (suck, gasp) Paratonia/ataxia
	Delirium/profound confusion Paranoia Disorientation in time and place Poor recall	Hyperreflcxia/extensor plantar? Seizures I ly per ventilation/incontinence Hypothermia /myoclonus
	Coma	D ece rcb oi tc/dec o rtica te posturing Brick oculoccpbalic reflexes

Source: Modified with permission from Rothstcin, J. D. 6c, Herlong, H. 1989, "Neurologic manifestations of hepatic disease," *Neurol Clin,* vol. 7, p. 564.

Management includes treating the precipitating event, restricting dietary protein intake, and altering the intestinal flora. Liver transplantation is a consideration and is successful in 55-89% of patients.

liver Transplantation

In one review of complications associated with (all ot livet) organ transplantation, neurological complications occurred in 30-60% of patients of adult ages. Neurological complications occurred in 20-30% of children undergoing liver transplantation (Ghaus, Bohlega, and Rczeig 2001). Complications of organ transplantation may be considered in terms of (1) the underlying disease, (2) the transplantation ptoccdure, (3) the effects of associated infection, and (4) the adverse effects of immunosuppressive agents.

Congenital biliary atresia is the most common reason for liver transplantation in children. Other causes are biliary micronodular cirrhosis, viral hepatitis, Alagille syndrome, and several rare genetic disorders. The main potential surgical complication of liver transplantation is excessive blood loss. Prolonged periods of hypotension may result in hypoxic-ischemic brain injury in watershed areas. Peripheral nerve and brachial plexus injuries can occur intraoperativcly. After organ transplantation, a steteotyped pattern of infection may occur at three different times: the first month after transplant; 1-6 months post-transplant; and 6 months or longer after transplantation. Infection with *Mycobacterium tuberculosis, Strongyloides stercorals,* and systemic mycoses characterizes the immediate postoperative period. The greatest tisk for infection is the second period. The responsible agents are viruses, especially herpesviruses and hepatitis virus, and opportunistic pathogens such as *Listeria monocytogenes, Nocardia asteroides,* and *Aspergillus fumlgatus.* Six months post-transplant, the risk is from infection secondaty to immunosuppression. The infectious agents include *Cryptococcus, L. monocytogenes,* and *Mycobacterium tuberculosis.*

Adverse neurological complications occur as a direct effect of immunosuppressive agents. The most commonly administered agents are cyclosporin A, corticosteroids,

methotrexate, high-dose cytarabine (ara-C), and OKT3 monoclonal antibody. Neurological complications occur in 10-25% of children treated with cyclosporin A. Seizures are the most common complication. Others arc tremor, burning dysesthesias of the palms and soles, ataxia, quadriparesis, behavioral disorders, and leukocncephalopathy.

The adverse neurological effects of corticosteroids are mental status changes, myopathy, hypertension, and abnormalities of fat metabolism. Methotrexate, an antifolate metabolite, causes aseptic meningitis in 10—38% of children treated intrathecally. Other symptoms are headache, photophobia, fever, meningismus, vomiting, and lethargy. Transverse myelopathy is a rare complication. Leukoencephalopathy, the most serious complication, is usually the consequence of repeated doses of intravenous high-dose methotrexate, or intrathecal methotrexate.

Intravenous and intrathecal administration of ara-C may cause myelopathy, peripheral neuropathy, encephalopathy, and cerebellar dysfunction. The cerebellar syndrome is characterized by dysarthria and both truncal and limb ataxia. High-dose ara-C administration is a potential cause of a Guillain-Barrc-like syndrome and a sensorimotor neuropathy. OKT3 administration is associated with fever, headache, and photophobia, which resolve when the drug is discontinued. Intracranial hemorrhage developed in 6 of 30 children treated with OLTx. One child had a basilar artery thrombosis and four developed pituitary gland necrosis. On postmortem examination, 22 had Alzheimer type II astrocytes and two had central pontine myelinolysis. Other neuropathological findings included neuraxonal dystrophy and phagocytic nodules, thought to represent disseminated fungal or viral infections.

Whipple's Disease

Whipple's disease is mainly an adult multisystem disorder. Early clinical features include fever and arthralgia, followed by features of intestinal malabsorption. Small intestine biopsy shows an accumulation of periodic-acid-Schiff staining histiocytes, which also occur in the brain and spinal cord. Neurological complications include intellectual impairment, ophthalmoplegia, ataxia, and spastic paraparesis. Polydipsia and abnormalities of the sleep-wake cycle indicate hypothalamic involvement.

ENDOCRINE DISORDERS

Thyroid Disorders

The thyroid gland and brain are intimately associated through the anterior hypothalamus. The hypothalamus regulates thyroxine levels by producing thyroid-stimulating hormone. Thyroid hormone is involved in the early neurodevelopment of dendritic growth and arborization, neural migration, and synaptogencsis. The clinical features of thyroid deficiency depend on the age at onset. Two syndromes, each with subtypes, are defined: congenital hypothyroidism and acquired juvenile hypothyroidism. The incidence of congenital hypothyroidism is 1 in 4000 live births. Affected newborns have little or no clinical evidence of thyroid hormone deficiency, and the diagnosis depends on newborn screening programs. These are mandatory in the United States and much of the Western world.

Most children with congenital hypothyroidism have thyroid dysgenesis of unknown etiology. The disorder is sporadic and the female-to-male ratio is 2:1. The thyroid is hypoplastic, ectopic, or absent. Affected infants usually have a rather pale skin, a hoarse cry, an enlarged protruding tongue, prolonged neonatal jaundice, umbilical hernia, and large anterior and posterior fontanelles. They often appear lethargic and have difficulty feeding, constipation, and diminished spontaneous movements. Within 1 or 2 months, it becomes increasingly apparent that these infants are inordinately apathetic and hypotonic and have a hoarse cry. Sensorineural deafness is common and early testing and diagnosis avoids potential problems in speech and language development. Delayed psychomotor development and ataxia are sometimes associated (Morin et al. 2002). One form of congenital hypothyroidism (Kocher-Dcbre-Semelaigne syndrome) is associated with muscular enlargement, weakness, and slow movements.

Acquired hypothyroidism develops at any age in previously normal children. Females are more often affected than males. Circulating antithyroid antibodies are present in a significant number, reflecting an immune-mediated process (I lashimoto's thyroiditis). Nonimmune causes include exposure to goitrogenic factors, inborn errors of thyroid metabolism, and acquired hypothalamic or pituitary disease. Pcndrcd described two deaf sisters with goiter from a nonendemic goiter area and this condition, now known as Pendrcd's syndrome, has a prevalence of 1.5-3 per 100,000 school-age children. Affected children have high-frequency or complete sensorineural deafness and goiter and arc either euthyroid or mildly hypothyroid. The pathogenesis is not established.

Endemic cretinism is the most severe form of dietary iodine deficiency. Neurological features include mental retardation and pyramidal and extrapyramidal dysfunction. The gait is unusual and thought to result from pyramidal and extrapyramidal dysfunction, as well as joint laxity. Deafness is common in children with endemic cretinism and significantly improves after iodine prophylaxis. Lcvothyroxine is the treatment of choice and results in normal growth and development if treatment commences within the first weeks postpartum (Selva et al. 2002). The ultimate intellectual development depends on the time of diagnosis and treatment and the severity of hypothyroidism (Hopwood 2002).

Hyperthyroidism (Graves' disease) usually results from autonomous thyroid stimulation by thyroid-stimulating

immunoglobulin. The thyroid is diffusely hyperplastic. A rare form of congenital hyperthyroidism has an insidious onset and the female-to-male ration is 6:1. Affected patients become increasingly irritahle and have a short attention span, difficulty concentrating, and an increased appetite. Behavioral problems at home or in school are common. The most common physical sign is unilateral or bilateral exophthalmos. Other ocular signs that are common in adults such as lid lag, difficulty with convergence, infrequent blinking, and the appearance of staring are uncommon in children. The thyroid gland is enlarged and easily palpable. Tremor and increased tendon reflexes are common and chorea may be present. Neuromuscular diseases (e.g., weakness, myasthenia, and hypokalemic periodic paralysis) arc less common in children than in adults.

Serum concentrations of Tj and T_4 are elevated. Propylthiouracil is the usual treatment of thyrotoxicosis. Neurological symptoms and signs resolve when the patient becomes euthyroid.

Parathyroid Disorders

Hypoparathyroidism results from deficiency of parathyroid hormone {PTH} or lack of responsiveness of the end organs to PTH (pseudohypoparathyroidism). The typical feature is hypocalcemia. In adults, deficiency of PTH is usually the result of inadvertent removal of the parathyroid glands during thyroid surgery or other surgical procedures about the neck. The Di George's syndrome is a congenital form of hypoparathyroidism resulting from abnormal embryogenesis. The characteristic features are thymic hypoplasia, congenital heart defects, and structural abnormalities of the brain.

Hypercalcemia as a consequence of hyperparathyroidism is uncommon in children. Nausea, vomiting, weight loss, lethargy, and weakness occur when serum calcium levels exceed 12 mg/dL. Attention deficit, depression, weakness, and hyper-reflexia may be associated.

Adrenal Gland Dysfunction

Excessive production of glucocorticoids occurs in adrenocorticotropic ic hormone (ACTH)-secreting pituitary adenomas, other intracerebral tumors, and adrenal adenomas. Excessive weight gain and proximal weakness follows initial growth failure. Tendon reflexes are decreased and electrophysiological studies show normal or low-amplitude, short-duration motor unit potentials. Muscle biopsy reveals type II atrophy. A cushingoid appearance is typical, with adipose tissue over the posterior neck (bison hump), thinning of skin with prominent capillaries, increased pigmentation of flexor skin creases, and sometimes purple striae on the trunk. Pubic hair may appear early. The measurement of serum Cortisol, ACTH, and their metabolites before and after dexamethasone suppression establishes the diagnosis.

High-dose glucocorticoids are used to treat acute head injury and some intractable myoclonic epilepsies such as infantile spasms. The mechanism of action is unknown. Pseudotumor cerebri (idiopathic increased intracranial pressure) can occur during the administration of high-dose glucocorticoids. The characteristic syndrome is headache, papilledema, and enlargement of the blind spot on visual field testing. Transitory visual obscurations may be associated. Some children develop reversible behavioral disturbances during the time of steroid administration. Withdrawal of ACTH should be carried out slowly and periods of stress are covered by exogenous corticosteroid administration.

Glucocorticoid Deficiency

Glucocorticoid and mineralocorticoid deficiency characterizes Addison's disease, originally described as a complication of adrenal gland tuberculosis. Adrenal failure can also result from pituitary diseases, prolonged administration of exogenous corticosteroids, or other destructive disorders of the adrenal such as hemorrhage, infection, or tumor. Hyperpigmcntation of the flexor surfaces, gingival, and mucous membranes occurs secondary to excess ACTH production. Affected children experience anorexia, vomiting, weight loss, apathy, irritability, and headache. Some children develop confusion, seizures, and coma.

Pituitary Disorders

Neurological disorders secondary to pituitary gland dysfunction can result from pathological processes of the gland, the pituitary stalk, or the pcriscllar region. The main features result from increased intracranial pressure and disorders of endocrine function.

The characteristic features of septo-optic dysplasia (De Morsier's syndrome) are absence of the septum pellucidum and other midline structures and failure of the interhemisphcric commissures (corpus callosum and anterior commissure) to form. Other midline anomalies include optic nerve hypoplasia and neuroendocrine disorders. Associated neurological abnormalities include mental retardation, microcephaly, visual impairment, nystagmus, spasticity, and seizures. Children with mild forms of the syndrome may have normal intelligence.

The Laurence-Moon-Biedl syndrome is thought to be associated with pituitary dysfunction. It is characterized by mental retardation, retinitis pigmentosa, syndactyly and Polydactyly, hypoplastic genitalia, and obesity. This syndrome, and similar syndromes, is probably a genetic disorder transmitted as an autosomal recessive trait. The mechanism of hypogonadism was considered unresponsiveness of target organs to gonadal hormones

(primary end-organ failure), hypothalamic dysfunction, or pituitary fail Lire, The pituitary is morphologically normal and the numbers and immunoreactivity of adenohypophyseal cells is normal.

Cerebral gigantism (Sotos' syndrome) is characterized by large body weight at birth and in early childhood, mental retardation, macroccphaly, and an unusual face with a broad forehead and a sharp chin. Bone age is advanced, the hands and feet are enlarged, and rapid growth occurs during infancy that slows by late childhood. Serum growth hormone concentrations are normal. Most cases are sporadic, but some show autosomal recessive inheritance.

Diabetes Mcllitus

Diabetes mcllitus is the most common endocrine disorder of childhood. Late complications include abnormalities of higher cortical function and disorders of the peripheral nerves, eyes, and kidneys. Insulin-dependent diabetes mellitus (IDDM) is the most common type of diabetes mcllitus encountered in children. Inadequate insulin production is secondary to circulating antibodies against pancreatic cell components. It occurs in association with other autoimmune diseases. A tendency to develop ketosis exists that may lead to ketoacidosis.

Peripheral neuropathy is the most common neurological complication of IDDM and is thought to affect 10% of children with chronic diabetes mellitus. The polyneuropathy is usually asymptomatic, but careful neurological examination often reveals mild weakness of distal muscles and decreased stretch reflexes. In one prospective study, nerve conduction and autonomic function was evaluated in 144 diabetic children. Neurophysiologies! recording of nerve conduction and parasympathetic function (R-R variations) were determined after 2, 5, and 10 years. Low sensory nerve conduction velocities and autonomic dysfunction were found in 25% of children at the onset of diabetes when patients were not in remission. An initial improvement of sensory conduction velocities was found from 0-2 years, hut after 2 years, sensory and motor nerve conduction velocities and autonomic nerve function deteriorated. A correlation existed between peripheral nerve conduction velocities and control of blood sugar concentration. Spinal somatosensory evoked potentials and peripheral nerve conduction velocities were measured in 46 neurologically normal, insulin-dependent juvenile diabetics. These children, without clinical evidence of neurological involvement, showed defects in spinal afferent transmission. In general, a correlation exists with the existence of neuropathy and the duration of the diabetes mellitus and the degree of blood sugar conttol.

Although adult patients with IDDM can develop cranial neuropathies, particularly cranial nerves III, IV, and VI, this is rare in children. Polyradiculopathy, a well-documented complication of diabetes in adults, is rarely encountered in children, usually juveniles, with diabetes mcllitus.

A small group of children with IDDM who had experienced hypoglycemic seizures were evaluated at 1, 3, and 7 years. They showed significant decline in verbal but not visuospatial skills. Later assessment showed deficits in perceptual, motor, memory, and attention tasks. Other studies have found no effect on cognitive performance from diabetes or from severe hypoglycemia in children with late-onset diabetes, whereas early onset diabetes was associated with psychomotor efficiency and attention.

Diabetes mellitus can result in a severe metabolic encephalopathy from diabetic ketoacidosis (DKA). DKA is the most serious complication of IDDM and the most common cause of death. The pathogenesis is unknown. Severe cerebral edema can occur even after administration of appropriate insulin and fluid correction and at a time when glucose levels are decreasing and circulation seems normal. Severe and abrupt clinical deterioration occurs secondary to cerebral edema resulting in central or uncal herniation. Emergency treatment includes the administration of mannitol, endotracheal intubation, and hyperventilation.

RENAL DISORDERS

Renal Failure

Renal failure results in an encephalopathy with clinical features similar to those of other metabolic encephalopathies. The pathogenesis is unknown. Several compounds including urea, creatinine, guanidine, and parathyroid hormone have been considered at least partially responsible for the neurological disorder, but the specific explanation is not established. The clinical manifestations of uremic encephalopathy are characterized by disturbances of cognition and motor function, which are usually accompanied by electroencephalographic abnormalities (Palmer 2002). Awareness of the environment is diminished and the child appears apathetic, if not preoccupied, and lethargic. Concentration is impaired and simple arithmetic becomes difficult. As the encephalopathy worsens, recent memory is impaired and the child becomes confused if dialysis is not instituted. Further deterioration results in lethargy, stupor, and apnea. Motor features include tremor, asterixis, muscle cramps, neuromuscular excitability, and weakness. Seizures and myoclonus are present in advanced uremic encephalopathy. Peripheral nerve involvement is common and can result in sensory or sensorimotor polyneuropathy. Clinical evidence of polyneuropathy is common before dialysis. Peroneal motor nerve conduction velocities are reduced in children undergoing chronic hemodialysis even without clinical evidence of peripheral nerve involvement. The velocities did not improve during the next 6-12 months. Nerve biopsies from children with chronic renal failure show acute axonal neuropathy, progressive axonal

neuropathy with secondary segmental demyelination, and a primary demyelinative polyneuropathy.

The degree of renal function does not correlate with cognitive function in children with chronic renal failure since infancy, who had early dialysis (mean age of 18 months) and early transplantation (mean age of 28 months). Although head circumference was normal at hi nil, mosi had microccphaK by 1 year of age. As a rule. neurodcvclopmcntal outcome tends to be better when renal impairment begins at an older age. The median intelligence quotient scores of children who experienced onset of chronic renal failure before the age of 1 year are lower than those whose diagnoses were made after the age ol 3 years (Qvist et al. 2002).

Treatment of children with chronic renal failure demands management and control of fluid and electrolyte balance, use of peritoneal or hemodialysis, and in some cases renal transplantation (Smith, Ho, and McDonald 2002). Seizures are best managed by using phenobarbital or phenytoin at the usual therapeutic doses, recognizing that protein binding is decreased in uremic patients.

Neurological Complications of Dialysis and Transplant

The neurological complications of dialysis and renal transplantation in children are the same as those described in Chapter *55A,*

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Chapter 56
Trauma of the Nervous System

A. BASIC NEUROSCIENCE OF NEUROTRAUMA

W. Dalton Dietrich and Helen M. Bramlett

Traumatic brain injury (TBI) is a leading cause of death and disability among children and young adults. In addition head injury in older adults as a result of falls is a growing clinical concern. To investigate the pathophysiology of brain injury and to develop novel thetapcutic strategies to treat this condition, experimental models of TBI have been established. Although no experimental model completely mimics the human condition, individual models produce many features of human brain injury. Based on these models, therapeutic strategies directed at specific pathomcchanisms have been initiated. This chapter reviews the basic science of neurotrauma and summarizes the various experimental strategics used to investigate and treat TBI.

EXPERIMENTAL MODELS OF TRAUMATIC BRAIN INJURY

Severe closed-head injury produces a range of cerebral lesions that may be divided into four general categories: (1) diffuse axonal injury; (2) vascular lesions, including subdural hematoma; (3) contusion; and (4) neuronal degeneration in selectively vulnerable regions. In a review of animal models of head injury, Gennarelli (1994) classified models of head injury according to the method of producing injury. Fluid percussion (FP) and rigid indentation models are characterized as percussion concussion, whereas inertial injury models and impact acceleration models are considered acceleration concussion. In an attempt to investigate the effects of mechanical deformation on specific cell types, in vitro models of stretch-induced injury have also been developed.

Percussion Concussion

The central, lateral, and parasagittal FP models are characterized by brief behavioral responsiveness (e.g., coma), metabolic alterations, changes in local cerebral blood flow (LCBF) and blood-brain barrier (BBB) permeability, and behavioral deficits. The central FP model tends to have variable and small contusions in the vicinity of the fluid pulse and scattered axonal damage, mostly limited to the brainstem. In contrast, lateral and parasagittal FP is characterized by a lateral cortical contusion that is remote from the impact site. Evidence of axonal damage is seen throughout the white matter tracts in the ipsilateral cerebral hemisphere, and tissue tears are seen at gray matter-white matter interfaces. Hippocampal damage is pronounced in the lateral and parasagittal IP injury models with little brainstem damage. The FP injury model thus produces a range of disorders, including contusion, widespread axonal injury, and selective neuronal necrosis. In addition, varying injury severity, including mild (1.1-1.3 atm), moderate (2.0-2.3 atm), and severe (2.4—2,6 atm), can be studied in a reproducible fashion. This is an important model

characteristic because of the heterogeneous nature of human TBI and the possibility that treatment strategies may vary with injury seventy,

Another commonly used rodent TBI model is controlled cortical impact injury. In this model, a bone flap is removed and the impact device is vertically driven into the cerebral cortex to produce tissue displacement. This model produces a well-demarcated cortical contusion with variable degrees of hippocampal involvement dependent on velocity and defotmation depth. An advantage of the controlled cortical impact model is that it can be used in mice and allows the testing of genetically altered mice to help determine the cause-and-effect relationships between gene expression and cell injury.

Acceleration Concussion

Inertia! acceleration models can produce pure acute subdural hematomas and diffuse axonal injury. Tissue tear hemorrhages occur in the central white matter, and gliding contusions occur in the parasagittal gray matter-white matter junctions. These models ate characterized by a variable period of coma and axonal damage in the upper brainstem and cetebellum. Impact acceleration models produce prolonged coma and widespread axonal damage. These models are characterized by variable and somewhat uncontrolled skull fractures.

Cerebral contusion is the most common head injury. In this regard, both acceleration and concussion models reproduce this histopathological outcome. Diffuse brain injury is an important phenomenon with regard to patients who die or remain in a persistent vegetative state. The parasagittal FP model produces widespread axonal perturbations in forcbrain structures and tissue tears in white matter. An optic nerve model of traumatic axonal injury has also been investigated. This approach produces axonal injury by a rapid elongation of the nerve in situ. First developed in guinea pigs, rats, and mice, this model is advantageous for clarifying the pathophysiology of traumatic axonal injury. Human head injury is never as pure as an experimental model, and the total human injury condition may not be addressed adequately with a single animal model. However, once a particular feature of human brain injury is produced in an experimental model, the pathogenesis of the injury can be critically investigated.

In Vitro Models

A shortcoming of animal models is that they preclude a critical assessment of individual cell responses to trauma. In animal experiments, for example, the initial cellular response to injury may be a consequence of both ptimary and secondary events initiated by a complex cascade of cellular interactions. Therefore to critically investigate the consequences of injury on a specific cell type in the absence of confounding cellular and systemic factors, several in vitro cell culture models have been developed. Models range from scratching the culture with a pipette tip to inducing cellular deformation by stretching cultured cells.

Using these apptoaches, investigators have found that trauma induces a wide range of primary cellular alterations. Astrocytic responses include hyperplasia, hypertrophy, and increased glial fibrillary acidic protein content. Increases in intracellular calcium occur, which arc blocked by specific-receptor antagonists. Traumatized astrocytes also produce interleukins and neurotrophic factors. Neonatal cottical neurons that arc stretched undetgo delayed depolarization that depends on the activation of specific teceptor populations. Combined mechanical trauma and metabolic impairment in vivo also induces N-methyl-o-aspartate receptor-dependent neuronal cell death and caspase-3-dcpcndent apoptosis. In vitro experimental approaches provide novel data concerning mechanisms underlying cellular responses to trauma and the role of specific cell types in the pathophysiology of brain trauma.

NEURONAL DAMAGE AFTER TRAUMATIC BRAIN INJURY

Temporal Patterns of Neuronal Death

The ncuropathological sequelae of human TBI have been well described. In experimental TBI, temporal patterns of neuronal damage have also been characterized. As early as 6 hours after cortical contusion injury, the contused tissue appears edematous, and pyknotic neurons are apparent at the injury site (Cortez, Mcintosh, and Oble 1989). By 8 days, a cortical cavity has developed that is surrounded by a border containing necrotic tissue, a glial scar, or both. The temporal profile of neuronal damage after parasagittal FP brain injury has also been assessed with light and electron microscopy (Dietrich, Alonso, and Hallcy 1994). As early as 1 hour after impact, dark, shrunken neurons indicative of irreversible damage are seen in cortical layers overlying the gliding contusion that displays BBB breakdown to protein tracers. Ultrastructural studies demonstrate that early BBB dysfunction results from mechanical damage of small venules in vulnerable regions, including the external capsule. In some brain regions, focal sites of acute neuronal da mage an[1] associated with exrravasated protein, whereas neuronal damage in other regions appears to occur without overt BBB breakdown. Astrocytic swelling is observed early after injury, with increased glial fibrillary acidic protein immunoreactivity apparent at later times in areas, demonstrating histopathological damage (Diettich, Alonso, and Halley 1994; Figure 56A.1). In terms of neuroprotection, the acuteness of this damage limits the potential for therapeutic interventions directed against the early neuronal and glial response to TBI.

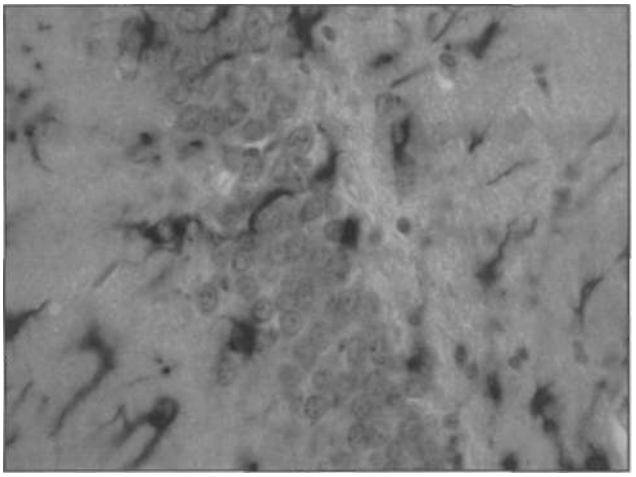

FIGURE 56A.1 Three days after fluid percussion injury, glial fibrillary acidic protein-positive astrocytes and processes are prominent in the hippocampus (x!200).

More subacute patterns of neuronal injury have been documented in various TBI models. At 3 days aftet moderate parasagittal FP brain injury, scattered necrotic neurons are present throughout the frontoparietal cerebral cortex remote from the impact site (Figure 56A.2), In addition, selective neuronal damage is seen in the CA3 and CA4 hippocampal subsectors, the dentate hilus, and lateral thalamus ipsilateral to the trauma. These patterns of selective neuronal damage are associated with a well-demarcated contusion overlying the lateral external capsule. Ultrastructural changes consistent with apoptosis have been described aftet TBI. Thctcfore delayed patterns of neuronal cell death may involve necrotic and programmed cell death processes.

Selective Neuronal Vulnerability

Damage to the hippocampus is commonly reported in autopsy studies of head-injured patients. Clinical and expetimental studies describe cognitive abnormalities thought to be associated with hippocampal dysfunction. In an acceleration model of brain injury in nonhuman primates, CAl hippocampal histopathologic^] damage was reported in the majority of animals, CA1 damage was not produced by secondary global ischemia, elevated intracranial pressure, or seizure activity. In this regard, CAl

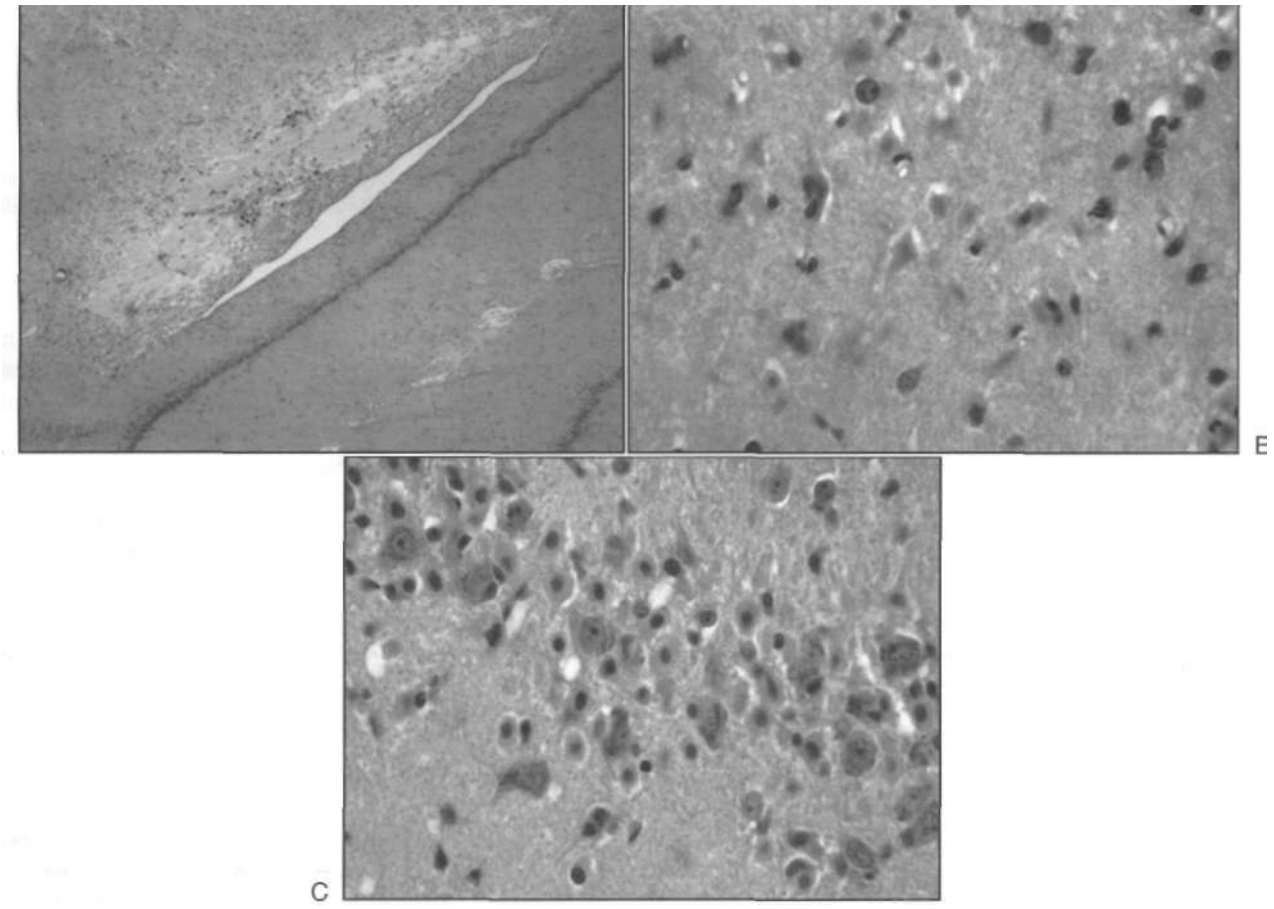

FIGURE S6A.2 Photomicrographs of rat brain 3 days after fluid percussion injury, (A) Focal contusion at gray-white interface (xl20). (B) Damaged cortical neurons overlying the contusion (xl20u). (C) Damaged and eosinophilic neurons in CA3 hippocampus (x 1200).

hippocampal damage is not routinely reported in other TBI models, including cortical contusion and moderate FP injury. However, midline FP injury followed by a delayed sublethal global ischemic insult leads to CA1 neuronal damage. It has been reported that moderate FP injury followed by a secondary hypoxic insult also results in significant CA1 damage. Also, in contrast to moderate FP injury, severe trauma causes hemodynamic reductions that reach ischemic levels and significant CA1 neuronal damage. Taken together, these findings indicate the importance of injury severity on outcome and the vulnerability of the post-traumatic brain to secondary insults. Finally, the dentate gyrus and CA3 hippocampus have also been reported to be selectively damaged in FP models, with bilateral damage to dentate hilus reported after FP injury,

Thalamic damage after brain injury is described in clinical and experimental studies. In human brain injury, the loss of inhibitory thalamic reticular neurons is proposed to underlie some forms of attention deficits. In radiographic studies of patients with TBI using magnetic resonance imaging, relationships between injury severity, lesion volume, ventricle-to-brain ratio, and thalamic volume have been teported. Patients with moderate to severe injuries have smaller thalamic volumes and greater venti ide-to-brain ratios than do patients with mild to moderate injuries. Decreased thalamic volumes suggest that subcortical brain structures may be susceptible to transneuronal degeneration after cortical damage. Focal damage to thalamic nuclei seen after long-term FP injury may result from progressive circuit degeneration after axonal damage, from neuronal cell death, or from the lack of neurotrophic delivery.

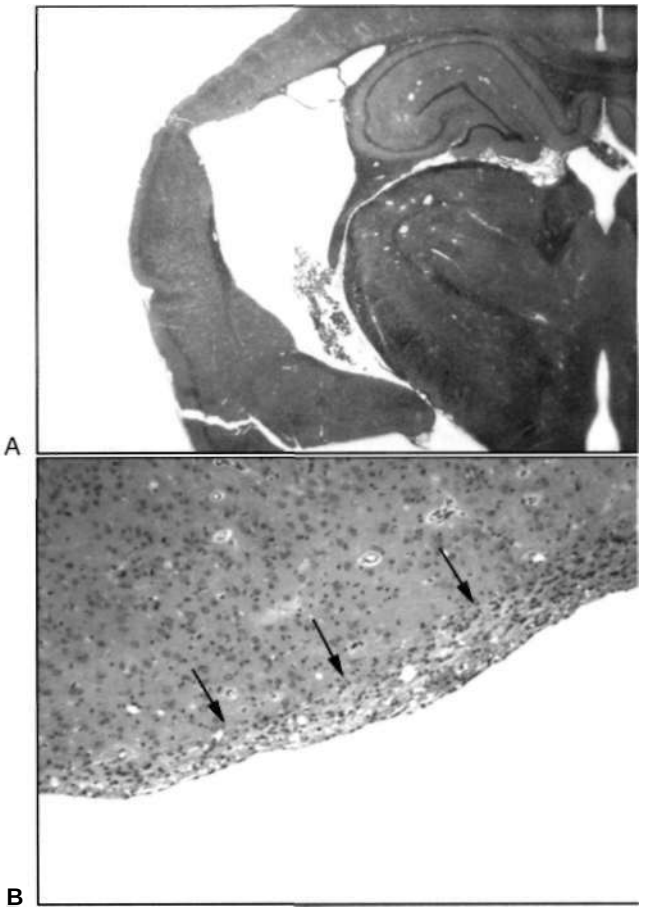

FIGURE 56A.3 Photomicrographs of rat brain 1 year after fluid-percussion injury (x30). (A) Brain shows gross atrophy with marked expansion of lateral cortex. (B) Severe loss of white matter in external capsule *{arrows,* x300).

Progressive Damage

Only recently has the progressive nature of the histopathological consequences of TBI been appteciated (Bramlett and Dietrich 2002). At *2* months after moderate parasagittal FP injury, significant atrophy of the cerebral cortex, hippocampus, and thalamus is apparent in histological sections (Figure 56A.3A). Progressive tissue loss in the cortex and hippocampus at various times up to 1 year after lateral FP injury have been reported. Similar findings have been found in a model of controlled cortical impact injury. At 3 weeks and 1 year after injury, analysis demonstrated a significant hemispheric volume loss and expansion of ipsilateral lateral ventricle. Thus atrophy of gray matter structures is associated with a significant enlargement of the lateral ventricle,

Ventricular expansion not associated with hydrocephalus or increased intracranial pressure is felt to be a sensitive indicator of structural damage and an indirect measure of white matter atrophy. Indeed, ventricular size has been correlated with memory disturbances, when patients with the highest ventricular volumes demonstrated significantly lower memory scores. Recent findings provide direct evidence of progressive white matter damage after FP brain injury (Bramlett and Dietrich 2002). At 1 yeat after TBI, severe atrophy of specific tracts including the external capsule in cerebral peduncle was documented (Figure 56A.3B). The importance of a progressive injury cascade after TBI in terms of other neurological conditions merits consideration. For example, if mild head trauma leads to a progressive reduction in neuronal reserve, would the person who sustained such trauma be more susceptible than others to neurodegenerative processes associated with aging? Indeed, some epidemiologic studies have indicated that a history of brain trauma is a risk factor for Alzheimer's disease.

Secondary and Repetitive Damage

A challenging problem faced by medical personnel responsible for the health care of amateur and professional athletes is the recognition and management of mild head injury. Returning an injured athlete to competition when the brain needs time to recover is an obvious concern. Also,

the basic understanding of the post-traumatic consequences affecting the vulnerability of the btain to secondary or repeated head injury remains unknown. This is a clinically important issue because TBI often is associated with respiratory suppression, resulting in secondary hypoxic insults (Chestnut 1995). Recently, experimental studies have documented the detrimental consequences of secondary insults after mild to moderate TBI. The effects of secondary hypoxia on histopathological and behavioral outcome were investigated. Secondary hypoxia induced immediately after moderate FP injury resulted in significantly greater cortical and hippocampal CA1 damage and sensorimotor and cognitive deficits than wete found in normoxic animals. Most recently, mild hypotension after TBI was reported to also worsen traumatic outcome. Taken together, these findings indicate the enhanced vulnerability of the post-traumatic brain to mild secondary insults.

Clinical studies indicate that patients with mild head injury may he at risk if they have a subsequent head injury (secondary impact syndrome). Recently, an animal model was developed to investigate the behaviotal and pathological changes associated with repetitive head injury. The consequences of single and repetitive injury induced 24 hours apart were assessed. Repetitive head injury led to gteater functional impairment and structural damage than was found in the single-injury group. In another study, repetitive injury in transgenic mice that expressed mutant human A/3 precursor protein produced elevated *Afi* levels and increased A/J deposition, thus linking TBI to the mechanisms of Alzheimer's disease. The known risk of developing neurodegenerative disease later in life is greater after repetitive brain trauma and makes this type of investigation extremely important.

Axonal and Dendritic Injury

In 1992, Povlishock wrote that axonal injuty exists as a spectrum involving widespread areas of the brain in experimental models of TBI. Patterns of teactive axonal change using monoclonal antibodies targeted at neurofilament subunits or ^-amyloid precursor protein have been characterized after HP brain injury and controlled cortical impact injury (Figure 56A.4; Povlishock, 1992). Within 1-2 hours of injury, reactive axonal change is most conspicuous in brainstem regions, including the pontomedullary junction. This pattern of axonal damage seen in experimental models is in contrast to the human condition, in which callosal and subcortical white mattet axonal damage predominates. In contrast, moderate parasagittal brain injury leads to widespread axonal damage in forebrain regions that represent reversible, irreversible, and delayed axonal perturbations. These findings may explain some ol the transient and delayed functional consequences of TBI.

In addition to axonal damage, studies indicate that TBI also leads to significant changes in neuronal dendrites. A common feature of damage of injured neurons is loss of microtubule-associated protein 2 (MAP2) antigenicity. MAP2 is an important microtubule cross-linking protein that is found predominantly in somatodendritic environments. Therefore changes in MAP2 may reflect damage to dendrites. Using this strategy, evidence of dendritic damage not necessarily associated with neuronal death has been obtained that may participate in some of the functional consequences of TBI.

The Importance of Gender

Recent clinical and experimental data have emphasized the importance of gender on the consequences of TBI (Stein 2001). In a study of 334 patients with TBI, female patients had a better predicted outcome at the time of discharge from an inpatient rehabilitation program. A meta-analysis of eight previous studies in which outcome was reported separately for men and women reported a worse outcome in women than in men. The impact of gender on TBI is an understudied area of clinical neurotrauma and should be emphasized in future trials.

In experimental models of TBI, gender also appears to influence traumatic outcome (Stein 2001; Bramlett and Dietrich 2001). The hemodynamic consequences of controlled cortical impact injury were reported to be less in female than in male rats. Also, contusion volume was significantly less in female than in male rats (Btamlett and Dietrich 2001). In this study, ovariectomy 10 days before TBI removed the volume differences between male and female rats. Thus intact females appear to have an endogenous neuroprotective mechanism that reduces the detrimental consequences of TBI (Stein 2001). In terms of testing neuroprotective strategies in models of TBI, gender differences must be stressed.

BASIC MECHANISMS OF INJURY

Primary Injury Mechanisms

Two major types of forces are responsible for brain injury: one localized at the impact site and a second characterized by rotational forces. Depending on the force and location of the primary impact, head trauma can produce acute damage to blood vessels and axonal projections. Contact phenomena generate superficial or contusional hemorrhages through coup and countercoup mechanisms. Direct injury is commonly superficial, and the coup-couutercoup hemorrhages may be adjacent or central.

Axonal shearing is a common lesion of the cerebral white matter, which occurs particularly in acceleration-deceleration injury. Only recently has morphological evidence of axonal shearing (primary axotomy) become available in FP models. Ultrastructural evidence demonstrates the tearing

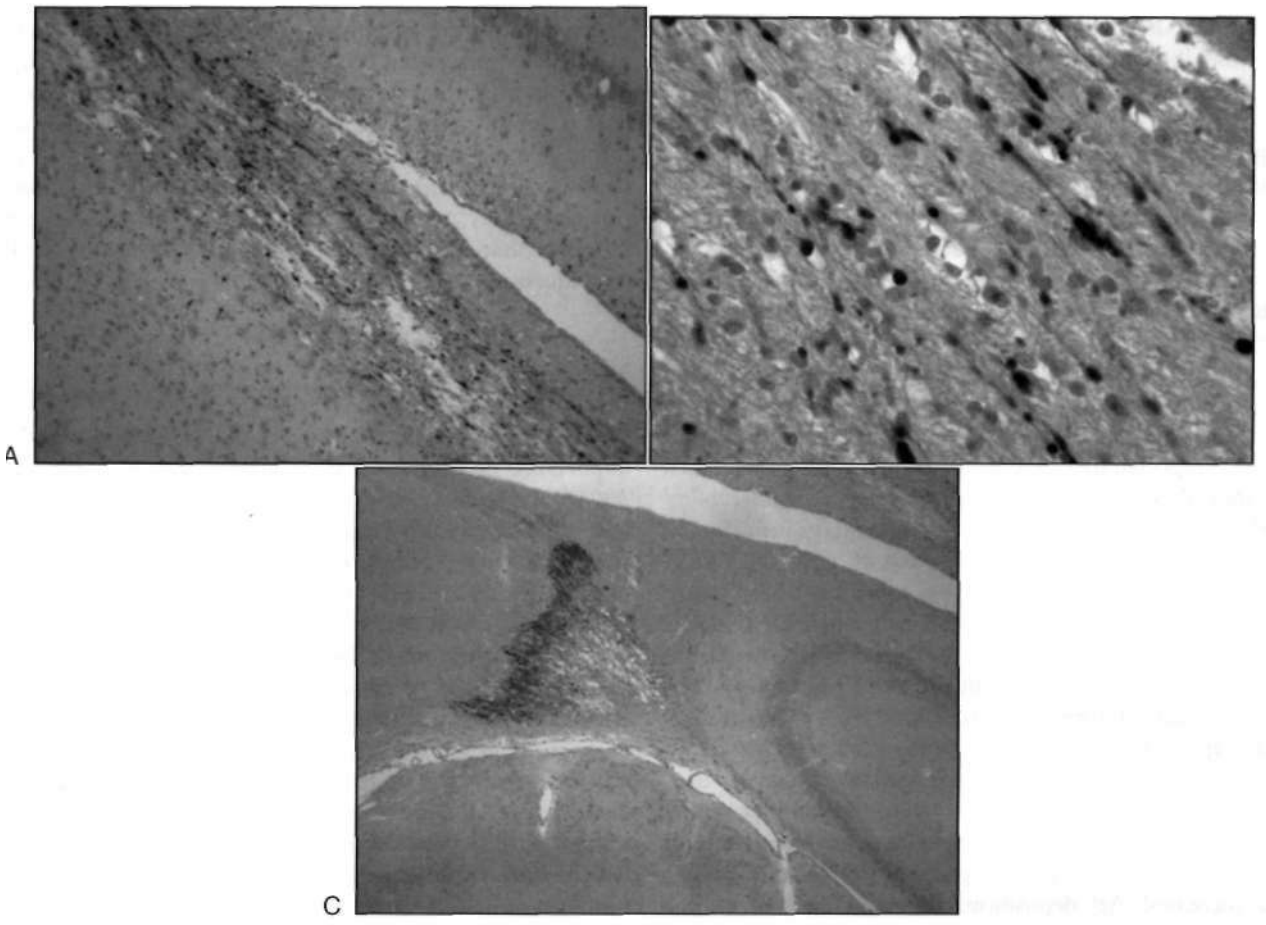

FIGURE 56A.4 /i-Amyloid precursor protein immunoreactivity after traumatic brain injury. (A) Large numbers of immnnoreactive profiles in external capsule (x 120). (B) High magnification of axonal swellings (x!200). (C) Dense reactive profiles within the fimbria of hippocampus consistent with primary axotomy (axonal shearing x 120).

or shearing of axons in nonhuman primates exposed to lateral acceleration. Pctturbations of the axolemma leading to the accumulation of cytoskeletal components and organelles or activation of intracellular mediators of injury such as calpain activation may represent secondary injury processes that can be treated.

Shearing strains may also damage blood vessels and cause petechial hemorrhages, deep intracerebral hematomas, and brain swelling. Mechanical damage to small venules resulting in focal BBB breakdown and platelet accumulation is reported immediately after FP injury (Dietrich, Alonso, and Halley 1994). Vascular damage leads to the formation of hemorrhagic contusions. Eatly vascular damage may increase neuronal vulnerability by causing post-traumatic perfusion deficits and the extravasation of potentially neurotoxic bloodbomc substances.

Secondary Injury Mechanisms

In many head-injured patients, the extent of neurological tecovery depends on the contribution of post-traumatic secondary insults (Chesnut 19951. In the clinical setting, secondary insults include hypotension, hypoxia, hyperglycemia, anemia, sepsis, and hyperthetmia. Experimental evidence indicates an increased susceptibility of the post-traumatic brain to secondary insults. For example, after midline FP brain injury, CA1 hippocampal vulnerability is enhanced with superimposed secondary ischemia. An important area of research regarding the treatment of brain injury involves the characterization of secondary injury processes, which may be targeted for intensive care management or pharmacotherapy.

A high frequency of hypoxic or ischemic brain damage occurs in patients who die as a result of nonmissile head injury. Hypoxic damage in the form of hemorrhagic infarction and diffuse neutonal necrosis is most common in arterial boundary zones between the major cerebral arteries. Hypoxic damage is also common in patients who have experienced an episode of intracranial hypertension. A significant cotrelation between hypoxic brain damage and arterial spasm in patients with nonmissile TBI has been reported. Post-traumatic hypoxia aggravates the BBB consequences of FP brain injuty.

Post-traumatic hemodynamic impairments represent another injury mechanism. Clinical and experimental investigations report moderate reductions in LCBF after TBI. After moderate parasagittal FP brain injury, widespread reductions in LCBF range from 40-80% of control. In contrast, severe FP injury leads to LCBF reductions that reach ischemic levels. Focal reductions in LCBF are associated with subarachnoid and intracerebral hemorrhage and local platelet accumulation. Reductions in LCBF result from the mechanical occlusion of cerebral vessels or the release of vasoactive substances, or possibly as a secondary consequence of reductions in neuronal activity or metabolism. Therefore injury severity is a critical factor in determining the hemodynamic and histopathological consequences of experimental TBI,

Hypotension is present in a significant number of patients with TBI. In severely injured patients, outcome is correlated with reduced mean arterial blood pressure. Hemorrhagic hypotension after FP injury results in more severe histopathological outcome than TBI alone. The increased sensitivity of the post-traumatic brain to moderate levels of hypotension may result from deficits in autorcgulation, which have been reported in patient and experimental studies. Hypotensive periods that may occur during surgical procedures and anesthesia may produce secondary insults and be hazardous to the head-injured patient.

Many patients experience fever after head injury, and clinical data indicate that hrain temperature may be higher than core or bladder temperature. Experimentally, post-traumatic brain hyperthermia induced artificially 24 hours after trauma increases mortality rate and aggravates histopathological outcome, including contusion size and axonal pathology (Dietrich et al. 1996). Thus in the clinical setting, post-traumatic hyperthermia may represent a secondary injury mechanism that might negate the beneficial effects of a therapeutic agent. Because delayed post-traumatic hyperthermia has been shown to have detrimental effects on outcome, aggressive attempts should be made to reduce brain temperature. Intravascular cooling devices may be used for temperature regulation in patients with central nervous system trauma.

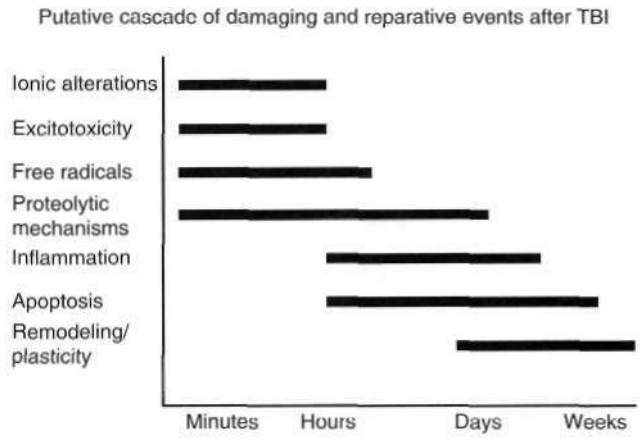

FIGURE 56A.5 *Paradigm for several time-dependent pathomechanisms and reparative events that may be targeted for therapeutic interventions (Adapted from Dirnagl, U., Iadecola, C., & Moskowitz, M. A. 1999, "Pathobiology of ischemic stroke: An integrated review," TINS, vol. 22, pp. 391-397).*

THERAPEUTIC INTERVENTIONS DIRECTED AGAINST PATHOPHYSIOLOGICAL PROCESSES

The pathophysiology of TBI has been investigated using a variety of animal models. Based on experimental data, new therapies have been initiated, some of which have been tested in the clinic. Several reviews summarize the agents that have been investigated in TBI (Mcintosh, Juhler, and Wieloch 1998). The problem of FBI involves injury pathways that arc common to other brain injuries, including cerebral ischemia. However, the pathogenesis of TBI is unique in other ways and necessitates therapeutic approaches specifically targeted at brain trauma (Figure 56A.5). The present discussion is limited to several of the major therapeutic strategics currently being assessed experimentally and clinically.

Glutamate Antagonists

Excitatory amino acid neurotransmitters have been implicated in the pathophysiology of TBI. Microdialysis techniques have documented elevated levels of extracellular amino acids, whereas N-mcthyl-u-aspartate (NMDA) receptor antagonists, including MK-801 (di?.OCilpine), provide behavioral and histopathological protection against brain trauma. The role of glutamate antagonists in treating central nervous system injury has been reviewed, and clinical stroke trials of the competitive NMDA antagonist MK-801 were withdrawn because of harmful side effects. Clinical data are still needed to determine whether NMDA receptor blockage will provide a significant benefit in clinical head trauma,

Free Radical Scavengers

The genesis of oxygen free radicals has also been implicated in the pathophysiology of TBI. Experimental FP injury increases the production of oxygen radicals, and free radical scavenger inhibitors have been reported to be protective in brain injury models. Sensitive indicators of hydroxy radical production and microdialysis have detected elevations in extracellular hydroxy radical production after FP injury. The free radical scavenger superoxide dismutase (SOD) reduces BBB opening and the genesis of

brain edema after TBI. Transgenic mice that ovcrcxprcss human copper-zinc SOD are protected against brain trauma. Clinical trials using polyethylene glycol SOD and free radical scavengers have been initiated in brain trauma, with little success.

The reason for these negative results is not known, although questions regarding brain penetration and limited therapeutic window have been discussed. In one experimental study, treatment with a potent inhibitor of lipid peroxidation and an antioxidant provided significant neuroprotection in a FP model when treatment was delayed 30 minutes but not 3 hours after TBI. Thus based on neurochemical and treatment studies, the therapeutic window for treatments that target free radical reactions and lipid peroxidation after moderate TBI seems to be short. Whether these treatments may protect against secondary insults remains to be investigated.

Neurotrophic Factors

A unique problem of brain trauma is diffuse axonal injury. Axonal injury leading to circuit disruption may not only produce immediate functional consequences but also may affect trophic signaling between neuronal populations. The addition of trophic factors after TBI may help maintain neuronal survival and promote circuit reorganization and functional recovery. Neurotrophins have been shown to be neuroprotective by in vitro and in vivo models of neuronal injury. After experimental TBI, delayed treatment with basic fibroblast growth factor significantly reduced histopathological damage and improved cognitive function. Several neurotrophic factors have also been shown to be protective when administered exogenously to animals after experimental TBI. For example, post-traumatic infusion of nerve growth factor (NGF) into the injured cortex or into the lateral ventricle was reported to improve learning and memory and to decrease apoptotic neuronal loss in septum of rats. The systemic administration of insulin-like growth factor-1 after TBI improved learning and neuromotor function. In contrast, brain-derived neurotrophic factor administration was not protective against behavioral or histopathological defects caused by TBI. In a recent publication, immortalized neural stem cells rcrrovirally transduced to produce NGF improved cognitive and neuromotor function and rescued hippocampa! CA3 neurons when transplanted into the injured brain. Therefore an important direction of future research will be to use engineered cell lines to produce neurotrophins that could synthesize and telease locally factors that enhance plasticity and circuit reorganization. If experimental studies continue to show a benefit of neuroprotection on neuronal injury and behavioral outcome in TBI models, this may be an important direction for future clinical trials in brain trauma.

Protection by Nitric Oxide-Related Species

In the nervous system, nitric oxide (NO) may serve as a neurotransmitter, a signal between cells, and an autocrine signal within a given cell. Aftet brain injury, an increase of neuronal calcium triggers constitutive NO synthase (cNOS) activity, leading to the release of NO that may enhance excitotoxicity. Studies of mutant mice deficient in neuronal (nNOS) or endothelial NOS (eNOS) activity have demonstrated that whereas nNOS exacerbates ischemic injury, eNOS protects against it.

Therapeutic strategies directed at the NO pathway have been reported in models of brain injury. Data indicate that FP injury leads to the acute activation of cNOS and that the selective inhibition of nNOS by 3-bromo-nitroindazole protects histopathologically and behaviorally. In addition, the inhibition of inducible NOS with aminoguanidine (selective iNOS inhibitor) also improved histopathological outcome. However, recent work using iNOS knockout mice has shown a beneficial role of iNOS in brain injury. Thus whereas early iNOS activity after brain trauma may contribute to secondary injury mechanisms, later or chronic activation may participate in reparative processes. These points regarding what processes should be targeted and when they should be inhibited are critical as novel strategics are developed to target NO-mediated cell injury. Additional studies using mutant mice deficient in nNOS, eNOS, or iNOS activity will be important to advance this area of investigation.

Inflammation

Inflammation is a host defense mechanism initiated by injury or infection through which blood-derived leukocytes (neutrophils, monocytes and macrophages, T cells) and soluble factors (cytokines, chemokines, complement) try to restore tissue homeostasis (Bethea and Dietrich 2002). Although evidence supports the beneficial role of inflammatory processes in acute injury, including the production of neurotrophic factors, inflammation is also thought to contribute to the tesulting neuropathology and secondary necrosis that occur after trauma. Brain trauma is associated with the production and release of proinflammatory cytokines, including tumor necrosis factor (TNF)-a, interleukin (IL)-l/3, and IL-6. The inhibition of cytokines such as IL-ljS and TNF-or has been reported to decrease lesion size and improve behavioral outcome after TBI. Also, treatment with the potent anti-inflammatory cytokine IL-10 was reported to improve outcome. However, absolute TNF-» inhibition in the form of knockout mice has yielded conflicting results regarding pathology and neurological outcome (Stahel et al. 2000). Again, these studies emphasize the diverse actions of cytokines and both the good and bad consequences of overexpression and inhibition.

Antiapoptotic Agents

Apoptosis is a mode of cell death in both physiological and pathological processes. Evidence of apoptotic cell death has also been observed after TBI. After FP injury, apoptotic cells have been identified in the ipsilateral cortex, hippocampus, and thalamus as soon as 4 hours after injury, and immunocytochemical markers for caspase-3, -8, and -9 activation have been reported (Figure 56A.6). The effects of l'T injury on the expression of the be 1-2 protein, which regulates developmental programmed cell death, have also been investigated. Evidence of apoptosis of oligodendroglia in long tracts undergoing Wallerian degeneration has been reported after SCI. Therefore demyelination of tracts after brain or spinal cord trauma may result from apoptotic death of oligodendrocytes. Importantly, indicators of apoptotic cell death have also been observed in human tissues.

Although the molecular events leading to apoptosis are not fully understood, the family of cysteine proteases (caspases) play an active role in its pathogenesis. In reference to neuroprotection, in vitro studies have demonstrated that protease inhibitors specific to caspase-3 inhibit apoptosis. Whereas some experimental data indicate that inhibition of caspasc-3 improves outcome after TBI, other studies suggest that this approach has limitations. Currently, emphasis is being placed on more upstream apoptotic processes in contrast to targeting caspase activation. Therefore more research is needed to clarify the various pathways involved in apoptotic cell death and determine which pathways may be most sensitive to therapeutic interventions. Using agents specific to apoptosis or in combination with agents that target necrosis is a potential research direction.

Therapeutic Hypothermia

Numerous studies have demonstrated that, although mild to moderate hypothermia is neuroprotective in models of TBI, mild hyperthctmia worsens outcome. After brain trauma, hypothermia has been shown to improve histopathological

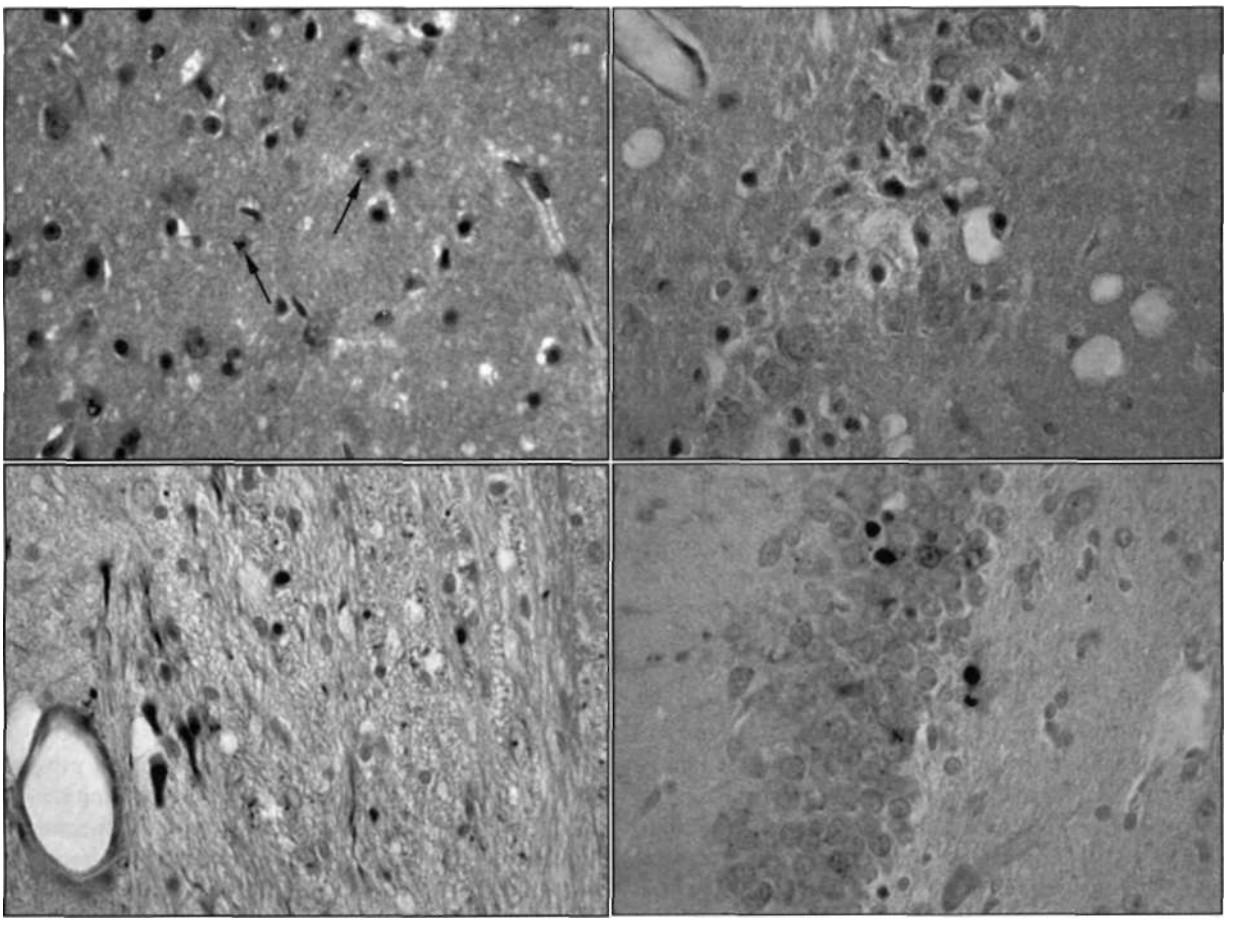

FIGURE S6A.6 Histopathological and lmniiinohistochemical evidence of apoptotic cell change 1 day after traumatic brain injury. (A) Hematoxylin and eosin-stained section showing apoptotic bodies (xl200). (B) Caspase-8 immunorcactivity (xl200), (C) Caspase-9 i mm u no reactivity in the thalamus (x!200). (D) Immurinhistochemistry of active caspasc-3 in dentate gyrus (x 1200).

and behavioral outcomes and to influence a wide range of injury processes (Dietrich et al. 1996). Microdialysis studies report that post-trauma tic hypothermia reduces the acute surge in levels of extracellular glutamatc and hydroxy free radicals after injury. Post-traumatic hypothermia protects against BBB dysfunction. In terms of long-term ourcome measures, hypothermia inhibits progressive cortical atrophy and subsequent ventricular enlargement. The ability of any therapeutic intervention to provide long-term protection is an important requirement for the advancement of any therapeutic strategy to the clinical setting,

As previously discussed, a significant number of patients with TBI sustain a secondary insult that may include hypotension, hypoxia, or hyperthermia. This fact has led to the use of complicated models to test novel neuroprotective agents before clinical trials. This point is important because experimental therapeutic strategies are commonly tested in simple models of brain injury as proof of concept (Mcintosh, Juhler, and Wieloch 1998). In this regard, post-traumatic hypothermia has been evaluated in TBI models complicated by secondary hypoxia. Taken together, these studies showed that hypothermia was protective in complicated models, but the degree of prorection depended on injury severity, duration of hypothermic period, and the rewarming procedure.

The use of moderate levels of hypothermia (>32^{C}C) also improves outcome in patient studies. Systemic hypothermia (32^{11} to 33^{C}C) begun within 6 hours of injury (Glasgow Coma Score 4-7} resulted in no cardiac or coagulopathy-related complications, a lower seizure frequency, and more patients in the good recovery to moderate disability category. In other head trauma studies, therapeutic hypothermia attenuated intracranial hypertension but did not affect the frequency of delayed intracerebral hemorrhage. Results from a recent multicenter TBI trial failed to demonstrate a protective effect of hypothermia on traumaric outcome. However, subgroup analysis showed that patients under age 45 coming into the emergency room hypothermic demonstrated an improvement with hypothermic treatment. Obviously, more experimental and clinical studies are needed to determine what factors are most important in providing protection when using hypothermic strategies. Temperature is known to affect many pathophysiological processes after TBI, and this characteristic may be advantageous because of the multifactorial nature of trauma pathomechanisms. The cooling and rewarming periods arc also important variables in determining the extent of neuroprotection. In TBI studies, prolonged periods of hypothermia (i.e., >24 hours) may therefore be necessary to protect the brain from primary and secondary injury processes. Because brain temperature can be elevated compared with bladder temperature in head-injured patients, normothcrmia or mild hypothermia should be maintained during critical postinjury periods.

RECOVERY OF FUNCTION

Environmental Enrichment

The effect of environmental enrichment (EE), which exposes animals to a complex, highly stimulatory, and social environment has been studied in a number of TBI models. Using a midline FP injury model that produced no noticeable histopathology, EE has been reported to improve cognitive function. In addition, EE has been shown to decrease overall contusion volume and improved performance in the Morris Water Maze task. The effects of EE have been suggested to be reflected in changes in dendritic arborization. Future studies combining EE with neuroprotective and reparative strategies probably will be needed to maximize improvement in outcome.

Reparative and Transplantation Strategics

Recent data indicate that after a variety of acute central nervous system injuries, there is a massive proliferation of stem or progenitor cells. Therefore the identification and origin of the fate of these cells is an area of intensive investigation. In a model of FP injury, the total number of proliferating cells as identified with 5-bromo-deoxyuridine, a marker of mitotic activity, was shown to significantly increase in areas of the subventricular zone and hippocampus. In that study, proliferating cells did not express cell markers and therefore appeared not to have begun to differentiate. Targeting this endogenous proliferative response to injury may be one way to enhance recovery following TBI.

In contrast to endogenous reparative events, the provision of new cells from exogenous sources is an alternative approach and may be necessary when neuronal loss and axonal injury are severe. Neural transplantation has been explored in TBI models (Soares et al. 1991, 1995). Fetal cortical tissue transplanted into the injury cavity improved motor function and transiently attenuated cognitive dysfunction alone and in combination with NGF infusion. Although the rccstablishmcnt of normal adult neural circuitry has not been demonstrated with fetal tissue grafts, one mechanism for improved function may be neuroprotection by release of trophic factors from the grafts (Soares et al. 1995). Recent studies have also attempted to provide cellular replacement and host-graft integration using self-renewing cell lines (Riess er al. 2002). Using immorralized neural progeniror cells derived from embryonic rat hippocampus (HiB5 cells), improved neuromotor and cognitive function and reduced hippocampal CA3 cell death after transplantation with cells transduced with the mouse NGF gene to secrete NGF have been reported. Continued study in this exciting field may establish transplantation procedures relevant to clinical strategies to promote recovery after TBI.

SUMMARY AND FUTURE DIRECTIONS

Continued experimental studies directed at investigating the pathogenesis of TBI will enhance our understanding of the neuroscicncc of brain trauma. The clarification of what injury processes dominate the injury cascade will improve our strategics directed at brain protection. The development of novel genetic mouse models of disease should also allow researchers to elucidate canse-and-effeet relationships between specific pathoinechanisms and cell death. The continued emphasis on determining how various factors, including age and gender, affect traumatic outcome should enhance the translation of experimental findings to the clinic. The relationship between early head injury and increased incidence of neurodegenerative disease is an important area for investigation as well. The determination of what genetic and environmental factors may interact to enhance the susceptibility of the post-traumatic brain to age-related disease processes is of utmost importance. Also, scientists from different laboratories need to assist in the replication of exciting data that will promote the design of successful clinical trials. Finally, the testing of combination therapies targeting multiple pathomechanisms must be encouraged. Strategies to protect vulnerable neurons, inhibit secondary injury mechanisms, and promote reparative processes must be considered in experimental studies. The continued communication between scientists involved in brain injury research and clinicians responsible for treating this patient population and designing clinical trials will advance our efforts toward these goals.

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Chapter 56
Trauma of the Nervous System

B. CRANIOCEREBRAL TRAUMA

Donald W. Marion, Michael C. Sharts, and Elizabeth C. Tyler-Kabara

Traumatic brain injury (TBI) is the leading cause of morbidity and mortality in the United States for people between the ages of I and 45 years. An estimated 1.6 million people sustain a TBI each year. Approximately 270,000 must be hospitalized, of whom 52,000 die of their injuries and 80,000 are left with severe neurological disabilities. Another 760,000 are treated and released from emergency departments or clinics, and it is estimated that approximately 400,000 people with mild ot moderate TBI do not even seek medical attention (Sosin, Sniezek, and Thurman 1996). The leading causes of TBI are motor vehicle crashes (MVCs), violence, and falls. Adolescents and older adults are most at risk. Falls are the leading cause of head injury in people 65 years and older, whereas MVCs are the leading cause of head injury in those 5-64 years old. At all ages, males arc at twice the risk of TBI as females. In the United States an estimated *5.3* million people are living with a permanent Tftl-related disability, the direct and indirect costs of which are estimated to exceed $4 billion a yeat (Ktaus and McArthur 1996). TBI-related death rates have been falling in the United States, with one study documenting a 22% decline from 1979 to 1992 (Sosin, Sniezek, and Waxweiler 1995). A significant teduction in MVC-related TBI is primarily responsible. However, some large cities are seeing a rise in gunshot wounds to the head, and deaths from this cause often exceed MVC-related fatalities.

PATHOPHYSIOLOGY

Trauma to the head causes primary injuries, such as skull fractures, cerebral contusions, and hemorrhage, that are a direct physical consequence of the impact. Within hours or days of the injury, secondary injury may also occur and may be *a* major determinant of the patient's ultimate neurological outcome.

TBI is caused by extetnal forces to the head that can be categorized as contact and inettial (Graham et al. 1995). Contact fotces typically cause focal injuties such as skull ftactutes, epidural or subdural hematomas, and contusions. Inertial forces set the head into acceleration (translational ot totational) with ot without a contact fotce. These forces may cause focal or diffuse brain injuries. Inertial forces with pure translational acceleration cause focal injuries such as contracoup contusions, intracctcbral hematomas, and subdural hematomas. Inertial forces with rotational ot angulat acceleration usually cause diffuse injuries and are common with high-speed MVCs. Extetnal signs of trauma such as scalp abrasions, lacerations, and hematomas are common with blunt fotce trauma to the head, but severe TBI can also result solely from acceleration and deceleration forces (e.g., MVC) without scalp injuries.

Skull fractures result ftom an impact to the head that is usually sevete enough to cause at least a brief loss of consciousness. The most common type of skull fracture is a linear fracture, typically over the lateral convexities of the skull. Linear skull fractures usually arc noudisplaced cracks through the skull, although very severe trauma can cause a gap, or diastases, between the fracture edges. Depressed skull fractures, with fragments of the skull pushed into the cranial vault, are most common with blunt force trauma to the head caused by an object with a small surface area, such as a hammer (Figure 56B.1). Severe blunt trauma to the forehead or the occiput can cause fractures through the base

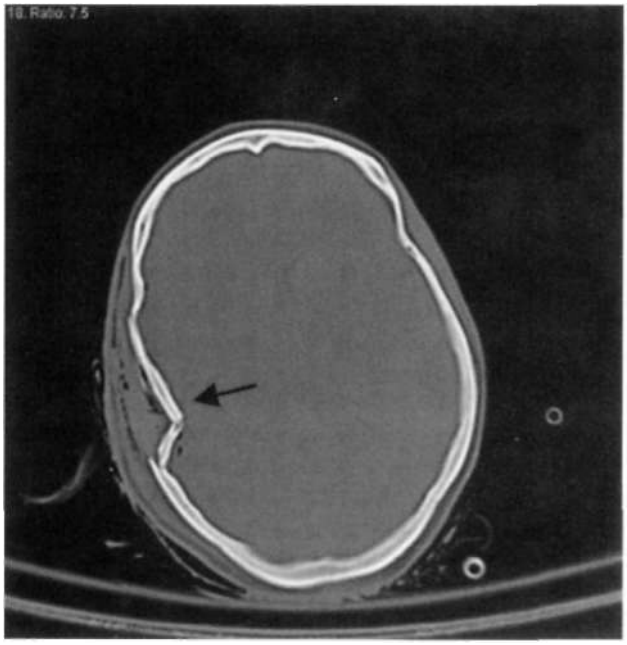

FIGURE 56B.1 A right temporal depressed skull fracture caused by an assault with a hammer. (Axial computed tomography scan, bone window.)

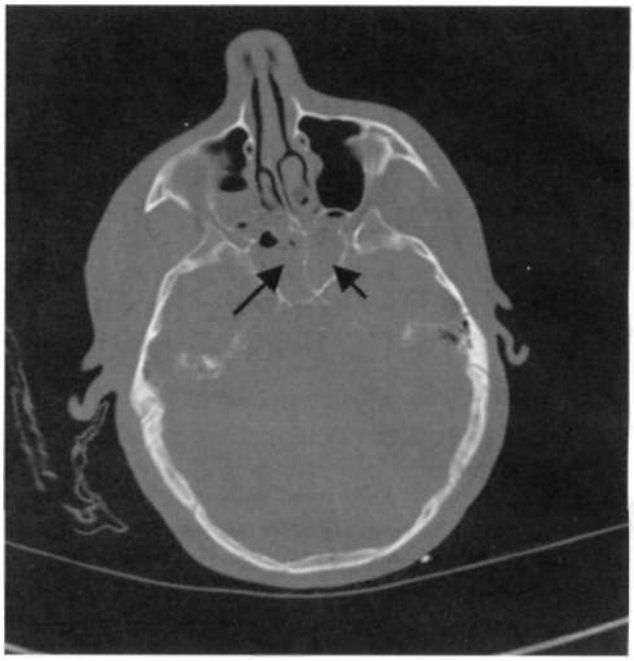

FIGURE S6B.2 Basilar skull fractures through the anterior skull base typically cause tears in the adjacent dura and cerebrospinal fluid rhiuorrhea. Computed tomography scans through the base of the skull may not show the fracture itself, but fluid in the sphenoid sinus *(arrows)* or the other paranasal sinuses is often seen. (Axial computed tomography scan, bone window.)

of the skull. Such basilar skull fractures are most common through the anterior skull base and often involve the cribriform plate, disrupting the olfactory nerves (Figure 56B.2). Posterior basilar skull fractures may extend through the petrous bone and internal auditory canal, thereby damaging the acoustic and facial nerves. The clinical significance of skull fractures is related more to the associated damage of underlying tissues or vessels than to the fracture itself. For example, linear skull fractures involving the squamous portion of the temporal bone often tear the middle meningeal artery, resulting in an epidural hematoma. Depressed skull fractures often are associated with contusions of the underlying brain tissue. If the scalp overlying the depressed skull fragment is lacerated, the depressed fragment of bone may be contaminated with bacteria. Basilar skull fractures often are associated with disruption of the dura underlying the fracture, resulting in a cerebrospinal fluid (CSF) fistulas and leakage of CSF from the nose or ear. Such fistulas are a conduit for bacterial contamination of the intracranial space from the nose, paranasal sinuses, or external auditory canal.

Typical post-traumatic intracranial lesions include hemorrhage, contusions, and diffuse brain injury, ultracrania] hem a to i n as arc classified as epidural, or hematomas that occur between the inner table of the skull and the dura matter; subdural, or hematomas that develop between the inner surface of the dura and the brain surface; and intraparencbymal, or hemorrhage that occurs in the brain substance itself. The most common intracranial hematoma is a subdural hematoma, found in 20-25% of all comatose patients with TBI {Figure 56B.3). The hematoma is thought to result from tearing of bridging veins over the surface of the cortex or from disruption of major venous sinuses or their tributaries. A subdural hematoma typically expands over most of the cerebral convexity. Spread to the contralateral hemisphere is limited b\ the Jural reflections of the falx cerebri. Because subdural hematomas often are associated with damage to the underlying brain tissue, swelling of the cerebral hemisphere also is common. In one scries, underlying contusions were observed in 67% of those with subdural hematomas. Subdural hematomas may be acute, subacute, or chronic, and each has a characteristic appearance on computed tomography (CT): Acute hematomas arc bright white, subacute lesions are isodense with brain tissue and often overlooked because of this, and chronic subdural hematomas are hypodense relative to the brain.

F.pidural hematomas arc located between the inner table of the skull and the dura and usually result from a tear of the middle meningeal artery or one of its branches caused by a skull fracture. They are less common than subdural hematomas and are found in 1-2% of all patients with TBI and 8-10% of those rendered comatose by the injury. The majority of epidural hematomas are located in the temporal or parietal regions, but they may also occur over the frontal or occipital lobes and rarely in the posterior fossa. They appear as hyperdense mass lesions on CT. Unlike that of

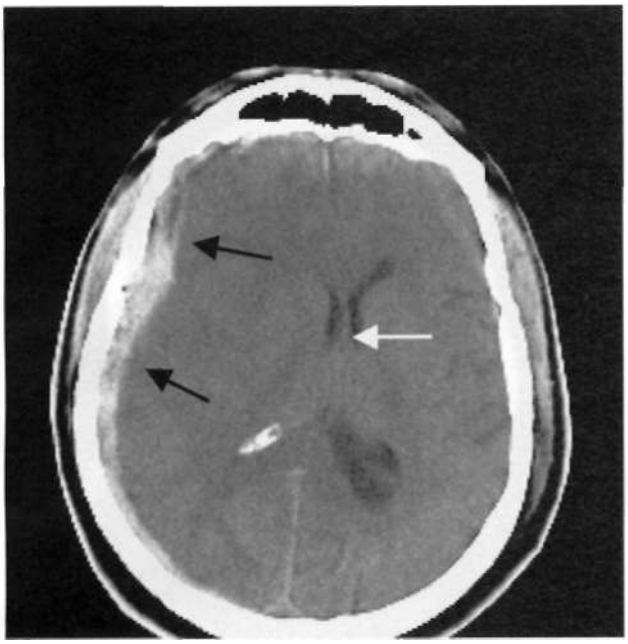

FIGURE 56B.3 An acute subdural hematoma typically spreads over the entire surface of the hemisphere *(black arrows)* and is associated with swelling of the hemisphere. As a result, shift of the midline structures away from the side of the hematoma may be greater than the thickness of the hematoma *{white arrow).* (Axial computed tomography scan.)

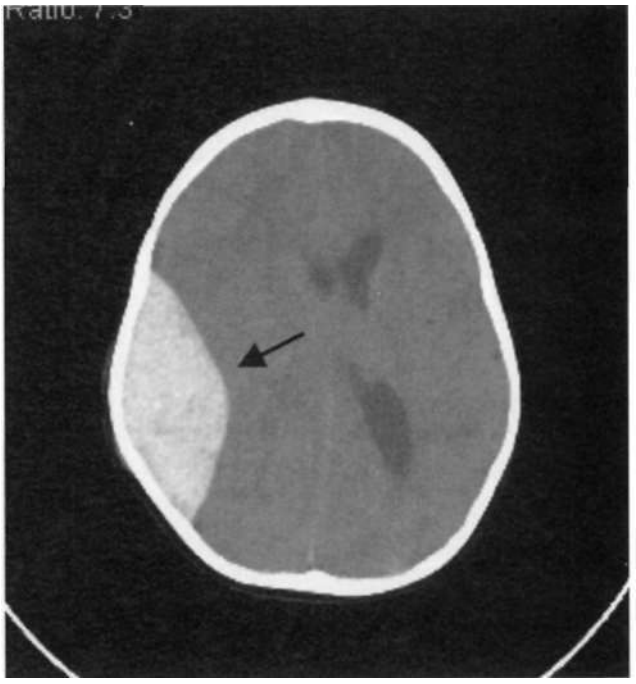

FIGURE 56B.4 Epidural hematomas have a lens-shaped appearance and smooth inner border because as they enlarge, they strip the dura away from the inner table of the skull. (Axial computed tomography scan.)

subdural hematomas, their spread is limited by the suture lines of the skull, where the dura is extremely adherent. Because there normally is no epidural space, the hematoma must sttip the dura away from the inner tahle of the skull as it enlarges, and this gives the classic biconvex or lenticular appearance (Figure 56B.4). Presumably because of the softer and more deformable skull in infants and toddlers and because of the very tight adherence of the dura to the skull in those over age 60 years, epidural hematomas are uncommon in these two age groups.

Ttaumatic subarachnoid hemorrhage (SAH) is common after severe TBI but does not produce a hematoma or mass effect (Scrvadci et al. 2002), It may be associated with a greater risk for post-traumatic vasospasm, however (Martin et al. 1992). Intraparenchymal hematomas occur after particularly severe TBI. They usually are associated with contusions of the surrounding brain tissue. Durct hemorrhage is hemorrhage into the base of the pons or midbrain thought to result from disruption of the perforating arteries at the time of uncal herniation. Brainstem hemorrhage such as this almost always results in death or vegetative survival.

Contusions are heterogeneous lesions consisting of areas of punctate hemorrhage, edema, and necrosis and are found in 20-25% of patients with severe TBI. There may be multiple contusions, often associated with other intracranial lesions. Contusions evolve over time and may he small or not apparent on the initial CT. They appear as areas of punctate hyperdensities (hemorrhages) with surrounding hypodensity (edema; Figure 56B.5A). Local neuronal damage and hemorrhage cause edema that may progress over 3-4 days. As contusions evolve they usually coalesce and appear more like intracerebral hematomas (Figure 56B.5B). Depending on size and location, they may cause significant mass effect with resultant midline shift, subfalcine herniation, or transtentorial herniation. Contusions most often occur in the inferior frontal cortex and the anterior temporal lobes. The surface of the inner table of the skull is very irregular at these locations, and shifting of the brain over the irregular skull at the time of impact causes the contusions. Direct blunt force trauma to the head also may cause a contusion in the brain tissue underlying the point of impact. If the head is in motion before impact with a rigid surface, contusions often arc found on the side of the brain opposite to the point of impact, and these contusions arc called contracoup contusions.

In high-speed MVCs where there is a severe rotational component to the injury, lacerations or punctate contusions at the interface between the gray and white matter may occur and are ofren called diffuse axonal injury (DAI; Figure 56B.6). Such punctate contusions are believed to result from the difference in density between the gray matter and white matter and the resulting difference in centripetal force associated with a rotational vector of injury. Nearly half of all severely head injured patients and a third of those who die have DAI, and this injury is a

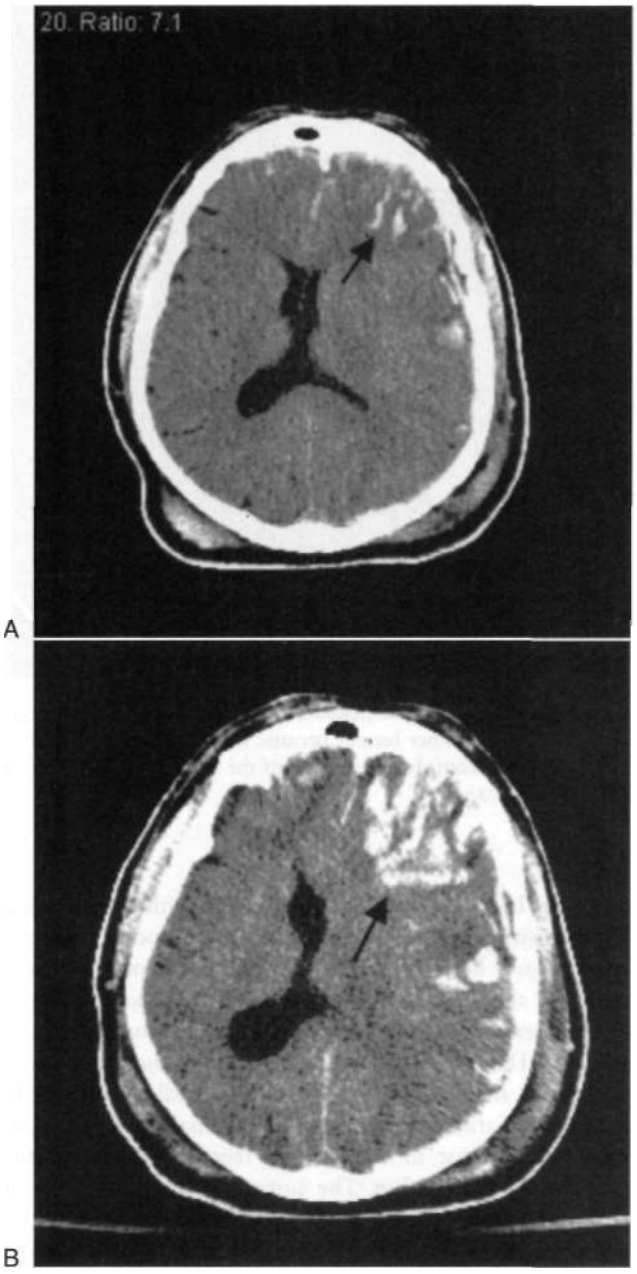

FIGURE 56B.5 Contusions most often occur in the inferior temporal and frontal *(arrow)* lobes. (A) In the first few hours after injury, they may appear only as punctate areas of hemorrhage mixed with edematous brain. But within 24-48 hours after injury hemorrhage may continue and cause significant enlargement of the contusion .mil hematoma. At its hours after injury this patieill had a sudden increase in 1CP and deterioration in the level of consciousness. (B) A repeat computed tomography scan revealed enlargement of the frontal contusion with mass effect, and the patient was taken to surgery for evacuation of the lesion. (Axial computed tomography scans.)

common cause of persistent vegetative state or prolonged coma. One study of 42 consecutive patients with TBI in a persistent vegetative state found evidence of DAI on magnetic resonance imaging in all of these patients. The

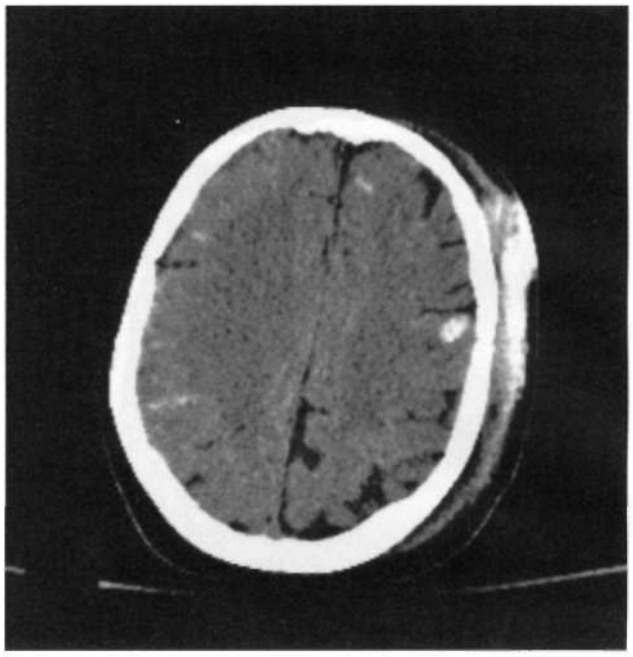

FIGURE 56B.6 Severe rotational vectors of force may cause diffuse punctate hemorrhages at the gray-white junction of the cortical mantle, as in this victim of a high-speed motor vehicle crash. (Axial computed tomography scan.)

most common locations of the lesions were the corpus callosum and the dorsolateral rostral brainstem. In the past, investigators thought that the mechanical disruption at the time of trauma was the sole cause of DAI, but recent evidence suggests that in some cases DAI may be a secondary manifestation of trauma (Povlishock and Christman 1995). They identified cases in which the histological footprints of DAI, such as fragmentation of axons and axonal swelling, do not appear until 24-48 hours after injury.

Post-traumatic intracranial lesions cause neurological deficits through direct and, in some cases, indirect mechanisms. Contusions and intraparenchymal hemorrhage destroy brain tissue •*Mtd* thereby cause neurological deficits directly related to the function of the tissue damaged. Another very important mechanism for temporary or permanent neurological dysfunction is brain herniation (Figure 56B.7), including uncal herniation. The intracranial contents are divided into compartments as a result of semirigid Jural reflections. The anterior and middle cranial fossae are separated from the posterior cranial fossa by the tentorium cerebelli. The brainstem, and specifically the miJbrain, traverses an opening in the anterior central portion of this partition (tentorial foramen). The medial portion of the temporal lobe, or uncus, lies on either side of this foramen. Because most traumatic injuries of the brain, such as hematomas or contusions, tend to occur over the lateral surfaces of the brain, and because the extreme lateral surface of the brain is the rigid skull, such lesions tend to

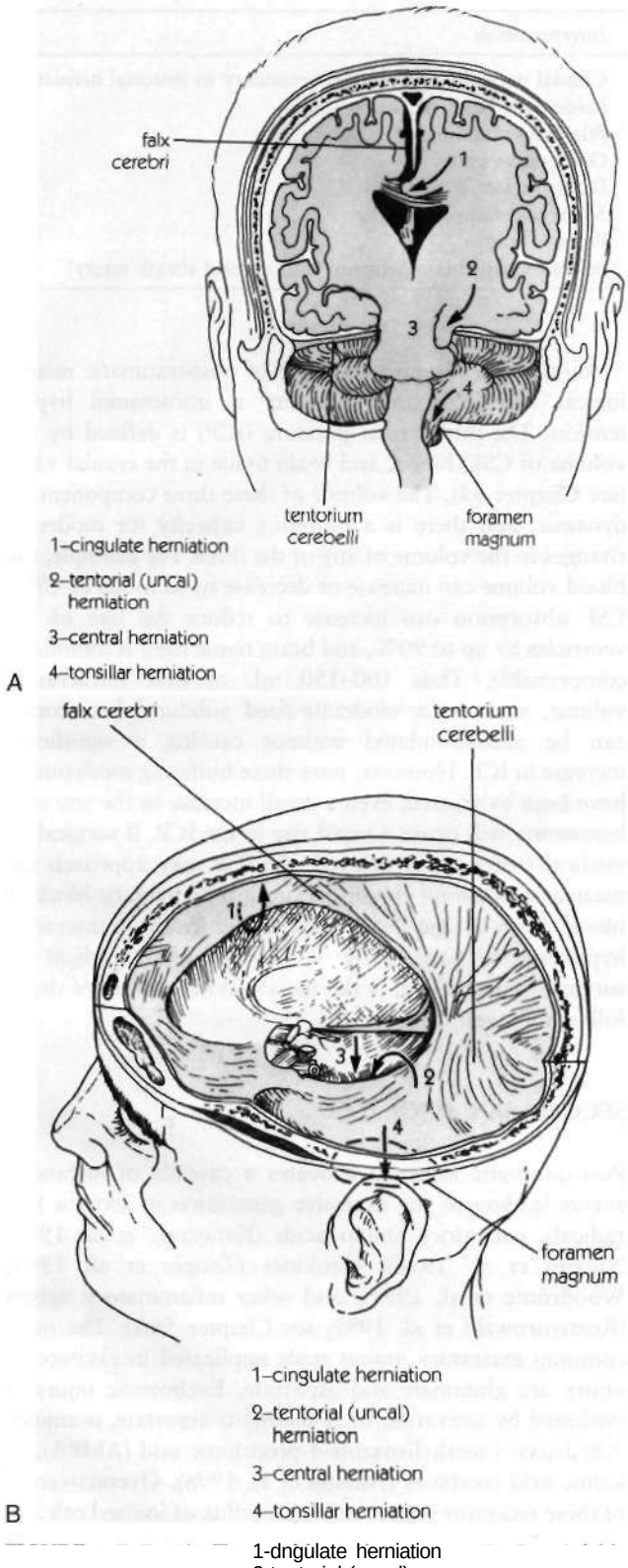

FIGURE 56B.7 (A) Types of brain herniation. (B) Dura] folds in the cranial cavity and associated herniation sites. (Reprinted with permission from Rengachary, S. S. & Duke, D. E. 1994, "Increased intracranial pressure, cerebral edema, and brain herniation," in *Principles of Neurosurgery,* eds S. S. Rengachary & R. H. Wilkens, McGraw-Hill, New York.)

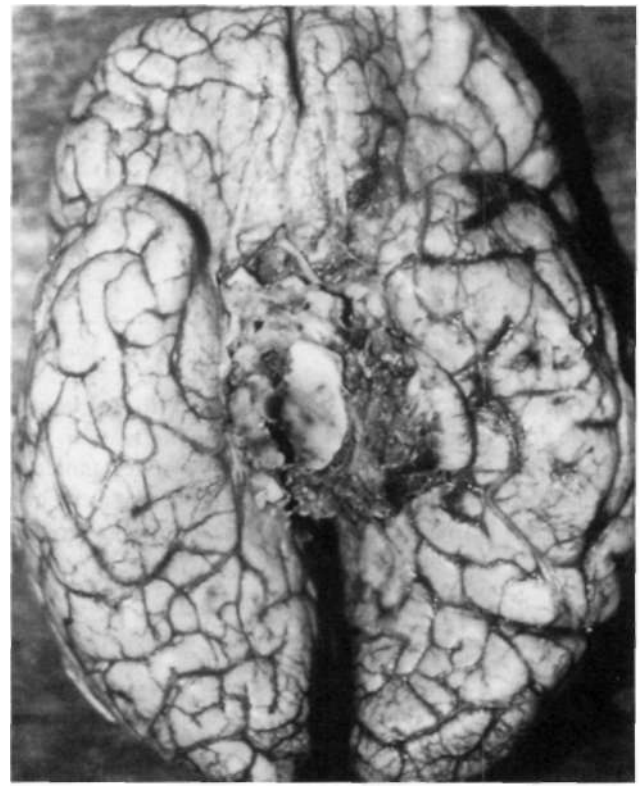

FIGURE S6B.8 Inferior view of the brain of patient with left cerebral hemisphere injury and swelling, showing the results of tentorial herniation, including the damage to the uncus and the hippocampus. Brainstem distortion and secondary hemorrhage (Duret's) have also taken place. (Reprinted with permission from the American Association of Neurologic Surgeons, Joint Section on Neurotrauma and Critical Care. 1995, *Guidelines for the Management of Severe Head Injury,* Brain Trauma Foundation, New York.)

depress the brain medially. As a result, a subdural hematoma over the surface of the temporal lobe, or hemorrhagic contusion of the temporal lobe itself, tends to displace the medial portion of the temporal lobe (uncus) into the tentorial foramen, compressing the midbrain (Figure 56B.8). Neurons that are part of the reticular activating system reside in the midbrain. At the base of the midbrain are the crus cerebri, carrying pyramidal fibers from the cortex, and the third cranial nerves, which exit the midbrain through the interpeduncular cistern. Compression of the midbrain from uncal herniation causes loss of consciousness by damaging the reticular activating system, pupil dilation and loss of the light reflex by stretching the third cranial nerve and its associated parasympathetic fibers (Table 56B.1), and abnormal posturing responses in the contralateral arm and leg from damage to the pyramidal fibers in the crus cerebri.

Medial displacement of a cerebral hemisphere caused by hemispheric swelling or a subdural or epidural hematoma also can cause herniation of the cingulate gyrus under the

Tabic 56B.1: Interpretation of pupillary findings in head-injured patients

Pupil size	*Light response*	*interpretation*
Unilaterally dilated	Sluggish or fixed	Cranial nerve HI compression secondary to tentorial herniation
Bilaterally dilated	Sluggish or fixed	Inadequate brain perfusion Bilateral cranial nerve III palsy
Unilaterally dilated or equal	Cross-re active (Marcus Gunn)	Optic nerve injury
Bilaterally constricted	May be difficult to determine	Drui's (opinio) Metabolic encephalopathy Pontine lesions
Unilaterally constricted	Preserved	injured sympathetic pathway (e.g., carotid sheath injury)

falx cerebri. This usually does not lead to permanent neurological dysfunction. However, the herniation may occlude one of the major intracranial arteries (anterior cerebral with cingulated herniation and posterior cerebral with uncal herniation), causing a secondary cerebral infarction (Figure 56B.9).

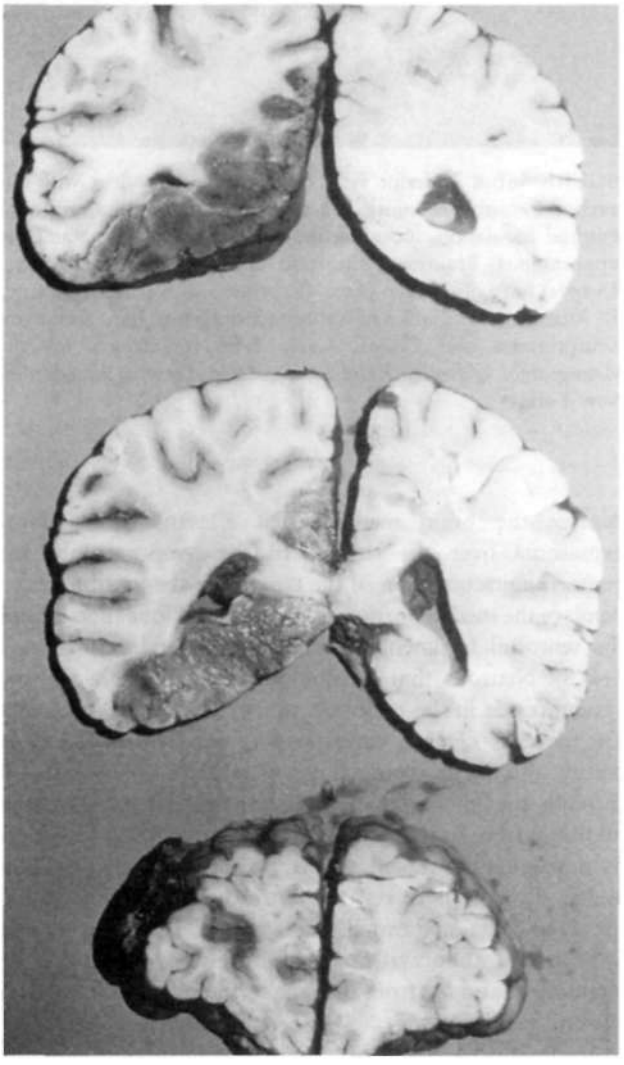

FIGURE 56B.9 Infarction of the occipital lobe as a result of tentorial herniation compressing the posterior cerebral artery.

Another very important cause of post-traumatic neurological morbidity and mortality is intracranial hypertension. The intracranial pressure (ICP) is defined by the volume of CSF, blood, and brain tissue in the cranial vault (see Chapter *65).* The volume of these three components is dynamic, and there is a buffering capacity for moderate changes in the volume of any of the three. For example, the blood volume can increase or decrease by as much as 40%, CSF absorption can increase to reduce the size of the ventricles by up to 90%, and brain tissue itself is minimally compressible. Thus 100-150 mL of new intracranial volume, such as a moderate sized subdural hematoma, can be accommodated without causing a significant increase in ICP. However, once these buffering mechanisms have been exhausted, even a small increase in the size of a hematoma will cause a rapid rise in the ICP. If surgical or medical treatment is delayed, the ICP may approach the mean arterial blood pressure, causing a hydrostatic block of blood flow to the brain and brain death. Intracranial hypertension, particularly if refractory to medical or surgical management, is the most common cause of death following severe TBI,

SFCONDARY INJURY

Post-traumatic ischemia activates a cascade of metabolic events leading to the excessive generation of oxygen free radicals, excitatory amino acids (Katayama ct al. 1990; Nilsson et al. 1996), cytokines (Taupin et al. 1993; Woodroofe et al. 1991), and other inflammatory agents (Rostworowski et al. 1997; see Chapter 56A). The most common excitatory amino acids implicated in exeitotoxic injury are glutamatc and aspartate. Fxcitotoxic injury is mediated by activation of N-methyl-D-aspartate, a-amino-3-hydroxy-5-mcthylisoazole-4-proprionic acid (AMPA), or kainic acid receptors (Nilsson et al. 1996). Overactivation of these receptors causes excessive influx of ionized calcium into the cytosol, and high levels of ionized intracellular calcium play a central role in neurodegcneration after central nervous system trauma (Fineman et al. 1993). Post-traumatic nonischemic events such as an increase in intracellular free $Ca^{'+}$, through receptor-gated or voltage-dependent ion channels, also induce the release of oxygen

free radicals from mitochondria. Excessive levels of highly reactive oxygen free radicals cause damage by lipid peroxidation of cell membranes, oxidation of intracellular proteins and nucleic acids, and activation of phospholipases A_2 and C, which hydrolyze membrane phospholipids, releasing arachidonic acid. The subsequent generation of excessive free fatty acids, leukotrienes, and thromboxane B_2 from the arachidonic acid cascade has been associated with neurodegencration and poor outcome after experi mental TBI. Inflammatory cytokines, particularly interleukin (IL)-l, IL-6, and tumor necrosis facror-«, also are produced in excess after TBI. Post-traumatic activation of microglia has been found to be an important source of these cytokines in animal models (Woodroofe et al, 1991). IL-1 and IL-6 induce an exuberant cellular inflammatory response thought to be responsible for astrogliosis, edema, and tissue destruction (Rostworowski et al. 1997; Schoettle et al. 1990).

High levels of extracellular potassium also are caused by TBI and result in an imbalance of intracellular and extracellular K^+, disruption of the Na-K^+-ATPasc cell membrane regulatory mechanisms, and subsequent eel! swelling. Clearance of excessive extracellular K^+ by astrocytes has been implicated as a cause of astrocyte swelling (Kimelberg 1995). In addition, high levels of extracellular K^+ have been implicated as the cause of widespread neuronal depolarization and spreading depression that has been observed after experimental TBI. Potassium also stimulates increased oxygen uptake in glial cells, potentially depriving adjacent neurons of oxygen. Severe TBI also causes a significant reduction in extracellular magnesium (Mg^{2+}) levels, thereby impairing normal glycolysis, cellular respiration, oxidative phosphorylation, and the biosyntheses of DNA, RNA, and protein. Because Mg^{2+} competes with $Ca^{24"}$ at voltage-gated cell membrane-associated Ca^{2+} channels, reduced levels of Mg^{2+} cause an abnormal influx of Ca^{2-r} into the cell.

PREHOSPITAL TRAUMATIC BRAIN INJURY MANAGEMENT

The acutely traumatized brain is vulnerable to further injury from systemic hypotension, cerebral hypoperfusion, hypercarbia, hypoxemia, and elevated ICP. Prevention of these physiological insults is essential for limiting secondary brain injury. Tbe initial prehospital evaluation of trauma patients should always begin with securing a patent airway and restoring normal breathing and circulation. Comatose patients usually benefit from early endotracheal intubation, but in the field this should be attempted only by experienced emergency medical providers. Securing and maintaining an airway is essential to providing optimal oxygenation and ventilation, and in patients with severe TBI early intubation has been shown ro reduce mortality (Winchell and Hoyt 1997). In patients with a Glasgow Coma Scale (GCS) score of 8 or less, those who were successfully intubated in the field had a mortality rate of 36%, compared with a mortality rate of 57% for a similar group of patients who did not have endotracheal intubation until they arrived at the trauma center. Orotracheal intubation usually is the easiest and safest method of securing an airway. Most emergency medical personnel are trained and experienced with this method of endotracheal intubation. Nasotracheal intubation is an altemarive route that may be necessary for those with severe maxillofacial trauma. It is less desirable, however, because it is a blind procedure. Irritation of the nasal passageways can cause a surge in blood pressure and ICP, and inadvertent passage of the tube into the brain is a possibility for those with severe anterior skull base fractures. A third alternative for securing the airway is the laryngeal mask airway, an easily learned and rapidly applied device that has undergone successful field trials (Sasada and Gabbott 1994). It does not protect against aspiration, however, and high airway pressures cannot be achieved with its use. A surgical airway, or cricothyroidotomy, should be considered only if all other attempts to secure an airway have failed and should be attempted only by experienced providers.

Before intubation the patient should be sedated and pharmacologically paralyzed because irritation of the oropharynx typically causes transient hypertension, tachycardia, ICP elevation, and agitation that can interfere with the procedure. Sedatives most commonly used include fentanyl, a short-acting opioid agonist that produces analgesia and sedation. The usual dosage is 3-5 pg per kilogram given intravenously 3 minutes before intubation, Etomidate is an alternative to opioids that provides adequate sedation bur is less likely to cause hypotension. Thiopental, an ultra-short-acting barbiturate, is preferred by some because its short duration of action makes it less likely to mask the patient's neurological status once he or she reaches the trauma center. However, it also is more likely than other agents to cause hypotension. Propofol has recently been introduced as a rapid onset, short-duration sedative that is very effective and unlikely to cause hypotension but is also very expensive. Neuromuscular blocking agents commonly used for endotracheal intubation include succinylcholine (1.5 mg per kilogram intravenously), which has the advantage of rapid onset, complete reliability, and a very short duration of action. This latter attribute is particularly important in the prehospital setting, where failed attempts at intubation are not uncommon. Vecuronium (0.01 mg per kilogram intravenously) is an alternative paralytic agent that has the theoretical advantage of being a nondepolarizing muscle relaxant. But because its duration of action is much longer (1-2 hours), it is less forgiving of failed attempts at intubation. Table 5 (SB. 2 si lows a recommended rapid sequence intubation pathway.

Tabic 56B.2; Recommended rapid sequence induction for the severely head-injured patient

1. Preoxygenation: 100% oxygen for 5 minutes or fout vital capacity breaths.
2. Presentment: fentanyl (3-5 ug/kg IV).
3. Wait 2-3 minutes if possible; continue preoxygenation.
4. Paralysis and sedation; succinylcholine (1.5 mg/kg IV).
5. Intubate with in-line cervical spine immobilization.
6. Positive-press LI re ventilation and consider rcparalysis with vecuronium if prolonged transport time is anticipated.

Supplemental oxygen should be provided before and immediately after intubation. Ventilatory rates of 10-12 breaths per minute for adults, 20 breaths per minute for children, and 25 breaths per minute for infants should provide adequate oxygenation. Hyperventilation should be avoided unless there is clear evidence of neurological deterioration during evaluation and transport. Aggressive hyperventilation can cause cerebral vasoconstriction, further reducing cerebral blood flow and potentially causing or worsening cerebral ischemia.

Rapid fluid resuscitation and restoration of a normal blood pressure also is critical in the prehospital setting because hypotension, and specifically a systolic blood pressure of less than 90 mm Hg, has been associated with a doubling of the mortality rate after severe TBI. The most likely cause of hypotension is hemorrhage, usually in the abdomen or chest, so hypovolemia should be assumed. Lactated Ringer's or normal saline solutions should be infused through large-bore intravenous catheters as quickly as possible until normotension is achieved. Recent preclinical studies suggest that hypertonic saline may be more effective than isotonic solutions for rapid volume resuscitation (Anderson ct al. 1997; Doyle, Davis, and Hoyt 2001), although several small clinical trials have not been convincing (Shack ford et al. 199S; Si in ma et al. 19'JSi.

All patients with a severe TBI should be treated as though they have a spinal fracture until adequate spinal evaluation proves otherwise. Those who survive long enough to reach the emergency department have a 2-6% chance of having a cervical spine fracture. Of greater concern, however, is that iatrogenic spinal cord injury during transport of the trauma patient is estimated to be the cause of up to 25% of all posttraumatic spinal cord injuries (Diliherti and I.iiidsey 1992). At the scene of the accident and after respiratory and hemodynamic stabilization, the patient should be placed in a neutral position on a flat, hard surface. If immediate endotracheal intubation is necessary, one person should provide in-line cervical spine immobilization while the second person intubates the patient. A rigid cervical spine collar should be placed as soon as possible. Next, the patient should be placed on a backboard, and the cervical spine can then be further immobilized with a buttress of foam or towels on either side of the bead. The patient should then be strapped to the board in multiple locations to prevent movement during transport.

Organization of emergency medical services and regional trauma programs has improved outcomes for trauma patients, and especially those with severe TBI. Designation as a level I or II trauma center by the American College of Surgeons Committee on Trauma or a state health department ensures that immediate neurosurgical coverage will be available when the patient arrives. Therefore every effort should be made to transport the patient with severe trauma directly to a designated trauma center. In some cases, however, the patient may need respiratory or hemodynamic stabilization .it .1 ne.irbv emergency department en route to the trauma center if an adequate airway or venous access cannot be obtained in the field.

EMERGENCY DEPARTMENT MANAGEMENT

Upon arrival at the emergency department of the trauma center the patient undergoes a thorough physical and radiological evaluation aimed at detecting all life-threatening injuries. The Advanced Trauma Life Support protocol usually is followed and provides a comprehensive routine that has proven successful in quickly identifying all major injuries (Subcommittee on Advanced Trauma Life Support of the American College of Surgeons Committee on Trauma 1993). As soon as the patient is brought into the trauma bay, emergency medical personnel provide a brief and concise review of their prehospital assessment and management, including mechanism of injury, stabilizing maneuvers, medications given, initial vital signs, GCS, and hemodynamic stability during transport. The airway is reassessed, and the need for endotracheal intubation carefully reconsidered. For those intubated in the field, proper placement of the endotracheal tube should be verified both clinically and radiographically. Once the airway is secure and adequate oxygenation is verified with the use of percutaneous oxygen saturation monitors or arterial blood gas analysis, two large-bore intravenous catheters should be inserted to provide sufficient venous access for high-volume fluid resuscitation. Isotonic saline solutions are infused to continue the volume replacement that usually was started in the field. Any life-threatening injuries such as overt hemorrhage, tension pneumothorax, or cardiac tamponade should be treated immediately upon discovery. A brief neurological examination is done and should include the GCS (Table 56B.3), pupillary size and reaction to light, and the symmetry and extent of extremity movements. The head is palpated for any fractures, lacerations, or penetrating wuunds. Lacerations are probed gently to evaluate for a depressed skull fracture or foreign body. Large lacerations should be compressed with pressure dressings or temporarily sutured to prevent further hemorrhage. Careful inspection of the head should determine the presence or absence of hemotympanum,

Tabic 56B.3: Glasgow coma scale

Speech	
Alert, oriented, and conversant	5
Confused, disoriented, but conversant	4
Intelligible words, not conversant	3
Unintelligible sounds	2
No verbalization, even with painful stimulus	1
Eye opening	
Spontaneous	4
To verbal stimuli	3
To painful stimuli	2
None. tun with painful stimuli	1
Motor	
Follows commands	6
Localizes painful stimulus	5
Withdraws from painful stimulus	4
Flexor posturing with central pain	3
F,xtensor posturing with central pain	2
No response to painful stimulus	1

Maximum sum score, 15; minimum score, 3. If asymmetrical motor or eye opening, the higher score is used.
Source: Teasdale, G. *&c* Jennett, B. 1974, "Assessment of coma and impaired consciousness. A practical scale," *Lancet,* vol. 2, pp. 81-84,

periorbital or mastoid ccchymosis, and CSF rhinorrhea or otorrhea.

During this primary examination there should be continuous catdiac and oxygen saturation monitoring and frequent measurements of the blood pressure. A Foley catheter should be placed to help monitor the fluid status, and an orogastric tube is inserted and connected to suction to decompress the stomach. Blood specimens are obtained and analyzed for glucose, electrolytes, complete blood count, platelets, and the prothrombin time, partial thromboplastin time, and international normalized ratio. Type and cross-match of a blood specimen should be considered and an arterial blood gas obtained. A serum and urine toxicology screen may be obtained if alcohol or substance abuse is a possibility, and a pregnancy test should be obtained for all women of childbcaring age.

Initial radiographic evaluation includes chest, pelvis, and lateral cervical spine films, which usually are obtained in the trauma bay during the primary survey. If the lateral cervical spine radiograph fails to visualize ihe lower ccr\ ical spine, a swimmer's view may be obtained, or this area can be imaged with axial CT. Once all life-threatening injuries have been identified and stabilized, all patients with suspected head injuries should undergo a CT scan of the head. Images should be obtained from the C2 vettebrae to the vertex at a minimum of 10-nini intervals. If the head CT does not reveal a surgical intracranial mass lesion, CT scans of the chest and abdomen may be obtained to detect occult hemorrhage in these cavities. However, if a surgical mass lesion is detected on the head CT scan, further imaging studies are postponed and the patient is taken directly to surgery for evacuation of the intracranial lesion. Often a diagnostic peritoneal lavage is done during the craniotomy to detect abdominal bleeding. Conversely, if hemodynamic instability necessitates that the patient be taken for emergent laparotomy or thoracotomy befotc a head CT scan can be obtained, and if intracranial injury is suspected, several diagnostic procedures can be performed in the operating room. An air ventriculogram will detect most large hematomas. With the patient in the supine position, a right coronal ventriculostomy is inserted. Preparations ate made fot an area postrema skull radiograph. fust before the radiograph is obtained, 3 ml, of air is injected into the ventticles. The air provides an outline of the ventricles, and distortion or shift of that outline suggests the ptesence and location of a hematoma. An alternative to obtaining an air ventticulogram is placement of diagnostic burr holes. This procedure is most appropriate if there are lateralizing neurological deficits, especially a unilateral fixed and dilated pupil. The initial butr hole is placed over the temporal lobe on the side ipsitateral to the dilated pupil. If no clot is derected, burr holes may then be placed over the frontal and parietal lobes. If a hematoma is encountered, the burr hole is enlarged to a craniotomy and the clot evacuated.

DEFINITIVE TREATMENT

The immediate concern in TBI is to determine the need tor craniotomy to evacuate an intracranial mass lesion such as a hematoma or contusion. In a subgroup of young patients, sutgery for decompressive craniotomy or temporal or frontal lobectomy may also be considered to treat tefractory intracranial hypertension. In addition to effectively treating elevated ICP, evacuation of post-traumatic mass lesions can prevent or reverse uncal herniation. The subsequent goal is to enhance cetebral perfusion and prevent ot limit secondary brain injury.

A reliable postres us citation GCS and assessment of pupil size and reactivity are critical for determining the severity ot the brain injury and for surgical decision making. CT scans of the head arc obtained to identify post-traumatic intracranial lesions, brain swelling, patency of the basal cisterns, and other charactetistics that will guide subsequent treatment. The need for a craniotomy is best determined by consideration of not only the CT images but also the post resuscitation GCS score and pupil status. For example, a patient with a moderate-sized subdural hematoma who has normal pupil size and reactivity and is able to follow commands might safely be treated nonoperatively. Convctscly, an elderly patient with fixed and dilated pupils and a GCS of 3 or 4 is unlikely to benefit from surgery regardless of bis or her CT findings. Thus when one is considering surgical evacuation of an acute subdural hematoma, scvetal factors must be weighed, including size and location of the hematoma, the presence and extent of

an underlying contusion or brain swelling, and the neurological examination. Deterioration of the neurological examination, particularly a decline in mental status, suggests enlargement of the hematoma, and a new CT scan should he promptly obtained. Hematomas less than 10 mm thick that cause less than 5 mm of midline shift usually can he observed, especially if they do not involve the middle cranial fossa (Servadei et al. 1998). If nonoperative management is elected in patients harboring an intracranial hematoma, they should be observed in the intensive care unit (ICU) with frequent neurological assessments. If the patient is unable to follow commands, ICP monitoring is recommended.

The classic presentation of a patient with an epidural hematoma is an initial period of unconsciousness immediately after impact to the head, followed by the so-called lucid interval in which the patient regains consciousness for a few minutes to an hour or more and then lapses into a coma. Less than a third of patients with epidural hematomas actually have a lucid interval, and most either remain conscious after the injury (smaller clots) or remain comatose.

Hematomas compressing the temporal lobes are particularly ominous and can rapidly cause uncal herniation with minimal enlargement. A lower threshold for surgical evacuation of these clots compared with that for hematomas in other locations is warranted. If the size of the clot is small enough not to necessitate evacuation, it should be observed with frequent CT scans in the first several days after injury. An increase in ICP may not always occur with enlargement of middle fossa hematomas, even those large enough to cause herniation, so ICP monitoring should not be relied upon to follow these clots.

Initial signs and symptoms of contusions vary greatly depending on the size, location, and associated lesions. Patients with small contusions may complain only of a headache and may have no symptoms. A small contusion may cause focal neurological symptoms if it is located in an eloquent area of the brain, such as the speech or motor areas. Larger contusions, particularly those involving the frontal lobes, typically cause increased ICP and coma. Patients with small or deep-seated contusions without mass effect initially can be managed nonoperatively. They should be followed closely with serial CT scans because there is a 20-30% chance that the contusion will enlarge in the ensuing 24-48 hours. Patients who are not following commands should have ICP monitoring. Like hematomas in the middle cranial fossa, contusions of the temporal lobes should be followed very closely with CT imaging. Enlargement of a temporal contusion to the point of uncal herniation can occur without a significant rise in ICP, and a low threshold for surgical evacuation of these lesions is warranted (Figure 56B.10). Unilateral fronral or temporal lobectomies usually are well toletatcd, do not cause measurable neurological deficits, and are effective in providing space for further swelling of the brain.

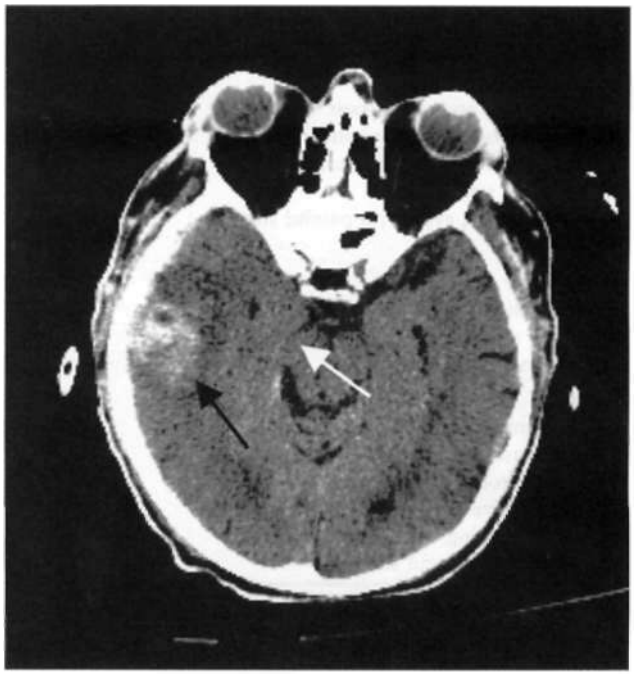

FIGURE 56B.10 Temporal lobe contusions *(black arrotv)* must be followed closely because even a slight enlargement can cause uncal herniation *(white arrow),* often without an increase in the intracranial pressure. (Axial computed tomography scan.)

CRITICAL CARE

In the ICU the primary goal is to prevent cerebral ischemia and thereby limit secondary brain injury. The most common potentially preventable causes of secondary injury are hypotension, hypoxia, and intracranial hypertension. It follows that optimal critical care of the patient entails comprehensive physiological monitoring to allow rapid detection and treatment of these physiological insults. Most comatose patients with TBI benefit from endotracheal intubation and mechanically controlled ventilation. Mechanical ventilation also should be considered for those with less severe TBI if they have pulmonary contusions or other causes of compromised respiration. Ventilator rates usually are set to provide an arterial PCO2 of approximately 35 mm Hg and the fraction of inspired O2 adjusted to provide an arterial P02 of 100 mm Hg.

Physiological Monitoring

The continuous monitoring of the end-tidal Pco_2 and frequent arterial blood gas analyses allow early detection of deterioration of the ventilatory status and appropriate adjustments of the ventilator. Continuous monitoring of oxygen saturation using pulse oximetry also is recommended. Continuous blood pressure monitoring is best accomplished with an indwelling arterial catheter fluid

coupled to a pressure transducer. The catheter is most commonly inserted into the radial artery and can also be used to obtain arterial blood samples for blood gas analysis. A common cause of hypotension after trauma is hypovolemia, which may result from overt hemorrhage usually detected early after injury, occult hemorrhage that may not be recognized for several hours or days, or soft tissue inflammation and swelling. Central venous pressure monitoring therefore should be considered for patients with severe TBI, especially those with significant non-central nervous system injuries. Indwelling subclavian or interna! jugular venous catheters coupled to pressure transducers are inserted for this purpose. In older adults or those with severe pulmonary contusions, pulmonary artery catheterization with a Swan-Ganz catheter may allow more accurate determinations of intravascular volume. Urine output monitoring also is essential for determining the patient's fluid status, so all of these patients should have an indwelling Foley catheter.

Continuous 1CP monitoring is essential for all patients who have a severe TBI and an abnormal CT scan of the head because 53-63% of these patients develop intracranial hypertension. Severe TBI is defined as a GCS of 3-8 and inability to follow commands. Comatose patients with TBI who arc older than 40 years and have unilateral or bilateral motor posturing or a systolic blood pressure less than 90 mm Hg also benefit from ICP monitoring even if their initial CT scan is normal. A ventricular catheter fluid coupled to an external strain gauge transducer is the gold standard against which all other ICP monitors are compared. It is not only accurate and reliable but also very inexpensive compared with newer self-contained pressure-sensing devices. Ventricular pressure monitoring also is considered more reflective of global ICP than subdural, subarachnoid, or epidural pressure measurements. Catheters placed in these extracerebral spaces arc more prone to occlusion and typically record a pressure that is lower than the global ICP because of the effects of compartmentalization. Other advantages of the ventriculostomy method of ICP monitoring are that the system can be re-zeroed after it has been inserted, something that is not possible with most of the newer self-contained devices, and CSF can be withdrawn to treat intracranial hypertension. The overall complication rate for ventricular ICP monitoring is 7.4% (infection, 6.3%; hemorrhage, 1.4%), and there is some evidence that the infection rate significantly increases for catheters that remain in place for more than 5 days.

Alternatives to the ventriculostomy technique of ICP monitoring have been developed that provide accurate measurements of global ICP, arc easier to insert, and may be associated with a lower complication rate. They include devices that contain a pressure-sensing transducer in the tip of the catheter that uses strain gauge or fiberoptic technology. These pressure sensors provide reliable ICP measurements even if they are inserted into the white matter and often arc used when it is difficult to insert a ventricular catheter because of small or collapsed ventricles. The primary disadvantage is that CSF drainage is not possible. They can be calibrated only once, before insertion, and some of the devices have been shown to have as much as 1-2 mm Hg of measurement drift per day.

The cerebral perfusion pressure (CPP) is a calculated physiological parameter that is used to describe actual cerebral perfusion and is defined as the difference between the mean arterial pressure (MAP) and the ICP. Some have suggested that maintaining a CPP above a certain threshold is more important than any particular MAP or ICP.

The adequacy of cerebral oxygenation can be assessed using brain tissue po_2 monitoring devices. These monitors provide continuous measurements of the tissue Po_2 in the small region of brain into which the device is inserted. The probes have been shown to be very sensitive to changes in the arterial P02, Pco_2, and medical interventions or physiological changes that may cause focal cerebral ischemia (Unterberg et al. 1997). Unfortunately, there are no methods for continuously monitoring global cerebral blood flow, although transcranial Doppler ultrasonography of the middle cerebral arteries can provide indirect information. Positron emission tomography and cerebral blood flow measurements with xenon, either as a radiolabeled agent or as CT contrast, can provide snapshots at different time intervals.

Treatment

Hypoxia is best avoided with the use of endotracheal intubation and mechanical ventilation. The fraction of inspired oxygen is titrated to achieve an arterial Po_2 of 100 mm Hg. Patients with severe chest injuries may develop a form of adult respiratory distress syndrome (ARDS), and positive end expiratory pressure (PEEP) is needed to maintain adequate oxygenation in these patients. Concern has been raised that the use of PEEP may increase the ICP in patients with TBI. But clinical studies find that, in the presence of ARDS, up to 15 em H_20 of PEEP can be used without measurable changes in ICP. This is probably because ARDS significantly reduces pulmonary compliance. Increased airway pressures are not transmitted to the chest cavity, so venous ourflow from the head is not restricted. Attention should also be paid to the oxygen delivery to the tissues. Maintaining an arterial Pco_2 of approximately 35 mm Hg is recommended to avoid the cerebral vasoconstriction associated with aggressive hyperventilation. Anemia must be treated aggressively, and a hematocrit of 30% or greater is recommended. Several ncurotrauma centers also are adjusting ventilatory and other rherapy to maintain a brain tissue P02 greater than 10 mm Hg, a threshold below which there may be an increased risk of tissue ischemia and worse outcomes {Kiening ct al. 1997).

Hypotension, defined as a MAP of less than 90 mm Hg, should he treated aggressively. Normovolemia should be restored by infusion of isotonic saline as needed to attain a central venous pressure of 7-12 cm H2O. Hypotonic intravenous solutions should be avoided because of the risk of worsening cerebral edema. If the patient is anemic, transfusions of packed red blood cells should also be used to restore the hematocrit to at least 30%. If hypotension persists despite adequate volume resuscitation, **a** continuous intravenous infusion of **a** vasopressor medication is recommended and the dosage titrated to elevate the MAP above 90 mm I Ig. Dopamine, Lcvophed, and norepinephrine are the preferred vasopressor agents.

Induced hypertension to elevate the CPP above 70 mm Hg is advocated by some, particularly if the ICP is elevated and difficult to treat (Rosner and Rosner 199.3). But a prospective randomized clinical trial in which a group of patients with TBI treated to maintain a CPP above 70 mm Hg was compared with a group in whom the CPP was allowed to drift to 60 mm Hg did not find any differences in 6-month clinical outcomes between the two groups (Robertson et al. 1999). Patients in the highcr-CPP group needed more vasopressor agents and had a significantly higher incidence of ARDS and other pulmonary complications than the group with the lower CPP. Others have measured brain tissue P02 in patients with TBI and found that there is typically not a fall in tissue P02 until the CPP drops below 60 mm Hg (Kiening ct al. 1997). Based on these findings, the current recommendation is to maintain a CPP above 60 mm Hg.

Intracranial hypertension is defined as sustained pressures greater than 20 mm Hg. Several clinical studies have found a significant increase in mortality and morbidity for patients with ICPs persistently above this threshold. Based on this association and the widely accepted premise that elevated ICP can compromise cerebral perfusion and cause ischemia, most believe it is important to treat intracranial hypertension aggressively. Before institution of therapy for intracranial hypertension, medical or physiological problems that can increase ICP should be considered and, if they exist, treated. They include seizures, fever, jugular venous outflow obstruction (e.g., poorly fitting cervical collars), and agitation.

Several medical and surgical options are available to lower ICP. Depending on the type of btain injury, some may be more effective than others, and each is associated with potential risks or side effects. The most commonly used treatment strategy involves a stepwise approach, with the use of the least toxic therapies first and addition of more toxic therapies only if the initial treatment is unsuccessful. Sedation and pharmacological paralysis often is an effective first treatment, particularly if the patient is agitated or posturing. We use a narcotic, such as morphine or fentanyl, for sedation and vecuronium bromide as the paralytic agent. Hypotension associated with the narcotic is avoided by ensuring normovolemia before treatment and using low dosages of the drug. The ability to obtain an accurate GCS is lost during this treatment, so the pupil examination, ICP, and CT scans must be monitored closely.

If intracranial hypertension persists after adequate sedation and paralysis, intermittent ventricular CSF drainage is used. Intermittent rather than continuous drainage allows reliable ICP monitoring. The next recommended treatment for intracranial hypertension refractory to these measures is mannitol. This osmotic diuretic lowers ICP and increases CPP by expanding the blood volume, reducing the blood viscosity, and increasing cerebral blood flow and oxygen delivery to the tissues within a few minutes of infusion. Its duration of effect averages 3-5 hours. Bolus administration of 0.25-1.0 g per kilogram every 3—4 hours as needed is recommended. Continuous mannitol infusions are more likely to lead to extravasation of the drug into brain tissue than bolus infusions, thereby causing a reverse osmotic gradient and increased edema and ICP. During mannitol administration the serum **osmolarity and sodium** should be monitored frequently and the drug discontinued if the serum sodium exceeds 160 mg/dL or the osmolarity exceeds 320 mOsm to minimize the risk of acute **tubular** necrosis and renal failure. The intravascular volume also should be monitored closely to prevent dehydration.

If the ICP remains above 20 mm Hg despite these measutes, the ventilator rate can be adjusted to reduce the $Paco_2$ to 30 mm Hg. But the use of hyperventilation in the first 24^4H hours aftet injury should be considered carefully because it will cause cerebral vasoconstriction at a time when cerebral blood flow already is critically reduced. Recent evidence also suggests that even brief periods of hyperventilation can increase extracellular lactate and glutamatc levels and thereby cause secondary brain iniury (Marion et al. 2002). Prophylactic hyperventilation in the absence of elevated ICP should always be avoided. A prospective randomized clinical trial comparing a group of patients with TBI who had prophylactic hyperventilation to a Paco2 of 25 **mm** Hg for 5 days with **a** group kept at a $Paco_2$ of 35 mm Hg found significantly worse **6-month** outcomes in the hyperventilated group (Muizelaar et al. I 991). If hyperventilation is used, monitoring of the brain tissue Po_2 or jugular venous oxygen saturation is recommended as a means of detecting cerebral ischemia that might be caused by the treatment,

If intracranial hypertension persists despite all these treatments, particularly if there is a rapid rise in ICP, or if the patient had a small contusion or hematoma on their original head CT scan, a repeat CTscan should be obtained immediately to determine whether the post-traumatic lesion has enlarged. Approximately 20-30% of contusions enlarge in the first 24-48 hours after injury. Even if the lesion has enlarged only slightly, emergent craniotomy and evacuation of the contusion or hematoma may be the best way to reduce the ICP quickly and effectively.

If the CT scan does not reveal a surgical intracranial mass lesion, the next recommended treatment for intracranial hypertension is high-dose barbiturate therapy. This medication is thought to act by reducing cerebral metabolic demand and blood flow, and preclinical studies suggest significant cerebral protective effects. Pentobarbital is the most commonly used drug for this purpose and is administered as an intravenous loading dosage of 10-15 mg per kilogram over 1-2 hours followed by a maintenance infusion of 1-2 mg per kilogram per hour. The dosage can then be increased until intracranial hypertension subsides or the MAP begins to fall. Others recommend continuous electroencephalographic monitoring and dosage increases until a burst suppression pattern is observed. The most common side effect of barbiturates is hypotension, but this can usually be avoided by ensuring a normal intravascular volume before administering the drug.

For patients with intracranial hypertension that persists despite all these measures, there are only a few remaining options, which are controversial and not embraced by all. Therapeutic moderate hypothermia has been used in several clinical trials over the last decade. The body temperature is reduced to 32-33"C as quickly as possible after injury and kept at that temperature for 24^48 hours using surface cooling techniques. Although clinical trials have not found that this treatment improves neurological outcome, they have consistently found that hypothermia significantly reduces ICP. And when its use is limited to 48 hours, hypothermia has not been shown to cause significant medical complications.

Decompressive craniectomies also are advocated by some and may include large lateral or bifrontal bone flaps with or without a generous temporal or frontal lobectomy. In one series of 29 patients with severe TBI, a subgroup that had large decompressive craniectomies was compared with a group that did not (Coplin et al. 2001). Six-month outcomes for the two groups were similar despite the craniectomy group having had a lower initial GCS and more severe radiographic injury. Importantly, the craniectomy group did not have a higher incidence of persistent vegetative state. Two other retrospective reports of patients with refractory intracranial hypertension treated with decompressive craniectomy as a last resort found good outcomes in *56-58%* (Guerra, Pick, and Gaab *1999;* Kunzc et al. 1998), and a third study suggested that decompressive temporal lobectomy improved outcomes for young patients when performed early after injury. However, others found that decompressive craniectomy did not improve ICP, CPP, or mortality {Munch et al. 2000).

Before decompressive surgery is considered, the salvageability of tin' patient should he considered carefully. Most agree that an intervention with a high probability of preventing brain death only to leave the patient in a persistent vegetative state is not a desirable intervention. Because age has such a profound impact on the likelihood of a meaningful recovery, these therapies are recommended only for those who arc less than 40 years old.

General Medical Care

Patients with TBI, particularly those who arc comatose or have significant non-central nervous system injuries, are at high risk of pneumonia, other infections, fever, malnutrition, seizures, deep venous thrombosis (DVT), pulmonary embolism, and other maladies endemic to the ICU. Most of these complications cause secondary brain injury and therefore should be diagnosed and treated rapidly. Fever is very common in the ICU and occurs in more than 90% of patients who are in the unit for 10 or more days (Kilpatrick et al. 2000}. Preclinical studies have shown that there is a logarithmic increase in neuronal cell death for every degree of brain temperature above 39 C in ischemic brain regions, and this effect is observed for 24 hours or more after injury (Baena et al. 1997). Clinical studies of patients with TBI reveal that the brain temperature often is 1-2 C higher than body temperature {Hcnkcr, Brown, and Marion 1998). Based on these findings, it is recommended that body temperarure be kept below 37°C at ail times and that infectious or other causes of fever be aggressively sought out and treated.

Comatose patients, those being treated with pharmacological paralysis, and those with pelvic and long bone fractures are at high risk for DVT and pulmonary embolism. The early use of DVT prophylaxis is recommended for this group of patients and typically includes the use of lower-extremity sequential compression devices and subcutaneous heparin or enoxaparin. The early use of minidosc heparin or low-molecular-weight heparins is safe and has not been found to cause or worsen intracranial hemorrhage after TBI (Kim et al. 2002; Norwood et al. 2002). If a pulmonary embolus occurs in the first 2-3 days after a TBI associated with intracranial contusion or hemorrhage, a vena cava filter usually is indicated. **After** the first few days, if serial CT scans verify that there is no further intracranial hemorrhage, full anticoagulation with heparin or Coumadin probably is safe. Malnutrition also is common after severe TBI when enteral feeding is poorly tolerated. The nonparalyzed patient with severe TBI typically has a 140% increase in resting metabolic expenditure (Young et al. 1985). Branched-chain amino acids from muscle protein are preferentially used for energy metabolism, potentially compromising the effectiveness of physical therapy. Nitrogen wasting also is increased, with excretion of as much as 9-12 g per day. Early enteral or parenteral feeding therefore is recommended, with the aim of providing at least 140% of the basal metabolic caloric needs each day by the third or fourth day after injury. For normal-sized adults, 2000-3000 kcal per day usually is needed. Because of the increased risk of infection with parenteral feeding, enteral administration is preferred.

Tf prolonged coma is anticipated, a surgical jejunostomy provides a convenient and well-tolerated route for tube feeding.

Post-traumatic contusions and subdural hematomas arc well-known causes of generalized seizures, so anticonvulsant prophylaxis is advocated for these and other patients with TBI. Most recommend treatment of all patients with TBI who have an abnormal CT scan with phenytoin for the first 7 days after injury. A prospective clinical trial did not find a benefit of longer prophylactic treatment (Temkin et al. 1990). A common side effect of phenytoin is fever, and this should be considered if infectious causes of fever have been excluded. The prolonged use of phenytoin also has been shown to significantly impair neuropsychological abilities after severe TBI. If seizures do occur, especially if they are prolonged, the associated cerebral hypermetabolism will cause secondary bram injury. Seizures therefore should be treated aggressively, including general anesrhesia if necessary. Patients who arc being pharmacologically paralyzed for treatment of intracranial hypertension may have seizures that are not readily apparent because they have no tonic-clonic extremity movements. Under these circumstances it is particularly important to provide anticonvulsant prophylaxis, and some even advocate continuous electroencephalographic monitoring. Clinically silent seizures should always be considered as a cause of an abrupt deterioration of cerebral oxygenation or a sudden increase in ICP, although the enlargement of an intracranial mass lesion still must be the first consideration.

PHYSICAL THERAPY AND REHABILITATION

The number of survivors of TBI is increasing with increasing successes in understanding and treating the disease and with improved injury prevention programs and technology. As a result, there is an increasing demand for high-quality, well-organized TBI rehabilitation programs. The primarv goal of these programs is to reintegrate patients with TBI back into their communities by cither restoring normal or near-normal functional capacities or teaching alternative strategies to help them function at a high level despite their disability. A multidisciplinary team of physical, occupational, and speech therapists, neuropsychologists, and social workers best accomplishes this (see Chapter 54). Ideally the team effort is coordinated by a physiatrist, or a neurologist with special training in rehabilitation. The team should be experienced in TBI rehabilitation and thoroughly understand the special needs of this group of patients. Programs that focus exclusively on TBI rehabilitation are far preferable to those that attempt to mix patients with TBI with patients suffering from stroke, neurodegenerative diseases, or tumors because the age groups affected are very different, as are the rehabilitative needs of these groups.

Rehabilitation of patients with TBI should begin in the ICU in the first few days after injury, with early consultation of the neurorehabilitation specialist and passive rangc-of-motion exercises of the extremities. Early mobilization of these patients helps prevent DVT formation, and there is evidence that early sitting of comatose patients may hasten return of consciousness. Administration of central neurostimulant medications as a supplement to physical therapy is being investigated for those with more severe injuries and minimal responsiveness (Meythaler et al. 2002). There obviously are many other critical aspects of TBI rehabilitation that are important for optimizing outcomes for these patients, but a thorough review is beyond the scope of this chapter.

PROGNOSIS

The early prediction of outcome after TBI can help guide acute and chronic care and help prepare family members for what is typically a prolonged recovery process. Just as importantly, further therapy may be determined to be futile, and expensive critical care or surgery can be reserved for those who are likely to benefit. It is obviously important that the early prediction of outcome be reliable, especially in cases in which life support withdrawal is considered. Several clinical and radiological characteristics have proven to be useful for outcome prediction, but they must be used in concert. Even with the use of these characteristics, prediction of death or vegetative survival is much more feasible than the accurate prediction of mild or no future disability and complete return to normalcy. The most powerful outcome predictors are age, initial GCS (particularly the moror component), pupil size and reaction to light, ICP, and the nature and extent of intracranial injuries. Age is perhaps the most important factor limiting good outcomes after TBI. In the Traumatic Coma Data Bank (TCDB) study of more than a thousand patients with severe TBI, the likelihood of death, persistent vegetative state, or severe disability was 92% for those older than 60 years, 86% for those older than 56, and 50% for younger patients. The older patients had a higher incidence of traumatic intracranial mass lesions, midline shift, and SAH, and the presence of these brain injuries was strongly correlated with poor outcomes. Subsequent studies confirm that the likelihood of a good recovery for patients over age 60 who present with a GCS score of 8 or less is very low.

The second most important predictor of outcome is the initial postresuscitation GCS score. Among the 746 patients with severe closed head injuries in the Traumaric Coma Data Bank study, good outcomes were observed in only 4.1% of those with an initial GCS of 3, 6.3% if their initial GCS was 4, and 12.2% if their initial GCS was 5. Again, subsequent clinical studies confirm a strong direct correlation between the initial GCS and likelihood of a good

outcome. The presence of unilateral or bilateral dilated pupils unrcactive to light also is important for outcome prediction, usually because it reflects uncal herniation and significant compression and damage of the brainstem. In several large clinical series, patients with bilaterally fixed and dilated pupils had a greater rlian 4JO"•:> likelihood of death or vegetative survival. Intracranial hypertension refractory to medical management is associated with a 43% mortality rate and 0% chance of a functional outcome.

The effect of the type and size of post-traumatic intracranial lesions on outcome has been analyzed in terms of both the specific lesions and CT-defined characteristics of the mass effect of these lesions. Subdural hematomas are associated with the worst prognosis, and in one study only 26% of patients with these clots had a functional recovery. Prognosis for those with subdural hematomas is related to the time it takes to evacuate the clot, however, and Seelig et al. observed a lower mortality in comatose patients with TBI who had operative decompression within 2 hours of injury compared with those who had surgery 6 or more hours after their injury (30% and 90%, respectively). The mortality for patients with epidural hematomas is much lower and usually results from *a* delay in the diagnosis and treatment of these lesions. The reason for the much better prognosis in those with an epidural hematoma compared with those with a subdural hematoma is that epidural hematomas usually are not associated with underlying cerebral contusions or swelling, whereas subdural hematomas often are. If left untreated, however, epidural hematomas can cause uncal herniation and death. One study found that the mortality rate increased from 17% to 65% if it took 2 or more hours to evacuate an epidural hematoma after onset of coma. Traumatic SAH also has been associated with 50% higher mortality than in patients with TBI who did not have SAH (Greene et al. 1996; Servadei et al. 2002). But the link between traumatic SAH and worse outcomes is controversial, and many believe that traumatic SAH is simply an indication of a more severe TBI and not directly responsible for outcomes.

Marshall et a), developed a CT-bascd classification scheme emphasizing the mass effect caused by post-traumatic intracranial lesions that has proven useful for outcome prediction when applied to the patients in the Traumatic Coma Data Bank (Marshall et al. 1991; Tables 56B.4 and 56B.5). As might be expected, those with large intracranial mass lesions and uncal herniation were found to have the worst outcomes. Based on these studies, one can say with certainty that an 80-ycar-old patient who presents with bilaterally fixed and dilated pupils, a CCS score of 3-4, and a large subdural hematoma will not have a functional outcome regardless of treatment. However, young patients with a higher GCS have a much better prognosis, and aggressive surgical and medical management usually is warranted.

Tabic 56B.4: Computed tomography (CT) classification of traumatic brain injury

Category	*Definition*
Diffuse injury I (no visible pathology)	No visible intracranial pathology seen on CT
Diffuse injury II	Cisterns are present with midline shift 0-5 mm; no high-density lesion >25 cc
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift 0-5 mm; no high-density lesion >25 cc
Diffuse injury IV (shift)	Midline shift >5 mm; no high-densiry lesion >25 cc
Evacuated mass lesion	Any lesion surgically evacuated
Nonevacuated mass lesion	High-density lesion >25 cc; not surgically evacuated

Source: Marshall, L. E., Marshall, S. B,, Klaubcr, M. R., & Clark, M. 1991, "A new classification of head injury based on computerized tomography," / *Neurosurg,* vol. 75, pp. SI4-S20.

PENETRATING HEAD TRAUMA

The most common cause of penetrating head injury is gunshot wounds. While the incidence of TBI caused by MVCs appears to be declining, probably as a result of increased use of passive restraint systems, the incidence of gunshot wounds to the head is increasing. From 1984 to 1992 the TBI death rate from MVCs declined by 25%, but the fire arm-re I a ted death rate increased by 13% (Sosin, Sme/ek, and Waxwcilcr 1995). In fact, in 1990 the number of firearm-re I a ted deaths surpassed MVCs as the single largest cause of death related to TBI.

Gunshot wounds to the head usually cause massive brain tissue destruction, severe brain swelling, and death. The wounding potential of a bullet depends primarily on its velocity at impact and its mass, although the shape of the

Tabic 56B.5: Relationship of computed tomography classification to outcome at discharge

	No. of patients	*Unfavorable outcome (D, VS, and SD)*	*Favorable outcome (MD and GR)*
Diffuse injury I	52	38%	62%
Diffuse injury II	177	65%	35%
Diffuse injury III	153	84%	16%
Diffuse injury IV	32	94%	6%
Evacuated mass	276	77%	23%
Nonevacuated mass	36	89%	11%

D = dcath; C R = good recovery; MD = moderate disability; SD = severe disability; VS = persistent vegetative state.
Source: Marshall, L. F., Marshall, S. B., Klauber, M. R., *fk* Clark, M. 1991, "A new classification of head injury based on computerized tomography," / *Neurosurg,* vol. 75, pp. S14-S20.

bullet and its lateral movements at impact also play a role. The relationship of bullet mass and velocity to the energy imparted to the head is described by the equation KE = j MV , where KE = kinetic energy, M = mass of the bullet, and V —impact velocity of the bullet. According to this equation the impact velocity is by far the most important determinant of the wounding potential of the bullet. It explains why high-velocity rifle wounds to the head are uniformly fatal, whereas low-velocity open-chambered handgun wounds often arc not. Once the bullet enters the skull it creates a variety of pressure waves in the brain, some of which can cause tissue pressures of nearly 100 atm, and these pressure waves produce more tissue injury. In addition to forward velocity, lateral motion of the bullet before and after impact also contributes to the severity of tissue destruction. Such motion is described as yaw, or the angle between the path of flight of the bullet and its long axis and precession and nutation, which arc circular rotations of the bullet around the center of its mass. These movements increase the bullet's relative surface area at the point of impact and allow it to pass more of its KE to the surrounding tissue. They increase the size of the entrance wound and cause greater cavitational injury. Bullets often fragment after impact with the skull and fracture a portion of tin- skull into multiple fragments. Both the bullet and bone fragments then become numerous secondary missiles that cause further tissue damage.

Low-velocity missile wounds, such as those caused by knives, ice picks, or arrows, do not cause the massive brain injuries seen with bullets, as might be predicted by the KE equation. Typically the only tissue damaged is that which lies in the immediate path of the missile, and complete neurological recovery after surgical extraction of the missile is not uncommon. Rarely, the missile damages a major intracranial artery or venous sinus, and these vascular injuries can result in large intracranial hematomas. Vascular injuries should always be considered in high- or low-velocity missile injuries to the head, especially those located near or in the base of the skull or the sylvian fissures.

The initial assessment and resuscitation of patients with penetrating head injuries is the same as for those with closed head injuries and is described in derail earlier in this chapter. Prompt and aggressive cardiopulmonary resuscitation is critical. Knives or other missiles protruding from the head should never be removed in the field or emergency department because they may be tamponading a damaged intracranial vessel, and removal could lead to intracranial hemorrhage. If there is a gunshot wound to the head, the neck, chest, and abdomen should be inspected carefully to ensure that there are no other gunshot wounds because wounds to the heart or great vessels in the chest or abdomen may be even more life threatening. A posrrcsuscitation GCS should always be obtained early after injury because it will guide future therapeutic decision making, A CT scan of the head defines the intracranial path of the missile and related skull and tissue damage (Figure 56B.11), but more importantly it identifies any large intracranial hematomas or contusions that, in some cases at least, may significantly contribute to outcome and should be evacuated rapidly. Cerebral angiography should be obtained if the missile trajectory is in or near the skull base or sylvian fissures, assuming the patient is deemed salvageable.

Most patients who are not thought to have lethal brain injuries need at least limited surgical management for their penetrating head injuries. Large intracranial hematomas should be evacuated quickly. Those with low-velocity

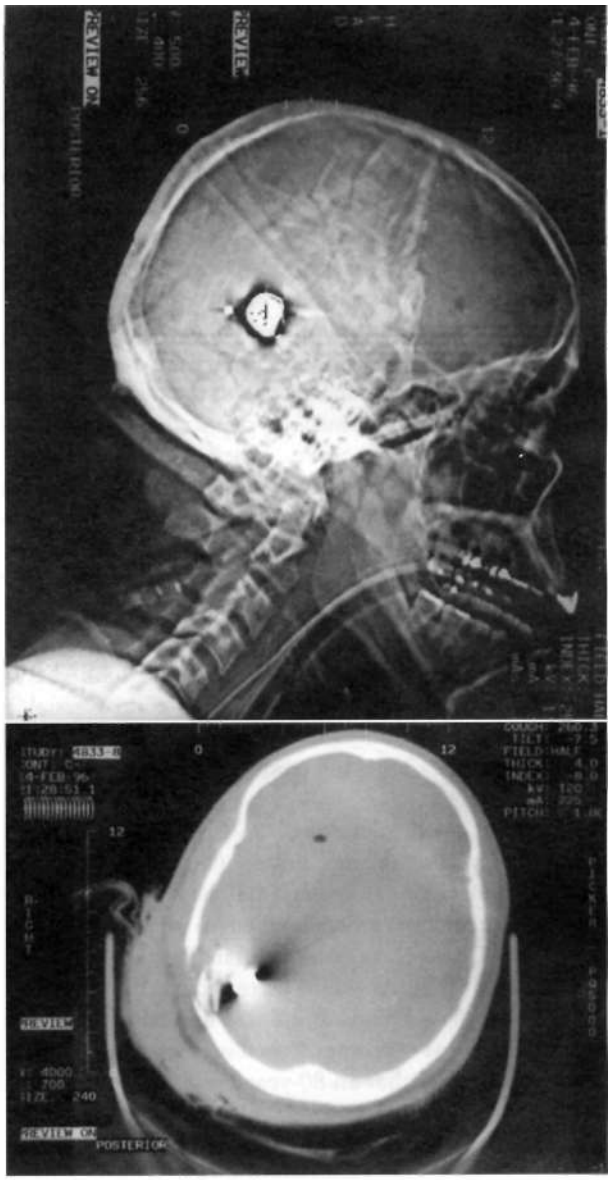

FIGURE 56B.11 (A) Scout view of bullet penetrating right parietal skull. (B) Axial computed tomographic view of same bullet.

missile wounds in which the object is still protruding from the head also should undergo a formal craniotomy. At surgery a segment of skull containing the missile, large enough to allow intracerebral exploration, is removed. The surgeon is then prepared to search for and immediately repair or occlude vascular injuries that may have been caused by the missile. Patients with gunshot wounds to the head should undergo a limited debridement of the scalp and skull wound. Scalp, bone, and bullet fragments penetrating the brain should bo removed only it rhey lie near the surface. Easily accessible necrotic brain is debrided, and meticulous hemostasis is achieved. Dura! closure is important because it reduces the risk of CSF leak and infection hut usually necessitates the use of a pericranial graft. The use of artificial dura! substitutes or allografts is not recommended because of the risk of infection.

Subsequent medical management of penetrating injuries is as described earlier in this chapter for patients with closed injuries. In addition, prophylactic antibiotics should be administered for at least 14 days because the missile usually carries skin and hair into the brain. By definition, all these patients have disruption and contusion of btain tissue and therefore should be treated with anticonvulsants.

The catly prediction of outcome and determination of salvageability are far less ambiguous for patients with penetrating injuries than for those with closed head injuries. The majority of those with gunshot wounds to the head die before or shortly after admission to the hospital. In one sctics of 314 patients with civilian craniocerebral gunshot wounds, the mortality rate was 92%, with 73% of that group pronounced dead at the scene of the injury and 12% dying within 3 hours of injury (Siccardi et al. 1991). The mortality tare among the 151 patients with gunshot wounds to the head that were entered into the Traumatic Coma Data Bank was 88%. No patient with an initial GCS of 8 or less achieved a normal neurological outcome, and only three recovered to the level of moderate disability, suggesting that the initial GCS score is an even more powerful predictor of outcome for these patients than it is fot those with closed TBI. In a meta-analysis of tecent clinical reports of civilian gunshot wounds to the head, only 5 of 490 patients with an initial GCS of 3-5 had favorable outcomes. The mortality rate was 51-87% for patients with GCS score of 8 or less and an unfavorable outcome rate of 61-94%. However, those who had an initial GCS score of 13-15 all survived and had a favorable outcome (Glasgow Outcome Scale of 4 or 5; Table 56B.6).

The extent of intracranial injury caused by the missile, as determined by CT scans, also has prognostic significance. CT findings of hypctdense lesions grcatct than 15 mL in volume, a midline shift of greater than 3 mm, compressed or absent basal cisterns, SAH, and intraventricular hemorrhage, as well as a bullet trajectory that traverses both hemisphctcs, the basal ganglia, or the posterior fossa, all are associated with mortality rates ranging from 80-90%. Additional clinical signs associated with death or poor outcome include fixed and dilated pupils, intracranial hypertension, and hypotension. Also, death is more likely if the gunshot wound is self-inflicted than if it is not.

MILD AND MODERATE BRAIN INJURY

Patients with a mild TBI have an initial GCS score of 14-15, and those with a modetate injury have a GCS score of 9-13. These injuries, often called concussions, typically involve a brief period of loss of consciousness at the time of impact to the head and some degtee of retrograde or post-traumatic amnesia. However, at the time of medical evaluation all of these patients are able to follow commands. Most patients with mild or moderate TBI do not have the complex intracranial pathology associated with severe TBI and thetefore have a very low likelihood of dying from their injury. However, the cognitive and neuropsychological injuries they may sustain ate magnified by the fact that of the estimated 220 victims of TBI per 100,000 population per year in the United States, 90%, or approximately 450,000, have mild or moderate injuries (Kraus and McArthur 1996). Although the mortality fate for those with mild injuries is nearly zero and for those with moderate injuries is approximately 4%, as many as 10% of those with mild injuties and 66% of those with modetate TBI have prolonged or permanent disabilities such that they ate unable to tetutn to work ot school.

Rotational acceleration and deceleration are common causes of these injuries, particularly those that cause loss of consciousness. However, the impact usually is not

Tabic 56B.6: Glasgow outcome scale

Unfavorable outcomes			*Favorable outcomes*	
1	*2*	*3*	*4*	*S*
Death Loss of life due to head injury	Persistent vegetative state Unresponsive, + steep cycles, + eye opening	Severe disability Conscious but disabled, dependent for daily care	Moderate disability Disabled but independent, able to care for self	Good recovery Resumes normal lite. minor residual deficits

severe enough to cause intracranial hematomas, cerebral contusions, skull fractures, or brain swelling. A small amount of traumatic SAH may be seen, usually in the sulci over the frontal ot temporal lobes. Most often, however, the CT scans are normal. Abnormal magnetic resonance imaging findings have been reported in as many as 30% of these patients, with diffuse hyperdense lesions on T2-weighted images the most common findings. These lesions are thought to represent focal or punctate contusions. Abnormal activation patterns often are identified with functional magnetic tcsonance imaging studies and are most common when there has been loss of consciousness or when the patient is symptomatic at the time of study.

The level of medical evaluation and management appropriate for patients with mild ot moderate injuries depends on several factors. Medical personnel should carefully evaluate any patient who lost consciousness at the time of impact ot has several minutes or more of retrograde or antegrade amnesia. Those with persistent headaches, confusion, dizziness or diplopia, or persistent weakness or numbness also should undergo a thorough medical assessment. Most of these patients benefit from a fotmal evaluation in the emergency department. If the patient is found to be n euro logically normal and asympto-matic after 1 hour or more of observation and serial evaluations, he or she usually can be safely discharged with careful instructions to return immediately if symptoms or signs of TBI develop. Ideally, the instructions are given both to the patient and a family member. Those with persistent symptoms or neurological deficits should have a CT scan of the head and be admitted to the hospital for observation. This is particularly important for those with a GCS score of 13 or less because the risk of an intracranial hematoma or contusion large enough to necessitate emergent craniotomy incteases as the GCS decreases. Of those with an initial GCS score of 9-13, as many as 40% have abnormal CT scans, and 8% need neurosurgical intervention (Stein and Ross 1992).

Athletes, particularly those involved in contact sporrs such as boxing, football, soccer, wrestling, and field hockey, are at high risk of mild and moderate TBI. In one recent report the incidence of concussion was estimated at 40,000 per year among high school football players (Powell and Bnrber-P'oss 1999). Multiple concussions, especially if they are sustained in a short period, are much more likely to cause prolonged or permanent neurological disability than a single concussion, and athletes also are at greater risk for multiple concussions. Second impact syndrome is a rare but potentially lethal problem and has been implicated as the cause of sudden death in several high school football players (Saunders and Harbaugh 1984). Because of these disabling and potentially life-threatening consequences of sports-re I a ted concussion, coaches and athletic trainers must carefully consider the advisability of return to play or retirement from athletic competition for each athlete immediately after a concussion. Several groups have devised concussion grading scales to be used to evaluate the severity of a concussion and have used these scales to develop guidelines for determining when an athlete can safely return to play. The most widely adopted scales are those developed by Jim Kelly at the University of Colotado (Colorado Guidelines; Kelly et al. 1991), Robert Cantu (Cantu Guidelines; Cantu 1998), and the American Academy of Neurology (AAN Guidelines; Goodman and Gactz 2002; Tables 56B.7 and 56B.8). In addition, most authorities recommend that the athlete be retired from play for at least one season if he or she sustains three or more grade I or II concussions during a season or two grade 111 concussions. Many athletic organizations at the high school, college, and professional levels also have adopted neuropsychological testing as a means of objectively evaluating the cognitive and neuropsychological conse-quences of each concussion (Maroon et al. 2002). When compared with preseason scores, such tests can provide a powerful tool for use in determining who should return to play and who should retire from the sport.

A common sequela of mild or moderate TBI is postconcussive syndrome, a constellation of symptoms that can be very disabling weeks or even months after the injury. The most common symptoms are headache, irritability, dizziness, tinnitus, lethargy, and sleep distur-bances (Ingebrigtsen et al. 1998). Approximately 30% of

Table 56R.7: Grading scales for concussion

	Grade of concussion		
Name of scale	*1*	*11*	***in***
Colorado (Kelly et al. 1991)	Confusion, no LOC, PTA <30 min	IOC o min, confusion, PTA >30 min	LOC >*S* min, PTA >24 hr
Cantu (199S)	PTA <30 min, no LOC	LOC <5 min, PTA 30 min-24 fir	LOC >5 min, PTA >24 hr
American Academy of Neurology (Goodman and Gaetz 2002)	Transient confusion, symptoms <15 min, no LOC	No LOC, transient confusion, symptoms >15 min	Any LOC

LOC = loss of consciousness; PTA = post-trauma tic amnesia.

Tabic 56B.8: Recommendations for return to play

Grade of concussion	*Colorado guidelines (Kelly et al. 1991)*	*Cantu guidelines (Cantu 1998)*	*American Academy of Neurology Guidelines (Goodman and Gaetz 2002)*
I	Return after 20 mm if norms I examination	Return the same day if normal at rest and exertion and after 7 days if symptomatic	Return the same day if normal at rest and exertion
II	Rmini alter 7 days if asymptomatic	Return after 2 wk if asymptomatic at rest and exertion for 7 days	Return after 7 days if asymptomatic
III	Evaluation by neurologist or neurosurgeon, return .liter *2* wk it asymptomatic and cleared by specialist	Return after 1 month if asymptomatic at rest and exertion for 7 days	Evaluation by neurologist or neurosurgeon; return after 2 wk if neurologieally cleared

patients with mild or moderate injuries have one or more of these symptoms 1 week after their injury, but they usually subside within 3 months (Levin et al. 1992). Only about 7% of patients still report residual symptoms after I year, and the most common is persistent headache. Postconcussive syndrome is best treated by primary care physicians or neuropsychologists, who thoroughly understand the syndrome. Cognitive testing is recommended for those who have symproms that last more than a few weeks because symptoms such as frustration and irritability often are linked to a cognitive inability to resume normal daily activities. If specific deficits are identified, cognitive rehabilitation is recommended. Persistent headaches, dizziness, and tinnitus are treated symptomatically after a head CT establishes that there are no intracranial lesions. Post-traumatic disturbances of the ossicles of the inner car semicircular canals can cause severe positional vertigo, and patients with vertigo or tinnitus often arc referred for evaluation by an otolaryngologist. Factors associated with an adverse long-term outcome after concussion include old age (Katz and Alexander 1994), long duration of post-traumatic amnesia (Lishman 1968), and a reduced premorbid intellectual capacity.

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Chapter 56
Trauma of the Nervous System

C. SPINAL CORD TRAUMA

Paul Santiago and Richard G. Fessler

Spinal cord injury (SCI), both in the acute and the delayed setting, is one of the most common clinical entities encountered by the neurologist and neurosurgeon. SCI often results in permanent neurological deficit and, depending on the level of injury, may leave the patient severely disabled. Delayed ot missed diagnosis, poot initial management, comorbidity, and age can significantly affect outcome. Early diagnosis, early stabilization of spinal fractures, aggressive management of comorbid disease, and multidisciplinary rehabilitation have increased sutvival rates and quality of life for these patients. Ttiage, management, and prognostication depend on a thorough understanding of the mechanism of injury, clinical examination, and diagnostic studies.

EPIDEMIOLOGY

Approximately 11,000 new cases of SCI are reported yearly in the United States (approximately 40 cases per million people). The incidence ranges from 11.5 to 53.4 cases per million people in developed countries across the world. These figures do not include patients who die at the time of injuty. About 1 in 40 patients admitted to a trauma centet has an SCI (Kraus et al. 1975; Kraus 1978; Fine et al. 1979; Woodruff and Baron 1994). SCI is also commonly associated with spinal injury. However, the majority of injuries to the spinal column occur without associated neurological deficit. Approximately 25% of patients with SCI have an associated head injury (Tator et a!. 1993), and 50% of patients with head injuries have an associated SCI, making it important that patients with SCI be treated in polytrauma units. Males make up approximately 85% of patients with SCI, and nearly 70% of patients with SCI are under the age of 40 (Table 56C.1; Tator et al. 1993). For patients sutviving to reach the hospital, reported mortality ranges from 4,4-16.7% (Tator etal. 1993). The estimated cost of care for patients with SCI in 1990 was estimated to be $4 billion (Tatot et al. 1993).

Roughly 55% of SCIs occur in the cervical region, with the remainder being evenly distributed in the thoracic, lumbar, and sacral regions. Thoracic spine injuries have been shown ro have a higher rare of complete SCI than injuries of the cervical and thoracolumbar spine. Recovery

Table 56C.1: Demographics of acute spinal cord injury

	Percentage of total
Age (yr)	
l'.inll-ll!	10
11-20	20
21-30	25
31-40	15
41-50	10
51-60	10
Over 60	10
Sex	
Male	Ss
Female	Li

Source: Modified from Tator, C. H., Duncan, E. G,, Edmonds, V. E., et al. 1993, "Changes in the epidemiology of acute spinal cord injury from 1947 to 1981," *Surg Neuro!,* vol. 40, pp. 207-215.

from complete injuries is mote likely in cervical spine injuries and poorest in thoracolumbar injuries. In all cases, the degree of permanent impairment directly correlates with extent of injury at admission.

The causes of SCI injury vary greatly between countries and even between age gtoups in a particular country. In developed countries traffic accidents and high-risk sports (e.g., rock climbing, surfing, and diving) have replaced work-related accidents as the leading cause of SCI. For example, diving results in approximately 1000 SCIs per year in the United States, with a 95% rate of quadriplcgia. Of note, alcohol has been implicated as a factor in as many as 25% of SCIs in the United States (Tatot et al. 1993). Increased awareness of the risk of SCI has significantly decreased the frequency of SCI at the workplace. Regional differences exist, however; SCI is particularly common in regions where high-risk occupations such as mining and logging are practiced. As the spine ages, it becomes more brittle and calcified, thereby increasing the chance that a fall will cause spinal fracture and SCI. Falls are the number-one cause of SCI among older adults. Violence, particularly gun-related violence, has become a much more common cause of SCI in the last two decades. Some authots report violence as the most common cause of SCI in certain parts of the United States (Sutherland 1993).

Iatrogenic SCI should be noted as a significant but often unrecognized cause of SCI. It is estimated that approximately 15% of patients with SCI worsen neurologically during the period immediately after admission to the hospital. A portion of these deteriorations may result from missed or poorly managed spinal injuries. Every patient possibly at risk for SCI should be treated as having an unstable spine injury until proven otherwise. In a patient with altered mental status this may not be easy in the acute phase. Workup should include a detailed physical examination and dynamic testing to rule out ligamentous injury, when indicated.

GRADING OF SPINAL CORD INJURY

Initial management of the patient with SCI includes not only a thorough neurological examination but also an accurate description of this examination in a standardized fashion. The currently adopted standard in the United States and most developed countries is the American Spinal Injury Association/International Medical Society of Pataplegia (ASIA/IMSOP) scale (Table 56C.2) in conjunction with the Medical Rcscatch Council muscle grading system (Table 56C.3; 1986). Several points should be made. These are not continuous scales, and there is a significant functional jump between grades. Secondly, muscle strength should be assessed on full range of motion across the affected joint, F'xaminers tend to grade patients on strength through partial range of motion, which results in some patients being given a motor scote that is too high. This i> a common source of confusion. Finally, the "+" and "-" subjective qualifiers are applied only to grade 4. The standard is to test 10 myotomes and 28 dermatomes bilaterally (Figure 56C.1). It is unfortunate that testing of the sacral dermatomes and myotomes (sensation at the anal mucocutaneous junction, deep anal sensation, and voluntary contraction of the anal sphincter) often is left to the most junior member of the team. Preservation of the sacral roots, or sacral sparing, has been associated with better outcome. The presence of sacral sparing has also been used as an indication fot emergent spinal decompression. The indication for emergent surgical decompression of incomplete traumatic SCI remains highly controversial.

Table 56C.2: ASIA/IMSOP impairment scale

Grade A	Complete	No motor or sensory function is preserved in the sacral segments S4-S5.
Grade B	Incomplete	Sensory but not motor function is preserved below the neurological level and extends through the sacral segments S4—S5.
Grade C	Incomplete	Motor function is preserved below the neurological level, and the majority of key muscles below the neurological level have a muscle grade <3.
Grade D	Incomplete	Motor function is preserved below the neurological level, and the majority of key muscles below the neurological level have a muscle grade >3.
Grade H	Normal	Minor and sensory functions are normal,

Source: Modified and reprinted with permission from the American Spinal Injury Society (ASIA) and International Medical Society of Paraplegia (IMSOP).

Table 56C.3: Medical Research Council muscle grading system

Grade	*Physical exam finding*
J	Full ROM against full resistance
4+	Full ROM against nearly full resistance
4	Full ROM against moderate resistance
4-	Full ROM against some resistance
3	Full ROM against gravity
2	Full ROM with gravity eliminated
1	Partial or trace muscle contraction
i)	No muscular contraction

ROM = range of motion.
Source: Modified from *Aids to the Examination of the Peripheral Nervous System,* liaillicre Tindall on behalf of the guarantors of brain, London, 1986.

The term *spina! cord level* is used to establish the functional level of injury in patients with SCI, The stricrcst definition of SCI level is based on the ASIA/IMSOP scales, in which sensory and motor levels are reported for both sides of the body, along with zones of partial preservation. The spinal cord level is defined as the caudalmost segment of the spinal cord demonstrating normal function. In practice, it is more common to report the level at which normal motor and sensory function exist on both sides of the body or to report rhc level at which motor function is graded at 3/5 or better. Ffficient communication requires that all parties use the same system. Because the spinal cord is shorter than the spinal column, there is often a significant disparity between the spinal cord and skeletal levels of injury.

Complete SCIs are injuries that meet the criteria for the ASIA/IMSOP scale grade A injury. Because there is often a zone of partial preservation below the lowest level considered normal, the definition includes patients with complete absence of normal motor and sensory function starting four levels below the caudalmost normal level. Incomplete injuries make up grades B, C, and D.

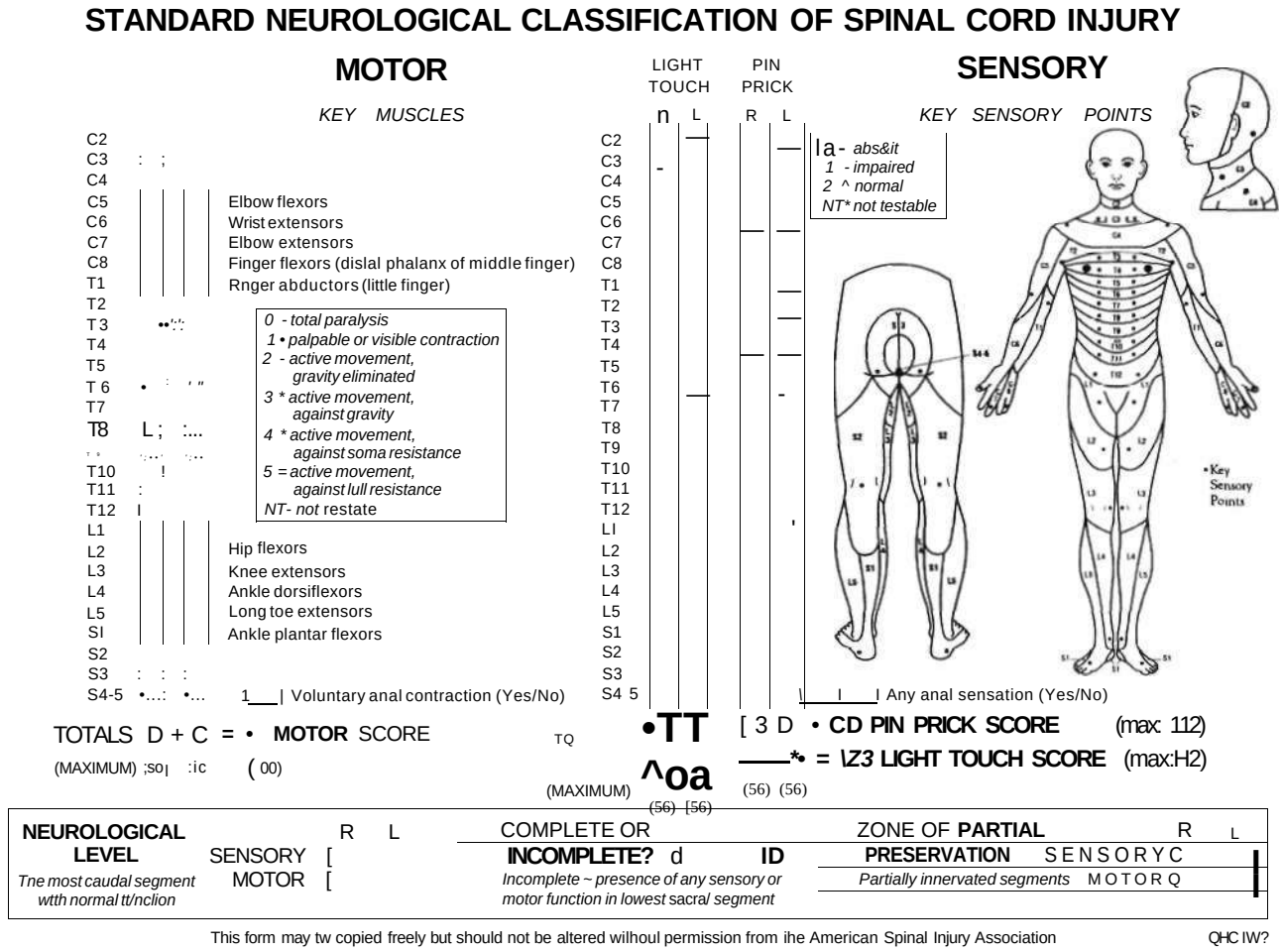

FIGURE 56C1 Template summarizing the spinal examination suggested by the American Spinal Injury Association (ASIA) and the International Medical Society of Paraplegia (IMSOP). This diagram contains the principal information about motor, sensory, and sphincter function necessary for accurate classification and scoring of acute spinal cord injuries. The 10 key muscles to be rested for the motor examination are shown on the left, along with the Medical Research Council grading system. The 28 dermatomes to be tested on each side for the sensory examination are shown on the right. The system for recording the neurological level, the completeness of the injury, and the zone of partial preservation (in complete injuries) is shown at the bottom. (Reprinted with permission.)

SPECTRUM OF DISEASE

SCI represents a spectrum of disease, not all of which is permanent. At one end of the spectrum are disorders such as "stingers" and transient paraplegia, most often encountered in young athletes, which represent self-limited injury to the spinal cord and nerve roots. In the middle of this spectrum are disorders such as the progressive myelopathy associated with severe cervical spinal stenosis and chronic progressive conditions with an insidious onset whose course can be arrested. At the other end of the spectrum are the disorders associated with immediate irreversible paralysis such as spinal cord transection and vascular injury. An understanding of the underlying pathophysiology of each condition is needed for a diagnosis and determination of the timing and course of treatment. Clearly, the evaluation and treatment of an otherwise healthy 18-year-old football player who presents with weak arms and legs after a tackle is different than that of a 78-yeat-old ex-miner who presents with the progressive lower extremity weakness. In the former case workup may reveal an acutely herniated disc compressing the spinal cord, an indication for emergent surgical decompression, with the hope of retutn of function. In the latter case, the presence of severe cervical stenosis, a chronic process, does not necessitate emergent intctvention. Rathet, a thorough discussion of the risks and benefits of surgical intervention is indicated. Surgical intervention in this case most often is aimed at preventing futthet loss of function rather than at improvement and carries a small risk of detetioration in level of function.

SCI is most often seen in the setting of pte-existing injury, even in young adults (Table 56C.4). The most common disorder associated with SCI is cervical spondylosis; studies have documented a prevalence of 10% cervical spondylosis among patients with SCI (Tator et al. 1993). Many of these disorders alter the biomechanics of the spinal column, affecting its ability to beat physiological and unphysiological loads, resulting in SCI when otherwise an SCI might not normally occur. For example, a 20-year-old tripping on the edge of a carpet and striking his forehead most often results in a btuise and some embatrassmenr. A normal spine is able to protect the underlying cervical cord during unphysiological hypcrcxtension of the cervical spine, dispersing the translated forces and cushioning the spinal cord with cctebtospinal fluid (CSF). This is very different from the case of a 20-year-old with Down syndrome and a congenital abnormality of occipital-cctvical junction. In this case, even a minor extension injury may result in a severe SCI because of the associated ligamentous laxity and cctvical stenosis.

Table 56C.4 Most common causes of acute and chronic spinal cord injury in clinical practice

- Trauma
- Spinal arthropathy
  - Cervical spondylosis
  - Ankylosing spondylitis
  - Cervical canal stenosis
- Malignancy or pathological fracture
- Infection
- Vascular
  - Direct injury
  - Arteriovenous fistula or malformation
  - Thromboembolic infarction
  - Fibrocartilaginous embolism
- Congenital abnormality

SCI in the setting of multisystem trauma deserves special mention. Only 20% of patients with SCI have isolated SCI, and approximately 20% of patients with SCI have other significant injuries, including ttaumatic brain injury, hemothotax or pneumothorax, extremity fractures, and intra-abdominal injury. These concomitant injuries present a numbct of short- and long-term management challenges. In genera], patients with isolated SCI have a better outcome than those with multiple injutics.

The so-called polytrauma patient often presents to the emergency room sedated, if not intubated and chemically paralyzed. In this setting it is nearly impossible to initially assess and determine a change in neurological function. SCI itself can tesult in hypotension and hypoxia through inrerruption of the autonomic nervous system and paralysis of the respiratory muscles, respectively. Undet sedation and chemical patalysis, the natural splinting mechanism provided by muscular spasm may not be present, and poor management in the field can result in the conversion of a spinal injury into an SCI or a partial SCI into a complete one. Patients needing intubation may have unstable cervical spmc fractures, adding SCI to the risks associated with emergent intubation. Additionally, polytrauma patients can present with hypotension caused by ongoing hemorrhage, decreasing the perfusion pressure to a potentially swollen, injured spinal cord. As with brain injury, prolonged hypoperfusion and hypoxia may be harbingers of poor outcome (Sentet and Venes 1979; Dolan and Tator 1982; Tator 1992, 1996; King, Gupta, and Narayan 2000). The systemic inflammatoty response syndrome associated with polytrauma can make it difficult to maintain tissue pctfusion, and injury to the lung parenchyma and adult respiratory distress syndrome can make it difficult to maintain tissue oxygenation. To further complicate matters, many polytrauma patients with spinal ftactutcs and SCI are unable to withstand the stress of general anesthesia and surgery in the acute setting. This results in the need to delay surgery and mobilization. For this reason, treatment of patients with SCI and polytrauma often entails constant interaction between subspecialties.

The examining physician should also keep in mind that just as polytrauma can have a negative impact on the management of SCI, the reverse is also true. Given that only 20% of patients with SCI present with isolated SCI, the clinician must be vigilant for the presence ot comorbidity,

Hypotension may be the result of occult hemorrhage, cardiac tamponade, or pneumothorax. Hypoventilation may be caused by hemothorax or pneumothorax, chest wall injury, or abdominal distension (abdominal compartment syndrome). These symptoms may be masked by the autonomic collapse and decreased tidal volumes associated with cervical SCI. Cervical and thoracic SCI can result in absence of sensation below the level of injury, delaying the diagnosis of intra-abdominal, pelvic, and extremity injuries, which would otherwise be severely painful. Special care should also be taken in the case of older adults, in whom low-energy collisions, such as falls from standing or **bed,** can produce significant injury. These low-impact events can result in bony fractures and bleeding, particularly in patients receiving anticoagulation therapy. Just as all polytrauma patients should be treated as if they had SCI until proven otherwise, all patients with traumatic SCI should be treated as if they had polytrauma until adequate screening is performed.

MECHANISMS OF TRAUMATIC INJURY

A detailed discussion of individual spinal fractures and dislocations is beyond the scope of this chapter. However, it is important to recognize that different fracture patterns carry different prognoses with respect to SCI.

There is a dramatic difference in the cross-sectional area of the spinal canal occupied by the spinal cord and the subarachnoid space (space available for the cord [SAC|) depending on the region of the spine in question. In the normal state, at the level of the foramen magnum and atlantoaxial unit (C'l/2), the subarachnoid space is large relative to the cross-sectional area of the spinal cord. Therefore most fractures of the occipital condyles, CI, and C2 do not result in SCI. The exception occurs in the case of atlantoaxial dissociation/dislocation (AOD), a predominantly ligamentous injury in which axial traction is applied to the spinal cord. Death is often the result of AOD, but in mild cases bulbar symptoms and patchy long tract findings can occur. The diagnosis often requires magnetic resonance imaging (MRI); surgical intervention is indicated,

In the lower cervical canal, the SAC decreases. Consequently, anterior dislocations and fracture dislocations result in decreased SAC and are more likely to be associated with SCI. Injuries such as laminar fractures (which can actually increase the SAC) and spinous process fractures usually are not associated with SCI. As the SAC reaches a minimum in the thoracic spine, thoracic dislocation and fracture dislocations carry a high risk of SCI.

As the spinal column transitions from the thoracic to the lumbar region, the spinal canal enlarges. At the level of the conus (usually at Ll/2) and lumbosacral enlargement of the spinal cord, a spectrum of injuries can occur, ranging from a ncurologically complete SCI to an isolated sacral root injury. The cauda equina is made up of nerve roots and has a smaller cross-sectional area in a wider spinal canal and therefore is more resistant to injury. It also has a greater potential for recovery after injury than the spinal cord. It is not uncommon to see burst fractures and fracture dislocations in the lumbar spine with greater than 75% canal compromise without associated neurological deficit.

COMPLETE VERSUS INCOMPLETE INJURY

Approximately two thirds of patients currently admitted with acute SCI have incomplete injuries, a significant change from the 1960s, when the majority of patients presented to tertiary care centers with complete injuries. This change has been attributed to a number of factors, including improved recognition and management of SCI in the field, improved treatment at referring hospitals, earlier referral to tertiary care centers, increased automobile and workplace safety, and better recognition of the difference in prognosis between complete and incomplete injuries.

Approximately 1-2% of patients with reportedly complete SCI can become ambulatory. This figure is controversial, with opponents arguing that these patients were wrongly diagnosed and should have been classified as having incomplete injuries. The difficulties associated with the initial diagnosis of SCI are reviewed earlier in this chapter. Alcohol, recreational drugs, sedatives, paralytics, lack of cooperation, and traumatic brain injury can make initial examination difficult. Proponents of the 1-2% recovery rate cite evidence of intact residual nerve fibers on electrophysiological testing of patients with clinically complete lesions ("dis-complete" syndrome; Dimitrijevic, Hsu, and McKay 1992). Given this, some argue for aggressive treatment of all patients with SCI, regardless of whether they are complete or incomplete on initial presentation.

SPINAL SHOCK

Spinal shock is the clinical syndrome often seen in major SCI to the cervical and upper thoracic spinal, characterized by complete loss of somatic motor, somatic sensory, and sympathetic autonomic function. The more severe and higher the SCI, the greater the duration and severity of the spinal shock. Typically, patients suffer from flaccid paralysis, loss of cutaneous and deep tendon reflexes, and anesthesia to all sensory modalities below the level of the inJury. Autonomic dysfunction is characterized by systemic hypotension, cutaneous hyperemia, and bradycardia caused by unopposed vagal tone. The exact mechanism of spinal shock remains unclear. Some propose a vascular event whereby some form of trauma induces hypoperfusion of the spinal cord. Another theory implicates abnormal neurotransmitter effects on impulse conduction.

The major difficulty in clinical practice occurs in the first few hours after SCI, when there is an admixture of the

Tabic 56C.5: Similarities and differences between neurogenic and hypovolemic shock

Neurogenic shock	*Hypovolemic shock*
Hypotension	Hypotension
Bradycardia	Tachycardia
Areflexia	Normal reflexes
Responsive to pressors	Responsive to volume replacement

temporary effects of spinal shock with the pathological, more permanent effects of the SCI. Another problem is the variable duration of spinal shock. In general, the loss of power and sensation that results from spinal shock resolves within I hour after injury. Therefore any weakness or numbness remaining after this time arc likely to indicate physical cord injury rather than spinal shock. The loss of reflexes and autonomic tone may last days to months, depending on the spinal level and severity of the initial injury.

By the time the average patient is evaluated in the field and transferred to a medical center, more than an hour has passed. Spinal shock generally is associated with severe SCI. The exception is the transient quadriplegia seen in athletes playing high-impact sports; in these cases the motor and sensory changes generally show improvement within minutes of symptom onset. If the signs of spinal shock are present, a diagnosis of severe SCI should be assumed and confirmed by diagnostic testing. The rapid changes that can occut within the first 24 hours of an SO underscore the need for frequent and systematic documentation of the neurological examination during that time. These changes also suggest that final prognostication should be delayed until the neurological deficit plateaus.

The clinician should not confuse the signs of spinal shock with those of hypovolemic shock (Table 56C.5). Hypovolemia-induced shock results in hypotension and tachycardia in an attempt to maintain cardiac output, and patients respond to volume repletion. In spinal shock the intravascular volume is normal, but the volume of the intravascular space is increased by loss of vascular tone. Although the heart could partially compensate for this by increasing cardiac output, the presence of unopposed vagotonia inhibits the normal physiological response of tachycardia. As a result, patients with spinal shock respond to sympathomimetic agents (e.g., phenylephrine) better than to volume replacement.

SPINAL CORD INJURY SYNDROMES

Knowledge of the functional organization of the tracts and nuclei that make up the spinal cord is crucial to understanding the effect of SCI at any given level. For several of the described SCI syndromes, however, the anatomical basis of the consequent deficits is poorly understood and the subject of much controversy. Table 56C.6 lists the commonly accepted SCI syndromes. A discussion of their anatomical basis and prognoses follows.

Cervicomedullary Syndrome

This SCI syndrome includes injuries that extend from the medulla to the mid-cervical cord, although injury may extend as far rostral as the pons and as far caudal as the lower cervical cord. The term *bulbar-cervical dissociation pattern* has also been used to describe these injuries. The neurological signs depend on the severity and level of injury. Respiratory arrest, loss of sensation in the C1-C4 dermatomes, quadriplegia, and hypotension damage to the spinal tract of CN V may result in facial numbness with an onionskin or Dejerine pattern of greater involvement posteriorly and perioral sparing or in sensory loss mainly in the brow area, depending on the details of the SCI. In the most extreme cases death can result. Proposed mechanisms of injury include direct stretch injuries (as in cases of atlanto-occipital dissociation), injury to the vertebral arteries, compression of the cord by a ruptured disc or vertebral burst fracture, and displacement of the odontoid peg.

The examination finding of an upper cervical sensory level in combination with facial numbness should lead to the conclusion that the lesion lies at the cervicomedullary junction. The spinal tract of CN V is organized in an onionskin pattern, with the fibers for perioral sensation crossing at the most rostral end of the tract and periauricular sensation at the most caudal end of the tract. Injury to the lower medulla and upper cervical spine results in injury to the most caudal fibers in the spinal tract of CN V, sparing the rostrally placed fibers subserving perioral sensation.

bell's cruciate paralysis should be included in any discussion of SCI at the cervicomedullary junction. This syndrome includes not only signs of the cervicomedullary syndrome but also quadriparesis characterized by arm greater than leg weakness. In the past, this pattern of injury was attributed to compression of the decussating pyramidal tracts in the ventrolateral aspect of the spinal cord at the level of the anterior rim of the foramen magnum and odontoid peg. The motor fibers to the upper extremities were postulated to decussate rostral and ventral to the

Table 56C.6: Most common incomplete spinal cord injury syndromes

Cervicomedullary syndrome
Central cord syndrome
Anterior cord syndrome
Posterior cord syndrome
Brown-Sequard syndrome
Con us medullar is syndrome
Cauda equina syndrome

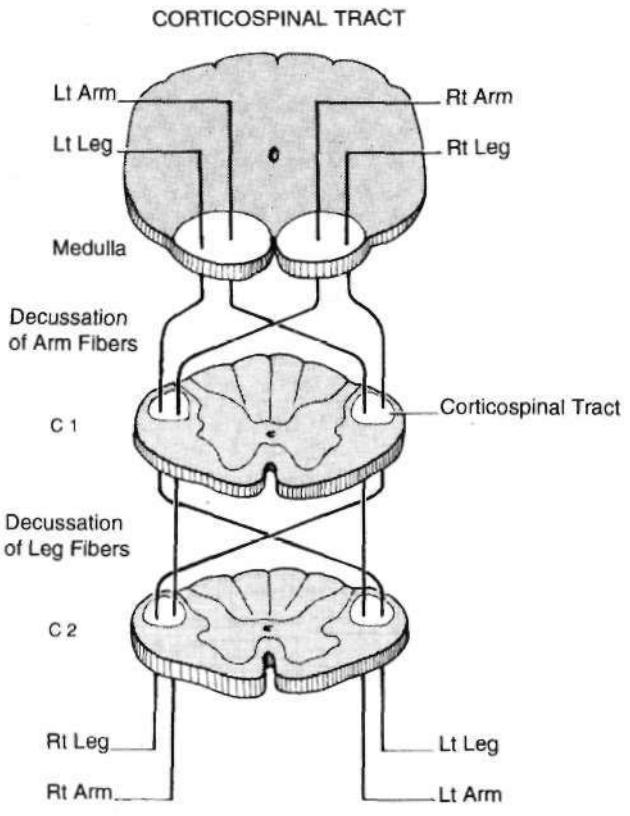

FIGURE 56C.2 The decussation of the axons in the corticospinal tracts. The upper, middle, and lower cross-sections show the medulla, the spinal cord at CI, and the spinal cord at C2, respectively. The axons subserving arm function cross the midline between the medulla and CI, whereas those subserving leg function cross between CI and C2. As noted in the text, recent evidence does not support the lamination concept in the corticospinal tract. (Reprinted with permission from Tator, C. H. 1994, "Classification of spinal cord injury based on neurological presentation," in *Neurotrauma,* eds R.J. Narayan, J. E. Wilberger Jr, & J. T. Povlishock, McGraw-Hill, New York, pp. 1059-1073.)

lower extremity fibers and to descend through the spinal cord in the medial aspect of the lateral corticospinal tracts. The upper-extremity fibers were believed to decussate between the foramen magnum and CI, whereas **the** lower-extremity fibers decussate more caudally between CI and C2. Consequently, the mote ventrally placed upper-extremity fibets would be more susceptible to injury at the level of the foramen magnum than the lower-extremity fibers. (Figure 56C.2 and Figure 56C.3) This anatomy of the injury remains controvetsial. No evidence has been found to support the theory that arm and leg fibers decussate at diffetent levels of the spinal cord. Indeed, there is evidence that the atm and leg fibers are intermingled at the **level of the decussation (Levi,** Tator, and Bunge 1996). Research in nonhuman primates suggests that only upper-extremity fibers may travel in the unctossed ventral corticospinal tracts and that injury of these venttally located ttacts at the level of the foramen magnum may

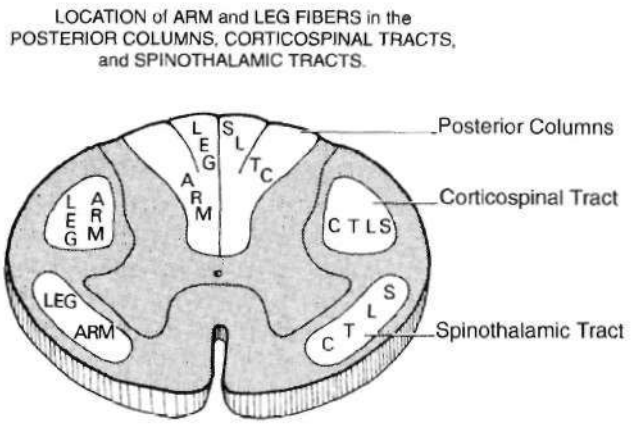

FIGURE 56C.3 Topographic distribution in the posterior columns, corticospinal tract, and spinothalamic tract. The locations of the axons subserving arm and leg function are shown in the three tracrs. Similarly, the locations of the axons subserving sacral (S), lumbar (L), thoracic (T), and cervical (C) function in the three tracrs are indicated. (Reprinted with permission from Tator, C. H. 1994, "Classification of spinal cord injury based on neurological presentation," in *Ncurotrauma,* eds R. J. Narayan, J. E. Wilberger Jr, & J. T. Povlishock, McGraw-Hill, New York, pp. 1059-1073.)

explain the ptefctential arm weakness seen in this syndrome. The prognosis for recovery usually is good.

Acute Central Cord Syndrome

Originally described by Schneider (1954), this SCI syndrome is characterized by arm greater than leg weakness, patchy sensory loss, dysesthesias, and areflexia. The injury is generally in the midcervical to lower cervical spine. Differentiating between an acute central cord syndrome and cruciate paralysis on clinical examination alone can be difficult. Computed tomography (CT) and MRI scanning have largely eliminated this difficulty, although the presence of cranial nerve abnormalities usually rules out an isolated central cord syndrome (Table 56C.7). The syndrome is commonly seen in cervical injuries in older adults with cervical spondylosis. The classic presentation is of an older adult with bruising of the forehead and quadriparesis caused by a fall forward, causing hyperextension of the neck. Schneider and colleagues hypothesised that during hypercxtension the cervical spinal cord in these patients is trapped anteriorly by an ostcophyric bar and posteriorly by hypertrophied ligamentum flavum, resulting in central hemaromyelia and necrosis with surrounding edema (Figure 56C.4). His theory was based on the premise that the corticospinal tracts are arranged in a topographic manner, such that the medial fibers subserving arm function are more medially placed than the fibers subserving leg function. As a tesult, in an injury to the central cord, the leg fibers would be injured less than the more centtally placed arm fibers. The anterior hotn cells would

Table 56C.7: Comparison of central cord syndrome with cruciate paralysis

	Central cord syndrome	*Cruciate paralysis*
Site of lesions	Midcervical to lower cervical Anterior horn cells Lateral corticospinal tract (medial part)	Lower medulla and upper cervical cord (anterior aspect) Corticospinal decussation caudal to the pyramids
Clinical manifestation	Arms weaker than legs; flaccid arms acutely; legs normal or variably weak; lower motor neuron deficits persist in upper limbs	Arms weaker than legs; flaccid arms acutely; legs normal or variably weak; upper motor neuron deficits develop in upper limbs +/- Trigeminal sensory deficit +/- Cranial nerve dysfunction
Prognosis for neurological recovery	Variable	Usually good

Source: Reprinted with permission from Tator, C. H., Duncan, E. G., Edmonds, V. E., et al. 1993, "Changes in epidemiology of acute spinal cord injury from 1947 to 1981," *Surg Neurol,* vol. 4, pp. 207-215.

also be damaged, resulting in a lower motor neuron (LMN) type of injury. In cases of central cord syndrome without spondylosis or obvious mechanical compression, Schneider later hypothesized that a vascular event involving the central aspect of the spina! cord could result in a similar injury. The anterior spinal, vertebral, and medullary arteries supply the ventral third of the spinal cord. During trauma these arteries can be stretched or transiently-occluded, resulting in ischemic injury to the spinal cord. The dorsal and lateral aspects of the spinal cord are less prone to ischemic injury because the pial mesh, supplied by both the anterior and posterior spinal arteries, serves them.

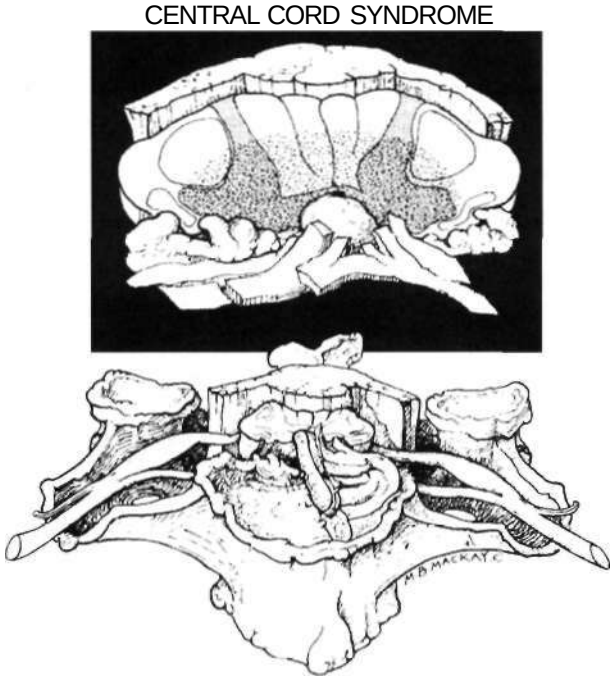

FIGURE 56C.4 Central cord syndrome. The drawing depicts a case of cervical spondylosis with osteoarthritis of the cervical spine, including anterior and posterior osteophytes and hypertrophy of the ligamentum flavum. Superimposed is an acute hyperextension injury that has caused rupture of the intervertebral disc and infolding of the ligamentum flavum. The spinal cord is ciimpressed anteriorly and posteriorly. The central portion of the cord *{rough stippling)* sustained the greatest damage. The damaged area includes the medial segments of the corticospinal tracts presumed to subserve arm function. (Reprinted with permission from Tator, C. H, 1994, "Classification of spinal cord injury based on neurological presentarion," in *Neurotrauma,* eds R. J. Narayan, J. E. Wilberge Jr, & J. T. Povlishock, McGraw-Hill, New York, pp. 1059-1073.)

Schneider's theory remains controversial. Anatomical studies have demonstrated the arm and leg fibers in the corticospinal tracts to be intermingled, as in the pyramidal decussation. More recent work using MRI and limited autopsy data has demonstrated a pattern of injury very different from that proposed by Schneider (Quencer et al. 1992). Both autopsy and MRI failed to demonstrate central cord necrosis or hematomyelia. Rather, the injury appeared to involve predominantly the white matter tracts, with evidence of edema and demyclination of large axons including but not limited to the corticospinal tracts, with little evidence of injury to the central gray matter. In fact, injury appeared to be concentrated along the posterolateral aspect of the cord. A unifying hypothesis explaining the pattern of injury in patients with an acute central cord syndrome docs not currently exist.

Prognosis for patients with acute central cord syndrome is fair. Recovery is rarely complete and depends on the pattern of injury. Patients with evidence of hematomyelia ot cord disruption on MRI have the worst prognosis. Recovery favors the lower extremities over the upper extremities. The upper extremities often are left severely weak and clumsy secondary to severe proprioceptive loss. Overall, 50% of patients with acute central cord syndrome and no evidence of hematomyelia will recover enough lower-extremity function to walk independently. There is no clear evidence that early surgical intervention improves outcome, but prospective, randomized trials are under way. If there is no evidence of bony or gross ligamentous instability, some surgeons place patients in cervical traction for 48-72 hours after injury. Thereafter, the patients are taken out of traction, and further imaging is obtained to

rule out occult instability. Many surgeons currently favor delayed surgery, waiting for the patients to reach the plateau phase of recovery, which usually occurs 6-12 weeks arret injury. Conservative treatment before surgical intervention generally includes the use of a hard cervical collar because it is believed that the swollen cord is more prone to injury from micromotion of the spine at the level of injury. Surgery is then offered to patients with significant spinal cord compression. For patients not considered surgical candidates, the cervical collar usually is discontinued after 12 weeks. Patients who present with gross instability usually are placed in traction and operated on within 48 hours. Emergent surgery is reserved for patients with abnormal alignment of the spinal column refractory to cervical traction and patients with acute disc herniation. The use of corticosteroids in SCI is highly controversial, although many centers favor the use of methylprcdnisolone within the first 8 hours after injury.

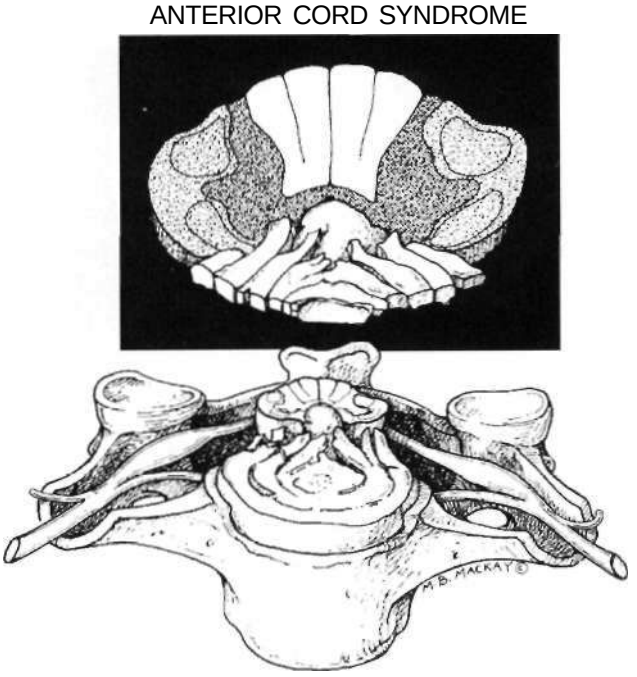

FIGURE 56C.5 Anterior cord syndrome. A large disc herniation is shown compressing the anterior aspect of the cord and resulting in damage *(rough stippling)* to the anterior and lateral white matter tracts and to the gray matter. The posterior columns remain intact. (Reprinted with permission from Tator, C. H. 1994, "Classification of spinal cord injury based on neurological presentation," in *Nettrotrauma,* eds R. J. Narayan, J. E. Wilberger Jr, J. T. Povlishock, McGraw-Hill, New York, pp. 1059-1073.)

Anterior Cord Syndrome

Acute anterior cord syndrome, also originally described by Schneider, is characterized by complete paralysis below and hypalgesia at the level of injury, with preservation of posterior column sensory modalities at and below the lesion. This syndrome may be associated with an anterior spinal artery occlusion or trauma. Typical injuries include large disc herniations and burst fractures with retropulscd bone fragments (Figure 56C.5). Acute surgical intervention usually is performed. Corticosteroid use is controvetsial. Prognosis for recovery of motor function is poor (10-20% recover functional motor control of the limbs), but some return of pain and temperature sensation can be expected.

Posterior Cord Syndrome

Acute posterior cord syndrome may not occur. It has been described as resulting from destruction of the posterior aspect of the cord, sparing the vcntrally placed spinothalamic tracts (Figure 56C.6). Patients with this syndrome can be expected to suffer complete paraplegia wirh loss of proprioception and vibration sense. Pain and temperature sensation and light touch are preserved.

Brown-Sequard Syndrome

A true Brown-Sequard syndrome, in which the patient suffers ipsilateral loss of motor control and posterior column function below the level of injury and contralatetal loss of pain and temperature sensation, usually one to two dermatomes below the level of proprioceptive loss (injury to fibers crossing the midline to join the ascending spinothalamic tract), is rare (Figure 56C.7). This pattern of sensory loss is often called dissociated, that is, with posterior column and spinothalamic tract loss being on opposite sides of the body. Loss of sphincteric function is variable and has a good prognosis for recovery. The mechanism of injury involves damage to one lateral half of the spinal cord, most commonly in the cervical cotd. Partial syndromes and combinations with other SCI syndromes ate common. Evolution from a bilateral complete injury to a Brown-Sequard syndrome has also been described. The causes of this injury are legion. Penetrating ttauma, spinal fracture, spinal dislocation, disc herniation, vasculitis, and radiation-induced injuty are common. The prognosis for recovery is good, with 90% of patients regaining the ability to walk independently.

Conus Mcdullaris Syndrome

Acute conus medullaris syndrome accounts for approximately 25% of all SCIs, These injuries can result in a range of lower-extremity dysfunction, usually with flaccid lower-extremity paralysis and loss of bladder and anal sphincter function. Sensory loss is variable. The anatomical basis of this injury pattern lies in the telationship between the conus

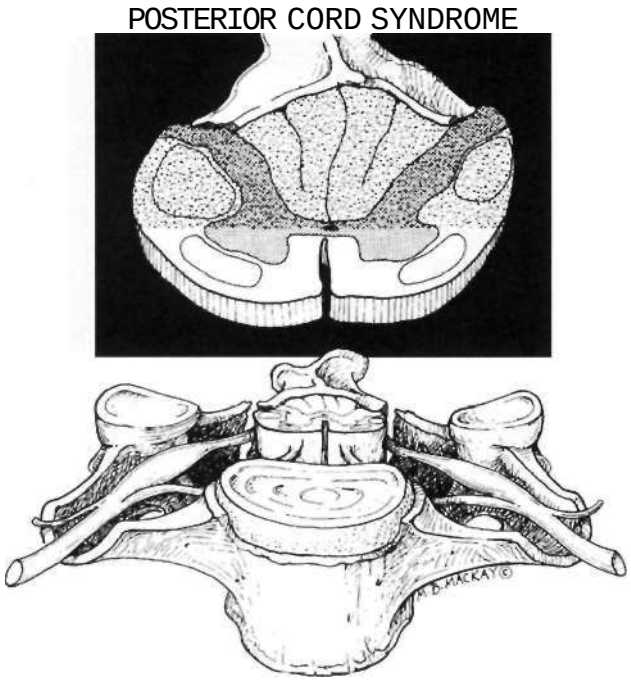

FIGURE 56C.6 Posterior cord syndrome. A laminar fracture is depicted with anterior displacement of the fractured bone and compression of the posterior aspect of the spinal cord. The damaged area of the cord *{rough stipphng)* includes the posterior columns and the posterior half of the lateral columns along with the corticospinal tracts. (Reprinted with permission from Tator, C. H. 1994, "Classification of spinal cord injury based on neurological presentation," in *Neurotrauma,* eds R.). Narayan, J. E. Wilherger Jr, & j. T. Povlishock, McGraw-Hill, New York, pp. 1059-1073.)

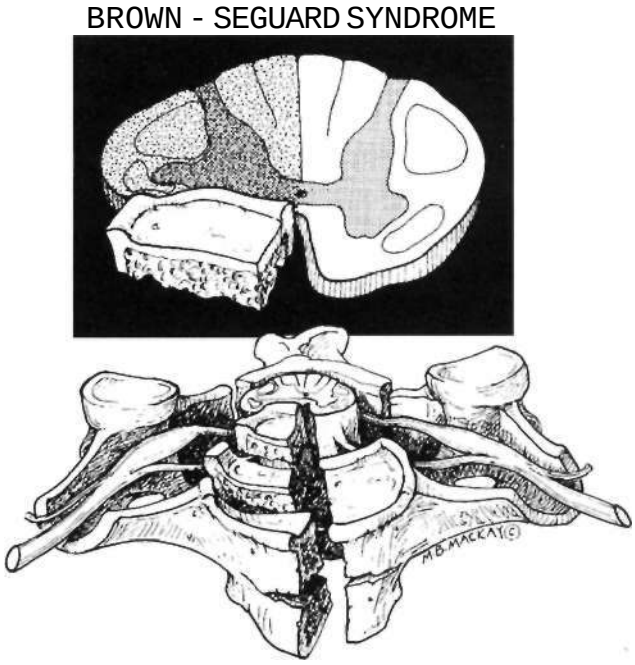

FIGURE 56C.7 Brown-Scquard syndrome. A burst fracture is depicted with posterior displacement of bone fragments and disc, resulting in unilateral compression and damage *(rough Stippling)* to one half of the spinal cord. (Reprinted with permission from Tator, C. H. 1994, "Classification of spinal cord injury hased on neurological presentation," in *Neurotrauma,* eds R. [. Narayan, J. E. Wilbcrgcr Jr, & J. T. Povlishock, McGraw-Hill, New York, pp. 1059-1073.)

medullaris and the thoracolumbar junction. In most patients, the conus lies directly opposite the vertebral bodies of T12 and LI, with the tip of conus not extending past the Ll/2 disc space, Biomechanically, this is a region of high stress, with the spinal column transitioning from the rigid thoracic spine to the more mobile lumbar spine. As a result, flexion-distraction and hurst fractures are common in this region (Figure 56C.8). These injuries produce a combination of upper and lower motor neuron deficits, including muscle atrophy, weakness, spasticity, and the development of a neurogenic bladder. Sensory abnormalities may vary. Recovery is variable. The use of corticosteroids remains controversial.

Cauda Equina Syndrome

The cauda equina normally begins at the level of the Ll/2 disc space, distal to the conus medullaris. This bundle of nerves is composed of the lumbar, sacral, and coccygeal nerve roots from L2 to CO. Injury to the cauda equina obviously is not a true SCI, but nevertheless the cauda equina syndrome is generally considered in the context of SCI. Partial and complete cauda equina syndromes are common. Rapid diagnosis and surgical intervention may improve outcome. The cauda equina is more resistant to injury than is die spinal cord. Typically, patients present with weak or flaccid lower extremities with at least partially preserved sensation. Knee and ankle jerks are absent. Sensory loss usually is asymmetrical and can be radicular, as opposed to the sensory impairments seen in the conus medullaris syndrome, which are more symmetrical. So-called saddle anesthesia is the most common sensory deficit. Saddle anesthesia denotes loss of sensation around the anus, genitals, perineum, buttocks, and posterior-superior thighs. Loss of bowel, bladder, and sexual function is also common. Urinary retention is the most common feature of a cauda equina syndrome; in the absence of urinary retention there is only a 1 in 1000 chance of having a cauda equina syndrome (OT.aoire, Crockard, and Thomas 1981; Kostuik et al. 1986). The cauda equina syndrome can be complete, albeit rarely. Sensory axons are much more resistant to injury than motor axons. The detailed signs depend on the level of the injury. A large, centrally herniated disc at L5/S1 can result in bladder and anal sphincteric dysfunction with associated perianal numbness and little or no other motor or sensory

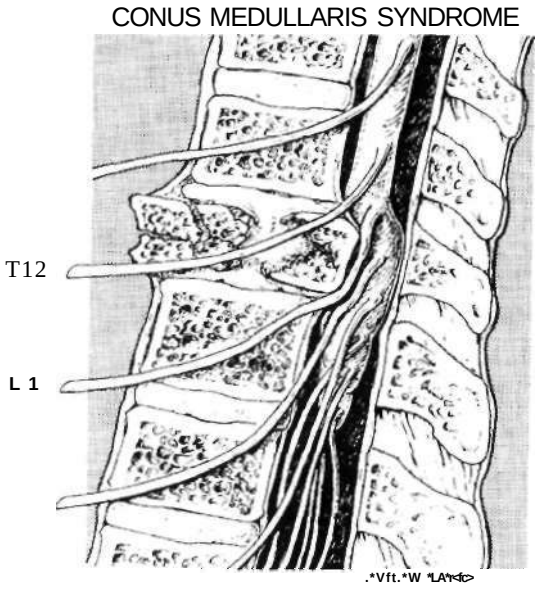

FIGURE 56C.8 Conus medullars syndrome. A burst fracture of T12 is depicted with posterior dislocation of bone fragments from the vertebral body into the spinal canal, resulting in compression of the conns medullars. Almost all the lumbar cord segments arc opposite the TI2 vertebral body, so a severe compression injury at this level could affect all the lumbar and sacral segments of the cord. (Reprinted with permission from Tator, C. H. 1994, "Classification of spinal cord injury based on neurological presentation," in *Neuroirauma,* eds R. J, Narayan, J. R. Wilberger Jr, &). T. Povlishock, McGraw-Hill, New York, pp. 1059-1073.)

dysfunction. Pain in cases of cauda equina syndrome can vary from absent to quite severe. In cases of severe pain, the pain is often asymmetrical and can be radicular.

The most common cause of a cauda equina syndrome is a large, acutely herniated disc (Figure 56C.9). However, absolute disc si?.e does not determine the extent of the cauda equina syndrome because it is possible for patients with underlying lumbar canal stenosis to present with a cauda equina syndrome from a moderately sized disc. Other causes include epidural compression from bony collapse, epidural tumor spread, epidural hematoma, and carcinomatous meningitis.

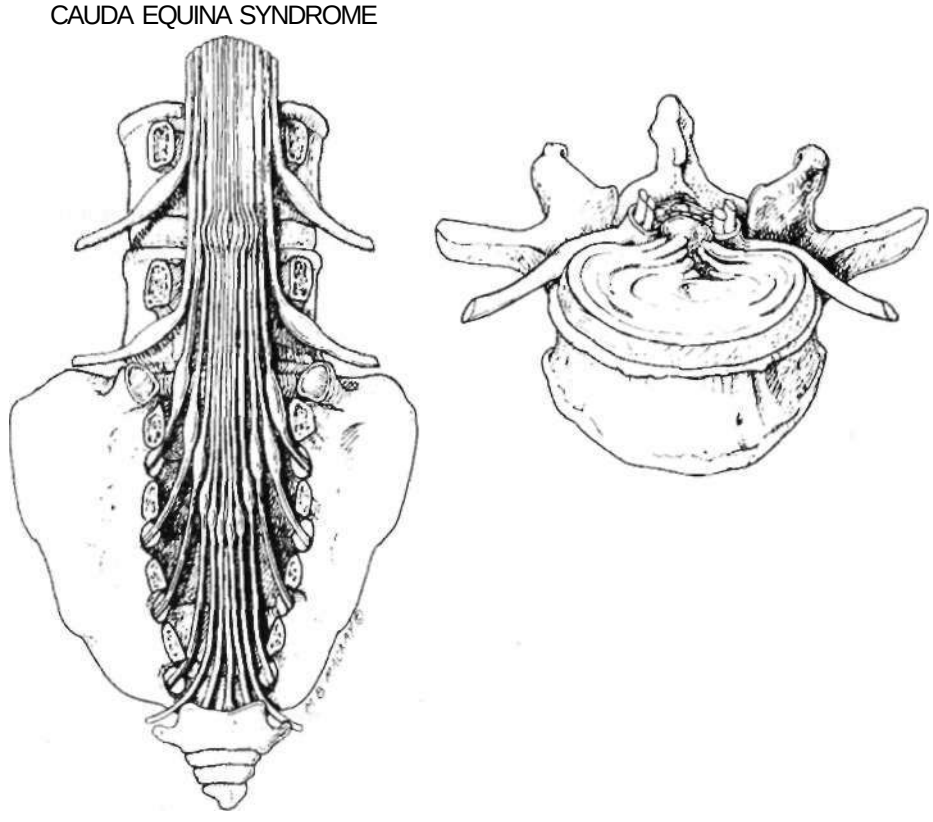

FIGURE 56C.9 Cauda equina syndrome. The drawing shows an acute central disc herniation of L4-L5 with major compression of the central aspect of the cauda equina. The medially placed sacral roots from S2 downward sustain the maximal compression, whereas tin- moiv laterally located L5 and SI roots are completely or partially spared. (Reprinted with permission from Tator, C. H. 1994, "Classification of spinal cord injury based on neurological presentation," in *Neurotrauma,* eds R. j. Narayan, J. E, Wilberger Jr, & J. T. Povlishock, McGraw-Hill, New York, pp. 1059-1073.)

Initial management should include a through neurological examination, including assessment of perineal sensation, anal sphincter function, and urinary retention. Urinary retention is easily assessed by measurement of the pnstvoid residua! (PVR). A PVR greater than 150 mL in adults indicates bladder dysfunction and may be caused by injury to the sacral roots. However, a large PVR may result from pharmacological blockade by anticholinergics or opiates. Therefore in a case of suspected cauda equina injury, a large PVR is a particularly sensitive but not specific indicator of injury. Imaging should include plain radiographs of the lumbar region and MRI of the thoracic and lumbar spine. In the absence of an MRI scan, a myelogram is indicated because a contrast-enhanced CT is much less sensitive. Care should be taken to ensure that the imaging includes the conus and at least screens the thoracic spine if no injury is evident below Tl2. Corticosteroids have not proven useful in most settings, although in some cases of carcinomatous meningitis, symptoms have improved with corticosteroids.

Outcome is variable but generally good compared with those of other incomplete SCIs. The earlier the decompression with emergent intervention, the better the prognosis. Motor and sensory changes have been known to improve dramatically. However, patients presenting with loss of perineal sensation and bowel or bladder difficulties often show little improvement in these symptoms.

Transient Spinal Cord Injury Syndromes

Transient SCI syndromes include a variety of conditions that have in common significant loss of neurological function with rapid return to normal function. These syndromes arc most commonly seen in young athletes.

The burning hand syndrome is characterized by transient paresthesias and dysesthesias in the upper extremities, often most severe in the hands. The symptoms usually are bilateral and symmetrical. This syndrome is often confused with "stingers," which are usually unilateral and felt to be secondary to unilateral nerve root or brachial plexus traction injury. The exact mechanism of injury is unclear, although some form of mild SCI secondary to cervical hyperextension has been suggested. These injuries tend to occur most often in patients with cervical spondylosis and congenital spinal stenosis. Though transient, these symptoms should raise concern, and for an athlete with repetitive episodes of burning hands, investigation should include cervical spine radiographs {including odontoid and flexion and extension views) and MRI of the cervical spine (including short TI inversion recovery sequences to help rule out ligamentous injury). In the acute setting, flexion and extension views should be obtained only after standard anteroposterior and lateral views do not demonstrate any significant injury. If the patient is in severe pain, we advise use of a cervical collar and delay of flexion and extension studies until they can be tolerated by the patient. In any case, the studies should be aborted if the patient develops worsening pain or neurological changes during the maneuver. CT scanning can be used to further define bony anatomy if any abnormality is detected on radiographs or MRI.

Transient quadriplegia or spinal cord concussion is also a transient SCI commonly seen in athletes. Unlike in the burning hand syndrome, which is limited to the upper extremities, patients present with loss of motot and sensory function in all four limbs. Most patients recover within minutes, all within hours, and those who do not do so have a more serious SCI. The exact mechanism of the transient syndrome is unclear, but it probably is caused by distortion of the nerve fibers of the spinal cord, which is of sufficient degree to produce conduction block but not to cause axonal degeneration (neurapraxia). Again, hyperextension injury in the setting of cervical stenosis or spondylosis has been implicated as the biomechanical mechanism of injury. Workup is as described for burning hand syndrome except that one episode is considered enough to warrant workup. If a cervical abnormality is found, a discussion should ensue regarding the risk of continuing contact sports. If no abnormality is present on plain film or MRI, other causes of quadriplegia should be considered, including head injury. A screening CT scan or MRI of the head should he obtained if there is any suspicion of a head injury. Although no hard data exist, there are rough guidelines for return to play after these transient syndromes (Torg 1987; Torg et al. 1997; Boockvar, Durham, and Sun 2001). Referral to a neurosurgeon or orthopedic surgeon specializing in spinal disorders is generally recommended.

Spinal Cord Injury Without Radiographic Abnormality and Spinal Cord Injury Without Radiological Evidence of Trauma

SCI without radiographic abnormality (SCIWORA) is most commonly seen in children, whereas SCI without radiological evidence of trauma (SCPWORET) is most commonly described in adults. The distinction between the two syndromes is subtle, and both syndromes may eventually cease to exist as the sensitivity of MRI continues to improve. Classically, radiographic evidence includes only plain films and CT. SCIWORA presents as a mild to moderate SCI with no evidence of bony injury. However, cases of complete SCI have also been reported. The laxity of the ligaments and paraspinous musculature has been implicated as an etiological factor in SCIWORA. Patients with SCIWORET have abnormal imaging of their spine on presentation but no evidence of trauma. Abnormalities such as cervical spondylosis, Klippel-Feil syndrome, and congenital spinal stenosis often are detected without evidence

of fracture or malalignment. In truth, many of these injuries may represent missed diagnoses. A hairline fracture, disc disruption, or epidural hematoma in the case of a patient with ankylosing spondylitis may be difficult to assess on plain film or CT.

An extremely rare cause of SCIWORA or SCIWORET is nucleus pulposus embolism. In this syndrome, trauma results in herniation of disc material into the venous channels in the adjacent vertebral body. This in turn may cause impairment of venous drainage of the spinal cord at that level. Spinal cord infarction may occur. CT and plain film may reveal a fracture of the vertebral endplatc but otherwise no bony abnormality to explain the extent of injury. This is believed to be an extremely rare cause of SCI and should remain a diagnosis of exclusion. Other causes of venous congestion and spinal cord infarction such as transverse myelitis and AV fistula should be considered before nucleus pulposus embolism is diagnosed.

Post-traumatic acute SCI without direct trauma to the spine is a nebulous syndrome that includes SCI caused by injuries to sites other than the spine and spinal cord. Penetrating trauma to the chest and abdomen can result in direct injury to the radicular feeding arteries of the spinal cord and cause hypotension and shock, resulting in a spinal cord infarct. Patients with severe atherosclerosis can undergo plaque embolism with a similar result. Unlike in SCIWORA or SCIWORET, the cause of injury is clear, although there is no evidence of SCI on plain film or CT.

Penetrating Spinal Cord Injury

The two most common penetrating injuries to the spine and spinal cord are missile injuries (particularly gunshot wounds) and stab wounds. Several general principles can be gathered from the management of gunshot wounds and stab wounds; these can later be extrapolated in to cover other clinical scenarios.

High-velocity missile injuries to the spine (e.g., 9 mm and fully jacketed rifle rounds) usually result in biomechanically stable injuries. This is not to imply that they are benign, however. Injury can be threefold. First, foreign material can be carried into the spine and spinal cord by the missile. This can include soil, plant matter, skin, blood, muscle, bone, and bowel contents depending on the missile trajectory, Such foreign material can result in osteomyelitis, epidural abscess, and meningitis, which may be chemical or infectious. Intestinal injury can lead to severe infection in the presence of a CSF leak, and fistulas between the extradural and intradural space have been reported. Second, a high-velocity missile can result in direct injury to the cord and surrounding tissues, usually leading to either complete or partial transection of the cord or possibly spinal compression by an epidural or subdural hematoma. Last, high-velocity missiles can cause a "blast effect" on the tissues surrounding the path of the missile. As a missile passes through an object, there is a transfer of energy from the missile to the surrounding tissue. Depending on the tissue and the velocity and nature of the missile, this energy can be dissipated over a large area. Fluid-filled structures tend to spread rhis energy over larger distances. As a result, a bullet passing from anterior to posterior and lodged in the T12 disc space can result in a complete injury to the conus without actually touching the conus. Diffuse hemorrhage in the white and gray matter can be identified on autopsy.

In the presence of bowel injury, antibiotic therapy is recommended. Persistent CSF leak may necessitate local debridement and repair. As noted earlier, the development of a CSF fistula can be a serious complication. In the absence of bowel injury and CSF leak, the use of antibiotics remains controversial because osteomyelitis and intradural infection arc quite rare. Corticosteroid use is contraindicated, given the concern for the possibility of infection.

Stab wounds to the spine rarely result in complete SCI. The spinal anatomy usually drives the offending blade to one side of the spinal cord or the other. This can result in the Brown-Sequard syndrome or a variant thereof, Dural laceration and CSF leak, epidural hematoma, nerve root injury, and brachial plexus injury have also been described. In acute stab wounds of the spine and spinal cord, the examiner should consider the presence of concomitant injury to the surrounding tissues.

Initial management of penetrating injuries to the spine and spinal cord should include plain films and CT, A screening CT of the area surrounding the site of injury should be performed to rule out occult injury to other structures in these regions. MRI scanning is generally of little use because of artifact from retained metal fragments. CT myelography may be substituted and indeed is preferred for evaluation of a CSF leak or nerve root injury. Foreign bodies should be left in situ until the patient is evaluated by the appropriate surgical specialists because significant hemorrhage from a previously tampo-naded vessel is theoretically possible upon removal of an imbedded foreign body. Antibiotic treatment is indicated, particularly in the setting of a CSF leak. Corticosteroids are contraindicated for the reasons described earlier. Persistent CSF leak may necessitate surgical exploration or lumbar drainage. Incomplete SCI in the setting of an intradural foreign body is generally considered an indication for surgical intervention. Depressed bone fragments may also necessitate surgical debridement. Recovery is generally good, in keeping with the incomplete nature of these injuries.

Delayed effects have been noted with penetrating as well as nonpenetrating SCI. As discussed later in this chapter, migration of bullet fragments, inflammatory responses to retained foreign bodies, and toxicity from metals such as copper and lead must be considered.

Delayed Post-Traumatic Spinal Cord Syndromes

Several SCI syndromes develop in the late stages (months to years after SCI). The most common of these is syringomyelia. These lesions typically result from the cystic degeneration of the injured spinal cord, particularly in cases of hemorrhagic necrosis and spinal cord infarct. The cysts spread rostrally and caudally, often involving the central region of the spinal cord. The abnormality may consist of a single cyst or multiple adjacent loculated cysts. The cysts may or may not communicate with the subarachnoid space and may be filled with protcinaccous fluid. Arachnoiditis is often seen in conjunction with post-traumatic syringomyelia, although the conditions may occur independently. The extent of injury correlates with development of both disorders: The more severe the injury, the more likely syringomyelia and arachnoiditis are to develop. Approximately 3% of patients with SCI develop syringomyelia. The most widely held theory relates to altered CSF flow whereby arachnoiditis leads to a blockage in the normal CSF flow pattern, resulting in accumulation of CSF in the central canal and surrounding gray matter. The CSF may he under absolutely increased pressure or may transmit venous, arterial, respiratory, or postural pressure effects. Symptoms include both motor and sensory abnormalities. Motor abnormalities include ascending [,MN abnormalities above and descending upper motor neuron (UMN) abnormalities below the level of injury in an incomplete injury. Sensory abnormalities involve the spinothalamic tracts as they cross in the region of central cord. Sensory abnormaliries may also include progressive chronic pain syndromes with causalgia-like symptoms. Bowel and bladder function may also deteriorate. However, asymptomatic syringomyelia is not uncommon, and the demonstration of progression is important in assessing its relevance. Therefore follow-up observation is often warranted. Baseline studies should include an MR1 scan of the complete neuroaxis. This will establish the anatomy of the syrinx and serve as a basis for later comparison. Special attention should be given to examination of the craniocervical junction to rule out a Chiari malformation and the need for posterior fossa decompression. Also, untreated hydrocephalus may contribute both to a Chiari malformation and syringomyelia. Further tests may include a cine-MRI to evaluate CSF flow patterns and myelography with immediate and delayed scanning to determine whether communication exists with the subarachnoid space. Some specialists obtain baseline and serial electromyography and spinal somatosensory evoked potential studies as objective measure of disease progression. Despite the array of potentially invasive and expensive diagnostic tests available, patient complaints remain the most sensitive measure of disease progression. Loss of any neurological function can be devastating to a patient with an SCI and can translate into significant loss of independence. Nonsurgical treatment is limited to observation and palliative care. Disease progression often occurs in a steplike fashion with long intervening plateau periods. A number of surgical approaches have been developed to treat this disorder, with mixed results. At best, symptoms show only temporary improvement; often there is only arrest of disease progression. Surgical approaches include dural augmentation and lysis of subarachnoid adhesions, cyst fenestration, and shunting. Multiple approaches have been used in the shunting of syrinxes, including syringo-subarachnoid, syringopleural, and syringoperitoneal shunt. Failure rates can be as high as 50% in the first 2 years. Low flow through the system has been implicated as the cause of shunt failure. Revision can be attempted, hut failure rates tend to increase with time. The overall prognosis for patients with progressive syringomyelia is poor.

Post-traumatic microcystic myelomalacia is another delayed syndrome encountered in patients with SCI. Symptoms can be similar to those of post-traumatic syringomyelia. MRI and direct observation reveal microcystic degeneration of the spinal cord. These observations have led to the name of *marshy cord syndrome.* Detailed pathological studies of the syndrome have yet to be performed. The disorder is not well characterized, and treatment options are limited. The prognosis is similar to that of syringomyelia.

Arachnoiditis has already been mentioned. As an independent finding, it is a rare complication of SCI. Although there is a loose correlation between severity of injury and the potential to develop arachnoiditis, many patients with severe SCI never develop the disorder, and patients with less severe insults (intraoperative durotomy during surgical decompression) may go on to suffer from arachnoiditis. Symptoms usually are progressive, and abnormalities generally spread to include previously unaffected areas. Abnormal connective tissue bands between the arachnoid and pia mater, arachnoid and spinal cord parenchyma, and nerve roots of the cauda equina lead to progressive strangulation of the normal spinal cord or nerve roots. Cases of tethered cord syndrome, similar to spinal dysraphism, have been described. Uutethering operations have had limited success. Patients generally describe progressive loss of neurological function. MRI scanning and myelography, in particular, best demonstrate the abnormality. There is currently no treatment, and the prognosis is poor, alrhough the severity of symptoms and degree of disease progression are highly variable.

A variety of pain syndromes have been described in the immediate period after SCI. Only 25% of patients go on to develop a chronic pain syndrome, mostly of the neuropathic type. Treatment consists of opiate and nonopiate medications, including tricyclic and selective serotonin reuptake inhibitors, antidepressants, and antiepileptic drugs. The mechanism or action of the antidepressants and antiepileptic drugs is considered in Chapter 50. Opiates can be delivered systemically or intrathecally. Intrathecal

delivery is accomplished by the use of an indwelling pump refilled at regular intervals.

MANAGEMENT OF ACUTE SPINAL CORD INJURY

The improvement in outcome for patients with acute SCI has resulted from better management both in the field and upon arrival at the hospital. Management in the field should include the assumption that all trauma patients suffer from spinal injuries and SCI until proven otherwise. Initial hospital management should also include the assumption that every patient has multiple systemic injuries until proven otherwise. Treatment of patients with acute spinal cord damage who have no history of injury poses more of a difficulty. In general, acute loss of any type of neurological function should be treated as a medical emergency. Rapid diagnosis and intervention may prevent further loss of function and lead to improvement. For the patient with a potential SCI, a detailed physical and neurological examination is mandatory. The decision to obtain imaging studies of the spine depends on the patient's history and physical examination findings. All patients with an altered mental status should undergo a complete diagnostic workup.

Management in the Field

All trauma patients should be treated as potentially unstable until proven otherwise. Initial management should include assessment of the airway, breathing, and circulation (ABCs). For patients with cervical spinal injuries, injury to the prevertebral soft tissues, hematoma, or edema of the retropharynx can lead to airway obstruction despite neurological ly intact muscles of respiration. The ability to speak is a rough indicator of adequate air movement through the airway. In the comatose patient, cyanosis, stridorous breath sounds, flaring of the nostrils, and tracheal deviation may all be signs of a compromised airway. Foreign bodies and vomitus are common causes of upper airway obstruction and can be readily cleared. Altered mental status may also result in dysfunction of the soft tissues of the upper airway, leading to obstruction. This often can be treated with the use of an oral or nasal airway. In cases of severe injury to the airway or airway edema, a field tracheostomy or cricothyroidectomy may be necessary. Despite an unobstructed airway, a high SCI or altered menial status secondary to traumatic brain injur) or intoxication may lead to impaired respiration. Lack of breath sounds may be caused by a pneumothorax and necessitate placement of a flutter valve in the field. Observation often reveals paradoxical breathing (abdominal breathing), shortness of breath, cyanosis, and a progressive decline in mental status. Such a patient may need endotracheal or nasotracheal intubation. Although maintaining normal tissue oxygenation is paramount in **the** treatment of trauma patients, there is a risk associated with manipulation of the cervical spine for intubation in patients with undiagnosed cervical spine injuries. The indications for nasotracheal and endotracheal intubation in trauma patients remain unclear. Good judgment and technique should be exercised at all times. Systemic blood pressure and heart rate should be assessed and an intravenous line placed as soon as possible. Patients with acute SCI may **not** respond to standard volume resuscitation; care should be taken to assess for spinal shock and autonomic dysfunction. In the case of bradycardia and hypotension unresponsive to fluid replacement, the use of vasopressors is indicated.

Once the ABCs have been addressed, extrication and mobilization should be considered. The patient's neck should be placed in a rigid cervical collar. If an adequate collar is unavailable, a rolled towel and tape can be used to secure the neck. Care should be taken to avoid airway obstruction. The patient's spine should be kept in as close to neutral alignment as possible. Once the patient has been extricated, a rigid backboard slum Id be used for i ran spurt. The head can be raped to the backboard or secured with sandbags for further stability. The possibility of hemodynamic instability, secondary to ongoing bleeding not identified before mobilization, or autonomic dysfunction should be noted. Intravenous fluids and pressors should be immediately available.

There are a few exceptions in the treatment of patients with traumatic SCI, as described earlier. In the very young patient care should be taken to avoid placing a collar or towel that may result in axial distraction (2002). If a properly fitting cervical collar is unavailable, sandbags or rolled towels and tape may suffice. Older adults with kyphotic deformities should not be forced into an anatomically neutral position, particularly those with ankylosing spondylitis. In this case, forcing the spine into neutral alignment may cause subluxation of the spine at the level of a fracture, leading to further neurological impairment. Immobilization of the spine rather than restoration of alignment should be stressed. Finally, rhe patient may be a danger to himself or herself. Patients who are agitated and uncooperative because of stress, head injury, or intoxication may need to be sedated or chemically paralyzed as well as intubated. This should be considered a measure of last resort in the field because once a patient is intubated, sedated, and chemically paralyzed, the opportunity for serial neurological examination is lost.

Initial Hospital Assessment

If the goal on transfer is stability, then the goal on arrival to the hospital is rapid diagnosis. Timely delivery of acute care can prevent complications, which can last a lifetime or be fatal. In most settings, a multidisciplinary trauma team is

needed. However, not all hospitals have access to the services available to a major trauma center. Often, patients are transferred to a local community hospital for initial screening and then possible transfer to a major trauma center, Despite the difference in resources, the initial evaluation at an outside hospital is critical to patient outcome.

Initial evaluation should consist of recapitulation of the ABCs. Further swelling of the airway, vomiting, or teeth dislodged during intubation may lead to airway obstruction not present in the field. Chest radiographs may reveal poor tube placement in the field. A delayed or intubation-related pneumothorax may necessitate placement of a chest tube. Placement of flutter valves in the field also necessitates placement of chest tubes in the hospital. Ongoing hypotension may necessitate the placement of central venous and arterial lines to monitor fluid resuscitation. Further discussion of initial trauma management is beyond the scope of this chapter. However, it must be stressed that all clinicians treating a patient with acute trauma should be aware of concomitant injury, and efficient dialogue between managing specialties is critical to good patient outcome.

Once the patient has cleared the ABCs, the detailed examination, or "D," follows. This should include a derailed neurological examination in all patients, which with practice can be performed in minutes. For the patient with a potential or actual spinal cord lesion, this must include assessment of cranial nerve, sensory, and motor function. Cranial nerve dysfunction may be a sign of brain injury or, in the presence of lower cranial nerve dysfunction, of a craniocervical junction abnormality. Because many health care decisions arc based on this early neurological examination and on serial neurological examinations, a standard approach is mandatory. The accepted standard is the AS1A/IMSOP scale, discussed earlier in this chapter. The presence of priapism should also be noted because its presence indicates SCI. The presence or absence of a bulbocavernosus reflex is of controversial utility because as many as 15% of normal patients have an absent reflex (Blaivas, Zayed, and Labib 1984),

The physical examination should also include examination of the patient's neck, abdomen, and back. Obvious deformities should be noted, Examination of the abdomen may reveal ecchymoses and rigidity, indicative of an intra-abdominal injury. The so-called scatbclt sign, a bruise in the distribution of a lap belt, should alert the examiner to the possibility of a flexion-distraction injury of the spine. Examination of the back may reveal bruising and a step-off, further evidence of ligamentous or bony injury. Although a thorough examination of the neck and back is a part of the complete examination of the trauma patient, care should be taken to minimize the number of times a patient is moved. For the patient with an unstable spinal injury, every move can increase the extent of SCI. If a patient must be rolled, the appropriate technique should be used. At least four people are needed. One person maintains the head in neutral alignment in relation to the body and applies gentle traction (in cases of suspected AOD, traction should be avoided), while two others roll the trunk. Those rolling the patient should cross arms in the middle in case one person loses his or her grip. The fourth person is then free to examine the back. Am dehns and clothing should be moved from beneath the patient. After a thorough examination the patient is gently rolled back into place.

In most instances, patients with presumed acute SCI will arrive at the hospital on a rigid backboard. These backboards allow safe and efficient patient transfer during transport and initial workup at the hospital. Backboards are uncomfortable to lie on for prolonged periods of time. Apart from discomfort, there is the risk of developing a decubitus ulcer, which may cause lifelong complications. Most centers try to limit the use of backboards to less than 2 hours.

It is often difficult to determine the level of bony injury from the neurological examination, given the anatomical differences between spinal cord level and spinal level. However, the standard is to report the cord level. In addition, head injury, sedation, peripheral nerve injury, and intoxication can cloud the initial assessment. This underscores the need for serial neurological examinations. Any condition that might affect the accuracy of the neurological examinations should be noted.

Radiographic Evaluation

Plain radiographs remain the standard in the initial evaluation of any patient with a possible SCI. A screening latetal cervical spine film is part of the immediate trauma workup. Knowledge of a significant cervical subluxation or AOD will affect the course of initial workup and prioritization of consultations. Once a patient has been evaluated and stabilized, further imaging workup should be obtained.

Radiographic and clinical clearance of the cervical spine is needed before a cervical collar can be removed. Many trauma centers require a full set of cervical spine films (anteroposterior, lateral, and open mouth odontoid views) on all trauma patients. The lateral view must include the top of the Tl vertebral body. If the Tl vertebral body is poorly visualized, a Swimmer's view should be obtained. If this is not possible, a CT scan thtough this level shun hi be obtained. Oblique films are useful for examination of the facets and neural foramina but are not considered standard. As access to helical CT scanning increases, so will the substitution of a screening spiral CT of the cervical spine for plain films. Screening helical CT of the cervical spine has been demonstrated to have at least the same sensitivity and specificity of plain films (Blackmorc ct al. 1999; Blackmore, Mann, and Wilson 2000; Hanson et al. 2000). To substitute for plain films the study must include coronal and sagittal reconstructions. Because many trauma patients

now undergo screening CT scans of the abdomen, pelvis, and head, a screening CT scan of the cervical spine adds only a few minutes to the time spent in the scanner, as opposed to 20-30 minutes to obtain plain films. Should physical examination of the neck reveal any sites of midline point tenderness, the recommendation is for fine cut CT studies (3 mm) through the appropriate levels. Any abnormality detected on plain film or screening CT scan should also be followed up with a fine cut study.

Recent recommendations by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons Joint Section on Disorders of the Spine and Peripheral Nerves dispute the need for cervical spine films in .ill trauma patients (Tabic 56C.8). Patients who meet all the criteria to he deemed asymptomatic can have their cervical spines cleared solely on the basis of history and physical examination. This decreases the number of radiological examinations performed and reduces the use of health care resources (2002).

In a patient with a normal neurological examination and no evidence of bony injury or malalignment on radiograph or CT scanning, a cervical collar can be removed if the following criteria are met. The patient must be fully conscious and able to complain of pain on palpation of posterior cervical spine and paraspinous musculature. If a patient is fully conscious and pain-free, the cervical collar may be removed. Strain and spasm of the cervical paraspinous musculature is a common post-traumatic disorder and is commonly called whiplash, a poorly characterized and poorly understood syndrome whose discussion is beyond the scope of this chapter. Significant pain in the absence of bony injury may also indicate a ligamentous injury. Ligamentous injuries heal poorly and are normally an indication for surgical stabilization. "Clearance" of the cervical spine in a patient with neck pain can be handled in one of several ways. If the pain is severe and the patient is unable to move his or her neck, the cervical collar should be replaced. The patient may then return for evaluation after the pain has subsided (usually 7-10 days). Lateral, anteroposterior, open mouth odontoid, flexion, and extension views of the cervical spine are then obtained without a cervical collar. Many centers require the presence of a physician during these studies. The patient should be instructed to flex and extend the neck slowly and to stop if pain, weakness, or sensory abnormality develops. If abnormal movement is not detected and the patient's pain has improved, the cervical collar can be removed and the patient referred to physical therapy. Persistent, severe pain usually is considered an indication for MRI. Flexion and extension studies may also be obtained in the acute setting if full range of motion is not hindered by pain. Many centers delay obtaining dynamic-radiographs because a physician may nor be available to accompany patients to radiology in a busy emergency room. Patients with altered mental status should remain in cervical collars until they can comply with physical examination. Patients unable to comply with examination for a prolonged period of time {weeks to months) may undergo an MRI, upright films, and passive flexion and extension studies under fluoroscopy to clear the cetvical spine. Protocols vary from center to center.

Tabic 56C.8: Criteria for classification of an asymptomatic trauma patient with respect to cervical spine injury

Neurologically normal: Patients must have a Glasgow Coma Scale score of 15 and must not have any of the following: disorientation to person, place, or time; inability to remember three objects at 5 minutes; delayed or inappropriate response to external stimuli; or any focal motor or sensory deficit.

Not intoxicated: Patients should be considered intoxicated if they have: a recent history of intoxication or intoxicating ingestion; evidence of intoxication on clinical examination; or laboratory evidence of the presence of drugs that alter the level of alertness, including blood alcohol levels higher than 0.08 mg/dL.

No *neck pain or midline tenderness:* Midline tenderness is present if the patient complains of pain on palpation of the posterior midline neck from the nuchal ridge to the first thoracic vertebra.

No *associated injury that is distracting to the patient:* Significant distracting injuries have been defined as long bone fractures; visceral injuries necessitating surgical consultation; large lacerations, degloving, or crush injuries; large burns; and any other injury that might impair the patient's ability to participate in a general physical, mental, and neurological examination.

Source: Adapted from Hoffman, J. R., Mower, W. R., Wolfson, A. B., et al. 2000, "Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma," N *Engl j Med,* 343, p. 9499.

The standard for imaging of the thoracolumbar spine in trauma patients is less rigid. In the absence of point tenderness or other localizing sign (e.g., bruising or step-off), screening films are not mandatory. Complaints of significant pain referable to the spine should be addressed with imaging studies. Despite negative plain films, a screening MRI scan of the thoracolumbar spine may demonstrate an occult fracture, which can be followed up with a fine cut CT scan. Patients with a significant injury mechanism (high-speed motor vehicle accident or fall from a significant height), patients with an altered mental status, or patients with a spine fracture or detectable ligamentous injury anywhere in the spine should have their complete spine surveyed (there is a 10-15% incidence of a concomitant fracture).

Conventional Tomography

In most instances, conventional tomography has been replaced by CT scanning. The large doses of radiation, the time of image acquisition, and the need for the decubitus position have led to its decline. However, conventional tomography remains the most sensitive way to study horizontally oriented vertebral fractures, particularly those involving the odontoid.

Computed Tomography

CT is the most useful imaging modality available for managing acute SCI. CT scans ate cheap, rapid, and easy to transfer electronically. CT is most sensitive in defining vcrtcbtal bony alignment, fracture pattern, and bony encroachment on the spinal canal. It is also useful in the diagnosis of acute epidural and subdural hematomas. CT allows not only detailed study in the axial plane but also study in the coronal and sagittal planes. Despite these advantages, CT has some significant limitations. In most circumstances, a patient must be transported to the CT scanner. Access to the patient may be limited during image acquisition, making CT scanning unsuitable for unstable patients. Plain radiographs of acceptable quality often can be obtained at the bedside in these patients. CT also does not adequately demonstrate soft tissue anatomy, making it difficult to identify spinal cord, ligamentous, and disc injuries.

CT remains more expensive than plain films. Combined use of plain films and CT is often the most effective use of resources. CT can be used to screen regions such as the cervicothoracic junction and thoracic spine, which can otherwise be difficult to study on plain films. In addition, vertically oriented fractures are best visualized on CT. Therefore in patients with persistent pain and symptoms localized to a particular spinal segment, CT scan of the suspected segment and adjacent segments can be an efficient confirmatory test.

Myelography

In the MR I era, myelography is seldom used in the setting of acute trauma. Despite the added resolution gained from postmyelography CT, the indications for its use are limited. Myelography can often be attempted as a substitute for MR1 when MRI is not possible, and when spinal canal compromise is in question. For example, CT myelography can be used as a substitute for MRI in the diagnosis of a traumatic disc herniation. Additionally, myelography remains the gold standard in evaluating nerve root avulsion {contrast leakage into the surrounding soft tissues can be readily identified).

Magnetic Resonance Imaging

Of the imaging modalities used in the diagnosis and management of SCI, MRI is the only modality capable of consistent and detailed imaging of the spinal cord parenchyma, spinal ligaments and discs, and paraspinal soft tissues. As opposed to myelography, which it has supplanted as the imaging modality of choice in SCI, MRI is noninvasive and can produce higher-quality images in a shorter period of time. MRI can also be useful in detecting occult boil)- injury b\ detecting changes in the bone marrow and soft tissues adjacent to a bony injury. Despite the greater sensitivity of MRI over CT in detecting injury, MRI does not provide adequate anatomical detail of bony structures. There are also several other drawbacks to MRI. MRI is expensive, and a radiologist often is needed to perform and interpret the study. Patients must be left deep in the bore of a large magnet for extended periods of time, precluding its use in unstable patients. Intubated patients must be switched to special ventilators, which often cannot provide complex ventilatory support. Patients must remain still during imaging, necessitating deep sedation or chemical paralysis in noncompliant patients.

Patients must be immobilized before MRI scanning. The commonly used cervical collars are all MRI compatible. Care should be taken to ensure that halos and tongs are MRI compatible (most new traction and halo devices are made of graphite for this reason). Patients with acute penetrating injuries often cannot be scanned because of the artifact from retained metallic fragments and the risk of migration of these fragments in the magnetic field.

Several different MRI sequences are useful in the diagnosis of spinal injury and SCI. Images can be acquired in the axial, sagittal, and coronal planes. Axial images provide detailed information about the cord parenchyma, particularly in latcralizing injury and determining the patency of the subarachnoid space. Sagittal imaging provides information regarding the rostral-can da I extent of injury, spina! alignment, and integrity of longitudinally oriented structures, such as the anterior and posterior longitudinal ligaments. Coronal imaging can be useful in patients with traumatic scoliosis and in studying the integrity of the nerve roots and brachial plexus. Images usually are acquired in 3- to 4-mm-thick slices. T1-weighted imaging provides the greatest anatomical detail and can serve as a reference for comparison with other sequences. T2-weighted imaging is the most sensitive for tissue edema and is often used to assess the extent of cord injury. However, edema often spreads several levels above and below the level of injury, making identification of the exact level of injury difficult on T2-weighted imaging. The extent of injury on acute T2-weighted imaging is not a good indicator of extent of injury in the long term. The presence of hematoma appears to be a much more sensitive predictor of long-term disability. The appearance of hematoma on MRI is very dependent on the interval between injury and imaging. The relative ratios of water, hemoglobin, and hemoglobin breakdown products in a clot at a given time determine its appearance on a particular imaging sequence. Hyperacute clots (up to 2 hours after injury) appear isointense with gray matter on Tl-weighted imaging and (because of their large quantities of protein-neb water) hyperintense on T2-weighted imaging. Acute hemorrhages (a few hours to days after injury) appear isointense on T1- and profoundly hypointense on T2-weighted imaging, in part because of the conversion of oxyhemoglobin to deoxyhemoglobin. Hemorrhages between a few days and

months after injury arc called subacute. ID the early subacute phase, methcmoglobin is contained in intact red blood cells, and hematomas appear bright on Tl- but hypointense on T2-weighted imaging. Late subacute hemorrhages contain a significant amount of extracellular methemoglobin, which appears hypcrintense on Tl- and T2-weighted imaging. In the chronic stage {more than a few months), hemorrhages appear hypcrintense on bothTl- and T2-weighted imaging, with a rim of hypointensity on T2-weighted imaging caused by hemosiderin deposition. Over the years hemosiderin can be cleared by tissue macrophages, but residual hemosiderin in glial cells results in an isointense signal on Tl- and hypointense signal on T2-wcighted imaging. These patterns are summarized in Table 56C.9.

MRI is also very sensitive for detecting injury in the marrow cavities and soft tissues of the spine. Vertebral body fractures result in edema of the marrow spaces, causing them to appear bright on 'I'2-weightcd imaging, Intervertebral disc disruption or herniation has been detected in as many as 54% of traumatic SCIs and appears as a bright signal on T2-weighted imaging (Flanders et al. 1992). If demonstrated, intervertebral disc herniation can be an indication for emergent surgical intervention. Shott Tl inversion tecovery sequences are helpful in the diagnosis of ligamentous injury. Again, depending on the level, significant ligamentous injury may be an indication for surgical stabilization. MRI is also the imaging modality of choice for serial examination of post-traumatic syringo-myelia and hydromyelia. Given the hyperemia associated with acute tiauma, gadolinium enhancement has not been demonstrated to add significantly to the management of acute SCI. However, gadolinium enhancement is quite useful in the workup of patients with SCI caused by malignancy and infection.

TREATMENT OF SPINAL CORD INJURY

The initial management of patients with acute SCI has already been discussed. Until a patient's spine has been declared stable, eithet by tilling out of a spinal injury or by surgical stabilization, care should be taken to maintain the spine in as neutral :i position as possible. Tins may necessitate the use of a cervical collar, traction tongs, or halo.

Cervical collars are cheap and readily available. They should be rigid, and care should be taken to ensure that they fit properly. Poorly fitting cervical collars can cause a decubitus ulcer, which can last a lifetime. Two general types of cervical collar are available: the disposable plastic collars used by emergency professionals in the field and the long-term composite collars used in the hospital, made of foam, cloth, and plastic. Both offer the same mechanical stability, but the disposable type is uncomfortable and can lead to the development of skin breakdown. The soft foam collars available over the counter provide no significant mechanical stability and are contra indicated fot use in patients with spinal injuries.

If a patient ptesents with a malaligned cervical spine fracture or SCI, the use of tong traction is indicated. Early reduction of a malaligned spinal injuty can result in significant pain reduction and return of neurological function (Evans 1961; Brunette and Rockswold 1987; Harrington, Likavec, and Smith 1991; Olerud and Jonsson 1991; Hadley et al. 1992; Lee, MacLean, and Newton 1994; Grant et al. 1999). Significant imptovement in function has been noted in the literature when reduction has been performed within 2 hours of arrival at a major medical center. Data from as late as 8 hours aftet injuty have also demonstrated a significant benefit to alignment restoration. Most advocate reduction aftet diagnosis of the malalignment on CT scan or plain film. The utility of prereduction MRI remains controversial because disc herniation is commonly seen. The bone windows of a head CT scan or at least plain films of the skull should be tevicwed before the tongs arc applied. A temporal or parietal skull fracture may necessitate the use of a halo ring. Radiographic facilities slum Id be immediately available, or if manual reduction is to be performed, the procedure is best performed under fluoroscopy. A conscious patient is ideal because he or she can report any change in neurological function immediately, but this may not be possible in a severely injured or noncompliant patient. Bilaterally, points two fingerbreadths above the pinna and in line with external auditoty meatus are marked and the

Tabic 56C.9: Relative intensity of blood and breakdown products on magnetic resonance imaging over time

	77	T2	*Proton density*
Hyperacute	Isointense	Hypcrintense	Hypcrintense
Acute	Isointense	Very hypointense	Hypointense
Subacute			
Early	Hyperintense rim	Very hypointense	Hypointense
Late	Hyperintense	Hyperintense	Hyperintense
Chronic			
Early	Hyperintense	Hypointense rim, hyperintense center	Hyperintense
Late	Isointense	Very hypointense	Very hypointense

Source: Osborne, A, G, 1994, "Intracranial hemorrhage," in *Diagnostic Neuroradiology*, Mosby, St Louis, pp. 154-198.

area around the sires prepared with antibiotic solution. Shaving usually is not necessary. A line through these points defines the neutral plane of the head and neck. The traction ring should be inspected before use. The ring should be large enough to allow fur swelling of the sculp but small enough to allow for tightening of the pins. Although older stainless steel models may be available for use in the operating room, trauma patients should be placed in an MRI-compatible apparatus. The "S" hook to which the traction cord will be tied should be placed on the tongs before application. Two screws are used. One screw is a set-screw, and the other has a built-in tension pin. Local anesthetic is injected into the pin sites several minutes before application. If reduction of a spinal injury is to be attempted, sedation and intravenous analgesia can be administered. Diazepine can be quite useful as a muscle relaxant, reducing the amount of weight necessary for reduction. Once the patient is ready, both screws are tightened simultaneously until the tension pin protrudes by 1 mm (approximately 30 lb of pressure). The pins should find purchase in the outer cortex of the skull (>150 lb of pressure at the pin sites is needed to penetrate the inner cortex of a normal skull).

After application of the traction apparatus, baseline radiographs should be obtained with no weight attached. In patienrs with SCI and normal alignment, 10-15 lb of traction can be applied. The purpose of traction in these patients is to maintain alignment and to remind caregivers of the presence of an SCI. In patients needing reduction, weight can be applied in 5- to 10-lb increments; the weight should be applied and a new radiograph obtained 5 minutes after application of the weight. This allows for fatigue of injured cervical soft tissues, which may prevent reduction. The amount of weight needed is controversial. Classically 3-5 lb per vertebral body level has been advocated (and 30 lb for a C5/C6 fracture or dislocation). However, in a large or muscular person this may prove inadequate. There is no established maximum weight. The safest technique is to monitor for distraction of the spinal column. Significant distraction at any disc level should prompt reduction in the amount of weight applied. If the malalignment has not been reduced, open reduction or manipulation of the spine must be considered. There are several practical concerns. The pins should be checked routinely to ensure that they maintain the desired amount of tension. Loose pins can pull out and result in significant injury to the scalp. As the amount of weight used increases, the patient may start to slide in the direction of the weight, necessitating the use of restraints. MRI-compatible screws do not have the same pull-out strength as stainless steel screws. If the applied weight exceeds 70 lb, an MRI-compatible halo ring should be considered. A greater amount of weight can be used, with four rather than two screws securing the halo to the skull. Once the malalignment has been reduced, the weight should he dropped to 15-20 lb. An immediate and then routine radiographs should be obtained to confirm that alignment is maintained. The tension pin should be examined daily. Inability to maintain alignment and an incomplete SCI level are indications for immediate surgical intervention (after emergent MRI).

Patients with suspected AOD can be placed emergently into a halo vest. Additionally, a halo vest can be used to immobilize the cervical spine when continuous traction is not feasible (e.g., long-distance transport to a tertiary care center). A health care provider with the appropriate training should apply the halo ring and vest.

Patients with grossly malaligncd spinal fractures of the thoracic and lumbar region are rare. Closed reduction of these fractures is not recommended; because the great vessels are closely associated with the thoracic and lumbar spine, there is a significant risk of injury to these structures with closed reduction. Threatened breakdown of the skin over a fracture is an indication for emergent open reduction and internal stabilization. Nonsurgical thoracolumbar spine fractures can be treated in a variety of orthoses, depending on the type of injury. A detailed discussion of the available bracing options is beyond the scope of this chapter.

In some patients, application of an orthosis, halo ring, or halo vest is the definitive means of spinal stabilization. These patients can then be mobilized within the constraints of their associated injuries. Patients in traction or awaiting surgical stabilization should be maintained under full spinal precautions. A rotating airbed is recommended to decrease the likelihood of decubitus ulcer formation. Early surgical stabilization is recommended. Indications for emergenl surgical intervention can be controversial and will be discussed separately. When possible, stabilization should he performed within 48 hours of injury. Acute trauma patients are at risk for the development of pneumonia, sepsis, deep vein thrombosis (DVT), pulmonary embolism, and skin breakdown. All can be exacerbated by the need for strict immobilization. The development of these morbidities can further delay surgery.

A comparison can be drawn between the injured spinal cord and brain injured by an ischemic stroke. A widely accepted stroke model describes an area of partially injured brain adjacent to the frank infarct. This endangered brain is called the ischemic penumbra. This area can survive if the necessary metabolic substrates are available. For this reason, care is taken to prevent hypoxia and anemia in patients with acute stroke. Similarly, patients with acute spinal injury should remain well ventilated with a Po^ and Pco_2 in the normal range. Furthermore, data exist to support maintaining the hematocrit above 30% and maintaining mean arterial pressure above 90 mm Hg in the acute period (2002). Although some authors advocate acute laminectomy in SCI to improve spinal cord perfusion pressure, the data do not support this argument.

The most important medical intervention that can be performed on the patient with an SCI is the prevention of

further injury. This can be accomplished with vigilance and adherence to spinal protocols.

Pharmacological Intervention

At least four pharmacological agents have undergone randomized controlled trials to determine their efficacy in improving outcome in patients with acute SCI. Two of these agents, methylprednisolone and tirilazad, arc corticosteroids. Naloxone is an opiate agonist that has shown some effect in patients with SCI. GM| ganglioside is a complex sugar that is a normal cell membrane component, Analysis of the data from multiple trials involving these drugs has failed to show consistent or clinically significant results. Nevertheless, the use of methylprednisolone in patients with SCI remains widespread, despite the fact that recent guidelines published by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons Joint Section on Disorders of the Spine and Peripheral Nerves does not advocate using any of these drugs to treat SCI (2002).

A number of animal models of acute SCI support the testing of corticosteroids in human SCI- The mechanism of action of corticosteroids remains unknown, but it is postulated to involve membrane stabilization, reduction of vasogenic edema, alteration of electrolyte concentration at the injury site, and inhibition of endorphin release. Tirilazad, in particular, has been postulated to act as potent free radical scavenger at the injury site. The National Acute SCI Study (NASC1S I), initiated in 1979 and reported in 1984, was the first attempt at a large, randomized, controlled trial of methylprednisolone in acute SCI (Bracken et al. 1984). The study design had significant flaws, including the dosage used. Based on animal data, the drug dosage used was too small to expect any effect (1000 mg bolus and 100 mg daily compared with 1000 mg bolus and 1000 mg daily for 10 days, no control). As a result, NASCIS II was initiated in 198.5 and repotted in 1990 (Bracken et al. 1990). Inclusion criteria were essentially the same for NASCIS I and II; no attempt was made to exclude injuries to the cauda equina or to exclude patients with normal motor examinations. Penetrating SCIs were excluded. In NASCIS II, patients were randomized to one of three groups within 12 hours of injury: methylprednisolone 30 mg/kg bolus, followed by 5.4 mg/kg per hour for 23 hours; naloxone 5.4 mg/kg bolus, followed by 4.0 mg/kg per hour for 23 hours; or placebo. Of the 487 patients (roughly evenly divided between the three groups), 62 of 162 receiving methylprednisolone demonstrated an improvement in sensory scores at 6 months and motot scores at 6 and 12 months. Furthermore, restratification of the data demonstrated that all 62 patients had received methylprednisolone within 8 hours of injury. Side effects were limited to wound healing problems and gastrointestinal bleeding. A numbet of significant criticisms have been raised. Many deal with the complex statistical analysis applied to the small responder group, without interpretation of this data in the context of the entire study-population. For example, the group of patients who received methylprednisolone 8 hours after injury had the same outcome as those who received placebo 8 hours after injury. No attempt was made to standardize other aspects of the medical and surgical management. Review of these aspects of care demonstrated a significant difference between treatment centcts. Finally, both NASCIS I and II lacked a functional outcome measure to determine whether the improvements in motor scores noted were of any clinical significance.

NASCIS III results were reported in 1997 (Bracken, Shepard et al. 1997), Patients were divided into three groups: methylprednisolone for a total of 24 hours, methylprednisolone for a total of 48 hours, and tirilazad for a total of 48 hours. All patients were treated within 8 hours of injury. There was no placebo group, and functional outcome was measured. The 499 patients were nearly evenly distributed between the three groups. Follow-up was performed at 6, 24, and 52 weeks. Analysis of the data suggested that improved motor scores were detected in patients who received 48 hours of methylprednisolone 3-8 hours after injury. No difference in motor score improvement was noted in any group treated within 3 hours of injury. Functional outcome was identical in all three groups, regardless of the timing of drug administration. Based on these data, the designers of NASCIS III recommended the administration of methylprednisolone for 48 hours when patients present 3-8 hours after injury. Like the previous two studies, NASCIS III has been plagued by criticism. Criticism stemmed from the arbitrary nature of the time cutoffs for treatment (<3 versus 3-8 hours after injury), the method used to score motor improvement, and the lack of significant clinical improvement in any group. Although not clinically significant, there is a suggestion of increased rates of pneumonia, sepsis, and death due to respiratory complications among patients who received 48 hours of methylprednisolone treatment.

GMi ganglioside is a complex carbohydrate and is a normal constituent of the neuronal cell membrane. GM_L ganglioside has been implicated in cell growth, development, and repair. Two North American multicenter clinical trials have failed to demonstrate a convincing benefit in patients with acute SCI (Geisler, Dorsey, and Coleman 1991a, 1991b; Gerhart ct al. 1995; Geisler et al. 2001). The data suggest that patients treated with GM| ganglioside may improve faster than controls, but long-term outcome has not been significantly different from that of control groups. For those wishing to administer GM| ganglioside despite the lack of proven clinical efficacy, the accepted protocol is methylprednisolone per the NASCIS II protocol within 8 hours of injury, followed immediately by a loading dose of GM| ganglioside 300 mg and a maintenance dosage of 100 mg per day for 56 days.

No significant randomized clinical trials have been carried out on the use of tirilazad and naloxone apart from their inclusion in the NASCIS studies. There currently is no recommendation regarding their use in acute SCI.

The use of methyl prednisolone and GM, ganglioside in acute SCI treatment remains one of the most controversial topics in the field of spinal cord disorders. Although the data do not suggest efficacy on the part of either agent, great benefit has been derived from these studies. With each phase of the NASCIS studies, the experimental design has become more rigorous and detailed. Only when clinical research is subjected to the same scientific standards as bench research will any significant strides in outcome research be made. Perhaps it is the lack of a medical or surgical treatment with any significant effect on acute SCI that drives clinicians to continue the use of methylpredm-soloue and (IM] ganglioside. Unfortunately, their use is not without risk.

Surgical Intervention

There tire two goals in the surgical management of patients with acute SCI: decompression of the neural elements and spinal stabilization. The timing of acute decompression is a controversial topic and can be influenced by the location of injury. Progressive neurological deterioration in the setting of ongoing compression is the most common justification for acute intervention. Interventions in patients with a fixed incomplete injury and ongoing neurological compression are more controversial. The controversy is likely to continue until the results of well-designed, randomized, controlled trials become available.

The classic teaching in the management of acute central cord syndrome is to avoid acute intervention whenever possible. In fact, in the absence of ongoing compression and neurological deterioration, acute intervention in cervical SCIs is generally accepted to be contra indicated. In the setting of cervical spondylosis, the practice of delayed surgery is based on the experience of Schneider in the 1950s (Schneider 1954). One must keep in mind that Schneider performed his procedures without the benefit of an operating microscope or detailed preoperative imaging. His approach to the cervical disc was from the posterior and involved sectioning of the dentate ligaments and mobilization of the injured spinal cord. However, the literature is rife with examples of miraculous improvement in the setting of acute decompression. Similarly, the 1992 study of thoracolumbar burst fractures by the Scoliosis Research Society reported a 25% complication rate for acute surgery compared with a 3% complication rate for nonoperative management (Gerr/bem 1992). Willi wound healing and instrumentation and graft complications considered, neurological deterioration caused by surgical intervention occurred in 0.6% of patients. Randomized controlled trials comparing early and late surgery are woefully absent in the literature. In one of the few studies available, no significant difference in length of stay or outcome was detected in patients undergoing early and late surgery for cervical SCIs (Vaccaro et al. 1997). In the absence of class I data, other retrospective reports in the literature suggest that early surgical intervention speeds recovery but may not have an effect on long-term outcome.

Traumatic injuries resulting in complete SCI are generally managed on a nonemergent basis with the following exceptions. Closed reduction of malaligned cervical spine injuries should be attempted cmcrgently. Evidence of a herniated disc, bony compression of the spinal cord, or inability to reduce a dislocation should be considered a surgical emergency. However, patients who present more than 24 hours after injury are unlikely to experience any improvement in neurological function. Elective stabilization of unstable injuries soon after injury (within 1 week) allows early mobilization. This may prevent some of the early complications of SCI: pneumonia, decubitus ulcer formarion, and DVT. Class I data in support of these recommendations are currently unavailable.

Acute surgery for incomplete traumatic lesions involving the thoracic spinal cord, conus, and cauda equina is controversial. There are few data to support acute intervention in these patients. Early decompression may shorten the recovery period but docs not appear to improve the extent of recovery. Many centers favor urgent decompression, that is, surgery within 72 hours of injury. This approach has the advantage of allowing the procedure to occur on an elective basis, allowing adequate workup and observation. Although some studies suggest that operative management of these injuries has a higher complication rate than nonoperative management, a closer look at the data reveals that the complications rarely involve injury to the cord. Rather, complications tend to be related to positioning, blood loss, and exacerbation of other injuries (e.g., pulmonary complications).

A detailed discussion of the surgical approaches, instrumentation, and nonoperative treatment strategies is beyond the scope of this chapter.

ACUTE **SPINAL CORD** INJURY SECONDARY TO INFECTION, HEMATOMAS, AND MALIGNANCY

The majority of patients who present with vertebral osteomyelitis, discitis, and epidural or paraspinal abscesses can be managed nonopcrativcly. A variety of surgical and nonsurgical options arc available tor treatment. Indications for surgery include signs of instability, progressive bony destruction despite appropriate therapy, and neurological dysfunction. Acute vertebral body collapse or large epidural collections can lead to compression of the neural elements. Acute loss of neurological function is a surgical emergency. Epidural collections can be drained without bony debridement if the surrounding bone is intact.

Collapsed or unstable vertebrae necessitate extensive debridement and fusion or instrumentation procedures.

In the absence of neurological symptoms and signs, patients with traumatic or spontaneous spinal epidural hematomas can be treated conservatively. Patients with spontaneous hematomas should be evaluated for clotting deficiencies and the underlying problem treated with blood products or factor replacement. Patients with progressive neurological deterioration should be referred emergently for surgical decompression.

Patients with metastatic or primary malignancies of the spine almost always need multidisciplinary treatment. Neurologists, neurosurgeons, and oncologists often find themselves crowded around the same patient. Patients presenting only with pain often can be treated conservatively and scheduled for elective surgery. Patients presenting with sensory changes and radiculopathy can be treated with radiation or chemotherapy and surgery on a semielective basis. High-dose corticosteroids and radiation therapy in many cases can control disease without surgery.

Acute or progressive loss of motor, bowel, or bladder function is a surgical emergency. Patients who present with paraplegia secondary to spinal cord compression (SCC) from malignancy usually have a life expectancy of months. Furthermore, patients with spinal cord compression can progress rapidly from symptoms of back pain to paraparesis and ultimately paraplegia. Patients presenting with paraplegia rarely become fully ambulatory after treatment. Pain is the most common presenting symptom of SCC. Therefore any patient with cancer and back pain has presumed SCC until proven otherwise. MRI is the imaging modality of choice. The entire spinal column should be screened. Plain films and CT should be performed as indicated. High-dose corticosteroid therapy should be initiated immediately. The dosage and type of corticosteroid administered has not been standardized (Cantu 1968; Posner, Howieson, andCvitkovic 1977;Delattreetal, 1989). Dcxamethasone dosages as high as a 100 mg inttavenous bolus followed by 24 mg intravenously every *6* hours for 3 days have been recommended. Corticosteroids often result in neurological improvement within 12 hours. The exact mechanism of action is unclear but may be related to decreasing edema in the injured spinal cord and an oncolytic effect {i.e., reduction in tumor volume). During this interval patients can undergo radiation or surgical therapy. After 3 days the corticosteroids should be weaned back to 4 mg intravenously or orally every 6 hours. High-dose corticosteroid administration is not without risk of complication. Known complications include gastrointestinal perforation and bleeding, infection, and poor wound healing. Patients who have not undergone some form of radiation or surgery in the 3-day treatment period are at risk of developing rebound edema and worsening of their symptoms. Patients presenting more than 48 hours after loss of function usually do not improve and can be treated on a semielective basis as indicated. Surgical techniques for tumor resection and stabilization have evolved over the past 20 years. If a patient's systemic tumor burden is under control, surgical intervention can improve pain control and maintain independence. Survival time plays a role only with respect to the length of postoperative rehabilitation necessary. Obviously, patients whose life expectancy does not extend beyond the anticipated postopetative recovery period arc not surgical candidates. Decision making therefore entails interaction not only between the surgeon and patient but also with oncologist treating the underlying disorder.

SPINAL CORD INJURY AND BLADDER FUNCTION

Complications from loss of normal bladder function arc the second leading cause of death among patients with SCI (Frankel et al. 1998). An improperly functioning bladder not only may cause social embarrassment and poor hygiene but also may lead to local infection, sepsis, hydronephrosis, renal and bladder calculi, vesiculourethral reflux, renal failure, and infertility (Benevento and Sipski 2002; Siroky 2002).

Normal bladder function depends on the coordination of inputs between the cerebral cortex, hypothalamus, brainstem, and spinal cord and their influence on the sympathetic, parasympathetic, and somatic nervous systems (see Chapter 42). The pontine micturition center (Barrington nucleus) directly excites motoneurons in the bladder while inhibiting contraction of the internal urethral sphincter. Nuclei in the periaqueductal gray receive input concerning bladder filling. The preoptic area of the hypothalamus may be involved in the initiation of micturition, whereas the cingulum and premotor area appear to inhibit micturition. Within the bladder wall is the detrusor muscle, a layer of smooth muscle responsible for bladder contraction. Contraction of the detrusor muscle is under control of the parasympathetic nervous system. Parasympathetic input is catried by the pelvic nerves and originates from nuclei in sacral spinal cord segments S2-S4. Sympathetic tone leads to bladder relaxation (/}-adrenergic reccptot) and contraction of the smooth muscle that makes up the internal urethral sphincter (a-adrenergic receptor). This input is carried by the hypogastric nerves and originates from spinal cord levels T11-L2. Finally, somatic efferents control contraction of the striated muscle that comprises the external urethral sphincter. These efferents originate in spinal cord segments S1-S4 (Onuf nucleus) and run in the pudendal nerves.

Normal micturition control is thought to begin with afferent signals from stretch receptors in the bladder wall traveling to the periaqueductal gray. These inputs then project to the hemispheres, where the urge to void is initiated. The cingulum and premotor areas then help to suppress this urge until it is convenient and socially appropriate to initiate micturition by causing increased

tone in the striated muscles that make up the external urethral sphincter (the guarding reflex). When appropriate, the nuclei in the pteoptic area of the hypothalamus initiate contraction of the bladder wall and relaxation of the smooth and striated muscle sphincters. The Barrington nucleus in the dorsomedial pontine tegmentum is believed to coordinate this activity.

Bladder injuries can be divided into two types: disorders of storage and disorders of emptying. Failure to properly store unne can be caused by a hyper-reflexic bladder. The high filling pressures that result from poor bladder compliance can then lead to failure of the bladder sphincters and incontinence. An areflexic bladder neck can also cause storage failure. In this case, there is no obstruction to urine flow. Failure of emptying can be caused by either a flaccid, hypotonic bladder or a hyperactive sphincter causing resistance to urine flow.

In general, the location of SCI dictates the type of bladder dysfunction observed. The action of the cortical, hypothalamic, and pontine micturition centers is to inhibit bladder contraction and coordinate bladder relaxation. Cervical, thoracic, and high lumbar cord injuries result in loss of this inhibitory reflex. In the acute period after an SCI, however, a period of spinal shock exists that may persist for several months. This results in a hypotonic, areflexic bladder. As spinal shock fades, the sacral segmental spinal bladder reflex becomes evident. Capsaicin-sensitive, unmyelinated C-fiber afferents determine bladder tone. The bladder becomes hyperactive and can develop high filling pressures. This contraction may or may not be associated with sphincter relaxation, which is the normal physiological sequela ot bladder contraction. This condition is called detrusor-sphincter dyssyncrgia, and in males it can lead to significant bladder obstruction (for unclear reasons it does not cause as significant a degree of obstruction in females). Up to 85% of patients with a lesion above the sacral cord suffer from this disorder. Although these patients may suffer from incontinence, the abnormal sphincter function leads to obstruction in the setting of high bladder pressures. Therefore these patients are at greatest risk of vesicourethral reflux and its sequelae. Patients with sacral cord or cauda equina lesions may suffer an LMN type of bladder impairment. In this case the bladder has little or no tone and the sphincters are incompetent, leading to incontinence, Both patterns of bladder dysfunction can range in severity that correlates with the severity of the underlying spinal cord or cauda equina injury. Additionally, one type of injury may over time develop into the other, and some patients may suffer from a mixed picture. Urodynamic testing is the screening tool of choice and can help determine the type of dysfunction present {see Chapter 42).

In the setting of acute SCI, the goal of bladder management should be to prevent the development of a dilated atonic bladder. Overstretching of the bladder may cause irreparable damage to any remaining bladder wall function. Prevention is best accomplished with the use of intermittent catheterization. Although patients with complete cord injuries have no sensation of bladder fullness, an over distended bladder can lead to episodes of autonomic dysreflexia, a potentially life-threatening condition caused by hypertension and bradycardia. Use of a long-term indwelling urethral catheter has been demonstrated to carry as high as 6.5 times the rate of urinary tract infection as the use of condom catheters and intermittent catheterization (Esclarin De Ruz, Garcia Leoni, and Herruzo Cabrera 2000). It is a generally accepted principle that the use of intermittent catheterization is superior to the use of both condom and indwelling catheterization. It should be noted that the rate of infection between condom and intermittent catheterization is approximately equal and that the rate of serious infection (e.g., pyelonephritis, urosepsis, and epididymitis) is identical for all three techniques of bladder drainage. Interestingly, some studies have suggested that assisted catheterization may carry a higher risk of infection than sclf-catheterination (Bakke and Vollset 1993). There is some evidence to support the concept that infections with normal perineal flora are the most common forms of infections and that with time the genitourinary tract may become resistant to infection with these organisms. Assisted catheterization may challenge the patient's immune system to an array of new pathogens to which the patient cannot develop immunity. Therefore patients with high cervical quadriplcgia may benefit more from the use of an indwelling catheter than assisted intermittent sel^catheterization, As in bowel care, adherence to a set regimen and good technique is the best way to reduce infection, regardless of the method of bladder drainage.

The chronic management of bladder dysfunction is beyond the scope of this chapter. The clinician has at his or her disposal a number of pharmacological, prosthetic, and surgical options. Studies are also under way in the use of inert bacterial strains to colonize the genitourinary tract and suppress the growth of other bacterial strains (Hull et al, 2000). The choice of treatment depends not only on the type of injury but also on the patient, comorbid disease, drug regimen, caregivers, socioeconomic setting, and desire for sexual function.

SPINAL CORD INJURY AND BOWEL FUNCTION

Bowel dysfunction in SCI can lead not only to the inconvenience and embarrassment of fecal incontinence but also to ileus, gastric ulcers, gastroesophageal reflux disease, discomfort, anorexia, diverticular disease, hemorrhoids, impaction, constipation, and autonomic dysreflexia (Benevento and Sipski 2002). Initiation of a strict bowel program can help prevent or minimize the effect of these complications.

Physiologically, the colon can be regarded as a tube of smooth muscle bounded by the ileocecal valve proximally

and the anal sphincter distally. Puborcctalis forms a sling of muscle around the rectum. Contraction of the puborcctalis muscle results in elevation of the rectum and formation of a more acute angle between the rectum and anus. This impedes the flow of liquid and feces through the rectum to the anus. The anal sphincter is made up of two regions: the internal anal sphincter (IAS) and the external anal sphincter (EAS). The IAS is made up of a band of continuous smooth muscle at the rectum end of the colon. The EAS is made up of a circumferential band of striated muscle continuous with the pelvic floor just proximal to the anus.

Continence is maintained by the resting tone of the IAS. A centrally mediated reflex causes the EAS and puborcctalis to contract during a Valsalva maneuver and coughing, helping to maintain continence. Colonic movement is mediated by a number of inputs. The gastrointestinal tract contains an intrinsic nervous system, which includes a plexus of nerves (Auerbach's plexus) situated between the layers of muscle forming the walls of the colon. The intrinsic plexus promotes peristaltic movement of luminal contents toward the tectum. The autonomic and somatic nctvous systems modulate the activity of the colon. Last, local chemical and tactile stimuli can modulate colonic motor activity and emptying. The sympathetic input to the colon is carried by the superior and inferior mesenteric nerves (spinal cord levels T9-T12) and hypogastric nerves (T12-L2). The vagus nerve carries parasympathetic input from the esophagus to the splenic flexure. The pelvic nerves (S2-S4) carry parasympathetic fibers to the descending colon and rectum. Somatic input to the rectum and pelvic floor travels in the pudendal nerves (S2-S4).

Peristaltic movement of the large intestine is primarily autonomous, with some spinal cord influence. Peristaltic waves push luminal contents both toward and away from the ileocecal valve in the ascending colon, but movement in the descending colon is primarily toward the anus. Gap junctions between smooth muscle cells in the wall of the colon help coordinate contraction. Breakdown products in the lumen of the colon help stimulate or inhibit contraction. Stretch of the smooth muscle wail results in a reflex involving Auerbaeh's plexus: The smooth muscle proximal to the area of luminal distension contracts while the region distal to the area of distension relaxes. In this fashion the bolus in the lumen is propelled forward in the descending colon. The vagus nerve and sacral parasympathetics stimulate colonic motility. The gastrocolic reflex increases colonic motility after a fatty or proteinaceous meal. The exact mechanism is unclear but may also involve the sacral parasympathetics.

The IAS and EAS are normally active in conjunction with the puborectalis muscle in maintaining an acute anal-rectal angle. This acts to maintain continence. The IAS normally maintains continence of gas and fluids, whereas the EAS maintains continence of solids. As the rectum fills and distends with stool, the IAS relaxes, and the tone of EAS increases. The sensation of the need to defecate is also relayed to the cerebral cortex. Voluntary contraction of the IAS helps to maintain continence until it is convenient and appropriate to initiate defecation. There is also reflexive contraction of the EAS and the puborectalis muscle during Valsalva and coughing. Voluntary relaxation of the puborectalis and the EAS results in involuntary movement of stool into the rectum. As stool fills the rectum, the anal rectal angle becomes less acute, making the passage of stool easier. Valsalva and increased peristalsis lead to further evacuation of stool.

Despite the presence of the autonomous enteric nervous system, SCI can have a profound impact on bowel function. Bowel dysfunction can be divided into two types: UMN and LMN dysfunction. In UMN dysfunction, a lesion exists in the spinal cord above the level of the conus medullaris. This results in a hyper-rcflcxic bowel, with increased colonic wall and anal tone. The connections between the sacral spinal cord segments and the colon remain intact, This results in reflex coordination and stool movement. Voluntary inhibition of the EAS is lost, and the anal sphincter remains tightly closed. This results in constipation and fecal retention. Involuntary emptying of the rectum can occur as stool builds up in the rectal vault. An LMN pattern exists when injury occurs at the level of the conus or cauda equina. Disruption of the parasympathetic outflow to the colon occurs. The result is in an areflexic colon. In this case peristalsis depends only on the myenteric plexus. Because of the slow transit time, stool tends to be rounder and drier. The nerves to the EAS and puborectalis muscles are also disrupted, resulting in loss of sphincter tone and a reduction in the anal rectal angle. This injury leads to constipation with frequent episodes of incontinence.

Patients with SCI have varying amounts of sensation with respect to defecation. Even in patients with a complete SCI there may still be a feeling of discomfort associated with a large amount of stool in the colon, as well as episodes of autonomic dysreflexia. In the acute setting, SCI can be associated with decreased motility throughout the gastrointestinal tract (ileus). Patients may need a nasogastric tube because gastric emptying may be significantly delayed. This decreased motility can result in abdominal distension to the extent that diaphragmatic excursion is inhibited, often further compromising respiratory function. Initiation of a bowel program early in the hospital course can prevent problems in the subacute period and shorten overall hospital stay.

Approximately 37% of patients with SCI need some form of assistance with bowel care. A detailed discussion of bowel management in chronic SCI is beyond the scope of this chapter. However, several key points can be summarized (Bryant 2000). Strict adherence to a bowel regimen is critical to success. Involvement of the patient, family, and caregivers is crucial. The seated position allows easier passage of stool because of the anatomical relationship between the puborectalis muscle and the rectum. The type of program used must take into account the type of injury

present (UMN or LMN). Patients with a UMN pattern of bowel dysfunction can benefit from stimulation of the anal sphincter and triggering of the normal sacral spinal cord reflexes. Stretching of the anal sphincter can result in autonomic dysreflexia in some patients, and caregivers should be prepared for this in high-risk patients. The goal of dietary and pharmacological management should he the formation of soft, well-formed stools that can be passed easily after digital stimulation. Patients with an LMN problem may need intermittent manual disimpaction to prevent incontinence. The goal of therapy is the formation of firm, well-formed stool that can be stored and easily removed manually. Dietary and pharmacological manipulation of bowel function is multifaceted. Patients often are given a warm beverage 30 minutes before the start of a bowel program to help stimulate the gastrocolic reflex, which can be partially preserved even in complete spinal cord lesions. Dietary control includes the inclusion of high-fiber foods and psyllium to give stools bulk and increase transit time. Pharmacological intervention can include stool softeners such docusate sodium, which emulsifies fat in the gastrointestinal tract. Senna tablets stimulate Aucrbach's plexus, increasing peristalsis. Bisacody) and similar suppositories act as mucosal irritants and can help stimulate colonic motility. Finally, gentle soapsud enemas can help to soften hard, impacted stool. Bowel care and hygiene can be intensely private matters. Care must be taken to protect a patient's privacy and dignity as much as possible. Surgical intervention can take the form of a colostomy or ileostomy in patients unable or unwilling to perform adequate bowel care.

SEXUAL DYSFUNCTION, SEXUALITY, AND **FERTILITY IN SPINAL** CORD **INJURY**

Sexual function and sexuality are complicated issues in the patient with SCI (see Chapter 42). Although the mechanics of sexual function may be partially preserved in patients with complete and incomplete SCI, libido often is adversely affected. Decreased libido probably is secondary to concerns regarding body image, poor sexual performance, and possibly concerns regarding continence during sexual activity. Pharmacological and prosthetic advancements have had a significant impact on the sex lives of patients with SCI, in addition to the strides made in counseling and support groups. A detailed review of the topic is beyond the scope of this chapter, but several key points deserve comment. Among these is the point that men and women demonstrate profound differences in the effect of SCI on sexual and reproductive function (Benevcnto and Sipski 2002).

One model of sexual function divides the sexual response into four phases: arousal, plateau, orgasm, and resolution (Masters and Johnson 1966}. Ejaculation normally is a component of the orgasm phase. Erection occurs during the arousal phase and can be stimulated in one of two ways. Direct stimulation of the penis and perineum results in an erection mediated by a spinal sacral parasympathetic reflex. An erection can also be stimulated psychogenic^lly. In this case erotic thoughts and nontactile stimuli result in erection. Nerve fibers in the hypogastric plexus (T11-L2) and sacral parasympathetics both play a role in tins type of erection. Therefore men with complete SCIs above Tl 1 lose the ability to have psychogenic erections but maintain the ability to have a reflex erection secondary to perineal stimulation. Men with incomplete injures above Til may retain the ability to develop an erection in response to psychogenic stimuli and retain reflexive erections. Men with complete injuries below spinal cord level L2 and those with cauda equina (LMN) injury often maintain the ability to develop psychogenic erections but lose reflexive erections. Incomplete LMN injuries result in a spectrum of erectile dysfunction, from nearly normal reflexive and psychogenic erection to complete impotence.

However, erection is only a single event in one phase of a four-phase process. During orgasm, involuntary smooth muscle contractions normally result in ejaculation of semen and the sensation of pleasure. The connections that trigger these sensations are unclear and may be carried via the autonomic nervous system. Data regarding orgasm and patients with SCI have been collected only through the use of questionnaires. No attempt has been made to standardize responses. However, several studies have demonstrated similar results (Bors and Comarr I960; Phelps et al. 1983; Alexander, Sipski, and Findley 1993). Approximately 45% of men with SCI reported achieving orgasm through coitus or masturbation. In one study 38% of patients with complete SCI reported achieving orgasm. Ejaculation involves the coordination of sympathetic, parasympathetic, and somatic nervous systems. Injury to any of these systems can result in difficulty with normal ejaculation. Retrograde ejaculation results in the delivery of semen into the bladder rather than out the penile meatus, thereby hindering fertility. Studies report that 4".. of patients with complete and 32% of patients with incomplete UMN lesions retain the ability to ejaculate (Bors and Comarr 1960). Eighteen percent of patients with complete and 70% with incomplete LMN lesions are reported to ejaculate normally.

The sexual response in women has been better studied in the laboratory than in men, albeit later (Sipski, Alexander, and Rosen 1995a, 1995b, 1997, 200 I; Sipski, Rosen, and Alexander 1996; Whipple, Cerdes, and Komisaruk 1996). The female sexual response can be divided into the same four phases as the male sexual response. Arousal can be measured by detection of clitoral engorgement and vaginal lubrication. As in men, arousal can be either reflexic or psychogenic. UMN lesions above the T11-12 spinal cord level appear to prevent psychogenic arousal while preserving reflexic arousal. Similarly, LMN lesions appear to prevent reflexic arousal but do not disturb psychogenic arousal. In one study, only 52% of women with SCI were able to stimulate themselves to orgasm (Sipski, Alexander,

and Rosen 1995). Women with complete LMN injures are the least likely to achieve orgasm, and women with SCI in general take longer to reach orgasm than women without SCI. The sensation of orgasm appears to be identical between injured and control patients. Finally, no episodes of autonomic dysreflexia were noted among women with SCI who are able to achieve orgasm. Orgasm in women also appears to involve an autonomic sacral reflex.

Treatment of sexual dysfunction has been limited to the treatment of erectile dysfunction (ED) in men. Although many men with SCI can develop erections, they often complain that they are unable to maintain erection and that their erections are not firm enough to allow intercourse. Prostheses, vacuum pumps, rings, and penile injections have all been successful in managing ED. The type of method used depends on the patient's comfort and type of dysfunction. Orally active vasoactive drugs such as sildenafil have had n dramatic effect on the treatment ot ED. Studies have demonstrated it to be safe in men with SCI. Little research has been undertaken to improve the female sexual response after SCI. Studies have suggested some benefit of sildenafil in the treatment of female sexual dysfunction (Sipski et al. 2000), but the benefit is not as dramatic as that observed in men.

Men with SCI injury have a number of obstacles to overcome with respect to fertility. First, SCI can have a dramatic effect on the ability to ejaculate. Furthermore, sperm from patients with SCI have impaired motility, and semen from the same patients may not provide the same substrate for conception when compared with controls (Bracket! et al. 1996), although the connection between SCI and poor sperm or semen quality had yet to be made at the time of study. Recurrent urinary tract infections and renal complications of SCI may also lead to infertility. Improved methods of harvesting sperm and semen have led to dramatic improvements in the ability of men with SCI to father children. SCI may not decrease fertility in females. However, pregnancy rates among women with SCI are lower than among age-matched controls. Whether this represents a physiological derangement or the decision of women with SCI not to have children remains to be determined.

AUTONOMIC DYSREFLEXIA

Distension of the bladder or bowel in patients with SCI may lead to episodes ol autonomic dysreflexia, a potentially life-threatening situation. Seen in patients with SCI at the midthoracic level or above, the syndrome may also be triggered by other noxious stimuli, including decubiti, nephrolithiasis, genitourinary infection, surgical procedures under local anesthesia, and biliary disease. The syndrome presents as chills, diaphoresis, piloerection, hypertension, reflex bradycardia, pupillary dilatation, headache, and pallor (Head and Riddock 1917; Kcndrick et al. 1953). Death can result from cardiac arrest caused by profound vagal overactivity. Symptoms can occur even years after SCI. The Threshold for the development of symptoms appears to decrease with successive episodes. Treatment should be directed at eliminating the noxious stimulus (e.g., bladder or bowel decompression). Antihypertensive agents or vagolytics (e.g., atropine) may be necessary in severe cases.

DEEP VEIN THROMBOSIS **AND** THROMBOEMBOLISM IN SPINAL CORD INJURY

There is little consensus in the literature and in clinical practice regarding the prevention of DVT and thromboembolism in patients with SCI (2002). The incidence of thromboembolic events in untreated or inadequately treated patients with SCI ranges from 7% to 100% (Perkash, Prakash, and Perkash 1978; Frlsbie and Sasahara 1981; Myllynen et al. 1985; Tator et al. 1987; Green et al. 1988; Merli et al. 1988; Waring and Karunas 1991; Kulkarni et al. 1992; Burns et al. 1993; Gunduz et al. 1993; Lamb et al. 1993; Geerts et al. 1994; Powell, Kirshblum, and O'Connor 1999). The complications of a thromboembolic event are significant, including cardiopulmonary arrest and death. Prophylactic therapy has included the use of rotating beds, pneumatic sleeves, low-dose unfractionatcd heparin, adjusted-dose un fractionated heparin, low-molecular-weight heparin, warfarin, electrical stimulation, aggressive physical therapy, and pcrcutaneously placed inferior vena cava (1VC) filters. In general, some form of prophylactic therapy appears to be superior to no therapy. Some therapies stand out, however, either because of ease of administration or increased efficacy in a particular situation. Rotating beds are commonly used during the acute phase of SCI before spinal stabilization. Patients benefit from the increased venous return and decreased pressure sore formation associated with frequent turning without the risk of injury to an unstable spine. Rotating beds arc not comfortable and arc poorly tolerated by conscious patients over the long term. Similarly, pneumatic compression sleeves are convenient in an immobile patient but impractical in a patient who is not confined to bed (e.g., a patient actively participating in spinal cord rehabilitation). The increased risk of bleeding associated with higher-dose anticoagulation regimens can outweigh the benefits of their use, particularly in patients with a ptevious history of bleeding or those who are prone to falls. IVC filter placement is associated with rare and even fatal complications. Filters can be placed in the acute period without concomitant anticoagulation in patients at high risk for bleeding or with short life expectancies. However, current recommendations include the need for lifelong anticoagulation (Becker, Philbrick, and Selby 1992). The cumulative lifetime risk of a major bleeding complication in a youne, person with an IVC filter ean he

quite high and calls into question the safety of IVC filter placement in younger patients. Finally, all studies investigating the efficacy of IVC filters have compared them with historical controls. No studies comparing the efficacy of IVC filter placement with current prophylactic regimens have been reported in the literature. Length of prophylactic therapy is also a subject of debate. A recent review of the literature demonstrates the reported risk of a thromboembolic event to be highest during the first 2-3 months after injury (2002). The risk declines significantly over time but never approaches that of controls. In fact, one study demonstrated the risk of dying from a pulmonary embolism to remain 20 times higher at *6* months for patients with a history of SCI than for control patients (DeVivo et al. 1989). The incidence has been reported to fall between 0.5% and 1% after 1 year (McKinley et al. 1999). Additionally, the risk of DVT decreases dramatically in patients with significant lower extremity motor function, and given the evidence in the medical literature, cessation of therapy earlier is warranted once such patients are mobile (Myllynen et al. 1985; 1997).

No studies have demonstrated a decreased risk of thromboembolic event in patients undergoing serial screening for DVT. In patients clinically suspected of having a DVT, venography remains the diagnostic gold standard. The invasive nature and cost of the procedure preclude its use as a screening tool. Fibrin degradation product (D-dimer) measurement, Doppler ultrasound, and venous occlusion plethysmography (VOP) have all been used in the diagnosis of DVT. Although the measurement of D-dimers has a high negative predictive value, the positive predictive value of this study has been documented to he 13% (Roussi et al. 1999). Doppler ultrasound and VOP demonstrate high positive and negative predictive values (Chu et al. 1985). Compared with venography, they are both cheap and readily available. Clinically significant pulmonary embolisms have been reported in the absence of a documented DVT. As a result, clinical suspicion of a pulmonary embolism should not be set aside after negative Doppler studies, VOP, or venography. Confirmatory tests for pulmonary embolism include ventilation/perfusion scanning and spiral chest CT. Ventilation/perfusion scanning is sensitive but not specific and may not be possible in patients with concomitant pulmonary disease. Spiral CT scanning is sensitive and specific, but some clinicians question the clinical significance of lesions detected by spiral CT. Clinical judgment should guide the decision to treat a radiographically documented pulmonary embolism.

Review of the existing data has led the American Association of Neurological Surgeons and the Congress of Neurological Surgeons Joint Section on the Disorders of the Spine and Peripheral Nerves to make the following recommendations. The prophylactic treatment of thromboembolism in patients with severe motor deficits caused by SCI is recommended. The use of low-molecular-weight heparin, rotating beds, pneumatic sleeves, adjusted-dose heparin, or combination therapy is recommended. Neither low-dose heparin nor oral anticoagulation monotherapy appears to be an effective treatment strategy. IVC filters are recommended only for patients who do not respond to anticoagulation or are not candidates for anticoagulation or mechanical devices. More research is needed to compare the efficacy of IVC filters and modern treatment paradigms. Surveillance scanning for DVT does not appear to reduce the rate of thromboembolism.

REHABILITATION AND LONG-TERM CARE

The impact of physiatry on the survival and quality of life of patients with SCI cannot be overemphasized. A detailed discussion on this topic can be found in Chapter 54,

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Chapter 56
Trauma of the Nervous System

D. PERIPHERAL NERVE TRAUMA

Brian Murray

Traumatic injury to the peripheral nervous system (PNS) is a common and under-recognized source of physical disability. Interest in PNS trauma has been recorded repeatedly through the centuries. Leonardo da Vinci made several detailed anatomical drawings of the brachial plexus, believing that this complex of nerves existed to ensure continued function of the upper extremity should one of its elements be severed (e.g., by a sword thrust). "Weir Mitchell and colleagues wrote the first systematic study of nerve injuries during the American Civil War, titled "Gunshot Wounds and Other Injuries of Nerves." By 1885, Duchcnnc, Erb, and Klumpkc had all made their landmark descriptions of various upper and lower trunk brachial plexus injuries. World Wars I and II generated further interest in peripheral nerve trauma, culminating in **both** the classification systems that arc still in use today and the development of microsurgical techniques in nerve repair.

There are many ways in which peripheral nerves may be lacerated, compressed, crushed, or stretched. In the modem world, most such injuries arise from motor vehicle accidents, but they are also distressingly common in sports, in the operaring room, from drug injections, and from gunshot wounds (both civilian and military). Also, nerves may be injured by exposure to extreme physical conditions such as freezing, electrical current, and radiation. Overall, up to 5% of all patients admitted to level I trauma centers have a peripheral nerve, nerve root, or plexus injury (Noble et al. 1998). Upper extremity nerve and plexus injuries arc more common than lower extremity injuries, with the radial, ulnar, and median nerves being most often affected. In the lower limb, the sciatic nerve and peroneal nerves are most often affected.

In this chapter, we discuss the relevant anatomy of the PNS to better understand the classification of peripheral nerve trauma and how elements of the PNS degenerate and regenerate in response to injury. Although both cranial and autonomic nerves are also part of the PNS, they are not covered in detail in this chapter; rather, the focus is on the spinal sensorimotor system that extends between nerve roots and target organs in the trunk and extremities. The most common mechanisms causing nerve trauma, their clinical evaluation, and the current techniques used in nerve repair are discussed, followed by an introduction to some of the fututc developments that may soon revolutionize the management of nerve injuries.

ANATOMY OF THE SPINAL NERVES OF **THE** PERIPHERAL NERVOUS SYSTEM

The PNS is composed of the neural elements, along with their support tissues, that extend between the central nervous system (CNS, in this case the spina! cotd) and their target organs. Thus the peripheral motor system (somatic efferents) extends in a segmental pattern from anterior horn cells lying in the anterior gray matter of

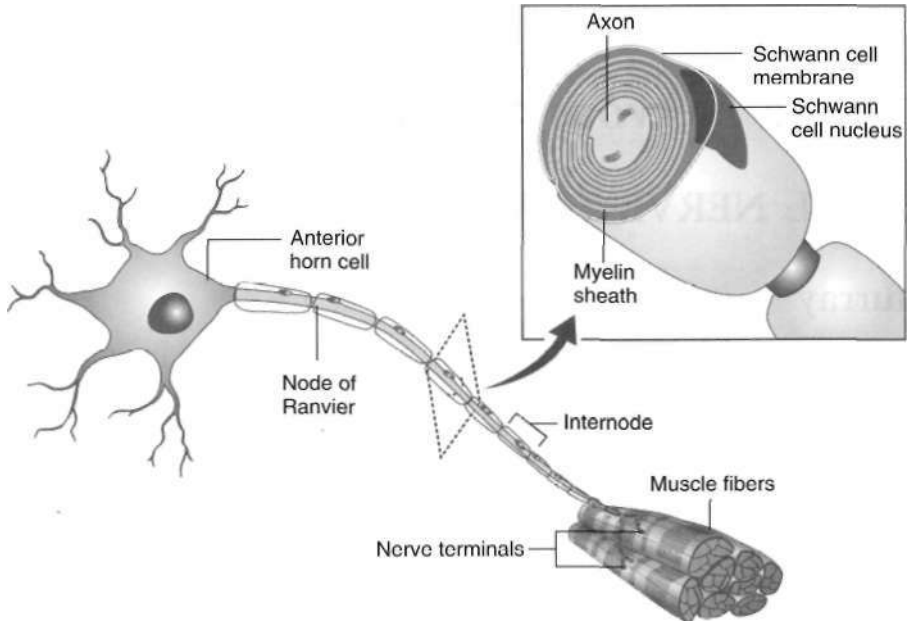

FIGURE 56D.1 The motor nerve cell body lies within the anterior horn of the spinal cord. A single axon extends from the anterior horn cell to its target muscle, making contact at the neuromuscular junction. Local support cells, called Schwann cells, generate a myelin sheath that is laid down at regular intervals around the axon; each interval is called an internode, and the intervening gap is called the node of Ranvier.

the spinal cord to muscles in the limbs and trunk (Figure 56D.1). Fibers of the peripheral sensory system (somatic afferents) extend from specialized sensory organs in skin, muscle, and viscera to their cell bodies lying in the dorsal root ganglia just outside the intervertebral foramina of the spinal column. Spinal nerves are formed when anterior (motor) and posterior (sensory) roots combine, After a brief intraforaminal course, posterior branches (posterior rami) extend backward to supply paravertebral muscles, whereas anterior branches (rami) extend forward to supply the trunk and also give rise to the roots of the plexuses (Figute 56D.2).

Some peripheral nerves, such as the anterior Interosseous nerve, are almost entirely composed of motot fibers,

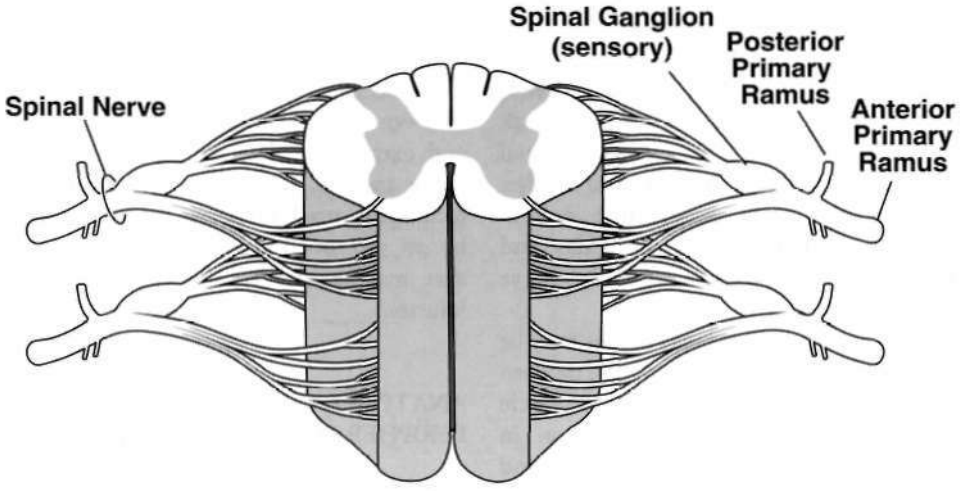

FIGURE 56D.2 Spinal nerves originate in segmental fashion as rootlets from the substance of the spinal cord. The anterior (efferent, motor) rootlets are derived from motor neurons in the anterior lion) ot the spinal cord. Afferent fibers from the periphery reach their cell body in the spinal ganglion in the intervertebral foramen, from which fibers extend as rootlets to the posterior horn of the spinal cord. Afferent and efferent fibers come together just distal to the dorsal root ganglion to form the spinal nerve. The spinal nerve divides into posterior and anterior primary rami; the anterior primary rami constitute the roots of the plexi,

whereas others, such as the sural nerve, arc purely sensory, Most spinal nerves, such as the sciatic nerve, are mixed (i.e., they contain both sensory and motor fibers). It should be remembered that motor nerves also contain small-diamctcr fusimotor fibers that supply the intrafusal muscle fibers. Furthermore, motor nerves are not pure motor nerves in the strictest sense; they also contain large-caliber afferent sensory fibers arising from the muscle spindles.

The core element of any nerve fiber is the axon, a thin tube of membrane-bound axoplasm that extends from the nerve cell body to the target otgan. This axon contains numerous mitochondria, along with a complex of cytoskeletal components such as mictotubules and neurofilaments. Through ionic current shifts mediated by a complex array of membrane ion channels, the axolemma is able to propagate an action potential along its length. The axon is invested in a layer of lipid-rich myelin that is made by a specialized I'NS support cell, the Schwann cell, the outer membrane and basal lamina of which are called the neurilemma.

Peripheral nerve axons may be classified as being unmyelinated or myelinated. The former are multiply arranged in and partially ensheathed by invaginations of the Schwann cell membrane, whereas the latter are enveloped in concentric lamellae of myelin to form a sheath {see Figure 56D.1). The latter serves a vital role in nerve impulse transmission, acting as an electrical insulator that significantly speeds up the conduction of an action potential along the entire length of the axon. The myelin sheath is not a continuous structure but is laid down in tubular segments called internodes, each derived from one Schwann cell, of varying lengths depending on the diameter of the axon. The small gap of naked axolemma between the myelin sheaths is called the node of Ranvier. This has a complex structure and is partly covered by finger-like processes of the adjacent Schwann cells and by basal lamina. The node is the site where ion flow takes place to maintain the action potential. In a process called saltatory conduction, these action potentials leap from node to node rather than travel in a continuous conduction process along the entire length of the axolemma. In this way, a myelinated large-caliber axon may conduct electrical impulses at up to 80 m pet second, whereas a small unmyelinated axon may conduct as slowly as 0.5 m per second.

It is important to be familiar with the various connective tissue components in a peripheral nerve trunk; they provide structure, tensile strength, and elasticity. The connective tissue elements of the nerve and the specialized perineurium provide the anatomical elements of the blood-nctvc barrier that maintains an immunologically privileged nerve microenvironment. After more severe grades of injury, the success or failure of nerve regeneration depends on the nature and degree of injury to connective tissue.

A thin layer of collagenous connective tissue called the endoneurium surrounds individual nerve fibers. This endoneurium is continuous with the subarachnoid space proximally. In the nerve trunk, endoneurium-encascd, myelinated and unmyelinated nerve fibers are arranged into bundles called fascicles. These fascicles, which vary greatly in size and number, are often artanged in an intertwining pattern (sometimes called Sunderland's plexus) in the more proximal portion of the nerve trunk but are arrayed m a more parallel pattern m the distal parts of the nerve. Each fascicle is invested in a layer of tough, specialized cells that have a basal lamina and that constitute part of the biood-nerve barrier, called the perineurium. A typical nerve trunk consists of a variable number of fascicles separated by interfascicular epineurium and surrounded by a tough layer of extrafascicular epineurium, which is in continuity with the dura mater proximally. Finally, the epineurium of the nerve trunk melds into surrounding structures via a loose layer of protective ateolar tissue called the mesoneurium. The latter structure is roughly equivalent to the adventitia of blood vessels and allows the nerve some degree of passive movement in the transverse and, most importantly, the longitudinal planes.

The arterial and venous blood supply of a peripheral nerve is segmental and enters the nerve proper at various sites along the length of the nerve via the mesoneurium. Longitudinally arranged arterioles travel along the interfascicular epineurium before they branch off to pierce the perineurium. It is the multilayered perineurium and the endoneurial capillary wall that form the blood-nerve barrier. The endoneurial capillaries have a larger diameter than typical capillaries in other organs and resemble end arterioles.

CLASSIFICATION OF NERVE TRAUMA

Based on observations made in wartime Britain in the 1940s, Seddon devised a thtee-tiered classification system for nerve trauma (Seddon 1942; Table 56D.1). In this system, the mildest form of injury is caused by a transient focal block in conduction along the nerve fiber caused by injury that is confined to the myelin and spares the axon. He called this neurapraxia, derived from the Greek word for *nonaction.* This type of injury has an excellent prognosis for complete recovery and is rarely clinically evident after *6* weeks; indeed, many patients return to normal within hours. A good clinical example of neurapraxia is Saturday night palsy, a wrist drop caused by compression of the radial nerve at the spiral groove of the humctus that classically involves the intoxicated person who goes to sleep with an arm hanging over the back of a chair. Seddon's second grade of injury, axonotmesis ("a cutting of the axon"), is an injury nor only to myelin but also to the axon itself so that "the sheath and the more intimate supporting structures of the nerve have not been completely divided, which means that the nerve as a mass of tissue is still in continuity" (Seddon 1942, p. 237). Axonotmesis is common in crush injuries and displaced bone fractures, and complete recovery is less likely than

Table 56D.1: Classifications of nerve trauma

Injured tissues	*Seddon*	*Sunderland*	*Modification (MacKinnon)*	*Modification (Millesi)*
Myelin	Neurapraxia	Grade 1	Grade I	Suffix A = epineurial fibrosis (e.g., IA, IIA)
Myelin, axon	Axonotmesis	Grade II	Grade II	Suffix B = interfascicular epineurial fibrosis (e.g., IB, IIB)
Myelin, axon, endoneurium		Grade III	Grade III	Sulfix C — endoneural scarring (e.g., II1C)
Myelin, axon, endoneurium, perineurium		Grade IV	Grade IV	
Myelin, axon, endoneurium, perineurium, epineurium	Neurotmesis	Grade V	Grade V	
Combination			Grade VI	

with neurapraxia. It triggers the process of wallerian degeneration and regeneration, the success of which depends in part on the preservation of connective tissues such as endoneurium and perineurium. Seddon's most severe type of injury is called neurotmesis ("a cutting of the nerve"), which entails damage to myelin, axon, and connective tissue. Seddon used this term to describe complete nerve transection in which "the injury produces a lesion which is in every sense complete" (Seddon 1942, p. 237). This is common after laceration injuries and has the worst prognosis for clinical recovery, ofren necessitating surgical intervention.

A second classification system for nerve trauma was devised by Sunderland to include additional information regarding the degree of injury to connective tissue. This system is divided into five grades, of which grades I and II are identical to Seddon's neurapraxia and axonotmesis, respectively. However, Sunderland subdivides Seddon's neurotmesis into three further levels of injury. Grade III entails injury to myelin, axon, and endoneurium, with sparing of the perineurium and cpineurium. Grade IV describes an injury to all nerve trunk elements except the epineurium, and grade V entails complete transection of all neural and connective tissue elements of the nerve trunk.

Modifications to these two systems have been devised, largely with the surgeon in mind. A further grade (grade VI) has been proposed to highlight the fact that in some injuries there may be a combination of Sunderland grades (e.g., some areas may be grade III and others grade IV) affecting different fascicles within a segment of nerve. Furthermore, a subclassification system has been devised to account for the degree of scarring present in the injury site. This is of vital importance to the surgeon in determining the likelihood of recovery from an injury; excessive scarring (fibrosis) may significantly impede axon.il regeneration. I his system may be used in conjunction with the Sunderland system. The suffix *A* refers to fibrosis that is located mainly in the epifascicular epineurium, so that, for example, IA injury implies that a conduction block has occurred (ncurapraxia, Sunderland grade I) together with epifascicular scarring, and IIA implies an axonotmesis lesion with epifascicular epineurial scarring. The suffix *B* refers to interfascicular epineurial fibrosis so that, for example, a IIB injury implies axonotmesis (Sunderland grade II) with interfascicular epineurial fibrosis; type C fibrosis occurs in the endoneural space and may occur with Sunderland grade III injuries (see Table 56D.1).

PERIPHERAL NERVE DEGENERATION AND REGENERATION

Large myelinated axons are the most vulnerable to traumatic injury. These axons predominate in motor nerves that supply extrafusal muscle fibers and sensory fibers subserving appreciation of vibration, position, and light touch. There arc three main ways in which peripheral nerve fibers may respond to injury: segmental demyelination, wallerian degeneration, and axonal degeneration. The first two of these processes are relevant to traumatic nerve injury and arc discussed in more detail in this chapter, whereas the latter is more characteristically seen in metabolic and toxic nerve disorders such as diabetes mellitus and renal failure, which arc discussed elsewhere (see Chapter 82).

Segmental Demyclination

Segmental demyclination typically occurs with nerve trauma at a focal segment of nerve that is subjected to a significant compressive force. The nerve segments that lie proximal and distal to the site of injury are not affected and function normally. Distortion of the myelin sheath may cause degeneration of one or several intcrnodes, which leak current and thus affect the ability of the sheath to act as an electrical insulator. If the myelin is only slightly damaged, there may be simply a widening of the node of Ranvier that causes a slowing of conduction velocity across the nerve segment. Such focal demyclination of axons within a nerve fascicle may affect some but not all

fibers, resulting in asynchronous conduction across the affected nerve segment. In this case, impulses eventually reach their destination after a delay, but the slowing may affect certain nerve functions that rely on highly synchronous firing, such as deep tendon reflexes and vibration sensation.

More severe degrees of compression may involve most, or indeed all, myelinated nerve fibers at the injury site and several internodes. In this situation there is blockade of conduction across that segment, which causes weakness or sensory disturbance. Ultrastructural studies of nerve segments that have been subjected to tourniquet compression reveal that the nodes of Ranvier are heavily distorted. Furthermore, the regions of myelin located at the edge of the tourniquet are deformed to a greater degree than the segment lying directly beneath the tourniquet. The tourniquet causes the underlying axon and myelin to telescope into a neighboring segment, which greatly distorts the paranodal segment of myelin to cause conduction slowing and, later, actual segmental demyelination and conduction block. Once a segment of myelin has been lost in this way, the Schwann cell divides and initiates remyclination. Conduction is re-established within a few weeks, but the new myelin sheath usually is thinner and has several internodes for each original internode.

Wallerian Degeneration and Regeneration

Interruption of axonal continuity triggers a carefully-orchestrated process called Wallerian degeneration that involves the axon, its cell body, its cellular connections, and surrounding connective tissues (Figure 56D.3).

Changes in the Distal Segment

After axotomy, the first changes that occur are in the axon distal to the site of injury. The initiating event for this

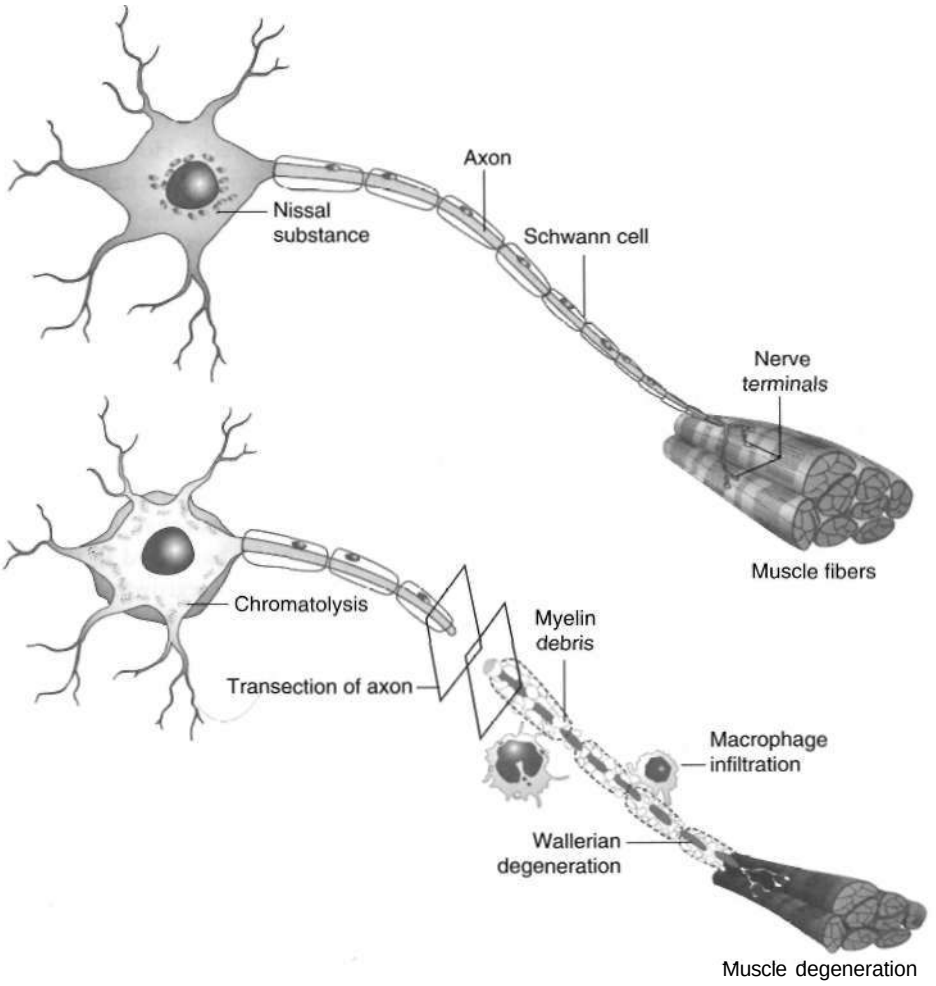

FIGURE S6D.3 Wallerian degeneration. After axotomy, the axon and myelin sheath distal to the transection begin to degenerate. Within a few days, macrophages are recruited into the injury site and digest the debris. Changes also occur proximal to the site of injury. A degree of wallerian degeneration takes place up to the first encountered node of Ranvier, and the cell body undergoes chroma to lysis, winch represents a switch in function of the cell body from axon maintenance to axon regeneration. If regeneration does not take place, the target tissue is not re innervated, and degeneration of the target organ eventually occurs,

process has yet to be defined, hut recent research supports an active father that passive process (i.e., degeneration does not occur simply because the axon cannot receive trophic support from the cell body). Many of the degenerative processes that take place share features with apoptosis. One of the key mechanisms mediating axon degeneration is an increase in the activity of calcium-activated proteinases (calpains). The axon immediately distal to the injury site leaks axoplasm, becomes swollen with organelles, and the plasma membrane develops blebs. By the third day, the nxophsm abruptly undergoes granular disintegration. which rapidly progresses distally.

Contact between the axon and its myelin sheath is compromised, so that within hours of the injury, the Schwann cell separates itself from the myelin sheath. The latter retracts from the node of Ranvicr before undergoing digestion by locally produced lipases and proteases. By day 3, myelin ovoids form in the distal segment. Mitogenic substances released after axotomy, such as glial growth factors and neuregulins, trigger a switch in Schwann cell gene expression so that it ceases production of myelin (which inhibits regeneration). Instead, the Schwann cells enter a proliferative phase, during which they dedifferentiate and upregulate the expression of adhesion molecules and neurotrophins that are necessary for the regenerative phase soon to follow. These denervated Schwann cells form cords aligned along the original basal laminal tubes of the myelinated axons in structures called bands of Bungner that form a pathway along which new axons are destined to grow. They also migrate from the proximal stump across any discontinuity in the basal laminal tubes to assist in guiding axon regrowth.

By day 3, lipases and proteinases, initially produced by the Schwann cell and later by activated macrophages, begin to digest myelin. There is activation of cells of the monocyte-macro phage system within the endoneurium. Additional macrophages are recruited from the circulation into the milieu of the distal degenerating nerve. The likely trigger to this process is the production of chemokines and inrerleukin-10 from local tissues. Myelin debris accumulates in the distal nerve and is slowly removed by phagocytosis.

Changes Proximal to the Site of Injury

A limited degree of axonal breakdown occurs proximal to the injury site, usually up to the level of the first encountered node of Ranvier. Very proximal injury may lead to apoptosis of the cell body itself, but the more common consequence of axotomy is for the cell body to go through a series of dramatic structural changes that set the stage for the upcoming regenerative phase. The trigger for this response has yet to he defined but appears to be related to retrograde transport of injury signals, including nerve growth factor, from the proximal stump together with increased local levels of the Schwann cell injury factor, ciliary neurotrophic factor. The cell body reaction is known as central chromatolysis ("loss of color"), wherein it swells with new proteins that force the nucleus into an eccentric position, and ribosomes become dispersed rather than clumped into Nissl bodies (and therefore can no longer be identified when stained with cationic dyes). One of the earliest axotomy-induced molecular events in the cell body is increased nuclear expression of transcription factors, such as c-Jun, that change the pattern of gene expression from that of axon maintenance to that of protein synthesis. The full complement of proteins generated in this process has yet to be determined. However, certain substances have already been identified with putative roles in the stimulation and regulation of nerve regrowth, including GAP-43 (growth-associated protein of 43 kDa), alpha tubulin, dynein, kinesin, SPRR1A, TOAD-64, ninjunn, and Reg-2.

Studies of axotomized facial nerve show that microglial cells in the CNS migrate to and proliferate around chromatolytic motor neurons. Synaptic connections between the motor neuron and other CNS neurons are lost and displaced by foot processes from local glial cells. This process is known as synaptic stripping.

The entire process of wallerian degeneration takes approximately 1 week. However, the distal segment of axon remains electrically excitable for the first *3-5* days of this process. Usually by the eighth day, the distal (and a small part of the proximal) axon has been completely digested, debris has been cleared from the site, bands of Bungner are in place, and the process of regeneration begins.

Regeneration

The PNS has a significantly greater regenerative capacity than the mature CNS. This results from a multitude of both neuronal and non-ncuronal factors. Furthermore, CNS axons appear to be hampered in their regenerative efforts by inhibitors of axon regrowth, such as Nogo-66 protein, which is expressed on the surface of CNS oligodendrocytes, and chondroitin sulfate proteoglycans, which are present in CNS scar tissue.

Regeneration is a slow process; axonal sprouts grow from the proximal to the distal stump at a rate of 1-2 mm per day (or 1 inch per month). Thousands of these nascent axon sprouts appear at the proximal nerve stump. The tip of the axon sprout is called the growth cone and is a highly motile structure, packed with mitochondria and cytoskcletal components, that emerges just proximal to the severed axon tip in response to regulated shifts in calcium concentrations in the local microenvironment. Under guidance from trophic factors, chemokines, and cell adhesion proteins produced by local tissues, the growth cone navigates through the bands of Bungner to make contact with the distal target organs (Figure 56D.4). These signals induce rapid alterations in the shape and

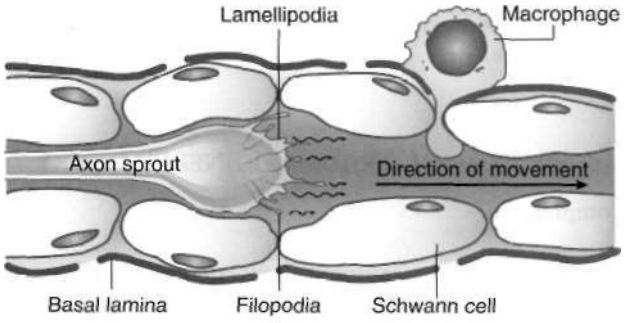

FIGURE 56D.4 Schematic diagram of axonal regeneration. The axon sprout grows out from the proximal stump and proceeds toward the degenerated distal axon stump via the bands of Bungner (formed by proliferating Schwann cells and bounded by the intact basal lamina). Macrophages migrate through the basal lamina into the injury site to phagocytose myelin ovoids and axoual debris. This clears the way for the axon sprout to progress distally. The motile tip of the axon sprout is called the growrh cone, which bears receptor-rich lamellipodia (sheetlike) and filopodia (finger-like). These structures are guided through the bands of Bungner to their target by multiple signals in the microenvironment.

conformation of the internal cytoskeleton, which lead to the extension of finger-like filopodia and sheetlike lamellipodia. Once adequate connections have been established, Schwann cells generate a fresh myelin sheath, which is thinner and has universally short internodes compared with the original sheath. The final stage in regeneration is the development of mature contacts with the target organs, be they motor endplates or sensory receptors.

At the molecular level, several mechanisms regulate and mediate peripheral nerve regeneration, which are summarized here:

- The Schwann cells and surrounding basal lamina that make up the bands of Bungner arc critically important in nerve regeneration. Once an axon has been severed, Schwann cells upregulatc expression of several adhesion factors including cadherins, immunoglobulin superfamily factors, and laminin, which promote the migration of axon sprouts from the proximal stump. In addition, special cytokines called neurotrophic factors are produced by the Schwann cells, including nerve growth factor (NGF), brain-derived neurotrophic factor, insulin-like neurotrophic factor, and ciliary neurotrophic factor. These nerve "fertilizers" promote the growth of axon sprouts.
- Neurotrophic factors such as brain-derived neurotrophic factor, adhesion molecules such as nmjurin, and cytokines and chemotaxins such as osteopontin are present in the tegion of the distal Stump to guide the advancing growth cone of axon sprouts in the correct tissue plane. Other locally produced substances such as nitric oxide and fibrin are also important in the regulation of axonal regeneration and cemyelination.
- It is important that axon sprouts do not stray off the correct path as they migrate from the proximal to the distal stump. In addition to the aforementioned positive chemical signals, inhibitory molecules, such as the semaphorins and nctrins, are produced by the Schwann cell and surrounding tissues to prevent misdirected growth of axon sprouts.
- The basal laminae of target muscle membranes release chemoattractant substances so that new motor axons make contact at the precise points where previous synapses were present. Recent research shows that non-neural elements, probably Schwann cells, are viral in guiding these terminal motor axons to such precise points on the target muscle (Nguyen, Sanes, and Lichtman 2002). Furthermore, Schwann cells at these motor terminals can extend processes to adjacent motor endplates, which increase the degree of muscle fiber innervation. It is important to note that prolonged denervation leads to irreversible degeneration of intramuscular nerve sheaths.

A number of factors dictate the success or failure of nerve regeneration. First and foremost is the nature of the injury itself. A clean transection of a nerve from a scalpel blade creates a small, debris-free, well-perfused gap. Conversely, a crush injury may not only cause extensive damage to surrounding connective tissues and blood vessels but also create an extensive gap between the healthy nerve stumps. In the latter situation, there is often a delay in initiating axonal sprouting as the proximal stump undergoes retrograde degeneration for about 1 cm (a process that can take up to 1 week). Complications are common in such injuries (usually Sunderland grade III and above), not the least of which is the formation of a neuroma. The latter is a multicompartmentalized mass of axon sprouts, fibrotic tissue, Schwann and perineuria! cells, and capillaries caused by disorganized regrowth across a ragged injury site. Neuroma in continuity is unable to satisfactorily conduct electrical impulses to or from the cell body but, when directly stimulated, can discharge spontaneously, causing significant local pain.

Regeneration is rarely 100% efficient. Even in the best functional outcomes, patients often note subtle residual deficits such as loss of dexterity or vague sensory disturbances. There are several plausible reasons why this might be so. Synaptic stripping has reduced the number of neural connections making contact with the cell body, and regenerated myelin sheaths are thinner and more variable in length than previously. New motor axons destined for muscle may inadvertently make their way into sensory-tracts in the distal stump. Motor fibers may fail to reinnervate all the dencrvated muscle fibers and may even reinnervate the wrong muscle entirely. This is known

as aberrant regeneration and produces the clinical sign called synkinesis. For example, after facial nerve injury, there may be aberrant reinnervation of the orbicularis oculi muscle by fibers intended for the orbicularis oris muscle, thus causing involuntary eye closure during voluntary oral movements. Facial nerve visceromotor fibers intended for the salivary glands may instead make their way to the lacrimal gland, thus causing the production of tears during meals.

The premorbid health of the patient is another crucial factor; patients with metabolic disease may not enjoy the same amount of successful regeneration as their healthier counterparts. Recent molecular research shows that certain immediate early genes are not activated adequately after injury in diabetic patients, so vital trophic factors are not produced quickly enough at the injury site to enable maximum nerve axon sprouting. In addition, impaired axonal regeneration in injured diabetic nerve may be related to altered expression of cytoskeletal components, including tubulin and neurofilament proteins, together with either failure or delay in re-establishing an adequate microcirculation,

After 24-36 months, a target muscle will be completely replaced by fibrotic tissue, so functional reinnervation is no longer possible. The rate at which this occurs varies from muscle to muscle; it appears to be prolonged in many of the larger muscles of the body, including the quadriceps, triceps, and biceps. Sensory organs are hardier than motor units and may be intact for up to 7 years after loss of contact with the cell body. Thus even late sensory reinnervation may be able to restore useful protective function to a limb. Neurophysiological, neuropsychological, and functional neuroimaging studies have identified a reorganization of the central motor and sensory pathways in the aftermath of peripheral nerve injury or repair,

Chronic denervation leads to extensive reorganization of representational maps in the sensory cortex, perhaps through redistribution of afferents from adjacent cortical regions. This may involve growth of new collateral sprouts and synapses or the recruitment of neural inputs that were dormant before the injury. There appears to be an age-related deterioration in sensory relearning after peripheral nerve injury: After repair of peripheral nerve lesions in the hand, cortical sensory relearning peaks in children under age 10. Traumatic injury of peripheral motor fibers induces an enlargement of the motor cortex output area. After a nerve transfer surgical procedure, there is a shift in the activity of the motor cortex representing the axon donor (e.g., the intercostal region) to that of the axon recipient (e.g., the elbow region). This plasticity is not limited to cortical structures; there appears to be a limited degree of reorganization within subcortical structures, such as the sensory relay stations in the dorsal columns and thalamus. Indeed, some peripheral nerve injuries may be followed by movement disorders in the affected limb, such as dystonia, choreoathetosis, and tremor, although this remains the subject of debate.

MECHANISMS OF TRAUMATIC NERVE INJURY

Compression

Compressive nerve injuries most commonly affect the nerves that cross over bony protuberances at exposed positions, such as the ulnar nerve at the elbow and the common peroneal nerve at the fibular head (Table 56D.2). Large-caliber myelinated nerve fibers are most susceptible to compression. More often than not compression neuropathies occur in patients who have been sedated or unconscious in a single position for an extended period of time. The classic example is the aforementioned Saturday night palsy, in which the patient characteristically awakens with a wrist and finger drop. Because the primary underlying pathophysiology is that of demyelinating conduction block, there is generally an excellent recovery in the following days to weeks. If a functional deficit remains after an 8-week period, however, it is likely that compression was severe enough to cause an additional element of axon loss. A similar problem can be recognized in the postoperative setting. For example, a patient may awaken from general anesthesia with complete upper limb paralysis caused by compression and stretch of brachial plexus elements between the clavicle and first rib while the arm is extended and hyperabducted intraoperatively. The deficit characteristically reduces to a pure upper trunk distribution in the first 1-2 days and in 2-3 months has fully resolved. Electrophysiological examination may reveal a combination of upper trunk demyelinating conduction block and a lesser component of axon loss. Anesthesiologists take care to protect potentially compressible nerves in patients who are undergoing general anesthesia.

Stretch

Peripheral nerves are vulnerable to serious injury from excessive stretch or traction. As the stretching force increases, the clastic properties of the nerve are overcome and a rupture occurs involving myelin, axon, and connective tissue. In addition, it has heen shown in an in vivo rat sciatic model that an 8% elongation of a nerve increases mtrancurial pressure to the point that blood flow is reduced about 50% (Clark et al. 1992).

An important example of a closed traction or stretch injury is Erb-Duchenne palsy caused by difficult delivery of an infant with consequent excessive traction forces applied to the child's C5-C6 roots and fibers of the upper trunk of the brachial plexus. Significant axonal injury characteristically occurs, which may leave the child with permanent

Table 56D.2: Examples of predominantly compressive nerve injuries

Nerve and site of injury	*Clinical picture*	*Pathophysiology*
Radial nerve at spiral groove of humerus; compression	Saturday night palsy; wrist and finger drop with sparing of triceps function	Demyelinating conduction block Generally recovers over 6-8 wk
Common peroneal nerve at fibular head; compression	Acute footdrop: weakness of ankle dorsiflexion, foot evcrsion, great toe extension; sensory loss on dorsum of ankle and foot	Demyelinating conduction block Generally recovers over 6-8 wk
Upper trunk of brachial plexus between clavicle and first rib; compression or traction	Classic postoperative brachial plexopathy Paralysis of shoulder abduction and elevation Paresthesias into lateral forearm	Predominantly demyelinating conduction block; lesser component of axon loss Usually recovers over 3 mo; can be delayed recovery up to 1 yr
Infraclavicular brachial plexus by pseudoaneurysm or hematoma secondary to transaxillary arteriography; compression	Median neuropathy Combined median and ulnar neuropathy Combined median, ulnar, axillary, and musculocutaneous neuropathies	Predominantly demyelinating conduction block if decompressed within first few hours Axon loss if not repaired
Ulnar nerve at olecranon groove or in cubital tunnel; compression	Paresthesias, pain in medial hand, and weakness of intrinsic hand muscles	Varies between demyelinating conduction block and axon loss; combined conduction block and axon loss

paralysis of upper arm flexors and forearm supinators; the arm is held in the waiter's tip position.

Particularly severe stretch ptoduced by distraction of the neck from the shoulder may cause an avulsion injury of the intraspinal rootlets from the spinal cord. Avulsion injuries most often occur in motor vehicle and motorcycle accidents and generally affect cervical root and brachial plexus fibers rather than components of the lumbosacral plexus or roots. The prognosis is poor; avulsed preganglionic sensory fibers fail to make contact with the spinal cord, and the distance between the site of motor nerve root injury and **the** target musculature is too long for effective regeneration. Furthermore, patients may suffer a severe pain syndrome that is notoriously difficult to treat. A vivid description of this deafferentation pain was by a physician who suffered a brachial plexus avulsion injury himself, having been struck by a window cleaner who had fallen from the fourth floot of a building as he was passing: "The pain is continuous; it does not stop cither day or night. It is either burning or compressing (like a vise) or dragging (a sense of weight) in character, or a combination of all these at the same time" (Murray and Wilbourn 2002, p. 1187).

Laceration

A laceration implies that a nerve has been partially or completely severed by a sharp object. Knife wounds are a common source ol such injuries, but they also can be caused by scalpel blades, broken glass, metal shards, chainsaw blades, wood splinters, and even animal bites. In general, the sharper the blade, the neater the injury and the shorter the distance between proximal and distal nerve stumps, and hence a greater likelihood of a satisfactory functional recovery. An example is the inadvertent transection of branches of the spinal accessory nerve during surgical removal of a mass in the posterior triangle of the neck.

Crush

A crush injury may arise from a sudden, significant force applied to the nerve by a blunt object such as a surgical clamp, lead pipe, baseball bat, or motor vehicle component. Mild degrees of crush may cause a predominantly demyelinating conduction block injury, but axon loss usually is prominent in most cases. Experimental work on animal nerves using smooth-tipped forceps have shown that axon and myelin debris is displaced longitudinally by the crush force, whereas the Schwann cell and its membranes remain intact. After removal of the crush force, axon and myelin tissues flow back into the crush site. Wallerian degeneration and regeneration may be satisfactory if the distance between the proximal and distal healthy matgins is not too great. The nerve remains in continuity, but neuroma formation is common at lengthy injury sites.

Gunshot Injuries

It is important to distinguish between low-velocity and high-velocity gunshot injuries. Low-velocity weapons are more often used in the civilian setting, and their missiles typically cause laceration, compression, and stretch injuries to localized segments of nerve and tissue. High-velocity weapons are used in both the military and civilian settings.

Missiles fired from such weapons are surrounded by a high-pressure zone, the explosive force of which causes extensive damage to both local and distant nerves, together with other tissues such as muscle, bone, organs, and blood vessels. As a consequence, all grades of nerve injury may occur concurrently in and around the wound site. Although neurotmesis lesions may be clearly apparent upon first inspection of the wound, one must consider the very real likelihood of additional areas of neurapraxia and axonotmesis. Therefore it is vital that these patients be serially followed clinically and by electrophysiological studies after the injury.

Radiation

One of the most common radiation-induced nerve injuries is to the infraclavicular brachial plexus during radiotherapy of the axillary chain of lymph nodes for breast cancer, There is a delay in the onset of 6 months to 4 years after therapy, and it most commonly starts with paresthesias in the index or middle finger, followed by weakness in muscles derived mainly from the lateral cord. Progression over time is the rule, so that the involved limb may eventually flail. This form of plexopathy is characterized by the initial development of demyelinating conduction blocks, which actually portend a poor prognosis and thus differ considerably from the neurapraxias associated with acute compression injuries (Wilbourn 1998).

Cold Injury

Peripheral nerves are especially prone to damage from excessively cold temperatures. Frostbite may affect a nerve that has been exposed to ambient temperatures her ween —2.5"C and +10°C for several hours. In the initial stages, the underlying pathophysiology is primarily that of demyelinating conduction block, but continued exposure to low ambient temperatures causes increasingly severe degrees of axon injury. The endoneurium becomes particularly edematous, which raises intraneural pressure to the point at which blood flow is compromised, further compounding the injury. Freezing temperatures cause necrosis of all exposed tissues.

Electrical Injury

Both the CNS and PNS are excellent conductors of electricity. Although this is of obvious physiological importance, it predisposes people to severe neurological injury if injured by an electrical current at home, in the workplace, or by lightning strike. Overall, the severity of an electrical injury is most dependent on voltage. High voltages (>1000 V) may cause frank necrosis of all tissues, including nerve, with subsequent loss of the limb or part thereof. Low voltages (<1000 V) portend a better prognosis and may or may not be associated with cutaneous burns. Most peripheral nerve injuries occur in association with third- and or fourth-degree electrical burns and include mononeuropathies, polyneuropathies, and plexopathics, which may be either early or delayed and often bilateral, depending on entry and exir point locations. The median and ulnar nerves are most commonly affected. Indeed, symptoms and signs may be similar to those of focal compression neuropathies, occurring at sites of minimal limb cross-sectional area where nerves cross over bony protuberances, joule's law predicts ihai maximal heal production should occur at such sites, and it has recently been proposed that perineuria! fibrosis may occur at these sites, giving rise to neuropathies that may be relieved by surgical decompression.

Injection Injury

One of the most severe forms of peripheral nerve injury is that caused by injection of a drug (prescribed or illicit) or toxin. Unfortunately, these injuries are common and are a direct effect of needle insertion into the nerve or, more often, of the drug itself (or its associated buffer and solvent). The presence of a toxic drug around a nerve may stimulate an intense inflammatory reaction, which may cause extensive degrees of epineurial scarring and distortion of the architecture of the nerve trunk. In general, an intact blood-nerve barrier (i.e., an intact perineurial-endoneurial border) will prevent diffusion of drug or toxin into the nerve fibers themselves. However, direct injection of drug into nerve may cause severe endoneural fibrosis with neural ischemia and axon loss. The degree of injury and the pattern observed (diffuse versus focal) vary from drug to drug. The radial and sciatic nerves are the most commonly affected, but injection injuries have also been described in the median, femoral, and ulnar nerves. The first symptoms often are immediate pain, paresthesias, and paralysis, but in some patients the onset apparently is delayed. Patients who do not show signs of recovery within 5 months or who have persistent pain need surgical intervention.

EVALUATION OF NERVE TRAUMA

Clinical and Electrodiagnostic Examination

The assessment of any traumaric nerve injury begins with a careful bedside history and clinical examination and is preferably carried out by those with particular expertise in the area. There are certain key elements to record in the history; the most important is the time interval that has elapsed between the injury and presentation. For example, if

4 years have elapsed from the time of injury, it is very unlikely that any significant motor recovery will take place despite surgical intervention because of extensive degeneration of muscle fibers. The mechanism of the injury is also important; intraoperative transection of a nerve by a scalpel is likely to portend a better prognosis than a laceration by a chainsaw. Elderly patients and those with metabolic disorders such as diabetes and renal failure are less likely to enjoy a good functional outcome after nerve injury.

A detailed knowledge of peripheral neuroanatomy is needed to appreciate the nature, extent, and likely consequences of a nerve injury. During examination one should also focus on whether the wound is open or closed, whether other tissues are involved, whether wound contamination or infection is present, and whether the vascular supply of the region might he compromised. An estimation of the distance between the injury and its target organ (e.g., muscle) is also of prime importance. For example, if the target organ is 3 inches from the injury site on the nerve, there is a reasonable likelihood of a good outcome over the next 3 months. The reverse is true of nerve injures that occur at a great distance from the target muscle; a lower trunk brachial plexus injury may be 16 inches or more from target intrinsic hand muscles. Tinel's sign, a tingling induced by mechanical distortion of the distal terminus of a regenerating axon (elicited by tapping the nerve with a finger or tendon hammer), is a useful bedside test that may help discern the site and rate of nerve regrowth after nerve injury or nerve repair.

Additional investigations are important in defining any nerve injury. (. hie I among these is the eleetrodia gnostic examination (EDX), which consists of nerve conduction studies (NCSs) and needle electrode examination (NEE; sec-Chapter 37B). The two main components of the NCS are assessment of sensory nerve action potentials (SNAPs) and compound muscle action potentials (CMAPs}, although late responses, including F waves and the H reflex, also provide useful information, particularly about the proximal portions of nerves. The EDX provides information about the site of the injury, its underlying pathophysiology, and the rate of recovery.

The timing of this complex test is vital and is of both practical and prognostic importance. If it is performed too soon after the injury, there may not have been sufficient time for EDX signs of axon loss to develop, and the physician cannot judge whether a nerve lesion is caused primarily by demyelinating conduction block or axon loss. In the case of a severe axon loss injury, CMAPs and SNAPs are entirely normal for the first 2 days despite the presence of an obvious clinical deficit and an inability of the patient to voluntarily recruit motor units during NEE. By day 3, however, wallerian degeneration should cause some loss of the distal CMAP amplitude, and by day 9 the CMAP may have further diminished ot even disappeared. By days 11-12 the SNAP amplitude also is diminished (the reason for the earlier loss of CMAP amplitude relates to the early failure of neuromuscular junction transmission). Finally, after a few weeks, there should be clear evidence of active denervation in the form of fibrillation potentials and positive sharp waves during NEE.

If the lesion is caused by conduction block, one should detect a significantly (e.g., >50%) lower proximal as compared with distal CMAP amplitude, with abnormal neurogenic motor unit action potentials or even their complete absence. The distal CMAP amplitude (if stimulating and recording beyond the site of conduction block) should be within normal limits in cases of conduction block. There may be a limited amount of axon loss if injury has occurred to some axons at the site of the conduction block. Therefore there may be some positive sharp waves or fibrillation potentials on NEE. It is important to remember that many nerve injuries involve components of both conduction block and axon loss (Wilbourn 1998).

There is no way to clearly differentiate a predominantly demyelinating conduction block process from an axon loss lesion on the basis of clinical symptoms or signs or of an EDX performed within 7 days of the injury.

An avulsion injury that involves both anterior and posterior preganglionic segments ma) produce a characteristic EDX pattern; there will be loss of CMAP amplitudes but preservation of SNAP amplitudes. This is because the lesion affects the dorsal root proximal to the ganglion that lies outside the spinal canal in the intervertebral foramen.

Repeat examination should always be performed to assess for electrophysiological recovery or worsening. One must assess for recovery of SNAP and CMAP amplitudes; during regeneration, the SNAP amplitude characteristically recovers before the motor amplitude. Furthermore, one may appreciate some degree of normalization of motor unit recruitment and morphology. One particularly important NEE feature is the appearance of low-amplitude, polyphasic unstable nascent motor unit potentials, which is important EDX evidence of early motor unit reinnervation.

Somatosensory evoked potentials (SSEPs) resulting from distal stimulation of the injured nerve may also be useful in evaluating peripheral nerve trauma, giving information about the integrity of posterior sensory tracts in the spinal cord and therefore useful in evaluating suspected posterior nerve root avulsion. However, the presence of an intact SSEP does not reliably indicate satisfactory nerve root function. SSEPs are so sensitive that they may yield positive waveforms in the presence of only a few hundred intact nerve root axons (Kline 2000). Furthermore, they do not provide enough localizing information to be of great assistance in postganglionic peripheral nerve injuries and do not provide information about injury to anterior (motor) rootlets in the spinal canal. Intraoperative SSEPs have been shown not to decrease the incidence of iatrogenic sciatic neuropathies during surgical repair ot acetabular fractures.

Neuroradiology Assessment

Even the most careful clinical and EDX examinations may be limited in certain situations. A very proximal injury to the sciatic nerve or brachial plexus may be inaccessible to a proximal motor stimulation point, thus pteventing assessment of proximal conduction. It may be difficult to accurately localize axon loss lesions either clinically or by EDX in certain sections of a peripheral nerve; for example, the ulnar nerve lacks any motor branch above the elbow. Furthetmore, in the earliest stages of closed-wound nerve trauma, it is not possible to differentiate a nerve transection from a lesion that remains in continuity. Radiological techniques have always had a part to play in nerve trauma evaluation, in cases of multiple trauma, plain films of the skull base, spine, and long bones may disclose fractures at sites that may compromise local nerve structures. Computed tomography myelogtaphy often is used to diagnose nerve root avulsions; conttast may be seen passing through the torn meningeal sheaths of avulsed nerve roots (pseudomeningoceles). Magnetic resonance imaging (MRI) of the spinal cotd has replaced computed tomography myelography as the first-line investigation in cases of suspected nerve root avulsion.

The most exciting advances have been in the emerging field of MRI neurography, which is based on the longitudinally orientated water diffusion properties of nerve as opposed to surrounding tissues. Diffusion images of nerve require high-field-strength MRI scanners, but one may also obtain detailed images using 1.5-Tesla scanners in conjunction with phased atray coils. For example, signal hypcrintensity can be seen on T2-weighted and short time inversion tecovery images of traumatized netve segments; abnormal high signal is seen both at and **distal** to the injury site. This MRI modality can diffetentiate between axonotmesis and neutotmesis lesions and also detect neutoma formation at nerve repair sites; using specialized phased array coils, one may even be able to identify which fascicles in a nerve trunk are injured and which are spared. These signal changes may be ttansient in cases of mild nerve injury or may be prolonged (up to many years) in severe preganglionic brachial plexus avulsion injuries. Early (within 1 week) signal hyperintensity may also be seen in denervated muscle on T2-weightcd and shott time inversion recovery (STIR) images, which will persist if nerve discontinuity picvents reinnervation (Figure 56D.5}.

MRI neurography is still a developing field, As the technique is perfected and experience grows, it will become a standard part of the evaluation of nerve injury,

SURGICAL REPAIR OF NERVE TRAUMA

The necessity for peripheral nerve surgery depends on several key factors, including the nature of the injury, the site of the injury, and the likelihood of satisfactory functional recovery. Surgical intervention is not indicated in an obvious case of neurapraxia because it is likely that the patient will enjoy an excellent outcome. However, one cannot be certain in cases of axonotmesis, which account for approximately 70% of all setious nerve injuries. Although connective tissue elements are intact and therefore the lesion is in continuity, a neuroma may develop that bars the progress of axonal sprouts from the proximal to the distal stump. One may suspect such a problem in a patient who docs not make a clinical recovery at the expected rate or in the patient who complains of significant spontaneous pain at the site of the injury. It is important for the surgeon to be aware that neuromas often are invisible to the naked eye and impalpable during wound exploration.

A specialized intraoperative technique called nerve action potential (NAP) recording has been developed to enable the surgeon to locate abnormal sites of nerve conduction caused by axon loss or neurapraxia and to define the healthy margins of the nerve. This technique entails placing stimulating and recording electtodes directly onto the nerve surface proximal and distal to an obvious or suspected site of nerve trauma that has remained in continuity. If the netve is healthy, the segment will transmit a normal NAP between the stimulation point and the recording point. NAP recordings provide evidence of regeneration within 8 weeks of a focal in-continuity lesion; the presence of a reasonable NAP in the distal segment indicates the ptesenee of 3000-5000 moderate-diameter myelinated axons at the recording site (Spinner and Kline 2000). Conversely, a neuroma or severely scarred intraneural site may fail to transmit an impulse and will manifest as a dropout in NAP waveform at the recording point. Absence of a NAP 6 weeks or more after the injury generally indicates a Sunderland grade IV lesion and is an indication for surgical repair of the injury.

Neurotmesis lesions do not regenerate spontaneously and necessitate some form of surgical intervention, the extent and timing of which depend on the severity of the injury. If the wound is open, it may be easy to inspect the site and make an immediate decision about the need for repair. For example, a nerve transection caused by a sharp blade in a clean wound may be repaired within 72 hours by direct end-to-end anastomosis (primary repair). A rapidly worsening neurological deficit in a closed wound may indicate the need for early intervention; one must also considet vascular lesions such as pscudoancurysms, expanding hematomas, or arteriovenous fistulas that may damage the netve in the wound site. Furthermore, the incteased interstitial pressures characteristic of compartment syndrome may cause a rapidly worsening neurological deficit necessitating emergency fasciotomy.

On the other hand, a blunt nerve laceration with a ragged epineurium (e.g., from a propeller blade) should be formally repaired at a later stage when it is easier to judge

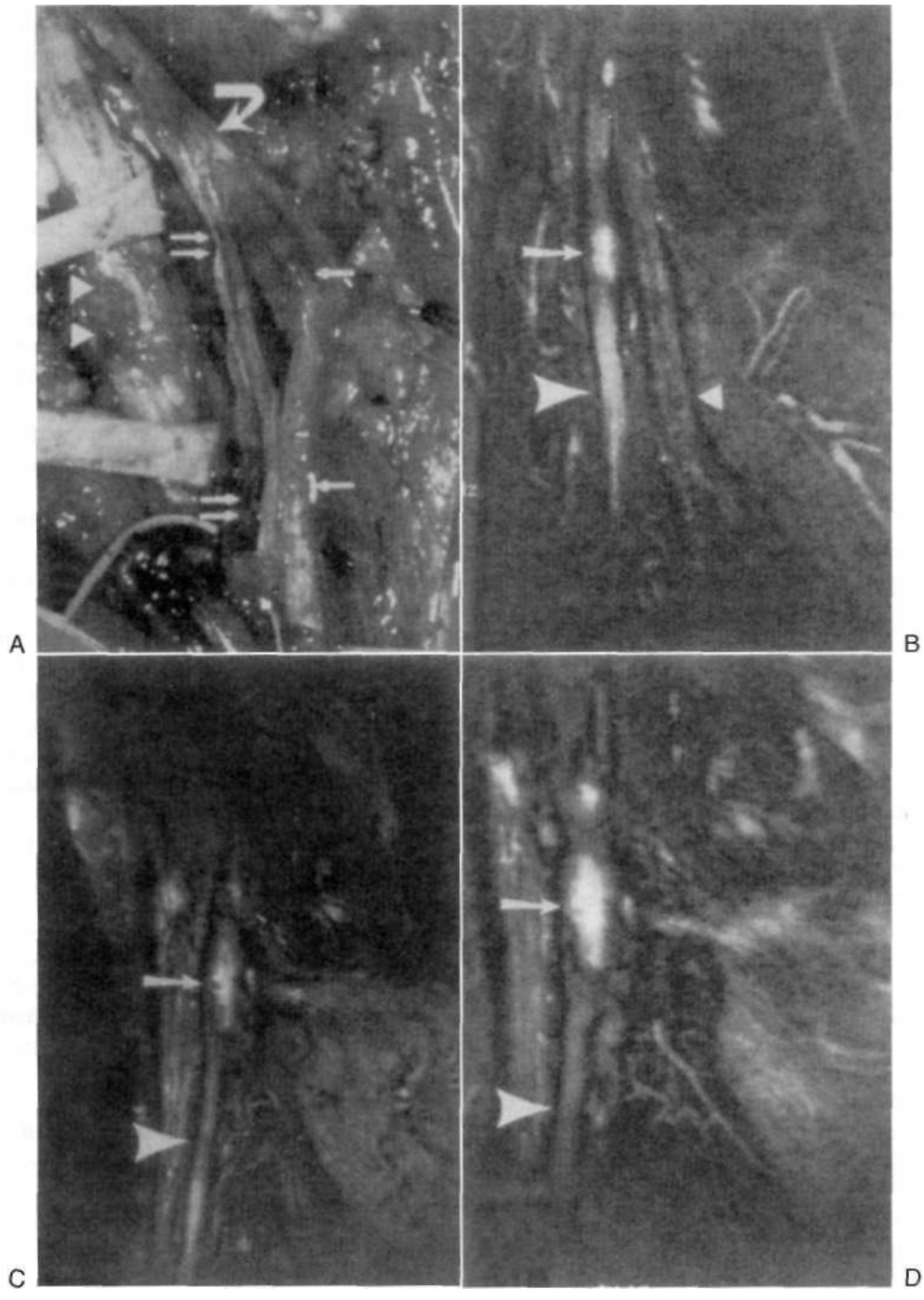

FIGURE 56D.5 MRl in nerve injury. (A) A scarred suture repair site after a laceration injury to the peroneal nerve was repaired using two sural nerve grafts *(double white arrows).* (B) High signal (T2-weighted) both at *[small arrow)* and distal to *(large arrowhead)* the scarred suture repair site 6 months after the original injury and suture repair but before the graft repair. (C) incomplete resolution of high signal seen several months after graft repair. Patient showing signs of clinical improvement. (D) 16 months later, the patient has made significant recovery. Almost complete resolution of high signal from the distal nerve segment *(large arrowhead).* High signal remains at the graft repair site *(arrow).* (Reproduced with permission from Grant, G. A., Britz, G. W., Goodkin, R., et a I. 2002, "The utility of magnetic resonance imaging in evaluating peripheral nerve disorders," *Muscle Nerve,* vol. 25, no. 3, pp. 314-331, Figure 10, p. 327. Wiley Periodicals, Inc., 2002.)

the true extent of the injury. For example, there may be a long segment of in-continuity injury proximal and distal to the transection or other areas of compression or axonotmesis at distant sites. One must also account for injury to vascular structures, bone, and soft tissues in the wound site. In such situations, it is prudent to delay formal nerve repair for at least 2 weeks. At the initial surgical debridement of the wound, the surgeon tacks the proximal and distal nerve stumps to local healthy fascial and muscular tissue and later reinspects the wound at a time when wallerian degeneration has occutred, the stumps have retracted, and easily detectable neuromas have formed. This is called a delayed primary repair.

Most nerve injuries occur in closed wounds and thetefore are more difficult to judge. One must pay close attention to clinical or EDX signs of recovery during serial evaluation; one should follow the patient for 2-3 months in the case of a suspected focal lesion and 4-5 months for a suspected lengthy lesion. Failure to progtess usually indicates a mote severe injury that warrants surgical inspection (Spinner and Kline 2000). In general, surgical repair of nerve trauma is needed for most grade IV and all grade V injuries.

Surgical Procedures

Great advances in peripheral nerve surgery have been made since the introduction and refinement of microsurgical techniques in the last half century. A detailed account of peripheral nerve surgery is beyond the scope of this chapter, but the basic techniques that are currently used in most specialized centers are outlined in the following sections.

Neurolysis (External and Internal)

The presence of scar tissue either around or within the nerve can significantly impede regeneration. Therefore one of the most important ptocedures is debridement of the wound, isolation of the nerve injury site, and mobilization of vascular and connective tissues above and below the nerve injury. This external neurolysis frees the nerve from surrounding scar tissue and may be sufficient to manage in-continuity lesions with recordable NAPs. Incomplete lesions may include scat tissue that involves the cpifascicular epineurium or the interfascicular epineurium. Internal neurolysis entails surgically freeing the nerve trunk or fascicles from such scar tissues using the surgical microscope. If the epifascicular epineurium is the only site of scat formation, a longitudinal incision called an epineurotomy may be sufficient. However, interfascicular scars may necessitate more intricate separation of involved from uninvolved nerve fascicles. The latter procedure usually is performed as part of the preparation for nerve graft repairs during which NAPs are used to identify damaged nerve fascicles. Review of outcomes after neurolysis of in-continuity radial and median nerve injuries at a major nerve trauma center showed good motor functional recovery in 98% and *95%* of cases, respectively,

Primary Neurorrhaphy

Primary repair (primary neurorrhaphy) of a neurotmesis lesion involves the direct suturing of the proximal to the distal stump and is the procedure of choice. If the parent nerve trunk contains few fascicles that are easy to align, an epineurial repair often is the preferred option. Consequently, this kind of repair usually is carried out on the distal segments of smaller nerves in the distal upper and lower extremity (e.g., digital nerves). Sutures are placed through the epineurium of the proximal and distal stumps, which ate then tightened into approximation without causing undue tension on the newly repaired nerve. Local landmarks, such as the orientation of blood vessels, are used to ensure the correct alignment of the nerve endings.

As mentioned previously, the proximal portions of larger nerves may have a complex intetlaced fascicular pattern (Sunderland's plexus), making it difficult to align transected whole nerve endings. If one were to carry out a whole nerve coaption and fail to pay attention to the fascicular pattern, a predominantly motor fascicle in the proximal stump could come into contact with a predominantly sensory fascicle in the distal stump, which would result in an unsatisfactoty functional outcome. In fascicular repair, the preferred technique in such proximal extremity nerve injuries, the surgeon coapts the proximal and distal ends of individual fascicles rather than the entire nerve trunk. Sutures are placed through the fascicular perineurium (Figure 56D.6). Histochemical staining of stumps, local landmark orientation, and intraoperative NAPs help the surgeon to choose the correct fascicular stumps.

Overall, good functional outcome is seen in about 70% of primary neurorrhaphies, but results vary. In one major nerve trauma center, good functional outcome was observed in 91% of radial and 86% of median nerve injuries repaired by primary neurorrhaphy.

Nerve Grafts

If there is a significant gap between the proximal and distal stump, as in a sevete neurotmesis lesion from a high-velocity gunshot, it may not be possible to perform primary neurorrhaphy because excessive tension will be placed on the nerve. This will increase intraneural pressure to the point at which blood flow is compromised. Excessive stretch leads to scat formation, especially when there is passive stretch across bony protuberances and joints. In Mich situations, nerve grafting is the preferred choice. This entails suturing a piece ot nerve harvested from elsewhere between the proximal and distal stumps of the injured nerve. In most centers, an autologous nerve graft is used

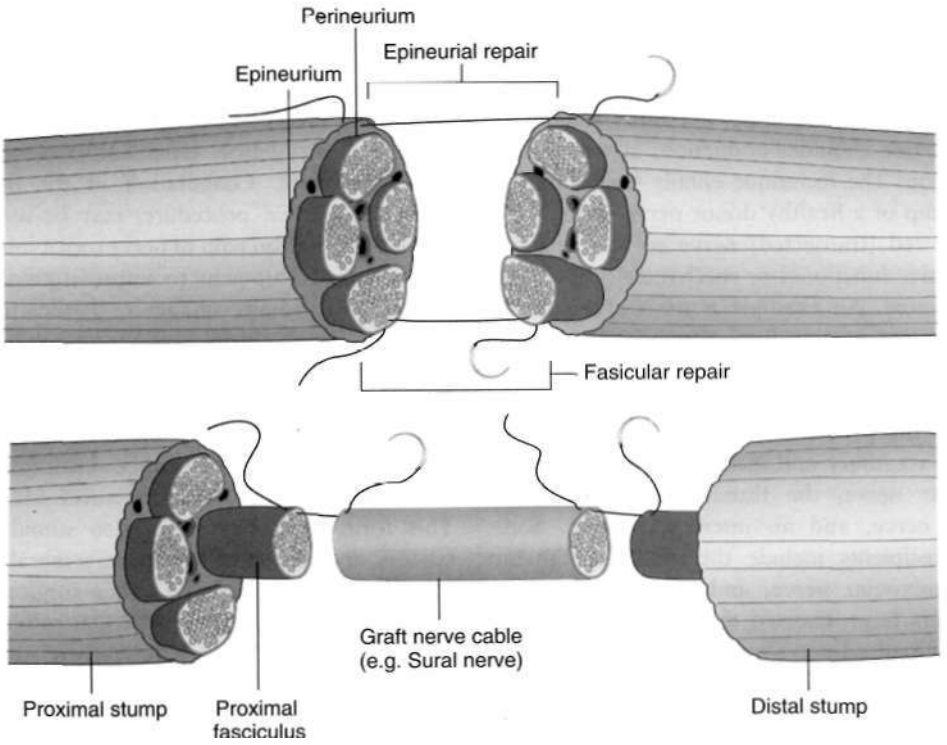

FIGURE 56D.6 Basic techniques in surgical repair. Schematic diagram illustrating the basic concepts of epineurial, fascicular, and graft repair. Direct end-to-end neurorrhaphy of small distal nerves usually is carried out using an epineurial repair approach *(top),* which entails placing sutures through the epifascicular cpincurium and bringing the nerve stumps into approximation. Fascicular repair *(top)* is preferred for more proximal nerves that have a more complex interlaced fascicular pattern. Stumps are approximated using sutures that have been placed through the perineurium. Graft repairs *{bottom)* are performed when direct end-to-end neurorrhaphy would cause excessive tension on the repair site. The graft material is harvesred from a nonessential sensory nerve (e.g., the sural nerve), which is then sutured between fascicles.

(i.e., a healthy segment of nerve is removed from the patient's body and sutured between the stumps at the trauma site; Millesi 1998). In general, these grafts are sutured via a fascicular rather than an epineurial approach (see Figure 56D.6). Common donor nerves are those that are nonessential and largely sensory in function such as the sural nerve, lateral antebrachial cutaneous nerve, and lateral tumoral cutaneous nerve. It is important to counsel the patient that once such a nerve is sacrificed, there will be an area of permanent sensory loss in the sensory distribution of the donor nerve.

The success rate of nerve grafting varies, but a satisfactory functional outcome occurs in about 50% of cases. Results vary depending on the experience and skill of the nerve trauma team and the particular nerve involved. For example, good functional recovery of motor function was observed in 68-75% of median and 80% of radial nerve injuries that were repaired by nerve grafting at one major nerve trauma center. Retrospective review of functional outcomes after repair of sciatic nerve injuries at the same center reported good outcomes after repair of tibial but not peroneal *(<3>6%)* division injuries. A number of factors influence whether successful functional regeneration takes place after graft repair, such as the distance between the proximal and distal stump and the type of nerve graft or conduit used. However, a recent primate study showed that the single most important prognostic factor is the time interval between the nerve injury and reinnervation of the target motor or sensory organ. The authors of this study postulate that there may be a time-dependent degeneration of Schwann cells in the bands of Biingner together with fragmentation of the basal lamina in the distal nerve. In addition, the neuron proximal to the injury site may also lose some of its ability to support axon regeneration. They suggest that, at least in nonhuman primates, the optimum time to successful reinnervation of the target organ using nerve grafts occurs within 100 days of sustaining the nerve lesion (Krarup, Archibald, and Madison 2002).

In general, a better outcome is seen in younger, healthier patients. Regeneration is better across shorter nerve grafts. Pure motor and pure sensory nerves recover more satisfactotily than mixed nerves.

Nerve Transfers

Avulsion injuries create a special problem in nerve repair because there is often no proximal stump with which an anastomosis may be made to a distal stump or an

intervening nerve graft. A specialized nerve transfer technique, also called neurotization, has been developed to improve the outcome of these functionally debilitating injuries. Neurotizations in the upper extremity usually are performed to provide shoulder abduction, elbow flexion, and hand sensation. The technique entails the transfer of the prn\im;i] stump of .1 healthy donor nerve to the distal stump of an injured (transected) nerve so that a target muscle of particular functional or mechanical importance becomes reinnervated. An example is the transfer of the spinal accessory nerve to the distal stump of the injured musculocutaneous nerve in a case of proximal upper extremity nerve root avulsion; the patient gains useful elhow flexion in the process. Other axon donor nerves depend on the exact injury and include the phrenic nerve, the suprascapular nerve, the thoracodorsal nerve, the medial pectoral nerve, and an intercostal nerve. Some common axon recipients include the musculocutaneous nerve, the suprascapular nerve, and the axillary nerve. Certain researchers have assessed the feasibility of direct reimplantation of avulsed nerve roots back into the spinal cord, with mixed results. Although some patients regain useful function of proximal limb muscles, more distal hand muscles are not successfully reinnervated, and there is a risk of causing operative injury to spinothalamic tracts within the spinal curd.

A similar problem also arises when the very terminal segments of a nerve have lost contact with the target organ, thus failing to leave a distal stump for reanastomosis. Although it is performed in highly specialized centers, a technique has been developed in which the distal nerve stump is split into fascicles, which are then implanted directly into the endplate region of the target muscle belly. One may even transfer an entire muscle together with its blood and nerve supply to the site of a functionally more important muscle that is nonfunctioning through prior injury. For example, a chronically denervated and degenerated biceps muscle in the upper extremity may be replaced by a neurotized and vascularized gracilis muscle that has been harvested from the lower extremity.

OTHER ASPECTS **OF NERVE INJURY MANAGEMENT**

Patients often complain of pain in the distribution of an affected nerve, which may be deep-seated, burning, stabbing, or ice cold in nature. Such pain may be caused by persistent distortion, compression, or ischemia of the nerve and may also represent a subtype of complex regional pain syndrome (type I or II) or post-traumatic neuralgia or in others may be psychological in origin. Some patients also complain of pain for secondary gain, which may or may not be apparent in the history. For many patients it is the most significant symptom of their injury and affects all aspects of daily living. The most severe pain syndrome is seen after avulsion of preganglionic posterior nerve roots and is very difficult to treat. A number of pharmacological and surgical procedures may assist these patients. Some of the mote commonly prescribed agents include amitriptyline, **carba-**mazepine, mexiletinc, gabapentin, clonazepam, opioids, and topiramate. Coagulation of the dorsal root entry zones (the DREZ procedure) may be useful in managing the deafferentation pain of nerve root avulsion. Novel drugs are under development to improve pain, including modulators of sodium channels, modulators of nicotinic acetylcholine receptors, and N-type voltage-sensitive calcium channel blockers. Physical and occupational therapy are integral parts of nerve injury management for **both** surgical and nonsurgical patients. It is imperative that range of motion exercises be instituted early after an injury to prevent joint contractures and muscle wasting, This form of therapy may also stimulate and enhance sensory and motor relearning in cerebral cortex. **It** is **best** to allow a brief interlude after a surgical nerve repair to allow wound healing and revascularization before performing full physical therapy, but passive movements may be instituted early. A range of specialized assist devices and splints are available to ensure adequate functional positioning of a weak limb. It is preferable to custom fit these lightweight devices so that agonist muscles are not overstretched and antagonists arc not excessively shortened.

FUTURE DIRECTIONS

Although the gold standard in nerve gap management is the autologous nerve graft, there are some disadvantages to its use. As already mentioned, the technique requires that a perfectly functioning nerve from elsewhere be sacrificed to repair the injured nerve. This may present a significant problem if multiple nerve trauma occurs or the gap between stumps is very great. Furthermore, nerve regeneration across the graft may not be as effective as across a direct end-to-end repair; the regenerating axon must make its way across two suture lines and the intervening graft tissue before making contact with the distal stump. The intrafascicular pattern may be very different between the nerve and graft stumps, and although the graft is from the same patient, it may not produce as much tropic and trophic support as local nerve tissue. The more suture lines present, the greater the chance of in situ neuroma formation, and in cases of severe multiple trauma there is the possibility of an inadequately vascularized graft bed. One approach may be to use human cadaveric nerve grafts (allografts) rather than autologous nerve grafts, which would obviate the sacrifice of perfectly healthy nerves from the patient to treat a damaged nerve and would also provide a more plentiful supply in the event that multiple grafts are needed. However, this foreign material triggers graft rejection, which necessitates the administration of potent immunosuppressive therapy.

For these reasons, there have been moves to develop alternative conduits to bridge the gap between separated nerve stumps. Much of this research has been carried out in animal models using many absorbable and nonabsorbable synthetic, semisynthetic, and biological devices, including collagen, epincurium, mesothelium, muscle, vein, glycolide trimethylene carbonate, silicone, poly-3-hydroxybutyrate, and poly-L-lactic acid. Although the results have been variable, most such devices have not been quite as effective as autologous grafts; nevertheless, they hold promise for the future. A recenr randomized prospective trial in humans showed favorable results using polyglycolic acid conduits for repair of digital nerves. Superior functional sensory outcome was observed when conduits were used to repair gaps of 4 mm or less compared with primary neurorrhaphy, and superior results occurred when conduits were used to repair gaps of 8 mm or more compared with autologous nerve grafts.

A number of ingenious modifications have been used to improve the effectiveness of conduits, the most widely reported of which is to seed the lumen of the entubulation device with a monolayer or scaffold of Schwann cells. Research in cell cultures and animals indicates that these seeded grafts may approach autologous graft levels in their ability to support nerve regeneration.

Another experimental approach is to seed synthetic conduits not with whole cells but with molecules, such as neurotrophic factors, that are known to promote regrowth of axons. For example, nerve growth factor has been studied extensively in the treatment of peripheral neuropathy. It is selectively trophic for small-caliber, unmyelinated sensory and autonomic (sympathetic) nerve fibers, and reduced levels may play a significant part in the pathogenesis of small fiber sensory neuropathy. Several trials have already been undertaken to assess the potential effect of subcutaneous recombinant human nerve growth factor in the management of diabetic and HIV-rclated small fiber polyneuropathies, but despite promising early results a placebo-controlled phase III trial did not show any clear benefit in the treatment of diabetic neuropathy. However, when one considers this in the context of nerve trauma repair, the delivery of neurotrophic factors via a local matrix bypasses many of the problems of systemic administration and also ensures a steady local concentration of agent along the course of the conduit. There is additional early evidence that vascularizing synthetic conduits containing vascular endothelial growth factor may also improve target organ reinnervation.

As further inroads arc made into the understanding of the molecular basis of nerve injury and regeneration, it is likely that other novel drug treatments will be evaluated in human trials to maximize functional recovery in both surgical and nonsurgical settings. Such agents may include modulators of cell signaling, cell adhesion, or inflammation and immunosuppressant drugs such as cyclosporine and rapamycin that also promote axon regeneration. Non-pharmacological strategies may also be of benefit. For example, it has been shown in an animal model of nerve injury that it may be possible to rescue muscles from denervation-induccd degeneration by transplanting embryonic anterior spinal cord cells into peripheral nerve. Furthermore, there is some evidence that continuous electrical stimulation using an implantable device may improve functional outcome after nerve injury. A gene therapy approach may be used to deliver neurotrophic and other substances to target tissue, bypassing the problems encountered by systemic administration, such as low bioavailability, short half-life, and frequent side effects caused by high dosage needs. Several groups have reported beneficial effects in animal models of nerve root avulsion using viral vectors to deliver the coding sequences of adhesion molecules, antiapoptotic proteins, and neurotrophic factors to both glial and neuronal cells in the dorsal and ventral horns of the spinal cord. Other advances undoubtedly will include detailed studies on brain plasticity after nerve injury and how this might be enhanced by various stimulation techniques to improve functional outcome. Magnetoencephalography is an exciting new technique that may prove invaluable in the finely detailed mapping of cortical responses to peripheral nerve injury.

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Chapter 57
Vascular Diseases of the Nervous System

A. ISCHEMIC CEREBROVASCULAR DISEASE

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EPIDEMIOLOGY AND RISK FACTORS

Every year, at least 750,000 Americans experience a new or recurrent stroke. Despite gradual declines in overall stroke death rates in many industrialized countries, stroke remains the third leading cause of death, with 160,000 stroke-related fatalities annually in the United States. Stroke is also the leading cause of disability in adults. Of the hundreds of thousands of stroke survivors each year, approximately 30% require assistance with activities of daily living, 20% require assistance with ambulation, and 16% require institutional care. The human and financial costs of stroke are immense, and its estimated annual economic impact on our society, both directly in health care and indirectly in lost income, is approximately $41 billion.

Steep decreases in stroke incidence and mortality have occurred in industrialized nations in recent years. The reduction in stroke mortality in the United States has been attributed to a declining stroke incidence, with suggestive evidence favoring a trend in declining stroke severity. Despite these trends in developed countries, stroke mortality and incidence are still high in many other countries. Socioeconomic factors, dietary and lifestyle behaviors, different patterns of risk factors, and environmental conditions may explain the different incidences of stroke observed in different parts of the world.

A number of factors that may be classified as modifiable and unmodifiablc increase the risk of ischemic stroke (Table 57A.1). Risk factors for stroke include older age, male gender, black ethnicity, low socioeconomic status, family history, arterial hypertension, diabetes mellitus, dyslipidemia, heart disease, cigarette smoking, excessive alcohol intake, and **body** mass index. Clinicians cannot assume that these risk factors express themselves exclusively by accelerating atherosclerosis. There are also considerable data implicating hemostatic and microcirculatory disorders in stroke as well as circadian and environmental factors.

The incidence of stroke increases dramatically with advancing age, and increasing age is the most powerful risk factor for stroke. The incidence of stroke doubles each decade past *55* years of age. Half of all srrokes occur in people older than 70 to 75 years. Men develop ischemic strokes at higher rates than women up to the age of 75 years. With an estimated 20% of the population being older than age *65,* and with greater than 10 million octogenarians, and an increasing life expectancy in the United States, it is predicted that in the near future, the incidence of stroke will reach 1 million per year. The rate of cerebral infarction is higher in blacks than in whites; this could be partially explained by the higher prevalence of diabetes and arterial hypertension experienced by blacks.

Table 57A.1: Risk factors for ischemic stroke

Nonmodifiable	*Modifiable*
Age	Arterial hypertension
Gender	i'r.siiMrnl ischemic ;imicks
Race/ethnicity	Prior stroke
Family history	Asymptomatic carotid hruit/sluisusis
Genetics	Cardiac disease
	Aortic arch atheromatosis
	Diabetes mellitus
	Dyslipidemia
	Cigarette smoking
	Alcohol consumption
	Increased fibrinogen
	Elevated homocyst(e)ine
	Low serum folate
	Elevated anticardiolipin antibodies
	Oral contraceptive use
	Obesity

Blacks also have higher rates of intracranial atherosclerotic occlusive disease, compared with whites (Sacco et al. 1995). **The** stroke incidence and case fatality rates are also markedly different among the major ethnic groups in Auckland, New Zealand. Maori and Pacific Islands people have a higher mortality within 28 days of stroke when compared with Europeans, especially men (Bonita ct al. 1997}.

Heredity seems to play a minor role in the pathogenesis of cerebral infarction. However, an increased risk is seen with a family history of stroke among first-degree relatives. There are also a number of genetic causes of stroke. Some inherited diseases, such as the hereditary dyslipoprotein-emias, predispose to accelerated atherosclerosis. A number of inherited diseases ate associated **with non**atherosclerotic vasculopathies, including Ehlcrs-Danlos (especially type IV) syndrome, Marfan's syndrome, Rendu-Osler-Weber disease, and Sturgc-Wcbcr syndrome. Familial atrial myxomas, hereditary cardiomyopathies, and hereditary cardiac conduction disorders are examples of inherited cardiac disorders that predispose to stroke. Deficiencies of protein C and S or antithrombin (AT) **III** are examples of inherited hematological abnormalities that can cause stroke. Finally, rare inherited metabolic disorders that can cause stroke include mitochondrial encephalopathy, /actic acidosis, and stroke-like episodes (MELAS), Fabry's disease, and homocysrinuria. Controversial evidence shows that the presence of the apolipoprotein K2 allele in elderly individuals and deletion of the gene for the angiotensin-converting enzyme may increase the risk of stroke (Slooter et al. 1997).

At least 25% of the adult population has arterial hypertension, defined as systolic blood pressure (SBP) greater than 140 mm Hg, or diastolic blood pressure (DBP) greater than 90 mm Hg. High notmal blood pressure is defined as SBP between 130-139 mm Hg or DBP between 85-89 mm Hg; normal blood press Lire as SBP less than 130 mm Hg and DBP less than 85 mm Hg, and optimal blood pressure as SBP less than 120 mm Hg, and DBP less than 80 mm Hg (National Institutes of Health |NIH| 1997), Arterial hypertension predisposes to ischemic stroke by aggravating atherosclerosis and accelerating heart disease, increasing the relative risk of stroke three- to fourfold. The risk is greater for patients with isolated systolic hypertension and elevated pulse pressure. Arterial hypertension is also the most important modifiable risk factor for stroke and the most powerful risk factor for all forms of vascular dementia. Lowering blood pressure in stroke survivors helps prevent recurrent stroke and is more important than the specific hypotensive agent used. Blood pressure treatment, resulting in a reduction in SBP of 10-12 mm Hg and *5-6* mm Hg diastolic, is associated with a 38% reduction in stroke incidence (MacMahon et al. 1996). Treatment of isolated systolic hypertension in the elderly is also effective in reducing stroke risk. The Systolic Hypertension in the Elderly Program showed a 36% reduction in nonfatal plus fatal stroke over 5 years in the age 60 and older group when isolated systolic hypertension was treated. Treating systolic hypertension also slows the progression of carotid artery stenosis. The PROGRESS Trial evaluated the effects of perindopril and indapamide on the risk of stroke in patients with histories of stroke or transient ischemic attack (TIA). Regardless of blood pressure at entry, patients clearly benefitted from treatment (PROGRESS Collaborative Group 2001).

Six million Americans have diabetes mellitus, and there are at least 5 million more people in which it is undiagnosed. Diabetes mellitus increases the risk of ischemic cerebrovascular disease two- to fourfold compared with the risk in people without diabetes. In addition, diabetes mellitus increases morbidity and mortality after stroke. Macrovascular disease is the leading cause of death among patients with diabetes mellitus. The mechanisms of stroke secondary to diabetes may be caused by cerebrovascular atherosclerosis, cardiac embolism, or rheological abnormalities. The excess stroke risk is independent of age or blood pressure status. Diabetes associated with arterial hypertension adds significantly to stroke risk. There is a fourfold increase in the relative risk of cardiovascular event among patients with diabetes and hypertension than among those without the two conditions (Hypertension in Diabetes Study [HDS] 1993). Diabetic persons with retinopathy and autonomic neuropathy appear to be a group at particularly high risk for ischemic stroke. High insulin levels increase the risk for atherosclerosis and may represent a pathogenetic factor in cerebral small vessel disease. However, presently no evidence exists that tighter diabetic control or normal HbA_u. levels over time decrease the risk of stroke or stroke recurrence.

High total cholesterol and high low-density lipoprotein (LDL) concentration are correlated with atherosclerosis. Although overwhelming evidence relates low levels of

high-density lipoprotein (HDL) cholesterol with coronary heart disease, the association with cerebrovascular disease is less clear. Some studies have shown a positive relationship between serum cholesterol levels and death resulting from nonhemorrhagic stroke. The relationship has not been consistent, however, possibly because different risks are associated with different lipoprotein subtypes. Lipid-modifying therapy with 3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitors (statins) have definitively established that reduction of LDL cholesterol reduces cardiovascular risk. Statins appear likely to benefit stroke survivors as well. The frequency of hemorrhagic strokes is not increased by the use of statins. Lipid-lowcring agents may slow progression of atherosclerotic plaque growth and may possibly cause a regression in plaque formation.

The Scandinavian Simvastatin Survival Study (4S) (Scandinavian Simvastatin Survival Study Group 1999} investigated cholesterol lowering in persons with coronary heart disease and hypercholesterolemia and reported a highly significant relative reduction in the total mortality rate, major coronary events, and number of cardiac revascularization procedures. Post hoc analysis also showed a 28% reduction in fatal or nonfatal stroke and TIAs (Pedersen et al. 1998).

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study investigated cholesterol lowering with pravastatin in patients with a previous myocardial infarction or unstable angina who had cholesterol levels between 155 and 271 mg/dL, and reported a remarkable reduction in myocardial infarction, cardiac tevascularizations, and cardiovascular deaths, as well as a 20% reduction in the risk of stroke (The Long-Term Intervention with Pravastatin in Ischaemic Disease [LIPID] Study Group 1998).

An estimated 1 to 2 million Americans have chronic nonvalvular atrial fibrillation (NVAF), a condition that is associated with an overall risk of stroke of approximately five to sixfold, and a mortality of approximately twice that of age- and sex-matched individuals without atrial fibrillation. The prevalence of atrial fibrillation increases with advancing age and is 0.5% for patients aged 50 to 59 years and 8.8% for those aged 80 to 89 years (Wolf et al. 1991). Approximately 70% of individuals with atrial fibrillation are between 65 and 85 years of age. NVAF is associated with a substantial risk of stroke. Heart failure, arterial hypertension, diabetes, prior stroke or TIA, and age older than 75 years increase the risk of embolism in patients with NVAF. High-risk patients have a 5-7% yearly risk of thromboembolism. The use of warfarin therapy with the international normalized ratio (INR) adjusted to between 2.0 to 3.0 decreases the relative risk of stroke in patients with NVAF by approximately two thirds. Left atrial enlargement increases the risk of stroke in men. Likewise, left ventricular hypertrophy as demonstrated by electrocardiography (KCG) in men with pre-existing ischemic heart disease is a major risk factor for stroke.

Smoking is the leading cause of preventable death in the United States. Cigarette smoking is a major risk factor for coronary artery disease, stroke, and peripheral arterial disease. Cigarette smoking is an independent risk factor for ischemic stroke in men and women of all ages, and a leading risk factor of carotid atherosclerosis in men. The risk of stroke in smokers is two to three times greater than in nonsmokers. The mechanisms of enhanced atherogenesis promoted by cigarette smoking are incompletely understood, but include reduced capacity of the blood to deliver oxygen, cardiac arrhythmias, and triggering of arterial thrombosis and arterial spasm. More than 5 years may be required before a reduction in stroke risk is observed aftet cessation of smoking. Switching to pipe or cigar smoking is of no benefit. Nicotine replacement therapy and bupropion are efficacious smoking cessation treatments.

There is a J-shaped association between alcohol consumption and ischemic stroke; light to moderate use (up to two drinks a day) evenly distributed throughout the week offers a reduced risk, whereas heavy drinking is associated with an increased risk of total stroke. Heavy drinking may precipitate cardiogenic brain embolism. Alcohol consumption increases the risk of hemorrhagic stroke; alcohol-induced hypertension predisposes to spontaneous intracranial hemorrhage. Furthermore, active drinkers have a higher frequency of obstructive apneas and more severe hypoxemia. Conversely, moderate alcohol consumption may reduce the risk of ischemic stroke and may elevate HDL concentration.

The prevalence of obesity (body mass index of 30 or higher) has increased nationwide. More than 61% of adult Americans are overweight, and 27% are obese. Obesity, particularly abdominal or truncal, is an important risk factor for cardiovascular disease in men and women of all ages. There is some evidence that physical activity can teduce the risk of stroke. Regular exercise lowers blood pressure, decreases insulin resistance, increases HDL cholesterol, and is associated with lower cardiovascular morbidity and mortality. Habitual snoring increases the risk of stroke and adversely affects outcome of patients admitted to the hospital with stroke. Mounting evidence also suggests that inflammation, impaired fibrinolysis, and increased thrombotic potential are important nontraditional cardiovascular risk factors.

Atherosclerotic lesions of the carotid bifurcation are a common cause of stroke. Asymptomatic carotid disease carries a greater risk of vascular death from coronary artery disease than from stroke. Persons with an asymptomatic carotid bruit have an estimated annual risk of stroke of 1.5% at 1 year and 7.5% at 5 years. Asymptomatic carotid artery stenosis less than 75% carries a stroke risk of 1.3% annually; with stenosis greater than 75%, the combined TIA and stroke rate is 10.5% per year, with most events occurring ipsilatcral to the stenosed carotid artery. Plaque composition may be an important factor in the pathophysiology of carotid artery disease. Plaque structure rather

than degree of carotid artery stenosis may be a critical factor in determining stroke risk. Ultrasonographic carotid artery plaque morphology may identify a subgroup of patients at high risk of stroke. Ulcerated, echoluccnt, and heterogeneous plaques with a soft core represent unstable plaques at high risk for producing arterioarterial embolism.

Patients who suffer TIAs are at greater risk than normal controls for stroke or death from vascular causes. The risk of stroke is approximately three times higher. Symptomatic carotid artery stenosis greater than 70% carries an annual risk of stroke of approximately 15%. Approximately 10-15% of those experiencing a stroke have TIAs before theit stroke. Patients with hemispheric TIAs arc at greater risk of ipsilatctal stroke than patients with tetinal TIAs. Patients with a first stroke arc at greater risk of recurrent stroke, especially, but not exclusively, early aftet the first stroke. Those who suffer a recurrent stroke have a higher mortality than patients with first stroke. If the recurrence is contralateral to the first stroke, prognosis for functional recovery is poor. The risk of stroke recurrence is increased also by the presence of underlying dementia.

The aorta is the most frequent site of atherosclerosis. Protruding atheroma may be the cause of otherwise unexplained TIAs ot strokes. Aortic arch atheromatosis detected by transesophageal echocardiography is an independent risk factor for cerebral ischemia; the association is particularly strong with mobile and thick atherosclerotic plaques measuring greater than or equal to 4 mm in thickness (The French Study of Aortic Plaques in Stroke Group 1996).

Hemostatic factors may be important in assessing the risk of cerebrovascular disease. Elevated hematocrit, hemoglobin concentration, and increased blood viscosity may be indicators of risk for ischemic stroke. Elevation of plasma fibrinogen is an independent risk factor for the development of cerebral infarction. An elevated plasma fibrinogen level may reflect progression of atherogenesis. Plasminogen activator inhibitor-! excess and factor VII are independent risk factors for coronary heart disease. Compared with while Americans, black Americans have higher mean levels of fibrinogen, factor VIII, von Willebrand's factor, and AT, and lower mean levels of protein C. Fibrinogen levels are closely correlated with other stroke risk factors such as cigarette smoking, arterial hypertension, diabetes, obesity, hematocrit levels, and spontaneous echocardiographic contrast. Antiphospholipid (aPL) antibodies are a marker for an increased risk of thrombosis, including TIAs and stroke, particularly in those younger than 50 years of age. The factor V Leiden mutation is associated with deep venous thrombosis in otherwise healthy individuals with additional prothtombotic risk factors. An overall association of the factor V Leiden mutation and arterial thrombosis has not been found. Elevated von Willebrand's factor is a risk factor for myocardial infarction and ischemic stroke. Elevated levels of fasting total homocysteine (normal 5-15 mmol/L), a sulfhydryl-containing amino acid, have been associated with an increased risk of stroke and thrombotic events in case-controlled studies. Metabolism of homocysteine requires vitamin B_6 (pyridoxine), vitamin Bi_2 (cobalamine), folate, and betaine. Plasma homocysteine concentrations may be reduced by folic acid alone or in combination with vitamin B_6 and vitamin $B|_2$. Conversely, serum folate concentrations less than or equal to 9.2 nmol/liter have been associated with elevated plasma levels of homocysteine, and a decreased folate concentration alone may be a risk factor for ischemic stroke, particularly among blacks (Giles et al. 1995).

Stroke is uncommon among women of childbearing age. The relative risk of stroke is increased among users of high-dose estrogen oral contraceptives, particularly with coexistent arterial hypertension, cigarette smoking, and increasing age. New agents containing lower doses of estrogen and progestogen have reduced the frequency of oral contraceptive-related cerebral infarction. Two recent postmenopausal hormone replacement studies with equine estrogen (Premarin) showed no benefit in reducing the incidence of stroke in a cohort of women with coronary heart disease (Hulley et al. 1998; Herrington et al. 2000). In addition, the Women's Health Initiative, a prospective randomized trial of estrogen therapy in healthy postmenopausal women, was halted prematurely because the risks outweighed the benefits. Absolute excess risks per 10,000 person-years attributable to estrogen plus progestin were sevenfold for coronary heart disease events, eightfold for strokes, eightfold for pulmonary thromboembolisms, and eightfold for invasive cancers, whereas absolute risk reductions per 10,000 person-years were sixfold for colorectal cancers and fivefold for hip fractures (Writing Group for the Women's Health Initiative Investigators. 2002). The risk of thrombosis associated with pregnancy is high in the postpartum period. The risk of cerebral infarction is increased in the 6 weeks after delivery but not during pregnancy.

A diurnal and seasonal variation of ischemic events occurs. Orcadian changes in physical activity, catecholamine levels, blood pressure, blood viscosity, platelet aggregability, blood coagulability, and fibrinolytic activity may explain the circadian variations in onset of myocardial and cerebral infarction. Although an early morning peak occurs for all subtypes of stroke, most clinical trials on the use of platelet antiaggregants or other antithrombotic agents do not take these circadian variations into account. Rhythmometric analyses support the notion that stroke is a chrono-risk disease, in which cold temperatures also represent a risk factor. A history of recent infection, particularly of bacterial origin and within 1 week of the event, is also a risk factor for ischemic stroke in patients of all ages. A number of recent reports suggest that *Chlamydia pneumoniae,* a causative organism of respiratory infections, has a role in carotid and coronary atherosclerosis. Some studies have also identified an association with chronic

infections with *Helicobacter pylori* and cytomegalovirus (Ross 1999;Bittner 1998).

PATHOPHYSIOLOGY OF CEREBRAL **ISCHEMIA**

Except for the lack of an external elastica lamina in the intracranial arteries, the morphological structure of the cerebral vessels is similar to those in other vascular beds. The arterial wall consists of three layers: the outer layer, or adventitia; the middle layer, or media; and the inner layer, or intima. The intima is a smooth monolayer of endothelial cells providing a nonthrombotic surface for blood flow. One of the major functions of the endothelium is active inhibition of coagulation and thrombosis.

The brain microcirculation comprises the smallest components of the vascular system, including arterioles, capillaries, and venules. The arterioles are composed primarily of smooth muscle cells around the endothclial-lincd lumen, and are the major sites of resistance to blood flow in the arterial tree. The capillary wall consists of a thin monolayer of endothelial cells. Nutrients and metabolites diffuse across the capillary bed. The venules are composed of endothelium and a fragile smooth muscle wall and function as collecting tubules. The cerebral microcirculation distributes blood to its target organ by regulating blood flow and distributing oxygen and glucose to the brain while removing by-products of metabolism.

A cascade of complex biochemical events occurs seconds to minutes after cerebral ischemia. Cerebral ischemia is caused by reduced blood supply to the microcirculation. Ischemia causes impairment of brain energy metabolism, loss of aerobic glycolysis, intracellular accumulation of sodium and calcium ions, release of excitotoxic neurotransmitters, elevation of lactate levels with local acidosis, free radical production, cell swelling, overactivation of lipases and proteases, and cell death. Many neurons undergo apoptosis after focal brain ischemia (Choi 1996). Ischemic brain injury is exacerbated by leukocyte infiltration and development of brain edema. Exciting new treatments for stroke target these biochemical changes.

Complete interruption of cerebral blood flow causes suppression of the electrical activity within 12-15 seconds, inhibition of synaptic excitability of cortical neurons after 2-4 minutes, and inhibition of electrical excitability after 4-6 minutes. Normal cerebral blood flow at rest in the normal adult brain is approximately 50-55 mL/100 g per mmute, and the cerebral metabolic rate of oxygen is 165 mmol/100 g per minute. There are certain ischemic flow thresholds in experimental focal brain ischemia. When blood flow-decreases to 18 mL/100 g per minute, the brain reaches a threshold for electrical failure. Although these neurons are not functioning normally, they do have the potential for recovery. The second level, known as the *threshold of membrane failure,* occurs when blood flow decreases to 8 mIV100 g per minute. Cell death can result. These thresholds mark the upper and lower blood flow limits of the ischemic penumbra. The ischemic penumbra, or area of misery perfusion, is the area of the ischemic brain between these two flow thresholds in which there are some neurons that are functionally silent but structurally intact and potentially salvageable.

PATHOLOGY OF **ISCHEMIC STROKE**

The pathological characteristics of ischemic stroke depend on the mechanism of stroke, the size of the obstructed artery, and the availability of collateral blood flow. There may be advanced changes of atherosclerosis visible within arteries. The surface of the brain in the area of infarction appears pale. With ischemia caused by hypotension or hemodynamic changes, the arterial border (or watershed) zones may be involved. A wedge-shaped area of infarction in the center of an arterial territory may result if there is occlusion of a main artery in the presence of collateral blood flow. In the absence of collateral blood flow, the entire territory supplied by an artery may be infarcted. With occlusion of a major artery, such as the internal carotid artery, there may be a multilobar infarction with surrounding edema. There may be evidence of flattening of the gyri and obliteration of the sulci caused by cerebral edema. A lacunar infarction, with a size of *1.5* cm or less, in subcortical areas or in the brainstem may be barely visible in the macroscopic analysis of the cut brain. Emboli to the brain tend to lodge at the junction between the **cerebral** cortex and the white matter. Early reperfusion of the infarct may occur when the clot lyses, leading to hemorrhagic transformation,

The microscopic changes after cerebral infarction are well documented. The observed changes depend on the age of the infarction. The changes do not occur immediately and may be delayed up to 6 hours after the infarction. There is neuronal swelling initially, which is followed by shrinkage, hyperchromasia, and pyknosis. Chromatolysis appears and the nuclei become eccentric. Swelling and fragmentation of the astrocytes and endothelial swelling occur. Neutrophils infiltrate appear as early as 4 hours after the ischemia and become abundant by 36 hours. Within 48 bouts, the microglia proliferate and ingest the products of myelin breakdown and form foamy macrophages. Later, there is neovascularity with proliferation of capillaries and increased prominence of the existing capillaries. The elements in the area of necrosis are gradually reabsorbed and a cavity, consisting of glial and fibrovascalar elements, forms. In a large infarction, there are three distinct zones: an inner area of coagulativc necrosis; a middle zone of vacuolated neuropil, leukocytic infiltrates, swollen axons, and thickened capillaries; and an outer marginal zone of hyperplastic astrocytes and variable changes in nuclear staining.

CLINICAL SYNDROMES OF CEREBRAL ISCHEMIA

A number of syndromes result from ischemia involving the central nervous system (Brazis et al. 2001).

Transient Ischemic Attacks

Approximately 80% of ischemic strokes occur in the carorid (or anterior) circulation, and 20% occur in the vertebrobasilar (or posterior) circulation. A TIA is a prognostic indicator of stroke, with one third of untreated TIA patients having a stroke within 5 years. The interval from the last TIA is an important predictor of stroke risk; of all patients who subsequently experience stroke, 21% do so within 1 month and 51% do so within 1 year of the last TIA. Cardiac events are the principal cause of death in patients who have had a TIA. The 5-6% annual mortality after TIA is mainly caused by myocardial infarction, similar to the 4% annual cardiac mortality in patients with stable angina pectoris.

A TIA is a temporary, focal, and "nonmarching" neurological deficit of sudden onset; related to ischemia of the brain, retina, or cochlea; and lasting less than 24 hours. Yet most TIAs last only 5-20 minutes. Episodes that last longer than 1 hour are usually caused by small infarctions. The onset of symptoms is sudden, reaching maximum intensity almost immediately. To qualify as a TIA, the episode should be followed by complete recovery. TIAs involving the carotid circulation should be distinguished from those involving the vertebrobasilar circulation. Headache is a frequent symptom in patients with TIAs. The following symptoms are considered typical of TIAs in the carotid circulation: ipsilateral amaurosis fugax, contralateral sensory or motor dysfunction limited to one side of the body, aphasia, contralateral homonymous hemianopia, or any combination thereof. The following symptoms represent typical TIAs in the vertebrobasilar system: bilateral or shifting motor or sensory dysfunction, complete or partial loss of vision in the homonymous fields of both eyes, or any combination of these symptoms. Perioral numbness also occurs. Isolated diplopia, vertigo, dysarthria, and dysphagia should not be considered as being caused by a TIA, unless they occur in combination with one another, or with any of the othet symptoms just listed (Table 57A.2).

Table S7A.2: Recognition of carotid and vertebrobasilar transient ischemic attacks

Symptoms suggestive of carotid transient ischemic attacks
Transient ipsilateral monocular blindness (amaurosis fugax)
Contralateral body weakness or clumsiness
Contralateral body sensory loss or paresthesias
Aphasia with dominant hemisphere involvement
Various degrees of contralateral homonymous visual field defects
Dysarthria (not in isolation)
Symptoms suggestive of vertebrobasilar transient ischemic attacks
Usually bilateral weakness or clumsiness, but may he unilateral or shifting
Bilateral, shitting, or crossed (ipsilateral face and con era lateral body) sensory loss or paresthesias
Bilateral or contralateral homonymous visual field defects or binocular vision loss
Two or more of the following symptoms: vertigo, diplopia, dysphagia, dysarthria, and ataxia
Symptoms not acceptable as evidence of transient ischemic attack
Syncope, dizziness, confusion, urinary or fecal incontinence, and generalized weakness
Isolated occurrence of vertigo, diplopia, dysphagia, ataxia, tinnitus, amnesia, drop attacks, or dysarthria

Occlusive disease in the subclavian arteries or the innominate artery can give rise to extracranial steal syndromes. The most well-defined syndrome is rhe subclavian steal syndrome. In this syndrome, reversal of flow in the vertebral artery is caused by a high-grade subclavian artery stenosis or occlusion proximal to the origin of the vertebral artety from the aortic arch or innominate artery, with resultant symptoms of brainstem ischemia, usually precipitated by actively exercising the ipsilateral arm. The left side is involved most frequently. With innominate artery occlusion, the origin of the right carotid is also subject to the consequences of reduced pressure. The subclavian steal syndrome can be suspected by the presence of a reduced or delayed radial pulse and diminished blood pressure in the affected arm relative to the contralateral arm. A subclavian steal may he symptomatic or asymptomatic. Many patients have angiographic evidence of reversed vertebral blood flow without ischemic symptoms. Transcranial Dopplcr sonography may detect transient retrograde basilar blood flow. Retrograde vertebral artery flow is a benign entity. Brainstem infarction is an uncommon complication of the subclavian steal syndrome.

Transient global amnesia {TGA) is characterized by a reversible anregrade and retrograde memory loss, except for a total amnesia of events that occur during the attacks, and inability to learn newly acquired information. During the attacks, patients remain alert without motor or sensory impairments and often ask the same questions repeatedly. Patients are able to retain personal identity and carry on complex activities. TGA most commonly affects patients in their 50s and older. Men are affected more commonly than women. The attacks begin abruptly and without warning. A typical attack lasts several hours (mean, 3-6 hours) but seldom longer than 12 hours. Onset of TGA may follow physical exertion, sudden exposure to cold or heat, or sexual intercourse. Although a large number of conditions have been associated with transient episodes of amnesia, in most instances TGA is of primary or unknown cause. TGA has been documented in association with epilepsy, migraine, intracranial tumors, overdose of diazepam, cardiac arrhythmias secondary to digitalis intoxication, and as a complication of cerebral and coronary angiography. Many reports

have suggested a vascular causal factor for this heterogeneous syndrome. Bilateral hippocampal and parahippocampal complex ischemia, possibly of migrainous origin, in the distribution of the posterior cerebral arteries is a potential mechanism. Acute confusional migraine in children and TGA have a number of similar features. Others have suggested an epileptic causal factor for a minority of patients. Transient amnesias have been divided into pure TGA, probable epileptic amnesia, and probable transient ischemic amnesia. In contrast to patients with TIAs, the prognosis of persons with pure TGA is benign, with no apparent increased risk for vascular endpoints. Recurrences are uncommon. Extensive evaluations are not required. Treatment with platelet antiaggregants is not indicated in most patients unless there is a suspicion for transient ischemic amnesia. The use of prophylactic calcium-channel blockers may be justified in patients with a potential migtainous causal factor.

Drop attacks are charactetized by the sudden loss of muscle tone and strength. The attacks cause the patients to unexpectedly fall to the ground. Consciousness is preserved. Most attacks occut while standing or walking and often follow head or neck motion. Drop attacks have been considetcd a symptom of vertebrobasilar ischemia, but many of these patients have other coexistent disotdcts that could otherwise explain their symptoms. In rare instances, drop attacks may indeed be caused by ischemia of the corticospinal tract or reticular formation. However, isolated drop attacks are seldom a manifestation of vertebrobasilar occlusive disease. In most instances these attacks ate secondaty to akinetic seizures, high cervical spine or foramen magnum lesions, postural hypotension, Tumarkin's otolithic ctises (in Meniere's disease), or near syncope.

TIAs may result from atherothromboembolism that originates from ulcerated extracranial arteries, emboli of cardiac origin, occlusion of small penetrating arteries that arise from the large surface arteties of the circle of Willis, altered local blood flow (perfusion failure) caused by severe arterial stenosis, nonatherosclerotic vasculopathies, or hypercoagulable states. Pteceding TIAs occur in large numbers of patients with brain infarction. In published series of cases of stroke, TIAs occurred before 25-50% of a the ro thrombotic infarcts, in 11-30% of cardiocmbolic infarcts, and in 11-14% of lacunar infarcts. Lacunar TIAs in general share the same pathogenetic mechanisms of lacunar infarcts and are associated with a substantially better prognosis than are nonlacunar TIAs.

Crescendo episodes of cerebral ischemia that increase in frequency, severity, or duration may be most threatening. A small subset of ctcsccndo TIAs is the capsular warning syndrome, characterized by restricted stereotyped, repeated episodes of capsular ischemia, causing contralateral symptoms involving face, arm, and leg. When capsular infarction develops, it is usually a lacunar-type stroke and involves a single penetrating vessel. Occasionally, striatocapsular or anrcrior-choroidal artery territory infarction occurs. Typically, these patients are refractoty to conventional forms of therapy (Donnan et al. 1993).

Rational treatment of patients with TIAs depends on a careful history and derailed physical examination. The neurovascular examination may disclose a well-localized bruit in the mid- or upper-cervical area. Bruits arise when normal laminar blood flow is disturbed. However, the presence of a cervical bruit does not necessatily indicate undeilying carotid atherosclerosis. Correlation with angiography or ultrasound studies show only 60% agreement with cervical auscultation in predicting the presence of arterial stenosis. Radiated cardiac murmurs, hyperdynamic states, nonathetosclerotic carotid arterial lesions, and venous hums can produce cervical murmurs. The absence of a bruit has little diagnostic value; the bruit may disappear when the stenosis is advanced. Convetsely, a cervical bruit may be heard contralateral to an internal carotid artery occlusion.

Different types of microemboli (e.g., cholesterol crystals, platelet fibrin, calcium, and so forth) can be seen in the retinal arterioles during or between attacks of transient monocular visual loss. Engorgement of conjunctival and episcleral vessels, conical edema and rubeosis irides, and anterior chamber cells flare arc indicative of an underlying ischemic oculopathy. Asymmetrical hypertensive retinal changes noted on funduscopy ate suggestive of a high-gtade carotid artery stenosis or occlusion on the side of the less severely involved retina. Venous stasis retinopathy may occut with high-grade carotid stenosis or occlusion and is characterized by diminished or absent venous pulsations, dilatated and tortuous retinal veins, peripheral microaneurysms, and blossom-shaped hemorrhages in the mid-peripheral retina. Corneal arcus senilis may be less obvious or absent on the side of low perfusion.

Many conditions can tesemblc a TIA. Space-occupying lesions; subdural, intracerebral, or subarachnoid hemorrhage; seizures; hypoglycemia; migraine; syncope; and labyrinthine disorders are among the divctse conditions in the differential diagnosis when TIA is considered. Symptoms of a transient neurological dysfunction that resolve incompletely should lead the physician to question the diagnosis of TIA. Similarly, a migration or march of symptoms from one part of the body to another is rare during a TIA and more indicative of a focal seizure or migraine. Fortification phenomena or scintillating bright visual symptoms are suggestive of migraine. In rare instances, involuntary limb shaking movements can occur, but, in general, involuntary movements reflect convulsive activity rather than a TIA.

Carotid Artery System Syndromes

Amaurosis fugax may he described as a sudden onset of a fog, haze, scum, curtain, shade, blur, cloud, or mist. A curtain or shade pattern with the loss of vision moving

superiorly to interiorly is described only in 15-20% of patients. Less commonly, a concentric vision loss, presumed to be caused by marginal perfusion, can diminish blood flow to the retina. The vision loss is sudden, often brief, and painless. The duration of vision loss is usually 1-5 minutes and rarely lasts more than .30 minutes. After an episode of amaurosis fugax, the vision is usually fully restored, although some patients may have permanent vision loss caused by a retinal infarction (see Chapters 14 and 15).

The sole feature that distinguishes the middle cerebral artery (MCA) syndrome from the carotid artery syndrome is amaurosis fugax. An MCA infarction is one of the most common manifestations of cerebrovascular disease. The clinical picture with an MCA infarction is varied and depends on whether the site of the occlusion is in the stem, superior division, inferior division, or lenticulostriate branches, and whether there is good collateral blood flow.

When the stem of the MCA is occluded, there is usually a large infarction with contralateral hemiplegia, conjugate eye deviation toward the side of the infarct, hemianesthesia, and homonymous hemianopia. Associated global aphasia occurs if the dominant hemisphere is involved and hemineglect with nondominant hemispheric lesions. The difference between an upper division MCA infarction and an MCA stem lesion is that the hemiparesis usually affects the face and arm more than the leg with upper division infarction. A Broca-type aphasia is more common in upper division infarcts because of the preferential involvement of the anterior branches of the upper division in occlusions. With lower division MCA syndromes, a Wernicke-type aphasia is seen with dominant hemisphere infarction and behavioral disturbances are seen with nondominant infarction. A homonymous hemianopia may be present. A lenticulostriate branch occlusion may cause a lacunar infarction with involvement of the inrernal capsule producing a syndrome of pure motor hemiparesis. These syndromes are variable and depend on the presence of collaterals or whether brain edema is present.

Alexia with agraphia may occur with left-sided angular gyrus involvement. Gerstmann's syndrome, which consists of finger agnosia, acalculia, right-left disorientation, and agraphia, may be seen with dominant hemisphere parietal lesions. The aphasias with dominant hemispheric infarctions may be of the Broca, Wernicke, conduction, transcortical, or global type, depending on the site and extent of involvement. Anosognosia, the denial of hemiparesis, most commonly is associated with right hemispheric strokes. Nondominant infarction may cause hemi-inattention, tactile extinction, visual extinction, anosognosia, anosodiaphoria, apraxia, impaired prosody, and rarely acute confusion and agitated delirium. A contralateral homonymous hemianopia or contralateral inferior quadrantanopia can occur with infarctions in cither hemisphere.

Anterior cerebral artery (ACA) territory infarctions are uncommon (Figure 57A.1). They occur in patients with vasospasm after subarachnoid hemorrhage caused by ACA or anterior communicating artery aneurysm. Excluding these causes, the percentage of acute cerebral infarcts that are in the ACA territory is less than 3%. The characteristics of ACA infarction vary according to the site of involvement and the extent of collateral blood flow. Contralateral weakness involving primarily the lower extremity, and to a lesser extent, the arm, is characteristic of infarction in the territory of the hemispheric branches of the ACA. Other characteristics include abulia, akinetic mutism (with bilateral mesiofronral damage), impaired memory or emotional disturbances, transcortical motor aphasia (with dominant hemispheric lesions), deviation of the head and eyes toward the lesion, paratonia (gegenhaltcn), discriminative and proprioceptive sensory loss (primarily in the lower extremity), and sphincter incontinence. An anterior disconnection syndrome with left arm apraxia caused by involvement of the anterior corpus callosum can be seen. Pericallosal branch involvement can cause apraxia, agraphia, and tactile anomia of the left hand. Infarction of the basal branches of the ACA can cause memory disorders, anxiety, and agitation. Infarction in the territory of the medial lenticulostriate artery (artery of Heubner) causes more pronounced weakness of the face and arm without sensory loss caused by this artery's supply of portions of the anterior limb of the internal capsule.

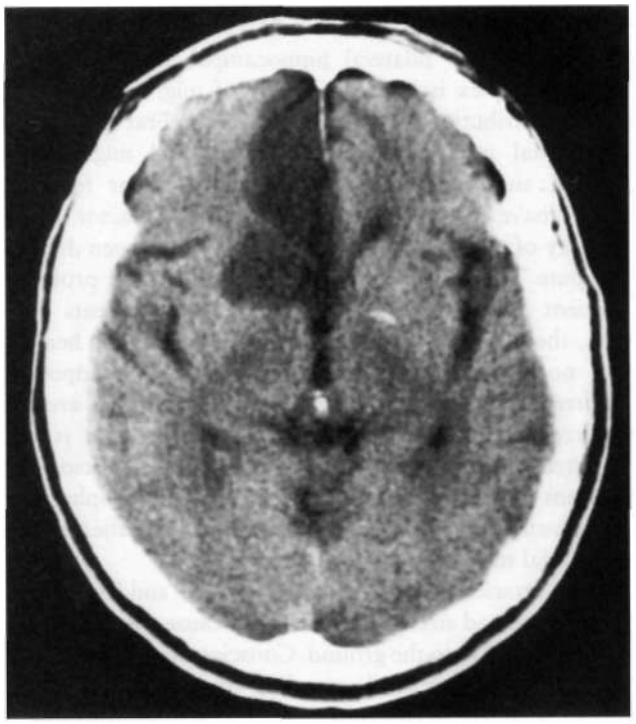

FIGURE *57* A.I N on enhanced axial computed tomographic scan of a 63-year-old man with left-sided weakness and abulia demonstrates a right anterior cerebral artery (ACA) territory infarction. More superior images showed the entire ACA distribution was in famed.

The anterior choroidal artery syndrome is often characterized by hemiparesis caused by involvement of the

posterior limb of the internal capsule, hemisensory loss caused by involvement of the posterolateral nucleus of the thalamus or thalamocortical fibers, and hemianopia secondary to involvement of the lateral geniculate body or the gcniculocalcarine tract. The visual field defect with anterior choroidal artery syndrome infarcts is characterized by a homonymous defect in the superior and inferior visual fields that spares the horizontal meridian. In a small number of patients left spatial hemineglcct with right hemispheric infarctions and a mild language disorder with left hemispheric infarctions may occur. With bilateral infarctions in the anterior choroidal artery syndrome territory, there can be pseudobulbar mutism, and a variety of other features including facial diplegia, hemisensory loss, lethargy, neglect, and affect changes.

LACUNAR SYNDROMES

Ischemic strokes resulting from small vessel or penetrating artery disease (lacunes) have unique clinical, radiological, and pathological features. Lacunar infarcts are small ischemic infarctions in the deep regions of the brain or brainstem that range in diameter from 0.5-15.0 mm. These infarctions result from occlusion of the penetrating arteries, chiefly the anterior choroidal, middle cerebral, posterior cerebral, and basilar arteries. Lacunar infarcts could also be the result of occlusion of penetrating arteries by atherosclerosis of the parent artery or microembolism. Lacunes may be single or multiple, symptomatic or asymptomatic. At least 20 lacunar syndromes have been described. Lacunar syndromes are highly predictive of lacunar infarcts, with a positive predictive value of approximately 84% to 90% (Can et al. 1997). The five best recognized syndromes are (1) pure motor hemiparesis, (2) pure sensory stroke, (3) sensory-motor stroke, (4) homolateral ataxia and crural paresis (ataxic hemiparesis), and (5) dysarthria-clumsy hand syndrome. Multiple lacunes may be associated with acquired cognitive decline. Headaches arc uncommon in patients with lacunar infarcts.

Pure motor hemiparesis is often caused by an internal capsule, basis pontis, or corona radiata lacune and is characterized by a contralateral hemiparesis or hemiplegia involving the face, arm, and to a lesser extent, the leg, accompanied by mild dysarthria, particularly at onset of stroke. There should be no aphasia, apraxia, or agnosia, and there are no sensory, visual, or other higher cortical disturbances. Pure sensory stroke is often caused by a lacuna involving the ventroposterolateral nucleus of the thalamus. It is characterized by paresthesias, numbness, and a unilateral hemisensory deficit involving the face, arm, trunk, and leg. Sensory-motor stroke is often caused by a lacuna involving the internal capsule and thalamus or posterior limb of the internal capsule; large striatocapsular infarcts also can cause a similar syndrome. It is characterized by a contralateral unilateral motor deficit with a superimposed hemisensory deficit. Homolateral ataxia and crural paresis are often caused by a lacuna either in the contralateral posterior limb of the internal capsule or the contralateral basis pontis. It is characterized by weakness, predominantly in the lower extremity, and ipsilateral incoordination of the arm and leg. Dysarthrla-clumsy hand syndrome is often caused by a lacuna involving the deep areas of the basis pontis and is characterized by supranuclear facial weakness, dysarthria, dysphagia, loss of fine motor control of the hand, and Rabinski's sign.

Vertebrobasilar System Syndromes

The areas of the cerebellum supplied by the posterior inferior cerebellar artery (PICA) are variable. There are several different patterns of PICA territory cerebellar infarctions. If the medial branch territory is affected, involving the vermis and vestibulocerebellum, the clinical findings include prominent vertigo, ataxia, and nystagmus. If the lateral cerebellar hemisphere is involved, patients can have vertigo, gait ataxia, limb dysmetria and ataxia, nausea, vomiting, conjugate or dysconjugate gaze palsies, miosis, and dysarthria. If the infarction is large, altered consciousness or confusion may occur. Hydrocephalus or herniation may develop. Although a PICA occlusion can be the cause of Wallenberg's (lateral medullary) syndrome, this syndrome is more often caused by an intracranial vertebral artery occlusion.

The anterior inferior cerebellar artery (AICA) syndrome causes a ventral cerebellar infarction. The signs and symptoms include vertigo, nausea, vomiting, and nystagmus caused by involvement of the vestibular nuclei. There may be ipsilateral facial hypalgesia and thermoanesthesia and corneal hypesthesia because of involvement of the trigeminal spinal nucleus and tract. Ipsilateral deafness and facial paralysis occurs because of involvement of the lateral pontomedullary tegmentum. An ipsilateral Horner's syndrome is present because of compromise of the descending oculosympathetic fibers. Contralateral trunk and extremity hypalgesia occurs and thermoanesthesia caused by involvement of the lateral spinothalamic tract. Finally, ipsilateral ataxia and asynergia is caused by involvement of the cerebellar peduncle and cerebellum.

Infarction in the territory of the superior cerebellar artery (SCA) produces a dorsal cerebellar syndrome (Hgure 57A.2). Vertigo may be present, although it is less common with SCA infarcts than with the other cerebellar syndromes. Nystagmus is caused by involvement of the medial longitudinal fasciculus and the cerebellar pathways. An ipsilateral Horner's syndrome is caused by involvement of the descending sympathetic tract. Ipsilateral ataxia and asynergia and gait ataxia are caused by involvement of the superior cerebellar peduncle, brachium pontis, superior cerebellar hemisphere, and dentate nucleus. There is an intention tremor caused by involvement of the dentate

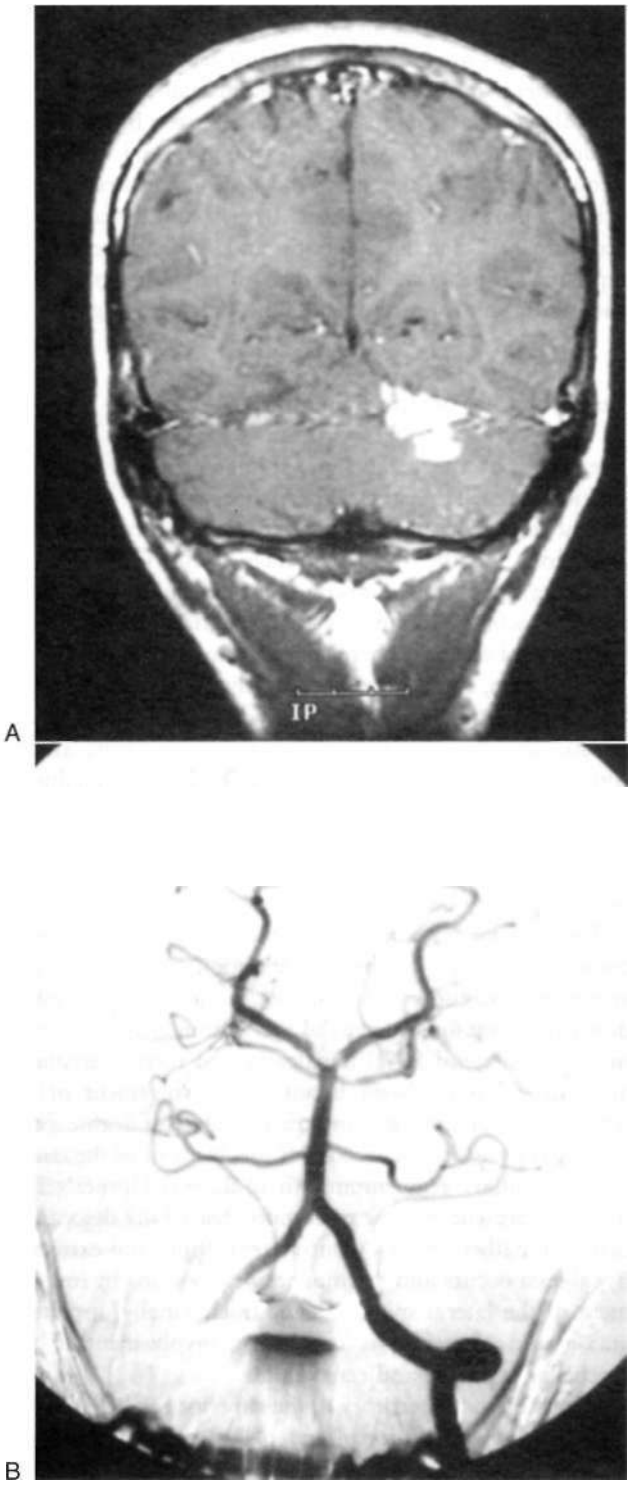

FIGURE 57A.2 A 15-year-old boy had vomiting, tinnitus, and unsteadiness. (A) Tl coronal postgadolinium magnetic resonance imaging shows enhancing lesions in the superior aspect of the left cerebellar hemisphere consistent with superior cerebellar artery infarct. (B) Anteroposterior view left vertebral artery injection shows a filling defect of the basilar apex also involving the proximal left superior cerebellar artery consistent with thromboembolus,

nucleus and superior cerebellar peduncle. Choreiform dyskinesias may be present ipsilarerally. Contra laterally, there is hearing loss caused by lateral lemniscus disruption and trunk and extremity hypalgesia and thermoanesthesia caused by spinothalamic tract involvement,

Weber's syndrome is caused by infarction in the distribution of the penetrating branches of the posterior cerebral artery (PCA) affecting the cerebral peduncle, especially medially, with damage to the fascicle of cranial nerve III and the pyramidal fibers. The resultant clinical findings are contralateral hemiplegia of the face, arm, and leg caused by corticospinal and corticobulbar tract involvement and ipsilateral oculomotor paresis, including a dilated pupil. A slight variation of this syndrome is the midbrain syndrome of Foville in which the supranuclear fibers for horizontal gaze are interrupted in the medial peduncle, causing a conjugate gaze palsy to the opposite side. Bcncdikt's syndrome is caused by a lesion affecting the mesencephalic tegmentum in its ventral portion, with involvement of the red nucleus, brachium conjunctivum, and fascicle of cranial nerve III. This syndrome is caused by infarction in the distribution of the penetrating branches of the PCA to the midbrain. The clinical ma infestations are ipsilateral oculomotor paresis, usually with pupillary dilation and contralateral involuntary movements, including intention tremor, hemiathcrosis, or hemichorca. Claude's syndrome is caused by lesions that are more dorsally placed in the midbrain tegmentum than with Benedikt's syndrome. There is injury to the dorsal red nucleus, which results in more prominent cerebellar signs without the involuntary movements. Oculomotor paresis occurs (see Table 76.1 for variations of these syndromes). Nothnagel's syndrome is characterized by an ipsilateral oculomotor palsy with contralateral cerebellar ataxia. Infarctions in the distribution of the penetrating branches of the PCA to the midbrain is the cause of this syndrome. Pannaud's syndrome can result from infarctions in the midbrain territory of the PCA penetrating branches. This syndrome is characterized by supranuclear paralysis of eye elevation, defective convergence, convergence-retraction nystagmus, light-near dissociation, lid retraction, and skew deviation (see Chapter 22).

Top of the basilar syndrome (sec Chapter 22) is caused by infarction of the midbrain, thalamus, and portions of the temporal and occipital lobes. It is caused by occlusive vascular disease, often embolic in nature, of the rostral basilar artery. The following signs may occur: Behavioral abnormalities include somnolence, peduncular hallucinosis, memory disturbances, or agitated delirium.

Ocular findings include unilateral or bilateral paralysis of upward or downward gaze; impaired convergence; pseudoabducens palsy; convergence-retraction nystagmus; abnormalities of abduction; Collier's sign, which consists of elevation and retraction of the upper eyelids; skew deviation; and oscillatory eye movements. Visual defects that may be present include hemianopia, cortical blindness, and Balint's syndrome.

Pupillary abnormalities are variable, and may be either large or small, reactive, or fixed. Motor deficits may also occur.

Although there are many named pontine syndromes, the most beneficial categorization is based on neuroanaromical divisions. Locked-in syndrome is the result of bilateral ventral pontine lesions that produce quadriplegia, aphonia, and impairment of the horizontal eye movements in some patients. Wakefulness and normal sleep-wake cycles are maintained because of sparing of the reticular formation, The patient can move his or her eyes vertically and can blink because the supranuclear ocular motor pathways lie more dorsally. In some patients with symptomatic basilar artery occlusive disease, there may be a herald hemiparesis that suggests a hemispheric lesion (Fisher 1988). However, within a few hours, there is progression to bilateral hemiplegia and cranial nerve findings associated with the locked-in syndrome. Pure motor hemiparesis and ataxia-hemiparesis caused by pontine lesions are discussed with the lacunar syndromes.

Occlusion of the AICA can lead to the lateral inferior pontine syndrome. Findings with this syndrome include ipsilateral facial paralysis, impaired facial sensation, paralysis of conjugate gaze to the side of the lesion, deafness, tinnitus, and ataxia. Contralateral to the lesion, there is hemibody impairment to pain and temperature, which in some instances includes the face. There may be horizontal and vertical nystagmus and oscillopsia. The medial inferior pontine syndrome is caused by occlusion of a paramedian branch of the basilar artery. With this syndrome, there is ipsilateral paralysis of conjugate gaze to the side of the lesion, abducens palsy, nystagmus, and ataxia. Contralateral to the lesion, there is hemibody impairment of tactile and proprioceptive sensation and paralysis of the face, arm, and leg. An occlusion of the AICA may lead to the total unilateral inferior pontine syndrome, a combination of the symptoms and signs seen with the lateral and medial pontine syndromes.

The lateral pontomedullary syndrome can occur with occlusion of the vertebral artery. The manifestations are a combination of the medial and lateral inferior pontine syndromes. Occlusion of the paramedian branch of the midbasilar artery can lead to ipsilateral impaired sensory and motor function of the trigeminal nerve with limb ataxia, characteristics of the lateral midpontine syndrome. Ischemia of the medial midpontine region is caused by occlusion of the paramedian branch of the midbasilar artery and can lead to ipsilateral limb ataxia. Contralateral to the lesion, eye deviation and paralysis of the face, arm, and leg occur. Although there are predominant motor symptoms, variable impaired touch and proprioception may occur. The lateral superior pontine syndrome may occur with occlusion of the SCA and produces a characteristic syndrome of ipsilateral Horner's syndrome, horizontal nystagmus, paresis of conjugate gaze, occasional deafness, and severe ataxia of the limbs and gait. Contralateral to the lesion, there is hemibody impairment to pain and temperature, skew deviation, and impaired tactile, vibratory, and proprioceptive sensation in the leg greater than in the arm.

The lateral medullary syndrome (Wallenberg's syndrome) is most often caused by occlusion of the intracranial segment of the vertebral artery (Figure 57A.3). Less commonly, it is caused by occlusion of PICA, This syndrome produces an ipsilateral Horner's syndrome; loss of pain and temperature sensation in the face; weakness of the palate, pharynx, and vocal cords; and cerebellar ataxia. Contralateral to the lesion, there is hemibody loss of pain and temperature sensation. The medial medullary (Dejerine) syndrome is less common and may be caused by occlusion of the distal vertebral artery, a branch of the vertebral artery, or the lower basilar artery. Vertebral artery dissection, dolichoectasia of the vertebrobasilar system, or embolism are less common causes of the medial medullary syndrome. The findings with this Syndrome include an ipsilateral lower motor neuron paralysis of the tongue and contralateral paralysis of the arm and leg. The face is often spared. In addition, there is contralateral hemibody loss of tactile, vibratory, and position sense. Occlusion of the intracranial vertebral artery can lead to a total unilateral medullary syndrome (of Babinski-Nageotte), a combination of medial and lateral medullary syndromes.

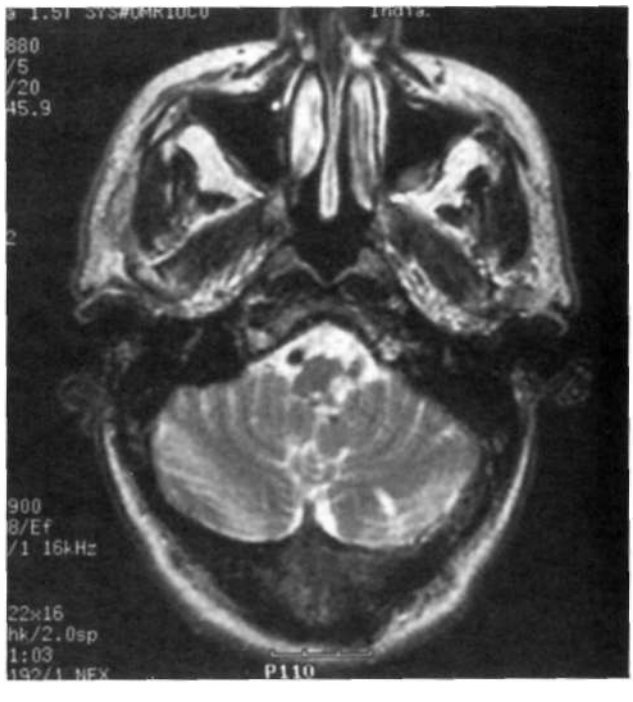

FIGURE 57A.3 A 74-year-old man had sudden onset of vertigo, vomiting, and gait unsteadiness. T2-weighted axial magnetic resonance imaging of the brain demonstrates an infarct in the posterolateral side of the medulla and a small cerebellar infarct in the distribution of the left posterior inferior cerebellar artery. There is poor flow void seen in the left vertebral artery.

The manifestations with PCA territory infarctions are variable, depending on the site of the occlusion and the availability of collateral blood flow. Occlusion of the precommunal PI segment causes midbrain, thalamic, and hemispheric infarction. Occlusion of the PCA in the proximal ambient segment before branching in the thalamogeniculate pedicle causes lateral thalamic and hemispheral symptoms. Occlusions also may affect a single PCA branch, primarily rhc calcarine artery, or cause a large hemispheric infarction of the PCA territory. Unilateral infarctions in the distribution of the hemispheral branches of the PCA may produce a contralateral homonymous hemianopia caused by infarction of the striate cortex, the optic radiations, or the lateral geniculate body. There is partial or complete macular sparing if the infarction does not reach the occipital pole. The visual field defect may be limited to a quadrantanopia. A superior quadrantanopia is caused by infarction of the striate cortex inferior to the calcarine fissure or the inferior optic radiations in the ternporo-occipital lobes. An inferior quadrantanopia is the result of an infarction of the striate cortex superior to the calcarine fissure or the superior optic radiations in the parieto-occipital lobes.

More complex visual changes may occur, including formed or unformed visual hallucinations, visual ami color agnosias, or prosopagnosia. Finally, some alteration of sensation with PCA hemispheral infarctions occurs, including paresthesias or altered position, pain, and temperature sensations. Infarction in the distribution of the callosal branches of the PCA involving the left occipital region and the splenium of the corpus callosum produces alexia without agraphia (Figure 57A.4). In this syndrome, patients can write, speak, and spell normally, but are unable to read words and sentences. The ability to name letters and numbers may be intact, but there can be inability to name colors, objects, and photographs. Right hemispheric PCA territory infarctions may cause contralateral visual field neglect. Amnesia may be present with PCA infarctions that involve the left medial temporal lobe or when there are bilateral mesiotemporal infarctions. In addition, an agitated delirium may occur with unilateral or bilateral penetrating mesiotemporal infarctions. Large infarctions of the left posterior temporal artery territory may produce an anomic or transcortical sensory aphasia.

Infarctions in the distribution of the penetrating branches of the PCA to the thalamus can cause aphasia if the left pulvinar is involved, akinetic mutism, global amnesia, and the Dejerine-Roussy syndrome. In the latter syndrome, the patient has contralateral sensory loss to all modalities, severe dysesthesias on the involved side (thalamic pain), vasomotor disturbances, transient contralateral hemiparesis, and chorcoathetoid or ballistic movements. A number of syndromes that can result from infarctions in the distribution of the penetrating branches of the PCA to the midbrain were previously discussed with the midbrain syndromes.

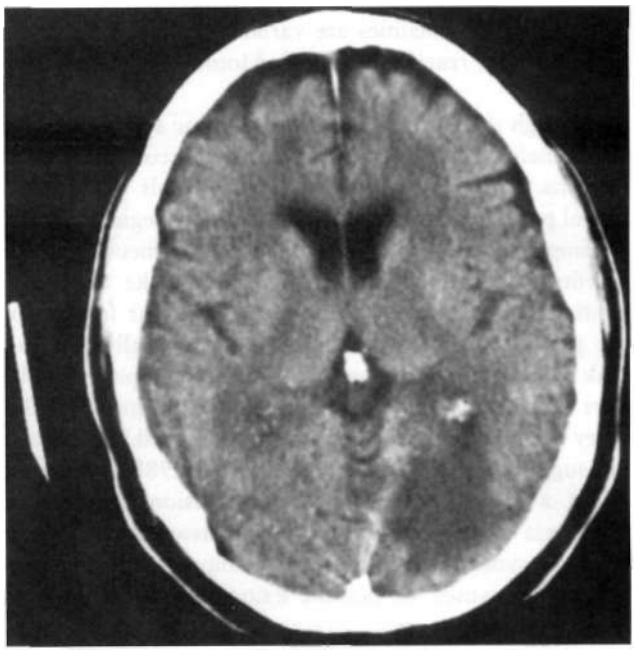

FIGURE 57A.4 A 77-year-old man had alexia without agraphia, right homonymous hemianopia, and antegrade amnesia. Nonenhanced axial cranial computed tomography demonstrates an area of decreased parenchymal attenuation in the left occipito-parii-ral region.

Bilateral infarctions in the distribution of the hemispheric branches of the PCAs may cause bilateral homonymous hemianopias. Bilateral occipital or occipitoparietal infarctions can cause cortical blindness, often with denial or unawareness of blindness (Anton's syndrome). Another syndrome, Balint's syndrome, seen with bilateral occipital or parieto-occipital infarctions, consists of optic ataxia, psychic paralysis of fixation with inability to look to the peripheral field and disturbance of visual attention, and simu I tan agnosia.

Syndromes of Thalamic Infarction

The main thalamic blood supply comes from the posterior communicating arteries and the perimesencephalic segment of the PCA. Thalamic infarctions typically involve one of four major vascular regions: posterolateral, anterior, paramedian, and dorsal. Posterolateral thalamic infarctions result from occlusion of the thalamogeniculate branches arising from the P2 segment of the PCA. Three common clinical syndromes may occur: pure sensory stroke, sensorimotor stroke, and the thalamic syndrome of Dcjcrine-Roussy. Anterior thalamic infarction results from occlusion of the polar or tuberothalamic artery. The main clinical manifesrations consist of neuropsychological disturbances, emotional-facial paresis, occasional hemiparcsis, and visual field deficits. Left-sided infarcts are associated with dysphasia, whereas neglect is seen primarily in patients

with right-sided lesions. Paramedian thalamic infarctions result from occlusion of the paramedian, thalamic, and subthalamic arteries. The main clinical manifestations include the classic triad of decreased level of consciousness, memory loss, and vertical gaze abnormalities. Dorsal thalamic infarctions result from occlusion of the posterior choroidal arteries. These infarctions are characterized by the presence of homonymous quadrantanopia or horizontal sectoranopias. Involvement of the pulvinar may account for thalamic aphasia.

Watershed Ischemic Syndromes

Watershed infarcts occur in the border zone between adjacent arterial perfusion beds. During or after cardiac surgery or after an episode of sustained and severe arterial hypotension after cardiac arrest, prolonged hypoxemia, or bilateral severe carotid artery disease, ischemia may occur in the watershed areas between the major circulations. Watershed infarctions also may be unilateral when there is some degree of hemodynamic failure in patients with underlying severe arterial stenosis or occlusion. Watershed infarcts also may be caused by microembolism or hyperviscosity states.

Ischemia in the border zone or junctional territory of the ACA, MCA, and PCA may result in bilateral parieto-occipital infarcts. There can be a variety of visual manifestations, including bilateral lower altitudinal field defects, optic ataxia, cortical blindness, and difficulty in judging size, distance, and movement. Ischemia between the territories of the ACA and MCA bilaterally may result in bibrachial cortical sensorimotor impairment (man-in-a-barrel), and impaired saccadic eye movements caused by compromise of the frontal eye fields. Ischemia on the border zone regions between the MCA and PCA may cause bilateral parietotemporal infarctions. Initially there is cortical blindness that may improve, but defects such as dyslexia, dyscalculia, dysgraphia, and memory defects for verbal and nonverbal material may persist.

Watershed infarcrs are also recognized between the territorial supply of the PICA, AICA, and SCA. Watershed infarctions may also involve the internal watershed region in the centrum semiovalc adjacent to, and slightly above, the body of the lateral ventricles.

DIAGNOSIS AND TREATMENT OF THREATENED ISCHEMIC STROKE

An ischemic stroke develops when there is interrupted cerebral blood flow to an area of the brain. Ischemic strokes account for approximately 80-85% of all strokes. Ischemic strokes may result from (1) large artery atheroscleroric disease resulting in stenosis or occlusion, (2) small vessel or penetrating artery disease (lacunes), (3) cardiogenic or artery-to-artery embolism, (4) nonatheioselerotic vasculopathies, (5) hypcrcoagulablc disorders, and *(6)* infarcts of undetermined causes. However, a rigid classification of ischemic stroke subtypes is difficult to establish because of the frequent occurrence of mixed syndromes.

LARGE ARTERY ATHEROTHROMBOTIC INFARCTIONS

Large artery atherothrombotic infarctions almost always occur in patients who already have significant risk factors for cerebrovascular atherosclerosis (see Table 57A.1). A tli ero thrombosis is multifactorial, comorbidities frequently overlap, and risk factors are often additive. For example, arterial hypertension is often associated with hyperlipidemia, hyperglycemia, elevated fibrinogen levels, excessive weight, and left ventricular hypertrophy on ECG. A resting ankle-brachial index less than 0.90 is indicative of generalized atherosclerosis (Zheng et al. 1997). Persons with a stroke are at high risk for development of other vascular complications. After a stroke, rhere is a 25% chance of a fatal thrombotic event in 3 years. Many of these deaths are caused by myocardial infarction. The mechanisms of large artery atherothrombotic infarction often reflect plaque complication; ulceration with artery-to-artery embolization (Figure 57A.5), or thrombosis in rhc setting of pre-existing arterial stenosis. Arteriogenic embolism is a common mechanism of cerebral ischemia. Embolism from ulcerated carotid artery atherosclerotic plaques is a common cause of cerebral infarction. In situ thrombosis occurs in the proximal carotid, distal vertebral artery, and lower or middle basilar artery (Figures 57A.6A and 57A.6B). Atherosclerotic involvement of the intracranial portion of the vertebrobasilar system frequently occurs in tandem and is the common pathological mechanism associated with the syndrome of vertebrobasilar territory infarction; this may arise in association with hypercoagulable states. Hypoperfusion secondary to hemodynamic alterations also may trigger these events. Whether the pathogenesis of stroke caused by intracranial arterial stenosis is different from that caused by extracranial aire rial disease is unsettled.

In patients with risk factors for atherosclerosis, the cholesterol-rich minimally raised fatty streak may progress to a fibrous plaque rhat can evolve into a complicated plaque with intraplaque hemorrhage, extensive necrosis, calcification, and subsequent thrombosis (Figure 57A.7). The infiltrarion of the fibrous cap by foam cells may contribute to the rupture of the atherosclerotic carotid artery plaque. Atherosclerosis is often segmental and asymmetrical, and earlier lesions tend to occur in areas of low shear stress, such as the outer aspect of the carotid artery bulb. Atherosclerosis primarily affects the larger extracranial and intracranial vessels, particularly the carotid siphon, MCA stem, origin of the vertebral arteries

FIGURE 57A..S Right common carotid angiogram shows 17% right internal carotid artery stenosis (North American Symptomatic Carotid Endarectomy Trial criteria) just superior to a large carotid ulceration. (Courtesy Vincent Mathews, MD.)

(Vi), intracranial segment of the vertebral arteries (V_4), and basilar artery. The distribution of cerebral atherosclerosis is different in certain ethnic groups. Stenosis of **major** intracranial arteries is more prevalent among blacks and **Asians** than in **whites.**

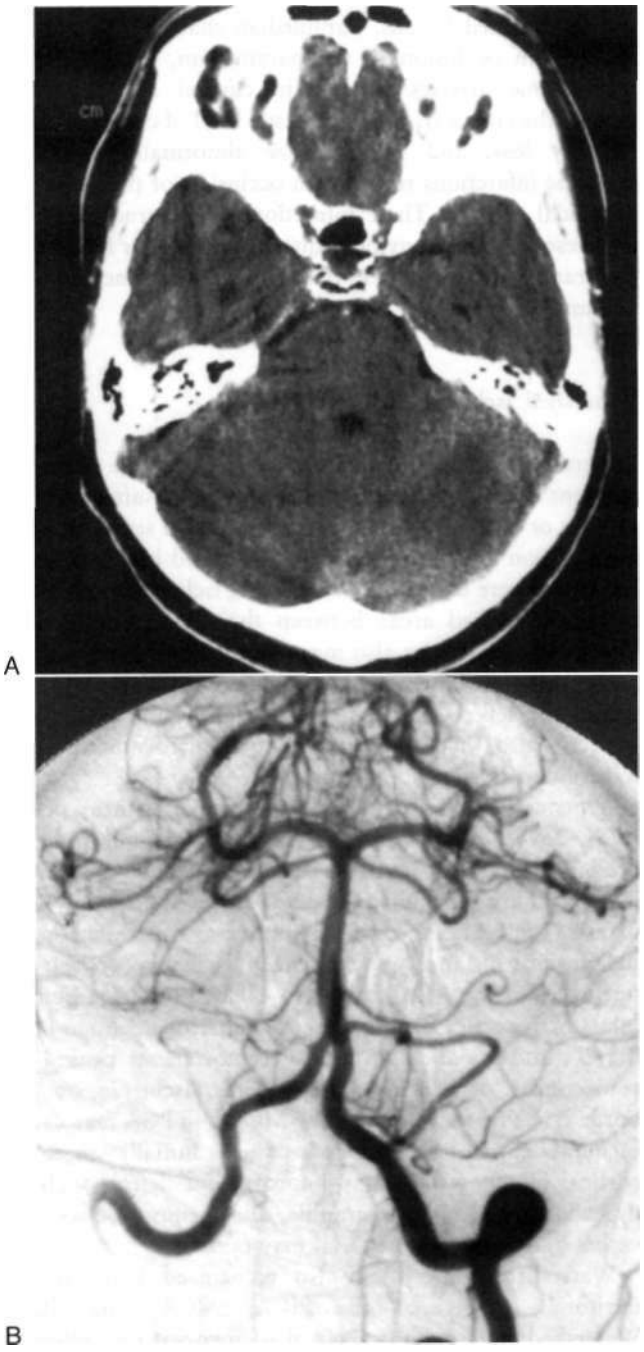

FIGURE 57A.6 (A) Nonenhanced axial computed tomographic scan shows bilateral cerebellar and pontine infarcts. (B) Anteroposterior view of vertebrobasilar angiogram shows a large filling defect on the basilar artery, consistent with partial thrombosis. (Courtesy Vincent Mathews, MD.)

SMALL VESSEL OR PENETRATING ARTERY DISEASE

Lacunes usually occur in patients with long-standing arterial hypertension, current cigarette smoking, and diabetes mellitus. The most frequent sites of involvement are the putamen, basis pontis, thalamus, posterior limb of the internal capsule, and caudate nucleus. Multiple lacuna are associated strongly with arterial hypertension and diabetes mellitus. Available evidence suggests that structural **changes** of **the cerebral** vasculature caused by arterial hypertension are characterized by fibrinoid angiopathy, lipohyalinosis, and microaneurysm formation. Accelerated hypertensive arteriolar damage of the small penetrating arteries is operative in a large number of patients with lacunar infarction. Microatheroma of **the** ostium of a penetrating artery, embolism, or changes in hemorrheology

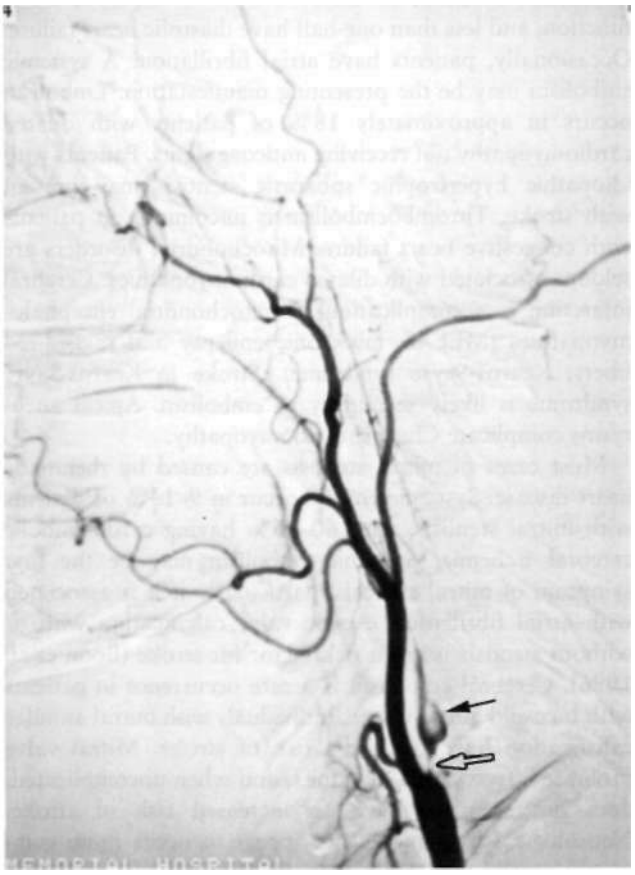

FIGURE 57A.7 Left carotid angiogram (lateral view) shows severe stenosis *[open arrow)* of origin of tlic left internal carotid artery with an intraluminal thrombus *[arrow).* **The artery was occluded in other images. (Courtesy Vincent Mathews, MD.)**

are pathophysiological^ operative in the remainder of cases. However, rhe mere association of a lacunar syndrome in a patient with arterial hypertension and diabetes is not sufficient for a diagnosis of a lacunar infarct, and other causes of ischemic stroke must be excluded, Large striatocapsular infarctions should be distinguished from lacunar infarcts, because they frequently have potential cardioembolic sources or coexistent severe carotid or MCA stenosis and often present with signs and symptoms of cortical dysfunction (Nicolai et al. 1996). Control of hypertension, prevention of microangiopathy, a better understanding of the ideal hemodynamic profile, and judicious use of platelet antiaggregants are essential in the management of patients with lacunar infarcts.

CARDIOGENIC EMBOLISM

Cerebrovascular events are a serious complication of a diverse group of cardiac disorders. Cardioembolic strokes are associated with substantial morbidity and mortality. Embolism of cardiac origin accounts for approximately 15-20% of all ischemic strokes. Cardiac emboli may be composed of platelet, fibrin, platelet-fibrin, calcium, microorganisms, or neoplastic fragments. The most common substrate for cerebral embolism in older individuals is atrial fibrillation, accounting for two thirds of emboli of cardiac origin. Other cardiac conditions with high embolic potential include acute myocardial infarction, infective endocarditis, rheumatic mitral stenosis, mechanical prosthetic heart valves, dilated cardiomyopathy, and cardiac tumors. Low or uncertain embolic risk disorders include mitral valve prolapse, mitral annulus calcification, aortic valve calcification, calcific aortic stenosis, remote myocardial infarction, left ventricular aneurysm, hypertrophic cardiomyopathy, patent foramen ovale (PFO), atrial septal aneurysm (ASA), atrial flutter, valvular strands, and Chiari network,

Congenital heart disease is probably the most common cardiac disorder causing ischemic stroke in children. Children with congenital heart disease and a low hemoglobin concentration are at special risk for arterial strokes; those with a high hematocrit are more likely to experience cerebral venous thrombosis (Perloff 1998). Emboli from cardiac sources may be silent or cause severe neurological deficit or death. Although most types of heart disease may produce cerebral embolism, certain cardiac disorders are more likely to be associated with emboli (Table 57A.3). Cardioembolic cerebral infarcts arc often large, multiple, bilateral, and wedge shaped. Sudden, unheralded, focal neurological deficits worse at onset are often presenting manifestations. Any vascular territory may be affected. Ischemic strokes with a potential cardiac source are more often associated with Wernicke's aphasia, homonymous hemianopia without hemiparesis or hemisensory disturbances, and ideomotor apraxia. Other features suggestive of a potential cardiac source of embolism include posterior division of the MCA, ACA, or cerebellar compromise; involvement of multiple vascular territories; or a hemorrhagic component of the infarction. Reliable clinical determination of a cardioembolic source of stroke may be hampered by a variety of problems. Identification of a potential embolic cardiac source is not by itself sufficient to diagnose a brain infarct as cardioembolic because (1) many cardiac problems may coexist with cerebrovascular atherosclerosis, {2) cardiac arrhythmias may occur after arrhythmogenic lesions such as parietoinsular and brainstem infarcts, (3) computed tomographic (CT) scan differentiation between cardioembolic and atherosclerotic causes of cerebral infarction is not always reliable, and (4) cardiac changes derected by echocardiography are prevalent in control populations.

An embolic stroke occurs in approximately 1% of hospitalized patients with acute myocardial infarction. Left ventricular thrombi are commonly associated with recent anterior wall transmural myocardial infarction. Echocardiography studies have demonstrated that approximately one third to one half of acute anterior myocardial infarctions, but less than 4% of acute inferior myocardial

Table 57A.J: Sources of cardioembolism

Acute myocardial infarction
Left ventricular aneurysm
Dilatated cardiomyopathy
Cardiac arrhythmias
Atrial fibrillation
Sick sinus syndrome
Valvular heart disease
Rheumatic mitral valve disease
Calcific aortic stenosis
Mitral annulus calcification
Mitral valve prolapse
Infective endocarditis
Nonbacterial thrombotic endocarditis
Prosthetic heart valves
Filamentous strands of the mitral valve
Giant Lambl's excrescences
Aneurysms of the sinus of Valsalva
Intracardiac tumors (atrial myxoma, rhabdomyoma, papillary fibroelastoma)
Intracardiac defects with paradoxical embolism
Patent foramen ovale
Atrial septal aneurysm
Atrial septal defect
Cyanotic Congenital heart disease
Eontan procedure or its modifications (cavopulmonary anastomosis)
Mitochondrial encephalomyopathics (mitochondrial encephalopathy, lactic acidosis, and strokelike episodes; myoclonic epilepsy and ragged-red fibers; Kearns-Sayre syndrome)
Coronary artery bypass grafting
VVI pacing
Heart transplantation
Artificial hearts
Cardioversion for atrial fibrillation
Balloon angioplasty
Ventricular support devices
Extracorporeal membrane oxygenator

infarctions, develop left ventricular thrombi. Almost all episodes of embolism occur within 3 months following acute myocardial infarction, with 85% of emboli developing in the first 4 weeks. A decreased ejection fraction is an independent predictor of an increased risk of stroke following myocardial infarction (Loll ct al. 1997). Patients with acute myocardial infarction who receive thrombolytic therapy have a small risk of stroke. A direct comparison of tissue plasminogen activator (tPA) and streptokinase (SK) shows an excess of strokes with tPA. Myocardial infarction is rare in young adults. Although the prevalence of left ventricular thrombi in individuals with left ventricular aneurysms is high, the frequency of systemic embolism is low. Dilated or congestive cardiomyopathy may result from arterial hypertension or a variety of inflammatory, infectious, immune, metabolic, toxic, and neuromuscular disorders. The global impairment of ventricular performance predisposes to stasis and thrombus formation. Patients commonly have signs of impaired left ventricular systolic function, and less than one hall haw-diastolic heart failure. Occasionally, patients have atrial fibrillation. A systemic embolism may be the presenting manifestation. Embolism occurs in approximately 18% of patients with dilated cardiomyopathy not receiving anticoagulants. Patients with idiopathic hypertrophic subaortic stenosis may present with stroke. Thromboembolism is uncommon in patients with congestive heart failure. Mitochondrial disorders are seldom associated with dilated cardiomyopathies. Cerebral infarction is a complication of mitochondrial enccphalomyopathies (MELAS; myoclonic epilepsy and ragged-red fibers; Kearns-Sayre syndrome). Stroke in Kearns-Sayre syndrome is likely secondary to embolism. Apical aneurysms complicate Chagas' cardiomyopathy.

Most cases of mitral stenosis are caused by rheumatic heart disease. Systemic emboli occur in 9-14% of patients with mitral stenosis, with 60-75% having cardioembolic cerebral ischemia. Systemic embolism may be the first symptom of mitral stenosis, particularly if it is associated with atrial fibrillation. Aortic valve calcification with or without stenosis is not a risk factor for stroke (Boon et al. 1996). Cerebral embolism is a rare occurrence in patients with bicuspid aortic valves. Individuals with mitral annular calcification have twice the risk of stroke. Mitral valve prolapse affects 3^4% of adults, and when uncomplicated, does not seem to have an increased risk of stroke. Neurological ischemic events appear to occur more commonly among men older than 50 years with auscultatory findings of a systolic murmur and thick mitral valve leaflets on echocardiography. Thromboembolic phenomena complicating infective endocarditis may be systemic (left-sided endocarditis) or pulmonan (right-sided endocarditis). Vegetations are detected by transthoracic echocardiography in 54-87% of patients with infective endocarditis and are associated with an increased risk of embolism (Eishi et al. 1995). Systemic emboli may occur in nearly one half of patients with nonbacterial thrombotic endocarditis, a condition characterized by the presence of multiple, small, sterile thrombotic vegetations most frequently involving the mitral and aortic valves. The risk of thromboembolism is higher with mechanical prosthetic heart valves than with biological prosthetic heart valves. Thromboemboli are more common with prosthetic heart valves in the mitral position than with prosthetic heart valves in the aortic position. The rate of systemic embolism in patients with mechanical heart valves receiving anticoagulant therapy is 4% per year in the mitral position, and 2% per year in the aortic position. Filamentous strands attached to the mitral valve appear to represent a risk for cerebral embolism, particularly in young patients, but the risk of recurrent cerebral ischemia is incompletely understood. The association of giant Lambl's excrescences or aneurysms of the sinus of Valsalva and cerebral embolism is low.

Atrial fibrillation is the most common arrhythmia requiring hospitalization in the United States. The incidence of thromboembolism in patients with atrial fibrillation is

4-7.5% per year (Atrial Fibrillation Investigators 1994). Patients with NVAF, the leading source of cardioembolic infarctions in older adults, have a five- to sixfold increase in stroke incidence, with a cumulative risk of 35% over a lifetime. Patients with rheumatic atrial fibrillation have a 17-fold increase in stroke incidence. However, individuals younger than 65 years with lone atrial fibrillation have a low embolic potential. Stroke patients with atrial fibrillation are also at high risk of death during the acute phase of stroke and during the subsequent year after stroke. A dramatic increase in the rate of atrial fibrillation occurs with age, from 0.2 cases per 1000 patients aged 30-39 years to 39 cases per 1000 patients aged 80-89 years. The proportion of strokes caused by atrial fibrillation also steadily increases, from 6.7% of all strokes in patients aged 50-59 to 36.2% in those aged 80-89. The risk of embolism is increased among patients with atrial fibrillation and hyperthyroidism, who also have an increased sensitivity to warfarin,

Cerebral and systemic embolism may occur also in the setting of the sick sinus syndrome. Patients at greatest risk for embolization have bradytachyarrhythmias; left atrial spontaneous echocardiography contrast and decreased atrial ejection force increase stroke risk (Mattioli et al. 1997). Patients with sick sinus syndrome may experience cerebral ischemia or systemic embolism, even after pacemaker insertion. VVf pacing is associated with a higher risk of embolic complications than atrial or dual-chamber pacing. The risk of thromboembolism is also higher among patients in chronic atrial flutter (Wood et al. 1997; Seidl et al. 1998).

Atrial myxomas are rare cardiac tumors complicated by postural syncope and systemic and embolic manifestations. Embolic complications are a presenting symptom in one third of patients with atrial myxoma. Recurrent emboli before surgery are common. Peripheral and multiple cerebral arterial aneurysms also have been diagnosed years following the initial embolic manifestations from atrial myxoma. Treatment of atrial myxomas consists of prompt surgical resection of the cardiac mass. Cardiac rhabdomyomas are associated closely with tuberous sclerosis; systemic embolism is unusual. Mitral valve papillary fibroe la stoma, an uncommon valvular tumor, is complicated rarely by stroke.

A paradoxical embolism caused by a right-to-left shunt through a PFO or ASA can be responsible for stroke and other ischemic cerebral events. A PFO is present in 35% of subjects between the ages of 1 and 29 years, in 25% of people between ages 30 and 79, and in 20% between ages 80 and *99* years. A PFO provides opportunity for right-to-left shunting during transient increases in the right atrial pressure. PFO is more common in patients with stroke than in matched controls. Patients with no identifiable cause for ischemic stroke and PFO usually have a larger PFO with more extensive right-to-left shunting than patients with stroke of determined cause. Platelet antiaggregants, oral anticoagulants, transcathctcr closure of the PFO, or surgical closure of the PFO have been recommended. A recent study found no difference in the time to primary endpoints between aspirin and warfarin (mean INR = 2.04) (Homma et al. 2002). ASA also might be a source of cerebral emboli. The coexistence of PFO and ASA increases the risk of embolic stroke. PFO and ASA have been associated also with mitral valve prolapse. Strokes are often severe but recurrences are uncommon. Pulmonary arteriovenous malformations occur in 15-20% of patients with Rcndu-Oslcr-Weber syndrome and can be the source of paradoxical embolism causing cerebral ischemia.

Spontaneous echocardiographic contrast is associated with elevated fibrinogen levels and plasma viscosity and is a potential risk factor for cardioembolic stroke. Spontaneous cchocardiographical contrast is highly associated with previous stroke or peripheral embolism in patients with atrial fibrillation or mitral stenosis and increased left atrial size. The risk of cerebrovascular events is increased in adults with cyanotic congenital heart disease in the presence of arterial hypertension, atrial fibrillation, history of phlebotomy, and particularly with microcytosis (Perloff etal. 1993).

The preponderance of posterior circulation ischemia following cardiac catheterization is unexplained. Stroke occurs after coronary artery bypass grafting with a frequency ranging between 1% and 5% (Figure 57A.8). Two thirds of strokes occur by the second postoperative day, and predominantly involve the cerebral hemispheres; brainstem/cerebellar infarcts and lacunar strokes are less common. The cause of postoperative stroke is multifactorial; hypoperfusion, ventricular thrombus, and emboli are probable causal factors, although embolic causes are the most likely mechanisms. Clamp manipulation during coronary artery bypass surgery also may favor the release of aortic atheromatous debris. Epiaortic ultrasound studies demonstrate an increased stroke rate associated with an increased severity of aortic atherosclerosis. Strokes rarely relate to carotid artery stenosis. Carotid artery occlusion, but not carotid artery stenosis, increases the risk for stroke following coronary artery bypass grafting (Micklcborough et al. 1996). Thromboembolic phenomena can complicate cardiac surgery using cardiopulmonary bypass with deep hypothermia and cardiac arrest. Stroke is a potential complication of cardioversion for atrial fibrillation. Cerebral embolism may also complicate valvuloplasty; the risk is greater for aortic rather than mitral valvuloplasty. Strokes may follow heart transplantation, the use of ventricular support systems and artificial hearts, and the use of the extracorporeal membrane oxygenator. Stroke following inadvertently placed left-sided heart pacemaker leads is an unusual complication. Ischemic myelopathy is a rare complication of intra-aortic balloon pump. Aortic dissection or hematoma may lead to an occlusion of a major radicular branch or local occlusion of the artery of Adainkiewicz (see Chapter 57F),

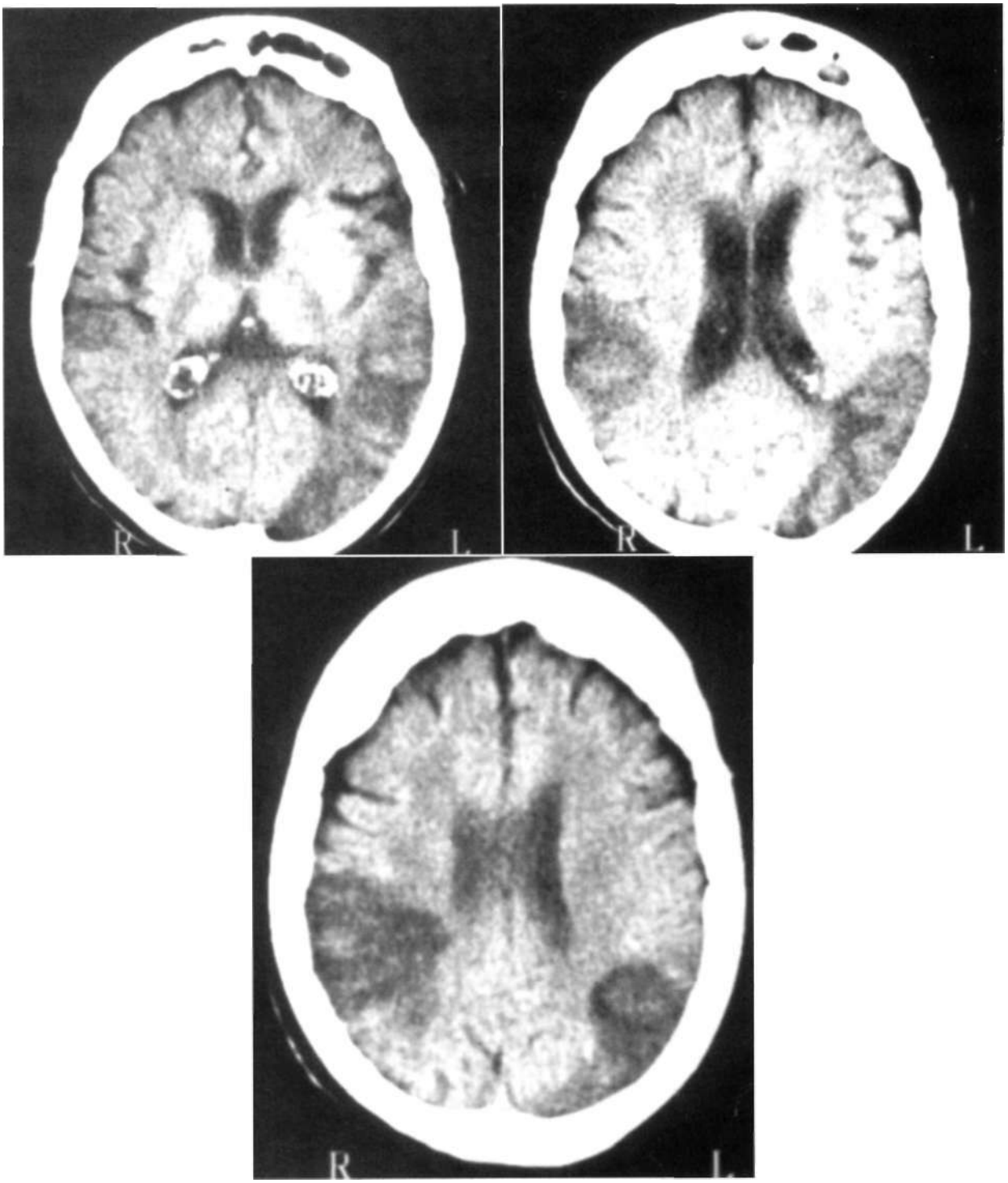

FIGURE 57A.8 An 80-year-old woman remained unresponsive with left-sided hemiplegia and right-sided hemiparesis after coronary-artery bypass grafting and aortic valve replacement. Noncnhanccd axial computed tomography demonstrates large left temporo-paricto-occipital and right frontoparietal infarctions.

NONATHEROSCLEROTIC VASCULOPATHIES

Although the majority of arterial disorders leading to stroke is caused by atherosclerosis, several nonathcrosclerotic vasculopathies can be responsible for a minority of ischemic strokes. These vasculopathies include ccrvicocephalic arterial dissections, traumatic cerebrovascular disease, radiarion vasciiloparhy, moyamoya, fibromuscular dysplasia (FMD), and cerebral vasculitis (Tables 57A.4 and 57A.5}. Together, these uncommon conditions represent 5% of all

Table 57A.4: Selected nonathcrosclerotic vasculopathies

Cervicocephalic arterial dissections
Traumatic cerebrovascular disease
Radiation-induced vasculoparhy
Moyamoya disease
Fibromuscular dysplasia
Vasculitis
Migrainous infarction

ischemic strokes. They are relatively more common in children and young adults.

Cervicocephalic arterial dissections are one of the most frequent n on atherosclerotic vasculopathies causing ischemic stroke in young adults. A dissection is produced by subincimal penetration of blood in a cc r vie ocep ha lie- vessel with subsequent longitudinal extension of the intramural hematoma between its layers. Most dissections involve the extracranial segment of the internal carotid artery or extracranial vertebral arteries. Intracranial carotid and vertebrobasilar dissections are less common; intracra- nial dissections are usually subintimal, and may follow trivial trauma, closed head trauma, basilar skull fractute, or penetrating injuries. The recurrence rate of extracranial cervicocephalic arterial dissections is approximately 1% per year. The risk of recurrent dissections is increased in younger patients and in patients with family history of arterial dissections.

Tabic S7A.5: Classification of cerebral vasculitides

Infectious vasculitis
Bacterial, fungal, parasitic
Spirochetal (syphilis, Lyme disease)
Viral, rickettsial, mycobacterial
Cysticercosis, free-living amebae
Necrotizing vasculitides
Classic polyarteritis nodosa
Wegener's granulomatosis
Allergic angiitis and granulomatosis (Churg-Strauss)
Necrotizing systemic vasculitis-overlap syndrome
Lymphomatoid granulomatosis
Vasculitis associated with collagen vascular disease
Systemic lupus erythematosus
Rheumatoid arthritis
Scleroderma
Sjogren's syndrome
Vasculitis associated with other systemic diseases
Behcet's disease
Ulcerative colitis
Sarcoidosis
Relapsing polychondritis
Kohlmeier-Degos disease (malignant atrophic papulosis)
Giant cell artcritides
Takayasu's arteritis
Temporal (cranial) arteritis
Hypersensitivity vasculitides
Henoch-Schonlein's purpura
Drug-induced vasculitides
Chemical vasculitides
Essential mixed cryoglobulinemia
Miscellaneous
Vasculitis associated with neoplasia
Vasculitis associated with radiation
Cogan's syndrome
Der m a to my o s i ti s polymyositis
X-linked lymphoproliferative syndrome
Thromboangiitis obliterans
Kawasaki's syndrome
Primary central nervous system vasculitis

Source: Reprinted with permission from Biller, J. *ik.* Sparks, I . H. 1993, "Diagnosis and management of cerebral vasculitis," in *Handbook of Cerebrovascular Diseases,* ed H. P. Adams Jr., Marcel Dekker, New York.

Cervicocephalic artetial dissections have been reported after blunt or penetrating trauma and also are associated with FMD, Marfan's syndrome, Ehlers-Danlos syndrome type IV, pseudoxanthoma elasticum, coarctation of the aorta, Menkes' disease, or [-antitrypsin deficiency, cystic medial degeneration, reticular fiber deficiency, accumula- tion of mucopolysaccharides, osteogenesis imperfecta, adult polycystic kidney disease, elevated arterial elastase content (Thai et al. 1997), lentiginosis, atherosclerosis, extreme vessel tortuosity, moyamoya syndrome, homocystinuria, pharyngeal infections, sympathomimetic drug abuse, and luetic arteritis. Not infrequently, cervicocephalic arterial dissections occur spontaneously.

Dissection of the cervicocephalic vessels may cause transient retinal, hemispheric, or posterior fossa ischemia, Horner's syndrome, hemicranial pain, cranial nerve palsies, cerebral infarction, or subarachnoid hemorrhage. Ischemic symptoms result from arterial occlusion or secondary embolization. In addition to a postganglionic Horner, neuro-ophthalmological manifestations of internal carotid artery dissections may also include central retinal artery occlusion, ophthalmic artery occlusion, ischemic optic neuropathy, homonymous hernia no pia, and ocular motor nerve palsies (cranial nerve ICN] III, IV, and VI). In addition to a first-order neuron Horner syndrome, other ncuro-ophthalmological manifestations of vertebrobasilar dissections include diplopia, nystagmus, oscillopsia, ocular misalignment, skew deviation, ocular motor nerve palsies (CN III, IV, and VI), lateral gaze palsy, internuclear ophthalmoplegia, and homonymous visual field defects.

Cervicocephalic arterial dissections should be considered in the differential diagnosis of ischemic stroke in any young adult, particularly when traditional risk factors are absent. Diagnosis is based on artcriographical findings, although high-resolution magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), computed tomog- raphy angiography, and extracranial and transcranial Doppler ultrasound are rapidly replacing contrast angiog- raphy for the diagnosis of cervicocephalic arterial dissec- tions, particularly in cases of carotid artery involvement (Figure 57A.9).

Arteriographical features include the presence of a pearl and string sign; double-lumen sign; short, smooth, tapered

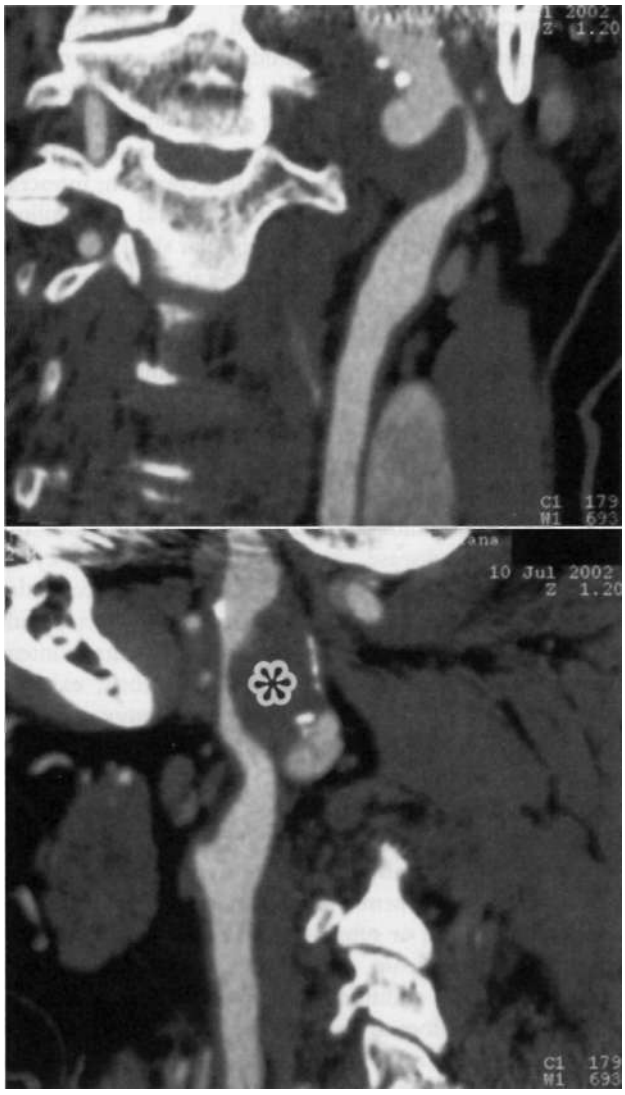

FIGURE 57A.9 Following the intravenous administration of iodinated contrast, spiral CT images were obtained using 1.3 mm collimation and 0.5 mm image reconstruction intervals. A pseudoaneurysm of the left internal carotid artery is noted. This pseudoaneurysm measures 1.9 x 2.9 cm in greatest axial dimensions. There is calcification in the wall of the aneutysm. There is extensive mural thrombus such that the aneurysm lumen containing contrast measures 12.5 x 10.7 mm (*). The internal carotid artery is severely narrowed just proximal to its entry site into the aneutysm.

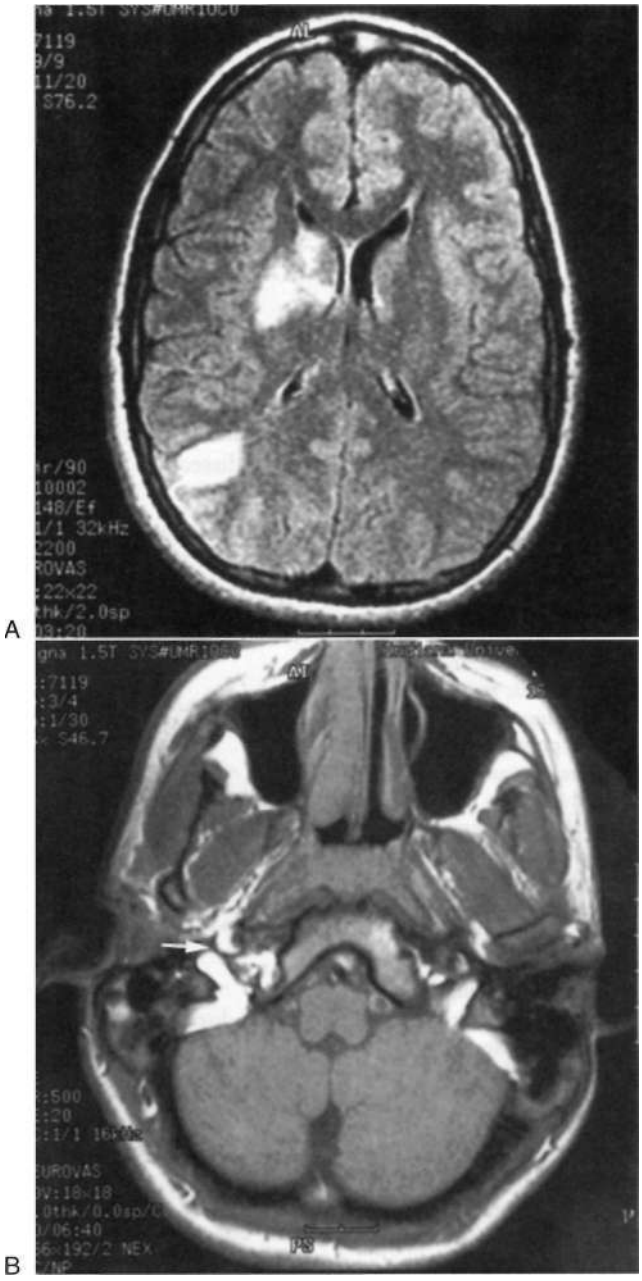

FIGURE 57A.10 A 16-ycar-old boy collapsed to the ground after experiencing right eye pain and left-sided weakness. (A) Axial T2-weighted magnetic resonance imaging of the brain shows ischemic areas in the right basal ganglia and right posterior parietal region, (B) associated with a crescent sign *(arrow)* of high signal consistent with intraluminal blood products on the right internal carotid artery suggestive of a dissection.

occlusion; or pseudoaneurysm formation. MRI demonstrates the intramural hematoma and the false lumen of the dissected artery (Figure 57A.10), Ultrasound studies can be helpful in monitoring their course.

Therapeutic interventions have included immediate anticoagulation with heparin followed by a 3- to 6-month course of warfarin; platelet atitiaggregants; or surgical correction for selected individuals with pseudoaneurysms or those who fail to respond to medical therapy. Although anticoagulants are often empirically recommended, their value in patients with extracranial cervicoccphalic arterial dissections has not been firmly established. Anticoagulation should be withheld in patients with intracranial dissections (particularly involving the vertebrobasilar circulation) because of the risk of subarachnoid hemorrhage.

Trauma is a leading cause of cerebrovascular mortality in the United States. Blunt or penetrating traumatic cerebrovascular disease may result in cervicocephalic arterial

dissection, arterial thrombosis, arterial rupture, pscudo-aneurysm formation, or development of an arteriovenous fistula. Internal carotid artery thrombosis also may follow maxillary and mandibular angle fractures. Carotid artery trauma may cause hematoma formation of the lateral neck, retinal or hemispheric ischemia, and a Horner's syndrome. Neurological deficits may be mild or devastating. Comatose patients with carotid arterial injuries with a Glasgow Coma Scale score of 8 or less do poorly regardless of management (see Chapter 5, Table 5.4). Missing the diagnosis may lead to devastating results. A thorough evaluation of the airway, oropharynx, and esophagus is needed. Arteriography is indicated in most instances, and surgical repair may be needed.

Injury to the endothelial cells by high-intensity radiation may cause accelerated atherosclerotic changes, particularly in the presence of hyperlipidemia. These changes may occur months to years after completion of radiation therapy. Radiation vasculopathy correlates with radiation dose and age at time of radiation therapy. Lesions develop in locations that are unusual for atherosclerosis and may involve the extracranial or intracranial vessels. Patients who receive therapeutic radiation therapy for lymphoma, Hodgkin's disease, or thyroid carcinoma are at risk for involvement of the extracranial circulation. Follow-up ultrasound carotid and MRI studies are recommended in these patients. Radiation therapy also may cause an occlusive vasculopathy of small and large intracranial arteries following irradiation of craniopharyngiomas, germinomas, pituitary tumors, or other intracranial neoplasms. Intracranial arterial stenosis also may follow stereotactic radiosurgery.

Moyamoya is a chronic progressive non-atherosclerotic, non-inflammatory, non-amyloid occlusive intracranial vasculopathy of unknown cause. Pathologically, there is fibrocellular intimal thickening and smooth muscle cell proliferation and increased elastin accumulation resulting in stenosis of the suprasellar intracranial internal carotid arteries. There is also thinning of the media, and a tortuous and often multilayered internal elastic lamina. Thrombotic lesions may be seen in major cerebral arteries. There are also numerous, perforating and anastomotic branches around the circle of Willis. Intracranial aneurysms may be seen at the circle of Willis or in the peripheral vessels (Yamamoto et al. 1997). Cases have been associated with neonatal anoxia, trauma, basilar meningitis, tuberculous meningitis, leptospirosis, cranial radiation therapy for optic pathway gliomas, neurofibromatosis type-1, tuberous sclerosis, encephalotrigeminal angiomatosis (Sturge-Weber syndrome), phakomatosis pigmentovascularis type Illb, brain tumors, FMD, polyarteritis nodosa, Marfan's syndrome, Turner's syndrome, pseudoxanthoma clasticum, hypomelanosis of Ito, Williams' syndrome, cerebral dissecting and saccular aneurysms, sickle cell disease, *0*-thalassemia, Fanconi's anemia, hereditary spherocytosis, lupus anticoagulant, Sneddon's syndrome, homocystinuria, oral contraceptives, factor XII deficiency, type I glycogenosis, reduced form of nicotinamide-adenine dinuclcotide phosphate-coenzyme Q reductase deficiency, renal artery stenosis, Down's syndrome, Apert's syndrome, Graves' disease, coarctation of the aorta, Alagille syndrome, hyperphosphatasia, Schimke's immunosseous dysplasia, primary oxalosis, pulmonary sarcoidosis, and Hirschprung's disease.

Moyamoya disease may cause TIAs, including hemodynamic paraparetic TIAs secondary to watershed paracentral lobule ischemia, headaches, seizures, movement disorders (chorea, hemidystonia, hemichorcoathetosis), mental deterioration, cerebral infarction, or intracranial hemorrhage. TIAs are often precipitated by crying, blowing, or hyperventilation.

Moyamoya disease has a bimodal age distribution with peaks in the first and fourth decades of life. Childhood moyamoya is characterized by ischemic manifestations, whereas adult moyamoya disease presents with hemorrhagic manifestations. Moyamoya affects children, adolescents, and young adults most frequently. Diagnosis is based on a distinct arteriographical appearance as described by Suzuki's six angiographic stages: (1) stenosis of the carotid fork, (2) initial appearance of moyamoya vessels at the base of the brain, (3) inrensification of moyamoya vessels, (4) minimization of moyamoya vessels, (5) reduction of moyamoya vessels, and (6) disappearance of moyamoya vessels (collaterals only from external carotid arteries) (Figure .S7A.11). Moyamoya is characterized by progressive, bilateral stenosis of the distal internal carotid arteries

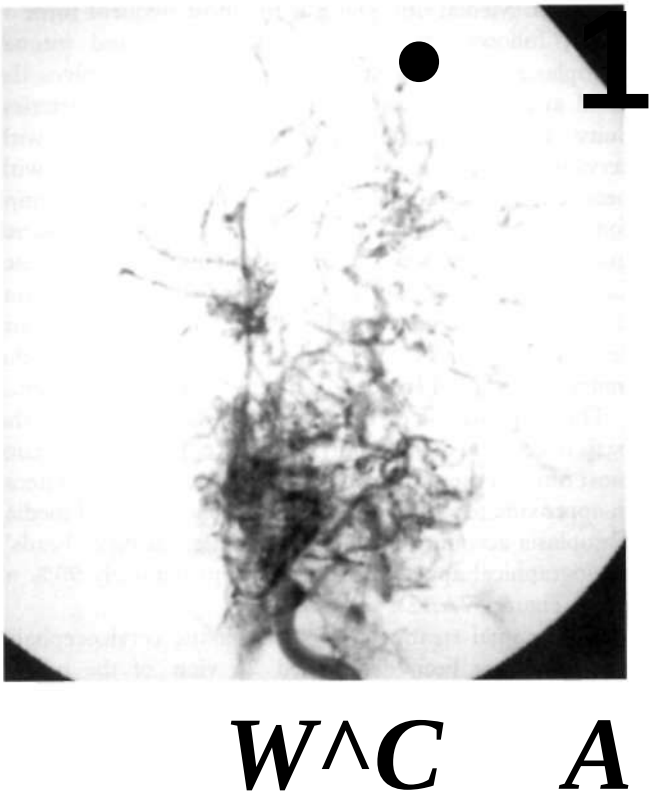

FIGURE 57A.11 Left carotid angiogram (anteroposterior view) shows occlusion of the supraclinoid internal carotid artery and innumerable moyamoya vessels. (Courtesy Vincent Mathews, MD.)

extending to the proximal ACA and MCA, often with involvement of the circle of Willis and development of an extensive collatetal {parenchymal, leptomeningeal, and transdural) network at the base of the brain like a cloud or puff of smoke (moyamoya). Intracranial aneurysms, particularly located in the posterior circulation, may be present.

The optimal treatment of ischemic moyamoya has not been determined. Platelet antiaggregants, vasodilators, calcium-channel blockers, and corticosteroids have been used with variable results. Anticoagulants are not useful. Good results have been reported with superficial temporal artery to MCA anastomosis and other indirect or combined surgical revascularization procedures. No clear superior therapy to ptevent rebleeding has been shown in the hemorrhagic type of moyamoya disease.

FMD is a segmental, non-athcromatous dyspiastic, noninflammatory angiopathy affecting predominantly young and middle-aged women. Cervicocephalic HMD affects less than 1% of the population, occuts mote often in whites than in blacks, and predominantly involves the cervical carotid arteries at the level of the CI to C2 vertebral bodies. FMD of the intracranial arteries is rare and mainly limited to the intrapetrosal internal carotid artery or carotid artery siphon. The cause of FMD is unknown. Immunological and estrogenic effects on the arterial wall may be causal mechanisms. An association with ofl-antitrypsin deficiency has been reported. Four distinct histological types ate recognized: intimal fibroplasia, medial hypetplasia, medial fibroplasia, and perimedial dysplasia. Medial fibroplasia is the most frequent form of FMD, followed by perimedial dysplasia, and intimal fibroplasia. The majority of cases of FMD involves the renal arteries, followed by the carotid and iliac arteries. Some cases are familial. Most often, patients with cervicocephalic FMD are asymptomatic or present with headaches, neck pain, carotidynia, tinnitus, vettigo, asymptomatic carotid bruits, transient retinal or cerebral ischemia, cerebral infarction, or subarachnoid hemorrhage. Cervicocephalic FMD may be associated with atterial dissection. Hypertensive patients may have concomitant renal FMD, Cerebral ischemia is usually related to the underlying atterial stenosis or artetial thromboembolism.

The diagnosis of cervicocephalic FMD is made on the basis of cerebral angiography. Cervicocephalic FMD occurs most often in the extracranial carotid artery and is bilateral in approximately two thirds of cases. The lesions of medial fibroplasia account for the characteristic "siting of beads" angiographical appearance seen in approximately 90% of cases (Figute 57A.12).

The optimal treatment of symptomatic cervicocephalic FMD has not been determined. In view of the benign natural history of this condition, platelet antiaggtegants arc recommended. Surgical intervention with angioplasty and stenting, gradual arterial dilatation, tcsection and reconstruction, or interposition grafting is seldom warranted.

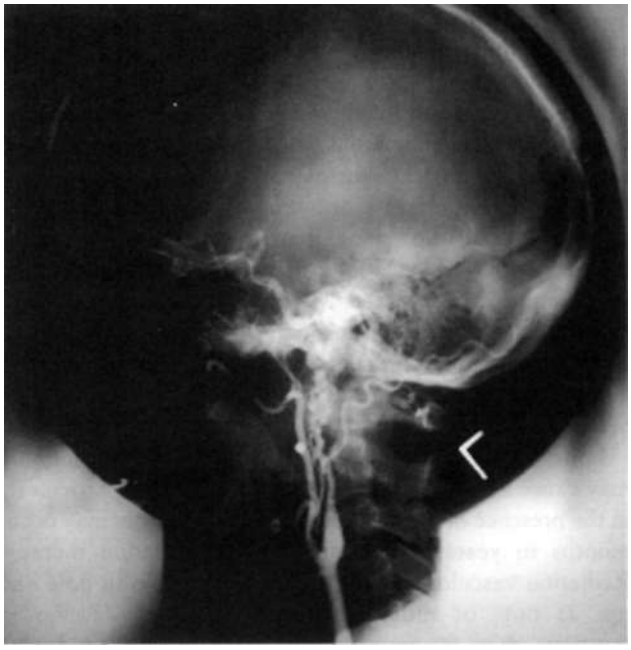

FIGURE 57A.12 Lateral left carotid angiogram in a patient with FMD. Note "string of pearls" appearance at around the C2 level.

Inflammatory vasculitides can involve any size of vessel, including the precapillary arterioles and postcapillary venules. Many infectious and multisystem noninfectious inflammatory diseases cause cerebral vasculitis (see Table 57A.5). Cerebral vasculitis is a consideration in young patients with ischemic ot hemorrhagic stroke; patients with recurrent stroke; patients with stroke associated with encephalopathic featutes; and patients with stroke accompanied by fever, multifocal neurological events, mononeuritis multiplex, palpable purpura, or abnormal urinary sediment. Other manifestations of cerebral vasculitis include headaches, seizures, and cognitive deterioration. Laboratory studies typically show anemia of chronic disease, leukocytosis, and an elevated erythrocyte sedimentation tatc. The diagnosis of vasculitis usually requires confirmation by arteriography or biopsy. Overall, these disorders have a poor prognosis, but corticosteroids and alkylating agents have improved the survival rate.

Intracranial vasculitis and stroke can result from meningovascular syphilis; prodromal manifestations are common before stroke. The MCA territory is most commonly affected. Spinal cord infarction may result from meningomyelitis. Other neurological manifestations in patients with secondary syphilis include headaches, meningismus, mental status changes, and ctanial nerve abnormalities. The cerebrospinal fluid (CSF) may show a modest lymphocytic pleocytosis, elevated protein content, and a positive Venerea! Disease Research Laboratory (VDRL) test result. Concurrent human immunodeficiency virus (HIV-1) infection can lead to rapid progression of early syphilis to neurosyphilis. Luetic aneurysms of the

ascending aorta can extend to involve the origin of the great vessels and can lead to stroke. Treatment schedules for syphilis are listed in standard textbooks; patients with concurrent HIV-1 infection and meningovascular syphilis may require prolonged antibiotic treatment. Worldwide, an estimated 1 billion people arc infected with *Mycobacterium tuberculosis.* Neurotuberculosis affects predominantly the basilar meninges. Predisposing conditions include alcoholism, substance abuse, corticosteroid use, and HIV 1 infection. Strokes can result from tuberculous endarteritis. The exudative basilar inflammation entraps the cranial nerves at the base of the brain, most frequently the third, fourth, and sixth cranial nerves. The basilar arteriolitis most commonly involves penetrating branches of the ACA, MCA, and PCA (medial and lateral lenticulostriate, anterior choroidal, thalamoperforators, and thalamogeniculate arteries). There is usually a modest lymphocytic and mononuclear pleocytosis. The CSF protein is usually elevated, and the glucose level is depressed. In the early stages, a predominantly neutrophilic response may be noted. Smears of CSF demonstrate M. *tuberculosis* in 10-20% of cases. Repeated CSF examinations increase the yield considerably.

Fungal arteritis may result in aneurysms, pseudoaneurysms, thrombus formation, and cerebral infarction. Complications of acute purulent meningitis include intracranial arteritis and thrombophlebitis of the major venous sinuses and cortical veins. Intracranial arterial stenoses have been associated with a complicated clinical course. Varicella-zoster may cause a virus-induced necrotizing arteritis similar to granulomatous angiitis. Cerebral infarction is a complication of the acquired immunodeficiency syndrome (AIDS), and may result from vasculitis, meningovascular syphilis, varicella-zoster virus vasculitis, opportunistic infections, infective endocarditis, aneurysmal dilation of major cerebral arteries, nonbacterial thrombotic endocarditis, aPL antibodies, or other hypercoagulable states, hyperlipidemia resulting from protease inhibitors, and other factors such as HIV-1-related malignancy, cancer chemotherapy, and thrombotic thrombocytopenic purpura (TIP). Large artery cerebrovascular occlusions have been found in association with meningoencephalitis caused by free living amebae. Other infectious agents known to produce cerebral infarcts include *Mycoplasma pneumoniae,* coxsackie 9 virus, California encephalitis virus, mumps paramyxovirus, hepatitis C virus, *Borrelia burgdorferi, Rickettsia typhi* group, cat-scratch disease, *Trichinella* infection, and the larval stage (cysticercus) of *Taenia solium.* Cerebrovascular involvement in ncurocysticercosis is usually ischemic and is caused by chronic meningitis, arteritis, or endarteritis of small vessels (Alarcon et al. 1992). Unilateral or bilateral carotid artery occlusion can complicate necrotizing fasciitis of the parapharyngeal space. Infection with *Chlamydia pneumoniae* accelerates the process of atherosclerosis in animal studies; treatment with azithromycin has been shown to reduce the degree of atherosclerotic lesions in a rabbit model (Moazed et al. 1999; Muhlestein et al. 1998).

Ischemic stroke is a complication of illicit drug use and over-thc-couutet sympathomimetic drugs. Stroke mechanisms associated with the use of illicit drugs are multifactorial, including foreign body embolization, vasculitis, vasospasm, acute onset of arterial hypertension or arterial hypotension, endothelial damage, accelerated atherosclerosis, hyper- or hypocoagulabiliry, cardiac arrhythmias, embolism from a myocardial infarction, or AIDS. The substances implicated most commonly are the amphetamines, cocaine (free-base or "crack"), phenylpropanolamine, pentazocine (Talwin) in combination with pyribenzamine ("T's" and "blues"), phencyclidine, heroin, anabolic steroids, and glue sniffing. Ischemic or hemorrhagic strokes may follow within hours of cocaine use, whether the drug is smoked, snorted, or injected (Figure 57A.13) (see Chapters 57G and 64B). The risk of intracerebral hemorrhage, especially among young women, has led to removal from the American market of phenylpropanolamine (Kernan et al. 2000). Ephedra, also called Ma Huang, widely used in weight-loss products, has been associated with high blood pressure, heart attacks, and strokes. Stroke in young athletes may also be the result of

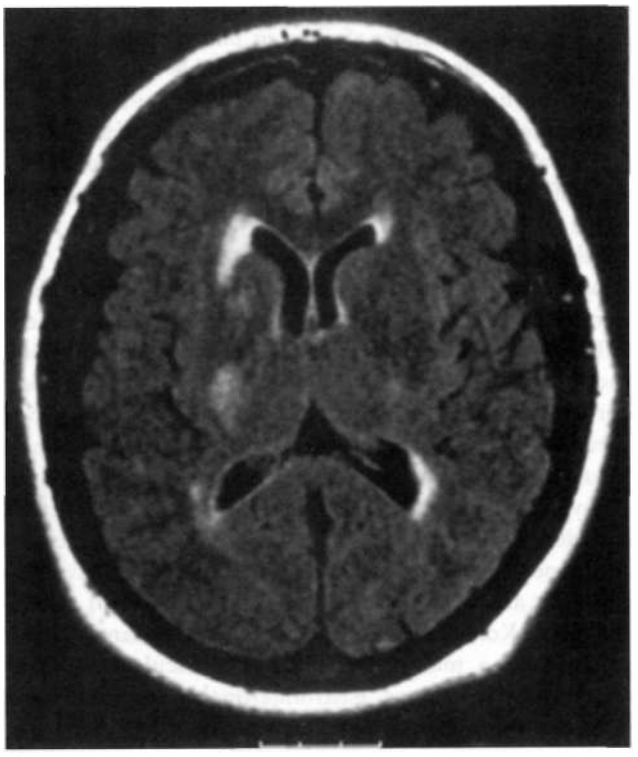

FIGURE 57A. 13 A 41-year-old woman with a history of cocaine ahuse had acute onset of left-sided hemiplegia, left hemibody sensory deficit, and a left homonymous visual field deficit. Axial flu id-attenuated inversion recovery images of the brain demonstrates an area of infarction in the posterior limb of the right internal capsule in the distribution of the anterior choroidal artery territory. There is associated periventricular ischemia.

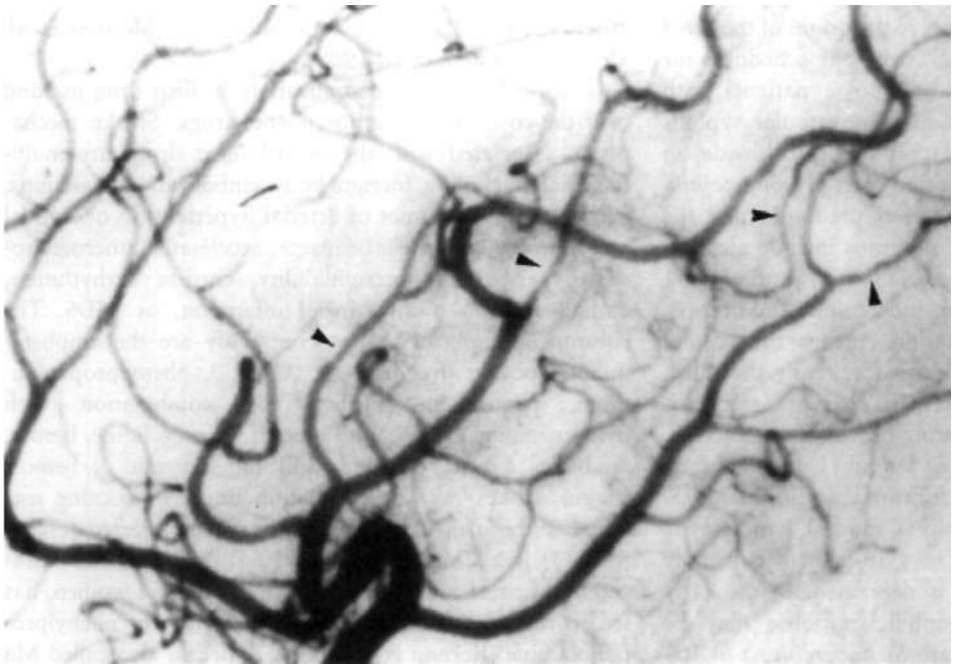

FIGURE 57A.14 Lateral carotid angiogram demonstrates irregular beading appearance *[arrowheads)* of large and medium branches of the anterior, middle, and posterior cerebral arteries in a patient with systemic lupus erythematosus. (Courtesy Vincent Mathews, MD.)

anabolic-androgen steroid abuse and recombinant erythropoietin ("blood doping") administration.

Ischemic stroke is also a complication of a variety of multisystem vasculitides. Stroke in patients with systemic lupus erythematosus may be attributable to cardiogenic embolism (nonbacterial verrucous or I.ibman-Sacks endocarditis, winch occurs in the ventricular surface of the mitral valve), aPL antibodies, underlying vasculopathy, or less often to an immune-mediated vasculitis (Figure 57A.14) (see Chapter 55A).

Behcet's syndrome may involve vessels of any size. Venous thrombosis is more frequent than occlusive arterial compromise. Affected patients arc mainly of Mediterranean or East Asian origin and may have a history of iritis, uveitis, and oral, genital, and mucocutaneous ulcerations. Cerebrovascular complications include strokes, carotid aneurysm formation, and cerebral venous thrombosis, Cogan's syndrome is a rare condition characterized by nonsyphilitic interstitial keratitis, vestibular dysfunction, and deafness. Complications include aortic insufficiency and mesenteric ischemia. The angiitic form of sarcoidosis primarily affects the eyes, meninges, and cerebral arteries and veins, Kohlmeier-Degos disease or malignant atrophic papulosis is a multisystem occlusive vasculopathy characterized by cutaneous, gastrointestinal, and neurological manifestations; it may be complicated by ischemic or hemorrhagic strokes. Cerebral vasculitis may also complicate the course of children with acute poststreptococcal glomerulonephritis. The multisystem vasculitides ate described in more detail in Chapter 55A,

Takayasu's arteritis is a chronic inflammatory artcriopathy of the aorta and its major branches, as well as the pulmonary artery. The cause is unknown, but an immune mechanism is suspected. The disease, prevalent in young women of Asian, Mexican, or Native American ancestry, develops insidiously, causing stenosis, occlusion, aneurysmal dilatation, or coarctation of the involved vessels. The disease has two phases. In the acute ot ptcpulsclcss phase, nonspecific systemic manifestations are present. Patients have skin rashes, erythema nodosum, fever, myalgias, arthritis, pleuritis, carotidynia, and elevated erythrocyte sedimentation rate. Months or years later, the second or occlusive phase develops and is characterized by multiple arterial occlusions. Patients may have cervical bruits, absent carotid or radial pulses, asymmetrical blood pressure recordings, and arterial hypertension. Neurological symptoms result from central nervous system or retinal ischemia associated with stenosis or occlusion of the aortic arch and arch vessels, or arterial hypertension caused by aortic coarctation or renal artery stenosis. Visual disturbances are most often bilateral. The diagnosis can be confirmed by MR A, but the most accurate assessment still requires aortography {Figure 57A.15).

Patients with active disease are treated with oral glucocorticoids; cyclophosphamide, a/athioprine, or methotrexate may be needed in special circumstances. Surgical treatment (angioplasty or bypass) of severely stenotic vessels may be required (Kerr ct al. 1999).

Cranial (giant cell or temporal) arteritis is a polysymptomatic systemic large vessel arteritis with a predilection to involve carotid artery branches (see Chapter 75). Thromboangiitis obliterans, also known as *Ruergcfs disease,* is a rare, segmental inflammatory, oblitcrativc angiopathy of unknown cause. The condition involves small and medium arteries and veins. It is suspected in young men who smoke and have a history of superficial

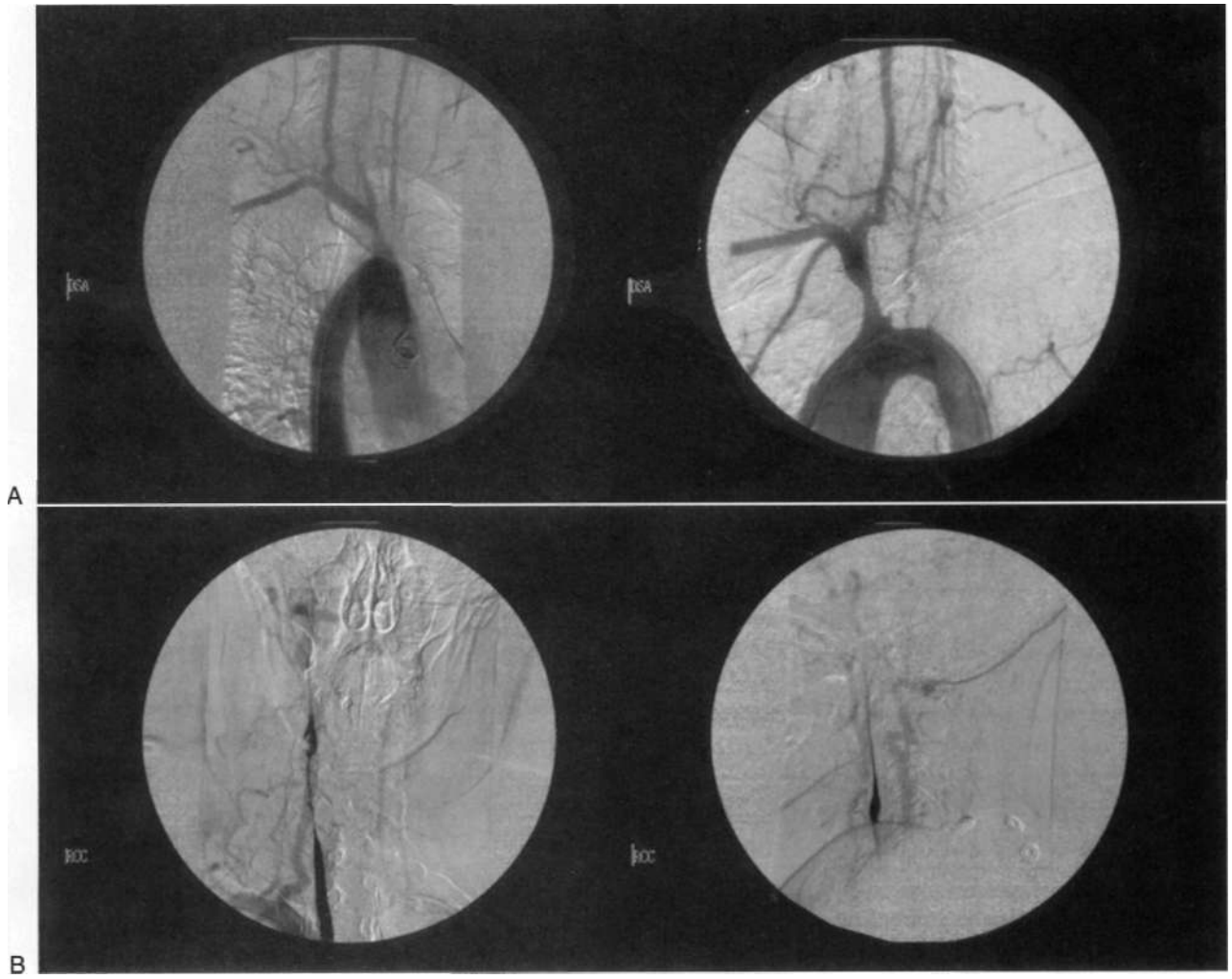

FIGURE 57A.15 (A) Aortogram demonstrates a nonocclusive stenosis of the brachiocephalic artery. There is complete occlusion of the left subclavian artery. The left vertebra is absent or occluded. (B) The right common carotid artery shows a long segment of critical stenosis extending from C3 to C5. *Continued*

migratory thrombophlebitis presenting with distal limb ischemia accompanied by digital gangrene. The disorder is characterized by remissions and exacerbations. Cerebral involvement is uncommon. Strokes can result from isolated angiitis of the central nervous system. Symptoms of large-vessel involvement include strokelike presentations. Small-vessel involvement may be manifested as a mass lesion in the brain or multifocal encephalopathy (Figure 57A.16A and Figure 57A.16B). The erythrocyte sedimentation rate is usually normal or minimally elevated (see Chapter 57G).

Migraine (see Chapters 21 and 75) affects women more often than men, and may start during childhood or adolescence. Epidemiological studies suggest a nonrandom association of both headache and migraine with stroke, particularly among young women. This rare association was limited to women younger than age 35 in a large Italian case-controlled study (Carolci ct al. 1996). The possible association between migraine headache and stroke was also evaluated by the Physician's Health Study; physicians reporting migraine had increased risks of subsequent rotal stroke and ischemic stroke compared with those not reporting migraines (Buring et al. 1995).

The International Headache Society Classification and Diagnostic Criteria require that, to establish a diagnosis of migrainous infarction, one or more migrainous aura symptoms must be present and not fully reversed within 7 days from onset, associated with neuroimaging confirmation of ischemic infarction (see Chapter 75). This definition implies that a firm diagnosis of migraine with aura has been made in the past. Also, the clinical manifestations judged to be the result of a migrainous infarction must be those typical of previous attacks for that individual, and finally, other causes of infarction, including those related to migraine therapy, need to be excluded by appropriate investigations.

Headache accompanies a number of embolic or thrombotic causes of stroke, including cervicocephalic arterial dissections. Migraines also can be a prominent symptom in the aPL antibody syndrome (APAS). Symptomatic migraine

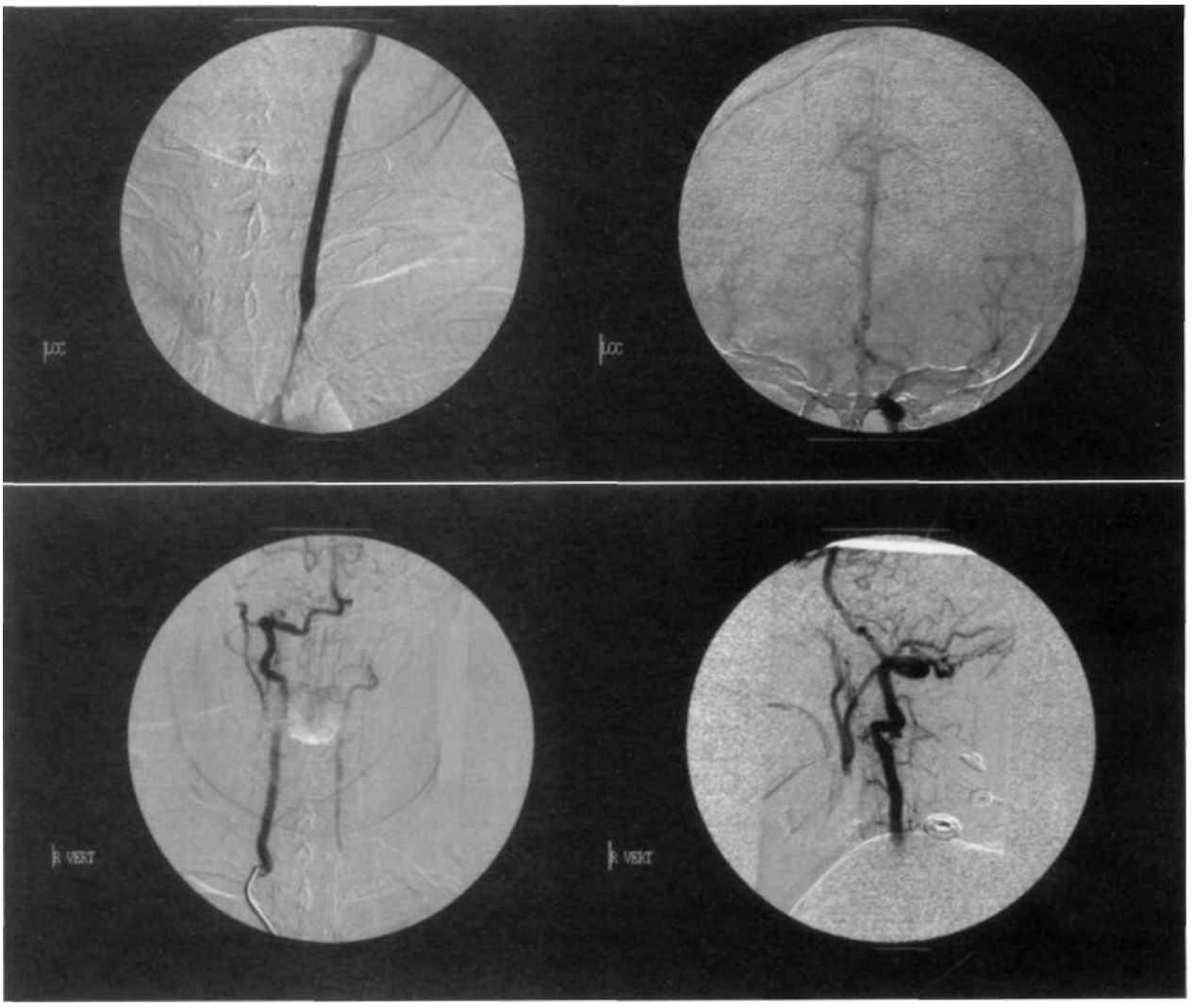

FIGURE 57A.15, cont'd. (C) There is also a very long stenosis of the left common carotid artery. (D) A larger cervical right vertebral artery provides vigorous filling of the intracranial right internal carotid circulation.

attacks are more frequent than migraine-induced ischemic insults. The presence of headache with a stroke is therefore not sufficient to make the diagnosis of migraine as the cause of the patient's symptoms. Furthermore, patchy subcortical abnormalities on MRI in patients with migraine with aura should be interpreted with caution. In other words, migrainous infarction remains a diagnosis of exclusion.

The pathogenesis of migrainous infarction is controversial. Cerebral infarcts complicating migraine are mostly cortical and involve the distribution of the PCA. The usual scenario of migrainous infarction is one of recurrent episodes of gradual buildup of unilateral throbbing headaches, associated with stereotyped visual phenomena occurring in both visual fields simultaneously, in one of which the vision loss becomes permanent. Migrainous infarctions have been subdivided as definite when all the International Headache Society criteria arc fulfilled, and possible when some, but not all criteria, are fulfilled. Patients with migrainous infarction arc at increased risk for recurrent stroke.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a familial nonarteriosclerotic, nonamyloid microangiopathy characterized by migraine with auta, tccurrent subcortical ischemic strokes starting in mid-adulthood, leading to pseudobulbar palsy, cognitive decline, subcortical dementia, and early white matter hyperintensities on MRI. CADASIL is caused by simple missense mutations or small deletions in Notch 3 gene on chromosome 19q12 encoding a transmembrane receptor Notch 3. Pathologically, there is a characteristic gtanular osmiophilic matctial in arterial walls, including dermal arteries (Kalimo et al. 2002}. A subtype of migraine, known as familial hcmiplegic migraine, characterized by transient weakness or frank paralysis during the aura, has also been mapped close to the CADASIL locus (Hutchinson et al. 1995).

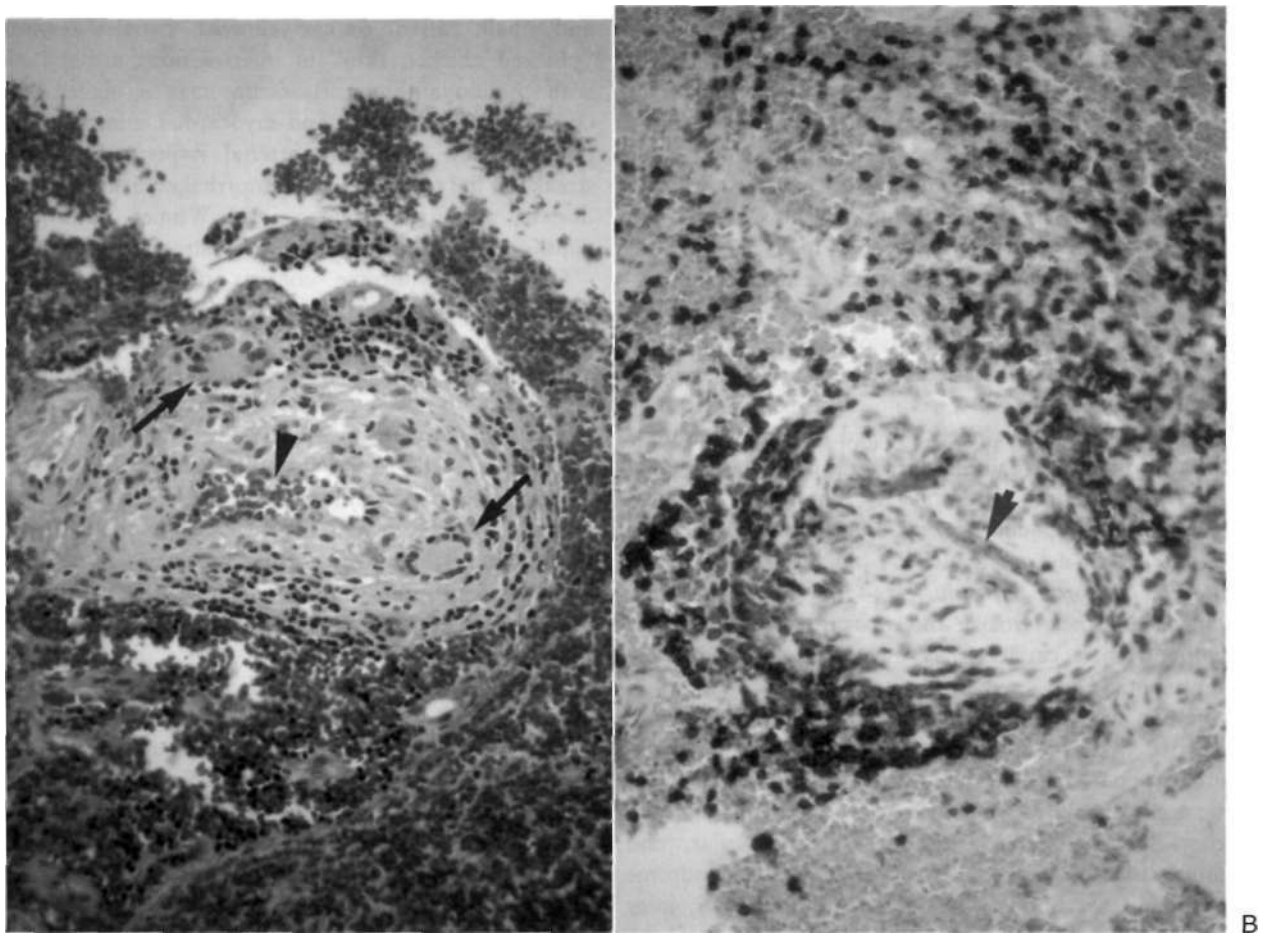

FIGURE 57A.16 Cerebellum. (A) Within an area of recent hemorrhage there is a small blood vessel showing focal infiltration with lymphocytes and a couple of multinucleated giant cells *(arrows).* The lumen of the vessel is marked with an *arrowhead* (x 680 H&E) Cerebellum. (B) The same vessel as in A. Immunostain with CD 3 demonstrates intense perivascular infiltration with T lymphocytes (x 680).

The newer acronym, cerebral autosomal dominant adenopathy with subcortical infarcts, leukoencephalopathy, and migraine, refers to a subvariety of CADASIL characterized by the high frequency of migraine (Verin et al. 1995),

INHERITED AND MISCELLANEOUS DISORDERS

Homocysrinuria, an inborn error of amino acid metabolism, is an unusual cause of stroke {Table 57A.6). Three specific enzyme deficiencies responsible for homocysrinuria have been identified: cystathionine ^-synthetase, homocysteine methyltransferasc, and methylene tetrahydrofolate reductase. The accumulation of homocysteine in the blood leads to endothelial injury and premature atherosclerosis. Patients with homocystinuria may display a marfanoid habitus, malar flush, livedo reticularis, ectopia lentis, myopia, glaucoma, optic atrophy, psychiatric abnormalities, mental retardation, spasticity, seizures, osteoporosis, and a propensity for intracranial arterial or venous

Tabic 57A.6: Inherited and miscellaneous disorders causing cerebral infarction

Homocystinuria
Fabry's disease
Marfan's syndrome
Killers-Polios' syndrome
Pseudoxanthoma clasticum
Sneddon's syndrome
Rendu-Osler-Weber's syndrome
Neoplastic angioendotheliomatosis
Susac's syndrome
Eales' disease
Reversible cerebral segmental vasoconstriction
Hypcreosinophilic syndrome
Cerebral amyloid angiopathy
Coils and kinks
Arterial dolichoectasia
Complications of coarctation of the aorta
Air, fat, amniotic fluid, bone marrow, and foreign particle embolism

thrombosis. Death may result from pulmonary embolism, myocardial infarction, or stroke. Raised levels of plasma homocysteine may be an independent risk factor for cerebrovascular disease, coronary, and peripheral arterial occlusive disease. Elevated levels of homocysteine can be effectively reduced with the administration of folic acid, occasionally requiring the addition of pyridoxine (vitamin BJ and vitamin B12. Other agents that may reduce homocysteine include choline, betaine, estrogen, and N-acetylcysteine.

Fabry's disease is an X-linkcd disorder of glycosphingolipid metabolism characterized by deficient lysosomal *a*-galactosidase activity. As a result, deposits of ceramidc trihexosidasc accumulate in endothelial and smooth muscle cells. Patients have a painful peripheral neuropathy, renal disease, hypertension, cardiomegaly, autonomic dysfunction, and corneal opacifications. Characteristic dark-red or blue lesions that do not blanch on pressure, called *angiokeratoma corporis diffusum,* are found between the umbilicus and knees. Stroke and myocardial infarction are common. Female carriers may have mild disease or are asymptomatic.

Marfan's syndrome is an autosomal dominant inherited connective tissue disease associated with qualitative and quantitative defects of fibrillin. Histopathological studies of aortic segments show cystic medial necrosis. This disorder is characterized by a variety of skeletal, ocular, and cardiovascular findings. Patients with Marfan's syndrome may display arachnodactyly, extreme limb length, joint laxity, pectus excavatum or carinatum, subluxation of the lens, and aortic valvular insufficiency. Marfan's syndrome is associated with a high incidence of dilatation of the aortic root. Other cardiovascular abnormalities include coarctation of the aorta, mitral valve prolapse, and mitral annulus calcification with regurgitation. Progressive dilatation of the aortic root may lead to dissection of the ascending aorta, resulting in ischemia to the brain, spinal cord, or peripheral nerves. Saccular intracranial aneurysms or dissection of the carotid artery can occur. Annual echocardiography studies arc recommended. Patients should avoid contact sports.

Patients with Ehlers-Danlos' syndrome, a fairly common heritable connective tissue disorder, display hyperextensibility of the skin, hypermobile joints, and vascular fragility leading to a bleeding diathesis. Arterial complications have been reported in association with Fhlcrs-Danlos' syndrome types I, III, and IV, especially type IV. Complications include dissections, arteriovenous fistulae, and aneurysms. Other cardiovascular abnormalities in patients with type IV Ehlers-Danlos' syndrome include ventricular and atrial septal defects, aortic insufficiency, bicuspid aortic valve, mitral valve prolapse, and papillary muscle dysfunction, Arteriography carries special risks and should be avoided if possible.

Patients with pseudoxanthoma elasticum, an inherited group of disorders of clastic tissue, often display loose skin and small, raised, orange-yellowish papules resembling "plucked chicken skin" in intertriginous areas. Patients with pseudoxanthoma elasticum have a higher risk of coronary artery disease and myocardial infarction. These patients may also have arterial hypertension, angioid streaks of the retina, retinal hemorrhages, arterial occlusive disease, and arterial dissections. Women with pseudoxanthoma elasticum should avoid estrogens.

Sneddon's syndrome consists of widespread livedo reticularis and ischemic cerebrovascular manifestations. A number of reports have documented a hereditary transmission and a link between Sneddon's syndrome and aPL antibodies. However, the etiopathogenesis remains unknown, although an immune mechanism is suspected. Endothelial cells could be the primary target tissue. Anticndothelial cell antibodies may be present (Frances et al. 1995).

Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease) is a familial disorder transmitted as an autosomal dominant trait. Ischemic stroke as a presenting manifestation of Rendu-Osier-Weber's disease has been reported infrequently. Paradoxical venous emboli passing through a pulmonary arteriovenous malformation can be the source of cerebral ischemia or abscess. Other potential causes leading to cerebral ischemia include air embolism and hyperviscosity secondary to polycythemia.

Neoplastic angioendotheliomatosis, also called *intravascular malignant lymphomatosis* or *angiotropic lymphoma,* is a rare disease characterized by multiple small- and large-vessel occlusion by neoplastic cell of lymphoid origin without an obvious primary tumor. Intravascular lymphomatosis has been reported to involve the skin, lungs, kidneys, adrenal glands, liver, pancreas, gastrointestinal tract, ovary, prostate, testicles, heart, thyroid, and parathyroid glands. Bone marrow, spleen, and lymph nodes arc usually spared. Simultaneous involvement of blood vessels throughout the body and compromise of different cerebral arterial territories is common with this disorder. Patients may present with recurrent multifocal cerebral infarctions, dementia, or myelopathy. Diagnosis requires skin, liver, renal, or brain-leptomcningeal biopsy. Combination chemotherapy has been recommended. Autologous peripheral blood stem cell transplantation after chemotherapy may be useful.

Microangiopathy ot brain, retina, and inner ear (Susac's syndrome), also known as retinocochleocerebral vasculopathy, is a rare microcirculatory syndrome that affects mainly adult women (Petty et al. 1998). The syndrome is unrelated to arterial hypertension or diabetes and is characterized by arteriolar branch occlusions of the brain, retina, and inner ear, with resultant encephalopathy, vision loss, vestibular dysfunction, tinnitus, vertigo, and asymmetrical sensorineural hearing loss. CSF examination may be normal orshow mild inflammatory response. Brain biopsy may show multifocal brain microinfarcts in both gray and white matter. The causal agent is unknown but has been

attributed to a disturbance of coagulation, microemholism, or both. Treatment with corticosteroids, cyclophosphamide, azathioprinc, plasmapheresis, or anticoagulant therapy is empiric, but branch retinal artery occlusions and central nervous system infarctions may recur despite the treatment. Hyperbaric oxygen treatment may be an option for refractory visual symptoms.

Eales' disease, commonly reported in India and the Middle East, is a rare, noninflammatory occlusive disease of the retinal vasculature characterized by repeated retinal and vitreous hemorrhages. The disorder affects mainly young men. Brain infarctions are rare.

Idiopathic reversible cerebral segmental vasoconstriction is an unusual clinical angiographical syndrome characterized by recurrent headaches, and transient motor and sensory findings associated with reversible arterial narrowing and dilatation involving predominantly the arteries around the circle of Willis. The cause is unknown.

The hypereosinophilic syndrome is a rare disorder caused by bone marrow overproduction of eosinophils that lodge in endothelial cells in the microcirculation primarily of heart, brain, kidney, lungs, gastrointestinal tract, and skin. Neurological complications include emboli from involved endocardium and heart valves, and neurological manifestations may result also from a hypercoagulable state with cerebral thromboses, and microcirculatory inflammation and occlusion by eosinophils. Cerebral infarction is a rare complication.

Cerebral amyloid angiopathy occurs both sporadically or in rave instances as a hereditary disorder. Cerebral amyloid angiopathy is characterized by the localized deposition of amyloid in the media and adventitia of small arteries and arterioles of the cerebral cortex and meninges in the elderly. Cerebral amyloid angiopathy is more commonly associated with lobar hemorrhage than with ischemic stroke, but has been associated with an increased frequency of cerebral infarction in patients with Alzheimer's disease (Olichney et al. 1995). Biopsy of the involved cortex and leptomeninges is the only definitive way to diagnose cerebral amyloid angiopathy.

Redundant length of the cervical carotid artery causes coils and kinks and other forms of tortuosity. Occasionally associated with FMD, kinks and coils of the carotid artery are an infrequent cause of cerebral ischemia. Arterial kinking seldom affects the vertebrobasilar circulation. Cerebral ischemia associated with kinking is attributable to a combination of flow reduction caused by obstruction, neck rotation, and distal embolization. Dolichoectasia is an unusual vascular disease that causes enlargement and elongation of arteries, particularly the basilar artery. This arteriopathy causes false aneurysm that leads to ischemic stroke, brainstem compression, cervicomedullary compression, cranial nerve palsies, cerebellar dysfunction, central sleep apnea, and hydrocephalus. The mechanisms of stroke arc penetrating artery occlusion, basilar artery thrombosis, or embolism from the dolichoectatic artery.

Ischemic stroke and intracranial hemorrhage, the latter caused by arterial hypertension or ruptured intracranial aneurysm, are important complications of coarctation of the aorta. Spinal cord ischemia may also complicate surgery for aortic coarctation. Neurological complications can result also from aortic rupture, infective aortitis or endarteritis, associated aortic bicuspid valve, and dissection of the aorta proximal to the coarctation.

Atheromatous emboli (cholesterol emboli syndrome) may follow manipulation of an atherosclerotic aorta during catheterization or surgery. Clinical presentation may include TIAs, stroke, retinal embolism pancreatitis, renal failure, and livedo reticularis. Purple toes may occur also as a result of small cholesterol emboli lodging in the digital arteries. Pedal pulses are normal. Patients also have a low-grade fever, eosinophilia, anemia, elevated erythrocyte sedimentation rate, and elevated serum amylase, Anticoagulation may exacerbate further embolization, and its use should be discouraged.

Accidental introduction of air into the systemic circulation can be a cause of cerebral or retinal ischemia. Air embolism is a dreaded complication of surgical procedures, including intracranial operations in the sitting position; open heart surgery; surgery of the lungs, pleura, sinuses, neck, and axilla; hemodialysis; thoracocentesis; arteriography; central venous catheters; and scuba diving. Symptoms include seizures and multifocal neurological findings such as cerebral edema, confusion, memory loss, and coma. CT scan may be useful in visualizing the gaseous bubbles. Treatment includes prompt resuscitative measures, placement of the patient in the left lateral position, inotropic agents, anticonvulsants, anti-edema agents, and hyperbaric oxygen. Caisson's disease can occur in persons who are scuba diving. Neurological features are caused by multiple small nitrogen emboli leading to ischemia of the brain and spinal cord; signs of spinal cord dysfunction are prominent. Hyperbaric oxygen therapy is the usual treatment.

Fat embolism to the brain complicates long bone fractures, sickle cell disease, cardiopulmonary bypass, soft tissue injuries, and blood transfusions. This syndrome-occurs suddenly within hours to 3 or 4 days after injury and is characterized by dyspnea, fever, tachycardia, tachypnea, cyanosis, cutaneous petcchiae, and coagulopathy. Neurological manifestations arc confusion, disorientation, delirium, hemiparesis, aphasia, and coma. Petechia) hemorrhages may be apparent on funduscopy, conjunctivae, base of the neck, and axillary region. Vigorous respiratory supportive therapy is essential.

Amniotic fluid embolism is a rare catastrophic obstetrical complication caused by the entry of amniotic fluid into the maternal bloodstream during parturition. Vigorous supportive therapy with intravenous fluids and blood replacement to treat shock, correction of respiratory distress syndrome, disseminated intravascular coagulation, and underlying fibrinolytic state are essential. Among other causes of emboli are large intracranial saccular aneurysms

or extracranial false aneurysms of the internal carotid artery. Tumor emboli to the brain have been reported with osteosarcoma, atrial myxoma, and with carcinoma of the lung, breast, pharynx, or esophagus. Talc, cornstarch, and other foreign particles injected as adulterants in illicit drugs can embolize to the brain or retina. Paradoxical embolism during bone marrow infusion is an infrequent complication.

HYPERCOAGULABLE DISORDERS

Alterations in hemostasis are associated with an increased risk of cerebrovascular events, particularly those of an ischemic nature and may account for a considerable number of cryptogenic strokes (Table 57A.7). These disorders account for 1% of all strokes and for 2-7% of ischemic strokes in young patients (Kitchens 1994).

Primary f lypercoagulable States

Inherited disorders predisposing to thrombosis especially affect the venous circulation. These disorders include AT-III deficiency, protein C and protein S deficiencies, activated protein C (APC) resistance, abnormalities of fibrinogen (dysfibrinogencmia), and abnormalities of fibrinolysis. Inherited thrombophilia should be suspected in patients with recurrent episodes of deep venous thrombosis, recurrent pulmonary emboli, family history of thrombotic events, unusual sites of venous (mesenteric, portal, or cerebral) or arterial thromboses, or in patients with thrombotic events occurring during childhood, adolescence, or early adulthood. Approximately one half of all thrombotic episodes occur spontaneously, although these patients arc at greatest risk when exposed to additional risk factors such as pregnancy, surgery, trauma, or oral contraceptive therapy.

Table 57A.7: Hypercoagulahle states

Primary hypercoagulahle states
Antitlirombin III deficiency
Protein C deficiency
Protein S deficiency
Activated protein C resistance with or without factor V Leiden mutation
Prothrombin G20210 mutation
Afibrinogenemia
Hypofibrinogenemia
D ysfi b r i nogenem i a
Hypoplasminogencmia
Abnormal plasminogen
Plasminogen activators deficiency
Lupus anticoagulant and antieardiolipin antibodies
Secondary hypercoagulable states
Malignancy
P regn a ncy/pu erpe r i u m
Oral contraceptive use
(karinii liypcr^rmnilation syndrome
Other hormonal treatments
Nephrotic syndrome
Polycythemia vera
Essential thrombocythenna
Paroxysmal nocturnal hemoglobinuria
Diabetes mellitus
Heparin-induced thrombocytopenia
Homocystinuria
Sickle tell disease (sickle cell anemia, sickle cell-hemoglobin C)
Thrombotic thrombocytopenic purpura
Chemotherapeutic agents

AT-III deficiency is inherited in an autosomal dominant fashion, thus affecting both sexes. There are three categories of inherited AT-III deficiency: classic or type I, characterized by decreased immunological and biological activity of AT-III; type II, characterized by low biological activity of AT-III but essentially normal immunological activity; and type III, characterized by normal AT-III activity in the absence of heparin, but reduced in heparin-dependent assays. Acquired AT-III deficiency may follow acute thrombosis and disseminated intravascular coagulation. It has been associated also with nephrotic syndrome, liver cirrhosis, eclampsia, various malignancies, the use of estrogens or oral contraceptives, L-asparaginase, tamoxifen, and heparin therapy. A normal level of AT-III activity obtained at the time of an acute thrombotic event is sufficient to exclude a primary deficiency. However, a low level of AT-III activity must be confirmed by repeat testing, after resolution of the thrombotic episode and discontinuation of anticoagulant therapy. Confirmation of a low plasma level of AT-III activity on repeat resting is compatible with a primary deficiency and is an indication to investigate other family members. Thrombotic episodes associated with AT-III deficiency are treated acutely with heparin with or without adjunctive AT-III concentrate. Prophylactic therapy in patients with recurrent thrombosis consists of long-term warfarin administration, keeping the therapeutic INK range between 2,0 and .i.O.

Protein C deficiency is inherited in an autosomal dominant fashion. Homozygous protein C deficiency presents in infancy as purpura fulminans neonatalis. Heterozygotes are predisposed to recurrent thrombosis. Thrombotic manifestations are predominantly venous, Acquired protein C deficiency has been associated with the administration of L-asparaginase, warfarin therapy, liver disease, disseminated intravascular coagulation, postoperative state, bone marrow transplantation, and the adult respiratory distress syndrome. Testing for immunological and functional assays of protein C should be performed after oral anticoagulation has been discontinued for at least a week. Heparin does not modify the levels of protein C. Warfarin-induced skin necrosis is a serious potential complication of protein C-deficient patients at the initiation of warfarin therapy; this syndrome often occurs in association with large loading doses of warfarin. The acute

management of thrombosis associated with protein C deficiency consists of prompt administration of heparin followed by incremental doses of warfarin, starting with low doses until adequate anticoagulation is achieved. Long-term management requires the administration of warfarin.

Protein S deficiency also has an autosomal dominant mode of inheritance. Protein S exists in plasma in two forms; approximately 40% of the total protein S is functionally active or free, and the remaining is complexed to a binding protein. Homozygous protein S deficiency presents with venous thromboembolic disease. Heterozygotes are prone to recurrent thrombosis including cerebral venous thrombosis. Acquired protein S deficiency occurs during pregnancy, in association with acute thromboembolic episodes, disseminated intravascular coagulation, nephrotic syndrome, systemic lupus erythematosus, and with the administration of oral contraceptives, oral anticoagulants, and L-asparaginase. Testing for immunological assays of total and free protein S, and functional assay of protein S, should be confirmed after resolution of the thrombotic episode and discontinuation of oral anticoagulants. Heparin therapy is effective in the management of acute thrombotic events associated with protein S deficiency, whereas watfarin is advocated for patients with recurrent thromboembolism.

Resistance to APC is one of the most common identifiable risk factors for venous thromboembolic disease, including cerebral venous thrombosis. The relation of APC resistance to arterial disease is not well established. APC resistance has been identified as 5 to 10 times more common than deficiencies of AT-III, protein C, or protein S. APC resistance also has an autosomal dominant mode of inheritance. APC resistance is associated in most patients with a single point mutation in the factor V gene (factor V Leiden), which involves the replacement of arginine 506 with glutamine 506 (Arg 506 Gin). Testing for resistance to APC must be done after discontinuation of anticoagulants. There are conflicting results about factor V Leiden gene mutation and the risk for acute cerebral arterial thromboses. The contribution of factor V Leiden or prothrombin G20210A to ischemic stroke in the young is less clear. Conversely, both factor V Leiden and prothrombin G20020A mutations are associated with an increased risk for cerebral venous thrombosis (Ludemann et al. 1998; Peuner et al. 1998; Cushman et al. 1998). In the Physicians' Health Study, no association between factor V Leiden or prothrombin G20210A and ischemic stroke was found (Ridker et al. 1995).

Abnormalities of fibrinogen account for approximately 1% of all inherited thrombotic disorders. Fibrinogen cross-links platelets during thrombosis and is an important component of atherosclerotic plaques. High concentrations of fibrinogen increase the risk for stroke and myocardial infarction. Afibrinogenemia is probably transmitted as an autosomal recessive trait; complications include umbilical cord bleeding, gastrointestinal hemorrhage, and intracranial hemorrhage. Hypofibnnogenemia represents the heterozygous lorm of afibrinogenemia; bleeding is rare. Dysfibrinogcnemia reflects a qualitative disorder in the fibrinogen molecule and may be associared with hemorrhagic or thrombotic episodes. Hereditary dysfibrinogcnemia is inherited in an autosomal dominant fashion. Decreased concentrations of fibrinogen are associated with disseminated intravascular coagulation, liver failure, snake bite, treatment with t.-asparaginase, Ancrod, fibrinolytic drugs, and valproate. Treatment consists of infusions of cryoprecipitate.

Decreased levels of plasminogen (hypoplasminogcnemia), qualitative abnormalities in the plasminogen molecule (dysplasminogencmias), and defective release of plasminogen activators occur in families with recurrent thrombotic events. Cerebral venous thrombosis occurs with disorders of plasminogen. Prophylactic therapy in patients with recurrent thrombosis consists of lifelong anticoagulation.

Lupus anticoagulants and anticardiolipin (aCL) antibodies are known collectively as *antipbvspbolipid antibodies* and have a pathogenetic role in arterial and venous thrombosis. Ischemic stroke is the most common arterial thrombotic event in patients with APAS. APAS associates the presence of aPL antibodies in high titers with recurrent arterial or venous thromboses, feral loss, and livedo reticularis. Several aPL antibodies have been described in immunoglobulin (Ig)G, IgA, or IgM isorypes: aCL, antiphosphatidylcthanolaminc (aPL), antiphosphatidylserine, and antiphosphatidykholinc. Affinity-purified aCLs do not bind to cardiolipin in the absence of seium or plasma. The component required for aCL binding is £2-gIycoprotein 1 (/32GP1). It is the 02-GPl -dependent aCL of the IgG isotype that has been significantly associated with sttokes and myocardial infarcts (Brey et al. 2001). Other stroke studies have reported an association with aPE (Gonzales-Portillo et al. 2001).

APL antibodies arc present in patients with systemic lupus erythematosus and related autoimmune disorders, Sneddon's syndrome, acute and chronic infections (including HIV-1), neoplasias, inflammatory bowel disease, administration of certain drugs, early onset severe preeclampsia, liver transplantation, and also in individuals without demonstrable underlying disorders. A distinct group of patients has a *primary* APAS; its association with ischemic cerebrovascular disease is rare.

APL antibodies arc associated with recurrent fetal loss, a prolongation of the activated partial thromboplastin time (aPTT) that does not correct on 1 to 1 mixing with normal plasma, thrombocytopenia, a false-positive VDRL test result, and livedo reticularis. They may also be associated with cerebral and ocular ischemia, cerebral venous thrombosis, migraine, vascular dementia, chorea, transverse myelopathy, myocardial infarction, peripheral arterial thromboembolism, venous thrombosis, pulmonary embolism, and Degos' disease. Multiple cerebral infarctions are

common in patients with aPL antibodies; a subset of patients may present with vascular dementia (Figure 57A. 17). Still another group may have an acute or progressive thrombotic ischemic encephalopathy. Pathological studies of cerebral arteries involved in association with aPL antibodies demonstrate the presence of a chronic thrombotic microangiopathy, but no evidence of vasculitis. Patients with a PI. antibodies have an increased frequency of mitral and aortic vegetations. There are findings resembling verrucous endocarditis (Libman-Sacks endocarditis). Left ventricular thrombus formation is a rare occurrence, Treatment for arterial thrombosis associated with aPL antibodies is not well established. One casc-conttolled study found that high-intensity warfarin (INR > 3.0), with or without aspirin, was more effective in preventing thrombotic recurrences than low-intensity warfarin, with or without aspirin, or aspirin alone (Khamashta et al. 1995). Guidelines published in the United Kingdom have recommended an INR target of 3,5 (British Committee for Standards in Hematology 1998) or 2.5 (Greaves et al. 2000). In the Warfarin Aspirin Recurrent Stroke Study (WARSS), warfarin (median **INR** = 2.09) did not provide additional benefit over aspirin in preventing recurrent ischemic stroke among ischemic stroke patients who were

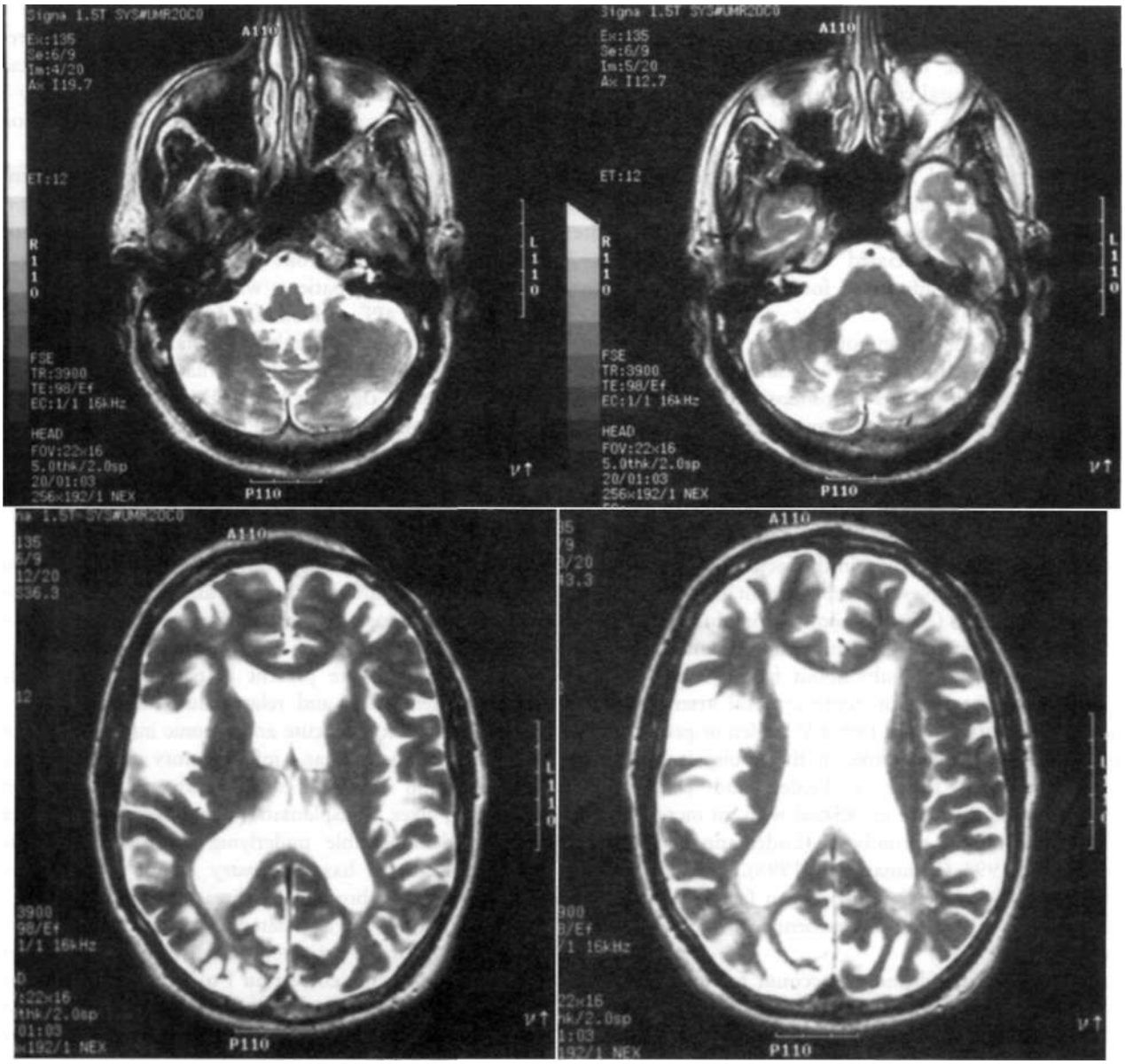

FIGURE 57A.17 A 44-year-old man with elevated anticardiolipin antibodies had a branch retinal vein occlusion in the left eye, progressive balance problems, poor memory, and an overall decline in cognitive functioning, Echocardiography showed thickened mitral valve without significant stenosis, T2-weighted axial magnetic resonance imaging of the brain demonstrates confluent hyperintensities in the periventricular region and basal ganglia consistent with ischemia. There are also bilateral hyperintensities in the cerebellum consistent with infarcts. Cortical ischemic changes are also present bilaterally in the occipital lobes and in the right frontal lobe.

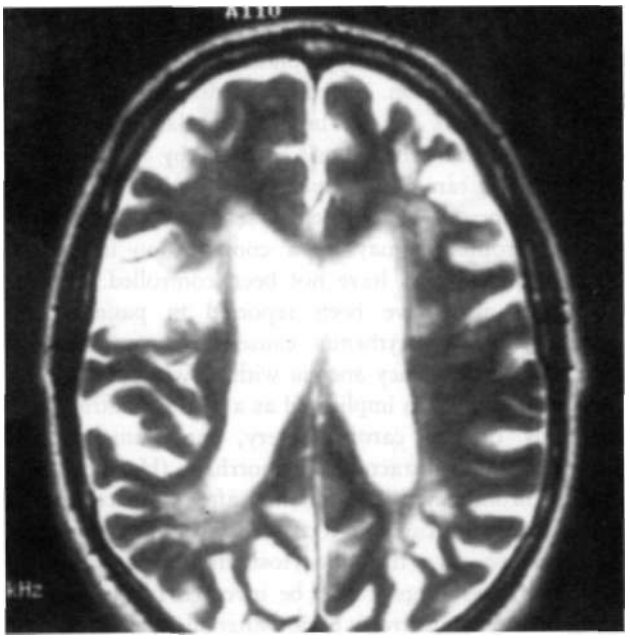

FIGURE 57A.17, cont'd.

aPl. antibody-positive at baseline (Levine et al. 2002). Pregnant patients are often treated with prednisone and low-dose aspirin.

Secondary Hypercoagulable States

Strokes may complicate the clinical course of malignancies. In rare instances, stroke may be the initial manifestation of cancer. Cerebral infarction mostly complicates lymphomas, catcinomas, and solid tumors. Cerebral hemorrhages are more common with leukemia. Hypercoagulability is not an uncommon finding in patients with malignancy, especially with mucin-producing carcinomas of the pancreas, gastrointestinal tract, and lung; myeloproliferative disorders; acute promyelocytic leukemia; and brain tumors. Mucinous adenocarcinomas of the gastrointestinal tract, lung, and ovary may produce infarcts from widespread cerebral arterial occlusions by mucin. The cause of the hypercoagulable state is often multifactorial. The pathophysiology is believed to be a state of low-grade disseminated intravascular coagulation and secondary fibrinolysis, but with the balance shifted toward clotting. Atherosclerosis is still the leading cause of infarction in patients with malignancy. Cerebral infarction in patients with malignancy also may be caused by tumor emboli, bone marrow embolization, emboli originating from mural thrombi, or emboli arising from marantic vegetations associated with nonbacterial thrombotic endocarditis. Many patients with nonbacterial thrombotic endocarditis have associated disseminated inttavascular coagulation, which may cause capillary occlusion of multiple organs, especially the lungs, kidneys, gastrointestinal tract, heart, and brain. Neurological manifestations produce a diffuse encephalopathy secondary to disseminated microinfarcts. Other patients with malignancy and cerebral infarction may have cerebral venous occlusive disease caused by thrombi, tumor invasion, or stroke associated with chemotherapy. In addition, cancer-en ha need arhcrothrombosis, neoplastic angioendotheliomatosis, arterial compression by tumor, occlusive vascular disease secondary to irradiation, intercurrent angiitis, and arterial rupture also may be responsible for cerebral infarction in some patients. Treatment consists of management of the underlying malignancy. Anticoagulants and platelet antiaggregants are used with variable success.

The postpartum period is a hypcrcoagulable state. Characteristically, arterial causes of stroke are more common during pregnancy, whereas venous causes of stroke are more common during the puerperium (sec Chapter 87).

Oral contraceptives cause alterations of the vessel wall with intimal hyperplasia. They also increase blood viscosity. (here arc decreased levels of protein S, AT-III activity, and plasminogen activator content in women taking oral contraceptives. There also may be an increase in the levels of fibrinogen, factors VII and X. Oral contraceptive therapy may enhance arrerial hypertension. Women taking oral contraceptives have an estimated ninefold increased risk of thrombotic stroke. This risk is increased by prolonged use, high dosage of the estrogen component, cigarette smoking, concomitant diabetes, arterial hypertension, hyperlipidcmia, and age older than 35 years. Current users of oral contraceptives are at increased risk of stroke. One study showed that oral contraceptives containing 30-40 ^g of estrogen are associated with a one third reduced risk compared with preparations containing 50 ng. The occurrence of intracranial venous thrombosis as a complication of oral contraceptives is well recognized. A patient on oral contraceptives occasionally presents with stroke caused by paradoxical embolism associated with deep venous thrombosis. Oral contraceptives also increase the risk of subarachnoid hemorrhage.

Oral contraceptives probably should be avoided in women with arterial hypertension. They should also be avoided in the first 2 weeks after delivery. Women older than 35 years of age who smoke cigarettes probably should be advised to choose a different contraceptive method. As part of primary stroke prevention efforts, women who smoke should not use oral contraceptives. The ovarian hypersrimularion syndrome occurs in women after induction of ovulation with clomiphene, human menopausal gonadotropin, human follicle-stimulating hormone extracted from human pituitary, and human chorionic gonadotropin. Evidence of body fluid shifts and hypercoagulability exist with this syndrome, reflected in thromboembolic events. Stroke is a rare but serious consequence of severe ovarian hyperstimillation syndrome.

Thromboembolic events are a feared complication of hormone treatment in ttansscxuals. Cerebral infarction has

occurred as a side effect of exogenous estrogen in a male-to-female transsexual. Likewise, TIAs and cerebral infarction may follow the administration of anabolic steroids for the treatment of hypogonadism and hypoplastic anemias. Cerebral ischemia has occurred also following the use of human recombinant erythropoietin in the treatment of anemia of patients on hemodialysis.

The nephrotic syndrome may be accompanied by venous and arterial thromboses, including cerebral arterial and venous occlusive disease. Ischemic stroke can be the presenting manifestation. The mechanism by which nephrotic syndrome causes hypercoagulability is multifactorial and includes elevated levels of fibrinogen, raised levels of factors V, VII, VIII, and X, thrombocytosis, enhanced platelet aggregation, and reduced levels of AT-III and protein S. The exact role of hyperlipidemia, corticosteroids, and diuretic use is uncertain. Nephrotic syndrome should be considered as a contributing mechanism in any patient with ischemic stroke and pre-existing renal disease. A urinalysis is the initial clue to the diagnosis. The presence of severe proteinuria and a low serum albumin should prompt consideration of a hypercoagulable state. Treatment of thromboembolism associated with nephrotic syndrome consists of anticoagulants until remission of the renal condition.

Polycythemia vera and primary or essential rhrombocythemia are typically disorders of middle-aged or elderly patients. Polycythemia vera is characterized by increased red blood cell mass and normal arterial oxygen saturation. Patients have ruddy cyanosis, painful pruritus, hypertension, splenomegaly, elevated hemoglobin, high hematocrit value, thrombocytosis, leukocytosis, and elevated serum B12 levels. Typically, the bone marrow is hypercellular. Secondary polycythemia may occur in association with cerebral hemangioblastoma, hepatoma, hypernephroma, uterine fibroids, benign renal cysts, carbon monoxide exposure, and administtation of androgens. Cerebral blood flow is reduced, and cerebral hemorrhage, and arterial or venous thrombosis, can complicate the condition. The majority of the intracranial events are thrombotic in origin, the larger cerebral arteries being the most frequently involved. The risk of stroke parallels the hemoglobin level: The higher the hemoglobin and hematocrit values, the greater the risk of stroke. Headaches, dizziness, vertigo, tinnitus, visual disturbances, carotid and vertebrobasilar TIAs, chorea, and fluctuating cognitive impairment are we 11-recognized features of patients with polycythemia vera. Spinal cord infarction is a rare complication. Cautious lowering of the hematocrit is a reasonable therapeutic approach. Because of the potential risk of hemorrhagic intracranial complications, aspirin therapy should be used cautiously.

Cerebral thrombotic and hemorrhagic complications are not uncommon in primary or essential thrombocythemia. Patients may have splenomegaly, mucocutaneous hemorrhagic diathesis, persistently elevated platelet count, usually in excess of 1 million per pi, giant platelets, and a bone marrow megakaryocyte hyperplasia. Neurological complications are common. Headaches, dizziness, amaurosis fugax, and TIAs of the brain are relatively frequent. Cerebral arterial thrombosis caused by platelet-fibrin thrombi is a rare but serious complication of essential thrombocythemia. Papilledema secondary to cerebral venous thrombosis may be a complication in patients whose platelet levels have not been controlled. Cerebral infarctions also have been reported in patients with secondary thrombocythemia caused by iron deficiency anemia. Iron deficiency anemia with or without thrombocytosis also has been implicated as a cause of intraluminal thrombus of the carotid artery, intracranial venous thrombosis, and intracranial hemorrhage (Hartficld et al. 1997), Thrombocytosis is common after splenectomy, but does not seem to catty an inctcascd thromboembolic risk. However, reactive thrombocytosis following cardiopulmonary bypass surgery may be involved in the cause of stroke in the late recovery period after surgery. The role of rebound thrombocytosis in ischemic stroke among heavy alcohol drinkers is uncertain. Treatment of primary thrombocythemia includes hydroxyurea, plateletpheresis, recombinant interferon-a, and aspirin. Vigorous correction of the anemia is indicated for those patients with thrombocytosis associated with iron deficiency anemia,

Paroxysmal nocturnal hemoglobinuria is an acquired clonal stem cell disorder characterized by severe hemolytic anemia and hemosiderinuria. A feared complication is cerebral venous thrombosis. Thrombosis of major cerebral veins or dural sinuses and portal vein thrombosis are the most frequent causes of death. Acute thrombotic episodes involving the cerebral veins may be treated with thrombolytic agents, unless contraindicated, or anticoagulant therapy. High-dose cyclophosphamide and granulocyte-colony stimulating factor are being studied for the treatment of paroxysmal nocturnal hemoglobinuria.

Diabetes is a well-established risk factor for ischemic stroke. Diabetes associated with arterial hypertension or hyperlipidemia adds significantly to stroke risk. There are a variety of platelet, theological, coagulation, and fibrinolytic abnormalities thai may play a role in the pathogenesis ol stroke in diabetic patients. Numerous hemorrheological disturbances appear to affect the development of diabetic microvascular disease and may contribute to cerebrovascular ischemic events. Hemorrheological alterations producing increased blood viscosity may include increased fibrinogen values, increased hematocrit, elevated factors V and VII, increased platelet aggregation, increased platelet adhesion, increased release of /i-thromboglobulin, decreased red blood cell deformability, and decreased fibrinolytic activity.

Heparin-induced thrombocytopenia can cause high morbidity and mortality from thrombotic complications. Heparin therapy may induce two types of thrombocytopenia. The most frequently observed is type I heparin-induced

thrombocytopenia, which is a mild and benign condition with platelet counts around 100,000 per pi. This thrombocytopenia tends to occur early and resolve spontaneously. Complications are rare. Type II heparin-induccd thrombocytopenia is a major, albeit infrequent (< 3% with unfractionated heparin and < 1% with low-molecular weight heparins), adverse side effect of heparin therapy with a delayed onset (5-15 days after heparin administration). An immune-mediated disorder characterized by increased levels of platelet-associated IgG and IgM, it increases the risk for venous and arterial thrombotic complications involving the brain, heart, and limbs. Fatalities arc high, and hemorrhagic complications are rare. Unlike drug-induced immune TTP, petechiae are not seen in cases of heparin-induced thrombocytopenia with thrombosis. Prevention is paramount, requiring an optimal reduction of the time of exposure to heparin to less than 5 days when possible, and daily platelet counts during heparin administration. Treatment requires immediate discontinuation of heparin. If anticoagulant therapy is still needed, the use of danaparoid, recombinant hirudin or argatroban should be considered.

Elevated plasma homocysteine levels are an independent risk factor for atherosclerotic disease. Patients with high plasma homocysteine levels have a greater likelihood of occlusive disease of the extracranial carotid arteries, cerebral arteries, peripheral vascular and coronary beds when compared with the general population. Diagnosis of hyperhomo cy stein cmia may be made by demonstrating elevated basal plasma levels of homocysteine or raised levels after methionine loading. Reduction of homocysteine levels in plasma requires the supplementation of folate, vitamin B<„ and vitamin Bj?. Homocystinuria is covered earlier in this chapter under Inherited and Miscellaneous Disorders.

Cerebrovascular disease is a major cause of morbidity and mortality in sickle cell disease. Strokes in sickle cell anemia (hemoglobin SS [HbSS]) patients manifest as ischemic strokes in children and as intracerebral and subarachnoid hemorrhage in adults. The most common presentations of stroke in patients with sickle cell disease are hemiparesis, seizures, language or visual impairments, and coma. Cognitive impairment may result from silent infarcts. Coma is more suggestive of intracranial hemorrhage rather than cerebral infarction. Patients at greatest risk of stroke are those with (HbSS) severe anemia, higher reticulocyte counts, and lower hemoglobin F levels. Sickle cell disease leads to a hyperviscous condition within the microvasculature. At low oxygen tensions, erythrocytes containing hemoglobin S assume a sicklclike appearance. Sludging in small vessels occurs, resulting in microinfarctions in the affected organs. Although there is pathological evidence that microvascular occlusion and sludging caused by sickling does occur in the brain, the clinical and neurodiagnostic findings are consistent with a large vessel arterial occlusive (intimal hyperplasia with superimposed thrombosis) disease affecting the major intracranial arteries, frequently involving the arterial border zones between major cerebral arteries and adjacent deep white matter. Infarcts are more common in the ACA-MCA boundary zone. Sickle cell disease commonly causes a moyamoya-like angiographic pattern. Sickle cell disease may be accompanied by thrombotic cerebral infarction, cerebral venous occlusive disease, or subarachnoid, intracerebral, or intraventricular hemorrhage. Delayed intracranial hemorrhage may Inllow cerebral infnivrion and lias been described as a complication of bone marrow transplantation. Spinal cord infarction is extremely rare. Neurological symptoms may be triggered by hypoxia, sepsis, dehydration, or acidosis.

The evaluation of the stroke patient with sickle cell anemia must be carefully individualized. Blood cell count, peripheral blood smear, hemoglobin electrophoresis, and sickling test are essential. MRI, MRA, and transcranial Doppler studies are valuable investigations in sickle cell patients; transcranial Doppler is useful in detecting the intracranial vasculoparhy and may make it possible to detect patients at highest risk for cerebral infarction and to initiate treatment prior to stroke. Cerebral angiography can be done safely with the use of low-osmolar contrast media after partial exchange transfusion is performed to avoid complications associated with contrast material. The Stroke Prevention Trial in Sickle Cell Anemia evaluated children with sickle cell anemia and no history of stroke. Children were screened with transcranial Doppler ultrasonography. The trial was prematurely stopped by the National Heart, Lung and Blood Institute after 11 strokes (10 cerebral infarctions and one cerebral hemorrhage) occurred among the standard of care group, while only one ischemic stroke occurred among the transfused group. Maintenance of hemoglobin S below 30% was effective in reducing the risk of cerebral infarction in children with sickle cell anemia (Pegelow et al. 1995). Meticulous hydration, adequate oxygenation, and analgesia are necessary. Iron overload may be prevented by subcutaneous chelation with deferoxamine. If snoring is also identified as a risk factor for stroke patients with sickle cell disease, a more aggressive approach to upper airway obstruction, including surgery, may be indicated.

TTP is a life-threatening, generalized microcirculatory condition of undetermined cause, characterized by fever, tln-ombocytopcmic purpura, microangiopathic hemolytic anemia, renal dysfunction, and fluctuating neurological signs. TTP is exceedingly rare, with a reported incidence of 1 person in 1 million annually. Most cases are idiopathic, but TTP also may be caused by drug exposure or it may be associated with pregnancy and the postpartum state, connective tissue disorders, infective endocarditis, or neoplasms. The pathological response is caused by widespread segmental hyaline microthrombi in the microvasculature. Neurological symptomatology is protean and fleeting. Patients frequently have headaches, visual disturbances, cranial nerve palsies, delirium, seizures, aphasia, paresis,

and coma. Treatment is with infusions of fresh frozen plasma, plasmapheresis, corticosteroids, and platelet anri-aggregants singly or in combination have been used also. If plasma exchange fails, splenectomy combined with corticosteroids and intravenous vincristine may be used.

INFARCTS OF UNDETERMINED CAUSE

Despite an extensive workup, in a considerable percentage of persons with ischemic stroke a causal factor cannot be determined. This percentage is possibly higher in patients younger than 45 years of age. Some of these ischemic strokes may result from asymptomatic episodes of paroxysmal atrial fibrillation; electrophysiological testing may be useful under those circumstances. The role of thrombophilia is also often under-recognized and warrants more detailed investigation in selected patients. The risk of recurrence of stroke of undetermined cause appears to be slightly less than that of ischemic strokes of other types.

ESSENTIAL INVESTIGATIONS FOR PATIENTS WrTH THREATENED STROKES

A basic workup, to be done in all patients with TIAs or evolving ischemic stroke, includes full blood cell count with differential white cell and platelet counts, erythrocyte sedimentation rate, prothrombin time (PT), aPTT, plasma glucose level, blood urea nitrogen, serum creatinine, lipid and cholesterol analyses, luetic serology, urinalysis, chest roentgenography, and ECG. Nonenhanced cranial CT is also being done in all patients because it may detect hemorrhagic or mass lesions that can present as a TIA or evolving stroke (Biller 1994). Approximately 10-40% of patients with TIAs have evidence of cerebral infarction on CT. Attention to early CT signs of ischemic stroke in the MCA territory such as loss of gray-white matter differentiation, sulcal effacement, effacement of the Sylvian fissure, and obscuration of the lentiform nucleus is critical. The horizontal part of the MCA is occasionally hyperdense in the noncontrast CT (dense MCA sign) before the infarction becomes visible (Figure *57A.* 18). This finding is indicative of a thrombotic or embolic occlusion of the MCA. The dense MCA sign often predicts a large cortical infarct, but is not always a poor prognostic indicator. MRI and intracranial and extracranial MRA improve the ability to localize an acute stroke and provide powerful noninvasive means to evaluate the pathological changes that occur following acute ischemic stroke (Figures 57A.19 and 57A.20). MRI is superior to CT in cerebral ischemia. The sensitivity of MRI in differentiating infarction or other lesions from normal tissue depends primarily on changes in tissue Tl and T2 relaxation times, which are related to tissue water content. Diffusion-weighted MRI allows early detection of acute cerebral ischemia,

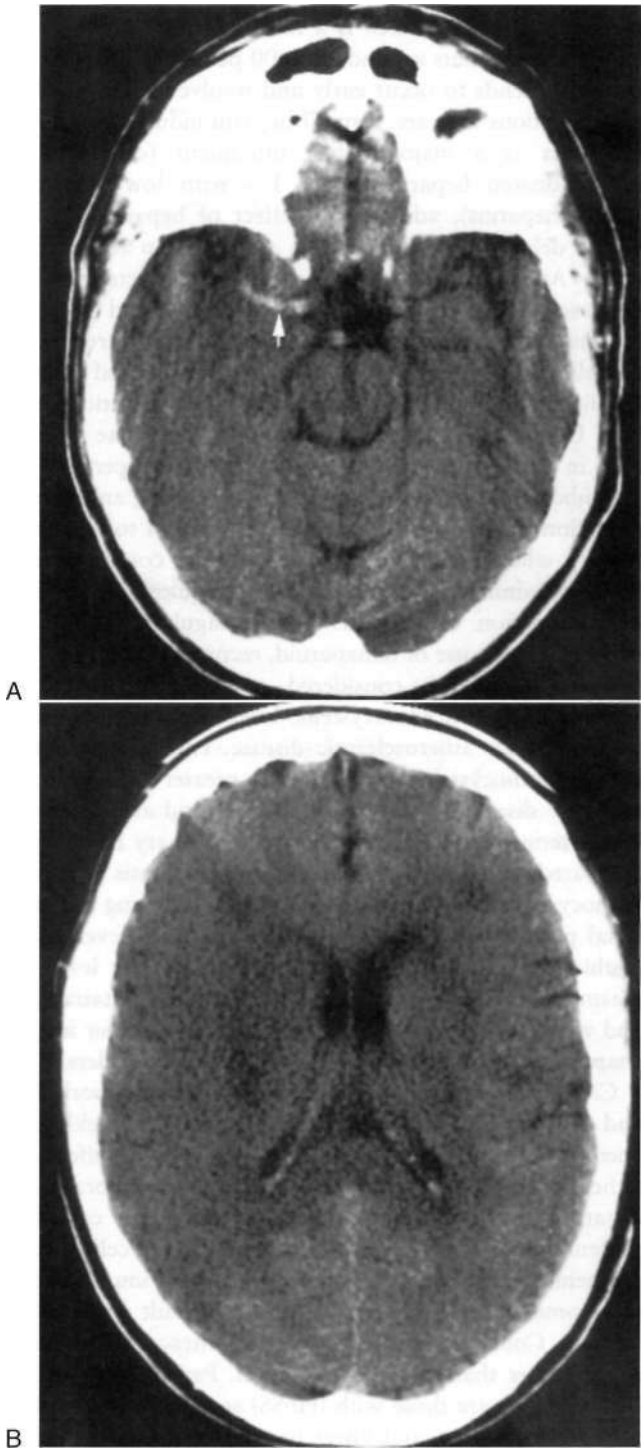

FIGURE 57A.1S Nonenhanced axial computed tomographic scans show (A) a dense right middle cerebral artery (MCA) sign *[arrow)* on the Ml segment and (B) a complete right MCA territory infarction. (Courtesy Vincent Mathews, Ml).)

while also differentiating acute from chronic stroke. Although the reliability of perfusion/diffusion MR imaging for brain tissue in the setting of thrombolytic therapy remains to be determined, studies are highly suggestive that

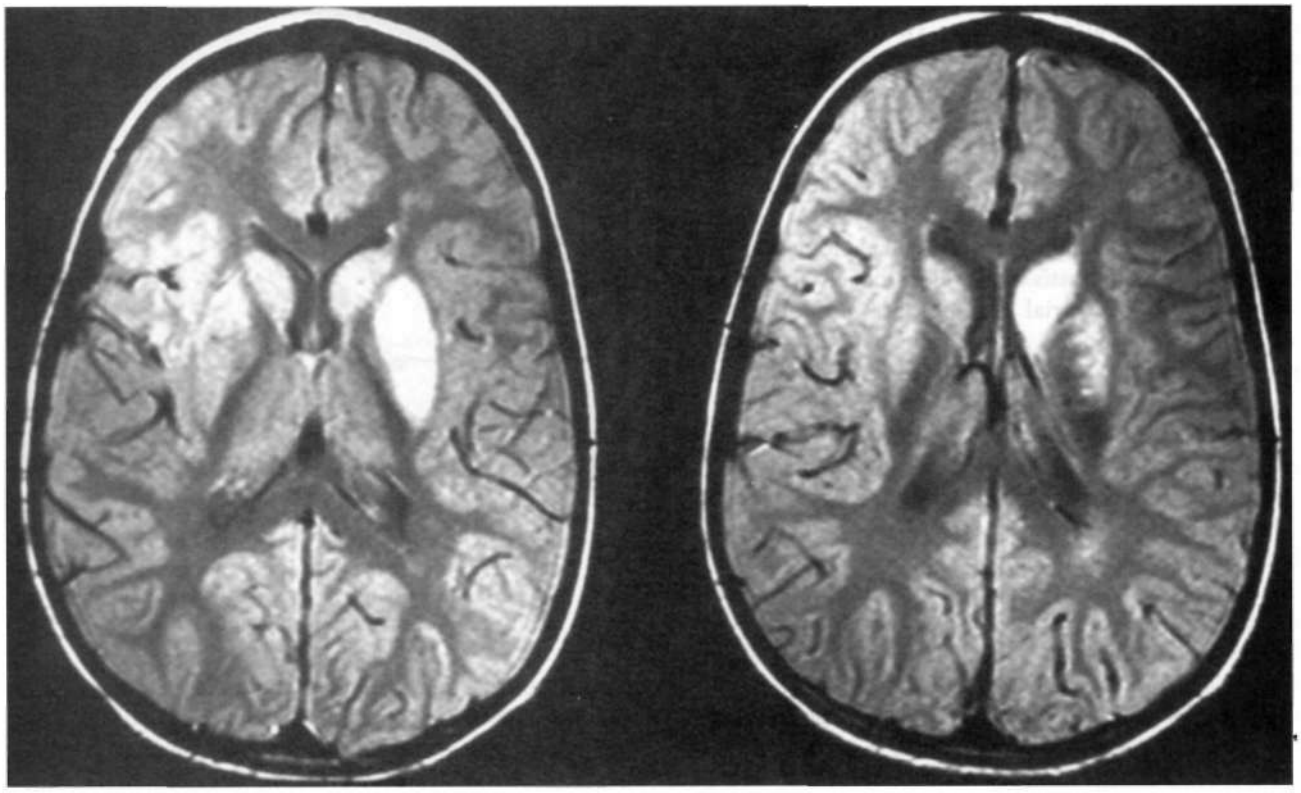

FIGURE 57A.19 Axial proton density magnetic resonance imaging demonstrates areas of increased signal intensity involving the head of the left caudate nucleus and the left lenticular nucleus consistent with infarction. The internal portion of the globus pallidus is spared.

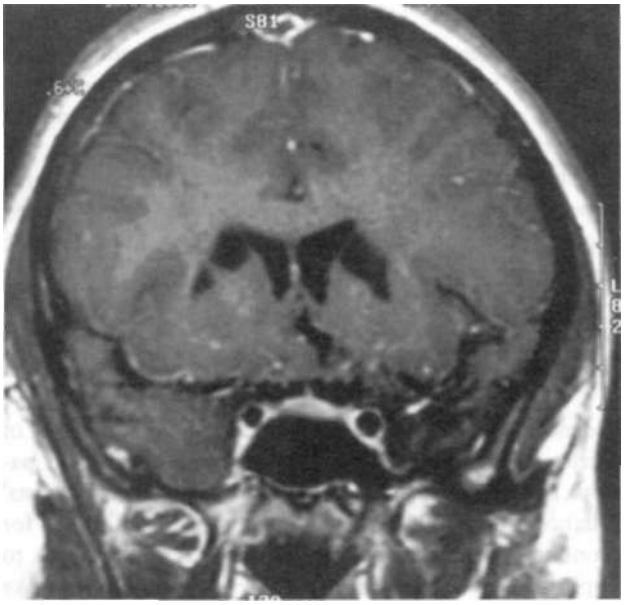

FIGURE 57A.20 Coronal Tl-weighted magnetic resonance imaging with contrast of a 14-year-old boy demonstrates bilateral recurrent artery of Heubner territory infarcts with involvement of the head of the caudate nucleus and anterior limb of the internal capsule. (Courtesy Vincent Mathews, MD.)

diffusion/per fusion mismatches are indicative of brain at risk {Mathews et al. 2001}.

The emphasis in screening is on noninvasive testing, including Doppler imaging, B-mode scanning, duplex scanning, and transcranial Doppler imaging (see Chapter 37D). In studies of duplex Doppler ultrasonography, sensitivity for detection of greater than 50% diameter stenosis ranged from *87-96%* and specificity ranged from 81-96%. Clinicians, however, need to be aware of the practical limitations of the ultrasound techniques. Severe stenosis or occlusion of an artery cannot he determined confidently by sonography. These methods also may fail to detect an intraluminal thrombus or a small atherosclerotic plaque, and some lesions arc anatomically beyond the reach of the scanner. Transcranial Doppler sonography assists in the evaluation of blood flow velocities and patency of the main intracranial arteries and in the identification of high-intensity transient microembolic signals.

Cardiac investigations to determine whether emboli have a cardiac source are advised in selected circumstances. Noninvasive cardiac imaging has expanded the ability to diagnose and assess a variety of cardiac conditions, many of which have been implicated as potential causes of TIA and evolving stroke. These imaging techniques differ widely in the information they provide about the morphology, function, and metabolic status of the heart. Most institutions currently use serial two-dimensional echocardiography to

detect left ventricular thrombus. The morphology of the thrombus predicts its embolic potential; left ventricular thrombi that have a protruding and mobile appearance on echocardiography are most likely to embolize. The sensitivity of two-dimensional echocardiography in detecting left ventricular thrombi varies from 77-92%; specificity varies from 84-94%, and predictive accuracy is 79%.

Patients with atrial fibrillation are likely to develop atrial thrombi caused by stasis of blood in the left atrium or left atrial appendage. Atria! thrombi are not always well visualized with routine studies. The left atrium, and in particular, the left atrial appendage, is often difficult to visualize with M-mode echocardiography. Left atrial thrombi can be detected successfully with two-dimensional echocardiography, but sensitivity and specificity of this technique are difficult to ascertain. Transesophageal echocardiography is used in selected individuals, particularly when the transthoracic images are technically inadequate for the evaluation of mitral and aortic prosthetic valves or vegetations; whenever there is a need for better visualization of the left atrial appendage or interatrial septum; or when a right-to-left shunt, left atrial spontaneous contrast, or aortic atherosclerosis is suspected. Continuous (Holter) ECG monitoring is seldom indicated, except when the history suggests paroxysmal disturbances of cardiac rhythm.

Most patients with TIAs or evolving stroke have cerebrovascular atherosclerosis. The gold standard for establishing the extent of vascular disease remains conventional angiography or intra-artenal digital subtraction angiography. Hither method can accurately determine the size and location of atherosclerotic lesions and aid in reliably assessing the vasculature, detecting tandem arterial lesions and the collateral circulation.

Angiography is not without complications, and its use is being challenged by the increasingly improving quality of MRA. A main disadvantage of MRA is that it overestimates the degree of stenosis related to turbulent flow. Although the risks associated with cerebral angiography have been gradually decreasing, the risk of any complication is approximately 1-5%, of which one half are minor groin hematomas. The risk of permanent neurological disability is approximately 0.2%, and the risk of death has been estimated to be 0.05%.

Cerebral angiography is indicated in several circumstances, particularly when the diagnosis remains uncertain, When a patient's workup fails to confirm the diagnosis, angiography is recommended to differentiate between atherosclerotic cerebrovascular occlusive disease and non-atherosclerotic vasculopathies, such as FMD, cervicocephalic arterial dissections, vasculitis, and moyamoya disease, as well as intracranial aneurysms or vascular malformations (Figure 57A.21).

Angiography is indicated when surgical treatment is planned. A full display of the extracranial and intracranial vasculature is important once potential surgical candidates

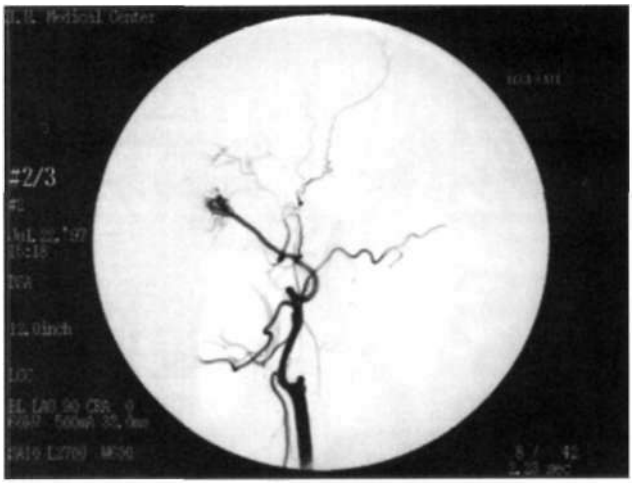

FIGURE S7A.21 A 43-year-old woman with a history of hypertension, hypercholesterolemia, and tobacco use had right-sided hemiparesis. Cerebral angiogram demonstrates an occlusion of the left internal carotid artery just past the bifurcation. There is partial reconstitution via ethmoid collaterals.

are identified. Angiography is indicated in patients with very early evolving stroke symptoms or frequent TIAs. Angiography is also indicated when distinctions affecting treatment are unclear; for example, angiography can assist in cases in which differentiation between carotid and vertebrobasilar TIA or evolving stroke is uncertain on clinical grounds only.

PREVENTING STROKE RECURRENCE: MEDICAL THERAPY

At present, general measures, including control of associated risk factors such as hypertension, hyperlipidemia, cigarette smoking, and the use of antithrombotic agents (platelet antiaggregants and anticoagulants), remain the mainstays of medical therapy for stroke prevention, A large proportion of strokes should be preventable by controlling blood pressure, treating atrial fibrillation, and stopping cigarette smoking,

Platelet Antiaggregants

Evidence from several clinical studies favors the use of platelet antiaggregants as the first line of therapy in patients at high risk for stroke (Antithrombotic Trialists' Collaboration 2002). These agents are indicated for secondary prevention of stroke. There is no evidence to support the use of aspirin in primary prevention of stroke among low-risk, middle-aged people. Although aspirin did not offer a long-term protective effect among 372 asymptomatic patients with carotid bruits and greater than 50% carotid stenosis on duplex ultrasonography, many physicians continue its use in patients with catotid

bruits or asymptomatic carotid stenosis under the assumption that it may be effective. Data regarding intraplaque hemorrhage caused by platelet antiaggregants are conflicting.

Aspirin, the oldest and most commonly used nonprescription drug in the world, is the standard medical therapy for prevention of stroke in patients with transient cerebral ischemia, as well as for reducing the risk of recurrent stroke and postoperative strokes after carotid end antrectomy (CEA). Aspirin is effective, inexpensive, and safe if started within 48 hours of acute ischemic stroke (International Stroke Trial Collaborative Group 1997; Chinese Acute Stroke Trial [CAST] 1997). Meta-analyses have shown that aspirin reduces the combined risk of stroke, myocardial infarction, and vascular death by approximately *25%.* The optimal dose of aspirin remains a source of controversy among neurologists. The range of acceptable management includes daily doses ranging between 50 and 1300 mg of aspirin. There is a suggestion that aspirin is also effective in doses as low as 30 mg daily. Results of primary prevention trials do not support the use of aspirin for primary stroke prevention {Patrono et al. 2001; Hebert ct al. 2000).

The mechanism of action of aspirin is the irreversible inhibition of platelet function by inactivation of cyclooxygenase. The atitiaggrcgant effect is seen within one hour after administration. Aspirin is also anti-inflammatory, antioxidant, and may increase fibrinolytic activity up to 4 hours after administration. The main side effect of aspirin is gastric discomfort. Gastrointestinal hemorrhage occurs in 1-5% of cases.

In the Aspirin in Carotid Endartcrcctomy (ACE) Trial, 2849 patients who were scheduled for CEA were randomly assigned to compare the benefits of low-dose aspirin {81-325 mg daily) with high-dose aspirin (650 or 1300 mg daily). The primary endpoints in the ACE Trial were stroke, myocardial infarction, or death. At 3 months after surgery, the risk of stroke, myocardial infarction, or death was 6.2% in the low-dose aspirin group, compared with 8.4% in the high-dose aspirin group. The difference was less apparent when only stroke or death was evaluated as the endpoint (Taylor et al. 1999).

Ticlopidine and ciopidogrel are structurally related thien©pyridines that have antiplatelet effects. Ticlopidine reduces the relative risk of death or nonfatal stroke by 12% in comparison with aspirin. Ticlopidine acts primarily by irreversibly inhibiting the adenosine 5^1 diphosphate pathways of the platelet membrane. Ticlopidine also reduces plasma fibrinogen levels and increases erythrocyte deformability. The recommended dosage of ticlopidine is 250 mg twice a day. Ticlopidine has more side effects than aspirin, including diarrhea, nausea, dyspepsia, and rash. These side effects tend to occur during the first few months of therapy. The dosage can be temporarily reduced to lessen the side effects for a few weeks, then brought back to 250 mg twice a day administered with food. A more worrisome adverse reaction is reversible neutropenia, which occurs in 2.4% of cases and is severe in 0.85%. This reaction can be encountered during the first 3 months of treatment, and for this reason a complete blood cell count must be obtained every 2 weeks during this period. The drug must be discontinued if the neutrophil count falls below 1200 per u.L. Rarely, thrombocytopenia and thrombotic TTP may occur. One case of TTP has been described for every 2000—4000 patients treated with ticlopidine,

The Ciopidogrel versus Aspirin in Patients at Risk of Ischemic Events study assessed the relative efficacy of ciopidogrel (75 mg daily) and aspirin (325 mg daily) in reducing the incidence of ischemic stroke, myocardial infarction, or symptomatic atherosclerotic peripheral arterial disease. The results of this study showed that ciopidogrel was modestly more effective (8.7% relative risk reduction) than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, and vascular death in patients with atherosclerotic disease. Ciopidogrel is a platelet adenosine diphosphate receptor antagonist. Overall, the tolerabiliry of ciopidogrel was excellent, with no increased incidence of neutropenia, and a lower incidence of gastrointestinal hemorrhage and peptic, gastric, or duodenal ulcers when compared with aspirin.

Bennett et al. (2000) studied the association of ciopidogrel with thrombotic TTP in 11 patients. In the majority of patients, ciopidogrel had been used for less than 14 days before the onset of thrombotic TTP. Several patients were taking concomitant medications, including statins in five patients, atenolol in three patients, and cyclosporine in one patient. How this serious, potentially fatal, complication will affect the clinical use of ciopidogrel remains to be seen (Bennett et al. 2000). The rate of diarrhea, rash, and pruritus is higher with ciopidogrel than with aspirin (Ciopidogrel versus Aspirin in Patients at Risk of Ischemic Events [CAPRIE] Steering Committee 1996).

Dipyridamole is a cyclic nucleotide phosphodiesterase inhibitor that increases the levels of the cyclic adenosine monophosphate. The European Stroke Prevention Study 2 (ESPS-2), a multicenter, randomized, double-blind, factorial, placebo-controlled trial, randomized patients with stroke or TIA within the previous 3 months to treatment with aspirin alone (25 mg twice a day), modified-rclease dipyridamole alone (200 mg twice a day), the two agents in combination, or placebo. The ESPS-2 investigators concluded that both low-dose aspirin and high-dose dipyridamole in a modified-release form alone were superior to placebo, and that the combination was significantly superior to each drug alone. The ESPS-2 investigators reported an additive effect of the modified-release dipyridamole when prescribed with aspirin with a remarkable 37% relative risk reduction in fatal and nonfatal stroke at 2 years. Benefit was limited to stroke prevention in patients with prior stroke or TIA. There was little effect on fatal stroke and myocardial infarction. The main side effects of dipyridamole are headaches and gastrointestinal distress. The use of low-dose aspirin did not reduce the risk of

bleeding (Diener et al. 1996). The European and Australian Stroke Prevention Reversible Ischaemia trial is currently randomizing patients with TIAs or minor ischemic stroke to oral anticoagulants, the combination of aspirin (30-325 mg) plus dipyridamole (400 mg daily) and aspirin alone (DeSchryer et al. 2000).

There is no persuasive evidence from current or past trials that patients benefit from the use of sulfinpyrazone or suloctidil. GP lib—Ilia antagonists, like abciximab (ReoPro), inhibit platelet aggregation and may have additional anticoagulant, fibrinolytic, and anti-inflammatory activities. In acute ischemic stroke, a dose escalation study of abciximab demonstrated the safety of this agent (The Abciximab in Ischemic Stroke Investigators 2000). A phase II trial of abciximab in acute ischemic stroke of less than 6 hours duration is currently under investigation. Long-chain polyunsaturated omega-3 fatty acids may be considered in patients unable to receive platelet anitaggregants or other antithrombotic agents.

Oral Anticoagulants

Oral anticoagulation with warfarin is indicated for primary and secondary prevention of stroke in patients with NVAF. Six randomized studies evaluated the primary and secondary prevention of stroke in patients with NVAF. Three of these studies also evaluated aspirin at daily doses of 75, 300, and 325 mg. These six studies demonstrated that the relative risk of stroke is reduced by 68% with the use of warfarin (Koefoed et al. 1997). Advancing age increases the risk of major hemorrhage in patients given warfarin for stroke prevention; patients older than 75 years are at greater risk of hemorrhagic complications. The relative risk reduction with aspirin therapy was 21% (18-44%) (The Atrial Fibrillation Investigators 1997). Therefore NVAF patients at high risk of stroke should be treated with dose-adjusted warfarin (INR 2.0-3.0); INR values less than 2.0 and greater than 4.0 should be avoided. Patients younger than 65 years without other risk factors can be given aspirin 325 mg per day. Low-intensity, fixed-dose warfarin plus aspirin is inadequate for stroke prevention in high-risk patients with NVAF. Anticoagulation is also recommended for patients with atrial fibrillation and hyperthyroidism. Patients who cannot tolerate pharmacological cardioversion may benefit from electrophysiological or surgical procedures. Anticoagulant rbiT.ipv has a protective effect against stroke following acute myocardial infarction. To prevent arterial embolism, immediate anticoagulation with heparin is initiated followed by oral anticoagulation for 6 months following an anterior wall myocardial infarction, or a myocardial infarction with apical wall motion abnormalities or left ventricular thrombus. Patients with mechanical prosthetic heart valves should receive lifelong therapy with oral anticoagulants to prolong the INR to a target of 3.5. Patients undergoing cardioversion for atrial fibrillation should receive anticoagulation for 3 weeks before and 4 weeks after cardioversion. Use of long-term anticoagulation in patients with left ventricular aneurysms and mural thrombi is not indicated because of the low risk of embolization. The WARSS randomized 2206 patients to warfarin (1103) or aspirin (1103) 325 mg daily. Warfarin (INR = 1.4 - 2.8) did not offer additional benefit in preventing recurrent ischemic stroke in patients with noncardioembolic infarcts (Mohr et al. 2001). Uncertainty persists about the use of warfarin in the management of patients with symptomatic stenosis of a major intracranial artery.

TREATMENT OF ACUTE ISCHEMIC STROKE

Modern therapy for acute ischemic stroke is currently being approached in four different ways. First, and most important, arc general measures aimed at prevention and treatment of complications. Second are those reperfusion strategies directed at arterial rccanalization. Third are cy to protective strategies aimed at cellular and metabolic targets. The fourth approach aims at the inhibition of the inflammatory processes associated with cerebral ischemia. Eventually, combined therapy will be used for acute ischemic stroke treatment.

Randomized studies of unfractionatcd heparin, low-molecular-weight heparins, or heparinoids for the treatment of acute ischemic stroke showed no proven benefits in the reduction of either stroke-related mortality, stroke-related morbidity, early stroke recurrence, or stroke prognosis. The time window from stroke onset varied from 12 hours to 48 hours in these studies.

Results are available from a randomized double-blind controlled trial of nadroparin-calcium (Fraxiparin), a low-molecular-weight heparin. In this trial, 312 patients were randomized within 48 hours of stroke to receive nadroparin-calcium 4100 antifactor Xa IU subcutaneously either once or twice daily, or placebo. Treatment was continued for 10 days. After 10 days, all patients received aspirin, 100 mg per day. There was no difference between the groups at 3 months. However, after 6 months, there was a significant dose-dependent reduction in the rate of poor outcome among the three study groups in favor of patients treated with nadroparin-calcium twice daily compared with those who received treatment once daily or placebo (Kay et al. 1995). A second randomized double-blind study involving 750 patients in 120 centers (FISS bis) failed to confirm these initial observations.

The International Stroke Trial studied approximately 20,000 patients who were randomized within 48 hours of ischemic stroke onset to receive fixed dose 10,000 or 25,000 units of unfractionated heparin subcutaneously daily (compared with no heparin). Treatment was continued for 14 days or until hospital discharge if shorter. There was no significant difference in the rate of death or

recurrent ischemic or hemorrhagic stroke at 2 weeks (11.7% with unfr actions ted heparin and 12.0% without unftactionated heparin). Patients receiving unfractionated heparin had significantly fewer recurrent ischemic strokes at 2 weeks, but this was negated by a similar increase in hemorrhagic strokes (International Stroke Trial Collaborative Group 1997). This trial used subcutaneous rather than intravenous unfractionated heparin.

Definite data regarding the safety and efficacy of intravenous heparin for acute ischemic stroke or cardioembolic stroke are lacking, but intravenous heparin is sometimes given to some patients with small cardioembolic infarcts associated with intracardiac thrombi, diagnosed by echocardiography, to prevent recurrence. In a small trial performed by the Cerebral Embolism Study Group, 45 patients with acute cardioembolic stroke who presented within 48 hours of symptom onset were randomized to receive either early or delayed treatment. The early treatment group received an intravenous heparin bolus of 5000-10,000 units followed by a maintenance infusion for at least 96 hours before the patient was switched to warfarin. Patients in the control group received no heparin and were given platelet antiaggregants or warfarin 10 days poststrokc. None of the 24 patients who received heparin experienced stroke recurrence or hemorrhage within the 96-hour treatment period. Of the 21 patients who received delayed anticoagulation, 2 experienced early recurrent embolic cerebral infarcts, 1 had a deep venous thrombosis, 2 had hemorrhagic transformations, and 3 died. The study suggested that heparin might be helpful, but the study was terminated prematurely. Heparin should not be used if a patient has a septic embolus or if the CT shows a hemorrhagic or large infarction. When intravenous heparin is given, most physicians do not currently use an intravenous bolus and aim for a target aPTT of 55-75 seconds, or 1.5-2.0 times control.

Intravenous unfractionated heparin appears to be ineffective in patients with acute partial stable stroke. A large randomized study evaluated unfractionated heparin in 225 patients with noncardioembolic stroke. Patients who had progressing deficit in the first hour of observation were excluded from the study because of the prevailing belief, at that time, that stroke in evolution should be anticoagulatcd. There was no significant difference in stroke progression or death at 7 days. The current status of antithrombotic therapy of cerebral ischemia is shown in Table 57A.8.

Although convincing statistical proof is still lacking, anecdotal evidence supports early initiation of intravenous unfractionated heparin to prevent stroke recurrence in several uncommon situations. These indications include cerebral infarction in the setting of inherited or acquired hypercoagulable states, intraluminal arterial thrombus, and extracranial cervicocephalic arterial dissections. Outcome of cerebral venous thrombosis is improved with heparin therapy with improvement beginning early in the course of therapy (Bousser et al. 1985; Kinhaupl et al. 1991).

Table S7A.8: Current status of antithrombotic therapy of cerebral ischemia

Therapy	*Coticius/orl*
Antithrombotic Agents	
Aspirin	Positive
Clopidogrel	Positive
Ticlopidine	Positive
Slow-release dipyridamole and aspirin	Positive
Sulfinpyrazone	Negative
Suloctidil	Negative
Glycoprotein Ilb/IIIa receptor antagonists	
Warfarin	Positive*
Warfarin	Negative*
Heparin	Negative
Fraxiparin	Negative
Ualteparin	Negative
Certoparin	Negative
i'in/.aparin	Negative
Dauaparoid	Negative

Tor primary and secondary prevention in patients with nonvalvular atrial fibrillation.

[1]No additional benefit {international normalized ratio = 1.4-2.8) in preventing recurrent ischemic stroke in patients with noncardioembolic infarcts.

Thrombolytic Therapy

If patients meet appropriate criteria, thrombolytic therapy may be administered. Thrombolytic therapy is able to recanalizc acute intracranial occlusions, but the question remains whether thrombolytic therapy can recanalizc occlusions of large extracranial or other large intracranial vessels (e.g., carotid terminus). A strong correlation has been shown between arterial recanalization and neurological improvement in acute cerebral ischemia.

In June *1996,* the Food and Drug Administration approved the use of intravenous tPA for ischemic stroke within 3 hours of symptom onset. As late as 2002, only the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA (recombinant tissue plasminogen activator) Stroke Study Group showed that treatment with intravenous tPA within 3 hours of onset of ischemic stroke improved clinical outcome (minimal or no disability on the clinical assessment scales) at 3 months (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995).

In the NINDS tPA study, treatment did not lessen death rates or account for an excess mortality. The frequency of symptomatic intracerebral hemorrhage was 10 times greater in patients given tPA (6.4% in the treatment group compared with 0.6% in the placebo group). Most hemorrhages occurred within 36 hours of treatment. Intravenous tPA should be administered only by physicians with experience in the diagnosis and management of stroke and who are familiar with the potential hemorrhagic complications associated with thrombolytic therapy.

Subsequent asscssmi-nt of the NINDS ll'A trial using *a* global statistic also demonstrated a sustained benefit of intravenous rt-PA at 6 and 12 months after the intervention in patients treated within 3 hours after onset of ischemic stroke symptoms (Kwiatkowski et al. 1999).

Inclusion criteria for administration of tPA in the NINDS tPA trial were acute ischemic stroke with a clearly defined time of onset (<3 hours), neurological deficit measurable on the NIH Stroke Scale, and CT scan without evidence of intracranial hemorrhage. Exclusion criteria for administration of tPA were rapidly improving or isolated minor neurological deficits, seizute at the onset of stroke, prior intracranial hemorrhage, symptoms suggestive of subarachnoid hemorrhage, blood glucose level less than 50 mg/dL (2.7 mmol/L) or greater than 400 mg/dL (22.2 mmol/L), gastrointestinal or genitourinary bleeding within the .3 weeks before stroke, recent myocardial infarction, current use of oral anticoagulants (PT >15 seconds or INR >1.7), a prolonged aPTT or use of heparin in the previous 48 hours, platelet count less than 100,000 pet j.iL, another stroke or serious head injury in the previous 3 months, major surgery within the previous 14 days, arterial puncture at a noncompressible site within the previous 7 days, or pretreatment SBP greater than 185 mm Hg or DBP greatet than 110 mm Hg.

The use of intravenous rt-PA for Alteplasc Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke trial was terminated early because of non statistical efficacy at interim analysis (Clatk et al. 1999). Favorable outcome at 3 months was 42.3% for those treated with tPA versus 38.9% for those treated with placebo. Mortality at 3 months was 11.0% for tPA-treated patients versus 6.9% fot those patients receiving placebo. Symptomatic intracranial hemorrhage occurred in 7.0% of tPA-treated patients. The Second European-Australasian Acute Stroke Study investigators recently assessed the safety and efficacy of intravenous alteplasc {0.9 mg/kg of body weight) administered within 6 hours of ischemic stroke onset and failed to confitm a statistical benefit for alteplasc; symptomatic intracranial hemorrhage occurred in 8.8% of altcplasc-treated paricnts and in 3.4% of placebo-treated patients (Hacke et al. 1998). An earlier study, using a dose of TPA of 1.1 mg/kg, also failed to demonstrate therapeutic efficacy among 620 patients treated within 6 hours from ischemic stroke onset (Hacke et a I. 1995). Favorable outcome at 3 months was 35.7% for those treated with tPA vctsus 24.3% for those receiving placebo. Mortality at 3 months was 22.4% for tPA-treated patients vetsus 15.8% for those treated with placebo (Clark et al. 1999; Hacke et al. 1998).

Thrombolysis-related intracranial hemorrhages are usually large volume lobar bleeds, often multiple, with blood/fluid levels; intraventricular and subarachnoid extension is not uncommon. The rate of symptomatic intracranial hemorthage in several phase IV series of tPA in the community setting was similar to that seen in the NINDS Trial (Chiu et al. 1998; Albers et al. 2000). Protocol violations have been associated with higher rates of symptomatic intracranial hemorrhages (Katzan et al. 2000; Buchan et al. 2000).

In spite of a consistently lower frequency of intracerebral hemorrhage with the use of SK rather than tPA, in patients with acute myocardial infarction, current data do not support the use of intravenous SK, 1.5 million units, in acute ischemic stroke.

Recombinant ptoutokinase (r-pro-UK) was tested in the Proutokinase in Acute Cerebral Thromboembolism II trial. In this multicenter, phase III, randomized, controlled trial, 180 patients with angiographically proven occlusion of the MCA (Ml or M2 MCA occlusion) wete given local intra-arterial pro-UK within 6 hours of symptom onset. Of the treated patients, 40% were functionally independent, compared with 25% of the placebo group patients 3 months after treatment {p — .04). The efficacy of treatment seemed to fall off after approximately *5* hours. Treated patients, however, also encountered a higher risk of intracranial hemorrhage with neurological detetioration within 24 hours of treatment (10% versus 2% in the control group; p = .06) (Furlan et al. 1999). The potential therapeutic benefit of intra-arterial thrombolysis and of the combination of thrombolytic and ncuroprotectant agents is being studied. Whether the combined use of intravenous and intra-arterial t-PA in acute ischemic stroke is safe or effective has yet to be determined. Mechanical thrombo-aspiration with newer catheter techniques is being actively explotcd.

The following seem to be predictors of favorable outcome with intravenous thrombolytic therapy for acute ischemic stroke: treatment within 90 minutes of symptom onset, normal baseline CT scan, milder baseline stroke severity, no history of diabetes mellitus, notmal prctrcatment blood glucose level, and normal pretreatment blood pressure. The following seem to portend a less favorable outcome and/or increased risk for cerebral hemorrhage; extended area of low attenuation with mass effect or low attenuation on one third or more of the MCA territory on pretreatment CT scan; advanced age; prior head injury; diabetes mellitus; marked elevation of the blood pressure before, during, and after treatment; hypertension requiring postrandomization antihypertensive treatment; severe pretreatment neurological deficits; and protocol violations according to the NINDS study protocol (Kocnnecke H-C 2002). Although no strict age cutoff exists for administering thrombolytics for ischemic stroke, physicians need to balance the increased risk of hemorrhage in patients aged 75 and older with potential benefit.

Defibtinogciiating Agents

Ancrod, an enzyme extracted from the venom of the Malayan pit viper, lowers fibrinogen and blood viscosity,

Table 57A.9: Current status of thrombolytic therapy of cerebral ischemia

Therapy	*Conclusion*
Thrombolytic therapy	
Streptokinase	Negative
tPA	Positive (within 3 hr of stroke onset; intravenous use)
r-prourokinase	Positive (within 6 hr of stroke onset; intra-arterial use)*
Hemorheological therapy	
Hcmodilution	Negative
Pentoxifylline	Negative
Ancrod	Positive (within 3 hr of stroke onset; intravenous use)*

"Currently, neither r-prourokinase nor Ancrod is available or approved by the U.S. Food and Drug Administration for use in acute ischemic stroke.
tPA = tissue plasminogen activator.

inhibits erythrocyte aggregation, indirectly stimulates thrombolysis, and possibly causes local vasodilatation. It also has a weak anticoagulant effect at high dosages.

Its potential as a treatment for ischemic stroke was shown to be beneficial when initiated within 3 hours of stroke onset in the multicentcr Stroke Treatment with Ancrod Trial (Sherman et al. 2000).

The positive results of this study were not replicated in a European Trial. Currently, neither r-pro-UK nor Ancrod are available or approved by the U.S. Food and Drug Administration for use in acute ischemic stroke. Hemorheologic therapy with isovolemic, hypovolemic, or hypervolemic hcmodilution has been ineffective (Table 57A.9).

Neuroprotective Agents

Despite widespread interest in neuroprotective drug therapy and positive results in experimental animals, no neuroprotective agent has been approved to date by the U.S. Food and Drug Administration for acute ischemic stroke.

Almost 120 controlled clinical trials involving more than 21,000 subjects, and investigating more than 50 neuroprotective interventions, have yielded negative results. New agents (spinal tap agents, oxygenated fluorocarbon nutrient emulsions, a-amino-3-hydroxy-5-merhyl-4-isoxazole propionic acid antagonists, and potassium channel openers) have been proposed.

Intracellular adhesion molecules (ICAMs) arc molecules to which leukocytes adhere and which facilitate migration of leukocytes through the endothelium. Some of these molecules are expressed in the cerebral vasculature during ischemia. Neutrophils in particular can contribute to tissue injury by obstructing capillaries and possibly by liberating cytotoxic products. Prevention of neutrophil adhesion by infusion of monoclonal antibodies directed at ICAMs improved neurological outcome in animal models of transient ischemia, but clinical trials yielded negative results. The sudden decrease in blood flow after ischemia provokes a cascade of events eventually leading to cell death. These events include the release of excitatory amino acids (F.AAs) with secondary opening of ion channels, which leads to an increase in intracellular calcium concentration, activation of enzymes, and generation of free radicals. Several agents have been shown in vitro and in animal studies to interfere at various steps of this cascade, thus potentially protecting the cells from ischemia.

Cerebroselectivc calcium-channel blockers such as nimodipine have been tested in acute stroke, but the benefits for patients with acute ischemic stroke remain unproven.

Endogenous EAA neurotransmitters play a major role in the pathogenesis of cerebral ischemia. In animals, EAA antagonists reduce the size of an infarct after occlusion of a maior artery. From preliminary studies, some of these compounds appear to be safe in humans, but their efficacy has not been demonstrated, and several clinical trials yielded negative tesults. Optimal protective regimens may necessitate blockading of both N-methyl-u-aspartate (NMDA) and non-NMDA receptors.

Free radicals produced during ischemia can degrade polyunsaturated lipids, which arc building blocks of cellular membranes, by means of lipid peroxidation. The central nervous system appears particularly susceptible to free radical injury. The 21 aminosteroid compounds inhibit lipid peroxidation by scavenging free radicals. Tirilazad is one such compound that decreases damage secondary to global ischemia in experimental animal models, but its clinical application in the treatment of patients with ischemic stroke has not been established.

Neurotrophins are factors known to promote cell growth in certain neuronal populations. Studies have shown that some of these factors given intraventricular^ to animals during ischemia reduce infarct size. The mechanism of action is still unknown but could be related to interaction with EAAs.

Calpains are cytosomal enzymes that are normally quiescent but become activated by increases in intracellular calcium concentration. These enzymes have many proteins as their targets, and thus their activation can cause considerable damage. In experimental models of stroke in animals, intra-arterial infusion of calpain inhibitors given after onset of ischemia significantly reduced infarct size compared with controls. The value of calpain inhibitors in humans has not been established.

The value of intravenous magnesium (which is an NMDA antagonist) is under investigation. Treatments with gangliosides, barbiturates, prostacyclin, opiate antagonists, aminophylline, ^-adrenergic receptor blockers, vasopressor therapy, naftidrofuryl, clometbiazole, inhibitors of leukocyte adhesion, fosphenytoin, lubeluzole, basic fibroblast growth factor, and citicolinc have been ineffective (Table 57A.10).

Tabic 57A.10: Current status of neuroprotection of cerebral ischemia: results of selected therapies

Ni modi pi tie	Negative
Tirilazad	Negative
Excitatory amino acid antagonists	Negative
Neurotrophins	Negative
Calpain inhibitors	Negative
Other agents	
Gangliosides	Negative
Barbiturates	Negative
Prostacyclin	Negative
Opiate antagonists	Negative
Aminophylline	Negative
/(-Adrenergic receptor blockers	Negative
Vasopressor therapy	Negative
Anti-ICA.M antibodies	Negative
Lubcluzole	Negative
Fosphcnytoin	Negative
Enlimomab	Negative
Basic fibroblast growth factor	Negative
Naftidrofuryl	Negative
Magnesium (intravenous)	Under investigation
Glyceryl trinitrate	Under investigation
Astrocyte inhibitors (ONO-2506)	Under investigation
Serotonin agonists (repinotan)	Under investigation

ICAM = intracellular adhesion molecule.

Surgical Therapy

Symptomatic Carotid Artery Stenosis

Stroke is often caused by atherosclerotic lesions of the carotid artery bifurcation; approximately 15% of ischemic strokes are caused by extracranial internal carotid artery stenosis. Carotid atherosclerosis develops in areas of low vessel-wall shear stress, most commonly the carotid bulb. In addition to the degree of carotid artery stenosis, plaque structure has been postulated as a critical factor in defining stroke risk. Ulcers found during CEA have been associated with cerebral artery microemboli detected by transcranial Doppler (Sitzer et al. 1995). Echoluccnt carotid artery plaques may also be associated with an increased risk of stroke. CEA, by removing the atherosclerotic plaque, restores cerebral blood flow and reduces the risk of cerebral ischemia, Results from three major prospective contemporary studies provide compelling evidence of the benefit of CEA performed by experienced surgeons in improving the chance of stroke-free survival in high-risk symptomatic patients. Timely surgical intervention in selected patients with hemispheric TTAs, amaurosis fugax, or completed nondisabling carotid terrirory strokes within the previous 6 months, and with 70-99% diameter-reducing carotid stenosis, can significantly reduce the risk of recurrent cerebral ischemia or death. Other factors that increase the risk of ipsilateral stroke are hemispheric (rather than retinal) site of ischemia, ulcerative nature of the stenosis, presence of contralateral carotid artery occlusion, and vascular risk factors. Benefits of CEA are similar for men and women. Advanced age by itself should not be considered a contraindication for properly selected patients with symptomatic high-grade carotid artery stenosis.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) confirmed the effectiveness of CEA for preventing stroke in 659 symptomatic patients with TIAs or minor strokes with high-grade (70-99%) diameter-reducing carotid artery stenosis. A uniform and strict technique measured carotid artery stenosis from an arteriogram. For different endpoints, absolute risk reductions in favor of surgery were 17.0% for ipsilateral stroke; 15.0% for all strokes; 16.5% for the combined outcomes of all strokes and death; 10.6% for major ipsilateral stroke; 9.4% for all major strokes; and 10.1% for major stroke and death. CEA was also beneficial and not more dangerous in symptomatic patients with atheromatous carotid artery pseudo-occlusion (carotid string sign). Longer term outcome was also better for surgically treated patients despite an occluded contralateral carotid artery. Morbidity and mortality of early CEA were similar to that of delayed surgery. The European Carotid Surgery Trial (ECST) also indicated the benefit from CEA compared with medical therapy in patients with mild carotid territory ischemic events associated with a diameter-reducing proximal internal carotid stenosis between 70% and 99%. The cumulative risk of any ipsilateral stroke at 3 years was 10.3% for the surgical group and 16.8% for the medical group. The ECST trial used different criteria than NASCET for measurement of carotid artery stenosis on angiography.

A diameter-reducing carotid artery stenosis of 70-99% by NASCET criteria is equivalent to a stenosis of 82-99% by ECST methodology; likewise a stenosis of 70-99% by ECST criteria is equivalent to a stenosis of 50-99% by NASCET criteria (Rothwell et al. 1994).

These methodological differences were more important with mild carotid artery stenosis. The Veterans Administration Trial of Carotid Endarterecromy in Symptomatic Carotid Stenosis was terminated early because of the positive results of NASCET and ECST. The Veterans Administration study also showed that CEA improved outcome in selected symptomatic patients with high-grade extracranial carotid artery stenosis. Among symptomatic patients with less than 30% stenosis, results from the ECST trial favor the use of medical therapy with platelet antiaggrcgants.

The utility of CEA for symptomatic patients with 30-69% carotid artery stenosis has recently been determined. Results were analyzed separately for those patients with 30-49% and those with 50-69% stenosis. Analysis from 1599 patients suggests that CEA is not indicated in most of these patients (European Carotid Surgery Tria lists' Collaborative Group 1996).

With a low surgical risk, CEA also provides modest benefit in symptomatic patients with carotid artery stenosis of 50-69% (Barnett et al. 1998), especially among men with hemispheric ischemia who are not diabetic. CEA

provides no benefit if the stenosis is less than 50% (50% by NASCET criteria is equal to 75% stenosis by ECST criteria). The benefit of CEA is highly dependent on surgical risk. Mortality and morbidity caused by CEA are significantly lower for asymptomatic patients. The acceptable level of surgical risk varies with the indication for carotid artery surgery. Maximal acceptable limits of surgical risks for combined perioperative neurological morbidity and mortality are 3% for asymptomatic patients, 5% for patients with TIAs, 7% for patients with stroke, and 10% for patients with recurrent stenosis.

Whether selected patients should undergo CEA on the basis of duplex scanning alone (without cerebral angiography), or duplex scanning complemented by MRA remains controversial. Carotid artery angioplasty and s ten ting may offer an alternative treatment to CEA, particularly in patients with internal carotid artery stenosis that is in an anatomically high location in the neck, carotid artery restenosis following prior CEA, radiation-induced carotid artery stenosis, and among certain high-risk patients with serious medical comorbidities. Carotid artery angioplasty and stenting should still be regarded as experimental. Results from randomized trials are needed before these techniques can be recommended. The Carotid Revascularization Endarterectomy versus Stent Trial is currently comparing the efficacy of CEA and carotid artery stenting among good-risk symptomatic patients with stenosis of more than 50%.

Asymptomatic Carotid Artery Stenosis

Asymptomatic carotid artery atherosclerosis is prevalent in the general population, especially in the elderly. Compared with symptomatic stenosis, asymptomatic carotid artery stenosis is associated with a relatively low risk of ipsilateral cerebral infarction. Data from four randomized clinical trials concerning the efficacy of CEA in patients with asymptomatic carotid artery stenosis are now available. The study by Clagett and colleagues was a fairly small study that followed only 57 asymptomatic patients with cervical bruits and abnormal ocular pneumoplcthysmography; only 29 were truly randomized to aspirin therapy or CEA. More unfavorable outcomes were noted in those patients undergoing CEA and the authors concluded that most asymptomatic patients with cervical bruits and abnormal ocular pneumopathy sinography are appropriately managed without CEA (Clagett et al. 1984), The Carotid Artery Surgery Asymptomatic Narrowing Operations versus Aspirin trial enrolled asymptomatic patients with 50-90% carotid artery stenosis. Patients with greater than 90% carotid artery stenosis were excluded on the basis of presumed surgical benefit. Overall, the trial showed no difference between the medically and surgically treated groups. The Mayo Asymptomatic Carotid Endarterectomy Trial (Mayo, 1992) was terminated early because of higher rates of myocardial infarction and TIAs in the surgical group. Patients in the surgical group did not receive aspirin, probably explaining those results. The Veterans Affairs Asymptomatic Carotid Endarterectomy Trial evaluated 444 asymptomatic patients with angiographicslly proven carotid stenosis of 50-99%. The study showed n relative risk reduction in the incidence of ipsilateral neurological events in favor of surgery when both TIA and stroke were included as composite end points. However, when ipsilateral stroke was considered alone, only a nonsignificant trend favoring surgery was noted. For the combined outcome of stroke and death, no significant differences were found between the two treatment arms (Hobson et al. 1993). The fifth randomized clinical trial, the Asymptomatic Carotid Atherosclerosis Study (ACAS), found that CEA combined with aspirin and risk-factor reduction is superior to aspirin and risk-factor reduction alone in preventing ipsilateral stroke in patients younger than 80 years who had greater than 60% asymptomatic carotid artery stenosis. The ACAS angiographieal methods were similar to NASCET. All patients randomized to the surgical arm of the study had a catheter angiogram but it was not mandatory in the medically treated patients. The aggregate morbidity and mortality of the ACAS participating surgeons were extremely low. Based on a 5-year projection, ACAS showed that CEA reduced the absolute risk of stroke by *5.9%* (which corresponds to an absolute risk reduction of only 1% per year), and the relative risk of stroke and death by 53%. The surgical benefit incorporated a perioperative stroke and death rate of 2.3% including a permanent artcriographical complication rate of 1.2%. It is also important to note that all patients with a *60—99%* stenosis were analyzed together in this study.

In spite of these results, controversy surrounds the selection of asymptomatic patients for CEA. Based on the low risk of stroke for all deciles until 80-89% carotid artery stenosis demonstrated by the European Carotid Artery Surgery Trialists (The European Carotid Surgery Trialists[1] Collaborative Group 1995), some experts recommend surgery only when the degree of stenosis is greater than 80%, provided that the operation is performed by an experienced surgeon with a complication rate (combined artcriographical and surgical) of 3% or less.

The value of impaired cerebral vasomotor reactivity using intravenous administration of acetazolamide as a predictor of stroke risk in patients with asymptomatic carotid artery stenosis is controversial. The necessity for widespread screening of patients with asymptomatic carotid artery stenosis is not supported by available data. Although concomitant CEA and coronary artery bypass grafting can be achieved with acceptably low operative risk, the best management for symptomatic carotid stenosis patients with coexisting severe carotid and coronary artery disease is still unknown. The risk seems to be low for asymptomatic carotid stenosis patients, and the available data do not justify preoperative prophylactic CEA in patients requiring coronary angioplasty.

GENERAL MANAGEMENT OF ACUTE ISCHEMIC STROKE

Rapid diagnosis of stroke and initiation of treatment are important to maximize recovery, prevent recurrence of stroke, and prevent complications. Patients with an acute stroke should be admitted to the hospital for emergency evaluation and treatment, preferably in a stroke unit or intensive care unit where close medical and nursing observation is available. Treatment of unselected acute stroke patients in specialized stroke units correlated with a lower mortality, reduced length of hospital stay, reduced frequency of discharge to a nursing home, and potentially reduced cost (see Chapter 54). Development of a stroke team is advantageous to expedite emergency care. Emergency care involves attention to the protect ion ol the airway to avoid obstruction, hypoventilation, and aspiration pneumonia. Pulse oximetry or arterial blood gases may be indicated. Supplemental oxygen and ventilatory assistance should be added if needed. Mild hypothermia protects the brain from ischemic injury; mild hyperthermia worsens ischemic outcome. Prevention of pulmonary complications is necessary in (lie bedridden patient or in the patient with impaired oropharyngeal function. The mortality from pneumonia is as high as 15-25% in stroke patients. Aspiration was documented by videofluoroscopical modified barium swallow examination in more than one third of patients with brainstem strokes, in one fourth with bilateral hemispheric, and in one tenth of patients with unilateral hemispheric strokes. It is important to place a temporary enteral feeding tube if there is evidence of oropharyngeal dysfunction to minimize the risk of aspiration. Patients with oropharyngeal dysfunction, even if it appears to be mild, should receive nothing by mouth until evaluation by an experienced speech pathologist and until appropriate swallowing studies arc completed. Good pulmonary toilet is needed.

The next step is assessment of the circulation. This involves evaluation of cardiac function and blood pressure. Because of the high frequency of cardiac dysfunction associated with stroke, cardiac monitoring is recommended for the first 24—48 hours after stroke. An immediate ECG should be obtained. Concomitant cerebral and myocardial ischemia can occur in approximately 3% of cases. Ischemic stroke can be complicated by a variety of cardiac arrhythmias. If ischemic F.CG changes occur, serial creatine kinase and lactate dehydrogenase isoenzymes are indicated. In patients with stroke, the blood pressure should be monitored frequently or even continuously for the first 48-72 hours. It is not unusual for the blood pressure to be transiently elevated after a stroke. One study showed that pharmacological elevation of SBP to a mean of 156 mm Hg appeared to be safe and may improve neurological symptoms in some patients with thrombotic stroke (Rordorf et al. 1997). Within a few days, the blood pressure may return to prestroke levels. Whether transient elevations should be treated is controversial, it is important not to overtreat the blood pressure and cause hypotension. The most important objective is to maintain adequate cerebral blood flow in the presence of impaired autoregulation. If urgent lowering of the blood pressure is indicated, intravenous labetalol can be given (e.g., 10 mg over 1-2 minutes, repeated or doubled every 10-20 minutes until the desired response has been achieved or a maximum dosage of 300 mg has been administered). Contraindications to the use of labetalol include congestive heart failure, asthma, second- or third-degree heart block, or cocaine use. The use of immediate release preparations of nifedipine should be strongly discouraged, because they lower the blood pressure in an unpredictable and sometimes dramatic fashion, and have caused major cerehral infarcts.

Immediately after the patient's arrival in the emergency room, blood should be sent for appropriate studies including a complete blood cell count, PT (INR), aPTT, and a general chemistry screen. A focused neurological examination should be performed to assess neurological stability and to determine the extent of infarction. General signs that point toward a large infarction are forced eye deviation, hemiplegia, and altered consciousness. A National Institutes of Health Stroke Scale value of greater than 15 is another general indicator of a large infarction. Once stability of the airway, breathing, and circulation is determined and a focused neurological examination is performed to assess neurological stability, the patient should be sent immediately for an emergent cranial CT scan without contrast. This can point the way to treat the patient with tPA, or to avoid anticoagulants in patients with intracranial bleeds.

Attention should be directed not only to the treatment of the stroke, but also to the prevention of complications. A variety of neurological and medical complications can arise after a stroke. During the first week after an acute cerebral infarction, the most common cause of deterioration is development of brain edema. Brain edema begins to develop within the first several hours after an ischemic event. The edema reaches its peak 72-120 hours after the stroke. Ischemic edema is initially cytotoxic and later vasogenic. Cytotoxic edema involves predominantly the gray matter, whereas vasogenic edema involves predominantly the white matter. Those at the greatest risk for development of edema are younger patients and those with large infarctions, often caused by large artery occlusions. There is no specific pharmacological agent that has been proven effective against ischemic cerebral edema. Traditional treatment of increased intracranial pressure associated with acute ischemic stroke is shown in Table 57A.11. For cerebellar strokes with edema and herniation, posterior fossa decompression may be life saving. Ventriculostomy may also be performed, but has the risk of upward herniation of the cerebellum and brainstem.

In the second through the fourth weeks, pneumonia is the most common cause of non-neurological death. Many cases

Table 57A.11: Medical management guidelines for elevated intracranial pressure in patients with acute ischemic stroke

Correction of factors exacerbating increased intracranial pressure
Hyperearbia
Hypoxia
Hyperthermia
Acidosis
Hypotension
Hypovolemia
Positional
Avoidance of head and neck positions compressing jugular veins
Avoidance of flat supine position; elevation of head of the bed 15-30 degrees
Medical therapy
Endotracheal intubation and mechanical ventilation, if Glasgow Coma Scale <8
Hyperventilation to a Pco_2 of 30-35 mm Hg (if herniating)
Administration of mannitol (20% solution), 1 g/kg over 30-60 min q4-6 hr, depending on clinical status, serum osmolality, volume status, and intracranial pressure measurements with goal of dehydrating the brain and not the patient; maintenance of serum osmolality around 300-310 mOsm/L
Fluid restriction
Maintenance of euvolemia with isotonic solutions using notmal saline; avoidance of glucose-containing solutions because hyperglycemia is associated with worse prognosis for stroke; replacement of urinary losses with normal saline in patients receiving mannitol

of pneumonia are caused by aspiration of food, saliva or regurgitated gastric secretions, inert substances, or bacterial pathogens in saliva. Rasal ganglia infarcts seem to predispose patients to pneumonia because of frequent aspiration during sleep. Other potential complications include seizures, cardiac arrhythmias, myocardial infarction, deep venous thrombosis, electrolyte disturbances, decubitus ulcers, and urosepsis. Cardiac dysfunction can manifest as ECG changes, arrhythmias, or myocardial ischemia.

Frequent neurological checks are essential for the early recognition of neurological changes associated with herniation, recurrent or progressive stroke, or complications such as seizures. Seizures occur in a small percentage (<5%) of patients after an ischemic stroke. Anticonvulsant medications should be initiated if a seizure occurs.

Lower extremity deep venous thrombosis in the hemiparetic limb is common if prophylaxis is not initiated. The risk of venous thromboembolism persists into the post-stroke period {Brandstater et al. 1992). If there are no contraindications, low-dose subcutaneous unfractionated heparin at a dosage of 5000 units twice a day or low-molecular weight heparin is used. If heparin is contraindicated, intermittent pneumatic compression of the lower extremities is recommended. Prophylactic doses of heparin can safely be given to patients receiving aspirin.

The patient's nutritional status and fluid requirements should be assessed. Patients with a large ischemic stroke may need a fluid restriction of two-thirds maintenance during the first few days. Swallowing function should be assessed before intake of fluid or food is initiated. Patients who have significant oropharyngeal dysfunction require parenteral or tube feeding.

Although urinary incontinence is not uncommon in **the** acute phase of stroke, indwelling catheters should be placed only if absolutely necessary and should be removed at the earliest possible time to avoid urosepsis. The chronic use of an indwelling catheter should be limited to patients with incontinence or urinary retention that is refractory to other treatments. In the presence of an indwelling catheter, treatment of asymptomatic bactcriuria is usually not indicated. However, for significant clinical infections with pyuria and fever, treatment is recommended.

Approximately 15% of patients develop pressure sores after a stroke. Steps to avoid this complication include frequent inspection of the skin, skin cleansing, frequent turning, use of special mattresses and protective dressings, maintaining adequate nutritional status, and trying to improve the patient's mobility early on.

One of the most common causes of injury to the patient with a stroke is falling. Assessments of the risk for falling should be made at regular intervals during the acute hospitalization and also during the chronic rehabilitation phase. Reduction of postprandial SBP has been associated with a higher incidence of falls and syncope. Measures should be instituted to minimize the risk of falls,

Shoulder subluxation can occur in hemiplcgic patients. Chronic sequelae can be minimized if therapy is initiated before severe restriction of movement develops.

Rehabilitation after stroke begins as soon as the diagnosis of stroke is established and as soon as any life-threatening neurological or medical complications have been stabilized (see Chapter 54). Patients are screened to evaluate whether they are candidates for rehabilitation. The criteria used to make this decision, including the stroke survivor's clinical and neurological status and social and environmental factors, are complex (Post-Stroke Rehabilitation Cuideline Panel 1995). The available evidence on the effectiveness of rehabilitation suggests that rehabilitation is beneficial to some patients, but the superiority of one type or the characteristics of patients most likely to benefit are not clear.

Depressive symptoms are common after stroke, occurring in more than 25% of patients. Stroke patients should be questioned and screened for depression. Depression is more common following left hemispheric infarcts, especially in the frontal lobe, possibly caused by disruption of catecholamine pathways. Treatment with antidepressants is often successful in ameliorating symptoms.

CEREBRAL VENOUS THROMBOSIS

Intracranial sinovenous occlusive disease is an infrequent condition with a variety of causes. The increasing

recognition of this condition is probably because of an enhanced clinical awareness and the use of MRI. Intracranial venous thrombosis can be aseptic or septic. Septic intracranial venous thrombosis (resulting from skull osteomyelitis, suppurative infections of the inner ear, and erysipelas) is relatively infrequent in modern times, and **most** often involves the cavernous sinus. Cavernous sinus thrombosis is typically a complication of a facial or orbital infection and often presents with proptosis, chemosis, and painful ophthalmoplegia. Septic lateral sinus thrombosis is an infrequent complication of otitis media or mastoiditis and often presents with headaches, fever, otalgia, vertigo, papilledema, and abducens nerve palsy (Figure 57A.22).

Aseptic intracranial venous thrombosis is divided into dural venous sinus thrombosis, deep venous thrombosis, and superficial or cortical vein thrombosis. The superior sagittal sinus is most frequently involved (Figure 57A.23). Causal factors are protean and the onset often insidious. The most common causa! factors are listed in Table 57A.12. However, in approximately 20% of cases, no cause is found (Bousser ct al. *1997).* Although rare, cerebral venous thrombosis is a well-recognized disorder in children,

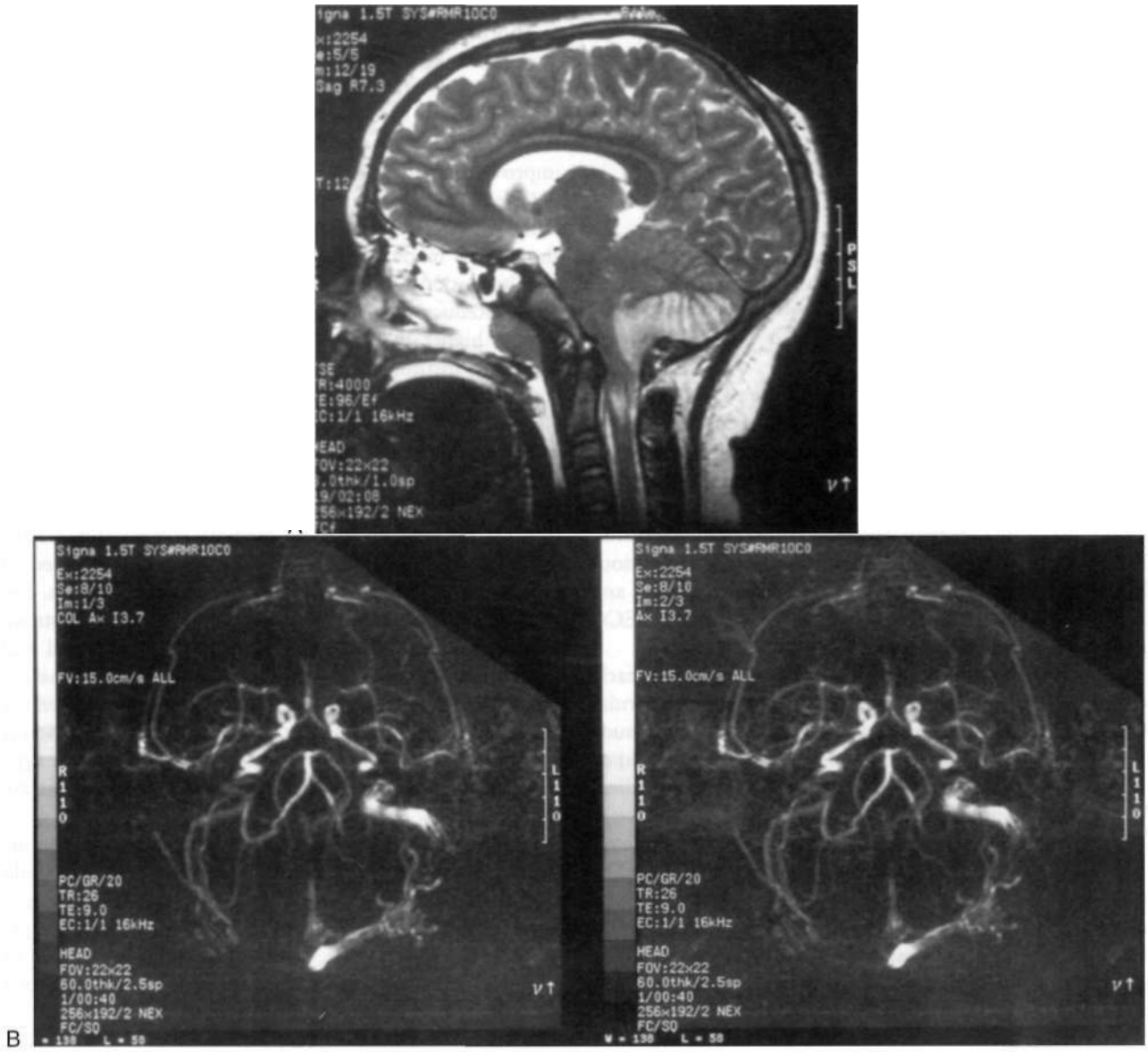

FIGURE 57A.22 A 10-year-old girl with otomastoiditis was evaluated hecause of unresponsiveness. Magnetic resonance imaging shows areas of increased signal in the right cerebellum greater than the left cerebellum, consistent with infarctions. The cerebellar tonsils are herniated. (A) Associated edema occurs in the superior cervical cord and inferior medulla. Phase contrast magnetic tesonance angiographical images demonstrate lack of flow in the straight sinus and the right transverse sinus. Only a small amount of signal in the region of the right sigmoid and internal jugular vein is seen. (B) Some arterial flow is represented in the examination.

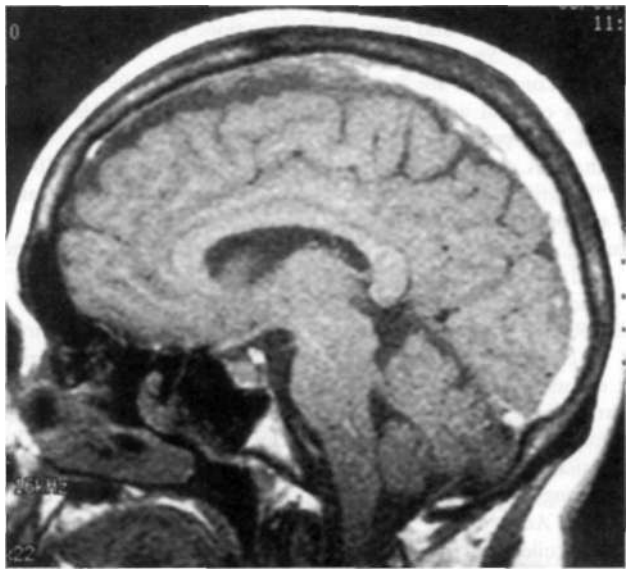

FIGURE 57A.23 Unenhanced sagittal Tl-weighted magnetic resonance imaging shows an area of increased signal and enlargement of the superior sagittal sinus throughout most of its course consistent with superior sagittal sinus thrombosis. It also involves the region of the torcula.

with approximately half of the cases occurring in neonates and young infants (deVeber et al. 1998).

Intracranial venous thrombosis may occur at any time from infancy to old age, but most reported modern cases have been in adult women in association with the pucrperium. Onset of symptoms may be acute, subacute, or chronic. Cerebral venous infarction is the most serious consequence of cerebral venous thrombosis. Intracranial venous thrombosis should be considered a potential cause for pseudotumor cerebri or unexplained hemorrhagic infarctions. Venous infarctions are often multifocal and bilateral, affecting both the gray matter and the subcortical white matter. Evidence of cerebral edema is unusual. Cerebral venous thrombosis may present without focal signs. Chief complaints arc headaches, vomiting, transient visual obscurations, focal or generalized seizures, lethargy, or coma. Papilledema is common. There may be alternating focal deficits, hemiparesis or paraparesis, or other focal neurological deficits according to the location of the venous structure involved. Salient radiological features are the presence of low-density areas of infarction, hemorrhages, and small ventricles. There may be visualization of thrombus within the sinus on postcontrast images (empty-delta sign) or direct visualization of the clot. The availability of MR venography makes it possible to diagnose early and atypical cases. MR venography is a reliable diagnostic tool and has replaced angiography for the diagnosis of cerebral venous thrombosis. Patients with intracranial venous occlusive disease should be screened for thrombophilia.

Accepted therapeutic measures include reduction of increased intracranial pressure, prophylactic anticonvulsants, and antibiotics in cases involving a septic causal factor. Most recent reviews on the subject recommend heparin anticoagulation followed by warfarin for the treatment of intracranial venous thrombosis. The efficacy of heparin has been shown, even in patients who have evidence of some intracranial hemorrhage by neuroimaging studies (Einhaupl ct al. 1991; Ameri et al. 1992).

Table 57A.12: Causes of intracranial sinovenous occlusive disease

Facial/orbital/paranasal sinuses/middle ear infections
Ptegnaney and pucrperium
Carcinoma
Dehydration
Matasmus
Sqisi>
Acute lymphoblastic leukemia
[.-Asparaginase therapy
Androgen therapy
Cisplatin and etoposide therapy
£-Aminocaproic acid therapy
Intravenous cadteters, cardiac pacemakers
Polyarteritis nodosa
Systemic lupus erythematosus
Wegener's granulomatosis
Behcet's disease
Kohlmcicr-Degos' disease (malignant atrophic papulosis)
Osteopetrosis
Inflammatory bowel disease
Sarcoidosis
Osteoporosis
Congestive heart failure
Nephrotic syndrome
Rudd-Chiari syndrome
Chronic lung disease
Trichinosis
Diabetes mellitus
Cerebral arterial occlusions
Homocystinuria
Head injury
Paroxysmal nocturnal hemoglobinuria
Sickle cell disease and trait
Polycythemia vera
Essential thrombocythemia
Iron deficiency anemia
Hypoplasminogcnemia
Afibrinogenemia
I iryoriliriuoiii'iifiiiia
Antiphospholipid antibody syndrome
Disseminated intravascular coagulation
Antithrombin III deficiency
Protein S deficiency
Protein C deficiency
Combined deficiencies (protein C, protein S, and antithrombin Iil)
Activated protein C resistance
Factor V Leiden mutation
Prothrombin G200210 mutation
Elevated Factor VIII plasma levels
Heparin-inducedthrombocytopenia
Arteriovenous malformations
Sturge-Weber syndrome
Idiopathic

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Chapter 57
Vascular Diseases of the Nervous System

B. INTRACEREBRAL HEMORRHAGE

Carlos S. Kase

Intracerebral hemorrhage (ICH) accounts for approximately 10% of strokes. Its clinical importance derives from its frequency and high mortality. Although the latter is strongly dependent on hematoma size and, to a lesser extent, location, the overall mortality for this stroke subtype varies between 25% and 60%. There has been a general decline since the 1980s in the incidence of stroke, including ICH, as a result of improved detection and treatment of hypertension. However, ICH continues to be a major public **health** problem, especially in populations at high risk, such as young and middle-aged blacks and Hispanics, in whom this stroke subtype occurs significantly more frequently than in whites, and the medically indigent who lack hypertension treatment. A growing body of evidence suggests that genetic factors, such as the possession of the 2 and 4 alleles of the apolipoprotein I., play an important role in the occurrence of certain forms of ICH, such as lobar hemorrhages (O'Donnell et al. 2000), Finally, the management of **ICH** is controversial because the value of surgical or nonsurgical treatment of the various types of ICH has not been defined by properly designed prospective clinical trials.

MECHANISMS OF INTRACEREBRAL HEMORRHAGE

Hypertension

The main cause of ICH is hypertension. The primary role of hypertension in ICH is supported by a high frequency (72-81%) of history of hypertension, significantly higher admission blood pressure measurements as compared with patients with other stroke subtypes, and a high frequency of left ventricular hypertrophy.

Broderick et al. *{\993),* studying 188 patients with primary ICH (i.e., with exclusion of patients with hemorrhage associated with ruptured arteriovenous malformations |AVMsj, tumor, anticoagulant and thrombolytic therapy, and cocaine ingestion), determined the cause to be hypertension in 72% of patients. Further support for the importance of hypertension in the pathogenesis of ICH is the steady increase in ICH incidence with advancing age, which is associated also with an increase in the prevalence of hypertension. The role of hypertension as a cause of **ICH** is most relevant for the nonlobar locations, which may be due to hypertension in approximately 50% of the cases (Woo et al. 2002). In both hypertensive and nonhypertcnsive patients, the circadian rhythm of ICH onset, with peaks at 8 AM and 8 PM (Casetta et al. 2002), coincides with the physiological daily peaks of blood pressure, pointing to the importance of blood pressure rises in the pathogenesis of ICH.

The actual vascular lesion produced by chronic hypertension that leads to arterial rupture and ICH is probably lipohyalinosis of small intraparenchymal arteries (Caplan 1994a). The role of microaneurysms of Charcot and Bouchard is uncertain, although their anatomical location at sites preferentially affected by ICH supports their causal importance. The nonhypertensivc causes of ICH are listed in Table 57B.1.

Table 57B.1: Non hypertensive causes of intracerebral hemorrhage

Vascular malformations (saccular or mycotic aneurysms, arteriovenous malformations, cavernous angiomas)
Intracranial tumors
Bleeding disorders, anticoagulant and fibrinolytic treatment
Cerebral amyloid angiopathy
Granulomatous angiitis of the central nervous system and other Viisculitides, Midi as polyarteritis nodosa
Sympathomimetic agents (including amphetamine and cocaine)
Hemorrhagic infarction
Trauma

Vascular Malformations

Because a detailed discussion of intracranial aneurysms and AVMs (see Chapters 57C and 57D) is provided elsewhere, we limit the analysis here to the role of small vascular malformations in the pathogenesis of ICH. These lesions are often documented either by magnetic resonance imaging (MRI), by pathological examination of specimens obtained at the time of surgical drainage of ICHs or at autopsy. However, cerebtal angiography also plays an important role in the diagnosis of these lesions. In a group of 38 young ICH paricnts (mean age, 46 years) subjected to angiography, Halpin et al. *(1994)* documented AVMs in 23 patients and aneurysms in *9* (a total of 32 of 38, or 84%). The ICH in these 38 patients had computed tomographic (CT) characteristics suggestive of an underlying structural lesion (associated subarachnoid or intraventricular bleeding, calcification, prominent vascular structures, atypical ICH location). However, in a group of 42 patients lacking these CT features, angiography still documented vascular abnormalities in 10 (AVMs in 8, aneurysm in 2).

ICHs caused by small AVMs or cavernous angiomas arc frequently located in the subcortical white mattet of the cerebral hemispheres. The clinical presentation of the ICH in this setting has a few distinctive characteristics. The hematoma is generally smaller and symptoms develop more slowly compared with hypertensive ICH. The presence of associated subarachnoid hemorrhage on CT scan suggests an aneurysm or AVM as the cause in a case of lobar ICH. In addition, those ICHs associated with small vascular malformations generally tend to occur in younger patients when compated with those with hypertensive ICH, and have a female preponderance.

Cavernous angiomas are being increasingly recognized as a cause of ICH in the subcortical portions of the cerebral hemispheres and in the pons, as a result of the high diagnostic yield of MRI. This technique demonstrates a characteristic pattern on T2- weigh ted images, with a central nidus of irregular bright signal intensity mixed with mottled hypointensity. surrounded by a peripheral hypointense ting corresponding to hemosidctin deposits

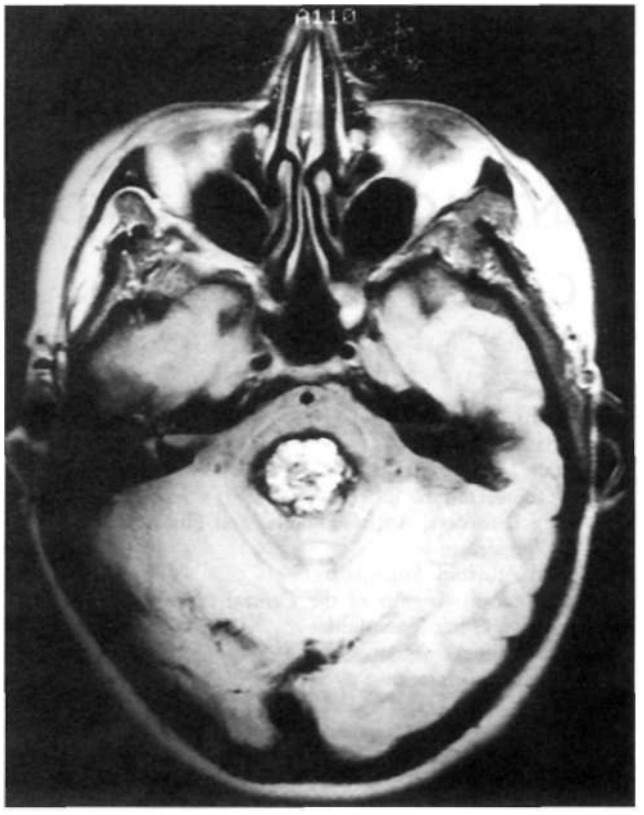


FIGURE .S7B.1 Magnetic resonance imaging (proton density) of large cavernous angioma of the midpons in axial view, showing mixed signal central nidus with peripheral hemosiderin ring.

(Figure 57B. 1), reflecting previous episodes of bleeding, These lesions are predominantly supratentorial, favoring the temporal, frontal, and parietal lobes, whereas the less frequent infratentorial locations favor the pons. They ate generally single lesions, but multiplicity is not uncommon, especially in patients with familial cavernous angiomas. The latter is common among individuals of Mexican-American descent, in whom cavernous angiomas are inherited in an autosomal dominant pattern, linked to a mutation in chromosome 7q. Their clinical presentation is with cithct seizures (27-70%), ICH (10-30%), or progressive neurological deficits *(35%).* Seizures are the most common ptesenting feature of supratentorial cavernous angiomas; ICH occurs in both the supratentorial and infratentorial varieties; and progressive neurological deficits arc a more common presentation of postetiot fossa (especially pontine) malformations. A progressive course, caused by recurrent small hemorrhages within and around the malformation, can evolve over protracted periods, at times suggesting a diagnosis of multiple sclerosis or a slowly growing brainstem glioma.

A clinical profile thus can be suggested for cases of ICH caused by small vascular malformations. These occur in generally young, predominantly female patients, who present with a syndrome of lobar ICH in which

CT scan can document a superficial lobar hematoma with adjacent local subarachnoid hemorrhage or MRI demonstrates the characteristic features of a small AVM or cavernous angioma. Lack of documentation of the vascular malformation on angiography is not uncommon, and definite diagnosis requires cither MRI or the histological examination of a sample of the hematoma and its wall.

Intracranial Tumors

Bleeding into an underlying brain tumor is relatively rare in series of patients presenting with ICH, accounting for less than 10% of the cases. The tumor types most likely to lead to this complication are glioblastoma multiforme or metastases from melanoma, bronchogenic carcinoma, choriocarcinoma, or renal cell carcinoma (Figure 57B.2}. The ICHs produced in this setting may have clinical and imaging characteristics that should raise the suspicion of an underlying brain tumor, including (1) the presence of papilledema on presentation; (2) the location of ICH in sites that are rarely affected in hypertensive ICH, such as the corpus callosum, which in turn is commonly involved in malignant gliomas; (3) the presence of ICH in multiple sites simultaneously; (4) a CT scan characterized by a ring of high-density hemorrhage surrounding a low-density center in a noncontrast study; (5) a disproportionate amount of surrounding edema and mass effect associated with the acute hematoma (Figure 57B.3); (6) enhancing nodules adjacent to the hemorrhage on contrast CT scan; and (7) an MRI pattern of heterogeneous signal changes within a mass lesion, surrounded by a hemosiderin hypointense ring and bright signal edema at the periphery on T2-weighted sequences. In these circumstances, a search for a primary or metastatic brain tumor should follow, including evaluation for systemic malignancy and, if there is none, cerebral angiography, and eventually craniotomy for biopsy of the wall of the hematoma cavity. The confirmation of the diagnosis of ICH secondary to malignant brain tumor carries a dismal prognosis, with a 30-day mortality in the 90% range.

Bleeding Disorders, Anticoagulants, and Fibrinolytic Treatment

Bleeding disorders caused by abnormalities of coagulation are rare causes of ICH. Hemophilia caused by factor VIII deficiency leads to ICH in approximately 2.5-6.0% of patients, one half with ICH and one half with subdural hematomas. The majority of these hemorrhages occur in young patients, generally younger than age 18, and their mortality is high, on the order of 10%. for subdural hematomas and 65% for ICH. Immune-mediated thrombocytopenia, especially idiopathic thrombocytopenic purpura, is associated with life-threatening ICH in approximately 1% of patients. Bleeding can occur when the platelet count drops below 10,000/ul, and the hemorrhages may occur anywhere in the brain. Acute leukemia, especially the acute lymphocytic vatiety, is a common cause of ICH that favors the lobar white matter of the cerebral hemispheres. The occurrence of ICH frequently coincides with systemic bleeding, mostly mucocutaneous and gastrointestinal. These bleeding complications of acute lymphocytic leukemia ate often accompanied by both thrombocytopenia (platelet counts of 50,000/uL or less) and rapidly increasing numbers of abnormal circulating leukocytes of 300,000/uL, or more (blastic crisis). Acute promyelocytic leukemia, a variant of acute myelogenous leukemia, has a particular propensity to produce ICH as a result of disseminated intravascular coagulation, caused by the release of a procoagulant factor from the promyelocyte granules.

Treatment with oral anticoagulants increases the risk of ICH by eight- to 11-fold, in comparison with non-anticoagulated individuals with otherwise similar risk factors for ICH. Anticoagulant-related cases account for 9-11% of ICHs. Potential risk factors for intracranial bleeding in anticoagulated patients include advanced age, hypertension, preceding cerebral infarction, head trauma, and excessive prolongation of the prothrombin time. The latter factor plays a major role in the pathogenesis of ICH in patients receiving oral anticoagulants. In the secondary stroke prevention trial Stroke Prevention in Reversible Ischemia Trial (SPIRIT), 651 patients assigned to warfarin were maintained at an international normalized ratio (INR) of 3.0-4.5, resulting in 24 instances of ICH (14 fatal), in comparison with three ICHs (one fatal) in the gtoup of 665 patients treated daily with 30 mg of aspirin (The Stroke Prevention in Reversible Ischemia Trial Study Group 1997), These data further support the recommendation that oral anticoagulation in patients with cerebrovascular disease should aim at an INR of 2-3 to reduce the frequency of this complication. The presence of severe leukoaraiosis on CT scan is an additional factor that independently increases the risk of ICH in patients on oral anticoagulants (Smith et al. 2002).

These hemorrhages have certain distinctive clinical characteristics. They tend to present with a slowly progressive course, at times over periods as long as 48-72 hours, in contrast with the usually more rapidly evolving p resell rati on of hypertensive ICH. Ik-cause of this longer course, hematomas in anticoagulated patients tend to reach volumes that are, on average, larger than those of hypertensive ICH, in turn resulting in the higher mortality of approximately 65%. Signs of systemic bleeding rarely accompany ICH. Anticoagulant-related ICH may represent bleeding from vessels different from those involved in ICH of hypertensive origin (Hart ct al. 1995). Certain angi opathics with bleeding potential, such as cerebral amyloid angiopathy (CAA), may play a causal role in the ICHs that

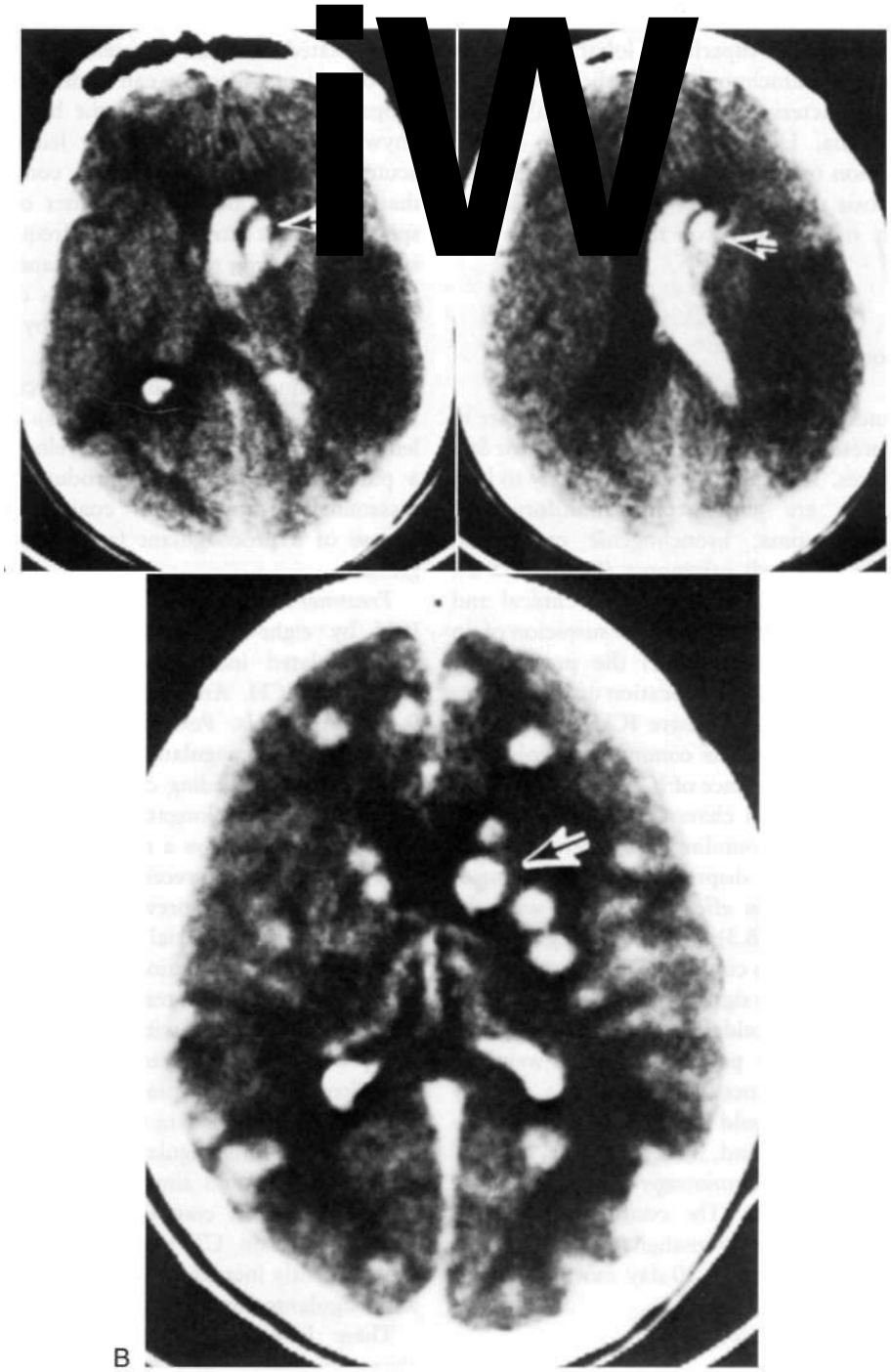


FIGURE 57B.2 (A) I ietnorrhage in the head of the left caudate nucleus *{arrow)*, with extension into the lateral ventricle. Also shown is an unrelated old infarct in the left middle cerebral artery distribution. Noncontrast computed tomographic (CT) scan. (B) 1'ostcontrast infusion CT scan of the same case, showing multiple enhancing metastases from bronchogenic carcinoma. The lesion shown in the area of the head of the caudate nucleus *(arrow)* was related to the hemorrhage shown in A.

occur in patients treated with anticoagulants (Rosand et al. 2000).

In addition to the anticoagulants, other substances with the potential for altering clot formation mechanisms are occasionally associated with ICH. These include *drugs with fibrinolytic properties* such as streptokinase and tissue-type plasminogen activator (t-PA). The use of t-PA for coronary thrombolysis in the early phases of myocardial infarction has been associated with a small (approximately 0.5-0.6%) risk of ICH with the currently recommended dose of lOOmg.

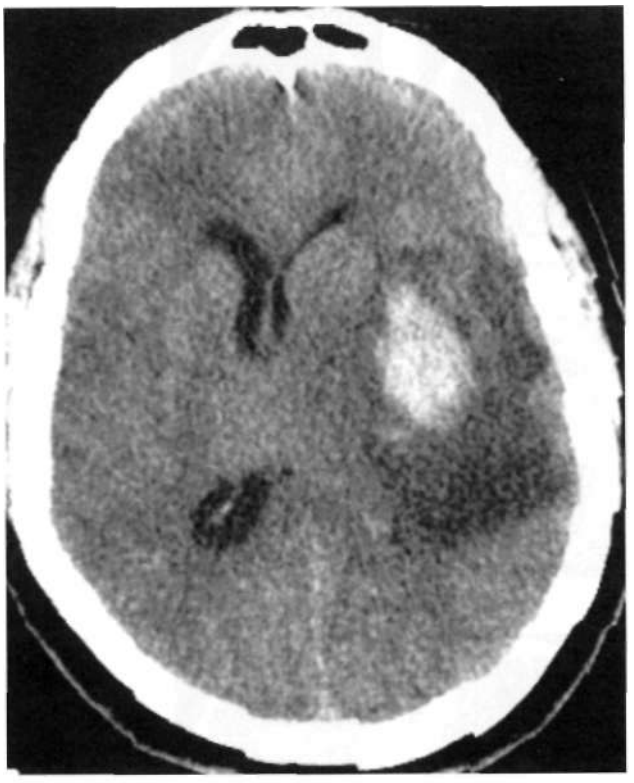


FIGURE 57B.3 Noncontrast computed tomographic (CT) scan of acute left putanunal intracerebral hemorrhage (CTdone3 hours after symptom onset) with a large amount of surrounding hypodensity edema and mass effect. Biopsy of tissue adjacent to the hemorrhage .11 the time nt surgical drainage revealed typical features of gliobastoma multiforme.

There is evidence to suggest that this complication of thrombolytic therapy may be favored by pre-existcnt vasculopathies with bleeding potential, such as CAA. The role of other factors, such as the simultaneous use of heparin anticoagulation and aspirin to prevent coronary reocclusion, is uncertain.

Recombinant t-PA for the treatment of acute ischemic stroke was complicated with ICH in 6.4% of cases (The National Institute of Neurological Diseases and Stroke [NINDS] rt-PA Stroke Study Group 1995}, which is 10 times higher than in untreated patients. Risk factors for ICH in this setting include a severe neurological deficit at presentation and documentation of hypodensity or mass effect on CT before treatment (The NINDS t-PA Stroke-Study Group 1997). Intra-artcrial thrombolysis of middle cerebral artery occlusion with prourokinase leads to improved clinical outcomes, but is associated with an 11% rate of early symptomatic ICH (Furlan et al. 1999). These hemorrhages occur at the site of the preceding cerebral infarct, are generally large (Figure 57B.4), and carry a dismal prognosis (Kase et al. 2001). Hyperglycemia at pretreatment baseline has been identified as a potential risk factor for ICH in patients treated with either intra-arte rial prourokinase (Kase ct al. 2001) or intravenous t-PA (Bruno et al. 2002}. Another potential risk factor for ICH after intraarterial thrombolysis is the presence of incidental "microhemorrhages" (Figure 57B.5), which can be easily detected with gradient-echo (or "susceptibility-weighted") MRI sequences (Kidwell et al. 2002).

Cerebral Amyloid Angiopathy

CAA is characterized by selective deposition of amyloid in cerebral vessels, primarily small and medium-sized arteries of the cortex and leptomeninges. Because the frequency of CAA increases steadily with age, reaching 60% in unselected autopsies of individuals older than 90 years, it characteristically causes ICH in the elderly and is rarely documented before the age of 55 years. In addition, the superficial location of the affected vessels in the cortex and leptomeninges is responsible for a predominantly lobar location of the ICHs. The widespread character of the angiopathy is responsible for the observation of both recurrent and multiple simultaneous, predominantly lobar hemorrhages in elderly patients. An additional characteristic of CAA is its association with histopathological features of Alzheimer's disease. There is clinical and progressive dementia in 10-30% of patients with CAA, and neuritic plaques in approximately 50% of the cases. CAA may present with features other than ICH, such as episodes of transient focal neurological deficit clinically suggestive of either transient ischemic attacks or partial seizures. These often occur days, weeks, or months before the episode of major lobar ICH and may correspond to small foci of hemorrhage that may be documented at multiple cortical sites by gradient-echo MRI sequences.

The histological lesion in CAA is deposition of Congo red-positive, birefriugent amyloid material in the media and adventitia of small cortical and leptomeningeal arteries. The actual mechanism of rupture of an affected artery may be either a weakening of the wall or the formation of microaneurysms at sites of amyloid deposition, particularly when hypertensive fibrinoid necrosis develops in the same location. Other conditions may combine with CAA to produce rupture of affected vessels, including head trauma, neurosurgical procedures, concomitant granulomatous angiitis of the central nervous system (CNS), and use of anticoagulant and fibrinolytic agents.

Granulomatous Angiitis of the Central Nervous System and Other Vasculitidcs

Granulomatous angiitis of the CNS, also referred to as *isolated angiitis of the CNS,* is characterized by

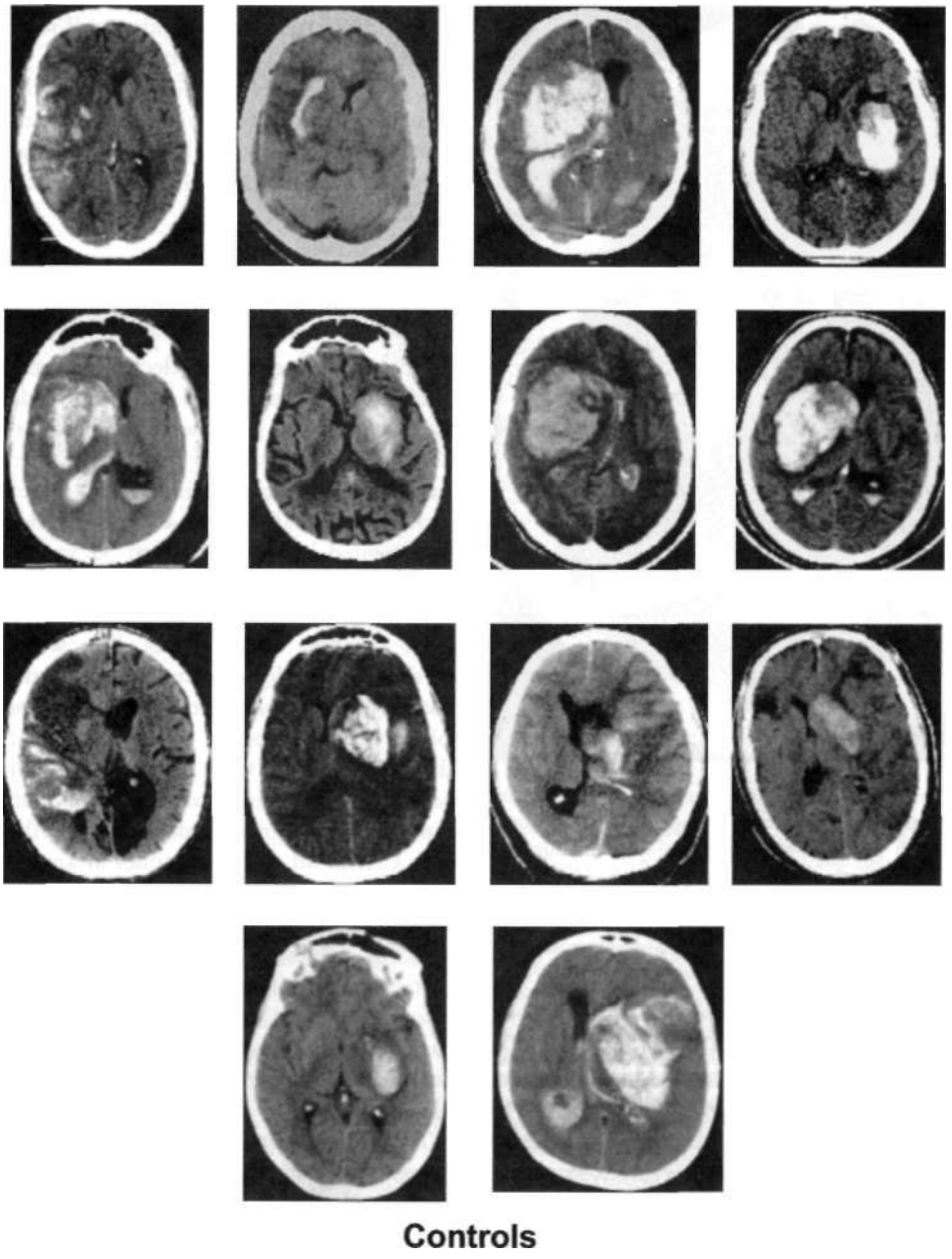


FIGURE 57B.4 Symptomatic intracerebral hemorrhages after infra-arterial thrombolysis of middle cerebral artery occlusion with pmurokinase. (Repriuti'd will) pinimMon from k.tse, C S., 1'mhn, A. |., WVdisli/r, 1, K„ el al. 200], "Cerebral lu-inorrliane after intra-arterial thrombolysis for ischemic stroke: The PRO ACT II trial," *Neurology,* vol. 57, pp. 1603-1610.)

mononuclear inflammation with giant cell formation in the media and adventitia of small and medium-sized intracraniaI arteries and veins (see Chaptet 57G). An associated element of intimal hyperplasia leads frequently to cerebral infarcts and occasionally ICH.

Among the vasculitides, the other variety that is known to present with ICH is polyarteritis nodosa. As opposed to granulomatous angiitis of the CNS, this form of necrotizing vasculitis depicts prominent signs of systemic involvement, including fever, malaise, weight loss, anemia, elevated sedimentation rate, and renal impairment with hypertension (see Chapter 55A),

Sympathomimetic Agents

Amphetamines cause ICH after intravenous, oral, or intranasal use (see Chapter 64B). The hemorrhages have occurred within minutes to a few hours after drug use, and the majority has been located in the subcortical white

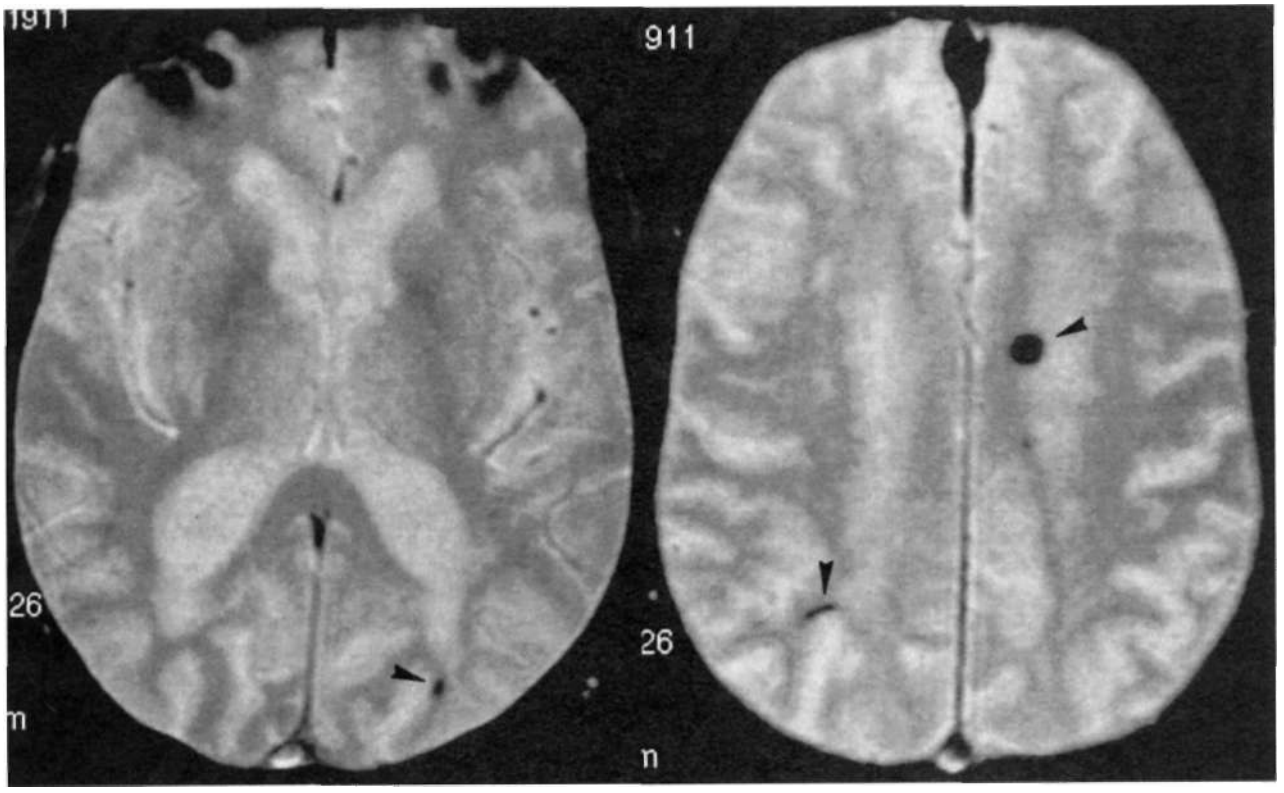


FIGURE 57B.5 Cortical microhcmorrhages *(arrowheads)* on gradient-echo magnetic resonance imaging scan.

matter of the cerebral hemispheres. In approximately one half of the reported cases, transient hypertension has been documented, as well as multifocal areas of spasm and dilatation (beading) of intraeniin.il arteries on angiography. Although the latter is frequently referred to as a *vasculitis* or *arteritis,* histological proof is lacking, and this angiographic picture probably represents multifocal spasm secondary to the drug. The decongestant and appetite-suppressant phenylpropanolamine has been associated with ICH in young patients (median age in the early 30s), predominantly women (Kernan et al. 2000), usually without a history of hypertension but with acute hypertension on admission in one third of patients. Beading of intracranial arteries is frequent on angiography.

Cocaine (see Chapter 64B) has become the most common sympathomimetic agent associated with ICH. Both ICH and subarachnoid hemorrhage can occur within short periods (generally minutes) of the use of both the alkaloidal (free-base) form of cocaine and its precipitate form known as *crack.* The ICHs favor the subcortical white matter, but occasionally occur in the deep portions of the hemispheres (Figure 57B.6). **There** may be multiple simultaneous ICHs, both deep and superficial, the mechanism of which remains unknown. In some instances, the origin of the ICH can be traced to a coexistent AVM or aneurysm, whereas the remainder are probably associated with either cocaine-induced vasoconstriction followed by reperfusion,

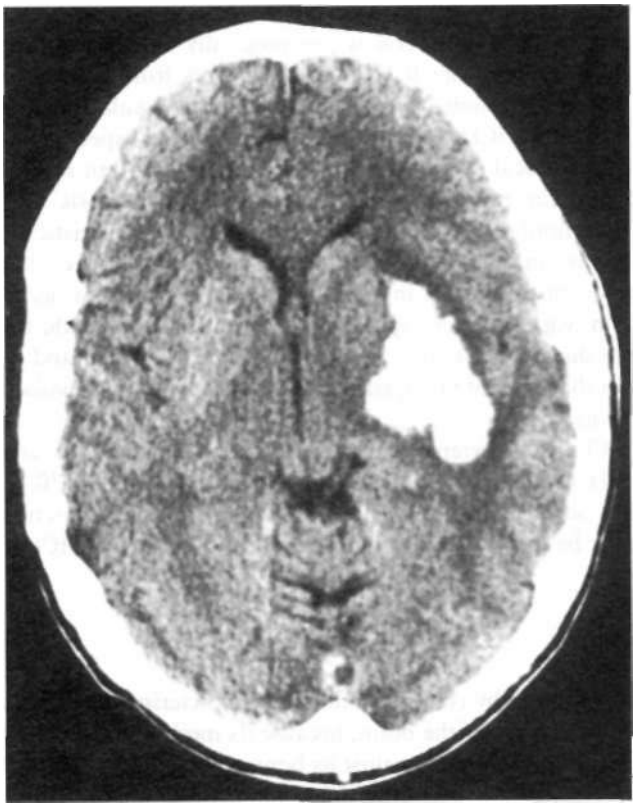


FIGURE 57B.6 Left putainina1 hemorrhage after use of crack cocaine. (Courtesy of Susan S. Pausing, MD)

Table 57B.2: Differences between intracerebral hemorrhage and hemorrhagic infarction

	Intracerebral hemorrhage	*Hemorrhagic infarction (embolic)*
Clinical		
Onset	Sudden, followed by progression	Maximal from onset
Raised intracranial pressure	Prominent	Absent
Embolic source	No	Yes
Computed tomographic scan		
High attenuation	Dense, homogeneous	Spotted, mottled
Mass effect	Prominent	Absent or mild
Location	Subcortical, deep (gray nuclei)	Cortex more than subcortical white matter
Distribution	Beyond arterial territories	Along branch distribution
Late enhancement	Ring-type	Gyral-typc
Ventricular blood	Yes	No
Magnetic resonance imaging*		
Hypointcnse blood (T2}	Homogeneous	Patchy, mottled
Hyperintense edema (T2)	Thin peripheral halo	Extensive, in vascular territory
Angiogram/magnecic resonance angiography	Mass effect (avascular)	Branch occlusion

^Magnetic resonance imaging depicts the same features as computed tomographic (CT) scanning in regard to mass effect, location, distribution, late enhancement, and ventricular blood. This table lists only the features that magnetic resonance imaging adds to those of CT.

Source: Reprinted with permission from Kasc, C. S., Mobr, J. P,, Caplan, L. R. 1998, "Intracerebral hemorrhage," in *Stroke: Pathophysiology, Diagnosis, and Management,* eds H. J. M. Barnett, J. P. Mohr, B. M. Stein, et al., Saunders, Philadelphia.

heavy alcohol intake, or rarely, a drug-induced cerebral vasculitis.

Hemorrhagic Infarction

Hemorrhagic infarction is pathologically and pathogenic-.illy different from 1CH in that it results from arterial or venous occlusion, rather than from the vascular rupture that causes 1CH, As a result, its pathological aspect is one of multifocal petechial hemorrhagic staining of an area of the brain primarily affected by ischemic necrosis (i.e., infarction). Hemorrhagic infarction characteristically occurs in the setting of cerebral embolism or, less frequently, cerebral infarction secondary to venous occlusion (e.g., superior sagittal sinus thrombosis); in both, the bleeding reflects the mechanism of the infarct and is not the result of therapeutic measures such as anticoagulant drugs.

Clinical differences between hemorrhagic infarction and ICH usually permit their clear distinction (Table 57B.2), but severe and confluent foci of hemorrhagic infarction may be difficult to distinguish from foci of primary ICH.

Trauma

ICH caused by cerebral contusion characteristically occurs in the surface of the btain, because its mechanism is one of direct brain trauma against its bony covering at the time of an acceleration-deceleration head injury (see Chapter 56A), This explains the sites of predilection for traumatic brain hemorrhages in the basal frontal, anterior temporal, and occipital areas, resulting from the coup and contrecoup mechanisms. Thus traumatic brain hemorrhages are frequently multiple.

CLINICAL FEATURES OF INTRACEREBRAL **HEMORRHAGE**

The clinical presentation of ICH has two main elements: symptoms that reflect the effects of intracranial hypertension, and those that are specific for the location of the hematoma. The general clinical manifestations of ICH related to increased intracranial pressure (ICP) (headache, vomiting, and depressed level of consciousness) are variable in their frequency at onset of ICH. The correlation of these symptoms, especially abnormal level of consciousness, with hematoma size applies to all anatomical varieties of **ICH,** which, in turn, relates directly to mortality.

A characteristic of ICH at presentation is the frequent progression of the focal neurological deficits over periods of hours. This early course reflects the progressive enlargement of the hematoma (Figure 57B.7), which at times amounts to volume increments of more than 300%, as measured by serial CT scans (Brott et al. 1997). Seizures at the time of presentation of ICH are rare, except for lobar ICH, in which they occur in as many as 28% of patients. The subcortical hemorrhage probably creates an area of partially isolated cortex, which reacts with sustained paroxysmal activity.

The CT scan is sensitive to the high-density fresh blood in the brain parenchyma, along with associated features of local mass effect and ventricular extension. MRI adds further precision, especially in determining the time elapsed

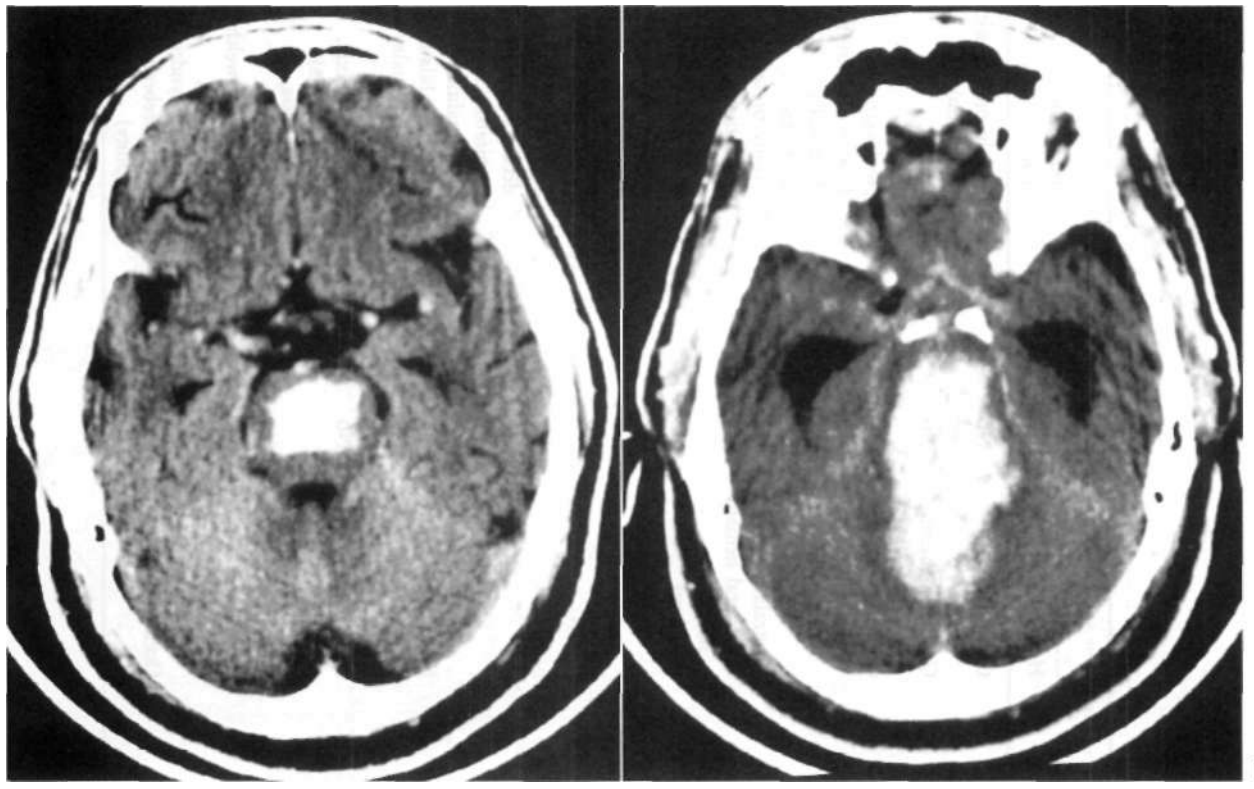


FIGURE 57B.7 (A) Basal-tegmental pontine hemorrhage at the time of admission. (B) Massive enlargement of hemorrhage with extension into the fourth ventricle and hydrocephalus of temporal horns, 6 hours later.

Tabic 57B.3: Temporal changes in magnetic i esonance imaging features of intracerebral hemorrhage

		Magnetic resonance imaging signal intensity	
Stage of intrai-.erebral hemorrhage	*Type of hemoglobin*	*T1 -weighted*	*Tl-wcighted*
First hours	Oxyhemoglobin	Same or *	+
t lours to days	Dcoxy hemoglobin	Same or *	
First days	Methemoglobin, intracellular	+	
Several days to months	Methemoglobin, extracellular	++	\ \
Several days to indefinitely	Ferritin/hemosiderin	Same or *	

Same = equal signal with surrounding brain; - hypointense to brain; + = hyperintense to brain; : marked hypointensity; ++ = marked hyperintensity.

between onset and time of MRI examination. The type of signal intensity change depicted by Tl- and T2-weighted MRI sequences can be correlated with the hyperacute, acute, subacute, and chronic stages of evolution of an intracerebral hematoma (Table 57B.3).

The physical examination findings that relate to the different anatomical locations of ICH are summarized in Table 57B.4.

Putaminai Hemorrhage

The most common variety of ICH, putaminai hemorrhage, represents approximately *35%* of the cases (Kase et ah 1998) (Figure 57B.8). A wide spectrum of clinical severity relates to hematoma size, from minimally symptomatic cases presenting with pure motor hemiparcsis, or slight hemiparesis and dysarthria, to the extreme of coma with decerebrate rigidity in instances of massive hematomas with rupture into the ventricles. Modern CT scan series of putaminai hemorrhage document a mortality of 37%, in contrast to 65-75% from pre-CT data. This difference reflects the description of the full spectrum of hematoma size in recent reports, including smaller hematomas with benign outcomes, which were misdiagnosed as infarcts in the pre-CT scan era.

Ventricular extension carries an invariably poor prognosis in putaminai hemorrhage. This feature in part reflects

Table 57B.4: Clinical features of anatomical forms of intracerebral hemorrhage

Type of intracerebral hemorrhage	*Hemiplegia*	*Hemisensory syndrome*	*Aphasia*	*Homonymous visual defects*	*G*
					Horizontal
Putaminal	Generally dense	Frequent	Global > motor > conduction	In larger hematomas	Contralateral
Caudate	Absent or mild, transient	Absent	No	No	Generally absent
Thalamic	Generally dense	Frequent, prominent	Occasional, thalamic variety	In larger hematomas	Contralateral, occasionally ipsi lateral
Lobar	Prominent in frontoparietal location	Prominent in fronto-parietal location	In dominant temporoparietal location	In occipital hematomas	Contralateral in frontal hematomas
Cerebellar	Absent	Absent	N<.	No	Ipsi lateral
Pontine	Variable, usually bilateral	Variable, usually bilateral	No	No	Bilateral
Mesencephalic	Variable, usually present	Rare	No	No	No
Medullary	Generally absent	Occasional	No	No	No
Intraventricular	Generally absent	Rare	No	No	Occasional

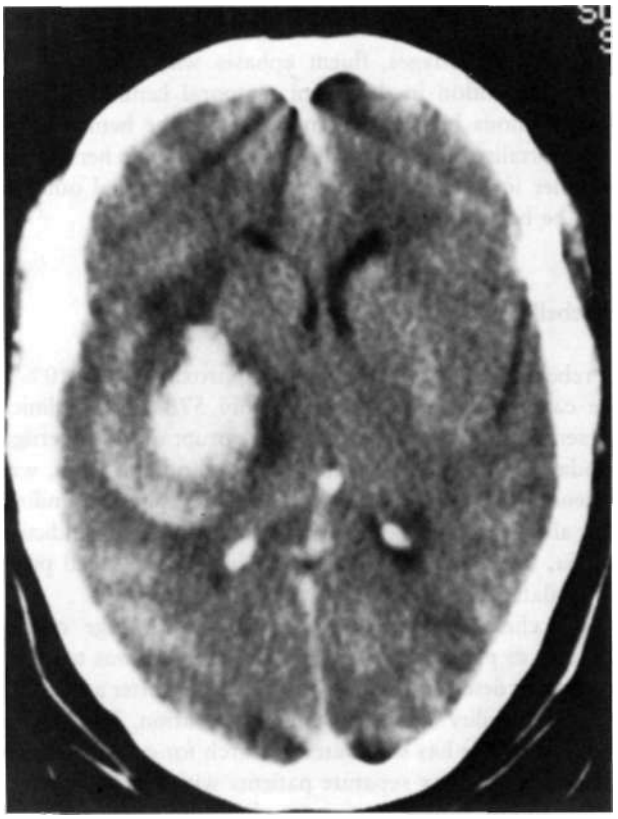


FIGURE 57B.8 Right putaminal hemorrhage.

the larger size of hematomas that track from the laterally placed putamen to the medially placed ventricular system.

Caudate Hemorrhage

Caudate hemorrhage is a rare variety of ICH that accounts for only approximately 5% of the cases (Kase et ah 1998) (Figute 57B.9). It results from rupture of penetrating arteries from the anterior and middle cerebral arteries, and its most common cause is hypertension. Presentation is similar to that of subarachnoid hemorrhage in that the clinical picture is dominated by signs of intracranial hypertension and meningeal irritation, with focal neurological deficits (hemiparesis, horizontal gaze palsy, Homer's syndrome) being minimal and transient, or altogether absent. The main differential diagnosis of caudate ICH is ruptured anterior communicating artery aneurysm with bleeding through the septum pellucidum into the ventricular system. In this instance, CT scan shows blood in the inter/hemispheric fissure and in the lowermost frontal cuts, as opposed to the higher location of the unilateral clot in the head of one caudate nucleus in primary caudate ICH. Ventricular extension of the hemorrhage is a regular feature in caudate ICH, and hydtoccphalus is usually present. Nevertheless, the outcome is generally good. The majority of patients recover without neurological sequelae, because

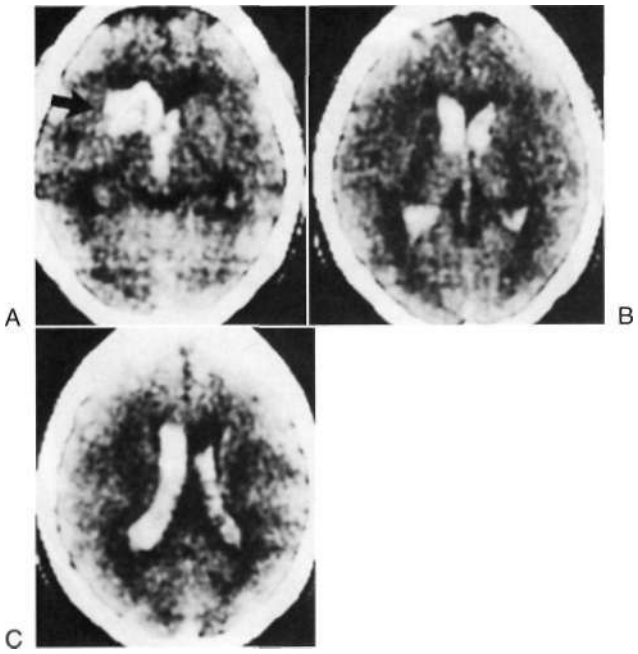


FIGURE S7B.9 Right caudate hemorrhage *(arrow)* (A), with extension into the lateral and third ventricles (A-C).

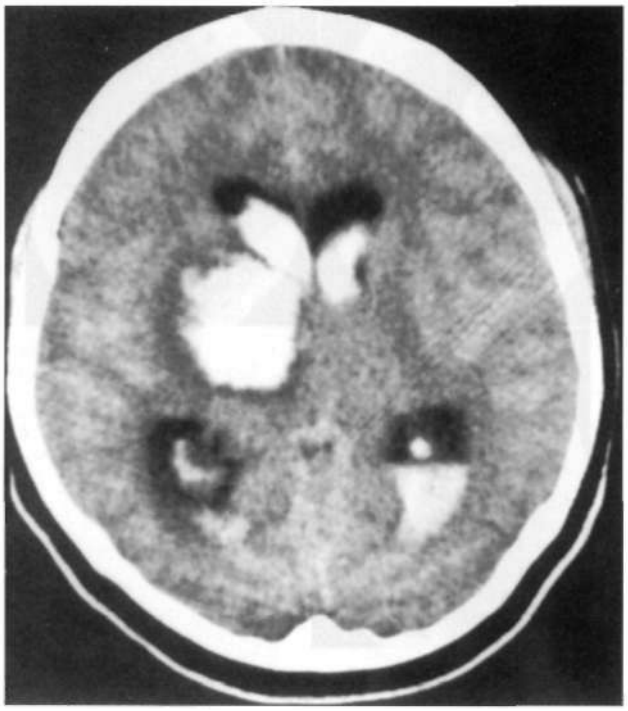
this type of ICH causes minimal parenchymal destruction, as compared with other forms of supratentorial ICH.

Thalamic Hemorrhage

Thalamic hemorrhage represents 10-15% of the cases of ICH (Kase et ah 1998) (Figure 57B.10). Its onset tends to be more abrupt than that of putaminal hemorrhage, and slow progression of deficits is less common. These features may reflect early communication of the medially located hematoma with the third ventricle. The prognosis in thalamic hemorrhage relates to hematoma size. Thete is a lack of correlation between survival and ventricular cxiciiMtin "i the hemorrhage, again documenting that hematoma size, not ventricular extension per sc, is the most crucial factor related to the vital ptognosis in ICH. Another reliable sign of poor prognosis in thalamic ICH is the presence of hydrocephalus, a complication that occasionally occurs abruptly, as a result of aqucductal obstruction by an intraventricular clot; here, however, ventriculostomy may result in a reversal of symptoms.

Lobar Hemorrhage

Lobar hemorrhage is second to putaminal hemorrhage in frequency, accounting for approximately 25% of the cases (Kase et al. 1998) (Figure 57B.11). Nonhypertensive mechanisms, including AVMs, sympathomimetic agents (in young patients), and CAA (in elderly patients) are frequent causes. The peripheral (subcortical) location of



HGURE 57B.10 Right thalamic hemorrhage with ventricular extension.

these hematomas explains the lower frequency of coma at onset, as compared with the deep ganglionic forms of supratentorial ICH. The clinical fearures reflect location: hemiparesis of upper limb predominance in frontal hematomas, sensorimotor deficit and hemianopia in parietal hemorrhages, fluent aphasia with relatively preserved repetition in dominant temporal hematomas, and homonymous hemianopia in occipital lobe hemorrhages. The mortality rate in lobar ICH is lower than in hematomas in other locations, and the long-term functional outcome may be better also.

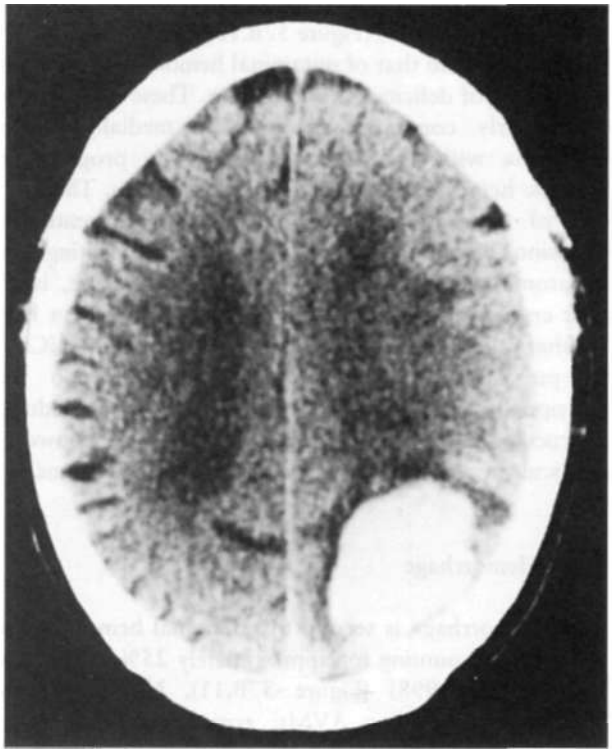


FIGURE 57B.11 Ijeft parieto-ou-ipital lobar hemorrhage.

Cerebellar Hemorrhage

Cerebellar hemorrhage represents approximately 5-10% of the cases {Kase et al. 1998) (Figure 57B.12). Its clinical presentation is characteristic, with abrupt onset of vertigo, headache, vomiting, and inability to stand and walk, with absence of hemiparesis or hemiplegia. The physical findings that allow its clinical diagnosis are the triad of appendicular ataxia, horizontal gaze palsy, and peripheral facial palsy, all ipsilateral to the hemorrhage.

The clinical course in cerebellar hemorrhage can he difficult to predict at onset. There is a notorious tendency for abrupt deterioration to coma and death after a period of clinical stability under hospital observation. This unpredictable course has stimulated a search for early clinical or CT signs that may separate patients with benign outcome from those who deteriorate clinically with onset of brainstem compression and high mortality.

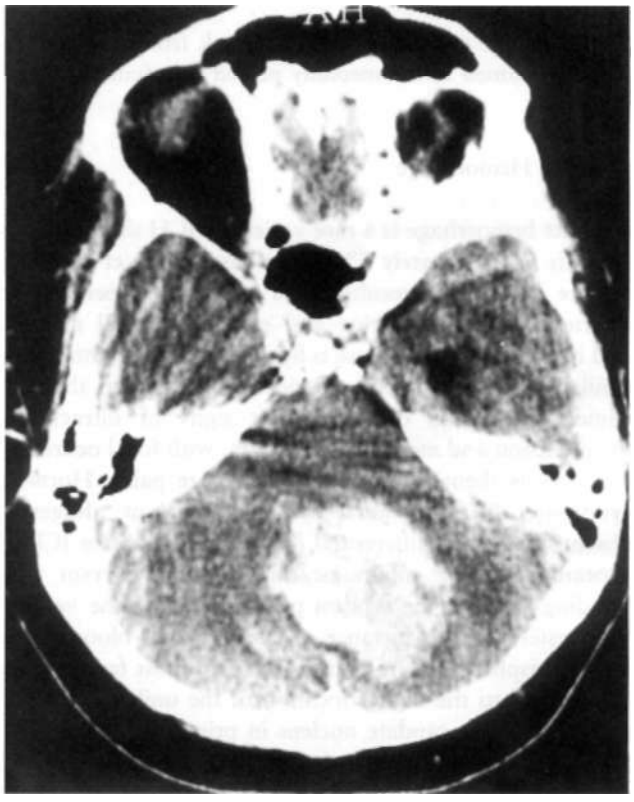


FIGURE 57B.12 Large midline and left-sided hemispheric cerebellar hemorrhage.

Pontine Hemorrhage

Pontine hemorrhage represents approximately 5% of the cases (Kasc et al. 1998) (Figure 57B.13). The massive, bilateral basal-tegmental variety produces the classic picture of coma, quadriplegia, decerebrate posturing, horizontal ophthalmoplegia, ocular bobbing, pinpoint reactive pupils (for which a magnifying glass may be required to allow detection of the light reflex), abnormalities of respiratory rhythm, and preterminal hyperthermia. Since the introduction of CT and MRI scanning, less severe forms of pontine hemorrhage are recognized that are compatible with survival. These hemorrhages are frequently located in the tegmentum, lateral to the midline (Figure 57B, 14), and thus produce syndromes of predominantly unilateral pontine cranial nerve involvement ("one-and-a-half" syndrome, internuclear ophthalmoplegia, fifth and seventh nerve palsies), with variable degrees of long-tract interruption. These hematomas probably result from rupture of distal tegmental branches of a long circumferential artery originating from the basilar trunk.

Mesencephalic Hemorrhage

Mesencephalic hemorrhage is exceptionally rare (Kase et al. 1998). The causal mechanism is hypertension or ruptured AVM in one half of the reported cases, the others being of undetermined cause. Occasional unilateral hematomas (Figure 57B.15) can present with ipsilateral third nerve palsy and cerebellar ataxia, with contralateral hemiparesis. Bilateral cases frequently have prominent tecta I -tegmental signs, with bilateral ptosis, paralysis of upward gaze, and small pupils with light-near dissociation (see Chapter 22). Most patients survive without surgical treatment, but with persistent sequelae.

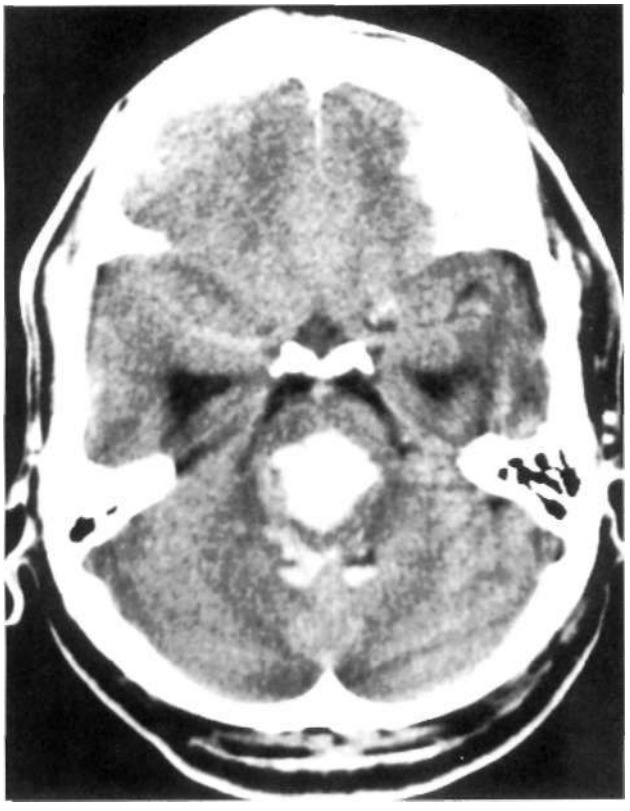


FIGURE 57B. 13 Large tegmental basal pontine hemorrhage with hydrocephalus of temporal horns.

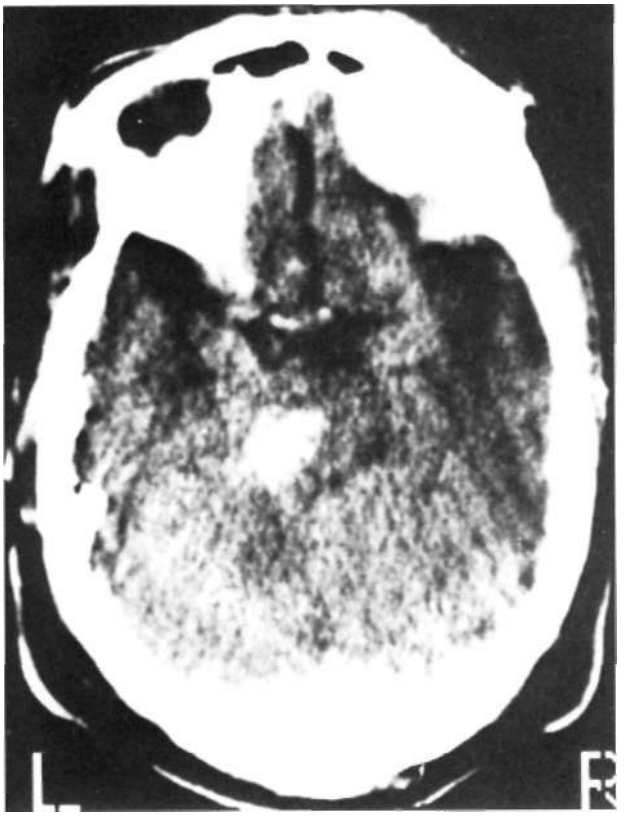


FIGURE 57B.14 Left tegmental pontine hemorrhage.

Medullary Hemorrhage

Examples of pure primary ICH involving the medulla alone are rare, with most reported cases representing medullary extension of caudal pontine hematomas. The clinical presentation of primary medullary hemorrhage reflects the location of the lesion on one half of the medulla, generally extending beyond the dorsolateral region, both medially (resulting in ipsilateral hypoglossal nerve palsy) and ventrnlly (resulting in contralateral hemiparesis). These two features distinguish most examples of medullary hemorrhage from the classical presentations of Wallenberg's lateral medullary syndrome, caused by infarction rather than hemorrhage (sec Chapter 22).

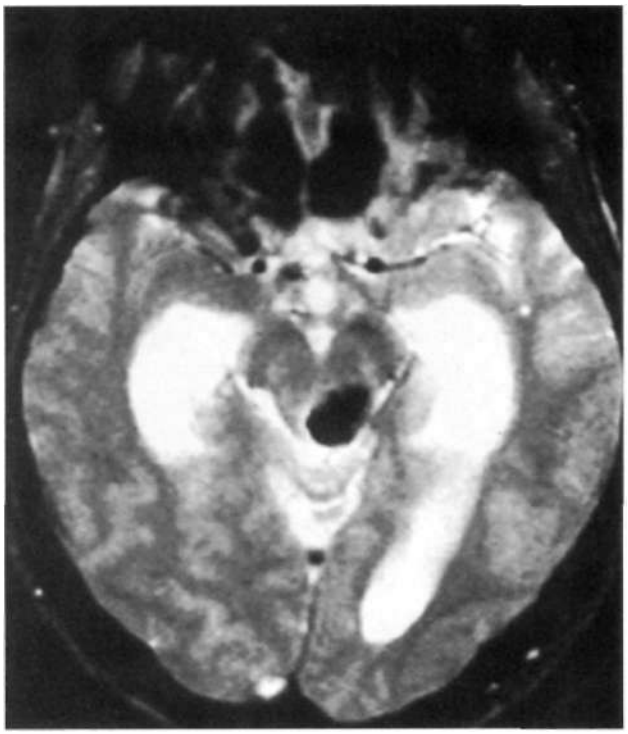


FIGURE S7B.15 Gradient-echo (T2) magnetic resonance imaging scan of left tegmental midbrain hemorrhage.

Intraventricular Hemorrhage

Extension of hemorrhage into the ventricular system is a common feature of caudate and thalamic hemorrhages and of large putaminal and lobar hemorrhages. As a primary form, not associated with a component of intra parenchymal bleeding, intraventricular hemorrhage is rare, accounting for only approximately 3% of ICHs. The site of origin of the hemorrhage is thought to be the vasculature of the subependymal region, and rarely the source can be identified in the choroid plexus.

The causes of intraventricular hemorrhage are similar to those of ICH elsewhere, including hypertension, aneurysm, AVM, coagulation disorders, cerebral tumors, cocaine use, and rare vasculopathies such as moyamoya disease. Those from aneurysm rupture are generally caused by an anterior communicating artery aneurysm rhat ruprures in an upward direction, bleeding directly into one of the lateral vcntticles; in these instances, basal frontal subarachnoid hemorrhage and interhemispheric hemorrhage accompany the intraventricular hemorrhage and should always raise the diagnostic suspicion of a ruptured aneurysm. AVMs that cause purely intraventricular hemorrhage are generally small and located in the medial aspect ut the basal ganglia or thalamus. Rarely, an inrravcntricular AVM or cavernous angioma may cause a primary inrravenrricular hemorrhage.

The clinical presentation of intraventricular hemorrhage is with acute onset of headache, nausea, vomiting, and decreased level of consciousness, with focal neurological deficits cither minimal or altogether absent (Marti-babreg.is et al. 1999). This presentation is identical to that of subarachnoid hemorrhage from ruptured aneurysm or AVM. If focal deficits such as hemiparesis or ocular motor disturbances are prominent, the picture is not strictly that of a pure intraventricular hemorrhage, but rather one of primary ICH with ventricular extension.

Intraventricular hemorrhage can be diagnosed reliably with CT and MRI, the latter being more sensitive for the detection of a small component of subependymal, intta-parenchymal hemorrhage. Also, MRI can suggest a diagnosis of aneurysm, AVM, or cavernous angioma as the mechanism of the hemorrhage. Even after extensive testing, many intraventricular hemorrhages remain of unknown mechanism.

The prognosis of intraventricular hemorrhage is strongly dependent on the severity of the initial presentation and its mechanism. Patients who are comatose as a result of the initial hemorrhage generally succumb, especially if they have early signs of brainstem involvement (ophthalmoparesis, loss of pupillary reflexes, decerebrate rigidity). Those who remain alert or obtunded, without signs of parenchymal involvement, tend to recover without neurological sequelae, although memory disturbances may be a relatively frequent residual deficit (Marti-Fabregas et al. 1999). Patients with the idiopathic form of intraventricular hemorrhage have the best prognosis.

TREATMENT OF INTRACEREBRAL HEMORRHAGE

Issues related to treatment of ICH have been dominated by two main considerations: (1) the type and intensity of medical interventions required to improve the functional and vital prognosis, and (2) the choice between medical and Surgical therapy. To a great extent, these two important aspects of treatment remain unclarified, largely as the result of a remarkable paucity of prospective clinical trials. These two issues are discussed separately.

General Management of Intracerebral Hemorrhage

Because ICH is associated frequently with increased ICP, most of the therapies used in this setting are directed at lowering ICP or preventing its increase. Among the many medications and procedures available, a small group has come into customary use in most institutions, despite their value not being proven in properly controlled studies.

Initial Evaluation

On arrival in the emergency department, patients with ICH need to be immediately evaluated for stabilization of vital signs and airway protection. If the patient has a depressed

level of consciousness, with a Glasgow Coma Scale score of 8 or less, endotracheal intubation should follow. This is best performed with the concomitant administration of short-acting agents such as thiopental (1-5 mg/kg) or lidocaine (1 mg/kg) to block the increases in ICP that result from tracheal stimulation.

Following emergent evaluation of the vital signs and laboratory studies, clinical examination and CT arc needed to establish the topography and size of the ICH, which determine the plan for further management, These decisions are made in conjunction with a neurosurgical consultant.

Labotatory test data on presentation with ICH should include coagulation studies, especially in instances of hemorrhage in patients receiving anticoagulants or previously treated with thrombolytic agents. Coagulation abnormalities in patients receiving anticoagulants should be treated emergently, because if anticoagulation is not reversed it can lead to progressive enlargement of the hematoma. Patients with ICH in the setting of heparin anticoagulation should be treated with protamine sulfate, 1 mg per 100 units of heparin estimated in plasma, whereas those on warfatin should receive .5-25 mg of parenteral vitamin K| and, most important, fresh frozen plasma (10-20 mL/kg). In view of the expected delays in having fresh frozen plasma immediately ready in these instances, the tecent availability of recombinant factor Vila for intravenous injection offers the option of a more rapid reversal of rhe abnormally prolonged INR in cases of warfarin-related ICH (Deveras and Kcssler 2002), Instances of ICH after thrombolytic therapy are best tteated with 4-6 units of ctyoprecipitate, or fresh frozen plasma, as well as single donor platelets,

General Measures for Prevention of Further Elevation of Intracranial Pressure

General measures include control of hypertension and treatment of seizures. The former can be necessary because persistent hypertension, by causing increased cerebral perfusion pressure, may produce an increase in cerebral edema around the ICH, with further elevation of ICP. However, this potential benefit of antihypertensive therapy must be balanced against the possible harmful effects of drug-induced hypotension with resulting cerebral ischemia and further neurological deterioration. This difficult clinical problem is compounded by the lack of knowledge concerning optimal balance between adequate cerebral perfusion and control of ICP. Pharmacological correction of severe hypertension is mandatory in the acute phases of ICH, with the aim being maintenance of normal cctcbral perfusion pressure levels, on the otder of 50-70 mm Hg, and a mean arterial pressure below 130 mm Hg (Broderick et al. 1999). These parameters for blood pressure control after acute ICH are safe, and do not compromise cerebral blood flow (Powers et al, 2001}, The antihypertensive agent of choice in this setting is the intravenous *0*- and a-blocking agent labetalol, often used in combination with loop diuretics. Although theoretically contraindicated because of their cerebral vasodilator properties, nitroprusside and hydralazine are the most appropriate choices when labetalol fails to control the blood pressure. These agents, in particular nitroprusside, have the advantage of being very effective and easy to titrate, and the feared side effect of increased ICP caused by cerebral vasodilation is rarely, if ever, of clinical consequence,

Seizures, a feature of the lobar rather than deep ganglionic vatieties of ICH, typically occur at onset. In patients who did not have early seizures, there is a negligible risk of late epilepsy. Thus the routine prophylactic use of anticonvulsants in patients with ICH is not justified. Early tonic - clonic convulsions need immediate control because they can contribute to increased ICP. The major anticonvulsants are of comparable value in this situation.

Specific Treatment of Increased Intracranial Pressure

The mainstays of treatment of intracranial hypertension have been hyperventilation, diuretic therapy, and corticosteroids. Hyperventilation is most effective in rapidly lowering intracranial hypertension, usually within minutes of achieving levels of hypocapnia in the range of 25-30 mm Hg. Inttavcnous mannitol (0,25-1.0 g/kg), a rapid and reliable way of lowering ICP, may be used along with hyperventilation in situations of neurological deterioration with impending herniation. Although dexamethasonc is frequently given with the purpose of decreasing intracranial hypertension by reducing cerebral edema, its use is not supported by data from a controlled clinical trial (Poungvarin et al. 1987).

Intensive monitoring of ICP with aggressive medical treatment of intracranial hypertension appears to improve the outcome of comatose patients with ICH. In addition, failure to control raised ICP with these measures can be used as an objective indicator that surgical evacuation of the hematoma is required, because persistently elevated ICP under these circumstances results invariably in progression to coma and death.

Choice between Medical and Surgical Therapy in Intracerebral Hemorrhage

A direct surgical approach is considered frequently in patients with superficial (lobar) hematomas of the cerebral hemispheres or with cerebellar hemorrhage, whereas patients with deep hemorrhages (caudate, thalamic, pontine, mesencephalic, and medullary in location) arc rarely, if ever, surgical candidates. Putaminal hemotrhage occupies an intetmediatc position and is most controversial. Few scientific data are available to assist the clinician in this therapeutic choice.

Six randomized clinical trials compared surgical with nonsurgical treatment of ICH, and the results were generally inconclusive, mostly because of methodological

issues (Fernandas ct al. 2000). A well-designed, prospective, multicenter clinical trial is required to answer rhis important clinical question, and at the same time evaluate conventional craniotomy against other newer surgical approaches.

A promising technique for surgical treatment of intracerebral hematomas involves the stereotactic drainage of the hemorrhage with the aid of local instillation of a fibrinolytic agent (Qureshi etal. 2001). The introduction of the draining cannula is done under local anesthesia and CT guidance, and the procedure allows repeated drainage of liquefied portions of the hematoma following local urokinase or tPA infusion. This can achieve the removal of as much as 80% of the hematoma, without the need for craniotomy. This technique may have a role in the surgical management of deep-seated thalamic or puraminal hematomas, as well as in patients considered to be too high risk for hematoma drainage through a craniotomy under general anesthesia.

Because of the lack of prospective data on tandomized trials of therapy in ICH, most patients are currently treated nonsurgically, with the exception of those with puraminal and lobar hemorrhage with progressive deterioration in the level of consciousness, and most instances of cerebellar hemorrhage. Patients with putaminal and lobar ICH who undergo a steady decline in level of consciousness, with onset of coma, have a mortality of 100% with medical therapy. On the basis of this consideration, occasional patients with putaminal ICH arc treated surgically, with a slight improvement in survival rates, but without any demonstrated improvement in functional outcome. This raises a difficult ethical dilemma conttasting improved survival with poor quality of life in patients with massive basal ganglionic ICHs, in whom severe hemiplegia, hemisensory loss, and aphasia or hemi-inattention syndromes arc the expected permanent sequelae. A somewhat less pessimistic picture exists in the case of lobat ICH with progressing mass effect. The surgically more accessible superficial hematomas suggest the potential for less devastating neurological sequelae, thus justifying surgery in selected cases. The most likely candidates for surgery are patients with lobar hemorrhages of intermediate size (hematoma volumes between 20 and 40 mL), who have a decline in level of consciousness or marked mass effect by CT scan. In addition, the presence ol a lesion with potential tor causing recurrence of ICH, such as an AVM, aneurysm, or cavernous angioma, is another indication for surgical therapy (Broderick et al. I 999).

Hie other group for whom surgery is frequently considered includes patients with cerebellar hemorrhage. Although a benign outcome without surgical evacuation is well documented in small cerebellar hemorrhages, the potential for sudden deterioration to coma and death, not infrequently after a clinically stable course under hospital observation, is well recogni/.ed. CT criteria for early selection of candidates for surgical therapy are large hematomas (diameter of 3 cm or more), presence of hydrocephalus, and obliteration of the quadrigcminal

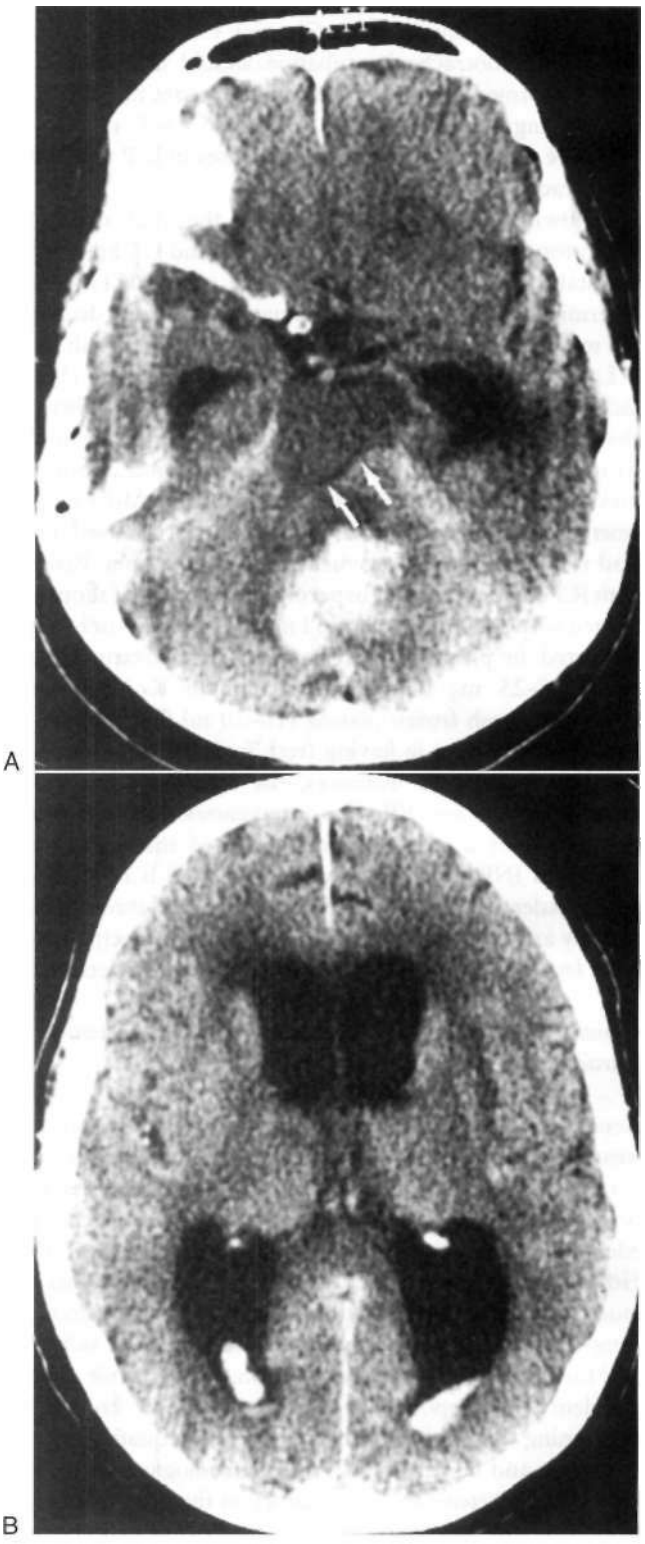


FIGURE 57B.16 Midline cerebellar hemorrhage with brainstem distortion, obliteration of quadrigeminal cistern *[arrows)* (A), and supratentorial hydrocephalus (B).

cistern (Figure 57B.16). In addition to these CT features, early signs of pontine tegmental compression and development of obtundation and extensor plantar responses constitute indications for emergency surgical therapy, hecausc the outcome is otherwise uniformly fatal.

In addition to direct evacuation of a hematoma, there is the option of ventricular drainage for the relief of hydrocephalus and increased ICP in cases of cerebellar, thalamic, and caudate ICH. In cerebellar hemorrhage, massive hydrocephalus can be a major cause of clinical dererioration, and ventricular drainage may provide dramatic improvement. Because ventricular drainage does not diminish compression of the brainstem, and because of the potential for upward transtentorial cerebellar herniation following decompression of the supratcntorial ventricular system, this approach is only rarely the sole form of surgical treatment. It may, however, be used immediately before occipital craniectomy for wide decompression of the posterior fossa and hematoma drainage. Patients with thalamic hemorrhage occasionally show a dramatic reversal of oculomotor signs, coma, or both, after ventricular drainage.

The value of these methods of management of ICH needs assessment by a prospective, multicenter, randomized trial of surgical versus nonsurgical treatment of ICH.

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Chapter 57
Vascular Diseases of the Nervous System

C. INTRACRANIAL ANEURYSMS AND SUBARACHNOID HEMORRHAGE

Warren R. Selman, Jeffrey L. Sunshine, Robert W. Tarr, and Robert A. Ratcheson

The importance of proper management of patients with intracranial aneurysms cannot be overestimated. The spectrum of neurological disorders produced by aneurysms ranges from the asymptomatic unruptured aneurysm to the ruptured aneurysm that produces debilitating stroke and death. The most devastating consequences of intracranial aneurysms are from the complications of subarachnoid hemorrhage (SAH). This chapter emphasizes strategies to prevent or ameliorate these complications.

CLINICAL SYNDROMES

The classic manifestations of a major aneurysmal rupture include a sudden explosive headache, decreased level of consciousness, photophobia, moiingisnnis, nausea, and vomiting. Because the prognosis is better if treatment occurs before these manifestations develop, it is important to recognize the signs and symptoms associated with aneurysmal expansion or a minor hemorrhage.

Headaches are one of the most important warning symptoms of aneurysmal rupture. Sentinel headaches occur in approximately one half of patients before rupture. Other associated symptoms may include nausea, neck pain, lethargy, and photophobia.

These symptoms are presumably caused by a noncatastrophic leak of the aneurysm and may be confirmed by demonstrating red blood cells or xanthochromia in the cerebrospinal fluid. Hemorrhage into the wall of an aneurysm can produce thunderclap headache associated with aneurysmal enlargement in the absence of red blood cells in the cerebrospinal fluid (Ostergaard 1993). Thus the absence of blood in the cerebrospinal fluid in a patient with a characteristic history docs not exclude the possibility of a symptomatic aneurysm. Such patients should undergo, at least, noninvasive imaging of the cerebral vessels with magnetic resonance angiography (MRA) or spiral computed tomographic (CT) angiography, and, if these studies are inadequate or if questions remain, then formal cerebral angiography.

Aneurysms may demonstrate evidence of their presence or of growth, before rupture, in other ways besides headache. Premonitory manifestations depend on the location of the aneurysm and include diplopia, visual field deficits, or facial pain (Weir 1994). The difficulty of diagnosing an aneurysm before a major hemorrhage occurs can be appreciated by considering the common occurrence of the alternative diagnoses, including migraine or tension-type headache, meningitis, sinusitis, and influenza. The high morbidity and morality associated with SAH mandates a

high degree of suspicion to allow appropriate treatment of patients whose symptoms indicate they may harbor intracranial aneurysms.

PHYSICAL FINDINGS

Unruptured Aneurysms

Because aneurysms can produce catastrophic hemorrhage before they reach a size that would produce neurological deficits, the lack of clinical findings should not preclude further diagnostic evaluation. The physical findings in patients with unruptured aneurysms are determined in part by the size and location of the aneurysm, although few aneurysms can be diagnosed with confidence on the basis of clinical presentation alone. Thus aneurysms arising from the anterior communicating artery can produce visual field defects, endocrine dysfunction, or localized immal headache. Aneurysms of the internal carotid artery can produce oculomotor paresis, visual field deficits, impaired visual acuity, endocrine dysfunction, and localized facial pain. Aneurysms of the internal catotid artcty in the cavernous sinus can produce a cavernous sinus syndrome when they reach a sufficient size. Those of the middle cerebral artery can produce aphasia, focal arm weakness, or paresthesias. Basilar bifurcation aneurysm can be associated with oculomotor patesis, although the clinical features of posterior circulation aneurysms seldom permit diagnosis before they rupture.

Of primary importance is altered oculomotor nerve function. This nerve is affected most commonly by an internal carotid artery aneurysm arising at or near the origin of the posterior communicating artery. Much less frequently, an aneurysm of the posterior circulation may affect this nerve. A third nerve palsy secondary to an aneurysm usually is associated with a dilated pupil and ptosis, which contrasts with those caused by an ischemic lesion of the nerve, such as might occur in patients with diabetes, in whom pupillary function is usualh preserved. However, this distinction is not uniformly reliable, and aneurysms should be suspected in all cases of new onset painful third nerve dysfunction.

Subarachnoid Hemorrhage

The physical findings in patients with ruptured aneurysms depend in part on the amount and location of the hemorrhage. Aneurysmal rupture can result in hemorrhage into the subarachnoid space alone or in combination with subdural hematoma, intracerebral hematoma, or intraventricular hemorrhage. Thus the immediate physical findings can vary from slight meningismus to profound neurological deficits with coma or death. Because treatment and prognosis depend to a great extent on the clinical Status of the patient, a grading scale based on the neurological presentation of the patient is used routinely. These grading scales are simple to use and should be noted for all patients presenting with subarachnoid hemorrhage. The two systems that are in most common use are the Hunt and Hess classification and the World Federation of Neurological Surgeons grading scale (Table 57C.1), which is based in part on the Glasgow Coma Scale (see Chapter 5, Table 5.4).

Table 57C.1: Hunt and Hess and World Federation of Neurological Surgeons Scale

Hunt and Hess Scale
Grade 0: Asymptomatic
Grade 1: Slight headache, no neurological deficit
Grade II: Severe headache but no neurological deficit other than perhaps a cranial nerve palsy
tirade III: Drowsiness and mild deficit
Grade IV: Stupor, moderate to severe hemiparesis, and possible early rigidity and vegetative disturbances
Grade V: Deep coma, decerebrate rigidity, and moribund appearance
World Federation of Neurological Surgeons Scale
Grade I: GCS 15; motor deficit absent
tirade II: GCS 13 or 14; motor deficit absent
Grade III: GCS 13 or 14; motor deficit present
Grade IV: GCS 7-12; motor deficit absent or present
tirade V: GCS *3-6;* motor deficit absent or present

GCS = Glasgow Coma Scale.

LABORATORY STUDIES

The laboratory evaluation of patients suspected of having a ruptured or unruptured intracranial aneurysm uses a combination of CT scan, magnetic resonance imaging (MRI), lumbar puncture, and angiography.

Unruptured Aneurysms

A conventional CT scan may, on occasion, demonstrate an intracranial aneurysm (Figure 57C.1). Most frequently, these are large or giant aneurysms with peripheral calcification on an unenhanced scan, and central dense enhancement on contrasted studies. Such aneurysms may be quite large and mimic intracranial neoplasms. Smaller aneurysms also have been detected with high-resolution CT.

The CT scanner can also be used in conjunction with software-based reconstruction techniques of maximal intensity projections, surface-shaded displays, or multiplanar reconstructions to produce three-dimensional CT angiograms. These images not only provide documentation of the aneurysm, but can be a useful aid to understanding the morphology of the aneurysm and its relationship to adjacent normal vessels (Plates 57C.I and 57C.II). CT angiography is able to detect calcium within the wall or

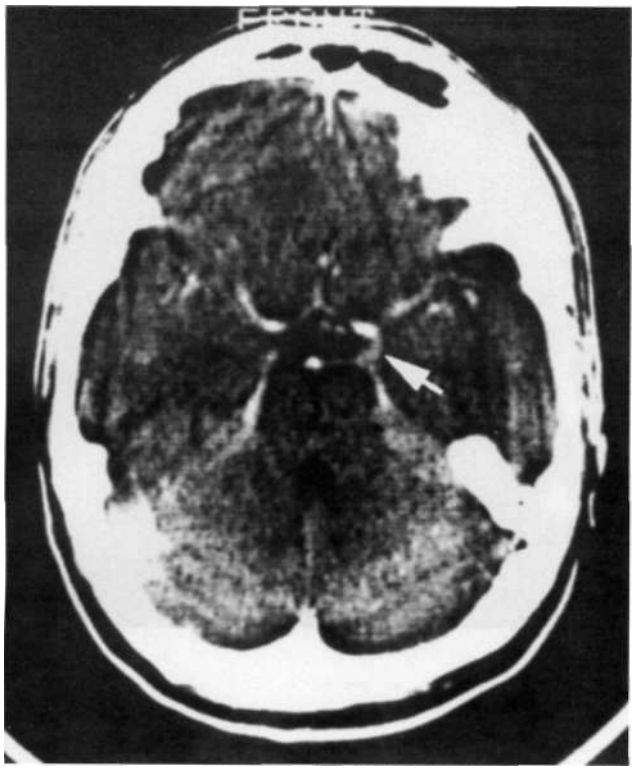


FIGURE 57C.1 Postcontrast computed tomographic scan demonstrating a left posterior communicating artery aneurysm *[arrow).*

neck of an aneurysm, a finding that may have an effect on therapeutic options.

MRI also can detect intracranial aneurysms (Figure 57C.2). Specialized pulse sequences and postprocessing techniques are used to produce MRAs that can visualize aneurysms as small as 4 mm and, unlike CT angiography, does not require administtation of contrast material. Both of these studies are considered noninvasive, and are not associated with the risks of conventional cerebral angiography.

Subarachnoid Hemorrhage

The conventional CT scan is indispensable for delineating the amount and location of blood in the subarachnoid space (Figure 57C.3). The sooner the CT scan is performed in relation to the suspected hemorrhage, the greater the likelihood of visualizing blood. In the setting of a suspected acute SAH, the CT remains the procedure of choice because MRI is less effective in detecting blood early after **the** rupture of an aneurysm. The location of the blood can indicate the site of aneurysmal rupture. Blood in the basal cisterns is seen with ruptured aneurysms in any location, but is most common with those of the internal carotid and basilar artery. Blood in the sylvian fissure is most common in middle cerebral artery aneurysms. Intraventricular blood is associated with anterior communicating and basilar artery aneurysms. Intracerebral hemorrhages of the frontal lobe can be seen with anterior communicating artery aneurysms, and those of the temporal lobe with middle cerebral artery aneurysms.

SAH is not always detected by CT scan. The amount of extravasated blood and the time interval between the SAH and the scan affect the percentage of negative study results. Modern-generation CT scanners can detect the presence of acute SAH in 90-95% of patients who undergo a scan within 24 hours after the hemorrhage. The sensitivity decreases to 80% at 72 hours. A negative CT scan result in a patient with the appropriate history of SAH should he followed by a lumbar puncture. If the CT scan demonstrates a characteristic SAH, there is lirtle to be gained by performing a lumbar puncture.

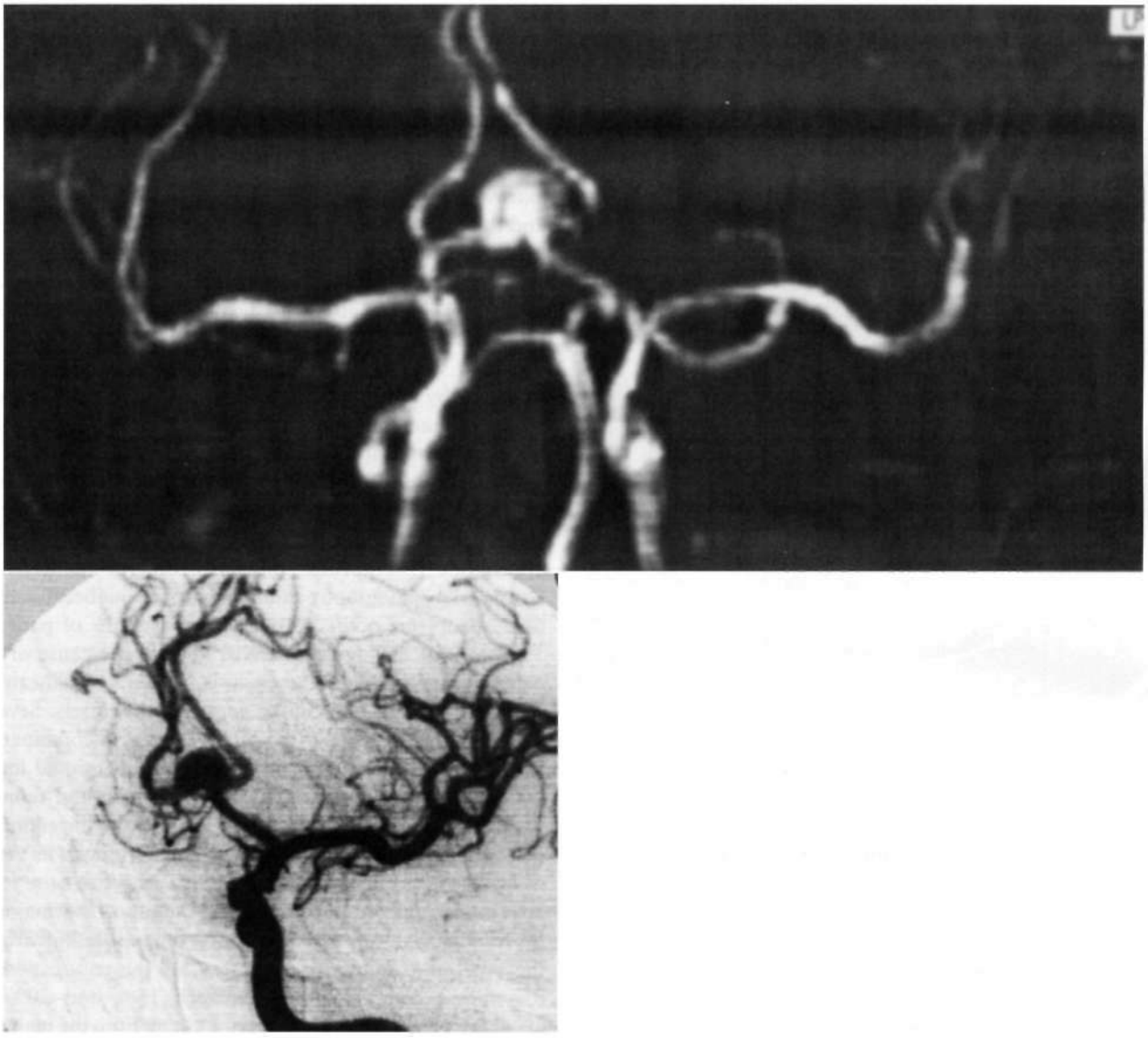
If either the CT scan or the lumbar puncture is positive for SAH, an angiogram should be obtained. Angiography should be performed as soon as reasonably possible so that appropriate therapeutic measures can be undertaken. Four-vessel angiography should be carried out because multiple aneurysms occur in approximately 20% of patients. The goals of angiography are to identify the cause of the hemorrhage and, if an aneurysm is present, to delineate its neck and the relationship to surrounding vessels. Several views may be required to fulfill these goals. A combination of conventional angiography and three-dimensional imaging techniques is often useful in determining and refining treatment strategies for microsurgical clipping or endovascular coiling. The aneurysm is named according to its vessel of origin. Approximately 80-85% of aneurysms arise from arreries located in the anterior circulation, the majority of which occur on the posterior communicating artery, the anterior communicating artery, or the trifurcation of the middle cerebral artery. Between 15% and 20% of aneurysms arise from rhe posterior circulation, the majority of which occur at the bifurcation of rhe basilar artery or at the origin of the posterior inferior cerebellar artery on the vertebral artery.

ANEURYSM PATHOGENESIS AND CAUSE

Several classifications of aneurysms have been proposed. Thar suggested by Weir (1985) is summarized in Table 57C.2. This morphological classification is helpful in defining the different natural history of these lesions. Intracranial aneurysms are classified on the basis of their morphology as saccular, fusiform, or dissecting. Further classification on the basis of presumed cause is also possible.

Saccular Aneurysms

Saccular, or berry, aneurysms are the most common form of aneurysms and are most often responsible for



B

FIGURE S7C.2 (A) Three-dimensional time-of-flight magnetic resonance angiogram reveals an aneurysm of the anterior communicating artery. (B) Left internal carotid artery angiogram, which confirmed the anterior communicating artery aneurysm demonstrated on the magnetic resonance angiogram.

aneurysmal subarachnoid hemorrhage. Saccular aneurysms may arise from defects in the muscular layer of cerebral arteries that occur at vessel bifurcations and from degenerative changes that damage the internal elastic membrane, resulting in weakness of the vessel wall. They usually occur on the first- or second-order arterial branches of the vessel emanating from the circle of Willis. Evidence suggests that both genetic and environmental factors contribute to the development of saccular aneurysms. The evidence that genetic factors are important comes from the documented association of intracranial aneurysms with heritable connective tissue disorders such as autosomal dominant polycystic kidney disease, Ehlers-Danlos' syndrome type IV, neurofibromatosis type I, and Marfan's syndrome. The familial occurrence of intracranial aneurysms also points to a role for genetic factors. In those patients who have a first-degree relative with an aneurysmal SAH, the tisk of a ruptured aneurysm is four times higher than the risk in the general population. A role for acquired factors in the pathogenesis of saccular aneurysm is suggested by the mean age of 50 for patients with aneurysmal SAH, and the increased incidence of hemorrhage occurring with age. Cigarette smoking is a risk factor in all population studies, and a role for systemic hypertension, although not as strong as that of cigarette smoking, in the cause of aneurysm formation appears likely.

Saccular aneurysms may also be caused by infection, trauma, or neoplasm. Mycotic aneurysms result from infected emboli that lodge in the arterial intima or the

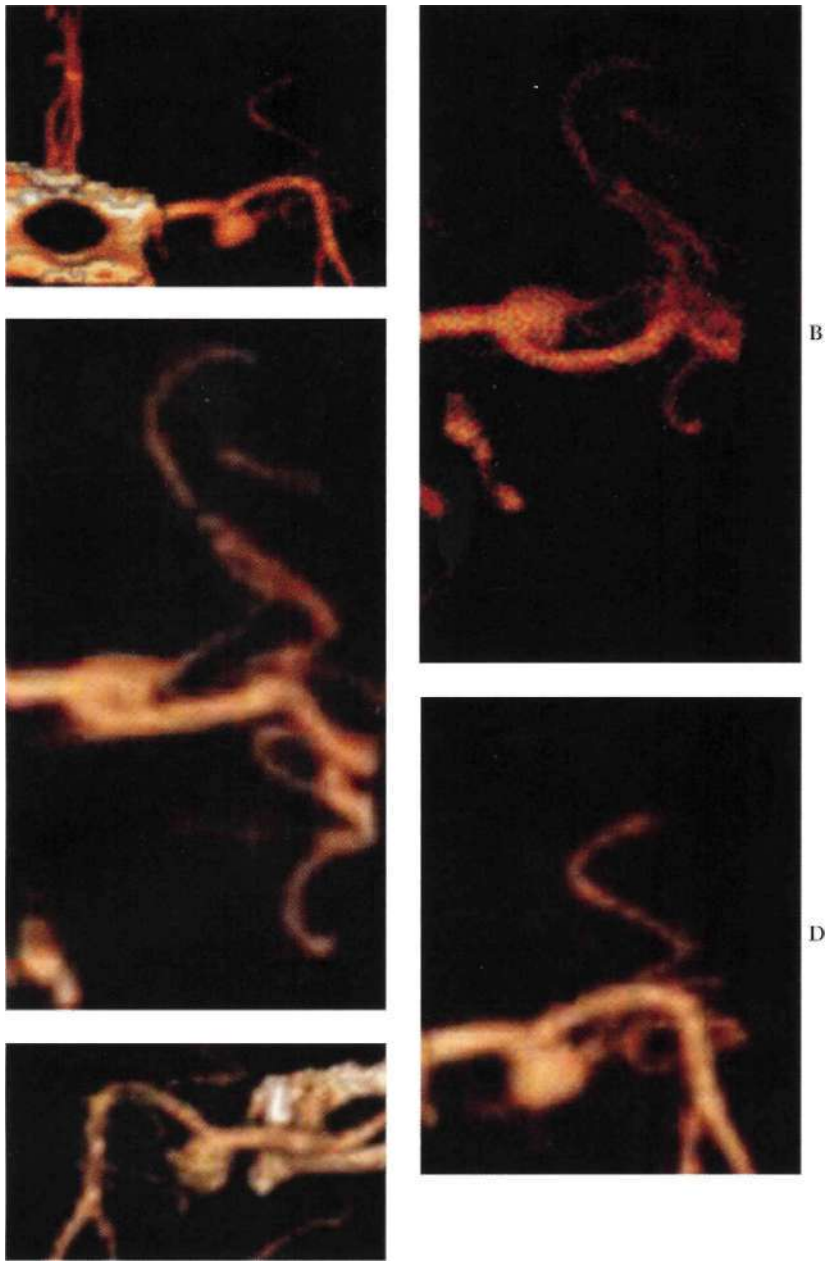


PLATE 57C.T (A-E) Four-dimensional surface shaded display computed tomographic angiogram with progressive rotation of views demonstrates a left middle cerebral artery trifurcation aneurysm. (E) Rotated and inverted view of the aneurysm demonstrates an M2 middle cerebral artery branch rising from rhe base of the aneurysm and wrapping around the posterior dome.

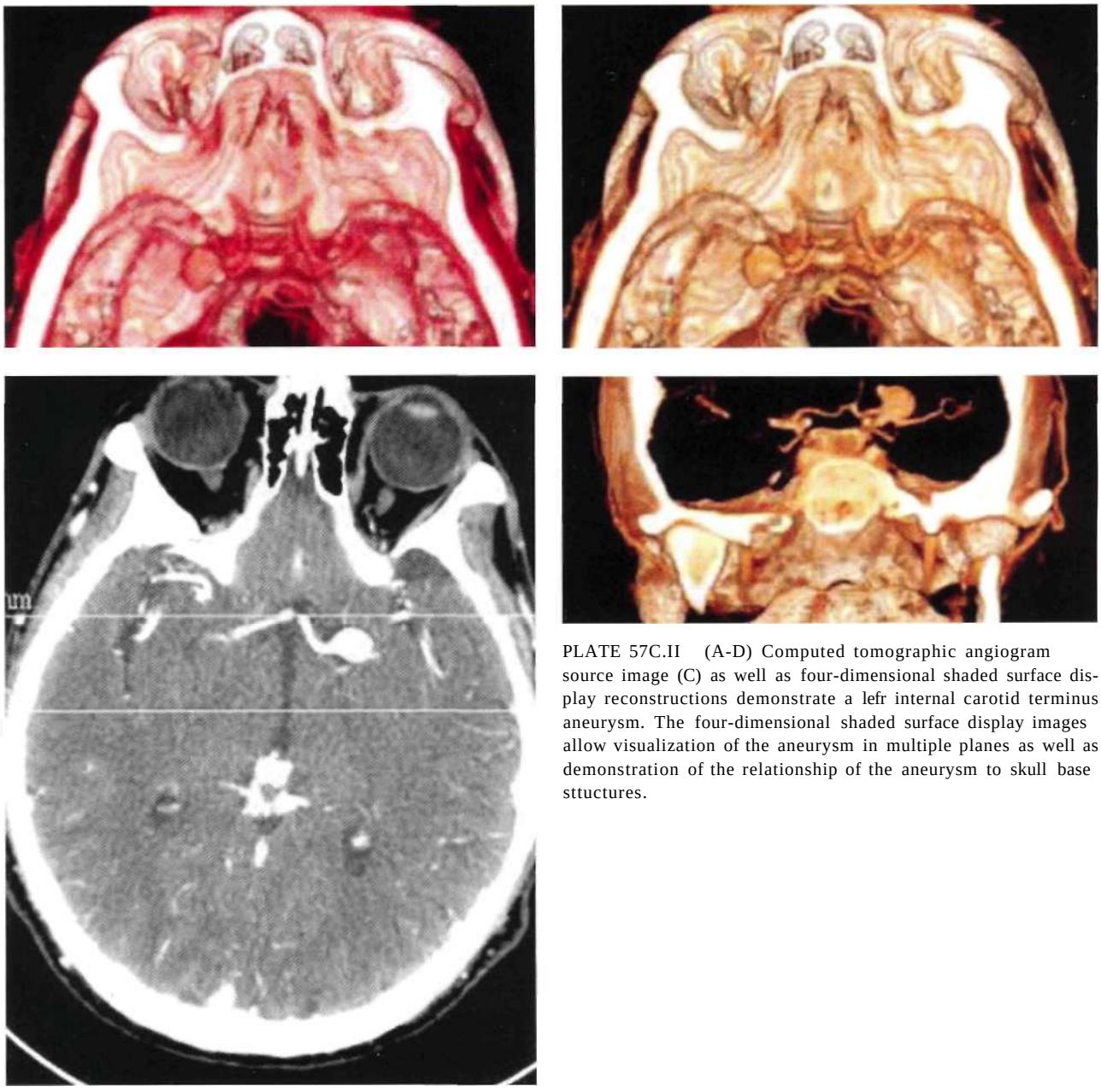


PLATE 57C.II (A-D) Computed tomographic angiogram source image (C) as well as four-dimensional shaded surface display reconstructions demonstrate a lefr internal carotid terminus aneurysm. The four-dimensional shaded surface display images allow visualization of the aneurysm in multiple planes as well as demonstration of the relationship of the aneurysm to skull base sttuctures.

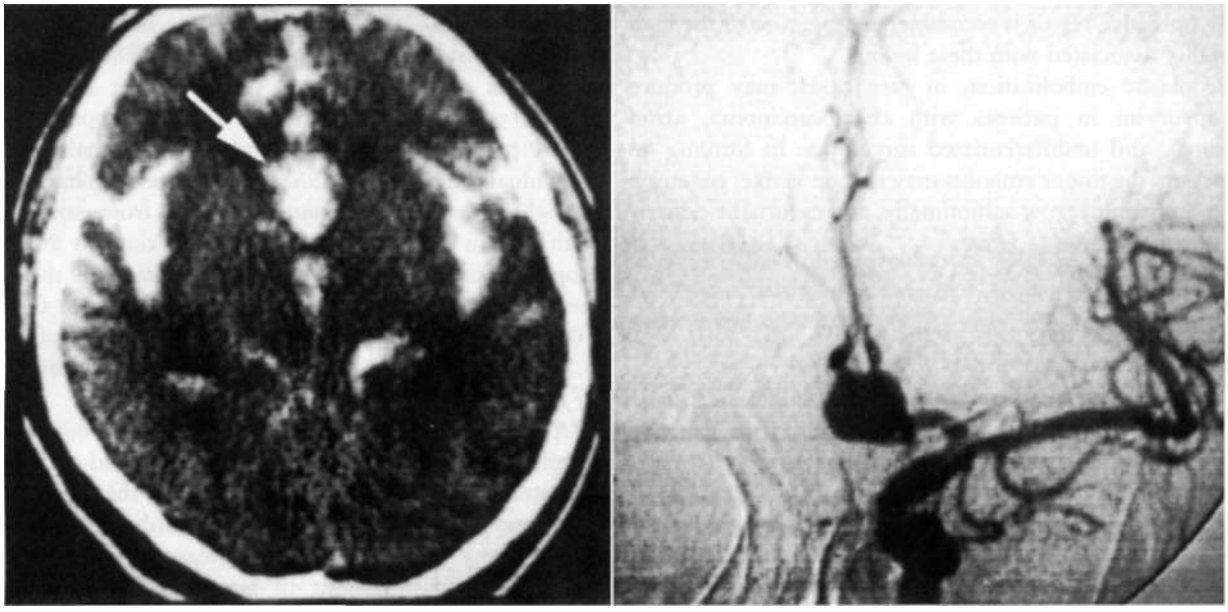


FIGURE 57C.3 (A) Uucontrasted computed tomography shows diffuse subarachnoid hemorrhage. Note blood in the septum pellueidum indicative of an anterior communicating artery aneurysm. (B) Left internal carotid artery angiogram confirmed the location of the anterior communicating artery aneurysm.

vasa vasorum and account for approximately 5% of all intracranial aneurysms. They occur most frequently in patients with subacute bacterial endocarditis, congenital heart disease, or a history of intravenous drug use, and are usually located on more distal branches of the cerebral vasculature. Proper management includes appropriate intravenous antibiotic therapy, with surgery in selected cases. Fungal aneurysms, which are much rarer than bacterial, usually are associated with arteritis and thrombosis and have been uniformly fatal.

Traumatic aneurysms are rare but can be caused by either blunt or penetrating head injury. Such aneurysms occur at sites other than bifurcations. Angiograms are not routinely performed following head trauma, and these lesions may not be detected, hut they should be considered in patients who suffer delayed deterioration.

Table 57C.2: Surgical classification of intracranial arterial aneurysms

Morphology
Saccular
Fusiform
Dissecting
Size
<3 mm
3-6 mm
7-10 mm
11-25 mm
>25 mm (giant)
Location
Anterior circulation arteries
Internal carotid
Carotid canal
Intracavernous
Paraclinoid (ophthalmic)
Posterior communicating region
Anterior choroidal region
Carotid bifurcation
Anterior cerebral
A1 (main branch)
Anterior communicating region
A2 (distal): callosomarginal region or distal pcricallosal
Middle cerebral
Ml (main branch): lcnticulostriate or temporal branch regions
Bifurcation
Peripheral
Posterior circulation arteries
Vertebral
Main trunk
Posterior inferior cerebellar artery region
Basilar
Bifurcation
Superior cerebellar artery region
Anterior inferior cerebellar artery region
Basilar trunk
Vertebrobasilar junction region
Posterior cerebral
PI (first branches of basilar—distal to apex)
P2 (distal posterior cerebral)

Source: Reprinted with permission from Weir, B. 1985, "Intracranial aneurysms and subarachnoid hemorrhage; An overview," in *Neurosurgery,* eds R. H. Wilkins, S. S. Rengachary, McGraw-Hill, New York.

Early operative repair is recommended because of the high mortality associated with these lesions.

Neoplastic embolization, in rare cases, may produce an aneurysm in patients with choriocarcinoma, atrial myxoma, and undifferentiated carcinoma. In forming an aneurysm, the tumor embolus may remain viable, penetrate the endothelium, grow subintimally, and eventually destroy the arterial wall.

Fusiform Aneurysms

Fusiform or dolichoectatic aneurysms are classified separately from saccular aneurysms, although in some patients these types may overlap. The basilar artery is most commonly affected, although these aneurysms also can be seen in the anterior circulation. Only rarely are these lesions associated with SAH. Their presentation is characterized by cranial nerve or brainstem dysfunction secondary to direct compression or by embolization from intraluminal thrombus.

Dissecting Aneurysms

Dissecting aneurysms result from cystic medial necrosis or a traumatic tear in the endothelium and subadjacent layers of the artery, allowing the formation of a false lumen. The false lumen may connect with the true lumen distally or may rupture through the remaining external arterial wall. Such aneurysms can occur in any portion of the extracranial or intracranial arterial circulation. Trauma is a common cause in the neck and anterior circulation, but is a rare cause in the posterior circulation. Connective tissue diseases such as Marfan's syndrome and other disorders such as fibromuscular dysplasia predispose to arterial dissections. The treatment of these lesions has not been standardized; patent artery occlusion, with or without bypass grafting, using conventional microsurgical or neuroendovascular techniques may be necessary. The use of endovascular stent placement, with or without direct aneurysm obliteration, can eliminate the need for patent vessel occlusion in many instances.

EPIDEMIOLOGY

The incidence and prevalence of unruptured intracranial aneurysms and aneurysmal SAH should be considered separately. Intracranial aneurysms are found on postmortem examination in between 1% and 6% of adults in large autopsy series (Schicvink 1997). The frequency of intracranial aneurysm seen during angiography for patients not suspected of harboring an aneurysm is between 0.5% and 1.0%. The overall incidence of SAH from aneurysms is approximately 7-10 per 100,000 people per year (Mcnghini et al. 1998), but this figure includes children, who have a very low incidence of rupture. The mean age of rupture is approximately 50 years. Among adults older than 30 years of age, the incidence of SAH is approximately 40-50 per 100,000 per year, and nearly one half of these individuals die from their SAH. Various reviews have noted a slight female predominance of SAH from aneurysms, with a mean age of hemorrhage of approximately 50 years. Ruptured aneurysms rarely occur in children, and there is a steady increase in the incidence of rupture from 0.3 per 10,000 persons per year between 25 and 34 years of age to 3.7 per 10,000 persons per year for patients 65 years of age or older.

A special category of patients are those who have a family history of aneurysms and SAH. Familial occurrence of intracranial aneurysms is defined by the presence of aneurysms in two or more first- to third-degree relatives without any known hereditary disease. It is not known whether the pathogenesis of familial intracranial aneurysms differs from that of the general population (Ronkainen ct al. 1998). In a community-based study from Rochester, MN, the relative risk of SAH among first-degree relatives of patients with the familial form of SAH was four times higher than the general population. Other studies have shown that in patients with familial intracranial aneurysms, there is a lower mean age at the time of rupture compared with SAH in the general population (Ronkainen et al, 1998). Screening studies, with MRA, CT angiography, or conventional angiography, for the presence of aneurysms in this group of patients appears warranted.

COURSE OF ANEURYSMAL SUBARACHNOID HEMORRHAGE

The International Cooperative Study on the Timing of Aneurysm Surgery used the Glasgow Outcome Scale to report on Outcomes at 6 months following SAH for 3521 patients and noted the following: 57.6% had good recovery; 9.1% were moderately disabled; 5.5% were severely disabled; 1,8% had vegetative survival; and 26.0% died. Approximately 12% of patients died before reaching a hospital, and approximately 40% of patients who were hospitalized died within 30 days {Olafsson et al. 1997). The total mortality rate in the first year was 63% and was 72% within the first 5 years. The authors noted little change in the initial mortality and morbidity of patients suffering an SAH over the past several decades and concluded that only the detection and treatment of intracranial aneurysms prior to rupture has any influence on the frequency of sudden death from SAH. The subject of detection and treatment of unruptured aneurysms is discussed in the following section of this chapter.

In a study of late morbidity and mortality in patients treated nonoperatively following SAI1 from a single

aneurysm, the main cause of death in patients surviving 6 months was recurrent hemorrhage. Rebieeding occurred at a rate of 3.5% per year during the first decade.

Functional outcome also must be considered when assessing patient management. Subtle cognitive dysfunction and psychosocial impairment can prevent the return to premorbid lifestyle in up to 20% of survivors. Neuropsychological deficits and cognitive dysfunction arc common among survivors after SAH. Cognitive impairment is highest among those patients who experience global cerebral edema, and those who suffer left-sided infarcts (Kreitcr et a I. 2002). Long-term quality of life may be diminished in many SAH survivors in that 41% have memory problems, 35% experience fatigue, 48% undergo personality changes, and 26% complain of insomnia {Ogden et al. 1997). The combination of these changes adversely **affects the** ability of patients who suffer an SAH to return to work, and approximately one half of survivors do not return to previous full-time employment. Wiebers et al. (1992) reported the annual estimated lifetime cost of aneurysmal SAH in the United States to be 1.8 billion dollars.

TREATMENT AND PROGNOSIS

Elimination of an intracranial aneurysm is the cornerstone of therapy. The risk reduction for subsequent SAH afforded by surgery is well documented in population-based studies (Olafsson et al. 1997). Every effort should be made to direct appropriately selected patients toward surgery as soon as possible. In general, patients in good condition are best managed by *early Intervention to secure the aneurysm.* The benefits of early treatment include prevention of rebieeding, improved prevention and management of delayed ischemic deficits from vasospasm, and a shorter hospital course with potentially fewer complications.

The major complications following SAH are the following: ischemic deficits, 27%; hydrocephalus, 12%; brain swelling, 12%; recurrent hemorrhage, 11%; intracranial hematoma, 8%; pneumonia, 8%; seizures, 5%; gastrointestinal hemorrhage, 4%; syndrome of inappropriate antidiuretic hormone (SIADH) secretion, 4%; and pulmonary edema, 1%. As detailed in the following section, the initial management of SAH patients must proceed rapidly and comprehensively to prevent or lessen the chance of demise because of any of these conditions, but especially the two that produce the greatest morbidity and mortality, rebieeding and delayed ischemic deficits. Both immediate and delayed effects must be anticipated and treated (Mayberg et al. 1994; Ratcheson and Wirth 1994; Bederson 1997).

The importance of appropriate intensive care management of SAH patients cannot be overestimated, because secondary **insults are** associated with negative clinical outcomes (Enblad and Pcrsson 1997).

Although aneurysm rupture almost universally results in SAH, the location of the hemorrhage is not confined to the subarachnoid space. Patients with massive intraventricular hemorrhage or intracerebral hematomas tend to die earlier than those with blood in other locations. **The** consequences of bleeding into the brain parenchyma or ventricles include an elevation of intracranial pressure caused by mass effect and acute hydrocephalus. Either of these conditions may require immediate treatment separately or in combination with definitive aneurysm treatment.

Central Nervous System Complications

Hydrocephalus caused by SAH can be immediate or delayed iMcConnick l[L>>L]J-i. Acme dilatation occurs in 20% of patients; it is caused by increased ventricular outflow resistance, appears within 3 days of the SAH, and requires immediate treatment. Delayed ventricular dilatation usually occurs after the tenth day, and is seen in 23% of patients. The development of acute hydrocephalus appears to be related to the degree of intraventricular blood, whereas delayed hydrocephalus can be correlated with the amount of SAH. The amount of cisternal blood on the initial CT, the presence of ventricular blood, and long-term treatment with antifibrinolytic agents are significantly related to the development of hydrocephalus.

Of patients with SAH, 3—5% have seizures during their hospitalisation. The use of anticonvulsants in the acute stage is considered standard therapy for the prevention of seizures, although there is no documentation that prophylactic anticonvulsant therapy has any influence on the development of chronic seizures. Epilepsy develops in approximately 15% of patients who suffer an SAH, and it develops within the first 18 months in more than 90% of these patients. The greatest risk factors for the development of late epilepsy are poor neurological grade on admission, rupture of a middle cerebral artery aneurysm, cerebral infarction secondary to vasospasm, and shunt-dependent hydrocephalus.

Systemic **Complications**

Neurogenic pulmonary edema, considered to be a mixed pressure and permeability edema characterized by the rapid onset of respirarory failure with a protein concentration greater than 4.5 g/dL in the edema fluid, may develop in SAH patients. Most patients with neurogenic pulmonary edema from SAH are comatose. Although initially believed to be secondary to a massive sympathetic discharge producing generalized vasoconstriction, more recent studies suggest that a direct neurogenic effect on the lungs causes pulmonary capillary endothelial damage. Treatment includes monitoring and, if possible, reduction of intracranial pressure, mechanical ventilation with positive

end-expiratory pressure, and monitoring the cardiovascular status to attain the lowest pulmonary wedge pressure **that** maintains an effective cardiac output.

Alterations of the electrocardiogram are the most frequent cardiac abnormality in patients with SAH. The most common changes include prolongation of the QT interval, ST-segment elevation or depression, and increased amplitude or deep inversion of the T waves (neurogenic T waves). These abnormalities are believed to result from disturbances of ventricular repolarization caused by a derangement of autonomic control of the heart. They represent epiphenoniena that reflect intracranial abnormalities without contributing directly to morbidity or mortality, although subendocardial hemorrhages arc common in patients dying from SAH.

Hyponatremia usually is associated with the SIADH secretion, but in some patients with SAH, a ttue natturesis or cerebral salt-wasting syndrome may occur. Assessment of the intravasculat volume status, body weight, and blood volume can differentiate these disorders and allow proper treatment. Patients with a true natrurcsis have evidence of postural hypotension and tachycardia, decreased blood and intravascular volume, elevated hematocrit, and decreased body weight; sodium and volume replacement are needed for proper treatment. SIADH, on the other hand, is associated with a normal cardiovascular status, a normal or low hematocrit, and notmal or increased body weight; the hyponatremia seen in this condition is dilutional or false, as opposed ro the true hyponatremia seen with cerebral salt wasting. Symptoms of SIADH depend on both the level of hyponatremia and the fate at which it develops. Although the best therapy is fluid restriction, this is often balanced by the need to maintain a high intravascular volume to prevent the development of delayed ischemic deficits secondary to vasospasm. In either case, rapid correction is rarely needed, and no more than one half the sodium deficit should be replaced during the first 24 hours.

Prevention of Repeat Hemorrhage and Delayed Ischemic Deficits

Rebleeding

Historically, the most feared complication for survivors of the initial hemorrhage had been recurrent bleeding, which occurred in approximately 15-20% of patients, and was associated with a 40-78% mortality. Treatment of the aneurysm was believed to be best when delayed, because early operative intervention was deemed to be too dangerous. In recent years, a tendency toward early treatment has substantially teduced the tisk of teblccding (Figure 57C.4).

The improved outcome may be related not only to a decrease in the devastating consequences of tchemorrhage, but also to the ability ro provide more effective treatment of vasospasm after the aneurysm has been obliterated. It was believed that cerebral vasospasm and ischemia, the leading

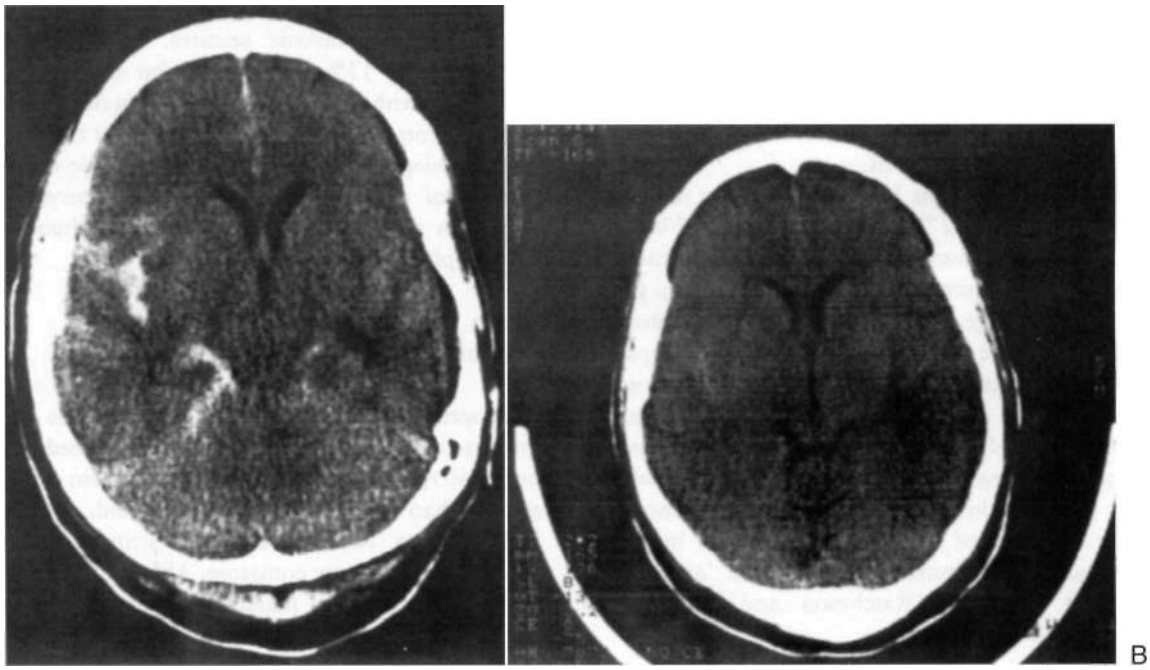


FIGURE S7C.4 (A) Uncontested computed tomography shows a subarachnoid hemorrhage in the right sylvian fissure. (B) The patient suffered a deterioration in neurological status, and a repeat uneontrasted computed tomographic scan performed 2 hours later shows increased blood indicative of aneurysmal rebleeding.

causes of death and disability among survivors of an initial aneurysm rupture, were increased by early surgery and, as such, would negate the benefits of reduced rebleeding following early operation. This was prior to the availability of new treatment options for the prevention and treatment of vasospasm following SAH. According to The International Cooperative Study on the Timing of Aneurysm Surgery (Kassell et al. 1990), 13.5% of all patients who experience aneurysmal SAH suffer delayed cerebral ischemia resulting in permanent disability or death. Of the 1494 patients in that study who died or became disabled, delayed ischemia caused by cerebral vasospasm accounted for 32% of the total; in compatison, the direct effect of aneurysmal rupture resulted in 25% and rebleeding in 17.6% of such outcomes.

Although rehemorrhage can be an immediate, devastating, and itrevcrsible event, the consequences of vasospasm evolve more slowly and are now more predictable, preventable, and treatable. Early aneurysm treatment should be considered for the majority of patients who suffet an aneutysmal SAH. A prospective study from three centers indicates that despite attempts at early surgery, rebleeding is still a significant problem, because only approximately one half of the patients were operared on within 72 hours, and 35% of the patients with a poor outcome had suffered from rebleeding (Roos er a I. 1997). Early recognition of aneurysmal rupture, and prompt treatment at, or transfer to, a facility, with a high volume of SAH patients (Bardach et al. 2002), which is equipped to provide the comprehensive care needed to manage these patients is of utmost importance.

Pharmacological means to prevent rebleeding may be used prior to definitive therapy. Inhibition of the breakdown of the blood clot around and within the ruptured aneurysm wall should lessen the chance of rehemorrhage, and antifibrinolytic agents can reduce the rebleeding rate, but, with long-term use, are associated with increased vasospasm and delayed ischemic neurological deterioration. Thus there was no change in the overall mortality from SAH when antifibrinolytic agents were used in conjunction with delayed sutgery because the decrease in mortality from rebleeding was offset by an increased mortality from ischemic complications. The use of short-tetm antifibrinolytic therapy, however, can prevent rebleeding without provoking increased ischemic complications, and may improve outcome (Hillman et al. 2002).

The definitive method for prevenrion of rebleeding is to secure the aneurysm as soon as possible. Two forms of treatment are widely used for mosr inrracranial aneurysms: microsurgical clipping and endovascular coiling. Surgical clipping is considered the treatment of choice for most intracranial aneurysms. Advances in microsurgical techniques, operative approaches, and clip design have improved the safety of craniotomy for aneurysm clipping. The most common technique for endovascular treatment of intracranial aneurysms involves the placement of detachable coils within the aneurysm sac (Figures 57C.5 and 57C.6). The results of aneurysm occlusion using this method suggest that it is most effective in treating aneurysms smaller than 25 mm in diameter, and with neck width smallct than one half the dome width. In a series of 403 patients with acute SAH treated at eight centers in the United States, complete

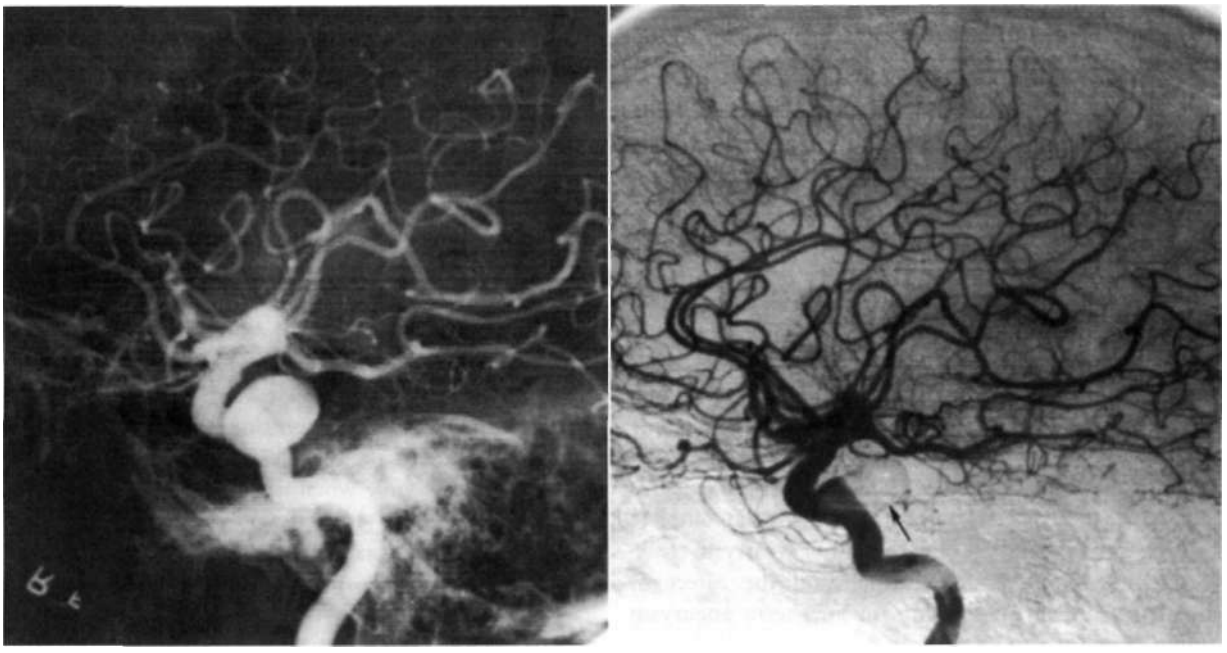


FIGURE 57C.5 (A) Lateral right internal carotid angiogram reveals a large cavernous carotid artery aneurysm. (R) Lateral right internal carotid artery angiogram following balloon embolization *(arrow)* shows almost complete obliteration of the aneurysm.

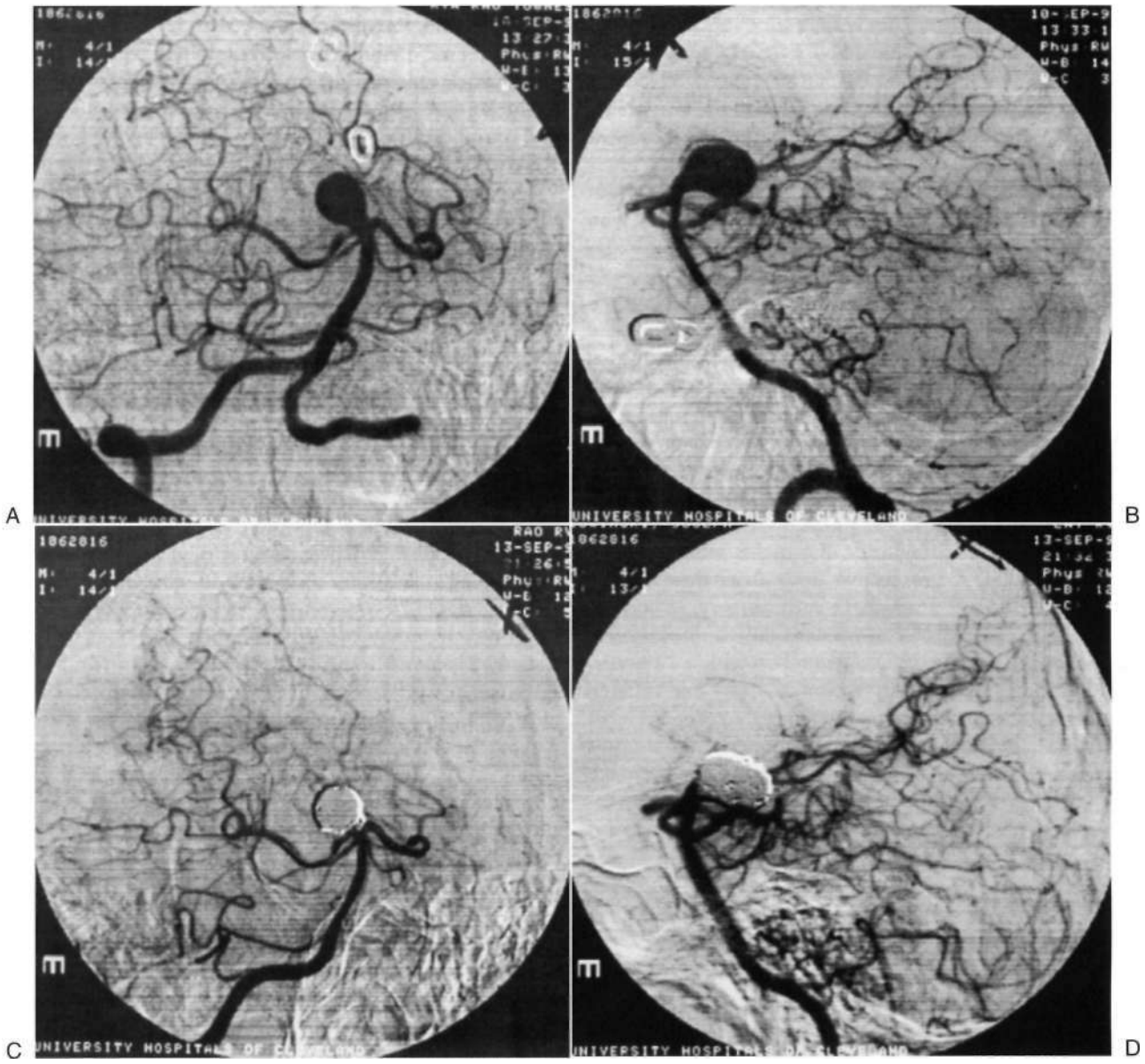


FIGURE 57C.6 Right anterior ohlique (A) and lateral left vertebral artery (B) angiogram demonstrating a large basilar tip aneurysm. Right anterior oblique (C) and lateral angiograms (D) following treatment with Guglielmi detachable coils show obliteration of the aneurysm.

aneurysm obliteration was achieved in 70.8% of aneurysms with a small neck and 35.0% of large aneurysms, and there was an 8.9% immediate procedural morbidity (Vihuelaetal. 1997). Despite advances in coil design and technology, complete aneurysm obliteration rates have remained stable at 29-31% in several recent studies (Gruber et al. 1999; Raftopaulos et al. 2000; Lott et al. 1999). Karly aneurysm rebleeding was not adversely affected by incomplete obliteration in these studies, hut the goal of aneurysm treatment remains complete obliteration, and the affect of incomplete aneurysm obliteration on long-term aneurysm rebleeding remains a concern.

The results of the first prospective randomized trial comparing craniotomy for aneurysm clipping and cndovascular coiling for ruptured intracranial aneurysm by The International Subarachnoid Aneurysm Trial (ISAT) were published in 2002. At 1 year following treatment, patients with aneurysms that were judged by both the neurosurgeon and the interventional neuroradiologist to be suitable for cither clipping or coiling had a reduction in the risk of poor outcome when treated with coiling compared with those patients treated with clipping. The primary outcome measure was the proportion of patients dead or disabled, defined by a modified Rankin scale score of 3-6, at 1 year. Recruitment was stopped after randomization of 2143 eligible patients were selected from 9278 patients with a subarachnoid hemorrhage. Analysis of these paticnts demonstrated an absolute risk reduction of 6.9%

(22.6% relative risk reduction) of dependency or death at 1 year with endovascular treatment. The ISAT report is an important step in defining the roles of endovascular and microsurgical treatment of intracranial aneurysms, although conclusions drawn from this study cannot be generalized to all ruptured and unruptured intracranial aneurysms, and certain caveats are needed in interpreting the results of this study. As noted in the accompanying editorial, "clinical equipoise" did not exist in 80% of the 9278 patients, and in the 7135 patients not randomized, for which follow-up was not available, more patients underwent craniotomy for aneurysm clipping than endovascular aneurysm coiling (Nichols er al. 2002). The differences in outcome between treatments were mainly in the modified Rankin scale score of 3 (significant testriction in lifestyle) and modified Rankin scale score of 2 (some restriction of lifestyle) groups, and there was no difference in mortality. The ability of a questionnaire to reliably differentiate moderate from moderately severe functional disability is uncertain (Nichols et al. 2002). Definitive treatment of an aneurysm should eliminate the risk of post-treatment rebleeding. Post-treatment rebleeding of the treated aneurysm within 1 year occurred in 2.4% (26/1048) endovascular cases, and in 1.0% (10/994) surgical cases. In addition, 139 patients treated by coiling required further treatment compared with 31 patients treated by clipping. Concerns about durability remain with respect to rebleeding rates, risk of recanalization of the aneurysm, and the need for repeat procedures. These issues highlight the necessity of long-term follow-up to determine which of these two forms of treatment is safer and more effective for this subgroup of patients with ruptured aneurysms over their lifetimes. In most comprehensive cerebrovascular centers, these two treatment techniques are considered complementary, and optimal patient care is best achieved by careful consideration of the aforementioned factors in selecting which treatment is most appropriate for each individual patient.

Early treatment to secure an aneurysm can decrease the complications associated with prolonged bed rest, avoid the need for prolonged antifibrinolytic therapy and its attendant complications, and permit more aggressive prevention and treatment of vasospasm and ischemia with blood volume and pressure manipulation, and balloon angioplasty, Advances in microsurgical and endovascular surgery and perioperative management have made carU intervention safer. There is ample evidence that surgery can be performed safely in the time immediately following aneurysmal rupture and may improve outcome (de Gans et al. 2002; Ross et al. 2002).

Early surgery may not be appropriate for every patient with an aneurysmal SAH, but every attempt should be made to secure the aneurysm as soon as possible to prevent rebleeding. Patient selection with respect to grade and timing of intervention is still a matter to be decided by the individual surgeon. Some consider early operation only for patients with good grade aneurysms, whereas others believe the high management mortality associated with patients with grades IV and V hemorrhage, especially younger patients, can be lowered only by early intervention and aggressive postoperative management.

Vasospasm and Delayed Ischemic Neurological Deficits

As indicated earlier, a major cause of morbidity and mortality after SAH is delayed ischemic deterioration. Approximately 5 days after SAH, any or all of the major branches of the circle of Willis that are exposed to blood may develop vasospasm, which may lasr for 1-2 weeks or longer.

SAH can alter the mechanisms that control cerebral blood flow and metabolism (Bcderson 1997). Chemical control of blood flow by carbon dioxide is altered in patients with SAH. Autorcgulation is commonly lost after SAH. Because the degree of impairment of autoregulation may be different in different regions of the brain, a reduction in cerebral perfusion pressure may cause extreme ischemia in some areas but not in others. These changes in the intrinsic control of cerebral blood flow are particularly deleterious because several factors may operate to reduce cerebral blood flow after SAH, including decreased cerebral perfusion pressure from the raised intracranial pressure as a result of acute hydrocephalus or clot formation.

Blood in the subarachnoid space triggers a pathological process that results in spasm of the vessels of the major branches of the circle of Willis. Thus vasospasm can dramatically decrease the caliber of the cerebral vessels and result in a decreased cerebral blood flow. Correlation of pathological specimens from patients with angiographical narrowing has demonstrated changes in vessel morphology, including subintimal cellular proliferation. Specimens obtained the second week after SAH demonstrate thickening of the arterial wall with medial necrosis. However, angiographics I narrowing is reversible and, on the basis of experimental studies, is more likely to be caused by prolonged but reversible smooth muscle contraction. Because flow in a vessel is inversely proportional to the fourth power of the radius, small changes in vessel caliber can have profound effects. If regional flow decreases below the critical thresholds for membrane integrity, ischemic edema formation and infarction can occur. Focal regions of edema can further impair local blood flow despite an overall normal intracranial pressure.

The term *vasospasm* is often used interchangeably to refer to the clinical condition of delayed ischemic neurological deficits and to the vascular narrowing seen on angiography. This terminology is unfortunate in that angiographic findings do not invariably correlate with the clinical picture. Whether such discrepancies are caused by different thresholds of ischemic tolerance, or to other factors, is not clear. This lack of stricr correlation should

not detract from an appreciation of the importance of delayed ischemic deterioration as a cause of serious morbidity and mortality, because its prevention and treatment are clearly a matter of life or death.

Ischemic complications occur in 24-32% of patients after SAH. The amount of blood in the subarachnoid space is an important prognostic factor, and thus the CT scan is critical to predicting the occurrence of vasospasm, A study of 47 patients with aneurysmal SAH who had CT evaluation within 4 days of the initial bleed found that the amount of blood present on the CT scan correlated well with the location and severity of vasospasm. Of the 18 patients with no blood in the subarachnoid space, only one developed spasm. In the presence of subarachnoid blood clots larger than 5 mm by 3 mm, or layers of blood greater than 1 mm thick in the fissures and basal cisterns, severe spasm occurred in 23 of 24 patients.

The modern management of patients with subarachnoid hemorrhage for prevention and treatment of cerebral vasospasm is based on the optimization of volume status and cardiac output (Findlay 1997). In addition, vasospasm appears to be related to an inhibition of reuptake of calcium, which leads to continued vascular smooth muscle contraction. A meta-analysis of nimodipine, a relatively selective cerebral vasculature calcium channel blocker, in the treatment of patients at high risk for cerebral arterial spasm has confirmed the efficacy of the drug for the prevention of delayed ischemia deficits (Barker and Ogilvy 1996). Despite a decrease in severe neurological deficits, there is no reduction in the degree of angiographical vasospasm. It is not clear whether this implies action on smaller vessels than those visualized angiographically, or Other direct anti-ischemic effects of nimodipine. Recently attention has focused on the beneficial effects of magnesium sulfate in the prevention and treatment of vasospasm. Magnesium sulfate may have a role in the prevention or reversal of vasospasm induced by SAH. $MgS0_4$ may prevent vasospasm by acting as a Ca^{2+} antagonist, because Ca^{+} and Mg^{2+} have opposing effects on vascular tone. $MgS0_4$ may have a similar action in blocking the activation of smooth-muscle contraction, as with the dilating effect on cerebral blood vessels exerted by Ca^{2+} channel antagonists. It may also produce beneficial effects by antagonizing the damaging actions of increased intracellular Ca^{2+} concentration induced by cerebral ischemia; the putative mechanism being Mg^{+} competing with Ca^{2+} for intracellular sites or limiting the influx of Ca from damaged cellular membranes (Vcyna et al. 2002).

Despite improvements in hemodynamic augmentation and medical treatment, the development of vasospasm is still a harbinger of potential deterioration from ischemic deficits. New methods of predicting and detecting vasospasm permit the use of more aggressive treatment modalities such as endovascular balloon dilatation of spastic arteries. Transcranial Dopplcr studies permit bedside evaluation of blood flow velocity (which increases with a reduction in vessel diameter) in the intracranial portion of the internal carotid artery and proximal branches of the circle of Willis. With early detection of velocity changes, it is possible to select patients who should be considered for treatment prior to the development of fixed neurological deficits. Other physiological techniques such as positron emission tomography (PET), single photon-emission computed tomography (SPECT), or Xenon CT may be more accurate depicters of cerebral blood flow in patients with threatened vasospasm, but have the disadvantage of not being available at the bedside.

Endovascular treatment, such as angioplasty with a silicone balloon to treat vasospasm, has become an indispensable treatment modality in the comprehensive management of SAH patients, and can provide dramatic improvement in the function of these patients (Eskridge et al. 1998) (Figure 57C.7). Intra-arte rial administration of vasodilators such as papaverine has somewhat unpredictable results. Although it may be useful for distal spasm, questions remain regarding the longevity of the response of intracerebral blood vessels. Additionally, intra-arterial papaverine may have deleterious effects such as increasing intracranial pressure or inducing systemic hypotension (McAuliffe et al. 1995). F.arly experience with intra-artcrial infusion of verapamil appears to be free of these potentially harmful side effects (Lei et al. 2002).

SPECIAL TREATMENT CONSIDERATIONS

Unruptured Aneurysms

The only method of lowering the initial mortality from SAH is to detect and treat unruptured aneurysms, especially in those patients deemed to be at high risk for aneurysm rupture. Because of the poor overall outcome of patients with intracranial aneurysms after SAH, a strong case can be made for surgical treatment of unruptured aneurysms.

The International Study of Unruptured Intracranial Aneurysms (ISUIA) (1998) examined the issue of treatment for unruptured aneurysms. This study, which included both a retrospective and a prospective component and involved 2621 patients enrolled at 53 participating centers, is the largest study on the natural history and the risks of intervention in patients with unruptured intracranial aneurysms. It revealed a lower rate of rupture of unruptured intracranial aneurysms than was previously thought, and an apparently higher rate of combined morbidity and mortality from treatment than reported in most surgical series. The risk of rupture of an aneurysm of less than 10 mm was 0.05% per year. The risk of rupture was increased to 0.5% per year in patients with a history of previous SAH. Aneurysms greater than 10 mm had an approximately 1% per year risk of rupture, with or without a previous history of subarachnoid hemorrhage.

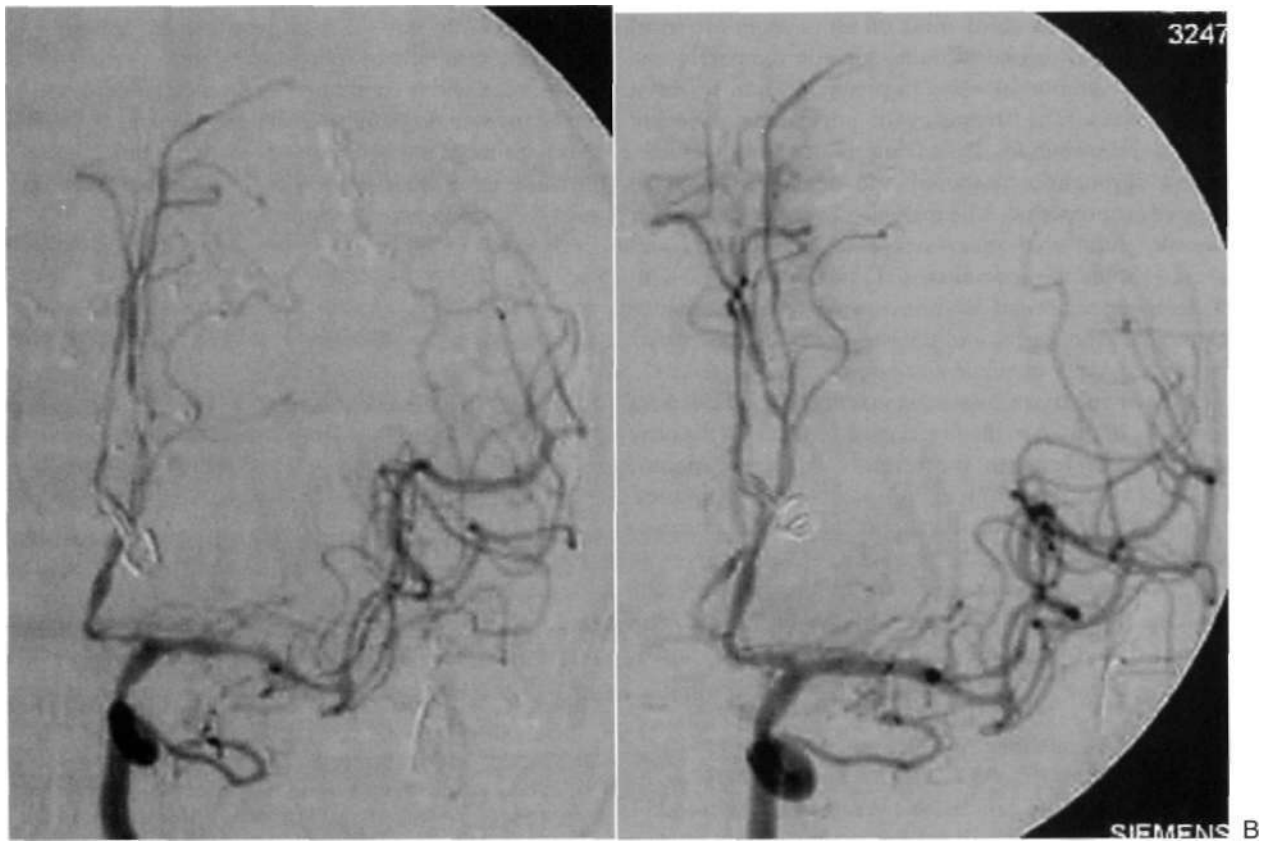


FIGURE S7C.7 (A) Posterior-anterior left internal carotid artery angiogram demonstrates moderate vasospasm of the supraclinoid segment of the left internal carotid artery, the Ml segment of the left middle cerebral artery, the Al segment of the left anterior cerebral artery, as well as multiple segments of the distal left anterior cerebral artery. (B) Posterior-anterior left internal carotid angiogram following angioplasty and intra-arterial papaverine infusion demonstrates improved vessel caliber.

Issues of a selection bias may have influenced the low incidence of ruptute noted in the ISUIA, and the large number of ruptured aneurysms that are smaller than 10 mm argues strongly against accepting a benign prognosis for all lesions below this size (Caplan 1998), Other recent studies noted a higher tate of ruptute of unruptured aneurysms, between 1-2% per year, which is in keeping with rates proposed by earlier investigators (Juvela ct a I. 2000; Tsutsumi et al. 2000; Winn et al. 2002). In a thorough review of the literature, "Weir (2002) noted that although the latgest diameter of an aneurysm is an important factor, the current state of knowledge about unruptuted aneurysms does not support the use of the size of the lesion as the sole criterion on which to base treatment decisions.

The decision to treat an unruptured aneurysm depends on several factors and is complicated because the rupture of an incidental aneurysm is a long-term risk spread out over many years, whereas the risk of surgery is immediate. Factots to be considered are the size of the aneurysm, the morbidity and mortality after SAH, the surgical morbidity and mortality, experience of the surgeon and institution, the life expectancy of the patient, and the attitude of the patient toward shott-term and long-term risk. In the prospective atm of the ISUIA study, the ovetall surgical morbidity and mottality at 1 yeat ranged between 13,1-15.7%. This combined surgical morbidity and mortality rate included analyses of the Rankin score and cognitive status. A meta-analysis of 28 surgical series containing 733 patients undetgoing elective surgery for asymptomatic, unruptured intracranial aneurysms found a morbidity of 4.1 % (95% confidence interval 2.8, 5.8%), and a mortality of 1.0% *(95%* confidence interval 0.4, 2.0%) (King et al, 1994). Elective aneurysm surgery has been demonstrated to be cost effective, provided that the surgical morbidity and mortality remain at low levels, that patient life expectancy is at least 13 years, and that the patient's quality of life is decreased by the knowledge of the aneutysm (King et al. 1995). In light of the devastating consequences of aneurysmal rupture, there must he strong contraindications not to considet the surgical treatment of incidentally discoveted aneurysms in young patients.

Subarachnoid Hemorrhage in Pregnancy

Special consideration needs to be given to the management of SAH during pregnancy (see Chapter 87). The frequency of discovery of cerebral aneurysms is increased during

pregnancy. SAH, the third most common nonobstetrical cause of maternal death, accounts for approximately one half of all intracranial bleeding in pregnancy and carries a grave prognosis. The frequency of aneurysmal bleeding parallels the elevation in cardiac output and blood volume, increasing throughout gestation and extending into the early postpartum period. The management of patients with incidentally discoveted aneurysms is not well defined and treatment should he individualized, but in patients with SAH neurosurgical consideration should take precedence over obstetrical concerns, and the patient should be treated in the same manner as those who are not pregnant.

The time of aneurysm rupture in normal pregnancies is as follows: 8% ruptured in the first 3 months, 22% in the next 3 months, *59%* between the seventh and tenth month, 3% during labor, and 8% in the puerperium. Ruptured aneurysms should probably be clipped as soon as possible, regardless of the state of the pregnancy. If the patient is near term, an expeditious cesarean section may prevent the burden of labor being added to the difficult course following aneurysm rupture and repair.

Subarachnoid Hemorrhage of Unknown Cause

A normal angiogram can be seen in patients with SAH because, occasionally, localized hemorrhage with intense spasm or thrombosis can prevent filling of the aneurysm. Because of the drastic consequences of missing a ruptured aneurysm, repeat angiography 7-10 days later is recommended. Repeat angiography reveals an aneurysm in 19% of patients in whom it was not visualized by the initial angiogram (Kaim 1996). Despite a thorough and complete angiographical evaluation, diagnostic studies fail to reveal a cause for the SAH in a substantial number of patients (see Perimesencephalic Hemorrhage, later in this chapter). Although trauma is the most common cause for SAH, the difference in distribution of blood and the antecedent history rarely make the distinction from aneurysmal SAH difficult. Other causes for nonaneurysmal subarachnoid hemorrhage include angiographically occult vascular malformations, hemorrhagic infarctions, and hypertensive hemorrhages. SAH of unknown cause is not associated with the high morbidity and mortality of aneurysmal SAH, and the risk of fatal rebleeding is well under 1% per year.

Perimesencephalic Hemorrhage

A distinct pattern of SAH that can occur without a detectable aneurysm is perimesencephalic hemorrhage. This entity may be caused by rupture of a capillary telangiectasia of the pons (Wijdicks and Schievink 1997). Patients with this pattern of hemorrhage and a normal angiogram should be considered to have a distinct subset of SAH and generally do not suffer from repeat hemorrhage. These patients have a relatively benign clinical course, although symptomatic vasospasm may occur. Although knowledge of this condition can provide an explanation for a negative angiogram result in the presence of definitive SAH, it should not be used as a reason to omit angiography because localized perimesencephalic hemorrhage can be seen with aneurysmal rupture.

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Chapter 57
Vascular Diseases of the Nervous System

D. ARTERIOVENOUS MALFORMATIONS

Warren R. Selman, Robert W. Tarr, Jeffrey L. Sunshine, and Robert A. Ratcheson

Arteriovenous malformations (AVMs) are developmental abnormalities of blood vessels in which one or more primitive direct communications between otherwise normal arterial and venous channels are preserved. The most devastating consequences of these lesions occur as a result of intracranial hemorrhage. Prior to a hemorrhage, these lesions may be uncovered in patients with seizures or may be discovered fortuitously during evaluation for an unrelated disorder. The proper management of AVMs is complex and requires an understanding of their natural history, their effect on cerebral circulation and metabolism, and the capabilities and limitations of the treatment options, including microsurgical resection, neuroendovascular embolization, and stereotactic tadiosurgery.

PATHOLOGICAL CHARACTERISTICS

Vascular malformations may be divided into four major types: (1) venous angiomas, (2) cavernous malformations, (3) capillary telangiectases, and (4) AVMs.

Venous angiomas, which are the most common type of vascular malformation, are composed entirely of venous structures and are almost always clinically silent. The presence of a large dilatated enhancing vein extending to the cortical or cpendymal surface with a radial configuration of smaller veins, as seen on a contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), is diagnostic (Figure 57D.1). Angiography is rarely needed to confirm the diagnosis.

Cavernous malformations are low-flow vascular anomalies consisting of sinusoidal vascular channels lined by a single layer of endothelium. The walls of the dilatated vessels are thin and contain no smooth muscle or elastic tissue. Marked hyalinization of the vascular channels is common. There is no intervening brain parenchyma within the collagenous stroma separating the individual vascular channels. Of all the vascular anomalies, cavernous malformations are most likely to occur with other lesions, such as a venous angioma. As noted later, cavernous malformations are responsible for the clinical presentation in these mixed lesions.

Capillary telangiectases, or angiomas, are small, solitary groups of abnormally dilatated capillaries. They rarely give rise to spontaneous hemorrhage and usually are detected only in postmortem examinations. There is one case report that suggests that capillary telangiectasia may be associated with the syndrome of perimesencephalic hemorrhage (see Chapter 57C), but this finding awaits confirmation (Wijdicks and Schievink 1997).

True AVMs are congenital lesions that arise from aberrant connections within the primitive arterial and venous plexus overlying the developing cortical mantle. This area of altered vasculature becomes incorporated into the brain parenchyma. The AVM itself is composed of abnormal arteries and veins. Larger vessels resemble veins in that they contain a small amount of muscularis and lack elastica. The amount of gliotic tissue that intervenes between the abnormal vessels varies greatly. Most AVMs show evidence of microscopic hemorrhage in this tissue regardless of whether the patient has experienced a symptomatic hemorrhage. There is no normal capillary bed in the nidus of an AVM.

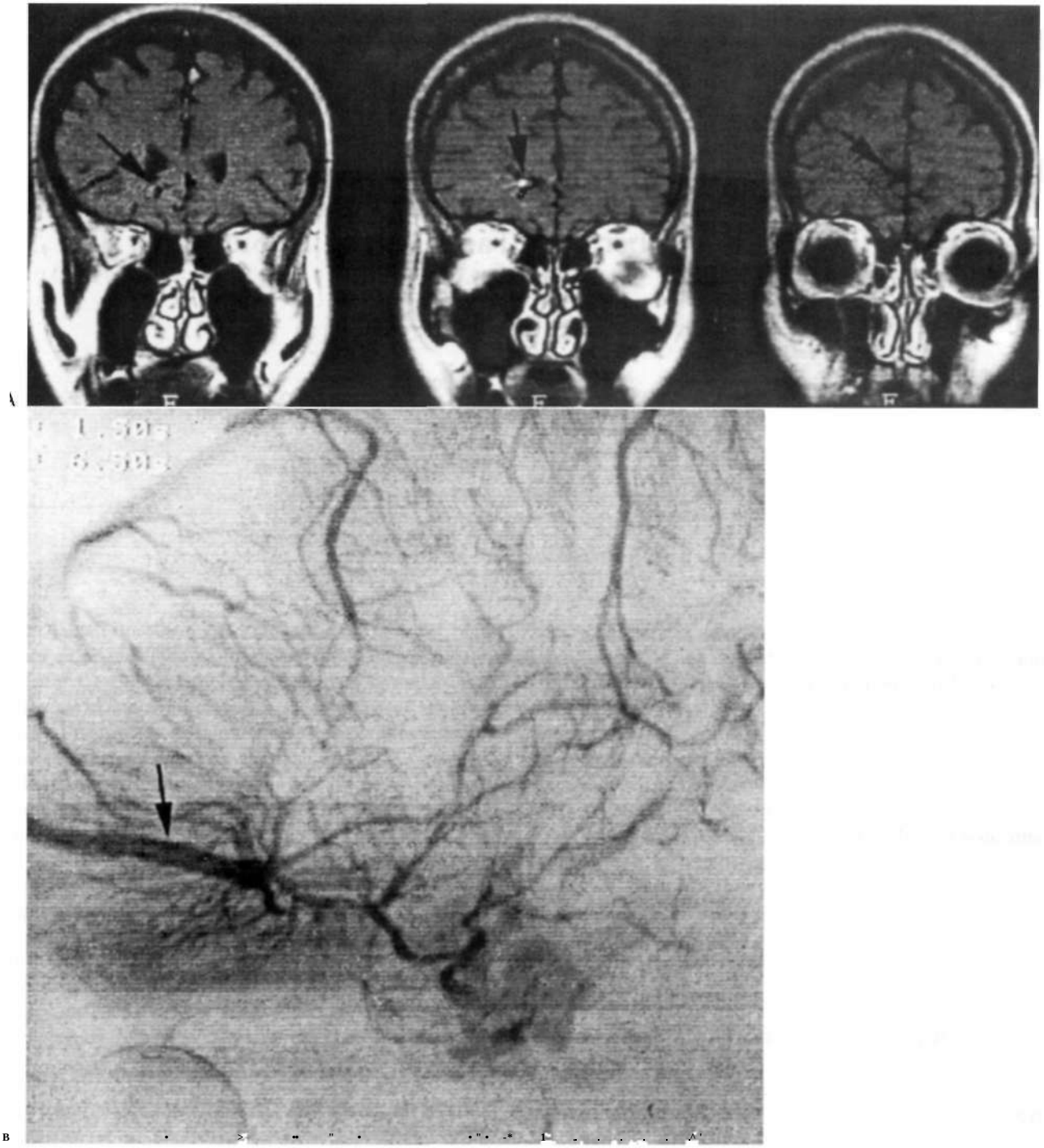

FIGURE 57D.I (A) Coronal Tl-weighted magnetic resonance images demonstrate the venous tributaries and large draining vein characteristic of a venous angioma *(arrows).* (B) Lateral venous phase from a right internal carotid artery angiogram confirms the right frontal venous angioma *(arrow)* draining toward the anterior portion of the superior sagittal sinus.

EPIDEMIOLOGY AND CLINICAL SIGNS

Cavernous Malformations

The frequency of cavernous malformations depends on the mode of study. In major autopsy series, the frequency is 0.02-0.53%. Studies based on MRI have reported a higher frequency of 0.4-0.9% (Maraire and Awad 1997). Familial forms of cavernous malformations, characterized by multiple lesions, appear to be transmitted in an autosomal dominant fashion (Notelet et al. 1997). Cavernous

malformations occur in all age groups, but the majority of patients present in the second to fourth decade of life. Most cavernous malformations are solitary lesions, but multiple lesions occur in approximately one thud of sporadic cases, and in more than two thirds of familial cases.

Cavernous malformations are dynamic lesions, and intralesional hemorrhage, thrombosis, organization, calcification, cyst formation, and involution of the caverns all contribute to the changes in these lesions. Cavernous malformations, unlike venous angiomas, have no distinctive CT scan appearance, but do have a characteristic MRI signature (Figure 57D.2). The MRI pattern of a central core of increased intensity surrounded by a rim of decreased intensity on T2-weighted sequences, or multiloculated rounded areas of increased signal on Tl-weighted sequences, allows their radiographical identification. Although the MRI picture is characteristic, the differential diagnosis should include cryptic or partially thrombosed AVMs, primary hemorrhagic or metastatic tumors, infectious and granulomatous diseases, and inflammatory lesions.

Cavernous malformations are rarely visualized on angiography because of the small size of the afferent vessels, the presence of thrombosis, and the relatively low flow in these lesions. *Cryptic malformation* is a term used to describe a small malformation that is undetectable by angiography but is demonstrated by pathological examination to be responsible for intracranial hemorrhage. Cavernous malformations account for 25-50% of such occult lesions. The remainder are considered to be angiographically occult AVMs. Because the natural history of the two lesions is different, in the presence of a new hemorrhage, follow-up angiography after the resolution of any mass effect may be needed to exclude the presence of a small AVM.

Solitary and multiple lesions may be clinically silent. The most common clinical manifestations of cavernous malformations are seizures, hemorrhage, and progressive neurological deficit. Seizures occur with approximately twice the frequency in patients with cavernous malformations compared with patients with AVMs and have been reported in between 38% and 100% in clinical series.

Cavernous lesions with calcification, evidence of chronic intralesional hemorrhage with thrombus organization, and thick pseudocapsules are more likely to present with seizures than gross hemorrhage. Women are more likely to present with gross hemorrhage and neurological deficits, whereas men are more likely to present with seizures.

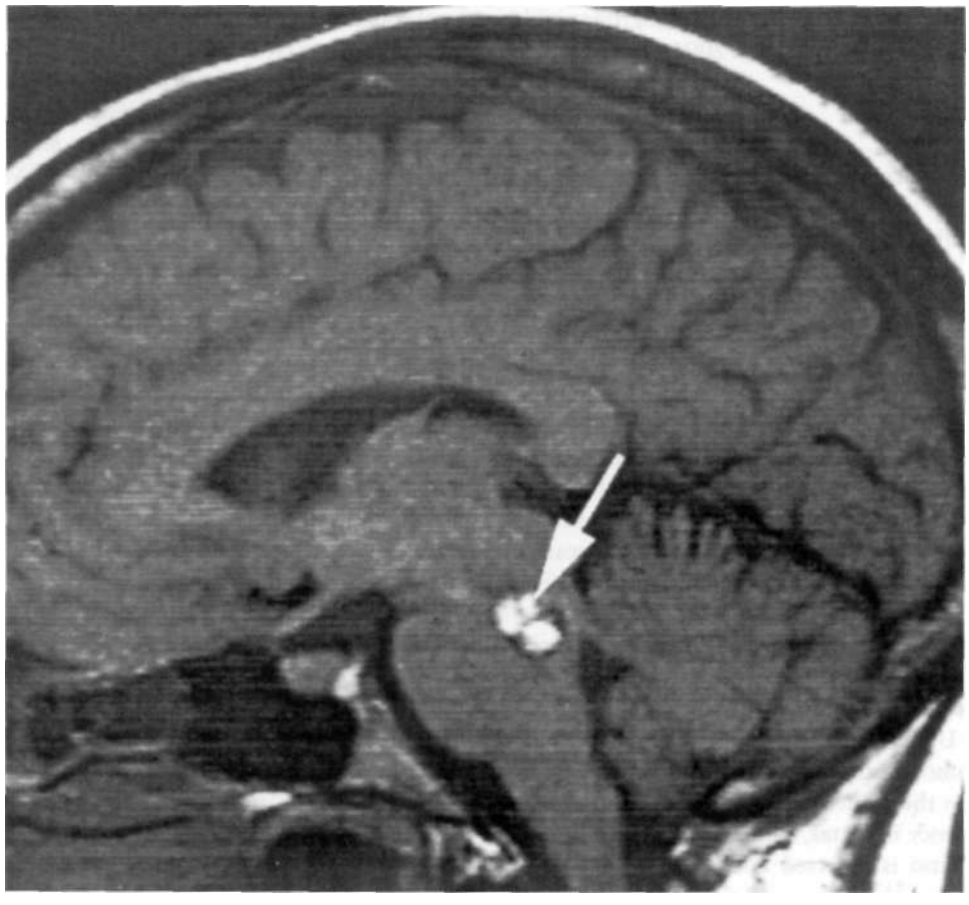

FIGURE 57D.2 Sagittal Tl-weighted magnetic resonance image demonstrates a cavernous angioma involving the dorsal midbrain *(arrow).* Note the characteristic surrounding areas of high signal intensity caused by walled-off microhemorrhages.

Clinically significant hemorrhage has been reported in between 8% and 37% of lesions in large clinical series (Maraire and Awad 1997). It is imporrant to distinguish between intralcsional and extralesional hemorrhages, and defining a clinical and radiological event as a bleeding episode is sometimes problematic. Although variable, the annualized risk of hemorrhage is between 1.6% and 3.1% per patient per year {Moriarity et al. 1999; Porter et al. 1997). In contrast to primary hemorrhage occurring from an AVM, the clinically significant bleeding noted with cavernous malformations is rarely life threatening, and the initial bleed is self-limited and patients usually have a good or fair outcome. There is, nonetheless, an increased risk of recurrent hemorrhage after an initial bleeding episode, which has been estimated to be between 207o and 85%. The risk of re hemorrhage has been shown to decrease over time. Cavernous malformations have a temporal clustering of hemorrhages where the rehemorrhagc rate is high initially, and decreases 2 to 3 years after a previous hemorrhage. In one study of 141 patients who presented with hemorrhage, during the first *iVi* years after a hemorrhage, the monthly hemorrhage hazard was 2%, and then the risk decreased to less than 1% per month (Barker et al. 2001). Most studies indicate that brainstem cavernous malformations have a rate of recurrent symptomatic hemorrhage up to 69%, and a significant morbidity; there may be some subgroups with a more benign course (Kupersmith et al. 2001; Moriarity etal. 1999; Porter et al. 1997).

Arteriovenous Malformations

AVMs occur with equal frequency in men and women, rarely produce clinical symptoms before the first decade, and commonly present in the second and third decades of life. Because many remain asymptomatic throughout life, determining the prevalence of AVM is extremely difficult. Autopsy series, showing prevalence rates between 500-600 per 100,000 undoubtedly reflect selection bias. Currently, we can only estimate the detection rate for symptomatic AVMs, which is 0.94 per 100,000 person years (Berman et al. 2000). Determining the prevalence of asymptomatic AVMs would necessitate performing random MRI scans on more than 1 million people, and would disclose a figure only within 20% of the true rate.

The ratio of AVMs to aneurysms in different populations is influenced by geography and ethnicity, as well as by referral patterns that probably distort the true figures. For instance, in the United States, aneurysms are more than 5 times more common than AVMs, but arc almost 14 times more common in the United Kingdom, and seem to occur with equal frequency in Qatar, Saudi Arabia, and China. In Singapore, the ratio is reversed and AVMs may be four times more common than aneurysms {Ohacghulam 2001).

Patients with AVMs may seek medical attention for one or a combination of the following problems: (1) intracranial hemorrhage, (2) seizures, (3) focal neurological deficits, (4) impairment of higher cortical function, {5) headache, and (6) bruit.

Headaches may occur in 5-35% of patients with AVMs. They characteristically begin during the second decade of life; they may be generalized, unilateral, focal, continuous, or intermittent. They are nonspecific and, in the absence of hemorrhage or hydrocephalus, the relation of the headache to the AVM is not always apparent.

In contrast to aneurysms, which produce predominantly subarachnoid hemorrhage, AVMs tend to produce localized intracerebral hemorrhage. Intraventricular, or subarachnoid hemorrhage, also may be present. The resulting neurological deficit depends on the location and size of the hemorrhage. There is no characteristic clinical picture that is specific for AVM hemorrhage. In most cases there is nothing remarkable about the history other than the sudden onset of severe headache, which is characteristic of any intracerebral hemorrhage.

Seizures may occur in patients at any age. Seizures are the presenting feature in 28-67% of patients with AVMs. More than 50% of patients found to have an AVM are likely to have had at least one seizure by the age of 30. A seizure is more common as an initial symptom between the ages of 11 and 20 years; hemorrhage is more common as an initial symptom between the ages of 21 and 30 years. Patients with large AVMs are twice as likely to have seizures in contrast to hemorrhage as their presenting symptom, with the converse relation holding for smaller lesions.

In addition to headaches, seizures, and hemorrhage, less frequent clinical manifestations of AVMs include focal neurological deficits caused by ischemia (steal phenomenon); cardiomegaly; and high-output congestive failure caused by the high-volume shunt, obstructive hydrocephalus, communicating hydrocephalus, and cranial nerve compression. The occurrence of these problems is in part related to the patient's age. Cardiomegaly and cardiac failure are usually manifested only during infancy and early childhood in a patient with a vein of Galen aneurysm, which is something of a misnomer because the underlying lesion is an AVM. Similarly, obstructive hydrocephalus is usually a disease of childhood secondary to aqueductal compression from an enlarged vein of Galen aneurysm or AVM, but communicating hydrocephalus may occur at any age from an intraventricular hemorrhage.

PHYSICAL FINDINGS

The physical examination should be tailored to the age of presentation. In infancy, evidence of a hyperdynamic cardiovascular state should be sought. It is necessary to measure head circumference. At any age, auscultation of the head may reveal a bruit, which may often be of some help in localization. Finally, the presence and character of a neurological deficit can localize the site of hemorrhage.

PHYSIOLOGY AND METABOLISM

In 1928 Cushing and Dandy both described alterations of normal blood flow patterns in the brain surrounding AVMs. They reasoned, on the basis of finding red blood (arterialization) in the venous channels, that the brain was not using the flow for metabolic purposes. The paucity of filling of surrounding cortex in the presence of an AVM, as noted on angiography, was described as *cerebral steal.*

Blood flow to and from AVMs is conducted through normally located channels. Because there is not a separate AVM circulation, the relationship between cortical nutrient branches and the arteries diverting blood into an AVM is important. A simplified model to describe the relationship of pressure in nutrient branches of a feeding vessel to AVM flow is depicted in Figure 57D.3. A decrease in pressure along a feeding artery is directly proportional to the time-average velocity of flow and the length of the artery. Thus the higher the flow to the AVM, the less the pressure in the nutrient arteries. Increased venous pressure associated with an AVM also leads to a further decrease in nutrient flow.

Although many high-flow AVMs demonstrate angiographic cerebral steal, not all produce ischemic symptoms (Taylor et al. 2002). This is explained in part by the auto regulatory response of the normal cerebral vasculature to a decrease in local perfusion pressure. In addition, neurons maintain normal electrophysiological function until flow is reduced from normal levels of 50 mL/100 g per minute to less than 20 mL/100 g per minute. Nonetheless, chronic hypoperfusion in the nutrient vessels surrounding an AVM may result in maximal dilation such that autoregulation is lost in this area. Such changes make the involved territory susceptible to alterations in systemic pressure and could result in cerebral ischemia.

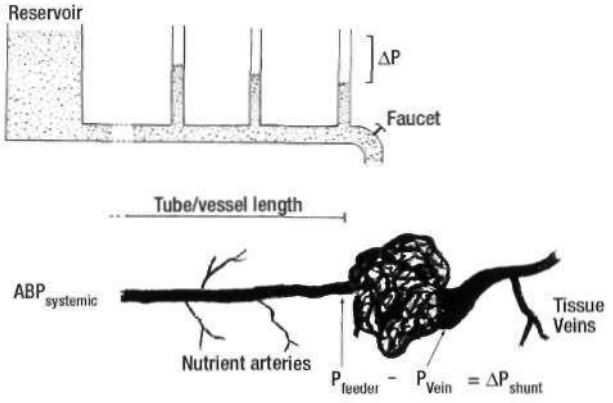

FIGURE 57D.3 Relationship of pressure (P) in the nutrient branches (those supplying surrounding normal cortex) to the flow in the feeding vessel supplying an arteriovenous malformation. (ABP =i arterial blood pressure.) (Adapted from Nornes, H. & Grip, A. 1980, "Hemodynamic aspects of cerebral arteriovenous malformation," 7 *Neurosurg,* vol. 53, p. 456.)

LABORATORY STUDIES

The identification of patients suspected of having an AVM has been made easier by the development of modern noninvasive diagnostic imaging techniques including CT scan, CT angiography, MRI scan, and magnetic resonance (MR) angiography (see Chapter 37B). If an AVM is found, conventional angiography (see Chapter 37C) is essential in determining the optimal treatment. An AVM may receive arterial input from any of the major cerebral arteries. If the AVM is located solely within the territory of a single cerebral artery, then the blood supply to the malformation may come solely from that artery. In larger AVMs, or those bordering more than one territory, the arterial supply is usually from more than one arterial distribution. Thus complete four-vessel angiography is needed to define these lesions. The venous drainage may be through the superficial or deep venous system, or directly into a major sinus, or some combination of these patterns.

The CT scan is often the first study that suggests the presence of a vascular malformation in a patient with headaches, seizures, or a neurological deficit. Information can be gained from both noncontrast and contrast-enhanced scans. The noncontrast scan can establish the presence and location of hemorrhage. A lobar hemorrhage should increase the suspicion of a vascular malformation as the underlying cause. Other diagnostic considerations include hypertensive hemorrhage, aneurysmal rupture, and hemorrhage into a tumor. Enhancement occurs because of collection of the contrast material in the intravascular compartment as well as in surrounding areas with altered blood-brain barrier permeability. The presence of a serpentine enhancement pattern is highly characteristic. High-resolution (2.0-min slice thickness) dynamic CT imaging after contrast administration allows accurate measurement of the size of the AVM nidus (Figure 57D.4).

Standard sequences such as Tl- and T2-weighted MRIs provide precise information on the size and location of an AVM (Figure 57D.5). The relation of feeding arteries and draining veins can be appreciated using MR angiography. Three-dimensional tlme-of-flight techniques are especially helpful for visualizing arterial flow, and two-dimensional time-of-flight is best for showing the slower flow in the venous drainage (Figure 57D.6).

Functional imaging (see Chapter 37E) is helpful in determining the effects of the AVM on the blood flow and regulatory capacity of the surrounding brain. Stable xenon CT scanning has been used to delineate the response to acetazolamide. The presence of a steal phenomenon may indicate a loss of autoregulation in the brain surrounding the AVM (Figure 57D.7). The relation of the AVM to vital cortical areas can be appreciated by the use of functional MRI (Figure 57D.8). These newer imaging modalities provide information that influences therapeutic planning.

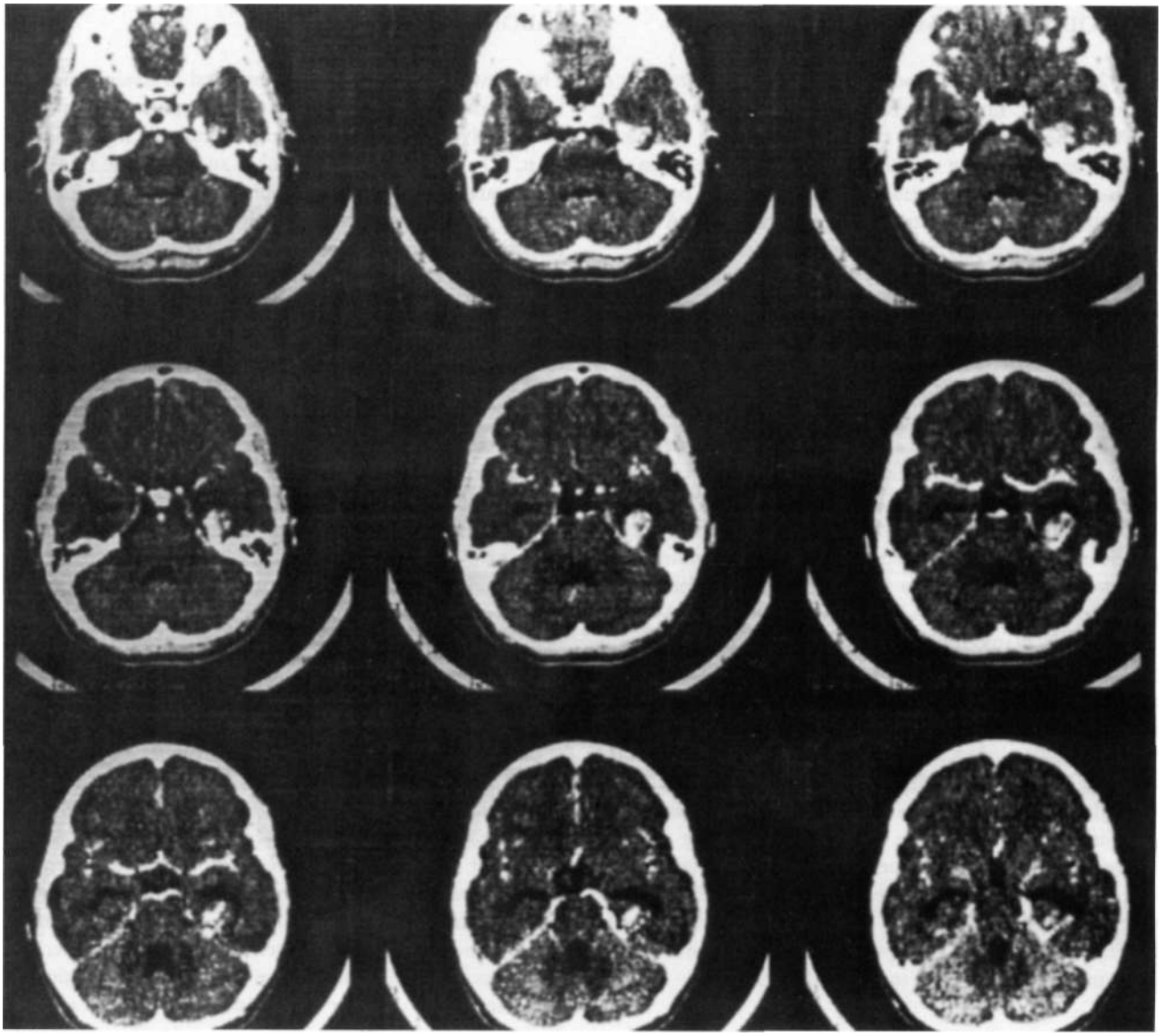

FIGURE 57D.4 Dynamic contrast enhanced computed tomography (2-mm slice thickness) delineates the nidus of a left posterior temporal lohc arteriovenous malformation. Standard sequences such as Tl- and T2-wcightcd magnetic resonance imaging provide precise information on the size and location of an arteriovenous malformation (see Figure 57D.5). The relation of feeding arteries and draining veins can be appreciated using magnetic resonance angiography. Three-dimensional timc-of-flight techniques are especially helpful for visualizing arterial flow, and two-dimensional time-of-flight is best for showing the slower flow in the venous drainage (see Figure 57D.6).

COURSE AND PROGNOSIS

Intracranial hemorrhage is the most significant clinical manifestation of an AVM. All studies have demonstrated a relatively constant and high risk of hemorrhage associated with AVMs. It is important to stress that the cumulative rate of hemorrhage is the same regardless of the presentation. Even an unruptured AVM carries a 4% yearly risk of hemorrhage. The mortality from the first hemorrhage varies between 6% and 14%. Once an AVM has bled, the likelihood of recurrent hemorrhage is approximately *6%* for the first year and 4% for subsequent years. Any estimate of the risk of hemorrhage for an individual patient must take into account specific considerations that may not be entirely reflected in cumulative data. For example, untreated AVMs in the posterior fossa appear to have a particularly poor prognosis. Children arc at relatively greater long-term risk for rehemorrhage, in that they normally have a longer lifespan during which rehemorrhage may occur. Patients with smaller AVMs, because of differences in the flow patterns and pressure within the nidus, may be more likely to hemorrhage than large AVMs.

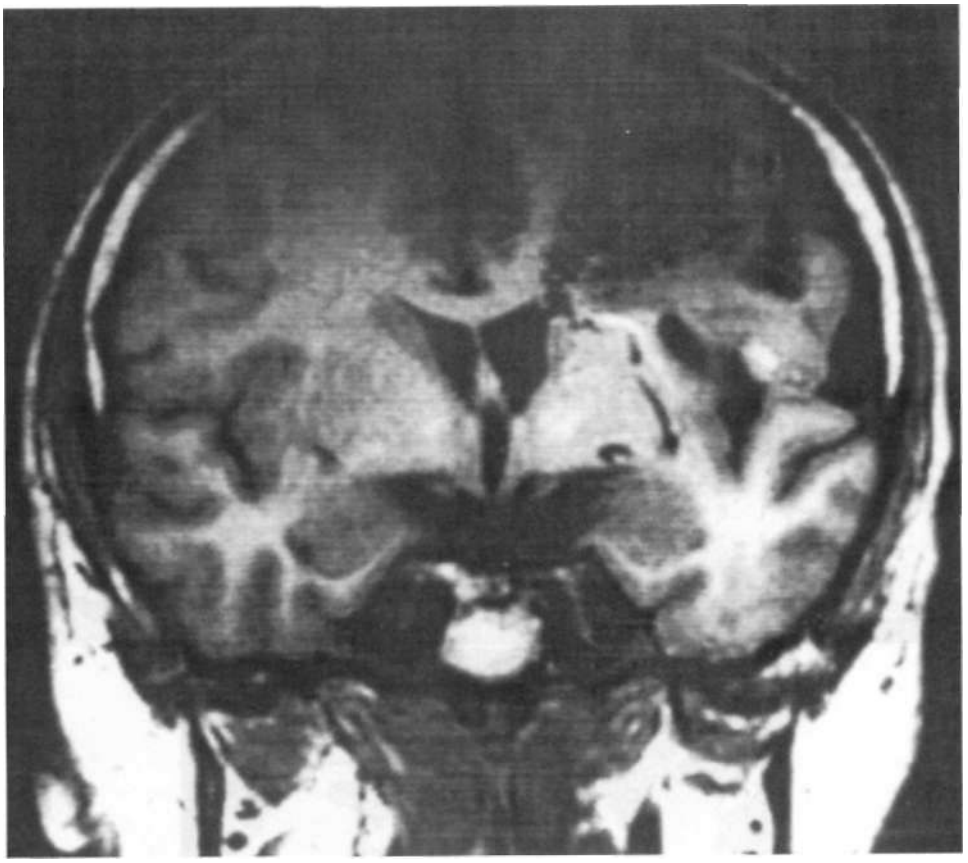

FIGURE 57D.5 Coronal Tl-weighted magnetic resonance image demonstrates a left frontal arteriovenous malformation nidus that extends to the ventricular surface.

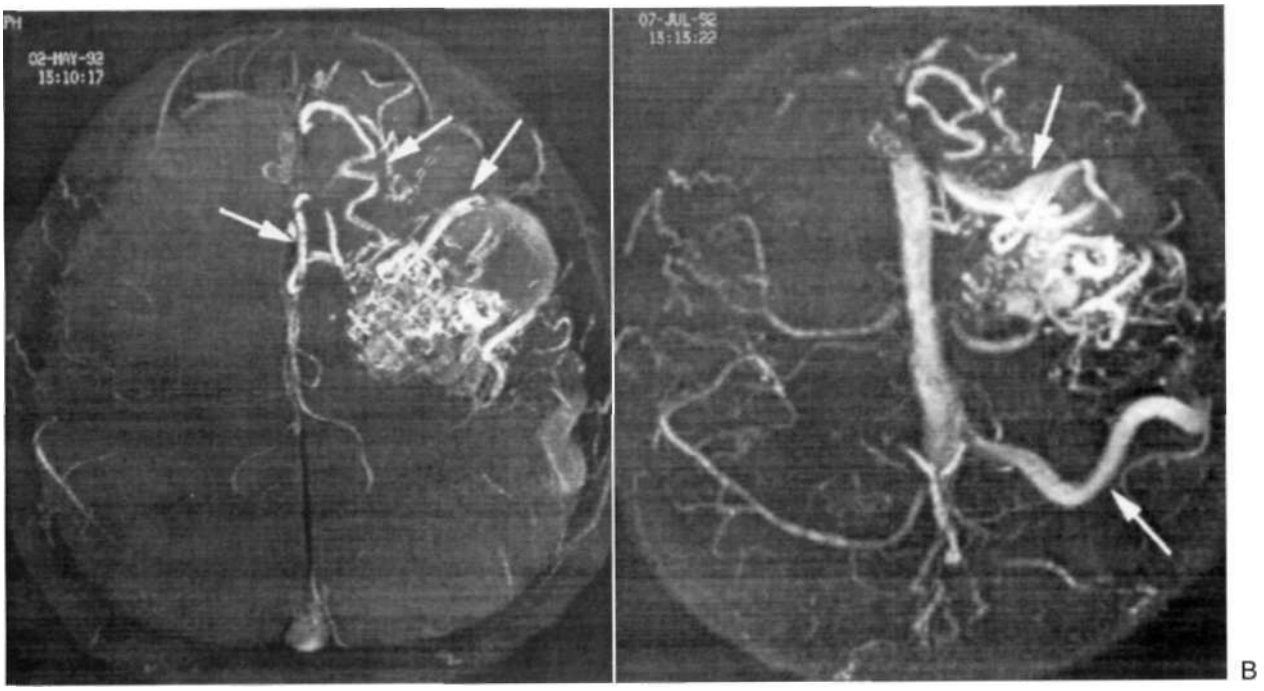

FIGURE S7D.6 (A) Three-dimensional time-of-flight magnetic resonance angiography demonstrates arterial pedicles *(arrows)* as well as a venous varix. The entire venous drainage pattern cannot be defined on this study. (B) Two-dimensional time-of-flight magnetic resonance angiography of the same patient details the venous drainage of the arteriovenous malfotmation into the superior sagittal sinus *(arrows).*

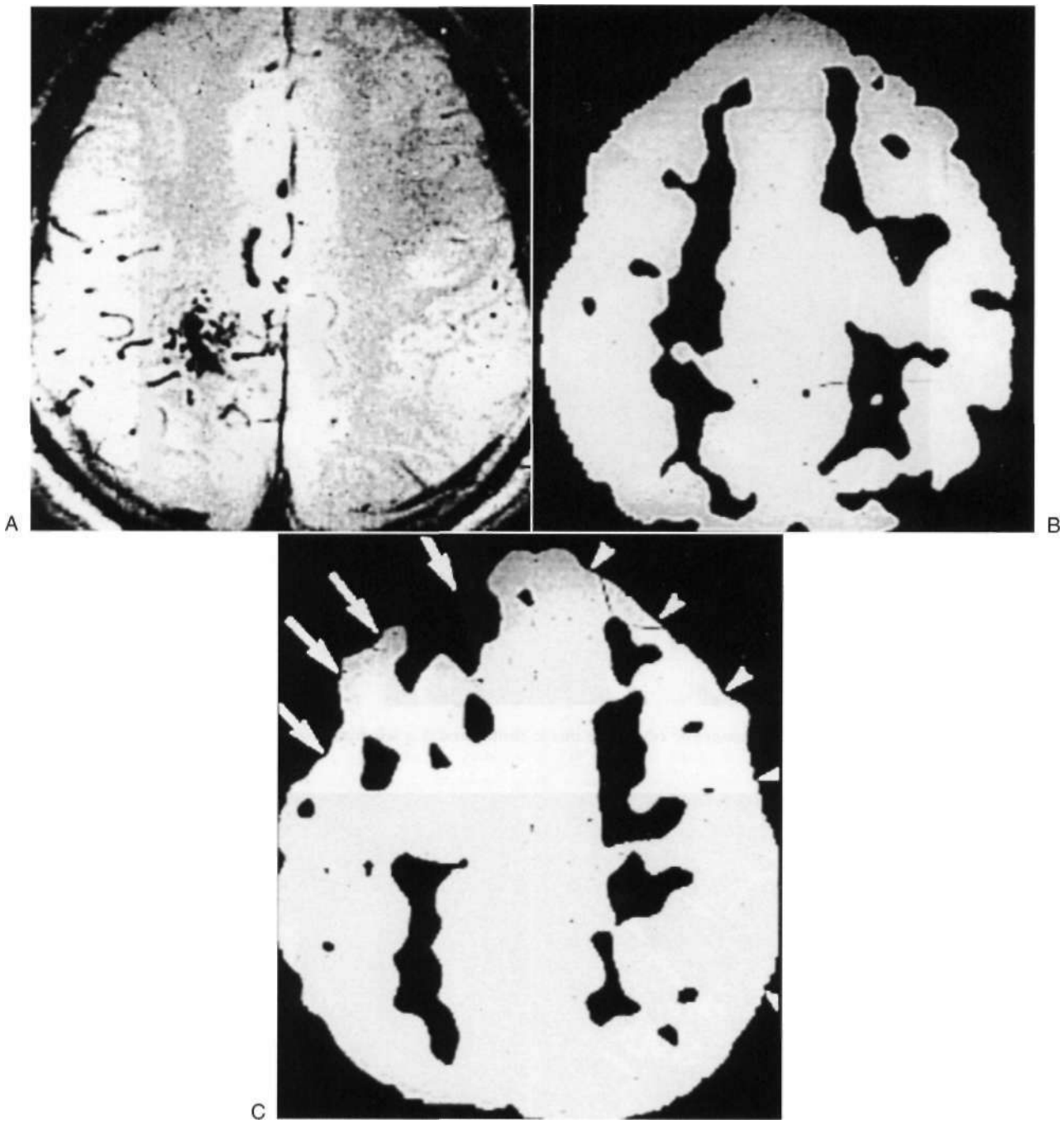

FIGURE 57D.7 (AJ Axial proton density-weighted magnetic resonance image shows a right parietal lobe arteriovenous malformation. Xenon computed tomographic scan cerebral blood flow analysis (B) before and (C) after the administration of acetazolamide (Diamox) demonstrates normal augmentation of blood flow with acetazolamide in the left hemisphere *{arrowheads}*, but a diminution of flow or vascular steal phenomenon *(arrows)* in the right ftontal lobe.

Systemic hypertension increases the risk of AVM hemorrhage. AVMs that have aneurysms on intranidal vessels, and those that have areas of venous outflow restriction, are more prone to hemorrhage (Figure 57D.9).

The overall course of patients harboring an AVM is not benign. In addition to the effects of a major hemorrhage, neuronal damage from repeated minor hemorrhages or ischemia of adjacent brain from cerebral steal can result in progressive neurological deterioration. The yearly mortality in a large series with long-term follow-up was 1-2%; the rate of mortality plus morbidity was 5%; the rate of morbidity alone was 3.5%. Other series have reported a mortality of approximately 0.9% per year. Mortality and morbidity for individuals younger than 20 years and

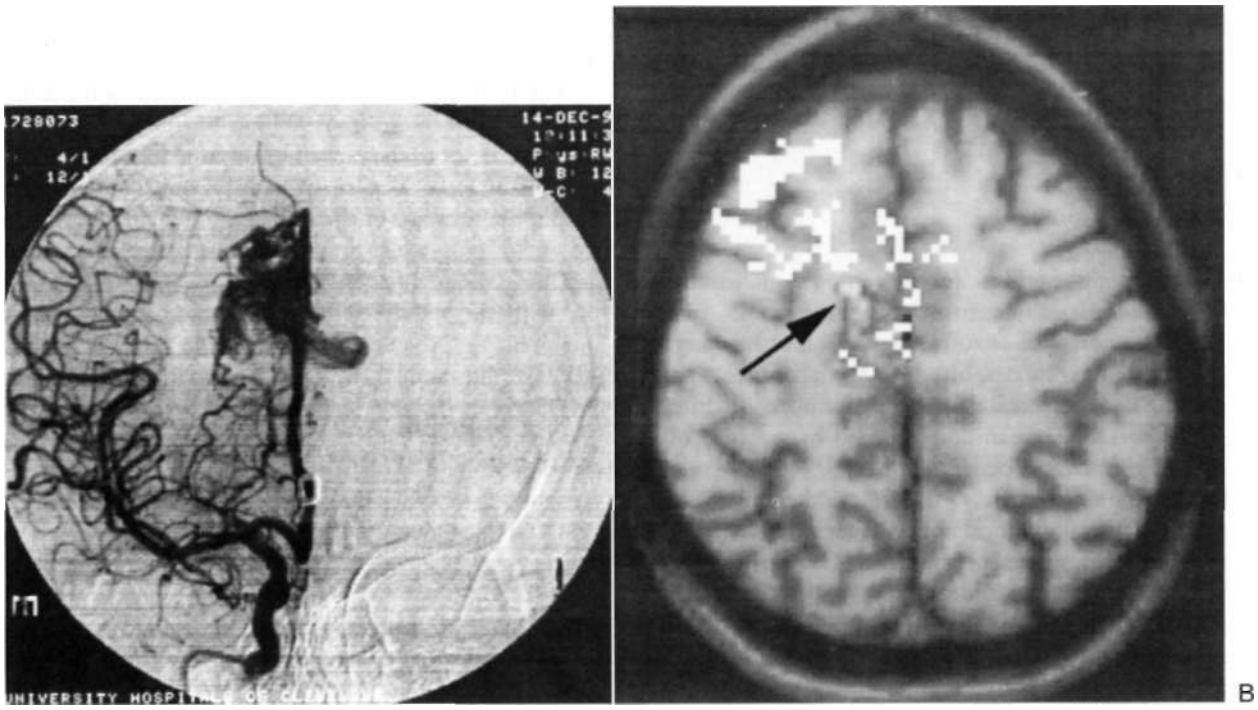

FIGURE 57D.8 (A) Right internal carotid artery angiogram shows a right frontal arteriovenous malformation. (B) Functional magnetic resonance imaging with left leg activation. Note the proximity of the arteriovenous malformation nidus *(arrow)* to the left leg motor cortex.

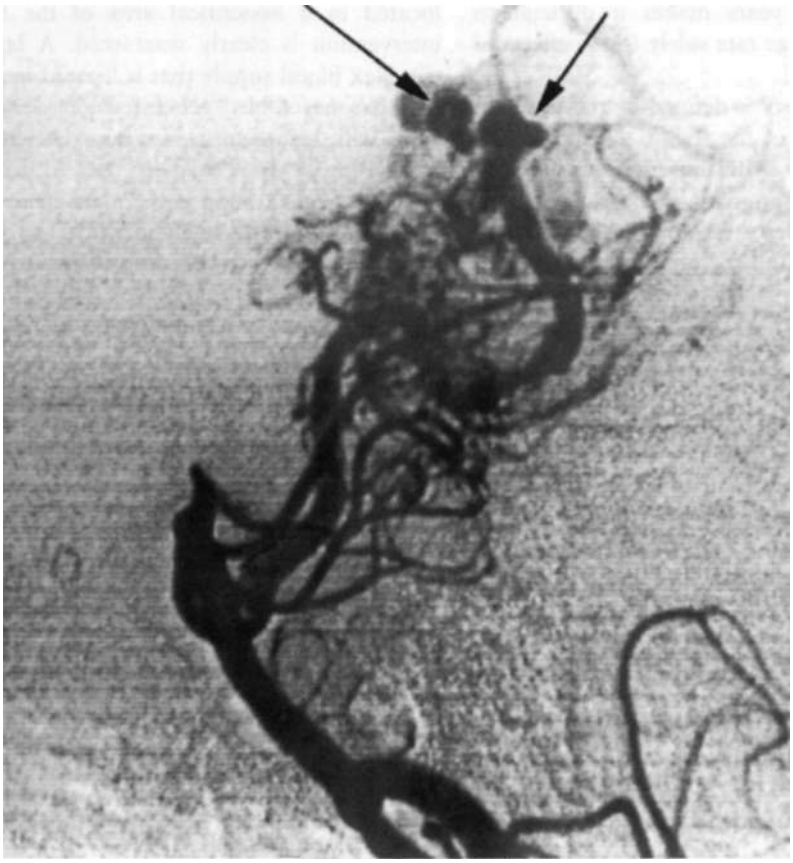

FIGURE 57D.9 Left vertebral artery angiogram shows several intranidal aneurysms *(arrows)* associated with this arteriovenous malformation nidus.

older than 40 may be lower than in the intervening age group.

TREATMENT

Cavernous Malformations

The therapeutic options for cavernous malformations include medical management of seizures or surgical excision for control of seizures, prevention of hemorrhage, or prevention of recurrent bleeding. With seizures, surgical therapy is used if medical management is unsuccessful, or if medical management can be optimized by removal of the lesion and the seizure focus.

The use of stereotactic radiosurgical therapy for treatment of cavernous malformations is being investigated, but the standard doses used for true AVMs are associated with a poor clinical response and a high complication rate. With lower doses, there are fewer complications reported, bur the i'] id points for therapeutic success are harder to define than with the criteria of angiographic obliteration used for true AVMs. Although some reports indicate that there is a reduction in the risk of reblccding 2 years following stereotactic radiosurgery for cavernous malformations (Hasegawa et al. 2002) the natural history of reduced hemorrhage risk after two years makes it difficult to ascribe the reduced hemorrhage rate solely to the effects of treatment (Barker et al. 2001).

In general, the role of surgery is defined by the status of the patient and the location of the lesion. Asymptomatic lesions are usually followed with observation only. In patients presenting with asymptomatic hemorrhage, surgical resection should be considered for any accessible lesion in the supratentorial region, and for any brainstem lesion that has a presentation on the pial surface or the floor of the fourth ventricle (Maraire and Awad 1997; Porter et al. 1997; Moriarity et al. 1999).

Arteriovenous Malformations

In light of a better understanding of the natural history of AVMs, and with refinements in therapeutic options, consideration of treatment should be given to most patients who harbor an AVM. With respect to determining which mode of therapy is optimal, microsurgery, radiosurgery, and endovascular surgery are all compatible and complementary (Ogilvy et al. 2001).

Although the mam indication for treatment is prevention of neurological morbidity caused by hemorrhage, there is a reduction in the occurrence of seizures with successful AVM treatment, whether microsurgical or radiosurgical (Ogilvy et al. 2001). As noted in the previous section, the major morbidity and mortality from an AVM result from hemorrhage, and surgical excision is the most direct and immediate method of eliminating the risk of subsequent hemorrhage.

The factors to be considered in determining the difficulty of surgically excising an AVM include the size of the lesion, the number of feeding arteries, the amount of flow through the lesion, the degree of steal from the surrounding brain, the location of the lesion, the functional importance of the surrounding brain, and the path of the venous drainage. Some of these variables are inter-related, and to facilitate surgical decision making, grading systems are used for predicting the operative risks in patients with different AVMs. The scale used most commonly is the Spetzler-Martin scale {Spet/ler and Martin 1986), which, for ease of grading, focuses on size, pattern of venous drainage, and the function of the surrounding brain. A sum of points assigned determines the grade of the AVM (Table 57D.1). Both retrospective and prospective experience have demonstrated a correlation between the grade of the AVM and the surgical risk, although the confidence intervals for these correlations are continuing to be defined.

The decision to pursue treatment must be made in light of a comparison between the natural history of AVMs and the risks of therapy for each individual. The wide variations both in the natural history and in treatment outcomes mandate careful consideration of diverse factors. If a hemorrhage has occurred from a small, accessible AVM located in a noncritical area of the brain, therapeutic intervention is clearly warranted. A large lesion with a complex blood supply that is located in a critical area and that has never bled generates considerably more controversy with regard to its best management.

Decision analysis has been used to determine the role of microsurgical excision in the management of patients with AVMs. The hazards of an uncritical use of decision analysis are evident when applied to AVM treatment. Decision-analysis techniques suggest that unless surgical mortality is on the order of 1% and surgical morbidity no more than 7%, nonoperative therapy is the preferred method of management. For these calculations, a 20-year follow-up was used, and the bleeding rate was assumed to be 1% per year. There are several problems with this application

Table S7D.1: Spet/ler-Martin gradi ng scale

	Points
Size	
0-3 cm	1
3.1-6.0 cm	2
>6 cm	3
Location	
No neloquent	0
Eloquent	ı
Deep venous drainage	
Not present	0
Ptesent	1

of decision analysis to AVM management. First, the probability of bleeding is a critical issue. With longer periods of follow-up, it has become apparent that the rate of rebleeding is higher than previously believed. Thus a 1% rate of bleeding severely underestimates the 4% per year rate of hemorrhage now known to occur in patients who present with or without hemorrhage. Second, an observation period of 20 years may be too short for general application. As stated previously, most AVMs are detected in the second, third, and fourth decades of life. Longer periods of observation, compatible with a normal life expectancy in the nonoperated group, necessarily increases the overall probability of hemorrhage. Furthermore, the likelihood of hemorrhage appears to be increased during these early decades, whereas patients in this age group, in general, are considered low-risk surgical candidates. Individual factors that may influence the frequency of hemorrhage and microsurgical outcome are not always considered in treatment algorithms. For example, small lesions are more likely to bleed, and these lesions also are associated with a lower surgical morbidity and mortality. Finally, surgical series of between 70 and 100 patients have reported outcomes compatible with decision analyses favoring operative intervention, with mortalities of approximately 1% and morbidity of well less than 7%. Thus although decision-analysis schemes may help to provide a framework for considering the optimal management of AVMs, care must be taken to accurately estimate the risk of all of the factors that can influence the decision for each individual.

The role of surgery in the management of AVMs is expanding. Sisti and colleagues *(1993)* reviewed their experience with *67* AVMs less than 3 cm in diameter and reported angiographic obliteration in 94%, with a surgical morbidity of 1.5% and no operative mortality. Of these lesions, 45% were in regions that some would consider surgically inaccessible, such as the thalamus, brainstem, medial hemisphere, and paraventricular regions. The immediate protection against hemorrhage provided by microsurgical removal and the avoidance of any risk of development of delayed radiation related brain injury are distinct advantages over stereotactic radiosurgery. These results emphasize that small size and location should not dictate which form of treatment is offered to a patient.

Large lesions previously classified as unresectable also may be managed surgically by using a regimen of preoperative embolization and staged resection. Preoperative embolization can cause thrombosis of much of the vascular nidus and decrease the number of feeding arteries. The role of endovascular techniques in the management of AVMs is continuing to expand with the development of improved catheters and embolization material (n-BCA Trial Investigators 2002). In particular, the preoperative use of both diagnostic and therapeutic endovascular techniques has allowed safer and more effective use of microsurgery and radiosurgery for the treatment of complex AVMs {Dion and Mathis 1994).

Radiosurgery has become an important tool for the treatment of some AVMs. The role of stereotactic radiation in the treatment of AVMs is both expanding and being better defined (Figure 57D.10). The results of the previous series demonstrate that stereotactic radiation is most effective in the obliteration of small AVMs. Because of the delayed reaction of the vessels, the patient remains at risk for bleeding until complete thrombosis is attained. The patient also should be advised of the possibilities of incomplete AVM obliteration and the risk of delayed development of radiation-induced brain injury. Even in the most favorable circumstances with a lesion less than 3 cm in diameter, the percent of lesions completely obliterated after 3 years is approximately 85%. An analysis of microsurgical and radiosurgical treatments concluded that microsurgical treatment of AVMs of grades I through III was associated with significantly fewer postoperative hemorrhages, fewer post-treatment neurological deficits, and fewer deaths. A life-table analysis confirmed the statistically significant difference in hemorrhage-free survival time between the microsurgical and stereotactic radiosurgical treatment groups (Pikus et al. 1998). The risks and benefits of the therapeutic options for patients with AVMs can he appreciated by direct comparison (Table 57D.2).

Special consideration must be given to the management of AVMs in pregnant women (see Chapter 87). Intracranial hemorrhage in pregnancy is caused as often by AVMs as by aneurysms. Although increased blood volume and venous pressure may be important in the pathogenesis of AVM hemorrhage, the time of hemorrhage does not always occur with the peak in cardiovascular changes of pregnancy. Labor and delivery is a high-risk period for AVM-associated hemorrhage, when 11% of these incidents occur. The decision about the diagnostic workup, time of surgery, and preoperative management should be based on neurosurgical rather than obstetrical criteria. If a hemorrhage has occurred during pregnancy, the risk of repeat hemorrhage is higher than in the patients who are not pregnant. Because of this high rate of reblccd, some have suggested that surgical excision of AVMs that have ruptured should be undertaken as soon as the patient is stable. The stage of pregnancy must be considered also; for those near term, an elective cesarean section at 38 weeks' gestation may carry the smallest combined risk to mother and child.

In general, to ensure that patients with AVMs receive appropriate therapy, the importance of a comprehensive team approach, which includes specialists with expertise in microvascular neurosurgery, endovascular techniques, and stereotactic radiation, cannot be overemphasized. Large lesions previously classified as unresectable may be safely managed with a combination of endovascular techniques, followed by surgical excision, and small lesions can be immediately and effectively eliminated with microsurgery.

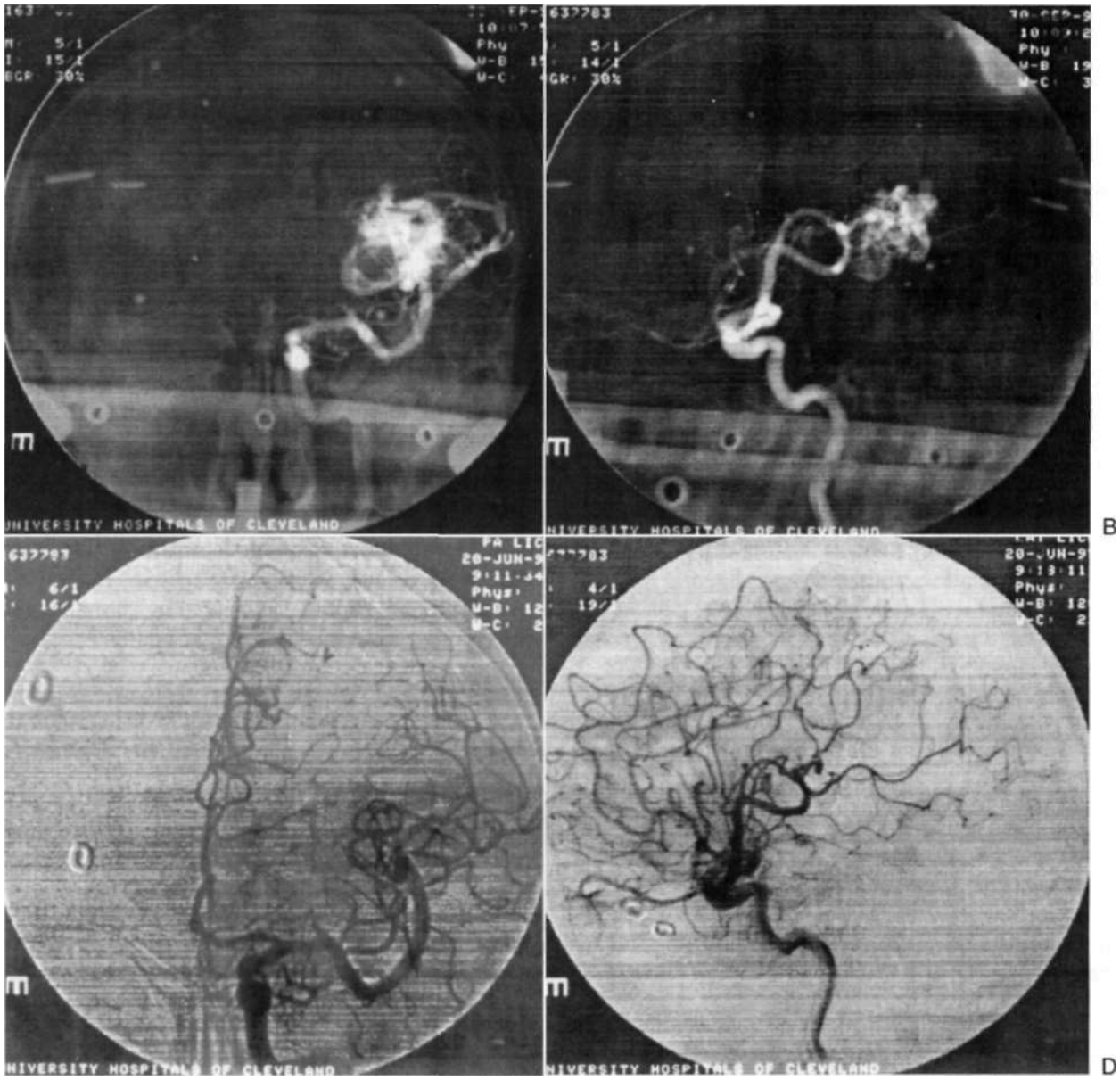

FIGURE 57D.10 (A) Posteroanterior and (B) lateral stereotactic left internal carotid artery angiogram demonstrates a left temporal arteriovenous malformation supplied by the left middle cerebral artery. Two-year follow-up (C) posteroanterior and (D) lateral left internal carotid attery angiograms after radiosurgery show obliteration of the arteriovenous malformation.

Table 57D.2: Comparison of tteatment modalities

Treatment modality	*Advantages*	*Disadvantages*
Microsurgical excision	Immediate elimination of risk of hemorrhage	Risk of immediate new neurological deficit
Endovascular embolization	Immediate reduction in size of AVM; immediate closure of intra n id a I aneurysms; no general anesthesia; short hospitalization	Rarely achieves total and permanent obliteration of AVM; risk of immediate new neurological deficit from hemorrhage or ischemia
Stereotactic radiosurgery	Noninvasive treatment; short hospitalization	Latency of 13 yr with risk of hemorrhage until complete obliteration ol AVM; risk ot delayed neurological deficit from radiation damage

AVM = arteriovenous malformation.
Source: Adapted from Steinberg, G. K. Sc Marks, M. P. 1997, "lnttaetanial arteriovenous malformation: Therapeutic options," in *Cerebrovascular Disease,* eds H. H. Batjcr, L. R. Caplan, & L. Fribcrg, Lippincott-Raven, Philadelphia.

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Chapter 57
Vascular Diseases of the Nervous System

E. STROKE IN CHILDREN

Meredith R. Golomb and Jose Biller

STROKE AND THE DEVELOPING CEREBROVASCULAR SYSTEM

Stroke in the older adult is usually due at least in part to chronic vascular injury. Obesity, cigarette smoking, arterial hypertension, diabetes mellitus, and a sedentary lifestyle are contributory to the majority of strokes in this population. In most children with sttoke, chronic lifestyle factots make little contribution to the cause of stroke. Developmental, genetic, and environmental factors are all possible contributors to cerebrovascular injury in the child.

EPIDEMIOLOGY

Premature and Term Neonates

Neonates are at higher risk for sttoke than older children, with risks for different stroke types partially determined by gestational age. The germinal matrix, an important site of neutonal development in the developing fetus, is highly vascularized with thin-walled vessels prone to rupture with increases in blood pressure. Premature infants often experience such shifts in blood pressure as a result of ventilators and othet sttessors, putting them at high tisk for intraventricular hemorrhage (IVH). Thorp et al. (2001) found that severe intracranial hemorrhages affected 2.9% of premature neonates 34 weeks' gestational age and younget, and 7.2% of premature neonates under 1500 g. (IVH in the premature neonate is discussed in further detail in Chaptet 86.) Neonates with gestational age older than 36 weeks are at lower risk of IVH. Gradnitzer et al. (2002) found that intracranial hemorrhage affects 1 in 100 term neonates.

Term and near-tctm neonates may also be at relatively high risk of arterial ischemic infarction when compared with older children, for reasons which are not completely clear. Lynch et al. (2001) at the National Institutes of Health estimated rates of 1 in 4000 and 1 in 5600 term births, but Gunthet et al. (2000) in Germany found a rate of only 1.35 per 100,000 tetm births.

There are few studies looking at the rate of cerebral venous thrombosis (CVT) in neonates. DeVeber et al. (2001) found a tate of 0.67 cases per 100,000 children per year, with neonates making up 43% of cases; the tates were not described in relation to the number of term births.

The General Population of Children

Estimates of the incidence of all pediatric stroke have ranged from 2.5 to 13 cases per 100,000 children per year

(Giroud ct al. 1995), with some variation among studies on the inclusion of neonates, traumatic strokes, and meningitis. ,md whether to use 16 or 18 as the age cut-off for pediatric stroke. There is also variation among studies as to whether hemorrhagic or ischemic strokes predominate. Estimates of the rate of hemorrhagic stroke have varied between 1.2 and 5 per 100,000 children per year (Giroud et al. 1995), and estimates of the rates of ischemic stroke have varied between 0.6 and 8 per 100,000 children per year (Giroud et al. 1995; deVeber 2002).

High-Risk Subgroups

Certain subgroups of children are at high risk of stroke, with rates approaching or surpassing those in older adults. Some medical conditions place children at risk for intracranial hemorrhage, ischemic stroke, or both,

Vascular malformations may present with intracranial hemorrhage. At the Hospital for Sick Children in Toronto, 80% of children diagnosed with arteriovenous malformations presented with spontaneous intracranial hemorrhage (Humphreys et al. 1996). It is not clear what percentage of children with arteriovenous malformations never have hemorrhage or other neurological signs, because neuroimaging is generally precipitated by neurological symptoms. Cavernous malformations and aneurysms may run in families and can present in childhood (Figure 57E.1). Risk may vary depending on the mutation involved. Intracranial hemorrhage may lead to vasospasm and resultant ischemic stroke, but may be rarer in children than in adults.

Children with bleeding disorders are at high risk for intracerebral hemorrhage. Of patients with hemophilia, 4% have intracranial bleeds, and 48% of these bleeds are intracerebral (Klinge et al. 1999).

Children with sickle cell anemia are at risk for ischemic stroke because sickling red blood cells may lead to thrombosis, and in some patients may be associated with moyamoya. The rate of stroke in children with sickle cell anemia has been estimated at 285/100,000 children per year (Earley et al. 1998), which is higher than the stroke rate reported in several adult stroke registries. Of children with sickle cell anemia, 11% have strokes and 17% have clinically silent infarcts (Figure 57E.2) (Pegelow 2001). Children with sickle cell anemia may also develop aneurysms and resultant hemotrhage, but this is more common in adults with sickle cell.

Children treated with extracorporeal membrane oxygenation (ECMO) are at high risk for both intracranial hemorrhage and embolic ischemic stroke. The rates of infarction after ECMO vary dramatically between scries, with rates ranging from 0% to 26%; Jarjour et al. (1994) examined the brains of 44 patients dying while on ECMO, and found evidence of focal ischemic infarct in 50% and intracranial hemorrhage in 52%.

Children with complex congenital heart disease arc at risk fot cardioembolic stroke, thrombotic stroke, watershed infarcts from drops in perfusion pressure, and CVT {Figure 57E.3). The rates of stroke in children with complex congenital heart disease also vary among series, with some of the variation resulting from the severity of the malfotmation, the number of corrective surgeries required, anesthetic techniques during surgery, patient selection, and length of follow-up. Miller et al. (1994) found evidence of focal infarction in *6* of 20 children with magnetic resonance imaging (MRI) performed at least 2 years after surgery. However, their data suggested that the patents of childten

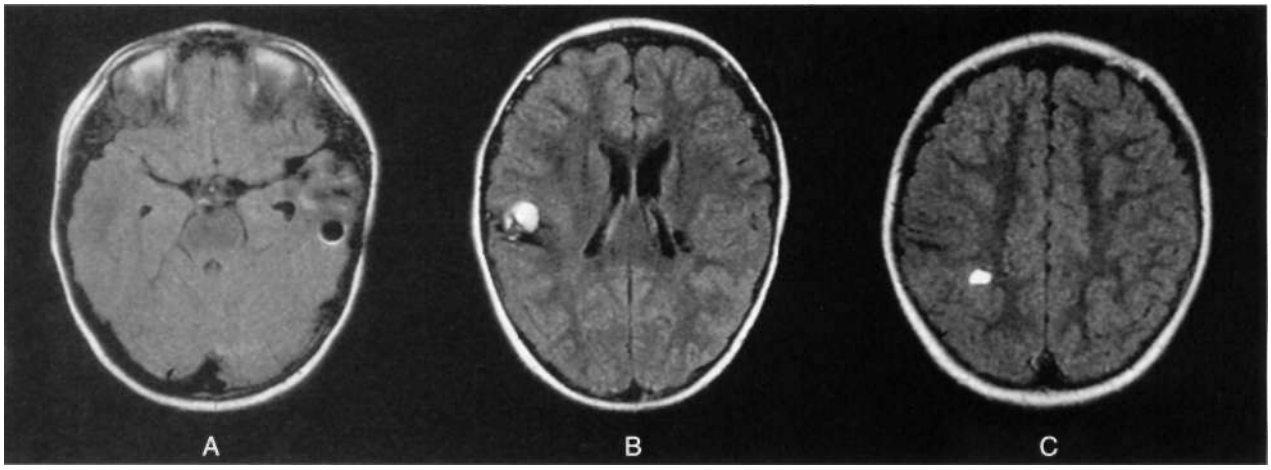

FIGURE .i71'.. 1 [his is ;i 5-ycar-oUI hoy with a history ot multiple cavernous malformations ami partial temporal lobectomy for resection of a cavernous malformation who presented with seizures. (A-C), Fast spin echo inversion recovery magnetic resonance imaging demonstrates multiple h y peri n tense new and hypo intense old parenchymal hemorrhages consistent with cavernous malformations, with evidence of recent hemorrhage and increased size of the right posterior frontal lesion and a new small hemorrhage in the right centrum semiovale. (Courtesy Section of Neuroradiology at Riley Hospital for Children, Indianapolis, Indiana.)

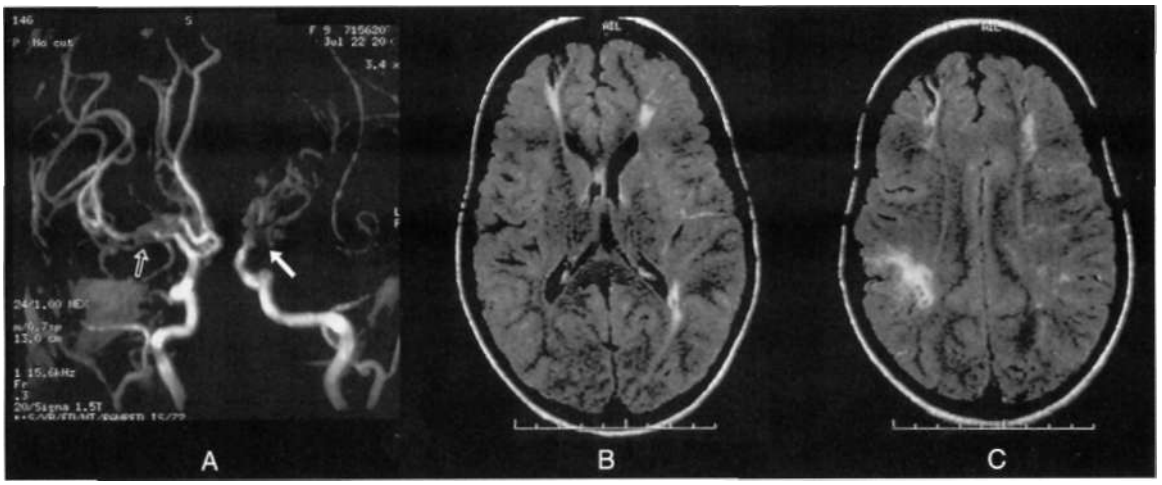

FIGURE 57E.2 This is a 10-year-old girl with sickle cell anemia. At age 5 she presented with a left hemiparesis. Magnetic resonance imaging (MR!) then showed acute ischemia in the right middle cerebral artery (MCA) territory and chronic ischemic changes in the left cerebral hemisphere. Magnetic resonance angiography (MRA) showed stenoses in both anterior circulations. These stenoses progressed over time, and she was treated with pial synangiosis and burr holes. There was no clear progression of ischemic lesions. (A) MRA demonstrates complete occlusion of the left Ml segment of the MCA *{solid arrow),* and severe stenosis of the M1 segment of the right MCA *[open arrow)* and both Al segments of the anterior cerebral arteries. There are multiple small vessels at the stenotic sites consistent with moyamoya. There appears to be an anastomosis between the left superficial temporal branches and the distal left M1. (B and C) Fast spin echo inversion recovery MRI demonstrates multiple old infarcts in the bilateral frontal and parieto-occipital regions and centrum semiovale. (Courtesy Section of Neuroradiology at Riley Hospital for Children, Indianapolis, Indiana.)

with minimal neurological impairment were less likely to participate in their study; the parents of 20 of 104 children with congenital heart disease declined participation in a long-term study, and the families of 37 of the 57 children who received psychometric assessment declined MRI. Mayer et al. (2002) found evidence of cerebrovascular complications in 5 of 77 *(6.5%)* pediatric patients with heart transplants and an average of 59.2 months of follow-up;

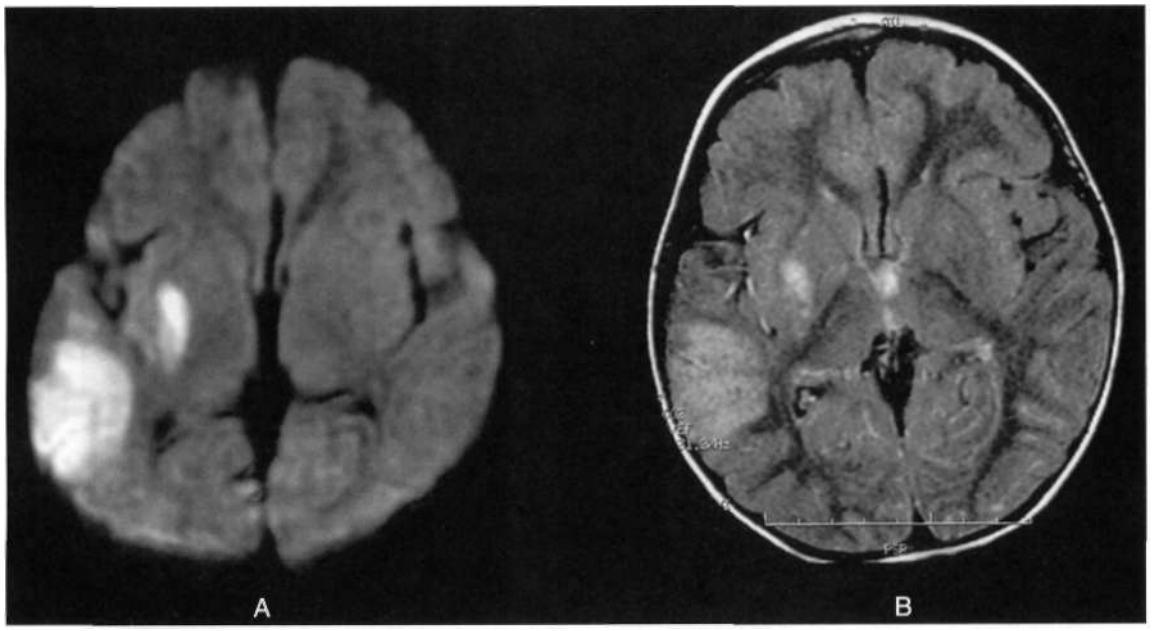

FIGURE 57E.3 This is a 3-year-old girl with a history of complex congenital heart disease. At age 10 months she had a procedure to repair a double inlet left ventricle and left transposition of the great arteries. She presented with seizures and dysconjugate ga?e 3 weeks later, and was diagnosed with an acute right pontine infarct. Magnetic resonance angiography and catheter angiography demonstrated narrowing of the distal basilar artery and the right superior cerebellar artery. At age 3 she presented with acute left hemiparesis and the following imaging: (A) Diffusion-weighred-imaging magnetic resonance imaging (MRI) and (B) fast spin echo inversion recovery MRI demonstrate multiple infarctions in the right temporal lobe, inferior parietal region, and Icntiform nucleus, consistent with cardiocmbolic stroke. (Courtesy Section of Neuroradiology at Riley Hospital for Children, Indianapolis, Indiana.)

25 of the 77 patients (32.5%) died. The times of greatest risk for children with congenital heart disease occur at the time of surgery or cardiac catheterization (Roach 2000a).

Children with cancer are at risk for both intracranial hemorrhage and ischemic infarction. Intracranial hemorrhage may occur secondary to thrombocytopenia from bone marrow suppression and/or bleeding of brain metastases or primary tumors. Children with cancer may develop ischemic infarction or CVT as a result of leukostasis in the setting of leukoma; complications oi chemotherapy Mich as with [.-asparaginase, which causes decreases in antirhrombin, fibrinogen, and plasminogen (Figure 57E.4); fungal or bacterial meningitis leading to arteritis; vasculopathy secondary to radiation; or complications of intracranial surgery. Bowers et al. (2002) observed 807 pediatric brain tumor patients for ;i ror.il of *M'14* uonpenoperarive years and found that 1.6% had a nonperioperative stroke.

Children with certain syndromes are at increased risk for stroke, sometimes for multiple reasons. Those with Down syndrome have higher than average rates of leukemia, which may lead to hemorrhagic stroke; moyamoya, which may lead to ischemic or hemorrhagic stroke; complex congenital heart disease, which may lead to cardioembolic stroke; and atlantoaxial instability and other abnormalities of the cervical spine, which may place them at increased risk for vertebral artery dissection. Children with neurofibromatosis type 1 also have higher than average rates of moyamoya and other occlusive vasculopathics that are sometimes associated with radiation. Connective tissue disorders, such as Marfan's syndrome, Ehlers-Danlos syndrome, and pseudoxanthoma elasticum may predispose to cervicocephalic arterial dissection or aneurysmal dilatation. Metabolic syndromes that damage the endothelium such as homocystinuria, Fabry's disease, and the familial hyperlipemias, may predispose to vascular damage and thrombosis.

PR] SLNTATIONS

The most common presentation of IVHs, arterial ischemic strokes, and CVT in term neonates is seizures. Seizures are a presenting sign for 6S% of term neonates with IVH, for at least 80% of term neonates with arterial ischemic stroke (Volpe 2001), and for at least 70% of neonates with CVT (deVeber et al. 2001). Other presenting signs include apnea, irritability, jirteriness, lethargy, and bulging fontanel. **The** immature central nervous system may not demonstrate focal signs, and hemiparcsis may not be apparent until a child is older than 6 months of age.

Children older than 6 months of age may present with seizures or focal signs similar to those seen in adult stroke, with hcmiparesis, ataxia, or aphasia. Although severe headaches such as those seen with intracranial hemorrhages often prompt parents to seek medical attention, parents may not detect focal motor weakness seen with a young child who has not yet started to walk, or aphasia in a young child who is just starting to speak. Parents may interpret the sudden onset of focal neurological signs as behavioral rather than neurological. It is easier to detect focal neurological signs and symptoms in older children, but these are also often missed in the first minutes to hours, possibly because many parents do not realize that children can have strokes.

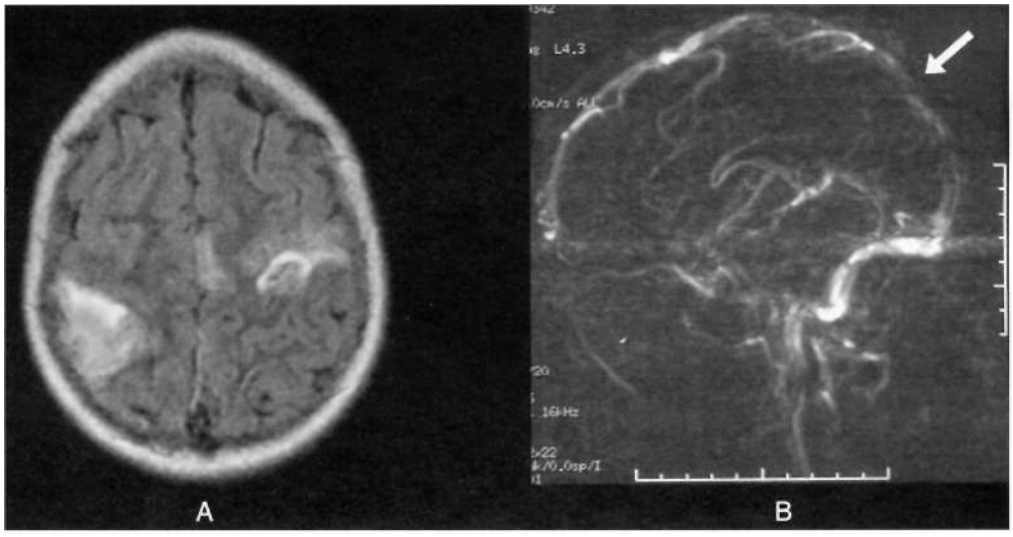

FIGURE 57E.4 This is an 8-year-old boy with leukemia who developed headaches and left hand numbness during induction chemotherapy with L-asparaginase. (A) Fast spin echo inversion recovery magnetic resonance imaging demonstrates multifocal bilateral hemorrhagic infarctions. (Bj Magnetic resonance venogram demonstrates irregularity of the superior sagittal sinus consistent with thrombosis *(arrow).* (Courtesy Section of Neuroradiology at Riley Hospital for Children, Indianapolis, Indiana.)

Some children may have no symptoms, or only gradual onset of developmental delay. As described previously, up to 17% of those with sickle cell disease have silent infarcts. The rates of silent infarction in other cerebrovascular disorders are not clear because radiological investigations are usually not initiated in the absence of clinical symptoms.

CAUSES

Cardiac Causes

Complex congenital heart disease may lead to thrombosis and ischemic stroke through several mechanisms. Abnormal cardiac anatomy or associated cardiac arrhythmias lead to abnormal flow and may predispose to the formation of intracardiac thrombi. Septal defects may lead to right-to-left shunts that allow venous thrombi to cross to the arterial side and cause cerebral infarction. Surgery and cardiac catheterization can disrupt the endothelium and lead to thrombosis. Cardiac surgery in itself may lead to a temporary prothrombotic state {Petaja ct al. 1996). An abnormal heart valve can serve as a nidus for bacterial vegetations that may cause cardioembolic stroke. Chronic hypoxemia in severe cases of congenital heart disease may lead to polycythemia, and the increased blood viscosity may promote thrombosis. Patent foramen ovale is associated with arterial infarction in both children and adults, again because of presumed right-to-left shunting.

Hematological Causes

Any hematological disorder that disrupts coagulation can place a child at risk for hemorrhagic stroke. Newborns have lower levels of coagulation factors and have a drop in the vitamin-K-dependent factors in the first days of life. Bleeding caused by vitamin K deficiency was more common before intramuscular or oral administration to neonates became widespread; Cornelissen et al. (1996) found that administering vitamin K lowered the incidence of vitamin K deficiency bleeding from 7 to 1.1 per 100,000 births per year. Accidental ingestion or overdose of warfarin has the same effect as a vitamin K deficiency, and may occur when a young child finds an older family member's medications. Congenital coagulation factor deficiencies may place the child at risk for abnormal bleeding. The most common are deficiencies of coagulation factor VIII (hemophilia A), coagulation factor IX (hemophilia B), and von Willcbrand's factor. Intracranial hemorrhage remains the most common cause of death from bleeding in patients with hemophilia.

A deficiency of factors involved in regulating coagulation may place the child at risk for thrombosis. Pediatric ischemic stroke is associated with deficiencies of protein C, protein S, and antithrombin III; activated protein C resistance caused by the factor V Leiden mutation; the prothrombin gene 20210 mutation, the methylene tctrahydrofolatc reductase (MTHFR) gene defect, and elevated lipoprotein (a); the plasminogen activator inhibitor promoter polymorphism (PAI 1); elevated antiphospholipid antibodies and lupus anticoagulant; elevated factor VIII levels; and low plasminogen or high fibrinogen levels.

Abnormalities of blood cells or blood cell concentration may place the child at risk for hemorrhagic or ischemic stroke. Low platelet count resulting from autoimmune thrombocytopenia or bone marrow suppression may lead to hemorrhage. Anything that increases blood viscosity, such as sicklcd cells, polycythemia, or chronic hypoxia, may predispose to arterial or venous infarct. Dehydration is associated with arterial strokes and CVT, possibly because it increases viscosity. Anemia is a risk factor for arterial ischemic infarction and CVT, possibly because of alterations in hemodynamics or imbalances in thrombotic pathways.

Trauma

Trauma can injure vessels directly, leading to hemorrhage from torn vessels and thrombosis in damaged intima (Figure 57E.5). The role of trauma in neonatal stroke is controversial; there is one clear, highly cited pathology case report documenting a neonatal stroke caused by forceps trauma (Roessmann et al. 1980). Subdural hemorrhages, subarachnoid hemorrhages, and ischemic infarctions all occur in both accidental and nonaccidenta! head injury. It is important to ascertain the cause of the trauma; 95% of serious intracranial injuries in children younger than 1 year of age are due to abuse, and *5%* of children who return to abusive parents without any intervention are killed (Johnson 2000). Bony abnormalities of the verrebrae, or abnormalities of vessel walls resulting from collagen-vascular disease or metabolic disease may predispose to cervicocephalic arterial dissection after mild rrauma. There may also be a prothrombotic state associated with trauma that can promote thrombosis and worsen outcome; disseminated intravascular coagulation worsens the outcome in trauma patients.

Infection

Bacterial meningitis may lead to disseminated intravascular coagulopathy and vascular inflammation, and subsequent arterial or venous thrombosis and infarction. Group B streptococcus meningitis is an important cause of stroke in neonates and may be transmitted vertically from the mother or horizontally by nursery staff. During the first 2 months of life, infants arc susceptible to bacteria found in maternal flora or in the local environment, including group B streptococcus, gram-negative enteric bacilli, and *Listeria*

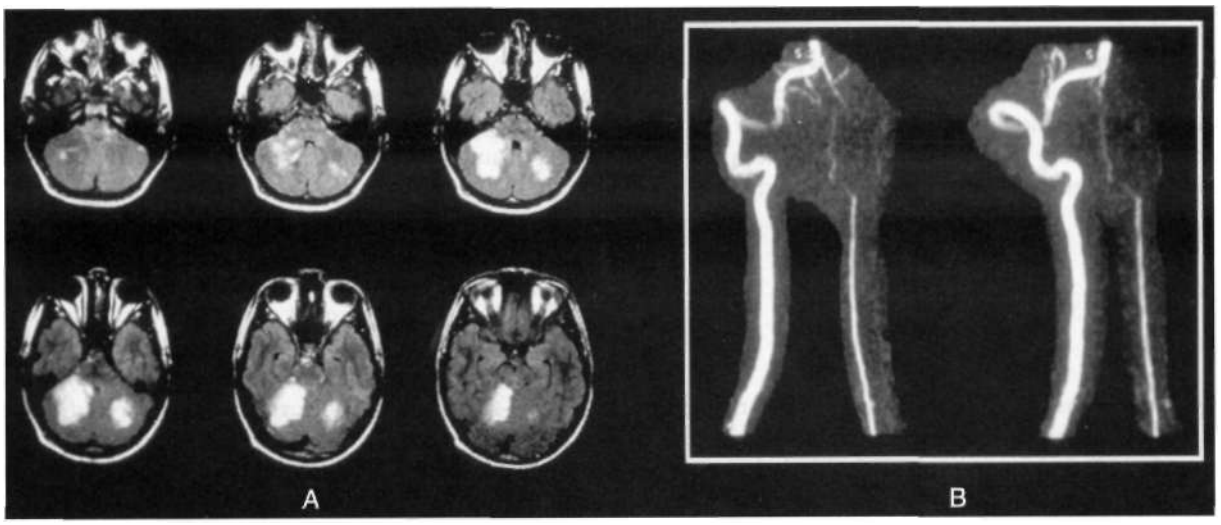

FIGURE S7E.5 A previously healthy 14-year-old boy developed vertigo, emesis, dysarthria, right handed dysmctna, and impaired tandem gait. Four days previously, he fell during hockey practice. (A) Magnetic resonance imaging demonstrated multiple cerebellar infarcts; (B) magnetic resonance angiography demonstrated left vertebral artery dissection.

monocytogenes. After 2 months of age, *Streptococcus pneumoniae* and *Neisseria meningitidis* are the most common causes of bacterial meningitis. The institution of *Haemophilus influenzal* type B vaccination at 2 months of age has led to a dramatic drop in *H. influenzal* B meningitis, In immunosuppressed children with cancer or acquired immunodeficiency syndrome (AIDS), *Aspergillus* species may lead to vasculitis and infarction. Patients with AIDS may also develop arteriopathy of medium and small vessels or aneurysms, and although the presumed cause for most cases is direct or secondary infection, the exact pathophysiology is not always clear. Tuberculosis leads to meningitis in 1-2% of cases, and may lead to vasculitis and infarction. Lyme disease is a rare cause of infectious vasculitis and aneurysm formation. Varice 11a-zoster virus may cause vasculitis by direct infection of the arterial wall or by a postinfectious inflammatory reaction that manifests weeks to months after the primary infection.

Vascular Mai formations/Vasculopathy/Migraine

As discussed in the Trauma section, vascular malformations may present with intracerebral hemorrhage. Resulting vasospasm may lead to ischemic infarction.

There are rare reported cases of primary angiitis of the central nervous system in children that may be fatal unless treated with aggressive immunosuppression. There are more frequently reported cases of less virulent vasculopathics in children, often occurring after varicella infection, that respond to aspirin alone and do not require immunosuppression (Lanthier et al. 2001).

There are many case reports of ischemic stroke in children after migraine. Arterial vasospasm in some children with stroke may be due to migraine.

Drugs/Toxins

Maternal usi' ol cocaine may lend to vasospasm and cere bra I infarction in the fetus, and use of cocaine by children may lead to intracranial hemorrhage or ischemic stroke. Other drugs such as amphetamines, which lead to sudden increases in blood pressure or vasospasm, also raise the risk of infarction. Accidental ingestion or overdose of medications used to treat thrombosis may lead to hemorrhage,

Metabolic Causes

The mitochondrial diseases may lead to metabolic infarction, particularly during times of metabolic stress. MRI usually demonstrates infarction in nonvascular territories (Figure 57E.6}.

Other metabolic diseases lead to cerebral infarction by contributing to arterial damage that results in thrombosis. Homocystinuria may lead to infarction, presumably through elevated homocysteine levels and subsequent vascular injury. The MTHFR gene defect has been associated with childhood stroke. Study results vary regarding the degree of associated risk, and carriers do not always have elevated homocysteine levels at the time of infarction. Fabry's disease is an X-linked lysosomal storage disease that causes a deficiency of alpha galactosidase and resultant accumulation of glycolipids in the endothelial wall, Both male and female heterozygotes arc susceptible to cerebral thrombosis, possibly because of an increase in v a so reactivity in damaged vessels or endothelial and leukocyte activation. Men may be more severely affected, and rarely show cerebrovascular involvement before the third decade of life. a_L Antitrypsin deficiency may lead to decreased structural integrity of the arterial wall by

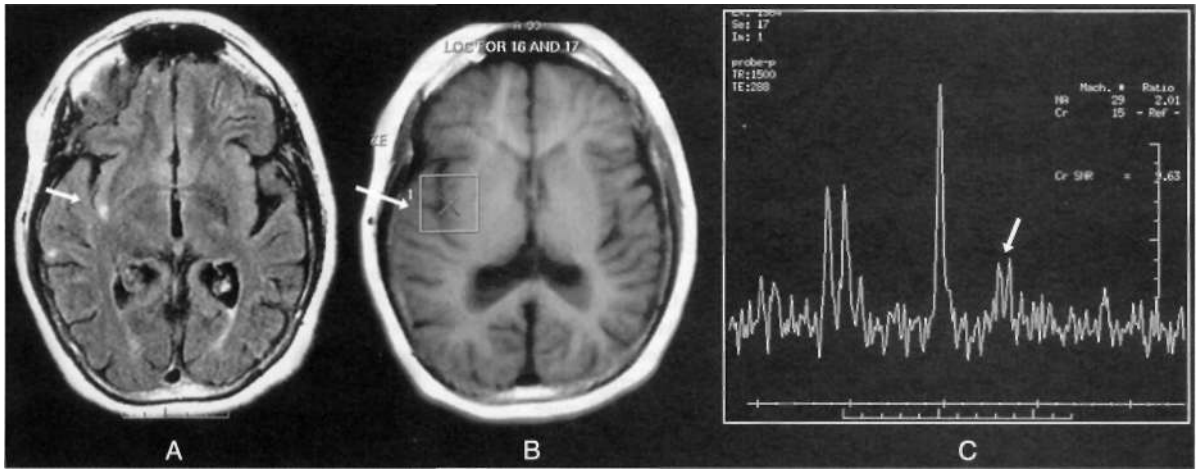

FIGURE 57E.6 This is an 18-year-old girl who presented at age 12 with headaches and went on to develop hilateral incoordination, decreased attention span, decline in school performance, and fatigability. (A) Fluid spin echo inversion recovery magnetic resonance imaging demonstrates multiple hilateral lesions not in vascular territories. (B) A M-ution of the involved area is selected for evaluation using magnetic resonance (MR) spectroscopy. (C) MR spectroscopy demonstrates a lactate doublet peak consistent with mitochondrial disease in an area of signal abnormality *(arrows).*

disrupting the balance of activity between proteases and antiprorcases. a_t Antitrypsin deficiency has been associated with aneurysm formation, arterial dissection, and vascular changes consistent with fibromuscular dysplasia. The hypcrlipidcmias may lead to atherosclerotic vascular changes in children similar to those seen in older adults.

Combinations of Multiple Factors

Some children have more than one factor contributing to the cause of their stroke. Hemorrhages in children with hemophilia are often precipitated by trauma. Children with ischemic stroke may have multiple prothrombotic abnormalities. Children with congenital heart disease or with leukemia may be at higher risk for developing thrombotic complications during hospitalization if they also have a prothrombotic abnormality.

Differential Diagnosis

Children with stroke often present with seizures. In the first hours after a seizure, before cranial imaging is performed, it can be difficult to determine whether a new hemiparesis is due to a temporary postictal Todd's paresis or to infarction. A Todd's paresis usually does not last more than 24 hours, although in rare cases it may persist for several days. Migraine may lead to temporary motor impairment or infarction and permanent weakness. A strong family history of hemiplegic migraine or documentation of a missense mutation of the CACNAIA calcium channel on chromosome 19*p*\3 may help diagnose familial hemiplegic migraine (Terwindt et al. 2002). However, there is variation in mutations among families; many families with familial hemiplegic migraine have a different gene locus. Alternating hemiplegia of childhood is a progressive neurodegenerative condition. The pathological condition is generally unclear, although cerebrovascular factors and mitochondrial disease may be contributory in some cases. Neuroimaging studies in alternating hemiplegia of childhood are usually normal. Edema, bleeding, or shifting of brain tumor may cause sudden onset of neurological signs, Encephalitis or meningoencephalitis may lead to sudden onset of focal neurological symptoms. Several metabolic diseases, including glutaric aciduria and carbohydrate-deficient glycoprotein syndrome can present with strokelike episodes; serum and urine testing and MRI help make the diagnosis. Acute disseminated encephalomyelitis (ADEM), multiple sclerosis, and vasculitis can all cause sudden onset of focal or multifocal neurological symptoms, and all cause multiple T2 bright lesions on MRI. Although ADEM lesions tend to occur more commonly at the grey-white junction than vasculitis lesions, and multiple sclerosis usually affects the periventricular areas in addition to other white matter tracts, the MRI findings may overlap.

EVALUATION

History and Physical Examination

In the young patient, the history should include questions about delivery and pctinatal period, attainment of hand preference, and basic developmental milestones. Prematurity places the child at increased risk of stroke, as described earlier, and a history of neonatal seizures may have been the first sign of neonatal stroke. Development of a hand preference before I year of age may be a sign of a

Table 57E.1: The physical examination in the child with stroke

Finding	*Possible significance/suggestive of:*
Head circumference	
Macrocephaly	Hydrocephalus caused by IVH, SDH, SAH, or vascular malformation
Microcephaly	Failure of brain growth resulting from stroke or genetic disorder
Eyes	
External/Iris	
Epicanthal folds, Rrushfield's spots	Down syndrome
Horner's syndrome	Carotid dissection (post ganglionicj/vertebral dissection (central)
Pulsating exophthalmos	Carotid-cavernous fistula
Lens subluxation	Marfan's syndrome, homocystinuria
Aiigioid streaks	Pseudoxanthoma elasticum
Xanthelasma on lids, corneal arcus	Hyperlipidemia
Corneal opacity	Fabry's disease
Retina	
Papilledema	Increased ICP resulting from hydrocephalus, vascular malformation, or acute edema
Hemorrhages	Trauma (consider child abuse), bleeding diathesis, ruptured aneurysm, collagen disease, emboli
Vasculopathy	Systemic vasculitis
Angioid streaks	Pseudoxanthoma elasticum. Paget's disease, sickle cell
A in; ion l.i	Familial cavernous angiomatosis, von Hippel-l.indau disease
Skin	
Bruising	Weeding diathesis (consider child abuse)
Petechia e	Platelet count low or dysfunction; DIC
Purpura	Henoch-Schonlein purpura
Pallor	Anemia
Erythema	Polycythemia
Cyanosis	Complex congenital heart disease, other cause of hypoxia
Skin necrosis	Meningococcemia
Cafe-au-lait spors	Neurofibromatosis type 1
1 lypopigmented macules, shagreen patches, facial angiofibromas	Tuberous sclerosis
Yellow papules	Pseudoxanthoma elasticum
Premature aging	Progeria

Continued

mild hemiparesis in the nondominant hand that could be due to what is presumed to be a perinatal infarction. Any early hemorrhagic or ischemic infarction may lead to slowed development. Medical history should include questions about previous hemorrhages, abnormal bruising, petechiae, or thromboses, and about other medical conditions that may raise the risk of early stroke, such as complex congenital heart disease, renal failure, or sickle cell anemia. Family history should include questions about abnormal bleeding in other family members, strokes or heart attacks before age 4.5, peripheral arteriopathy, or deep venous thrombosis. A history of multiple miscarriages may be suggestive of antiphospholipid antibody syndrome.

Physical examination should include examination of the face for signs of dysmorphic features suggestive of a genetic syndrome. Head circumference should be assessed. **Early** stroke may lead to macroccphaly caused by hydrocephalus or microcephaly caused by tissue loss and poor brain growth from infarction. Examination of the skin should document signs of bruising or petechiae; livedo reticularis suggestive of Sneddon's syndrome, systemic lupus erythematosus, or other autoimmune disorders; cafe au lait spots for neurofibromatosis type 1; hypopigmented macules for tuberous sclerosis; excess skin laxity for a collagen disorder such as Ehlcrs-Danlos' syndrome; cyanosis for heart failure and anoxia; and pallor for anemia. Head and neck should be auscultated for vascular bruits, the heart should he auscultated for murmurs and arrhythmias, peripheral pulses should be compared, and the abdomen should be auscultated for renal bruits suggesting a more systemic-vascular disorder. Neurological examination should be used to detect signs of focal abnormality, with the caveat that signs may not localize well in the very young child, or may be difficult to assess in the frightened or uncooperative child (Table 57E.1).

Imaging Studies

Ultrasound is useful in assessing IVH or periventricular leukomalacia in the premature infant, or assessing carotid

Table 57E.1: The physical examination in the child with stroke—cont'd

Finding	*Possible significance/suggestive of:*
Malar rash	Systemic lupus erythematosus
Skin laxity	Ehlcrs-Danlos syndrome type IV
Telangiectasias	Oslcr-Wcber-Rendu disease (hereditary hemorrhagic telangiectasia)
Oral/genital ulcers	Behcet's disease
Angiokeratomas	Fabry's disease
Lentigines in non-sun-exposed areas	Predisposition to dissection or to cardiac atrial myxoma, which may lead to cardioembolic stroke
Discoloration of fingers with cold: white, blue, then red	Raynaud's phenomenon as sign of collagen disease ot systemic lupus erythematosus
Subcutaneous nodules on elbows, forehead, tendons	Rheumaric fever, systemic lupus erythematosus, rheumatoid arthritis
Erythematous macules that evolve to clear, fluid-filled vesicles	Acute varicella (chicken pox); shingles if in a dermatomal distribution
Multiple round, white, puckered sc:irs	Past varicella infection
Needle tracks	IV drug addiction, with risk for endocardiris and HIV
Mouth	
High, arched palate	Mar fan's syndrome
Petechial hemorrhages	Infecrive endocarditis
Heart and Peripheral Pukes	
Murmur	Complex congenital hcarr disease, valve abnormality
Decreased pulses	Takayasu's arteritis
Increased pulses	Hypertension
Abdomen	
Hepatomegaly	Infection, cancer, liver failure
Bruit	Renal artery stenosis
Back	
Scoliosis, vettebral anomalies	Possible increased risk of dissection
Hands	
Long, tapering fingers	Marian's syndrome
Other anomalies of bones of hands	May be seen in association with congenital heart disease
Clubbing of fingers	Congenital heart disease
Joints	
Painful, with restricted movement	Arthritis due to autoimmune disease, past bleeds (hemophilia)
Warm	Autoimmune disease, infection
Overall Size	
Tall	Marfan's syndrome, homocystinuria
Short	Progeria, mitochondrial disease, dwarfism (risk of vertebral anomalies)

DIC = disseminated inttavascular coagulation; HIV = human immunodeficiency virus; ICP = increased intracranial pressure; rv = intravenous; IVH intraventricular hemorrhage; SAH = subarachnoid hemorrhage; SDH = subdural hematoma.

flow in any child, but its sensitivity for detecting arterial stroke in the neonate is probably less than 50% (Goiomb er al. 2003). Power Dopplcr ultrasound may be useful in detecting CVT in the neonate.

Cranial computed tomography (CT) is better at assessing hemorrhage in the older child and ischemic stroke in the neonate and older child, but may not detect arterial stroke until 24 hours or more after the event.

MRI is the imaging tool of choice for most types of childhood stroke, and diffusion-weighted imaging (DWl) can detect brain ischemia within hours. DWI stays bright for approximately 2 weeks in the older child or adult, bin ma\ "normalize" ipseuJonnrm.ili/.irion) within days in the neonate (Mader et al. 2002). Stroke imaging at any age should include DWI, T2, and fluid attenuated inversion recovery of (FLAIR) to detect areas of early infarction. Magnetic resonance angiography may be helpful in diagnosing vasculitis and dissection involving larger vessels.

Magnetic resonance proton spectroscopy and single photon emission CT demonstrate changes in regional blood flow and may be helpful in assessing patients with moyamoya disease and other sources of vasculopathy. Magnetic resonance spectroscopy provides the earliest detection of ischemic lesions.

Conventional angiography can clarify the structure of vascular malformations and is the most accurate method for detecting vasculitis and dissection. An interventional radiologist experienced in cranial angiographyis required, and angiography may not always be possible in the acutely ill child. All forms of ncuroimaging should be used in combination with other laboratory and physical findings, because no one technique has perfect sensitivity or specificity for detecting vasculopathy.

Prothrombotic Evaluation

The basic evaluation for prothrombotic disorders may include prothrombin time (international normalized ratio) and activated partial thromboplastin time; a complete blood cell count including platelets, protein C, protein S, and antithrombin III levels; activated protein C resistance; plasminogen, fibrinogen, and homocysteine levels; anti-phospholipid antibody screen; lipoprotein a level, and a cholesterol panel. Genetic testing may include screening for the factor V Leiden mutation, the prothrombin 20210A gene, and the MTHFR mutation (Andrew and de Verber 1999); genetic counseling should be provided before these tests are ordered, however {see the section Caveat for Genetic Workup).

Cardiac Evaluation

The basic cardiac evaluation may include electrocardiogram with rhythm strip and a transthoracic echocardiogram with injection of agitated saline to screen for a patent foramen ovale. If there is any suspicion for cardiocmbolic events and those two studies are unrcvcaling, transesophageal echocardiography and a Holter monitor study should be performed.

Other Studies

Electroencephalogram may help localize the lesion in children with seizures, and is helpful for evaluating cerebral function in the unresponsive, and possibly locked-in, patient with a brainstem stroke. Visual evoked potentials and brainstem auditory evoked potentials may be particularly helpful in evaluating the very young or somnolent patient.

Serum and plasma studies may help identify the cause of the stroke. Thrombocytopenia, deficiencies of factors I, VII, VIII, IX and XIII, and deficiency of von Willebrand factor are all risk factors for intracranial hemorrhage, whereas polycythemia, thrombocythemia, and anemia are all risk factors for ischemic stroke. Abnormalities in platelet count and fibrinogen may be markers for disseminated intravascular coagulation, which may lead to thrombosis and ischemic stroke. Elevated serum lactate is a marker for mitochondrial disease, but not all patients with mitochondrial disease have elevated serum lactate, and genetic tests may be required to confirm the diagnosis. Serum studies for plasma «-galacrosidase identify Fabry's disease. Serum ammonia, amino acids, and organic acids may help identify metabolic disease that can lead to stroke, such as hyperhomocysteinemia and mitochondria! diseases. Skin biopsy is often necessary to confirm the diagnosis of collagen vascular disease. Muscle biopsy may help confirm mitochondrial disease.

Caveat for Genetic Workups

Identifying a patient as having a genetic disorder may affect current ami future medical, life, and disability insurance status. In some cultures, genetic disorders stigmatize a family and affect social interactions and ability to marry within the group. Screening a family may identify asymptomatic patients who may stay asymptomatic. Whereas the risk with some genetic disorders, such as protein C deficiency, is clear and warrants screening other family members, the degree of risk attached to pediatric carriers of the factor V Leiden mutation are not clear, particularly if the carriers are nonsmokers and do not use oral contraceptives. Some mutations are very common, and the number of asymptomatic carriers may be very high; more than 40% of healthy children in a European study were either homozygous or heterozygous for the MTHFR mutation (Koch et al. 1999). These issues should be discussed with the family before genetic tests are ordered on asymptomatic family members.

THERAPIES

The Acute Period

Children with intracranial hemorrhage or hemorrhagic stroke require close observation in the first hours. Children with hemophilia need immediate factor replacement and may require blood transfusion. Children with large hematomas with significant mass effect may need surgery. Any child presenting with unexplained or poorly explained intracranial hemorrhage should also be evaluated for child abuse and other sites of injury.

There are only a handful of case reports describing children with ischemic stroke treated with intra-arterial or intravenous tissue plasminogen activator. Few children present within the mandated 3 hours of infarct onset. There are currently no clear guidelines on using intravenous or intra-arterial thrombolytics in children. It may not be helpful in neonates, who have lower levels of plasminogen than older children. Centers trying thrombolytic therapy in children should have stroke neurologists experienced in its use to assist in management, 24 hour access to a CT scanner to monitor for intracranial hemorrhage, and a pediatric neurosurgeon and operating room on-call in case of disastrous intracranial hemorrhagic complication.

There also arc no clear guidelines on the use of heparin in pediatric arterial stroke and SVT patients. Pilot studies and case series have described good results with heparin and low molecular-weight heparin (dcVcbcr et al. 1998). Large-scale studies with catheter-related, noncranial thrombosis have shown good results (Andrew et al. 2000). Other low-molecular weight beparinoids such as danaparoid are currently being studied, and may be good alternatives for patients with heparin-induced thrombocytopenia.

In sickle cell anemia, acute stroke is usually treated with exchange traiislusimi. Tin.' Srroko Prevention in Sickle Cell Trial showed that in children with evidence of vasculopathy by transcranial Doppler ultrasound screening, treating with regular transfusions reduced the risk of recurrent stroke by 90% (Adams 2000). However, chronic transfusions carry the risk of infection and cause increases in serum ferritin. Some children require treatment with deferoxamine chelation to prevent iron overload,

Attempts at treating and preventing metabolic stroke and cerebrovascular disease have been made by addressing the pathological defects in metabolic pathways. Therapy with coenzyme Q10 and other antioxidant vitamins for different mitochondrial diseases have had varying results. Folate, vitamin B_6, and vitamin Bj2 all play a role in homocysteine metabolism, which is impaired in homocystinuria and in carriers of the MTHFR gene defect. Several different enzyme abnormalities may lead to homocystinuria, and the enzyme affected determines whether supplementation with folate, vitamin B_{ft}, or vitamin $B|_2$ are helpful. Dietary supplementation with folate lowers serum homocysteine levels in adults with the MTHFR gene defect, and may also be helpful in children. Enzyme replacement with alpha galactosidasc decreases the symptoms of Fabry's disease, normalizes cerebrovascular reactivity (Moore et al. 2002), and may decrease the risk ot stroke.

There are several case reports and pilot studies dealing with replacing deficient coagulation pathway proteins. Protein C concentrate has been tried for protein C deficiency secondary to meningococcemia (Ettingshausen et al. 1999} and protein C deficiency (Dreyfus et al. 1995). Antithrombin concentrate has been used to treat consumptive coagulopathy and patients with antithrombin III deficiency at the time of acute stroke with good results, but it does not appear to prevent thrombosis in leukemia patients treated with L-asparaginase (Hongo et al. 2002).

Chronic Therapy

Patients with hemophilia and severe bleeding may require prophylaxis with regular factor transfusions. Young or ataxic children with hemophilia may need to wear protective helmets until their balance improves.

Patients with genetic, chronic thrombotic abnormalities such as protein C or S deficiency, or with lupus anticoagulant, may require long-term care with low-molecular-weight heparin or warfarin (Andrew et al. 2000), but for many patients, the best long-term therapy is not clear. Low-molecular-weight heparin may be used for 3-6 months after cervicoccphalic arterial dissection or CVT (Andrew and dc Verber 1999). Warfarin or aspirin arc more often used for long-term therapy (Andrew et al. 2000). Families of children on warfarin need to be counseled about regulating vitamin K levels in the diet, bony changes, possible teratogenicity, and the risks of under- or over-treatment. Families of children on aspirin are generally concerned about Reye's syndrome, but no cases have been reported in children taking aspirin for stroke prophylaxis (Roach 2000b).

There arc few clinical trials in this area. Stratcr ctal. (2001) did a prospective follow-up study of 135 children with first onset of ischemic stroke. The children received prophylactic treatment with either low-dose, low-molecular-weight heparin or aspirin and were followed for a median of 36 months. Low-dose, low-molecular-weight heparin was not superior to aspirin in preventing stroke recurrence.

Surgery or interventional procedures play a role in treating some types of cerebrovascular disease. Surgical procedures such as encephalodurosynangiosis or arterial bypass may be used to treat children with moyamoya disease. Surgery or neurointerventional procedures may be used to treat vascular aneurysms or malformations that place the patient at risk for intracranial hemorrhage.

Other Issues

Pregnancy often occurs in adolescent women, but carries special risks for women with a history of hemorrhagic or ischemic stroke. Ideally, such pregnancies should be planned, and patients should meet with their physician and a high-risk obstetrician before conception. Other medications used by women with stroke, such as warfarin and antiepileptic medicines such as valproate, may act as teratogens. This should be explicitly discussed with patients and their families, preferably before patients become sexually active. If pregnancy is accidental, a meeting with a high-risk obstetrician should be arranged as soon as possible, and neurologist, hematologist, and obstetrician should work together in planning care.

Oral contraceptives carry a very small risk for the general population, but may carry more risk for women with pro thrombotic disorders (Glueck et al. 2001). Oral contraceptive use raises the risk of both peripheral and cerebral venous thrombosis. These issues should also be explicitly discussed with patients and their families, preferably before adolescence, because some oral contraceptives are used to treat acne or menstrual disorders in adolescent women.

The issue of physical restrictions on stroke patients is a difficult one. Hemophiliacs are already restricted from contact sports because of their tendency to easily bruise and bleed. Ischemic stroke patients may make good motor recoveries, and the issue of physical restrictions should be discussed early. The cause of the stroke and the medications required to treat it should be considered.

OUTCOMES

The outcomes of childhood stroke can be very difficult to predict. Children with stroke are at risk for future cognitive

impairment, motor impairment, and epilepsy. Preterm infants are at particularly high risk; their outcomes are described in more detail in Chapter 86.

In term neonates, it is difficult to predict outcome based on initial cranial imaging. It is not clear whether the side of the infarct affects language development, because studies have not agreed. It is difficult to predict degree of hemiplegia from initial cranial imaging. Evidence of degeneration of corticospinal tracts and resulting asymmetry in the midbrain seen on MRl performed during the second 6 months of life does predict hemiplegia.

Studies in both infants and older children show that larger infarcts and multiple infarcts are more likely to cause cognitive impairment, as well as motor impairment and epilepsy. Overall, **the** intelligence of children with stroke falls within the normal range, but some children with stroke require extra help in school. Involvement of the cortex, internal capsule, and basal ganglia together is more likely to cause motor impairment than involvement of one of those alone.

The prognosis for children with progressive cerebrovascular diseases is much less benign. Children with severe forms of sickle cell or moyamoya disease who are **not** treated or do not respond to therapy may be left with significant cognitive and motor disabilities and epilepsy.

FUTURE DIRECTIONS

Screening and Prevention

As we begin to understand more about why children have strokes, we will begin to understand how to prevent them. The improved understanding of thrombotic disorders has helped some families prevent thrombotic events through screening and medical therapy. However, there are other causal factors that have yet to be discovered.

Therapy

Clinical trials are needed to assess the best therapies for children with stroke, and to form the infrastructure needed to assess new therapies used to treat adult stroke. Children may be able to benefit from some of the therapies developed for adults.

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Chapter 57
Vascular Diseases of the Nervous System

F. SPINAL CORD VASCULAR DISEASE

David S. Geldmacher and Brian C. Bowen

The spinal cord is subject to many of the same vascular diseases that involve the brain, but its anatomy and embryology render it susceptible to some syndromes that do not have intracranial counterparts.

VASCULAR ANATOMY OF THE SPINAL CORD*

The embryonic arterial supply to the spinal cord derives from radicular arteries that enter at each spinal level and divide to follow the dorsal and ventral roots. The ventral radicular branches join along the midline to form the anterior spinal artery. Irregular anastomoses among the dorsal roots, as they enter the cord on each side, form paired posterior spinal arteries. The anterior and posterior spinal artetics constitute longitudinal arterial plexuses. Circumflex vessels (arteria vasocorona) connect the anterior and posterior arterial systems around the lateral margins of the cord (Figure 57F.1).

During development, a few predominant radicular arteries provide most of the flow to the spinal cord through the anterior spinal artery. Five to eight large anterior radicular arteries and a similar number of posterior radicular arteries exist in adults. The largest and most frequently identified of the anterior vessels is the arteria radicularis magna or great artery of Adamkiewicz, which courses along one of the lower thoracic or upper lumbar anterior roots to join the anterior spinal artery (Figure 57F.2). It provides a major portion of the blood flow to the lower thoracic cord and the lumbar enlargement. The sacral cord, conns medullaris, and cauda equina are supplied by small lower segmental arteries. The cervical and upper thoracic spinal cord is richly vascularized by a plexus arising from branches of the ascending cervical and vertebral arteries.

In contrast to the lumbar and cervical regions, the blood supply to the midthoracic cord is relatively tenuous, often consisting of only one significant radicular vessel. At thoracic levels, the anastomotic network is less intricate, and the anterior spinal artery may become discontinuous. The midthoracic region of the spinal cord is considered traditionally to be the most vulnerable to compromise from hypoperfusion or occlusion of a single artery, but more recent evidence suggests that lower cord levels are at greatest risk (Duggal 5c" Lach 2002}.

The main blood supply to spinal gray matter, as well as to anterior and lateral funiculi, is derived from anterior sulcal arteries. These arise from the anterior spinal artery in

"The nomenclature for spinal vessels is potentially confusing. In the section on Vascular Anatomy presented here, the term *radicular* refers to intradural vessels that follow the course of a corresponding nerve root. Some anatomists identify arteries or veins that supply or drain the spinal cord at sevetal vertebral levels as *medullary* vessels, which are distinguished from the much smaller radicular vessels that supply or drain the nerve roots at every vertebral level (Gil I Man 1970). However, in the neuroimaging litetature, medullary vessels are sometimes referred to as *radkuktmedullary* vessels and the terms *radicular, medullary,* and *radiculomedullary* are often used interchangeably. Thus the "radicular" vessels described in Figure 57F. 1 and Figure 57F.2 correspond to the medullary vessels as defined by Gillilan (1970) and others (Bowen et al. 1996), which are shown in Figure parts 57F.5C and 57F.5D.

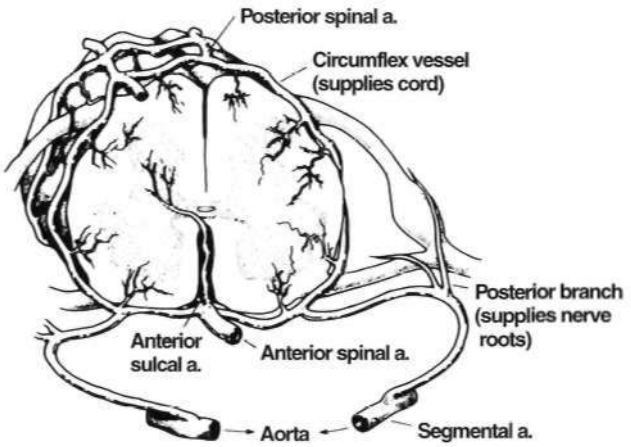

FIGURE 57F.1 Arterial supply to the spinal cord and nerve roots at rhe level of a radicular, artery. (Adapted from Henson, R. A., Parsons, M, 1967, "Ischaemic lesions of the spinal cord: An illustrated review," *QJM*, vol. 36, pp. 205-222.)

the midline and course into the ventral median fissure. Each anterior sulcal artery distributes blood to only the left or right half of the spinal cord. The greatest distance between sulcal arteries is in the thoracic segments; the vascularity is proportional to the numbers of neurons located throughout the cord at that level. The dorsal columns and extreme dorsal horns (approximately one third of the cord cross section) are supplied by penetrating branches from the posterior spinal arteries. The superficial white matter also receives blood flow via the circumflex anastomotic vessels (sec figure **57K** 1).

The venous system of the spinal cord parallels the arterial supply. A group of radial veins flows outward to the surface of the cord, ending in a coronal plexus, and deep parenchymal veins empty into central sulcal veins in the median fissure. Unlike the arteries, however, each parenchymal vein drains both the right and left sides of the **cord.** There are few venous anastomoses within the substance of the cord, but sulcal veins often have intersegmental anastomoses. The anterior median spinal vein, which lies external to its corresponding artery, is filled from the sulcal veins. As with the other spinal veins, the median spinal vein is more irregular than the corresponding artery and may be doubled. Extramedullary venous channels are also prominent along the dorsal cord, and the dominant vessel is usually the posterior median spinal vein. There is no corresponding artery in the midline. Paramedian and posterolateral veins are variably observed. The posterolateral veins may have segments that course adjacent to the posterior spinal arteries, but the veins and arteries do not parallel each other in general. Eight to 12 major anterior radicular veins arise from the anterior median spinal vein. They are joined by anterolateral anastomoses from the coronal venous plexus at the nerve roots before passing through the dura. There is typically a large vein that drains the levels of the lumbar enlargement {vena radicularis magna). Posterior radicular veins are present throughout, but are particularly prominent in the cervical region, Venous blood from the entire cord runs into the epidural and paravertebral venous plexuses, forming a large, valveless system from sacrum to occiput (Batson's plexus). The absence of valves to resist retrograde flow in this continuous venous network may be a factor in the pathogenesis of some spinal cord vascular disease.

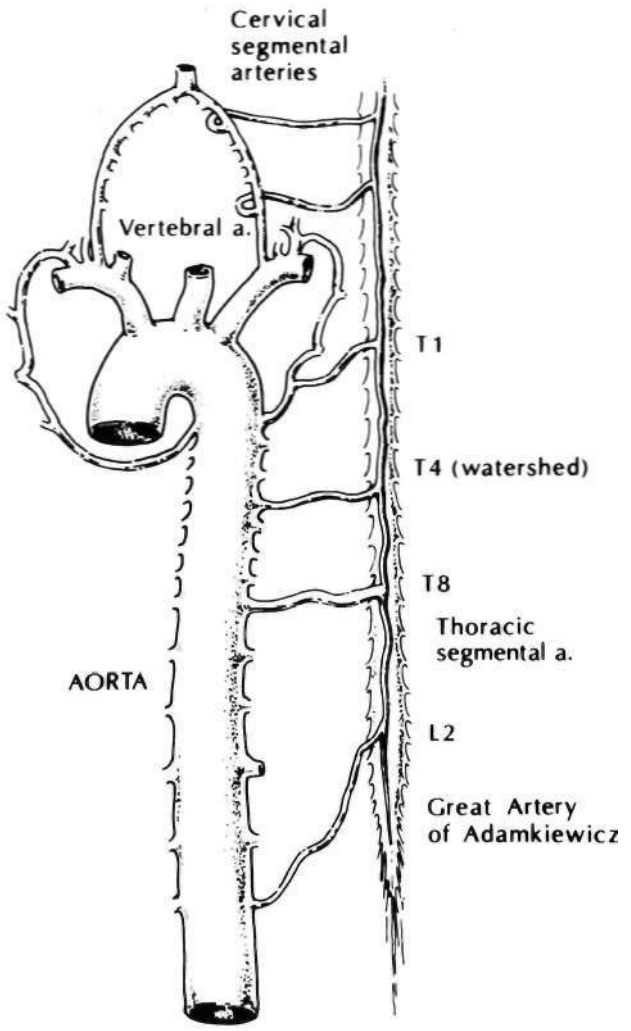

FIGURE 57F.2 Relationship of rypical anterior radicular arteries and spinal cord segments.

SPINAL CORD ISCHEMIA

Animal studies of aortic compression resulting in paralysis were reported as early as 1667, and, clinically, paraparesis resulting from aortic obstruction was recognized in the mid-1800s. By the early twentieth century, cardiac embolism, atheromatous disease, and decompression sickness were described as causes of spinal cord ischemia. Although it is less common than cerebral vascular disease, the

true prevalence of spinal cord infarction is not known. It probably represents less than 1% of all acute strokes.

Clinical Presentation and Course

Weakness, numbness, pain, and urinary complaints are common presenting symptoms of spinal cord ischemia. The weakness may progress gradually over hours or be maximal at onset. Because of the vulnerability of the thoracic cord to flow-related ischemia, paraparesis is more frequent than quadriparesis. Numbness, accompanied by paresthesias, often parallels the weakness and occasionally precedes it. Back pain in a radicular distribution is common. Visceral referred pain can mistakenly suggest an intra-abdominal process. Urinary dysfunction is typical, usually in the form of retention, but bladder and bowel incontinence may develop after the initial spinal shock resolves.

Examination of the patient initially reveals flaccid paresis with diminished superficial (abdominal, cremasteric) and tendon reflexes below the level of ischemia. Spasticity and hyper-reflexia, accompanied by extensor plantar responses, usually evolve with ischemia above the lumbar segments. A posterior spinal artery syndrome occurs only rarely and is notable for preservation of strength and reflexes.

Sensory loss is nearly universal in spinal cord ischemia. The location of a lesion may be predicted by the cutaneous distribution of sensory loss and the modalities involved. Occlusion of the anterior spinal artery impairs pain and temperature perception below the lesion, whereas in a posterior spinal syndrome there is derangement of touch, vibration, and proprioceptive senses below the lesion. A smaller lesion, such as that from the occlusion of a central sulcal artery, can present with a partial Brown-Sequard's syndrome or a suspended dissociated sensory loss (loss of pain and temperature sensation over the segment affected by the lesion, with preserved sensation above and below the lesion).

The course of spina! ischemic syndromes is variable. Transient ischemic attacks of the cord may occur, with weakness and numbness lasting 15 minutes. A slowly progressive myelopathy attributed to chronic constriction of radicular vessels in the neck has been suggested, but not established. Infarction of the spinal cord typically becomes evident as paresis within minutes of the initial symptoms or precipitating event. Intervals of many hours from the onset of pain, however, are recognized. Pain is often persistent and is a major contributor to long-term disability in spinal cord vascular syndromes. Return of function depends on the degree of parenchymal damage; there may be complete recovery. The duration of dysfunction is useful in determining prognosis. Unless significant motor recovery occurs in the first 24 hours, the likelihood of major improvement is low. The clinical presentation of spinal cord syndromes is presented in more detail in Chapter 27.

Investigations

Magnetic resonance imaging (MRI) is the imaging procedure of choice for detecting spinal cord ischemia, although the results can be normal even in the presence of significant symptoms. The pattern of signal changes, and their time course, are similar to those for cerebral infarction (Mascalchi et al. 1998; Rovira et al. 1998). After spinal cord infarction, typical spin-echo MRI findings are cord enlargement and hyperintense signal on T2-weighted images initially (8 hours to several days), with or without gadolinium enhancement, followed by cord atrophy months later. Abnormal signal and enhancement may demonstrate a double-dot ("owl's eyes") pattern in the region of the anterior horns, an H-shape pattern involving the central gray matter, or a more diffuse pattern involving both gray and white matter (Figure 57F.3). The diffuse pattern may be difficult to distinguish from venous infarction. When cord infarction results from compromise of a segmental artery, branches supplying the ipsilateral half of the vertebral body may be affected also. Vertebral body infarct is best detected on sagittal T2-wcighted images, usually appearing as a triangular area of increased signal near the endplate, the deep medullary portion of the vertebral body, or both. Other laboratory and radiographic studies are not diagnostic in noncomprcssive spinal cord ischemia. Myelography is usually normal. In many cases, the cerebrospinal fluid (CSF) protein is elevated, but CSF pleocytosis is rare.

Causes of Spinal Cord Ischemia

Typical causes of spinal ischemia are summarized in Table 57F.1.

Regional hemodynamic compromise from mechanical disruption of the aorta is the most common cause of spinal cord infarction, accounting for nearly 40% of one series of 44 patients (Cheshire et al. 1996). Complications of aortic aneurysm repair represent the largest proportion of those cases. Clamping of the aorta above the renal arteries for more than 20-30 minutes or operative ligation of lower thoracic intercostal vessels places the cord at risk for ischemia and infarction. Thoracoabdominal aortic aneurysm repairs arc associated with 5-20% risk of significant neurological deficits. There is emerging evidence to suggest that intraoperative interventions, like distal aortic perfusion and CSF drainage, may contribute to a lowered complication rate (Estrera et al. 2001). Modern endovascular aneurysmal repair techniques continue to present risks for spinal cord ischemia (Gravereaux et al. 2001). Aneurysmal aortic dissection causes spinal ischemia by diversion of blood flow around the ostia of intercostal and segmental arteries. In this condition, there is infarction of gray matter with preservation of superficial white matter. The longitudinal anastomotic network is apparently able to

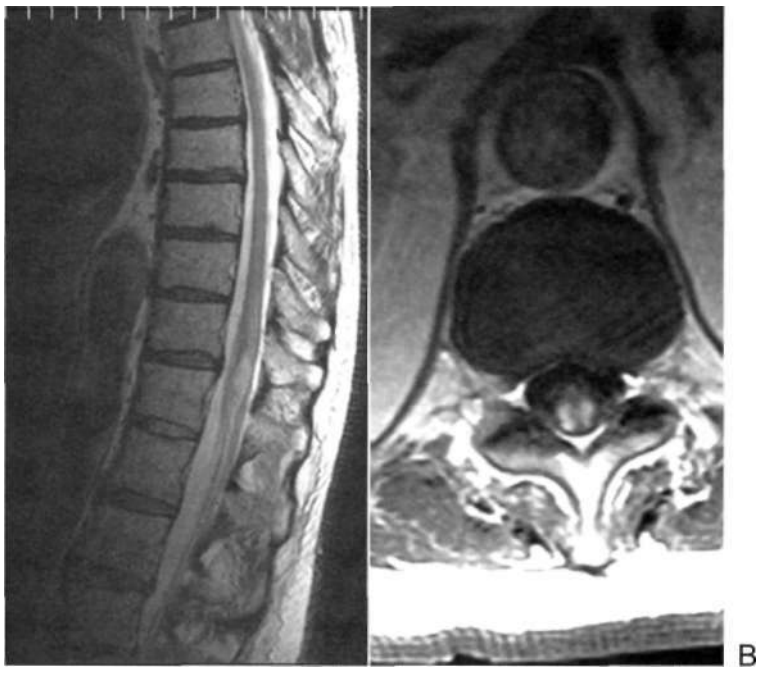

FIGURE 57F.3 Magnetic resonance imaging of a subacute, arterial infarction of the conus medLilians. A 69-year-old man had sudden onset of paraparesis and loss of bowel and bladder function 8 days prior to the magnetic resonance study. (A) T2-weighted, fast-spin-echo image shows focal enlargement and hyperintense signal within the conus medullaris. (8) Postcontrast Tl-weightcd axial image (T12 level) shows abnormal enhancement in an H-shaped pattern involving the central gray matter. (From Bourn, Ji, (. '. , . Saraf-Lavi, E. 2003, "Imaging of spinal vascular lesions," in *Advanced Imaging and Image-Guided Therapy of the Nervous System,* eds R. **E.** Latchaw, J. Kucharc/yk, M. E. Moseley, Mosby, Philadelphia. With permission.)

maintain sufficient blood supply to perfuse the perimeter of the cord, but not its central zones. Vertebral artery dissection may also lead to posterior cervical cord infarction. Nonpenetrating aortic trauma may cause torsional occlusion of vessels supplying the cord, with resultant ischemia.

Systemic hypotension produces cord ischemia, but because encephalopathy is common after resuscitation, isolated spinal cord syndromes are infrequent. Lower cord levels are especially susceptible to hypoperfusion. If there is prolonged hypoxemia, however, the pathological lesions arc distributed diffusely throughout the spinal gray matter. Localized thoracic cord ischemia may result from disordered autoregulation following percutaneous radiofrequency spinal rhizotomy.

Atherosclerotic plaques in the aorta may overlie the origin of branches to the spinal cord and diminish their blood flow or be a source of embolism. Transesophageal echocardiography may identify such plaques in the descending aorra. The spinal cord vessels are of a size that is generally not subject to occlusive atheromatous disease, but they are prone to luminal narrowing from arteriosclerotic hyalinization. Either of these conditions may result in intermittent claudication of the spinal cord manifested by activity-induced, transient symptoms of myelopathy. As with cerebral vascular disease, these transient ischemic attacks may precede spinal cord infarction. Intermittent spinal claudication may respond positively to aortobifemoral bypass.

Radiotherapy may produce myelopathy in part from occlusive changes in parenchymal spinal cord arterioles. The degree of myelopathy depends on the total radiation dose, dose per fraction, and the length of the irradiated segment of the cord.

Thromboembolism causes both acute and stepwise spinal cord dysfunction. Emboli arising from the mitral valve in rheumatic heart disease and from acute bacterial endocarditis may cause acute paraplegia. Similarly, thromboembolism from an atrial myxoma may cause multiple spinal cord infarcts. Myelopathy associated with decompression sickness results from circulating nitrogen bubbles that block small spin;i] aru'riev Spinal cord ischemia also may complicate therapeutic renal or bronchial artery embolizations.

Fibrocartilaginous emboli from inter vertebral disks are occasionally the cause of an ischemic syndrome unique to the spinal cord. The anterior portion of the cervical cord is the site of multiple arterial and venous microcmboli from a ruptured intervertebral disk in up to 70% of such cases. Women are affected twice as often as men. Fragments of disk material are traumatically forced into bone marrow sinusoids by local fracture and increased tissue pressure may introduce the emboli into the spinal vertebral

Table S7F.1: Causes of spinal cord ischemic syndromes

Regional hemodynamic compromise
Systemic hypotension
Occlusive vascular disease
Thromboembolism
Undo vascular procedures
Fibrocartilaginous (intervertebral disk) embolism
Vasculitis
Arterial dissection
Thrombosis
Venous occlusion

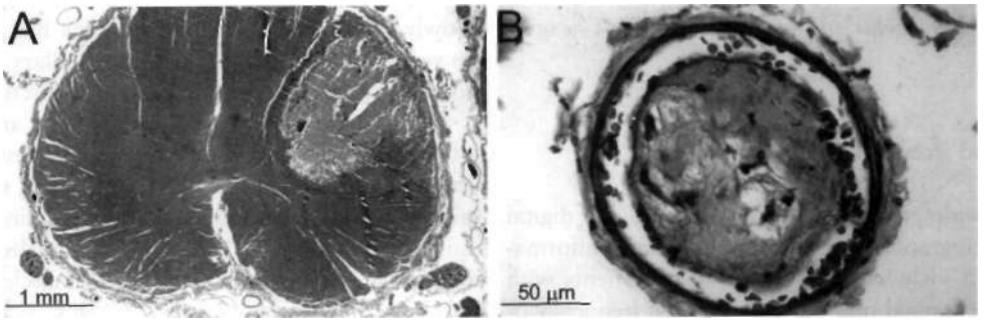

FIGURE 57F.4 Pathological sections from a 19-year-old man who died after tervical fibrocartilaginous embolism. (A) Segmental infarction in the posterolateral cord. (B) Intraluminal fibrocartilaginous material in the infarcted region. (From Fre yal den hove n, T. E., Mrak, R. E. 2001, "Fibrocartilaginous embolization," *Neurology,* vol. 56, p, 1354. With permission.)

plexus and arterial channels leading to cord infarction (Freyaldenhoven and Mrak 2001) (Figure 57F.4) Approximately one half of these events ate purely arterial; the rest have mixed arterial and venous involvement.

Vasculitic and thrombotic causes of spinal cord ischemia are well known. Before the antibiotic eta, meningovasculat syphilis was a common cause of anterior spinal artery ischemic syndromes and spinal meningitis continues to be occasionally associated with pataplcgia of vasculat origin. Systemic inflammatory conditions such as Crohn's disease, polyarteritis nodosa, and giant cell arteritis may also lead to myelopathy. Sickle cell disease, intrathecal chemical irritants, angiographic contrast material, the postpartum state, and intravascular neoplastic invasion all predispose to thrombosis and spinal cord infarction.

Venous infarction without hemotrhage is clinically indistinguishable from the arterial ischemic syndromes. There may be an associated systemic thrombophlebitis that propagates into the spinal canal via the venous plexus. A subacute necrotizing myelitis (Foix-Alajouanine's syndrome), causing stepwise spinal cord dysfunction, may occur with extensive spinal cotd thrombophlebitis and no systemic foci of venous inflammation, or in association with chronic obsttuctive pulmonary disease, or a neoplasm (usually of the lung). This condition may also be the end-stage tesult of chronic venous hypertension and congestion secondary to dural venous fistula. Polycythemia rubra vera may be associated with noninflammatory spinal venous thrombosis that results in cord ischemia,

Treatment

'['he medical management of spinal cord ischemia is generally supportive and focused on reducing risk for recurrence. This includes maintenance of adequate blood ptessute, early bed rest, and reversal of proximate causes such as hypovolemia or arrhythmias. Acute thrombolytic and antithrombotic therapy (e.g., heparin) have not been systematically studied. Such interventions will continue to be difficult to study because of the low incidence of spinal cord infarction and the variability of its natural course. Over the longer term, care is directed toward minimizing the complications of autonomic dysfunction and immobility. Physical and occupational therapy are useful in promoting functional recovery. Overall mortality is approximately 20%, and more than minimal improvement can be expected in only 35^0% of spinal infarction (Cheshire et al. 1996). Nonetheless, with appropriate rehabilitation, most patients are able to return to home.

SPINAL VASCULAR MALFORMATIONS

Spinal vascular malformations consist of normal-sized to enlatgcd arteries and enlarged, tortuous veins without an intervening capillary network. A commonly accepted classification system (Anson and Spetzlet 1993) categorizes spinal vascular malformations into four types:

1. Type I—dural arteriovenous fistula (AVF); subtypes IA (single feeding artery) and IB (multiple feeding arteries).
2. Type II—intramedullary glomus-type arteriovenous malformation (AVM).
3. Type III—intramedullary juvenile-type AVM, which is more extensive than a glomus-type AVM, frequently having an extramedullary component and sometimes an extradural component.
4. Type IV—intradural, extramedullary (pcrimedullary) AVF: subtypes IVA, IVB, and IVC correspond to lesions with progtessively increased arteriovenous shunting manifested as increased number, size, and tortuosity of feeding arteries.

Spinal vascular malfotmations not included in this tadiological-pathological classification system include cavernous angiomas (or cavernous malformations), venous angiomas (or preferably "developmental venous anomalies"), and epidural/paraspinal AVMs. Other classifications are based on whether the malformations are

amenable to cndovascular surgical intervention (Caraginc etal. 2002).

Distribution and Prevalence

Prior to the widespread use of selective spinal digital subtraction angiography, patients with vascular malformations were often included as a subgroup of patients with manifestations of spinal tumors. The reported frequency of vascular malformations as a subset of spinal tumors ranged from 3-11 %. The frequency could be higher because patients with small, asymptomatic or misdiagnosed lesions may be overlooked. Spinal dural AVF, which is the most common type of spinal vascular malformation in the previously noted classification, is typically found in older adult men, accounting for a reported prevalence of up to 9 to 1 for vascular malformations in men compared with women. For the same reason, the diagnosis of vascular malformation is nude most freqiiuurly between ages 3(1 and 70. When symptoms develop during childhood, the vascular malformation is more likely to be an AVM (Type II or III vascular malformation). The predominant locations for vascular malformations arc the lower thoracic and lumbar spine regions, again because these are the favored locations for dural AVFs. These usually drain to the dorsal surface of the cord.

Clinical Presentation and Course

Spinal vasculat malformations, especially dural AVFs, are frequently misdiagnosed. The onset of manifestations can be acute or insidious and the course may include remissions and relapses. The most common complaints at onset are pain, weakness, and sensory symptoms. The predilection of spinal vascular malformations for the lower thoracic and lumbar regions results in complaints referable to those levels. Later, the initial signs and symptoms persist and are joined by bowel and bladder complaints. The onset of symptoms is frequently associated with trauma, exercise, pregnancy, or menstruation. Misdiagnosis, especially as demyelinating disease, was common before MRI of the spine. Nonetheless, the interval between symptom onset and accurate diagnosis may be years. Severe locomotor disability develops in approximately 20% by *6* months after onset of symptoms and in 50% by 3 years. Once leg weakness or gait difficulties start, they tend to progress rapidly.

The signs and symptoms of spinal vascular malformations are attributable to mass effect and ischemia. Although it is unusual for an unruptured spinal AVM to cause sufficient mass effect to cause spinal cord dysfunction, epidural, subdural, and intramedullary hemorrhage can occur and produce spinal cord compression. Dural AVF rarely produces hemorrhage and typically presents as a slowly progressive myelopathy, which has been attributed to venous hypertension and intramedullary venous congestion that eventually can progress to infarction.

Pain may be local, radicular, diffuse, or any combination of these. There may be upper motor neuron weakness, lower motor neuron weakness, or both. A spinal bruit is a highly specific, though uncommon, finding that is diagnostic of a spinal AVM. Vascular malformations may coexist in the skin or paraspinal muscles. In cutaneomeningospinal angiomatosis (Cobb's syndrome}, dural angioma may coexist with a cutaneous angioma in the corresponding dermatome. Foix-Alajouanine's syndrome (see Causes of Spinal Cord Ischemia, earlier in this chapter) has been associated with end-stage dural AVF with thrombosis and venous infarction. Spinal hemorrhage usually has an abrupt onset and may be associated with the typical symptoms of spinal subarachnoid hemorrhage {SAH), including headache, meningeal infection, and cord and nerve root damage. Even in the absence of SAH, the CSF may be abnormal, with mild pleocytosis and elevated protein.

Vascular malformations (AVMs and dural AVFs) may cause increased local venous pressure, decreased perfusion pressure, decreased tissue perfusion, and finally tissue ischemia. This explains the coexistence of deficits in more than a single arterial territory and the symptomatic improvement that results from ligation of feeding vessels. The sometimes confusing and widely varied presentation of spinal vascular malformations results in a large differential diagnosis, which includes neoplasms, herniated discs, multiple sclerosis, intracranial SAH, subacute combined degeneration, meningovascular syphilis, and transverse myelitis (sec Chapter 27).

Investigations

MRI, with contrast-enhanced three-dimensional magnetic resonance angiography (MRA) (see Chapter 37B), is the diagnostic procedure of choice in the initial evaluation of suspected spinal vascular malformations. MRI can discriminate extramedullar from intramedullary lesions, document thtombosis of the malformation following ligation or embolization of the feeding vessels, and demonstrate changes in the spinal cord (edema, hemorrhage) distinct from, yet caused by, the vasculat malformation.

Routine MRI is sensitive in detecting intramedullary AVMs (Types II and III vascular malfomations). The findings include intramedullary low signal with surrounding normal cord tissue, focal cord enlargement at the location of the nidus, and serpentine signal voids within the subarachnoid space in the region of the nidus (Figure 57F.5). MRA augments the MRI study by confirming the locaton of the nidus and allowing better visualization of the AVM drainage to the coronal venous plexus (perimedullary veins) on the surface of the spinal cord. Preliminary studies

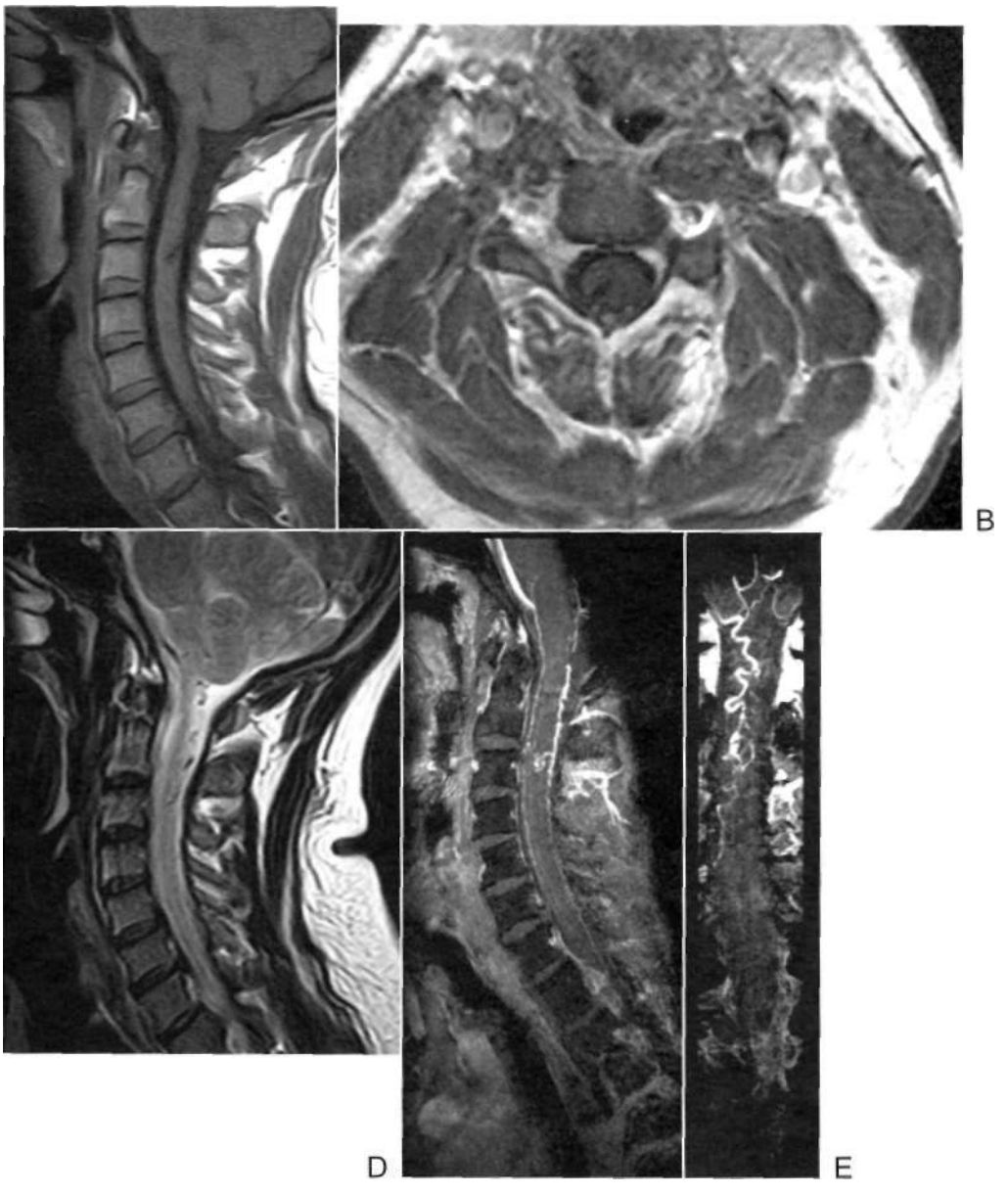

FIGURE 57F.5 Magnetic resonance imaging and contrast-enhanced three-dimensional magnetic resonance angiography (MRA) of a cervical intramedullary, glomus-type arteriovenous malformation. (A) Precontrast Tl-weighted sagittal image shows a focal hypointense intramedullary lesion at C3. The cord is not enlarged. (B) Posteontrast Tl-weighted axial image confirms the intramedullary location of the lesion. (C) T2-weighted, fast-spin-echo sagittal image shows serpentine flow voids posterior to the cervical cord from CI to C3. (D, E) Sagittal (D) and coronal (E) targeted MRA demonstrate the intramedullary nidus communicating with an enlarged posterior median vein. (From Rowen, B. C. & Saraf-Lavi, E. 2003, "Imaging of spinal vascular lesions," in *Advanced Imaging and Image-Guided Therapy of the Nervous System,"* eds R. E. Latchaw, J. Kucharczyk, M. E. Moseley, Mosby, Philadelphia. With permission.)

using newer dynamic contrast-enhanced MRA techniques have shown improved detection of the feeding arteries of AVMs compared with older techniques.

In cases of dural AVF (Figure 57F.6), **MRI** abnormalities involving the spinal cord have heen observed with variable frequency: slight enlargement of the cord; cord hypoiintensity on Tl-weighted images and h y peri men sity on T2-wcighted images involving the central region of the cord and extending over several levels; scalloping of the cord contours on sagittal images; and enhancement of the cord on posteontrast Tl-weighted images. Of these findings, the most consistently observed is hypcrintensity within the center of the cord on T2-wcighted images. In general, however, these findings are nonspecific and, like the clinical findings, can mimic those of cord neoplasm, infection, or ischemia from arterial occlusive disease. Thus detection of blood flow related signal abnormalities in the subarachnoid space is crucial to achieving high diagnostic accuracy for dural AVF, As shown by Saraf-l.avi and colleagues (2002), the detection of intradural flow voids on T2-weighted

images and the detection of intradural serpentine enhancement on T1-weighted images, extending for more than three contiguous vertebral levels, are each associated with the presence of dural AVF. Contrast-enhanced three-dimensional spinal MRA provides more direct and extensive visualization of the abnormal intradural vessels (veins), and when added to standard MRI can improve detection of dural fistula. The principal benefit of MRA is in the improved localization of the vertebral level of the fistula, which potentially expedites the subsequent invasive catheter angiograph) study.

In the pretreatment evaluation of vascular malformations, plain radiography is rarely helpful. Supine myelography, which, with careful technique, is able to detect the serpentine filling defects caused by abnotmal intradural vessels (although these may be confused with nerve roots in the lumbar region), has been supplanted by MRI with MRA. I hr definitive radiological procedure in the pretreatment evaluation of vascular malformations is selective spinal (catheter) angiography using digital subtraction techniques. Many institutions perform this procedure while the patient is intubated and under general anesthesia. Selective spinal angiography is tedious and typically requires that each segmental artery in the region being examined be injected. The effect of noninvasive spinal MRA on the of the indications for and performance of catheter angiography has yet to be reported in the neuroimaging literature. Catheter angiography remains the gold standard for characterizing vascular malformations in terms of location, size, configuration, blood flow, feeding arteries, and draining veins (see Figure 57F.6).

Treatment

The treatment of spinal vascular malformations is by surgical resection and/or angiographically directed embolization

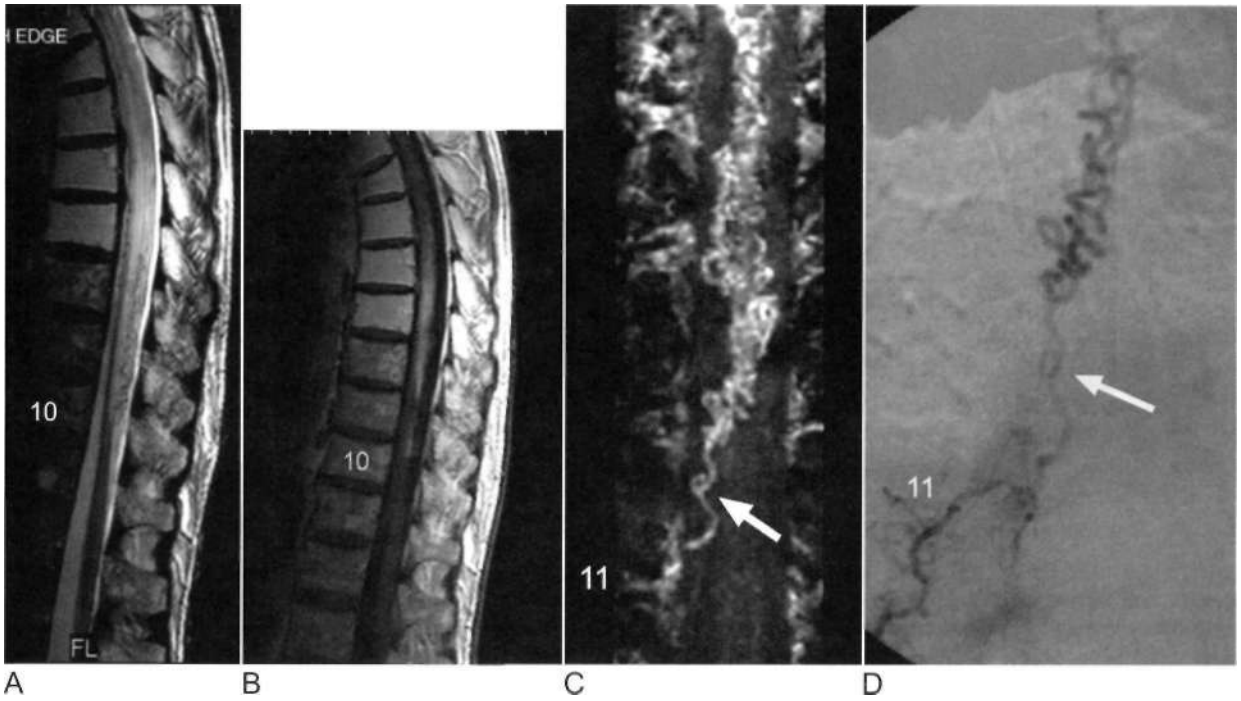

FIGURE 57F.6 Magnetic resonance imaging (MRI) and contrast-enhanced three-dimensional magnetic resonance angiography (MRA) of a right Til dural arteriovenous fistula. At the time of the MRI study, this 68-year-old man had a 3-year history of progressive myelopathy. His symptoms began approximately 6 months after radiotherapy and surgical excision of a carcinoma of the right lung apex. His progressive neurological deficits were initially attributed to radiation myelitis of the upper thoracic cord. After surgical obliteration of the fistula, his symptoms improved. (A) Fast-spin-echo T2-weighted image shows hyperintense cord from T6 to T10 and serpentine flow voids, consistent with enlarged intradural vessels, posterior to the cord from TS to T10. (B) Postconttast Tl -weighted image shows hyperintense vertebral bodies from T4 to T7, as seen in A, and consistent with radiation changes. There is patchy enhancement within the cord from T6 to T10. (Q MRA (tatgeted to posterior half of the spinal canal) demonstrates an enlarged, tortuous vessel *{arrow}* extending ftom the right Til foramen to the posterior cord surface, where numerous, convoluted vessels are seen. The right Tl 1 vessel corresponds to the posterior medullary vein draining the fistula. (D) Digital subtraction (catheter) angiogram (anteroposterior view) following injection of the right Til posterior intercostal artery demonstrates a fistula in the region of the right neural foramen with drainage into the canal via the medullary vein *(arrow).* (From Kowen, B. C. & Pattany, P. M. 1999, "Vascular anatomy and disorders of the lumbar spine and spinal cord," in *The Lumbar Spine,* ed J. Ross, Magnetic Resonance Imaging Clinics of North America, W.B, Saunders Co., Philadelphia. With permission.)

of the malformation. Once lodged within the abnormal vessels, these iatrogenic emboli promote thrombosis and decrease blood flow. A sequential approach of embolization, followed by definitive surgical therapy, is common (Caragine et al. 2002).

SPINAL HEMORRHAGE

Subarachnoid, intramedullary, subdural, and epidural hemorrhage may affect the spinal cord and its meninges. The onset is usually sudden and painful and most commonly is related to trauma or vascular malformations.

Subarachnoid Hemorrhage

Spinal SAH accounts for less than 1% of all SAHs. The most common cause is a spinal angioma, but these account for only approximately 10% of the total. Other associated conditions include coarctation of the aorta, rupture of a spinal artery, mycotic and other aneurysms of the spinal artery, polyarteritis nodosa, spinal tumors, lumbar puncture, blood dyscrasias, and therapeutic thrombolytics and anticoagulants.

Clinical presentation of spinal SAH is characterized hy the sudden onset of severe back pain, which is often localized near the level of the hemorrhage. Within minutes. the pain becomes diffuse and signs of meningeal irritation become prominent. Multiple radiculopathies and myelopathy may be present. Headache, cranial neuropathies, and a decreased level of consciousness are associated with diffusion of blood above the foramen magnum. The CSF is grossly bloody, intracranial pressure is frequently elevated, and papilledema may be present.

Correct diagnosis requires a strong clinical suspicion. The evaluation of spinal SAH frequently follows negative radiological studies of the intracranial structures. 11istory- may reveal the initial severe back pain or prior anticoagulant use. Physical examination may reveal a spinal bruit, cutaneous angioma, sensory level, the stigmata of collagen vascular disease, or evidence suggesting septicemia. Radiological studies arc discussed under spinal vascular malformations. Treatment is directed toward the underlying CailSC.

Hematomyelia

Intramedullary spinal hemorrhage most often results from trauma. Hematomyelia may follow direct trauma to the spinal column or hyperextension injuries of the cervical spine. Spontaneous hematomyelia is caused usually by bleeding of a spinal vascular malformation, hemorrhage into a spinal tumor or syrinx, a bleeding diathesis, anticoagulant drugs, or venous infarction. The hemorrhage tends to disrupt spinal gray matter rather than white matter. There are no recognized intraspinal counterparts to intracerebral hypertensive hemorrhage and amyloid angiopathy, Hematomyelia most commonly presents as spinal shock associated with the sudden onset of severe back pain, which is often radicular. Spasticity develops below the level of the lesion and fasciculations, atrophy, and areflexia may occur in the myotomes corresponding to the lesion.

MRI is the best imaging modality to detect intramedullary hemorrhage. Lumbar puncture may be consistent with SAH. The initial treatment is supportive. Laminectomy and drainage of the hematoma, followed by resection of the tumor or vascular malformation, can be performed if neurological deficits are incomplete or progressive.

Spinal Epidural and Subdural Hemorrhage

Spinal epidural hemorrhage (SEH) occurs more frequently than spinal subdural hemorrhage (SSH). SF.H is more commonly observed in men and has a bimodal distribution, with peaks during childhood and the fifth and sixth decades of life. Cervical lesions are more common in childhood, whereas thoracic and lumbar lesions predominate in adults. Hemorrhages can he spontaneous but often occur following trivial exertion or minor trauma. SFH is ;i complication of both lumbar puncture and epidural anesthesia and is more likely in patients who arc anticoagulatcd. Other causes include blood dyscrasia, thrombocytopenia, neoplasms, and vascular malformations.

SSH is most common in women. It may occur at any age but tends to predominate in the sixth decade. Most occur in the thoracic and lumbar regions. Hemorrhagic diatheses, including treatment with anticoagulants, blood dyscrasias, and thrombocytopenia, ate the precipitating factors most commonly associated with SSH. Other factors include trauma, lumbar puncture, vascular malformation, and spinal surgery.

The clinical presentations of SEH and SSH are indistinguishable. Tin- initial symptom is severe back pain at the level of the bleed. Myelopathy or cauda equina syndrome with motor and sensory findings corresponding to the level of the lesion develops over hours to days. The diagnosis should be suspected in patients with disorders of coagulation who have undergone recent lumbar puncture and develop back pain or signs of spinal cord or root dysfunction. Patients with a rapidly decreasing platelet count or less than 20,000 platelets/uL are at particular risk of developing SEH or SSH with a spinal tap and should receive a platelet transfusion prior to lumbar puncture. Clotting studies and a platelet count are important in the initial evaluation. In SEH and SSH, the CSF may be normal, xanthochromic, or contain increased protein,

MRI, the imaging modality of choice, delineates the hematoma and its location referable to the dura. In addition, gadolinium-enhanced MRI and MRA may show

an underlying vascular malformation. In patients unable to tolerate MRI or where it is unavailable in the acute phase of the illness, myelography with computed tomographic scanning provides an alternative. Myelography reveals a filling defect or complete blockage to the flow of contrast material at the level of the lesion. The myelographic appearanees of SEH and SSH may be indistinguishable.

Treatment is directed toward the underlying defect. Laminectomy with evacuation of the clot should be performed as soon as possible. The prognosis for recovery is better when surgery is performed early and the pre-operative deficits are not severe.

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Chapter 57
Vascular Diseases of the Nervous System

G. CENTRAL NERVOUS SYSTEM VASCULITIS

James W. Schmidley

Isolated vasculitis of the central nervous system (CNS) is rare. Only one or two cases are encountered each year in large medical centers, but it is frequently among differential diagnoses, which puts the neurologist on the hotns of a dilemma. There are no characteristic clinical features; the results of routine laboratory investigations, both medical and neurological, are either normal or nonspecific. The single test, short of a biopsy, that is sometimes helpful in establishing the diagnosis is catheter angiography. This invasive test has the drawbacks of low sensitivity and specificity: The result may be negative in pathologically documented cases of CNS vasculitis. The consequence of missing the diagnosis is the death of the patient; the consequence of delay in diagnosis is likely to be severe disability. The only therapies that appear to be effective are also highly toxic, and one should feel uneasy administering them without solid evidence supporting vasculitis.

TYPES OF CENTRAL NERVOUS SYSTEM VASCULITIS

When vasculitis is clinically and pathologically restricted to the CNS, it is referred to as a *primary* or *isolated* CNS vasculitis. Early descriptions of this disorder included the term *granulomatous,* but this histological feature, although frequent, is not required for diagnosis. This section covers isolated CNS vasculitis and the CNS vasculitides associated with cutaneous herpes zoster infections, drug abuse, lymphomas, and amyloid angiopathy.

The CNS also may be involved by widespread systemic vasculitis, usually polyarteritis nodosa or Wegener's granulomatosis. These disorders, which are discussed in Chapter 55A, rarely present with isolated CNS manifestations.

Isolated Central Nervous System Vasculitis

The mode of onset is acute or subacute. Although the classic picture is one of progressive, cumulative, and multifocal neurological dysfunction, there are abundant exceptions, including patients whose presentation suggests cerebral tumor, chronic meningitis, demyelinating disease, acute encephalitis, myelopathy, simple dementia, and degenerative disorders. When isolated CNS angiitis presents as a stroke, it is usually because of intracerebral hemorrhage, which occurs in approximately 15% of patients at some time in the illness. The disease rarely causes cerebral infarcts or transient ischemic attacks in the absence of clinical or laboratory evidence of a widespread CNS inflammatory disorder, such as a cerebrospinal fluid (CSF) plcocytosis.

Nonfocal symptoms such as headache and confusion are the most common presentation. Aside from confusion, the most common sign at presentation is hemiparesis. Ataxia of limbs or gait, focal cortical dysfunction including aphasia, and seizures are also frequent. Virtually every neurological sign or symptom has been reported at least once (Calabrese et al. 1997), Nonspecific visual complaints occur in approximately 15% of patients, but disorders of specific ocular motor nerves, optic nerve, or visual fields are much less common. Systemic symptoms are generally absent. Fully developed cases almost invariably show signs and symptoms of progressive, widespread neurological dysfunction; however, occasional patients present with a multiple sclerosis-like course of early relapses and remissions, or

clinical manifestations largely restricted to one part of the nervous system, such as the spinal cord or cerebellum.

Pathology of Isolated Central Nervous System Vasculitis

The vascular inflammation is usually of a chronic granulomatous nature, with monocytes and histiocytes, lymphocytes, and plasma cells infiltrating the walls of small (200 urn) arteries and veins, particularly in the leptomeninges. Larger vessels may be involved but never to an extent exceeding that of smaller ones. Although present in most autopsy cases, giant cells are not required to make a diagnosis. There is no predilection for bifurcations, as in polyarteritis nodosa, although fibrinoid necrosis can occur; eosinophils are not present in large numbers. Small, clinically silent, foci of vasculitis are occasionally present in one or more viscera but, by definition, produce neither laboratory nor symptomatic evidence of organ dysfunction.

Cause and pathogenesis are unknown. Many vasculitis syndromes are a result of deposition of immune complexes, but there is little support for this mechanism in isolated CNS vasculitis. The infiltrating cells have been $CD4^+$ T lymphocytes in the few cases in which leukocyte typing has been done. There is no convincing evidence of infection with *Mycoplasma,* or any other microorganism, in human CNS vasculitis, although *Mycoplasma* does cause CNS vasculitis in animals.

Laboratory Findings in Isolated Central Nervous System Vasculitis

General medical laboratory investigations are usually unremarkable. Some patients have an elevated sedimentation rate, but usually not to the degree seen in temporal arteritis. The laboratory is of use only in eliminating systemic vasculitis, neoplasm, infection, or other alternate diagnoses. Electroencephalography and computed tomographic scan are not specific, although they are usually abnormal; there is less experience with magnetic resonance imaging (MRI), but it is unlikely to be any more specific. Although some literature has stressed the contrary, the CSF has been abnormal (in some way) in almost all autopsy-documented cases. Unfortunately, the abnormalities are totally nonspecific, namely a mild lymphocytic plcocytosis and a mild to moderate elevation in protein. Oligocional bands and elevated immunoglobulin (lg)G index are occasionally encountered, as are low glucose values and leukocyte counts of several hundred per pi. The major value of CSF examination in investigating suspected CNS vasculitis is to rule out infections, including syphilis, or neoplastic infiltration of the meninges.

Although some publications emphasize the value of angiography in making the diagnosis, (1) cerebral angiography has been entirely normal in many pathologically documented cases, and (2} the arteriography changes of vasculitis, when seen, are not specific (Alhalabi and Moore 1994). Given its lower spatial resolution, magnetic resonance angiography is unlikely to be useful.

The typical findings of vasculitis in cerebral angiography are widespread segmental changes in the contour and caliber of vessels. Small aneurysms, usually on vessels much smaller than those bearing congenital saccular aneurysms, arc occasionally present, but cannot be distinguished from aneurysms complicating atrial myxoma or infective endocarditis. Occlusion of large cerebral vessels is rare.

It is my opinion that many published cases of angiographically diagnosed CNS vasculitis, including the so-called isolated, benign variant, represent misinterpretation or overintcrprctation of nonspecific angiographic changes, unconfirmed by a tissue diagnosis. Until the pathological processes underlying these cases are established, the use of more circumspect terms such as *reversible cerebral vasoconstriction* or *cerebral angiopathy* is appropriate.

APPROACH TO DIAGNOSIS

All patients in whom CNS vasculitis is suspected should be evaluated thoroughly to exclude a systemic vasculitis. A careful history and physical examination, with attention to the skin, eyes, testicles, paranasal sinuses, and lungs, are likely to be more revealing than a "shotgun" laboratory approach. The CSF should be examined in all cases to exclude infectious and neoplastic meningitis. An MRI scan should be performed to exclude other diagnoses such as multiple cerebral metastases, multicentric primary CNS tumors, hydrocephalus, or demyelinating diseases. Other conditions mimicking CNS vasculitis may include atrial myxoma, cholesterol embolization to the CNS, infectious endocarditis, Sneddon's syndrome, the antiphospholipid-antibody syndrome, encephalitis, neoplastic angioendotheliosis, malignant hypertension, and eclampsia.

Patients whose neurological illness is compatible with isolated CNS vasculitis, but which resists diagnosis by physical examination, routine laboratory testing, imaging, and CSF analysis, should be studied with catheter angiography. Although nonspecific and present in only a minority of proven cases, the classic angiographic picture can be supportive of a diagnosis of CNS vasculitis provided that the many other conditions capable of producing an identical appearance have been excluded. In my opinion, if therapy with cyclophosphamide or another potent immunosuppressive agent is contemplated, then the diagnosis must be confirmed by biopsy. If possible, the biopsy should be directed to lesions visible on MRI, and the specimen should include lep to meninges. If no lesion is available for biopsy, then the nondominant frontal or temporal pole should be sampled, again taking care to ensure that leptomeninges are included.

Among 30 brain biopsies examined at Duke University to rule out vasculitis, Chu et al. (1998) found nine with

isolated, noninfectious, CNS vasculitis. No diagnosis was possible on five specimens; the remainder had non-vasculitic conditions. Of the 30 patients, 22 had cerebral angiography, which proved to be an extremely poor predictor of pathological findings. Multifocal stenoses, with "sausaging" of luminal profiles—considered to be the typical picture of CNS vasculitis by many—was seen more often in the patients with other diagnoses, or negative biopsies, than in those with histologically proven CNS vasculitis.

Alrawi et al. (1999) reported a similar distribution of findings among 61 patients who underwent biopsy at the University of Michigan (28% revealed definite CNS vasculitis, and 8% revealed probable CNS vasculitis). More important, biopsy results that were negative for vasculitis provided another diagnosis, often with entirely different therapeutic implications, in an equal number of patients. The most frequent nonvasculitic diagnoses were neoplastic and infectious. Angiography in 14 patients showed the classic abnormalities of vasculitis in four patients with and in five without biopsy-proven vasculitis.

Both papers agreed on MRPs lack of specificity. Only the University of Michigan study (Alrawi et al. 1999) analyzed clinical features and concluded that the presence of CSF pleocytosis, headache, or both, predicted a biopsy with positive results. They experienced no complications of the biopsies, 75% of which were done stereotactically. The complication rate in the Duke University study (Chu et al. 1998) was 20%, with one persistent hemiparesis. More than 90% (28 of 30) of the biopsies in the Duke study were open-wedge resections. Whether these complication rates reflect differences in technique or more careful scrutiny is not clear. Only the Michigan series had sufficient numbers to allow comparison, and the yield of a diagnostic biopsy was similar with both approaches. The authors of both papers concluded that brain biopsy, although not infallible, was the most reliable method for establishing a diagnosis of isolated CNS vasculitis. Both studies also emphasized the lack of specificity of angiography and the importance of considering the entire clinical picture.

Therapy

High-dose prednisone plus cyclophosphamide is currently the treatment of choice (Calabrese et al. 1997). Some patients recover or stabilize on corticosteroid therapy alone, but most progress. The results of therapy are difficult to interpret because of (1) the rarity of the disorder, so that centers do not accumulate large numbers of patients; (2) the difficulty of unequivocally establishing the diagnosis, other than by biopsy; (3) the inclusion of patients with the so-called benign form of CNS vasculitis; and (4) the inclusion of patients with diagnoses based only on angiography. Intravenous Ig has been administered with success a few times, but in poorly documented cases.

CENTRAL NERVOUS SYSTEM VASCULITIS ASSOCIATED **WITH** SYSTEMIC DISORDERS

Cutaneous Herpes Zoster Infection

CNS vasculitis associated with herpes zoster usually presents as a severe hemispheric stroke in the weeks or months following an ipsilateral ophthalmic division infection in an older adult patient (Cilden et al. 2002). Angiography shows ipsilateral segmental stenoses of proximal middle and anterior cerebral arteries. Evidence of varicella zoster virus is found in the same segments of these vessels, although histologically, necrosis has been more prominent than inflammation. Presumably, the virus reaches the affected arterial segments via intracranial projections of the ophthalmic division of the trigeminal nerve. The effectiveness of acyclovir and corticosteroids for this syndrome is unknown, but their use seems reasonable. A second type of cerebral vasculitis associated with herpes zoster is less common and less well understood. It is a diffuse, small-vessel vasculitis, in the absence of parenchymal infection, which can follow noncephalic, as well as ophthalmic, eruptions of zoster.

Intravenous Drug Abuse

The usual scenario in CNS vasculitis associated with intravenous drug abuse is subarachnoid or intracerebral hemorrhage following the use of intravenous, or even oral, methamphetamine or another sympathomimetic, including "look -a like," diet pills. It is uncertain whether the "vasculitis" reported in the angiograms of these patients is a true inflammatory process or a vasculopathy induced by an unusual reaction to the drug, hypertension, or other factors. When the case reports are examined critically, it becomes obvious that (1) in only one has vasculitis been pathologically documented; (2) the "vasculitis" has sometimes occurred after first use of the drug, an event unlikely to be immunologically mediated; and (3) the course is usually monophasic rather than progressive and multifocal, as one would expect in a true vasculitis. Because drug abusers (to say nothing of dealers) are famously unreliable, it is sometimes difficult to be certain what illicit drugs actually were used and in what doses, and it is virtually impossible to trace inert substances used as fillers, which nonetheless might be responsible for the clinical events in some cases.

Experimental animals given sympathomimetic drugs chronically do nut. in mosl models, develop a CNS vasculitis. Many case reports claim cure using corticosteroids, but this may only represent the natural history of the

syndrome. Before entertaining this diagnosis in intravenous drug users, it is also important to exclude the other, definitely treatable causes of stroke in this population, subacute and acute bacterial endocarditis being the most important. Additional causes of cerebral embolization in drug abusers include talc and air emboli, the latter caused by inadvertent injection of air into the internal or common carotid artery while attempting to puncture the internal jugular vein in the neck. Intravenous drug abusers are at risk for hepatitis-associated polyarteritis nodosa, which can involve either the peripheral, or the central, nervous systems. A rather nonspecific cerebral vasculitis may occur in cocaine users, although vasculitis is not present in the brains of most patients with cocaine-associated strokes (Aggarwal et al. 1996).

Lymphoma

Patients with systemic lymphoma, nearly always Hodgkm's disease, rarely also have an isolated CNS vasculitis, in the absence of parenchymal or meningeal involvement by lymphoma (Yuen and Johnson 1996). This association, not noted for other malignant neoplasms, naturally leads to speculation that the Hodgkin's disease somehow triggers or provokes the vasculitis. In some patients, the CNS vasculitis has developed concurrent with, or following, disseminated herpes zoster infection, further confounding the picture. In the nonzoster cases, the CNS disorder improves with remission of the Hodgkin's disease brought about by chemotherapy or radiotherapy.

Amyloid

Cerebrovascular amyloid may coexist with a CNS vasculitis (Fountain and Ebcrhard 1996). In most instances, the vascular amyloid is the same type that accumulates in senile plaques as well as vessels in Alzheimer's disease. The relationship, if any, between these two usually distinct processes is not clear. Amyloid deposited in any location frequently evokes a limited degree of giant cell macrophage response and may elicit a sparse lymphocytic infiltrate as well. Thctcforc the vasculitis may just represent an excessive degree of inflammatory response to the vascular amyloid. The vasculitis also could cause amyloid deposition. Cytokines, such as interleukin-1, increase production of amyloid precursor protein by endothelium, at least in vitro. If cytokines or other by-products of inflammation cause amyloid deposition in vessel walls, they seem to do so only in the vasculature of the CNS. When they oceut independently, both amyloid and vasculitis preferentially affect cortical and leptomeningeal vessels; the fact that the two are found together in approximately the same distribution makes it difficult to draw conclusions as to which is cause and which is effect. In some cases, amyloid deposits are found in the walls of noninflamed vessels, suggesting they cannot be the result of the inflammation. However, even these cases have not been studied in serial histological sections.

Most pa lien Is have presented with a progressive cluneal picture consistent with vasculitis, including abnormal spinal fluid. Although cerebrovascular amyloid angiopathy without vasculitis almost always presents with inrrapa-rcnchymal hemorrhage (see Chapter 57B), this is true in only approximately 30% of patients with amyloid-associated CNS vasculitis. In the absence of a better understanding of this disorder, treatment should be the same as for isolated CNS vasculitis.

GRAFT-VERSUS-HOST DISEASE

A CNS vasculitis may occur in survivors of leukemia who have chronic graft-versus-host disease (GvHD) after allogeneic bone marrow transplantation (Padovan et al. 1999). CNS disease of any kind is regarded as rare in GvHD, but the same authors, in another study, found a correlation between GvHD and clinical and imaging abnormalities, suggesting CNS dysfunction (Padovan et al. 1998).

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Chapter 58
Cancer and the Nervous System

Tracy T. Batchelor

Neuro-oncology is an interdisciplinary medical specialty involving neurologists, neuropathologists, neurosurgeons, oncologists, and radiation oncologists in the care of patients with brain tumors. The number of newly diagnosed primary brain tumors continues to increase on a yearly basis in the United States, with an estimated 39,455 patients diagnosed in 2002. It was estimated that 359,000 persons with primary brain tumors were living in the United States in 2000 (Central Brain Tumor Registry of the United States [CBTRUS| 2002), In addition, the prevalence of neurological complications from systemic cancer continues to increase as the number of patients diagnosed with cancer increases and patients survive for longer periods. These observations strongly indicate that neuro-oncology patients will represent an increasing fraction of general neurology practices in the future. Thus neurologists need to become more informed about the basic clinical features and management of this group of disorders.

Neuro-oncology as an academic discipline is growing rapidly in the United States and abroad. Most university or academic medical centers have developed neuro-oncology programs, and most programs employ neurologists as the primary physicians. A growing number of these institutions now offer clinical and research training fellowships in neuro-oncology. Two periodicals *(journal of Neuro-Oncology* and *Neuro-Oncology)* are now devoted exclusively to neuro-oncology, and the biomedical literature on the biology, epidemiology, and treatment of brain tumors is rapidly increasing. Three federally funded clinical trials consortia have been formed for the study of adult and pediatric brain tumors (www.nabtc.org, www.nabtt.org, and www.phtc.org). An intramural neuro-oncology branch was formed at the National Institutes of Health in 2000 under the sponsorship of the National Cancer Institute and the National Institute of Neurological Disorders and Stroke. A successful and expanding academic organization, The Society for Neuro-Oncology (www.soc-neuro-onc.org), exists and serves as a forum for exchange of scientific and clinical information.

In this section, "Cancer and the Nervous System," leading experts have compiled a thorough review of neuro-oncology geared toward the neurologist. The first six chapters focus on primary nervous system tumors while the final two chapters cover metastatic tumors of the nervous system and paraneoplastic disorders of the nervous system. The rising incidence of primary brain tumors and the frustrating search for the cause of brain tumors are discussed in Chapter 58A. Very little is understood about the causation of primary brain tumors. Despite a large number of observational studies, important environmental risk factors for this tumor have not been identified. However, ongoing, prospective cohort studies may offer future insight into the causation of primary brain tumors. The biology, classification, and pathology of primary brain tumors are reviewed in Chapter 58B. The molecular mechanisms of tumor infiltration, progression, and resistance to therapy are becoming increasingly well understood for this diverse group of neoplasms. Based on a better understanding of the molecular pathology of these tumors, entirely new classes of anti-tumor therapies are being developed, including angiogenesis inhibitors, tyrosine kinase inhibitors, and anti-invasion drugs. These new classes of anti-tumor therapies offer hope that effective treatments for these tumors are on the horizon. The clinical features of brain tumors, as well as some of the common medical and neurological complications that occur in this patient population, are reviewed in Chapter *SHC* It is critical for physicians to understand the significant risk of venous thromboembolism in this patient population and the proper method in which to manage such a complication. It is also important for physicians treating seizures and epilepsy in these patients to understand the potential interaction of cytochromc-P450 inducing anti-epileptic drugs with chemotherapcutic agents. The characteristic neuroimaging features of the common nervous system tumors are reviewed in Chapter 5SD. The critical radiographic distinction between primary central nervous system lymphoma versus other types of brain tumors is discussed in this chapter. The multidisciplinary management of nervous system tumors in adults and children are reviewed in Chapters 58E and 58F. The potential roles of surgery, radiation, and chemotherapy are reviewed for each of the major tumor types in adults and children, '['lie chapters on primary brain tumors are followed by a review of metastatic disease of the nervous system in Chapter 58G and paraneoplastic neurological disorders in Chapter 58H. In the latter chapters the major metastatic complications, including brain metastases, epidural metastases, and spinal cord compression, as well as leptomeningeal metastases, are

discussed. Finally, the major paraneoplastic disorders that affect the nervous system are reviewed.

These chapters will hopefully provide a practical yet thorough review of the major clinical topics in neuro-oncology. Readers interested in further material **are** referred to some of the standard textbooks cited in the following Bibliography.

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Chapter 58
Cancer and the Nervous System

A. EPIDEMIOLOGY OF PRIMARY BRAIN TUMORS

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Primary brain tumors are a diverse group of neoplasms arising from different cells of the central nervous system (CNS). Light microscopy is used to classify these tumors according to predominant cell type, and to grade them for malignancy based on the presence or absence of standard pathological features. Gliomas are the most common brain tumors and may arise from astrocytes (astrocytomas), oligodendrocytes (oligodendrogliomas), or ependymal cells (ependymomas). Astrocytomas account for approximately 80% of all malignant brain tumors. The cause of brain tumors remains unknown despite a large number of epidemiological studies. This type of cancer is associated with a unique set of challenges for observational study designs (Table 58A.1). Despite a slow start, observational brain tumor studies may yet yield important clues into the pathogenesis of this cancer.

CLASSIFICATION

Histopathological Classification

The different cellular origins of brain tumors have contributed to the difficulty in achieving a single, widely accepted classification system. Historical attempts at developing a classification system for brain tumors date back to the 1830s. The German pathologist Rudolf Virchow introduced the term *glioma* in 1860 and was the first to attempt a correlation of microscopic to macroscopic features of CNS tumors.

Bailey and Gushing devised the first major classification system for brain tumors in 1926 and proposed that this type of cancer arose from primitive neuroectoderm. Their system consisted of fourteen distinct tumor types, each arising from a cell arrested at a different stage of neuronal development, and morphologically different from its normal counterpart. In 1912 Tooth argued that their histological features determined the biological characteristics of brain tumors. Yet, it was not until 1949 that Kcruohan and colleagues suggested that different histopathologic appearances do not represent separate tumor types but rather degrees of tumor differentiation. The Ringertz system of 1950 was based on the notion that different brain cells give rise to different histological types of brain tumors. In addition, Ringert/ proposed that astrocytoma consisted of three different grades: astrocytoma, astrocytoma with anaplastic foci, and glioblastoma multiforme (GBM). In 1981 Daumas-Duport and colleagues organized a tumor grading system (St. Anne-Mayo system) based on the absence or presence of four criteria: nuclear atypia, mitoses, endothelial cell proliferation, and necrosis. In 1979 the World Health Organization (WHO) published a classification system that encompassed all CNS tumors. The WHO classification system was subsequently revised in 1993 and 2000, and includes 10 major categories and 126 subcategories of brain tumors (Klcihues et al. 2000). In this system, the most common type of glioma, astrocytoma, is assigned different grades of malignancy (I-IV) based on the presence or absence of the criteria previously described. Malignant astrocytomas (anaplastic astrocytoma |III/IV| and GBM |IV/IV]) are the

Table 58A.1: Challenges in brain tumor epidemiology studies

1. Uncommon form of cancer
2. Diversity of histological brain tumor types
3. Lack of uniformly accepted classification system
4. Changing methods of ascertainment (clinical, radiographic, histological)
5. Variable reliability of exposure assessment (cognitive impairment of subjects, remote exposures)

most common subtypes and account for 80% of all malignant brain tumors. Table 58A.2 shows a comparison of the major classification systems currently in use.

Molecular Classification

Interest in a genetic classification of gliomas is based on studies demonstrating a predictable set of genetic changes in the progression from low-grade to high-grade gliomas and the observation that certain genetic changes predict prognosis better than histopathological characteristics for specific brain tumor types. Formation of brain tumors involves an accumulation of lesions in genes important for the regulation of cell proliferation, differentiation, and death (Table 58A.3).

As with other types of cancer, both oncogenes and tumor suppressor genes play critical roles in glioma pathogenesis. Oncogenes are dominantly acting genes coding for protein products that accelerate cell growth and proliferation. Typically, genetic alterations of oncogenes involve amplification and activating mutations, Conversely, protein products coded by tumor suppressor genes repress cell growth. Alteration of these genes by physical elimination (deletions) or inactivating mutations leads to cell proliferation.

Low-gtade astrocytomas (WHO grades I/IV and II/IV) are characterized by a high frequency of imitations in the p53 tumor suppressor gene (^50%) and amplification of the oncogene, platelet-derived growth factor (=^60%) (Kleihucs et al. 2000). Progression to anaplastic astrocytoma (AA) is associated with loss of heterozygosity (I.OH) on chromosome 19q and alterations in the retinoblastoma tumor suppressor gene. Progression to GBM (^80%) correlates with I.OH on chromosome lOq and amplification of epidermal growth factor receptor (EGFR). Two studies examining these genetic alterations have suggested possible prognostic significance in GBM. Leenstra et al. (1998) reported shorter survival among GBM patients with I.OH on chromosome 10 (60-85% of GBMs) and EGFR amplification (40%) (Batchelor and Louis 2001). Similarly, Lin et al. (1998) reported LOH at the PTEN/MMAC1 (25% of cases) locus was more common in high-grade astrocytomas and was predictive of shorter survival. Another study has demonstrated the age-dependent prognostic effects of specific genetic alterations. For example, EGFR amplification is a negative prognostic marker in young patients, but associated with a better prognosis in the elderly (Simmons et al. 2001). Future classification will undoubtedly incorporate many of these genetic markers of prognosis.

DESCRIPTIVE EPIDEMIOLOGY

Incidence

The traditional source of descriptive data on brain tumors has been the Surveillance, Epidemiology and End Results (SEER) program sponsored by the National Cancer Institute. This program collects population-based cancer data on approximately 26% of the U.S. population (including 15 state cancer registries) to gauge national trends in cancer incidence and survival (Ries et al. 1998). However, this data encompasses only *malignant* tumors. In contrast, the Central Brain Tumor Registry of the United States (CBTRUS) includes both benign *and* malignant brain tumors. The CBTRUS, established in 1992, is the nation's largest population-based registry of primary brain tumors, compiling information from 16 state cancer registries (Central Brain Tumor Registry of the United States [CBTRUS] 2002).

Incidence estimates differ according to the inclusion or exclusion of benign brain tumors. SEER data estimated approximately 17,000 new primary brain tumor cases in the United States for 2002 (Ries et al. 2002). CBTRUS

Tabic 58A.2: Pathological grading systems for astrocytomas

WHO	*Modified Ringertz*	*UCSF*	*St. Anne-Mayo*
		Mildly anaplastic astrocytoma	AMIncyiom.i grade I
Astrocytoma (grade II)	Astrocytoma (grade 1)	Moderately anaplastic astrocytoma	Astrocytoma grade 2
Anaplastic astrocytoma (grade III)	Anaplastic astrocytoma (grade 2)	Highly anaplastic astrocytoma	Astrocytoma grade 3
		Gemistocytic astrocytoma	
Glioblastoma multiforme (grade IV)	Glioblastoma multiforme (grade 3)	Glioblastoma multiforme	Astrocytoma grade 4

WHO = World I lealth Organization; UCSF = University of California, San Francisco.
Source: Adapted from Wen, P. Y., Fine, H. A., Black P. M., Shrieve, D. C, et al. 1995, "High-grade astrocytomas," *Neurol Clin,* vol. 13, pp. 875-900.

Table 58A.3: Gene and chromosomal alterations in gliomas

Ccne	*Gene function*	*Chromosome*	*Comment*
p53	Tumor suppressor	17pl3.1	33% of all grades of astrocytomas, 65% of low-grade astrocytomas
MDM2	Tumor suppressor	12ql4.3-ql5	10% of glioshlastoma
p!5 and p16	Tumor suppressor	9p21	IVlitrd 111 ()""•,. ni j-liom.i cell lines
CDK4 and CDK6	Promoter of cell proliferation	I2ql3-14 and 7q21-22	Amplified in 15% of cases without pi 5 or p!6 mutations
Retinoblastoma	Tumor suppressor	13ql4	33% of high-grade astrocytoma
		19	Frequent in high-grade astrocytomas
		22q	20-30% of all grades of astrocytomas
EGFR	Oncogene	7	33-50% of high-grade astrocytomas, always associated with 10 loss
PDGF	Oncogene		Expressed in all grades of astrocytomas
	Tumor suppressor	l0q	80% of all glioblastomas
		lp	Nearly all oligodendrogliomas, usually associated with 19q loss

EGFR = epidermal growth factor receptor; GBM = glioblastoma multiforme; PDGF = platelet-derived growth factor.

data estimated approximately 35,550 new cases of both malignant and benign brain tumors for the same year. The annual incidence of malignant brain cancer for all races from 1995-1999 was 6.8 per 100,000 person-years, compared with 4.2 per 100,000 person-years for primary benign brain tumors.

Mortality and Prognostic Factors

Although brain tumors account for only 2% of all cancers and are one fifth as common as breast or lung cancer, they result in a disproportionate share of cancer morbidity and mortality. The 5-year survival rates for brain tumors are the sixth lowest among all types of cancer (following pancreas, liver, esophagus, lung, and stomach, respectively) (Legler et al. 1999). The 5-year survival rates for the most common histological subtypes, A A and GBM, are 30.0% and *33%,* respectively. The U.S. mortality rate for malignant brain cancer was 4.7 per 100,000 persons for 1999 and represented a *46%* increase in mortality since 1950 (CBTRUS 2002). Approximately 13,100 deaths will be attributed to malignant brain and nervous system tumors in 2002; this number has been increasing for the last 30 years. Age-specific mortality rates from brain tumors among all races demonstrate gradual increases with each decade until the age of 55, after which the rate increases dramatically. When stratified by race or gender, these trends arc present, although whites exhibited greater mortality (5,1 per 100,000 persons) than blacks (2.8 per 100,000 persons) from 1995-1999 (Figure 58A.1). Finally, for all primary brain tumors, the 5-year survival rates have risen from 22% to 32% over the past 30 years.

Young age, high Karnofsky performance status, and lower pathological grade are favorable prognostic factors for primary brain tumors. Less significant predictors of favorable prognosis include long duration of symptoms, absence of mental changes at the time of diagnosis, cerebellar location of tumor, small preoperative tumor size, and completeness of surgical resection.

Gender and Race

There is a slight male predominance in the incidence of malignant brain tumors (8.02 per 100,000 person-years for men versus 5.62 per 100,000 person-years for women). However, when all brain and CNS tumor types are examined, the disparity between the sexes is less apparent (14.22 per 100,000 person-years for men versus 13.86 per 100,000 person-years for women) (Ries et al. 2002). This is partially explained by the predominance of meningiomas, a benign brain tumor, in women (5.19 per 100,000 person-years) as compared with men (2.66 per 100,000 person-years). Figure 58A.2 compares the incidence rates of malignant brain tumors among white and black individuals. Whites have a higher incidence of malignant brain tumors as compared with blacks for both genders: white males have an incidence rate of 9.1 per 100,000 person-years compared with black males at 5.1 per 100,000 person-years, whereas white females have an annual incidence of 6.1 per 100,000 person-years versus an annual incidence rim- nf 2.8 per 1 00.000 person years among black females (CBTRUS 2002). Comparisons between other racial groups within the United States are difficult because of the small numbers of cases, but malignant brain tumor incidence rates among Asian Americans, Latinos, and Native Americans arc lower than those of cither whites or blacks.

Temporal Trends

Several studies have documented rising incidence rates for brain tumors in several industrialized countries. These increases seem confined mainly to the older adult population with no clear ethnic, gender, or geographical differences. Overall, the incidence increased 18% from 1973-1994 and 80% from 1950-1994 (white population only). However, other population-based data suggest that incidence rates have recently stabilized among all age groups (Legler et al. 1999). From 1992-1999, the incidence of all

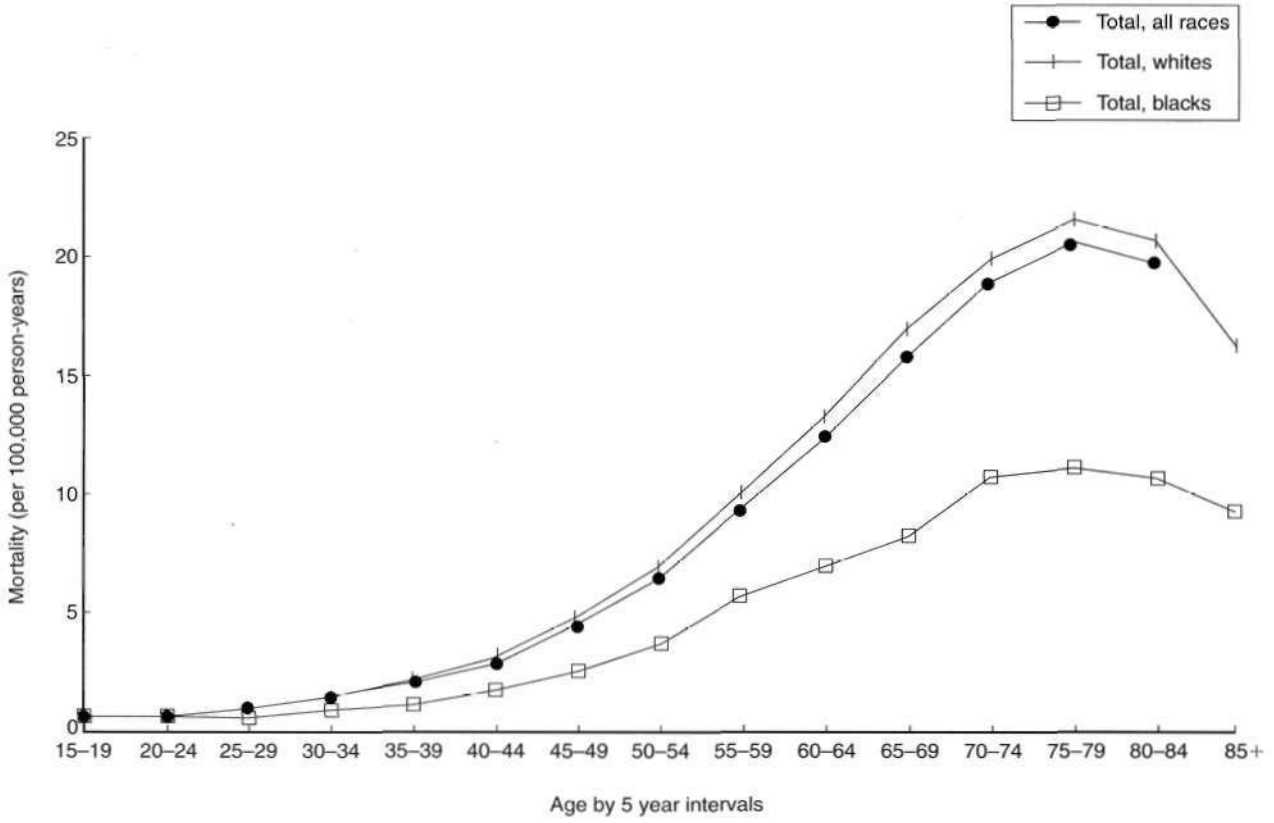

FIGURE 58A.1 1995–1999 invasive brain tumor mortality rates for U.S. whites and blacks, stratified by age. (From Ries, L. A. G., Eisner, M. P., Kosary, C. L., et al., eds. 2002, *SEER Cancer Statistics Review, 1973–1999*, National Cancer Institute, Bethesda, MD.)

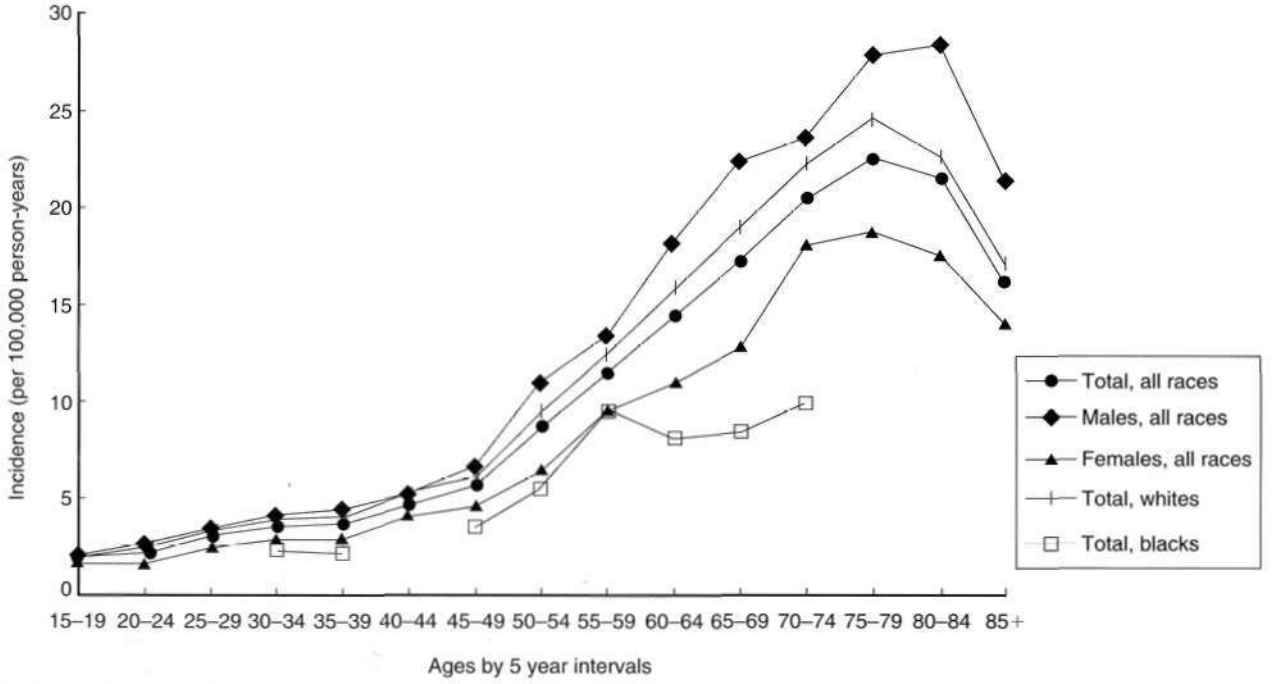

FIGURE 58A.2 1995–1999 invasive brain tumor incidence rates for U.S. whites and blacks, stratified by age. (From Ries, L. A. G., Eisner, M. P., Kosary, C. L., et al., eds. 2002, *SEER Cancer Statistics Review, 1973–1999*, National Cancer Institute, Bethesda, MD.)

malignant brain tumors decreased by 0.4%. This reduction in incidence was observed in both males (—0.7%) and females (—0.1 %) and was associated with a reduction in mortality resulting from brain tumors across all races (-0.5%). These data support the concept that the increasing incidence observed prior to 1992 may have been the result of better ascertainment.

The increases in incidence observed in the United States for all age strata and racial groups are in accordance with observations in other parts of the world. Although the responsible factors remain unclear, there is agreement that at least part of the increase is the result of more complere case ascertainment because of improved diagnostic technology, better access to health care, and clinical specializarion. Some investigators have argued that the increase in brain tumor incidence correlates with the introduction of noninvasive diagnostic technology including computerized tomography (CT) in the 1970s and magnetic resonance imaging (MRI) in the 1980s. Medicare data from 1986-1994 suggest that although the use of CT and MRI has stabilized among the 85-years-and-older age group, the use of CT continues to increase among the younger-than-85 age group. This may reflect a more aggressive diagnostic approach to the very elderly and may account for the stabilization of brain tumor incidence rates in people 85 years of age and younger, and a continued increase among those older than 85. Other contributing factors include access to better health care for older adulrs and increased availability' of neurological physicians. The number of neurologists in the United States increased 3.6-fold from 1970 to 1987 (Preston-Martin and Mack 1996). However, others have concluded that improved diagnostic capability does not fully account for the magnitude of the observed increase and that changing environmental exposures may play a role.

Geographical Trends and Migrant Studies

Increasing brain tumor incidence rates have been observed in many orher counrrics during the last 30 years. The highest rates are noted in industrialized nations such as the United States, Canada, Australia, and the United Kingdom, whereas developing nations have lower incidence rares. Generally, it appears that brain tumor incidence is associated with the level of economic development, and concomitant differences in the availability of diagnostic-methodology (CT, MRI, neurosurgical technology) may account for some of the observed disparities. Even within the United States, a significant variation in the incidence of brain tumors exists between the states. Hawaii has the lowest rate for males (5.1 per 100,000 person-years) and for females (4.1 per 100,000 person-years) (CBTRUS 2001). Maine has the highest rate (9.9 per 100,000 person-years) for males and Montana (7.3 per 100,000 person-years) has the highest rate for females. In contrast to international trends, a clear relationship between these rates and economic conditions does nor exist.

Migrant srudies have typically exhibited elevated incidence rates in the host country compared with the country of origin, with increases in brain tumor incidence and mortality developing among migrants. This suggests environmental factors may influence the development of brain tumors. However, disparities in case ascerrainment in the countries under study complicate the interpretation of this data.

Primary Central Nervous System Lymphoma

The descriptive epidemiology of primary CNS lymphoma (PCNSL), a type of non-Hodgkin's lymphoma (NHL), deserves special comment. A dramatic increase in the incidence of PCNSL has occurred during the past few decades. This parallels a doubling of the incidence rate of systemic NHL during the past four decades (Preston-Martin and Mack 1996). The incidence of PCNSL peaked in the early 1990s and has since decreased. The primary factor behind the rising incidence is the acquired immunodeficiency syndrome (AIDS) epidemic. Of individuals with AIDS, 2-6% develop PCNSL at some point in their disease course (Fine and Loeffler 1999). The incidence of AIDS has decreased along with the rate of PCNSL since the beginning of the 1990s. However, AIDS does not fully account for the total increase in incidence. In a population-based study that excluded never-married males, a group previously considered at highest risk for HIV infection, there was nearly a threefold increase in the incidence rate of PCNSL from the 1970s to the 1980s. This increase was reported among both young and older adult populations, with a clear predilection toward males (71%) and whites (83%) (Kadan-Lottick ct al. 2002). Some have speculated that PCNSL may become the most common primary brain tumor; however, such speculation may be premature because some cancer centers are reporting decreased numbers since the early 1990s (Corn et al. 1997). Clearly, updared, population-based data will be needed to address this issue.

ANALYTIC EPIDEMIOLOGY

Study Designs

Analytic epidemiology involves the application of case control and cohorr study designs to identify risk factors for particular diseases. The *case control study* has been the most commonly used study design in the search for risk factors for brain tumors. In a case-control study, subjects are classified based on the presence (case) or absence (control) of the outcome of interest (e.g., brain tumor). An exposure of inrerest (e.g., head trauma) is then determined in a uniform manner for cases and controls. An odds rario (OR) of disease for the exposed compared with the

unexposed is generated. Case control studies are most useful in the study of uncommon diseases (brain tumors) or those with a long period between the exposure of interest and the development of disease. In a *cohort study* subjects are classified on the basis of the presence or absence of a particular exposure and are followed forward in time to ascertain the development of the outcome or disease of interest. Cohort studies are most useful when the outcome under study is common. Because brain tumors are uncommon, ven few cohnn studies ol risk ['actors for brain tumors have been accomplished.

Methodological Challenges

Because brain tumors are an uncommon and heterogeneous form of cancer, prospective cohort studies have not been feasible and most case control studies have small numbers of cases. Despite these limitations, several case control studies have examined putative risk factors for brain tumors. In addition to the usual problem of selection bias with the case control study design, recall bias may be an especially important limitation in retrospective case control studies of this population. Individuals with brain tumors often have cognitive and language difficulties and reliable exposure assessment are therefore difficult to achieve. Another shortcoming of observational studies in this population has been the tendency to group all brain tumors together as one entity. Although this may identify risk factors common to all brain tumors, it will potentially miss important exposures for specific histopathological types. Although exceptions exist, most exposures analyzed are characterized by small effects and marked inconsistencies across studies. The major categories of exposures are reviewed in the following text.

Occupational Studies

A large number of occupational studies of brain tumor risk were conducted in cohorts of workers presumed to share common exposures. Most of these studies report standardized incidence or mortality ratios using expected rates from the general population. Detection bias is a risk in these studies because working adults with health insurance may be more likely to have diagnostic tests. This may lead to better ascertainment of brain tumors in the worker cohort as compared with the general population. Overestimation of the true association may then occur.

In general, the data on occupational exposures and brain tumors are inconsistent. Small numbers of cases, imprecise methods of exposure assessment, potential confounding, and bias have complicated the interpretation of many studies. Study validity is often weakened by the lack of biological measures of exposure and specific chemical identities, and the tendency to group all types of brain tumors into one category. However, moderate risks cannot be excluded for most of these occupational exposures and well-designed case control studies are needed to further address this issue.

Observational studies have found that workers in "white collar'" professions have higher rates of brain tumors. Some of these occupations involve chemical exposures of some type, such as laboratory researchers and health professionals. However, the existence of detection bias is real because these professionals arc more likely to have health insurance and seek medical attention (Carozza et al. 2000). McLaughlin (19H7) analyzed the potential effect of detection bias in a Swedish study where health care is free and available to all citizens. Despite universal access, higher reported brain tumor rates among professionals suggest that detection bias docs not fully account for this observation.

Electrical workers have been the subject of several occupational cohort studies based on possible exposures to electromagnetic fields (EMFs). A review of seventeen studies concluded that few were of sufficient size and design to ascertain KMF exposure accurately. Despite these limitations, most have failed to detect a significant association between EMF exposure and risk of brain tumors. However, a study of Swiss railway workers found that exposure to low frequency EMF among shunting yard engineers may accounr for the higher mortality of brain tumors in this group. Yet the study failed to yield a dose-response relation between brain tumor mortality and similar exposure to low frequency EMF (Minder and Pfluger 2001).

At least 10 occupational cohort studies of workers in the oil refinery industry have reported an increased risk of brain tumors. However, a working group from the International Agency for Research on Cancer concluded that only I of these 10 studies was without significant methodological or statistical limitations. This single study reported an increased risk of brain tumors only among oil refinery workers employed in the industry for a short duration of time, raising doubts about the validity of the results. No specific chemical exposure has been identified as a risk factor in these studies, and the weight of the evidence to date does not establish employment in this industry as a risk for the development of brain tumors.

Agricultural workers are exposed to a large number of chemicals in the form of pesticides, herbicides, and fungicides. However, each of these categories consists of many different combinations of chemicals. Similar to other occupational cohort studies, one limitation of studies among these workers is the use of job classification as a proxy for nonspecific chemical exposures. Biological markers ot exposure are lacking in most studies. Farming as an occupation and residence on a farm have been associated with an increased risk of brain tumors. An increased risk of brain tumors has been reported among Italian farmers exposed to fungicides and copper sulfate (RR = 2.0, 95% CI 1.22-3.23), Swedish horticulturists (standardized mortality ratio |SV1R| 3.2, 95% CI 1.6-5.7),

and Chinese farming women exposed to pesticides (standardized incidence ratio = *3.6, 95%* CI 1.2-8.5). However, no consistent evidence exists to indicate that any one chemical exposure is responsible for the apparent increased risk of brain tumors among agricultural workers.

Increased risks are also reported for workers in the vinyl chloride, petrochemical, and rubber industries. Other studies have found an increased risk among aircraft pilots, firefighters, welders, glass manufacturers, tile makers, and metal cutters. However, these findings have been in con si stent over nine.

Despite the large number of studies in several occupational settings, an increased risk of developing a brain tumor based on occupational status is not established. The studies conducted to date, characterized by significant design flaws, have yielded conflicting results.

Radiation

Ionizing radiation and two forms of nonionizing radiation (electromagnetic radiation [EMR| and radiofrcquency |RF] radiation) have been studied as potential risk factors for brain tumors. Ionizing radiation exposure from radiation therapy has been established as a cause of certain types of brain tumors, especially meningiomas and nerve sheath tumors. Biological studies have suggested meningeal cells may be more susceptible to radiation than other parts of the body. A cohort of 10,000 children treated with 1.5 Gy of cranial radiation for tinea capitis had elevated risks of nerve sheath tumors (RR = 33.1, 95% CI 9.4-116.5) and meningiomas (RR = 9.5, 95% CI 3.5-25.7), but less elevation of risk for malignant gliomas (RR = 2.6, *95%* CI 0.8-8.6). Ionizing radiation was also associated with an increased risk of pituitary adenoma in a study of patients with tinea capitis who received scalp irradiation at doses ranging from 1-2 Gy (mean 1.4 Gy) (Juven and Sadetzki 2002). Less dramatic but still significant elevations of risk for meningiomas and nerve sheath tumors have been reported in individuals treated with variable doses of ionizing radiation for thymic enlargement, enlarged tonsils and adenoids, and thyroid and nasopharyngeal conditions. In a mutagen sensitivity assay, peripheral blood lymphocytes from glioma subjects were more prone to chromosomal damage when exposed to y-radiation. In this study, mutagen sensitivity of lymphocytes was associated with an increased risk of glioma (OR = 2.09, *95%* CI 1.43, 3.06) (Bondy et al. 2001).

Exposure to diagnostic x-rays as a risk factor for brain tumor development is less well established. Dental x-rays have been the subject of at least 10 studies with ORs of brain tumor risk ranging from 0.4-4.0 (Preston-Martin and Mack 1996). Three U.S. studies and an Australian study have demonstrated an increased risk of meningioma associated with frequent dental x-ray examinations. This effect was strongest for younger age of exposure and exposure in the remote past when doses were higher. Prior to the introduction of fast speed film in 1956, exposures were several orders of magnitude higher than exposures used today. All such studies showed only modest elevations in glioma risk.

Since an initial report in 1979 suggested that electric wiring configurations may be associated with increased risks for leukemia and brain tumors, occupational cohort studies have also suggested an increased risk of brain tumors among electric utility workers, possibly because of the effects of EMR. Two large occupational cohort studies of electric utility workers with direct measurements of magnetic fields have demonstrated elevated risks of brain tumors with apparent dose response relationships (RR = 2,6, 95% CI 1.4-4.9 and RR = 3.0, 95% CI 1.0-8.8 in highest exposure groups). However, the role of other occupational carcinogens cannot be excluded in these studies. Other studies have not found an excess risk of brain tumors among electrical workers. Twenty-one studies of EMF exposure of varying methodology, starting as early as 1948, have reported ORs from 0.3-13.1 and SMRs ranging from 1 14-340 (Preston-Manii] and Mack 1996), Other observations have cast doubt on the possibility that EMR causes brain tumors. Biological plausibility is yet to be established, subsequent studies have reported conflicting results, and the probable roles of bias and confounding in earlier studies have been emphasized. Studies using more rigorous methodology, including direct in-home measurement of EMR, have concluded that EMR does not increase the risk of adult and childhood brain tumors.

RF radiation exposures mainly involve microwave and radar equipment, and occupational exposures (sealers, plastic welders, amateur radio operators, medical personnel, and telecommunications workers). Biological plausibility of RF radiation as a risk factor for cancer is not established. The limited data available are equivocal with respect to any cancer risk.

Cellular telephones are a source of RF exposure and have received attention as a potential risk factor for brain tumors. This is based, presumably, on exposure of the head of the user to RF energy. Unlike mobile cellular phones, portable cellular phones include an antenna as part of the headset, theoretically increasing cranial exposure to RF energy. Despite limited biological plausibility and little human data, coverage in the popular media has caused public concern. Several epidemiological studies have addressed this controversial issue. FLxposure to RF energy is difficult to quantify, even under laboratory conditions (Rothman et al. 1996). Therefore proper assessment of exposure will involve a proxy measure such as phone billing records. Studies to validate billing records as an accurate measure of exposure to cellular phone use are published. In a cohort of 250,000 portable and mobile cellular phone customers, the age-specific rates of mortality were similar between the groups (portable/mobile mortality ratio of 0.86, 95% *(A* 0.47-1.53} (Rothman et al. 1996).

In a large case control study, there was no evidence for an increased risk of astrocytomas, meningiomas, or acoustic neuromas among those subjects who used these devices for an extended time (Inskip et al. 2001). Additionally, the side of the tumor and the side of the cranium exposed did not correlate. These data do not support cell phone use as an important risk factor for primary brain tumors.

In summary, biological and epidemiological studies have established ionizing radiation as a cause of brain tumors in animal models and humans. Credible evidence supports causation of meningiomas and nerve sheath tumors, while support for causation of the most common type of primary brain tumor, glioma, is equivocal. Although some support from occupational cohort studies exists for an increased risk of brain tumors among electric utility workers, presumably resulting from KMR, the weight of evidence does not support EMF/EMR as an important causal factor. Less evidence is available supporting RF radiation as a risk factor for cancer. Biological plausibility is not established for these nonionizing forms of radiation. Despite the evidence supporting ionizing radiation as a cause of brain tumors, this exposure is responsible for only a tiny fraction of brain tumors in the United Stales.

Trauma

Head trauma has been implicated as a potential risk factor for brain tumor development. The evidence is strongest for meningiomas and less convincing for gliomas (Wrcnschet al, 2000; Nygren et al. 2001). Anecdotal reports of brain tumors arrsing after head trauma date back to the reports of Harvey Cushing in 1922. Gushing reported the presence of a head scar or skull depression in 8% of meningioma patients. Experimental studies have also implicated physical trauma as a cocarcinogen. Certain occupations with increased risk of head trauma {e.g., farmers, carpenters) are associated with a possible excess of brain tumors. An excess risk of meningiomas in persons with a history of serious or repetitive head trauma has been reported in three case-control studies (Preston-Martin et al. 1998). Childhood brain tumors may be more common in firstborn children because of a higher risk of birth trauma and in children with a documented history of birth trauma (e.g., forceps delivery, prolonged labor, and cacsarian section). Other studies have not confirmed an increased risk among these groups.

Studies of head trauma and brain tumors may be confounded by ionizing radiation. Individuals with a history of head trauma are more likely to have had skull x-ray examinations. Recall bias is another factor complicating interpretation of case control studies of head trauma and risk of brain tumors. Persons with brain tumors may be more likely to recall minor and major episodes of head injury than controls. One study reporting a positive association between head trauma and risk of brain tumors found no association when the definition of head trauma was restricted to episodes requiring medical attention. Future studies should standardize the definition of head trauma to include only episodes requiring medical attention and should document concurrent x-ray studies.

Acoustic neuroma (nerve sheath tumor of the VHI/ auditory cranial nerve) was associated with acoustic noise of 10 years' duration in a case control study (OR = 2.2, *95%* CI 1.12-4.67). Noise exposure was based on a blinded review of job histories. A dose response relationship was observed in this study because 20 or more years of exposure was associated with an OR of 13.2 (95% CI 2.01-86.98) (Ries et al. 1998). Experimental studies of tissue destruction and repair following acoustic trauma support the biological plausibility of this association.

N-Nitroso Compounds

N-nitroso compounds (NOCs) are broadly acting and potent carcinogens in animal models (Lijinsky 1999), It has been known for 40 years that NOCs arc present in foods treated with sodium nitrite. Although NOC levels in many foods have declined during the last 20 years, even small amounts may be important because humans are more sensitive than laboratory rodents to the carcinogenic effects of NOCs. A prevalent and long-standing hypothesis in the epidemiology of gliomas is that NOC exposure may increase risk. NOCs include nitrosamines, which require metabolic activation to a carcinogenic form, and nitrosamides, which do not. Transplacental exposure to ethylnitrosourea, a nitrosamide, results in formation of brain tumors, including gliomas, in rodents and primates. The addition of vitamin C to the diet prevents tumor formation in this model. Human NOC exposures are divided equally between exogenous and endogenous sources. The exogenous (environmental) sources of NOC exposure arc best established for nitrosamines: tobacco (mainly second-hand smoke), cosmetics, automobile interiors, and cured meats (Preston-Martin and Mack 1996). Other sources include rubber products {e.g., baby pacifiers, bottle nipples) and certain drugs, including antihistamines, diuretics, oral hypoglycemic agents, antibiotics, tranquilizers, and narcotics. N-nitrodiethanolaminc, a carcinogen in animal models, occurs mainly as a contaminant in cosmetic products, soaps, shampoos, and hand lotions (Batchelor et al. 2001). Some environmental sources may contain both nitrosamines and nitrosamides (Preston-Martin and Mack 1996). Endogenous formation of NOCs is a complex process that occurs in the stomach. This process depends on the presence of NOC precursors, gastric pH, the presence of bacteria, and othct physiological parameters (Davis and Preston-Martin 1998).

Measurement of NOC exposure is difficult, given the many exogenous and endogenous sources. Thus Reclassification of exposure is a major limitation for any

study of this topic. However, because processed and cured meats arc sources of exogenous NOC exposure, dietary assessment may serve as a useful surrogate marker of this form of NOC exposure. These foods contain nitrates and nitrites that can react with secondary amines or amides to form NOCs.

The NOC hypothesis is controversial. Some studies report an increased risk of gliomas in persons exposed to environmental sources of NOC and others do not. F.pidemiological support for NOC exposure as a risk factor for brain tumors comes mainly from nine studies of pediatric brain tumors and childhood and maternal diet. Studies in children present fewer methodological challenges because dietary exposures arc relatively recent or characterized by a fixed period of interest (e.g., gestation). An elevated risk of brain tumors in children has been reported for increased maternal consumption of nitrite-cured or processed meats (e.g., cooked ham, processed pork, corned beef, and fried bacon) (Bunin 1998). Studies of dietary NOC exposures and risk of gliomas in adults yield inconsistent results. Retrospective, casc-comvol studies in adults are complicated by inaccurate measurement of remote diet. Moreover, many studies of diet and risk of brain tumors have not used valid, reliable instruments to measure dietary intake over time. A population-based, retrospective case control study in Germany (115 gliomas, 418 controls) reported a significantly increased risk of glioma in adults with higher levels of dietary meat, processed pork, fried bacon, and cooked ham. In a smaller case control study in Los Angeles County in the United States (94 gliomas, 94 controls), an increased risk of glioma was associated with consumption of cured meats, especially bacon (Blowers et al. 1997). In a case control study in the San Francisco Bay area, higher consumption of cured foods was associated with an increased risk of glioma in men but not women (Lee ct al. 1997). Case control studies of glioma risk and other environmental sources of NOC like drinking water, tobacco, and medications, have yielded inconsistent but mainly negative results. Despite the existence of both experimental and observational data that NOC exposure may increase the risk of glioma, this hypothesis remains tenuous. In addition to the problem of inaccurate measurement of the exposure in these studies, all of these retrospective case control studies are subject to recall bias. The magnitude and direction of errors in dietary recall data may be influenced by disease status, casting doubt on the results of many retrospective studies (Wilkins and Bunn 1997). Some authorities have called for studies with prospective cohorts as the best method to address definitively the NOC hypothesis (Blot ct al. 1999),

Vitamins and Fruit Juices

Indirect support for the NOC hypothesis includes the observation that certain modulators of the nitrosation process, vitamins (C, E) and fruit juices, appear to reduce brain tumor risk in adults and children. Dietary studies show a reduced risk of brain tumors in children and meningiomas in male adults who consume increased amounts of fruits and fruit juices (Preston-Martin e\ Mack).

Tobacco and Alcohol

The presence of nitrosamines in tobacco smoke has stimulated interest in tobacco exposure as a potential risk factor for brain tumors. Studies of active and passive smoking and brain tumor risk have been inconclusive. A 1970 case control study suggested a protective effect of smoking, but was flawed because exposure was assessed after diagnosis and probably reflected persons who stopped smoking after learning their diagnosis. Subsequent case control studies in Los Angeles found no association of smoking and risk of glioma or meningioma (Ries ct al. 1998). Studies of maternal smoking (active and passive) and risk of brain tumors in offspring have also resulted in conflicting results. Conclusive evidence is not available that establishes cither active or passive smoking as a risk factor for brain tumors (Filippini et al. 2002; Zheng et al. 2001).

Because beer and liquor contain nitrosamines, there has been speculation that consumption of alcoholic beverages may increase the risk of brain tumors. In one study, a correlation was established between childhood brain tumors and paternal use of hard alcohol (white distilled alcohol up to 60% by volume) (RR = 3.72, 95% CI = 1.91-7.26) for less than 15 years, and an even more elevated risk of 4.06 (95% CI = 1.09-15.21) for greater than sixteen years of hard liquor use (Hu et al. 2000). However, no consistent association between maternal consumption of alcoholic beverages and risk of gliomas or meningiomas has been demonstrated (Preston-Martin and Mack 1996).

Infections

Although several reports have implicated infectious agents in the development of different types of brain tumors, these associations have been inconsistent.

The detection of viruses and virus-like particles in brain tumor specimens has resulted in speculation that viral infection may be a risk factor for brain tumor development. Interest in simian virus 40 (SV40), a polyoma virus, was stimulated by animal studies documenting brain tumor development after intracerebral inoculation with SV40 and human studies in which SV40 was isolated from brain tumor tissue. Poliomyelitis vaccine administered between 1955 and 1962 was contaminated with SV40. This cohort has been studied over subsequent decades. These individuals did not experience an overall increase in brain tumors during the ensuing 20 years, but some uncommon brain

tumor types (mcdulloblastoma and spongioblastoma) appeared more often than expected (Klein at al. 2002). Other nonpolyoma viruses (adenovirus, cytomegalovirus, other herpes viruses, arboviruses, and retroviruses) are known to induce brain tumors in experimental animal models. Most of these vituses have not been subjected to rigorous cpidemioiogical study as possible risk factors for brain tumors. Human cytomegalovirus (HCMV) is a /J-herpes virus that has been implicated in glioma development. In one study, HCMV gene products were found in 27 of 27 malignant glioma specimens, but were not found in other types of CNS tumors or non-neoplastic neurological diseases (Cobbs et al. 2002). The investigators raised the possibility that HCMV could play a causative factor in glioma growth. However, one cannot exclude the possibility that infection with HCMV could have occurred after glioma formation.

Studies of maternal infection have generally found no increased risk of brain tumors in offspring of mothers infected with varicella, rubella, or mumps during pregnancy. One large case control study reported an increased rink (R!l 2.4, 95% CI 1.5-4.0) of all types of brain rumors after different neonatal infections (Linct et al. 1996).

Infection with *Toxoplasma gondii* has been associated with an increased risk of meningioma and astrocytoma in two case control studies. However, despite this parasite's propensity to infect the nervous system, it has not been established as a risk factor for the development of brain tumors.

At the present time, epidemiological evidence implicating infectious agents as important factors in the causation of brain tumors is not conclusive.

Genetic Syndromes

Approximately 1-5% of brain tumors are caused by genetic syndromes that increase the risk of nervous system tumors {Ries et al. 1998). Neurofibromatosis type I (NF I) occurs in I in every 3000 persons and is linked to a gene on chromosome 17. Approximately 5-10% of persons with NF I develop brain tumors, primarily nerve sheath tumors, astrocytomas, and meningiomas. NF II is defined by the presence of bilateral acoustic neuromas and a corresponding link ro a gene on chromosome 22. Individuals with NF II also have astrocytomas and other brain tumor types. Table 58A.4 reviews other inherited syndromes associated with an increased risk of nervous system tumors.

Several familial cancer syndromes are associated with an inctcascd risk of brain tumors. Li-Fraumcni's syndrome, an autosomal dominant condition, may involve a mutation in the tumot suppressor gene p53, conferring an increased risk of brain tumors, sarcomas, and breast cancer (Chomprct 2002). Persons with nevoid basal-cell carcinoma (Gorlin's syndrome) and Wilms' tumor have an incteased risk of mcdulloblastoma. Turcot\s syndrome is associated with adenomatous polyps and increased risk of mcdulloblastoma and GBM. Familial clustering of brain tumors is also recognized outside of these defined syndromes. The chance of having a family member with a brain tumor is twice as high in adult brain tumor patients (8%) as in controls (4%). This familial clustering is even more pronounced for children and certain histological types of brain tumors (mcdulloblastoma). Although genetic syndromes account for only a small fraction of brain tumors in the United States, further study of the affected genes may provide insight into the molecular pathogenesis of sporadic brain tumors.

Genetic Polymorphisms

Genetic polymorphisms in specific detoxification and metabolic enzymes have been implicated in the pathogenesis of certain neoplasms. Despite conflicting results from the small number of studies, a sound rationale exists for further investigation into this category of potential risk factors (Kelsey et al. 1997; Trizna et al. 1998). In addition to the possible association of NOC and gliomas, other xenobiotics, including polycyclic aromatic hydrocarbons, have been shown to induce brain tumors in animal models. These associations between chemical carcinogens and brain tumors in experimental models raise the possibility that susceptibility may be related to genetic polymorphisms at loci encoding phase I cytochrome P450 (CYP450) and phase II glutathione 5-transferase enzymes. Several potential ncurocarcinogens (polycyclic aromatic hydrocarbons, nitrosoureas, and methyl halide) are substrates for these enzymes. Several case control studies of brain tumors have assessed other polymorphic enzymes (GSTT1, GSTM1, GSTP1, CYP2D6, NAT2, HRAS1) implicated in the activation or detoxification of potential neurocarcinogens.

Tabic 58A.4: Genetic syndromes associated with nervous system tumors

Syndrome	*Chromosome*	*Inheritance*	*CNS tumors*
NFI	17ql	**Al)**	Glioma, meningioma, nerve sheath tumors
NF1I	22 q	A I)	Nerve sheath, optic glioma, meningioma
Tuberous sclerosis	9q32-34	Al)	Ependymoma, astrocytoma, ganglioneuroma
Von Hippel-Lindau syndrome	3pl3-143 3p25-26	AD	Hemangioblastoma
St urge-Weber disease		AD	Choroid plexus papilloma

AD = autosomal dominant; CNS = central nervous system; NF = neurofibromatosis.

Tabic 58A.5: Metabolic polymorphisms and risk of astrocytoma and meningioma

Tumor	*Enzyme system*	*Polymorphism*	*Cases*	*Controls*	*OR [95% CIj*
Astrocytoma	CYP450	CYP2D6 PM	109	412	4.17 [1.57, 11.09]
Meningioma	CYP450	CYP2D6 PM	48	412	4.90 11.39, 17.26]
Astrocytoma	Glutathione S-transferase	GSTTl Null	109	494	2.67 [1.53, 4.65]
Meningioma	Glutathione S-transferase	GSTTl Null	47	494	4.52(2.18,9.34]
Gliomas	HRAS	"Rare" HRAS1	52	109	2.72 [1.17-6.32]

OR = odds ratio.

In most studies, an elevated risk of glioma and other primary brain tumors has been associated with polymorphisms in these enzymes {Table S8A.5). The study of genetic polymorphisms in different detoxification and metabolic enzymes as potential risk factors for brain tumors is a new and promising area of investigation.

CONCLUSION

Brain tumors are an uncommon but especially lethal form of cancer, and their incidence has increased dramatically over the past five decades. The only established environmental risk factor, ionizing radiation, accounts for only a small fraction of incident cases, and genetic predisposition exists in only a small percentage of cases. The study of brain tumors has been complicated by several factors. Brain tumors are an uncommon form of cancer, making centralized reporting and multi-institutional collaboration essential for effective observational study. Such reporting and collaboration are recent developments and promise improved study design and execution in the future. Because brain tumors arc a heterogeneous group of cancers arising from different cell types, perhaps by different molecular mechanisms, future studies of brain tumors should focus on biologically distinct tumor types such as astrocytoma and meningioma. Molecular classification of these tumors may allow even greater refinement of tumor classification. The WHO system is now the most widely accepted histopathological classification system with high inter-rater reliability (94%) and serves as the basis of reporting to the CBTRUS. Use of WHO criteria supplemented with genetic classification will improve case definition in future studies.

Future studies of brain tumors are needed to explore more fully the role of dietary NOC compounds, physical trauma, and viral infection. Collaboration and centralized reporting will improve these studies. Ongoing prospective cohort studies arc likely to accumulate enough eases in the future for more detailed assessment of diet, comorbid illnesses, and drug exposures as potential risk factors. Understanding the molecular pathology "I gliomas may also allow correlation of candidate exposures with specific molecular subtypes o! tumors that nia\ shed light on the molecular mechanisms of disease causation and progression.

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Chapter 58
Cancer and the Nervous System

B. PATHOLOGY AND MOLECULAR GENETICS OF NERVOUS SYSTEM TUMORS

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GENERAL PRINCIPLES OF NERVOUS SYSTEM TUMOR BIOLOGY

Nervous system tumors, like other human neoplasms, are clonal proliferations that develop as a result of changes in key growth regulatory genes. Such genes fall into several different classes: (1) growth-promoting oncogenes, which are abnormally activated in tumors; (2) growth-checking tumor suppressor genes, which are inactivated in tumors; (3) cell death genes, which are impaired in rumors; and (4) DNA repair genes, which arc improperly regulated in tumors. In combination, these genetic changes result in a powerful growth advantage that enables the cells to proliferate, evolve, and disseminate (Maherctal. 2001).

The specific genes affected in human nervous system tumors are in the discovery stage and are discussed in the following text with each tumor type. Most of these genes are also deregulated in othct types of human cancers, and the manner in which the deregulation specifically affects nervous system cells remains unclear. Certain nervous system cells are probably more susceptible to neoplastic transformation than others. For example, the far greater frequency of gliomas over neuronal tumors has been attributed to the greater "neoplastic vulnerability" of glial cells; because oncogenic transformation requires cell division, postmitotic cells such as neurons should not be susceptible to tumorigenic events. However, it remains possible that nervous system tumors arise when oncogenic changes occur in precursor cells rather than in mature glial

cells or neurons; such precursors are now known to reside in the brain even into adult life. In this sense, the greater frequency of gliomas may relate to the particular paths of differentiation that are followed after specific tumorigenic genetic changes {Bachoo et al. 2002); in other words, transformed neuroepithelial progenitors may have to undergo specific molecular events to become tumors, with these same events essentially restricting cells to glial differentiation.

It is not clear why nervous system cells, rather than other cells, are transformed, because the cause of brain tumors remains unknown. At this time, ionizing radiation and hereditary predisposition arc the only two clear causal factors implicated in the genesis of nervous system tumors. Prior therapeutic irradiation of the nervous system for other tumors is a risk factor for the development of gliomas, meningiomas and schwannomas. Hereditary brain tumor predisposition is rare and confined to the neurocutaneous syndromes: neurofibromatosis (NF) 1 and 2, tuberous sclerosis (TS), von Hippel-Lindau (vHL) disease, Li-Fraumeni's syndrome, Turcot's syndrome and Gorlin's syndrome. These conditions highlight the critical roles played by specific genes in brain tumorigenesis.

HISTORY OF NERVOUS SYSTEM TUMOR CLASSIFICATION

The first comprehensive classification of nervous system tumors, formulated by Percival Bailey and Harvey Cushing in 1926, was founded on presumed parallels between embryological and neoplastic cells. In large part, this hisrogenetic "cell of origin" model still forms the basis for today's nomenclature. Interest in the role of developmental pathways in tumorigenesis has recently been renewed. In 1949, as a means of enhancing the clinical utility of tumor classification, Kernohan contributed a tumor grading system for the purpose of assessing patient prognosis. Russell and Rubinstein modified and updated the Bailey and Cushing system during the 1960s, 1970s, and 1980s. Further updates were incorporated into the World Health Organization (WHO) classification, first completed in 1979 and then revised in 1993 and 2000 (Kleihues and Gavenee 2000). Although not universally accepted, the WHO classification is currently the one most widely used by neuropathologists.

The WHO currently lists more than 100 types of nervous system tumors and their variants (Kleihues and Cavcncc 2000). This level of complexity seems daunting at first, but consideration of key clinical and imaging characteristics typically narrows the differential diagnosis to a few common possibilities (Table 58B.1). For example, the differential varies substantially for suprarentorial versus infra tentorial diagnosis, pediatric versus adult, and enhan cing versus nonenhancing tumors. The following sections ilisaiss basic techniques and histopathologic^! terms used in the diagnosis of nervous system tumors.

GENERAL HISTOPATHOLOGIC AL FEATURES AND TECHNIQUES

General Histopathological Features

Most classification and grading schemes of nervous system tumors are based on light microscopic examination of hematoxylin and eosin-stained sections. The approach to nervous system neoplasia follows the standard approach to classifying human tumors from other parts of the body. Therefore many neuropathological terms are borrowed from the discipline of general pathology. The lexicon that follows includes the terms most frequently used in clinical practice.

Anaplasia

Anaplasia suggests that tumor cells have gone from a more differentiated to a less differentiated state. Anaplasia is recognized by a histological appearance characterized by lack of cytoplasmic differentiation, a high nuclear-to-cytoplasmic ratio, increased nuclear size, and marked pleomorphism.

Tumor Grading

The fundamental concept of tumor grading is that the level of tumoral differentiation predicts biological behavior. In the WHO scheme, grade I is equivalent to benign; II is low-grade malignant; III is intermediate-grade malignant, often associated with the term "anaplastic"; and IV is high-grade malignant. Grading, which depends on histological assessment, should not be confused with tumor staging, which depends on gross and radiographic characteristics and the extent of tumoral spread. Staging of central nervous system (CNS) tumors has been defined and systematized primarily for use in clinical trials. Computed tomography (CT) and magnetic resonance imaging (MRI) have increased the accuracy of tumor staging,

Palisading and Pseudnpalisading

Palisading or lining up of tumor cells is characteristic of schwannomas, where collections of palisaded nuclei are referred to as *Verocay bodies.* The term describes a collection of neoplastic cells arranged in parallel arrays or palisades. Necrosis never occurs in true palisading, but pseudopalisades consist of serpiginous zones of necrosis lined by hypcrccllular, viable tumor nuclei, Pseudopalisading necrosis is often found in glioblastoma (Figure 58B.1) and may rarely be seen in other malignant CNS tumors.

Rosettes

The term *rosette* is confusing because it has been applied to several histological structures. The two most commonly

Table 5SB.1: Common central nervous system tumor diagnoses by location

Location	*Chitd/young adult*	*Older adult*
Cerebral/supratentorial	Ganglioglioma	Gr. 11-111 glioma (NE)
	DNT	Glioblastoma (ring E)
	PNET	Mets (E)
	AT/R1	Lymphoma (E)
Cerebellar/infratentorial	Pilocytic Astrocytoma	Mets (E)
	Medulloblastoma	I lemangiohlasroma
	Ependymoma	Choroid plexus papilloma
	Choroid plexus papilloma	
	AT/RT	
Brain stem	"BS glioma"	Gliomatosis cerebri
	Pilocytic astrocytoma	
Spinal cord (intra-axial)	Ependymoma	Ependymoma
	Pilocytic astrocytoma	Diffuse astrocytoma (ill-defined)
		Paraganglioma
Exrra-axial/dural	Secondary lymphoma/leukemia	Meningioma
		Mets
		Secondary lymphoma/leukemia
Intra sellar	Pituitary adenoma	Pituitary adenoma
	Craniopharyngioma	Rathke's cleft cyst
	Radike's cleft cyst	
Suprascllar/hypothalamie/optic patbway/third v.	Germi 110ma/germ cell tumor	Colloid cyst
	Craniopharyngioma	
	Pilocytic astrocytoma	
Pineal	Germinoma/germ cell tumor	Pineocytoma
	Pineocytoma	Pineal cyst
	Pineoblastoma	
	Pineal cyst	
Thalamus	Pilocytic astrocytoma	AA/glioblastoma
	AA/glioblastoma	Lymphoma
Cerebellopontine angle	Vestibular schwannoma (NF2)	Vestibular schwannoma
		Meningioma
Lateral ventricle	Central neurocytoma	Central neurocytoma
	SEGA (tuberous sclerosis)	SEGA (tuberous sclerosis)
	Choroid plexus papilloma	Choroid plexus papilloma
	Choroid plexus carcinoma (infant)	Subependymoma
Nerve root/pa raspinal	Neurofibroma (NFl)	Schwannoma
	MPNST (NFl)	Meningioma
		Secondary lymphoma
		Neurofibroma (NFl)
		MPNST

AA = anaplastic astrocytoma; AT/RT = atypical teratoid/rhabdoid tumor; DNT = dysembryoplasric neuroepithelial tumor; E = enhancing tumor; Gr. • grade; Mets •• metastases; MPNS1 • malignant peripheral nerve sheath tumor; NE • non-enhancing tumor: NFl = neurofibromatosis type 1; NF2 = neurofibromatosis type 2; PNET = primitive neuroectodermal tumor; SEGA= subependymal giant cell astrocytoma.

encountered rosettes are Homer Wright rosettes and perivascular rosettes. A Homer Wright or neuroblastic rosette is a ring of cells surrounding neuropil (i.e., delicate fibrillary processes) and represents axon formation by primitive neuronal elements. Because Homer Wright rosettes are identical to those encountered in neuroblastomas of the peripheral nervous system, their presence is oken Liken .is evidence of neuroblastic differentiation. They are associated, as a focal finding, in primitive neuroectodermal tumors (PNETs) such as medulloblastoma and pineoblastoma. CNS tumors with extensive Homer Wright and neuropil formation are sometimes referred to as *central* or *cerebellar neuroblastomas.*

Perivascular pseu do rosettes are characterized by a peripheral ring of tumor nuclei, surrounding a central blood vessel with a nuclear-free eosinophilic zone between (Figure 58B.2). The nuclear-free zone is derived from tapering cellular processes that radiate from the tumor cells to the vessel. Perivascular rosettes are typical of ependymomas and the perivascular processes are highlighted with glial fibrillary acidic protein (GFAP) immunostains. Similar axon-bearing structures may occasionally be seen

in neuronal tumors, such as central neurocytomas, pinc-ocytomas, and various forms of PNET.

Desmoplasia

Desmoplasia is a form of fibrosis induced by resident fibroblasts within regions of the CNS that normally harbor them, such as the meninges and perivascular spaces. Desmoplasia is a reactive rather than a neoplastic change and may be seen in any tumor as it infiltrates the lep-tomeninges. It also represents a characteristic feature of certain tumor types, such us desmoplastic gangliogliomas and medulloblastomas.

Microvascular Proliferation

Microvascular (endothelial and pcricytic/smooth muscle cell) proliferation represents an important and interesting response to tumor- and hypoxia-associatcd angiogenesis factors. It is encountered in both benign and malignant CNS neoplasms, but is more common in malignant tumors. In pilocytic astrocytoma, the new vessels often take on a glomeruloid configuration, usually with a single-layered flat endothelial lining. In malignant tumors, such as glioblastoma, these vessels are also glomeruloid, but additionally display multilayering with enlarged or "hyper-plastic" endothelial cells (Figure 5KB.3). In either case, these neovascular structures lack the tight junctions that nor-mally contribute to the blood-brain barrier and typically leak intravascular contrast material. This accounts for the tumor-associated enhancement detected radiologically.

Frozen Sections and Touch Imprints/Smears

Intraoperative frozen sections are more difficult to interpret than fixed tissue sections, but have the advantage of speed, requiring only minutes to prepare. They are requested for several reasons that include simple curiosity and a desire to provide rapid feedback to the patients and their families. However, the most important reasons for performing this technique are to ensure that a representative sample is obtained for permanent sections and to provide informa-tion that may affect the surgical procedure. For example, a neurosurgeon may stop at a limited biopsy for a suspected lymphoma, aggressively resect an ependymoma, or send additional material to the microbiology laboratory for an abscess. Because the process of tissue freezing produces significant cytological artifacts, another popular technique has been the preparation of touch imprints or smears from fresh tissue. Although the underlying architecture is lost, the tissue requirements are minimal and the cytologic preservation is excellent (Figure 58B.4). This may be critical for diagnoses based primarily on nuclear cytology, such as reactive gliosis versus low-grade diffuse glioma. It is also important to realize that the frozen section technique

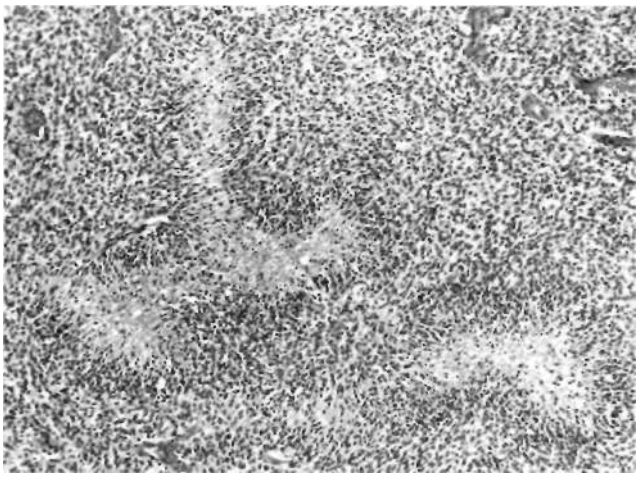


FIGURE 58B.1 Glioblastoma. Nuclear pseudopalisading surrounding foci of central necrosis (hematoxylin-eosin stain; xlOO).

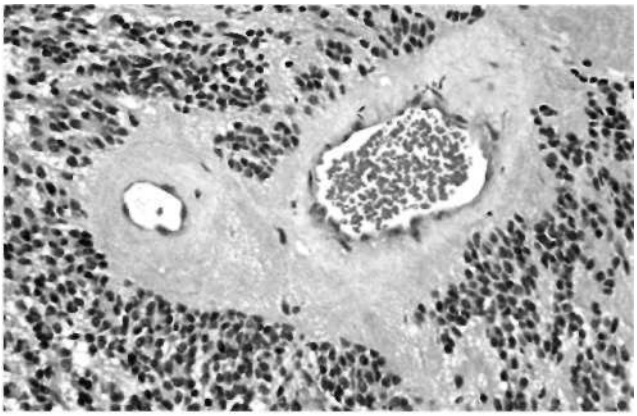


FIGURE 58B.2 Ependymoma. Characteristic perivascular pseu-dorosette characterized by a fibrillary-appearing perivascular nuclear-free zone (hematoxylin-eosin stain; ×200).

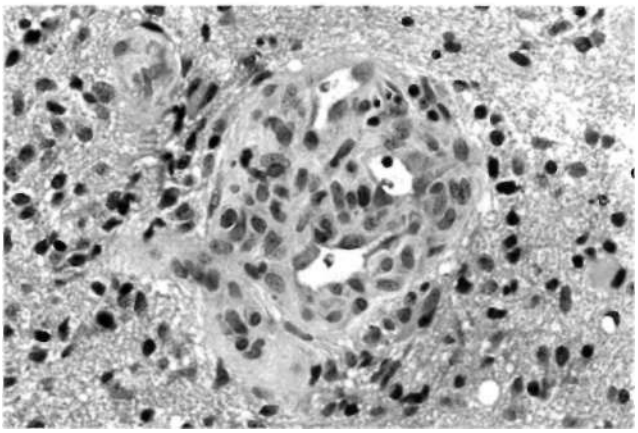


FIGURE 58B.3 Glioblastoma. Focus of endothelial hyperplasia with glomeruloid, multilayered vessel (hematoxylin-eosin stain; x400).

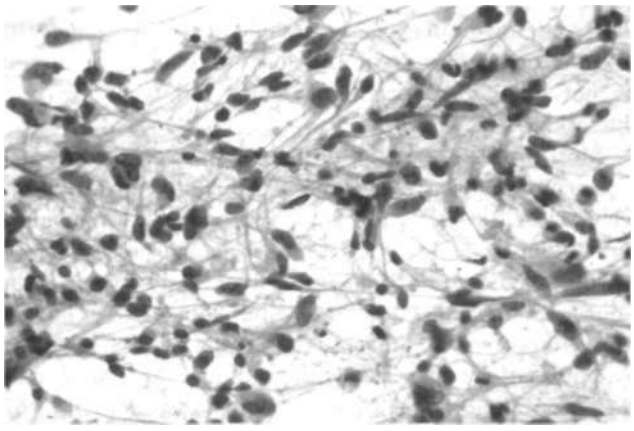


FIGURE 58B.4 Diffuse astrocytoma on an intraoperative smear. Cyrological preservation is superior to that of a typical frozen section and cytoplasmic processes are easier to discern. The oval to spindled, hyperchromatic nuclei arc typical of diffuse astrocytoma (hematoxylin-eosin stain; x400).

results in substantial tissue loss and morphological artifacts in the thawed residual specimen. Therefore it is best omitted in limited biopsies for which the surgical procedure will not be altered and supplemented by additional tissue. In other words, it is impetative that at least some optimally fixed, nonfrozen tissue is saved for final diagnosis on permanent sections.

Electron Microscopy (Ultrastructural Pathology}

The use of electron microscopy in the diagnosis of tumors is labor intensive, time consuming, and expensive, with interpretation typically delayed by 1-2 weeks. For these reasons, it has been supplanted by immunohistochemistry in most pathology laboratories. Nevertheless, it is extremely valuable in the diagnosis of certain tumors and remains the only method capable of proving epcndymal differentiation. Ultrastructural pathology is used to gain insight into forms of diffctcntiation, primarily by visualizing specific organelles and other components of the cytoplasm and cell sutfacc (intermediate filaments, neurosecretory granules, synapses, pinocytotic vesicles, intercellular junctions, cilia, microvilli, basement membrane, and so on), and is therefore of particular utility in the diagnosis of poorly differentiated neoplasms.

Immunohistochemistry

Immunohistochemistry is an ancillary diagnostic technique for detecting protein expression within tumor nuclei, cytoplasm, and cell membranes. It is used most commonly to determine lines of cellular differentiation, proliferation indices, oncogene overexpression, or losses of tumor suppressor expression. Monoclonal antibody technology and recently improved antigen-retrieval methods have greatly expanded the versatility of this technique in routine formalin-fixed paraffin-embedded tissue. However, several pitfalls remain and considerable experience is needed for accurate determinations. Commercial antibodies vary greatly in terms of sensitivities, specificities, and clinical utilities. Most laboratories use the immunoperoxidase staining technique with horseradish peroxidase and a brown diaminobenzidine dye, because staining is permanent and the reaction is visible by conventional light microscopy. Several antibodies are commonly applied to die study of CNS tumors.

Glial Markers

Immunorcactivity for GFAP, an intermediate filament, is fairly specific for the glial lineage. Although it is commonly considered an astrocytic marker, it docs not reliably distinguish astrocytic from oligodendroglial or epcndymal ontogeny. Some degree of glial differentiation and/or GFAP expression may also be encountered in choroid plexus tumors, mcdulloblastomas/PNFTs, gangliogliomas, and even some peripheral nerve sheath and cartilaginous tumors. Lastly, some astrocytomas are associated with minimal cytoplasm ot intermediate filament synthesis and may appear GFAP-negative as a result. S-100 protein provides a useful, though less specific, glial marker in such cases.

Neuronal Markers

Neurofilaments are heteropolymers composed of three subunits, with molecular weights of 68, 150, and 200 kD that are unique to neurons and their axonal processes. Each triplet protein is immunochemically distinct and is the product of a different gene. Normal neurons and mature neuronal tumors (e.g., gangliogliomas) stain for neurofilament protein, but primitive neuronal tumors such as mediilloblastoma arc often negative. Nevertheless, the staining of axons is also of great utility for highlighting a tumor's growth pattern. For example, discrete tumors, such as metastases and ependymomas push axon-bearing parenchyma to the side, whereas diffuse gliomas contain entrapped neurofilament-positive axons within their substance.

Another commonly used neuronal cell marker is synaptophysin, a 38-kD glycosylated polypeptide, which is a component of presynaptic vesicle membranes. Thought to be an oligomeric protein that avidly binds calcium within the neurotransmitter vesicles, synaptophysin is important in the calcium ion-depcudent release of neurotransmitter molecules. It is a relatively reliable marker of neuronal differentiation and is typically found even in the most primitive neuronal tumors, such as mediilloblastoma and PNET. The characteristic staining of neuropil on synaptophysin immunohistochemistry, however, sometimes makes it difficult to decipher whether the synaptophysin-positive neuropil belongs to the tumor or represents entrapped nonneoplastic tissue. This marker, along with chromogranin,

is useful for highlighting normal and neoplastic ganglion cells, as well as neuroendocrine tumors, such as pituitary adenomas, carcinoids, and paragangliomas. Neu-N, a marker of relatively mature neuronal differentiation, has the advantage of clearly marking tumor nuclei rather than surrounding neuropil.

Epithelial Markers

Cytokeratins are a class of intermediate filaments with molecular weights of 40-67 kD, primarily located in epithelial cells. Antibodies against cytokeratin are most commonly used in the diagnosis of metastatic carcinomas, but can also be used to identify craniopharyngiomas, chordomas, and choroid plexus tumors. Epithelial membrane antigen (EMA) is a glycoprotein constituent of normal and neoplastic epithelial cells. In the CNS, EMA is a particularly useful marker for meningiomas, which, unlike true epithelial tumors, display minimal to no cytokeratin expression in most cases, except in the secretory meningioma.

S-100 Protein

S-100 protein is a soluble 21-kD protein, composed of three antigenically distinct portions. It is common to neuroectodermal cells, including melanocytes, glia, Schwann cells, chondrocytes, and the sustentacular cells in tumors such as paraganglioma, pheochromocytoma, and olfactory neuroblastoma. To a lesser extent, it also stains neuronal tumors and fibrous meningiomas. Therefore as a glial marker it typically displays a higher sensitivity and a considerably lower specificity than GFAP. The S-100 protein is also particularly useful for demonstrating Schwann cell differentiation in benign and malignant peripheral nerve sheath tumors (MPNSTs).

Methods of Assessing Cell Proliferation

The simplest and least expensive method for estimating cellular proliferation is the mitotic index, usually expressed as cither the average or maximal attainable count per 10 high-powered fields (HPF). Difficulties stem from pyknotic nuclei mimicking mitoses in poorly preserved specimens, variable field sizes among microscopes, and lack of uniform methods for counting. The proliferation index is often underestimated as well, given that the cells undergoing mitosis represent only a small fraction of cycling cells within a tumor.

Flow cytometry (FCM) is a method by which cells suspended in fluid move in single file past sensors that record selected physical or chemical characteristics. Tumor assessment by FCM uses mainly fresh or frozen tissues and body fluids, but newer modifications allow the use of fixed or paraffin-embedded specimens. It has the advantage of rapid assessment of thousands of cells, but it is a labor-intensive and expensive technique, which precludes its routine use. Furthermore, because morphology is lost, it is not possible to determine which cell types arc proliferating,

Most proliferation antigens are nuclear constituents that are manifest during one or more proliferative phases in the cell cycle, allowing the recognition of cycling cells by routine immunohistochemistry. These markers are already valued in the diagnosis and management of brain tumors. The murine monoclonal antibody Ki-67 binds to a human nuclear protein in the growth fraction (Gi, S, G2, and M phases of the cell cycle), with maximum expression in the M phase but not in the Go phase, MIB-1, a variant of Ki-67 that works in paraffin sections, is gaining popularity as an ancillary marker for tumor grading (Giannini et al. 1999a). In most tumor types, the Ki-67 or MIB-1 labeling index increases with degree of malignancy.

Molecular Diagnostics

As previously stated, tumors arise when alterations occur in key growth regulatory molecules. It is anticipated that measurements of such molecular alterations will change the way tumors arc classified. Molecular changes can be detected at the genomic DNA, messenger RNA (mRNA) or protein levels. In situ hybridization can be used to detect tumor related mRNAs. For example, diagnostic elevations of hormone specific mRNAs are detectable in pituitary adenomas, and the same techniques could be useful in other CNS tumors. Other gene products, such as proliferation antigens, growth factors, and their receptors, are similarly identifiable by RNA probes, although the degradation that occurs in paraffin-embedded tissue makes this technique somewhat challenging for archival or routinely processed tissue specimens.

Molecular DNA probes are also well suited to the study of chromosomes and genes, alterations of which are central to the development of neoplasia. Some tumors are associated with "signature" cytogenetic abnormalities, such as chromosomal translocations and deletions. However, abnormalities at the submicroscopic or molecular levels, such as gene rearrangements and single gene defects that may affect oncogenes and tumor suppressor genes, cannot be detected by routine karyotyping (conventional cytogenetics). The most common and practical approaches to detect deletions of chromosomal regions or specific tumor suppressor genes include loss of heterozygosity (LOH), fluorescence in situ hybridization (FISH), and quantitative polymerase chain reaction (PCR) techniques, for detection of oncogene amplification, FISH, Southern blot, and quantitative PCR are most practical. Thus far, no specific translocations of fusion transcripts are associated with primary CNS neoplasms, as in hematopoietic and soft tissue tumors. Comparative genomic hybridization (CGH), CGH microarray, spectral karyotyping/multiplex FISH, and oligonucleotide

or complementary DNA expression profiling techniques are **also** very useful techniques for surveying entire genomes for abnormalities, but these techniques are still primarily used for research, rather than diagnostic pathology.

Few molecular diagnostic tests have become routinely used or "standard of care" in neuro-oneology. The most notable is the use of chromosome lp and 19q testing as a prognostic/management tool for patients with oligodcn-droglial tumors; this is currently performed in only a few laboratories. Nevertheless, the clinical interest in this test is growing and it is expected to soon become commonplace. FISH has the advantage of simplicity, morphological preservation, minimal tissue and purity requirements, and lacks the requirement for microdissection or matching blood and nonneoplastic tissue. However, accurate interpretation requires experience, especially in cases with ancuploid populations of tumor cells. It also uses large probes (100-300 Kb) and is insensitive to very small deletions. LOH has the advantage of simplicity, and the probes arc smaller and capable of detecting losses even in the presence of mitotic recombination (loss of wild type allele and duplication of mutant allele), but it requires normal DNA for comparison and may yield false negative results if the tumor sample is not relatively pure. Other clinical applications of FISH include epidermal growth factor receptor (EGFR) amplification to distinguish small-cell glioblastoma from anaplastic oligodendroglioma, 22q deletion ro distinguish atypical teratoid/rhabdoid tumor (AT/RT) from variants of medulloblastoma, and meningioma-associated deletions *{NF2, DAL1,* lp, 14q) to distinguish anaplastic meningiomas from other malignancies or benign meningiomas from foci of meningothelial hyperplasia. Ir is likely that many more applications of molecular diagnostics will become incorporated into diagnostic neuropathology laboratories in the near future.

PRIMARY NEUROEPITHELIAL TUMORS

Primary neuroepithelial tumors are those nervous system neoplasms that arise from the primary cells of the nervous system (i.e., glia, neurons, or their precursors). From both a clinical and pathological standpoint, gliomas constitute the largest and most heterogeneous group of neuroepithelial tumors. The term *astrocytoma* has been applied broadly, but only four types have clinical importance: diffuse astrocyroma, pilocytic astrocytoma, pleomorphic xanthoastrocytoma (PXA), and subependymal giant cell astrocytoma (SEGA). Each has a distinctive topography, histology, and natural history. Diffuse astrocytoma (grade II), anaplastic astrocytoma (grade III), and glioblastoma (grade IV) form a continuum of malignancy for the diffuse astrocytoma, whereas the other forms are considered distinct entities. The term *diffuse glioma* is also used commonly in neuro-oncology to encompass the diffuse astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas (OAs) (grades I1-1V), all infiltrative gliomas with overlapping clinical, radiographic, and histological features.

Diffuse Astrocytoma (WHO Grade **II)**

Referred to loosely as well-differentiated, low-grade, diffuse, grade II, or simply "astrocytoma," this slow-growing tumor regularly undergoes malignant progression to anaplastic astrocytoma and GBM. Survivals of 5-10 years are expected, but a remarkably wide range exists among individual patients. The median age of onset is roughly 35 years, and young patients have a considerably better prognosis than older patients. Radiographically, these tumors are ill-defined, nonenhancing cerebral masses, often with a subcortical epicenter. A much smaller proportion of diffuse astrocytomas occur in the spinal cord, cerebellum, or brain stem. Brain stem gliomas deserve special mention, because these tumors typically present in childhood, expand the pons, and have a uniformly poor prognosis, regardless of the histological grade.

Diffuse astrocytomas are poorly circumscribed, and, although the CNS parenchyma may be expanded, the overall anatomy is minimally disrupted. Given its diffusely infiltrative nature and lack of solid mass formation, large portions of the tumor are not seen by gross inspection or on radiographs (i.e., microscopic disease). The infiltrative growth pattern makes therapy challenging, because microscopic foci of disease cannot be adequately treated with surgery, radiation, or chemotherapy. Widespread infiltration involving multiple lobes and even the brain stem *(gliomatosis cerebri)* is rare and has a poor prognosis regardless of histological grade.

Microscopically, there is a slight to moderate increase in cellulariry and the primary distinction from reactive astrocytosis rests on the finding of cytological atypia. Diffuse astrocytoma cells can take on several morphological types, including fibrillary, gemistocytic and protoplasmic. The fibrillary type is most common and consists of irregular, elongated, hyperchromatic nuclei, eirher appearing "naked" in an otherwise fibrillary background or displaying discernible cytoplasmic processes (see Figure 58B.4). The latter may be highlighted by imnumohistochemical stains for GFAP, but this is neither absolutely sensitive nor specific for the following reasons: (1) Some astrocytomas harbor minimal quantities of GFAP-positivc cytoplasm, (2) interpretation may be difficult as a result of staining of non-neoplastk astrocytic elements or high background in general, and (3) other gliomas display GFAP immunoreactivity. By definition, grade II astrocytomas lack mitotic activity, microvascular proliferation, and necrosis. Ancillary staining for M1B-1 (Ki-67) generally reveals a low proliferative index as well.

Chromosome 17p losses and mutations of *TPS3* are seen in roughly half of the cases. Those with *TI'53* gene

mutations usually display strong nuclear immunostaining for p53 protein, although the association is imperfect because die protein can be stabilized by other mechanisms and many immunopositive cases lack *TPS3* mutations (Louis et al. 1993). Those cases that evolve to glioblastoma (secondary glioblastoma) typically retain evidence of *'IPS 3* mutation and may even show additional *TP53* gene mutations or clonal expansion of the tumot cells with mutation (on the other hand, *de novo,* or primary glioblastomas, rarely display such mutations; see the following text}. Other common alterations include the over-expression of platelet-derived growth factot teccptor alpha in astrocytomas of all grades and losses of chromosome 22. Other than these two events, little is known about the earliest changes in these low-grade gliomas, their progenitor cells, or the .cause of transformation. The only known risk factors for the development of astrocytomas are prior therapeutic radiation to the brain and rare hereditary brain tumor syndromes such as Li-Fraumeni syndrome, Turcot's syndrome and NFl. By the time a patient comes to clinical attention with a diffuse astrocytoma, it is likely thai the tumor has been growing for years.

Anaplastic Astrocytoma (WHO Grade III)

The clinical ptesentation and radiographic features of anaplastic astrocytoma are similar to those of grade II astrocytoma, except the mean age of presentation is roughly a decade later and more cases show contrast enhancement. The average survival is 3 years after diagnosis, with great in ret- individual variability. Patient age is one of the most powetful prognostic variables and younger patients survive significantly longer than older ones.

Histologically, anaplastic astrocytomas ate more cellulat than grade II astrocytomas and display a greater degree of proliferation. They are primarily defined by the ptesence of mitotic figures. Some cases display endothelial prominence or hypertrophy, but lack the multilayered microvascular proliferation and necrosis of glioblastomas. The gemistocytic ("stuffed cell") astrocytoma is an astrocytoma variant that commonly ptcscnts at the anaplastic level. Characterized by strongly GFAP-positive cells with eccentric bellies of eosinophilic cytoplasm, this tumor type has a high incidence of progression to glioblastoma. Interestingly, it is primarily the small cell astrocytoma elements in the background that constitute the proliferating element, Another feature that may hklp to distinguish anaplastic astrocytomas from gtade II astrocytomas is the generally higher Ki-67 or MIB-1 proliferative index on immunostains (Giannini ct al. 1999a).

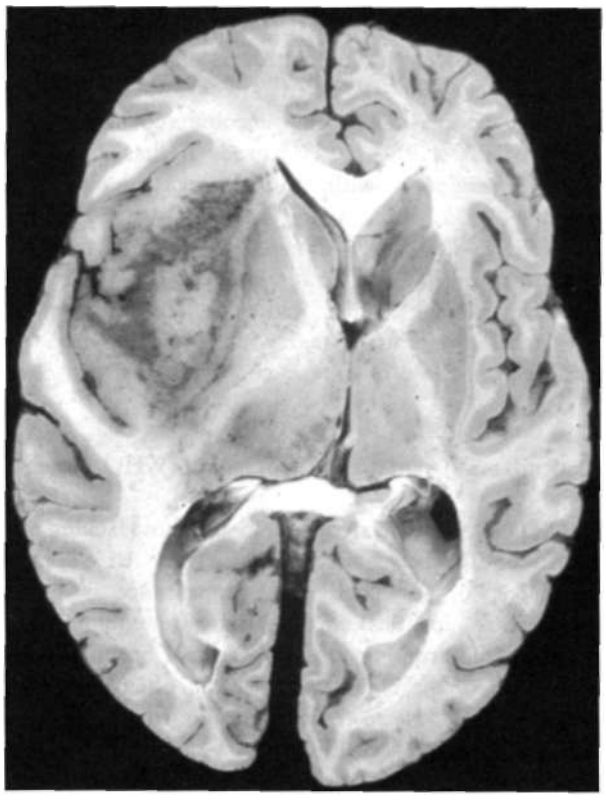
Anaplastic astrocytomas share the high frequency of *TPS3* mutations seen in grade II astrocytomas. Inactivation of the *Rb* cell cycle regulatory pathway is also common and may be ptimarily responsible tor the increased proliferation observed histologically. Homozygous deletion of the *CDKN2A/pl6* gene is the most common mechanism for disabling this pathway, although deletions of the *KB* gene and *CDK4* amplifications are alternate aberrations (Ueki et al. 1996). Amplifications of the *EGFR* gene and losses of phosphatidylinositol phosphate 3'-phosphatase *(PTEN)* on lOq occur less frequently in anaplastic astrocytomas than glioblastomas, and when present, may suggest eithet a worse prognosis or the possibility of undersampling or undergrading in a glioblastoma.

Glioblastoma (WHO Grade IV)

Glioblastoma (previously known as glioblastoma multiforme) is the most common primary brain tumor in adults, comprising approximately 50% of all gliomas. The peak age at onset is 50-60 years, roughly a decade later than anaplastic astrocytoma. Unfortunately, scvetal decades of basic and clinical research have had little impact on the prognosis of glioblastoma. The avctage sutvival remains approximately 1 year after treatment with radiation,

Glioblastoma most commonly occurs in the deep white matter, hasal ganglia, or thalamus and is rarely found in the cerebellum or spinal cord. As the designation *multiforme* implies, the gross and microscopic appearances are heterogeneous. The affected portion of the brain is usually replaced hy a single mass that grossly may appear well circumscribed, but microscopically infiltrates widely, often spreading to the opposite hemisphere via the corpus callosum ("butterfly lesion"). Multifocal tumors may occut and in most cases likely tepresent separate regions of malignant transformation within a widely disseminated lowet-grade astrocytoma, such as gliomatosis cetebti. In advanced stages, the tumor may extend into the meninges or the ventricle. Seeding of the neutaxis as multiple implants in the brain or ventricular surfaces is an atypical growth pattern and extracranial metastases ate extremely rare.

The cut surface has a variegated appearance (Figure 58B.5), characterized by central yellow or white zones of necrosis and hemorrhage surrounded by a hyperemic ring (endothelial hyperplasia) and "edematous" brain with varying mixtures of edema, gliosis, and tumor infiltrates. Microscopically, all the features of anaplastic astrocytoma plus endothelial hyperplasia and/or necrosis characterize GBM. Endothelial hyperplasia is defined as thickened or glomeruloid vessels with multilayering (see Figure 58B.3). It is a form of tumor-induced angiogenesis and a potential target for novel thetapies. The necrosis is often associated with a characteristic serpiginous distribution and associated nucleat pscudopalisading (sec Figure 58B.1). Several histological variants are recognized, including giant cell glioblastoma, small cell glioblastoma, and gliosarcoma. The latter is characterized by a sarcomatous clement, currently believed to arise from mesenchymal metaplasia within a glioblastoma. No significant clinical differences have been identified in these variants when



F1GURF, 58B.5 Glioblastoma (cut in axial imaging plane). This patient's right hemispheric glioblastoma demonstrates central necrosis, a deceptively demarcated hyperemic rim (endothelial hyperplasia), and an infiltrative component that extends well beyond the grossly discernible margins (note the expansion of the right thalamus with blurring of the grey-white junctions).

compared with conventional glioblastoma, although gliosarcomas arc more frequently noted in the temporal lobes.

Glioblastomas are among the genetically best characterized CNS tumors and often harbor numerous cytogenetic and molecular genetic aberrations (Maher et al. 2001). Mutations of *TP53* are less common than in diffuse astrocytomas or anaplastic astrocytomas and are primarily seen in "secondary glioblastomas" arising in younger patients after malignant transformation of a lower-grade precursor (Louis et al. 2001). In contrast, 30^40% of glioblastomas harbor EGER amplifications, often with an associated constitutively activating mutation. These are mainly encountered in the "primary" or "de novo" glioblastoma (Louis el al. 2001). The latter is defined by the lack of a precursor lesion, typically in an older patient with rapid clinical onset. Such gene amplifications are also particularly common (—70%) in the small-cell variant of glioblastoma. These tumors are composed of small round cells with minimal cytoplasm and a remarkably brisk mitotic index. They are sometimes misdiagnosed as anaplastic oligodendrogliomas because of their rounded, more uniform nuclei. However, they share the demographic features and dismal prognosis of glioblastomas and do not harbor the Ip and 19q deletions seen in oligodendrogliomas (see the following text). Alterations of the *pl6/CDK4/RB* pathway are nearly universal in glioblastoma and many cases harbor chromosome 10 losses (mostly primary glioblastomas). The PTENgeneon 10q23 is mutated in a subset of these and may have prognostic significance in certain patient populations. Additional tumor suppressor genes on both the long and short arms of chromosome 10 are suspected in the remaining group of PTEN-wild type tumors wirh demonstrable LOH. The list of additional glioblastoma-associated alterations is growing rapidly and a detailed discussion is beyond the scope of this text. Nevertheless, intensive research is currently focused on mechanisms of invasion, cellular migration, proliferation, angiogenesis, apoptosis dysregulation, and therapeutic resistance {Maher et al. 2001).

Circumscribed ("Favorable") Astrocytomas

Pilocytic astrocytoma, PXA, and SEGA are examples of circumscribed or "favorable" astrocytomas that grow slowly, with relatively discrete demarcation and a significantly better prognosis than the diffuse astrocytomas. These tumors are more common in children and young adults.

Pilocytic Astrocytoma (WHO Grade I)

Pilocytic astrocytomas are usually well circumscribed grossly and radiologically, although limited degrees of infiltration are nearly always found microscopically. They are most commonly found in the cerebellum, hypothalamus, third ventricle, optic nerve, spinal cord, and dorsal brainstem, but may also involve the cerebrum. Nonspecific clinical terms such as *cerebellar astrocytoma, optic nerve glioma,* and *tectal glioma* generally refer to pilocytic astrocytomas, but should be avoided because diffuse gliomas can also present in these sites. Likewise, the adjective *juvenile* often added to pilocytic astrocytoma is misleading, because most adult cases are histologically and clinically indistinguishable from those in children. Outcome depends on the surgical accessibility of the tumor, but is usually excellent (80% 20-year survival) and many are curable with surgery alone. The gross appearance varies somewhat with anatomic location. Cerebellar tumors, which arc often hemispheric, are typically composed of a large, fluid-filled cyst with an enhancing mural nodule. Hypothalamic and optic nerve tumors are usually solid. Optic nerve gliomas appear as a focal, segmental nerve swelling. Both unilateral and bilateral optic nerve gliomas are particularly common in NKl, a setting in which most are indolent and do not require surgical intervention.

The distinctive histological feature of pilocytic astrocytoma is a biphasic pattern with compact pilocytic areas interspersed with microcystic, spongy, or loose areas (Figure 58B.6). Dense portions contain piloid (hairlike) or bipolar astrocytes with long, spindle-shaped processes.

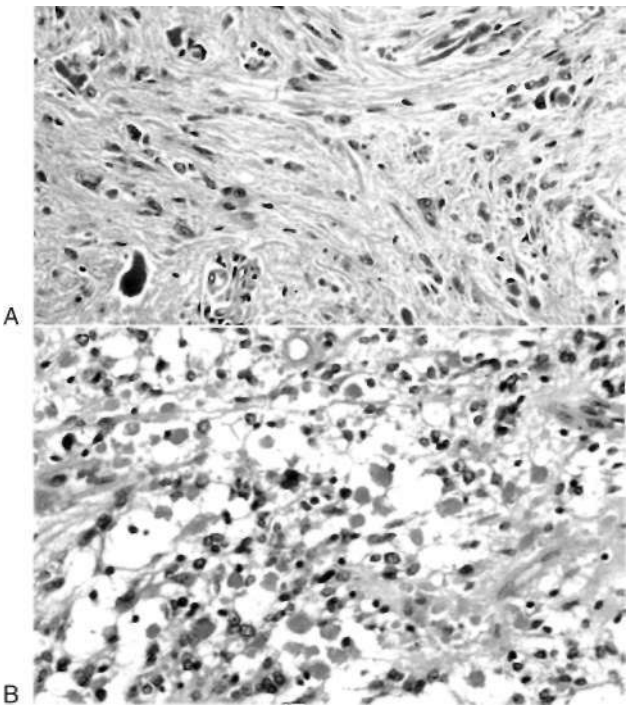


FIGURE 5 SB.6 Pilocytic astrocytoma. Classic examples are hiphasic wiih druse IAI ;nij lonw iO) regions. Helpful markers include bright red, corkscrew-shaped Rosenthal fibers (A) and mul berry-shaped eosinophilic granular bodies (B) (hematoxylin-cosin stain; x200).

Rosenthal fibers (RFs) are common. These arc masses of intracellular astrocytic filaments that are fusiform or corkscrew-shaped, with a hyaline appearance {Figure 58B.6A). Mu I berry-shaped eosinophilic granular bodies (EGBs) are also found in most cases (Figure 58B.6B). Although not entirely specific, both RFs and EGBs are generally signs of an indolent process and represent important diagnostic clues that distinguish pilocytic from diffuse astrocytomas. Evidence for *NF1* gene inactivation has been found in Nil-associated pilocytic astrocytomas, hut not in sporadic tumors. Little else is known about the molecular pathology of this tumor type.

Pleomorphic Xanthoastrocytoma (WHO Grades II or III)

PXA is a rare and distinctive form of "favorable" astrocytoma, often misdiagnosed in the past as GBM. The average age at diagnosis is 26 years, and history of seizures often precedes diagnosis (Giannini et al. 19991}). PXA usually involves the cerebral cortex and overlying meninges, and the preferred site is the temporal lobe. The histological features are hypercellulanty with many atypical and pleomorphic tumor astrocytes. Bizarre giant cells are present, but mitoses are unusual. Probably the most helpful finding is that of EGBs, because these arc generally not seen in glioblastomas. Despite its name, xanthomatous cells (lipidized astrocytes) with foamy, lipid-filled cytoplasm are only encountered in roughly a quarter of cases. PXA (WHO grade II) has a relatively favorable prognosis with postoperative survival times averaging 81% at 5 years and 70% at 10 years. However, 15-20% are estimated to undergo malignant transformation (WHO grade III) and/or follow an aggressive clinical course. Little is known about the tumorigenic events associated with PXA, hut they seem to differ from those of diffuse astrocytomas.

Subependymal Giant Cell Astrocytoma (WHO Grade I)

Most SEGAs arc associated with TS and those lacking other features of TS may have a form fruste. An elongated, sausagelikc, or lobulated gross appearance is typical. Histologically, identical smaller masses resembling candle gutterings (the drippings of tallow from a burning candle) on the wall of the lateral ventricle are often seen in TS-associated cases. Hydrocephalus results from obstruction of the foramen of Monro.

The rich vascularity of the tumor gives the cut surfaces a red and beefy appearance. Calcification is an almost constant feature and is so extensive at times that the mass becomes hard as a stone. The tumors are moderately cellular, consisting of closely packed astrocytes with abundant cytoplasm. Tumor cells are often arranged in sweeping fascicles or around blood vessels, analogous to the pseudorosettes in ependymomas, and may have a gemistocyte-like or spindled morphology.

Some tumor cells are clearly of astrocytic origin and the cytoplasm is filled with GFAP. Other tumor cells resemble neurons having prominent nucleoli and many have intermediate features with astrocytoma-like cytoplasm and neuronal-like nuclei. Neuronal differentiation is further suggested by positive immunohistochemical staining for 68-kD neurofilament protein. Tumor cells may stain with both neuronal and glial markers or with neither, explaining the preference of some neuropathologists for the term subependymal giant cell *tumor* rather than SEGA. Because TS is characterized by hamartomas of many organs, SF.GAs may also be hamartomas rather than neoplasms. This is consistent with their benign behavior.

Oligodendroglioma (WHO Grades II or III)

As opposed to astrocytomas, most of which are high-grade at the time of diagnosis, oligodendrogliomas usually present at the grade II stage. They typically present in young to middle-aged adults and are distinctly uncommon in children. The majority are hemispheric masses, mainly in the frontal lobe, and location in the brain stem, cerebellum,

and spinal cord is unusual. The prognosis for grade II oligodendrogliomas is significantly better than for grade II astrocytomas, with average survival times of 10 years or more after diagnosis and inter-individual improved chemosensitivity profiles. As with astrocytoma[1];, individual variability exists in time to progression and overall survival.

The most classic and uniformly accepted oligodendroglial features include uniformly round nuclei, bland chromatin, clear perinuclear haloes imparting a "fried egg" appearance, and a rich, branching capillary network reminiscent of chicken wire (Figure 58B.7). Less specific findings include cortical involvement, microcalcifications, mucin-nch microcystic spaces, and perineuronal satellitosis. Although helpful in diagnosis, the "fried egg" appearance is a formalin fixation artifact that is neither necessary for diagnosis nor encountered in frozen sections or rapidly fixed specimens. The morphological spectrum includes two strongly GFAP-positive cells: mini- or microgemistocytes and gliofibrillary oligodendrocytes. The former are gemistocytc-like cells with small bellies of eosinophilic cytoplasm, round, bland nuclei resembling those of classic oligodendroglioma nuclei, and no cytoplasmic processes. The latter arc histologically identical to classic oligodendroglioma cells, but exhibit a thin perinuclear rim of GFAP immunoreactivity. These two cell types (1) ate commonly encountered in otherwise classic-appearing oligodendrogliomas, (2) are reminiscent of normal GFAP-positive oligodendroglial precursor cells, and (3) do not impact negatively on prognosis (although the presence of numerous microgemistocytes should prompt a cateful search for anaplastic features), Anaplastic- oligodendroglioma (grade III) is defined by hypercellularity, numerous mitoses, and microvascular proliferation. Some oligodendrogliomas have regions that are histologically similar to diffuse astrocytoma, which can cause diagnostic difficulties because no specific oligodendroglioma markers arc available.

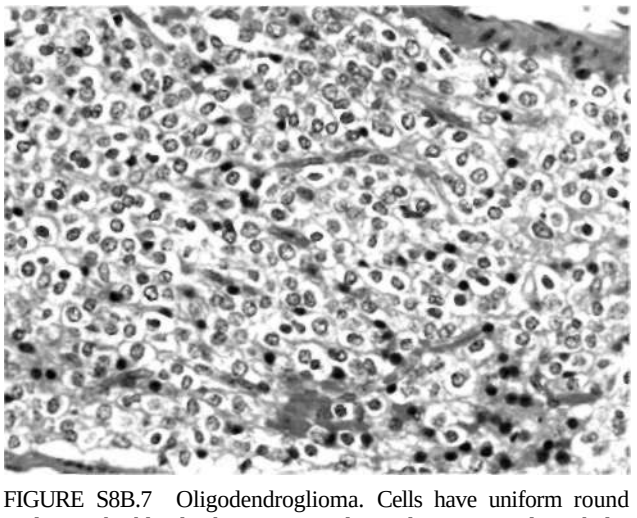


FIGURE S8B.7 Oligodendroglioma. Cells have uniform round nuclei with bland chromatin and a clear perinuclear halo, producing a fried-egg appearance. The rich, branching capillary network has been likened to chicken wire (hematoxylin-eosin stain; x200).

The genetic characterization of oligodendrogliomas has provided some of our most important clues in the diagnosis and treatment of diffuse gliomas. A characteristic loss of chromosomal arms Ip and 19q is found in 50-80% of cases. More importantly, this genetic signature is associated with both prolonged survival and a favorable response to procarbazine, chloroerhyleyelohcxylnitrosourea, vincristine chemotherapy and/or radiation therapy (Gairncross etal. 1998). Based on these findings, ancillary testing for Ip and 19q status is often requested by both clinicians and patients, with some centers now performing genetic testing routinely. The most commonly used techniques include FISH and LOH, each with advantages and disadvantages (Perry et al. 2003). Additional progression-associated alterations, such as those commonly seen in astrocytomas, are occasionally reported in anaplastic oligodendrogliomas as well.

Oligoastrocytoma (WHO Grades II or III)

As a group, patients with OA have survival rates intermediate between those of pure astrocytomas and oligodendrogliomas. Of all the gliomas, OAs remain the most difficult to define and most likely to receive discordant diagnoses from expert neuropathologists. Nevertheless, the WHO recognizes two basic patterns: (1) a biphasic ("compact") variant in which the two elements arc spatially distinct, and (2) an intermingled ("diffuse") variant in which the cell types are interspersed (Kleihues and Gavencc 20001. Although the biphasic form is easier to accept and conceptualize, the intermingled variant is more common. Cases are most often characterized by the presence of some rounded nuclei (? oligodendroglial), some irregular hyperchromatic nuclei (? astrocytic), and many difficult to characterize cells with intermediate or indeterminate features (i.e., morphologically ambiguous). The diagnosis of "diffuse glioma, not otherwise specified" is appropriate in some of these cases. Nonetheless, these tumors are usually graded and treated in the same fashion as pure oligodendrogliomas.

Generally, OAs and morphologically ambiguous diffuse gliomas have been understudied genetically, precisely because the typical study design is to exclude the cases with diagnostic uncertainty. A few have focused on the biphasic variant, in which microdissection is feasible (Maintz et al, 1997). In these, the same mutations have characteristically been found in both components, consistent with a monoclonal process, rather than a collision tumor (i.e., coexistence of two neoplastic clones). Therefore most biphasic OAs have genetically resembled either pure oligodendroglioma or astrocytoma, with only rare cases showing mixed patterns.

Ependymoma (WHO Grade II or III)

Ependymomas compose 4% of all brain tumors and arc die third most common CNS tumor in children. They may occur at any age, bur in children they are most frequent in the first decade. Patients younger than 3 years of age have a significantly worse prognosis. Ninety percent of tumors are in the brain, with an infratentorial site twice as common as a supratentorial site, and 10% are in the spinal cord, often in adults. The typical infratentorial ependymoma occupies the fourth ventricle. Obstructive hydrocephalus develops when rumors are large enough to obstruct the flow of cerebrospinal fluid (CSF). Some are periventricular or may not have any obvious association with native ependyma (e.g., spinal cord or cerebral hemispheres).

Ependymomas are remarkably well-circumscribed masses that tend to compress rather than infiltrate the adjacent parenchyma. As such, some tumors may be surgically curable and the extent of resection constitutes a much more important prognostic variable in ependymomas than in diffuse gliomas. Cystic tumors are more likely to be found in the cerebrum. Ependymomas in contact with CSF pathways may seed subarachnoid spaces and generate drop metastases in approximately 5% of cases. This is associated with a poor prognosis. Ependymomas are characterized by sheers of cells interrupted by perivascular rosettes, and by nuclear free /.ones surrounding a central blood vessel (sec Figure 58B.2). True ependyma! rosettes (i.e., containing a central lumen) and canals (i.e., slitlike structures resembling small ventricles) are more specific, but encountered in only approximately 10% of cases. Ependymoma is one of the few remaining tumors in which the diagnosis in morphologically ambiguous cases can only be verified by ultrastructural examination. Electron microscopy shows a combined glial and epithelial-like appearance with intermediate filaments (GEAP), microvilli, zipperlike intercellular junctions, intracellular lumina, cilia, and their basal attachments, known as basal bodies or blepharoplasts. Immunohistochemistry for CFAP may be particularly helpful in highlighting the thin processes radiating toward vessels in pseudorosetr.es. Anaplastic ependymoma (grade III) is diagnosed in the presence of hypercclularity, increased mitotic activity, and microvascular proliferation. Regions of infarctlike necrosis are fairly common in tumors that otherwise appear to be low-grade, and this is not a reliable grading criterion. In fact, the predictive value of histological grading of ependymomas is questionable, because its prognostic significance has not been consistent in reported series,

Ependymomas arc often aneuploid with complex, albeit nonspecific alterations. Chromosome 22q deletions are among the most common, with associated *NF2* mutations primarily restricted to spmal examples, a fact that fits with the spinal localization of most ependymomas in NF2 patients (Singh et al. 2002).

Myxopapillary Ependymoma (WHO Grade I)

Myxopapillary ependymoma is a distinct variant that is virtually restricted to the filum terminale. These tumors may also occur in the presacral soft tissue. They are more common in adults than in children, and have a red appearance because of their lush vascularity. They have a variably papillary architecture with numerous hyalinized vessels, surrounded by mucin and an outside layer of tumor cells. A thin collagenous capsule typically surrounds the tumor. The prognosis is excellent, particularly when the capsule has not been breached intraoperativeiy. Those removed piecemeal with mucin spillage have a higher likelihood of recurrence. These tumors may metastasize to the lungs or other sites, despite their benign appearance.

Subcpendymoma (WHO Grade I)

Subcpcndymomas are slow-growing tumors that are increasingly detected by MRI in the absence of clinical manifestations. Among subependymomas, 90% occur in adults, in whom they are small and incidental. In children, subependymomas are more likely to be large and symptomatic. Subependymomas appear as glistening, pearly whirr, tabulated, intraventricular protuberances, most often in the fourth ventricle. Earge tumors may obstruct the ventricle and cause hydrocephalus. Microscopically, they are characterized by clusters of bland, rounded nuclei, embedded in a fibrillary matrix with microcysts and foci of calcification. The proliferative index is typically low. Rare cases contain foci of classic ependymoma and are referred to as mixed ependymoma/subependymoma. These cases are graded and treated according to the potentially more aggressive ependymoma component. The histogenesis of subependymomas remains controversial, with candidates including subependymal glia, astrocytes, ependymal cells, or some mixrure of these. Genetic changes are largely unknown.

Choroid Plexus Tumors

Choroid Plexus Papilloma (WHO Grade I)

Choroid plexus papillomas compose only 0.5% of intracranial tumors. As a rule, they are confined to the portion of the ventricular system that contains normal choroid plexus. Approximately half arc in the fourth ventricle; in adults, they often occupy the cerebellopontine angle. Tumors in the lateral ventricle arc more common in children and may cause hydrocephalus by a combination of outflow obstruction and excess CSF production. The onset of symptoms is usually in the first decade and may be congenital, hi most cases, papillomas arc surgically curable tumors.

Choroid plexus papillomas have a pink or red, highly vascular polypoid or cauliflower appearance, often with chalky calcifications (Figure 58B.8). Large tumors in the third or fourth ventricles may occlude or even distend the ventricle, causing hydrocephalus. Histologically, choroid plexus papillomas resemble normal choroid plexus in terms of a well-formed papillary structure, with true fibrovascular cores and in most cases, a single-layered epithelial covering. However, the lining of papillomas lacks the cobblestone-like appearance of normal choroid plexus, and tends to form instead a uniform layer of tall cuboidal to columnat cells without intervening spaces. Calcifications and clear intracytoplasmic vacuoles are common. The mitotic index is low.

Immunohistochemically, they are consistently positive for cytokcratin, sometimes revealing a paranuclear ball-like pattern of staining, Immunoreactivity for transthyretin/prealbumin is also typical. A subset expresses GFAP focally and this is thought to reflect cpendymal differentiation.

Choroid Plexus Carcinoma (WHO Grade III)

The diagnosis of choroid plexus carcinoma in adults is exceedingly rare and should be made only after exclusion of metastatic adenocarcinoma, most often from the lung. Carcinoma of the choroid plexus tends to arise in the lateral ventricle of infants and then invade the adjacent brain parenchyma and seed throughout the subarachnoid space. Systemic metastases occur occasionally. The clinical course is generally quite aggressive and mortality rates are high.

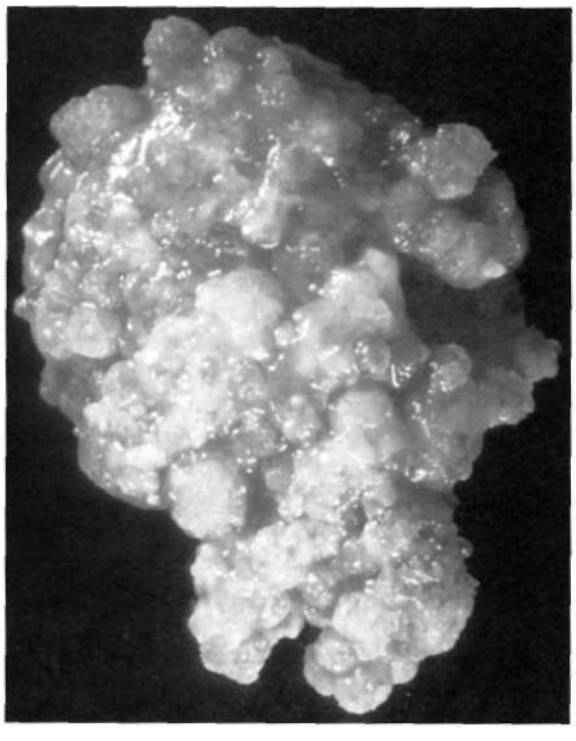


FIGURE 58R.8 Choroid plexus papilloma. Polypoid or cauliflower-like lesion with a nodular and partially calcified surface taken from the fourth ventricle.

Histologically, choroid plexus carcinoma resembles high-grade papillary adenocarcinoma, but docs not sectete mucin, an important distinction from the majority of metastatic adenocarcinomas. Some cases have a small-cell appearance reminiscent of PNET or rhabdoid cells similar to AT/RT (see the following text). Little is known about the genetics of these high-grade malignancies, although the possible involvement of the *INI-l/hSNF5* gene on 22qll.2 has recently been raised; if shown in other studies, this could suggest genetic similarities to AT/RT.

Neuronal/Glioneuronal Tumors

GangUoglioma/Gangliocytoma (WHO Grades 1, II, or III)

Most gangliogliomas occur before age 21 and compose 4-8% of pediatric brain tumors. They grow slowly and tend to be benign in their biological behavior. The temporal lobe is the most common site of occurrence, but other lobes of the cerebral hemispheres, the cerebellum, and the spinal cord are sometimes affected. Seizures are a typical clinical feature. The tumots are often cystic, well circumscribed, and extend to the surface of the brain. The solid portions are firm, gray, and gritty as a result of calcific deposits that are evident on CT.

Portions of the tumor resemble a low-grade astrocytoma, either pilocytic or fibrillary in nature. Unlike native entrapped neurons within an infiltrative glioma, some of the tumor ganglion cells have a dysmorphic appearance, as evidenced by their lack of polarity, clustering, cytoplasmic vacuolation, increased nuclear pleomorphism, or multinucleation (Figure 58B.9). Binucleate or multinucleate neurons are particularly helpful, when present. Otherwise, the most useful features in the distinction from diffuse gliomas include relative circumscription and EGBs. Perivascular lymphocytic cuffing, microcystic spaces, and fibrosis with collagen deposition are other common findings and RFs are found in many cases, particularly at the edges of the lesion. Those without an obvious astrocytic component are sometimes referred to as *gangliocytoma*, although it is not yet clear that this distinction has any clinical relevance. The term *ganglion cell tumor* is less committal and incorporates both entities. Rare cases demonstrate signs of anaplasia (grade II or III), most often in the glial component, but the grading criteria and their predictive value have yet to be firmly established. GFAP activity is abundant in the astrocytic component, whereas the ganglion cell component expresses most markers of mature neurons, such as synaptophysin, chromogranin, neurofilament, and Neu-N. Tumor genetics remain largely unknown.

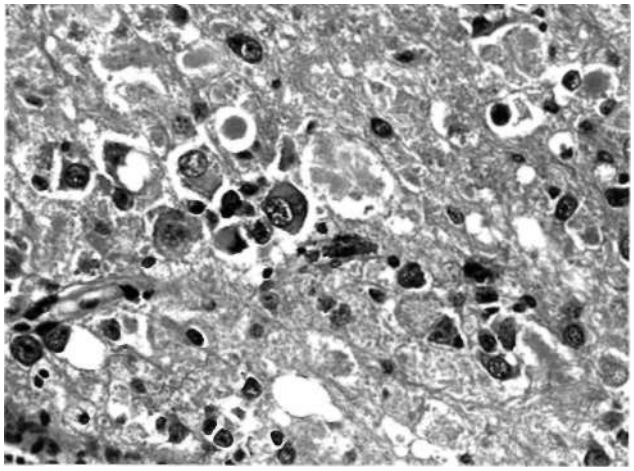


FIGURE S8B.9 Ganglioglioma. Haphazardly arranged and clustered dysmorphic ganglion cells, including the binucleate Form seen centrally (hematoxylin-eosin stain; x400).

Dysembryoplastic Neuroepithelial Tumor (WHO Grade I)

Dysembryoplastic neuroepithelial tumor (DNT) is a benign, quasihamartomatous tumor with an excellent prognosis. DNTs occur throughout childhood and early adulthood, with a mean age of onset of 9 years. They are usually supratentorial and intracortical in location and arc often associated with a long history of intractable seizures. The temporal lobe is the most common location for DNTs, although histologically similar tumors have been described in rarer sites, such as the basal ganglia, thalamus, lateral ventricle, septum pellucidum, and brain stem. They are we 11-demarcated, multinodular intracortical growths that may be associated with adjacent cortical dysplasia.

Histologically, there is a wide range of appearances, although the most characteristic features include patterned (i.e., with ribbons or arcades) mucin-rich cortical nodules and "floating neurons," the latter consisting of ganglion cells that appear to float within a lacunelike, mucin-filled space. The cytology of tumor cells varies, although most resemble oligodendroglioma cells. In fact, on a small biopsy, it may he virtually impossible to distinguish these two entities, but the presence of diffuse cortical and subcortical invasion on larger samples argues against a diagnosis of DNT. Little is known regarding the genetic basis of this tumor, although recent studies suggest that they do not carry the lp and 19q deletions, typical of oligodendroglioma {Perry et al. 2003).

Central Neurocytoma (WHO Grade II)

Central neurocytomas are slow-growing tumors, located in the lateral or third ventricle near the foramen of Monro, frequently involving the septum pellucidum (Schild et al. 1997). Age at onset is usually in the second or third decade. They are usually sharply demarcated, sometimes lobulated masses that fill the ventricular space without significant infiltration of the surrounding brain.

The main histological feature is a proliferation of uniformly rounded tumor cells that mimic oligodendroglioma. Unlike oligodendrogliomas, however, they often display "neurocytic rosettes," exaggerated or irregular Homer Wright-like rosettes with central axon-rich neuropil. These rosettes are indistinguishable from the pinocytic rosettes encountered in pineocytoma, another tumor of small, mature neurons with cytological features similat to those of central neurocytomas. Ultrastructurally, their cytoplasm contains microtubules, synapses, and neurosecretory granules, belying their neuronal nature. Further, central neurocytomas are generally immunoreactive for the neuronal markers synaptophysin and Neu-N. Central neurocytomas with elevated proliferative indices (e.g., >2%) and vascular hyperplasia tend to have a higher rate of recurrence and are sometimes referred to as *atypical neurocytomas,* although grading criteria have not been firmly established. Rare examples of extravcntricular neurocytomas and liponeurocytomas {with fat metaplasia) have been described in the cerebral hemispheres, cerebellum, and spinal cord, but it has yet to be determined whether these represent the same family of tumors. The WHO, however, has recognized the cerebellar liponeurocytoma as a distinct entity. The genetic alterations of neurocytoma are largely unknown, although, as expected, central neurocytomas do not harbor the lp and 19q deletions seen in oligodendrogliomas (Perry et al. 2003).

Embryonal Tumors/Primitive Neuroectodermal Tumors

The precise definition of PNET has long been debated among the philosophic lumpers and splitters of medicine, but basically refers to an extra cerebellar "small, blue, cell tumor" which othctwise resembles medulloblastoma and in most cases shows evidence for primarily neuronal differentiation, albeit immature. Glial, mesenchymal, and melanotic elements may be seen as well. Sometimes referred to as *cerebellar PNET,* the medulloblastoma therefore represents the prototype and most common member of the PNET family. Adding further confusion to the nomenclature is the existence of a peripheral nervous system PNET, which is felt to represent a completely different small, blue, cell tumor type with homologous genotypic and phenotypic features to those of Ewing's sarcoma (t[l I;22][q24;q12| with *EWS-FLI1* or variant fusion products). Other than medulloblastomas, the CNS variants are relatively uncommon and may include supratentorial PNET (sPNET), pineoblastoma, central neuroblastoma, ependymoblastoma, and medulloepithelioma. Despite the morphologic and immunohistochemical overlap among these entities, and the convenience of using an umbrella term of PNET fot all of them, this is likely over simplistic, lr is now known,

for example, that sPNETs have a significantly worse prognosis than medul lob la stomas and seem to differ genetically (Reddy et al. 2000). Therefore the overall heading of *embryonal CNS neoplasms* may be preferable to discuss this group of tumors, **and** this term allows the inclusion of an important and newly recognized member, the AT/RT. In a somewhat looser context, this includes PNETs of specialized sensory organs, such as retinoblastoma and olfactory neuroblastoma.

Tumors resembling PNET can be induced in animals with various viruses or genetic manipulations, such as transgenic or knockout mice. In humans, the importance of genetic factors is exemplified by retinoblastoma, from which Knudsen's two-hit hypothesis was formulated and the tumor suppressor gene *Rb* was identified on chromosome 13. Much has been learned recently about the genetic alterations of medulloblastomas and its variants (see the following text). For the rarer forms of PNET, the molecular pathogenesis is still a mystery.

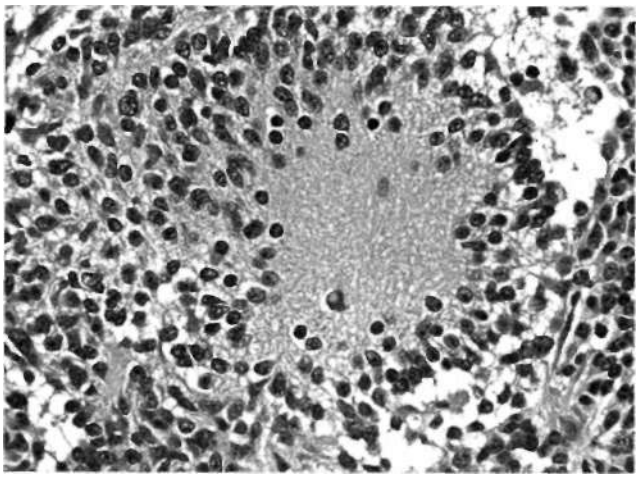


FIGURE 58B.10 Medulloblastoma. Cellular tumor composed of small, poorly differentiated cells with Homer Wright (ncuroblastic) rosette formation (hematoxylin-eosin stain; x400).

Medulloblastoma **(WHO** Grade IV)

The name *medulloblastoma* is misleading because it is doubtful that any cell identifiable as a mcdulloblasi exists during histogenesis. Instead, research suggests that medulloblastomas arise from the external granular layer (e.g., desmoplastic variant), subependymal matrix cells of the fourth ventricle (e.g., classic variant), or both. Much progress has been made in the multimodality treatment of medulloblastomas, with 5-year survival rates often quoted to be as high as 70-80%. Unfortunately, life-saving therapy, such as craniospinal irradiation, may be associated with significant long-term toxicities to the developing brain, with cognitive decline, psychomotor and growth retardation, or hormonal deficits.

Medullohlastoma is thi- most common torm of I'NKT. More than 50% of medulloblastomas occur in children younger than 10 years of age. A second, smaller frequency peak occurs between the ages of 18 and 25. Medulloblastoma, by definition, originates in the cerebellum. It is generally well defined, soft, friable, and focally necrotic. Medulloblastomas have a proclivity to invade the ventricle and disseminate along CSF pathways. The potential aggressiveness of medulloblastomas is affirmed by rare reports of metastases to bone, lymph nodes, and other extracranial sites.

Classic medulloblastomas consist of small, immature cells with hyperchromatic round- to carrot-shaped nuclei with minimal cytoplasm, as well as numerous mitoses and apoptotic bodies. They typically display limited degrees of neuronal maturation with neuropil formation, synaptophysin immunoreactivity, and occasional Homer Wright (ncuroblastic) rosettes (Figure 58B.10). Cases with extensive rosette formation or neuronal maturation are sometimes referred to as cerebellar neuroblastomas or ganglioneuroblastomas, respectively. Recently recognized variants with clinical significance include the anaplastic/large cell variant (poor prognosis) and the extensively nodular variant (favorable prognosis) (Eberhart et al. 2002). There is also some evidence that the nodular or desmoplastic variant is encountered most frequently in adults, in the lateral cerebellar hemispheres, and in patients with Gorlin's nevoid basal cell carcinoma syndrome (NBCCS). There is decreased proliferation and a greater degree of neuronal maturation within the center of these nodules or pale islands. Glial differentiation is also fairly common and it is unclear whether cases with prominent glial features have a worse prognosis. Rarer forms of differentiation are encountered most often in infants and include mesenchymal (e.g., medullomyoblastoma) and melanin-producing neuroectodermal forms (e.g., melanotic medulloblastoma).

Much has been learned in recent years regarding medulloblastoma tumor biology, and the reader is referred to a recent review for greater detail (Ellison 2002). Familial forms of medulloblastoma have provided some of the important clues for both inherited and sporadic forms of the disease. These include the hedgehog/patched signaling pathway implicated from studies of NBCCS and the *APCJ Wttt* pathway associated with a form of Turcot's syndrome (polyposis coli and brain tumors). Unfortunately, medulloblastoma appears to be a fairly heterogeneous disease genetically, with no single alteration accounting for the majority of the cases. Cytogenetically, a characteristic isochromosome 17q has been reported in one third to one half of cases. The *Tl'S.i* gene has essentially been excluded as a potential 17p-associated tumor suppressor and other regions of the short arm are currently being investigated. Both A1YCC and MYCN gene amplifications have been associated with particulatly aggressive medulloblastomas and are more commonly encountered in the anaplastic/large cell variant. On the other hand, expression

of the neurotrophin receptor, TrkC, is associated with a significantly better prognosis. Interestingly, genomic screening with expression profile mictoarrays that characterize thousands of genes simultaneously may be a useful method for predicting biologic behavior (Pomeroy et al. 2002). Tberefotc the routine diagnostic workup of medulloblastoma may soon involve a number of histopathologic and genetic techniques for furthet sttatification and individualized therapy.

Atypical Teratoid/Rhabdoid Tumor (WHO Grade IV)

AT/RT is a relatively recently recognized form of embryonal CNS neoplasm that has been often misdiagnosed as medulloblastoma or PNET, because of the prominence of small, blue cells in many cases (Packer et al. 2002), Irs awkward name derives from the fact that it may resemble either epithelial tumors ("tetatoid") or the malignant thabdoid tumor (MRT) seen in the kidney, soft tissue, and other organ sites throughout the body. Mostly restricted to infants, AT/RT is one of the most aggressive human tumors. Average survival times are in the range of 6-8 months following diagnosis, and they typically do not tespond to conventional medulloblastoma-associated therapies. Because of these dramatic biologic differences, it is critical to distinguish AT/RT from medulloblastoma, and it is probable that part of the poor prognosis reported in patients with medulloblastoma who are younger than 3 years of age stems from prior inclusion of misdiagnosed AT/RTs.

Although small, blue cells are common and may predominate in some cases, the defining feature is the rhabdoid cell, an enlarged cell with an eccentric oval- to kidney-shaped nucleus with vesicular (open or clear) chromatin, as well as an eosinophilic rounded, paranuclear inclusion, often highlighted by imniLinostains for vimentin. Carcinoma-like and sarcoma-like foci are also evident in some cases. Ultrastructurally, the paranuclear inclusions consist of whorled bundles of intermediate filaments. AT/RT teprcsents a classic example of "polyphenotypic tumot," defined by the coexpression of antigens normally associated with differing liistogenetie line (e.g., epithelial, mesenchymal, neuronal, glial, and so on). The list of potentially positive immunostains is long, but as opposed to PNET, the vast majority of AT/RTs express EMA, smooth muscle antigen, and vimentin. Despite the name *teratoid,* these tumors are not related to germ cell tumors and generally do not express germ cell markers.

Genetically, AT/RTs are known to harbor monosomy 22 or 22q deletions in the majority of cases. Recently, the *iNl-l/bSNFS* tumor suppressor gene on 22qll.2 was identified and the inactivation of this gene is thought to be involved in the formation of these tumors and malignant rhabdoid tumors (MRTs). Germline mutations have also been reported in familial or disseminated forms of this disease.

MEN1NGEAL/EXTRA-AXIA1, TUMORS

The most common extra-axial brain and spinal tumors ate meningiomas, although hemangiopericytomas, sarcomas, lymphomas, metastatic tumors, schwannomas, and inflammatory masses also occut adjacent to the brain and spinal cord.

Meningioma (WHO Grade I)

Meningiomas compose 20-25% of all intracranial tumors. They are most ptcvalent after age 50 and constitute less than 2% of CNS tumors in children. The female-to-male ratio is 2 to 1 in adults, nearly 10 to 1 in the spinal cord and 1 to 1 in pediatric or malignant forms. Although most (roughly 80%) are benign, a subset are aggressive with high-grade histology, recurrences, and substantial morbidity and mortality. Even some of the histologically benign meningiomas ate associated with disfigurement, neurological deficits, and ma jot therapeutic challenges, particularly when located in sites at the skull base that prevent complete resection. Because growth is typically slow, tecurrences many years after primary resection are not uncommon, and long follow-up times are required to determine whether a surgical cure has been achieved. Generally, the extent of surgical resection and histological grade represent the most important prognostic variables. For example, the 5-year recurrence rates are roughly 5% for gross totally resected versus 30% for subtotally resected benign meningiomas. In contrast, this figure rises to 40% in atypical meningiomas, even when they are believed to be totally resected (see the following text).

The locations of meningiomas, in descending order of frequency, are the cerebral convexity, parasagittal tegion, sphenoid wing, parasellar region, and spinal canal. Postetior fossa and lateral ventricle locations arc mote common in children. Multiple meningiomas suggest the possibility of NF2, although non-NF2 associated forms are also encountered. Interestingly, a number of such cases show identical mutations in each of the meningiomas atising from a single patient, suggesting that dura! dissemination may account for multifocality in some patients, despite a histologically benign appearance.

Benign meningiomas are well demarcated and compress father than invade the adjacent brain or spinal cord. Nevertheless, bone and soft tissue invasion may occur and is typically associated with hyperostosis. Notably, this type of invasion does not constitute evidence for malignancy and those that are gross totally resected share the same excellent prognosis as those without invasion. A pattern of diffuse, carpetlike tumor spread along the dural surface is referred to as *meningioma en-plaque.* Meningiomas are generally firm in consistency and often gritty because of the presence of sandlike calcifications, referred to as psammoma bodies.

Meningiomas are hisrologically heterogeneous; the most recent WHO classification includes 13 morphological types {Kleihues and Cavenee 2000). Four rare variants are considered more aggressive by definition: clear cell (grade 11), chordoid (grade II), papillary (grade III), and rhabdoid (grade III). The other nine subtypes arc considered benign, unless they fulfill additional criteria for atypical (grade II) or anaplastic (grade **IIII)** meningioma. The majority of meningiomas have two basic histological patterns: meningothelial or fibroblastic, with the transitional variant having features of both. Meningothelial tumors are composed of arachnoidal epithelioid cells, arranged in lobules, often with prominent whorls and psammoma bodies (Figure J8B.11), which represent laminated calcifications "I degenerated meningothelial whorls. Fibroblastic meningiomas are distinguished by theit spindled appearance, fascicular or storiform architecture, and abundant collagen deposition. The most helpful immunohistochemical marker is EMA, which can be detected at least focally in the vast majority of meningiomas.

Meningioma was one of the first solid tumors to be characterized by a cytogenetic alteration. More than half are associated with losses of chromosome 22, or portions thereof. The tumor suppressor gene primarily involved in most of these cases is *NF2,* a finding that correlates well with the fact that meningiomas are the second most common tumor type in NF2 patients. A second gene with a high degree of homology, *DAIJ* or protein 4.IB on 18pll.3, has recently been implicated as well (Gutmann et al. 2000), Losses of both *NF2* and ptotcin 4.IB are common in meningiomas of all grades, suggesting they are early events. Progesterone receptors (PRs) arc present in more than 50% of cases. Their significance is unclear, other than the fact that meningiomas can enlarge dramatically with pregnancy and regress after delivery.

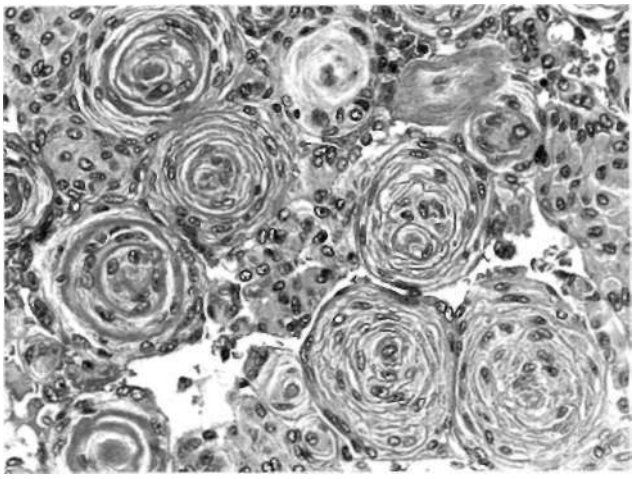


FIGURE 58B.11 Meningioma. Typical meningothelial nests and whorls with focal hyalinization, the first step in the formation of concentrically laminated calcifications or psammoma bodies (hematoxylin-eosin stain; x400).

Atypical Meningioma {WHO Grade **II)**

The intermediate grade category of atypical meningioma was created to define a meningioma type that has considerably increased risk of recurrence, even when gross rotal resection is achieved. These tumors are also associated with a slight, but statistically significant increase in mortality, when compared with age and sex matched controls. Using current criteria, atypical meningiomas account for 15-20% of all meningiomas.

In most pathology series, the mitotic or proliferative index is the most powerful predictor of outcome. Based on a large Mayo Clinic series, the finding of at least 4 mitoses per 10 HPFs, even focally, qualifies for the diagnosis of atypical meningioma (Perry et a!. 1999). With fewer mitoses, the presence of at least 3 of 5 additional parameters (sheeting architecture, hypercellularity, macronucleoli, small-cell formation, necrosis) also suffices. The issue of brain invasion has also been debated, and, although once considered the ultimate manifestation of malignancy, recent studies suggest that in the absence of frank anaplasia, these tumors have similar recurrence and mortality rates as those of atypical meningioma. Similar to mitotic counts, **MIB-1** (Ki-67) labeling indices may be helpful for predicting the risk of recurrence, particularly in borderline atypical cases. Meningioma grade is also inversely proportional to PR expression, so that in general, fewer atypical meningiomas are PR immunoreactive than their benign counterparts.

A growing number of cytogenetic alterations have been associated with malignant progression of meningiomas, although the genes have yet to be identified. Most common in atypical meningiomas ate deletions of lp, 6q, 10, and 14q (Weber et al. 1997).

Anaplastic Meningioma (WHO Grade **111)**

With the omission of brain invasion as a criterion for anaplastic meningioma, these tumors have become quite rare, accounting for no more than 1-2% of all cases. Many of these tumors start as benign or atypical meningiomas and progress over time, although de novo presentation is also encounteted. As a group, they are highly aggressive, rapidly-growing, and highly infiltrative with an associated median patient survival rate of less than 2 years (Perry et al. 1999). Nevertheless, extent of resection remains important and long-term survival is still possible in a subset. Subsequent to surgical and radiotherapeutic failure, effective treatment options are generally lacking for these patients.

Histologically, anaplastic meningiomas ate defined by the presence of excessive mitotic activity (>20 per 10 HPF) and/or frank anaplasia with a carcinoma-like or sarcoma-like appearance. They are highly cellular tumors with extensive sheeting, necrosis, and nuclear atypia. Lower grade elements, more easily recognizable as meningioma, are

often seen. For those lacking this feature, immunohistochemistry or electron microscopy arc often necessary to exclude hemangiopericytoma, other dural-based sarcomas, metastatic carcinoma, or melanoma.

Anaplastic meningiomas shatc the genetic features of lower-grade meningiomas, but additionally harbor chromosome 17q gains/amplifications and 9p/pl6 losses in many cases. In most, the MIB-1 (Ki-67) labeling index is markedly elevated and there is no discernible PR expression.

Hemangiopericytoma (WHO Grade II or III)

Hemangiopericytoma, once considered a variant of meningioma, is now generally accepted to be a highly vasculat dural-based sarcoma, analogous to those encountered in soft tissue sites. Despite the implication of pericytic origin, they remain of uncertain histogenesis. They occur at all ages, peaking in the foutth to sixth decades. Unlike meningiomas, one gender is not affected more than another, they are EMA-negative, and no association exists with NF2 or any other meningioma-associated genetic alterations. Hemangiopericytoma is also a more aggressive tumor with recurrences rate of 60-80% and systemic metastasis rates as high as 25%.

Histologically, the tumor is a highly cellular, reticulin-rich neoplasm with numerous, characteristically branching ("staghom") thin-walled vessels. Tumor cells are oval to spindled and display variable proliferative indices. Using Armed Forces Institute of Pathology (AFIP) criteria, those with more than 5 mitoses/10 HPF and/or hemorrhage/necrosis are considered high-grade (grade III), although even the low-grade (grade II) examples are considered malignant by definition (Mena et al. 1991).

NERVE SHEATH TUMORS

Schwannomas and neurofibromas represent the most common peripheral nerve sheath tumors, but may be encountered "centrally" when they arise from paraspinal nerve roots or cranial nerves. Multiple neurofibromas or schwannomas should suggest NF1 and NF2, respectively, particularly in younger individuals. Even the most cellular and mitotically active schwannoma virtually never undergoes malignant transformation, although plexiform and intraneural neurofibromas harbor a small but significant risk of this complication, MPNST may therefore develop de novo or within a pre-existing tumor, most often a plexiform neurofibroma from a patient with NF1. The risk of developing MPNST is also increased in previously irradiated tissue (e.g., mediastinal radiation for Hodgkin's lymphoma), both in patients with and without NF1. Generally, MPNSTs are encountered in soft tissue sites, but may be seen more centrally, because of paraspinal localization. These sarcomas are usually high-grade and have a dismal prognosis.

Schwannoma (Neurilemoma) (WHO Grade I)

The frequency of schwannomas peaks in the fourth and fifth decades. Most are located on the vestibular portion of the eighth cranial nerve. Other cranial nerves, particularly the trigeminal, are much less frequent sites. Bilateta! vestibular schwannomas (acoustic neuroma) are diagnostic of NF2, Vestibular schwannomas erode the internal auditory meatus and occupy the cerebellopontine angle; with increasing si/.e, they compress and deform the pons. Spinal schwannomas compose approximately 30% of intraspinal tumors. Most arise from the dorsal roots, preferring sensory nerves, like their cranial counterparts. Spinal schwannomas may extend through the dura or, in some cases, through the intervertebral foramen as a dumbbell-shaped mass that is partly within and partly outside the spinal canal.

As opposed to neurofibromas, schwannomas are pure Schwann cell proliferations, typically arranged in two architectural patterns. Cellular, dense zones, known as Antoni A areas, contain spindle-shaped ceils arranged in nuclear palisades, termed *Veroaty's bodies.* Antoni B areas arc myxoid and microcystic in appearance with thin, wavy cells and foci of collagenization, highly reminiscent of neurofibromas. Degenerative changes are common and include hemorrhage, cystic breakdown, vascular hyalinization, and calcification. As opposed to neurofibromas, schwannomas typically have a discernible capsule and push the parent nerve aside rather than invading it. Immunohistochemical studies reveal strong and diffuse S-100 immunoreactivity, diffuse collagen IV positivity teflecting the rich network of Schwann cell-associated basement membrane, and a relative lack of neurofilament-positive entrapped axons.

The vast majority of both sporadic and familial schwannomas are associated with loss of expression for the NF2 protein product, merlin or schwannoma (Stemmer-Rachamimov et al. 1997}. *NF2* gene deletions and LOH are common, although other mechanisms may also be involved.

Neurofibroma (WHO Grade I)

Neurofibromas arc less commonly located in the CNS" than are schwannomas. Multiple spinal nerve root involvement is virtually pathognomonic of NFL They more typically originate from nerve terminals in the dermis and from large nerve trunks, such as the brachial plexus. Unlike the eccenttic globular growth pattern of schwannomas, neurofibromas grow within the substance of a nerve, generating a fusiform intraneural mass. A plexiform ("bag of worms")

growth pattern results from the involvement of multiple nerve fascicles and is virtually diagnostic of NF1. On gross inspection, neurofibromas are typically gray and gelatinous.

Histologically, bundles of thin, wavy cells with thin wavy nuclei are suspended haphazardly in a myxoid or mucin-rich stroma. The degree of collagen ization is variable, depending on the age of the lesion. The resulting hyaline silhouettes arc likened to "shredded carrots," As opposed to schwannomas, neurofibromas are a mixture of cell types that includes not only Schwann cells, but also fibroblasts, perineurial-like cells, mast cells, and entrapped elements from the parent nerve. Most cases are hypocellular, and therefore foci of marked cellularity, increased cell size, and mitotic activity should cause concern for malignant transformation to MPNST. Immunostains demonstrate patchy S-100 and collagen IV expression, because only a portion of the inttatumoral cells are Schwann cells. Entrapped neurofilament-positive axons are nearly always found except in dermal neurofibromas. The MIB-1 (Ki-67) index is generally low and p53 protein is negative, except in foci of transformation to MPNST.

Studies suggest that the Schwann cell is the neoplastic component of neurofibromas, and thar the remaining cell types are probably reactive or entrapped elements (Perry et al. 2001). Deletions of the *NF1* gene and losses of its protein product, neurofibromin, have been detected in a subset of both familial and sporadic neurofibromas.

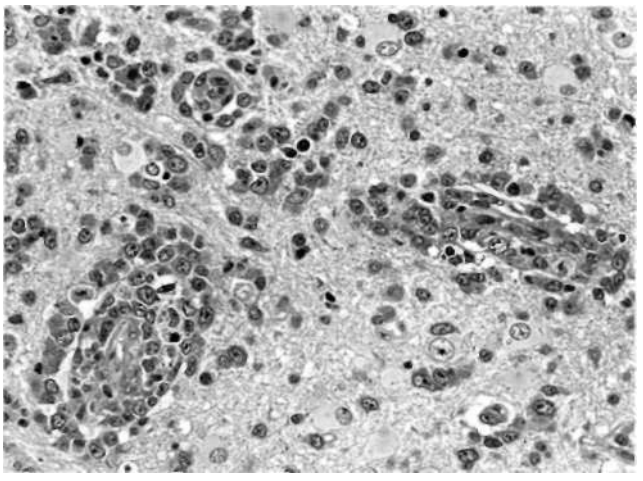


FIGURE 58K.12 Central nervous system lymphoma. Infiltrative neoplasm with distinctive a ngioccn tricky (aggregating around and within the vessel walls), composed of immature lymphoid elements with high nuclear to cytoplasmic (N/C) ratio, vesicular nuclei, and prominent nucleoli (hematoxylin-eosin stain; x400).

MISCELLANEOUS TUMORS

CNS Lymphoma

CNS involvement by lymphoma may be cither primary or secondary. Secondary CNS involvement occurs in 25-30% of systemic non-Hodgkin\ lymphomas, but is exceptional in Hodgkin's disease. Systemic lymphomas tend to infiltrate the leptomeninges and spare the parenchyma. The epidural spine is a favored site and spinal compression is a common complication. In contrast, primary CNS lymphomas typically present deep in the brain parenchyma (e.g., periventricular) and usually spare the leptomeninges, which may explain why the CSF cytological examinations contain tumor cells in a minority of patients. The incidence of lymphoma is increased in immunodeficicnt patients, such as patients with acquired immunodeficiency syndrome and organ transplant recipients. Such cases are typically associated with Epstein-Barr virus (LBV) and CSF PCR studies take advantage of this common finding. Primary CNS lymphoma is also increasing in the older adult, immunocompetent population for reasons that are poorly understood. These cases are generally unassociatcd with EBV. Survival without treatment is typically less than 1 year, but prolonged survivals are now being reported with methotrexate-hased chemotherapy regimens. Primary CNS lymphoma is unique in that approximately half are multifocal, they may disappear entirely after steroid therapy (in the early forms of disease), and they often recur in a completely different site from that of the initial lesion.

The vast majority of primary CNS lymphomas are diffuse large cell lymphomas of B-ccll type. They show a distinctive angiocentric pattern, in which malignant cells surround and invade blood vessels in concentric layers (Figure 58B.J2). Reactive T cells are often numerous as well. Cases from immunosuppressed patients are characteristically necrotizing and KBV immunoreactivc, whereas those from immunocompetent patients are not. Biopsies from patients treated preoperatively with steroids are a diagnostic challenge for pathologists, because the tumor cells often die, leaving behind a reactive component that resembles either an inflammatory or dcmyelinating disorder. In such cases, an accurate diagnosis may be delayed until the time of recurrence. Also, because of the sometimes low cellularity in comparison to lymph node biopsies and the typically mixed infiltrate, wherein reactive T cells may outnumber tumor cells, FCM is often less sensitive for establishing the diagnosis than routine histology and may waste a considerable amount of precious tissue. The molecular profiles of primary CNS lymphomas have not been extensively studied, although a recent study suggests that coinactivation of the 9p tumor suppressors, p16 and $p14^{ARt;}$ may be important in tumorigenesis (Nakamura er al. 2001),

Germ Cell Tumors

Nervous system germ cell tumors are most common in school-aged children, and they arc analogous to germ cell tumors in the gonads, retroperitoneum, and mediastinum. The pineal region is the most common site of occurrence, followed by the suprasellar/hypothalamic region. Germ cell

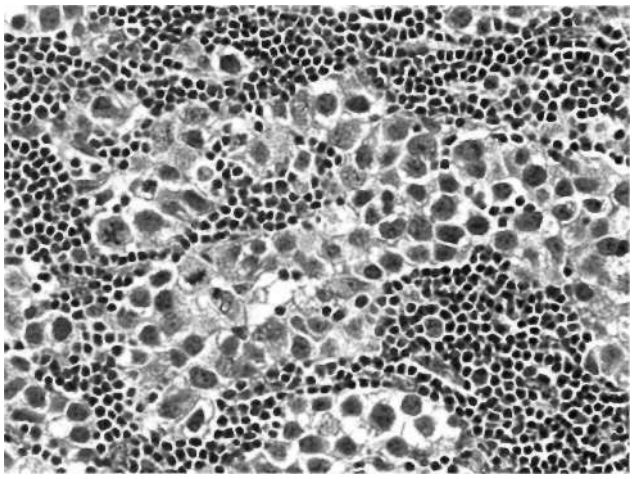


FIGURE 58B.13 Pineal germinoma. The dual cellular population consists of numerous small, reactive lymphocytes and large clear tumor cells, which resemble primordial germ cells (hematoxylin-eosin stain; x400).

tumors as a group grow rapidly, with a propensity to seed the subarachnoid space. *CSV* examination for both cytology and marker levels may be diagnostic. Elevations of placental alkaline phosphatase (PLAP) are most suggestive of germinoma, ^-fetoprotein of yolk sac tumor, and #-human chotionic gonadotropin (jft-HCG) of choriocarcinoma or a syncytiotrophoblastic element. For reasons that are not understood, pineal germ cell tumors arc virtually restricted to hoys and in some cases, the clinicoradiographic features may be deemed so typical that a biopsy is not felt to be necessary prior to therapy. Pure germinoma is most common, and is virtually 100% curable because of its exquisite radiosensirivity. Mature teratoma is less often a pure tumot, and is slow growing, cystic, and does not respond well to chemotherapy or radiation. However, these tumors are often well demarcated and may be surgically curable. Most of the remaining cases consist of mixed germ cell tumors with various malignant elements, such as embryonal carcinoma, yolk sac tumor, choriocarcinoma, and immature teratoma. Such cases have a significantly worse prognosis, but survival rates have improved with multiple agent chcmothcrapcutic regimens. In occasional cases that are successfully treated, the only viable element remaining on "recurrence" is matute teratoma.

Histologically, germinomas are identical to tcsticulat seminoma and ovarian dysgerminoma, with two distinct cell populations (see Figure 58B.13). The neoplastic clement tcscmbles primordial germ cells with abundant glycogcn-ncll clear cytoplasm and PI.AT' immunorcactivity. The stroma is often rich in reactive lymphocytes, primarily T cells. Sarcoidlike granulomas are also quite common and may obscure the diagnosis in biopsies in which the tumot cells are overshadowed by the teactive response. Embryonal carcinoma resembles a poorly differentiated catcinoma. Endodermal sinus tumor (yolk sac tumor) forms lose papillary epithelial sttuctutes, known as Schiller-Duvall bodies. Choriocarcinoma is characterized by a combination of mononucleate cytottophohlasts and multinucleate syncytiotrophoblasts. It is highly vascular and particularly prone to massive hemorrhage. Teratomas differentiate into elements from all thtee germ layers. The common benign form contains mature components (teeth, hait, muscle, cartilage, and bronchial wall) arranged in a haphazard, nonfunctional manner. Immature teratoma contains the same elements, but its appearance is fetal rather than mature. Foci of immature brain, with neural tubclike structures arc particularly common.

Hemangioblastoma (WHO Grade I)

Hemaiigi obi a stomas arc benign, highly vascular tumors <i uncertain histogenesis. Approximately 10% of patients with hemangioblastoma have VHL disease. The rest are considered to be sporadic in origin. The age at diagnosis ranges from adolescence to the sixth decade, with the peak incidence at 40 years. Hemangioblastomas are more common in men. The tumor usually presents as a cyst with an enhancing mural nodule in the cerebellum, and is the most common primary cerebellar neoplasm in adults, Hemangioblastomas are sometimes located in the tetina, brainstem, spinal cord, or paraspinal nerve roots, sites commonly involved in association with VHL disease.

Hemangioblastomas are cystic and sharply demarcated, often allowing total surgical resection. The cyst contents arc usually clear and yellow; a rusty color indicates previous bleeding. Solid portions of the tumor are dark red because of an elaborate vascular supply, which predisposes to spontaneous hemorrhage. Histological examination shows abundant capillaries coursing throughout the tumor mass, although the actual tumor cell is believed to be the foamy, lipid-laden stromal cells in between. These cells consistently stained positive for S-100 protein and neuron-specific enolase (NSE). Patchy GFAP expression is also encountered occasionally. An eryrhropoietin-like substance is identified in the cyst fluid of 20% of tumors. It may be associated with pure red cell hyperplasia in the patient and extramedullary hematopoiesis in the tumor.

The *VHL* gene on 3p25-26 is a growth regulator that behaves as a classic tumor suppressor gene, with patients with VHL hathoring a germlinc mutation ("first hit"). In these patients, it predisposes to a variety of tumors and malformativc lesions, but the majority of the morbidity and mortality result from renal cell carcinomas, CNS hemangioblastomas, and in a subset of patients, phcochromoeytomas.

Craniopharyngioma (WHO Grade I)

Craniopharyngiomas compose 2-5% of CNS tumors. Most become symptomatic in the first two decades but can occur at any age. Craniopharyngiomas are thought to arise from

cell rests of Rathkc's pouch, an evagination of the primitive stomatodeum. Remnants of Rathke's pouch may be identified as nests of squamous epithelium on the anterior surface of the infundibulum and the pars tuberalis in infants and adults. Craniopharyngiomas may he intrascllar or more frequently suprasellar in location, often involving the hypothalamus and the optic nerve or chiasm. The expanding mass causes hydrocephalus by encroaching on the third ventricle.

The advancing margins of the craniopharyngioma may appear deceptively sharp but microscopic finger like extensions into surrounding tissue are common. Both solid and cystic areas arc intermingled. The cysts can become large and are typically filled with a dark, viscous, cholesterol-rich fluid, likened to motor oil. Irregularly shaped calcific deposits, varying in size from grains of sand to fine gravel, are found in approximately 75% of cases. The microscopic appearance has been compared to that of adamantinoma of the tibia and ameloblastoma of the jaw. Therefore the classic craniopharyngioma is sometimes referred to as adamantinomatous craniopharyngioma. The tumor demonstrates benign-appearing epithelium with central cobweb-like loosening ("stellate rcticulin") and peripheral palisading. Squamoid foci may be seen and the pattern of kcratinization with ghostlike nests of keratinocytes is known as *wet keratin.* Wet keratin differs from the dry, flaky keratin of epidermoid and dermoid cysts (see the following text) and is unique to craniopharyngioma. Therefore it is diagnostic on a biopsy, even without the presence of viable epithelium. A rarer variant is the papillary craniopharyngioma. These often present in the third ventricles of young adults. They are characterized by a true, nonkeratinizing squamous lining over fibrovascular cores. Goblet cells may also be seen. It is still uncertain whether this variant has a better prognosis,

Epidermoid and Dermoid Cysts

Epidermoid and dermoid cysts are presumed implantation or sequestration cysts derived from misplaced ectoderm. They may he congenital or acquired. The congenital type is caused by inclusion of ectodermal tissue during embryonic closure of the neural groove or during coalescence of epithelial fusion lines in the cranium. Sequestration cysts accompany dysraphism, such as spina bifida, and may communicate with the skin surface through a sinus tract.

Epidermoid cysts occur in young adults and are usually found in the cerebellopontine angle or skull. Dermoids are more common in children and tend to occur near the midline m the cerebellar vermis, parasellar or parapoiitmc region, and spinal canal, especially in the lumbosacral region. Intact tumors are enveloped by a fibrous capsule that has a glistening white surface, like mother-of-pearl, and are thus called *pearly tumors.* The lining and contents of the epidermoid are composed of keratinizing squamous epithelium that may be attenuated or focally stratified. The thin wisps of flaky intraluminal keratin are known as *dry keratin,* in contrast to the type seen in craniopharyngiomas. The adjacent collagenous wall is often partially calcified, producing a linear or speckled pattern on CT images. The inner layer of a dermoid is also composed of squamous epithelium, but the presence of hair follicles and other skin appendages distinguishes dermoid cysts from epidermoid cysts. The cyst contents, once introduced into the meninges by spontaneous rupture or during surgery, can incite a severe chemical meningitis that is typically granulomatous.

Neuroenteric, Colloid, and Rathke's Cleft Cysts

Cysts lined by cuboidal to columnar, mucin-producing epithelial cells, resembling those of respiratory or enteric lining may occur in several sites throughout the CNS. Such cysts are referred to as Rathke's cleft cyst in the sella, colloid cyst in the third ventricle, and neuroenteric (also known as enterogenous, bronchogenic, neuroepithelial, and so on) cyst when they occur in the anterior spinal region or rarely at intracranial sites. These cysts are thought to be developmental rather than neoplastic, but their precise origin has not been established. Although the presumed embryology may differ at these sites, the histological appearance is otherwise similar.

Lipomas

Most lipomas are located in the midline and are sometimes associated with other developmental abnormalities, such as agenesis of the corpus callosum. Typical locations include the dors.il aspect ol the midbrain, cerebellar vermis, and spinal cord. The most common location is the surface of the corpus callosum. Lipomas of the spinal cord often become symptomatic by causing cotd compression, but lipomas of the brain arc usually asymptomatic and are incidental findings on neuroimaging studies and on postmortem examination.

Lipomas are yellow and resemble normal fat. Tumors of the brain, particularly those adjacent to the corpus callosum, may seem to infiltrate the parenchyma, but are benign in histological appearance and biological behavior. Lipomas of the spinal canal are almost invariably in an epidural or subdural position and are well demarcated from the adjacent spinal cord.

METASTATIC TUMORS

Metastatic tumors are actually more common than primary brain tumors. Most occur in middle-aged and older adults, with multiple CNS metastases detected commonly. Metastases often lodge in the corticomedullary junction,

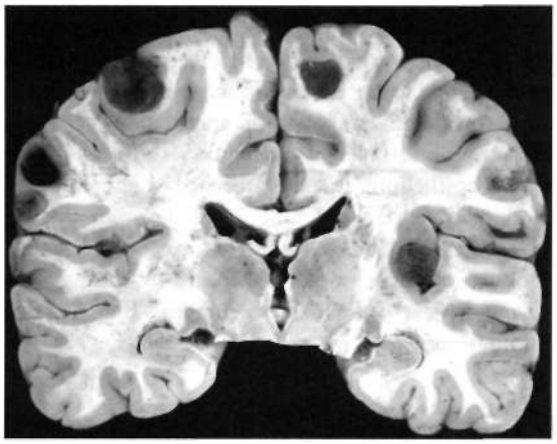


FIGURE 58B.14 Metastatic small cell carcinoma. Foci of well demarcated tumor, primarily localized to corricomcdullary junctions.

A zone of edema customarily surrounds even small metastatic lesions,

The typical metastasis is round and sharply demarcated with central necrosis or hemorrhage (Figure 5SB.14). Spontaneous bleeding is characteristic of choriocarcinoma, melanoma, or renal carcinoma metastases. However, lung carcinoma, the most common primary to metastasize to the brain, accounts for many hemorrhagic cases. Most other primaries metastasize to the lung before they gain access to the brain. The histological appearance is variable and recapitulates the morphology of the primary tumor. Most metastatic lesions are carcinomas or melanomas, rather than sarcomas or lymphomas,

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Chapter 58
Cancer and the Nervous System

C. CLINICAL FEATURES AND COMPLICATIONS

Pierre Giglio and Mark R. Gilbert

Primary and metastatic brain tumors may present with acute changes in neurological function, like seizures or sudden confusion, or with gradual and progressive changes in motor or sensory function, personality, or cognition. Both patient and physician may overlook initial symptoms, especially when slowly ptogrcssivc and not severe. Headache is probably the most common initial symptom. Unfottunately, the cause of the headache is often misdiagnosed as migraine, stress, tension headache, or neuralgia. This chapter discusses the clinical features of brain tumors with an emphasis on useful indicators for suspecting an intracranial tumot in clinical practice.

HEADACHES

Headaches are an important indicator of increased intracranial pressutc in patients with brain tumots. Howcvet, increased intracranial pressure is not always the mechanism of brain tumor headache. In the absence of incteased intracranial pressure, direct impingement or traction of pa in-sensitive structures, such as the meninges or blood vessels, is the explanation of the headache mechanism. A "referred" frontal headache may occur secondary to a supratentorial tumor impinging on cranial nerve-innervated structures, whereas postetior fossa tumors may cause cervical pain from irritation of sttuctures innervated by cranial nerves IX and X {Wall ct al. 2001}.

Approximately 20% of patients with brain tumots have headache at ptesentation, usually in association with some other symptom or symptoms. La let in the course, approximately 60% eventually develop headache. The incidence is higher in patients with posterior fossa tumors. The description of headache is usually a dull ache or pressure, often resulting in an initial diagnosis of tension headache. In others, the headache is throbbing and intetmittent, simulating migraine headache. Head pain with features of cluster headache are less common and occur with pituitary tumots (Porta-Etessam 2001). Most headaches seen in practice are bilateral and sometimes desctibed as a "band" around the head.

Some patients desctibe a progressive increase in the severity of their headache or an increase in frequency of intermittent headaches. Such a history should always arouse suspicion, even in patients with a history of prior migraine or tension headaches. Acute headache may be a presenting featutc of hemorrhage into a tumor, but also occuts as a presenting feature of a brain tumor without evidence of hemotrhage on imaging.

An often cited and important feature of headaches in brain tumor is increased severity in the morning, with a tendency toward improvement by afternoon or evening. The explanation of this phenomenon is increased intracranial pressure with nocturnal recumbence, but this is, by no means, a constant characteristic of brain tumor headaches. Many patients describe little or no relationship of headache severity to time of day.

Changes in position, coughing, sttaining, and Valsalva's maneuver may exacerbate headache. Analgesics and anti-migraine medications may make the headache better and result in a delay in diagnosis. A good response to simple

analgesics is often reported, and brain tumor headache maybe relieved with triptans (Pascual 2000),

SEIZURES

The recorded incidence of seizures in patients with brain tumors is as high as *35%*. Seizures are often the feature that precedes brain tumor diagnosis. Seizures may be focal at onset and reflect the brain tumor location, or may be generalized secondarily from a primary irritative focus. Temporal lobe tumors may present as stereotyped automatisms, such as lip smacking. Focal motor activity may follow, and in more than half the cases, secondary generalization occurs. After the episode, confusion and retrograde amnesia arc common. Some patients with brain tumors describe auras of anxiety, fear, or euphoria as their "warning." Viscerosensory auras arc probably the most common auras in seizures of temporal lobe onset (Palmini andGloor 1992).

Frontal lobe tumors may also present with seizures and accompanying auras. Depending on the location (anterior versus posterior frontal), speech arrest or motor manifestations may be more prominent. Common auras reported in frontal lobe seizures are dizziness, a rising epigastric sensation, and fear (Qucsncy 1990).

Visual auras may precede seizures arising from tumors in the occipital lobe. Secondary generalization, in at least some of the episodes, is common in patients with brain tumors. Sensorimotor phenomena often herald parietal lobe seizures.

COGNITIVE DYSFUNCTION

Cognitive dysfunction is probably the most common problem in patients with brain tumors. Initially, this dysfunction is often overlooked. Subtle problems with language function, such as word finding difficulty or memory failure, are attributed to stress or fatigue. As with seizures, tumor location determines the specific clinical features. Frontal lobe tumors often cause executive dysfunction. Similar dysfunction is also encountered in patients with tumors in other locations (Lilja et al. 1992), probably because of a disconnection syndrome involving the frontal lobes. Memory problems may also be present. With left hemispheric tumors, language dysfunction is often noted concurrently. Right hemispheric tumors may result in problems with visual perception and scanning; patients may report getting lost while driving in familiar places (Schicbcl et al. 1996).

The his to pathology of a brain tumor influences the development of cognitive dysfunction. Low-grade tumors may not cause appreciable deficits despite their location (Meyers etal. 1992). Cerebral plasticity and reorganization allow for transfer of function when the underlying process develops slowly. In children, this plasticity may be striking. The functional magnetic resonance imaging (MRI) scan in Plate 58C.I shows right hemisphetic activation with motor function of both arms in a patient with *a* low-grade astrocytoma of the left frontal lobe diagnosed about 10 years earlier. Compensation of language, memory, and other cognitive domains may be similar. High-grade tumors such as glioblastoma multiforme grow rapidly and cause focal cognitive deficits based on location, as well as more generalized impairment secondary to mass effect and increased intracranial pressure.

NAUSEA AND VOMITING

Nausea and vomiting may result from increased intracranial pressure. In addition, tumors of the posterior fossa may have a direct effect on the emetic centers near the fourth ventricle (area postrema). In such cases, vomiting is usually repetitive and intractable but may respond ro focused radiation therapy to the posterior fossa (Cohen et al. 2002),

SYMPTOMS RELATED TO ENDOCRINE DYSFUNCTION

Hypothyroidism, decreased libido, and other symptoms of endocrine dysfunction may follow treatment of brain tumors. In some cases, endocrine dysfunction is the initial feature. Tumors of the hypothalamic-pituitary axis may cause gonadotrophs and growth hormone deficiency as well as hypopituitarism (Paja et al. 1995).

VISUAL SYMPTOMS

When brain tumor patients complain of visual blurring or other visual complaints, the precise nature of the complaint must be fully explored. Contralateral flashing lights may be due to seizures from an occipital lobe tumor, whereas loss of vision on one side may indicate a visual field loss from a tumor more anteriorly placed in the parietal or temporal lobes. The complaint of diplopia may indicate increased intracranial pressure, especially when associated with nausea and vomiting, as in patients with a brainstem glioma.

SYMPTOMS FROM PLATEAU WAVES

Patients with brain tumors may complain of transitory episodes of altered consciousness and visual disturbances. The cause of such episodes may be transitory elevations of intracranial pressure. These elevations or "plateau waves," first described by Lundberg, are important to recognize because they are treatable with acctazolamidc

(Watling and Cairncross 2002). A correct diagnosis also prevents unnecessary treatment with anticonvulsants. The episodes are often mistaken for seizures.

CLINICAL EVALUATION AND INVESTIGATIONS IN BRAIN TUMOR PATIENTS

Clinical Evaluation

Careful examination for evidence of cognitive or other neurological dysfunction is required for patients with symptoms that are suspicious for intracranial tumors. Besides helping to guide investigative procedures, a good clinical examination serves as part of a baseline assessment that helps determine the efficacy of any treatment. A bedside mental status assessment is mandatory in all patients. In cases presenting with evidence of cognitive decline, a more formal neuropsychological assessment may be useful.

Neurological examination must focus on the elicitation of signs that help confirm localization based on symptoms. In patients presenting with personality changes and occasional word finding difficulties, a rigorous language assessment, evaluation for apraxia, unilateral weakness, and frontal release signs are important. Prominent visual symptoms may indicate an occipital lobe tumor or pressure on the optic chiasm. Careful documentation of either visual field deficits or diminished visual acuity may then constitute the most important part of the assessment.

Investigations in Brain Tumor Patients

Imaging (Computed Tomography Scan and Magnetic Resonance Imaging)

If clinical suspicion for an intracranial tumor is high, MRI is the investigation of choice. In many cases, computed tomography (CT) scans are obtained first, particularly when patients present acutely with seizures or severe headache. CT scans can be helpful in excluding hemorrhage into an intracranial mass as well as provide some estimation of the degree of mass effect and midline shift caused by the mass. Vasogenic edema surrounding a tumor typically appears as abnormal, fingerlike white matter hypodense areas. Resolution and artifact, especially "beam hardening," limit the use of CT, particularly in the posterior fossa. The size and number of lesions may be underestimated, especially with regard to metastasis.

MRI scans provide better definition of brain tumor size, edema, mass effect, and midline shift, as well as evidence of herniation (Figure 58C.1). These studies allow distinction between intra-axial and extra-axial mass lesions. Meningiomas and other dural-based lesions are more easily distinguished from parenchymal tumors such as gliomas.

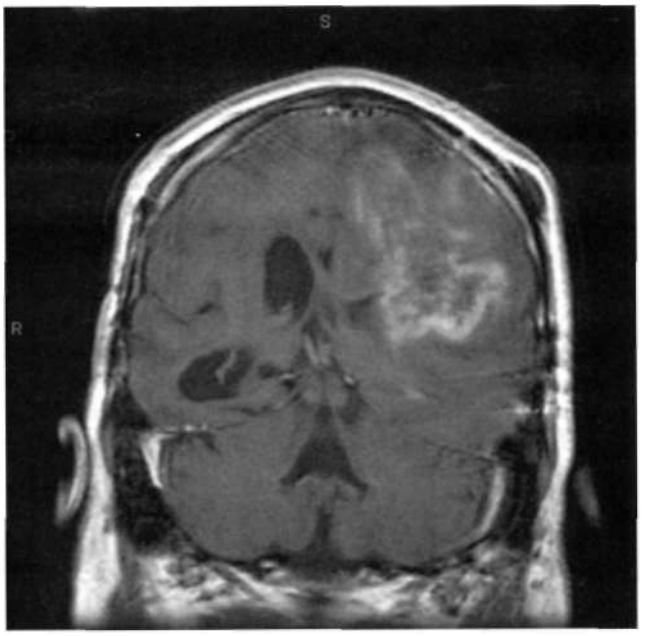


FIGURE 58C.1 Magnetic resonance imaging scan with mass effect and subfalcine herniation from a left glioblastoma multiforme.

Another obvious advantage of MRI is its sensitivity for leptomeningcal disease, which produces abnormal linear and nodular enhancement of the leptomeninges and T-2 signal abnormalities.

Electroencephalograph y

Often, electroencephalography (EEG) is obtained when patients present with seizure activity, particularly when the postictal state (drowsiness, confusion) is prolonged and nonconvulsive status epilepticus is suspected. Routine EEG studies are not indicated in patients in whom seizure activity is controlled.

Evaluation for Primary Tumors in Suspected Metastases

Intracranial masses consistent with metastatic lesions should prompt investigation for evidence of systemic cancct. Traditionally, contrast CT scans of the neck, chest, abdomen, and pelvis have been used to look for the primary cancer. More recently, positron emission tomography has been used in an attempt to increase the sensitivity for detection of primary tumors such as lung cancer (Chin et al. 2002) as well as melanoma (Holder et al. 1998).

Lumbar Puncture

In cases in which clinical evaluation or imaging is suggestive of leptomeningcal metastases, examination of the cerebrospinal fluid is warranted. Imaging should always precede this and in patients with evidence of increased

intracranial pressure, mass effect, or midline shift, lumbar puncture is contra indicated.

THE DIAGNOSIS AND MANAGEMENT OF BRAIN TUMOR-RELATED COMPLICATIONS

Seizures, cerebral edema, and deep venous thromboses may complicate the course of patients with brain tumors. These complications may lead to tumor diagnosis in some cases, or develop during the course of tumor evaluation and management in others. Management of these symptoms can be challenging, but timely investigation and treatment can dramatically improve quality of life in these patients.

Seizures

The clinical presentation of seizures in brain tumor patients was discussed previously in this chapter. This section covers management.

Surgery

Improved seizure control often follows surgical removal of the tumor. A more controversial issue has been the need to resect surrounding "epileptogenic" cortex identified by electrocorticography. Some investigators have favored epilepsy surgery where possible, consisting of a mass resection and a subtotal lobectomy. Others have advocated "mass" surgery only. The extent of surgery is individualized based on the eloquence of the area where the **tumor** is located and the expertise of the neurosurgical team.

Radiation Therapy

Both conventional and stereotactic radiation therapy may result in better seizure control. In contrast, seizures may increase in frequency during radiation therapy, probably as part of the "immediate" response to radiation. This has been reported in radiosurgery patients and often responds to adjustments in corticosteroid dosage (Werner-Wasik et al. 1999).

Corticosteroids

A reduction in the inflammatory response around a tumor may help in reducing seizures. The management of cerebral vasogenic edema is discussed in the following text.

Antiepileptic Drugs

Broadly speaking, antiepileptic drugs may be subdivided into "conventional" versus "new" and enzyme-inducing versus nonenzyme inducing (see Table 58C.1). In patients

Tabic **S8C.1:** Anticonvulsants introduced before and after 1990

Pre-1990	*Post-1990*
Phcno barbital	Felbamate""*
Phenytoin	Gahapentin*
Primidone	Lamotrigine
Diazepam	Topiramate
Carba maze pine	Levetiracetam*
Valproic acid	Oxcarbazepine

'Denotes a nonen/yme-inducing anticonvulsant drug.
•^Usc restricted because of hepatic toxicity,

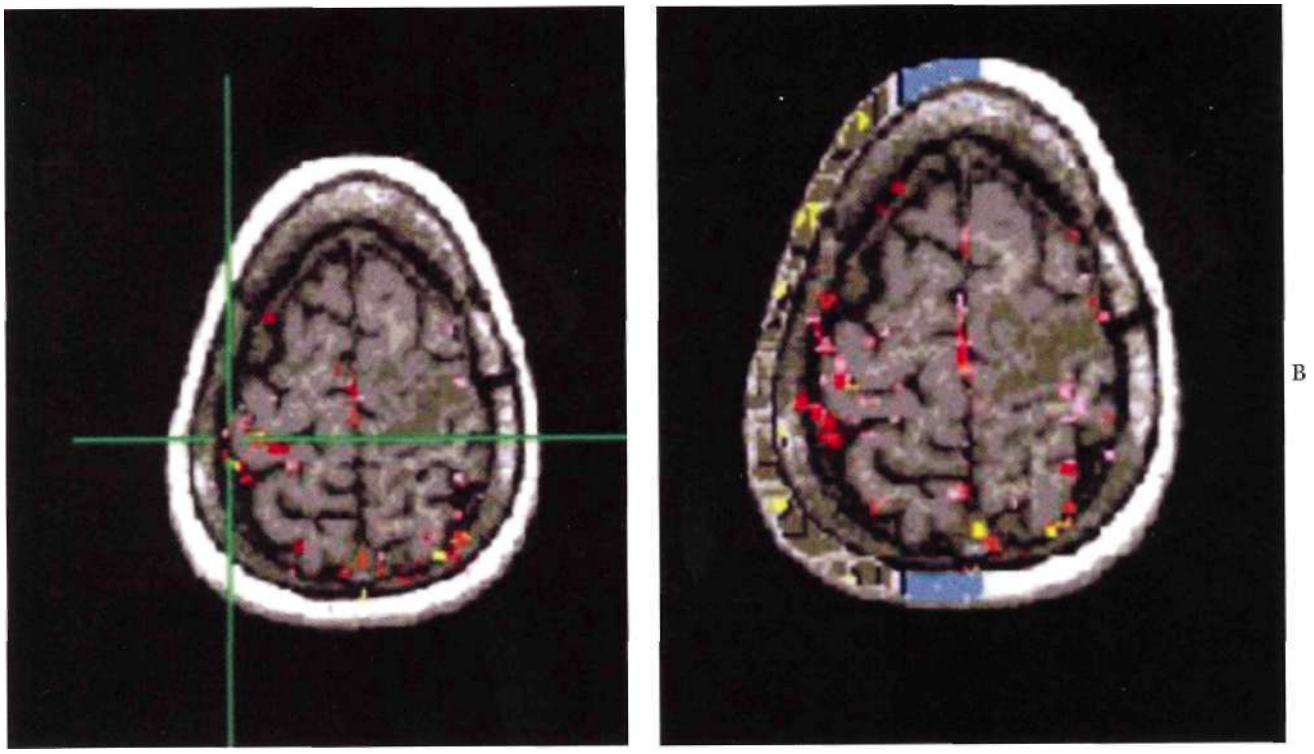
with brain tumors presenting with seizures, the emetgent administration of an intravenous antiepileptic drug such as fosphenytoin is usual. The dtug is often maintained in cases with good seizure control. Increasingly, however, newer antiepileptic drugs are being used because of better tolerance in some patients. The newet generation of antiepileptic drugs is sometimes preferred because of less potential for drug interactions. Gahapentin and levetiracetam are examples of nonenzyme-i inducing Lintiepileptic drugs (NE1AED). Because most brain tumot patients ate tteatcd with chemotherapeutic agents, drugs that do not interfere with hepatic metabolism, and thctcfotc with bioavailability of chemotherapy, represenr an advantage, particulatly with chemothctapy agents such as vincristine (Villikka et al. 1999), CPT-11" (Mathijsscn et al. 2002), and paclitaxel (Chang et al. 1998), This effect is so important that patients enrolled into brain tumor trials ate often stratified according to whether they are using an enzyme-inducing antiepileptic dtug or an NEIAED.

Cerebral Edema

Both primary brain tumors and metastases usually induce cetcbral edema. This may result in headache, altered mental status, and neurological deterioration. Brain tumor edema is usually of the *vasogenic* type; that is, it results from passage of fluid from the intravascular compartment to the interstitial space. When brain tumors cause obstructive hydrocephalus, increases in intraventricular pressure may result in transependymal spread of fluid into the periventricular interstitial space, or *interstitial* edema.

Management of Cerebral Edema

Vasogenic edema may result in acme increased intracranial pressure. Such patients usually tequire hospitalization and, in severe cases, arc best managed in an intensive care unit. In this setting, intravenous mannitol is often used to reduce intracranial pressure. By effecting an osmotic diuresis, the drug results in intravascular volume depiction, resulting in fluid return to the intravascular compartment. The side



PLATK 58C.I Functional magnetic resonance imaging scan shows activation of right motor area for the hand with activity of both the right hand (A) and left hand (B). Notice the abnormal signal related to low-grade tumor in left frontal lobe.

effects of hypovolemia and electrolyte imhalance limit repeated dosing of mannitol. The benefit of mannitol is short-lived, lasting on average 24-48 hours befote a rebound increase in intracranial pressure occurs.

Urea and glycerol are also used to achieve the same effect as mannitol, an osmotic diuresis. In practice, both drugs are used less often than mannitol. The osmotic diuretic effect of urea and glycerol is also short-lived and a rebound phenomenon may occur with both agents when they are stopped. Glycerol is usually better tolerated than urea, which may cause prominent nausea. The usual oral dosage of glycerol is 1.5 g/kg per day in divided doses.

Corticosteroids are the mainstay of treatment in patients symptomatic from vasogenic cerebral edema. Unlike osmotic diuretics, the effect of corticosteroids is sustained. Unfortunately, the long-term use of corticosteroids is associated with a multitude of side effects, including hyperglycemia, osteopenia, proximal muscle weakness, and limb swelling. In patients with severe cerebral edema and increased intracranial pressure, very high doses of dexamethasone (30-36 mg daily in divided doses) are used. The dexamethasone dosage is tapered once clinical improvement is noted.

Venous Thrombosis

Deep venous thrombosis is a common complication in brain tumor patients. In a retrospective study of 381 patients with malignant glioma, 97 (36.7%) were found to have venous thrombosis confirmed by venography {Ruff and Posner 1983). The reasons for this high incidence are probably multiple. An obvious explanation in some patients may be the immobility following hospitalization for surgery or immobility of limbs secondary to hemiplegia, although deep venous thrombosis also occurs in patients with malignant brain tumors who have retained mobility. Intracranial neoplasms have also been shown to inhibit purified plasmin in an in vitro assay (Sawaya et al. 1984).

Clinical Presentation

The typical initial feature is unilateral foot, calf, or thigh pain or swelling. Likewise, arm or forearm swelling and pain may be prominent in upper extremity thrombosis. Superficial venous distension, increased temperature, and erythema may be present. Some patients present with symptoms of pulmonary thromboembolism, pleuritic chest pain and shottness of breath that may be accompanied by changes in the lower extremities. Corticosteroids may blunt symptoms related to inflammation. In such cases, local swelling and erythema at the site of thrombosis may be minimal and pulmonary symptoms absent. Anxiety may be the only initial manifestation of pulmonary thromboembolic disease.

Investigation

When deep venous thrombosis is suspected, venous Doppler studies of the lower extremities are required. Both lower extremities should be studied. Ventilation-perfusion scans or CT angiograms should be ordered when Doppler studies are positive or when symptoms suggest pulmonary embolism,

Management

Despite the high frequency of deep venous thrombosis in brain tumor patients, there are aspects of management that are still controversial. The most important aspect of management is prevention. Intermittent pneumatic compression of the calf reduces the incidence of venous thrombosis in the perioperative period. Low-molecular weight heparin is also used, but some investigators have found a significant increase in postoperative intracranial hemorrhage when used at typical doses for prophylaxis (Dickinson et al. 1998). Passive and active physical therapy should be incorporated in the prevention of deep venous thrombosis.

Immediate anticoagulation is indicated once deep venous thrombosis is confirmed. Patients are anticoagulated with low-molecular weight or fractionated heparin and started on warfarin. In deep venous thrombosis, oral anticoagulation is continued for at least 6 months. When pulmonary embolism has occurred, treatment is continued indefinitely. Another method that is often used in the management of deep venous thrombosis is vena caval interruption. A recent review on the indications for vena caval interruption indicated two accepted indications for the procedure: a temporary or definitive contraindication to anticoagulant treatment and failure of anticoagulation (Girard et al. 2000). Vena caval interruption is usually achieved with Greenfield titanium or steel filters. Although filter placement may be considered convenient in patients who may be at high risk of bleeding, thrombosis at or above the filter site may result in pulmonary embolism. Extensive inferior vena caval thrombosis may sometimes complicate filter placement, resulting in severe venous insufficiency, lower extremity gangrene, sepsis, and death (Figure 58C2), Decousus et al. (1998) examined vena caval filters in the prevention of pulmonary embolism m a multicenter, randomized open trial comparing vena caval filter with no filter and anticoagulation. This study demonstrated initial efficacy of vena cava) filters in preventing pulmonary embolism. However, at 2 years, an excess recurrence of deep vein thrombosis was noted in the vena caval filter group. There was also no effect on immediate or long-term mortality in this group. Our clinical experience has been that thrombosis at the filter site may be a frequent problem unless patients are also maintained on low-molecular weight heparin at prophylactic doses or warfarin after filter placement {see Figures 58C.2 and 58C.3).

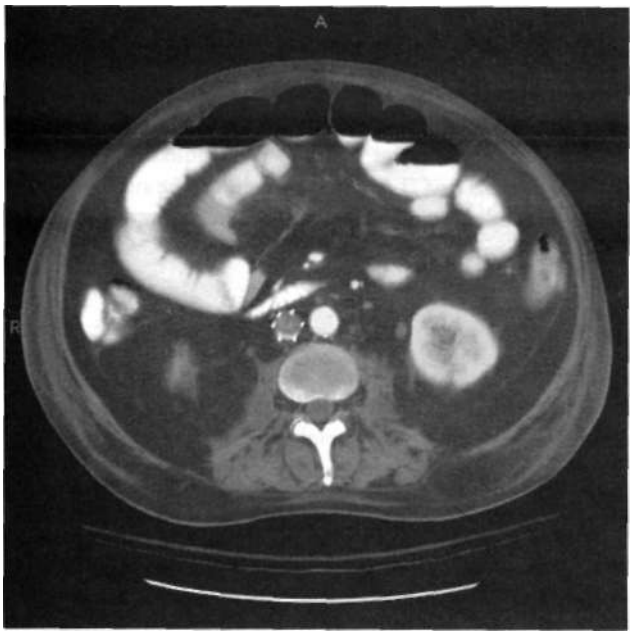


FIGURE S8C.2 Extensive clot formation at the site of an inferior vena caval filter. Note the small elliptical area of contrast in the vein indicating flow and the hypodense area within the vein representing clot formation.

SUMMARY

Brain tumors can present in a dramatic way, such as with seizure activity or in a more progressive fashion with worsening headache, weakness, and numbness. In either case, modern imaging facilitates the diagnosis, although a careful clinical assessment is critical in assessing performance status, suitability for experimental or conventional therapies, and determining practical needs such as walking aids and home safety alterations. Because cognitive dysfunction is often present in patients with brain tumors, bedside cognitive evaluation is mandatory in all patients and formal neuropsychological evaluation is necessary in a few. Until therapies that are more effective are developed, the emphasis of follow-up care musr be on the quality of life of patients. Besides ascertaining cognitive and physical function, this requires monitoring for brain tumor complications and preventing or treating them in a timely fashion. The use of anticonvulsants, prophylactic anticoagulation, physical therapy, and corticosteroids may help patients achieve a better quality of life with control of symptoms and prevention of complications.

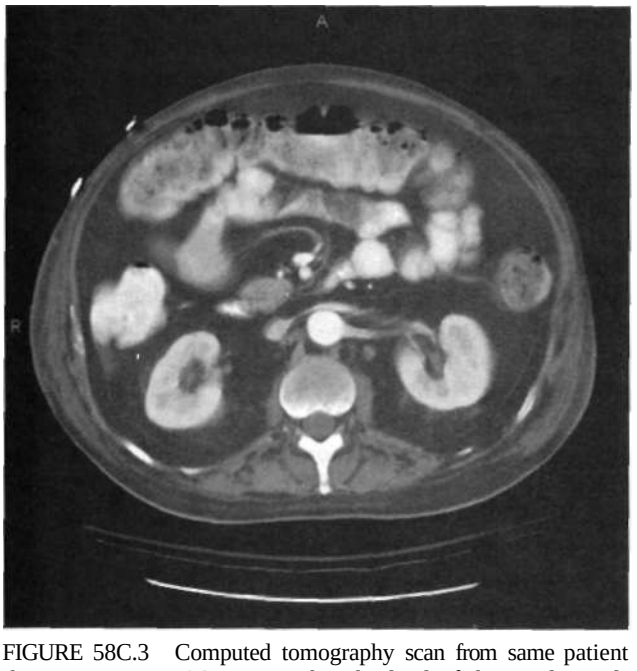


FIGURE 58C.3 Computed tomography scan from same patient shown in Figure 58C.2. Note that the level of the renal vessels above the filter flow is patent as indicated by contrast enhancement within the renal vein.

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Chapter 58
Cancer and the Nervous System

D. NEUROIMAGING

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Neuroimaging has many important roles in neuro-oncology, including preoperative differential diagnosis, operative planning, assessment of response and tumor progression, and identification of treatment-related side effects. In the practice of neuro-oncology, gadolinium-enhanced magnetic resonance imaging (MR1) is the imaging modality of choice. It is extremely sensitive to pathological alterations in brain tissue and the anatomic resolution is significantly better than computed tomography (CT) (Atlas et al. 2002). Despite significant advances in imaging technology, several significant limitations exist in the specificity of imaging for determining tumor type, tumor grade, response to treatment, and detecting treatment-related complications. Functional and spectroscopic MRI techniques hold the promise of increased imaging specificity, as well as allowing better understanding of tumor physiology.

CENTRAL NERVOUS SYSTEM METASTASIS

Brain Metastasis (Figure 58D.1)

Brain metastasis may arise from almost any primary tumor in the body. Prostate cancer and skin tumors other than melanoma are exceptions; brain metastases are highly unusual in both. Lung, breast, and melanoma are the most common sites of primary tumors in patients with brain metastasis. Melanoma comprises only 1% of all cancers, and thus has a clear predilection to produce brain metastasis. Brain metastases typically occur in patients with advanced systemic metastatic disease. In such patients, the presence of a typical appearing brain lesion on imaging is sufficient for the diagnosis of brain metastasis. However, the first sign of cancer in 10% of patients with lung cancer is metastasis. Therefore a broader ncuroradiological differential diagnosis is required in the absence of known metastatic cancer. The peak age incidence of brain metastasis mirrors that of the primary tumor. In 50% of patients, metastases are multiple and distributed to various brain regions according to relative blood flow. Brain metastases arc most commonly located at the gray-white junction, but also appear in the white matter and other sites. The lesions have prominent, well-circumscribed homogeneous or ring enhancement, and typically are associated with a substantial degree of vasogenic edema. Hemorrhage and cystic changes may occur, but calcification is rare.

Leptomeningcal Metastasis (Figure 58D.2)

Leptomeningcal metastasis (LM) results in multifocal neurological deficits. Similar to other metastatic complications,

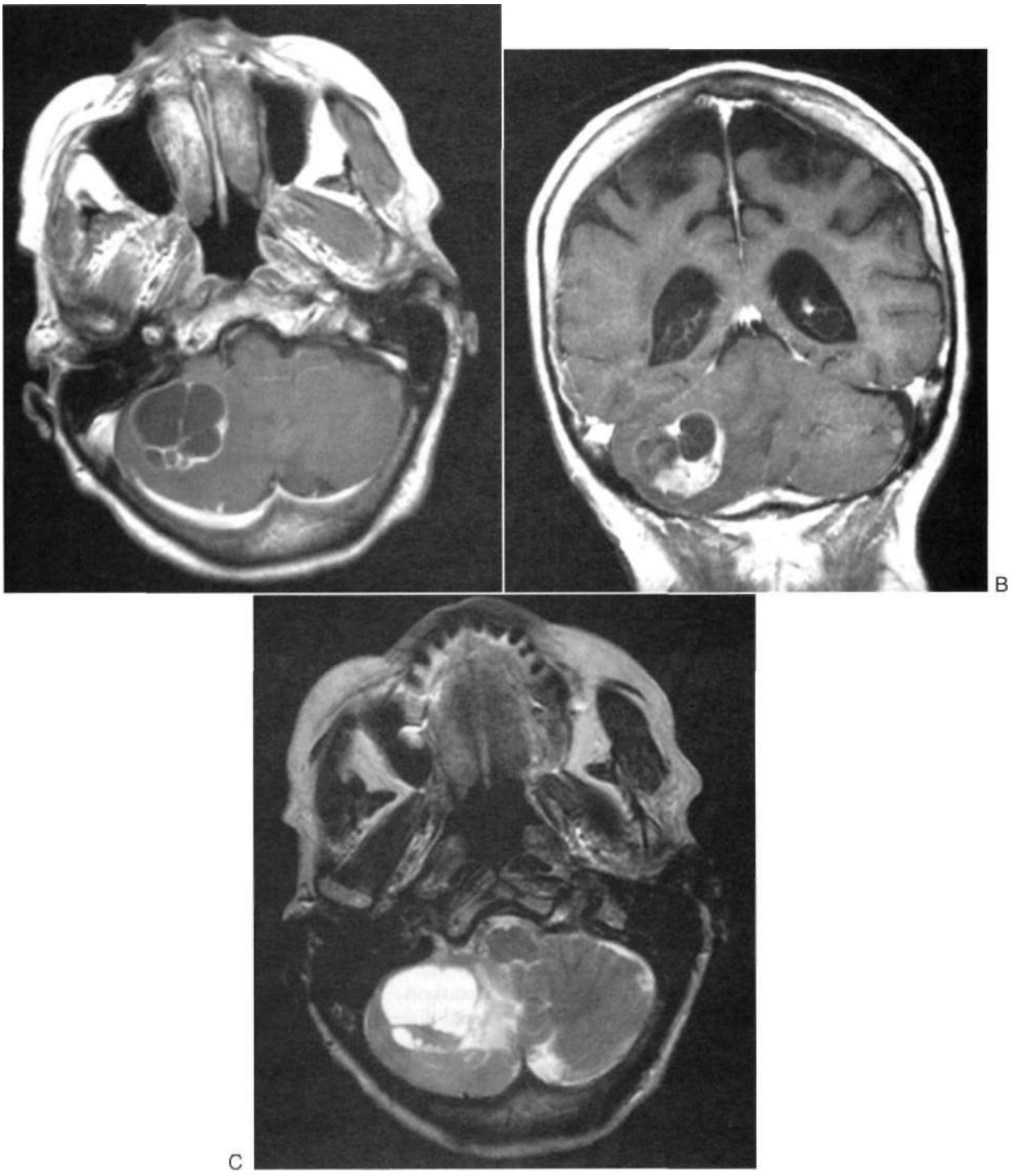


FIGURE 58D.1 Brain metastasis. A gadolinium-enhanced T1W1 in a 79-year-old woman with metastatic ovarian adenocarcinoma shows a septated, cystic-appearing lesion with an inferior mural nodule (A, B). There is mass effect on the fourth ventricle and medulla. Hyperintense T2-weighted signal is seen wirhin the cystic portion of the lesion, whereas the solid portion of the lesion is isointense to brain (C).

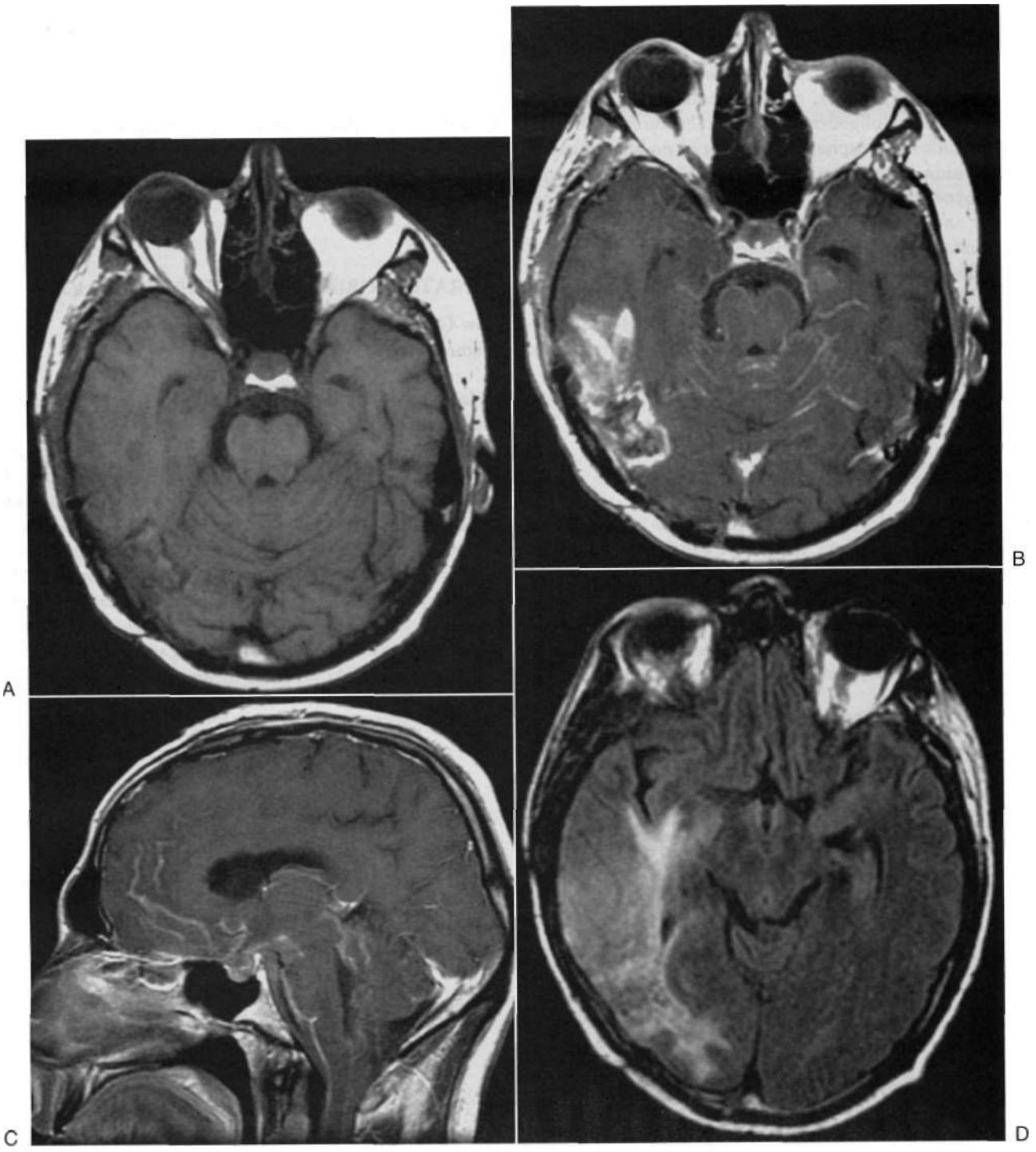


FIGURE 58D.2 Lcptomeningeal metastasis. A 34-year-old man developed multifocal symptoms along the neuraxis 1 year after diagnosis of a glioblastoma arising in oligodendroglioma. There had been three craniotomies for tumor resection. No abnormalities are detected in the subarachnoid spaces on T1WI prior to gadolinium administration (A). After gadolinium, prominent linear enhancement is seen on the surface of the midbrain and along the cerebellar folia (B), in sulci in the frontal lobes and along the ventral pons and medulla (C), Fluid-attenuated inversion recovery (FLAIR) images do not show clearly hyperintense signal in the subarachnoid spaces (D), although this finding is often seen in cases of leptomeningcal tumor spread.

LM usually occurs in patients with advanced systemic cancer. In addition, several primary brain tumors can produce LM, including primitive neuroectodermal tumors (PNETs), ependymomas, primary central nervous system lymphoma, and oligodendrogliomas. Features of LM on MRI include hydrocephalus and linear or nodular enhancement within the subarachnoid space. FLAIR images may show hyperintense signal within the subarachnoid space (Singer and Atlas 1998). Gadolinium-enhanced imaging of the cauda equina may be particularly useful in patients with clinical features suggestive of LM but with normal brain MRI and cerebrospinal fluid (CSF) cytology. In the appropriate clinical setting, the presence of nodular enhancement along the cauda equina is strong evidence to support the diagnosis of LM.

Metastatic Epidural Spinal Cord Compression (Figure 58D.3)

Epidural spinal cord compression (ESCC) is also a late complication of systemic metastatic cancer. Patients typically present with a few weeks of back pain followed by lower limb weakness. On rare occasion, FSCC may be the initial manifestation of cancer. The most common mechanism of ESCC is a vertebral body metastasis with extension into the adjacent spinal canal. Paraspinal tumors may also gain access to the epidural space by growing through neural foramina. The radiological evaluation of a patient with suspected ESCC! requires sagittal II and T2WI through the entire spine, because a 25% incidence of synchronous lesions exists. Axial images through the epidural mass permit further assessment of the severity of cord compression and are valuable for surgical and radiation planning.

SUPRATENTORIAL PRIMARY BRAIN TUMORS

Low-Grade Diffuse Fibrillary Astrocytomas (Figure 58D.4)

Mildly in creased eel hilarity and tumor cell infiltration into surrounding brain tissue characterizes low-grade astrocytoma (LGA). Vascular endothelial proliferation, mitotic activity, and necrosis do not occur. The average age at diagnosis is 34 years, although the age range is quite wide (Kleihues and Cavence 2000). On MRI, LGA demonstrates ill-defined T2WI hyperintensity in white matter and cortex, with mild mass effect. Vasogenic edema is minimal. The periphery of the lesion may show linear enhancement, but enhancement within the mass suggests high-grade histology. However, the absence of gadolinium enhancement is not reliable evidence of low-grade histology; one

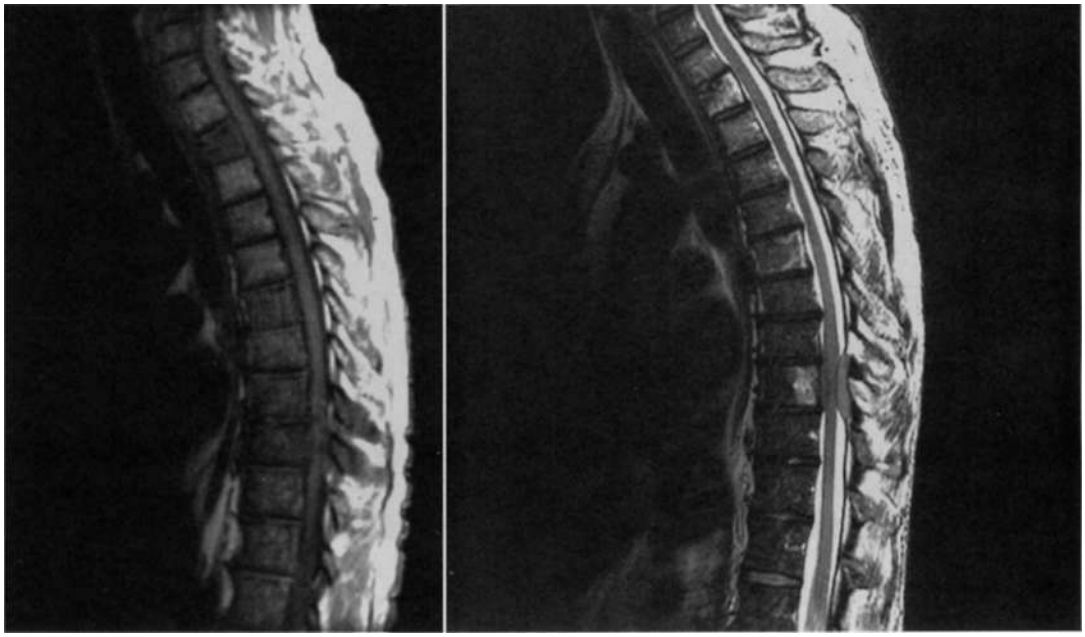
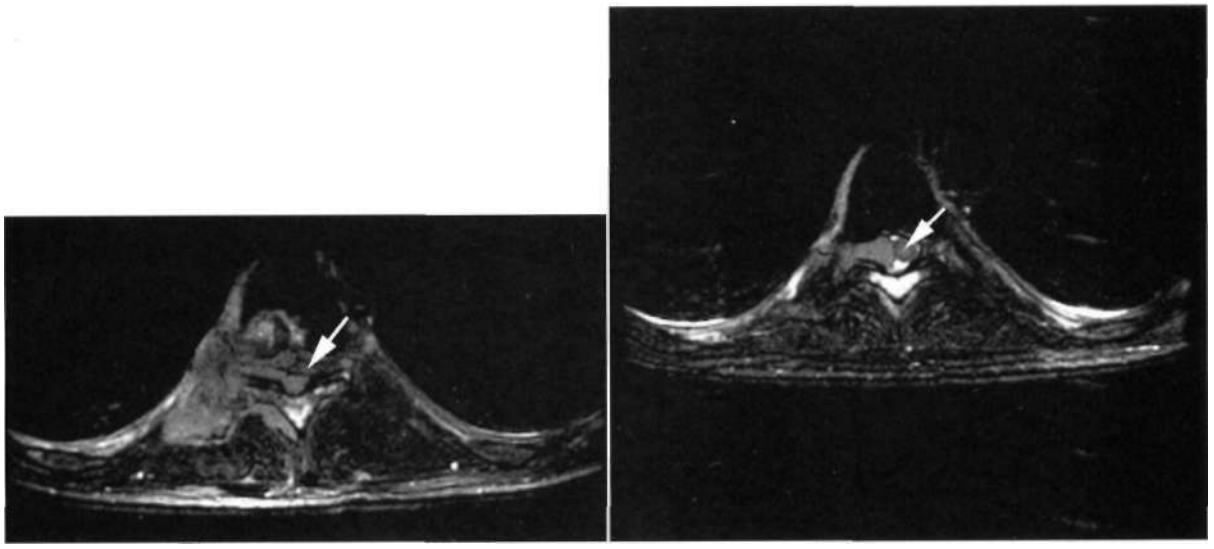


FIGURE 58D.3 Metastatic epidural spinal cord compression. A 45-year-old man with progressive systemic non-Hodgfcin's lymphoma complained of thoracic back pain and lower extremity weakness. Sagittal T1WI (A) and T2WI (B) reveal an epidural mass lesion compressing the thoracic spinal cord at T8. There is minimal, if any, abnormal 12 weighted signal abnormality in the spinal cord parenchyma. Marrow signal is abnormal in the dorsal aspect of the T8 vertebral body. Axial T1WI (C) and T2W1 (D) show a right paraspinal mass with invasion of tumor into the spinal canal via a neural foramen. There is also a lesion in the dorsal right vertebral body. The thoracic spinal cord (C, D, *arrows)* is deviated to the left, but there is residual surrounding cerebrospinal fluid space remaining. The more common mechanism of metastatic epidural cord compression is direct extension of a vertebral lesion into the spinal canal.



third of patients with nonenhancing gliomas have high-grade tumors at biopsy (Barker et al. 1997). Cyst formation is common. Calcification is uncommon except with oligodendroglioma.

Repeat imaging studies are useful to follow tumor activity, particularly to detect anaplastic progression to a higher-grade astrocytoma. Comparison of new studies with the postoperative baseline examination, and to the most recent prior study, is the best method to detect the gradual growth ot I GA. New foci of contrast enhancement suggest anaplastic progression, but transitory radiation-induced enhancement and radiation necrosis are also

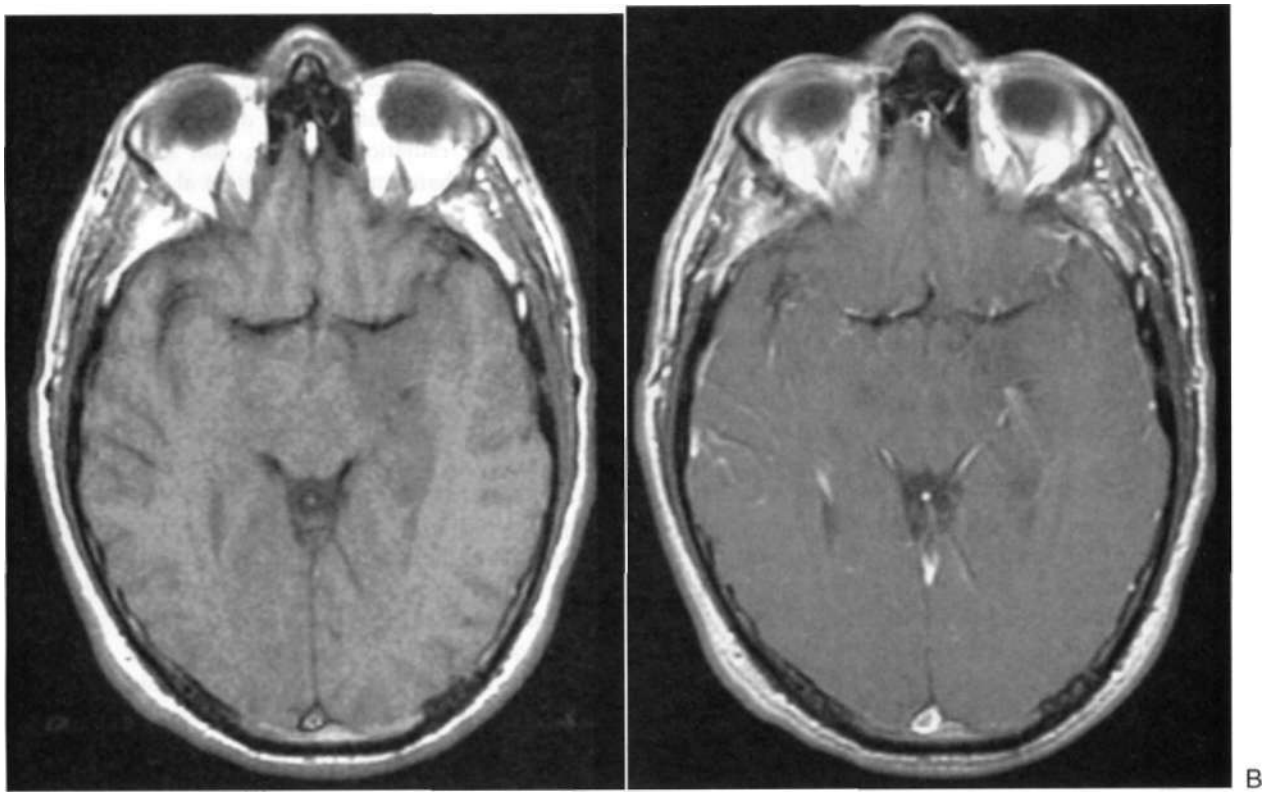


FIGURE 58D.4 Low-grade diffuse fibrillary astrocytoma. Axial T1WI in a 43-year-old man with new onset partial complex seizures demonstrates a slightly hypointense mass lesion within the medial left temporal lobe (A). There is no evidence of enhancement after gadolinium administration (B). A poorly circumscribed, hyperintense lesion expanding cortex and white matter of the medial lobe is seen on T2WI (C) and FLAIR (D) images. There is no evidence of vasogenic edema. Serial follow-up magnetic resonance imaging scans revealed an enhancing nodule and extension of the T2-weightcd signal abnormality 6 months after diagnosis (not shown). Low-grade astrocytomas in middle aged and older adults should be followed closely for evidence of early anaplastic progression.

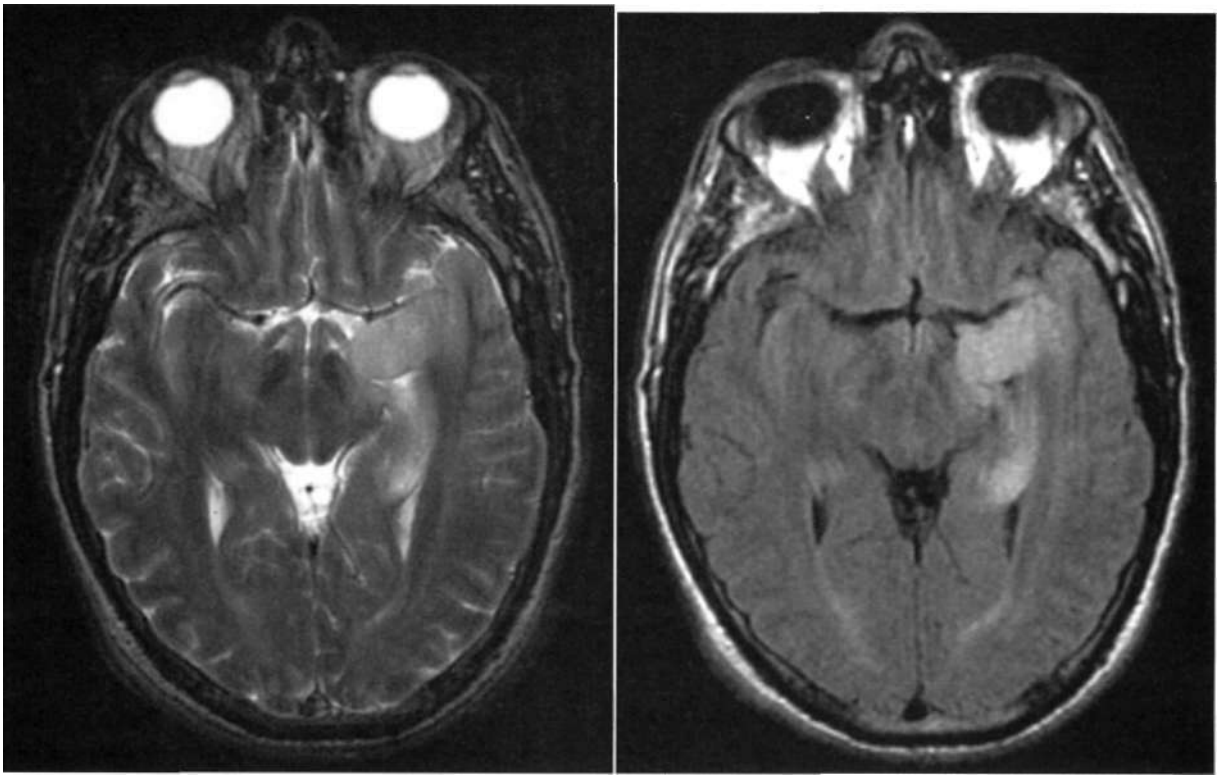


FIGURE 58D.4, cont'd.

considerations in patients who have received irradiation (Peterson et al. 1995).

Anaplastic Astrocytoma (Figure 58D.5) and Glioblastoma Multiforme (Figure 58D.6)

Anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM) are both high-grade diffuse fibrillary astrocytomas and have high cell density, mitotic figutes, and vascular endothelial proliferation. GBMs also show necrosis. Five percent of high-grade astrocytomas are multifocal. The peak age incidence is 41 years for AA and *53* years for GBM (Kleihues and Cavcnee 2000). More mass effect occurs than in LGA, and areas of hemorrhage may produce heterogeneous signal on T1WI and T2WI. Irregular ring-enhancement after gadolinium administration implies the presence of necrosis and is suggestive of GBM. Fluid-filled cystic structures may show smooth linear enhancement. A combination of vasogenic edema and infiltrating tumor cells produces extensive surrounding areas of hyperinteusity within the white matter surrounding the tumor on T2WI. As noted previously, high-grade gliomas occasionally do not demonstrate enhancement after administration of gadolinium.

Most high-grade astrocytomas do not exhibit marked shrinkage following treatment. However, glucocorticoid therapy for peritumoral edema can lead to a significant decrease in the size of both the contrast-enhancing component and the peritumoral edema. Enlarging areas of contrast enhancement are common findings on follow-up studies. The differential diagnosis includes tumor progression, radiation necrosis, and transient radiation-associated enhancement (Peterson et al. 1995).

Low-Grade Oligodendroglioma (Figure 58D.7)

Low-grade oligodendrogliomas (LGOs) are tumors of low to moderate cell density with abundant proliferation of capillaries and absence of necrosis. The cortex and white matter are prominently involved, and calcification is common. Peak age incidence is 42 years (Kleihues and Cavencc 2000). On MRI, LGO are hypointense on T1WI and hyperintense on T2WI, and margins are well defined and may expand the cortex. Vasogenic edema is minimal. Contrast enhancement, calcification, and cyst formation may be present. Gradual enlargement may occur over several years, and comparison of new studies with a postoperative baseline examination is valuable. Unlike astrocytoma, oligodendroglioma may shrink significantly after treatment.

Anaplastic Oligodendroglioma

Anaplastic oligodendrogliomas (AOs) usually show more mass effect, contrast-enhancement, and vasogenic edema than LGO. Ring-enhancement may portend a more aggressive and less responsive tumor than does more

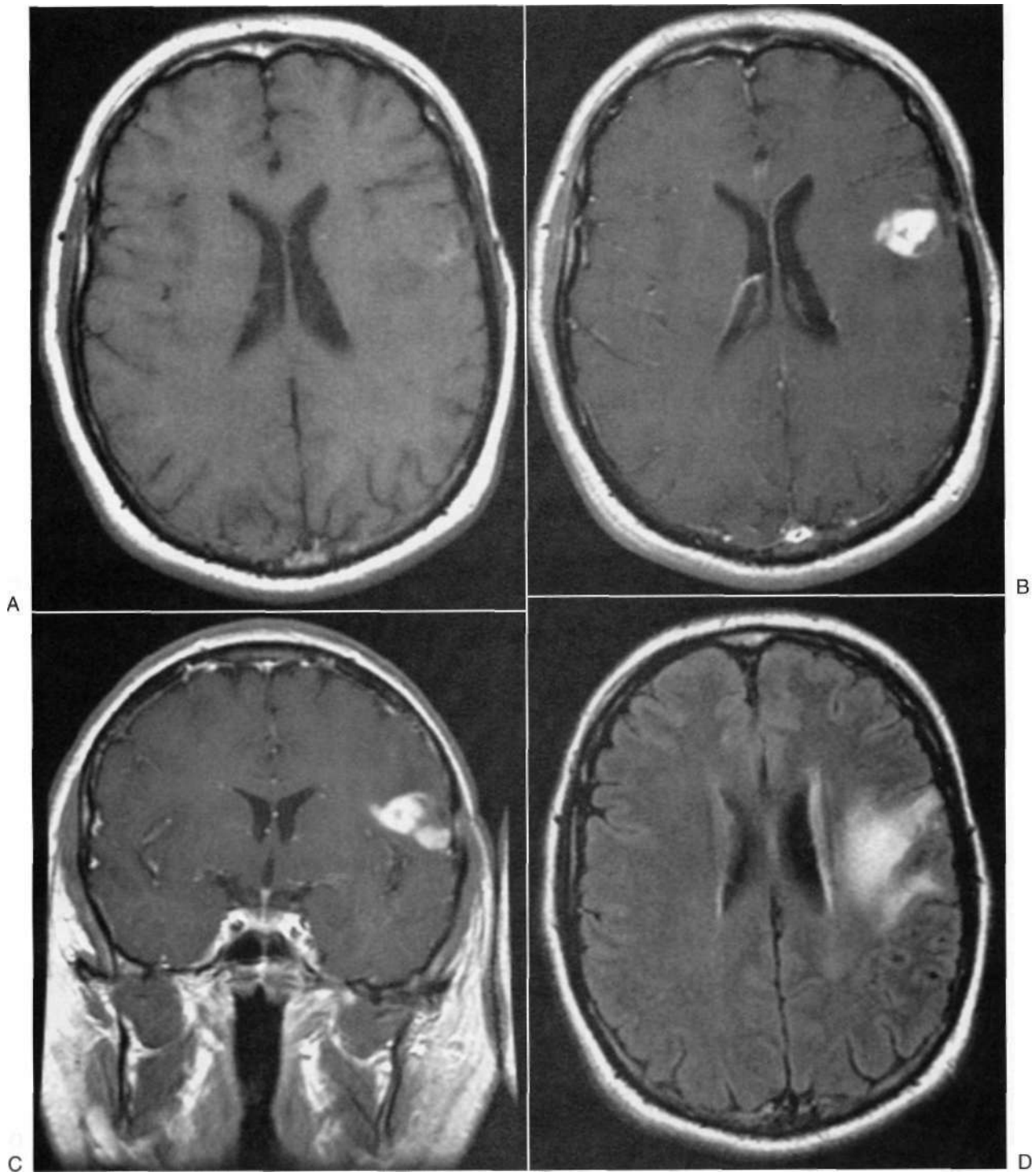


FIGURE 5SU.5 Anaplastic astrocytoma. TIWI before (A) and after (B, C) gadolinium administration in a 36-ycar-old man with brief episodes of aphasia demonstrate a small area of minimal hypointensity in the left frontal lobe that exhibits focal enhancement. There is no clear evidence of ring enhancement. A FLAIR image (D) shows a poorly circumscribed area of heterogeneous hyperintensity centered within the white matter and cortex.

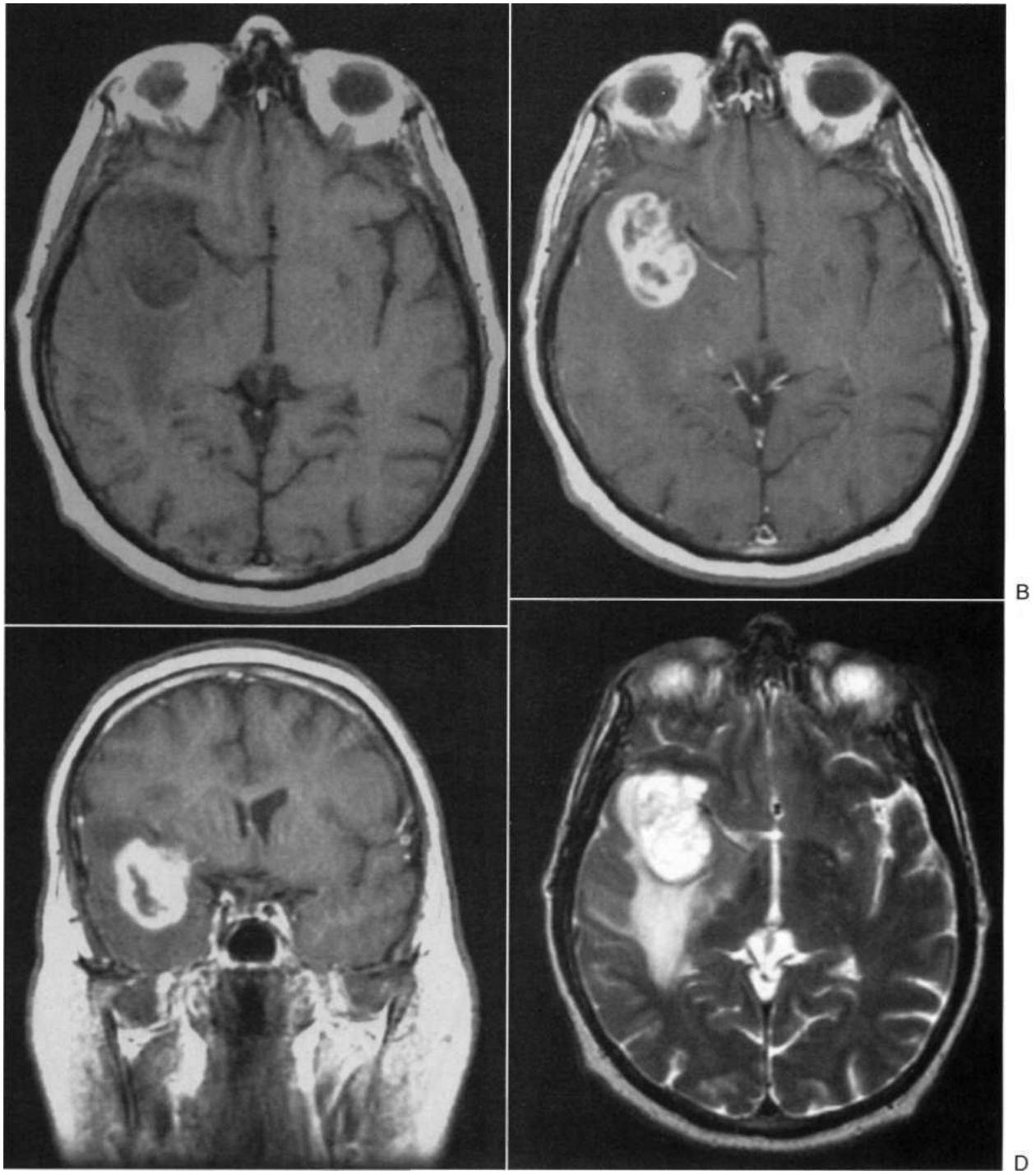


FIGURE 58D.6 Glioblastoma multiforme. A 64-year-old man developed partial complex seizures that included olfactory hallucinations. T1WI before gadolinium (A) shows a hypointense mass lesion within the right temporal lobe that has a central, cystic-appearing region of even lower intensity. Irregular ring enhancement is seen after administtation of gadolinium (B, C). T2WI (D) demonstrates that the cystic-a p pea ring component of the lesion is vety hyperintense, representing a large area of necrosis, as confirmed at the time of surgery. Vasogenic edema and infiltrating tumor produce a posterior region of milder hyperintensity with ill-defined margins within the white matter.

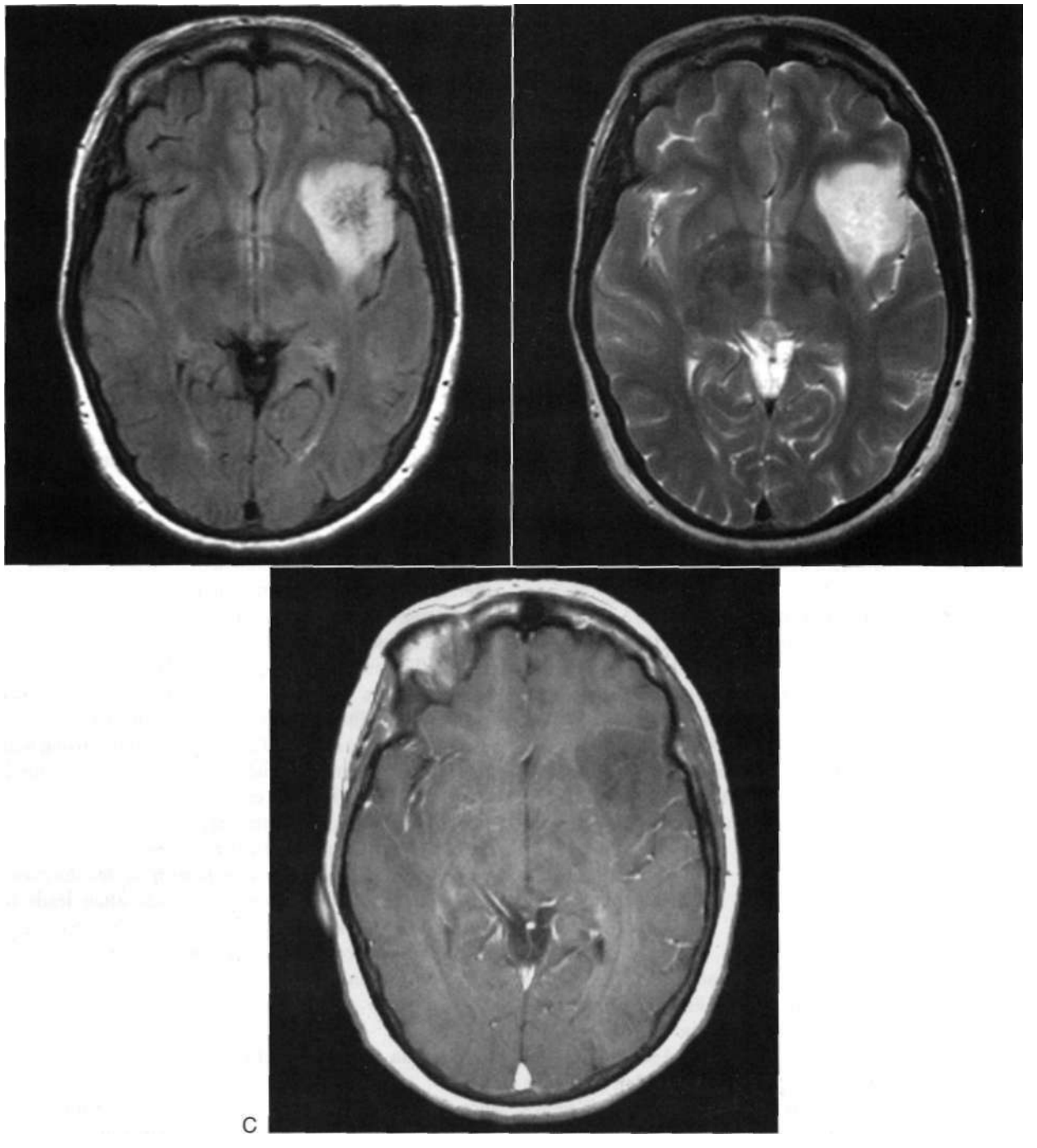


FIGURE 58D.7 Low-grade oligodendroglioma. Axial FLAIR images (A) and T2W1 (B) demonstrate a well-circumscribed lesion within the left frontal insular region in a 50-year-old woman who had a 10-month history of episodes of aphasia and right hemi paresis. There is prominent cortical expansion as well as involvement of white matter, effacement of sulci in the left frontal region, but no evidence of significant surrounding vasogenic edema or mass effect on the left lateral ventricle. After administration of gadolinium, there is no evidence of enhancement (C). Low-grade oligodendrogliomas often demonstrate some enhancement. Computed tomography showed no evidence of calcification (not shown).

homogeneous enhancement (Cairncross et al. 1998). Seventy-five percent of AOs exhibit a marked response to therapy. This prominent response correlates with the loss of heterozygosity on the short arm of chromosome 1p.

Optic Pathway Glioma (Figure 58D.8)

The origin of optic pathway glioma is most commonly as a pilocytic astrocytoma in the optic nerves and optic chiasm of children. These tumors are usually of low malignant potential. Bilateral optic nerve gliomas are associated with neurofibromatosis (NF) type 1 (Klcihues and Cavenee 2000). Adults have a more aggressive, higher-grade, diffuse astrocytoma. High-grade tumors enlarge the affected optic pathway structures and show contrast enhancement (Kornreich et al. 2001). Hyper intensity on T2WI that extends posteriorly along the optic tracts indicates tumor infiltration and vasogenic edema.

Subependymal Giant Cell Astrocytoma

Subependymal giant cell astrocytomas (SEGAs) develop at the foramen of Monroe in approximately 10% of patients with tuberous sclerosis (TS) by age 20. Neurological complications usually result from hydrocephalus. Because of a high rate of spontaneous mutation, only one half of patients have a family history of TS (Kleihues and Cavenee 2000). Enhancement is present, and calcification and hemorrhage may be seen (Nishio et al. 2001). Other features of TS, cortical tubers and subependymal nodules, are present as well.

Ganglioglioma

Gangliogliomas contain a combination of dysplastic large neurons and neoplastic astrocytic cells. They are designated *anaplastic ganglioglioma* when the glial component appears to have high-grade features. Age at time of diagnosis may range from childhood to adult life. The temporal lobes arc the most common location (Kleihues and Cavenee 2000). Calcification and cystic changes are common. On MRI, these tumors show nodular areas of contrast enhancement and may be solid or cystic.

Dysembryoplastic Neuroepithelial Tumor

Composed of glial and neuronal elements, dysembryoplastic neuroepithelial tumors (DNETs) are benign lesions that rarely regrow after total or even subtotal surgical resection. They are most often located in the medial aspect of the temporal lobes. Peak age incidence is the second and third decades (Kleihues and Cavenee 2000). DNETs usually expand the cortex and subcortical white matter, and may have small rings of enhancement. Calcification is common, whereas macroscopic cyst formation is rare.

Central Neurocytoma (Figure 58D.9)

Intraventricular masses arising from the region of the foramen of Monro, central neurocytomas are slow growing, densely calcified tumors that contain homogenous populations of small round cells, histologically indistinguishable from oligodendroglioma (Kleihues and Cavenee 2000). However, tumor cells express neuronal proteins. Average-age at diagnosis is 29 years, with a wide range. Hydrocephalus is common.

Primary Central Nervous System Lymphoma (Figure 58D.10)

Primary central nervous system lymphoma (PCNSL) is a non-Hodgkin's B-cell lymphoma that arises in the brain and often involves the eye (intraocular lymphoma). This tumor has become much more common over the past several decades. Peak age of incidence is from 50 years to late sixties. Twenty-five percent of PCNSLs are multifocal. Tumor masses favor deep cerebral and periventricular structures (Kleihues and Cavenee 2000). The lesions are relatively hypointensc on T2WI, demonstrate strong homogeneous enhancement, and have extensive surrounding vasogenic edema (Buhring et al. 2001). Abnormal diffusion, a common finding, probably represents dense ccllularity. PCNSL may shrink markedly or even disappear after administration of glucocorticoids such as dexamethasone. Preoperative administration of steroids often leads to a nondiagnostic brain biopsy. The likelihood of leptomeningeal dissemination requires gadolinium-enhanced imaging of the entire spine.

Germinoma (Figure 58D.11)

Intracranial gcrminomas may arise in the suprasellar or pineal regions. In the suprasellar location, pure germinomas are more common than mixed germinomas and arc highly radiosensitive lesions that Jo noi secrete tumor markers. Mixed germinomas are more common in the pineal region, may secrete ^-fetoprotein or jft-human chorionic gonadotropin, and are highly resistant to treatment. Peak age incidence is 10 years (Kleihues and Cavenee 2000). Gcrminomas are hyperdense on CT and show strong enhancement. Invasion of adjacent brain is common (Liang etal. 2002}. Teratomas, a type ol mixed germinoma, may contain calcification and fat. The high incidence of leptomeningeal dissemination requires gadolinium-enhanced imaging of the entire spine for staging purposes.

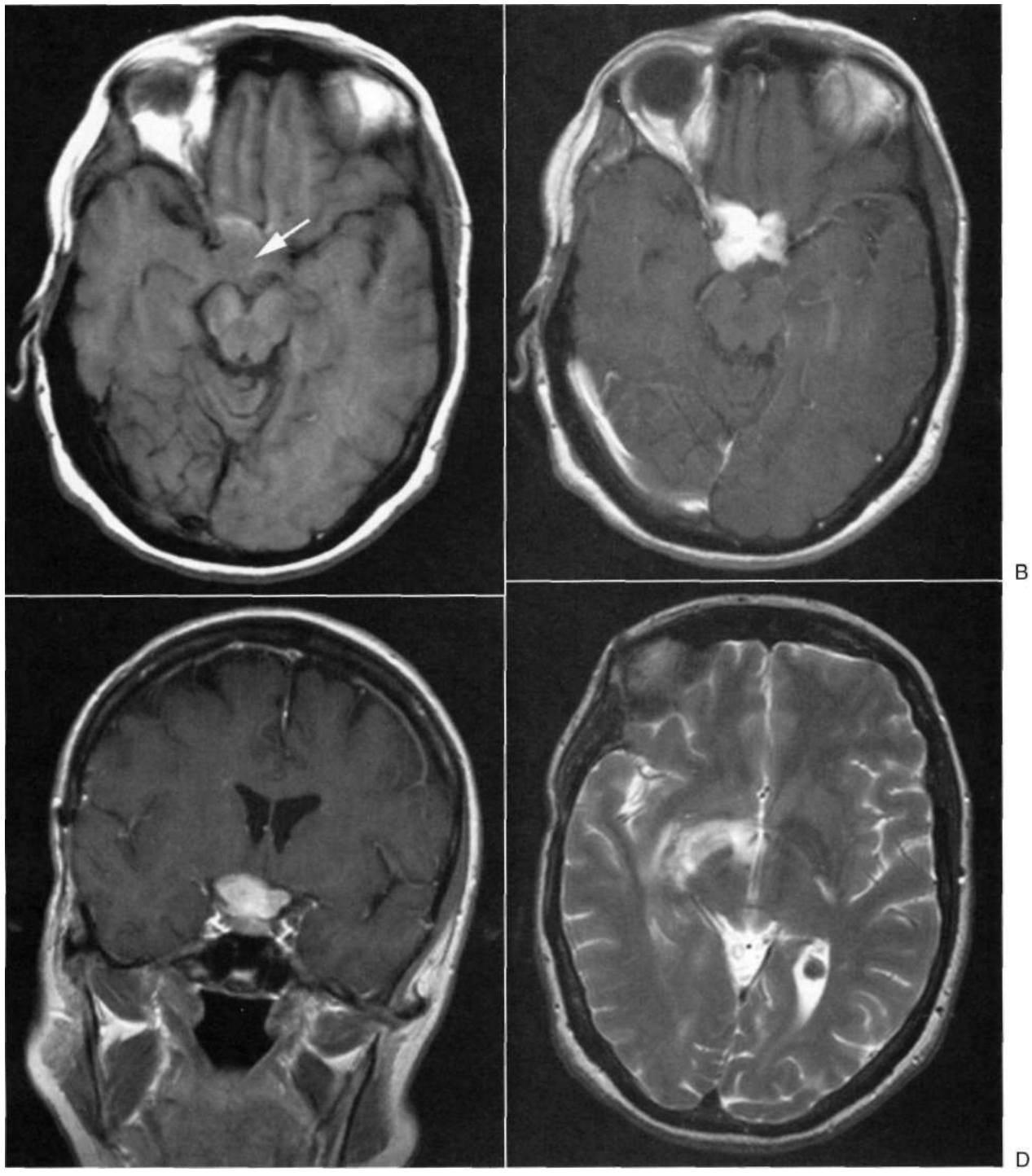


FIGURE 58D.8 Optic pathway anaplastic astrocytoma. T1WI before gadolinium (A) shows an isointense mass centered in the optic chiasm *{arrow)* with extension along bilateral optic nerves and tracts in a 54-year-old woman with several weeks of progressive blurring of vision in both eyes. There is heterogeneous contrast enhancement (B, C). The mass fills the majority of the suprasellar cistern. On T2WI (D) the rumor shows hypei intensity within the lesion, as well as hyperintense signal in the optic ttacts and the medial right temporal kibe. Involvement of the adjacent temporal lobe occurs by direct extension from the optic tracts. Tumor may sometimes spread posteriorly to the lateral geniculate nucleus.

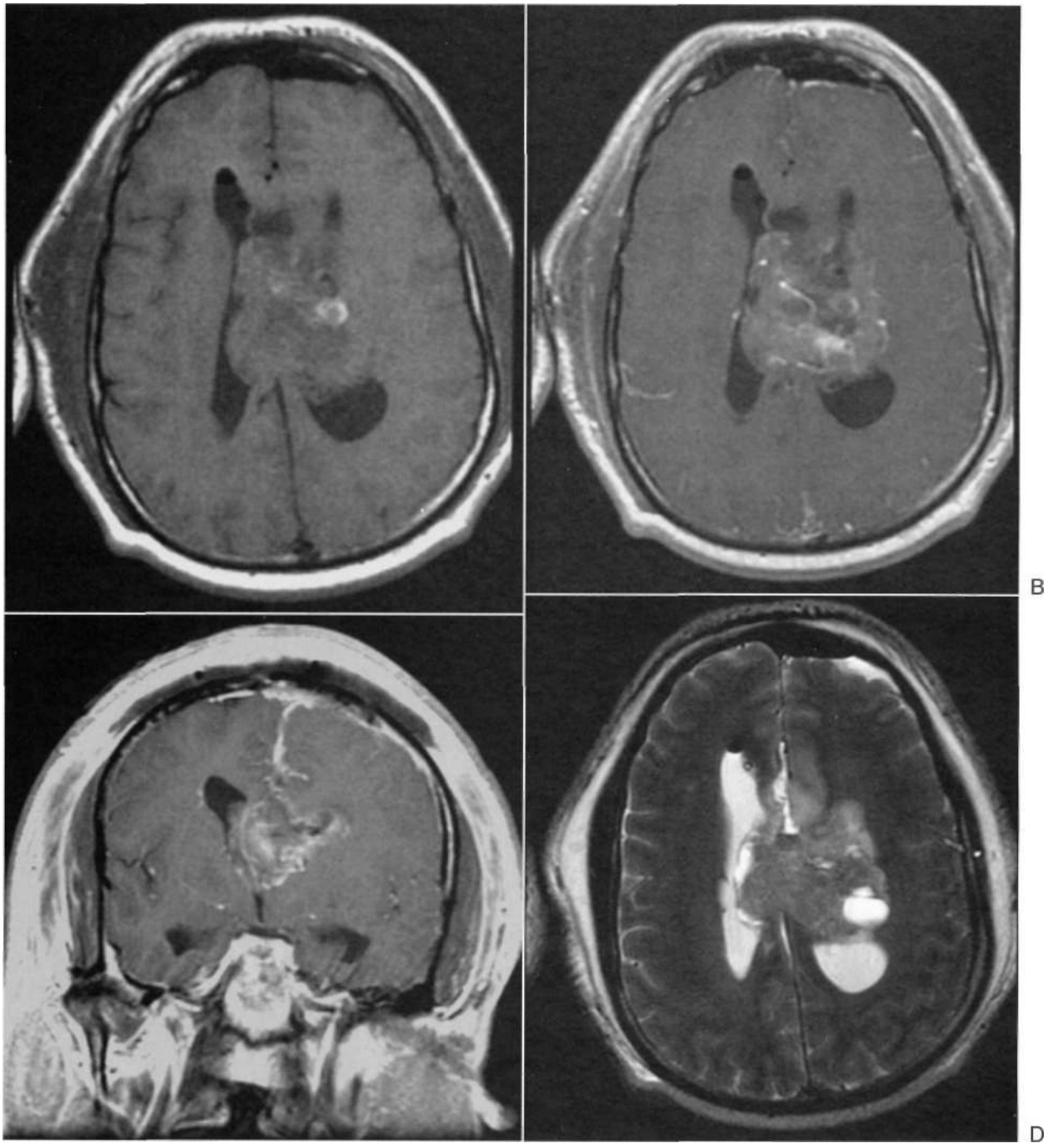


FIGURE 58D.9 Central neurocytoma. On T1 Wl (A) rumor is seen as a heterogeneous-signal mass lesion within the left lareral ventricle in a 45-year-old man with several weeks of headache, heaviness in his legs, and decreased visual acuity. Areas of hyperintensity likely represent calcification. After administration of gadolinium (B, Q, there is mild heterogeneous enhancement. The temporal horns of the lateral ventricle are dilated. On T2WI (D), the tumor is isointense to brain, with small areas of hyperintensity resulting from cystic change. A small amount of postbiopsy air is present within the frontal horn of the right lateral ventricle. Foci of dense calcification arc seen on computed tomography (E).

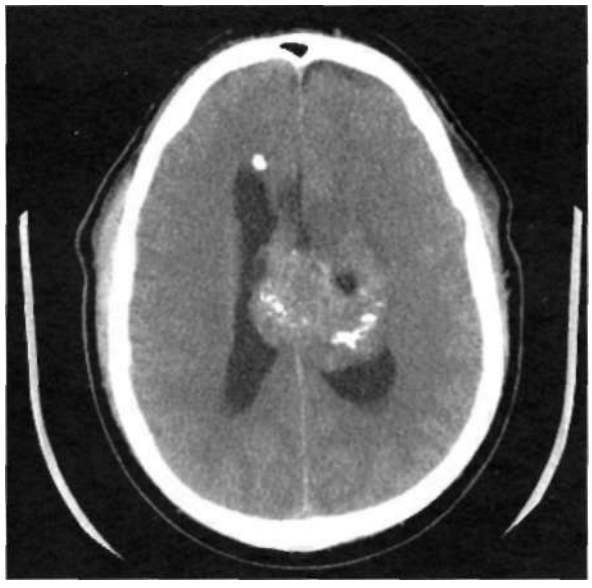


FIGURE S8D.9, cont'd.

Choroid Plexus Papilloma (Figure 58D.12)

Papillomas of the choroid plexus arise in the lateral ventricles (50%), third ventricle (5%), and fourth ventricle (40%). This is usually a tumor of childhood and young adulthood (Kleihues and Cavenee 2000). MRI shows a lobulated, well-circumscribed, enhancing, intraventricular lesion, often associated with hydrocephalus (Pencalet et al. 1998). Calcification is uncommon. Choroid plexus carcinoma is rare and shows brain invasion and necrosis.

Colloid Cyst (Figure 58D.13)

Colloid cyst is a rare lesion of adults in early middle age. Chronic or intermittent symptoms of hydrocephalus bring the tumor to clinical attention. The cyst arises in the anterior aspect of the third ventricle (Kleihues and Cavenee 2000). High concentrations of protein and cholesterol are present within the cyst, producing variable signal intensity on TIWI and T2WI. Peripheral enhancement may be present (Armao et al. 2000).

INFRATENTORIAL PRIMARY TUMORS

Ependymoma and Anaplastic Ependymoma (Figure 58D.14)

Ependymomas arise from cpendymal cells lining the surfaces of the ventricles. The most common location is the fourth ventricle. Spinal, lateral ventricular, and

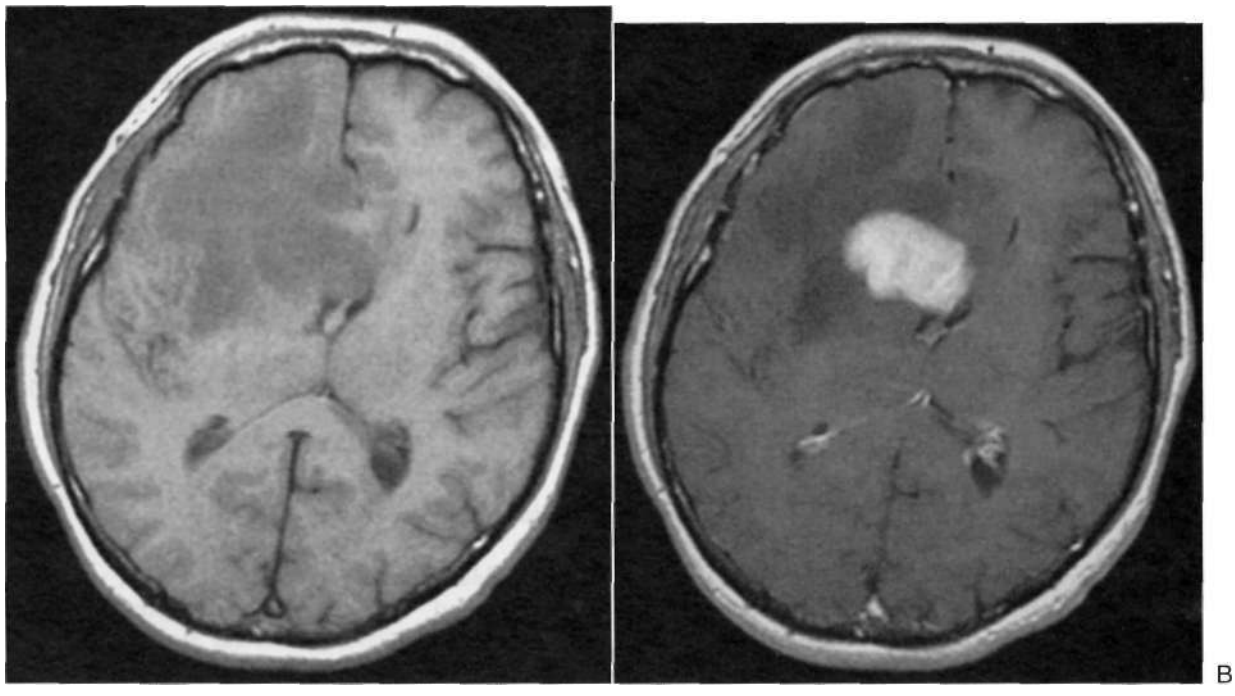


FIGURE 58D.10 Primary central nervous system lymphoma. TIWI before gadolinium (A) shows a single, minimally hypointense mass lesion in the region of the right caudate head, producing marked midline shift and subfaleine herniation in a 65-year-old man with 3 weeks of progressive cognitive changes and gait ataxia. There is strong, homogeneous contrast enhancement (H). On T2WI (C), the tumor is isointense to normal brain and is surrounded by a large area of vasogenic edema. Markedly abnormal diffusion is seen on diffusion-weighted images (D), suggesting high cell density.

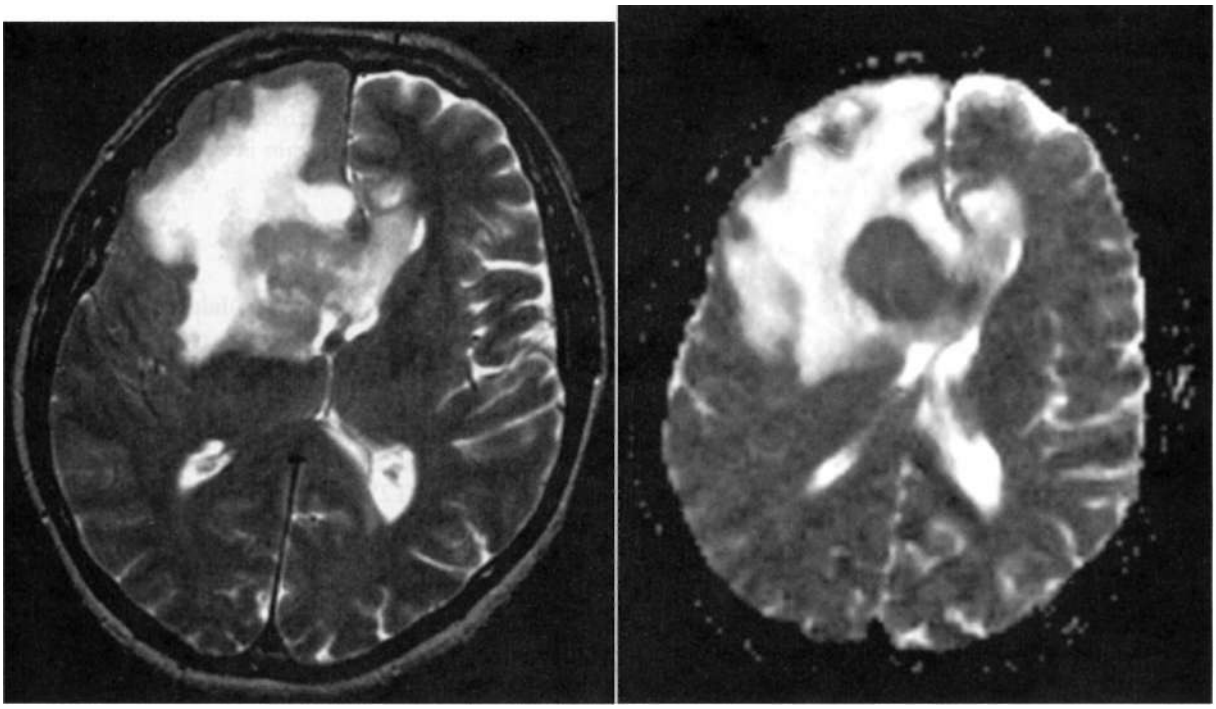


FIGURE 58D.10, cont'd.

extraventricular supratentorial tumors are less common. These lesions expand the fourth ventricle (Kleihues and Cavenee 2000). They are well circumscribed and show variable amounts of enhancement. The risk of leptomcningeal spread requires spinal imaging as part of staging.

Subependymoma

Subependymomas arise as a nodular mass lesion along the ventricular surface in middle to late adulthood, usually along the floor of the fourth ventricle (Kleihues and Cavenee 2000). Calcification and enhancement arc sometimes present. They are rarely symptomatic and the prognosis is excellent.

Juvenile Pilocytic Astrocytoma (Figure 58D.15)

Juvenile pilocytic astrocytoma (JPA) is a low-grade pilocytic astrocytoma of childhood. It usually arises as a cystic mass lesion with a mural nodule within the posterior fossa or the hypothalamic region. These tumors do not show aggressive growth or brain invasion (Kleihues and Cavenee 2000). The lesions arc hypointense on TIWI and hypcrintense on T2WI, and associated vasogenic edema is minimal. The cystic component may follow CSF signal. A nodule or mass lesion that shows strong, homogenous enhancement is present. Occasionally, tumors lack a cystic component.

Brainstem Glioma (Figure 58D.16)

Diffuse pontine astrocytomas are childhood tumors that enlarge the pons, show indistinct margins, and do not enhance. This type of brainstem glioma is the most common and has the poorest prognosis (Guillamo et al. 2001; Kleihues and Cavenee 2000). Cervicomedullary junction tumors are less common and grow more slowly. They are nonenhancing, well circumscribed, and have an exophytic component. The least common and most benign type of brainstem glioma is the tectal astrocytoma, a nonenhancing lesion that enlarges the tectal plate and produces obstructive hydrocephalus. Enhancement in a brainstem glioma usually indicates a high-grade tumor. In adults, brainstem gliomas may occur as low-grade, diffuse pontomedullary lesions, or as enhancing high-grade lesions.

Medulloblastoma (Figure 58D.17)

Medullobla stomas arc malignant cerebellar vermis tumors of childhood that have a pronounced tendency for leptomeningeal invasion. Peak age at diagnosis is 7 years. Adult mcdulloblastomas are much less common, and tend to arise in a lateral cerebellar hemisphere location. The fourth ventricle is compressed rather than expanded (Kleihues and Cavenee 2000). Medullobla stoma may be hypointense on T2WI and have abnormal diffusion due to high cell density (Tortori-Donati et al. 1996). They are rarely

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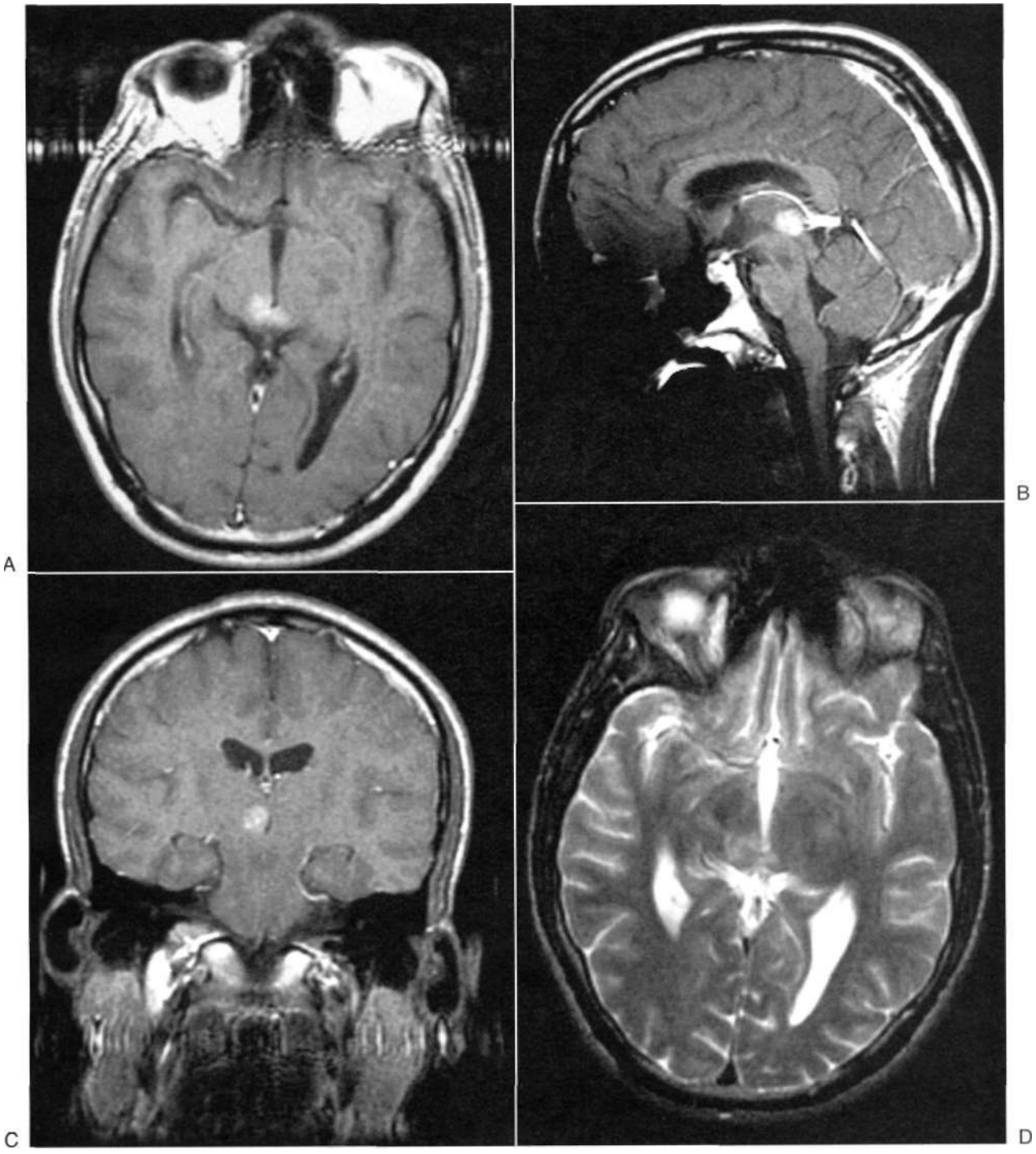

FIGURE 58D.11 I'ineal region germinoma. Gadolinium-enhanced T1WI (A, B, C) show a homogeneously enhancing lesion within the pineal region and walls of the posterior third ventricle in a 19-year-old man with 3 weeks of intermittent lightheadedness and vertical diplopia. There is invasion of the medial thalamic nuclei. On T2W1 (D), the tumor is mildly hyperintense.

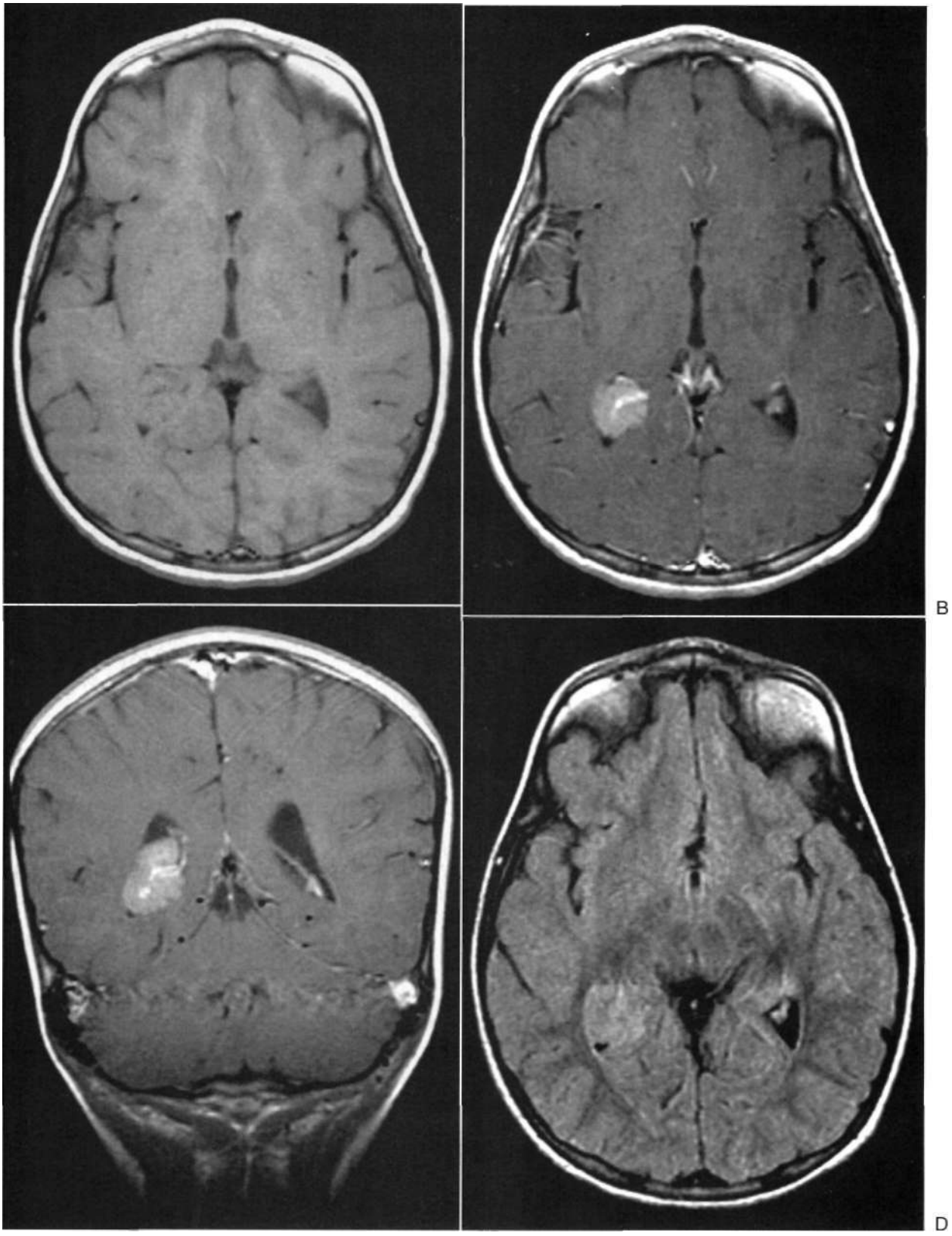

FIGURE 58D.12 Choroid plexus papilloma. T1WI before gadolinium (A) shows an isointense mass lesion within the trigone of the right lateral ventricle in an asymptomatic 4-year-old boy. The border of the lesion appears lobulated. There is homogenous enhancement (B, C). The tumor is mildly hyperintense on FLAIR (D). There is no evidence of brain invasion, vasogenic edema, or hydrocephalus. These tumors are commonly associated with hydrocephalus,

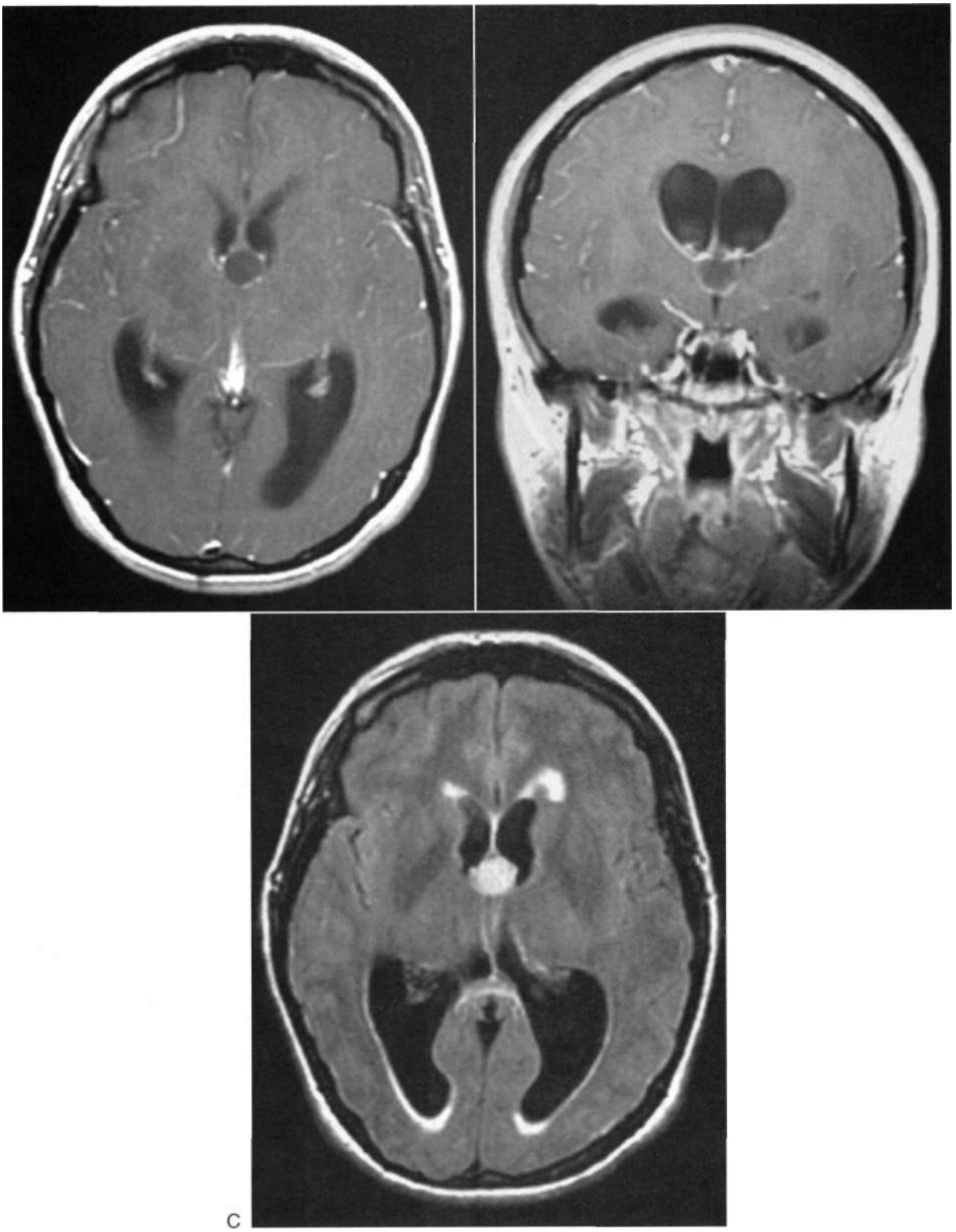

FIGURE 58D.13 Colloid cyst. A spherical, centrally hypo in tense structure with mild peripheral enhancement is present in the region of the foramen of Monro on the gadolinium-enhanced axial (A) and coronal (B) TIWI of a 35-year-old woman with 2 weeks of severe headache, nausea, and vomiting. The lateral ventricles arc dilated. The lesion is hyper in tense on an axial Fl.AIR image (C). TIWI and T2W1 signal intensities of colloid cysts are variable, depending on the concentrations of protein and cholesterol.

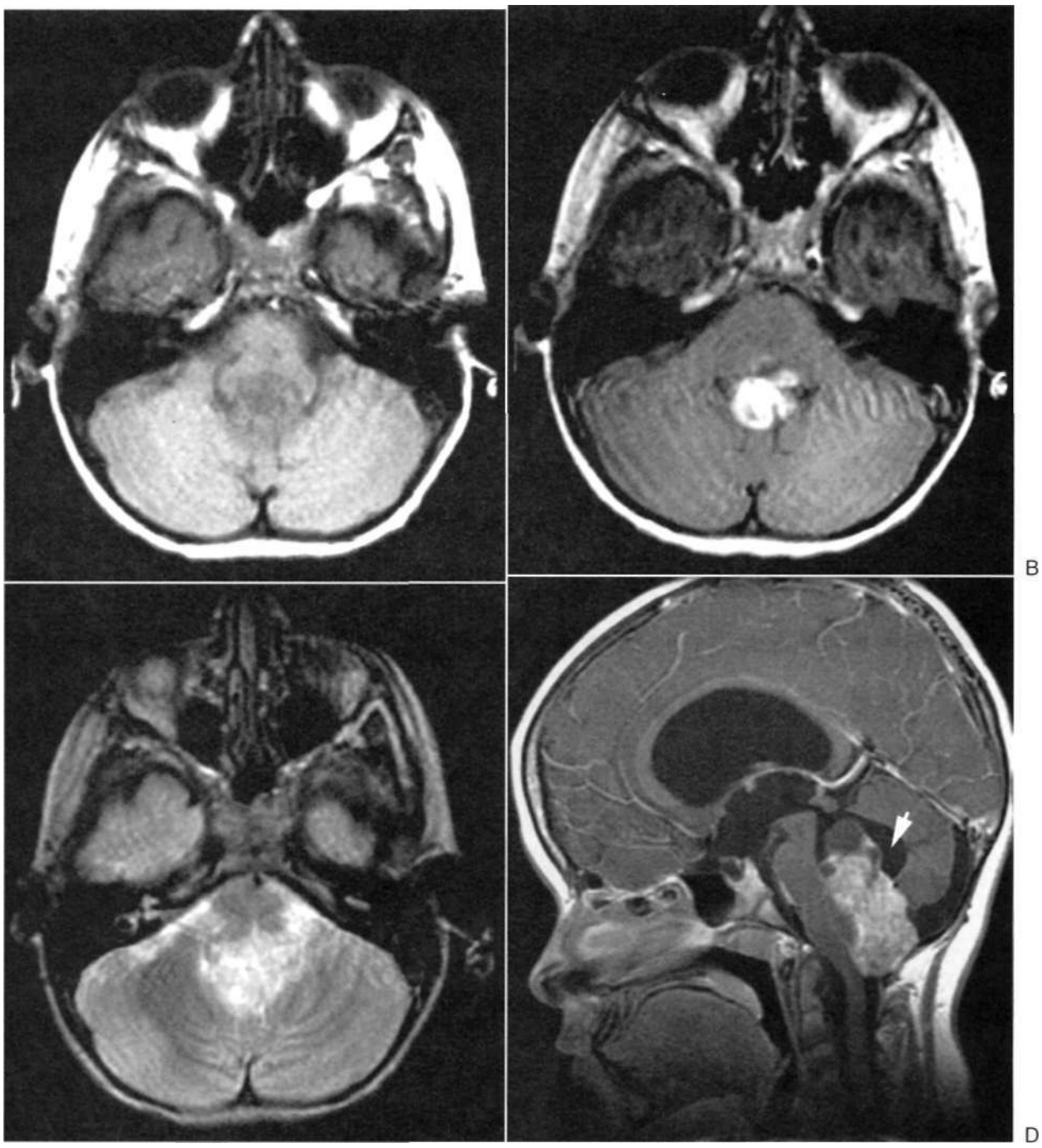

FIGURE 58D.14 Ependymoma. TIWI (A) shows a hypointense mass lesion within the fourth ventricle with well-circumscribed margins in a 5-year-old boy with a 5-month history of worsening nausea and vomiting. After gadolinium (B), the lesion shows strong enhancement. On T2WI (C) the lesion shows heterogeneous hyperintensity compared with brain. A sagittal, gadolinium-enhanced TIWI (D) in another patient with ependymoma clearly demonstrates expansion and filling of the fourth ventricle *(arrow).*

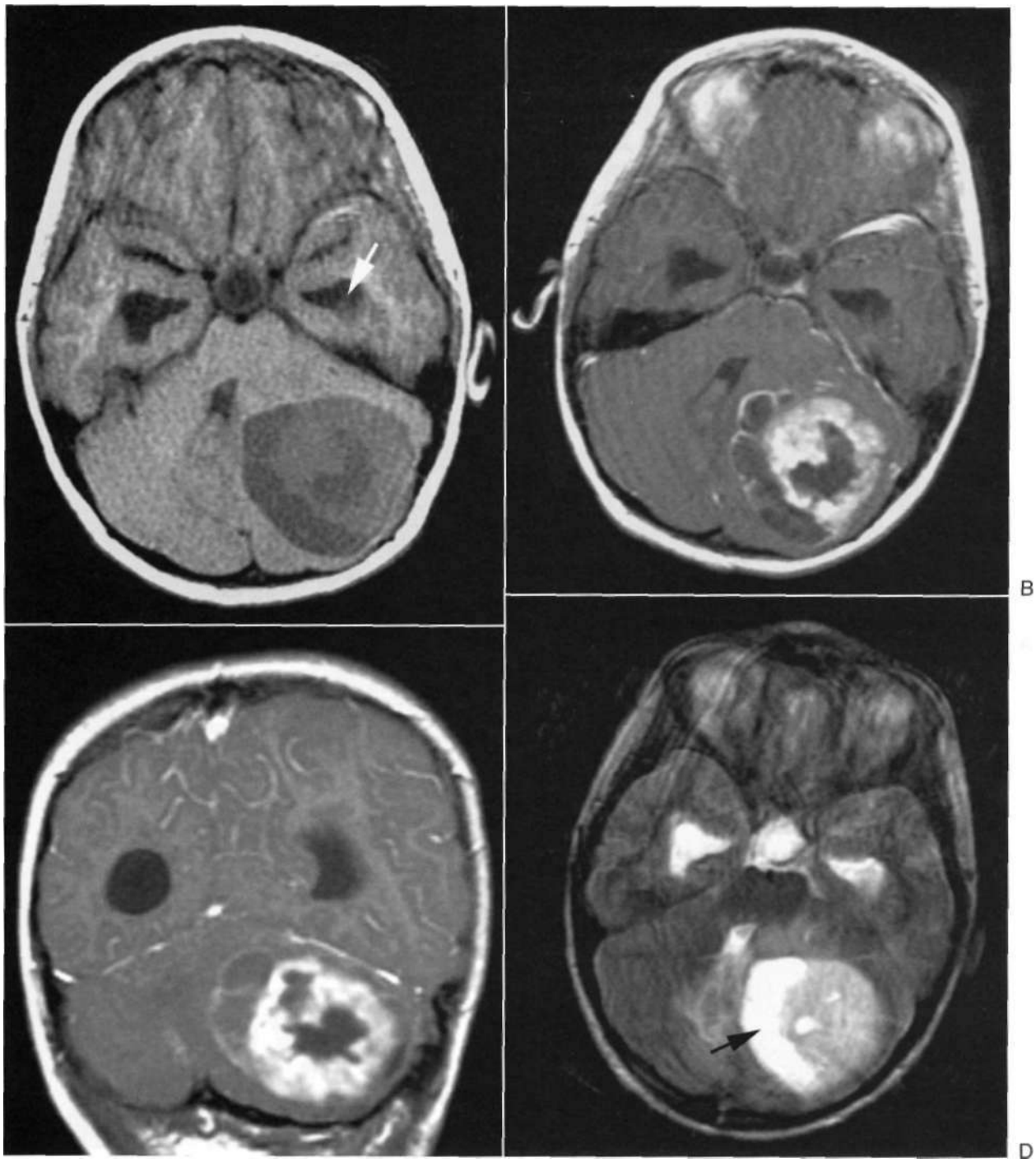

FIGURE 58D.15 Juvenile pilocytic astrocytoma. An 8-year-old child had a 7-month history of progressive headache and clumsiness. Axial **T1WI** before gadolinium (A) shows a we 11-circumscribed, hypointense lesion with internal signal heterogeneity in the left cerebellar hemisphere. There is compression of the fourth ventricle and dilation of the temporal horns of the lateral ventricles *[arrow).* Irregular ring enhancement is seen after administration of gadolinium on axial (B) and coronal (C) T1WI. There is thin, smooth enhancement of the medial, multicystic appearing structures. On T2WI (D), the bulk of the tumor (lateral aspect of the mass) is mildly hyperintense to brain. The medial, cystic areas are markedly hyperintense *[arrow),*

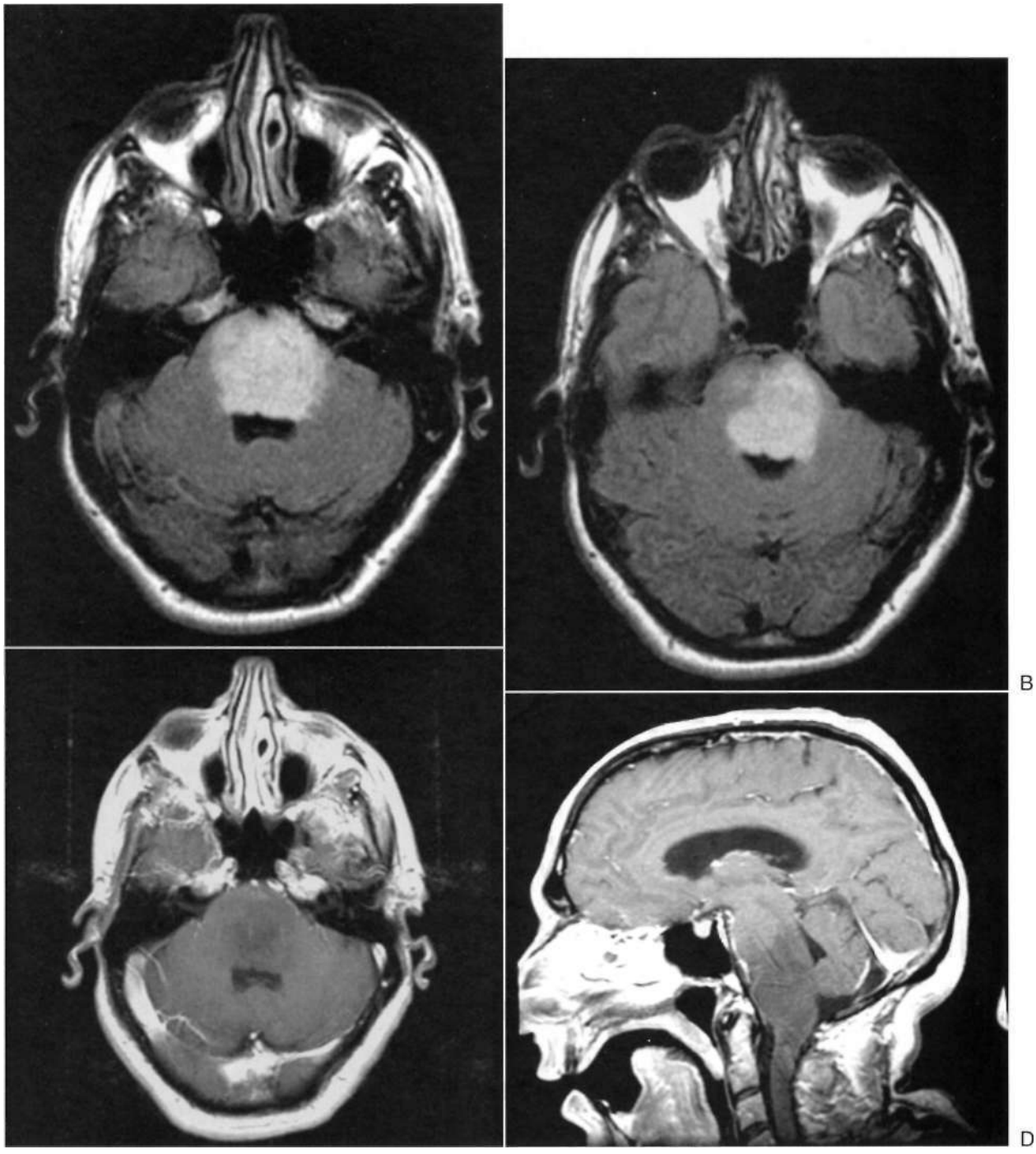

FIGURE 58D.16 Brainstem glioma. A T2 hypcrititcnsc mass lesion with ill-defined margins is seen to expand **the** pons on serial axial FLAIR images I A, B) in a 54-year-old **man** with a 2-month history of progressive gait ataxia *i\i\d* slurred speech. After administration of gadolinium, there is no evidence of enhancement on axial (C) or saginal (D) TIWI within the pontomedullary tumor.

nonenhancing. Gadolinium-enhanced spinal imaging is important for staging.

Hemangioblastoma (Figure 58D.18)

Hem a ngi obi a stomas arc cystic tumors with a mural nodule that occur in the posterior fossa and spinal cord. When multiple, these tumors arc associated with von Hippcl-I.indau disease, an autosomal dominant trait (Kleihucs and Cavenee 2000). The cystic component usually follows CSF signal, and an associated enhancing tumor nodule or mass lesion is present (Conway et al. 2001). Hemorrhage is rare, even on susceptibility images. Lesions may enlarge after years of quiescence, and new lesions may appear, necessitating life-long surveillance.

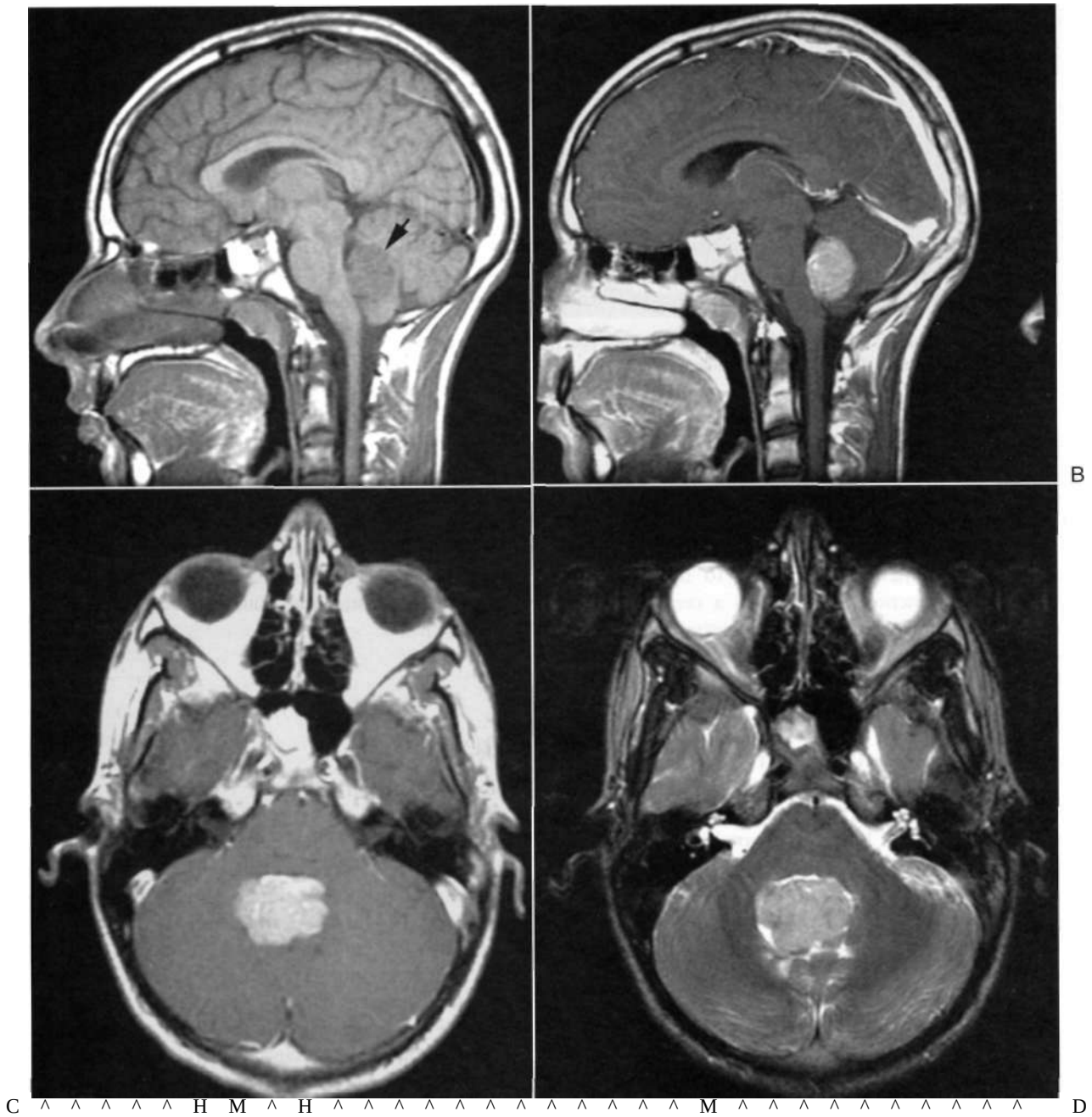

FIGURE **58D.17** Medulloblastoma, Sagittal T1WI (A) before contrast administration demonstrates a well-demarcated, hypomrense mass lesion *(arrow)* expanding the fourth ventricle in a 15-year-old boy who had a 2-week history of gait ataxia, nausea, and vomiting. There is moderate heterogeneous gadolinium enhancement (B, C). The tumor is slightly hypetintense on T2WI (D).

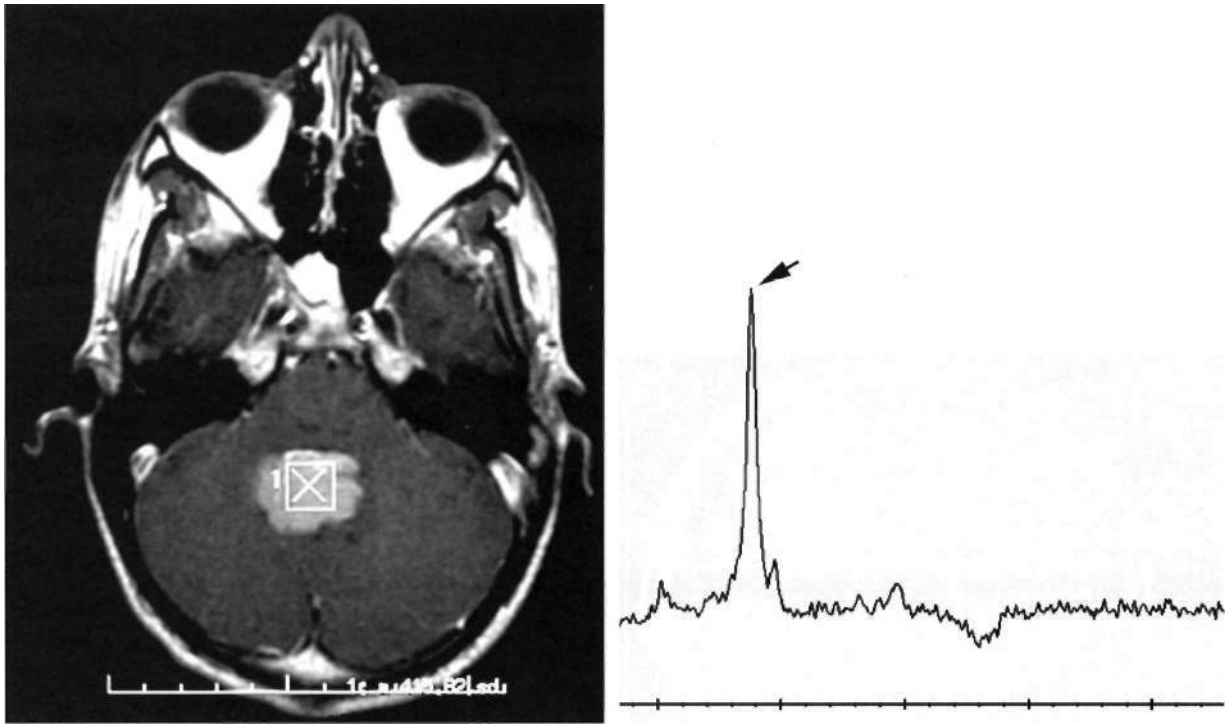

FIGURE 58D.17, cont'd. Single-voxel magnetic resonance spectroscopy (E, F) shows high choline *(arrow),* extreme elevation of the choline/creatine ratio, and absence of N-acetyl aspartate.

Lhermitte-Duclos' Disease (Figure 58D.19)

Dysplastic cerebellar gangliocyroma, or Lhermitte-Duclos' (LD) disease, is a hamartoma of neuronal cells rather than a true neoplasm (Kleihues and Cavenee 2000). LD disease comes to clinical attention secondary to hydrocephalus or cerebellar dysfunction. MRI shows a cerebellar mass lesion, without evidence of contrast enhancement, or vasogenic edema. A characteristic linear striated appearance on T2WI is characteristic (Klisch et al. 2001).

Vestibular Schwannoma (Figure 58D.20)

Vestibular schwannoma (VS) may occur as unilateral, sporadic tumors or as bilateral tumors as part of NF2 (Kleihues and Cavenee 2000). Schwannomas are mildly hypointense on T1WI, show heterogeneous, mild hyperintensity on T2WI, and have strong, heterogeneous enhancement (Somers et al. 2001). Cystic changes may occur.

Epidermoid

Epidermoids and dermoids are ectodermal heterotopias rather than neoplastic masses. Epidermoids usually arise in the cerebellopontine angle; a parasellar location is next most common. Dermoids are midline in location and contain fat. Epidermoids often come to attention as a result of cranial nerve dysfunction as the cyst gradually enlarges (Kleihues and Cavenee 2000). The cyst follows CSF intensity on T1WI and T2WI, but may be hyperintense to CSF on FLAIR images. Importantly, diffusion-weighted images show very hyperintense signal, permitting easy distinction from an arachnoid cyst (Annet et al. 2002).

OTHER TUMORS

Meningiomas (Figure 58D.21)

Meningiomas arise from the leptomeninges, and therefore may occur in supra tentorial, infratemorial, or spinal locations. Rarely, these tumors occur along the optic nerve sheath or within the trigone of the lateral ventricle, where they arise from meningothelial cells in the choroid plexus (Kleihues and Cavenee 2000). Meningiomas are dural-based mass lesions, which are relatively isointense to brain on T1WI and T2WI and demonstrate strong, homogeneous enhancement (Nakano et al. 2002). The amount of vasogenic edema in the adjacent brain is variable. Dural tails, when seen, are a nonspecific characteristic of many dural-based tumors. Calcification is common. Brain invasion suggests a malignant meningioma.

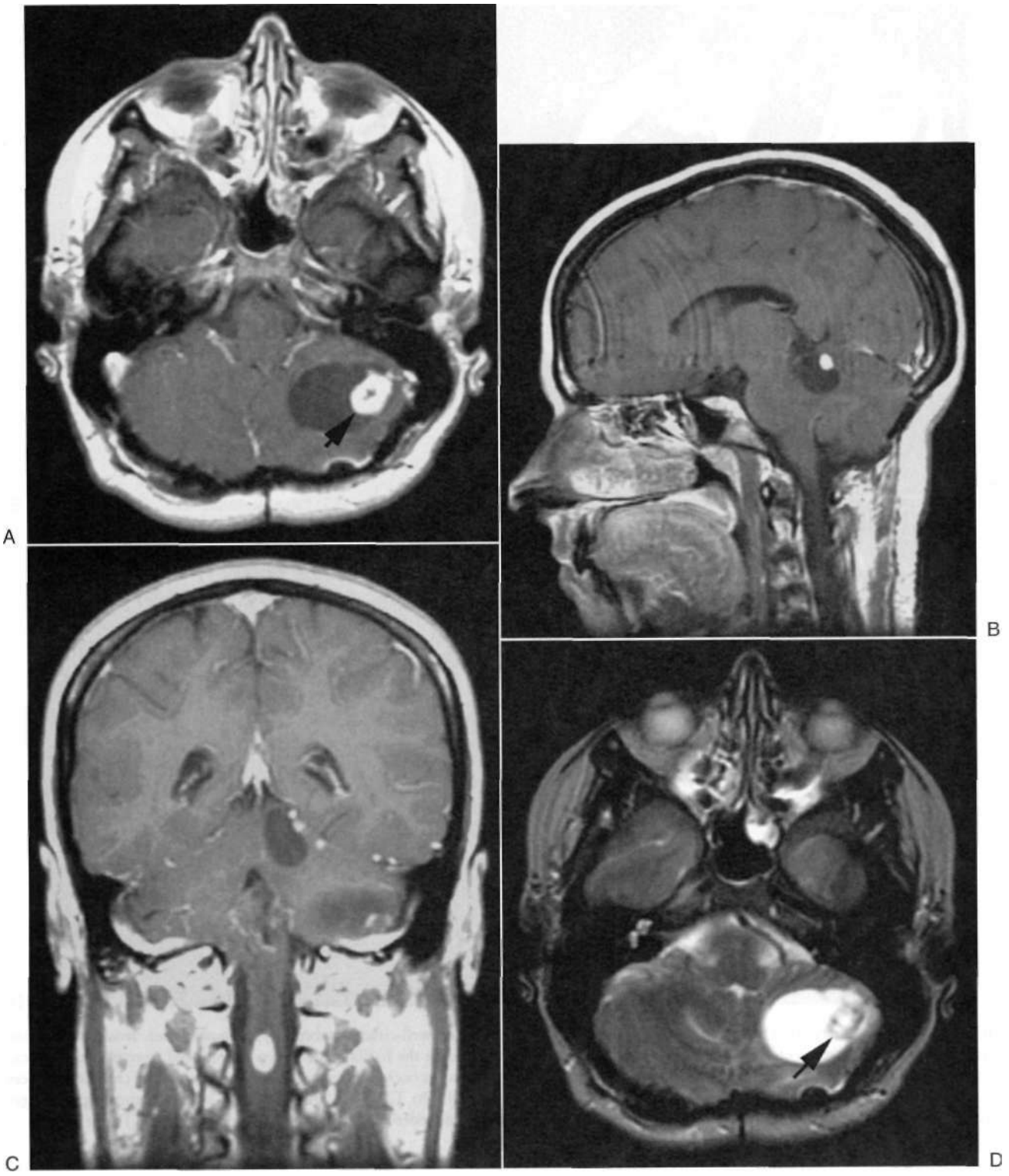

FIGURE 58D.18 Hemaneioblasroma. Gadolinium-enhanced TlWl (A, B, C) show multiple cystic lesions within the cerebellum and cervical spinal cord, with associated nodules *(arrow)* of densely enhancing hemangioblastoma, in a 35-year-old woman with *1* weeks of severe headache and a history of von HippeHJndau disease. There is minimal enhancement of the cyst walls. A T2W1 (D) shows the mural nodule *(arrow)* is heterogeneous in signal intensity.

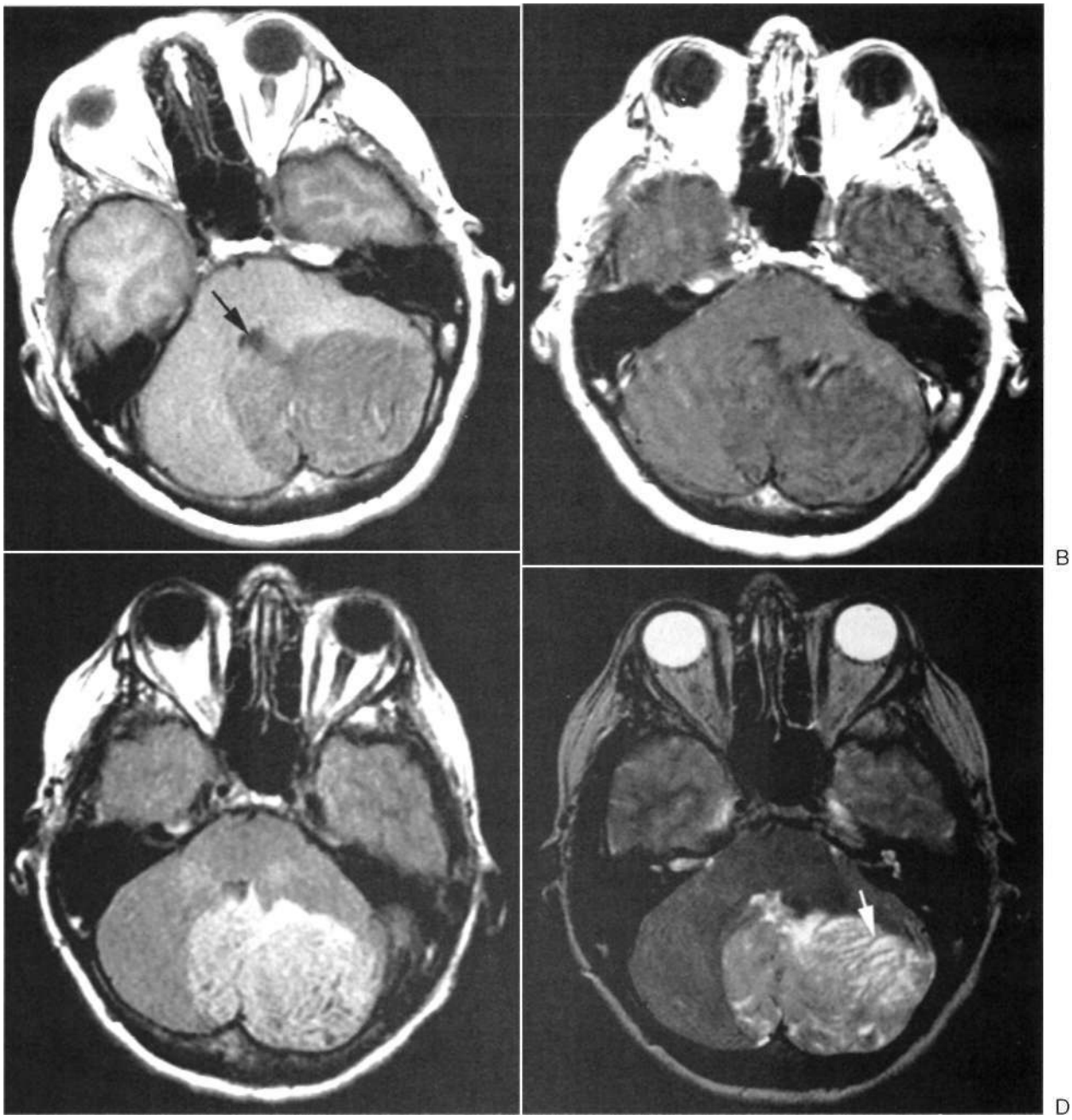

FIGURE 58D.19 Lhcrmitte-Duclos' disease. T1WI (A) shows a large, well-circumscribed, hypo intense mass lesion within the cerebellum, producing mass effect on the fourth ventricle *(arrow)* and effacing the basilar cistern in a 52-year-old woman with a 2-ycar history of gait difficulty. Linear foci of hypoiutcnsity arc seen, and the adjacent occipital bone is remodeled, suggesting chronicity. There is no evidence of enhancement after administration of gadolinium (B, C). On T2WI (D) there is linear heterogeneous signal ("tiger stripes") within the mass *[arrow*), but no evidence of surrounding vasogenic edema. Calcification was detected on CT (not shown},

Pituitary Adenoma (Figure 58D.22)

Pituitary adenomas are slow-growing tumors of the adenohypophysis. They are located within the gland, disrrihuted in accordance with the normal cells from which they arise. Prolactinoma (lateral location) and non-functioning tumors comprise more than one half of cases. Thyroid-stimulating hormone-producing tumors arc the least common. Microadenomas, defined as less than 10 mm in greatest diameter, arc much more common than are macroadenomas. Endocrine dysfunction is the usual presentation. Macroadenomas (10 mm or larger) produce symptoms from compression of parasellar structures. Onset is at all ages. Microadenomas show subtle

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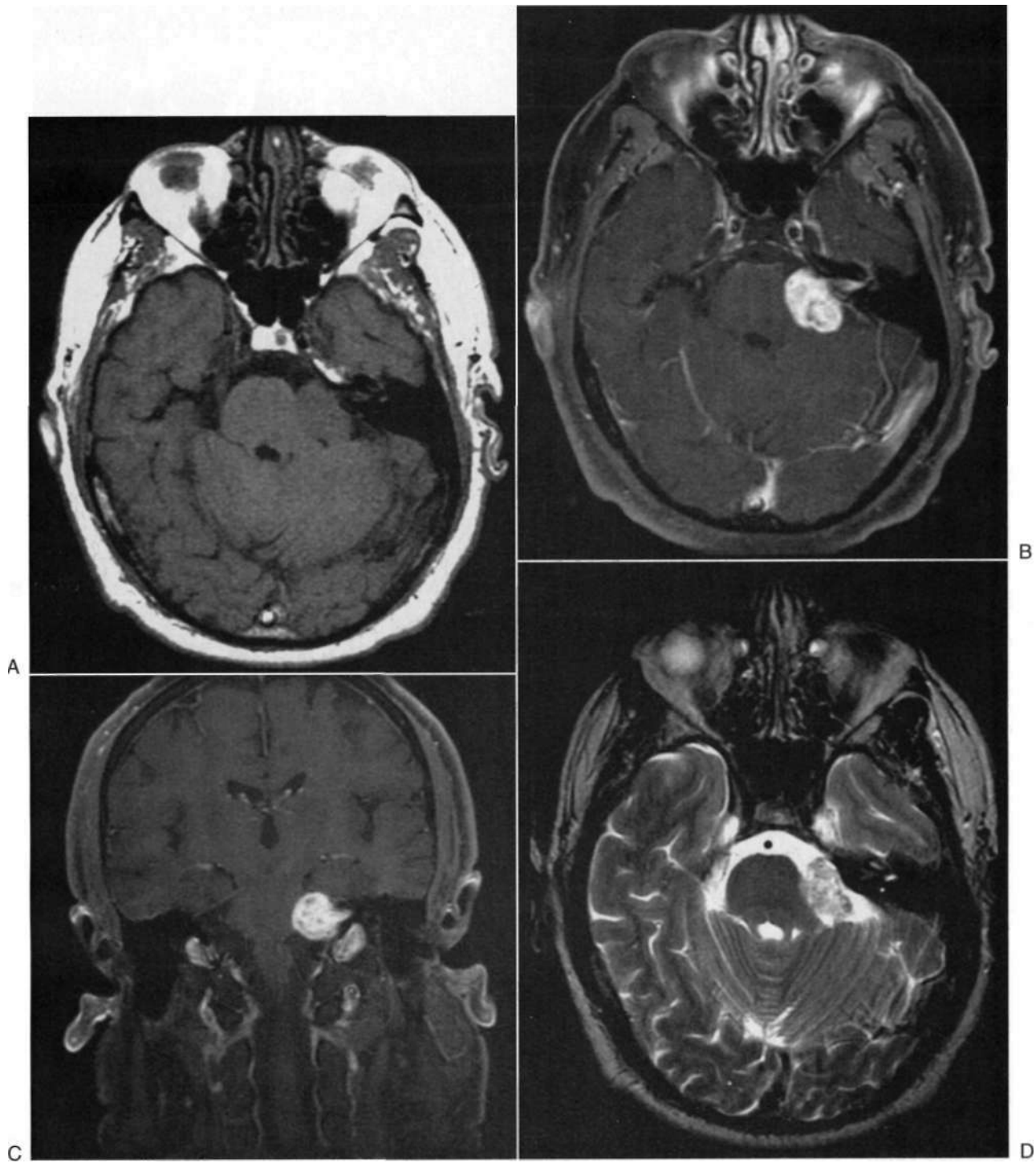

FIGURF 58D.20 Vestibular schwannoma. T1W1 (A) shows an isointcnsc mass lesion within the left cerebellopontine angle, with mass effect on the adjacent brainstem and middle cerebellar peduncle and extension into **the** left internal auditory canal in a 58-year-old man who had a several-year history of hearing loss and tinnitus in the left ear. The tumor demonstrates heterogeneous gadolinium enhancement (B, C). T2WI (D) shows heterogeneous signal intensity. Vestibular schwannomas often show cystic changes, and may-occasional ly calcify.

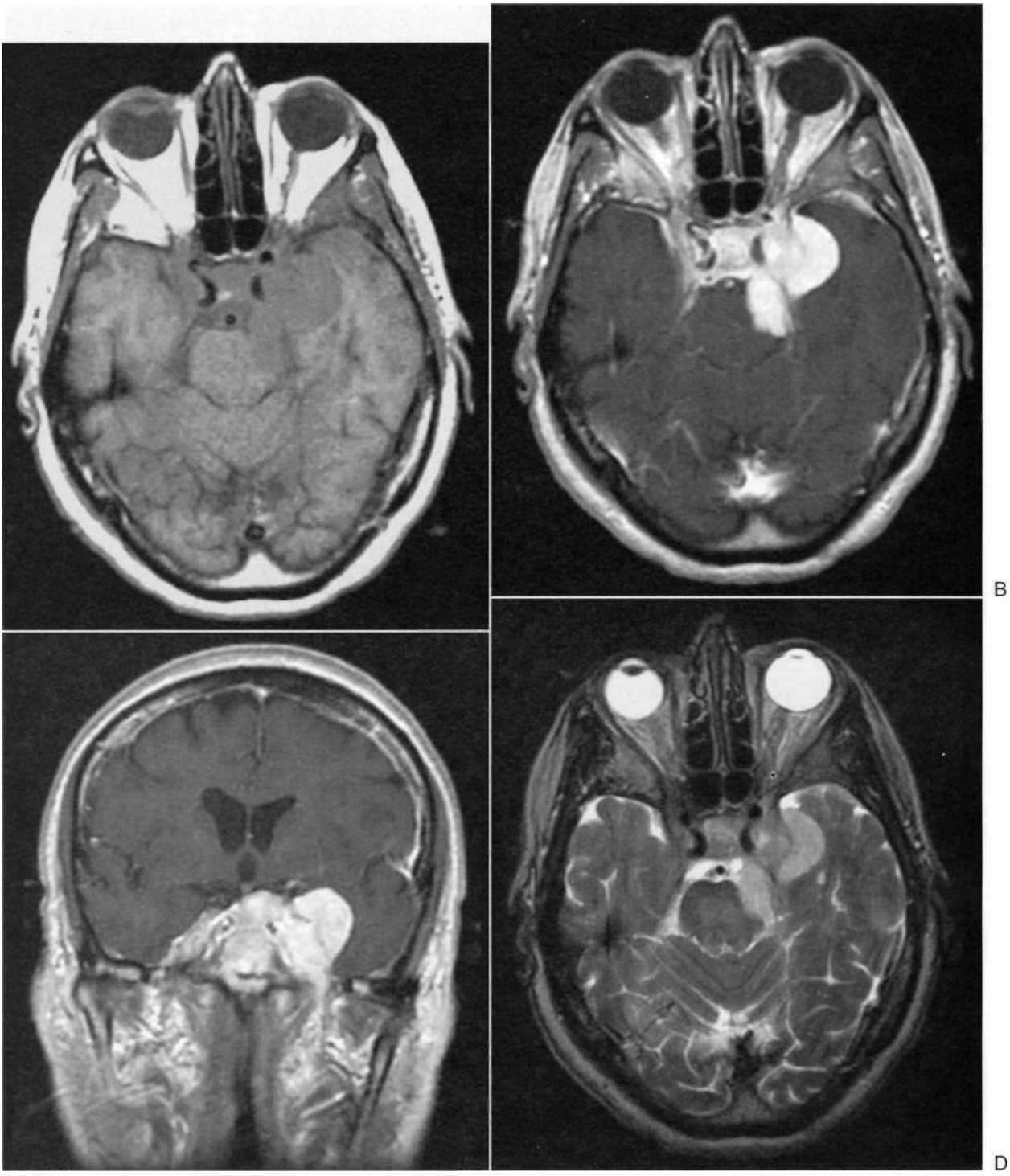

FIGURE 58D.21 Meningioma. A **TIWI** shows an isointense mass lesion, centered in the left cavernous sinus (A), with extension into the sella, right cavernous sinus, and middle cranial fossa and posterior fossa in a 77-year-old woman with a 2-year history of diplopia. There is mass effect on adjacent brain without evidence of brain invasion. Homogeneous enhancement is seen after gadolinium administration (B, C). There may be extension into the left foramen of ovale, and vascular structures are encased. Dural tails are present. The mass is mildly hyperintense to brain on T2W1 (D).

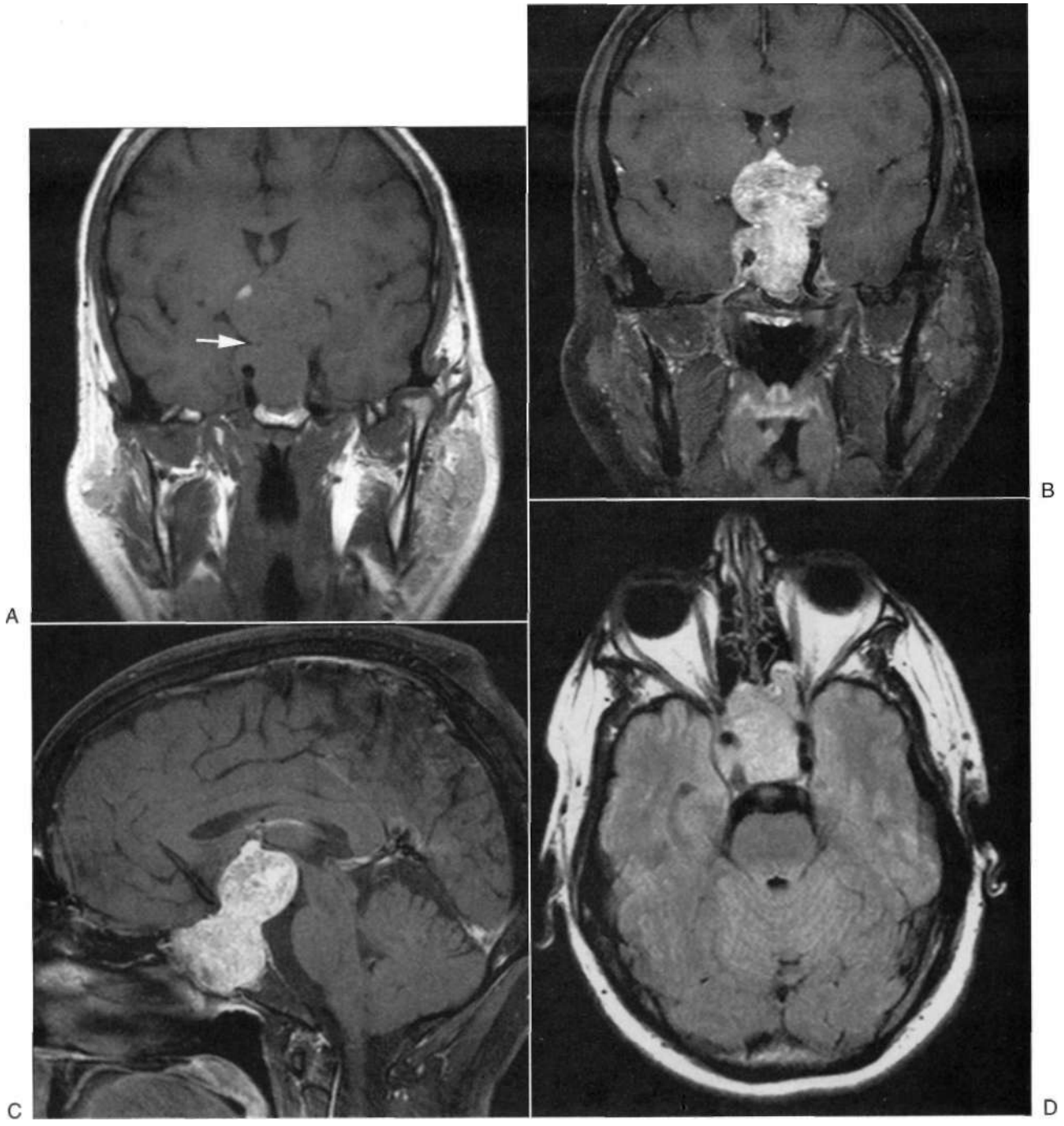

FIGURE 58D.22 Pituitary microadenoma. A ITWl (A) demonstrates a large, isointense mass lesion expanding the sella turcica and filling the suprasellar cistern in an asymptomatic 42-year-old man who participated in a magnetic resonance imaging study. The tumor is constricted into a waistline by the diaphragma sella *(arrow).* There is heterogeneous enhancement after administration of gadolinium (B, C). There is mass effect on the floor of the third ventricle and encasement of the left internal carotid artery. The optic chiasm is deviated superiorly. FLAIR (D) shows the lesion to he isointense to brain.

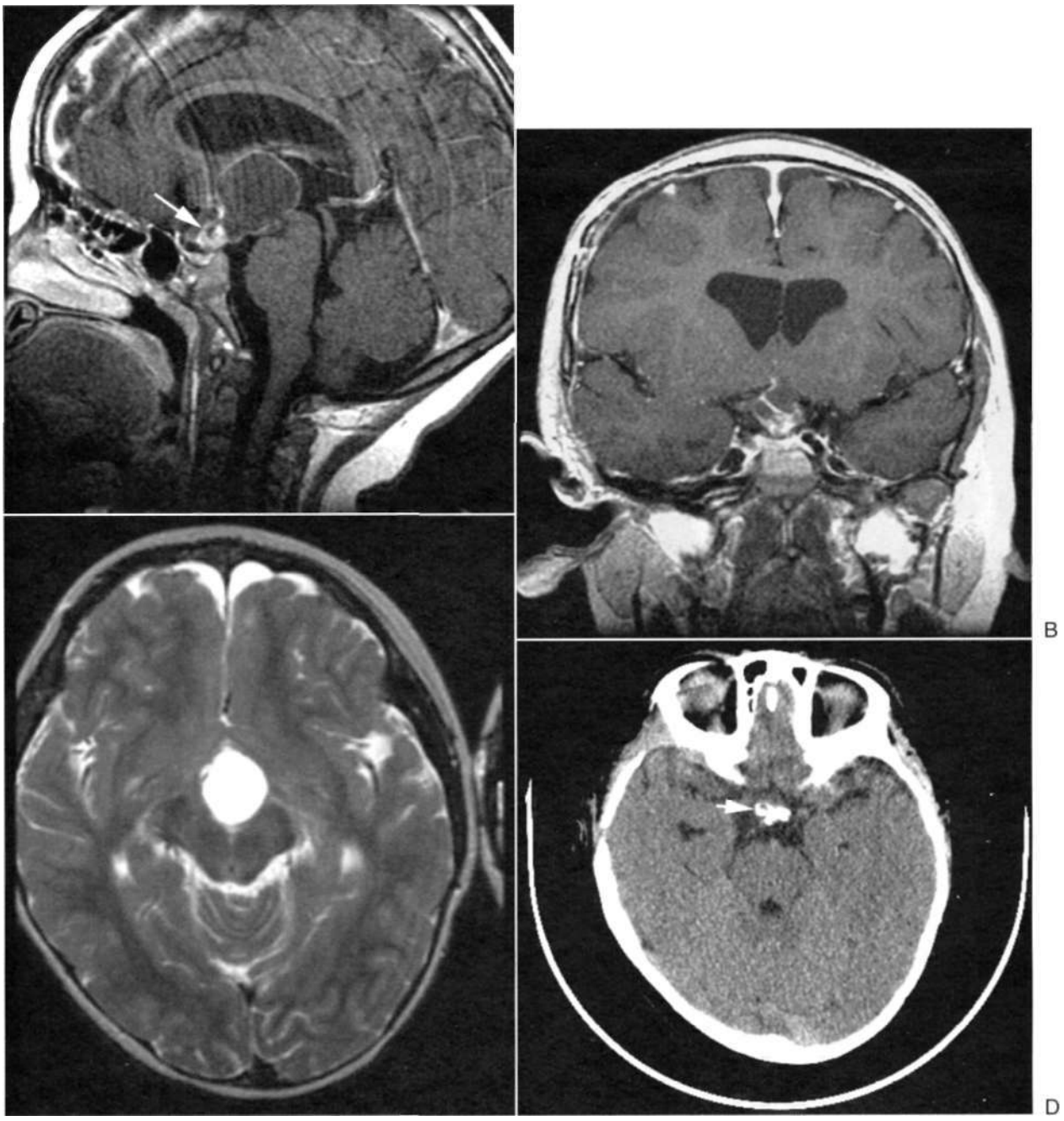

FIGURE 58D.23 Suprasellar adamantinomatous craniopharyngioma. Gadolinium-enhanced T1WI (A, B} show a mass lesion within the suprasellar cistern that has an inferior, enhancing, nodular component *(arrow)* and a superior, cystic-appearing structure that produces mass effect on the floor of the third ventricle. The patient was a 4-year-old boy with headache, lethargy, and vomiting. The cyst has a smooth rim of peripheral enhancement. T2WI (C) shows marked hyperintensity in the cystic component. There is dense calcification in the region of the enhancing nodule *(arrow)* on CT (D).

hypointensiry to the normal gland on TIWI (Rand et al. 1996). T2W1 are less sensitive. For a short interval after administration of gadolinium, adenomas enhance less than the normal gland. Indentation of the floor of the sella and deviation of the infundibulum are secondary evidence of tumor.

Craniopharyngioma (Figure 58D.23)

(iraninpliaryngioma arises as a suprasellar, cystic, epithelial tumor that may originate from Rathke's pouch (Kleihues and Cavenee 2000). The common form of craniopharyngioma, called *adamantinomatous craniopharyngioma,* arises in children, is located in the suprasellar cistern, and is calcified and cystic (Sartoretti-Schefer et al. 1997).

ACKNOWLEDGMENT

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Chapter 58
Cancer and the Nervous System

E. MANAGEMENT OF PRIMARY NERVOUS SYSTEM TUMORS IN ADULTS

Joachim M. Baehring and Fred H. Hochberg

High-grade gliomas, which account for the majority of primary brain tumors diagnosed each year in the United States, carry a grim prognosis. Most patients with glioblastoma multiforme die within 1 year of diagnosis. The exceptions are younger patients with completely resectable tumors and minimal neurological dysfunction. Despite the provision of radiation therapy and chemotherapy as adjuvant treatment, fewer than 10% of patients are alive 2 years after diagnosis. Because these tumors are rare and therapies complicated to perform, muchofthe burden of patient care has shitted from the general oncntogisi and ncurologisl to tertiary centers with collaboration among radiation oncologists, neurosurgeons and neuro-oncologists. These specialists often provide novel therapies under the sponsorship of the National Cancer Institute as part of collaborative brain tumor programs such as the New Approaches to Brain Tumor Therapy consortium, the North American Brain Tumor Consortium, the Pediatric Brain Tumor Consortium, or the Radiation Therapy Oncology Group.

Novel approaches to therapy have been designed to address issues specific to brain tumors. The blood-brain barrier (BBB) prevents access to the brain by hydrophilic chemotherapeutic agents and large molecules. Cells of brain tumors arc uniquely able to resist chemotherapeutic agents by overexpressing membrane proteins that eliminate these drugs or by inducing enzymes to inactivate them. Even when drugs enter brain tumors, not all cells are sensitive. The hypoxic areas of tumors are in cell-cycle arrest and resistant to cell cycle-dependent agents ot radiation. Other factors confounding therapy include corticosteroids that alter the BBB penetration of drugs, the host immunologic reaction to the tumor, as well as the cytotoxic effects of chemotherapy. There is a cascade of molecular events that carry benign tumors toward malignancy; thus inhibition of a single pathway may not induce cell cycle arrest ot apoptosis. Despite these factors, there have been improvements in treatment. Surgical techniques have been refined and now allow the use of the operating microscope and intraoperative magnetic resonance imaging (MRI) to achieve microscopic decompression. Operative morbidity has been reduced by the performance of operations done with the patient awake and talking, with available intraopetative cortical stimulation and functional mapping or electroenccphalographic monitoring. Functional MRI or positron emission tomography (PET) studies provide precise delineation of speech or motor areas in proximity to tumors. As surgery has become more precise, so has radiation therapy. Highly focused external radiation

strategies have improved local tumor control with reduced damage to contiguous normal brain. Chemotherapy, long unproductive, now improves survival and function of patients with lymphoma or oligodendroglioma of the brain.

This chapter is an overview of current therapy for brain tumors in adults. The physician, awate of current therapies as well as the rationale for future therapies, is provided an approach to specific brain tumors.

TREATMENT STRATEGIES

Surgery

Surgery is the primary modality of management for patients with brain masses. Stereotactic or open biopsy provides indispensable diagnostic information necessary for treatment planning. Surgery can be curative for brain tumors such as meningioma or ganglioglioma. Operative intervention may also alleviate symptoms of mass effect or obstruction of cerebrospinal fluid (CSF) circulation. Similarly, surgery often affords time in which other therapies can he provided or serves as a method to insert cither drugs or viral therapies into brain tumors. More controversial is the subtotal resection of infiltrative brain tumors.

Biopsy

A histological diagnosis is necessary prior to rational therapy. Up to 10% of clinically apparent neoplasms may actually be of infectious or demyelinative origin. Stereotactic biopsy uses targets acquired by computed tomography (CT) or MRl. A stereotactic frame or fiducial markers placed on the patient's head provide precise sampling strategy. Prior to biopsy "activation," MRI or PET studies are performed to identify contiguous, eloquent areas of the brain. These studies can be coregistcred on three-dimensional MRI reconstructions from which biopsy coordinates are drawn. A probe is then passed through a small drill hole that retrieves cylindrical samples 1 cm in length and 1-2 mm in diameter. The procedure is safe, commonly performed in most large hospitals, and is associated with less than a 2% risk of seizure, hemorrhage, or infection. In many centers, a neuropathologist in the operating room provides immediate analysis of frozen or smear preparations to confirm the tumor,

Resection

A number of brain tumors can be cured by complete surgical resection (grade I gliomas such as ganglioglioma, papilloma of the choroid plexus, pleomorphic xanthoastrocytoma (PXA), pilocytic astrocytoma of the cerebellum, dysembryoplastic neuroepithelial tumor, pituitary adenoma, meningioma). Less clear is the benefit of resecting the infiltrating diffuse astrocytoma or "partial" decompression of an aggressive tumor. Resection provides prolonged survival for oligodendrogliomas and oligoastrocytomas and most clinicians support "subtotal" resection in the setting of increased intracranial pressure; steroid-obligating mass effect, hemorrhage or impending herniation; the presence of necrotic tumor cysts; and uncontrollable seizures. Often the decision to operate depends on preoperative MRI mapping of both gray and white matter functions. Aids to the surgeon also include tumor resection based on intraoperative MR] or "MRI roadmaps," intraoperative cortical stimulation mapping, and monitoting of somatosensory evoked potentials. It is often argued that surgery will reduce the burden of tumor prone to malignant degeneration, but this view is countered by tbc occurrence of infiltrates of tumot extending at distances from the main mass. The advocates of subtotal resection often cite the diminished likelihood of the sampling error associated with stereotactic biopsy. Carefully performed tumor resection, with the patient awake and within an operating room offering MRI guidance, commonly improves clinical deficits; in general, resection benefits tumors lying in the poles of the frontal or temporal cortex.

Following operation, within 48 hours, a contrast-enhanced MRI is recommended as an objective mcasiifc of residual tumor. After 48 hours, perioperative changes occur in the brain and prevent accurate determination of residual tumor.

Radiation Therapy

Radiation therapy is commonly provided to treat brain tumors. Some tumors, such as gcrminomas, can be cured and others are slowed in their progression. Survival is improved in many glial and nonglial tumors, and symptoms, including seizures, are reduced. Palliation is the goal for older adult patients or those with leptomeningcal tumor.

The target for radiation cell death is DNA within the cell. High-energy beams cause breaks in the DNA double strand either by ionization of the target atom of by production of free radicals. The effect of radiation depends on the dose applied, how often it is applied, and how much time is available for the target to repair the damage. Dividing cells are more susceptible to itradiation than ate nondividing cells, especially during the M-(mitotic) and G2 phase of the cell cycle.

Photons are the most commonly used particles 111 the radiation therapy of brain tumors. Examples of nonphoton irradiation modalities (available in experimental facilities) include neutrons, protons, helium ions, pions, and heavy-ions (carbon, argon, neon).

External Beam Radiation Therapy

Radiation therapy is most commonly delivered by a linear accelerator (LINAC), which uses high-frequency

electromagnetic waves to accelerate electrons to high energies. The electron beam is used directly for the treatment of superficial tumors or indirectly by producing x-ray beams for the treatment of dccp-scatcd lesions. Shielding blocks are built for each patient to restrict the beam to the target volume. The size of the treatment field depends on the tumor type. For infiltrative tumors, such as malignant gliomas, therapy is provided to the volume of enhancement V or T_2 abnormality on MRI and a margin of 1-3 cm. For sharply demarcated cystic astrocytomas, a margin of 0.5 cm suffices. On the other hand, whole-brain radiation therapy (WBRT) is provided to treat multifocal infiltrating tumors seen in gliomatosis cerebri, the multiple masses of recurrent brain lymphoma, and the potential seeds within the neuraxis of primitive neuroectodermal tumors (FNETs). Numerous strategies, mainly of experimental nature, have been developed to improve tumor cell kill and minimize damage to normal tissue. These include increasing the number of treatment fractions to two or more per day (thereby reducing the time for tumor repair of damage), the use of multiple fields (to diminish damage to normal tissue), the use of radiosensitizing agents, localized high-field strength sources (brachytberapy or radiosurgery), and MRI-based treatment planning (to reduce damage to contiguous sensitive areas such as the optic chiasm).

Conventional Fractionated Radiotherapy

Conventional radiation therapy is provided in daily fractions of 1.8 to 2.0 Gy. The total dose seldom exceeds 60 Gy, at which point there is an increased risk of radiation necrosis, or damage to normal brain. Fractionation is more likely to leave surviving cells compared with single fraction irradiation. However, tumor, as early responding tissue, is more likely damaged than is nondividing normal brain (late responding tissue).

"Hypcrfractionation" protocols decrease the dose per fraction, but increase the number of fractions per day. With accelerated fractionation, the dose is applied over a shorter period by increasing the number of daily treatments. In theory, this reduces repopulation of tumor cells during irradiation. Fractionation strategics require immobilization devices such as bite blocks and thermoplast molds that allow reproducible positioning of the patient with each treatment. The use of multiple radiation fields or three-dimensional conformal irradiation limits the exposure of overlying skin and normal brain tissue.

Brachytberapy

In brachytberapy, radiation is delivctcd by implanting the irradiation source close to or into the target tissue (Brain Tumor Cooperative Group 2002). Interstitial therapy uses iridium-192 or iodine-125 seeds. Iridium-192 has a longer half-life (74 days) and penetrates deeper into the surrounding brain tissue. Scalp infections have been described after therapy with high activity brachythcrapy seeds, and there is a 50% risk of the development of contrast-enhancing necrotic tissue in the radiation site. Nearly half of patients require a second craniotomy after seed implantation. Intratumoral positioning of miniature x-ray-gencrating devices or intracavitary application of radionuclide is another form of local radiation delivery.

Sensitization of Tumor Cells to Ionizing Radiatton

Hypoxic tumor cells likely evade the lethal effect of irradiation. Rapidly growing tumors such as malignant gliomas contain a significant fraction of hypoxic cells that in.i\ represent one third ot the tumor burden. Fractionation of irradiation allows reoxygenation of tumor tissue during the resting intervals. In addition, these cells can be manipulated through pharmacological and physical strategies. Drug strategies include nitroimidazoles such as metronidazole, misonidazolc, or etanidazole, and the hypoxic cytotoxin tirapazamine. Increased oxygen can be carried to the tumor by the application of hyperbaric oxygen or the provision of agents that alter hemoglobin-oxygen dissociation curves (RSR13). Examples for non-hypoxic radiosensitizers are halogenated pyrimidines such as 5-bromodeoxyuridine and hydroxyurea. Flalogenated pyrimidines are incorporated into dividing cells and thus selectively increase radiation sensitivity of tumor cells. Radiosensitization is also provided by certain chemotherapeutk agents (cis dianunincdichloroplatinum [ei.spl.um! *:>v* doxorubicin); the antitrypanosomal agent suramin, or the angiogenesis inhibitor thalidomide.

Stereotactic Radiosurgery Techniques

Radiosurgery is the name given to single fractions of stereotactic radiosurgery (SRS) and multiple fractions of stereotactic radiation therapy (SRT). These techniques deliver large doses of radiation to well-circumscribed tumor sites while minimizing exposure to normal tissue. Three types of facilities are typically used. *LINAC radiosurgery* uses a modified LINAC to produce high-energy photon beams. The radiation source moves through multiple noncoplanar arcs, as a flashlight would move around the perimeter of a circle. Heavy charged particle beams such as helium or protons *{proton radiosurgery)* offer optimal physical characteristics for stereotactic applications. The beam penetration into tissue reflects the energy-imparted to the particle. The particle penetrates to relatively finite depths (Bragg peak), after which there is a sharp dose decrease. ('The "flashlight beam" penetrates only so far and no further, thus protecting surrounding normal tissue.) An onsite cyclotron is needed to generate high-energy heavy particle beams restricting its use. *Gamma knife* provides irradiation using 200 separate and collimated cobalt-60 sources in a hemispherical array aimed at the target tumor (multiple "flashlights" all aimed at the target).

These radiosurgery techniques require some means of fixation of the patient's head in space. These devices include immobilization masks, rigid frames affixed to the patient's skull or fitted mouthpieces. The acute complications of these therapies include cerebral edema and seizures. The major late complication is radiation necrosis manifested as early as 2-4 months after treatment, but maximal at 18 months. The mass, indistinguishable from viable-tumor, may have characteristic neuroimaging features like low choline/creatine ratios and increased lactate peak on magnetic resonance (MR) spectroscopy, and does not accumulate FDG isotopes on PET scans. Surgical biopsy or decompression may be required for this complication.

Chemotherapy

Chemotherapy is provided to most patients with malignant brain tumors. Less commonly treated are nonresected low-grade but symptomatic tumors prior to or following radiation therapy. Chemotherapy is becoming increasingly important for patients with brain lymphoma or anaplastic oligodendroglial tumors.

An exhaustive description of chcmothcrapcuric agents is beyond the scope of this chapter; the reader is referred to texts that list both commonly provided and experimental drugs.

Alkylating Agents

Alkylating agents are the major agents used against brain tumors. The antitumot effect of this class of drugs is based on covalent binding of alkyl groups to DNA, which results in DNA intra- and interstrand crosslinks. However, gliomas are prone to resist these effects by reducing drug uptake, ovcrexprcssion of cellular sulfhydryl groups, and elimination of alkylated nucleosides by cellular repair mechanisms. The active metabolites of these drugs often produce myclosupprcssion, whose variable time course indicates that alkylating agents affect hematopoicsis at different levels of differentiation. Nausea and vomiting are frequent, but can be avoided; however, male sterility and teratogenicity are sources of profound morbidity. Secondary malignancies occur in 5-10% of patients, but commonly the tisk is cited as 2% pet yeat aftet exposure.

Nitrogen Mustards

Nitrogen mustard derivatives of mechlorethamine are administered orally or intravenously. Cyclophosphamide and ifosfamide are activated by the microsomal mixed oxidase system of the liver, which is the main site of clearance. Characteristic dose-limiting toxicity is leukopenia, which occurs 10-12 days after the drug is given. However, cyclophosphamide does not suppress hematopoietic stem cells and thus cumulative damage is rarely seen or is reversed with the use of bone marrow stimulating agents. The dtugs cause alopecia and may induce sterility and bladder damage. Cyclophosphamide is used with carboplatin and E topoxide VP-16 to treat PNETs and I'lop'i-.ide esthesinneiu-tibkisiiiuia before radiation is given. Ifosfamide is an analogue of cyclophosphamide used to treat soft-tissue sarcomas such as those of muscle or peripheral nerve sheath. The hemorrhagic cystitis that follows both drugs as a result of the active metabolites present in the urine, can be prevented by hydration, frequent bladder emptying, and use of mercaptoethane sulfonare (MESNA).

Thio-TEPA

Trierhylenethiophosphoramide (Thio-TEPA), the pro-drug, is converted to TEPA and other alkylating moieties in the liver by microsomal oxygenases. It is used as an intrathecal agent to treat leptomeningeal tumors as well as primary central nervous system (CNS) lymphoma. Dose-limiting toxicity ismyelosuppression (leukopenia nadir after 2 weeks, thrombocytopenia nadit aftet 3 weeks).

Nitrosoureas

BCNU, CCNU. The chloroethylnitrosoureas, intravenous bischloroethy I nitrosourea (carmustine, BCNU) and oral cyclohexylchloroethylnitrosourea (lomustine, CCNU) are lipid soluble and readily cross the BBB. These agents have represented the major drugs provided for grade 3 or 4 glioma and add 4-8 weeks of survival to patients with glioblastoma multiforme. Resistance to these agents reflects induction of guaninc-O -alkyl transferase. This resistance is reduced by concomitant treatment with O^6 benzyl guanine. Delayed myelosupptession occurs on day 21 after treatment with reductions of granulocytes and platelets. With prolonged therapy, cumulative myclosuppression (usually by cycle 5 after standard doses) occurs, as well as lung, liver, and rena! .llleianniis eniimicmly .lipidoses approaching 1200 mg/m^{-}). Alternative modes of drug administration include implantable wafers of BCNU (polifeprosan 20 with carmustine implant |Cliadel]l and intra-arterial BCNU.

Nonclassic Alkylating Agents

Procarbazine

Procarbazine (PCZ), an oral agent, represents a major active agent in the procarbazine-CCNU-vincrisrinc (PCV) regimen provided to patients with oligodendroglial tumors. As with other alkylating agents, it requires activation and induces resistance through guanine-O -alky] transferase. Cells deficient in DNA mismatch repair are not susceptible to *PCZ.*. Limiting usefulness are extended interactions with

drugs and foods, as well as interaction with drugs that share or induce rhe hepatic microsomal cytochrome P4S0 (CYP450) oxidoreductasc system. Dose-escalation trials in patients on CYP450-inducing seizure medications have shown that high doses may be required above those commonly used. PCZ, an inhibitor of monoamine oxidase, cannot be used concomitantly with tricyclic antidepressants, tyramine-rich food or alcohol. Side effects include nausea, mild leukopenia, and thrombocytopenia 1 week after treatment. Transient central and peripheral neurotoxicity has been observed. Hypersensitivity reactions can frequently be controlled with corticosteroids. The toxic effects on gonads are profound and can be irreversible, PCZ is currently being used as a single drug or in combination protocols for malignant gliomas and the salvage therapy of primary CNS lymphoma.

Antifolates

Methotrexate

Methotrexate is a potent inhibitor of dihydrofolate reductase (DHFR), an enzyme necessary for the synthesis of tetrahvdrofolates. These are one-carbon carriers essential for synthesis of thymidylatc and purines. After transportation into the cell along the reduced-tolate carrier system, methotrexate (or a variety of analogues) undergoes polyglutamation. Cytotoxicity reflects the duration of cell exposure to the drug as well as drug concentration. Thus the area under the concentration x time curve correlates with response. To achieve therapeutic concentrations within the brain, spinal fluid, nerve roots, and eye, methotrexate is given by vein in gram-equivalent doses. These doses, above 3.5 g/m^2, and commonly 8 g/m^2, are used for the treatment of primary CNS lymphoma (PCNSU and primary sarcomas of the nervous system. The drug mandates the establishment of alkaline diuresis, because concenttations in urine can exceed the level of solubility depending on urine pH. Methotrexate is excreted in the proximal tubule and reabsorbed in the distal tubule. Competing for this excretion are other organic acids such as acetyl salicylic acid, penicillin C or probenecid, which should be avoided during treatment, The drug has a two-phase pattern in plasma—an initial half life of 2-3 hours, and another of 8-10 hours. A late component of excretion exists in those with a third space or obesity. Thus potential toxicities include the kidney (from late excretion or precipitation of metabolites with low solubility), mucosa, and liver, where hepatocytes may store polyglutamated metabolites for months after treatment. With diminished renal function, enteral elimination can be facilitated by administration of cholestyramine or can be circumvented by dialysis of the drug,

Neurotoxicity reflects the prior use of radiation therapy or localized accentuated drug concentrations around ventricular catheters in the brain. A myoclonic dementia is reflective of microcalcifications in white matter. Cellular mechanisms of resistance result from altered transmembrane transport of the drug, decreased affinity of DHFR, or ovcrexpression of the enzyme.

Cytidine Analogues

Cytosine Arabinoside

The deoxycytidine analogue cytosine arabinoside (ara-C) is used as a second-line intrathecal or high-dose intravenous agent to treat primary CNS lymphoma. Its active phosphorylated metabolite (arabinosylcytosine triphosphate) competitively inhibits DNA polymerase A. After incorporation into DNA, there is inhibition of chain elongation and template function. This water-soluble drug can achieve therapeutic concentrations within the brain parenchyma and spinal fluid, where it is eliminated by deaminases, Molecular mechanisms underlying ara-C resistance in humans have not been clearly identified. It is presumed that downregulation of enzymes required for pro-drug activation, upregulation of inactivating enzymes, and modifications in the cellular response to ara-C-mediatcd DNA damage are involved. Toxicities include early and severe myelotoxicity (after intravenous use), gastrointestinal side effects, and encephalopathy, particularly at high doses and in patients older than 40 years.

Ara-C provided by lumbar puncture or through an Ommaya reservoir in continuity with the subarachnoid space or ventricle treats leptomeningeal lymphoma or esthesioneutoblastoma. Doses between 30 and 50 mg/m are given. This approach, requiring twice-weekly administration, has led to the provision of drug encapsulated in microscopic lipid-based particles that release the drug over 2 weeks' time. Seizures and chemical leptomeningitis can complicate intrathecal administration and may require the use of anticonvulsants or oral corticosteroids.

Antimicrotubule Agents

Microti!bular components of the mitotic spindle apparatus can be inhibited within rumor cells with resulting reduction of cell division, intracellular transport, and secretion. Vinca alkaloids are used to treat glioma as well as PNET. However, it is unclear whether these drugs play any effective role in therapy.

Vinca Alkaloids

The vinca alkaloids, naturally found in *Catharantbus roseus*, inhibit polymerization of tubulin and the disassembly oi micro tub ILLS, .uid thus produce cell cycle arrest in metaphase. Vinca alkaloid resistance mechanisms include the overexpression of P-glycoprotein, a large

transmembrane protein encoded by the MDR1 gene that functions as a drug-pump transporting a variety of drugs from the intracellular to the extracellular compartment, Vinca alkaloids arc administered by bolus injection or short infusion. Complications are neurological and include noncumulative autonomic neurotoxicity, constipation, paralytic ileus, dysuria, and blood pressure in stability. The main cumulative side effect is peripheral neuropathy.

Vincristine

Vincristine as a bolus injection {1.4 mg/m" up to 2 mg) is metabolized in the liver and excreted into bile. This drug is part of PCV chemotherapy for the treatment of oligodendroglial tumors. The uncertainties regarding efficacy may reflect its poor penetration of the BBB. Toxicity to peripheral or cranial nerves ensues after cumulative doses higher than 5 to 6 mg. The nerve damage may be painful or dysesthetic. An encephalopathy with seizures has followed inadvertent high dose usage.

Compounds Based on Elemental Platinum

Platinum compounds form hifunctional bonds to DNA to produce intrastrand adducts linking two nucleotides. The cell repair of these links makes use of nucleotide excision-DNA repair. Defects in the DNA mismatch repair system may prevent recognition of platinum adducts and result in failure to initiate apoptosis. Platinum-based compounds, usually in combination with other drugs, are being used for the treatment of neuroblastomas, pineal parenchymal tumots, embryonal tumors and nongenninomatous germ cell tumors, as well as for salvage therapy of recurrent malignant gliomas.

Cisp latin

Cisplatin is administered intravenously at doses of 50-90 mg/m^2 every 2-3 weeks. The drug is eliminated mostly through renal excretion. Cisplatin is highly emctogenic. Othct significant adverse reactions include peripheral neuropathy, as well as central neurotoxic effects (papilledema, seizures), ototoxicity, renal toxicity resulting in loss of magnesium, calcium and heavy metal ions requiring prophylactic supplementation, and myelosuppression (particularly thrombocytopenia).

Carboplatin

The commonly used carboplatin dose is 4–6 mg/m^2 x min (area under the concentration x time curve). Virtually all of the intravenous dose is excreted in urine within 24 hours. In general, the agent is easier to use than cisplatin, having fewer side effects of emesis, neuropathy, confusion, and renal damage, but is likely more myclosuppressive. The drug is used alone by vein or artery or in high doses with stem cell support to treat glioma and as part of regimens for PNETs.

Topoisomcrasc Inhibitors

DNA is a dynamic molecule that coils and bends to form supercoils. To replicate, DNA must temporarily uncoil and link/unlink its double strands (catenation/decatenation). This process is catalyzed by topoisomcrascs. Topoisomerase I introduces single-strand breaks into the DNA molecule. Topoisomcrasc II catalyzes linking and unlinking by causing double strand breaks. The topoisomcrascs bind to the free ends of the cut DNA molecule using a specific tyrosine residue.

Topoisomcrasc I Inhibitors

A large number of eamprothecms are potent against glial cell lines in vitro. These drugs, y-aminocamptothecin, topotecan, irinotecan (CPT-11), and the experimental agents karcnitecin (BNP1350) and gimatecan (ST1481), inhibit topoisomerase I.

Topotecan

Topotecan is hydrolyzed to its active metabolite. It is inactivated by carboxylation and excreted rcnally. After a 30-minute infusion in doses of 1.5 mg/m^2 on days 1 to 5 of a 21-day cycle or 2.6 mg/m over 72 hours weekly, there is excellent penettation of the BBB. The agent is a second line drug fot methotrexate-resistant PCNSL, but has shown no effect on malignant gliomas. Dosing is limited by leukopenia and thrombocytopenia.

Irinotecan

Irinotecan (CPT-1 I) undergoes hydrolysis to form the active moiety, SN-38. The latter is inactivated by liver glucuronidation and passed into the bile. As this process is inhibired by valproic acid, this anti-epileptic drug is prohibited in CPT-11 recipients. Adverse reactions include an acute cholinergic syndrome, delayed diarrhea, myelosuppression, nausea, vomiting, and alopecia. The typical dosing schedule is 125 mg/m Avk for 4 weeks, followed by 2 weeks of rest, or 300-350 mg/m every 3 weeks.

Topoisomcrasc II Inhibitors

During the catenation/decatenation process, topoisomerase II forms a complex with two DNA double strands—the cleavage complex. Etoposide and teniposide, semisynthetic

derivatives of podophyllotoxin, a substance found in mayapple extracts, inhibit the re-ligation of DNA from the cleavage complex.

E *top oside*

Etoposidc (VP-16) is being used as part of polychemotherapy regimens against PNETs, ependymoma, pinealoma and pineocytoma, embryonal tumors, and nongerminomatous germ cell tumors, as well as a salvage treatment for malignant gliomas and PCNSL. As a bolus infusion of TOO to 150 mg/m on two or more consecutive days, it is without significant nonhematological toxicity. It is used experimentally as an intrathecal agent {new formulation), an oral agent (new formulation), and in high-dose chemotherapy protocols followed by stem-cell rescue. Cytotoxicity may depend on persistent cleavage complex formation. This is the rationale for prolonged oral administration of low-dose etoposide (50 mg/m) even in prior recipients of bolus etoposide chemotherapy. Penettation through the intact BBB is poor (CSF concentration less than 5% of plasma level). The drug is almost completely bound to plasma protein. Dose-limiting toxicity is myelosuppression. Leukopenia and thrombocytopenia are mild and occur during the second week after initiation of bolus treatment. Cell count nadir after a 21-day course of oral etoposide is reached within days after drug administration. Etoposide is eliminated in part unchanged through the kidney and in part metabolized in the liver, Resistance to etoposide is based on ATP-dependent transporters such as P-glycoprotein and mutations within the topoisomcrase gene.

Delivery Strategies

The major anatomical obstacle for chemotherapy of primary brain tumors is the BBB, which is composed of the endothelial cell layer of cerebral capillaries sealed by intercellular tight junctions, the vascular basal membrane, and astrocytic foot processes. Whether this barrier is functional in brain tumors is controversial; few studies have directly measured brain concenttations of systemically administered agents. Delivery strategies developed to circumvent the barrier include the following: (I) Intrathecal administration of methotrexate, thio-TEPA, or cytosine-arabinoside for leptomeningeal metastases from high-grade gliomas or esthesioneuroblastomas. However intraparenchymal brain and nerve root tumors in excess of 3 mm cannot be effectively treated via this route. (2) Intracarotid infusion of hypertonic solutions such as 25% mamiitol or 15".. glycerol to produce reversible opening ol the BBB. This approach, selectively used in specialized centers, produces 1-2 hours of barrier lysis during which hydrophilic cbemotberapeutic agents such as methotrexate or cyclophosphamide may penetrate the brain parenchyma. The permeability change favors normal brain over tumor tissue. This technique has been used to treat PCNSL and malignant glioma. The technology obligates general anesthesia and serial angiographic procedures and is associated with significant toxicity, including seizures and ttansient encephalopathy. (3) Biodegradable polymers impregnated with BCNU increase local drug concentration without notable systemic toxicity (Engelhard 2000). Dime-sized wafers of p-carboxyphenoxy (poly bis) propane and scbacii acid degrade over 7 in 10 days into tumor surrounding the resection site. The polymer-based delivery strategy is associated with survival improvements of less than 2 months in patients with recurrent malignant glioma. I lowevcr, the approach may benefit from the use of wafers containing higher concentrations of BCNU. Complications include infection, wound healing impairment, brain necrosis, and CSF leak. Future use of polymers may include the provision of antiseizure medications, corticosteroids, or other antineoplastic agents.

High-Dose Chemotherapy with Stem Cell Rescue

Mycloablative doses of chemotherapy followed by autologous bone marrow or peripheral blood stem cell transplantation have l.nled to produce higher response rates in malignant gliomas when compared with conventional adjuvant chemotherapy (Einlay 1996). Moreover, this approach is associated with significant treatment-related morbidity and mortality, and thus has not found widespread use. Early results of high-dose chemotherapy with peripheral blood stem cell rescue in patients with potentially chemosensitive brain tumors like anaplastic oligodendroglioma or PCNSI. are more promising.

New Treatment Strategies

Over the preceding decade, numerous new treatment strategies have been developed, mostly based on the rapidly growing insight into molecular mechanisms of tumorigenesis. The better understanding of tumor development has yet to result in prolonged survival and improvement of quality of life for patients with brain tumors. However, after decades of little progress in glioma therapy, a number of new approaches raises hope.

New Cytotoxic or Cytostatic Cbemotberapeutic Agents

Temozolomide is a nonclassic alkylating agent. It is spontaneously converted under physiological conditions to monomcthyltriazene imidazole carboxamide, the same intermediate obtained from metabolic degradation of dimethyltriazenyl imidazole carboxamide (DTTC, dacarbazinc). Its metabolism is much more predictable than that of other alkylating agents because it is independent

from interindividual differences in the rate of enzymatic conversion. It has shown mild to moderate efficacy in malignant glioma. Critical for its antineoplastic activity is the methylation at the O^{s} position of guanine. Resistance to temozolomide is the result of guanine-0 -alkyi transferase-incdiatcd repair of O"-methylated guanine residues, defects in the cellular DNA mismatch repair system, and induction of poly (adenosine diphosphate ribose) polymerase, a constituent of the nucleotide excision repair system. Oral bioavailability is excellent, and therapeutic concentrations are reached within brain parenchyma and spinal fluid. Dose limiting toxicity is myelosup press ion resulting in neutropenia and thrombocytopenia 3-4 weeks after initiation of each cycle.

Tumor Therapy Targeting Control of Cell Growth

How cells conttol theit growth is an essential issue in the development of primary brain tumors, STI-571, a synthetic inhibitor of the tyrosine kinase receptors abl and c-kit, has been of value in the therapy of chronic myelogenous leukemia and gastrointestinal stromal tumors. This has inspired the use of similar agents to target analogous brain tumor pathways. Cell growth control can be attacked at different levels: gtowth factors, growth factor receptors, intracellular signal transducers, nuclear transcription factors, and cell-cycle conttol proteins. Various strategies are available to interfere with proteins or the transcription/ translation of their encoding genes at each level. Antisense oligonucleotides injected into tumors hybridize with transcripts of growth control genes and inhibit their translation. Ribozymes degrade transcripts with high specificity. Monoclonal antibodies directly target growth control proteins. Gene therapy may restore the function of mutated cell-cycle control proteins. Modified peptides or peptidomimctics are molecules designed to bind to the active sites of proteins such as the tytosine kinase domain of growth factor teceptors. Modification of peptides is neccssaty to prevent rapid degradation by ubiquitous proteases. Pep ti do mime tics are small organic molecules that mimic peptides but are not subject to proteolytic degradation.

Growth Factor Receptors

Epidermal Growth Vector Receptor. Epidermal growth factor receptor (EGFR) is overexprcssed in patients whose glioblastoma multiforme is not the apparent product of malignant change of a more benign tumor *[de novo* glioblastoma multiforme). The rearranged EGFR gene results in aberrant transcripts. For instance, the in-frame deletion of exon 2 to 7 is translated into a ptotein with a truncated extracellular domain (EGERvIll). Although EGFRvIII does not bind epidermal growth factor (EGF), it is constitutivcly phosphor y la ted at its car boxy [-terminal tyrosine residues and thus may continuously transduce downstream signaling.

To target the mutated EGFR, monoclonal antibodies have been developed. These antibodies can be "cold" or conjugated to radioisotopes or cytotoxins. In clinical trials, either alone or with radiation therapy, are ZD1839 (Iressa) and ryrphostin (AG1478, [4-(3-chloroanilino)-6,7-dimethoxyquinazoline]}, small molecule inhibitors of EGFR tyrosine kinase that block downstream effects on cell growth control.

Platelet-Derived Growth Factor Receptor. STI-571 is a tyrosine kinase inhibitor of the 2-phenylaminopyrimidine class. In addition to its effects on abl and c-kit, it is a selective inhibitor of platelet-derived growth factor receptor (PDGFR). It is being evaluated in phase I trials either alone, with radiation therapy, or with tcmo/olomidc. Leflunomide (N-[4-(trifluoromethyl)phenyll 5-methylisox-a7.ole-4-carboxamide, SU-101) inhibits PDGER signaling. Because objective responses in a phase I trial were observed in malignant glioma patients, the dtug is being explored in phase II/III clinical trials.

Vascular Endothelial Growth Factor Receptors. Kinase insert domain receptor (KDR) and FMS-related tyrosine kinase 1 are tyrosine kinase receptors for vascular endothelial growth factor (VEGF). Treatments targeting these receptors are described in the section on antiangiogenic strategies.

Intracellular Signal Transducers

Inhibition of Protein Kinase C. Protein kinase C (PKC) is one of the plasma membrane serine threonine kinases essential for the signal transduction of growth factors and hormones. PKC alpha is overexpressed in high-grade gliomas. Inhibitor-; of PKC include antisense oligonucleotides and tamoxifen. Tamoxifen is an oral, nonsteroidal, mixed estrogen receptor agonist and antagonist that inhibits PKC via an estrogen receptor independent pathway. It is used in high doses (to 240 mg/day) for the treatment of recurrent malignant glioma, but catries the risk of venous thromboembolism.

Inhibition of the Ras Signaling Pathway. The Rasproteins (p2 1 tas) arc guanine nucleotide-binding proteins with guanosine triphosphatase activity. These proteins play a central role as signal transducers for a variety of critical processes such as proliferation and differentiation. Activation of the Ras pathway depends on signaling from tyrosine kinase receptors such as EGFR. Ovcrcxprcssion of Ras-proto-oncogene product has been found in malignant gliomas.

Proper functioning as a signal transducer requires anchoring of the protein in the inner leaflet of the cell membrane. This is mediated through a farnesyl moiety that is covalently linked to a cysteine terminus of the protein, Farnesyltransferase, the enzyme that catalyzes the bond formation between farnesylpyrophsophate and Ras protein, can be inhibited. Inhibition of this transferase reverts transformation of cells containing mutated Ras.

Farnesyl transferase inhibitors are currently in clinical trials, as are inhibitors of /i-hydroxymethylglutaryl coenzyme A reductase. Two surprising inhibitors of the Ras signaling pathway are lovastatin and simvastatin, which alter synthesis of steroids and polyisoprenoids such as farnesyl pyrophosphate or geranylpyrophosphate.

l'roteasome Inhibitors. The proteasome is a cellular protein degradation complex that recognizes and degrades polyubiquitinated substrates such as cell-cycle control proteins. Although a fairly nonspecific apparatus, the overall effect of some proteasome inhibitors such as PS-341, a dipeptidyl boionic acid derivative, is the induction of apoptosis. PS-341 is currently the subject of clinical trials for patients with recurrent malignant glioma.

New Delivery Strategies

New delivery strategies are designed to circumvent the BBB to treat malignant gliomas. The bradykinin analogue cereport (RMP-7) increases capillary permeability by inducing contraction of endothelial cells, loosening of tight junctions, and stimulating transendothelial transport. Intraoperative injection of resection margins with various therapeutic agents (viral vectors, oncolytic viruses) docs not depend on BBB permeability. Tissue penetration can be improved using convection-enhanced delivery. This technique requires intraoperative placement of infusion catheters in the wall of the resection cavity. Using microinfusion pumps, therapeutic agents are provided postoperatively.

Modulation of Drug Resistance

Several methods are under investigation to reduce resistance to alkylating agents. O^b-henzylguanine is a potent inhibitor of 0^6-alkyl-guanine-DNA-alkyirransfcrase. Chemotherapy with carmustine preceded by 0^6-benzylguaninc decreases the maximum tolerated dose of the alkylating agent because there is increased myelotoxicity. It remains to be shown whether this combination lends to increased survival. The rationale for combination therapy of temozolomide with other alkylating agents such as BCNU is the favorable toxicity profile combined with O^6-alkyl-guanine-DNA-alkyltransfcrase-deplcting properties of temozolomide.

Inhibitors of Angiogenesis and/or Ceil invasion

Gliomas greater than a few millimeters in size stimulate new blood vessel formation. This induction is affected by promoters including VEGF (hypoxia-inducible endothelial cell mitogen, vascular permeability factor), basic fibroblast growth factor (bFGF), platelet-derived growth factor, EGF, transforming growth factor (TGF), and tenascin. Endogenous inhibitors of angiogenesis include angiostatin, endostatin, thrombospondin, and heparin. FMS-relatcd tyrosine kinase 1 (Flt-1, VEGF-R1) and KDR (VEGF-R2) are tyrosine kinase receptors for VEGF.

Matrix metalloprotcinases (MMPs) are a family of more than 20 en do peptidases that degrade macromolecules of the extracellular matrix. They are produced by a variety of different cells, including inflammatory cells and endothelial cells and may influence tumor cell migration through brain parenchyma and the growth of new blood vessels. The control of the MMPs depends on tissue inhibitots in the vicinity of primary and metastatic brain tumors. Marimastat, Ag3340, and Col-3 (6-demethyl-4-dedimethyl-aminotetracycline) are synthetic inhibitors of MMP currently the subject of study in several clinical trials.

Thalidomide inhibits tumor necrosis factor-^ (TNF-u) and angiogenesis induced by VF.GF. Expression of *0*-integrins is decreased and endothelial cell migration is reduced. Daily doses to 1200 mg have been administered to treat recurrent malignant gliomas. SU5416 is an inhibitor of KDR (VEGF-R2) and FMS-related tyrosine kinase 1 (Flt-1, VF.GF-Rl). It has antitumor activity in xenograft glioblastoma models. O-chloro-acetyl-carbamoyl-fomagillol (TNP-470} is an analogue of material produced by the fungus *Aspergillus fumigatus fresenius.* It exerts growth arrest in endothelial cells. Angiostatin, an endogenous fragment of plasminogen, inhibits neovascularization. Administered pa rente rally over prolonged periods, it inhibits visceral tumor growth in animal models. Local administration can he achieved with direct intratumoral injection, or it can be delivered using adenovirus (Ad)-associated vectors. Kndostatin, a carboxyterminal fragment of collagen XVIII, shows promise as an antiangiogenic agent in animal experiments. Other potential therapies targeted to endothelial cells include squalamine, anti-VEGF antibodies, interleukin ((L) 12, cyclooxygenase II inhibitors, and EMD121974, a cyclic pentapeptide inducing apoptosis of growing endothelial cells through inhibition of their wvAi intcgrin interaction with the matrix proteins vitronectin and tenascin.

Gene Therapy

Gene therapy of brain tumors encompasses a wide spectrum of various sttategies (Lam et al. 2001). Viral vectors create localized inflammation while expressing transgenes that activate cytokines and chemotherapies. Transfection efficiency depends on the agent and the mode of introduction. Cells are killed not only by transfection but by the cellular reaction that damages adjacent tumor cells: the "bystander effect," The delivery of a therapeutic gene can be enhanced by improving the vector or delivering it through infusional clysis. Modified retroviral vectors lacking infectivity as a result of fusion of an envelope protein to a polypeptide through a protease sensitive linkage are locally activated by releasing the polypeptide in the vicinity of metalloproteinase rich tumors, l.igands or antibodies targeted at receptors expressed on tumor cells (EGFR, transferrin receptor,

integrin receptor) can be incorporated into the capsid of adenoviral vectors. Tumor-specific expression systems make use of the human telomerasc reverse transcriptase (hTERT) promotor. hTERT is the catalytic subunit of the telomerasc ribonucieoprotein and is expressed in glioma cells but not in normal glia cells. Delivery of recombinant proteins can be achieved by fusion with transducing proteins such as TAT protein of human immunodeficiency virus or VP22 of herpes simplex virus (HSV). Tumor selectivity can also be accomplished by using replication-conditional viral vectors, retroviruses, or placement of genes essential to virus replication under the control of promotors that are selectively active in gliomas (such as the nestin promotor).

Currently used vector systems are either replication-defective or replication-conditional and include recombinant HSV, Ad, retrovirus, and hybrid vectors. Replication-conditional vectors replicate selectively in tumor cells. Examples are recombinant HSV lacking the gene encoding thymidine kinase, the IISV double mutant G207 with defective y34.5 and ribonucleotide reductase gene, and Ad mutants that lack expression of the El B gene and thus replicate only in p.53 deficient cells (ONYX-015). Retroviruses replicate only in dividing cells. These viruses are unstable in body fluids. Transduction efficiency can be increased by using vector producer cells as delivery .systems.

Gene therapy delivery involves stereotactic injection into the tumor or intraoperative insertion into the wall of the resection cavity, intra-arterial or intraventricular application. Nonviral strategies have made use of naked DNA, polycationic polymers, and liposomes.

Transfection of Tumor Cells with Bacterial Enzymes Followed by Application of Pro-Drugs. The herpes simplex virus thymidine kinase gene has been inserted into tumor cells using adenoviral or retroviral vectors. Transfected cells phosphorylate systemiealty administered ganciclovir to form a nucleotide-like precursor, incorporation of which into the nascent DNA strand blocks DNA replication. Only dividing cells arc transfected limiting the cytotoxic effects on normal tissue. Transformation efficiency is low but n on trans fee ted tumor cells can be eliminated through the release of phosphorylatcd ganciclovir from dying adjacent tumor cells ("bystander effect"). Other examples of "suicide gene therapy" arc the *Escherichia coli* cytosine deaminase/5-fluorocytosine system and rat CYP450 2Bl/cyclophosphamide system. Cytosine deaminase converts 5-fluorocytosine into 5-fluorouracil. Because of its high membrane diffusibility, the "bystander effect" is pronounced. CYP450 2B1 converts cyclophosphamide to phosphoramide mustard. This "suicide gene therapy" concept is the basis for several ongoing phase I clinical trials.

Other Gene Therapy Concepts. Gene therapy concepts can target a poptosis-resistance mechanisms of glioma cells. Transfection of glioma cells with wild type p53 can restore tumor suppressor function and induce apoprosis. Synergies exist with radiation and chemotherapy. Similarly, apoptosis can be induced by transfection with dominant-negative forms of Ras or ribozymes against Ras messenger RNA, which leads to upregulation of Fas expression or by transfection of caspases or TNF-a. Transgenes can also block angiogenesis by providing dominant negative forms of the VEGF receptor (KDR/ELK1), VEGF antisensc oligonucleotides, and antagonists of the endothelial cell tyrosine kinase receptor TIE2. Other gene therapy strategies confer drug resistance to endogenous hematopoietic cells, thus allowing higher doses of chemotherapy without an increase in myelotoxicity.

Novel transgenes or gene therapy targets include the following: (1) fusogenic membrane glycoproteins (measles virus proteins F and H, mutated form of the retroviral envelope protein of the gibbon ape leukemia virus), which fuse tumor cells; (2) sodium iodide symporter gene transfer followed by I-I31 administration; (3) transfection of tumor cells with gap junction protein «-l (conncxin-43) to enhance intercellular communication; (4) tissue inhibitor of metalloproteinascs-2 and antisensc integrin /j-'l cDNA; (5) ovcrcxpression of tyrosine kinase receptor type 3 by mcdulloblastoma; (6) telomerase, which elongates telomeric DNA; (7) granulocyte-macrophage colony-stimulating factor cDNA that induces antitumor immune response, as can IL-12 or IL-4.

Immune-Mediated Therapy

Whether primary brain tumors suppress immune reaction, are poorly recognized by the immune system, or are protected by the immunosuppressive effects of concurrent glucocorticoid administration is uncertain. Therapies based on immune-mediated strategies aim to increase immune responses to the tumor. Extraneurally injected brain tumor cells ("tumor vaccination") and immune cells communicate in the absence or the presence of antigen presenting cells. The communication is mediated by rcccptor/ligand interaction or the production of cytokines. Cytokines have been used to increase the local tumor response to brain tumors by in vivo or ex vivo stimulation of cytotoxic I -lymphocytes. Recombinant cytotoxins combine receptor-mediated specificity with the toxicity of a bacterial protein. (.t)[ij-.iLV-IU'S ni antibodies with radioactive isotopes deliver cytotoxic doses of radiation to cells expressing surface antigens recognized by the antibody.

Vaccination Strategies. Tumor vaccination makes use of attenuated autologous tumor cells or dendritic cells loaded with tumor antigens. These tumor antigens create an immune reaction enhanced by irradiation, transfection with cytokine genes, or transfection with major histocompatibility complex (MHC) class II genes. The antigen

can be presented in subcutaneous tissues, after which cytotoxic T-cells infiltrate the site of injection as well as the brain.

Cytokines. Interferons are cytotoxic and indirectly immunomodulatory, Interferon *a* and *fi* have been administered alone or in chemotherapy combinations to treat recurrent malignant gliomas. Interferon *y* induces expression of MHC class I molecules on glioma cells as well as MHC class I and II molecules on immune cells. It potentiates lymphokiue-activated killer (LAK) cell attack on glioma cells and induces the expression of CD95 (Fas) to inhibit glioma cell growth,

IL-2 has been used in combination with LAK cells. Tumor-infiltrating T lymphocytes (TILs) express low levels of tlw IL-2 receptor. However, clinical trials using di:\vi injections of IL-2 did not improve tumor control.

Apoptotic pathways may be exploited to kill brain tumor cells (Roth ct al. 1999). TNF-a, CD95 ligand (FasL, ApolL), and Apo2 ligand cytokines induce apoptosis. Fas (CD95) is expressed on glioma cells. Fas-negative glioma cells can be transfeeted with Fas cDNA. CD95 is not present in normal brain. Thus CD95 is a logical target on glioma cells. The ligand Apo2L (TNF-related apoptosis-inducing ligand [TRAIL]), the receptors DR4 (TRAIL-R1), and DR.S (TRA1L-R2), as well as the decoy receptors DcRl (TRAIL-R3) and DcR2 (TRA1L-R4), are involved in apoptotic activities. Binding of Apo2L to DR4 or DR5 leads to induction of apoptotic cell death. Apo2L is expressed on malignant gliomas but not normal brain. These ligands lend themselves to local application within brain tumors.

Recombinant Cytotoxins. Cytokines can be linked to bacterial toxins as genetically engineered fusion proteins. Currently in phase I clinical trials are IL-4 and IL-13 linked to pseudomonas exotoxin. These constructs are injected into the wall of the resected tumor or administered through convection-enhanced delivery. The targets are glioma cells ex pressing II receptors (Puri et al. 1999),

Antibody- and Cell-Mediated Therapy of Gliomas. Antibodies alone or conjugated with toxins or radioactive isuropes cm target epitopes on tumor cells. These approaches are hampered by insufficient delivery, lack of tumor specificity, and concerns regarding ventricular or subarachnoid exposure.

Locoregional radioimmunotherapies currently use monoclonal antibodies against LGFR, neural cell adhesion molecule, or tenascin labeled with iodine-131 or yttrium-90 (Brady et al. 1992). Yttrium-90 is the favorable isotope because it delivers high-energy beta rays and provides a stable conjugate. The antibodies are injected by vein, artery, or into the operative site. With intracavitary injection, radiation doses to the cavity wall approaching 280 Gy have been achieved.

Iinimine cells can he used to target glioma eel Is. i \1\ cells can kill autologous glioma cells, but clinical results have been disappointing. Although it is possible to isolate and stimulate TILs, these strategies have not been translated to human use.

Restoration of Local and Systemic Immune Response in Glioma Patients

Although glioma biopsies reveal perivascular lymphocytes, it is generally assumed that there exists subtle glioma-related immunosuppression. Potential mediators include inhibitory cytokines (TGF-/J, prostaglandin F., IL-10) and defective cytokine receptors on tumor-infiltrating T cells. Glioblastoma can be made immunogenic by transfection with antisense TGF-^3 or decorin, a TGF-0-binding and TGF-/i-inhibiting proteoglycan. Although IL-2 transfection has been unrewarding, other cytokines have been used with success (IL-4: intratumoral delivery of IL-4 using a transfeeted plasmacytoma cell line, IL-7), Transfection of tumor cells with the costimulatory molecule B7 leads to inhibition of glioma cells. Other strategies improve antigen presentation and T-cell costimulation by using cytokines (interferon-)' and TNF-c) to enhance the expression of MHC class I and II molecules.

Insulin-like growth factor is integral to glioma proliferation. Antisense oligonucleotides directed against the insulin-like growth factor type I receptor restore a glioma-specific CD8-I- lymphocytic response. This approach has led to responses in a clinical human trial.

Oncolytic Viruses

Oncolytic viruses are modified viruses that preferentially replicate in and destroy cancer cells (Mineta et al. 1995). An example for this therapeutic strategy is a replication competent, EIB-attenuated adenovirus. E1B is a viral protein that binds and inactivates p53, a prerequisite for the virus's ability to replicate in its host cell. Ad lacking El B can only replicate in TP53-deficient cells. Loss of TP53 function is an early event in the pathogenesis of gliomas and thus renders them susceptible to lytic infection with this attenuated vitus (Alemany et al. 1999). Clinical trials have proven safe and continue.

Genetically Modified Neural Stem Cells

Neuroprogenitor cells may deliver vectors or therapeutic genes to tumors. Animal experiments have shown that systemically administered neural stem cells home to brain tumors. Progenitor cells have been found within experimental brain tumors following injection into the contralateral cerebral hemisphere—an observation that may indicate the stem cells' ability to track down migratory brain tumor cells (Noble et al. 2000).

MANAGEMENT OE SPECIFIC BRAIN TUMORS

Astrocytic Tumors

Low-Grade Astrocytomas

Clinicians arc divided into advocates of early biopsy followed by radiation thcrapv and tliose who prefer to observe their patients and not treat. Our approach is to provide early diagnostic biopsy or gross total resection. Radiation or chemotherapy is reserved for nonresectable, symptomatic patients.

Surgery establishes a diagnosis and identifies the existence of oligodendroglial-containing tumors. Symptoms are alleviated, including those associated with mass effect, hydrocephalus, hemorrhage, cyst formation, or seizure activity. Surgery reduces the cell pool at risk of malignant degeneration and removes potentially more aggressive foci within radiographically benign tumors. Less clear is the survival benefit of resection of infiltrating diffuse astrocytoma or "partial" decompression of a mass. Most surgeons safely resect tumors in the poles of the frontal or temporal cortex. The introduction of preoperative MRI mapping of gray and white matter functions as well as intraoperative monitoring, and resections performed under the guidance of intraoperative MRI have expanded the surgical options (Bcrgcr et al. 1997).

Radiation therapy has a limited role in the initial treatment of low-grade astrocytomas except in those eases with a high proliferative index (Yi-67 index), large tumor size, or tumor in proximity to vital structures. Asymptomatic individuals with incompletely resected or nonresectable diffuse astrocytomas are usually followed without treatment with quarterly MRI scans, and then scans every *6* months. Radiation is provided for patients with progressive symptoms or tumor expansion, uncontrolled seizures, or steroid dependence (Knisely et al. 1997). When the tumor exhibits changes suggestive of focal anaplasia (as gadolinium enhancement on MRI, glucose uptake on PET, or increased perfusion on single photon emission-computed tomography fSPECT] scans above 5%) proliferative index external beam radiation therapy in fractions of 180 to 200 cGy, 5 days per week, to a total dose of 50-60 Gy is an option. The radiation field includes the area of radiographically identifiable tumor (Fluid Attenuated Inversion Recovery |FLAIR] or T2 margin) and an additional margin of 1-2 cm. The latter includes presumed tumor infiltrates. The clinician should be **aware** of radiation therapy complications, which can become apparent within 2 years. These include acute, early-delayed and late-delayed toxicities. Within 10 days of the start of irradiation, patients may become fatigued and experience altered appetite and sleep patterns reflecting brain edema. I'here is likely demyelination seen as increased permeability to dye as well as FLAIR changes on MRI. Six to 18 months after radiation, contrast-enhanced masses reflect radiation-induced white matter necrosis. ^{lft}FDG-PET or ^{201}Thallium SPF(T disclose diminished uptake of lig.md. Th:s prvi,v^s often responds to corticosteroid treatment and surgery, Additional complications include pan-hypothalamic-pituitary dysfunction, elevated prolactin levels, impotence, or amenorrhea.

Chemotherapy for infiltrative astrocytomas is restricted to patients whose unresectable tumors arc progressively symptomatic, or in those tumors with anaplastic foci. Radiation therapy should be tried first in such cases unless an oligodendroglial component is present. Chemotherapy may be a logical approach to radiation-resistant multifocal low-grade tumors. Chemotherapy carries the long-term risk of inducing hematological malignancies (5% at *5* years) or sterility. Nitrosoureas are the most widely used group of chemotherapeutic agents. Carmustine as a single agent (dose of 200 mg/m^2 given as an intravenous infusion every 6 weeks) or lomustine (oral dose of 110 mg/m^2) in combination with PCZ (60 mg/m^2, days 8 through 21), and vincristine (1.4 mg/m^2, maximum dose 2 mg; days 8 and 29) (PCV) in 6 weekly cycles are considered standard treatment regimens. Temozolomide is currently undergoing clinical evaluation at different dosing schedules (e.g., 150 to 200 mg/nr on days 1 to 5 of a 28-day cycle) in the treatment of symptomatic infiltrative astrocytomas prior to and after irradiation,

After surgery, therapy with radiation or drugs does not prolong the recurrence-free interval (7 years) nor influence the expected survival (median up to 12 years). Favorable outcomes follow gross-total resection of tumors in young patients with high levels of performance (Piepmeyer et al. 1996). Less than one fourth of recipients of gross total resection are likely to relapse after 1 I years.

Pilocytic Astrocytoma. Composing 85% of infra tentorial astrocytomas, most pilocytic astrocytomas ate benign tumors located in the cerebellum. Surgical removal is often feasible and potentially curative (Dirven et al. 1997). Those growing in the hypothalamus, the walls of the third ventricle, the optic pathway, and the brainstem are not amenable to resection. Radiation thetapy is seldom administered because the 25-ycar survival rate is between 50% and 94% following surgical resection alone. For the unresectable case exhibiting progressive growth or symptoms refractory to treatment, involved field radiation therapy is given with a margin of 0.5 cm. Chemotherapy can be used prior to irradiation or for tumor progression, Malignant transformation of pilocytic astrocytoma is unusual and may reflect the effect of prior therapy with ionizing radiation.

Pleomorphic Xantho astrocytoma. PXA is a rare, usually benign, superficial cortical glioma. Complete resection is feasible in most patients and potentially curative. As w[r]ith other low-grade gliomas, radiation or chemotherapy is provided for aggressive or recurrent tumors. The survival is more than 80% after 5 years and 70% after 10 years,

with well-resected lesions faring the best. Anaplastic transformation occurs in 15-20% of patients for whom the natural history may be indistinguishable from that of glioblastoma.

Subependymal Giant Cell Astrocytoma. Subependymal giant cell astrocytoma occurs in patients with tuberous sclerosis. Hydrocephalus emerges before the third decade as tumors in the wall of the lateral ventricles or in the interventricular foramina obstruct CSF outflow. Surgery is curative and required when the masses outgrow the i on fines of the ventricle.

Neuroepithelial Tumors of Unknown Origin: Chordoid Glioma of the Third Ventricle. Chordoid gliomas occur in the third ventricle of adult women. As with other tumors in proximity to the hypothalamus or median eminence, there is hypogonadotropic hypogonadism, amenorrhea, hypothyroidism, or fluid-balance disorders requiring hormonal replacement. The excellent prognosis reflects the extent of surgical resection. This procedure has been aided by the use of endoscopic techniques or intraoperative MR] scanning.

High-Grade Astrocytomas

Anaplastic Astrocytoma, Glioblastoma. High-grade astrocytomas are the most common primary brain tumor in adults. Although surgical resection is often performed, total resection is seldom achieved; and resections greater than *95%* are the only ones that improve outcome. Gross total resection is recommended whenever feasible. Biopsy for histological confirmation is offered to older adult patients with lesions in proximity to sensitive cortical areas or deep-seated locations.

Radiation therapy, the most effective treatment for malignant glioma, doubles the median survival of patients with glioblastoma. The treatment consists of fractionated external beam irradiation provided at a daily dose of 1.8-2 Gy 5 days a week up to a total dose of 55-60 Gy. Stereotactic radiation is used in an attempt to reduce recurrence of malignant glioma within the field of standard radiation. Whether applied from external sources (SRS), radiation seeds (brachytherapy), or x-ray-emitting devices, control of the local tumor is improved in selected cases. SRS is noninvasive and reduces exposure of normal brain. Local infections and wound healing problems are not issues after SRS, and fewer patients require craniotomy for removal of necrotic tissue or recurrent tumor. When radiosurgery "boosts" are added to conventional radiation, selected patients experience a survival advantage. Thus patients with small, radiographically distinct areas of residual or recurrent tumor should be considered for additional stereotactic treatment (Alexander et al. 1998). The adverse effects of this aggressive approach include seizures, transient focal neurological deficits, and radiation-induced necrosis developing within 3-18 months. One third of patients treated with stereotactic radiation techniques have local recurrence; and half, a marginal recurrence (2-5 cm from the original tumor volume). Distant recurrences occur in the remainder. It is often difficult to distinguish tumor recurrence from radiation necrosis. The clinical presentation seldom varies, and imaging results {MRI, SPECT, PET) arc conclusive in only a minority of patients. Evidence of residual tumor is found in more than 90% of radiation necrosis specimens after stereotactic radiation.

The role of adjuvant chemotherapy in the management of high-grade astrocytic tumors is controversial. Since the early 1970s nitrosoureas have been the standard chemotherapeutic agents. Survival benefit has been shown in several clinical trials and in meta-analyses, but this benefit is marginal. The prognosis of patients more often reflects the tumor grade, age at diagnosis, and performance status prior to treatment. Those patients who live longer have grade III tumors, younger age (younger than 60 years), and Karnofsky performance score greater than 90%. The combination of drugs such as PCZ/lomustine/vincristine (PCV) may be superior compared with single drugs such as BCNU. Intra-artcrial drug delivery as well as marrow intensive regimens arc associated with toxicity and likely are not widely applicable. Temozolomide, unptoven in the therapy of glioblastoma, is an alternative to classical alkylating agents (Friedman et al. 2000). Given in 4-week cycles (150-200 mg/nr on days 1-5), the agent is increasingly used in clinical trails prior to or during radiation therapy, or at continuous low doses (75 mg/m^2). There arc relatively few side effects (leukopenia, thrombocytopenia, and emesis).

Neoadjuvant approaches are not standard treatment for malignant astrocytic tumors, but are increasingly used in clinical trials. At tumor recurrence, nitrosoureas arc still provided, but their benefits are limited by prior myelosuppression or drug resistance. Paclitaxel; combination chemotherapy with mechlorethamine, vincristine, and PCZ; PCZ monotherapy; platinum compounds (ciplatin, carboplatin); combination therapy with ifosfamide, carboplatin, and etoposidc; and CPT-11 among others have been evaluated as alternative salvage treatments. A detailed description of more recently developed treatment sttategies can be found in the first section of this chapter.

Median survival of glioblastoma is less than 1 year, with exceptional survivors beyond 2 years. The median survival of patients with anaplastic astrocytoma ranges from 2 to 5 years.

Others

Gliomatosis Cerebri. Patients with gliomatosis cerebri do not benefit from surgery because the tumor extends widely along white matter tracts. Symptoms reflecting brain swelling as well as focal areas of malignant degeneration determine the onset of therapeutic intervention. Involved

field or whole-brain radiation is standard therapy, but provides only marginal benefit. Thus chemotherapy is often used with agents including PCV or temo/.olomide. The infiltrating tumor may be slow growing. Therefore the clinician is advised to evaluate focal areas of glioblastoma, whoso control m.n bench! prognosis.

Oligodendroglial Tumors

Oligodendroglioma and Oligoastrocytoma

Gross total resection prolongs survival for patients with oligodendroglioma and oligoastrocytoma containing varying proportions of oligodendroglia and fibrillary or protoplasmic astrocytes. Microscopic infiltrates are likely always present. Debulking is needed for symptoms of mass effect and hemorrhage. A MIB-1 proliferation index greater than 5% even in grade 2 tumors predicts aggressive behavior. Benefit is achieved with adjuvant radiation therapy and chemotherapy. Oligodendrogliomas may respond to PCV chemotherapy. PCV may be administered to low-grade oligodendrogliomas that cannot be resected, are symptomatic, or contain more aggressive features. The median survival time of patients with oligodendrogliomas is between 4 and 11 years. Key prognostic variables are extent of resection and the provision of chemotherapy. Features suggesting more aggressive behavior include contrast enhancement with gadolinium, MR spectroscopy with choline/creatine ratio higher than 3:1, elevated MR perfusion, location in deep-seated areas of the brain, frequent mitoses, unci Ki 67 staining vales higher than S%.

Oligoastrocyromas are managed in a similar way as oligodendrogliomas.

Anaplastic Oligodendroglioma and Anaplastic Oiigoas trocytoma

Resection, radiation, and chemotherapy are important modalities of therapy for patients with anaplastic oligodendroglial tumors (anaplastic oligodendroglioma and anaplastic oligoastrocytoma). Gross total resection oi biopsy is followed by adjuvant radiation and chemotherapy. Grade III or IV "malignant" oligodendroglial tumors share with their low-grade counterparts remarkable sensitivity to various types of monochemotherapy or combination chemotherapy. The most widely studied regimen is PCV. The majority of patients have at least a partial response. Tumors with chromosome lp loss, or the combined loss of Ip ai:J l''\], are more likch to respond to l'C\ and live longer (Fortin et al. 1999). PCV administered prior to radiation may be as effective as postradiation chemotherapy, and may allow better tolerance of the drugs and improved delivery. Patients without residual postoperative, contrast-enhancing disease or with only residual FLAIR changes are often first treated with radiation therapy as an endpoint of chemotherapy benefit is difficult to define. Alternative treatment strategies include temozolomide, BCNU, or melphalan, or high-dose, myeloablative chemotherapy followed by peripheral stem cell rescue. However, the latter approach is still considered experimental in this disease setting.

Ependymal Tumors

Ependymoma and Anaplastic Ependymoma

Ependymomas occur along the neuraxis, usually in proximity to the ventricles or subarachnoid space. Intracranial ependymoma is more common in children (infratentorial more frequent than supratentorial), spinal ependymoma in adults. Ependymoma is the most common intramedullary spinal cord tumor in adults and is typically in proximity to the conus medullaris. In this location, most are of the myxopapillary subtype. Only a small fraction of ependymomas are high-grade. Local recurrence and leptomeningcal spread have been described in a small fraction of low-grade and a larger fraction of high-grade tumors.

Complete surgical removal is indicated and may cure the patient with a low-grade ependymoma. Resection of tumors in the conus medullaris is technically difficult because the masses adhere to nerve roots and have indistinct surgical "planes" or margins that separate them Iron- norm.-! tissue of the base ;>l the spina' cord Chant; er al. 2002). Radiation therapy is beneficial to patients with residual symptomatic tumor after operation, at recurrence, or with aggressive histology (Scbild et al. 1998). Low-grade tumors, especially those located within the spinal cord, require only involved field radiation. Craniospinal irradiation is needed if leptomeningcal spread occurs. The benefits of prophylactic craniospinal irradiation for high-grade ependymoma are unclear. Local failure tends to herald leptomeningcal spread. Chemotherapy for ependymoma includes carboplatin, PCV, combination chemotherapy with cisplatin, lomustine, and vincristine, or alternating cycles of cisplatin/etoposide and cyclophosphamide/ vincristine (Chamberlain 2002).

Siibependymoma

Subependymomas are benign tumors in proximity to the ventricles. Not uncommonly, their dereccion as calcific masses is incidental, and therapy is onl\ indicated v. hen symptoms ensue. The fourth ventricle is the most common location, followed by the septum pellucidum and the lateral ventricles. The tumor is well demarcated and surgical removal is curative. Subtornlly resected tumors should be followed with serial MRI studies. Symptomatic residual tumors and those that show progressive growth should be irradiated.

Choroid Plexus Tumors

Choroid Plexus Papilloma and Carcinoma

Choroid plexus papillomas are tumors of childhood. In adults they account for only 0.5% of all intracranial neoplasms. The tumor is located in the fourth ventricle, the lateral ventricles, or the cerebellopontine angle. Patients most commonly present with deficits of the eighth cranial nerve, signs of cerebellar dysfunction, or overproduction of CSF.

Total resection is accomplished in fewer than half of cases. Frequently the tumor is attached to lower cranial nerves. Thus morbidity of surgical intervention is significant. In one small series, transient worsening ot neurological deficits occurred in up to 25% of cases, and postoperative mortality approached 2(i%. Preoperative selective microembolization has been used. There is no role for adjuvant treatment modalities at diagnosis because long-term survival follows even subtotal resection. At progression or recurrence, treatment with conventional external beam radiation ot SRS is of benefit. Obstructive hydrocephalus, a frequent complication of choroid plexus papilloma, is relieved by tumor removal, and shunt procedures are only indicated in a few cases (Tacconi et al. 1996).

Choroid plexus carcinoma in adults is the subject of case reports only. Adjuvant treatment after surgical removal includes irradiation and chemotherapy. Therapeutic efficacy has been shown for lomustinc.

Neuronal and Mixed Neuronal-Glial Tumors

Ganglioglioma and Gangliocytoma

Gangliogliomas contain two cell populations: gangliocytes and mature glial elements derived from precursor cells that can differentiate into both elements. Although commonly benign, anaplastic changes develop in 4-32% of cases. Gross total resection results in survival ranging from 7 to 17 years. Thus adjuvant irradiation is not indicated. Radiation therapy is provided to tumors that are incompletely resected or those with anaplastic progression. These have a worse prognosis with an overall survival of 3 years or less (Hakim ct al. 1997). Chemotherapy is used with the assumption that the astrocytic component will respond. For the anaplastic glial component, regimens are identical to the ones used for high-grade gliomas.

Central Neurocytoma

Central neurocytoma, a neuronal tumor, occurs in young adults in proximity to the supratentorial ventricular system. The tumor arises from the fornix, septum pellucidum, or the walls of the lateral ventricles. A benign tumor, surgical removal is performed by operations through the corpus callosum or cortex with attendant memory and cognitive problems, which are transient, Fewer than 50% of patients experience cure; for the remainder there is bleeding or adherence of tumor to adjacent structures. However, long-term tumor control can be achieved with partial resection. Instances of anaplasia or dissemination along CSF pathways are rare. Thus radiation therapy is recommended for tumors with a high proliferative index or growth. For tumors smaller than 3 cm, SRS may be beneficial. Adjuvant chemotherapy benefits a minority of patients treated with a combination of cisplatin, etoposide, and cyclophosphamide (Schild et al, 1997; Brandes ct al. 2000).

Pineal Parenchymal Tumors

Although a variety of tumors appear in the region of the pineal gland or the subarachnoid space surrounding it, cells of "pineal" origin can form tumors: pineocytoma, pineal parenchymal tumors of intermediate grade, and pineobi asroma. The more malignant tumors are seen in younger patients; more than 90% of patients with pineoblastoma are younger than age 23, whereas in patients older than the age of 40 years, one third of the masses are tumors of low or intermediate grade (Chang et al. 2000).

There is uncertainty regarding the role of surgery. CT- or MR-based stereotactic biopsies are performed in many-centers. Tertiary neurosurgical hospitals advocate complete tumor resection. Radiation therapy to the pineal region and the craniospinal axis is provided to patients with high-grade neoplasms, residual tumor after surgery, and subarachnoid dissemination. Chemotherapy is used in the setting of pineoblastoma or parenchyma) tumors that are disseminated at onset or at recurrence. Commonly, preirradiation chemotherapy reduces tumor size. As with other neuroblasts tumors (esthesioneuroblastoma, mcdullobla stoma, PNET), platinum-based compounds are used, usually in combination with etoposide, alkylating agents (CCNU, PCZ, cyclophosphamide), or vincristine. Long-term responders are reported, but estimates of survival are based on literature reviews or small retrospective institutional series.

Peripheral Neuroblastic Tumors

Esthesioneuroblastoma

Esthesioneuroblastoma arises from the neuroepithelium of the upper nasal cavity. From there it invades the neurocramum through the cribriform plate, compresses the frontal lobes of the brain, and may infiltrate the brain parenchyma or subarachnoid spaces. A standardized therapeutic approach has not been established. Frequently, gross total resection via a craniofacial approach is followed by

adjuvant external beam radiation therapy unless the tumor is excised completely or is low grade (Eich ct a I. 2001). Because gratifying responses are seen with chemotherapy, patients with disseminated or recurrent disease and those with high-grade tumors are treated with combinations such as cisplatin-etoposide, cyclophosphamide-vincristine-doxorubicin, or alternating cycles of cisplatin-etoposide and cyclophosphamide-vincristine (McElroy et al. 1998). Advocates of radiation and chemotherapy prior to surgery cite decreased tumor burden and facilitation of gross total removal with decreased morbidity as benefits of this approach. Others recommend chemotherapy with cisplatin and etoposide after biopsy, followed by radiosurgery and postradiation chemotherapy.

Patients with low-grade tumors have progression-free survival exceeding 10 years, in comparison with less than 3 years for those with more aggressive tumors. Not uncommon are late local recurrences or metastases to cervical lymph nodes. When the tumor invades through the dura into the subarachnoid space, intrathecal methotrexate, cytosine-arabinosidc, or thio-TEPA may be used. Radiation is administered to symptomatic or nodular leptomeningeal recurrences,

Embryonal Tumors

Medulloblastoma

Medulloblastomas in adults are rare neoplasms. The majority of patients present before 40 years of age. Unlike childhood tumors, these are prone to the cerebellar hemispheres, less commonly in contiguity with the fourth ventricle. As a result, dissemination into the CSF is seen in fewer than one third of cases. In general, the natural history is less aggressive: Extraneural metastases have been reported in fewer than 150 patients, and then most frequently to bone (Chan et al. 2000). Multidisciplinary management is critical for the successful treatment of these tumors. Resection, craniospinal radiation, and adjuvant chemotherapy results in 10-year survival rates of *56%.* Obstructive hydrocephalus is a frequent complication of medulloblastoma. Ventrieulo-pcritoncal shunting is provided to symptomatic patients with occlusion of the fourth ventricle and dilatation of lateral ventricles. Often a filter is placed into the distal end of the shunt tubing to reduce the risk of peritoneal dissemination of tumor. Resection is followed by evaluation of CSF and lumbar spine for tumor spread, and craniospinal irradiation (posterior fossa 56 Gy, whole-brain 36 Gy, and spine 30-36 Gy). Chemotherapy benefits high-risk patients with significant residual tumor, brainstem infiltration, or leptomeningeal metastasis. Commonly used drugs cither prior to or following irradiation include cisplatin, cyclophosphamide, nitrosoureas, and etoposide. The Pediatric Oncology Group pioneered the use of alternating cycles of cisplatin (90 mg/m^2 on day 1 or 20 mg/m on days 1-5) and etoposide (100 mg/m on days 1-5) with cyclophosphamide (between 450 and 1580 mg/m on days 1 and 2) and vincristine (1.5 mg/m day 1). Rational administration of these drugs provides for their use before irradiation because craniospinal irradiation limits bone marrow reserve and the incidence of leukoencephalopathic complications is higher when chemotherapy follows radiation. However, radiation therapy should not be delayed by extended periods of myclosuppression from chemotherapy. Whether to offer prophylactic chemotherapy to low-risk patients is uncertain. Ultimately this issue will he addressed by formal study, but drugs are easily provided at diagnosis, and even "low-risk" patients are **seldom** cured, with relapse occurring years after initial diagnosis. Treatment of tumor recurrence after multimodality therapy is extremely difficult. Re-resection or SRS may be offered to selected patients. Alkylating agents are effective, and high-dose chemotherapy followed by stem cell rescue may benefit young patients.

Supratentorial Primitive Neuroectodermal Tumors

Supratentorial PNETs arc rarer than medulloblastomas. Well-delineated tumors with minimal residual tumor after surgery have a favorable prognosis. Surgical resection establishes the diagnosis and reduces the tumor burden. Adjuvant therapy consists of fractionated external beam radiation to the primary site and the craniospinal axis. However, because many of these masses are sensitive to chemotherapy, many centers have begun to treat high-risk patients with low-dose radiation in conjunction with chemotherapy. Drugs used include the PCV combination, cisplatin-etoposide alone, or alternating with cyclophosphamide-vincristine. Toxicity to bone marrow, gastrointestinal tract, and kidney accompanies the latter regimen, and thus these agents are provided prior to radiation therapy. Survival may exceed 5 years, but many patients succumb to their disease within a few years. Whether intrathecal chemotherapy with ara-C, methotrexate, or thio-TEPA confers any benefit to the patient with leptomcninge.il spread is uncertain. Treatment failure usually occurs locally. At recurrence, re-resection and salvage chemotherapy can be offered.

Tumors of Cranial and Peripheral Nerves

Schwannoma and Neurofibroma

Schwannomas and neurofibromas are benign tumors of the peripheral nerve sheath. Intracranial schwannomas arise commonly from the sensory branches of cranial nerves such as the acoustic or trigeminal nerves. However, these rarely occur within the parenchyma of cortex or medulla. Schwannomas most commonly affect the vestibular division of the eighth cranial nerve and may result in hearing

loss, vertigo, and facial numbness. However, the majority arc without symptoms and thus arc undetected. Small and stable asymptomatic tumors arc commonly followed with serial MRI scans on an annual basis. Symptomatic tumors are treated with microsurgical resection or SRS. Surgical risks include postoperative CSF leak, facial and trigeminal neuropathy, and deafness. These risks are directly related to tumor size (Kaylie et al. 2001}. The use of proton radiosurgery or fractionated SRT achieves tumor "control" without disappearance in more than 90% of patients, with hearing complications in approximately 20% (Harsh et al. 2002). Only a small fraction of schwannomas undergo malignant degeneration.

Malignant Peripheral Nerve Sheath Tumor

Malignant peripheral nerve sheath tumor (MPNST) is a rare neoplasm of peripheral nerves, including cranial nerves. Wide surgical excision is the treatment of choice, Average extent of resection depends on tumor location and ranges from 20% in paraspinal nerve root and plexus masses to nearly 100% in tumors of the distal extremities. Radiation therapy is provided for residua! disease in the form of external beam radiation alone or in combination with brachytherapy (iridium-192) or intraoperative high energy electron irradiation. Although amputation has been historically offered, these approaches have improved limb-sparing control. Twenty to forty percent of patients are treated with adjuvant chemotherapy at diagnosis (MESNA, doxorubicin [Adriamycin], ifosfamide, and dacarbazine, or single-drug regimens such as high-dose methotrexate). No • link/.! trials have been published and chemotherapy does not have a role in the initial treatment of completely resected MPNST.

Treatment failure in half the patients is local within 3 years, but late local recurrences at 25 years have been described. The median survival exceeds 2-5 years. Tumor size, extent of surgery, and age at diagnosis are predictors of survival.

Meningeal Tumors

Meningioma

Meningiomas are the most common nonglial intracranial tumors. These tumors have been found incidentally in 20% of autopsy series and affect women more than men. Management depends on location, coexistent motbidities, and the patient's age and health (Chamberlain 2001). Incidentally found asymptomatic meningiomas lacking mass effect or compression of a venous sinus can be followed conservatively with serial MRI evaluations. Many meningiomas will not grow over years, sparing older adult patients the need for craniotomy (Black et al. 1998). However, when seizures occur (20% risk), tumors grow (approximately one third of patients), or focal signs emerge, surgical resection can be curative, especially in meningiomas overlying the hemispheres. Although highly vascularized, preoperative embolization is usually not necessary. Technically more challenging are tumors invading dural venous sinuses, tumors arising from the dura overlying the medial portions of the sphenoid bone or other parts of the skull base, meningioma en plaque, posterior fossa meningiomas, and the rare intraventricular meningiomas. Complete surgical removal may not be possible in these situations and may be complicated by infection, CSF leakage, cerebral venous thrombosis, or cranial neuropathies. Less aggressive surgery in association with stereotactic radiation reduces treatment morbidity and may improve progress ion-free survival (Villavicencio et al. 2001). At recurrence or tumor progression, conventional external beam irradiation or SRS are the major treatment options.

Atypical (6%) and malignant meningiomas (2%) account for a small fraction of all meningiomas, but these tumors recur in spite of surgical resection and irradiation. Although meningiomas express estrogen and progesterone receptors, clinical trials with tamoxifen or progesterone receptor antagonists such as mifepristone (RU-486) have been disappointing. Some authors have reported partial responses or stable disease in patients with recurrent or malignant meningioma who receive hydroxyurea, alpha interferon, or drug regimens such as cyclophosphamide/ doxorubicin vincristine, ifosfamide/MESNA, or doxorubicin dacarbazine.

Hemangiopericytoma

Intracranial hemangiopericytoma, often confused **with** meningioma on imaging studies, is a rare meningeal neoplasm. Its high rate of local recurrence and predisposition to metastases to bone and liver make it unique in mcningeal-based neoplasms. Leptomcningeal spread has been described as have recurrences beyond 5 years of diagnosis. Gross total resection emphasizes removal of surrounding normal dura or brain. Radiation therapy (fractionated to 48-60 Gy) reduces the local recurrence rate and prolongs the progression-free and overall survival (Rastin et al. 1992). Unfortunately, as with meningioma and schwannoma, tumor shrinkage cannot be expected until years after therapy.

At tumor recurrence, options include surgical resection, conventional external beam radiation, and SRS. Chemotherapy may benefit the patient with systemic metastases or local therapy-refractory disease, but data are not available (Galams et al. 1998). Most protocols use doxorubicin in combination with cyclophosphamide, ifosfamide, cisplatin, and/or dacarbazine. Partial responses or stable disease for several months have been observed with these regimens. Up to 90% of tumors recur locally or systcmically within 9 years of initial manifestation.

Extraneural recurrence is predictive of worsened prognosis. Median survival after first tecurrcnce is between 4 and 5 years, but with aggressive management, long-term survival is possible.

Ncuraxis Tumors Derived from the Hematopoietic System

I'rimary Central Nervous System Lymphoma

Non-AIDS Related Disease. PCNSI, is a highly aggressive tumor. Left untreated, most patients succumb within *6* months. As with most brain malignancies, young age (younger than 60) conveys improved prognosis. Unfavorable prognostic factors include older age, low performance status, multiple brain lesions, evidence of leptomeningeal dissemination, lack of radiographic complete response to treatment, and elevated serum lactate dehydrogenase level. Methotrexate-based chemotherapy given in high doses (above 3.5 g/m^1) followed by leucovorin rescue has been shown to be the single most effective treatment for PCNSI,. Its introduction, either alone or in combination before radiation therapy, has resulted in response rates of 70-95% and survival durations in excess of 3 years. The treatment produces no alopecia, minimal to modest myelotoxicity, and is compatible with normal cognitive function. Other potentially efficacious agents include ara-C, rhio-TEPA, cyclophosphamide, ifosfamide, BCNU, PCV, CCNU, PCZ, temozolomide, and topotecan. Polychemotherapy tcgimens include inelkolitwalc. K.Z-, .i:id vn\ i ist ire with radiation therapy, and postradiation ara-C. Virtually all regimens share response rates and durations of response that are comparable to those provided by methotrexate monotherapy. However, combination regimens are associated with highet tisks of myelotoxicity and radiation-containing regimens increase the likelihood of clinically significant neurotoxicity, especially in older adult patients. Intraarterial administration of chemotherapy preceded by disruption of the BBB with manmtol is effective, but requires two-vessel angiography and general anesthesia with each treatment. The administration of intrathecal or intraocular chemotherapy is of uncettain benefit. High-dose intravenous methotrexate results in cytotoxic drug levels within the CSF and in the aqueous and vitteous humor of the eyes. However, high tumor burden within CSF may be associated with methotrexate resistance and thus intrathecal chemotherapy may postpone the need for craniospinal irradiation.

WBRT is now commonly deferred until the time of recurrence, given the high incidence of neurotoxicity, especially in patients older than the age of 60. Above doses of 35-45 Gy, escalation provides no survival benefit. Failures of radiation therapy occur within months and within the radiation field. Similarly, surgical resection provides no survival benefit and thus only biopsy is performed to establish the diagnosis.

In spite of major progress, there is still a need for refinement of therapy. This reflects several noteworthy features of the current natutal histoty: Most patients relapse, systemic dissemination is encountered in up to 8%, and the underlying hematogenous origin of the tumor is uncertain. At the time of recurrence there is likely benefit for retreatment. We have successfully used methotrexate at the time of relapse even in prior methotrexate recipients. Anecdotal responses at the time of relapse have also been reported with the use ci topotecan, NIU\II:LI1> (a chimerit antibody targeting CD20), temozolomide, PCV, or cytosine-arabinoside/etoposide, as well as intensive chemotherapy supported by autologous or allogeneic peripheral blood stem cell transplantation, WBRT is an option for patients who either fail or are not candidates for salvage chemothctapy. Meningeal or ocular relapse can be treated with radiation and chemotherapy (intrathecal or intravitreal).

AIDS-Related PCNSL. Patients with the acquited immunodeficiency syndrome (AIDS) develop PCNSL in the advanced stage of their disease. A severely compromised immune system and concomitant opportunistic infections frequently preclude chemotherapy. Thus WBRT has been the standard treatment for PCNSI. in AIDS patients. This approach has been associated with poor and nondurable responses. A subset of patients with low HIV burden and high CD4 T-cell counts are eligible to receive chemotherapy, The introduction of highly aggressive antiretroviral therapy has increased the patients in this category while reducing the incidence ot brain lymphoma.

Germ Cell Tumors

Germ cell tumors of the CNS are rare adult tumors (less than 0.1% of primary brain tumors) occurring commonly before the age ol 20 years. Nine times more common in Asia, the most common germ cell tumor occurring within the CNS is germinoma, which shares a common histology with testicular seminoma and ovarian dysgerminoma. Less common are nongerminomatous germ cell tumors (teratoma, embtyonal carcinoma, yolk sac tumor [endodermal sinus tumorl, choriocarcinoma, and mixed germ cell tumors). The entire group has a proclivity for the sellar and suprasellar region, walls of the third ventricle, and the pineal gland. Surgical access u difficult and often limits intervention to biopsy or empiric radiation/chemotherapy. The latter approach is usually avoided, given the high incidence of mixed neoplasms. Treatment planning depends on careful analysis of resected tissue, often with evaluation of serologic and CSF levels of ,8-human chorionic gonadotropin, a-fetoprotein and placental alkaline phosphatase. The major determinants of outcome are local tumor control and histological subtype. Treatment schedules are still being optimized.

Germinoma

Germinomas are infiltrative tumors with a tendency to subependymal and leptomeningeal spread. Traditionally, treatment has included surgical resection or biopsy followed by radiation therapy. The radiation is provided to the ventricular system, with craniospinal irradiation reserved for patients with cy to pathological or radiographic evidence of leptomeningeal spread. Preirradiation chemotherapy is given to high-risk patiencs to achieve complete responses and allows significant reduction of radiation dose (Matsutani et al, 1998; Sawamura et a I. 1998). The most commonly used agents are cisplatin, etoposide, and cyclophosphamide. Long-term survivors of radiation exceed 15 years with hypothalamic/pituitary neuroendocrine morbidities.

Nongerminomatous Germ Ceil Tumors

Gtoss total resection prolongs survival but is achieved in less than half the cases. Each of the nongerminomatous germ cell tumors is approached differently (Schild et al. 1996). Mature or immature teratomas are operated on and then uu'iu' invu!u'd held i.iLh.Ltic i:i ihcrap\ v, n:i *i.\<.ind* control, If the teratoma has undergone transformation to malignancy, there is an increased risk of leptomeningeal metastases. This argues strongly for prophylactic whole-brain or craniospinal irradiation. Other nonteratoma, nongerminomatous germ cell tumors are provided adjuvant radiation therapy (above 50 Gy) and cisplatin-based polychemothcrapy. The radiation therapy fields include the whole brain followed by a "boost" to the tumor bed. These approaches are associated with complications of anterior pituitary dysfunction and intellectual decline—changes that have spurred the use of localized, lower doses or hyper fraction a ted radiation in the setting of polychemothcrapy (cisplatin + etoposide; cisplatin + etoposide + ifosfamide). Prognosis for mature teratomas is excellent, Only 10-15% of patients with embryonal carcinoma, yolk sac tumor {endodermal sinus tumor), or choriocarcinoma survive 3 years a her diagnosis. Mixed germ cell tumors and immature teratomas fall in between these two extremes.

Tumors of the Scllar Region

Craniop baryngioma

Craniopharyngioma is a tumor derived from Rathke's pouch epithelium, which may be present both within the sella turcica as well as other skull base locations. Microsurgical resection via a frontoptetional or transsphenoidal approach is the primary treatment in symptomatic cases. External beam radiation therapy may extend progression-free survival after incomplete resection, although long-term survival can be accomplished with surgery alone. Masses may infiltrate the hypothalamus and multistage operative interventions are provided (van Effenterre et al. 2002).

Pituitary Adenoma

Surgical resection is the treatment of choice for pituitary adenomas larger than 1 cm in diameter, or those with compression of the optic chiasm, erosion of bone, or extension into the walls of the sella. The transsphenoidal approach (Hardy's procedure), preferable to the transcranial route (most often fight pterional craniotomy}, achieves gross total resection in one third of patients. Postoperative complications include diabetes insipidus, meningitis, hemorrhage, and persistent leak of CSt\ Improvement in microsurgical technique and imaging has reduced mortality to below 2%.

Radiation therapy is provided as primary treatment to older adult patients, those who are not surgical candidates, and following partial resection (Sasaki et al. 2000). Tumor shrinkage is seen only years after treatment. Adverse effects are infrequent and include necrosis of the adjacent portions of the temporal lobe, hearing loss, optic neutopathy, and radiation-induced sarcomas. Multiple field techniques and radiosurgery have reduced the incidence of these complications. However, the majority of patients treated with surgery and radiation require replacement of pituitary gland-dependent hormones. For recurrent adenomas, SRS or SRT have been used. Local control rates are higher than 80% for patients with nonsecreting pituitary adenomas. Prognosis for secreting adenomas is slightly worse.

Dopamine agonists such as bromocriptine, cabergoline, quinagolide, and pergolide can lead to a reduction in tumor size, improvement of symptoms, and normalization of prolactin levels in microprolactinomas as well as macroprolactinomas (Pinzone et al. 2000).

CONCLUSION

Management of patients with primary brain tumors is an interdisciplinary effort that includes neurosurgeons, neurologists, radiation oncologists, medical oncologists, neuroradiologists, and neuropathologists. Neurologists are involved in the clinical diagnosis of primary brain tumors and their neurological complications such as seizures and intracranial hypertension. An increasing number of neurologists treat brain tumors with chemotherapeutic agents or new medical strategies.

Progress has been made in diagnostic procedures, monitoring of therapeutic efficacy, understanding the pathogenesis of primary brain tumors, optimizing standard treatments for selected tumor subtypes, and developing new treatment concepts.

However, the outcome in the majority of primary brain tumors—the malignant gliomas—remains poor. A large number of new treatment strategies awaits further study. Clinical testing has been facilitated by multispceialty neuro-oncology centers and national brain tumor consortia, raising hope for an imminent breakthrough in the treatment of this tumor type.

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Chapter 58
Cancer and the Nervous System

F. MANAGEMENT OF PRIMARY NERVOUS SYSTEM TUMORS IN INFANTS AND CHILDREN

Alfredo D. Voloschin, Tracy T. Batchelor, and Jeffrey C. Allen

Primary brain tumors are the most common solid tumors of childhood, representing 20% of all childhood cancers in the United States. They are second only to leukemia in frequency among all childhood cancers (Swensen and Bushhouse 1998). Approximately 85% of primary brain tumors in children 2 years to 12 years of age arc located in the posterior fossa. Most primary brain tumors are located in the supratentorial compartment in children younger than 2 years and older than 12 years. Seventy percent of primary brain tumors are gliomas and only 5% of central nervous

system (CNS) tumors arise from the spinal cord. No geographical or ethnic predominance exists.

PRIMITIVE NEUROECTODERMAL TUMORS (MEDULLOBLASTOMAS, SUPRATENTORIAL PNETS, PINEOBI.ASTOMAS, AND EPENDYMOBLASTOMAS)

Background

Although original reports (Harvey Cushing, 1930) suggested that mcdulioblastomas originated from multipotential medulloblasts, the term *meduWoblastoma* is now a synonym for a primitive neuroectodermal tumor (PNET) of the posterior fossa. These tumors represent approximately 20% of all pediatric brain tumors. The incidence in boys is twice that of girls, and median age at diagnosis is 5 to 7 years. Supratentorial PNETs represent only 3% of all pediatric brain tumors. Eighty percent are diagnosed before 10 years of age. Although a slight male predilection exists, it is less than for mcdulioblastomas.

Etiology

No clear causc-and-effect association with dietary or environmental factors lias been found, but a genetic predisposition exists in rare syndromes such as Turcot's (associated with mutations in the APC gene on chromosome 5), Gorlin's (or nevoid basal cell carcinoma associated with abnormalities on chromosome 9q), and Ei-Fraumeni's.

Although most medulloblastomas are sporadic, familial cases, unrelated to the previously mentioned syndromes, are reported (von Koch et al. 2002). *Trilateral retinoblastoma* refers to a peculiar familial syndrome with bilateral retinoblastomas and a pineoblastoma with retinoblastic features (Finelli et al. 1995).

Clinical Presentation

Several of the clinical manifestations are the result of increased intracranial pressure (ICP). Headache is the most common symptom at presenrarion and usually precedes diagnosis by 4 to 8 weeks. Personality- changes, namely irritability, arc an early feature, but are difficult to recognize as a sign of a brain tumor. The features that most often lead to diagnosis arc morning nausea and vomiting, lethargy, diplopia, head tilt, and ataxia. The common signs on physical examination are papilledema, ataxia, dysmetna, and cranial nerve involvement. Clinically significant brainstem invasion at diagnosis is unusual. Abduccns nerve palsy secondary to raised ICP is a cause of diplopia and head tilt. Torticollis is a sign of cerebellar tonsillar herniation. Although magnetic resonance imaging (MRI) visualizes leptomeningeal metastases in 20-30% of children with PNETs at the time of diagnosis, clinical manifestations are uncommon. Back pain and radicular pain indicate the rare complication of spinal canal dissemination.

Among infants with posterior fossa tumors, the important features are changes in mood and personality as well as macrocephaly. Delay in milestone achievement or loss of previous!! achieved milestones and failure ic ilime uncharacteristic. Less commonly, intratumoral hemorrhage may lead to an apoplectic presentation.

The presenting features of supratentorial PNETs are progressive headache, nausea, vomiting, and lethargy secondary to increased ICP. Children with pineoblastomas often present with Parinaud's syndrome. The enhanced MRI of the brain typically shows a hctcrogcncously enhancing mass within the fourth ventricle, cerebellum, pineal region, or cerebrum. Obstructive hydrocephalus and, occasionally, intratumoral calcifications, hemorrhage or necrotic cysts, are often associated (Figure 58F.1).

The differential diagnosis relates to tumor site and age at diagnosis, and includes high-grade glioma, choroid plexus carcinoma, ependymoma, desmoplastic infantile ganglioglioma, neurocytoma, and germ cell tumors (when located in the pineal region).

Management

A high level of clinical suspicion is critical to make an early diagnosis. Neuroimaging is usually the first step. A computed tomography (CT) scan of the brain is usually obtained in the acute setting, but MRI of the brain and spine should be performed shortly thereafter in all children in whom the diagnosis of mcdulloblastoma is suspected. A contrast-en ha need brain MRI typically shows a heterogeneously enhancing mass in the fourth ventricle with obstructive hydrocephalus. Tumors that arise in the cerebellar hemispheres may not cause hydrocephalus as frequently. Spinal MRI is required in all cases to exclude leptomeningeal metastases. The differential diagnosis of a posterior fossa tumor in children includes inedulloblastoma, cerebellar astrocytoma, ependymoma, dorsally exophytic brain stem glioma, and choroid plexus carcinoma. The brain MRI in supratentorial or pineal region PNETs frequently shows a large heterogeneously enhancing mass. The differential diagnosis of such a pineal region mass includes a glioma such as an astrocytoma or ependymoma, as well as a germ cell tumor. Cerebrospinal fluid (CSF) obtained at the time of surgery or after resection is an important part of the staging evaluation. However, if the tumor is small and without significant mass effect, lumbar puncture to obtain a CSF sample for cytology and routine analysis before resection is recommended. The treatment consists of surgery, radiation therapy, and chemotherapy,

The gnuU of siirgen are to control IC P, achieve a gross total resection (if feasible), and prevent recurrence of

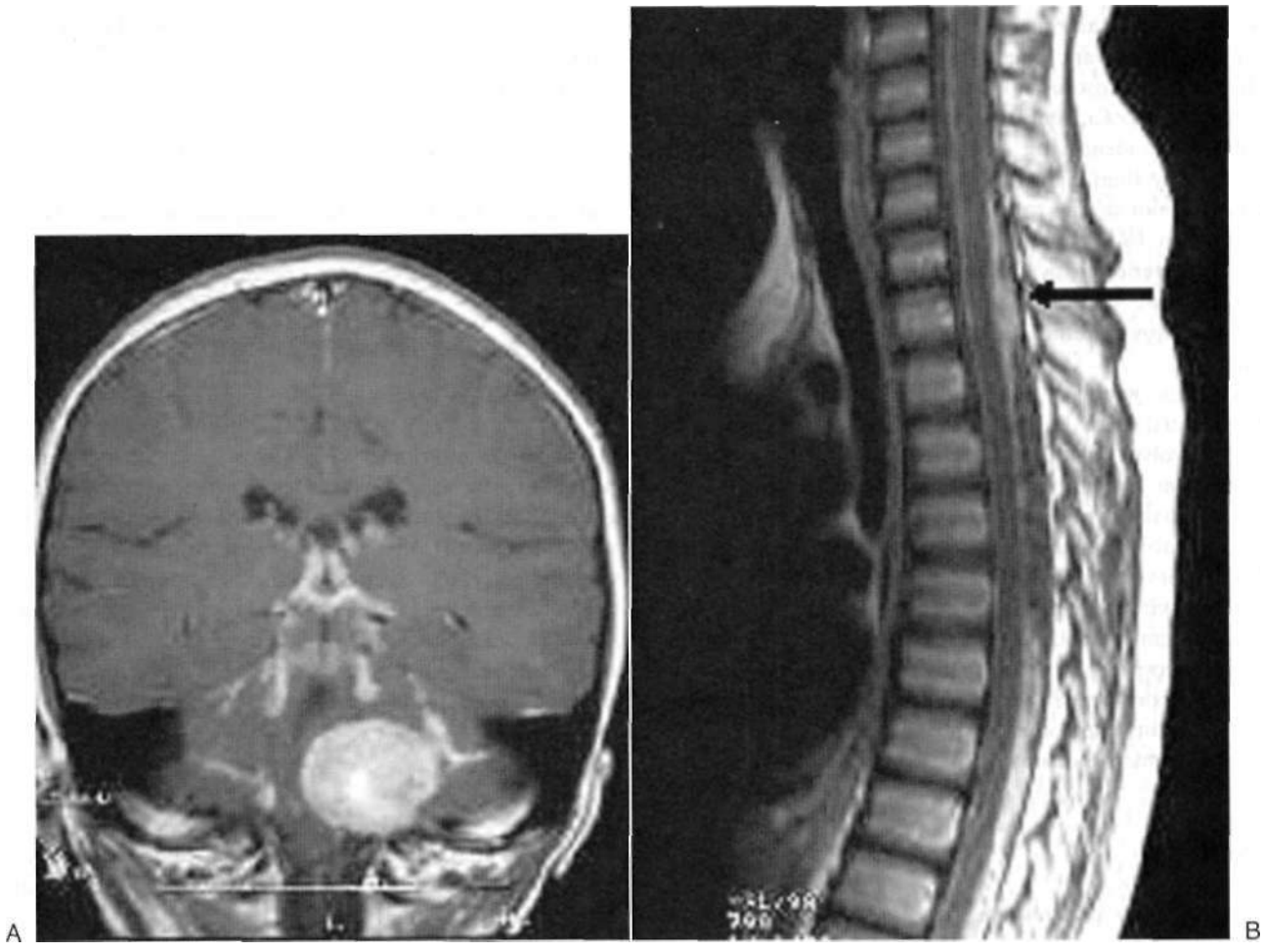

FIGURE 58F.1 Posterior fossa medul I obi a stoma with dissemination. This 7-year-old girl presented with a 6-week history of morning nausea and vomiting, left-sided hearing impairment, diplopia, dysphagia, ataxia, and back pain. Contrast-enhanced magnetic resonance imaging (MRl) (A) shows a large fourth-ventricle enhancing mass that extends laterally into the left cerebellopontine angle. There is diffuse leptomcningeal spread and extension into the left internal auditory canal (IAC). The contrast-enhanced, sagittal spine MRl (B) shows diffuse leptomeningeal metastases *Lunitf).*

obstructive hydrocephalus. A vemriculoperitoneal (VP) shunt may be necessary after surgery. Potential complications of posterior fossa surgery include cerebellar mutism, mainly seen with section of the vetmis, and aseptic meningitis. The posterior fossa or *cerebellar mutism syndrome* occurs in approximately 10-20 % of cases. The characteristics are reduced speech output or mutism, personality changes, hypotonia, ataxia, and reduced oral intake. Symptoms typically appear 1 or 2 days after surgery and may last for a few months with varying degrees of recovery.

Following the completion of the staging evaluation (MRl of brain and spine, CSF cytology), the patient is assigned to cither a high- or average-risk prognostic group. The major determinants of this risk categorization are age at diagnosis, metastasis or "M-stage," primary tumor site, and volume of residual postoperative disease. Distinction is made between age younger than 3 years versus older than 3 years, MO versus M+, cerebellar versus noncerebcllar primary-tumor, and postoperative residual tumors smaller than 1.5 cm^2 versus larger than 1.5 cm" (Table 58F. 1).

Adjuvant therapy depends on the age at diagnosis and risk group. Standard risk patients arc older than 3 years at diagnosis, have residual disease smaller than 1.5 cm , have a primary tumor in the cerebellum, and no evidence of metastasis (MO). Present treatment recommendations include craniospinal irradiation (24 Gy) with a boost to the primary tumor {54 Gy). Vincristine may be given

Table 58F.1: Staging

MO	No dissemination
Ml	Positive cytology on CSF
M2	Nodular seeding into cerebellum, cerebral subarachnoid space, or intraventricular cavity
M3	Nodular seeding into spinal subarachnoid space
M4	Extraneu ral metastases; rare, except in infants and young children

I. SI' cerebri spinal Kind.

Source: Keating, R. F., Goodrich, J. T., & Packer, R. J. 2001. *Tumors of the pediatric central nervous system,* Thieme, New York.

weekly during radiotherapy. Following radiotherapy, eight cycles of adjuvant chemotherapy (cisplatin, cyclohexyl-chloroethy I nitrosourea [CCNU], and vincristine) is usually administered. Current research in this group of patients consists of identifying adjuvant chemotherapy with less ototoxicity than cisplatin and less myelosuppression than CCNU. Pilot studies to lower the dose of craniospinal irradiation to 18 Gy and reduce the boost volume from the entire posterior fossa to the postoperative volume are also in ptogrcss. The use of protons rather photons for the radiotherapy minimizes the exposure of normal tissue to radiation.

Patients younger than 3 years of age at diagnosis are treated with chemotherapy alone or chemotherapy with involved field radiotherapy. Whether conventional multiagent chemotherapy or high-dose submyeloablative or myeloablative chemotherapy with stem cell support is preferable is under investigation (Dunkel and Finlay 2002). Several experimental protocols exist for older patients with high-risk disease (M+, residual tumor larger than 1.5 cm^2). Concepts under study include preirradiation chemotherapy, hyperfractionated radiorherapy (more than one fraction per day), reduced-dose radiotherapy with concomitant chemotherapy (Packer et al. 1999), and submyeloablative or myeloablative chemotherapy.

Prognosis

Standard risk patients have a 5-year survival between 60-70%; 5-year survival in high-risk patients is between 30-40%. Most initial recurrences occur at the primary site. Retrieval therapy is rarely curative, but long-term disease control may occur with high dose myeloablative chemotherapy. One histological variant, *anaplastic large cell medal lu-blastoma,* carries a poorer prognosis because of a higher risk for early metastatic involvement and recurrence (Ebcrhart 2002). The presence of dissemination is the single most important factor that correlates with outcome (Helton et al. 2002}.

Radiotherapy can cause significant adverse late effects in cognitive development (Mulhern et al. 1999), growth, and endocrine function. Repeated surveillance imaging is ret]uired throughout the patient's life time in anticipation of radiation-induced secondary malignancies such as an atypical meningioma.

ATYPICAL TERATOID/RHABDOID TUMOR

Background

Atypical teratoid/rhabdoid tumor is an uncommon tumor seen primarily in infants and young children (Bambakidts et al. 2002). Because only 150 cases have been reported, the true incidence is unknown. These tumors may arise anywhere in the body, but are most common in the kidney and CNS, primarily in the posterior fossa, either in isolation or in association with a renal tumor. The tumor is very aggressive and tends to present with high M stage. It rarely responds to adjuvant therapy and is uniformly fatal.

ASTROCYTOMAS

Low-grade glial and neuronal tumors include localized and diffuse subtypes (Table 58F.2). Their clinical features arc different (Table 58F.3).

JUVENILE PILOCYTIC ASTROCYTOMA

Background

Juvenile pilocytic astrocytomas (JPAs) are well-circum-scribed tumors, classified as grade 1 by the World Health

Table S8F.2: Low-grade glial and/or neuronal tumors

Gliomas	*Mixed glioneurona! tumors*	*Neuronal tumors*	*Miscellaneous*
JPA	DNET	Central neurocytoma	Dysplastic gangliocytoma of the cerebellum (Lliermittc-Ducios's syndrome)
PXA	GG	Gangliocytoma	
SEGCA	DIG		
DCAI			
Diffuse Tumors			
Grade '4 (Circumscribed, benign tumors, typically, pilocytic astrocytoma)			
Grade % (Low grade astrocytoma)			
Grade % (Anaplastic astrocytoma)			
Grade % (GEM)			

DCAI = desmoplastic cerebral astrocytoma of infancy; DIG = desmoplastic infantile ganglioglioma; DNET = dysembryoplastic neuroepithelial tumor; GBM = glioblastoma multiforme; GG = ganglioglioma; JPA = juvenile pilocytic astrocytoma; PXA = pleomorphic xanthoastrocytoma; SEGCA = subependymal giant cell astrocytoma.

Tahle 58F.3: Clinical findings with pediatric brain stem tumors

Clinical findings	*Diffuse tumors (60-80%)*	*Focal tumors*	*Dor sally exophytic (20%)*	*Cervicomedu ila ry*
Cranial nerves	Bilateral, asymmetric; sixth and seventh most often	Unilateral; depends on location in the brainstem	R.IIV	Lower cranial nerves -» dysphonia, dysphagia
Brainstem symptoms	Progressive gait ataxia, weakness, and long-tract signs	Usually spared	Nausea and vomiting; long-tract signs are rare	Chronic nausea, vomiting
Duration of symptoms before diagnosis	Short (6 weeks) because of aggressive behavior	Longer duration; more indolent course; chronic course	Gradual and chronic course	Chronic course
Anatomical location	Almost always in the pons	Anywhere in the brainstem, but usually midbrain	Floor of the fourth ventricle	Cervicomedu] hi in-junction
Pathology	Often malignant	Usually low-grade; solid or cystic	Usually low-grade	Usually low-grade
Imaging	Infiltrative lesion in the pons with rare enhancement	Occasional enhancement	Exophytic component strongly enhances on CT and MRI	May show homogeneous or heterogeneous enhancement
Other signs and symptoms	Spastic qu.idriparcsis	Contralateral hemiparesis; tectal tumors cause obstructive hydrocephalus	larly obstructive hydrocephalus, papilledema, ataxia and torticollis	Intractable neck pain, torticollis; hydrocephalus
Treatment	Palliative: radiation therapy (54Gy); chemotherapy: platinum-based, but no clear role as of yet	Aggressive resection; may need shunt; RT if progressive or malignant component	Resection of exophytic component; reoperation if recurrence; RT if malignant	Resection
Prognosis	Most die within IS months	Relatively good; chronic course.	Relatively good	Relatively good

CT = computed tomography; MRI - magnetic resonance imaging; RT = radiation therapy.

Organization (WHO). These tumors represent approximately 20% of all childhood brain tumors, without clear gender predominance. Neurofibromatosis (NF) type I is the best example of a condition associated with an increased risk of JPA. No other definite predisposing factors are known.

Clinical Presentation

JPAs commonly arise in the optic pathways, cerebellum, hypothalamus, basal ganglia, or cerebral hemispheres, but also occur in the brain stem and spinal cord. Therefore the spectrum of clinical manifestations depends on the structures involved, and may include visual deficits, obstructive hydrocephalus, ataxia, endocrine dysfunction, focal neurological deficits, seizures, long-tract signs, arid cranial nerve dysfunction.

Diagnosis

The diagnosis should be suspected when any of the previously noted features are found in a young patient. The history of illness is usually long and other signs of chronicity, such as bone remodeling, scoliosis, or hemihypotropby, are present depending on primary tumor location. The typical MRI appearance is an intensely homogeneously enhancing lesion with only minimal, associated edema. Intratumoral cysts are common, depending on location (i.e., cerebellum, cerebrum, midbrain, and spinal cord). Histological examination reveals both a compact and loose cellular array. The pathological hallmarks for diagnosis are Rosenthal's fibers and eosinophilic granular bodies. JPAs are glial fibrillary acid protein (OFAP)-positivc. Invasion of the overlying meninges is common, but is uol *A* negative prognostic factor. Mitoses are ran- and the MIB-1 labeling index is usually less than 4% (Dirven et al. 1998).

Management

Treatment consists mainly of surgery. Gross total resection is considered curative and radiation and chemotherapy are not required. Recurrent, progressive, or unresectable tumors may require adjuvant treatment such as chemotherapy for younger patients and radiation therapy for older patients.

Chemotherapy is assuming an increasingly important role in the management of recurrent and unresectable tumors, and various regimens such as cisplatin and vincristine or procarbazine, CCNU, and vincristine have produced consistent, durable responses. Surgery is contraindicatcd in typical optic pathway gliomas (OPGs) with expansion of the chiasm, with or without involvement of the proximal optic nerves, contiguous optic tracts, hypothalamus, or optic radiations.

Prognosis

The prognosis is excellent; 5-year survival is 100% after gross total resection. The main limitation is the anatomical location of the tumor. Complete resections are most difficult for tumors located in the brain stem, spinal cord, and hypothalamus. The quality of survival depends on multiple factors, including the tumor location and the side effects of surgery, chemotherapy, and radiotherapy.

PLEOMORPHIC XANTHO ASTROCYTOMA

Background

Pleomorphic xanthoastrocytomas (PXAs) are cortical tumors that mainly occur in children. The median age at the time of diagnosis is 14 years,

Clinical Presentation

PXAs are typically very large and superficially located. Seizures are the most common initial feature. Contrast-enhanced cranial MR! typically shows a large, enhancing tumor with occasional cystic components and calcification. The typical pathological findings are pleomorphism with significant cellular ntypia and bizarre multinucleated giant cells with intracellular lipid accumulation. The proliferative indices are usually low, although necrosis, endothelial proliferation, and mitoses are described, PXA can be confused with glioblastoma multiforme (GBM) because of the presence of multinucleated cells and occasional foci of necrosis (Giannini et al. 1999).

Diagnosis and Management

The clinical diagnosis of PXA should be suspected in children who present with new onset seizures, focal deficits, and a large, enhancing cortical mass on brain imaging. The goal of surgery is to achieve a gross total resection, which may be curative. Adjuvant therapy can be deferred while the patient is followed expectantly.

Prognosis

Several scries report a 5-year progress ion-free survival of greater than 70%. However, the presence of mitoses, endothelial proliferation, or necrosis on the pathological specimen, although very rare, may significantly alter the clinical behavior and prognosis (Sugira et al. 2000). Radiation therapy does not alter the poor outcome in these cases.

SUBEPENDYMAL GIANT CELL ASTROCYTOMA

Background

Subependymal giant cell astrocytomas (SEGCAs) usually originare in rhe ependymal walls of the lateral ventricles and are associated almost exclusively with tuberous sclerosis (TS). Sporadic cases are rare.

Clinical Manifestations

SEGC A is sometimes the presenting feature of TS in patients without the typical physical stigmata of rhe syndrome. These tumors tend to grow toward the foramen of Monro, leading to obstructive hydrocephalus, headaches, vomiting, and visual deficits. On physical examination, papilledema is common, as are focal neurological deficits such as hemiparesis. Other findings, related to TS, arc skin and retinal abnormalities. Small, subependymal calcified lesions as well as areas of gliosis, cortical tubers, and heterotopias are often associated with SEGCA in TS. Therefore both CT and MRI are essential for early and accurate diagnosis. Although the former is better for detecting small, calcified lesions, MRI is superior to CT in identifying areas of gliosis, heterotopia, and SEGCA, which gives the typical radiographic appearance of "candle dripping,"

Management

SEGCAs typically show diffuse contrast enhancement on both CT and MRI studies. Total gross resection is the treatment of choice for SEGCAs that are large, progressive, and cause obstructive hydrocephalus. The major risk is injury to the forniceal columns. Alternatively, a VP shunt can provide symptomatic relief. The benign behavior of these tumors warrants reoperation in the case of recurrence or progression, after subtotal resection.

Prognosis

SEGCAs are essentially benign tumors. Gross total resection should be curative. However, in some patients with TS,

multiple tumors may be present. The overall prognosis for patients with TS is good, despite an increased susceptibility to other tumors types, including rhabdomyomas of the myocardium and angiomyomas of the kidney, liver, adrenals, and pancreas.

DESMOPLASTIC CEREBRAL ASTROCYTOMA OE INFANCY

Desmoplastic cerebral astrocytomas of infancy (DCAI) are characterized by their large size and superficial/cortical location. These tumors may involve an entire hemisphere. The usual initial presentation is a seizure, although progressive focal deficits may be the first manifestation. The tumor is contrast-enhancing on MRI and usually has a large cystic component. Lepto meningeal invasion is common in patients with DCAI, classified as a grade 1 tumor by the WHO. Despite the malignant features, patients with DCAI have a good prognosis after gross total resection.

DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOR

Background

Dysembryoplastic neuroepithelial tumors (DNETs) represent 1% of all brain tumors in patients younger than 20 years of age. The wide variation in the reported incidence of DNET is perhaps due to the different criteria used for diagnosis. Two thirds of DNET are located in the temporal lobe and DNET are found in 5-15% of temporal lobe resections for intractable epilepsy. These lesions are classified as WHO grade 1 tumors.

Clinical Presentation

These tumors typically present with a long history of complex partial seizures. The average age at onset is 9 years. The superficial, cortical location of DNET may account for the high risk of seizures. Contrast-enhanced cranial MRI shows absence of edema and only minimal, if any, enhancement. The diagnosis of DNET is a consideration in children and young adults with either new-onset seizures or a long history of epilepsy. The pathological findings include a specific glioneuronal element manifested by GFAP-negative oligodendroglia-like cells and neurons in a mucinous eosinophilic background that give the appearance of "floating neurons." In addition, oligodendrocytes, astrocytes, or both, are found. The pathological differential diagnosis includes oligodendroglioma, mixed oligoastrocytoma, and ganglioglioma.

Management

These tumors have a benign course and gross total resection is often curative. Radiation and chemotherapy are not recommended.

Prognosis

The stable behavior of these tumors over time results in an excellent prognosis after either gross total or partial resection.

GANGLIOGLIOMA

Gangliogliomas represent 4-8% of primary brain tumors in children and 80% occur before age 30 years.

Clinical Presentation

Seizures are the first manifestation in half of the cases. Complex partial seizures are common because the typical tumor location is in the temporal lobe. Contrast-enhanced, cranial MRI shows a supratentorial cystic mass with an enhancing mural nodule. This appearance is similar to JPA and PXA. An infantile variant of ganglioglioma, desmoplastic infantile ganglioglioma (DIG), is characterized by a large size and a supratentorial location. Pathological studies show a synaptophysin positive ganglion cell component as well as a GFAP-positive astrocytic component (De Munnynck et al. 2002).

Management

Gross total resection is the treatment of choice. Recurrent or unresectable tumors are irradiated (Johnson et al. 1997). Ganglioglioma may be WHO grade 1 or 2. Some tumors show anaplastic features in the glial component. This tumor variant has responded to chemotherapy in clinical trials.

Prognosis

Gross total resection is usually curative. Thus location and extent of resection are the most important prognostic factors.

CENTRAL NEUROCYTOMA

Background

Central neurocytoma is a rare tumor of neural origin that usually has an intraventricular location. Obstructive

hydrocephalus or focal deficits are common presentations. MRI of the brain shows an isointense mass with minimal enhancement. On pathological study the presence of perinuclear halos on light microscopy may lead to a mistaken diagnosis of oligodendroglioma. The diagnosis is a consideration in every young patient with an intraventricular mass. Synaptophysin, a neuronal stain, positive in neurocytoma but negative in oligodendroglioma, is crucial to make the correct diagnosis. Very rare atypical forms with mitoses, necrosis, and endothelial pro I i (era t ion are reported (Soyletnezoglu et al. 1997). A MIB-1 labeling index is useful for prognostic purposes. Patients with a MIB-1 labeling index greater than 2% have a worse prognosis.

Management

Gross total resection can be curative for central neurocytomas. Radiation and chemotherapy are not necessary in typical cases. This emphasizes the importance of differentiating central neurocytoma from oligodendroglioma, a tumor that may require adjuvant radiation and chemotherapy. Radiotherapy is a consideration only for atypical forms with a high MIR-1 Libeling index and for recurrent, unresectable tumors.

Prognosis

Gross total resection of typical central neurocytoma is often curative. The outcome in atypical central neurocytomas is difficult to predict accurately because of the rarity of the tumor. Data is not available on response to chemotherapy or radiation therapy.

COLLOID CYST OF THE THIRD VLNTRICLL

Colloid cysts are typically located in the third ventricle. Less than 50 pediatric cases arc reported. The mean age at presentation in children is 11 years.

Clinical Presentation

A colloid cyst of the third ventricle may obstruct the foramen of Monro and result in acute obstructive hydrocephalus and sudden death. Headache, nausea, and vomiting may occut. Drop attacks and transient loss of consciousness is reported in adults. Mortality is higher in children than in adults. Contrast-enhanced cranial MRI typically shows an isointense or hyperintense lesion with a variable degree of enhancement. Viscous fluid within the cyst results in a hyperdense appearance on CT. The very slow tumor growth over time may explain the very low incidence in children.

Surgery is the treatment of choice. Several surgical approaches are possible (i.e., transcortical, transventricular, and endoscopic transcallosal). The latter is associated with less morbidity. Total resection is curative. Disconnection syndromes may occur after the transcallosal approach.

LOW-GRADE FIBRILLARY ASTROCYTOMA

Background

Low-grade astrocytomas (LGA) localized to the posterior fossa represent 12-18% of all pediatric intracranial tumors. Focal LGA represents 20-40% of all brainstem tumors. No gender predilection exists, and the peak age at diagnosis is 6—10 years. In contrast to the adult population, LGA are more common than high-grade astrocytomas (HGA) in children.

The incidence of LGA has increased over the past several years without an identified reason. A potential association of paternal exposure to chemical and electrical industries and tumor occurrence is reported (McKean-Cowdin et al. 1998).

Presentation

The initial symptoms vary depending on the location of the tumor. The prodrome is months to years.

LGAs in the brain stem are usually "focal" rather than diffuse. They tend to arise in the midbrain, cerebellar peduncles, medulla, or cervicomeduUary region. Diffuse pontine astrocytomas have a different clinical course and often undergo malignant transformation within months. This is much less likely in other locations.

Patients with medullary tumors may present with a long history of dysphagia, hoarseness, ataxia, and hemiparesis. CervicomeduUary tumors may cause medullary or upper cervical symptoms such as neck discomfort, weakness or numbness of the hands, and an asymmetric quadriparesis. Patients with midbrain tumors such as a tectal glioma often present with signs and symptoms of raised ICP. Other symptoms include diplopia and hemiparesis. In children with dorsally exophytic brainstem glioma, a component of the tumor arises in the medulla and grows exophytically in a dorsal direction resulting in noncommunicating hydrocephalus. Low-grade fibrillary astrocytomas car also arise in tile brain hut the clinical course may be more aggressive, especially when the thalamus is involved.

Most low-grade fibrillary astrocytomas appear isodense on CT without significant contrast enhancement. The tumor is hypointense on Tl-weighted MRI and hyperintense on T2-wcighted MRI, with minimal or no gadolinium enhancement with the exception of dorsally

exophytic brainstem tumors. Pathological examination may demonstrate some cellular plcomorphism but no mitoses, necrosis, or endothelial proliferation (i.e., histologic features of malignancy) (Table 58F.3).

Management

Management depends on the clinical prodrome and location of the primary tumor (F.rnestus et al. 1996). A rapidly evolving prodrome with an operable tumor usually warrants prompt neurosurgical intervention. The management of a tumor with a long history of indolent and mild symptoms is often done with close MRI and clinical surveillance. Patients with progressive neurological symptoms and MRI studies suggesting tumor growth tequire therapeutic intervention (Jallo et al, 2001). The likelihood of total resection of a diffuse fibrillary astrocytoma is minimal, especially when the tumor is located in the tectum or medulla. However, radical resection can often confer a long symptom-free outcome, especially in patients with suprarcntorial and dorsally exophytic brainstem tumors. If resection is not feasible, chemotherapy or radiotherapy may he indicated. Chemotherapy is reserved primarily for younger patients (Allen and Siffcrt 1996), and radiotherapy may be instituted in younger patients whose tumors progress during chemotherapy (Pollack et al, 1995). Radiotherapy may be used more liberally in older children.

Prognosis

The 10-year survival rate for completely resected supratcntorial LGA is excellent (higher than 90%). The prognosis for gemistocytic astrocytomas is less predictable because of the propensity of these tumors to rapidly degenerate into HGA. The prognosis for focal midbrain tumors is also favorable, in spite of the fact that complete resection is impossible.

OPTIC PATHWAYS GLIOMAS

Background

OPGs represent approximately 4% of all primary pediatric brain tumors. These rumors may involve various parts of the optic pathway such as the optic nerves, chiasm, optic tract, and optic radiations. The tumor may also infiltrate the adjacent hypothalamus and temporal lobes. Optic nerve gliomas are strongly associated with NF1. OPG in NF1 patients may have a more indolent course than those arising in patients without NF1 (Deliganis et al. 1996).

Clinical Presentation

Most OPGs are LGAs; 60% are pilocytic astrocytomas and 407o are fibrillary astrocytomas. Although most optic nerve and chiasm gliomas are LGAs, their clinical course may be aggressive when the optic pathways and hypothalamus are invaded. Age is an important prognostic factor; children younger than 5 years of age have a more aggressive course. Unilateral optic nerve gliomas present with the classic triad of visual loss, proptosis, and optic atrophy. Chiasmatic involvement may lead to visual loss, a bitemporal field defect, as well as to obstructive hydrocephalus as the tumor grows dorsally to obstruct CSF flow in the third ventricle. Further invasion into brain parenchyma may result in hemiparesis and seizures. t liinMLi.iiu- minors in infants prcscnl as ver\ large suprasellar masses that may also extend into the hypothalamus and third ventricle, producing hydrocephalus and endocrine abnormalities. The diencephalic syndrome consists of irritability, failure to thrive, nystagmus with visual loss, and hydrocephalus.

Management

The clinical diagnosis of an OPG is suspected when a child presents with visual impairment associated with nystagmus and optic atrophy. Contrast-enhanced cranial or orbital MRI typically shows a solid, cystic, or mixed type of tumor with gadolinium enhancement. MRI studies and clinical presentation may distinguish an OPG from other childhood tumors that arise in the suprasellar location such as a germ cell tumor or craniopharyngioma. The unpredictable clinical course of patients with OPGs has led to controversy regarding the optimal management of these tumors. The clinical course, age i>r onset, severity ot symptoms, size .rid extent of the tumor, and the presence of NF1 may all affect management decisions. Early treatment is started in younger patients, patients with progressive symptoms, and those with more extensive CNS involvement. The initial treatment of choice is chemotherapy, which may cause stabilization or regression (Silva et al. 2000), Combination therapy with cither cisplatin and vincristine (Kato et al. 1998) or thioguanine, procarbazine, CCNU, and vincristine have had comparable beneficial effects. Oral temn/nlonnde or etoposide may also be effective. Radiotherapy is reserved for older children or for those whose tumors progress after multiple chemotherapy regimens.

Prognosis

Although optic nerve gliomas are almost always low-grade histologically, their location often results in devastating morbidity. The growth rate, however, often slows in older

children and young adults. Patients with NFl-associated optic nerve gliomas may remain stable for several years, Close observation and symptomatic management are recommended.

HIGH-GRADE ASTROCYTOMAS

Background

HGAs are much less common in children than adults. These tumors consist of either anaplastic astrocytoma (III/1V) or GBM (1V/IV). The tumors arise in the brainstem, thalamus, and, less commonly, in the cerebrum. Hemispheric tumors account for 15-20% of all HGAs. Certain genetic syndromes, such as hereditary nonpolyposis colorectal carcinoma, are associated with HGAs. NFl is most frequently associated with pilocytic astrocytomas (Rodriguez et al. *1996).* Li-Fraumeni syndrome (P53 mutation), has also been associated with gliomas of different grades (LGA, anaplastic astrocytoma [AA], GBM), medulloblastoma, choroid plexus carcinoma, and supratentorial PNFT.

Clinical Presentation

The clinical manifestations of HGA depend on the anatomical location as well as the age of the patient. The clinical prodromes are usually short and rapidly evolving, although in some cases an HGA may arise in the setting of prolonged symptoms from a low-grade fibrillary astrocytoma.

Management

The diagnosis of an HGA should be suspected based on the clinical presentation, tumor location, and the MRI that shows combinadons of diffuse, nonenhancing signal abnormalities and focal, enhancing solid lesions. Intratumoral cysts often correlate with spontaneous necrosis. The T2 signal is often more diffuse, consistent with both infiltrative tumor and edema. Significant mass effect, hydrocephalus, and intratumoral hemorrhage may be present. Malignant features on pathological studies include nuclear pleomorphism, mitoses, necrosis, endothelial proliferation, and a high MIB-1 labeling index.

Gross total resection is the initial treatment goal (Pollack 1999). This facilitates a more accurate diagnosis and makes subsequent radiotherapy more tolerable. Chemotherapy has .in ; nuTi'.ir,;'. bin k'ss drilled role *:i:* pivsrnl. The prognosis for children with HGA is poor, but better than in adults. A report from the Children's Cancer Group (Wisoff et al. 1998) showed that the 5-year progress ion-free survival (PFS) rates for anaplastic astrocytoma were 44% ± 11% and 22% ± 6% for children who underwent radical resection versus other types of surgery, respectively. The 5-year PFS rates for GBM were 26% ± 9% and 4% ± 3% for children who underwent radical resection versus other types of surgery, respectively. Radical resection and the absence of P53 immunostaining are favorable risk factors. Thus patients with diffuse thalamic and pontine tumors have the worst prognosis (Reardon et al. 1998). Several studies have shown that chemotherapy may have a clinically beneficial role in children with HGA. The overall 5-year survival of children with supratentorial HGA treated with chemotherapy and radiation is approximately 43%, versus 18% for radiation alone. Prcirradialion chemotherapy has been studied with the goal of delaying radiation. This approach is especially important for children younger than 3 years of age. Treatment with high-dose chemotherapy and autologous bone marrow support has been conducted in children with HGA (Dunkel and Finlay 2002). The risk/benefit ratio is still under investigation, with initial reports of 23% overall response but a mortality rare of 16% (Finlay et al. 1996). Diffuse, infiltrating brainstem tumors have been treated with high dose chemotherapy (CCNU, vincristine, and prednisone, as well as platinum-based agents) and stem cell rescue, with disappointing results.

Prognosis

The extent of surgical resection contributes to prolonged progression-free survival (Campbell et al. 1996). Patients with anaplastic astrocytoma have a more favorable prognosis than those with GBM. New treatment approaches include radiosurgical boost to the postoperative tesidual tumor following external beam radiotherapy, radiosensitizing agents, and new adjuvant chemotherapy agents such as temozoiomidc (Friedman et al. 2000).

EPENDYMOMAS

Background

Ependymomas represent approximately 10% of all childhood intracranial neoplasms, constituting the third most common pediatric brain tumor, after medulloblastoma and astrocytoma. Ninety percent of pediatric ependymomas are intracranial and 75% arise in the posterior fossa. Most supratentorial ependymomas are located in the brain parenchyma away from the ependymal surface, in contrast to infratentorial ependymomas. Ependymomas represent less than 10% of pediatric intramedullary spinal cord tumors. In contrast, ependymomas represent more than 50% of intramedullary spinal cord tumors in adults. The association of intramedullary spinal cord ependymomas and NF2 are clear. In fact, ependymomas account for almost all spinal cord gliomas in NF2.

Clinical Presentation

The presenting symptoms of infra tentorial ependymomas relate to their origin from ependymal tissue lining the fourth ventricle. Hydrocephalus results when the tumor fills the fourth ventricle, causing headache, irritability, nausea, vomiting, ataxia, and papilledema. Tumors that extend out one of the foramens of Luschka compromise unilateral lower cranial nerves and cause hoarseness and dysphagia. If the tumor extends through the foramen of Magendie, the patient may complain of neck discomfort and have torticollis. The initial feature of the tumor in infants is increased head circumference. Other, less frequent, features include low back pain and leg weakness resulting from dissemination along the spine.

Spinal cord ependymomas are typically located in the cervical region. The most common presenting symptom is localized pain at the level of the lesion. The pain is worst' at night, presumably because of congestion of the spinal venous plexus in the recumbent position. The second most common symptom is radicular dysesthesias and a late manifestation is progressive spastic quadriparesis. Thoracic ependymomas are associated with scoliosis. Myxopapillary ependymomas of the conus medullaris and filum terminate may present with low back pain, radicular pain, saddle anesthesia, and sphincter dysfunction. A typical MRI appearance of a fourth ventricular ependymoma is that of a homogeneously enhancing solid mass extending out one of the foramens of Luschka or Magendie with obstructive hydrocephalus (Figure 58F.2). The characteristic microscopic feature of an ependymoma is dense eellularity with pen vascular pseudorosctrcs; a minority express true ependymal rosettes. The presence of mitoses, necrosis, and vascular proliferation is observed in malignant variants. GFAP is usually positive in most ependymomas and epithelial membrane antigen stains are positive in anaplastic variants. Myxopapillary ependymomas have a mucinous appearance and arise exclusively in the eauda equina. Malignant ependymomas are very rare in the spinal cord. Intracranial ependymoblastomas, a type of PNET, are malignant and arc similar to medulloblastoma, retinoblastoma and pineoblastoma in their clinical course.

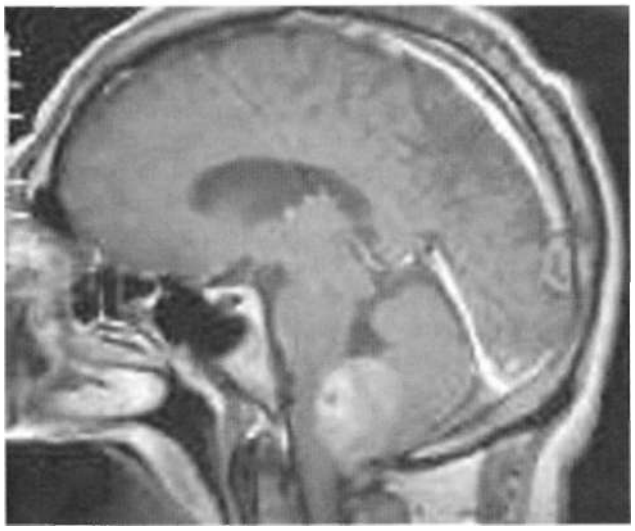

FIGURE 58F.2 Fourth ventricular ependymoma. A sagittal enhanced magnetic resonance image of a 6-year-old boy presenting with ataxia and morning nausea and vomiting. The tumor fills tin- low.r |i;irr .:! i:v lounl- •-.i.Tiliu •• .mil i.vrentk caudalh out the **foramen of Magendie,**

Management

The first line of treatment is surgery with a goal of curative gross total resection. Complete resection of spinal cord and supratentorial ependymomas is common. Technological advances such as the operating microscope, Cavitron ultrasonic aspirator, intraoperative ultrasound, and MRI, as well as electrophysiological monitoring, have reduced operative morbidity of spinal cord surgery. Overall, spinal cord ependymomas are more easily resectable than astrocytomas because of the presence of a better demarcated "cleavage plane."

The role of radiation therapy remains controversial and is reserved for patients in whom a gross total resection is not possible. Several studies suggest that radiotherapy-prolongs progression-free survival after subtotal resection of an ependymoma (McLaughlin et al. 1998). The usual dose of radiation is 5400 cGy to the posterior fossa. The role of radiotherapy for partially resected myxopapillary ependymomas is less clear.

Approximately 10-15% of fourth ventricular ependymomas present with subarachnoid metastases. Presently, no established role exists for chemotherapy in the management of ependymomas (Siffert and Allen 1998). Several small series in newly diagnosed and recurrent disease have shown objective responses to the following drugs: carboplatin, cisplatin, ifosfamide, and etoposidc. Chemotherapy is used for infants and younger children with incompletely resected or disseminated disease (Duffner et al. 1998).

Prognosis

The most important prognostic factors for both intracranial and spinal cord ependymoma are age and extent of surgical resection (Paulino er al. 2002; Pollack et ai. 1995b). The 5-year progress ion-free and overall survival for patients with subtotal versus total resections of posterior fossa ependymomas is 25% and 66%, respectively. Consequently, the prognosis of patients with disseminated disease is much worse (Finestus et al. 1996). Local radiation therapy improves survival as well (McLaughlin eral. 1998).

CHOROID PLEXUS TUMORS

Background

Although tumors of the choroid plexus represent only 1-2 % of all pediatric hrain tumors, more than ""()% of choroid plexus tumors occur in pediatric patients and half occur in children younger than 2 years of age. Seventy-five percent arise in the lateral ventricles and the remainder in the fourth ventricle.

Clinical Presentation

Initial symptoms are usually secondary to elevated ICP and hydrocephalus, and include headaches, nausea, and vomiting. Other possible manifestations include lethargy, seizures, and failure to thrive. On physical examination, papilledema is often present. Infants may show irritability, lethargy, vomiting, a tense fontanelle, and macrocephaly with splayed sutures. Diagnosis is suspected when a large enhancing tumor in the lateral ventricle is visualized on gadolinium-enhanced MRI, Multilobular, calcified, contrast-enhancing intraventricular masses are characteristic of choroid plexus tumors. Two histological types of tumors are recognized: choroid plexus papilloma, a low-grade variant, and choroid plexus carcinoma, a malignant variant that has a higher mitotic index and is more invasive (Pencalet ct al, 1998).

Management

The clinical diagnosis of a choroid plexus tumor is considered in a young child with features suggestive of hydrocephalus and increased ICP. Macrocephaly and lethargy indicate the need for a contrast-enhanced cranial MRI. Intraventricular enhancing masses with a peculiar "cauliflower" shape on MRI arc characteristic of choroid plexus tumors.

A major obstacle to the surgical removal of choroid plexus tumors is the rich vascular network within these tumors. The choroid plexus receives its blood supply from the anterior and posterior choroidal arteries, branches of the internal carotid artery and the posterior cerebral artery. The exrent of surgical resection is the single most important factor that determines the prognosis of choroid plexus papilloma.

The primary treatment objective for both low-grade and high-grade choroid plexus tumors is gross total resection. For choroid plexus papilloma, this is a curative procedure, For choroid plexus carcinoma, adjuvant therapy is often necessary. Because the majority of children diagnosed with choroid plexus carcinoma are younger than the age of 3 years, chemotherapy is the treatment of choice (Duffner et al. 1995), A variety of multiagent regimens have been explored, and preliminary evidence suggests that choroid plexus carcinomas are chemosenskive tumors. The role of adjuvant radiotherapy is controversial. Radiation is reserved for children older than 3 years who have had a subtotal resection, malignant features within the tumor, or dissemination of the tumor along the neuraxis.

Prognosis

Gross total resection is curative for papillomas. The prognosis in significantly worse for carcinomas and several adjuvant therapies are being investigated.

CRANIOPHARYNGIOMA

Background

Craniopharyngiomas are the most common nonglial tumors in children and account for 3-5% of all pediatric brain tumors. The peak age range for diagnosis of this tumor is 6-14 years,

Clinical Presentation

The typical onset is insidious and a 1- to 2-ycar history of slowly progressive symptoms is common. These symptoms may include progressive visual loss, delay in sexual maturation, growth failure, weight gain, and diabetes insipidus. Eventually, extension of the tumor into the hypothalamus, third ventricle, and limbic system produces endocrine dysfunction. More than 70% of children at time of diagnosis present with growth hormone deficiency, obstructive hydrocephalus, short-term memory deficits, and psychomotor slowing. The presenting feature in young adults is hypopituitarism, galactorrhea-amenorrhca syndrome in females, and impotence in males. Craniopharyngiomas arc subdivided into adamantinomatous and papillary types. The first gtoup is the more common and occurs in children and adults. Adamantinomatous craniopharyngiomas typically have cystic and solid areas with calcifications. Papillary tumors, seen almost exclusively in adults, arc predominantly solid without calcification and ate less infiltrative. MRI features include a multicystic and solid enhancing suprasellar mass, which, if large enough, causes hydrocephalus and stretching of the optic nerves and chiasm (Brunei et al. 2002). The CT usually reveals intratumoral calcifications (Figure 58F.3).

Management

Surgical removal of the tumor is the most effective treatment. Complete microsurgical resection is the treatment of choice for newly diagnosed craniopharyngiomas. Transcranial or transsphenoidal surgical approaches are commonly used.

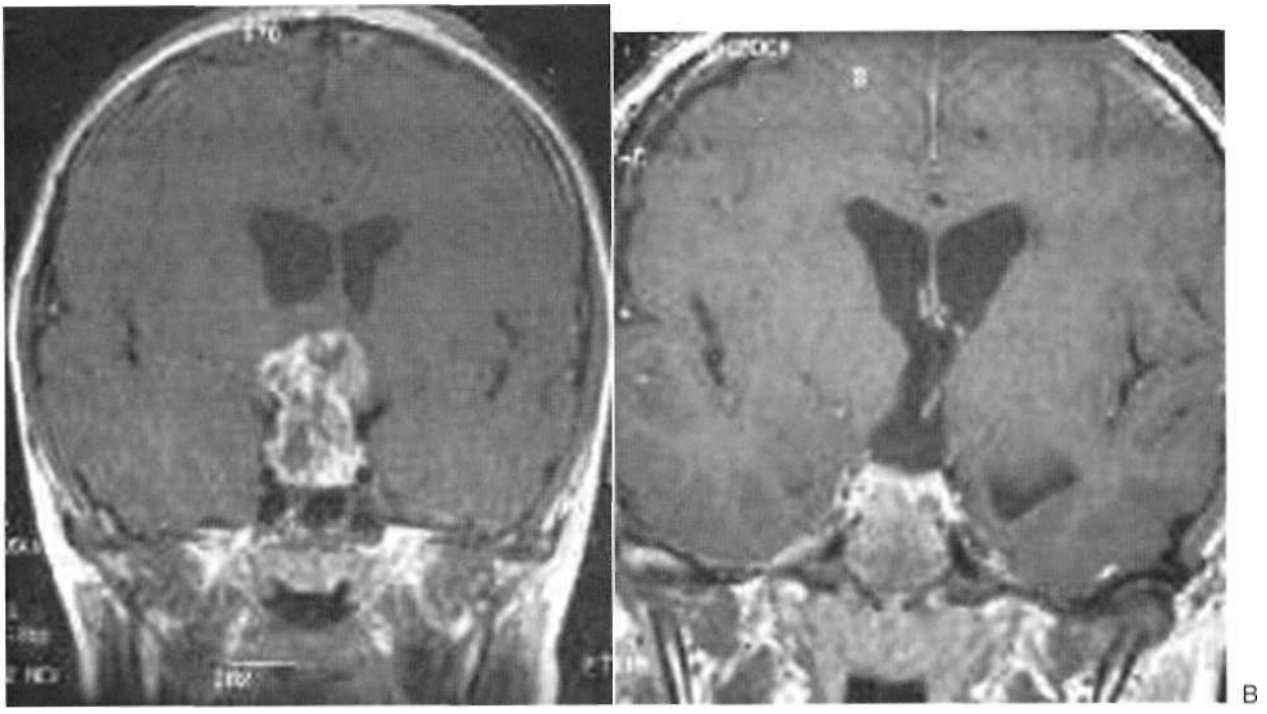

FIGURE 58F.3 Suprasellar craniopharyngioma. This 8-year-old girl presented with short stature, bitemporal field cuts, and headaches. The preoperative magnetic resonance imaging (MRI) (A) scan shows a cystic, enhancing suprasellar mass. Following ;i trnnssphenoid.il resection, the postoperative MRI (B) shows a gross total resection.

Transsphenoidal resection is the preferred method for tumors in a subdiaphragmatic location and is associated with a tower incidence of postoperative diabetes insipidus.

Radiosurgical techniques are in use for surgically unresectable or recurrent tumors. Long-term complications of radiation include secondary malignancies, optic neuropa thy and vascular injury leading to moyamoya disease, Intracavitary irradiation is also an option. ^{i2}P is the preferred agent because of less penetration of normal tissue and a longer half-life.

Recurrent craniopharyngiomas are treated with rcopcration, radiation, or chemotherapy. Intracavitary bleomycin is used for recurrent tumors. This form of local chemotherapy may also be beneficial as a supplement to surgery by thickening the cyst wall, making it resistant to tearing, and, in turn, facilitating resection.

Prognosis

The most important factors that correlate with PHS are the extent of resection and postoperative radiation. In fact, recurrence occurs in 30% of cases after total resection and in 57% cases aftet subtotal resection. The recurrence rate drops to 30% when subtotal resection is followed by radiation. Unfortunately, most long-tetm survivors experience significant morbidity related to panhypopituitarism, cognitive impairment, and obesity.

GpRMC£LL ANQ NONGERM CEL, TUMORS

Background

Tumors of the pineal region represent 3-5% of all pediatric brain tumors. Germ cell tumors include gcrminomas, which compose 60-70% of all pediatric germ cell tumors, and nongerminomatous germ cell tumors (NGGCT), NGGCT include embryonal cell carcinoma, teratomas, endodermal sinus tumor, choriocarcinoma, and mixed germ cell tumors such as teratocarcinoma. These tumors typically arise in midline locations such as the pineal or suprasellar regions. Germinomas are the most common tumors of the pineal region, but NGGCTs and germinomas arise with equal frequency in the suprasellar region. Intracranial germ cell tumors arise typically in the second and third decades of life. A male excess occurs in pineal region tumors, and both genders are equally affected in the suprasellar region. People of Japanese descent have a higher incidence of intracranial germ cell tumors. Other malignant tumors arising in this location include pincoblnstoma and pineocytoma. Pineoblastoma represents an aggressive tumor that resembles a PNET in terms of age at diagnosis and propensity to disseminate into the subatachnoid space. Pineoblastoma can also present as a component of the familial syndrome termed *trilateral retinoblastoma,* which includes bilateral retinoblastomas and a pineoblastoma with retinoblastic features {Finelli et al. *1995).* Pineocytoma usually presents during

Table 58F.4: Subtypes of germ cell and nongerm cell tumors

Germ ceil tumors		*Nongerm cell tumors*	
Germinomas	*Nongerminrmiiitiws*	*Pineal parenchyma*	*Others*
None	Embryonal cell carcinoma] LTilli HUilS Endodermal sinus tumor Choriocarcinoma Mixed: teratocarcinoma	Pineoblastoma Pineocytoma	Astrocytoma Ependymoma Oligodendroglioma Meningioma Neurocytoma Lipoma

adolescence and has a much less aggressive course (Table 58F.4).

Gliomas, low-grade and high-grade, are the second most common tumor type in the pineal region. Benign cystic lesions of the pineal region should be differentiated from low-grade cystic astrocytomas. The former should demonstrate no progression on serial ncuroimaging studies over time.

Clinical Presentation

The typical presentation of a patient with a suprasellar germ cell tumor, such as a germinoma, is a months-to-years long history of endocrine dysfunction: hypopituitarism manifested by polyuria, polydipsia, growth impairment, precocious puberty, and hypothyroidism. Visual loss may result from dorsal extension of the suprasellar tumors. Tumors arising in the pineal region may produce headache, nausea, and vomiting caused by obstructive hydrocephalus. Limitation of vertical gaze, convergence nystagmus, impaired pupillary reflexes, and double vision may occur as a result of compression of periaqueductal structures (Parinaud's syndrome), Papilledema is often present secondary to increased 1CP caused by obstructive hydrocephalus. Germ cell tumors can cause precocious puberty as a result of result of /{-human chorionic gonadotropin (/i-HCG).

Management

The classical presentation of a pineal-region tumor is a patient with signs and symptoms of increased ICP in association with Parinaud's syndrome. Because the differential diagnosis of tumors in this location is large, every patient should have some type of histological or chemical confirmation of a specific tumor type. Histological confirmation may not be necessary in patients with elevated CSF concentrations of tumor markers (o?-fetoprotein fAFPl, HCG) consistent with a NGGCT (Seregni et al. 2002).

Germ cell tumors typically show homogeneous enhancement with peripheral calcification on contrast-enhanced cranial MRI, in contrast to the intratumotal calcification typically seen in pineocytomas.

Tumor markers in CSF and serum may suggest the specific type of underlying tumor and are useful as parameters to follow during the course of therapy (Table 58F.5). Elevation of AFP occurs with endodermal sinus tumors and embryonal carcinomas, whereas a high level of /J-HCG suggests choriocarcinoma. Pure germinomas may have modest elevations of CSF HCG up to 50 mlU/ml. Lactate dehydrogenase isoenzymes and placental alkaline phosphatase are also detectable in CSF in germinoma patients. The current standard of care for pineal region tumors includes biopsy for tissue diagnosis, and possible resection, depending on rhe specific tumor type. Resection is not indicated for germinomas because of the extreme sensitivity of this tumor to radiation and chemotherapy. Preoperative evaluation should include contrast-enhanced cranial and spinal MRl, serum and CSF tumor markers (if lumbar puncture can be safely performed), CSF cytology, assessment of pituitary and endocrine function, and visual field assessment. In cases of obstructive hydrocephalus, preoperative third ventriculostomy eliminates the need for a VP shunt, which would carry a risk of in tec n on as well as peritoneal dissemination of the tumor. Furthermore, endoscopic biopsy of the tumor may be achieved during the third ventriculostomy,

Resection is the procedure of choice for nongerininomatous pineal region tumors once the diagnosis is established. It may be curative for benign lesions such as a pure teratoma and may improve prognosis for patients with malignant tumors. In addition, resection provides ample tissue to avoid potential diagnostic mistakes caused by sampling error, especially for mixed tumots. Spinal MRI, to rule out CSF dissemination, should be obtained either prior to surgery or 2 weeks after surgery. In contrast, a postopetative, contrast-enhanced cranial MRI should be obtained within 48 hours of surgery to assess the extent of resection. The most common complications of pineal gland surgery are ocular dysmotility, ataxia, and altered mental status. Other, less common complications include seizures, hemiparesis, visual field defects, aseptic meningitis, and intratumoral hemorrhage.

Sensitivity to radiation and outcome depend on histology. Germinomas are the most radiosensitive, with a 90% PFS at 5 years, whereas nongerminomatous malignant germ cell rumors have a 5-year survival rate of .30-40%.

Table 58.5: Tumor markers for germ cell tumors

Tumor	*AH}*	*0-HCG*	*LDH*	*PLAP*
Germinoma		+	++	++
Choriocarcinoma		+++		
Embryonal carcinoma	+	++		
Endodcrmal sinus rumors	-M-+			
Malignant teratomas	*+1—*			

AFP = a-fetoprotein; HCG = human chorionic gonadotropin; LDH = lactate dehydrogenase; PLAP = placental alkaline phosphatase.
Source: Keating, R. F., Goodrich, J. T,„ & Packer, R. J. 2001, *Tumors of the pediatric central nervous system,* Thieme, New York.

Several treatment alternatives exist regarding the management of intracranial germinomas. Radiotherapy alone is usually administered in relatively high doses and large volumes {whole ventricular or craniospinal) even for localized disease. Although the 10-year survival proportion ranges from 80-90%, children often suffer from the late consequences of radiotherapy. Alternatively, the use of chemotherapy followed by response-based radiotherapy permits a selective reduction in not only dose, but also volume of radiotherapy in patients whose tumors completely disappear after 2-4 courses of chemotherapy. For NGGCT, more aggressive chemotherapy (Kellie et al. 2002) and high dose/volume radiotherapy is required to improve survival. Patients with pineoblasromas are treated on protocols designed for patient with PNETs.

Prognosis

The prognosis for patients with pineal region tumors depends on the histology. Surgical resection may be curative for pineocytomas and ependymomas. Patients with anaplastic pineocytomas and pincoblastomas have a much worse prognosis. Germinomas have an excellent prognosis because of their sensitivity to radiation and chemotherapy. NGGCTs, however, tend to have a poor prognosis. Recurrent germ cell tumors may respond to salvage chemotherapy or radiation.

LATE EFFECTS OF THERAPY

Late effects of therapy sinmId be considered before deciding on a particular modality of treatment for an infant or child with a tumor of the nervous system. Indeed, it is often the profile of the potential late effects of one therapy versus another that determines which modality to apply. The particular importance of this concept in pediatric ncuro-oncology is twofold. (1) The developing nervous system is particularly vulnerable to the toxic effects of chemotherapy and radiation compared with adults, (2) The long-term survival of several types of pediatric brain tumors permits the development of some late effects (e.g., secondary malignancies) and has implications for the quality of life for these patients. The late effects of specific treatment modalities are reviewed below.

Surgery

Although gross total resection is the goal of sutgery for most U;H-S i'l brair Uin-ors, Lii:nplic;:lioii\, iikhkluig local injur) to eloquent neural tissue and postoperative complications such as infection, may result in greater neurological injury. Specific neurological syndromes such as cerebellar mutism are common after surgery for posterior fossa tumors. In addition, VP shunts are subject to infection and malfunction, which may require additional interventions.

Radiation

Radiation therapy may produce subacute and late effects on the CNS. The subacute effects include the radiation somnolence syndrome (RSS) and Lhermitte's syndrome. The RSS typically follows within 1-2 months of large-volume cerebral irradiation. Patients typically become lethargic and anorexic, and may develop symptoms that recapitulate the symptoms of the initial tumor. The syndrome spontaneously resolves within 3 months in most cases, but occasionally low-dose corticosteroids are required (Ryan 2000). Lhermitte's sign, electric shocks traveling down the spine on neck flexion, usually arises within several months of cervicothoracic spinal irradiation (Lewanski et al. 2000). This usually resolves spontaneously within months.

Late consequences may include subtle, progressive cognitive deficiencies such as memory impairment or learning disabilities (Mulhern et al. 1999). A leukoencephalopathy has been described in children with acute lymphoblastic leukemia who received intrathecal and intravenous methotrexate (Lovblad et al. 1998} and whole-brain irradiation (Hcrtzberg et al. *1997).* Patients develop subtle but progressive cognitive decline as well as seizures. Similar findings are reported with high dose cytosine arabinoside. In its severe form, the child becomes demented and incapacitated. The MRI and CT show a diffuse periventricular Icukomalacia with patchy necrosis and calcification. The administration of high-dose intravenous methotrexate following radiation therapy results in an especially high risk of leukoencephalopathy, and this sequence of treatments should be avoided. Radiation necrosis may occur after radiation delivery to the tumor and surrounding brain. The necrosis is characterized by necrotic brain and tumor tissue that can cause mass effect, edema, and contrast enhancement on MRI. This complication of radiation may be indistinguishable trom progressive or recurrent tumor on conventional neuroimaging studies.

In fact, cerebral radionccrosis can produce symptoms identical to that of an expanding tumor including progressive focal neurological deficits, seizures, and increased ICP. Treatment of cerebral radionecrosis with corticosteroids may result in improvement of clinical symptoms and reduction in contrast enhancement on CT or MRI studies. However, surgical debulking is often necessary to reduce mass effect and increased ICP. Involvement of small cerebral blood vessels may lead to ischemic strokes. Eventually, the development of multiple small collateral vessels may result in a moyamoya pattern of vascular abnormality that, in turn, increases the risk for stroke or cerebral hemorrhage.

Secondary malignancies, including high-grade gliomas, atypical meningiomas (Santoro et ah 2002), and schwannomas, have been observed within the treatment field several years after the completion of radiation therapy. Patients with Turcot's syndrome, Gorlin's syndrome and NF1 are more likely to develop a secondary malignant glioma after radiation therapy compared with patients without these conditions. This ptovides additional rationale to defer, when possible, radiation therapy for low-grade gliomas. Growth tetardation in children with brain tumors is usually multifactorial. Radiation involving the pituitary gland may affect the production and release of growth hormone. In addition, spinal radiation (as part of craniospinal treatment) affects the growth of the vertebral bones. Pituitary function may also be impaired by direct invasion of the gland by adjacent tumor.

Chemotherapy

Bone marrow suppression is the most common hematological side effect of chemotherapy. Although this toxicity is usually reversible after stopping chemotherapy, some patients develop prolonged cytopenias. These patients are at risk for recurrent and opportunistic infections caused by neutropenia; risks of hemorrhage, resulting from thrombocytopenia as well as fatigue; syncope; and risk for cerebral and cardiac ischemia caused by anemia.

Secondary malignancies are also a potential late effect of chemotherapy. In children, acute myelogenous leukemia is the most common type of secondary malignancy induced by chemotherapy. Alkylating agents, platinum-based drugs, and etoposide are most commonly involved.

Peripheral neuropathy is a common late effect of several chemotherapies (Quasthoff and Hartung 2002). Cisplatin mainly affects proprioception and spares pain and temperature sensation. The usual presenting symptoms are painful dysesthesias and tingling sensations in the roes and later in the fingers. Motor fibers are spared. In contrast, vincristine produces a sensorimotor neuropathy. The first symptoms are usually tingling in the toes and fingers. Loss of ankle jerks is typically the first objective sign. Continued use leads to areflexia and motor weakness involving the dorsiflexors of the feet. Patients with pre-existing neuropathies may become quadriparetic after treatment with vincristine. Cerebellar syndromes of acute onset may be seen with high-dose eytarabine and occasionally with 5-fluorouracih These complications are usually reversible within 2 weeks, but severe irreversible damage to Purkinje cells may occur if the drug is given for several months or if the drug is reintroduced (Friedman and Shetty 2001).

Transverse myelopathy may be seen with prolonged treatments with intrathecal methotrexate or eytarabine. The risk is higher when combined with spinal irradiation.

CONCLUSION

Pediatric brain tumors arc a distinct group of neoplasms with unique characteristics with respect to clinical presentation and management. In contrast to the location of primary brain tumors in adults, posterior fossa tumors predominate in children. Pediatric brain tumors present with a variety of symptoms, usually involving changes in personality, nausea, vomiting, :\]\t.\ morning headaches. Neurological deficits may not become evident until a month or two after the onset of symptoms.

An accurate pathological diagnosis is critical for the management of pediatric brain tumors. Indeed, certain neoplasms have a benign course and good prognosis after gross total resection, despite a malignant appearance on MRI and pathological examination (e.g., PXA). Likewise, other tumors such as a DNET or a centtal neurocytoma may be mistaken for oligodendrogliomas. Because of the potentially severe side effects of adjuvant radiation and chemotherapy, these modalities of treatment should be reserved for truly malignant tumors that carry a poor prognosis. The prognosis and management of pediatric brain tumors is determined by such factors as histopathology, extent of resection, age of the patient and the presence or absence of metastases. Chemotherapy is assuming an iiKTC.iMngK impoi Mill role Il'. the management oi many types of malignant tumors in children. In many cases, chemotherapy may improve survival and reduce rhe chances of neurotoxicity by delaying the need for radiation therapy in young children.

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Chapter 58
Cancer and the Nervous System

G. NERVOUS SYSTEM METASTASES

David Schiff and Patrick Wen

BRAIN METASTASES

Epidemiology

Parenchymal brain metastases are the most common direct neurological complication of systemic cancer. Their precise incidence is unknown; autopsy studies dating hack several decades suggested that brain metastases occurred in 15% of patients dying with cancer. Current estimates range from 20 to 40% (Posner 1995). Based on the greater than 500,000 cancer deaths yearly in the United States, these figures suggest a range of 75,000 to 200,000 new cases of brain metastases each year. For comparison, 35,000 new patients with primary brain tumors are diagnosed each year in the United States.

The incidence of brain metastases varies with the tumor type. For example, the chance of developing brain metastases is 1% in men with prostate cancer, whereas the figure is 3% in women with ovarian cancer. In contrast, the likelihood of developing brain metastases with melanoma ranges from 18-90%, whereas corresponding figures for lung cancer are 18-63% and for breast cancer 20-30%. Overall, lung cancer accounts for 40-50% of all patients with brain metastases and breast cancer accounts for 15-20% (Figure 58G.1). Melanoma, renal cell carcinoma, and gastrointestinal tumors each account for an additional 5-10% of cases (Lassman and DcAngelis 2003).

Brain metastases can arise anywhere in the brain, and their frequency in various locations reflects the relative proportion of cerebral blood flow. Thus 80% of metastases arise in the supratcntorial compartment. For unclear reasons, pelvic and gastrointestinal primary tumors are more likely to metastasize to the posterior fossa than to the supratcntorial region.

Although most patients develop brain metastases in the setting of known cancer, brain metastases are the initial manifestation of the underlying primary tumor in 10-30% of cases. Less than one fourth of these have clinical features pointing to the location of the primary tumor. Nonetheless, 80% will eventually have the primary site of tumor identified during their lifetime. Lung cancer is the most common cause of brain metastases presenting without a known primary, accounting for two thirds of cases. Among lung tumor metastases, two thirds are from non-small cell lung cancer (NSCLC) (Lc Chevalier et al. 1985). Gastrointestinal primaries account for an additional 10%. The high likelihood of a lung primary, and the fact that many patients with other primary tumors have lung

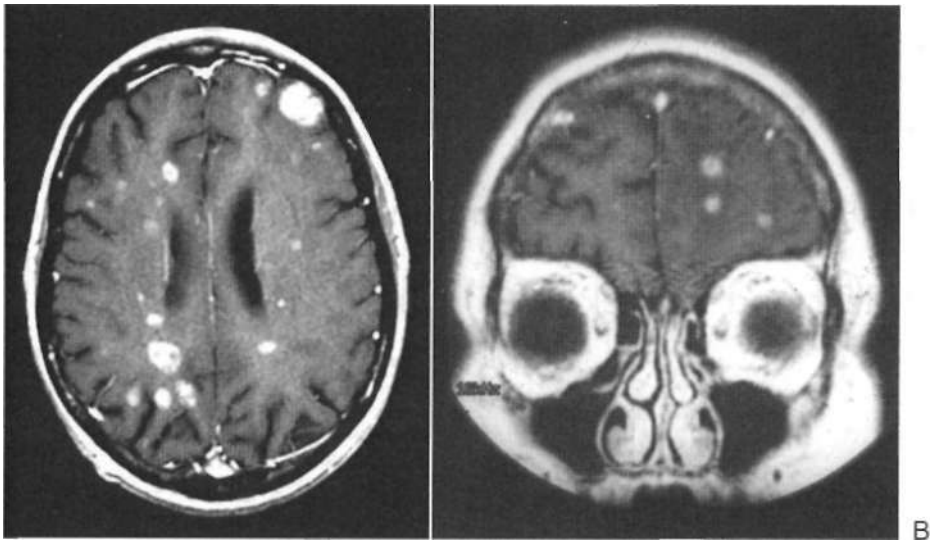

FIGURE 58G.1 (A) Axial and (B) coronal Tl-weighted, contrast-enhanced magnetic resonance image of the brain of a 58-year-old woman with breast cancer treated 1 year previously with whole-brain radiation therapy for brain metastases who presents with multiple recurrent lesions. The treatment options are limited to chemotherapy or reirradiation,

metastases by the time they develop brain metastases, makes restricting initial radiological studies to the chest the more cost-effective approach. Because most brain metastases are multiple, and most patients with brain metastases have a known cancer, only 15% of solitary intracranial masses in patients not known to have cancer turn out to be metastatic tumors (Voorhies et al. 1980).

Pathophysiology and Pathology

Parenchymal brain metastases generally arise from hematogenous spread, typically through the arterial circulation. Tumor emboli, like all emboli, tend to lodge at the gray-white junction because the caliber of blood vessels narrows at this site. These small emboli enlarge in a spherical fashion, eventually developing central necrosis as they outgrow theit blood supply. They are usually associated with substantial surrounding vasogenic edema and are well demarcated from the adjacent brain. The surrounding, normally functioning brain tissue is displaced, and herniation occurs if the displacement is not successfully treated.

The histopathology of brain metastases usually closely resembles that of the underlying systemic tumor. Brain metastases may have a highei labeling index (percentage of cells going through the cell cycle) than the corresponding systemic tumor, suggesting that their growth rate is faster.

Metastases from certain primary tumors (melanoma, choriocarcinoma, and renal cell carcinoma) have a tendency for intratumotal hemorrhage. This may be attributable to a tendency for neovascularization or because they invade blood vessels. Brain metastases from NSCLC also occasionally hemorrhage.

Clinical Presentations

Symptoms of brain metastases may arise as long as 20 years after discovery of the primary tumor, or may even antedate discovery of the underlying systemic cancer. The latter is common with lung cancer, whereas patients with systemic breast cancer and melanoma may enjoy years of apparent freedom from systemic cancer prior to discovery of cerebral metastasis (Henson and Urich 1982).

The presenting features are usually progressive over days to weeks, although occasional patients present acutely with seizures or intratumoral hemorrhage. I lalf of all patients complain of headache, and one third have mental status changes. Most headaches are indistinguishable from tension headache (Husain and Forsyth 2002). The "classic" brain tumor headache, which is worse in the mornings or awakens the patient from sleep, is uncommon, and its absence does not preclude the diagnosis of a brain tumor, Headache in the absence of other symptoms is more likely to be due to multiple metastases than a single metastasis, Over time, headache from brain metastasis becomes progressively more severe and may be accompanied by nausea, vomiting, and drowsiness. Unilateral weakness and gait disturbances are other common presenting complaints. Seizures are present at diagnosis in 18% of patients with brain metastases (Cohen et al. 1988).

Mental status changes and hemiparesis are the most common findings on neurological examination; each is present in approximately 60% of patients (Posner 1995),

Despite the frequent occurrence of increased intracranial pressure, papilledema is detected in only 10% of patients.

Differential Diagnosis

Several neurological conditions may mimic brain metastases both clinically and radiographically. A primary brain tumor must be considered, especially in patients with a single brain mass. This is a particularly important consideration in patients with breast cancer and a dural-based tumor (Schoenbcrg ct al, 1975). Abscess, demyelination, progressive multifocal leukoencephaloparhy, cerebrovascular disease, and the effects of radiation or chemotherapy also simulate brain metastases. Although the clinical syndroms ami ilic ncuroimaging studies usually provide a diagnosis, brain biopsy is sometimes required,

Ncuroimaging

Ncuroimaging advances since the early 1970s have made the diagnosis of brain metastases relatively easy in almost all cases. This topic is covered fully elsewhere in this section, and this discussion is limited to recent comparisons of various imaging modalities. Noncontrast magnetic resonance imaging (MRI) is as sensitive as contrast-enhanced computed tomography (CT) scan for detection of brain metastases. Metastases larger than 1 cm in diameter almost always produce an abnormality on T2-weighted images, whereas those smaller than 0,5 cm rarely do. Use of gadolinium-containing contrast agents dramatically improves the sensitivity of MRI, making it markedly superior to double-dose CT scanning with delayed imaging. Triple-dose administration of contrast further improves the sensitivity of MRI. Although the two dosages are equivalent for detecting metastases larger than 1 cm in diameter, triple dose studies demonstrate three times as many metastases smaller than 0.5 cm in diameter (Yuh et al. 1995). Delayed imaging after standard dose contrast is intermediate in sensitivity between single- and triple-dose gadolinium.

The differentiation of patients with one brain metastasis from those with multiple metastases has important therapeutic implications. In the pre-MRI era, approximately half of all patients had a single brain metastasis. Currently, 70-75% of patients with brain metastases have multiple metastases when studied with MRI. Lung cancer and melanoma are somewhat more likely to produce multiple cerebral metastases, whereas renal cell, breast, and colon cancer tend to produce single metastases. A distinction is made between single and solitary brain metastases: A solitary brain metastasis occurs in a patient with a single brain lesion and no systemic metastases, whereas single brain metastasis implies nothing about the extent of cancer elsewhere in the body.

Management

Supportive Care

Although the use of corticosteroids and antiepilcptic drugs (AEDs) are addressed in other chapters, a few comments pertinent to their rational use in brain metastases are appropriate. Corticosteroids improve symptoms associated with brain metastases in two thirds of patients. Their use improves median survival in otherwise untreated patients from 1 to 2 months. One randomized, controlled trial examined different doses in patients with brain metastases. These patients al! had a Karnofsky Performance Score (KPS) less than or equal to 80 (Tabic 58G.1). All patients received standardized whole-brain radiotherapy after receiving dcxamethasone for 1 week. In the first part of the trial, patients were randomized to receive either 8 or 16 mg daily in divided doses. The two groups did equally well, with slightly less toxicity related to steroids in the lower-dose group. Other patients were then randomized to either 4 or 16 mg daily. The lower-dose group did slightly less well at 7 days (although the difference was not significant) and better at 28 days, with significantly less toxicity than the high-dose group. The authors concluded that unless patients were in danger of herniation, 2 mg twice daily was an appropriate starting dose (Vecht et al. 1994).

Approximately 10-20% of patients with brain metastases present with seizures and require treatment with standard anticonvulsants. The use of prophylactic anticonvulsants in patients who have not had seizures is controversial. Fewer than 20% of these patients experience seizures later in the course of their illness, and this risk does not appear to be reduced with prophylactic anticonvulsants. Consequently, the American Academy of Neurology has issued a practice parameter recommending against the

Tabic 58G.1: Karnofsky performance status

KPS 100	Normal; no complaints; no evidence of disease
KPS 90	Able to carry on normal activity; minor signs or symptoms of disease
KPS Nn	Norma! activity with effort; some sign or symptoms of disease
KPS 70	Cares for self; unable to carry on normal activity or do active work
KPS 60	Requires occasional assistance, but is able to care for most personal needs
KPS 50	Requires considerable assistance and frequent medical care
KPS 40	Disabled; requires special care and assistance
KPS 30	Severely disabled; hospitalization is indicated, although death not imminent
KPS 20	Very sick; hospitalization necessary; active support treatment is necessary
KPS 10	Moribund; fatal processes progressing rapidly
KPS I'	Dead

prophylactic use of anticonvulsants in patients with brain metastases who have not had a seizure (Glantz et al. 2000). Potential exceptions to this guideline include patients with metastases from melanoma (which may be more epileptogenic because of multiplicity- or hemorrhage), tumors in motor cortex, or concomitant parenchymal and leptomeningeal brain metastases.

Management

Radiation Therapy. The goals of radiation therapy (RT) are to alleviate neurological deficits attributable to tumor and to shrink the tumors and prolong survival. In terms of meeting the first goal, approximately three fourths of patients undergoing RT experience symptom palliation, and two thirds maintain this improvement (('airik KISS el a I, 1980). With respect to tumor shrinkage, this depends on the size and radiosensitiviry of the metastasis. With standard doses of whole-brain radiation therapy (WBRT), 37% of patients with SCLC, 35% with breast cancer, 25% with squamous cell cancer, and 14% with nonbreast adenocarcinomas achieve a complete response (CR) (Nieder et al. 1997). Tumors with a pretreatment volume of less than 0.5 ml. had a 100% CR rate, whereas tumors with a pretreatment volume larger than 10 ml. had little likelihood of disappearing in the same study. These results highlight the unfortunate fact that CR of brain metastasis to WBRT is the exception, not the rule.

The Radiation Therapy Oncology Group (RTOG) has conducted a series of clinical trials exploring and comparing the results of different dose-fractionation schemes. Schedules ranging from 5 fractions of IOO cGy to 20 fractions of 250 cGy have resulted in similar outcomes. With all of the schedules, the median survival with WBRT is approximately 4 months, and the 1-year survival is 15%. Approximately 40% of patients succumb to their intracranial disease; the remainder die from progression of extracranial tumor.

The large RTOG database has permitted the application of statistical techniques such as recursive partitioning analysis (RPA) to separate patients with brain metastases treated with WBRT into different prognostic classes based on clinical features at presentation. Patients with brain metastases can be divided into three classes. Class 1 consists of patients with a KPS greater than or equal to 70 (see Table 58G.1), age younger than *65* years, primary site of tumor resected or controlled with treatment, and no extracranial sites of metastatic tumor. Such patients have a median survival of 7.1 months. Class 3 is composed of all patients whose KPS is less than 70; the median survival in this group is only 2.3 months. Class 2 contains all patients who do not fall into classes 1 and 3; class 2 patients have a median survival of 4.2 months (Caspar et al. 1997).

Radiation sensitizers with selective tumor uptake offer the theoretical promise of increasing the efficacy of WBRT. A recent randomi/.ed clinical trial of motexafin gadolinium administered prior to each radiation treatment did not find any prolongation of survival or time to intracranial tumor progression. However, patients with brain metastases from NSCI.C had significantly prolonged time to tumor progression with this agent. This finding requires confirmation. RSR-13, an allosteric modifier of hemoglobin that allows more oxygen to he released to hypoxic tissue, has shown promising results in phase II studies, and is currently being evaluated in a phase III trial.

Radiation Toxicity. With standard fractionation schemes, WBRT is tolerated well. Patients should expect temporary alopecia and fatigue. Headache and nausea occasionally occur, but are generally alleviated with corticosteroids and antiemetics.

Long-term survivors of brain metastases are at risk of suffering late complications of WBRT. Of WBRT recipients for brain metastases, 10-30% develop cognitive impairment by I year (Benin and Delattre 2002). Symptoms commonly include poor short-term memory, abulia, gait unsteadiness, and urinary urgency. MRI frequently reveals extensive, symmetric periventricular white matter changes termed radiation leukoencephalopathy, ventrieulomegaly, and sometimes cortical atrophy. The clinical picture may resemble normal-pressure hydrocephalus, but a positive durable response to ventriculoperitonea! shunt is uncommon (DcAngeiis et al. 1989). Because the risk of this complication is greater with larger fraction sizes, many radiation oncologists treat patients with good prognosis with 20 fractions of 200 cGy or similar regimens.

Prophylactic Cranial Irradiation. Brain metastases are extremely common in SCLC, being present in 10% of patients at diagnosis, increasing to 20% during therapy, and 35% at time of autopsy (Jeyapalan and Henson 2002). At 2 years postdiagnosis, the cumulative risk of brain metastasis is 47% for patients with limited disease and 69% for those with extensive disease. Presumably the brain is a pharmacologic sanctuary for microscopic tumor against systemic chemotherapy, which does not penetrate the intact blood-brain barrier. This has led to numerous trials designed to test whether prophylactic cranial irradiation (PCI) would decrease the incidence of brain relapse and improve survival in patients who achieved systemic CR. Typically, 24 to 36 Cy W^{f}BRT has been administered in 2-2.5 Gy fractious. A metaanalysis of these studies indicated that PCI reduced the risk of subsequent brain metastasis in half the patients and modestly increased 3-year survival from 15.3 to 20.7% {p = .01) (Auperin et al. 1999). Controversy still remains over whether the benefits of PCI outweigh its toxicities, particularly leukoencephalopathy. Two large prospective randomized trials of PCI did not document increased neuropsychological deficits among PCI recipients. Others have argued that the smalt numbers of long-term survivors in these trials

precluded accurate assessment of the risk of leukoencephalopathy, and that because PCI benefited only about one fourth of its recipients, it should not be considered standard therapy.

Surgery. For several decades, neurosurgeons resected single brain metastases in selected patients and argued that surgery produced better results, particularly noting improvement in the percentage of long-term survivors, than with radiotherapy alone. In 1990 a randomized controlled trial verified the neurosurgeons' contention. In this study, eligible patients had a single surgically accessible metastasis identified by contrast CT or MRI scan. Patients with highly radiosensitive primary rumors were excluded. Patients were randomized to biopsy followed by WBRT (36 Gy in 12 fractions) versus resection and radiotherapy. Patients who underwent surgical resection of the metastases followed by RT developed fewer local recurrences (20% versus 52%), and significantly improved survival (40 weeks versus 15 weeks) compared with those patients who received only a biopsy and RT. Patients who underwent surgical resection also had improved performance status and a reduced risk of dying as a result of neurological causes. Multivariate analysis showed that surgery and longer time between diagnosis of the primary tumor and the development of brain metastases were associated with increased survival, whereas disseminated disease and increasing age were associated with decreased survival (Patchell et al. 1990). Thus in patients with surgically accessible single brain metastases and absent or controlled systemic cancer, surgical resection has become the standard of care.

The role of WBRT following resection of a single metastasis is uncertain. In one trial, patients with a single metastasis on gadolinium MRI scan who underwent complete resection were randomized to receive either 50.4 Gy in 28 fractions versus no radiation (Patchell ct al. 1998). The recurrence rate either locally or distantly in the brain was significantly reduced in the radiation group (18%) compared with the observation group (70%). However, overall sin \ p. .il did not Jrlri M;;iii[ic.i:itly ktwivr [lirlwo groups. Radiation substantially reduced the death rate resulting from neurological causes; however, patients in the observation group who did not die of neurological causes appeared to live longer than similar patients in the radiotherapy group. There was no difference in how long patients maintained functional independence. In the absence of survival benefit to postoperative WBRT, its use must be decided on an individual case basis. For some patients and physicians, the reduction in recurrent brain metastasis and neurological death will outweigh the potential side effects of radiotherapy.

Stereotactic Radiosurgery. Like conventional surgery, stereotactic radiosurgery (SRS) has emerged as a means of enhancing long-term local control of brain metastases. SRS is a technique of external irradiation that uses multiple convergent beams to deliver a high single dose of radiation to a radiographically well-circumscribed treatment volume. SRS is generally administered either with a gamma knife apparatus or a modified linear accelerator. With either technique, the use of a stereotactic head frame and the radiation delivery system allows for great precision with a rapid drop-off in radiation dose within millimeters of the target lesion, sparing normal brain the potentially deleterious consequences "1 high ilos;[1] radiation.

Numerous single institution experiences with radiosurgery for single or oligometasraric brain lesions have been published. In a review summarizing published series comprising more than 2000 patients treated over 8 years in the 1990s, Locffler found that SRS achieved permanent local control in more than 80% of patients w[r]ith complications in fewer than 10%. Outcome appeared independent of the number of metastases treated {Loeffleret al. 1999). Median survival following SRS is approximately 9-10 months, very similar to surgical series. Radiosurgical treatment is also effective for metastases that have recurred following fractionated radiotherapy.

One consistent and remarkable finding across SRS series is that metastases from highly radio-resistant tumors like melanoma and renal cell carcinoma, which respond very poorly to fractionated radiotherapy, respond virtually as well to SRS as do tumors far more sensitive to conventional radiation.

SRS offers the potential of treating lesions in locations generally considered surgically inaccessible. Metastases in eloquent cortex, basal ganglia, thalamus, and even the brainstem can be treated with relatively low risk. A technical limitation of SRS compared with conventional surgery is the inability to treat metastases greater than 3.5 cm in median diameter. Another advantage of surgery is its ability to alleviate mass effect quickly. Approximately 7% of metastases treated with SRS transiently increase in diameter on scan, reflecting a radiation reaction.

Because the results for SRS appear similar to those from surgery, one might ask whether SRS has been proven to improve the patient's outcome, as has surgery, when administered with fractionated radiation. A recently concluded RTOG clinical trial has affirmed this hypothesis by randomizing patients with one to three brain metastases to WBRT with or without radiosurgery. Patients with a single brain metastasis had a significant survival benefit from the addition of radiosurgery, as did patients younger than 50 and those in RPA class 1.

The role of WBRT following radiosurgery for brain metastases is also uncertain. Two retrospective cohort studies have examined this issue. Pirzkall ct al. (1998) compared outcomes in 158 patients treated with radiosurgery alone versus 78 receiving radiosurgery plus fractionated WBRT. All patients had three or fewer brain metastases. The overall median survival was 5.5 months, with no difference between treatment groups. However,

median survival in patients without extracranial tumor was increased in pal ictus gelling both forms oi radiation (15.4 versus 8.3 months, $p = .08$), There was a trend for superior local control in patients getting combined therapy. A similar smaller study also found no difference in median survival (11 months) or I year progression-free survival. Brain relapse was significantly more common in patients receiving radiosurgery alone; however, most patients who did relapse could still be salvaged. A phase III clinical trial addressing this issue in patients with one to three brain metastases is underway.

The effectiveness of radiosurgery versus surgery in patients with brain metastases has never been ascertained. Although surgeons occasionally remove two or three brain metastases, surgery is generally restricted to single lesions. Radiosurgery appear?, more i osl i ffcclivc llian MHL> IV, although surgery alleviates symptoms of mass effect much more rapidly and reliably than SRS. Phase III trials comparing these two modalities have been proposed, but no major trial has yet been undertaken.

Treatment Options for Recurrent Brain Metastases

Rcirradiation. Several ease series have examined the safety and efficacy of administering a second course of fractionated WBRT to patients with recurrent or progressive brain metastases. In general, this option is considered only in patients who had a good and relatively durable response to their prior course of WBRT. Sometimes the entire brain is reirradiated, but if metastases are not widespread, fractionated radiation may be delivered to a limited portion of the brain. A majority of patients achieve symptom palliation, which lasts a median of 3 months. Because survival under these circumsrances is generally limited (median survival 4 months), clinical radiation-induced leukoencephalopathy is relatively uncommon (Wongetal. 1996).

Chemotherapy, The concepi of administering chemotherapy for brain metastases is attractive. Not only could systemic chemotherapy potentially treat all the brain metastases, it would reach the systemic tumors that are often present. One difficulty is that most patients have already received treatment with those drugs that are mosr active against their primary tumor. As a result, these drugs are often not effective in eradicating the brain metastases, ! lie relative miperme.ibilit) ot the blood brain barrier to many chemotherapeutic agents is another complicating factor, although the presence of contrast enhancement in virtually all brain metastases indicates that the blood-brain barrier is partially disrupted in brain metastases,

Numerous studies have been conducted with various chemotherapeutic regimens in lung, breast, and other primary tumors. The role for chemotherapy is perhaps clearest in germ cell tumors, in which chemotherapy can often provide a durable CR. SCLC is another relatively chemosensitive tumor. Unfortunately, it is exceptional for patients with brain metastases from NSCI.C, melanoma, and breast cancer to have a radiographic response or prolonged disease stabilization with currently available chemotherapy. The development of new, more active agents offets the hope of improvement.

SPINAL CORD COMPRESSION

Epidemiology

Epidural spinal cord compression (ESCC) refers to compression of the spinal cord or cauda equina from a neoplastic lesion outside the spinal dura. This complication of systemic cancer is estimated to affect approximately 25,000 Americans each year (Sehiff 2003). Although every type of cancer is capable of producing ESCC, several tumors predominate. Thus in most series breast, lung, and prostate cancer each account for about 20%, whereas renal cell carcinoma, non-Hodgkin's lymphoma (NHL), and multiple myeloma typically account for 5-10% each (Sehiff 2002). Ewing's sarcoma and neuroblastoma are particularly common causes in children. Of all ESCCs, 20% occur in patients not previously known to have cancer; among this group, lung cancer, lymphoma, and multiple myeloma are the typical underlying tumors.

Pathophysiology and Pathology

A protective ring of bones encloses the spinal cord. The ring is composed of the vertebral body anteriorly, and the lamina, pedicles, and spinous processes posteriorly. The thecal sac lies within this bony ring. The outermost layer of the thecal sac is composed of dura mater that is continuous with cranial dura mater and fuses with periosteum of the sacrum at S2. The spinal epidural space lies between the periosteum of the vertebral bones and the dura, and normally contains fat, connective tissue, and a venous plexus. Tumor cells generally seed the vertebral bones (usually the vertebral body) rhrough hematogenous dissemination via arteries or the valveless, low-pressure venous plexus of Batson. The tumor gradually expands and forms an epidural mass, producing compression of the spinal cord. The tumor takes the path of least resistance, frequently encircling rhe spinal cord. Collapse of the vertebral body may occur, exacerbating the severity of spinal cord compression. Less commonly, primary or metastatic tumor in the paravertebral region grows through the neural foramen to produce ESCC. Animal models suggest that both demyelination, produced with slowly expanding masses and often reversible, and venous infarction, play a role in spinal cord dysfunction. Of ESCCs, 60% arise in the thoracic spine and 30% in the lumbar spine (Sehiff 2002).

Clinical Presentations

Back pain, present in 83-95% of patients at the time of diagnosis, is usually the first symptom of ESCC (Schiff 2002), On average, the pain precedes the development of neurological symptoms by approximately 2 months. The duration of pain is often related to the rate of tumor growth, with slower growing tumors presenting with longer duration of pain. Most patients have local pain, related to disruption and stretching of cortical hone and periosteum. Cough, movement, and recumbency commonly exacerbate the pain. Eventually, the pain takes on a radicular distribution, which in the thoracic spine may produce a bilateral gripping sensation. Pain is often quite severe by the time ESCC is diagnosed.

Motor involvement, the must dreaded of F.SCC manifestations, is present in 80% of patients (Hclweg-Larsen and Sorensen 1994). Once weakness is present, ptogression is often rapid, and diagnostic workup and thetapy must proceed expeditiously. This is particularly impottant because pretreatment neurological function is a major predictor of post-treatment outcome. Approximately 50% of patients with ESCC are ambulatory, 35% are paraparetic, and 15% are paraplegic at diagnosis. Weakness is typically bilateral and symmetric; the iliopsoas muscles may be disproportionately affected.

Sensory loss is detectable in about 75% of patients at diagnosis, typically reflecting the extent of weakness. Patients frequently experience ascending numbness and paresthesias. A correlation exists between the extent of sensory loss and the inability to ambulate (Schiff 2002). Radicular sensory loss may help to localize the level of r.SCC. However, the spinal sensory level detected on examination is often sevetal levels below the responsible lesion (Posncr 1995). Lesions above the cauda equina generally result in sparing of saddle sensation, whereas cauda equina lesions may produce saddle sensory loss. Occasionally, ESCC in the cervical cord may be associated with Ehermitte's sign, which is characterized by an electrical sensation in the spine and extremities with neck flexion,

Bowel and bladder dysfunction arc evident in a majority of patients with ESCC, taking the form of urinary retention, incontinence, and constipation. However, isolated bowel or bladder disturbance in the absence of back pain, weakness, or sensory loss is rarely related to ESCC, Isolated gait ataxia is another uncommon manifestation of ESCC,

Differentia! Diagnosis

The differential diagnosis of ESCC in cancer patients is broad and can be separated into neoplastic and non-neoplastic causes (Table 58G.2). Spine metastases not impinging on the thecal sac can produce severe pain mimicking ESCC. These may be clinically indistinguishable from ESCC. Patients with radiographically high-grade ESCC may not show features of radiculopathy and myelopathy if cord compression has developed slowly. Intramedullary spinal cord metastases are rare as compared with ESCC. The clinical features are similar to ESCC, although many patients pass through a stage in which spinal cord dysfunction is unilateral or at least very asymmetric, unusual with ESCC. Leptomeningeal metastases (LMs), which, like intramedullary spinal metastases, are discussed later, occasionally produces a cauda equina syndrome which may resemble ESCC. Radicular pain predominates over local pain in this condition, and bowel and bladder involvement may be particularly prominent compared with ESCC. Neoplastic masses in the brachial or lumbosacral plexus may also simulate ESCC, although unilateral findings are the rule. Malignant plcxopathy often coexists with ESCC, given the proximity to the spinal cord (Figure 58G.2),

Two rare neurological conditions related to, but not a direct result of, cancer are radiation myelopathy and paraneoplastic myelopathy. Radiation myelopathy may occur if the spinal cord was included in prior radiotherapy treatment ports (Benin and Delattre 2002). The most common form, *chronic progressive radiation myelopathy*, generally develops 1 to 2 years after radiotherapy. Ascending numbness and pyramidal tract dysfunction often occur in an asymmetric fashion, suggesting the Btown-Scquard syndrome. The risk of myelopathy is increased by high radiation doses, long length of irradiated spinal cord, and a latge radiation fraction size. Paraneoplastic disorders are a rare cause of myelopathy. The most common clinical syndrome Is a painless myelopathy accompanied by encephalitis or sensory neuropathy.

Table 5S(!,2: Differential diagnosis of epidural spinal cord compression

Causes that should be considered in cancer patients
Vertebral metastases without ESCC
Intramedullary spinal cord metastases
Leptomeningeal metastases
Malignant plcxopathy
Radiation myelopathy
Paraneoplastic myelopathy
Benign causes
Osteoarthritis
Rheumatoid arthritis
Tophaceous gout
Spinal epidural abscess
Spinal epidural hematoma
Spinal epidural vascular malformation
Meningioma
Neurofibroma
Intramedullary hematopoiesis
KpiduiM lipomatosis
Sarcoidosis
Histiocytosis

ESCC = epidural spinal cord compression.

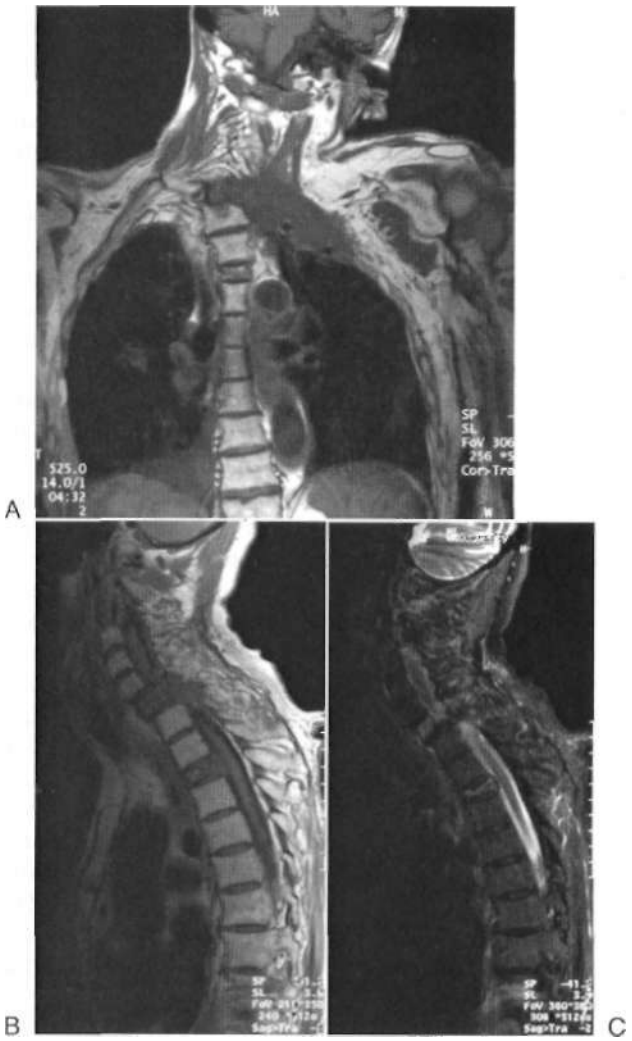

FIGURE 5 KG.2 This 65-year-old woman with lung cancer presented with a left apical lung tumor, and 3 months of distal left arm weakness and pain. She then developed distal right arm weakness consistent with C7, C8, and T1 pd/radiculopathy. Tl - and T2-weighted magnetic resonance imaging (MRI) scans demonstrate the apical mass extending into the neural foramina and vertehral bodies at C6 and C7, displacing [he cord anteriorly and to the right. Also seen is a pathological compression fractute at T3 producing moderate canal stenosis. (A) Coronal TI-weighted MRI showing left apical lung tumor extending into the neural foramina and vertebral bodies at Cfi and C7 *{arrow}*. (B) Sagittal Tl-weighted MRI showing tumor infiltrating vertebral bodies at C6 and C7 and displacing the spinal cord. Also seen is a pathological compression fracture at T3, producing moderate canal stenosis. (C) Sagittal T2-weighted MRI showing the same rumor infiltrating vertebral bodies at C6 and C7 and displacing the spinal cord. Also seen is a pathological compression fracture at T3, producing moderate canal stenosis.

A necrotizing myelopathy, without associated antibody or other serum markers, is also described with cancer.

Of the benign conditions that mimic ESCC, osteoarthritis is the most important. Features that may help differentiate the pain of FSCC from musculoskeletal disease include the frequent localization of pain from ESCC to the thoracic spine compared with the lumbosacral and cervical localization of pain from benign causes, and the tendency for recumbency to i\.Kerb a re the pain from I'SCC and relieve pain from benign causes. Other benign causes that should be considered in the differential diagnosis of ESCC include other types of arthritis such as rheumatoid arthritis and tophaceous gout, benign tumors such as meningiomas and neurofibromas, vascular malformations, epidural hematomas, extramedullary hematopoiesis, epidural lipomatosis, sarcoidosis, and histiocytosis.

Ncuroim aging

The availability of MRI has revolutionized the definitive diagnosis of ESCC (see Figures 58G.2B and 58G.2C). Prior to MRI, myelography with or without CT scanning was the gold standard. Prior to myelography, patients were often screened with plain radiographs or hone scans. Plain radiographs demonstrating vertebral collapse or pedicle erosion at a level corresponding to clinical findings were highly predictive of F'SCC. However, false negative studies were common. Radionuclide bone scanning was more sensitive, although this test could be normal in neoplasms without increased blood flow or new bone formation like multiple myeloma. Moreover, abnormal studies were frequently related to benign causes.

MRI and myelography are rhe only studies capable of demonstrating the thecal sac compression characteristic of ESCC. Myelography produces good images of the entire thecal sac as long as a complete block is not present; in that event, a second punctutc rostral to the block may be necessary to delineate the upper extent of epidural tumor. Disadvantages of myelography, in addition to its invasiveness, include its insensitivity to intramedullary pathological conditions and the potential risk of precipitating a cerebral or spinal herniation syndrome. Patients suspected of having cerebral metastases should undergo brain imaging prior to myelography. Additionally, neurosurgical consultation should be sought prior to the procedure in case patients with complete subarachnoid block deteriorate neurologically following the myelogram ("spinal coning"). Patients with pacemakers, certain aneurysm clips, and shrapnel who cannot undergo MR] remain dependent on myelography.

MRI produces excellent images of the spinal cord, thecal sac, and bony spine, demonstrating metastases in each of these areas when they are present. Typically radiologists perform scans in the sagittal plane, with selected axial images through regions of interest identified on the sagittal images. MRI allows the entire spine to be screened for epidural metastases, an important advantage because 30% of patients with ESCC have multiple epidural deposits. Noncontrast Tl- and T2-weighted MRIs are generally satisfactory to screen for abnormalities in the bone and epidural space. Gadolinium administration may be helpful

in delineating the epidural tumor and leptomeningeal metastases.

Management

Corticosteroids

A few years after the beneficial effect of corticostetoids on brain tumors was established, corticosteroids were observed to ameliorate the clinical features of ESCC. Since then corticosteroids have been routinely used in patients with ESCC. Subsequently, rodent models of ESCC confirmed a benefit with dexamethasone. One randomized controlled trial of dexamethasone in patients with carcinomatous ESCC undergoing radiation showed that the use of dexamethasone increased the likelihood of patients remaining ambulatory (Sorensen et al, 1994). The optimal dose of corticosteroids for ESCC remains unresolved. Based on extrapolation from a dose that was demonstrated to be effective in rodent models, some protocols have suggested an initial dose of 100 mg dexamethasone, followed by 24 mg four times daily. Retrospective cohort studies suggest that substantially lower doses (e.g., 10 mg initially and then 4 mg four times daily) achieve equivalent results with fewer serious corticosteroid complications such as gastrointestinal bleeding (Heimdal et al. 1992). If the higher dosage is used, one reasonable strategy is to taper the dose by 50% every 3 days so long as the patient is stable.

Radiotherapy

Radiotherapy is the treatment of choice for most patients with ESCC. By stopping tumor growth and sometimes shrinking the tumor, radiotherapy usually alleviates pain and stabilizes or improves neurological function. Radiation ports are created on the basis of the radiological studies, and traditionally extend one vertebral level above and below the site of epidural tumor. Ports arc widened when a paravertebral mass is known to be present. Radiation dose represents *A* compromise among tumor control, risk of radiation myelopathy, and treatment duration compatible with the patient's condition. No prospective controlled trial has examined different dose-fractionation schemes. Commonly, radiation oncologists deliver approximately 3000 cGy in 10 fractions over 2 weeks.

Prognosis with ESCC following radiotherapy depends most heavily on pretreatment neurological function. Another important factor is the radiosensitivity of the underlying tumor. Some cancers, like lymphoma, myeloma, and prostate cancer, are quite radiosensitive; others, including renal cell carcinoma and non-SCLC, are relatively radioresistant. Patients with radiosensitive rumors are much more likely to have tumor shrinkage and long-term local tumor control with radiotherapy than those with radioresistant ones. Finally, the degree of subarachnoid block is a prognostic factor; patients with high-grade block tend to fare worse than patients with minimal deformation of the thecal sac from epidural tumor.

In general, almost all patients who are ambulatory at the onset of radiorherapy remain ambulatory at its conclusion. Among patients who are Aira paretic and una Mi[1] u> W.LX, one third regain ambulation. Only 2-6% of patients regain the ability to walk when treatment is delayed until after the patient is paraplegic. Median survival following ESCC is approximately 6 months, and is better in patients who remain ambulatory. Eocally recurrent ESCC occurs in one half of 2-year survivors.

Recently, neurosurgeons and radiation oncologists have been working to modify radiation equipment to deliver SRS to the spine. Although few data have been reported in detail, and precision with high-dose radiation around the spinal cord will be crucial, such techniques offer the promise of treating rumors resistant to fractionated radiotherapy.

Surgery

Decompressive laminectomy had been standard practice for patients with ESCC. In the 1970s, it was widely recognized that the results from radiotherapy were at least as good as those from laminectomy with less morbidity. One of the major shortcomings of laminectomy was that epidural tumor usually arose anterior to the spinal cord in the vertebral body. In this situation, not only did laminectomy fail to provide exposure to debulk the main tumor mass, it removed one of the elements of the spinal column still providing stabilization.

More recently, surgeons have performed vertebral corpectomy to treat patients with ESCC. In this procedure, tumor in the vertebral body is curetted out from an anterior or lateral approach. The spine is then stabilized with methylmcthacrylate or hone graft and instrumentation. The complication rate of this procedure is relatively high and includes infection, stabilization failure, wound breakdown, and hemorrhage. However, it does allow for more complete tumor resection than laminectomy for anteriorly situated tumors. An ongoing clinical trial is comparing the outcome of vertebral corpectomy to radiotherapy. Vertebral corpectomy particularly should be considered in cases of spinal instability, rctropulsed bone within the spinal canal, local recurrence during or after radiotherapy, and radioresistant tumors when other sites of metastasis are limited.

Chemotherapy

Chemotherapy is a rational means of treating ESCC when the causative tumor is chemosensitive. Most common solid tumor causes of ESCC arc not chemosensitive. b'or Hodgkin's lymphoma, germ cell tumors, and neuroblastoma, chemotherapy may effectively treat both the ESCC

and other sites of disease. Hormonal manipulation has been documented to be of benefit in cases of ESCC from prostate and breast cancer.

INTRAMEDULLARY SPINAL CORD METASTASES

Metastases are capable of spreading to the substance of the spinal cord, either by hematogenous spread, or secondary to leptomeningcal invasion and subsequent centripetal growth. Intramedullary spinal cord metastases cause progressive myelopathy, which often initially takes the form of a *hemicord* syndrome *(Brown-Sequard syndrome)* with ipsilateral pyramidal weakness and posterior column sensory loss, and contralateral spinothalamic sensory loss. Lung cancer accounts for about half of all cases, with small cell histology being particularly common. Melanoma, lymphoma, and renal cell carcinoma are other common causes. MRI scanning generally reveals a contrast-enhancing mass with a larger surrounding region of T2 signal abnormality (edema). Most patients with this complication cither have concurrent or prior brain metastases. Treatment generally consists of corticosteroids and fractionated radiotherapy, which usually stabilize neurological function for several months (Schiff & O'Neill 1996).

LEPTOMENTNGEAL METASTASES

Involvement of the lep to meninges by tumor is an increasingly common problem in patients with cancer, and leads to significant morbidity and mortality (Mason 2002; Kesari and Barchelor 200.3). The factors that have contributed to the increased incidence are a greater awareness of the condition among oncologists, improved diagnostic tests, and longer survival among patients with systemic malignancies. Longer survival of patients with systemic cancers results in a higher incidence of central nervous system (CNS) metastases.

Epidemiology

Approximately 5% of cancer patients have LM (Posner 1995). The incidence varies with different tumor types. LM occurs in up to 8% of patients with solid tumors, 5-29% of patients with NHL, and 11-70% of leukemias (Wen and Fine 1937; Kesari and Batchelor 2003).

Among solid tumors, adenocarcinomas have a particular propensity to metastasize to the leptomeninges. In several large series, breast cancer accounted for 1 1-64% of patients with LM, followed by lung cancer (14-29%), melanoma (6-18%), and gastrointestinal cancers (4-14%). Primary brain rumors, especially medulloblastomas and high-grade gliomas, also have a tendency for cerebrospinal fluid (CSE) spread. Some solid tumors, such as head and neck cancer, thyroid cancer, prostate cancer, carcinoid, and bladder cancer rarely seed the leptomeninges (Wen and Line 1 997; Kesari and Batchelor 2003).

LM associated with acute lymphoblastic leukemia (ALL) in children was previously common, but CNS prophylaxis has reduced the incidence from 667u to 5%, The incidence of LM in adults with ALL remains high, despite similar prophylactic measures. Patients with acute myelogenous leukemia have a 20-50% risk of meningeal involvement, whereas LM is uncommon in patients with chronic myelogenous leukemia and hairy cell leukemia. Leptomeningcal involvement is present in up to 50% of patients with chronic lymphocytic leukemia at autopsy, although it is almost always asymptomatic during life (Grossman and Moynihan 1991).

Seeding of the leptomeninges occurs in approximately 6% of patients with NHL. The highest risk occurs in those with diffuse, lymphoblastic, or Burkitr's histology, or those who have involvement of the bone marrow, testes, or cxtranodal sites. Leptomeningcal disease is rare in patients with Hodgkin's disease, mycosis fungoides, and multiple myeloma (Grossman and Moynihan 1991).

Pathogenesis

Tumor cells usually reach the leptomeninges by direct extension from pre-existing tumor in the brain parenchyma or epidural space or by hematogenous spread (Posner 1*99S).* Tumor cells may also spread along spinal nerve roots from a paraspinal mass or along cranial nerves from a head and neck tumor. Once tumor cells reach the leptomeninges, they spread along the surface of the brain, spinal cord, and nerve roots (Figure 58G.3). Exfoliated tumor cells are carried by the flow of CSF to other parts of the ncuraxis, especially to the basal cisterns and Cauda equina, where they tend to settle as a result of gravity and slow CSF flow.

The presence of tumor cells in the leptomeninges produces neurological dysfunction in several ways. Direct invasion of spinal and cranial nerves can cause demyelination and subsequent axonal degeneration of the nerves. Tumor cells may also grow along the Virchow-Robin spaces and directly invade the brain or spinal cord, producing symptoms of confusion and seizures (Wasserstrom 1995). LM may also produce CNS dysfunction by causing hydrocephalus. Tumor cells can occlude the CSF outflow foramina of the fourth ventricle or impede the reabsorption of CSF through the arachnoid granulations, leading to hydrocephalus. Occasionally the intracranial pressure may be increased without enlargement of the ventricles, and, rarely, herniation may occur. Tumor cells may interfere with the blood supply, decreasing cerebral blood flow and even producing transient ischemic attacks and strokes. Tumor cells may also directly compete with neurons for oxygen and essential metabolites such as glucose. This is

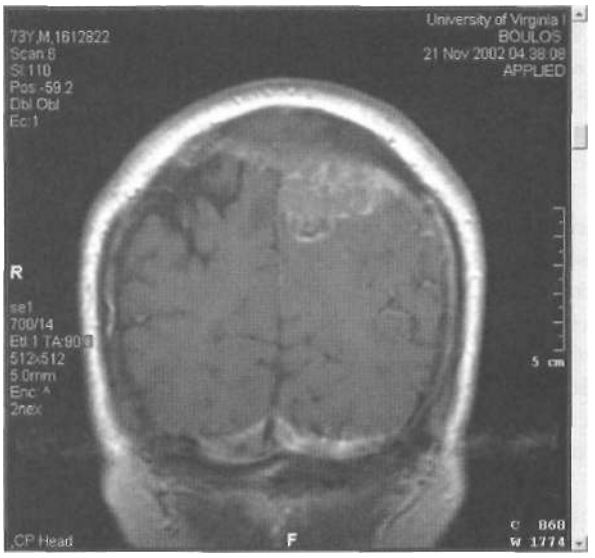

FIGURE 58G.3 Gross appearance of tumor infiltrate in the subarachnoid space as evidenced by clouding of the Ieptomeninges. (Courtesy of Dr. Umberto De Girolami, Division of Neuropathology, Brigham and Women's Hospital.)

the mechanism proposed for the weight gain seen in children with leukemic meningitis and infiltration oi the hypothalamus (Posner 1995).

Clinical Features

LM is usually a late complication of systemic cancer, occurring 6 months to 3 years after the diagnosis of the primary tumor (Wasserstrom 1995). In rare patients with breast carcinoma and melanoma, an interval of up to 10 years may exist between the diagnosis of the primary tumor and the Leptomeningeal relapse. LM usually occurs in the setting of active disease outside the nervous system, although as systemic therapy improves, increasing numbers of patients are developing LM as the sole site of relapsed disease. In 5% of patients, leptomeningeal involvement is the initial presentation of a neoplasm (Posner 1995).

The presentation of LM can be extremely variable and requires a high index ol suspicion. The diagnosis should be considered in any cancer patient, especially if there are symptoms and signs involving several different sites in the neuraxis.

Cerebral symptoms occur in up to 50% of patients (Kaplan et al. 1990; Wasserstrom 1995). The most common are headaches, which can be nonspecific or have features suggestive of increased intracranial pressure. Other symptoms include nausea, vomiting, cognitive changes, and occasionally seizures. Focal cerebral symptoms are relatively rare. Papilledema may occasionally be present in patients with hydrocephalus. Rarely, LM may produce a diencephalic syndrome, diabetes insipidus, central hypoventilation, cerebral infarction, and complex partial status epilepticus (Wen and Fine 1997).

Thirty percent of patients have cranial nerve symptoms and 50% have cranial nerve signs. Involvement of the third, fourth, and sixth nerves is most common, followed by facial weakness, decreased hearing, and involvement of the optic, trigeminal, and hypoglossal nerves.

Approximately 60% of patients have spinal symptoms, especially in the lumbosacral region, as a result of involvement of nerve roots. The most common symptoms are pain, weakness, and paresthesias. Sphincter dysfunction is less common. More than 70% of patients have signs of spinal cord dysfunction, including asymmetric weakness, sensory loss, and depressed reflexes.

Diagnostic Tests

The most useful tests for the diagnosis of LM are summarized in Table 58G.3.

Cerebrospinal Fluid Examination

Examination of the CSF is the most important test for the diagnosis of LM. The finding of malignant cells in the CSF is the definitive diagnosis. However, the CSF is almost always abnormal even if the cytological examination result is negative. These abnormalities may include lymphocytic pleocytosis, elevated opening pressure, increased CSF protein, and a decreased glucose concentration (Fosner 1995; Kesari and Batchelor 2003). In 3% of patients, the CSF is normal. This usually occurs in patients who have a block in the CSF pathway with the result that the area of CSF sampled (e.g., ventricular CSF) may not be connected

Table 58G.3: Diagnostic tests for leptomeningeal metastases

Test	*Measurement*	*Positive findings*
Lumbar puncture	Lymphocytic pleocytosis	>70%
	Elevated opening pressure	50%
	Elevated protein	75%
	Reduced glucose	30-40%
	Cytology after ILP	50%
	Cytology after 3LPs	90%
	CSF markers	Variable
	Immunohistochemistry	Variable
	PCR	Variable
Brain MRI	Meningeal enhancement	>50%
	Enlarged ventricles	<50%
Spine MRI/ myelogram	Subarachnoid masses	<25%
	Meningeal enhancement	>50%

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; PCR — polymerase chain reaction.

to the areas involved by leptomeningeal tumor (e.g., cauda equina).

The opening pressure is elevated in approximately 50% of patients with LM as a result of tumor cells obstructing CSF outflow from the ventricles or interfering with CSF reabsorption by the arachnoid granulations,

The CSF white blood cell count is elevated in more than 50% of patients with LM. This increase in cell count may range from a few cells to more than 1000. This is usually a lymphocytic pleocytosis, but occasionally polymorphonuclear cells may be found. Rarely, patients with Hodgkin's disease, NHL, and leukemia have eosinophils in the CSF.

The CSF protein is elevated in most patients as a result of a combination of disruption of the blood CSF barrier and exudation of serum protein into the CSF, and breakdown of tumor cells and lymphocytes. In most, the protein is moderately elevated, but levels in excess of 2 g/dl can be seen. Because normal levels of CSF protein are lower in the ventricle (10 mg/dl) than in the lumbar space (40-45 mg/dl), a CSF protein level of 40 mg/dl from an Ommaya's reservoir should be considered abnormal. In patients with leptomeningeal myeloma CSF immunoglobulin (Ig)M may be elevated.

Low CSF glucose (hypoglycorrhachia) is present in approximately 30% of patients with LM (Wassertrom et al. 1982). The precise cause of the low CSF glucose is unknown. Possible reasons include impaired carrier mediated transport of glucose across the blood-CSF barrier and increased utilization of glucose by tumor cells and reactive lymphocytes.

A positive CSF cytological examination result is diagnostic of LM. Ideally, fresh samples of CSF should be sent to the laboratory for cytological examination. When not possible, the CSF should be stored in a refrigerator until it can be analyzed. Positive cytological examination result is found in approximately 50-60% of patients with the initial lumbar puncture and in up to 90% of patients with repeated sampling (Posncr 1995). In general, the CSF cytological examination result is more likely to be positive when obtained from the lumbar CSF than ventricular CSF. The presence of malignant cells in CSF tends to correlate with more extensive leptomeningeal disease. In 8-10% of patients with LM, the CSF cytological result remains persistently negative. This may result from malignant cells remaining adherent to the leptomeninges without being shed into the CSF, or from a blockage in the CSF pathway so that the area from which CSF is being sampled is not in communication with the site of LM. In patients with subarachnoid blocks and cerebral or cranial nerve symptoms, a cisternal puncture may increase the diagnostic yield. Rarely, false positive cytological results may occur in parients who have brain metastases without leptomeningeal involvement, as a result of laboratory error, or when reactive lymphocytes are misinterpreted as malignanr.

When the CSF cytological examination result is negative, biochemical markers can sometimes be useful in assisting the diagnosis of LM and monitoring the response to therapy (Wen and Fine 1997; Kesan and Batchelor 2003). Some of the more commonly used markers are listed in Table 58C.4. Although some of these markers are fairly specific, their usefulness is often limited by their relative lack of sensitivity. Occasionally, parenchymal metastases adjacent to leptomeningeal or ependymal surfaces falsely elevare die levels of biochemical markers in the CSF.

In some patients immunocytochemistry can increase the sensitivity for detecting malignant cells. Monoclonal antibodies against surface markers on lymphocytes can be especially useful in distinguishing lymphoma cells, which are usually monoclonal B-cells, from reactive T lymphocytes. ITowever, because malignant lymphocytes can be mixed with reactive T cells, the presence of polyclonality does not exclude tumor. When the diagnosis of leptomeningeal lymphoma is difficult, polymerase chain reaction (PCR) techniques can be used to determine

Table 58G.4: Cerebrospinal fluid tumor markers in leptomeningeal metastases

Marker	*Tumor*
Relatively specific	
AFP	Tcratocarcinoma, yolk sac tumor, ECC, endodermal sinus tumor
CA-125	Ovarian cancer
CA-15-3	Breast cancer
CAI9-9	Adenocarcinoma, biliary disease
Creatine kinase BB	Small cell lung cancer
HCG /J-subunit (,8-HCG)	Choriocarcinoma, ECC, germ cell rumor
5-HIAA	Carcinoid
HPAP	Germinoma
IgM	Myeloma
Melanin	Melanoma
PSA	Prostate cancer
Tissue polypeptide antigen	Breast cancer
Nonspecific	
fii -microglobulin	Lymphoma, infection, other tumors
/(-glucuronidase	Nonspecific
CEA	Colon, ovarian, breast, bladder, lung
HMFG1 mAb	Nonspecific
l.DH isoenzymes	Carcinoma, non-specific
Tclomcrasc	Non-specific.
VEGF	Non-specific

AFP = alpha fetoprotein; CA = carbohydrate antigen; CEA = carcinoembryonic antigen; ECC = embryonal cell carcinoma; HCG = human chorionic gonadotropin; HIAA — hydroxyindoieacetic acid; HMFG — human milk fat globule; HPAP — human placental alkaline phosphatase; IgM = immunoglobulin M; LDH = lactate dehydrogenase; PSA = prostate specific antigen; VEGF = vascular endothelial growth factor,

whether the Ig gene rearrangement is identical in all the lymphocytes, suggesting a neoplastic process (Thomas ct al. 2000).

Neuroimaging

MR1 is the most sensitive neuroimaging test for detecting LM, Meningeal enhancement is present in half of patients with LM. Also observed arc small enhancing cortical nodules and communicating hydrocephalus from impaired CSF absorption. Rarely, focal LM may mimic a meningioma. Whenever possible, MR1 should be performed before lumbar puncture. Lumbar puncture occasionally results in intracranial hypotension and meningeal enhancement, which leads to an erroneous diagnosis of LM. Myelography shows thickening and nodularity of nerve roots in 25-33% of patients with LM, and may be helpful when MRI can not be done. Increasingly, the diagnosis of LM is established in patients with characteristic clinical and radiological findings, even if the CSF cytological examination result is negative (Freilich et al. 1995).

Other Tests

Cerebral angiography may show areas of narrowing resulting from spasm of pial vessels or infiltration of their walls by tumor, but is now rarely performed. Electroencephalography (EEG) is usually normal or shows nonspecific changes including focal or generalized slowing or sharp activity. Rarely, EEG shows triphasic waves or seizure activity. Electromyography (EMG) may show evidence of polyradiculopathy and prolonged F-wave latencies, but is rarely useful. When the diagnosis of LM is strongly suspected, but routine tests are all normal, a meningeal biopsy may be helpful.

Diagnosis

The diagnosis of LM is based on the combination of characteristic clinical, radiological, and CSF features, and ideally, the presence of a positive CSF cytological examination result. Other conditions causing subacute neurological deficits at multiple sites in the neuraxis may mimic LM (Table 58G.5). These include parenchymal and epidural tumor deposits and subacute and chronic meningitides such as syphilis, sarcoidosis, Lyme disease, and fungal and tuberculous meningitis. Routine imaging, CSF studies, and positive cytological examination result usually distinguishes other entities from LM. Specific serological tests arc also useful. These include Lyme antibody titers; serum angiotensin converting enzyme (sarcoidosis); fluorescent treponemal antibody (syphilis); cryptococcal antigen; fungal cultures; and PCR for herpes simplex, varicella zoster, and tuberculosis. A meningeal biopsy may be useful when the diagnosis remains in doubt.

Tabic 5SG.5: Differential diagnosis of LM

Neoplastic
Parenchymal metastases
Dural metastases
Castleman's disease
Infections
Bacterial/viral meningitis
Fungal infections, including eryptococcus
Lyme disease
Neu rocy stice rcosis
Tuberculosis
Granulomatous Disorders
Histiocytosis
Sarcoidosis
Wegener's granulomatosis
Inflammatory Disorders
Multiple sclerosis
Para ne o p 1 astie e n ccp h a 1 o myelitis
Relapsing polychondritis
Rheumatoid nodules
Vasculitis (including granulomatous angiitis)
Miscellaneous
Enhancing meningeal blood vessels
Post lumbar puncture changes (intracranial hypotension)

Treatment

Despite more than three decades of effort, the treatment options for LM remain limited. Reasons for the difficulty include (1) the need to treat the entire neuraxis because of widespread dissemination of tumor cells throughout the subarachnoid space; (2) the close proximity of the tumor cells to neural structures; (3) the need to limit the administered doses of radiation and chemotherapy because of potential neurotoxicity; (4) the blood-CSF barrier, which limits access of many systemically administered drugs into the CSF; and (5) the intrinsic resistance of many solid tumors.

The goal of therapy is to improve or stabilize the patient's neurological status and prolong survival. The specific treatment depends on the tumor type, the site of the leptomeningeal tumor, and the clinical condition of the patient. Without treatment, the median survival of patients with LM is 4 to 6 weeks. Death usually results from progressive neurological dysfunction. With treatment, the median survival is increased to 3-6 monrhs. The response rate is 50-60% for carcinomas, and more than 80% for **NHL** (Wen and Fine 1997). Although treatment often provides effective local control, LM usually occurs in the setting of systemic relapse, and most patients who survive beyond the first month (two thirds of the total) eventually die of their systemic disease. As systemic therapy improves, LM will become the sole site of relapse. LM will then become an increasingly important problem. The patients who benefit most from treatment are those with minimal neurological deficits, good performance status, slowly

Tabic 58G.6: Treatment of ieptomeningeal metastases

Radiation therapy to sites of symptomatic and bulky disease
Intrathecal chemotherapy
Methotrexate (10 mg twice weekly) + leucovorin
Thiotepa (10 mg twice weekly)
Cytarabine (50 mg twice weekly)
Cytarabine (DepoCyt) (50 mg every 2 weeks)
Systemic chemotherapy (e.g., high-dose methotrexate)
Optimal treatment of systemic disease

progressive systemic disease with little or no systemic metastases, and a diagnosis of NHL or breast cancer (Grossman and Moynihan 1991).

Because tumor cells are disseminated throughout the subarachnoid space, the entire neuraxis must be treated if therapy is to be effective. If only symptomatic sites are treated, early relapse is likely secondary to seeding from residual tumor cells in untreated areas of the leptomeninges. Currently, standard therapy for LM involves radiation to sites of symptomatic and bulky disease, intraventricular administration of chemotherapy via an Ommaya or Rickham reservoir, and optimal treatment of systemic disease (Table 58G.6).

Radiation Therapy

RT is limited to symptomatic areas and sites of bulky disease, where the penetration of intrathecal drugs is limited. Although RT is more effective than chemotherapy in treating tumor cells in the Virchow Robin's spaces and nerve root sleeves, the use of craniospinal radiation to the entire neuraxis is rare because of bone marrow suppression. This is of particular concern in patients with LM because many have systemic metastases that require treatment with chemotherapy. The dose of radiation is approximately 3000 cGy, administered over 2 weeks.

Chemotherapy

The administration of chemotherapy for LM is directly into the CSF, using an intraventricular cannula with a subcutaneous reservoir under the scalp (Ommaya or Rickham reservoirs) to bypass the blood-CSF barrier. Intraventricular administration of chemotherapy produces better CSF distribution than intrathecal (IT) therapy administered to the lumbar subarachnoid space. In addition, it is less uncomfortable and avoids epidural and subdural leakage of the drug. In many patients with extensive LM, obstruction of CSF flow in the subarachnoid space decreases the effectiveness of intrathecal chemotherapy, and increases the likelihood of toxicity. In these patients, ^{L11}Indium-DTPA CSF flow studies may be helpful in defining the CSF blocks (Mason et al. 1998). These blocks require treatment with RT.

Only a limited number of chemotherapeutic agents are available for IT administration (Wen and Fine 1997; Mason 2002; Kesan and Batchelor 2003). Methotrexate (MTX) is the most widely used drug. It is an antimetabolite and interferes with DNA synthesis by inhibiting dihydrofolate reductase. It is active against leukemia, lymphoma, breast cancer, and other solid tumors lo a much lesser extent. The typical treatment is 10-12 mg twice weekly for 5-8 treatments, or until the CSF clears. This is followed by weekly and then monthly maintenance therapy. The most effective duration of treatment is unclear, but standard recommendations suggest treatment for at least 3 to 6 months, and perhaps indefinitely. Therapeutic concentrations (>10" ^{A} molar) are attained in the CSF for 48 hours by administration of 12 mg of MTX. The MTX is gradually reabsorbed into the blood stream by bulk flow, and transport via the choroid plexus results in a low systemic concentration {peak systemic concentration of >10~ molar), which may cause myelosuppression and mucositis. To reduce these systemic side effects, leucovorin (10 mg orally twice daily) is often given for *3—4-* days after administration of MTX. Complications of IT MTX include aseptic meningitis, teukoencephalopathy, mucositis, myelosuppression, encephalopathy, and opportunistic infections (Kesari and Batchelor 2003). High-dose intravenous MTX may also be effective in some patients (Glantz et al. 1998).

Cytosinc arabinosidc (ara-C) is a synthetic pyrimidine nucleoside with activity against leukemias and lymphomas but not most solid tumors. The half-life of ara-C is very-short in the serum, but is significantly longer in the CSF because of low levels of cytidine deaminase. The standard IT dose of ara-C is 50 mg twice a week. Intrathecal ara-C has relatively little systemic toxicity because any drug reaching the systemic circulation is rapidly deaminated. Neurological complications associated with intrathecal ara-C include transverse myelopathy, aseptic meningitis, encephalopathy, headaches, and seizures (Kesari and Batchelor 2003).

A slow-release, liposomal formulation of cytarabine (DepoCyt) was recently approved for IT use in patients with lymphomatous meningitis (Glantz, Jaeckle et al. 1999; Giant/., LaFollette et al. 1999). An important advantage of this drug is that cytotoxic concentrations of cytarabine (>0.1 ng/mL) are maintained in the CSF for 2 weeks. In a randomized study of 28 patients with lymphomatous meningitis treated with either cytarabine (every 2 weeks) or ara-C (twice a week) for one month, the response rate in the cytarabine-treated patients was significantly higher compared with the ara-C treated patients (71% versus 15%) (Glantz, LaFollette et al. 1999). Patients treated with cytarabine also had increased time to neurological progression and improvement in KPS compared with those treated with ara-C. A second study compared the efficacy of IT MTX and cytarabine in the treatment of LM from solid tumors. Cytarabine was slightly more effective with respect to cytologieai response (26% verus 20%, p = .76) and median survival (105 days versus 78 days, p — .15).

Cytarabine treatment was significantly better in delaying the time to neurological progression (58 days versus 30 days, $p = 0.007$) (Glantz, Jaeckle et a). 1999; Kesari and Batchelor 2003). Arachnoiditis can occur in up to 60% of patients receiving cytarabine. Oral dexamcthasone (4 mg twice daily for 5 days) reduces the frequency of arachnoiditis significantly.

High-dose systemic ara-C (3 g/m^2 every 12 hours) penetrates well into the CNS and is sometimes used in patients with leukemia or NHL who have both systemic and CNS disease.

Thiotepa (N, N', N"-triethylenethiophosphoramide) is an alkylating agent with activity against a variety of tumors, including leukemia and breast cancer. The dosage is 10 mg administered twice weekly. The usefulness of thiotepa is potentially limited by its rapid clearance from the CSF. However, in one randomized trial of IT chemotherapy in patients with LM, thiotepa was as effective as MTX and less toxic (Grossman et al. 1993).

Unlike combination chemotherapy for many systemic cancers, combinations of IT agents have not been shown to be more effective than single agents and tend to be more toxic.

Although IT chemotherapy is generally considered standard treatment for LM in conjunction with radiotherapy, its usefulness has been challenged (Sicgal et al. 1994). Further studies will be required to define the precise role of IT chemotherapy.

Hormonal Therapy

Hormonal therapy may occasionally be of benefit in patients with LM caused by hormone sensitive tumors such as breast cancer and prostate cancer (Wen and Fine 1997).

Prognosis

Without treatment, patients with LM usually survive only 1-2 months, with occasional long-term survivals. With treatment, the median survival increases to 3-6 months (Posner 1995). Patients with NHL and breast cancer tend to respond better to treatment than those with other cancers, and the percentage of long-term survivors is increased. The 1-year survival rate for breast cancer is approximately 11%, whereas that for NHL is 6-23%. In general, fixed neurological deficits, such as cranial nerve palsies or paraplegia, do not improve significantly with therapy, but encephalopathies may improve dramatically.

Newer Therapies

More effective treatment programs for LM are under investigation. The strategies being evaluated include intrarhecal administration of drugs such as busulphan, gemcitabine, and mafosfamide; radiolabeled monoclonal antibodies; immunotoxins, interlcukin-2; and viral mediated gene therapy.

SKULL AND DURAL METASTASES

As with other nervous system metastases, the incidence of skull and dural metastases appears to increase with prolonged patient survival and improved neuroimaging (Posner 1995; Jansen and Sillevis Smitt 2002). Skull and dural metastases may he asymptomatic and detected incidentally on neuroimaging studies or produce symptoms by compression of adjacent neural structures (see Figure 58G.3). Treatment of these metastases is usually effective.

Skull Metastases

Skull metastases occur in 15-25% of all cancer patients, usually in the setting of bony metastases elsewhere in the body. At least half are asympromatic. Skull metastases usually arise from hematogenous spread via either the arterial circulation or Batson's plexus. The most common primary tumors that metastasize to the skull base and calvarium are breast, lung, and prostate, followed by renal, thyroid, and melanoma (Jansen and Sillevis Smitt 2002), Renal cell and thyroid carcinoma may produce solitary calvarial metastasis. Rarely, extracranial tumors may extend centrally along cranial nerve branches and enter the skull through foramina. Tumors with a predilection for perineural growth include squamous cell carcinoma of the nasopharynx, esthcsioneuroblastoma, lymphoma, nerve sheath tumors, and skin cancers.

Calvarial metastases are often asymptomatic. Occasionally they produce localized pain or a palpable mass. When metastases enlarge, they may cause focal neurological deficits or seizures. Rarely, calvarial metastases invade or compress cerebral venous sinuses, producing increased intracranial pressure and venous infarction.

Skull base metastases often present with characteristic clinical features (Greenberg et al. 1981) (Table 58G.7). The differential diagnosis includes leptomeningeal and parenchymal metastases, as well as benign conditions such as granulomatous or infectious diseases. Biopsy may be indicated if the diagnosis is not conclusive following clinical and radiological evaluation and CSF examination (to exclude leptomeningeal disease).

Calvarial metastases appear as irregular lucencies on skull radiographs. In 90% of patients, bony metastases are present elsewhere in the body. CT and JVlRI usually show lesions involving all three tables of the skull bone, and provide information regarding the extent of intracranial extension and relation to venous sinuses (Jansen and Sillevis Smitt 2002), The differential diagnosis of multiple skull defects includes normal structures such as venous

Table 58G.7: Classification of clinical syndromes caused by skull base metastasis

Site of skull base metastasis	*Symptoms and signs*
Orbital	Local pain, proptosis, sensory loss V[, diplopia, decreased vision (late)
Pa r ase 1 la r/ca ve rn o us sinus	Unilateral frontal headache, oculomotor palsies (III, IV, VI), sensory loss Vi
Middle cranial fossa	Facial numbness or pain (V23), sometimes abducens or facial nerve palsy (VI, VII)
Jugular foramen	Unilateral postauricular pain, hoarseness, dysphagia (IX, X), sternocleidomastoid or trapezius weakness (XI)
Occipital condyle	Unilateral occipital pain, stiff neck, unilateral tongue weakness (XII)

Source: From Greenberg, H, S., Deck M. D. F., Vikrara, B., Chu, F. C. H., et al. 1981, "Metastasis to the base of the skull: Clinical findings in 43 patients," *Neurology*, vol. 31, pp. 530-537.

lakes, pacchionian granulations, and parietal foramina. Pathological conditions include Langerhans' cell histiocytosis, hyperparathyroidism, osteomyelitis, and radiation necrosis. For single calvarial lesions, the differential diagnosis includes meningiomas (including primary intraosseous meningioma), hemangiomas, epidermoid cysrs, leptomenirigeal cysts (in children), Langerhans' cell histiocytosis, Paget's disease, postsurgical defect, and osteomyelitis (Jansen and Sillevis Smitt 2002). In patients not known to have cancer, comparison with prior imaging studies may he helpful.

Radiological diagnosis of skull base lesions tends to be more difficult. Contrast-enhanced MRI is the most useful diagnostic test, but CT scans with thin cuts through the skull base may help detect bony lesions. Occasionally, hone scans are useful.

Treatment of skull metastases depends largely on the presence of symptoms and the radiological findings. Asymptomatic metastases often require no specific therapy. Symptomatic lesions respond well to RT. CChemotherapy may be of benefit for chemosensitive tumors, and hormonal therapy may benefit subsets of breast and prostate cancers. Occasionally, surgery is necessary.

The prognosis of skull metastases depends on systemic tumor control as well as local factors, including invasion of venous sinus or dura, leptomeninges, and brain parenchyma (Jansen and Sillevis Smitt 2002). In general, better outcomes are associated with starting treatment less than 1 month after diagnosis.

Dural Metastases

Dural metastases occur in up to 20% of patients in autopsy studies (Posner 1995), but symptomatic lesions are much less frequent. The most common tumors giving rise to dural metastases arc NSCLC, prostate cancer, and breast cancer. Less commonly, melanoma, gastric, colon, SCLC, and renal cell carcinoma, pleural mesothelioma, carcinoid tumors, and lymphoma may be responsible (Rodas and Greenberg 1997), Metastases usually reach the dura by invasion from rumors in the adjacent skull or brain parenchyma, or by hematogenous spread.

Dural metastases cause symptoms by compressing or invading the underlying brain, by obstructing adjacent venous sinuses, ot by producing subdural fluid collections and hematomas (Rodas and Greenberg 1997). The subdural collections are often indistinguishable from subdural hematomas and hygromas from benign causes. The relation of the subdural collections to an underlying neoplasm may only be determined by finding malignant cells at surgery.

MRI usually establishes the diagnosis. However, small dural metastases arc often difficult to distinguish from meningiomas. This is especially important in patients with breast cancer who may have an increased incidence of meningiomas (Schoenberg et al. 1975).

Patients usually respond to treatment with RT, which may be either whole-brain radiation or focal irradiation. The indication for whole-brain radiation is the existence of concurrent intra parenchymal or leptomeningeal disease. Chemotherapy may he an effective alternative for some chemosensitive tumors such as lymphoma, SCLC, breast carcinoma, and germ cell tumors. Surgical resecrion is indicated for patients with a large symptomatic lesion, or in cases in which the differential diagnosis from meningioma is in doubt.

The prognosis for patients with dural metastases is slightly better than for parenchymal metastases (median survival of 24 weeks versus 18 weeks). The most important variable for prognosis of dural metastases is the extent of systemic disease (Jansen and Sillevis Smitt 2002).

PLEXUS METASTASES

Brachial Plexopathy

Invasion of the brachial plexus is by local spread of tumor from lung or breast carcinoma or axillary lymph nodes (Kori et al. 1981; Kori 1995; Briemberg and Amato 2003) (see Figure 58G.2A). Rarely, tumor may reach the brachial plexus by hematogenous or lymphatic spread. The lower trunk of the brachial plexus is usually involved. Most patients experience constant, severe pain radiating from the shoulder down the medial aspect of the arm into the fourth and fifth digits. Numbness and paresthesias may be associated. Examination shows weakness, atrophy, and sensory loss in the distribution of the lower trunk of the brachial plexus (C8-T1 nerve roots). Horner's syndrome is present in 50% of patients and reflects involvement of the

stellate ganglion. The main differential diagnosis is epidural and leptomeningeal disease affecting cervical nerve roots, and radiation plexopathy. Radiation plexopathy usually occurs 1 year or more (median 40 months) after RT with doses of 6000 cGy or more. Features suggesting radiation injury rather than tumor are the relative absence of pain, involvement of the upper trunk or entire brachial plexus, severe lymphoedema, slow progression or stabilization, absence of Horner's syndrome or associated epidural disease, and myokymic discharges (spontaneous rapid semi-rhythmic bursts of potentials} on EMC (Kori 1995). CT or MRI of the brachial plexus usually establishes the diagnosis. Occasionally, MRI of the cervical spine may be necessary to exclude epidural disease. When standard imaging studies and positron-emission tomography cannot establish the diagnosis, surgical exploration and biopsy of the brachial plexus may be necessary. The treatment for neoplastic brachial plexopathy is RT. Approximately half of patients experience improvement in pain but neither strength nor sensory symptoms improve.

Lumbosacral Plexopathy

Lumbosacral plexopathy usually results from direct extension of tumor or from metastases to local lymph nodes or bone. The most common tumors associated with lumbosacral plexopathy are colorectal cancer, lymphoma, cervical carcinoma, and sarcomas (Jaeckle et ah 1985). The initial features are pain, numbness, paresthesias, weakness, and edema of the leg. Impotence and incontinence may occur. Examination findings may include weakness, sensory loss, reflex asymmetry, leg edema, and rarely, a pelvic mass on rectal examination. Bilateral lumbosacral plexopathics occur in 25% of patients; the usual cause is metastatic breast cancer. Occasionally, patients develop isolated obturator neuropathy. MRI or CT scan of the lumbosacral spine and pelvis establish the diagnosis. A significant minority of patients have spread of tumor to the epidural space. Radiation injury to the lumbosacral plexus is less common than radiation injury to the brachial plexus, but is in the differential diagnosis, Radiation injuries tend to be less painful than tumor infiltration and LMG may show myokymia. Treatment of neoplastic lumbosacral plexopathy involves RT and, occasionally, surgery,

PERIPHERAL NERVE METASTASES

Very rarely, mononeuropathies, mononeuropathy multiplex, and even a symmetric polyneuropathy may result from direct nerve infiltration by tumor (BHemberg and Amato 2003). Lymphomas and leukemias, particularly chronic lymphocytic leukemia, have been associated with peripheral neuropathy resulting from malignant infiltration of nerve (Amato and Dumitru 2002).

CONCLUSION

Because patients with systemic malignancy survive longer, the incidence of nervous system metastases increases. These metastases must be distinguished from nonmetastatic complications of cancer, including metabolic disturbances, infections, complications of therapy, cerebrovascular disorders, and paraneoplastic syndromes. The widespread availability of MRI has greatly facilitated the diagnosis of brain and epidural metastases as well as spinal cord compression. For other nervous system metastases such as LM, the diagnosis remains difficult and requires careful clinical evaluation.

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Chapter 58
Cancer and the Nervous System

H. PARANEOPLASTIC DISORDERS OF THE NERVOUS SYSTEM

Myrna R. Rosenfeld and Josep Dalmau

Paraneoplastic neurological syndromes (PNSs) are a heterogeneous group of disorders caused by cancers not located in the central nervous system. The mechanism of PNS is other than metastases or any of the following complications of cancer: metabolic and nutritional deficits, infections, coagulopathy, and side effects of cancer treatment. PNSs may affect any part of the nervous system (Table 58H.1), and their frequency varies according to the type of syndrome and cancer.

In general, PNSs are difficult to diagnose and treat. The symptoms of PNS may occut before the presence of systemic cancer is known, making diagnosis all the more difficult. The onset of neurological features is often acme or subacute, followed by stabilization within a few weeks. This time course suggests that by the time most PNSs are diagnosed, the pathological damage is already irreversible. For all PNSs, treatment of the tumor is the most effective step in controlling, or at least stabilizing, the neurological disorder (Graus et al. 200 1 j.

PATHOGENESIS

Evidence is increasing that most PNSs are immune mediated (Dalmau et al. 1999). The current concept is that the expression of neuronal proteins by a tumor provokes an immune response against both the tumor and the nervous system. This hypothesis is supported by the frequent detection in the serum and cerebrospinal fluid (CSF) of antibodies reacting with antigens expressed by the tumor and nervous system (onconeuronal antigens) (Table 58H.2) (Dalmau et al. 1999). Most antibodies associated with PNSs of the central nervous system are considered highly specific for the presence of cancer. In contrast, antibodies associated with some PNSs of the neuromuscular junction and peripheral nerves (e.g., Lambert-Eaton myasthenic syndrome [LEMS], myasthenia gravis [MG], neuromyotonia) may occur with or without cancer.

The role of antineuronal antibodies in the pathogenesis of PNS remains uncertain for most syndromes. Antibodies with a ditect pathogenic effect are found in some disorders of the peripheral nerve or neuromuscular junction, and can also occur in the nonparancoplastic setting. These include antibodies to P/Q-type voltage-gated calcium channels (VGCCs) in patients with LEMS, antibodies to the acetylcholine teceptor in patients with MG, and antibodies to voltage-gated potassium channels (VGKCs) in patients with ncutomyotonia.

Data suggest that cytotoxic T-cell tesponses are important in the pathogenesis of PNS, especially of the ecnttal nervous system. These data include the presence of prominent infiltrates of CDS ' and $CD4^+$ T cells in the nervous system, and in vitro studies showing the cytotoxic effect of these lymphocytes on cells exptessing the onconeuronal antigens (Albert et al. 1998; Bcnyahia et al.

Tabic 58H.1: Paraneoplastic neurological syndromes

Syndromes affecting the central nervous system
Cerebellar degeneration
Ence pha 1 om yeli tis *
Opsoclonus-myoclonus
Stiff-man syndrome
Necrotizing myelopathy
Motor neuron syndromes[1,] (ALS; subacute motor ncuronopathy; upper motor neuron dysfunction)

Syndromes affecting the visual system
Retinopathy
Optic neuritis
Uveitis (usually in association with encephalomyelitis)

Syndromes affecting the peripheral nervous system
Sensory neuronopathy
Vasculitis of the nerve and muscle
Subacute or chronic sensorimotor peripheral neuropathy
Sensorimotor neuropathies associated with plasma cell dyscrasias and li-cdl lymphoma
Autonomic neuropathy[1,]
Brachial neuritis
Acute polyradiculoneuropathy (Guillain-Barre syndrome)
Peripheral nerve hyper excitability

Syndromes affecting the neuromuscular junction and muscle
Lambert-Eaton myasthenic syndrome
Myasthenia gravis
Derma tomyositis
Acute necrotizing myopathy
Carcinoid myopathy*
Cachectic myopathy[1]

"Includes focal cortical, limbic, and brainstem encephalitis, cerebellar dysfunction, and myelitis.
'Not discussed further in this chapter.
ALS — amyotrophic lateral sclerosis.

1999; Tanaka et al. 1999). Because the T-cell and humoral immune responses appear to be directed against the same antigens, it is likely that PNSs result from the cooperation of both arms of the immune response. The immune response has an antitumor effect in some PNSs (Gratis et al. 1997a).

GENERAL DIAGNOSTIC APPROACH

The specificity of paraneoplastic antineuronal antibodies for PNSs or some types of cancer makes them useful diagnostic tools (see Table 58H.2). In approximately 60% of patients with PNS, the neurological symptoms precede the tumor diagnosis. Therefore in the right clinical context the detection of a paraneoplastic antibody in the serum or CSF helps to diagnose the PNS and focus the search for the neoplasm.

Most paraneoplastic antineuronal antibodies can also be detected, usually at low titers, in the serum of a variable proportion of patients with cancer but without PMS. This should be considered when a paraneoplastic antineuronal antibody is identified in the serum or CSF of a patient suspected to have PNS. Other causes for the neurological dysfunction should be considered if the detected antibody is not usually associated with the neurological syndrome. Similarly, if the detected cancer is not the histological type typically found in association with the antibody (e.g., anti-Yo with lung cancer rather than breast or ovarian cancer), a second neoplasm should be suspected (Miyamoto et al. 2002). A search for another neoplasm is required if die tumor cells do not express the target antigen of the paraneoplastic antibody (Graus et al. 2001). Clinical experience

Table 58H.2: Paraneoplastic antineuronal antibodies, associated syndromes, and cancers

Antibody	*Syndroms*	*Associated cancers*
Anti-Hu	Focal encephalitis, PEM, PCD, PSN, autonomic dysfunction	SCLC, other
Anti-Yo	PCD	Gynecological, breast
Anti-Ri	PCD, opsoc 1 onus - my oclo n us	Breast, gynecological, SCLC
Anti-Tr	PCD	Hodgkin's lymphoma
Anti-CV2/CRMP5	PEM, PCD, peripheral neuropathy	SCLC, other
Anti-Ma proteins*	Limbic, brainstem encephalitis, PCD	Germ cell tumors of testis, other solid tumors
Antiamphiphysin	Stiff-man syndrome, PEM	Breast
Anti-VGCCf	LEMS	SCLC
Anti-AChRt	MG	Thymoma
Anti-VGKCt	PNH	Thymoma, others
Anti recover! m	Retinopathy	SCLC
Antibipolar cells of the retina	Retinopathy	Melanoma

[5]Patients with antibodies to Ma2 arc usually men with testicular cancer. Patients with additional antibodies to other Ma proteins are men or women with a variety of solid tumors.
These antibodies can occur with or without a cancer association,
tOther antibodies reported in a few or isolated cases include antibodies to tubby-like protein and the photorcceptor-spccific nuclear receptor.
AChR. = acetylcholine receptor; LEMS = Lambert-Eaton myasthenic syndrome; MG — myasthenia gravis; PCD = paraneoplastic cerebellar degeneration; PEM = paraneoplastic encephalomyelitis; PNH = peripheral nerve hyperexcit ability; PSN = paraneoplastic sensory neuronopathy; SCLC = small cell lung cancer; VGCC = voltage-gated calcium channels; VGKC = voltage-gated potassium channels,

suggests that finding high titers of paraneoplastic antibodies in the CSF is confirmatory evidence of PNS of the central nervous system.

The diagnosis of PNS is relatively straightforward for patients who develop symptoms of a well-defined syndrome that is typically associated with cancer. Patient age is important because symptoms that often associate with paraneoplastic mechanisms in adults (e.g., subacute cerebellar dysfunction) are less typical of paraneoplasia in children. Conversely, the development of opsoclonus in children is often paraneoplastic, but in adults, is usually due to other causes. In these settings, the detection of an antibody-known to be associated with PNS or cancer is practically-confirmatory of paraneoplasia. If a cancer is not discovered, rhe presence of an occult neoplasm is assumed unless proven otherwise. Body positron emission tomography scans may detect tumors that escape detection by other Standard imaging methods (Antoine et al. 2000; Recs et a). 2001). Although almost any neoplasm can cause PNS, the tumors most commonly involved are small cell lung cancer (SCLC), cancers of rhe breast, ovary, thymoma, neuroblastoma, and plasma cell tumors. The development of PNS frequently heralds tumor recurrence in patients with a history of cancer or those who have recently gone into tumor remission.

The diagnosis of PNS is more difficult in patients who develop less characteristic symptoms (e.g., brainstem dysfunction, myelopathy), especially if no antibodies are found in the serum or CSF. Most PNSs have an acute or subacute onset compared with noninflammatory neurodegenerative disorders that arc chronically progressive. If the patient is known to have cancer, the possibility of metastases and nonmetastatic neurological complications of cancer (side effects of tteatment, metabolic encephalopathy, infection, or cerebrovascular disorders resulting from coagulopathy) should be considered before the diagnosis of PNSs. Neuroimaging, in particular magnetic resonance imaging (MRI), can help to exclude some of these complications, although the MRI may be abnormal in some PNSs (best seen on T2 and FLAIR sequences) (Gultekin et al. 2000; Rosenfeld et al. 2001). The CSF profile in patients with PNS of the central nervous system often suggests an inflammatory process: pleocytosis, increased protein concentration, intrathecal synthesis of immunoglobulin (Ig)G, and oligoclonal bands. If paraneoplasia remains a consideration, every attempt should be made to find the associated neoplasm.

SPECIFIC PNSs AND THEIR TREATMENT

Paraneoplastic Cerebellar Degeneration

Clinical Findings

Paraneoplastic cerebellar degeneration (PCD) is characterized by the rapid development of severe pancerebeliar dysfunction. Clinical features include truncal and appendicular ataxia, dysarthria, and downbeat nystagmus. In adults, the subacute onset of PCD differentiates it from chronic degenerative diseases of the cerebellum. A subset of patients with SCLC develop PCD associated with LEMS, often before the tumor is diagnosed (Mason et al. 1997). LEMS may be overlooked unless it occurs prior to the onset of PCD.

Tumor Association

SCLC, cancer of the breast and ovary, and Hodgkin's disease are the most commonly associated tumors.

Immune Responses

Anti-Yo is the most frequent and well-characterized antibody associated with PCD. The antibody is usually associated with breast or gynecologic tumors (Peterson et al. 1992). Women with neither breast nor gynecological tumors are anti-Yo negative. Anti-Yo antibodies have been identified in a few male patients with PCD and cancer of the salivary gland, lung, and esophagus. Some patients with predominant truncal ataxia and ocular movement abnormalities may harbor an antibody called anti-Ri. In such cases, the tumor is usually a breast carcinoma or, less frequently, gynecological cancer, bladder cancer, or SCLC (Luque et al. 1991), These patients may also develop dementia, mixed peripheral neuropathy, axial rigidity, and myoclonus. PCD may occur as part of paraneoplastic encephalomyelitis (PFM) associated with anti-Hu antibodies. Patients with PCD associated with Hodgkin's disease may develop anti-Tr antibodies (Gratis et al. 1997b). The neurological disorder may develop before or after the diagnosis of the lymphoma, sometimes heralding tumor recurrence.

Treatment

Several single case reports describe patients with PCD who improved after trearment of the tumor, plasma exchange, intravenous immunoglobulin (IVIg), or immunosuppression with cyclophosphamide or steroids (Blaes et al. 1999; David et al. 1996). However, most patients with PCD do not improve with any of these treatments.

Paraneoplastic Encephalomyelitis (Including Limbic Encephalitis, Focal Cortical Encephalitis, Brainstem Encephalitis, Cerebellar Dysfunction, and Myelitis)

Symptoms

Patients with paraneoplastic encephalomyelitis (PFM) may develop clinical features of dysfunction at several different

levels of the neuraxis (Gratis et al. 2001). Many develop a sensory ncuronopathy (see paraneoplastic sensory neuronopathy [PSN]). Approximately 20% have symptoms of limbic encephalopathy. These include confusion, depression, agitation, anxiety, memory deficits, dementia, and partial complex seizures. Symptoms of cerebellar dysfunction, in particular gait ataxia, predominate in approximately 15% of patients. Most develop a pancerebellar syndrome and involvement of other areas of the nervous system. Brainstem encephalopathy characterized by oscillopsia, diplopia, dysarthria, dysphagia, gaze abnormalities, subacute hearing loss, and facial numbness develops in one third of patients. Lower motor neuron involvement secondary to myelitis occurs in approximately 20%; the presence of symptoms affecting other areas of the neuraxis helps to rule out pure motor neuron disorders. Approximately one fourth of patients with PEM develop autonomic nervous system dysfunction; symptoms include postural hypotension, gastroparesis and intestinal dysmotility, sweating abnormalities, neurogenic bladder, and impotence. Respiratory or autonomic failures are frequent causes of death.

Tumor Association

PEM, with or without PSN, can be associated with almost any tumor, but in the majority of patients the underlying tumor is lung carcinoma, particularly SCLC (Gratis et al. 2001).

Immune Responses

Patients with PEM/PSN and SCLC often have anti-Hu, and a much lower frequency of anti-CV2/CRMP5 antibodies, or both (Graus et al. 2001). In these patients, neurological symptoms usually precede the cancer diagnosis. Anti-CV2/CRMP5 antibodies are also associated with thymoma and other cancers. Patients younger than 45 years of age with symptoms of limbic, hypothalamic, and brainstem dysfunction with antibodies to Ma proteins usually have an underlying germ cell tumor of the testis. These antibodies are also encountered in older patients with similar neurological symptoms and other cancers (Gultekin etal. 2001).

Treatment

In genetal, PEM is poorly responsive to any type of treatment. Symptom stabilization or improvement may occur with prompt treatment of the tumor (Graus et al. *1999).* Limbic encephalitis is the most likely symptom to improve with tumor treatment and immunomodulation with steroids and IVIg (Gultekin et al. 2001). The therapeutic roles of plasma exchange or immunosuppression with cyclophosphamide and steroids are uncertain.

Paraneoplastic Opsoclonus-Myoclonus

Symptoms

Opsoclonus-myoclonus consists of spontaneous, arrhythmic, large-amplitude conjugate saccades occurring in all directions of gaze that are associated with myoclonus of the head, trunk, or extremities. In children, paraneoplastic opsoclonus-myoclonus usually has a subacute onset with frequent fluctuations and is accompanied by ataxia, hypotonia, and irritability (Russo et al. 1997). Although it may resolve spontaneously, most children are left with behavioral abnormalities and psychomotor retardation. In adults, symptoms range from opsoclonus with mild truncal ataxia to a more severe syndrome characterized by opsoclonus, myoclonus, ataxia, and encephalopathy that can lead to stupor and death. Spontaneous remissions rarely occur.

Tumor Association

In children, opsoclonus-myoclonus is usually a manifestation of neuroblastoma, although similar neurological symptoms may be associated with viral infections. The neurological symptoms precede the tumor diagnosis in 50% of patients. Children with neuroblastoma and opsoclonus have a better tumor prognosis than those without paraneoplastic symptoms. In adults several underlying tumors have been reported, but the most common is SCLC.

immune Responses

Some adult patients, in particular those with SCLC and 5—10% of children with neuroblastoma, have anti-Hu antibodies in their sera. Patients with breast and gynecological cancers may harbor anti-Ri antibodies {Luque et al, 1991). Antibodies to Ma proteins have been reported in a few patients with lung cancer (Rosenfeld et al. 2001). However, many adults and children with neuroblastoma do not have paraneoplastic antibodies.

Treatment

Neuroblastoma induced opsoclonus-myoclonus often responds to treatment of the tumor (chemotherapy), steroids, adrenocorticotrophic hormone, IVIg, or plasma exchange (Veneselli et al. 1998); however, developmental and neurological sequelae are common (Russo et al. 1997). Paraneoplastic opsoclonus-myoclonus in the adult may partially respond to immunosuppression and IVIg, Patients whose tumors are treated promptly have a better neurological outcome than those whose tumors are not treated (Bataller et al. 2001). In the latter group, the disorder often progresses to severe encephalopathy and death. Neurological improvement has been reported with

several treatments, which include depletion of serum IgG using protein-A columns, clonazepam, piracetam, valproic acid, and thiamine (Batchclor et ai, 1998).

Stiff-Man Syndrome

Symptoms

Stiff-man syndrome is characterized by fluctuating rigidity of the axial musculature with superimposed spasms. Muscle stiffness primarily affects the lower trunk and legs, but it can extend to the arms, shoulders, and neck. Muscle spasms are usually precipitated by emotional upset and auditory or somesthetic stimuli. Electrophysiological studies show continuous activity of motor units in the stiffened muscles " that improve after treatment with diazepam. The rigidity disappears during sleep and after local or general anesthesia. Muscle spasms and rigidity may-occur as a fragment of PEM.

Tumor Association

The paraneoplastic form of stiff-man syndrome is usually associated with breast and lung cancers and Hodgkin's disease (Folli et al. 1993).

immune Responses

The main autoantigen of the paraneoplastic form of the disorder is amphiphysin. However, in approximately 80% of patients with stiff-man syndrome, the disorder develops as a nonparaneoplastic phenomenon in association with diabetes and polyendocrinopathy and, often, antibodies to glutamic-acid decarboxylase (GAD) (Brown and Marsden 1999).

Treatment

Treatment of the tumor and the use of steroids may improve paraneoplastic stiff-man syndrome. IVIg is useful in patients with nonparaneoplastic stiff-man syndrome (Dalakas et al. 2001). Because GAD and amphiphysin are part of gamma aminoburyric acid/glycine inhibitory synapses and both are located at the presynaptic level, it is reasonable to suspect that IVIg may also improve symptoms in patients with autoimmunity to amphiphysin.

Paraneoplastic Necrotizing Myelopathy

Symptoms

Paraneoplastic necrotizing myelopathy is rare disorder that develops acutely or subacutely, first affecting the thoracic portion of the spinal cord and then progressively ascending or descending the spinal cord to involve the brainstem. Some patients present with back pain or pain radiating toward the legs, whereas others have no pain. Additional symptoms include sphincter dysfunction, segmental sensory deficits, and flaccid or spastic paraplegia that evolve to tetraplegia, and ultimately respiratory failure and death. The CSF shows elevated protein concentrations and, rarely, a mild pleocytosis. MRI studies may show enlargement of the spinal cord, T2-weighted abnormalities and, sometimes, contrast enhancement. Because paraneoplastic necrotizing myelopathy is extremely rare, other cancer-associated neurological complications should first be considered in the differential diagnosis. Leptomeningeal, epidural, or intramedullary metastases are distinguishable by the more consistent presence of pain, characteristic neuro-imaging findings, and positive CSh' cytological examination in cases of leptomeningeal metastases. A history of spinal or mantle irradiation should raise the suspicion of postradiation myelopathy. In patients with lymphoma and leukemia, a syndrome identical to paraneoplastic necrotizing myelopathy may be caused by viral infections, particularly the herpes group, as well as by toxic effects of intrathecal chemotherapy, and more rarely by septic infarcts.

Tumor Association

The syndrome has been reported in association with several carcinomas and lymphoma.

immune Responses

No antibodies or other biological markers are associated with paraneoplastic necrotizing myelopathy. In most instances, a definitive diagnosis cannot be established without postmortem study.

Treatment

Effective treatment is not available and supportive care should be offered.

Paraneoplastic Sensory Ncuronopathy

Symptoms

PSN is characterized by progressive sensory loss that may involve limbs, trunk, and face, and sometimes sensorineural hearing loss. Painful dysesthesias are common. At onset, symptoms are usually asymmetrical and can be confused with radiculopathy or polyneuropathy. All modalities of sensation are eventually affected, and, with progression, the sensory deficits result in ataxia, gait difficulty, and pscudoathetoid movements. PSN may develop alone or more commonly in association with PEM (Graus et al,

2001; Lucchinetti ct al. 1998). Neurological dysfunction precedes the cancer diagnosis in two thirds of patients. Typically, nerve conduction studies show small-amplitude or absent sensory nerve action potentials, although motor nerve and F-wave studies are usually normal. These findings arc consistent with the pathological involvement of the dorsal root ganglia, hut some patients also have electrophysiological evidence of axonal and demyelinating neuropathy (Camdessanehe et al. 2002). For patients with no known cancer, PSN should be suspected when sensory symptoms develop subacutely and asymmetrically, and involve the trunk and cranial nerves, particularly if the patient is a smoker. The CSF often shows an increased protein level with plcocytosis, oligoclonal bands, and intrathecal synthesis of IgG.

Tumor Association

Approximately 70% of patients with PSN have cancer of the lung, usually SCLC, but virtually any type of neoplasm may be found.

immune Responses

The anti-Hu antibody is almost always detected in the serum of patients with PSN and SCLC, but is rarely present in PSN associated with other tumors (Molinuevo et al. 1998). A few patients with PSN have been reported with antibodies to amphiphysin and CV2/CRMP5 (Antoine et al. 2001; Saw et al. 1999).

Treatment

A recent study of patients with SCLC and anti-Hu-associatcd PSN and PEM indicated that neurological symptoms in patients whose tumors completely responded to therapy were more likely to stabilize or improve as compared with those with untreated tumors or tumors that did not respond to therapy (Graus et al. 2001). In some patients, prompt treatment with steroids may partially improve sensory deficits (Oh ct al. 1997a).

Vasculitis of the Nerve and Muscle

Symptoms

Vasculitis of the nerve and muscle usually occurs in older men. A painful symmetric or asymmetric, subacute, sensorimotor polyneuropathy, or, less frequently, mono neuropathy multiplex develops (Oh 1997). Electrophysiological findings are compatible with axonal degeneration involving motor and sensory nerves. The erythrocyte sedimentation rate and the CSF protein concentration are elevated. Nerve and muscle histology shows intramural and perivascular inflammatory infiltrates composed of $CD8^+$ T cells.

Tumor Association

SCLC and lymphoma are the tumors most commonly associated.

Immune Responses

Serological markers of paraneoplasia arc not usually associated, although anti-Hu antibodies are found m some patients with SCLC.

Treatment

The vasculitis often responds to treatment with steroids, cyclophosphamide, or both (Oh 1997).

Subacute and Chronic Peripheral Neuropathies

Symptoms

A mild peripheral neuropathy is common in patients with cancer, especially in the advanced stages of the disease. The cause is multifactorial, and includes metabolic and nutrirional deficits and toxicity from chemorherapy. Paraneoplastic sensorimotor neuroparhy may develop before or after the diagnosis of cancer. The onset may be subacute or acute, and the course is usually progressive. A relapsing and remitting course suggests chronic inflammatory demyelinating polyneuropathy (CIDP) (Antoine et al, 1999).

Tumor Association

The tumors most commonly associated arc lung and breast cancers.

Immune Responses

Serum antineuronal antibodies are not usually present, although some patients with lung cancer and rhymoma may harbor CV2/CRMP5 antibodies (Antoine et al. 2001).

Treatment

Patients with electrophysiological signs of demyclination may improve with steroids or IVIg {Antoine ct al. 1999).

Peripheral Neuropathy Associated with Plasma Cell Dyscrasias and B-Cell Lymphoma

Several malignancies of plasma cells and lymphocytes are associated with neuropathy. Included are multiple myeloma, osteosclerotic myeloma, Waldenstrom's macroglobulinemia and B-cell lymphoma (Ropper and Gorson 1998).

A sensorimotor neuropathy may develop in patients with multiple myeloma that is similar to those seen in other advanced cancers. If the myeloma is complicated by amyloidosis, the neuropathic symptoms often include autonomic dysfunction and lancinating and burning dysesthesias (Ropper and Gorson 1998). In both cases, treatment of the myeloma does not affect the neurological symptoms.

Osteosclerotic myeloma is often associated with a symmetrical, distal sensorimotor neuropathy with predominant motor symptoms that resemble CIDP. Some patients with osteosclerotic myeloma and neuropathy develop additional symptoms indicative of the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, *M* protein, and skin changes). A radiological survey demonstrates a solitary or reduced number of osteosclerotic lesions that tend to involve the axial skeleton (truncal and proximal long bones) and spare the skull. Treatment of the osteosclerotic lesions with excision, radiation therapy, or chemotherapy may improve the neurological and systemic symptoms,

Among patients with Waldenstrom's macroglobulinemia, less than 10% develop a symmetrical, dcmyelinating, sensorimotor neuropathy predominantly involving large sensory fibers, especially those for vibration sense. The IgM paraprotein sometimes reacts with myelin-associated glycoprotein (Dimopoulos et al. 2000). The neuropathy may respond to treatment directed at Waldenstrom's macroglobulinemia, plasma exchange, IVIg, rituximab, chlorambucil, cyclophosphamide, or fludarabine (Latov 2000; Levine and Pestronk 1999).

Castleman's disease, or angiofollicular lymph node hyperplasia, is actually a group of lymphoproliferative disorders with common clinical and histological features. These are often accompanied by a severe systemic inflammatory response that can be complicated by acquired systemic amyloidosis. Multicentric Castleman's disease is associated with several neuropathies that include a painful sensorimotor neuropathy, a chronic relapsing sensorimotor neuropathy, and a predominantly motor neuropathy (Vingerhoets et al. 1995). Additional symptoms that indicate POEMS syndrome are common. Specific serum antibodies arc absent and serum levels of interleukin-6 are often elevated. Neurological improvement is reported with cyclophosphamide and prednisolone or immunosuppression.

Brachial neuritis, and an acute paraneoplastic polyradiculoneuropathy identical to Guillain-Barre syndrome may be associated with Hodgkin's disease. Evidence does not exist for an association with malignancy. The course of the neurological syndrome is independent of the lymphoma, and symptoms can develop either during active disease or during remission. The differential diagnosis of brachial neuropathy should include the more common causes of brachial plexopathy in cancer patients. These include tumor infiltration, radiation injury, ischemic neuropathy, and traumatic injury of the plexus. Treatment for both disorders is the same as in the noncanccr patient: and includes plasma exchange or IVIg.

Peripheral Nerve Hyper excitability

Symptoms

The term *peripheral nerve hyper excitability (PNH)* has been adopted to include a disorder previously described with several names (neuromyotonia, undulating myokymia, Isaac's syndrome) and the cramps-fasciculation syndrome (Hart et al. 2002). These terms characterize the motor manifestations of spontaneous and continuous muscle fiber activity of peripheral nerve origin that can be triggered by voluntary muscle contraction. Other symptoms include motor weakness and hyperhidrosis. Electromyographic studies show fibrillation, fasciculation, and myokymic electromyography (EMG) discharges (doublet, triplet, or multiplet motor unit discharges) in most patients. Patients with the cramps-fasciculation syndrome do not have myokymic EMG discharges.

Tumor Association

PN[r]II can develop without associated cancer, but when paraneoplastic, thymoma and lung cancers are the usual tumors. Patients with thymoma may also have MG.

Immune Responses

Many patients have antibodies to VGKCs that contribute to the nerve hypcrexcitability by increasing the release of acetylcholine resulting in prolongation of the action potential (Shillito et al. 1995). Patients with PNH and thymoma, with or without MG, may also harbor antibodies to acetylcholine receptors (Hart et al. 2002).

Treatment

Symptomatic improvement is reported with diphenylhydantoin, carbamazepine, and plasma exchange.

Lambert-Eaton Myasthenic Syndrome

.*Symptoms*

Neurological symptoms usually develop before the tumor diagnosis and gradually progress over weeks or months. Less often, the onset of symptoms is acute. The common features are fatigue, muscle weakness, myalgia, and paresthesias (O'Neill et al. 1988), More than half of patients have cholinergic dysautonomias that include dry mouth, erectile dysfunction, and blurry vision (O'SLiilleabhain et al. 1998). Transitory cranial nerve

dysfunction may produce diplopia, ptosis, or dysphagia. Neurological examination shows proximal weakness, occurring in the legs more than the arms, and absent or depressed tendon reflexes, which may potentiate after a brief muscle contraction. Strength may improve after brief exercise, but continued exercise increases weakness. The diagnosis is based on electrophysiological studies. Nerve conduction studies show small amplitude compound muscle action potentials. At slow rates of repetitive nerve stimulation (2-5 Hz), a decremental response of greater than 10% is obtained. At fast rates of repetitive nerve stimulation (20 Hz or greater) or after maximal voluntary muscle contraction, facilitation occurs and an incremental response of at least 100% is seen.

LEMS can develop in association with other paraneoplastic syndromes such as 1'CO and PEM (Mason et al. 1997). Recurrence of LEMS after remission often heralds tumor recurrence.

Tumor Association

Approximately 60% of patients with LEMS have SCLC or rarely other tumors, such as lymphoma.

Immune Responses

Patients with LEMS have scrum antibodies against P/Q type VGCCs (Motomura et al. 1997). The antibodies interfere with the quantal release of acetylcholine at the presynaptic neuromuscular junction, resulting in failure of neuromuscular transmission. When I.EMS develops in association with PEM, patients often have anti-Hu antibodies.

Treatment

Most patients with cancer improve neurologically with combined treatment of their cancer and therapy for LEMS. The latter includes medication to increase the release of acetylcholine and immunomodulation (Sanders 1995). The use of 3,4-diaminopyridine results in moderate to marked neurological improvement in 80% of patients. If 3,4-diaminopyridine is not available, a combination of pyridostigmine and guanidine may be beneficial (Oh et al. I 997b). Plasma exchange and fVIg are useful for treating severe weakness; strength improves within days or weeks, but the benefits are transient (Bain et al. 1996), Long-term immunosuppression with prednisone or azathioprine should be considered if symptoms continue despite the use of 3,4-diflminopyridine.

Myasthenia Gravis

Symptoms

MG is a postsynaptic disorder of neuromuscular transmission. The main features are weakness and fatigability of skeletal muscles that improves with rest and worsens with activity. Ptosis and diplopia occur in most patients, and symptoms remain localized to the extraocular and eyelid muscles in 15% of patients. In the rest, weakness becomes generalized and can impair respiration to the extent that mechanical ventilation is necessary. Tendon reflexes and sensation are normal.

Tumor Association

A thymic epithelial tumor (thymoma or thymic carcinoma) is found in 10% of patients with MG, and one third of patients with thymoma develop MG, In a few instances, MG has been reported in association with other tumors, including thyroid gland tumors, SCLC, breasr cancer, and lymphoma.

Immune Responses

Antibodies to acetylcholine receptors are found in 80-90%i of patients with generalized MG, and in 70% of those with ocular MG. Other antibodies found in patients with MG are antistriated muscle antibodies and antititin antibodies. The detection of antititin antibodies was thought to predict tumor bur this is not the case (Somnier and Engel 2002).

Treatment

Trearmcnt is firsr directed at the underlying tumor. Additional strategics include symptomatic treatment (e.g., anticholinesterase drugs), immunomodulation (plasma exchange, IVIg), and immunosuppression (steroids, azathioprine, and others).

Derma tomy o sitis

Symptoms

Dermatomyositis and polymyositis are immune-mediated inflammatory diseases of muscle. An association exists between cancer and dermatomyositis in adults, but not with polymyositis (Leow and Goh 1997). The symptoms of paraneoplastic dermatomyositis arc the same as those in patients without cancer. Cutaneous changes include purplish discoloration of the eyelids (heliotrope rash) with edema and erythematous lesions over the knuckles. The presence of necrotic skin ulcerations and pruritus are suggested to indicate an underlying cancer (Gallais et al. 1996). The typical presentation is the subacute onset of proximal muscle weakness. Neck flexors, pharyngeal and respiratory muscles, arc commonly involved and may lead to aspiration and hypoventilation. Tendon reflexes and sensation are normal. Scrum creatine kinase concentrations are often elevated, although normal levels are occasionally found, even in patients with profound muscle weakness. EMG shows increased spontaneous activity (fibrillations,

positive sharp waves, and complex repetitive discharges), and short duration, low-amplitude polyphasic units on voluntary activation. Muscle histology shows inflammatory infiltrates ($CD4^+$ T cells predominate in dermatomyositis and $CD8^+$ T cells in polymyositis) and muscle necrosis; the presence of peri fascicular atrophy is characteristic of dermatomyositis.

Tumor Association

Several tumors are associated with dermatomyositis; most common are breast, lung, ovarian, and gastric malignancies. Less frequently associated arc cancer of the pancreas, thymoma, germ cell tumors, melanoma, nasopharyngeal cancer, and lymphoma.

Immune Responses

Abnormalities of both humoral- and cellular-mediated immunity are found in patients with dermatomyositis, although the target antigen is not known. An antibody directed against histidyl-tRNA synthetase (anti-Jo-1) is present in approximately 50% of patients with dermatomyositis associated with interstitial lung disease.

Treatment

In some patients, muscle and dermatologicat symptoms improve coincidently with treatment of the tumor. No studies are available on the efficacy of immunosuppressants in cancer-associated dermatomyositis, hut it seems reasonable to use strategies similar to those used in nonparaneoplastic dermatomyositis (steroids, azathioprine, IVIg) (Amato and Barohn 1997).

Acute Necrotizing Myopathy

Symptoms

This rare disorder is characterized by the acute onset of painful proximal muscle weakness with rapid generalization and involvement of respiratory and pharyngeal muscles. Serum creatine kinase concentrations are markedly elevated and electrophysiological studies demonstrate myopathic findings. Muscle histology shows severe necrotic changes with minimal or no inflammatory infiltrates. The causes of an acute necrotizing myopathy in patients with cancer include chemotherapy and cytokine-induced rhabdomyolysis (Andetiini et al. 1995).

Tumor Association

Acute necrotizing myopathy occurs in association with several solid tumors including carcinoma of the lung, bladder, breast, and gastrointestinal tract (Levin et al. 1998).

Immune Responses

A specific immune response has not been identified.

Treatment

Only in rare instances does treatment of the tumor result in neurological improvement (Levin et al. 1998).

Paraneoplastic Visual Syndromes

Symptoms

Paraneoplastic involvement of the visual system may affect the retina, and less frequently, the uvea and optic nerves (Jacobson 1998). Because paraneoplastic visual syndromes are rare, the more important considerations are metastatic infiltration of the optic nerves, toxic effects of chemotherapy or radiation therapy, and severe anemia. The symptoms of paraneoplastic retinopathy are photosensitivity, progressive loss of vision and color perception, central or ring scotomas, and night blindness. Attenuation of photopic and scotopic responses is recorded on the elcctroretmogram (ERG). Funduscopic examination shows nonspecific arteriolar narrowing. When one eye is affected, the other becomes symptomatic within days or weeks. Imaging studies and evaluation of the CSF are not revealing.

Melanoma-associated retinopathy (MAR) affects patients with metastatic cutaneous melanoma (Boeck et al, 1997). Patients typically present with the acute onset of night blindness and shimmering, flickering, or pulsating photopsias. Symptoms often progress to complete visual loss. The ERG typically demonstrates reduction in the b-wave amplitude.

Paraneoplastic optic neuritis is very uncommon, and, although it may develop in isolation, it is usually associated with PEM. The onset is subacute with painless, bilateral visual loss. Papilledema may be presenr.

Tumor Association

SCLC is the tumor most commonly associated with paraneoplastic retinopathy, other than melanoma with MAR.

Immune Responses

Serum antibodies that specifically react with retinal proteins are detected in some patients. The term *cancer-associated retinopathy* was originally used to describe patients with antibodies to recoverin, a retinal-specific calcium binding protein. Antibodies to other retinal antigens, such as tubby-like protein 1 and the photoreccptor-specific nuclear recepror, have since been reported. Patients with MAR typically have antibodies that react with the bipolar cells of

the retina, Anti-CV2/CRMP5 antibodies are reported in some patients with PEM and uveitis.

Treatment

Although the paraneoplastic retinopathies rarely improve with treatment, responses to steroids, plasma exchange, and IVIg are reported.

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Chapter 59
Infections of the Nervous System

Ashok Verma

Infectious diseases remain a major cause of death and disability for millions of people around the world, despite decades of dramatic progress in their treatment and prevention. Each infectious agent can cause a spectrum of illnesses, which challenges the physician's diagnostic skills. Infections must be considered in the differential diagnosis of syndromes affecting many organ systems, including the central nervous system (CNS).

The CNS may appear protected from perturbations in the environment by a blood-brain barrier—a system of tight junctions around capillaries—that resists the entry of pathogens, inflammatory cells, and macromolccules into the subarachnoid space and the hrain. However, the barrier fails to resist the ingenuity of the microbial world. Many pathogens have devised highly specialized, yet poorly understood, mechanisms to breach this barrier. For example, certain highly encapsulated bacteria and fungi possess surface components that allow them to traverse the tight capillary junctions to enter into the brain. The degree of specialization required for this mechanism is demonstrated by the predilection for only certain serotypes of organisms within a species to cause meningitis. Type 3 strains of group B streptococci account for the vast majority of cases of neonatal meningitis caused by this organism, even though other serotypes cause much of the invasive disease outside the CNS. This disparity appears to be due solely to the arrangement of the component sugars of the capsular polysaccharide; other serotypes of group B streptococcus rarely cause neonatal meningitis, even though their capsules possess the same four component sugars in different structural arrangements. Another example of a unique strategy employed by organisms such as herpes simplex virus and rabies virus is to travel by retrograde axonal transport within the peripheral nerves to reach the CNS.

Many infectious pathogens exhibit highly specific tropism to a particular site or even a specific cell type in the CNS. In paralytic poliomyelitis, for example, the poliovirus is tropic only to the anterior horn cells of the spinal cord and the homologous motor neurons in the brainstem. Why only a minority of poliovirus infections affects the CNS is a mystery; paralytic poliomyelitis occurs in far less than 1% of all human poliovirus infections.

Under circumstances ideal for a given microorganism, nearly any known human pathogen can cause CNS infection. Old and established CNS infectious agents may appear in new places in this age of rapid travel and changing environment. West Nile virus, for example, has found new terrains in the United States. The potential for infectious agents to emerge in novel and unexpected ways requires that physicians and public health officials be knowledgeable, vigilant, and open minded in their approach to the consideration of unexplained brain diseases. Additionally, entirely new infectious agents have emerged in recent decades, and new CNS infectious diseases continue to be identified. The role of infectious agents in the etiology of brain diseases once believed to be noninfectious is being increasingly recognized. For example, it is now widely accepted that Epstein-Barr virus is the cause of primary CNS lymphoma in HIV-infected individuals.

The advent of antimicrobial agents led some to believe that infectious diseases would soon be eliminated and might become history. Hundreds of chemotherapcutic agents have been developed and are effective not only against bacteria, but also against viruses, fungi, and parasites. Nevertheless, we now realize that, as we developed new antimicrobial agents, microbes developed the ability to elude our best weapons and counteract them with new survival strategies. Antibiotic resistance occurs at an alarming rate among all classes of human pathogens. Diseases once thought to have been nearly eradicated from the developed world—CNS tuberculosis, for example—have rebounded in recent years. These pathogens have an incredible adaptability and diversity. Retroviruses such as human immunodeficiency virus (HIV) continue to humble us despite an understanding of their pathogenesis at the most basic molecular level.

Optimal therapy for CNS infections requires a broad knowledge of medicine, a close liaison with the microbiology laboratory and personnel, and careful clinical judgment. Many CNS infections, including bacterial meningitis, viral encephalitis, and cerebral malaria, are life-threatening conditions and must he treated emergently, often before the specific causative organism is definitively identified. Initial antimicrobial agents must be chosen empirically and must be active against the range of potential infectious agents consistent with the clinical scenario.

Bacterial diseases are considered in Chapter 59A, viral infections in Chapter 59B, fungal infections in Chapter 59C, and parasitic infections in Chapter 59D. HIV-related diseases of the CNS are discussed in Chapters 59E and 59F, and the spongiform encephalopathies (prionoses or protein conformation disorders) are covered in Chapter 59G. Sarcoidosis, a granulomatous disease of uncertain etiology, is not considered an infectious disease and is discussed in Chapter *55,*

Chapter 59
Infections of the Nervous System

A. BACTERIAL INFECTIONS

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Bacterial infections reach the intracranial structures in one of the three ways: by hematogenous spread (bacteremia, emboli of bacteria, or infected thrombi), by extension from juxtacranial structures (ears, paranasal sinuses, osteomyclitic foci in the skull, congenital sinus tracts, or penetrating cranial injuries), or from an iatrogenic source (brain or spine surgery, ventriculoperitoneal shunt, and rarely following lumbar puncture). However, in many cases of bacterial central nervous system (CNS) infections, the pathway of infection cannot be determined, even at autopsy.

Increasingly, infection in urban hospitals is nosocomial (i.e., acquired in-hospital); in large hospitals of developed countries, nosocomial meningitis is now at least as frequent as the community-acquired variety. Medical care may increase the sick patient's risk of acquiring systemic and CNS infections in a number of ways (Scheld et al. 1997; Cohen and Powderly 2003): (1) through contact with pathogens during hospitalization, (2) through breached barriers (surgical incisions, intravenous devices, endotracheal tubes, or bladder catheters), (3) through introduction of foreign bodies such as a pacemaker that provides a nidus for bacterial colonization, (4) through alteration of the natural flora by antibiotics, and (5) through treatment with immunosuppressive drugs.

With hematogenous infection usually a single type of virulent organism gains entry to the cranial cavity. In adults the most common pathogenic organisms are *Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, Listeria monocytogenes,* and staphylococcus. More common in neonates are *Escherichia coli* and other gram-negative bacilli and group B streptococcus, and in the infant and child, *H. influenzae* infections arc more common. By contrast, when septic material embolizes into the brain from an infection elsewhere, more than one type of pathogen common to these sources may be transmitted. The mechanism of meningitis and brain abscess from infection of the parameningeal structures occurs in one of the two ways: (1) infected thrombi may form in diploic veins and spread along these vessels into the dura! sinuses (into which the diploic veins flow) and from there, in retrograde fashion, along the meningeal veins into the brain, and (2) an osteomyelitic focus may form, with erosion of the inner table of bone and invasion of dura, subdural space, pia-arachnoid, and even the brain. Infections that follow neurosurgical procedures or the placement of an intracranial appliance are usually staphylococcal; a small number arc due to mixed flora, including anaerobes, or enteric organisms. Bacterial pathogens invading intracranial structures through any of these pathways can cause pyogenic meningitis, brain abscess, septic thrombophlebitis, epidural abscess, or subdural empyema. The age and the immune status of the patient, the clinical setting (community-acquired, nosocomial, or postsurgical), and evidence of systemic and local cranial disease all must be taken in account in determining the most likely invading intracranial organism and, thereby, the most appropriate empiric emergency therapy, before the exact pathogen is identified.

BACTERIAL MENINGITIS

Definition

Bacterial meningitis may be defined as an inflammatory response to bacterial infection of the pia-archnoid and cerebrospinal fluid (CSF) of the subarachnoid space. Because the subarachnoid space is continuous over the brain, spinal cord, and optic nerves, infection in this space extends throughout the cerebrospinal axis unless there is obstruction of the subarachnoid space. Ventriculitis to some degree is nearly always present in patients with bacterial meningitis, but frank ventriculitis is uncommon in meningitis because of the bulk flow of *CSV* from the ventricles into the subarachnoid space.

Epidemiology

Acute bacterial meningitis occurs throughout the world. Although precise figures are unavailable, the incidence of bacterial meningitis is between 3 and 5 per 100,000 people per year in the United States (Quagliarello and Scheld 1997). More than 2000 deaths due to bacterial meningitis are reported annually in the United States. The disease is more common and the mortality higher in the developing countries. The relative frequency of isolation of various bacterial species as a cause of meningitis varies with age. Worldwide, three main pathogens, *H. influenzae, S. pneumoniae,* and *N. meningitidis,* account for 75-80% of cases after the neonatal period. *E. coli* and other enteric bacilli, /„ *monocytogenes,* and group B streptococci are major pathogens in neonatal meningitis.

Before the introduction of the conjugate vaccines, *H. influenzae* type b was the most common cause of bacterial meningitis in the United States, causing 45% of cases. *S. pneumoniae* accounted for 18% of cases, and N. *meningitidis* for 14%. Widespread vaccination against *H. influenzae* type b since 1987 has markedly reduced the frequency of *H. influenzae* meningitis in children. With the resulting 82% reduction in *H. influenzae* meningitis between 1985 and 1991 among children under age 5 in the United States, *S. pneumoniae* and N. *meningitidis* have become the principal causes of meningitis in children older than 1 month (Quagliarello and Scheld 1997). However, *H. influenzae* bacteremia and meningitis are increasing in frequency among adults who test positive for human immunodeficiency virus (HIV) (Munoz et al. 1997).

In Africa, the meningococcal A + C polysaccharide vaccine has modified the cyclic pattern of epidemic meningococcal meningitis (Soriano-Gabarro ct al. 2002). The sub-Saharan (Sahel) regions of Africa between 5 and 15 degrees north latitude, with annual rainfall of 30-110 cm, constitute the African meningitis belt. Regional prevalence of meningococcal meningitis in epidemic years is 400-1000 cases per 100,000 of population. Used for prophylaxis and outbreak control, the vaccine has broken the earlier 8- to 14-year patterns of recurrence of meningococcal meningitis, with the appearance of smaller epidemics, with shortened interepidemic intervals in some countries, in addition to outbreaks of meningitis in countries outside the belt (Varaine et al. 1997).

Simultaneously, there has been a worldwide increase in infection with strains of *S. pneumoniae* resistant to penicillin (Koedel et al. 2002), other ^-lactam antibiotics (second- and third-generation cephalosporins), and even chloramphenicol. Altered penicillin-binding proteins, and not jfj-lactamase production, mediate penicillin resistance. Early reports of drug resistance from Spain, Hungary, and South Africa were followed by similar reports from Japan and multiple centers in the United States, In 1994, isolates from 25% of patients with invasive pneumococcal infection in Atlanta, Georgia, hospitals were resistant to penicillin. Moreover, 9% of pneumococci from this study group also were resistant to cefotaxime and cephtriaxone, third-generation cephalosporins commonly used to treat meningitis, highlighting the growing problem of antibiotic resistance (Quagliarello and Scheld 1997).

Pathogenesis

S. pneumoniae, N. meningitidis, and *H. influenzae* are spread by droplets or exchange of saliva. Bacterial meningitis develops most commonly when pathogens colonizing the nasopharynx cause bacteremia and breech the blood-brain barrier. However, meningitis can also arise as a consequence of parameningeal infection, after traumatic or surgical disruption of the blood-brain barrier, or when a cerebral abscess ruptures into the ventricular or subarachnoid space.

The immediate effect of bacteria or other microorganism in the subarachnoid space is to cause an inflammatory reaction in the pia and arachnoid membranes as well as in the CSF. The inflammation results in hyperemia of the meningeal venules and capillaries and an increased permeability of these vessels, resulting in exudation of proteins and the migration of neutrophils into the pia and subarachnoid space (Scheid ct al, 2002). If untreated, subarachnoid exudate increases rapidly, particularly over the cerebral convexities and at the base of the brain. The exudate extends into the sheaths of cranial and spinal nerves and, for a short distance, into the perivascular spaces of the cortex. During the first few days, polymorphonuclear infiltrates are the predominant cells. Within a few days, lymphocytes and histiocytes increase gradually in relative and absolute number. Although fibroblasts begin to proliferate early, they are not conspicuous until later, when they take part in the organization of the exudates, resulting in loculation of pockets of exudate. During the process of resolution, the inflammatory cells disappear in almost the same order as they had appeared. The completeness of resolution depends to a large extent on the stage at which the infection is arrested.

Clinical Features

The classical clinical presentation of adults with bacterial meningitis comprises headache, fever, and neck stiffness, often with signs of cerebral dysfunction; these manifestations are found in more than 85% of patients. Nausea, vomiting, myalgia, and photophobia are also common. The neck stiffness may be subtle or marked, accompanied by Kcrnig's and/or Brudzinski's signs. These signs are elicited in over half of adults, but less in neonates and elderly; absence of clinical meningeal signs does not rule out the diagnosis of bacterial meningitis. Cerebral dysfunction is manifested by confusion, delirium, and a declining level of consciousness that ranges from lethargy to coma. Seizures occur in approximately 40% of cases. Cranial nerve palsies involving III, VI, and VII are found in 10-20% of cases and result from direct damage to the nerve by the surrounding infection or endarteritis of the vasa nervorum, Occasionally there are other focal neurological deficits such as hemiparesis and dysphasia due to endarteritis obliterans of the major arteries passing through the pools of infected material in the subarachnoid spaces. Recurrent seizure activity and focal neurological deficits are more common in the early stages of pneumococcal meningitis than in H. *influenzae* or meningococcal disease. Bilateral Vt cranial nerve palsy may indicate raised intracranial pressure (ICP), Papilledema is rare in acute bacterial meningitis and should suggest a different diagnosis, such as a brain abscess. Focal neurological deficits, seizure activity, and encephalopathy may arise from cortical and subcortical ischemia and/or infarction, from increased 1CP, or from development of subdural empyema.

Classical clinical features of bacterial meningitis are commonly absent in neonates, and the only clinical clue in them may be listlessness, high-pitched crying, refusal to feed, irritability, or other nonspecific manifestations. In the elderly patients, meningitis often has an insidious onset with lethargy or obtundation and with variable signs of meningeal irritation and no fever. In this subgroup of patients, an altered mental status should not be ascribed to other causes until bacterial meningitis has been excluded by examination of CSF. Many of the signs of bacterial meningitis, including altered mental status, may be present in patients following neurosurgery or head trauma, Meningitis is difficult to judge in such a situation, and the physician should have a low threshold for performing CSF examination if any unexpected clinical deterioration occurs.

Certain clinical features may suggest a specific etiologic diagnosis in patients with meningitis. Meningococcemia with or without meningitis presents with a prominent rash, principally in the extremities. Farly in the disease process, the rash is often erythematous and macular, but typically it evolves quickly into a petechial phase with further coalescence into a purpuric form. A similar rash may be seen in other forms of meningitis (echovirus type 9, *S. aureus, Acinetobacter* spp.), in Rocky Mountain spotted fever and other rickcttsioses, in S. *aureus* endocarditis, in rapid overwhelming sepsis, and in some noninfectious disorders such as vasculitis and thrombotic thrombocytopenic purpura. An additional suppurative focus of infection, typically pneumonia, otitis media, or sinusitis, is seen in about 30% of patients with pneumococcal or *H. influenzae* meningitis. Patients in whom meningitis develops in the wake of a CSF leak may have rhinorrhea or otorrhea, and the causative organism is often 5. *pneumoniae.*

The likelihood of infection with a specific pathogen relates, in large part, to age of the patient (Table 59A.1). Group B streptococci, *Listeria,* and gram-negative bacilli cause meningitis and invasive disease at the extremes of life, in neonates and the elderly. In the United States, *N. meningitidis* is now the predominant pathogen among children aged 2-18 years and *S. pneumoniae* among adults (Schuchat et al. 1997).

Table 59A.1: Empiric antibiotic therapy of bacterial meningitis

Age of patient	*Likely organism*	*Antimicrobial therapy**	*Adverse effects*
0-12 weeks	Group B Streptococcus *E. colt* *L. monocytogenes*	Third-generation cephalosporin + ampicillin (+ dexamcthasonc first 2 days in >4-week-old infant)	Vomiting, diarrhea, maculopapular rash, cosinophilia, biliary pseudolithiasis
3 months-50 years	*S. pneumoniae* *N. meningitidis* *H. influenzae*	Third-generation cephalosporin -I- vancomycin (± ampicillin)	Nausea, vomiting, diarrhea, maculopapular rash, eosinophilia, biliary pseudolithiasis, leukopenia, "red man"[1]' syndrome
>.50 years	*S. pneumoniae* *L. monocytogenes* Gram-negative bacilli	Third-generation cephalosporin + vancomycin -I- ampicillin	Nausea, vomiting, diarrhea, maculopapular rash, cosinophilia, biliary pseudolithiasis, transient increase in liver enzymes, leukopenia, "red man" syndrome
Base of skull fracture	Staphylococci Gram-negative bacilli 5. *pneumoniae*	Third-generation cephalosporin -I- vancomycin	Nausea, vomiting, diarrhea, eosinophilia, biliary pseudolithiasis, leukopenia, "red man" syndrome
Head trauma, neurosurgery, CSF shunt	Staphylococci Gram-negative bacilli *S. pneumoniae*	Vancomycin -I- ceftazidime	Nausea, vomiting, diarrhea, transient increase in liver enzymes, leukopenia, "red man" syndrome
Immunocompromised state	*L. monocytogenes* Gram-negative bacilli *S. pneumoniae* *H. influenzae*	Vancomycin -I- ampicillin -I- ceftazidime	Nausea, vomiring, diarrhea, maculopapular rash, eosinophilia, biliary pseudolithiasis, transient increase in liver enzymes, leukopenia, "red man" syndrome

'Tor all age groups from 3 months onward, an alternative treatment is meropenem -I- vancomycin. In case of severe penicillin allergy, consider vancomycin + chloramphenicol for meningococcus and trimethoprim/sulfamethoxazole for listeria. A higher failure rate has been reported wirh chloramphenicol or regimen without vancomycin in meningitis with drug-resistant pneumococcus.

"Red man" syndrome ranges from mild, flushing of upper body and erythema, reported in up to 70%, wiiich may rarely extend to prutitic rash, high fever, and exfoliative dermatitis. Caused by hypersensitivity reaction to vancomycin and related antibiotics.

Diagnosis

The patient with suspected bacterial meningitis requires blood cultures and urgent lumbar puncture (LP). Cranial computed tomography (CT) before LP is indicated when focal findings or clinical evidence of raised ICP are present (Hasbun et al. 2001; Kastenbauer et al. 2002). When the need for CT scanning significantly delays LP, blood cultures should be obtained and empiric antibiotic therapy administered appropriate to the clinical setting (Figure 59A.1}. LP is then performed as soon as possible following CT.

CSF examination reveals elevated pressure (200-500 mm H_20) and protein (100-500 mg/dL, normal 15-45 mg/dL), decreased glucose (<40% scrum glucose), and marked pleocytosis (100-10,000 white blood cells [WBC]/uL, normal <5) with 60% or greater polymorphonuclear leukocytes. The CSF Gram stain result is positive in at least 60% of cases, and CSF culture results are positive in approximately 75%. The likelihood of finding Gram stain or culture-positive CSF may decrease to 5-40% if antibiotics were administered before the LP. However, antibiotics given 1-2 hours before the spinal tap do not decrease diagnostic sensitivity of CSF culture done in conjunction with blood cultures and latex particle agglutination and counterimmunoelectrophoresis testing of CSF for bacterial antigens. Latex agglutination detects the antigens of *H. influenzae* type b, *S. pneumoniae, N. meningitidis, E. colt* Kl, and group B streptococci. Some test kits may not include tests for group B meningococci because its coat polysaccharide is weakly antigenic (Chadwick and Lever 2002). Because antibiotic therapy takes longer than 12 hours to sterilize CSF, culture results are often positive for the first several hours after antibiotics. Early in disease, 10-20% of patients have CSF cell counts of less than 1000 cells/pL. Otherwise, cell counts below 1000 cells/pL in a patient with a compatible clinical syndrome indicate partially treated meningitis, concurrent immunosuppression, or a nonbacterial cause. Rarely, cell counts of less than 100 cells/uL are seen in the apurulent bacterial meningitis syndrome of pneumococcal meningitis (Felgenhauer and Kober 1985), with overwhelming bacterial meningeal infection and absent CSF neutrophil response. Blood cultures reveal the causative organism in 50% of bacterial meningitis cases, consistent with the importance of bacteremia in pathogenesis. Neuroimaging studies may be normal or reveal complications of bacterial meningitis, such as cerebral edema, communicating or obstructive hydrocephalus, infarction, or venous sinus thrombosis.

The differential diagnosis includes viral, rickettsial, tubercular, fungal, or parasitic meningitis; subarachnoid

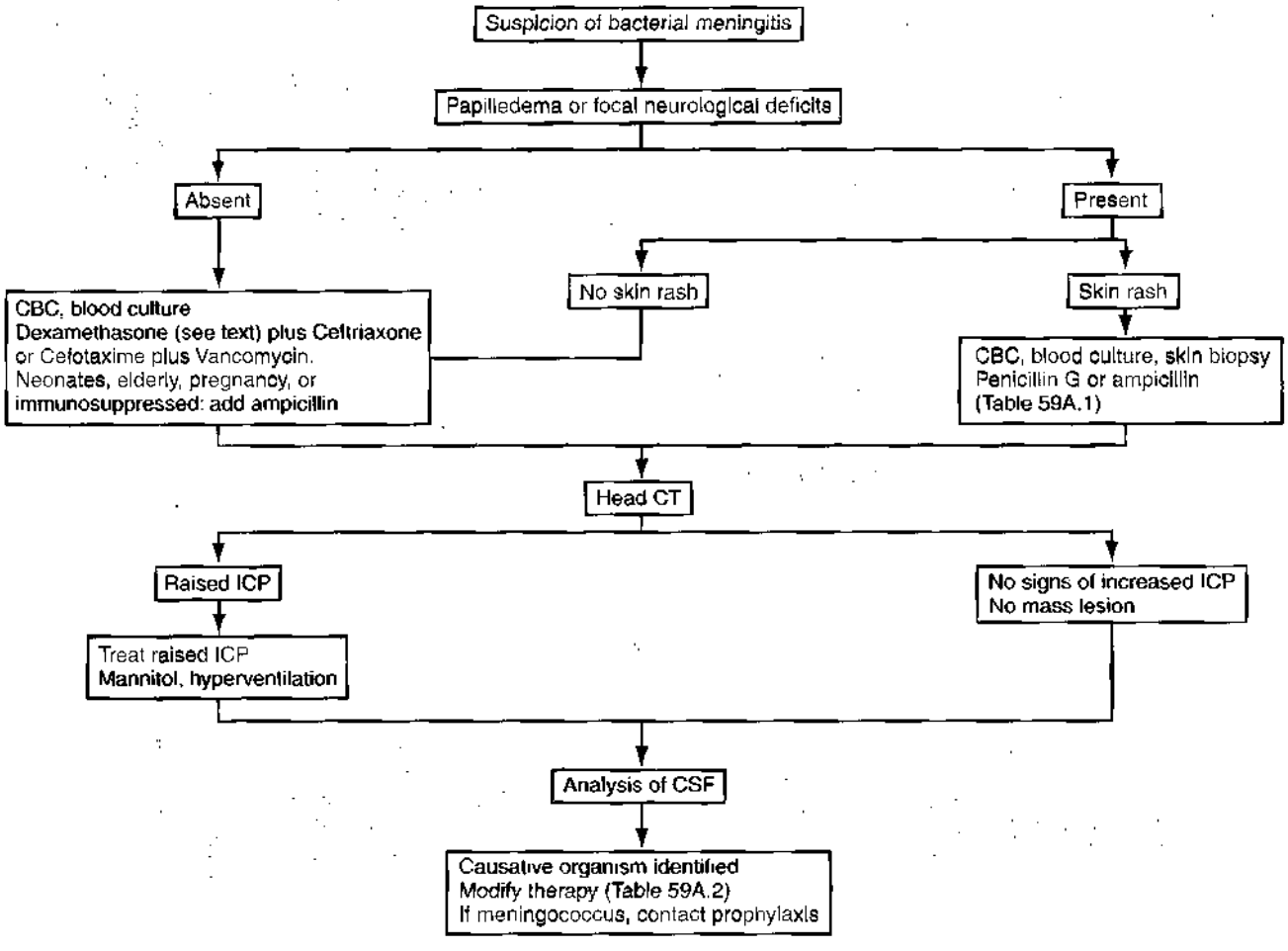


FIGURE 59A.1 Algorithm for the initial management of patients with acute bacterial meningitis. CBC = complete blood count; CSF : cerebrospinal filud; ICP = intracranial pressure.

hemorrhage; and carcinomatous meningitis. When meningeal signs are less prominent, cerebral or epidural abscess, subdural empyema, and viral encephalitis are additional diagnostic considerations.

Treatment

Antibiotic selection depends on the clinical setting in conjunction with allergies, local resistance patterns, and CSF results. When LP is delayed or the Gram stain result is nondiagnostic, empiric therapy is initiated (see Table 59A.1 and Figure 59A.1). Ampicillin or penicillin G and a third-generation cephalosporin ate typical first-line agents. Until recently, empiric coverage included ampicillin to cover most pneumococcus, meningococcus, and *Listeria* and a third-generation cephalosporin, such as cefotaxime, ceftriaxone, or ceftazidime, to cover gram-negative organisms and ampicillin-resistant *H. influenzae.* However, with the emergence of resistant pneumococcus, these recommendations are changing, and local resistance patterns influence empiric antibiotic coverage in adults with community-acquired meningitis. In patients with recent head trauma or neurosurgical procedures, vancomycin should he added to a third-generation cephalosporin to cover *S. aureus.* Ceftazidime, unlike other third-generation cephalosporins, covers pseudornonas and is reserved for situations in which meningitis with this organism is suspected or proven. Current antimicrobial recommendations for bacterial meningitis caused by specific bacterial pathogens are summarized in Table 59A.2.

When the CSF Gram stain result or culture reveals a particular bacterial pathogen, treatment is directed toward the specific pathogen. In meningitis caused by 5. *pneumoniae* of unknown antibiotic sensitivity, vancomycin combined with a third-gene rati on cephalosporin that achieves adequate CSF levels should be given, because of the emergence of penicillin-resistant pneumococcus. Therefore, bacterial meningitis with gram-positive cocci is treated with vancomycin plus a broad-spectrum cephalosporin. Gram-negative cocci are treated with penicillin G. Gram-positive bacilli are treated with ampicillin (or penicillin G) plus an aminoglycoside. Gram-negative bacilli are treated with a third-generation cephalosporin and an aminoglycoside.

Table 59A.2: Antibiotic treatment for bacterial meningitis*

Antibiotic	*Bactericidal/ bacteristatic*	*Therapeutic to toxic ratio*	*Cerebrospinal fluid penetration*	*Organism*	*Intraven (adult)*
Penicillins					
Penicillin G	Cell wall damaged; bactericidal	Wide, except in renal failure and the elderly	3+	N. *meningitidis,* some *S. pneumoniae,* group B Streptococcus	24 millio
Ampicillin	Bactericidal	Wide	3+	As for penicillin G + some H, *influenzae, L. monocytogenes,* 60-70% *E. coll*	12 g/day
Extended-spectrum penicillins	Bactericidal	Wide	3+	As for ampicillin + *P. aeruginosa, K. pneumoniae,* indole positive *Proteus, Serratia*	Carbem (q4h) 12-20 azloc and m 10-15
Ami staphylococcal penicillins	Bactericidal	Wide	2+	*S. aureus, S, epidermidis*	Methicil oxaci (q4h)
Vancomycin	Bactericidal	Narrow	3+	*S. aureus* including methicillin-resistant strains, S- *epidermidis,* penicillin-resistant pneumococci, enterococci, diphtheroids, and *F, meningosepticum*	3 g/day
Third-generation cephalosporins	Bactericidal	Wide	3+	Broad-spectrum; some gram-positive and especially gram-negative *E. coli, Klebsiella, Proteus, Serratia, N. meningitidis, H. influenzae* (including /J-lactamase-sccrcting strains)	Cefotaxi (q4h) Ceftri 4 g/d Cefta 8 g/da
Chloramphenicol	Bacteriostatic; hactericidal in therapeutic concentrations against *Haemophilus, S. pneumoniae,* and meningococcus	Narrow; peak serum levels should be maintained between 15 and 25 mg/liter	4 1	*H. influenzae, S. pneumoniae, N. meningitidis*	4 g/day admin *TV* pr vomit

Aminoglycosides	Bactericidal but not uniformly so because of acidic pH and low CSF levels	Narrow	f+; consider intrathecal or intraventricular administration	Gram-negative enteric organisms, *P. aeruginosa*	Netilmicin and gen 200 mg Kanam 1 g/day
Trimethoprim-sulfa met h-oxazolc	Bacteriostatic or bactericidal	Narrow	**4+**	Broad-spectrum *S. pneumoniae, H. influenzae,* meningococcus, gram-negatives, *Staphylococcus, L. monocytogenes, Nocardia*	Trimethop sulfam 6 g/day (trimet 15 mg/ ql2b}
Metronidazole	Bactericidal	Narrow	**4+**	Anaerobes	1.5 g/day
Rifampin	Bactericidal	Narrow	**4+**	Prophylaxis for meningococcus and *H. influenzae;* given with vancomycin for resistant *Staphylococcus* **and** *F, meningosepticutn*	600 mg/d
Fluoroquinolones	Bacterid da I	Narrow	Ciprofloxacin 1+; Ofloxacin 2+; Pofloxacin .3—	Gram-negative including *P. aeruginosa* and Staphylococcus; use selectively for multidrug-resistant gram negative bacteria and M. *tuberculosis;* prophylaxis for meningococcus	Ciproflox (q12h} Pefloxa 800 m
Unique ^-lactams	Bactericidal	Narrow	**2+, 3+**	Broad-spectrum most gram-positive and gram-negative nosocomial *Fonterobacter* and *Acinetobacte.r,* polymicrobial bacteremia	Imipenem

4+ = excellent; 3+ = very good; 2- = good; 1+ = poor; CSF = cerebrospinal fluid.

"Readers should check the product information sheet included in the package of each drug and follow those instructions.

^-Lactamase inhibitors (e.g., clavulanate or sulbactam) may be used with ampicillin, amoxicillin, or ticarcillin to inhibit ^-lactamases

^Ceftriaxone can be administered once a day if necessary. It is eliminated by kidneys and liver, and impaired function of either or

Ceftazidime is especially effective against *Pseudomonas* species. As single agents, ceftriaxone and cefotaxime arc the most frequently u

babies younger than 3 months because it displaces bilirubin.

[s] Avoid in newborns ("gray baby syndrome"). Serum levels should be monitored. Levels >40 mg/L are toxic. Levels >*25* mg/L can

Idiosyncratic irreversible marrow aplasia (1:30,000 patients) is the most feared complication.

'Also causes neuromuscular blockade—caution in myasthenia gravis, respiratory failure, and postoperatively when curare has been u

• CNS toxicity includes seizures (2-8% of patients).

Current antibiotic recommendations, when culture results reveal a specific pathogen, are listed in columns five and six of Table 59A.2,

Because bacteria! meningitis develops in an immunologically privileged site lacking a lymphatic system, bactericidal, rather than bacteriostatic, antibiotics that rapidly achieve adequate CSF levels should be selected. Therefore, antibiotic selection and reevaluation arc made in the context of several general pharmacological principles. Meningeal inflammation increases permeability of the blood-brain barrier to /^-lactam antibiotics from 0.5-2.0% to 5-10% of serum concentration. For more lipid-soluble antibiotics, such as chloramphenicol, rifampin (RIF), and trimethoprim/sulfamethoxazole (TMP/SMX), CSF levels reach 30-40% of serum concentrations even without meningeal inflammation. The low pFI of infected CSF impairs aminoglycoside activity, and increased CSF protein reduces the concentrations of active free drug for the ^-lactams, which are highly protein bound. Antibiotics used in meningitis, their relevant properties, and specific indications appear in summary form in Table 59A.2.

Optimal duration of therapy is not known for bacterial meningitis. Parenteral antibiotics are administered for 7-10 days for meningococcal and *H, influenzae* meningitis, 10-14 days for pneumococcus, and longer courses of 14-21 days for *L, monocytogenes* and Group R streptococci, and 21 days for gram-negative bacilli other than *H. influenzae* (Quagliarello and Scheld 1997). Treatment of bacterial meningitis sometimes extends to include family, medical personnel, and other contacts who may require che mo prophylaxis (vide infra). In many instances, proven or suspected bacterial meningitis requires notification of public health authorities to ensure accurate surveillance.

Adjunctive Therapy

Despite the availability of bactericidal antimicrobial therapy, the morbidity and mortality from bacterial meningitis remain unacceptably high. Recent studies have focused on the pathogenesis and pathophysiology of tissue injury in bacterial meningitis because the simple introduction of powerful antimicrobial agents may not improve the situation. Experimental evidence from animal models supports a role for inflammatory cytokines in the pathophysiology of bacterial meningitis (Scheld et al. 2002), The proinflammatory cytokines, interleukin 1 and 6, and TNF-a, produced by CSF leukocytes in response to a bacterial stimulus, whether whole organism, component, or toxin, mediate CNS inflammation, cerebral edema, cerebrovascular dysregulation, and brain injury in these models. Corticosteroids have a beneficial effect by inhibiting the synthesis of proinflammatory cytokines at the level of messenger RNA (mRNA) and by decreasing CSF outflow resistance and stabilizing the blood-brain barrier; therefore, their use in bacterial meningitis has been proposed. The available evidence on adjunctive dexamethasone therapy confirms a benefit for *H. influenzae* type b meningitis in reducing audiological sequelae and suggests a benefit in reducing audiological and neurological sequelae in pneumococcal meningitis in children. Adjunctive dexamethasone therapy, recommended in children over 3 months of age and many adults (Tunkel and Scheld 2002) with bacterial meningitis, should be started intravenously at the same time as, or shortly before, the first dose of antibiotic as 0.15 mg/kg body weight and administered every 6 hours for 2 to 4 days (Mclntyre et al. 1997; de Cans and Van de Beek 2002}. The rationale for giving dexamethasone before antibiotic therapy is that dexamethasone inhibits the production of TNF-a (mRNA level) if administered to macrophages and microglia before they are activated by bacterial cell wall components. Dexamethasone is unable to regulate TNF-a production once mRNA induction occurs.

Advantage of corticosteroid therapy for meningitis, especially pneumococcal, in adults is not as clear as in children with *H. influenzae.* In a single 1989 study, dexamethasone, 12 mg intravenously every 12 hours for 3 days, was beneficial in patients with pneumococcal meningitis. Flowever, with increasing pneumococcal resistance to antibiotics, the effect of corticosteroids on CSF antibiotic penetration would influence the recommendations for management of pneumococcal meningitis. For example, experimental evidence in animal models of meningitis shows that concurrent corticosteroid administration reduces vancomycin penetration into CSF. As a result, currently recommended treatment of pneumococcal meningitis in adults receiving adjuvant dexamethasone, pending antibiotic sensitivities, consists of ceftriaxone plus RIF. In treating penicillin-resistant pneumococcal meningitis, a second CSF study in 24-48 hours is recommended to document bacteriological improvement, because adjuvant dexamethasone may mask clinical signs of poor antibiotic response (Quagliarello and Scheld 1997).

Other adjunctive treatment may be useful in critically ill patients with bacterial meningitis. Patients with increased 1CP may benefit from the insertion of an ICP monitoring device and vigorous treatment of raised ICP. To avoid status epilepticus, seizures should be treated promptly with appropriate agents, such as lorazepam or diazepam and phenytoin. Treatment of shock and disseminated intravascular coagulation may be necessary. Plasma exchange has proved life saving in some patients with fulminant mcningococcemia, but this treatment must be considered experimental.

Complications

Focal cerebral signs such as hemiparesis usually imply arteritis, septic venous thrombophlebitis, ot cerebritis. Meningeal inflammatory processes in bacterial meningitis can cause cranial neuropathies. Cranial nerve VI palsy and a

deteriorating level of consciousness within the first 48 hours usually indicate an increase in ICP. Subdural effusions may develop in children, particularly with *H. influenzae* or other gram-negative meningitis. Indications for tapping and culturing a subdural effusion include persistent fever, rapidly enlarging head circumference in the absence of hydrocephalus, or focal neurological signs related to the effusion. Subdural effusions are aspirated under CT guidance. Sterile effusions often resolve spontaneously; subdural empyemas require more aggressive neurosurgical management (Bleck 2002). Depending on clinical circumstances, hydrocephalus may require intervention with serial LPs (if communicating) or external ventricular drainage. Obstructive hydrocephalus may be monitored expectantly with serial CTs.

SOME SPECIFIC PATHOGENS AND PUBLIC HEALTH ISSUES

Pneumococcus

Meningitis occurs in approximately 4% of patients with invasive *S. pneumoniae.* Associated conditions include otitis media, skull fractures, alcoholism, and sickle cell disease. Pneumovax, the pneumococcal vaccine composed of polysaccharides of 23 pneumococcal types, is recommended for patients with surgical or functional asplenia (such as sickle cell disease) and chronic illnesses. Of all blood culture isolates of pneumococci in the United States, 88% are contained in the 23-vaIent vaccine.

Rare pneumococcal meningitis cases have been classified as apurulent by the absence of CSF pleocytosis. Turbid CSF, masses of pneumococci, elevated protein, fewer than 100 cells/jiL, and low CSF glucose are characteristic. Within 24 hours after initiating antibiotic treatment, CSF cell counts can increase to more than 2000 cells/uL and the pneumococci disappear from the CSF.

Penicillin G and ampicillin are equally effective in treating meningitis caused by penicillin-sensitive strains of *S, pneumoniae.* For patients with *S. pneumoniae* resistant to both penicillin and ampicillin, treatment is by ceftriaxone combined with vancomycin. Consideration should be given to using intraventricular vancomycin in patients not responding to intravenous vancomycin. Intraventricular vancomycin is safe and is not associated with increased seizure activity.

Meningococcus

N. meningitidis infection may manifest as fever and bacteremia without sepsis, meningococcemia without meningitis, or meningitis with or without meningococcemia (Ferguson et al. 2002). Meningitis occurs in an estimated 48% of cases of invasive disease. Penicillin G is the antibiotic of choice for meningococcal meningitis; ampicillin may also be used. Rare NT. *meningitidis* isolates produce ^-lactamase or have altered penicillin-binding proteins. In the event of poor initial response to penicillin or ampicillin, isolates should be tested for sensitivities and therapy changed to ceftriaxone or cefotaxime. Treatment of systemic infection may not eliminate nasopharyngeal carriage. During widespread outbreaks or epidemics, when up to 1% of the population may be affected, a single injection of long-acting oily preparation of chloramphenicol (Tifomycine) at a dose of 3 g intramuscularly has been used successfully,

Current commercial vaccines include the quadrivalent vaccine with activity against serogroups A, C, Y, and W135. Protective antibodies persist for up to 5 years in adults, but only 1-2 years in children younger than 4 years. Vaccination is recommended for patients with complement deficiency or asplenia, as well as military recruits and travelers to hyperendemic or epidemic areas in Africa, Asia, and South America. Most vaccinations arc given during outbreaks. A vaccine against serogroup B has been developed in Cuba and used in some areas of South America.

Prophylaxis for meningococcal meningitis is recommended for the index case and all household members and medical personnel who may have had close contact with infected patients. A 2-day course of oral rifampin (RIF) is given in doses of 600 mg every 12 hours for adults, 10 mg/kg every 12 hours for children 1 month to 12 years old, and 5 mg/kg every 12 hours for infants younger than 1 month of age. Alternatives include ceftriaxone intramuscularly, recommended for pregnant and lactating women or children younger than 2 years (250 mg for adults, 125 mg for children), or minocycline or ciprofloxacin.

Haemophilus Influenzae

Meningitis complicates approximately 10% of *H. influenzae* infections, often in the setting of a paramemngeal ear or nose infection or basal skull fracture. The H. *influenzae* type b conjugate vaccine series is administered at 2, 4, and 12-18 months of age. Chemoprophylaxis with oral RIF is recommended for all household members under 4 years of age. The doses are the same as for meningococcal prophylaxis, but treatment is given for 4 days.

Listeria Monocytogenes

Listeria, a common meningeal pathogen in immunosuppressed hosts and neonates, also causes meningitis in the normal host. Meningitis develops in 36% of cases of invasive listeriosis. Ampicillin plus gentamicin is recommended for patients of all ages with *Listeria* meningitis, because neither ampicillin nor penicillin is bactericidal for *Listeria* in vitro, and third-generation cephalosporins are inactive against Listeria. TMP/SMX may be used in penicillin-allergic patients.

Listeria cerebritis or rhombencephalitis is a distinct nonmeningitic syndrome, which presents as headache,

fever, nausea, and vomiting, followed by cranial nerve palsies, decreased consciousness, seizures, and focal deficits. The CSF may contain few or no WBCs. CSF Gram stain and culture results are negative, but blood culture results are positive. *Listeria* cerebritis requires 6 weeks of treatment.

Nosocomial Agents

Increasing numbers of nosocom hilly acquired mlections, including meningitis, are encountered in hospitalized sick patients. Gram-negative bacteria of the *Enterobacteriaceae* family *(E. colt, K. pneumoniae), Pseudomonas* species, and gram-positive cocci (staphylococci, pneumococci) frequently cause hospital-acquired meningitis. Members of the genus *Acinetobacter,* especially multircsistant strains of *A. baumannii,* increasingly cause nosocomial pneumonia, bacteremia, and meningitis in the intensive care units (ICU). Associated systemic features include petechial rash in 30% of patients and Waterhouse-Friderichsen syndrome in some cases. *Acinetobacter* and meningococcus thus share clinical, as well as microbiological, features, leading to diagnostic confusion. *Acinetobacter* are rod-shaped gram-negative organisms during rapid growth and coccoid in the stationary stage. Most *A. baumannii* are now resistant to ampicillin, carbenicillin, cefotaxime, chloramphenicol, gentamicin, and other aminoglycosides. Imipenem, carbenicillin plus an aminoglycoside, and amoxiciilin-clavulanic acid are treatment alternatives.

Brain Abscess

Brain abscess is a focal suppurative process of brain parenchyma, accounting for an estimated 1 in 10,000 general hospital admissions. Brain abscesses develop most frequently by spread from a contiguous infected cranial site, such as ear, sinus, or teeth. Other predisposing causes include open head trauma, previous neurosurgical procedures, and craniofacial osteomyelitis. Hematogenous spread from a remote source also can cause brain abscesses, particularly in the setting of congenital heart disease with right-to-left shunt or pulmonary disorders such as lung abscess, bronchiectasis, or arteriovenous fistula. Metastatic, or blood-borne abscesses, are usually found at gray and white matter junctions, in the distribution of the middle cerebral artery, and are often multiple. However, 20% of abscesses are occult, without an additional source of infection (Anderson 1993). Classifying brain abscesses by likely entry point of infection allows physicians to predict likely pathogens and choose appropriate empiric therapy (Lu et al. 2002).

Frontal abscesses arise most often from paranasal sinus infection, temporal or cerebellar abscesses from an otogenic source, and multiple abscesses from a remote site. Experimental evidence suggests that bacteria require a damaged brain, such as the microscopic or macroscopic area of necrosis resulting from septic thrombophlebitis, emboli, or hypoxemia, to establish infection. The predilection of metastatic abscesses for gray-white matter junctions, for example, may be a consequence of the fluctuations in blood supply to those areas. Once infection is established, the abscess passes through the stages of cerebritis, central necrosis, capsule development, and maturity over a period of approximately 2 weeks or so.

Clinical Features

Patients with brain abscess present with signs and symptoms of an expanding mass lesion, with progressive headache, altered mentation, focal deficit, or seizures. About one half of patients develop nausea and vomiting. Approximately the same proportion has fever, and hence the diagnosis should not be excluded based on normal temperatute alone. Acute worsening of headache and nuchal pain, together with an increase in temperature, can signify rupture of the abscess into the subarachnoid space, with consequent pyogenic meningitis, a serious event.

Diagnosis

Neuroimaging studies reveal one or more ring-enhancing masses with surrounding edema (Figure 59A.2). The ring of enhancement may be thicker near the cortex and thinner near the ventricle; large abscesses tend to have thin, enhancing rings of relatively uniform thickness. Associated sinus or ear infection also may be identified by cranial imaging, though dedicated sinus or temporal bone CT may be necessary, in order to better visualize the primary site of infection. An early lesion in the cerebritis stage appears as a nonenhancing focal low-density area on CT scan or hypointensity on magnetic resonance imaging (MRf). Air within a brain mass, in the absence of recent neurosurgical procedures, suggests an abscess. An indium-labeled leukocyte scintillation scan demonstrating an active inflammatory focus may complement CT or MRI studies.

Peripheral leukocytosis may be mild or absent and should not be relied on for considering the diagnosis. Because of the risk of herniation or precipitating rupture, LP is contra indicated in suspected or proven brain abscesses. CSF reveals only nonspecific findings of elevated protein and lymphocytic pleocytosis with normal glucose and rarely yields positive culture results unless the abscess has ruptured into the subarachnoid space.

Pathogens

Occurring as mixed infections 30-60% of the time, brain abscess pathogens vary with the clinical setting. In immunocompetent patients the most commonly encountered aerobic organisms arc the a-hcmolytic and nonhemolytic

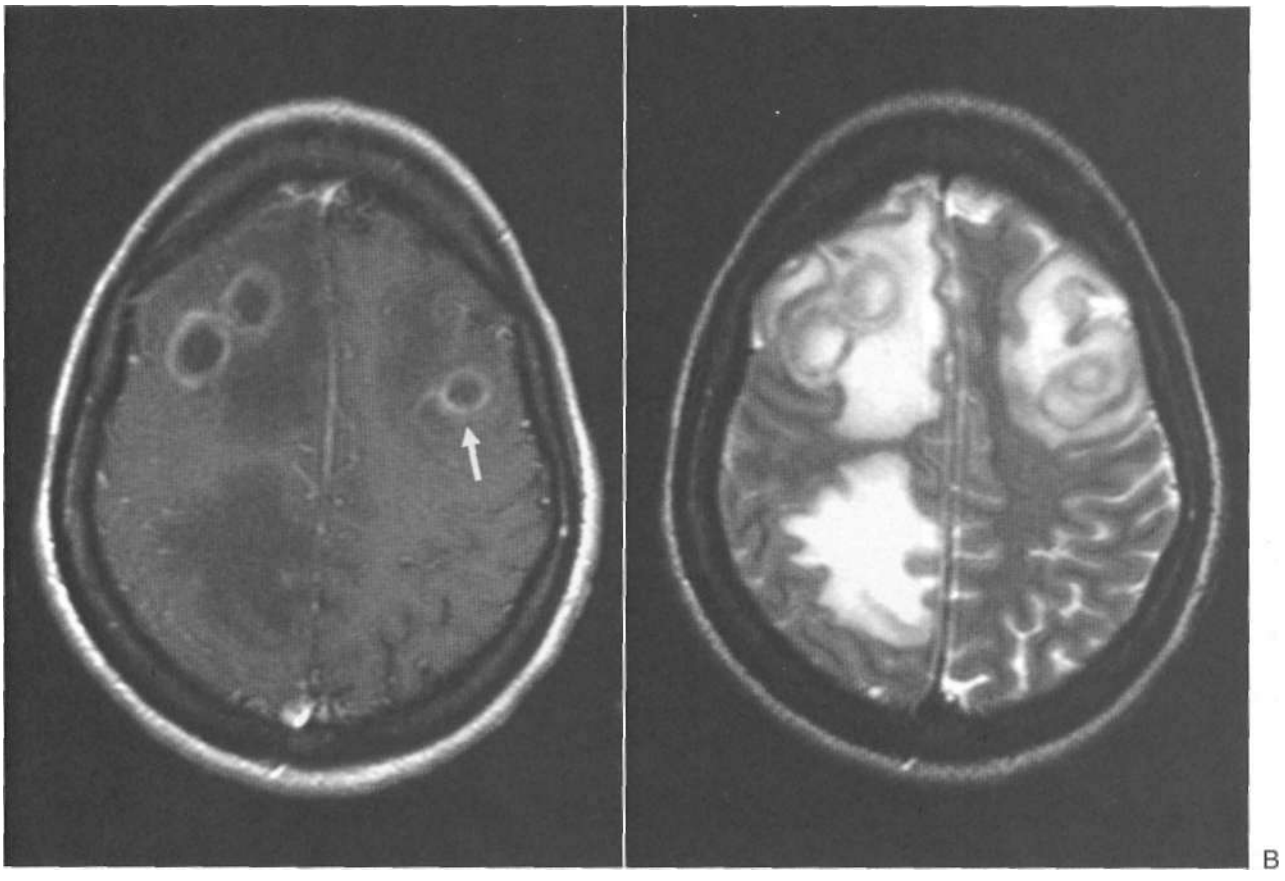


FIGURE 59A.2 Brain abscess. Postgadolinium axial T1W-MRI showing multiple ring-enhancing lesions (some multiloculated, *arrow,* A) with surrounding edema best seen in T2W sequence (B) and with associated intralesional diffusion restriction (DW-MRI, C). Prominent lactate *(arrow)* and inverted peak at 0.9 ppm *(arrowhead)* in single voxel from the lesion {H^1 spectroscopy, D and E) are typical of bacterial abscess. (Courtesy Dr. S. Ouanounou.) *Continued*

streptococci (such as *S. milleri), S. aureus,* and *Enterabacteriaceae.* Other important pathogens include anaerobes such as *Bacteroides., Fusobacterium, Peptostreptococcus,* and *Propionibacterium;* gram-negative bacteria such as *Eikenella, Actinobacitlus,* and *Haemophilus;* and enteric gram-negative bacteria such as *E. colt, Klebsiella,* and *Pseudomonas.* Several important associations include 5. *milleri* or pneumococcus with a sinus source; *Bacteroides, Enterobacter, Proteus,* streptococci, or *Pseudomonas* with an ear source; anaerobic streptococci with pulmonary infections; *Actinomyces* with dental procedures; and *S. aureus* in patients with head trauma, recent neurosurgical procedures, or cranial osteomyelitis. Various other bacteria may occasionally be found in brain abscesses, including *Clostridium* spp. after trauma and wound contamination by soil, C. *diversus* in neonates, *Salmonella* spp., .S. *moniliformis* (the agent of rat-bite fever), and *Brucella* spp. Except for pneumococcus and *H. influenzae,* typical bacterial meningitis pathogens irif requently cause brain abscess (Case Records 1993).

Geography and immune status are other important determinants of brain abscess microbiology and its differential diagnosis. Tuberculomas frequently cause space-occupying lesions in countries with high tuberculosis (TB) prevalence. Amcbae, toxoplasmosis, cysticcrcosis, or other helminths, including schistosomal species, Paragonimus, trichinosis, sparganosis, and echinococcosis, cause parasitic cerebral abscesses. *P. boydii* fungal abscess may follow a near-drowning episode by 2-4 weeks.

In immunocompromised patients with T-ccll or mononuclear phagocyte defects, causes of brain abscesses include L. *monocytogenes, N. asteroides, G, terrae* (an environmental actinomycete), *Mycobacterium* spp., and parasites such as *Toxoplasma, Acanthamoeba, Cryptococcus,* and T. *cruzi.* In HIV-infected patients, polymicrobial pyogenic abscesses with *S. bovis, Fusobacterium, Peptostreptococcus,* and group Gl streptococcus have been reported, along with abscesses with unusual combinations of organisms, such as *Candida* and staphylococci (Maniglia et al. 1997). Neutrophil abnormalities lead to an increased incidence of *Enterobacteriaceae* and *Pseudomonas* abscesses and fungal abscesses caused by *Aspergillus, Mucor,* or *Candida;* and *Strongyloides.*

Differential Diagnosis

In the febrile patient with headache, altered mentation, and laterali/.ing findings, the differential diagnosis includes

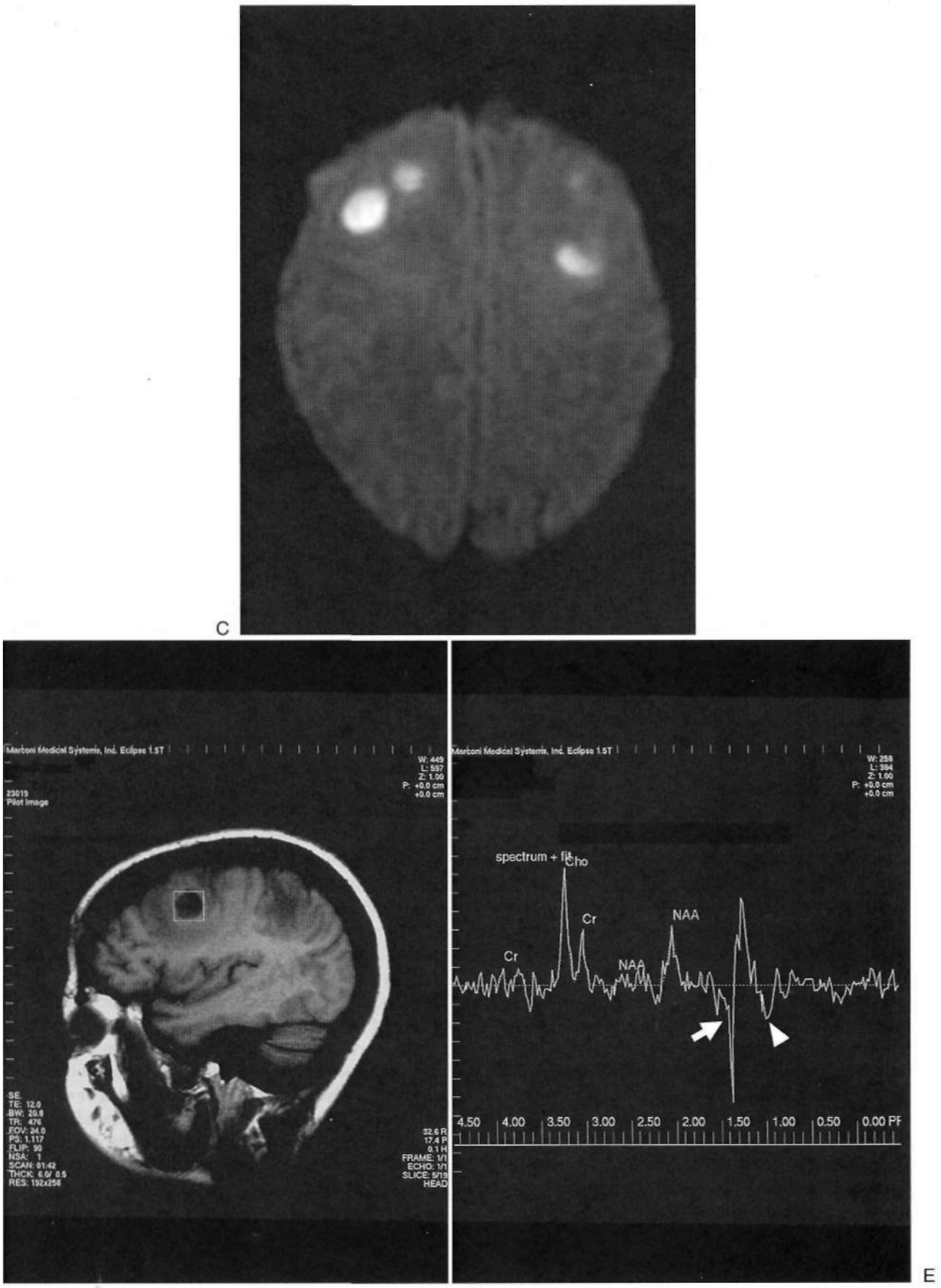


FIGURE 59A.2, cont'd. (Courtesy Dr. S. Ouanounou.)

other infectious etiologies, such as subdural empyema, epidural abscess, viral encephalitis, bacterial or acute aseptic meningitis, septic thrombophlebitis, and endocarditis with septic embolism or mycotic aneurysm rupture. When fever is low grade or absent, primary or metastatic brain tumor is also a consideration. Occasionally, demyelinating lesions presenting as focal deficits or seizures appear as ring-enhancing masses on neuroimaging studies. Resolving cerebral hemorrhages also appear as ring-enhancing lesions on neuroimaging studies, particularly brain CT. Brainstem infection with *L. monocytogenes* or *P. acnes* may produce brainstem encephalitis (rhombencephalitis) that clinically mimics brainstem abscess.

Treatment

Successful treatment of brain abscess requires antibiotics in all patients and surgery in many cases. Antibiotics must not only penetrate brain tissue, but also reach the abscess cavity and retain activity at its characteristically low pH. For years, standard brain abscess therapy combined high-dose penicillin (24 million U per day intravenously) with chloramphenicol (1 g every 6 hours). Because metronidazole (1 g loading dose, followed by 500 mg every 6 hours) provides excellent anaerobic coverage and penetrates well into brain abscesses, it has replaced chloramphenicol, which carries the additional risk of aplastic anemia. Hence, empiric antibiotic therapy for brain abscess usually includes metronidazole and either penicillin or a third-generation cephalosporin (cefotaxime, ceftriaxone, or ceftazidime), which covers the streptococci and aero-to let ant anaerobes resistant to metronidazole. Following head trauma or neurosurgical procedures, when *S. aureus* is a concern, an antistaphylococcal penicillin (nafcillin, methic.illin) or vancomycin is added.

Current recommendations for empiric therapy, based on location of abscess and inferred source of infection, are metronidazole with either penicillin or a third-generation cephalosporin for frontal abscesses; penicillin, metronidazole, and ceftazidime for temporal or cerebellar abscesses; nafcillin, metronidazole, and cefotaxime for multiple (metastatic) abscesses; nafcillin and cefotaxime for penetrating wounds; and vancomycin and ceftazidime for postoperative abscesses {Mathisen and Johnson 1997). Intravenous treatment must continue for 6-8 weeks and may be followed by oral therapy for 2-3 months. Surgical excision may shorten the time course of intravenous therapy by 1 or 2 weeks.

Optimal therapy usually requires neurosurgical intervention. Although controversy continues as to whether aspiration under stereotactic CT guidance or total excision yields better results, excision is recommended for gas-containing, multiloculated, or fungal abscesses. Patients for whom medical management alone may be the better choice include those with multiple, deep, or dominant hemisphere abscesses; simultaneous meningitis or ependymitis; abscesses measuring less than 3 cm; or abscesses that shrink after antimicrobial therapy. Surgery is not performed in the cerebritis stage until a capsule forms. Ear, nose, sinus, and dental infections should be evaluated and treated by the appropriate surgical specialists.

Adjunctive medical therapy for medical or surgical cases includes corticosteroids for mass effect, hyperosmolar agents for worsening cerebral edema and raised ICP, and prophylactic or symptomatic anticonvulsants. Decreased mortality from brain abscesses over the last two decades, from more than 50% to less than 10%, reflects improvements in neuroimaging and neurosurgical techniques. One half of survivors recover completely. Rapid disease progression before hospitalization and altered consciousness at the time of admission portend poor outcome. Intraventricular rupture of a brain abscess is associated with mortality exceeding 80%.

After treatment, patients are followed with neuroimaging studies at monthly intervals for approximately 6 months or until contrast enhancement disappears. Persistent contrast enhancement predicts recurrence in up to 20% of patients. Seizures occur in 25-50% of patients during their early period of hospitalization, and anticonvulsants initiated during hospitalization are continued for 6-12 months. When administered prophy tactically, anticonvulsants are continued for a minimum of 3 months after surgery.

Subdural Empyema

Subdural empyema is a collection of pus between the dura and arachnoid. It develops most commonly as a consequence of ear or sinus infection. Other causes include cranial osteomyelitis, penetrating head trauma or neurosurgery, infection of subdural effusions in childhood meningitis, and hematogenous spread from a remote source. Purulent material tracks over the brain surface of the hemispheres (Figure 59A.3), along the falx, or adjacent to the primary focus. Posterior fossa involvement is unusual; spinal subdural empyemas are rare and always meta static.

Clinical features

Patients typically present acutely with prominent headache, fever, stiff neck, seizures, focal neurological deficit, and rapid clinical deterioration. The diagnosis should be considered in all patients with meningeal signs and deficits indicating extensive, unilateral hemispheric dysfunction or in patients with sinusitis who develop meningeal signs. A parafalcine collection would be indicated by leg weakness, paraparesis, or sphincter disturbance. Children younger than 5 years may develop subdural empyemas after *H. influenzae* or gram-negative bacterial meningitis and present with irritability, poor feeding, and increasing head circumference. Radicular pain and signs of cord

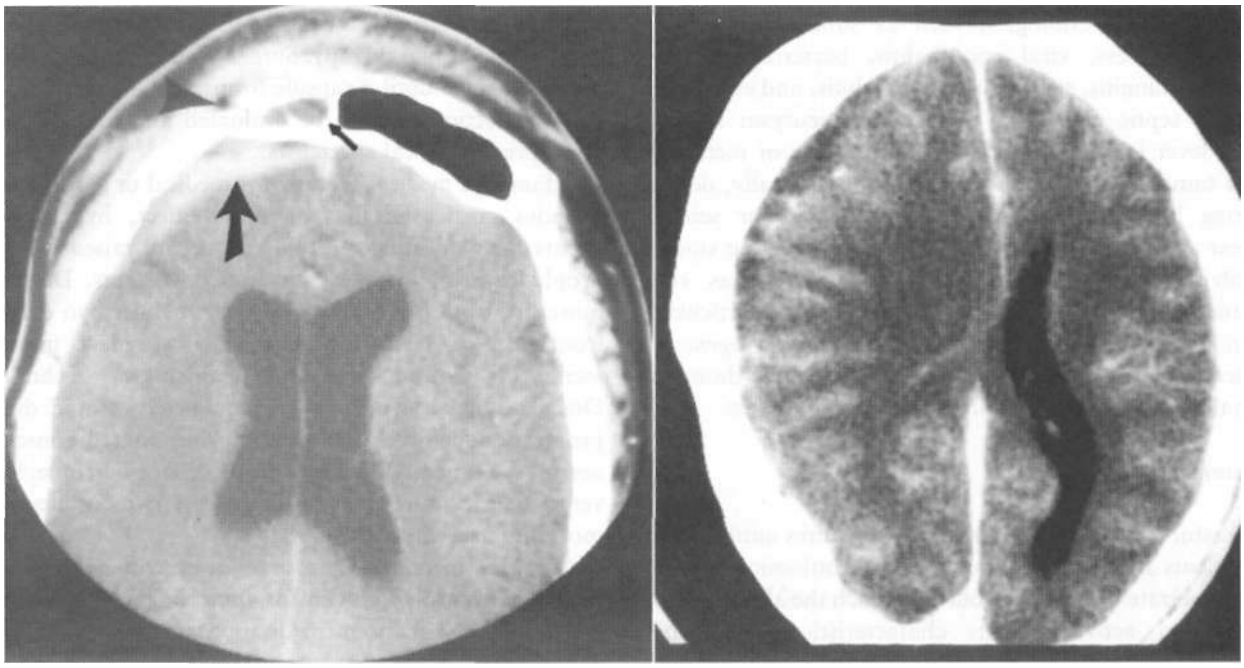


FIGURE 59A..1 Subdural empyema. (A) Contrast-enhanced computed tomographic scan showing right frontal sinus infection *(short arrow)* that has spread to the right subdural space *[long arrow)* and forehead *[arrowhead),* (B) In a second patient, the contrast-enhanced computed tomographic scan shows an extra-axial fluid collection and midline shift disproportionately greater than the size of the subdural collection,

compression in the absence of vertebral tenderness suggest spinal subdural empyema.

Diagnosis

Because there are similarities between subdural empyema and bacterial brain abscess with regard to pathogenesis and clinical presentation, the disorders share many aspects of diagnosis and management. Bacterial pathogens for both disorders are similar, although subdural empyemas are less often mixed. Neuroimaging studies help establish the diagnosis, but may underestimate the size of the empyema. In infants, the diagnosis may be made by subdural taps. The empyema fluid is usually too turbid to tran si Humiliate. Spinal cases are examined by MR! or myelography.

Treatment

Because subdural empyema progresses rapidly, combined medical and surgical management should proceed emergcntly (Bleck 2002), Untreated, subdural empyemas are uniformly fatal. Whether craniotomy or burr hole aspiration is the better surgical treatment remains controversial. Burr holes work well for early cases, but pus may reaccumulate. Craniotomy is recommended in posterior fossa cases or if cranial osteomyelitis coexists. Otitis or sinusitis may require simultaneous surgical therapy. Empyema fluid should be cultured, and antibiotic treatment is continued for at least 3 weeks. In as many as one fourth of cases, no organism can be cultured from pus (Anderson 1993).

Overall mortality is 14-18%. Rapid disease progression before hospitalization and depressed level of consciousness at admission arc associated with poor prognosis. Mortality is 75% in comatose patients. An estimated 42% of survivors develop seizures within 16 months.

Cranial Epidural Abscess

Cranial epidural abscess, an infection in the space between dura and skull (Figure 59A.4), begins as cranial osteomyelitis complicating ear, sinus, or orbital infection and nasopharyngeal malignancy. Diagnosis, urgent management, and prognosis are similar to subdural empyema. Because *S. aureus* is a frequent cause, particularly after trauma or surgery, antibiotics should cover *staphylococcus* as well as the aerobes, anaerobes, and gram-negative organisms encountered in brain abscesses and subdural empyemas. Brain abscess, subdural empyema, and epidural abscess may occur simultaneously in the same patient.

Septic Venous Sinus Thrombosis

Septic thrombosis of cerebral veins or venous sinuses may complicate meningitis or epidural or subdural abscesses or develop during the intracranial spread of infection from extracranial veins. Once established, infection and clot

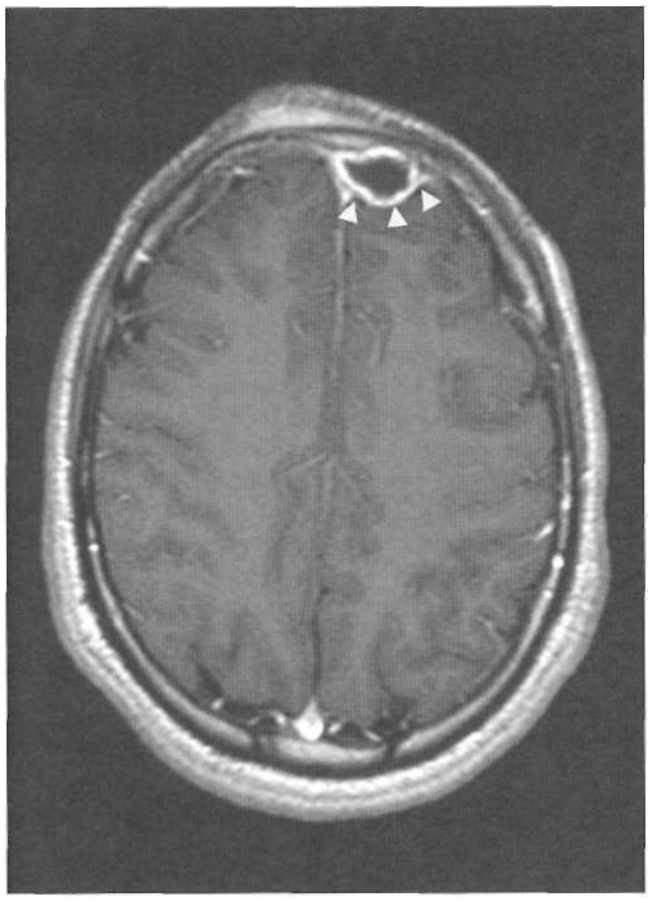


FIGURE 59A.4 Epidural abscess associated with frontal sinus disease. Postgadolinium axial T1W-MR1 showing thiek-wallcd enhancing epidural collection close to the inner table of the frontal bone *{arrowheads)* with adjacent soft tissue swelling. (Courtesy Dr. S. Ouanounou.)

spread through the venous system, aided by the absence of valves in intracranial veins. Fortunately, antibiotics have rendered this grim complication of facial, sinus, ear, dental infection, or bacterial meningitis itself less common. The most common bacterial pathogens depend on the source of initial infection; with sinusitis they arc *staphylococcus,* aerobic and microaerophilic streptococci, gram-negative E. *coli,* and/or anaerobes, whereas .*S. aureus* predominates when facial infection is the source. Otitis media or mastoiditis may be complicated by the development of the lateral sinus thrombosis.

Clinical Features

Thrombosis may develop in the cavernous, superior sagittal, or lateral sinuses, depending on the site of primary infection. Specific presenting features vary with the site involved and include headache, altered mentation, seizures, cranial neuropathies, fluctuating focal deficits, nonartcrial distribution strokes, and increased ICP. Cavernous sinus thrombosis is indicated by ipsilatcral proptosis and facial edema, retinal vein engorgement, retinal hemorrhages or papilledema, and clinical involvement of the third, fourth, sixth, and ophthalmic division of the fifth cranial nerves. Lateral (transverse) sinus thrombosis is accompanied by papilledema, extension to the jugular bulb with involvement of cranial nerves IX, X, and XI and extension to petrosal sinuses with involvement of cranial nerves V and VI. Sagittal sinus thrombosis is associated with papilledema, focal or generalized seizures, leg weakness, aphasia, or cortical sensory deficits.

Diagnosis

CT scan or **MRI** may demonstrate the primary infection or clot within the sinus. Clot within the sinus may appear as hyperdensity in the sinus on noncontrast CT, but may be missed by **MRI,** because acute thrombus may appear hypointense on T2-weighted images. **MR** venography or cerebral angiography with venous phase studies may be necessary to confirm the diagnosis.

Treatment

Treatment is directed towatd the primary infection. As with subdural and epidural empyema, empirical therapy is directed at gram-positive organisms, including staphylococci, aerobic gram-negative bacilli, and anaerobes. Anticoagulants are generally contraindicated because venous cerebral infarcts aire often hemorrhagic. However, they may help prevent clot propagation, particularly in early cases. Polycythemia, if present, is treated with volume expansion.

Spinal Epidural Abscess

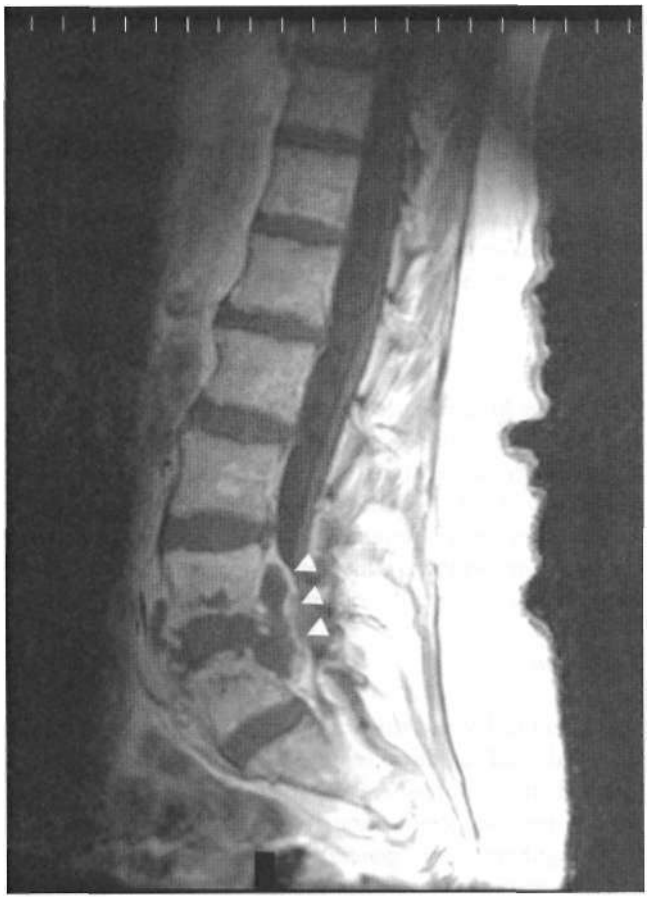
Spinal epidural abscess follows infection elsewhere in the body in most cases. Infection develops in the epidural space by direct extension of vertebral osteomyelitis or soft tissue infections (retroperitoneal, mediastinal, perinephric, psoas, or paraspinal abscess) following penetrating trauma or decubitus ulcers or by hematogenous spread from skin or parenteral drug use. Rarely, back or abdominal surgery, LP, or epidural anesthesia has been contributory.

Clinical Features

Localized back pain and radicular pain are common early symptoms, frequently overshadowed by rapid evolution of paraparesis or quadriparesis. The thoracic spine is involved in 50-80% of cases, lumbar in 17-38%, and cervical in 10-25%.

Diagnosis

The combination of fever, back pain with local spine tenderness, and radiculopathy or myelopathy mandates



FfGURE 59A.5 Spinal epidural abscess. Postgadolinium sagittal T1W-MRI of lumbar spine demonstrating enhancing epidural collection *[arrowheads]* with irregularity of the adjacent verrebral endplates suggesting discitis, osteomyelitis, and associated epidural abscess. (Courtesy Dr. S. Ouanounou.)

emergent evaluation. Peripheral WBC count and erythrocyte sedimentation tate are usually, but not always, elevated. The diagnosis depends on MRI or myelography, if MR! is not available. MRI is the test of choice because it is noninvasive and provides images of the cord and epidural space in sagittal and transverse planes, as well as direct visualization of inflammatory tissue (Figure 59A.5). LP risks spinal herniation or spreading infection to the subarachnoid space should the needle pass through the abscess. Even so, because outcome depends so heavily on early diagnosis, myelography should be performed in suspected cases when MRI cannot be obtained emergently. Blood culture results ate often positive and cotrelate well with abscess pathogens. Differential diagnosis includes transverse myelitis, spinal osteomyelitis, or less commonly, spinal subdural empyema, epidural hematoma or metastases, primary spinal tumots, spinal artery syndromes, and discitis. More chronic cases may resemble the hypertrophic spinal pachymeningitis (progressive dural fibrosis with motor root compression) associated with TB or syphilis.

Treatment

Once MRI or myelography has established the diagnosis, utgent surgical decompression and antibiotic thetapy are needed. Antibiotics to cover *S. aureus* and gram-negative bacilli are administered, pending definitive identification by cultures of blood or intraoperative specimens. *S. aureus* is the most common pathogen, detected in 50-90% of cases, followed by streptococci and gram-negative enteric bacilli in 10-20% of cases. Other pathogens include *M. tuberculosis, Salmonella, Listeria, Brucella, Actinomyces* spp,, *Nocardia,* fungi {cryptococcosis, aspergillosis, mucormycosis, coccidioidomycosis, blastomycosis), and parasites (cysticercosis, echinococcosis, schistosomiasis). Corticosteroids are frequently administered preoperative^- and postoperatively during the first week of treatment. Antibiotic treatment continues for 3-4 weeks in uncomplicated spinal epidural abscess and for 6-8 weeks if osteomyelitis is apparent. Prognosis for recovery is good if surgery is performed in the early stages. Neurological recovery is often dismal if surgery is performed more than 24 hours after the onset of paralysis.

Shunt Infections

S. epidermidis causes most infections of external ventricular catheters, ICP monitors, shunt devices, and Ommaya reservoirs, followed by *.S. aureus.* Infection, often within 2 weeks of installation, is signaled by fever, shunt malfunction, and wound infection (Figure 59A.6). Signs of meningitis may be absent, but CSF pleocytosis is present, Although CSF cell counts may be gteater in ventricular compared with lumbar CSF, both should be examined and cultured. Because most infections are hospital acquired, the organism should be assumed to be methiciilin resistant, and initial treatment is with vancomycin, combined with a third-generation cephalosporin and often an aminoglycoside, to cover gram-negative bacilli. Intraventricular vancomycin and aminoglycoside may be necessary, along with removal of the shunt (Kim and Pons 1994),

MYCOBACTERIAL DISEASES

Tuberculosis

Although TB most commonly involves the lungs, it can produce disease in nearly every organ system. Approximately 1% of TB infections arc complicated by neurological disease such as tuberculous meningitis, tuberculoma, or tuberculous involvement of the spine with myelopathy (Pott's disease). The TB bacilli are obligate aerobic organisms infecting humans and other animals. Two main species ate recognized, *M. tuberculosis* and *M. bovis.* Other less common species include M. *africanum*

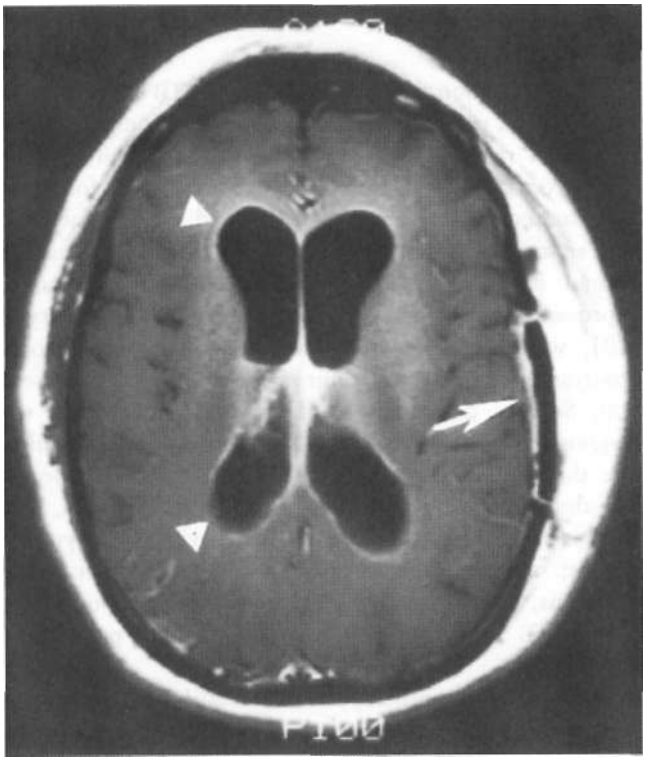


FIGURE 59A.6 Ependymitis secondary to shunt infection. Gadolinium-enhanced axial Tl-weighted magnetic resonance image showing abnormal contrast enhancement of ependymal lining of dilatated lateral ventricles *(arrowheads);* swollen, infected contrast-enhancing craniotomy site; and dural enhancement *(long arrow)* after removal of shunt.

in West and Central Africa and M. *ulcerans.* The atypical or nontuberculous mycobacteria, M. *avium-intracellulare,* arc widely distributed saprophytes and cause multisystem infections, including meningitis, in immunocompromised patients.

Epidemiology and Current Trends

TB is the most important infectious disease in the world, with an estimated one third of the population infected with the TB bacillus. As is the case for other infections introduced to new, susceptible populations, TB occurs in epidemic waves. Unfortunately, this wave is taking 300 years to pass and has not yet crested in many countries of Asia and Africa. Each year an estimated 8 million individuals around the world develop active TB. Approximately 70,000 of these patients worldwide and 4000 patients in the United States acquire TB meningitis. The majority of these individuals develop a subacute meningitis that if left untreated soon produces severe brain damage. HIV infection in recent decades has been associated with an increasing numbers of new cases and with a higher risk of extrapulmonary TB.

Pathogenesis

Neurological TB may develop during primary infection (Tung et al. 2002) or reactivate as a consequence of immunosuppression. TB meningitis develops most commonly after a two-stage process. Tubercle bacilli spread hematogenously from the lung or other organs fotm tubercles (Rich focus) in the brain parenchyma, and at a later stage, rupture into the subarachnoid or ventricular space. In other instances, meningitis may arise in the course of miliary TB or from parameningeal infection. Inflammatory exudate spreads along the subarachnoid space and pial vessels to the brain. Pott's disease, or spinal TB, develops when hematogenous spread of tubercle bacilli to the spine causes vertebral osteomyelitis, adjacent joint space infection, and subsequent paravertebral abscess.

Tuberculosis Meningitis

Clinical Features. TB meningitis typically follows a subacute course with low-grade fever, headache, and intermittent nausea and vomiting, followed by more severe headache, neck stiffness, altered mentation, and cranial (usually III, but also II, VII, and VIII) nerve palsies. Untreated disease progresses with more pronounced meningeal signs, seizures, and focal neurological deficits, including hemiparesis, increasing drowsiness, and signs of increased ICP. Other presentations of tuberculous meningitis include acute meningitis, behavioral or intellectual disturbances without meningeal signs, encephalopathy, seizures, isolated cranial neuropathies, stroke, increased ICP, and recurrent serous or aseptic meningitis. Overall, meningeal signs are present in approximately 70% of cases, cranial nerve palsy in 25%, and focal neurological findings in 16-18%. Purified protein derivative (PPD) testing is positive in 50% and active chest infection in some of the patients.

Diagnosis. Identifying tubercle bacilli on CSF acid-fast bacilli (AFB) smear or culture establishes the diagnosis. Serial LPs and centrifugation of specimens increases the yield of the AFB smear, a test that is diagnostic in only 10-30% of cases. CSF culture results arc positive for *M. tuberculosis* in 45-70% of patients but may take 6-8 weeks to become positive. Because a negative CSF AFB smear result does not rule out TB meningitis and the culture may not yield organisms for weeks, a presumptive diagnosis is often made based on other clinical criteria so that empiric anti-TB therapy can be started as early as possible.

CSF examination demonstrates normal or elevated opening pressure, elevated protein {80^400 mg/dL), low glucose (<40 mg/dL), and pleocytosis (averaging 200-400 WBC/uL with lymphocytic predominance). However, patients with miliary TB or CNS tuberculomas may have a normal CSF initially. CSF WBC counts of less than 5/u.L

have been reported in up to 11% of HIV-scropositive patients, and 5% of HIV-seronegative patients shown to have TB meningitis. In other instances, an early polymorphonuclear or eosinophilic CSF cellular response may be seen. The lack of sensitivity and specificity of standard CSF analysis and AFB smears has prompted the search for additional diagnostic tests. As a result, polymerase chain reaction (PCR) technique has been applied and is now routinely available for the diagnosis of TB meningitis, with reported sensitivities of 70-75%. Enzyme-linked immunosorbent assay (FLISA) and radioimmunoassay tests for and mycobacterial antibodies in the CSF have also been developed (LoBue and Catanzaro 1997).

Additional investigations should include general examination for lymphadenopathy and hepatosplenomegaly, retinal examination for choroidal tubercles, chest radiography for lung infection, tuberculin test, and brain neuroimaging study. Cranial CT or MRI showing basal meningeal and sylvian exudates and enhancement with hydrocephalus suggests the diagnosis.

Differential diagnosis includes untreated or partially-treated bacterial meningitis, other granulomatous meningitides (spirochetes, *Brucella,* most fungi, and parasites such as *Amoeba, Toxoplasma,* and trypanosomes), other conditions that elicit a subacute or chronic granulomatous response (CNS sarcoid, lupus, Behcet's, Vogt-Koyanagi-Harada disease, granulomatous angiitis), and lymphomatous or carcinomatous meningitis. TB should also be considered when suspected bacterial meningitis fails to resolve with antibacterial therapy.

Tuberculomas

Tuberculomas, the parenchymal form of TB, occur as single or multiple brain or spinal cord lesions and present with signs and symptoms of space-occupying lesions. On CT or MRI scan, the lesions may be of low or high intensity, with ring enhancement. Miliary disease is characterized by multiple small (1-2 mm) lesions. Open or stereotactic biopsy may be necessary if definitive diagnosis of TB cannot he made at an extraneural site. In regions in which TB is prevalent, the decision to initiate anti-TB therapy may be made without histological confirmation.

Spinal Tuberculosis

The most common site of involvement by TB of the spine is in midthorax region. Back pain is the chief complaint, and paraspinal muscle spasms or kyphotic deformity of the spine (from collapse of vertebra, a gibbus) may be found on examination. Plain films show decreased bone density and joint space destruction in long-standing disease, but may be normal in early disease. Radionuclide bone scanning improves detection of spinal TB, but the best modality is MRI, which simultaneously visualizes the spinal cord. Progressive paraparesis requires urgent surgical intervention. Surgery also may be indicated for biopsy if the diagnosis is in doubt or to obtain cultures for sensitivities. The differential diagnosis of vertebral bacterial diseases includes infections with staphylococci, streptococci, and typhoid and other gram-negative bacilli; paratyphoid disease; and brucellosis. Compared with other bony infections, there is less sclerosis in tuberculous spondylitis. Skeletal TB appears to be rare in HIV-infected patients.

Treatment. Chemotherapy for TB requires a combination of several bactericidal drugs to sterilize lesions and avoid inducing resistance. Commonly used anti-TB medications and their side effects arc summarized in Table 59A.3. Optimal drug combinations vary with region of the body, clinical setting, and local resistance patterns (Small and Fujiwata 2001). One recommended regimen for initial treatment of CNS TB is with isoniazid (INH), RIF, pyra/.inamide, and ethambutol or streptomycin (SM). RIF, SM, and INFI (when there is meningeal inflammation) penetrate to the CSF well. If there is satisfactory clinical improvement after 2 months, three- or four-drug regimens can be consolidated to two agents, usually INH and RIF, for an additional 10 months. In areas with high prevalence of drug-resistant disease and HIV infection, treatment begins with five to seven drugs until drug-susceptibility results are known. Additional agents include ethionamide, which penetrates CSF well, cycloserine, para-aminosalicylic acid, thiacetazone, clofazimine, ofloxacin, and rifabutin, which is active against *M. avium* infections and penetrates CSF well. Oral pyridoxine (25-50 mg/day) is given concurrently with INH to prevent neuropathy. Monthly

Table 59A3; Commonly used antimicrobial agents for tubercular meningitis

Drug	*Dose (tng/kg/day) and route*	*Major toxicity*
Isoniazid (INH)	.5-10 (max 300 mg) PO, add pyridoxine to prevent neuropathy (Child 25 mg/day PO, Adult 50 mg/day PO)	Hepatitis (1-2%), neuropathy (5%), seizures
Rifampin (RIF)	Child 15 PO, Adult 10 PO"	1 lepatiris : 1-2% i, hypt-i-si'iiMtivitv
Pyrazinamide	25 (max 2.5 g/day) PO	Arthralgia (5%!, hepatitis (1-5%), hyperuricemia, gout, rash
Streptomycin	Child 30 IM Adult 15 (max 1 g/day) IM	Hearing loss, vestibular imbalance (1-5%)
Ethambutol	15-25 (max 2.5 g/day) PO	Optic neuritis (3%), neuropathy (1-2%), rash

Source: Adapted from Davis, J. K. 2002, "Tuberculous meningitis," in *Current Therapy in Neurologic Disease,* 6th ed., eds R. T. Johnson, J. W. Griffin, and"J. C. McArther, Mosby, Philadelphia.

vision and color identification studies are recommended for patients taking ethambutol to monitor for toxic optic neuropathy. Monthly hearing evaluations are necessary when SM is used, and the drug should be stopped at signs of vestibular toxicity. Liver enzyme levels are monitored also, because INH, RIF, and pyrazinamide are hepatotoxic. Treatment can be continued with elevated liver enzyme levels if the patient remains anicteric or without other signs of liver toxicity. RIF induces cytochrome P450 and thus can alter levels of concurrently administered phenytoin, RIF also accelerates methadone metabolism and may precipitate withdrawal symptoms in patients receiving maintenance therapy.

During treatment CSF is reexamined to monitor treatment efficacy and drug levels. Neuroimaging studies are performed 2-3 months after the start of treatment and again at 3- to 6-month intervals to verify improvement in lesions. Two years of treatment may be necessary for tuberculomas. Chemotherapy alone is effective treatment for most spinal TB without cord involvement.

Complications. TB meningitis, particularly when advanced, can be an acute, life-threatening illness. Untreated, it is nearly always fatal, usually within 3-6 weeks of presentation. Even with treatment, a 21% mortality rate for immunocompetent patients and 33% for HIV-infected patients has been reported. Complications of untreated, late, or incompletely treated CNS TB include progressive hydrocephalus (Figure 59A.7), which may require shunting; blindness caused by damage to the optic nerves and chiasm in the suprasellar cistern; the syndrome of inappropriate secretion of antidiuretic hormone; tuberculoma-associated edema; vasculitis; stroke; arachnoiditis; spinal cord atrophy; and syringomyelia. Arachnoid adhesions may lead to abnormal CSF circulation or ventricular trapping (Figure 59A.8); CSF flow studies before shunt placement may be beneficial.

Although definitive clinical trial data are lacking, corticosteroid therapy has been generally accepted for specific indications: (1) increased ICP; (2) complicated meningitis with hydrocephalus, vasculitis, or arachnoiditis; (3) very high CSF protein with impending spinal block; (4) tuberculoma with surrounding edema; (5) destructive ocular lesions; (6) replacement therapy for adrenal insufficiency; and (7) severely debilitated patients with drug-sensitive strains. Dooley et al. (1997) analyzed data from seven studies conducted from 1955-1991 and concluded that adjuvant corticosteroids improve neurological outcome in patients with tuberculous meningitis of moderate severity (drowsiness, cranial nerve palsies, or hemiparesis, but not coma). Specifically, a regimen of dexamethasone at 8-12 mg per day (or prednisone equivalent) tapered over 6-8 weeks, hastened resolution of CSF abnormalities, reduced the appearance of new neurological complications, and improved long-term neurological and general function of patients with intermediate meningeal

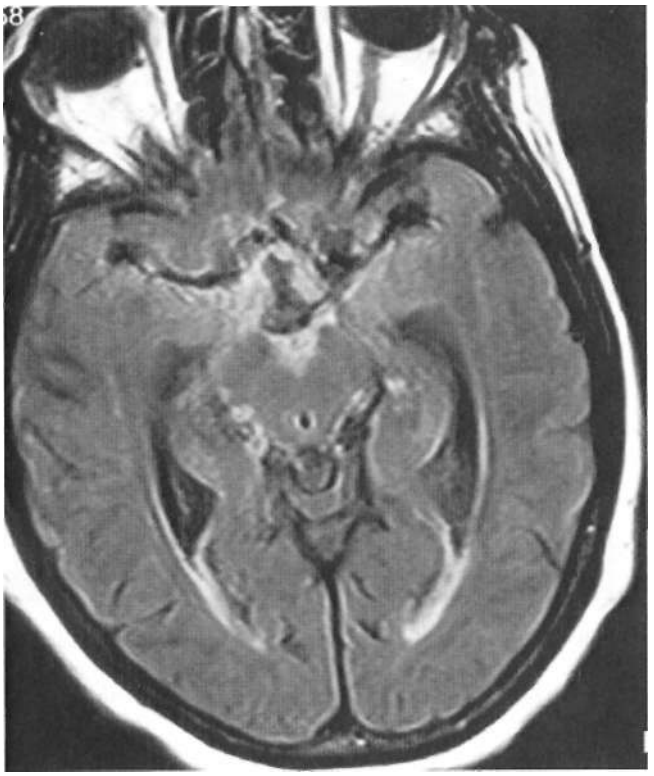


FIGURE 59A.7 Tubercular meningitis. Axial FLAIR-MR] showing marked hy peri n tensity of the basal eisterns and prominent temporal horns in a patient with mild communicating hydrocephalus. (Courtesy Dr. 6. Bowen.)

disease. Other treatment modalities including intrathecal streptomycin for meningitis and intrathecal hyaluronidase for spinal arachnoiditis have also been used.

Prevention. Vaccination is by intracutaneous injection of bacille Oalmettc-Guerin (BCG) vaccine. Enormous variation in protection, from 6-77%, has been reported, but BCG is thought to help in preventing meningitis in children in developed countries. As a live vaccine derived from *M. bovis,* BCG is contraindicated in immunocompromised patients and should not be administered with other live vaccines.

Leprosy (Hansen's Disease)

Leprosy, caused by the acid-fast bacterium M. *leprae,* is an infection of superficial tissues, primarily peripheral nerves and skin. Leprosy has been the most common cause of crippling hand disease in the world and is a frequent cause of blindness. There were an estimated 10-12 million cases worldwide in the early 1980s. By 1994, following the widespread use of multidrug therapy, numbers were reduced to 2.4 million. Leprosy cases are distributed nonhomogencously across South and Southeast Asia,

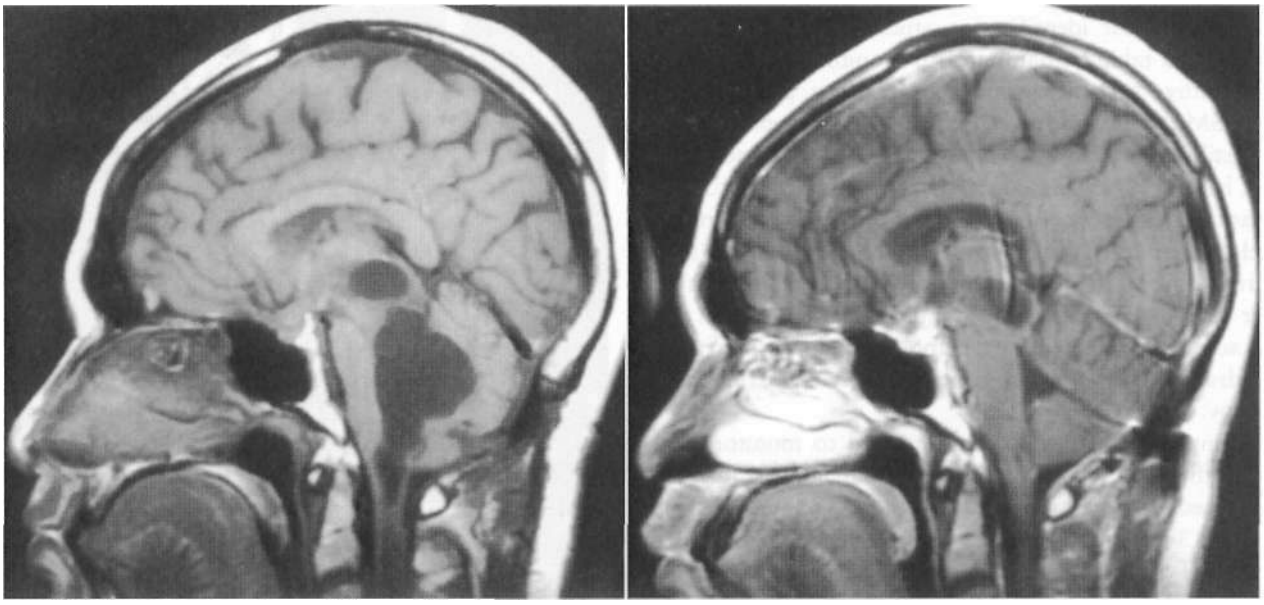


FIGURE 59A.8 Tuberculosis meningitis with arachnoid adhesions and trapped fourth ventricle. Preoperative (A) and postoperative (B) Tl-weighted sagittal magnetic resonance images showing dilatation of the fourth ventricle, posterior third ventricle, and a syrinx, resolving (B) after placement of right lateral and fourth ventricular shunts.

Africa, and Central and South America, with India, Indonesia, Myanmar, Nigeria, and Brazil collectively contributing nearly all registered cases. BCG vaccination, background prevalence of *M. tuberculosis,* and the atypical environmental mycobacteria influence leprosy epidemiology. In East Africa, for example, a reciprocal relationship between numbers of cases of TB and leprosy exists. Insufficient data exist to support the comorbidity of HIV and leprosy.

Leprosy is spread by the respiratory route or skin-to-skin contact, although transmission by insects has not been completely excluded. Most exposed individuals are naturally immune. Susceptible individuals develop one of three forms: lepromatous, borderline, or tuberculoid. All patients with leprosy manifest some degree of nerve involvement that varies with the immune response to the infection. Lepromatous leprosy is more common in Africa and Mexico, and tuberculoid leprosy is more frequent in India.

Clinical Features

The unique clinical features of leprosy result from the peripheral nerve tropism of *M. leprae* and its preference for temperatures 7" to 10°C lower than core body temperature. The long incubation period varies from *6* months to 40 years and is a consequence of its very slow growth, doubling only once every 11-13 days. Early signs include hypopigmented anesthetic skin patches, areas of cutaneous sensory loss without skin patches, and multifocal or diffuse skin infiltration. Sensory impairment proceeds in a predictable sequence, with loss of temperature sensation first, followed by pain, and then touch, with sparing of proprioception and vibration. Sweating is diminished also.

Patients with impaired cell-mediated immunity develop lepromatous leprosy. Bacilli distribute widely through skin and nerves, producing a symmetrical dermal and neural syndrome. Mulriple small macules, infiltrations, papules, and nodules appear, affecting cooler areas of the body first. Peripheral nerves thicken in the superficial, and thus cooler, portions of their course, but the strict correlation between skin lesions and anesthetic areas, characteristic of early and tuberculoid forms, does not apply in lepromatous cases. As disease progresses, sensory disturbances worsen, with sparing of sensation in the palms, soles, midchest, and midback until late in the course and after motor involvement begins. Visual impairment and blindness may result from exposure keratitis caused by lagophthalmos or corneal anesthesia, iritis, or cataracts, caused by intraocular bacteria. Destructive lesions of the respiratory tract above the larynx, testes, and structures of hands and feet develop, and diffuse systemic disease may cause lymphedema, hepatosplenomegaly, nephritis, and renal amyloidosis. Lucio reactions, sloughing ulcerations on the lower extremities or throughout the body, a consequence of arteriolar vasculitis and infarction, has been described in untreated Central or South American lepromatous patients.

Patients with good resistance develop tuberculoid leprosy, with multifocal, often asymmetrical, lesions of nerve and sometimes skin. Compared with lepromatous leprosy, infection is less disseminated, and anesthesia is confined to a few well-defined widely scattered hypopigmented or erythematous areas with palpable outer edges, hair loss, and anhidrosis. Thickening of the nerve supplying

sensation to the affected area may be found nearby. Nerve damage results from bacterial multiplication within Schwann cells or granulomatous damage to the perineurium. When more proximai nerve trunks are involved; a clinical syndrome resembling mononeuritis multiplex results. In tuberculoid leprosy, the ulnar nerve is involved most frequently, and nerves are more vulnerable than usual to trauma and pressure palsies. Radial motor involvement occurs late, owing to its deep course in the arm and forearm, whereas its distal superficial sensory portion may become thickened and palpable earlier. Painful granulomas or abscesses in the course of affected nerves may occur and require urgent medical and surgical attention. Loss of protective sensation in the hands and feet leads to traumatic, nonhealing injuries of the fingers and toes (acrodystrophic neuropathy). Sympathetic nerve injury also contributes to trophic and osteoporotic changes in the small bones of the hands and feet.

Borderline (dimorphous) leprosy, an intermediate form with features of both tuberculoid (localized) and lepromatous (widespread) disease, includes the polyneuritic form of leprosy.

Diagnosis

The diagnosis of leprosy should be considered in patients with transient, recurrent, or persistent numbness or paresthesias or when a chronic, asymptomatic, atypical skin rash does not respond to standard treatments. Palpable nerves commonly identified include greater auricular nerve in the neck, ulnar at the elbow, median at the wrist, terminal branch of the radial near the wrist, peroneal at the head of the fibula or in front of the ankle, posterior tibial below the inner malleolus, and sural on the lateral foot. Peripheral nerve electrophysiological studies demonstrate focal or multifocal neuropathy in tuberculoid cases or a more diffuse sensory neuropathy in lepromatous cases. Radial nerve sensory conduction study is one of the more sensitive indicators of disease. Absence of response to sweat tests or to intradermal pilocarpine or histamine confirms dermal sympathetic nerve involvement.

Demonstrating M. *leprae* in skin, nasal mucous membrane, or nerve biopsy establishes the diagnosis. In the slit-scrape method, smears of scrapings from skin lesions are stained for AFB. Skin biopsy facilitates correct classification and may be repeated to assess treatment response. Nerve biopsy is performed in purely neural cases or when a skin biopsy has not been diagnostic. The lepromin test can be used to classify the type of leprosy and to assess resistance to disease. Lepromin reagent, a suspension of killed *M. leprae* and cellular material from host tissue, is injected intra dermally in a dose of 0.1 mL. The early Fernandez reaction, read at 48 hours, is an allergic reaction similar to the tuberculin reaction. The degree of erythema and induration is assessed. The Fernandez reaction is positive in all forms of leprosy. The Mitsuda reaction, read at 4-5 weeks, is an indicator of resistance. It is positive in tuberculoid patients, weakly positive or negative in borderline patients, and negative in lepromatous patients. Because healthy individuals with no exposure to leprosy may have positive Mitsuda reactions, the test is not used for diagnosis.

The differential diagnosis includes other causes of hypertrophic neuropathy (Charcot-Marie-Tooth disease Type I, Refsum's disease, Dejerine-Sottas disease, primary amyloidosis, sarcoidosis, neurofibromatosis, chronic inflammatory demyelinating polyneuropathy), conditions causing distal anesthesia with ulcers and loss of digits (syringomyelia, tabes, diabetic pseudotabes, yaws, congenital in sensitivity to pain), and other causes of peripheral and multifocal neuropathies.

Treatment

Therapy should consist of two or more drugs and should begin as soon as the diagnosis is made and classification as multibacillary or paucibacillary is determined, Multibacillary leprosy is treated with RIF, 600 mg once a month; dapsone (a folate antagonist), 100 mg daily; and clofazimine, 50 mg daily plus 300 mg once a month for a minimum of 2 years, or until skin-smear results are negative, which typically takes approximately 5 years. Dapsone neuropathy, a symmetrical distal sensory neuropathy, may arise during long-term treatment, and clofazimine has been associated with retinopathy. Paucibacillary leprosy is treated with RIF, 600 mg once a month, and dapsone, 100 mg daily for 6 months. Additional drugs include the thioamides, fluoroquinolones, minocycline, and clarithromycin. Hemolytic reaction to dapsone is a concern in patients with glucose-6-phosphate dehydrogenase deficiency,

Reactions and Complications

Reversal, or type I reaction, develops after the initial therapy for borderline leprosy releases *M. leprae* antigen, Augmented cell-mediated immunity upgrades the disease toward the tuberculoid end of the clinical spectrum, and patients develop fever, inflammation within existing skin lesions, and neuritis. Urgent therapy prevents permanent nerve damage and consists of prednisone, 40-60 mg daily, tapered over 2-3 months. Antileprosy treatment is continued. Declining cell-mediated immunity in a patient with borderline leprosy leads to lepromatous disease, known as the downgrading response.

Erythema nodosum leprosum, or type 2 reaction, may be precipitated by treatment of lepromatous disease, intercurrent infection, or stress. Ninety percent of lepromatous leprosy patients experience erythema nodosum leprosum reactions after starting therapy. Antigen release from dying mycobacteria in the face of high circulating antibodies to *M. leprae* antigens provokes an Arthus-type reaction. Clinical manifestations include painful papules, neuritis,

fever, uveitis, and lymphadenitis. Mild reactions may be treated with chloroquine or salicylates, and more severe reactions with a short course of corticosteroids. Recurrent erythema nodosum Icprosum reactions arc treated with thalidomide, which inhibits TNF-a secretion, starting with 200^-00 mg as a single oral bedtime dose and followed by 50-100 mg daily after 1-2 weeks. Thalidomide must not be used in women of child bearing age because of the risk of producing phocomelia in the fetus. Long-term thalidomide therapy may produce a toxic neuropathy. Eye reactions, such as acute iridocyclitis, should be treated with topical atropine and corticosteroids.

Hands and feet require careful, regular inspection for swelling, ulceration, and functional or sensory loss during treatment. Protective footwear and wound care are provided as needed. Nerve abscesses may occur in tuberculoid or neural leprosy patients and require surgical decompression and drainage. Because relapses have been reported more than 8 years after triple-drug therapy, patients require long-term follow-up.

Prevention

Chemoprophylaxis of household contacts is not routine, although exceptions have been made for children in contact with a lepromatous patient, who then receive monthly R1F for 6 months. BCG or vaccines derived from killed or chemically modified *M. leprae* and research strains have been used. BCG's protective effect varied from 80% in Uganda to 20-30% in Myanmar and India.

Spirochetes

Spirochetes belonging to the genera *Treponema, Borrelia,* and *Leptospira* are important human pathogens. Except for the endemic treponemal diseases (yaws, pinta, bejel), all produce multiphasic or relapsing diseases with multifocal neurological involvement. Diagnosis and management of these infections, which are increasing in frequency throughout the world, are hampered by suboptimal diagnostic methods, incomplete treatment, and potential relapses, despite therapy.

Syphilis

Syphilis, a chronic multisystem disease caused by the spirochete *T. pallidum,* is spread venereally or vertically (i.e., mother to child). Venereally acquired disease is characterized by episodes of active disease separated by periods of latency, with neurological involvement in secondary and later stages. An estimated 4-9% of patients with untreated syphilis develop symptomatic neurosyphilis, with meningovascular syphilis in 2-3%, general paresis in 2-5%, and tabes dorsalis in 1-5%.

Clinical Features

Primary syphilis is characterized by one or more primary skin lesions, called chancres, which develop at the site of inoculation from 3-90 days {average, 20) after exposure. Spirochetes can be demonstrated in the lesions by darkfield microscopy. Neurological disease is not a feature of primary syphilis, although asymptomatic spread to the CNS has been documented in 30% of cases of early syphilis.

Secondary syphilis occurs 2-12 weeks after contact. Disseminated infection manifests clinically by constitutional symptoms such as fever, malaise, generalized lymphadenopathy, rash, and neurologically as syphilitic meningitis or cranial neuropathies, including hearing loss and ocular changes. Approximately 30% of secondary syphilis patients develop CSF changes indicating meningeal infection, but only 1-2% of patients are symptomatic. CSF shows lymphocytic pleocytosis, elevated protein, and low-to-normal glucose. Spirochetes can be detected by darkfield microscopic examination of secondary skin lesions and, occasionally, in CSF and the anterior chamber of the eye. After the second stage resolves, the patient enters a latent, asymptomatic period, with disease apparent only by serology. CSF at this stage is usually normal; abnormalities indicate asymptomatic neurosyphilis (Table 59A.4).

Up to one third of untreated patients develop late syphilis (tertiary syphilis), a slowly progressive inflammatory disease that includes gummatous (granulomatous), cardiovascular,

Table 59A.4: Algorithm for diagnosis and treatment for neurosyphilis

Lumbar puncture and CSF analysis if patient has any of the following
Clinical neurological involvement with syphilis
Concomitant HIV infection with syphilis of unknown duration
Active cxtraneural tertiary syphilis (aortitis, iritis, gumma etc.)
Treatment failure
Diagnostic CSF criteria for CNS syphilis
CSF pleocytosis (>5 cells/mm)
Reactive CSF VDRL test (CSF without blood contamination)
Positive CSF FTA-ABS test (highly sensitive but less specific)
No single test will diagnose all cases of neurosyphilis
Treatment recommendations
Penicillin G 18-24 million U/d (3-4 million U q 4hr IV for 10 to 14 days), or
Procaine Penicillin 2.4 million U/d 1M plus probenecid 500 g PO qjd for 10-14 days, or
Ceftriaxone *2 vjA* IM or IV for L0-.I4 d;n-s, plus hen/,athin;: penicillin 2.4 million U IM, one dose at 2 weeks
Follow-up monitoring
If CSF pleocytosis, repeat CSF every month until cell count is normal
If CSF cell count has not decreased after 6 months, or if CSF is not normal after 2 years, consider retrcatment

Source: Adapted from Rompalo, A. N. 2002, "Neurosyphilis," in *Current Therapy in Neurologic Disease,* 6th ed., eds R. T. Johnson, J. W. Griffin, & J. C. McArther, Mosby, Philadelphia.

and neurological forms. Early neurological manifestations of tertiary neurosyphilis include pure meningeal or meningovascular disease, with a 5- to 10-year latency from primary infection, and parenchymal forms, which occur 10-30 years after initial infection. General paresis refers ro parenchymal cerebral involvement and tabes dorsalis to syphilitic myeloneuropathy. Syphilitic gummas, granulomas that presenr as space-occupying lesions in brain or cord, may occur at any stage of disseminated disease.

Neurosyphilis spans all stages of disseminated disease. Meningeal, meningovascular, and parenchymal syndromes are perhaps best viewed as a continuum of disease, rather than as discrete disorders. Syphilitic meningitis, meningovascular syphilis, general paresis, and tabes are different clinical expressions of rhe same fundamental pathological events, specifically meningeal invasion, obliterative endarteritis, and parenchymal invasion. Especially in the antibiotic era, symptomatic neurosyphilis may present, not as one classic syndrome, but as mixed, subtle, or incomplete disease (Cintron and Pachner 1994). All of the neurological complications of syphilis have been reported in HIV disease, which may accelerate the onset and progression of neurosyphilis.

Syphilitic meningitis typically occurs earlier than other forms of neurosyphilis and is often asymptomatic. Rare complications of acute syphilitic meningitis include hydrocephalus, myelitis, or lumbosacral radiculitis. Meningovascular syphilis usually occurs 4-7 years after primary infection (range, 6 months to 12 years). In addition to stroke, involvement of large and small cerebral vessels also causes headache, vertigo, insomnia, and psychiatric or personality disorders.

General paresis, the encephalitic form of neurosyphilis, typically presents as progressive dementia beginning 15-20 years after original infection (tange, 3-30 years). The clinical picture also may include delusional or apathetic states, dysatthria, myoclonus, intention tremor, seizures, hyper-reflcxia, and Argyll Robertson pupils {small, irregular pupils that constrict with accommodation but not light). Disease manifestations may be remembered using the mnemonic *paresis:* personality, effect, reflexes, eye, sensorium, intellect, and speech.

Tabes dorsalis, the spinal form of syphilis, develops approximately 15-20 years after the original infection (range, 5-50 years). Tabes is characterized by lightning pains, autonomic dysfunction (urinary incontinence), and sensory ataxia. Affected patients have normal strength and lack reflexes in the legs; a positive Romberg's sign accompanies impaired proprioception. Pupils are abnormal in more than 90% of cases, with Argyll Robertson pupils observed in approximately one half. Other associated features include optic atrophy, ophthalmoplegia, ptosis, gastric or other visceral crises (pharyngeal, laryngeal, genitourinary, intestinal, rectal), impotence, fecal incontinence, and pain and temperature loss leading to trophic changes such as Gharcot's (neuropathic) joints and perforating foot ulcers.

Syphilitic inflammatory diseases of rhe eye include uveitis, chorioretinitis, and vasculitis. Each may accompany acute syphilitic meningitis or present as an isolated complication of secondary syphilis. Optic attophy evolves over months to years and may coexist with other forms of neurosyphilis, particularly tabes. Optic nerve degeneration usually begins peripherally and extends to the center of the nerve, producing progressive constriction of the visual fields with ptesetved acuity. Syphilitic otitis, an unusual manifestation, presents as unexplained hearing loss or vestibular abnormalities, with positive treponemal serology.

At birth, congenitally infected infants may show signs of serous nasal discharge (snuffles), rash, condylomas, hepatosplenomegaly, or osteochondritis. If left untreated, the classic stigmata of Hutchinson's teeth, saddle nose, interstitial keratitis, saber shins, mental retardation, hearing loss, and hydrocephalus develop.

Diagnosis

Syphilis can be diagnosed by demonstration of spirochetes in lesions of primary, secondary, or early congenital syphilis. More commonly, however, treponemal and nontreponemal serologic tests are used to make the diagnosis. Treponemal tests include fluorescent treponemal antibody absorption, microhemagglutination assay, fluorescent treponemal antibody-absorption double staining, hemagglutination treponemal test for syphilis, and T, *pallidum* immobilization. Treponemal test results become positive 3–4 weeks after inoculation and usually remain positive for life. Nontreponemal or reagin tests detect antibodies to membrane lipids of T, *pallidum,* using antigens such as cardiolipin, lecithin, or cholesterol, and include the Venereal Disease Research Laboratory (VDRL) test and rapid plasma reagin test. More sensitive but less specific than treponemal serologies, nontreponemal test results become positive 5-6 weeks after exposure and usually become negative in the year following adequate treatment.

Patients with classic neurosyphilis syndromes require serum serologies and CSF examination. Because syphilitic eye disease often is associated with neurosyphilis, patients with syphilis and oculat manifestations should also undergo LP. The Centers for Disease Control and Prevention (CDC) recommends CSF examination for all patients with syphilis who have neurological or ophthalmic symptoms and signs or active tertiary disease (aortitis, gumma, iritis) or have failed therapy (see Table 59A.4). In addition, the CDC advises that HIV-infected patients with late latent syphilis or latent syphilis of unknown duration undergo LP prior to treatment (Centers for Disease Control 1998; Pao et al. 2002).

The diagnosis of neurosyphilis depends on clinical evidence, CSF findings, and serology. CSF mononuclear pleocytosis (>5 cells per pi) and elevated protein support the

diagnosis of neurosyphilis. CSF-VDRL is very specific; it is more sensitive in meningovascular syphilis and general paresis than in asymptomatic neurosyphilis and tabes. False-positive CSF-VDRL may occur if blood contaminates CSF, as occurs with traumatic LP. Intrathecal *T. pallidum* antibody production, oligoclonal antibodies, IgM antibodies, or PCR-amplificd products may increase sensitivity of CSF examination (Cinque et al. 1997), Serum VDRL may be negative in up to 25% of patients with late neurosyphilis, but specific treponemal tests remain reactive. The CSF of patients with tabes may show less-pronounced inflammatory changes than other forms of neurosyphilis.

False-positive treponemal tests occur in Lyme borreliosis, nonvencreal treponematoses, genital herpes simplex, pregnancy, lupus, alcoholic cirrhosis, scleroderma, and mixed connective tissue disease. Transient false-positive reactions to nontreponemal tests can result from mycoplasma or enterovirus infection, mononucleosis, pregnancy, parenteral drug use, advanced TB, scarlet fever, subacute bacterial endocarditis, viral pneumonia, brucellosis, rat-bite fever, relapsing fever, leptospirosis, measles, mumps, lymphogranuloma venereum, malaria, trypanosomiasis, and varicella. Chronic false-positive reactions may be caused by malaria, leprosy, lupus, other connective tissue disorders, parenteral drug use, Hashimoto's thyroiditis, rheumatoid arthritis, reticuloendothelial malignancy, and advanced age.

The differential diagnosis of neurosyphilis includes other inflammatory meningovascular or CNS granulomatous diseases, such as TB or cryptococcal meningitis, brucellosis, Lyme disease, CNS sarcoid, and cerebral vasculitides.

Treatment

Diagnosis and treatment of neurosyphilis is summarized in Table 59A.4. Optimal treatment of neurosyphilis is aqueous penicillin G at doses of 18-24 million units per day intravenously {3-4 million units every 4 hours) for 10-14 days. The alternative, procaine benzyl penicillin, 2.4 million units intramuscularly daily, with probenecid, 500 mg orally four times daily, both for 10-14 days, has been associated with treatment failures. In penicillin-allergic patients, alternatives include oral doxycycline, 200 mg twice daily for 4 weeks, or skin testing to confirm allergy and consideration of desensitization. A patient with a positive serum treponemal antibody test result and neurological disease compatible with neurosyphilis should be treated with penicillin in doses adequate for neurosyphilis, even in the absence of CSF confirmation. Because of sequestration of spirochetes in the inner ear and poor antibiotic penetration to that area, syphilitic otitis may require a longer duration of thetapy, from *6* weeks to 3 months.

Patients with documented neurosyphilis should be followed after therapy. Clinical symptoms or signs of syphilis should prompt consideration of retreatment, as should fourfold increase of serum titers or failure of CSF titers greater than 1 to 32 to decrease at least fourfold by 12-24 months. If pleocytosis was present, LP should be performed every 6 months until cell count normalizes. Patients in whom CSF cell count does not decrease after 6 months, or in whom CSF does not return to normal after 2 years, may require retreatment.

Complications of and Response to Treatment

Jatisch-Herxheimer reactions most frequently complicate treatment in patients with early syphilis. Clinical features of this systemic response to release of heat-stable pyrogens from spirochetes include rigors, fever, hypotension, and leukopenia. The response to treatment varies according to the chronicity of the neurological damage. In meningovascular syphilis, signs that remain 6 months after treatment usually persist indefinitely. Treatment of general paresis may improve the cognitive or psychiatric disease in relatively early cases or arrest disease progression in approximately one half of advanced cases. Residual symptoms of tabes continue after the CSF has normalized and require symptomatic treatment of joint deformities with orthotics, visceral crises with atropine, and pain with anticonvulsants or amitriptyline. Pretreatment optic atrophy and extensive perioptic meningeal infiltrate may presage progressive vision loss during treatment. Adequate-treatment of a mother with syphilis before the sixteenth week of gestation prevents congenital syphilis.

Lyme Disease (Borreliosis)

Lyme disease, a systemic disease with dermatological, rheumatological, neurological, and cardiac manifestations, is caused by *Borrelia burgdorferi* and transmitted by the hard-shelled deer ticks: *Ixodes dammini* in the eastern United States, *Ixodes pacificus* in the western United States, and *Ixodes ricinus* in Europe.

Clinical Features

The existence of both early and late neurological manifestations, diagnostic uncertainty, and potential for relapse despite therapy have fueled continuing debate over the spectrum of Lyme-related neurological disease. Best agreement exists for the early neurological syndromes, which include lymphocytic meningitis, cranial neuropathy (commonly unilateral or bilateral Bell's palsy), and painful radiculoneuritis, which can occur alone or in combination. Optic neuritis, mononeuritis multiplex, and Guillain-Barre syndrome are other infrequent manifestations of early neurological involvement. Neurological complications of more advanced Lyme disease include encephalomyelitis, with predominant white matter involvement and peripheral neuropathy. Lymphocytic meningitis is usually acute, but may cause chronic or relapsing meningitis and communicating hydrocephalus. Radiculoneuritis, beginning as

a painful limb disorder, may continue with exacerbations and remissions for up to 6 months. Encephalopathy with memory or cognitive abnormalities, confusional states, accelerated dementia, and normal CSF study results may occur. Other psychiatric or fatigue syndromes appear less likely to be causally related to Lyme disease (Steere 2001).

The most common form of neuroborreliosis in Europe, radiculoneuritis {lymphocytic mcningoradiculitis, Bannwarth's syndrome), is rare in the United States. The meningitic forms of borreliosis may resemble CNS lymphoma, because the CSF may contain atypical lymphocytes. The differential diagnosis of *Borrelia* encephalomyelitis includes a first episode of multiple sclerosis. Bites from uninfected ticks may produce similar neuropathies (Garcia-Monco and Benach 1995).

Several systemic disorders support the diagnosis of Lyme borreliosis. Dermatotogical manifestations include erythema chronicum migrans, a painless expanding macular lesion present shortly after initial infection in approximately two thirds of patients, and acrodermatitis chronicum atrophicans, a bluish-red discoloration of the legs that occurs after the first year of infection. Other extraneural features include Borrelia lymphocytoma, occurring 6-12 months after infection, recurrent monoarthritis or polyarthritis, and second- or third-degree cardiac conduction block.

Diagnosis

The best clinical marker for the disease is the erythema chronicum migrans rash that occurs in 60-80% of patients. The diagnosis of active neuroborreliosis is made by the presence of consistent history, signs, and symptoms, together with CSF pleocytosis, serum anti-B. *burgdorferi* antibodies, and evidence of intrathecal antibody production. Serologic testing by ELISA is performed as an initial screen, followed by Western blot confirmation. Culture of organisms and PCR testing of CSF are also available.

Treatment

Borreliosis is treated with parenteral antibiotics if there is evidence that infection has crossed the blood-brain barrier. Ceftriaxone (2 g once daily intravenously) or penicillin (3-4 million units intravenously every *3-A* hours) for 2-4 weeks are first-line drugs. Tetracycline and chloramphenicol are alternatives in penicillin- or cephalosporin-allergic patients. Jarisch-Merxheimcr reactions may occur within 2 hours of initiating therapy. Mepta/inol, a drug with mixed opiate agonist and antagonist properties, may mitigate the attack. Routine use of corticosteroids is not indicated. Recommendations for the use of corticosteroids in neuroborreliosis generally have been limited to patients tteatcd aggressively with intravenous antibiotics with evidence of severe inflammation that fails to improve with time.

CSF examination should be performed toward the end of the 2- to 4-week treatment course to assess the need for continuing treatment and again 6 months after the conclusion of therapy. Intrathecal antibody production may persist for years following successful treatment and in isolation does not indicate active disease. Patients in whom CSF pleocytosis fails to resolve within *6* months, however, should be retreated.

Peripheral or cranial nerve involvement without CSF abnormalities may he treated with oral agents, either doxycycline, 100 mg twice daily for 14-21 days, or amoxicillin, 500 mg every 8 hours for 10-21 days.

Relapsing Fever

The term *relapsing fever* applies to two distinct borrelial diseases, louse-borne relapsing fever and tick-borne relapsing fever. Both are characterized by episodic fever and spirochetcmia, systemic symptoms, and variable presence of neurological complications. The human body louse transmits .0, *recurrentis* and soft ticks of the genus *Ornithodoros* transmit other *Borrelia* spp., including *B. duttoni.*

Clinical features

Overcrowding and poor hygiene predispose to louse-borne relapsing fever. Clinical featutes may he mild, but sevete febrile illness with mortality reaching 40% in epidemic situations also is seen. Hepatosplenomegaly, jaundice, respiratory symptoms (cough and dyspnea), and myocarditis ate more common than in the tick-borne syndrome, and neurological manifestations, including meningitis, meningoencephalitis, cerebral hemorrhage, or neuropathy, develop in approximately 30% of patients.

Neurological syndromes associated with tick-borne relapsing fever appear at the end of the first bout of fever or with relapses. Cranial neuritis is the most common neurological manifestation of tick-borne disease, with facial weakness affecting up to 22% of patients. Lymphocytic meningitis, subarachnoid hemorrhage, encephalitis, transient or permanent focal deficits, iritis, iridocyclitis, optic atrophy, and sciatic neuralgias also have been described.

Diagnosis

Demonstrating borreliae in the peripheral blood of febrile patients using darkfield microscopy and Wright's or Gicmsa's stained blood smears establish the diagnosis. Proteus OX-K agglutinin titers are elevated in relapsing fever. Nervous system disease is accompanied by CSF lymphocytic pleocytosis and elevated protein. Spirochetes may be detected in CSF by smear or animal inoculation in approximately 12% of patients with CNS signs. In the westetn United States, the diffetential diagnosis of tick-borne relapsing fever includes Colorado tick fever and Rocky Mountain spotted fever.

Treatment

Louse-borne relapsing fever is treated with a single oral dose (500 mg) of tetracycline; erythromycin in the same dose is also effective. Tick-borne relapsing fever is treated with oral tetracycline or erythromycin, 500 mg every 6 hours for 5-10 days.

Leptospirosis

Many wild and domestic animals carry *Leptospira interrogans.* Leptospirosis is a worldwide zoonotic infection transmitted direct!;- to humans by contact with urine of infected rodents or domestic animals or indirectly via water or soil contaminated by infected urine. The severity of disease varies widely; jaundice, hemorrhage, and renal failure develop in severe cases. Approximately 15% of patients develop signs and symptoms of meningitis, and many more have lymphocytic CSF.

Clinical Features

The illness often follows a biphasie course. The first bacteremic phase is characterized by fever, headache, myalgias, nausea, vomiting, and abdominal pain. Dissemination of the organism in the acute phase leads to meningeal invasion, during which leptospirae may be cultured from blood and CSF but not urine. A second immune phase develops in the second week, once the patient has mounted an antibody response to the organism. This stage is characterized by more severe systemic illness, with meningitis, uveitis, rash, and in severe cases, hepatorenal and hemorrhagic syndromes. Eighty percent to 90% of patients have CSF abnormalities consistent with aseptic meningitis. CSF examination reveals lymphocytic pleoeytosis, elevated protein, and normal glucose levels, but the leptospirae have been cleared from the CSF by tins stage. CSF pressure is usually normal, yet LP may improve the headache. More-severe forms of illness are accompanied by conjunctival suffusion, myositis with rhabdomyolysis, meningoencephalitis, or myelitis. In Weil's disease, the most severe form, hepatorenal dysfunction and myocarditis accompany depressed consciousness and, occasionally, intracerebral hemorrhage. Cerebral arteritis is an unusual late complication, and a form of moyamoya disease has been thought to occur as a result of obstruction of the internal carotid arteries near the circle of Willis. Mononeuritis multiplex and Guillain-Barre syndrome have been reported. Invasion of the eyes by leptospirae during the acute phase may produce uveitis weeks or months after recovery.

Diagnosis

Jaundice, renal failure, and elevated serum creatine kinase (CK) following a febrile illness suggest the diagnosis. Organisms can be isolated from blood or CSF during the first 10 days of illness and from urine during the first month of illness. Serological test results, based on macroscopic or microscopic agglutination procedures, arc positive after the first week.

Treatment

Severe leptospirosis is treated with penicillin G, 1.5 million units intravenously every 6 hours for at least 7 days. 1 ess-severe cases are treated with doxycycline, 100 mg twice daily for 5-7 days.

RICKETTSIAE AND RELATED ORGANISMS

Rickettsiae are obligate parasites that appear microscopically as coccobacilli. The major ones are maintained in nature by a cycle involving an animal reservoir, an insect vector (lice, fleas, mites, and ticks), and humans. Q fever is an exception and is probably contracted by inhalation. In the early twentieth century, the rickettsial diseases, epidemic typhus in particular, were common and of grave health concerns. In Eastern Europe, between 1915 and 1922, there were an estimated 30 million cases of typhus, with 3 million deaths. Now, as a result of insect control and antibiotic therapy, the rickettsial diseases are uncommon. In the United States these diseases are quite rare, bur they are important because up to one third of patients have neurological manifestations, mainly headache and meningoencephalitis. Rocky Mountain spotted fever is the commonest form in the United States, with about 200 cases each year. All rickettsial diseases share the clinical triad of high fever, skin rash, and headache, with meningoencephalitis developing during the second week of illness in some cases. Rickettsiae infect small blood vessels throughout the body causing endothelial wall inflammation and proliferation, thrombosis, and perivascular inflammation. The vasculitis is most prominent in skin, heart, skeletal muscle, kidney, and CNS.

Lpidemic (Louse-Borne) Typhus

K. prowazekii is transmitted by the human body louse from person to person, causing epidemic louse-borne typhus. A nonhuman reservoir, the southern flying squirrel in the eastern and south-central United States, has been recognized as an alternative source of infection, but the vector insect is not known.

Clinical Features

The illness begins within 12 days of a louse bite with abrupt fever, headache, limb pain, nausea, vomiting, facial swelling, and rash (Sexron and Kaye 2002), The rash

appears first in the axillae and upper trunk, spreading to become confluent and hemorrhagic, but sparing the face, palms, and soles. Vacant, placid expressions or agitation are described during the high, unremitting fever, whereas meningitis or meningoencephalitis with focal neurological deficits, delirium, or coma accompany severe disease and complicate up to 50% of cases. Tinnitus, hyperacusis, deafness, dysphagia, and midbrain stroke syndromes are recognized consequences of brainstem microinfarction. Transverse myelitis, hcraiparesis, painful peripheral neuropathy, akinetic mutism, and psychiatric disturbances have been reported in survivors. Systemic complications include vascular occlusions and gangrene, myocarditis, shock, and secondary infections.

Diagnosis

The combination of a cold weather environment, crowded conditions, and infrequent bathing and changing of clothes provides an ideal setting for louse-borne typhus. Clinical suspicion and serological demonstration of heterophilc antibodies to *Proteus mirabilis* OX-19 and OX-2 strains, the Weil-Felix reaction, assist in diagnosis. CSF may show modest elevations in protein and lymphocyte count, with normal glucose. Specialized laboratories can make a diagnosis by organism isolation, agglutination or EI .ISA serologic tests, or PCR amplification.

Treatment

Early and specific treatment is indicated to avoid a potentially fatal outcome. Effective therapies include oral or intravenous chloramphenicol, 500 mg every 6 hours intravenously for 7 days; oral or intravenous tetracycline, 500 mg every 6 hours intravenously for 7 days; or doxycycline in a single oral dose of 200 mg for adults. Relapses arc retreated with the same regimen. Formaldehyde-inactivated *R. prowazekii* vaccine is recommended for persons with potential occupational exposure.

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever, a tick-borne infection caused by *R. rickettsii,* is the most virulent of the spotted fevers, with fatality of 20% when treatment is delayed. Rocky Mountain spotted fever is present in the northwestern and eastern United States, Canada, Mexico, Colombia, and Brazil. Seasonality is predicted by activity of local ixodid tick species, including *Dermacentor andersoni* (wood tick) and *Dermacentor variabilis* in the western United States, *Amblyomma americanum* (lone-star tick) in the southern United States, *Rhipicephalus sanguineus* in Mexico, and *Amblyomma cajennense* in Brax.il and Colombia. Other forms of tick typhus, some in geographically overlapping areas, include *Rickettsia japonica* in japan, *Rickettsia australis* in Australia, Mediterranean spotted fever *(Rickettsia conorii)* in Asia, Africa, and the Mediterranean, and Siberian tick typhus *(R. siberica).*

Clinical Features

The illness begins with fever, headache, myalgia, and gastrointestinal symptoms 2-14 days after the tick bite. The rash appears first around the wrist and ankles from days 3-5 of the illness and spreads to the soles of the feet and forearms. Petechial and ecehymotic rashes, indicating microcirculatory injury, may foreshadow gangrene of the digits or rhabdomyolysis. Other complications include renal failure and pulmonary edema. CNS manifestations accompany severe cases. Meningitis or meningoencephalitis with microinfarcts causes focal neurological deficits, transient deafness, depressed consciousness, or coma. CSF examination reveals elevated protein and lymphocytic or polymorphonuclear plcocytosis in approximately 30% of patients, with low glucose in fewer than 10%. Electroencephalography shows diffuse abnormalities, which may persist into convalescence. Flame-shaped hemorrhages, venous engorgement, or arterial occlusion on ophthalmoscopic examination, indicate retinal vasculitis.

Diagnosis

R. rickettsii can be demonstrated by direct immunofluorescence or immunoperoxidase staining of skin biopsy in patients with rash. Other laboratory tests may indicate anemia, thrombocytopenia, coagulopathy, hyponatremia, and muscle tissue breakdown. Serology retrospectively confirms the diagnosis.

Rocky Mountain spotted fever and the other rickettsial diseases should be distinguished from other causes of meningoencephalitis with rash, insect exposure, or recurrent fever by tests specific for the alternative diagnoses: from meningococccmia by blood and CSF culture, viral hemorrhagic fevers or hemorrhagic measles by serology, relapsing fever and tularemia by blood culture, typhoid fever by blood or bone marrow culture, leptospirosis by clinical or laboratory evidence of myositis and hepatitis, Lyme disease by serology, malaria by blood films, secondary syphilis by serology, toxic shock syndrome by blood wound or vaginal culture, and thrombocytopenic purpuras and immune-mediated vasculitis by serological markers of collagen-vascular disease,

Treatment

Treatment is with oral or intravenous tetracycline (25-50 mg per kg per day) or chloramphenicol (50-75 mg per kg per day) in four divided doses or oral doxycycline, 100 mg twice a day for 7 days and continued for 2 days once the patient has become afebrile.

Other Rickettsial Diseases

Murine typhus is caused by *R. typhi.* The organism is harbored by rats worldwide and transmitted to humans by flea bites. Early disease is characterized by fever, headache, myalgia, nausea, and truncal rash in 18% of patients. Neurological symptoms, including confusion, drowsiness, seizures, and ataxia, and focal deficits may occur. Diagnosis is based on clinical suspicion, and the Weil-Felix reaction is the same as for louse-borne typhus. Treatment is with chloramphenicol, tetracycline, or doxyeycline.

Scrub typhus is a febrile disease in East and Southeast Asia with headache, painful adenopathy, eschars, and trunk and thigh rash. *R. tsutsugamushi,* the causative agent, is transmitted by the bite of larval-stage trombiculid mites (chiggers). Meningoencephalitis or myocarditis accompanies severe cases. Specific serological or PCR tests arc used for diagnosis when available. Treatment is with a single oral dose of doxyeycline, 200 mg for adults and 100 mg for children.

Q fever, an acute or chronic febrile illness that occurs worldwide, is caused by *Coxiella burnetii.* Cattle, sheep, and goats are the animal reservoirs. C. *burnetii,* though in the rickettsial family, differs from the other rickettsial infections by the aerosol route of transmission, absence of rash, and lack of cross-reacting antibodies to *Proteus* OX species. Characteristic clinical syndromes include atypical pneumonias or hepatitis. Also seen are endocarditis, vertebral osteomyelitis, and neurological syndromes, including aseptic meningitis and encephalitis. Diagnosis depends on ELISA or indirect fluorescent antibody serologic tests. Rarely, C. *burnetii* has been isolated from the CSF. Early, uncomplicated Q fever is treated with chloramphenicol, tetracycline, or doxyeycline. Endocarditis requires therapy with RIF and TMP/SMX or tetracycline. A formalinized vaccine is available for individuals with potential occupational exposure.

Ehrlichiosis

Ehrlichioses are tick-borne zoonotic infections caused by an intra leukocytic bacterium closely related to *Rickettsiae.* First recognized as a canine pathogen, two species of *Ehrlichia* have been associated with human disease, including a summertime meningitis, in the United States, and a third species with a mononucleosis-like illness in Japan.

In the United States, incidence peaks from spring through autumn. Patients presenr with fever, headache, myalgia, rash, and history of tick bite. Occasionally, meningitis is the sole clinical manifestation. Renal failure, disseminated intravascular coagulation, cardiomegaly, opportunistic infection, seizures, encephalopathy, or coma are among the serious complications in some cases (Fishbein et al. 1994).

Most patients have varying degrees of leukopenia, thrombocytopenia or anemia, and mild to moderate hepatic enzyme abnormalities. Diagnosis depends on epidemiological and clinical features, plus a high index of suspicion. Acute and convalescent sera confirm the diagnosis. PCR-based tests are available for early confirmation of acute infection. Treatment is with oral or intravenous doxyeycline, 100 mg twice daily, for 7 days.

Bartonella

Oroya fever and verruga peruana are two forms of the same disease, bartonellosis, caused by *Bartonella hacilliformis.* These two clinical forms were linked to bartoncllosis by the fatal self-inoculation experiment of the Peruvian medical student, Daniel Carrion, who, with the help of a colleague, injected himself with material from verruga peruana cutaneous lesions and contracted Oroya fever. Bartonellosis also is referred to as Carrion's disease. Oroya fever is associated with encephalitis and cerebral venous thromboses, and verruga peruana with intracranial nodules. These diseases occur in river valleys along the western slopes of the Andes in Peru, Ecuador, and Colombia at altitudes of 2000-8000 feet. Sandfly bite transmits the disorder.

B. hacilliformis can be seen in red blood cells in the acute febrile stage and in smears from verruga. The differential diagnosis for Oroya fever includes malaria, typhus, and typhoid. The verruga stage resembles yaws or secondary-syphilis. Chloramphenicol (4 g daily in divided doses) for at least 7 days is the drug of first choice. Penicillin, tetracycline, streptomycin, and eotrimoxazole are alternatives.

ZOONOSIS PATHOGENS AND RELATED ORGANISMS

Brucellosis

Brucellosis, a zoonosis caused by several *Brucella* species *(B. melitensis, B. abortus,* and *B. suis),* is a multisystem illness characterized by fever, frequent bone and joint disease (arthritis, sacroiliitis, spondylitis, osteomyelitis), and respiratory, gastrointestinal, cardiac, or neurological disease. Normally a disease of domestic and wild animals, Brucellosis is transmitted to humans by ingestion of infected unpasteurized milk, by aerosol spread, or by contact with infected animals or animal products. The disease exists worldwide, but is especially prevalent in Mediterranean regions, the Middle East, the Indian subcontinent, and Latin America. In the United States, the disease is rare, with less than 100 cases being reported annually since 1990.

Early complaints may include fatigue, sensations of malodorous sweat or abnormal taste, and symptoms of deptession. Untreated, an undulant fever pattern emerges in 2- to 4-week cycles. Meningitis can be the presenting manifestation, or it may occur late in disease. Acute or chronic meningitis, encephalitis, meningovascular disease, multifocal white matter disease, intracerebral or epidural abscess, subdural empyema, intracranial hypertension,

ruptured mycotic aneurysms, hydrocephalus, papilledema, cranial neuropathies, psychosis, parkinsonism, radiculopathies (usually lumbosacral) or myelopathy, peripheral neuropathies, and myositis have been reported. Endocarditis occurs in approximately 2% of cases.

Brucellosis figures in the differential diagnosis of nearly any neurological disease in endemic areas. Definitive-diagnosis depends on isolation of brucellae from blood, bone marrow, or other tissues. Because the organism is difficult to culture, diagnosis usually depends on (1) positive *Brucella* agglutination or FLISA test results with high titers of antibody in blood and CSF; (2) abnormal CSF with a lymphocytic pleocytosis, elevated protein, and low to normal glucose; and (3) response to therapy.

Uncomplicated brucellosis is treated with oral doxycyclinc, 200 rng daily, with streptomycin, 1 g intramuscularly daily, for 12 weeks, or another amino glycoside for the first 4 weeks, then followed by RIF (10-15 mg/kg per day) for an additional 4-8 weeks. Neurobrucellosis, endocarditis, and skeletal and other severe organ involvement are treated with three-drug therapy with doxycycline, an aminoglycoside, and RIF for at least 12 weeks. Children under 8 years of age are treated with trimethoprim/sulfamethoxazole (TMP-SMX) in combination with an aminoglycoside and RIF. Adjunctive corticosteroid therapy has been used for concurrent vasculitic or demyelinatiug disease.

Anthrax

Anthrax, caused by the gram-positive sporulating bacillus, *Bacillus anthracis,* is usually a disease of herbivores, acquired from contact with soil-containing spores. Less commonl\. anthrax causes hemorrhagic meningitis in humans after exposure to infected animals or their products. The three main forms of disease are cutaneous, respiratory, and gastrointestinal (Swartz 2001). Meningitis is seen in less than 5% of cases. For a diagnosis of anthrax meningitis, there should be a primary site of infection, such as a malignant pustule or pulmonary syndrome, plus CSF and blood containing *B. anthracis.* Treatment is with penicillin G, 4 million units cvety 4-6 hours for 7-10 days.

Plague

Plague, caused by *Yersinia pestis,* is a zoonotic infection of wild rodents, transmitted by the bites of infected fleas to humans, an accidental host. Meningitis is an unusual manifestation of plague, usually complicating bubonic plague, particularly if buboes are located in the axilla. Human infection takes the clinical forms of febrile lymphadenitis (bubonic plague), septicemic, pneumonic, or meningeal plague. Most meningitis cases follow inadequately treated bubonic plague by 9-15 days, but primary plague meningitis also occurs. Y. *pestis* can be found on CSF Gram stain and culture. Treatment of the primary infection is with streptomycin, 30 mg/kg per day intramuscularly in two divided doses for 10 days. Meningitis is treated with intravenous chloramphenicol, 25 mg/kg initially, followed by 60 mg/kg per day in four divided doses for 10 days, either alone or in combination with streptomycin.

Tularemia

Tularemia (rabbit fever, deer fly fever, Ohara's disease, yatobyo) is an infectious disease of rodents caused by *Francisella tularensis.* Tularemia is transmitted to humans by insect bite, handling infected animals, ingesting infected meat or water, or inhaling contaminated aerosols or dust. *F. tularensis* causes an acute febrile illness; classic forms include ulceroglandular, oculoglandular, pneumonic, pharyngeal, abdominal, or typhoidal (septicemic) disease. Dissemination may lead to meningitis or encephalitis with mononuclear pleocytosis, elevated protein, and low glucose. Encephalitis and Guillain-Barre syndrome accompanying the pneumonic and pleuritic form have been reported also. Clinical suspicion and serological studies aid in the diagnosis; culture and isolation of *F. tularensis* are difficult. Streptomycin, 1 g intramuscularly daily for 10-14 days, treats the infection. Gentamicin is an alternative.

Pasteurellosis

Pasteurellae, primarily animal pathogens carried in the nasopharynx or gastrointestinal tract of many domestic and wild mammals and birds worldwide, are rare causes of meningitis or brain abscess in humans during disseminated infections. Human *Pasleurella* infections, usually *P. multocida,* are either focal soft tissue infection after an animal bite, respiratory infection, or bacteremia. Diagnosis is by demonstration or culture of the organism from wound, sputum, or CSF, and treatment is with penicillin.

Glanders

Glanders, primarily an equine infection by *Pseudomonas mallei,* occasionally produces human disease consisting of suppurative infections, lymphadenopathy, and pulmonary disease. Meningitis or brain abscesses occur in up to one fourth of patients. A history of contact with horses, mules, or donkeys is typical, and transmission occurs through contamination of broken skin or mucosal surfaces by draining ulcers of an infected animal. Diagnosis is by microscopic examination of exudates. A 3-week course of sulfadiazine, 100 mg/kg daily in divided doses, is recommended.

Melioidosis

Melioidosis, caused by the ubiquitous soil saprophyte *Fseudomonas pseudomallei,* is a glanderslike infectious disease of animals and humans, with meningitis or brain abscess sometimes complicating disseminated forms (Woods et al. 1932). A role for a neurological toxin in the development of aseptic meningitis or brainstem encephalitis, bulbar and respiratory weakness, and peripheral motor neuropathy of Guillain-Barrc type, in the absence of direct CNS infection, has been suggested but not proven.

The diagnosis should be considered in patients with a radiological pattern of TB from which AFB-staining bacteria cannot be found. Melioidosis is diagnosed by identifying organisms with bacteriological staining and culture techniques. Patients are seropositive by indirect fluorescent antibody or ELISA tests. Septicemic forms are treated with TMP/SMX plus ceftazidime, 120 mg/kg per day, with intravenous therapy for 2 weeks and oral treatment for 6 months.

Cat-Scratch Disease

Cat-scratch disease, a slowly progressive regional adenitis caused by *Bartonella henselae* or, less often, *Afipia felts* is associated with aseptic meningitis in immunocompetent individuals and encephalitis, myelitis, or radiculoneuritis in HIV-infected patients. Several clinical patterns have been recognized. Immunocompetent individuals may have one or several bacteremic episodes with fever, arthralgias, headache, and aseptic meningitis, but the illness is self-limited in the majority of cases. HIV-infected patients with disseminated *B. henselae* infection may have bacillary angiomatosis (neovascular proliferative skin lesions), which resemble the cutaneous stigmata of verruga peruana or Kaposi's sarcoma, oculoglandular syndrome with preauricular adenitis, palpebral or conjunctival granulomas, anemia, hepatosplcnomcgaly, or encephalomyelitis. Direct plating of homogenized tissue of accessible lesions has yielded bacteria, but cultivation of *Bartonella* spp. is technically difficult and slow. ELISA tests and PCR amplification from infected tissues are available. Intravenous gentamicin is recommended for encephalitis and oral doxycycline, erythromycin, or ciprofloxacin for bacillary angiomatosis.

Rat-Bite Fever

Rat-bite fever is a systemic febrile illness caused by *Streptobacillus moniliformis,* which is transmitted by the bite of a rat or other small rodents. Patients develop rash or purpuric skin lesions, asymmetrical polyarthralgias, or septic arthritis, with the additional complications of meningitis, brain abscesses, endocarditis, or myocarditis. Diagnosis is by visualization or culture of organisms from blood, joint fluid, or purulent material. Treatment is with penicillin, streptomycin, or a cephalosporin in penicillin-allergic patients.

STAPHYLOCOCCAL SYNDROMES

Toxic Shock Syndrome

Toxic shock syndrome (TSS), epidcmiologically linked to several toxigenic *Staphylococcus aureus* strains, is a multisystem disorder characterized by desquamating skin rash, especially on the palms and soles, high fever, hypovolemic shock, vomiting or diarrhea, renal failure, hypcrcmic mucosal surfaces, thrombocytopenia, liver enzyme abnormalities, myalgias, and encephalopathy. Several related exotoxins, chiefly TSS toxin 1 (TSST-1), produced by isolates of 5. *aureus* from patients, cause the disease. TSS has been reported in children, in menstruating women using hyperabsorbent tampons, and following gynecological and other surgical procedures. CNS complications may be more frequent in nonmenstrual TSS.

Confusion, disorientation, agitation, or somnolence independent of anoxic or metabolic changes arc described. Other features include headache, generalized electroencephalographic abnormalities, poor concentration, memory impairment, and other cognitive dysfunction. CSF is usually normal. Serum CK levels, elevated in over one half of patients, reflect the severity of toxic myositis and convalescent-stage weakness. Although blood, vaginal fluid, or wounds may be cultured for *S. aureus* and isolates tested for production of TSST-1, TSS remains a clinically defined syndrome. Other febrile exanthems with hypotension, such as Rocky Mountain spotted fever, leptospirosis, meningococcemia, gram-negative sepsis, viral exanthems, and drug reaction, should be excluded. Management requires aggressive fluid replacement and treatment with a *fi*-lactamase-resisrant antistaphylococcal antibiotic or clindamycin, 300 mg intravenously every 8 hours for 10-14 days.

Tropica! Pyomyositis

Tropical pyomyositis is a subacute syndrome caused by staphylococcal infection, characterized by the spontaneous appearance of bacterial abscesses within the fascial boundaries of large-bulk skeletal muscles. Tropical pyomyositis accounts for 3^1% of surgical admissions to hospitals in sub-Saharan Africa. Although early staphylococcal pyomyositis may respond to an antistaphylococcal penicillin or vancomycin alone, drainage of abscess cavities is usually necessary. In temperate regions, a different, hyperacute pyomyositis, caused by group-A beta-hemolytic streptococcal infection, is recognized. When it occurs, it is usually the earliest sign of critical, potentially fatal, disseminated infection, designated streptococcal TSS.

Therapy includes penicillin or ampieillin, a third-generation cephalosporin, surgical drainage, and supportive treatment with volume expansion.

FILAMENTOUS BACTERIAL INFECTIONS (ACTINOMYCETOSIS)

Nocardiosis

Nocardiosis is a locally invasive or disseminated infection caused by the aerobic actinomycetes *Nocardia asteroides, N. otitidiscaviarum,* and *N. brasiliensts.* The organisms are soil saprophytes, spread to humans by inhalation, through broken skin, from the gut, or after dental procedures. Primary infection, typically manifests as pneumonia with cavitary pulmonary lesions, but sinusitis, keratitis, cutaneous abscesses and fistulae, septic arthritis, or vertebral osteoarthritis are seen also. Disseminated disease commonly involves the CNS. The CNS syndromes, including cerebral abscesses, meningitis, and rarely, hemorrhagic meningitis develop in approximately one third of all pulmonary cases and primary CNS infection in another 5-7%. Cerebral abscesses ofrcn appear as complex multiloculated structures with satellite extensions on neuroimaging studies. Brain abscesses tend to burrow into a ventricle or our to the subarachnoid space, so meningitis is often associated with abscesses.

Nocardia spp. appear as weakly gram-positive, branching filaments in sputum, drainage from fistulas, or histological specimens. Dense bacterial concentrations resemble Chinese calligraphy. *Nocardia,* when stained with modified acid-fast procedures, are partially acid fast. Because nocardiosis is an infection with a variable, often chronic, course, treatment with sulfonamides (TMP/SMX) may need to extend for months. The recommended intravenous dose is TMP (15 mg/kg per day) and SMX {75 mg/kg per day), rhc equivalent of two double-strength tablets every 8 hours. Second-line drugs include minocycline, imipenem, or an aminoglycoside in combination with a thitd-generation cephalosporin.

Actinomycosis

Actinomycosis, characterized by abscesses that cross fascial planes to form sinuses, is a rare cause of brain abscesses. Actinomycosis is caused by a variety of gram-positive anaerobic or microaerophilic rods of the genera *Actinomyces* (most commonly *Actinomyces israelii* and A, *arachnid,* normal mouth and female genital tract flora). Most infections are either cervicofacial, thoracic, abdominal, or pelvic. Cervicofacial actinomycosis or "lumpy jaw" is the most common form and may develop following dental procedures or oral mucosa trauma, as a complication of dental caries or periodontal disease, ot without antecedent trauma or predisposing infection. Abscesses and draining sinuses form and exudates contain sulfur granules, so named because they are yellow. Actinomyces reach the brain by direct extension of oral-cervicofacial disease or hematogenous sptead. Brain abscess is the most common CNS presentation. Abscesses may be single or multiple and may appear multiioculated with ring enhancement (Figure 59A.9) or more homogeneous enhancement on neuroimaging studies. Chronic meningitis may develop as a consequence of spread from a parameningeal extracranial site or paraventricular or parameningeal brain abscess. Spinal epidural abscess, dural sinus rhrombosis, and spinal cord subdural empyema also have been reported.

Macroscopic and microscopic examination of pus and granules, followed by culture, establishes the diagnosis. Actinomycosis resembles nocardiosis, but the latter does not form granules in visceral organs. Actinomycosis occurs in immunocompetent patients, whereas nocardiosis is a disease of immunosuppressed patients. Treatment is with penicillin, initially 18-24 million units in divided doses intravenously per day for 2-6 weeks, followed by oral penicillin or amoxicillin for 6-12 months. Surgical drainage and excision may be indicated. Clindamycin penetrates

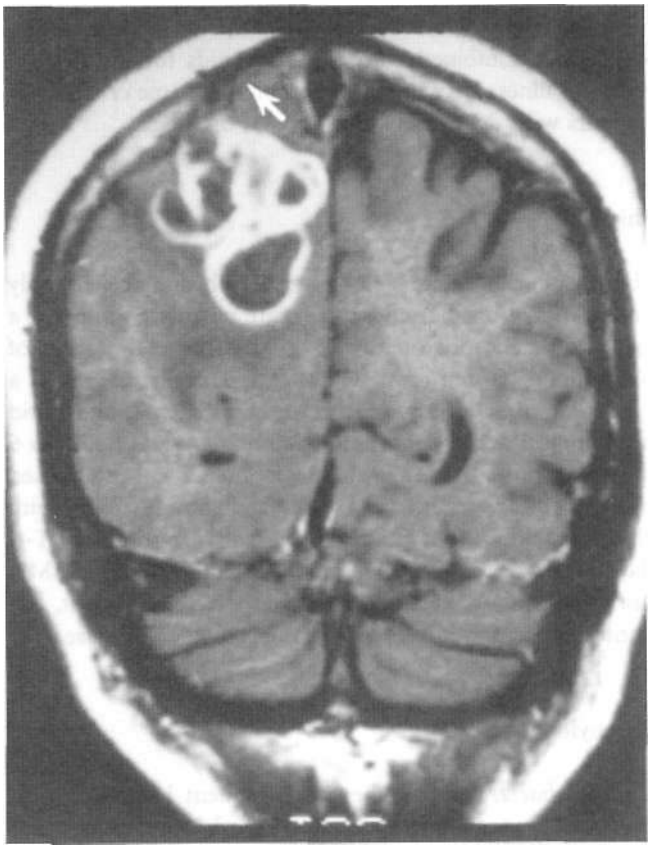


FIGURE 59A.9 Actinomycosis. Gadolinium-enhanced coronal Tl-weighted magnetic resonance image showing multiioculated, ring-enhancing lesion in a patient with intracerebral spread of actinomycosis abscesses from a skull infection. Skull involvement is indicated by resorption of normal fatty marrow signal *{arrow).*

bone well and may be the drug of choice if there is bony involvement.

ENTERIC BACTERIA

Salmonellosis

A common cause of neonatal meningitis, *Salmonella* species are associated also with brain abscess, subdural empyema, and recurrent bacteremia in HIV-infected parients, *Salmonella typhi* and *S. paratyphi* are recognized agenrs ot enteric fever, vascular (endothelial) infection leading to aortoduodenal fistulas and chronic carrier states. Disseminated intravascular coagulation complicates severe infections. Atypical manifestations include pneumonitis, pericarditis, sacroiliitis, arthritis, and osteomyelitis, the last being particularly common in patients with sickle cell hemoglobinopathies. Until recently, chloramphenicol was used to treat typhoid fever. However, because of outbreaks associated with resistant strains in Latin America, the Middle East, and South and Southeast Asia, ciprofloxacin for adults (500 mg orally twice a day for 10-14 days) or ceftriaxone for children (100 mg/kg per day intravenously or intramuscularly for 10-14 days) or adults (1-2 g daily) are considered better choices for patients in these areas. Antibiotics combined with corticosteroids for the first 48 hours of illness may improve outcome in some critically ill patients with delirium, stupor, coma, or shock.

Shigellosis

Shigella species, members of the Enterobacteriaceae family and agents of bacillary dysentery, are postulated to cause a fatal, toxic encephalopathy in children by elaboration of Shiga toxin (Goren et al. 1992). The encephalopathy is a syndrome of sudden headache, cerebral edema, and rapid neurological decompensation, beginning several hours to 6 days after onset of diarrheal illness. Shigellosis is diagnosed by stool culture. Enteric and systemic disease is treated with ciprofloxacin (500 mg orally twice daily for adults for 1-5 days) or TMP/SMX (160 mg of TMP and 800 mg of SMX orally twice daily in adults) and supportive treatment, but antibiotics may not influence the neurological disease.

Campy 1 obactcrios is

Campylobacter, among the most frequent bacterial infections of humans worldwide, causes both acute enteric and systemic illnesses. Sources of infection include raw milk, water, and poultry. *Campylobacter jejuni* has been identified as the most common antecedent pathogen for the Guillain-Barre syndrome, accounting for an estimated 20^10% of all cases. The onset of Guillain-Barre syndrome is usually 2-3 weeks after the diarrheal illness and follows an estimated I per 1000-2000 *Campylobacter* infections. The presence of anti-GMj antibodies in Guillain-Barre patients infected with C. *jejuni* Penner serogroup 19 and anti-GQlb ganglioside antibodies in Miller-Fisher variant patients infected with *C. jejuni* Lior serogroup 7 has led to the hypothesis that lipopolysaccharides of these *Campylobacter* isolates induce neuropathic disease by molecular mimicry (Yuki 1997; Yuki et al. 1997). *Campylobacter* infection is diagnosed by isolation and identification of the organism from stool or blood. Most strains are treated adequately with erythromycin, 250 mg orally four times daily for 5-7 days.

Whipple's Disease

Whipple's disease, caused by *Tropherym.a wbippelii,* is a multisystem disorder characterized by gastrointestinal disease (abdominal pain, diarrhea, weight loss), arthritis, lymphadenopathy, addisonian symptoms (hypotension, asthenia, cutaneous hyperpigmentation), and protean neurological manifestations including dementia, oculofaciomasticatory myorhythmia, supranuclear ophthalmoplegia, meningitis, neuropathy, and myopathy (Anderson 2000). Classically, the disease occurs as coexisting neurological and gastrointestinal disease, and the diagnosis is made by identifying periodic acid-Schiff-positive bacilli in macrophages in tissue obtained from duodenal or jejunal biopsy. Brain biopsy, demonstrating periodic acid-Schiff-positive material, has been used to establish the diagnosis in the absence of intestinal disease. For its numerous other presentations, sarcoidosis, collagen vascular disease, malabsorption syndromes, Addison's disease, frontotemporal dementia, Creutzfeldt-Jakob disease, progressive supranuclear palsy, or Wernicke's encephalopathy are differential diagnostic considerations. Treatment is with oral double-strength TMP-SMX twice daily for 1 year. Severely ill patients are treated with thrice daily TMP/SMX for the first 2 weeks, together with folinic acid. Oral chloramphenicol, parenteral ceftriaxone, or penicillin arc other treatment options for those who respond poorly.

RESPIRATORY PATHOGENS

Chlamydial Diseases

Each of the three chlamydial species, *Chlamydia psittaci, C. trachomatis,* and C. *pneumoniae* arc human pathogens, with C. *psittaci* most consistently associated with neurological complications.

Psittacosis (or ornithosis), caused by C. *psittaci,* is transmitted from bird to humans by the aerosol route. Fever, cough, myalgia, headache, and hepatomegaly are presenting clinical features, occasionally accompanied by

cranial nerve palsy, myelitis, meningoencephalitis, seizures, or cerebellar ataxia. CSF contains few or no lymphocytes and normal protein, although elevated protein has been reported with myelitis. Psittacosis is diagnosed by serology and treated with oral tetracycline or erythromycin, 500 mg four times per day for 10-14 days. In the absence of a firm diagnosis, erythromycin may be preferable, because it also covers other *Legionella* and *Mycoplasma,* which also cause atypical pneumonias with neurological symptoms.

C. trachomatis causes ocular and venereal disease. Treatment is with erythromycin or tetracycline.

Mycoplasma Syndromes

The human mycoplasmas are *Mycoplasma pneumoniae, M. hominis,* M. *urealyticum,* and M, *genitalium.. M. pneumoniae,* responsible for most clinical disease, causes respiratory infections. Systemic illness with cough and fever are the most consistent clinical presentations, 1 Extrapulmonary involvement includes rash, cardiac abnormalities, arthralgias, vascular diseases (Raynaud's phenomenon, internal carotid artery occlusion, stroke;-, and neurological syndromes (aseptic meningitis, meningoencephalitis, leukoencephalitis, transverse myelitis, brainstem syndromes, Guillain-Barre syndrome, and peripheral neuropathy). Diagnosis depends on recognizing the clinical syndrome and may be confirmed by demonstration of cold agglutinins or complement-fixing antibodies. Erythromycin, 500 mg every 6 hours in adults, 1 g per day in older children, and ."50-50 mg/kg per day in young children for 21 days is the recommended treatment. Tetracycline is an alternative in adults and children older than 8 years.

Legionellosis

Legionella pneumophila causes Legionnaires' disease, which can complicate myositis, encephalitis, and meningitis. *L. pneumophila* is transmitted to humans from its natural aquatic habitat by aerosol or airborne droplets, particularly where humidifiers or air conditioners are used. Legionnaires' disease is characterized by mild to severe pulmonary disease, gastrointestinal disease, hyponatremia, myalgias or myositis, and encephalomyelitis. Encephalopathy, manifesting as altered mental status, is the most common neurological abnormality; ataxia, cranial nerve palsy, mild inflammatory CSF changes, and electroencephalographical abnormalities, have been reported. The diagnosis is suspected in patients with pneumonia and purulent sputum with few or no organisms seen on Gram's stain or in patients who fail to respond to ^-lactam or aminoglycoside antibiotics. Diagnosis is made by culture, serology, or DNA probe. Treatment is with erythromycin, 1 g intravenously every 6 hours until clinical improvement, followed by 2 g orally in divided doses for 3 weeks. Alternative agents include clarithromycin, doxycycline, ciprofloxacin, and RIF.

Pertussis

Bordetella pertussis causes pertussis (whooping cough), an upper respiratory catarrhal infection followed by paroxysmal coughing in a series of short expiratory bursts and an inspiratory gasp. Pertussis is a severe disease in children younger than 1 year, associated with seizures and encephalopathy. Subconjunctival, scleral, or CNS hemorrhages can follow the increased intrathoracic and intra-abdominal pressures during violent coughing at any age. Definitive diagnosis is by isolation of *B. pertussis,* but because the organism is difficult to culture, a clinical case definition (cough of 2 weeks' duration in the setting of a community outbreak) is used. Treatment is with erythromycin at doses of 40-50 mg/kg per day for 14 days, and erythromycin for prophylaxis of household contacts may be necessary. A vaccine composed of one or more components of the organism combined with diphtheria and tetanus toxoids (DPT) is used for immunization.

CARDIAC INFECTIONS

Endocarditis

When cerebral emboli from all sources are counted, approximately 3% result from infective endocarditis. Common pathogens include enterococci, *Streptococcus viridans, S. aureus, S. epidermidis,* or *Pseudomonas aeruginosa.* Cerebral embolization occurs in at least one third of all infective endocarditis cases, commonly in middle cerebral artery territory. Bland or hemorrhagic cerebral infarcts, arteritis, single or multiple abscesses, mycotic aneurysms (often at bifurcation points of distal branches of the middle cerebral artery), intra parenchymal or subarachnoid hemorrhage, cerebritis, meningitis, and asymptomatic CSF pleocytosis can develop during active endocarditis.

Blood culture, a critical diagnostic test for endocarditis, may give negative results in 2.5-31.0% of cases. Reasons for culture-negative endocarditis include fungal endocarditis, slow growth of fastidious organisms such as *Haemophilus,* variant streptococci or *Brucella,* failure to culture intracellular pathogens such as chlamydiae or rickettsiae, right-sided endocarditis, and recent antibiotic use. CSF examination, if clinically indicated, most consistently shows increased numbers of polymorphonuclear leukocytes, red cells, elevated protein, and normal glucose levels. Treatment is with parenteral antibiotics for at least 4 weeks. Indications for valve replacement include more than one significant embolic episode or failure of antibiotic therapy; mycotic aneurysms may require neurosurgical intervention.

Rheumatic Fever

Rheumatic fever, a sequelae of group A streptococcal infection, is diagnosed by one or more clinical criteria (carditis, migratory polyarthritis, subcutaneous nodules, erythema marginatum, chorea), plus culture evidence of recent group A streptococcal infections or elevated anti-streptolysin O titers. The childhood chorea, Sydenham's chorea, occurs in less than 10% of patients. Onset may be immediate or several months after the index infection. Even patients with chorea only are treated, according to the American Heart Association guidelines, which advise prophylactic monthly intramuscular injections of 1.2 million units of benzathine penicillin G or daily oral penicillin V to prevent recurrent attacks.

DISORDERS DUE TO BACTERIAL TOXINS

Neurotoxigenic Clostridia: Botulism and Tetanus

Clostridia, strictly anaerobic gram-positive bacilli, form highly resilient spores that are ubiquitous in the environment. Unlike pathogens that cause neurological disease by inducing inflammation or forming mass lesions, and the consequent tissue injury, several clostridial species elaborate exotoxins that gain access to the nervous system by avid and specific binding to motor nerve terminals. The resulting clinical syndromes are motor disorders that often are accompanied by autonomic dysfunction. Botulism and tetanus require notification of public health authorities, both to obtain therapeutic antisera and to initiate appropriate epidemiological investigation. Knowledge of their characteristic clinical features facilitates early diagnosis of these rare, but rrearable, disorders.

Botulism

An unusual cause of acute generalized weakness, botulism develops when the extremely potent neurotoxin secreted by *Clostridium botulinum* blocks peripheral cholinergic transmission. *Clostridia botulinum* spores are widespread in soil and aquatic sediment. Seven botulinum toxin serotypes define the various C. *botulinum* strains (Case Records 1997). Types A, B, E, and rarely, F cause human disease. Types C and D cause botulism in animals, and type G does not appear to cause human or veterinary illness. Food-borne botulism, described in 1895 by van Ermengen, develops when preformed toxin is ingested from contaminated food. Wound botulism, first recognized in 1942, occurs when C. *botulinum* in an infected wound releases botulinum toxin directly into the tissue. Toxin production by C. *botulinum* colonizing the gut causes infantile botulism. Less commonly, gut colonization causes botulism in adults with pre-exisring gasrrointestinal disorders, such as intestinal surgery or inflammatory bowel disease (Midura 1996).

Pathogenesis and Pathophysiology

Borulinum toxin blocks acetylcholine release at peripheral synapses, leading to the paralytic and autonomic clinical manifestations of botulism (Montecucco and Schiavo 1994). With a median lethal dose as low as 1 ng/kg in mice, it is the most potent toxin known. Unlike C. *botulinum* spores, the toxin is heat-labile. Botulinum toxin is initially synthesized as a single 150-kD prorein chain and contains a single disulfide bond. Proteolysis forms heavy (100 kD) and light (50 kD) chains. The ("'-terminal region of the heavy chain binds tightly and specifically to presynaptic membranes, whereas the N-terminal domain governs internalization of the toxin into the motor neuron. Once internalized, botulinum toxin cannot be neutralized by therapeutically administered antibodies. After translocation across vesicular membranes into the cytosol, cleavage of the disulfide bond liberates the light chain, which contains the catalytic activity of botulinum toxin. The light chain is a zinc endopeptidase that targets various proteins mediating exocytosis. Hence, botulinum toxin causes irreversible blockade at peripheral cholinergic synapses. Recovery requires sprouring of new nerve Terminals, accounting for rhe protracted clinical course of botulism.

Public Health Issues

Although the disease is ubiquitous, five western states (California, Washington, Colorado, New Mexico, and Oregon) account for more than half of all reported outbreaks in the United States. First reported in 1976, infant botulism is now the most common form of botulism in the United States. Among adults, food-borne botulism is much more common than wound botulism. Outbreaks of poisoning are more often due to home-preserved than to commercially canned products, and vegetables are incriminated more commonly rhan any other food product. Since the late 1980s, injection drug use, specifically "skin popping" heroin, has been linked to wound botulism. Skin popping refers to subcutaneous injection, typically by chronic addicts whose poor venous access precludes inrravenous administration. Since 1990, a sharp increase in wound botulism in California has been associated with skin popping "black tar" heroin (Centers for Disease Control 1995).

Clinical Features

Whether toxin is ingested or elaborated in situ from gut colonization or an infected wound, common early symptoms of botulism include diplopia, ptosis, dysarthria, and dysphagia. Extraocular and bulbar muscle weakness

progresses rapidly to the limbs, typically symmetrically, and also to respiratory muscles. Alertness and cognition are normal, unless hypoxemia or hypercarbia supervene because of respiratory failure. Reflexes are depressed or absent, and sensation is normal. These symptoms and signs all indicate neuromuscular blockade. In botulism, impaired cholinergic transmission also involves autonomic synapses, as indicated by dilated poorly reactive pupils, dry mouth, paralytic ileus, and occasionally bradycardia.

In food-borne botulism, nausea, vomiting, and diarrhea often accompany early neurological symptoms, typically 12-36 hours after toxin ingestion. Gastrointestinal symptoms may be less prominent in early wound botulism. Clinical features of infantile botulism vary widely (Midura 1996). Constipation, poor suck, weak cry, and listicssness are common, and the baby often appears floppy. The incubation period may be as brief as a few days or as long as a month. A small percentage of cases of sudden infant death syndrome result from infant botulism. Honey has been implicated as the source of C. *botulinum* spores in infantile botulism. Dust is another important environmental source of spores; however, in most cases of infantile botulism, a source cannot be identified.

Diagnosis

The differential diagnosis includes other causes of acurc generalized weakness. Preserved alertness and lack of sensory or upper motor neuron signs help exclude acute brainstem disorders such as stroke, demyelinating syndromes, and encephalitis. The descending paralysis of botulism closely resembles the Miller-Fisher variant of Cuillain-Barre syndrome and overlaps with the clinical features of diphtheritic polyneuropathy. However, in botulism, sensation is normal, as is CSF. Electromyography and nerve conduction study results reveal changes indicating presynaptic neuromuscular blockade, in contrast to the often-elevated CSF protein and electrophysiological features that suggest the demyelinating neuropathies of Guillain-Barrc syndrome or diphtheria. Pupillary involvement and ileus help distinguish botulism from myasthenia gravis presenting in crisis. In addition, peripheral electrophysiological studies, particularly repetitive nerve stimulation, in myasthenia reveal a postsynaptic defect in neuromuscular transmission (decrement on slow repetitive stimulation; see Chapter 36B), rather than the presynaptic electrophysiological abnormalities that characterize botulism (increment on rapid repetitive stimulation). Normal CSF and prominent ocular signs differentiate botulism from poliomyelitis, in which pleocytosis is the rule and extraocular weakness and ptosis are rare. Tick paralysis also causes acute generalized weakness caused by impaired presynaptic neuromuscular transmission, but weakness typically ascends and spares extraocular muscles. Paralytic shellfish toxicity and organophosphate poisoning are other considerations; the latter causes a syndrome in which cholinergic, rather than anticholinergic, features predominate. The differential diagnosis of infantile botulism includes sepsis, pneumonia, failure ro thrive, myasthenia, polio, Guillafn-ftarre syndrome, brainstem encephalitis, meningitis, hypothyroidism, and metabolic disorders.

Symptoms and signs suggesting cholinergic blockade at both autonomic and neuromuscular synapses suggest the diagnosis of botulism. History of similar symptoms in family or acquaintances or of eating home-canned foods should be specifically sought, as should evidence of recent trauma or chronic infection. Alrhough many patients with wound botulism have a clinically obvious site of infection, it should be emphasized that the extremely high potency of botulinum toxin means that small, seemingly trivial abscesses can cause botulism.

In a patient with a compatible clinical syndrome, the diagnosis of botulism is confirmed by roxin assay or by culturing C. *botulinum.* Toxin detection requires mouse bioassay, which can be arranged through state health departments or the CDC. Appropriate samples for toxin assay include suspected food sources, blood, and stool in most instances, as well as gastric contents and enema fluid in infant botulism. Rapid determination of the source of toxin helps identify individuals at risk in fooddiorne cases. Because C. *botulinum* is a srrict anaerobe, culture specimens require special collection, transport, and culture procedures. Appropriate culture materials include suspected contaminated foods, wound specimens, and stool.

Treatment

Once taken up by neurons, botulinum toxin is invulnerable to antibody inactivation and irreversibly blocks exocytosis. Hence efforts to neutralize circulating antitoxin and eradicate its source often begin before roxin or culture results, which take days, are known (Burningham et al. 1994), In adults, trivalent (types A, B, E) equine antitoxin is given if initial testing reveals no hypersensitivity reaction. Nasogastric suctioning and enemas may help remove toxin in food-borne cases. In wound botulism, infected wounds, even if minor, should be debrided. Because the procedure could liberate more toxin, it may be prudent to debride wounds after antitoxin administration. Whether antibiotics active against C. *botulinum* should be given is controversial, because of the concern that bacterial lysis could release more toxin. If other intercurrent infections require antibiotic therapy, aminoglycosides are probably best avoided whenever possible, because they also impair presynaptic neuromuscular Transmission.

Meticulous supportive care plays a critical role. Close monitoring in an ICU is important, even in patients who do not require intubation at presentation, because respiratory decompensation can develop precipitously. Serial bedside pulmonary function tests are more sensitive than blood gas parameters in determining the need for mechanical ventilation, because vital capacity decreases before hypoxemia

and hypercarbia develop. Complications of prolonged immobility, such as stress ulcer, malnutrition, pneumonia, urosepsis, deep venous thromboembolism, and depression should be anticipated and managed appropriately. In infants, supportive care, including mechanical ventilation in many patients, is the mainstay of therapy. Treatment of infant botulism usually does not include antitoxin administration or antibiotics (Midura 1996).

Modern critical care has decreased mortality from 60% to 20% (Case Records 1997) in botulism. Because botulinum toxin irreversibly destroys the cellular apparatus responsible for acetylcholine release at neuromuscular junctions, motor recovery depends on motor axon sprouting, which takes weeks to months. Long-term ventilatory support and tracheostomy may be necessaty. Full recovery can take years.

Tetanus

Clostridium tetani secretes tetanospasmin, also known as tetanus toxin, and tetanolysin. The function of tetanolysin remains uncertain; tetanospasmin blocks release of inhibitory neurotransmitters by spinal interneurons, causing the dramatic muscle contractions that characterize tetanus. *C. tetani* spores can survive for years in soil and house dust. When introduced into the anaerobic environment of a suitable wound, conversion to the toxin-producing vegetative form may cause tetanus. Neonatal tetanus complicates umbilical sepsis, which is usually related to improper umbilical stump care. Septic procedures during pregnancy or abortion can cause maternal tetanus. Other circumstances favoring the growth of C. *tetani* include deep puncture wounds, chronic skin or dental infections, decubitus ulcers, and other contaminated, necrotic wounds. Although trauma precedes most cases, a responsible wound is not identified in 20% of patients. Tetanus, a preventable disease, is an important international public health problem, particularly in the developing world.

Pathogenesis and Pathophysiology

Tetanospasmin inhibits release of *y*- amino butyric acid and glycine, which are inhibitoty neurotransmitters in the brainstem and spinal cord (Ernst et al. 1997). A single type of tetanus neurotoxin exists, in contrast to the multiple scrorypes of botulinum toxin. Interestingly, though botulinum and tetanus toxins cause dramatically different clinical syndromes, they share many biochemical featutes (Montecucco and Schiavo 1994). Both are 1.50-kD zinc endopeptidases consisting of light and heavy chains connected by a disulfide bond. The binding specificity and translocation reside in the heavy chain, in the C- and N-termini, respectively. The light chain is the zinc endopeptidase, which blocks exocytosis. Unlike botulinum toxin, which remains in the motor axon terminal, tetanus toxin travels to the anterior horn cell by retrograde axonal transport, moves into the intersynaptic space, and enters inhibitory neurons. Impaired exocytosis in these spinal inhibitory neurons causes uncontrolled muscle contraction, a prominent clinical feature of tetanus. Similar disinhibition in the intermediolateral column of the spinal cord is thought to produce autonomic dysfunction.

Public Health issues

Underreporting is the rule for all forms of tetanus in both industrial and developing countries (Galazka and Gassc 1995). Neonatal tetanus remains a significant public health problem in the developing world. In industrialized nations, tetanus is rare, owing to toxoid immunization programs, which usually target children. As a result, tetanus has become particularly rare in children and young adults and is primarily a disease of the elderly in industrialized countries. Interestingly, immunization efforts also decrease mortality from neonatal tetanus. Since the 1980s, tetanus outbreaks have developed among heroin addicts in Hong Kong, reminiscent of similar outbreaks in New York City during the 1960s (Sun et al. 1994),

Clinical Features

The typical incubation period is 2 weeks but can range from hours to a month or more. Cardinal features include muscle rigidity and spasms, which may be accompanied by autonomic hyperactivity. Local tetanus, in which symptoms remain limited to a limb, is a rare form. Far more common is generalized tetanus, also called lockjaw, as trismus heralds the disorder in over 75% of cases. Tetanus resulting from infected head and neck wounds may present with facial or ocular muscle spasms, so-called cephalic tetanus. Sustained contraction of facial muscles causes a sneering grimace known as risus sardonicus. Other early symptoms include dysphagia and axial muscle involvement, such as neck stiffness, abdominal rigidity, and back pain. Early involvement of face, neck, and trunk muscles has been ascribed to the shorter axons of motor neurons supplying cranial and axial muscles, as compared with the limbs. Laryngospasm compromises ventilation and makes intubation extremely difficult. Sustained contraction of back muscles causes opisthotonos, an arching posture of the back. As tetanus progresses, reflex muscle spasms develop, triggered by sensory stimuli, movement, or emotion. Examination can be difficult, as it may prompt spasms.

Diagnosis

Differential diagnosis includes hypocalcemia, strychnine poisoning, dystonic reactions to neuroleptics or antiemetics, meningitis, encephalitis (including rabies), status epilepticus, and the acute abdomen. Oral infection or mandibular

fracture or dislocation may cause isolated trismus, without the generalized features of tetanus. Immunization status should be established, if possible, and a history of chronic infection should be sought. The characteristic muscle contractions elevate serum CK, but there are no pathognomonic laboratory abnormalities in tetanus. CSF is normal. Wound cultures must be interpreted cautiously. Positive culture results may indicate wound colonization, rather than true infection with subsequent toxin production. Moreover, in most established cases, wound cultures do not yield C. *tetani.*

Treatment

Therapeutic goals include protecting the airway, neutralizing circulating tetanospasmin and preventing its further production, managing spasms and dysautonomia, and general supportive care (Ernst et al. 1997; Reddy 2002). The risk for precipitous respiratory decompensation, even in mild cases, warrants ICU management for all patients with tetanus.

Initial management of most patients with generalized tetanus includes endotracheal intubation, because laryngospasm may appear abruptly even in mild cases. Human tetanus immune globulin, given as a single dose of at least 500 IU intramuscularly, neutralizes circulating toxin. Infected wounds should be debrided after human tetanus-immune globulin administration, because the procedure may release further toxin. Metronidazole or penicillin should be given to eradicate C *tetani.* Because minute amounts of tetanospasmin can produce clinical disease, affected patients frequently do not mount a protective immune response. Hence tetanus toxoid should be administered, either primary immunization series or booster injection as appropriate, to all patients with tetanus,

A paucity of randomized clinical trial data means that treatment recommendations for tetanus depend heavily on clinical experience. This is particularly true for managing sympathetic hyperactivity. A quiet, dark environment minimizes sensory stimulation that may precipitate spasms or hypertensive crises. Benzodiazepines, such as parenteral diazepam, lorazepam, or midazolam, reduce rigidity and spasms. Such agents also provide effective sedation, an important consideration because severe tetanus typically requires weeks or months of ICU care. Most patients also require treatment with neuromuscular blockers, such as pancuronium or vecuronium, to control spasms. Intravenous dantrolene and intrathecal baclofen also have been used successfully to manage muscle rigidity and spasms in tetanus. Hypertension and tachycardia often respond to beta blockers such as propranolol or labetalol, although treatment may be complicated by cardiac arrest or hypotension. As with all critically ill patients, optimal supportive care includes attention to nutritional status and measures to prevent stress ulcers, deep venous thrombosis, and decubitus ulcers.

Tetanus is a reportable illness whose complex management poses considerable challenges for neurointensivists. It is worth noting that tetanus could be largely prevented with simple modifications in peripartum and neonatal care and more widespread use of tetanus toxoid, which is both inexpensive and safe.

Complications

Without treatment, generalized tetanus is uniformly fatal, The overall case-fatality rate in the United States from 1991 through 1994 was 25%, with substantially higher rates among older patients (Izurieta et al. 1997). Complications include acute respiratory failure from laryngospasm, long-bone fractures from severe tetanospasm, and cardiac arrest from dysautonomia. Patients with protracted courses may require tracheostomy or develop seizures or other evidence of withdrawal related to long-term use of benzodiazepines, Most survivors recover fully. Because the disease is caused by the binding of tetanus toxin to receptors, immunodeficiency neither lengthens nor shortens the pure tetanus-related disease.

Diphtheria

Diphtheria is an acute infectious disease of the tonsils, pharynx, larynx, nose, other mucous membranes, or skin caused by *Corynebacterium diphtherial..* The potentially-fatal effects of diphtheria depend on the production of an exotoxin, by a lysogenie tox^+ phage. Although toxic to all tissues, the exotoxin's most dramatic activity is against heart and peripheral nerves. Approximately 20% of patients develop myocarditis and neuritis.

Faucial diphtheria is the most common form, presenting with fever, sore throat, membranous pharyngitis, cervical lymph adenopathy, and edema. In North America and Europe, skin infections with C. *dtphtheriae* are now more common than nasopharyngeal disease. Cutaneous diphtheria appears as a pustule or nonhealing ulcer with a gray, dirty membrane. Toxic complications of cutaneous infections are rare, with neuritis more likely than myocarditis.

The toxin inhibits protein synthesis, causing segmental demyelination of motor and sensory myelinated axons, producing a toxic cranial and peripheral neuropathy. Early lower cranial nerve signs and symptoms, within 2 weeks of the appearance of faucial disease, suggest IX and X nerve dysfunction with paralysis of the soft palate, nasal speech, and nasal regurgitation of fluids. Blurred vision, caused by ciliary paralysis of accommodation, or diplopia, caused by oculomotor nerve paralysis, appear in the third or fourth week of the disease. Peripheral polyneuritis, more likely in severe cases, typically begins between the sixth and seventh weeks of illness, when the patient may appear otherwise stable. The neuropathy vaties widely in severity. Phrenic and further vagal nerve involvement may produce a rapidly

descending paralysis of pharynx, larynx, and diaphragm, A subacute motor neuropathy, involving proximal groups first, sometimes evolves slowly, halting after 1-2 weeks, or rapidly generalizes to quadriplegia and respiratory paralysis. Vibratory, proprioceptive, and other cutaneous sensory loss may be limited to the hands and feet or extend over mueh of the body. Sphincter dysfunction sometimes develops; cardiac vagal denervation can result in arrhythmias or baroreceptor abnormalities. Conduction abnormalities may follow the onset of neurological symptoms by several weeks and peak after clinical recovery has begun. CSF may be normal or reveal elevated protein, which is not a poor prognostic sign, when there is radicular involvement. Primary cutaneous diphtheria is characterized by early, localized anesthesia surrounding the skin ulcer, followed by weakness of surrounding muscles, before progression to generalized disease.

Definitive diagnosis requires isolation and identification of the organism from infected sites, but treatment with diphtheria antitoxin (equine hyperimmune serum) should be started as soon as a presumptive diagnosis is made. Diphtheria antitoxin can only neutralize circulating toxin before it enters cells. Antitoxin dose depends on the site of primary infection: 20,000-40,000 units for faucial diphtheria of less than 48 hours, 40,000-80,000 units for faucial diphtheria of longer than 48 hours, and 80,000-100,000 units for extensive disease or neck swelling. Patients with sensitivity to horse serum receive a 1 to 10 dilution test dose first and can be desensitized with increasing doses of antiserum, with epinephrine readily available. Antibiotics terminate toxin production and prevent further proliferation of the organism. Hither parenteral or oral penicillin G, 100,000 U/kg twice daily, or erythromycin, 5 mg/kg four times daily for 14 days, are recommended. Additional treatment is largely supportive, with respiratory and eardiac monitoring. Neurological recovery is the rule, although arrhythmias or heart failure may be fatal.

Diphtheria is included in the triple vaccine DPT (diphtheria, pertussis, and tetanus), which is administered as three primary doses at 2-month intervals beginning at 6-8 weeks of age. A fourth dose is given 6-12 months after the third, and DT is given at school entry.

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Chapter 59
Infections of the Nervous System

B. VIRAL INFECTIONS

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Hundreds of viruses exhibit tropism for the central and/or peripheral nervous system. The clinical spectrum of viral diseases is broad. Signs of primary viral infection may range from asymptomatic infection to systemic febrile illness with or without central (CNS) or peripheral (PNS) nervous system involvement. In the case of many viruses, involvement of the CNS or PNS is the predominant feature of illness, whereas in others, involvement of the nervous system is a rare complication of more generalized illness. The manifestations of viral nervous system involvement are myriad, including meningitis (acute or chronic), encephalitis (acute or chronic forms such as subacute sclerosing panencephalitis [SSPE]), myelitis, ganglionitis, and polyradiculitis. By virtue of their existence as foreign antigenic stimuli, viruses may also incite para- or postinfectious CNS inflammatory or autoimmune syndromes, such as acute disseminated encephalomyelitis (ADEM). The basic clinical featutes of each of these major clinical syndromes are overviewed in Chapter 47 (Neuroendocrinology). In this chapter, the most common etiologies of each of the major clinical syndromes will be discussed, with a review of diagnosis and treatment.

The most common viruses causing nervous system disease in North America are listed in Table 59B.1 in the relative order of frequency with which they occur and with an indication of their relative propensity to cause meningitis, encephalitis, postinfectious encephalomyelitis, or myelitis. Causes of viral nervous system disease that should be considered in patients who have recently traveled abroad arc shown in Table 5.9B.2. In Europe and the United States, the most common causal agents of aseptic encephalitis and meningitis arc enteroviruses (coxsackie and echoviruses), arboviruses, and Herpes simplex virus (HSV). Worldwide, there are over 50,000 encephalitis deaths from rabies each year, and in Asia at least 35,000 cases and 10,000 deaths from Japanese encephalitis (JE). In the United States, nearly 4000 cases of West Nile Virus encephalitis, with 250 deaths, occurred in 2002. Although the basic clinical features of most types of viral meningitis and encephalitis are generally similar, specific skin, mucous membrane, or other physical examination findings may help to narrow the possible viral etiologies of nervous system disease (Tables 59B.3 and 59B.4), It is important to recognize that several nonviral diseases can mimic the clinical features of viral CNS infection (Table 59B.5) (DeBiasi and Tyler 2002). The treatment, prophylaxis, and immunotherapy of specific viral infections are summarized in Tables 59B.7 and 59B.8.

SPECIFIC VIRAL ENTITIES

Herpesviruses

Herpesviruses are ubiquitous and can infect many mammalian, bird, reptile, and amphibian species. These viruses cause acute infection, but also share the biological capacity of latency, the ability to remain quiescent for periods of time in the host and to be reactivated. Members of **the** herpesvirus family causing neurological diseases in humans include HSV-type 1 and type 2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstcin-Barr virus (EBV),

Tabic 59B.1: Primary causes of viral nervous system infection in North America

Agent		*Meningitis*	*Encephalitis*	*Postinfectious ADFM*	*Myelitis*
Konpolio enteroviruses	Ee ho virus	s $ *			
	Coxsackievirus	K-K-S			
Arboviruses (U.S. & Canada)					
Togavi ruses					
Flavivirus	Si. Louis encephalitis virus (SLE)	;-			
	West Nile Virus	;			
	Powassan				
Alpha virus	Eastern equine (REE)	^			
	Western equine (WEE)				
	Venezuelan equine (VEE)				
Reoviridae: orbivirus	Colorado tick fever	**			
Bunyavirus	California {La Crosse)	tf			
	Jamestown Canyon	*a-*			
	Snowshoc hare	*			
Herpes viruses	HSV-1	*			
	HSV-2	* ^			
	VZV	4	f If		
	CMV	*			
	EBV	fr			
	HHV-6	*			
	HHV-7				
	i n rv-8				
	Herpes B virus				
Lymphocytic choriomeningitis virus (LCMV)		* *			
Mumps virus		**			
HIV		**			
Rabies virus					
Measles virus					
Rubella virus					
Poliovirus (now eradicated from Western hemisphere)		*X*			
Adenovirus		*			
Vaccinia					
Influenza					
Parainfluenza		*			
Rotavirus		*			
Parvovirus B-19		*			

human herpes viruses {HHV-6, HHV-7, and HHV-S), and the simian {"monkey") Herpes B-virus.

Herpes Simplex Viruses Type 1 and 2 (HSV-1, HSV-2)

Herpes Simplex Encephalitis (HSE), HSV-1 encephalitis is the most common cause of sporadic, fatal encephalitis in the United States, accounting for approximately 10% of all eases of encephalitis. Early recognition is important hecause of the efficacy of the antiviral drug acyclovir in reducing morbidity and mortality. Mortality in untreated cases is 70% and is reduced to approximately 20% with rapid institution of antiviral therapy in a timely fashion. However, morbidity due to HSV-1 encephalitis, treated or untreated, remains high, with up to 70% of survivors demonstrating permanent neurological sequelae. HSV-1 strains are etiological agents in over 90% of cases of HSE in adults. Type 2 strains are more commonly isolated in monophasic or recurrent meningitis and congenitally acquired neonatal HSV meningoencephalitis. Both types 1 and 2 have been associated with myelitis. HSV-1 and -2 related CNS disease in immunosuppressed hosts is discussed in Chapter 59E.

HSV-1 is transmitted by respiratory or salivary secretions. Up to 33% of HSV-1 encephalitis cases may occur in conjunction with primary infection. In these cases, it has been postulated that virus may spread from the olfactory fibers in the nose to orbitofrontal cortex and temporal lobes. In the majority of cases, however, encephalitis is probably a consequence of reactivation and centripetal spread of virus latent in the trigeminal ganglia from a prior infection.

Fever and headache are consistent features of HSE. Onset of symptoms may be abrupt with focal or generalized seizures, or more protracted, with behavioral changes, an amnestic syndrome, aphasia, or other focal signs.

Tabic 59B.2: Additional causes of virai nervous system infection resulting from foreign exposures

Agent		*Geographic distribution*
Nipah virus		[rulonesia
Filovirus	Ebola	Africa
	Marburg	
Arbovirus		
Togavirus		
Mosquito-borne	Eastern equine	Caribbean and South America (plus U.S.)
	Venezuelan equine	Central and northern South America (plus U.S.)
	St. Louis	Caribbean, Central and northern South America (plus U.S.)
	Japanese B	Japan, China, S.E. Asia, India
	Kunjin	Australia
	Murray Valley	Australia and New Guinea
	West Nile	Africa and Middle East, Parts of Europe
	lilieus	South and Central America
	Rocio	Brazil
Tick-borne complex	Far Eastern	Eastern Russia
	Central European	Eastern and Central Europe, Scandinavia
	Kyasiinur Forest	India
	I.ouping 111	England, Scotland, and Northern Ireland
	Negislii	Japan
	Russian spring-summer	Eastern Europe, Asia
Bunyavirus	Tahyna	Czechoslovakia, Yugoslavia, Italy, Southern France
	Ink oo	Finland
	Rifr Valley	East Africa
Rhabdovirus	Rabies	Many developing countries

The diagnosis of HSE should be considered in any febrile patient with an altered level of consciousness, with or without other focal neutological deficits. The presence of hallucinations, particularly olfactory hallucinations, should suggest the possibility of HSE. There is no pathognomonic set of clinical findings of HSE. Focal signs, hemiparesis, hemisensory loss, ataxia, or focal seizures are seen in approximately one half of patients at presentation. Multiple conditions may mimic the clinical presentation of HSV encephalitis, including other viral and postviral

Table S9B.3: Skin/mucous membrane findings suggesting specific viral CNS diseases

Exantkem or mucous membrane change	*Viral agent*	*Specific changes*
Vesicular eruption	Enterovirus	"Hand, foot and mouth disease"—macules/papules/vcsicles on palms, soles, buttocks
	Herpes simplex	Grouped small (3 mm) vesicles on an erythematous base
	Varicella zoster virus	Zoster: Vesicles in dermatomai distribution
		Primary VZV; multiple vesicles, papules, pustules in various stages of eruption
Maculopapular eruption	Epstein-Barr virus	Diffuse maculopapular eruption following ampicillin treatment
	Measles	Diffuse maculopapular erythematous eruption beginning on face/chest and extending downward
	HHV-6	Roseola: Diffuse maculopapular eruption following 4 days of high fever
	Colorado tick fever	Maculopapular rash in 50%
	LCMV	Occasionally occurs with lymphadenopathy
Erythema multiforme	(Mycoplasma)	Many rypes of rash
Confluent macular rash	Parvovirus	Confluent erythema over cheeks ("slapped cheek") followed by lacy, reticular rash over extremities (late)
Purpura	Parvovirus	Rare "stocking glove syndrome—purpuric lesions on distal extremities"
Pharyngitis	Enterovirus	"Herpangina"—vesicles on soft palate
	Adenovirus	Pharyngoconjunctivitis
Conjunctivitis	St. Louis encephalitis	Conjunctivitis
	Adenovirus	Conjunctivitis with pharyngitis (see above)

Table 59B.4: Other specific findings associated with viruses causing CNS disease

binding	*Viruses*
Alopecia	LCMV
Arthritis	LCMV, Pitrvovirus
Biphasic Illness	LCMV, Colorado tick fever
Lymph adenopathy	LCMV, Mumps
Mastitis	Mumps
Mononucleosis	CMV, EBV
Myelitis	St. Louis encephalitis vims, VZV, Herpes B virus, LCMV
Myocarditis/pericarditis	Enterovirus, (Mumps, LCMV)
Orchitis/oophoritis	Mumps (LCMV, EBV)
Paresthesias	Colorado tick fever, LCMV, Rabies
Parotitis	Mumps (LCMV)
Pneumonia	Influenza, Parainfluenza
Retinitis	CMV
Tremors	Arbovirus
Urinary problems	St. Louis encephalitis virus, VZV, Herpes B virus, LCMV

encephalitides (particularly those with focal involvement), cryptococcal abscesses, toxoplasmosis, septic emboli from bacterial endocarditis, amebic meningoencephalitis, sagittal sinus or other cerebral vein thromboses, and mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS).

Examination of cerebrospinal fluid (CSF) is imperative, and the single most important diagnostic test in suspected cases of HSE. CSF is usually under increased pressure, with a lymphocytic pleocytosis of 10-1000 white blood count (WBC) per til.. Cases of documented HSE without CSF pleocytosis are tare, but can occur, particularly in neonatal disease or in immunocompromised patients. Red blood cells (often crenated) or xanthochromia may be present in the CSF, but this finding is neither sensitive nor specific for HSE. CSF protein is usually moderately elevated, and glucose is usuallv normal.

Virus may be cultured from the CSF in less than 5% of cases; however, HSV DNA can be detected in the CSF with polymerase chain reaction (PCR) techniques. CSF PCR testing has an estimated sensitivity of greater than 95% and a specificity approaching 100% for the diagnosis of IISV infections of the nervous system, including HSE (Whitley and Lakeman 1995; DeBiasi and Tyler 1999} and has replaced brain biopsy as the diagnostic test of choice for HSE (Table 59R.6). CSF HSV PCR is also useful in diagnosis of cases of HSV-2 brainstem encephalitis and myelitis. CSF PCR remains a sensitive technique for the detection of HSE even in patients who have received up to a week of antecedent antiviral therapy. Newer quantitative, real-time PCR methods, which allow rapid turnaround of CSF sample results within hours, should allow for improved accuracy and rapidity of diagnosis in patients with possible HSE (DeBiasi et ah 2002). Despite the sensitivity of PCR, several recent reports have emerged indicating that CSF PCR may yield false-negative results in patients in whom CSF is analyzed within the first 24 hours of illness (Weil et ah 2002). For this reason, HSV-specific antiviral therapy should not be discontinued m patients with suspected focal encephalitis on the basis of a single negative CSF PCR test if it is obtained within 72 hours of symptom onset, unless a suitable alternative diagnosis has been established.

CT and magnetic resonance imaging (MR1) have both been utilized to assist in the diagnosis of HSE, MRI is a more sensitive modality and is the preferred study. Up to 40% of patients with HSE with normal CT scans will have demonstrable abnormalities on MRI. MRI typically demon si rates focal abnormalities as areas of high signal intensity on T2-weigh ted images in fron to temporal regions (Figure 59B.1). Electroencephalogram (FFG) may be abnormal early in the course of disease, demonstrating diffuse slowing, focal abnormalities in the temporal regions, or periodic latcralizing epileptiform discharges (PLEDS). Brain biopsy is now only rarely performed for diagnosis of HSF. Biopsy is reserved for atypical cases in which the diagnosis remains in question or those who respond poorly to treatment. Biopsy specimens show hemorrhagic necrosis, HSV antigen in infected cells, and accumulations of viral particles forming acidophilic intranuclear inclusion bodies in neurons (Cowdry type A inclusions) (Plate 59B.I).

Because of its safety, empitic therapy with acyclovir should be instituted immediately in cases of focal encephalitis (see Table 59B.7). Acyclovir should be administered intravenously at a dose of 10 mg/kg every 8 hours in adults and 20 mg/kg every 8 hours in neonates and children. Treatment should be continued, unless a CSF HSV PCR (obtained 72 hours or later after onset of symptoms) is negative, and/or an alternative diagnosis is made, for a minimum of 14 days. Many experts favor a 21-day course of therapy in adults and neonates with HSV meningoencephalitis. Renal insufficiency is an infrequent, usually reversible, side effect of acyclovir therapy. Acyclovir dosing should be adjusted appropriately in patients with renal insufficiency. Treatment with acyclovir reduces mortality of HSF from 70% to 20%. Over one third of patients with HSE treated with acyclovir recover with mild or no neurological impairment. Relapses following treatment with acyclovir have been reported (more often in neonates and children than adults) and may be due to either immune-mediated mechanisms or continued active viral infection. These possibilities can be distinguished by CSF HSV PCR. Patients with immune-mediated relapse are PCR negative, whereas those with residual infection remain PCR positive. Patients with relapse who remain PCR positive should receive an additional course of acyclovir therapy and should be tested for the possibility ol acyclovir-resistant virus. Foscarnet is an alternative therapy for patients with suspected or proven acyclovir-resistant strains or with allergy to acyclovir. Vidarabine is no longer utilized as a treatment for HSF".

Table 5915.5: Diseases that can masquerade as viral nervous system disease

Etiology			*Suggestive features*
Infectious	Bacterial	Parameningcal focus (sinusitis, intracranial abscess)	Very mild pleocyrosis, focal neurological exam
		Partially treated bacterial meningitis	Prior antibiotic treatment, right shifted CSE
		Lyme disease	Tick exposure, arthritis, apnmpri.iie geography, erythema migrans
		Tuberculosis	Very high protein, hypoglycorrhachia
		Leptospirosis	Conjunctival suffusion, jaundice
		Syphilis	Chronic
		Brucella	Farm animal exposure
		Whipple's disease	GI complaints
		Bartonella (cat scratch disease)	Cat exposure, adenopathy
		Listeria	Brainstem encephalitis
		Typhoid fever	Exposure history, bradycardia
	Fungal	Cryptococcus	Usually immunocompromised pr.
		Coccidioides	Southwestern U.S. exposure, pulmonary symptoms
		Histoplasma	Pulmonary nodules
		Blastomycosis	Midwest, pulmonary symptoms
		Candida	Immunocompromised pt.
		Nocardia	Immunocompromised pt.
	Parasitic	Toxoplasma	Retinitis, cat exposure
		Cysticercosis	Calcified lesions
		Amoebic	Fresh water: Naegleria
		Malaria *(P. falciparum)*	Exposure history
	Rickettsial	Rocky Mountain spotted fever	Leukopenia, thrombocytopenia, hyponatremia, petechial rash
		Ehrlichia	See above
		Coxsiella brunetti (Q fever)	F.xposure to sheep, pulmonary disease
	Mycoplasma		Precedent pulmonary symptoms
Parainfectious	Acute disseminated encephalomyelitis (AD EM)		Characteristic MRI findings
Noninfectious	Connective tissue disorders	Systemic lupus erythematosis (SLE)	Malar rash, multisystem organ involvement
		Sarcoidosis	Hilar adenopathy, erythema nodosum
	Uveomeningitic syndromes	Behcet's	Genital/oral ulcers, uveitis
	Intracranial tumors and cysts		Recurrent episodes, dermal sinus tract
	Drugs	NSAIDs, antibiotics, immunomodulators, anticonvulsants	Exposure history
	Intracranial hemorrhage		
	Encephalopathy	Toxic or metabolic	

Neonatal Herpes Simplex Virus Meningoencephalitis

In contradistinction to adults, in which HSF is usually caused by HSV-1, HSV-2 is the most common causal agent of meningoencephalitis in neonates (although HSV-1 disease may also occur). Neonates who acquire HSV from the birth canal develop infection of the CNS in 50% of cases (Kimberlin et al. 2001), CNS disease occurs as either a componenr of an overwhelming sepsislike disseminated disease with multi-organ involvement (in the first week of life), or as isolated CNS disease, which usually presents later (weeks 2-10 of life), with or without accompanying vesicular skin, mucous membrane, or conjunctival lesions (skin, eye, mouth disease). The presence of vesicular skin or mucosal lesions in an infant of this age, even in the absence of fever or systemic symptoms, warranrs immediate evaluation of CSF for cell counts, chemistry, and HSV PCR because up to 30% of infants with presumed isolated skin, eye, and mouth disease may subsequently be identified as having CNS involvement. Neonates with possible HSV disease should be treated empirically with intravenous acyclovir 20 mg/kg every 8 hours while awaiting results of CSF HSV PCR. Treatment should be continued for 14 days in infants with isolated skin, eye, and mouth disease and 21 days in infants with sepsis or evidence of CNS involvement, Relapses of skin, eye, and mouth disease (with the potential for CNS involvement and subsequent neurological deficits) arc common in the first year of life following

Tabic 59B.6: PCR diagnosis of viral nervous system disease

Virus	*Sensitivity*	*Specificity*	*Comments*
denovirus	Unknown		
engue	Unknown		
itero virus	>95%	*>9S%*	
crpesvi ruses			
CMV	100% in immunocompromised >6Q% in congenital CMV infection		Quantitative available
EBV	98.5 as tumor marker in **HIV** patients with CNS lymphoma	100%	Predictive value in normals unclear
HSV-1 and-2	>95%	>95%	Quantitative available
HHV-6	*>95%*		Poor positive predictive value in disease (30% normals positive}
VZV	*>9S%*	*>9S%*	
IV	HIV RNA present at all stages	Excellent	Quantitative available disease progression? response to therapy? drug-resistance?
HTLV I and II	75%	98.5%	
Influenza	Unknown but > culture	Unknown	
Japanese encephalitis virus	Unknown	Unknown	
JC virus	50-90% in PML	98%	
LCMV	Unknown	Unknown	
Mumps	Unknown	Unknown	
Measles	Unknown	Unknown	
Parvovirus B-19	Unknown	Unknown	
Rabies	100%	Unknown	
West Nile	Poor	Unknown	

CNS or non-CNS presentations of neonatal HSV disease. For this reason, the continuation of oral acyclovir prophylaxis for 3-6 months following intravenous therapy is currently being studied in a randomized multicenter trial (Kimberlin 2001). In the future, quantitative HSV PCR techniques may allow more accurate analysis of response to therapy, required duration of therapy, and determination of prognosis.

Meningitis Due to Herpes Simplex Virus

At the time of their first episode of genital herpes (generally due to HSV-2), approximately 36% of women and 11% of men have symptoms of meningitis, including fever, headache, and nuchal rigidity. Of these patients, 20% will develop recurrent episodes of meningitis (see Mollaret's meningitis following). When aseptic meningitis occurs in this setting, genital lesions are present an average of 1 week before the CNS symptoms. CSF viral cultures are invariably negative during recurrent episodes of meningitis, although the virus may be isolated during the first (primary) episode. Other neurological complications, such as paresthesias, urinary retention, and transverse myelitis, have been described with HSV-2 infections.

Recurrent meningitis, or discrete episodes of meningitis, has been linked to other viruses (including human immunodeficiency virus [HIV] and EBV), other infectious agents (such as partially treated or atypical bacterial or fungal pathogens, such as *Borrelia burgdorferi),* drug exposure (nonsteroidal anti-inflammatory agents, IVIG, monoclonal antibodies), dermoid cysts within CSF pathways that are leaking, and idiopathic inflammatory conditions (sarcoid, uveomeningitis syndromes). Recurrent aseptic meningitis should be distinguished from recurrent bacterial meningitis, in which underlying abnormalities should be sought, such as CSF leak, skull base fracture, dermal sinus, parameningeal infection, or impaired B-cell immunity (DeBiasi and Tyler 2000).

CSF PCR has identified HSV-2 in a large subset of patients with the syndrome of benign recurrent lymphocytic meningitis, also known as Mollaret's meningitis. This syndrome may be associated with the presence in the CSF of Mollaret's cells, large cells of monocyte-macrophage lineage. In one of the largest series to date, 85% of patients had detectable HSV DNA, of which 91% were HSV-2 (Tedder et al. 1994). These patients were predominantly females and experienced 3-9 attacks of meningitis over a period of 2-23 years. Of these, only 23% had a history of

Table 59B.7: Treatment and prophylaxis of viral infections

Antviral class	*Antiviral agent*	*Dnse*	*Indications*
Nucleoside analogs	Acyclovir	10 mg/kg/dose (IV) q8h x 14-21 days	HSV encephalitis in adults
		20 mg/kg/dose (IV) q8h x 21 days	Neonatal HSV encephalitis
		500 mg/m^2/dose (IV) q8h x 21 days (equivalent to 10-12 mg/kg/dose in adults and up to 20 mg/kg/dose in infants)	VZV encephalitis in normal or immunocompromised pt
		15 mg/kg/dose (IV) q8h x 10-14 days	Herpes B virus
		800 mg (PO) JX/day x 7 days	Dcrmatomal zoster or primary V in immunocompromised pt
	Famciclovir	200 mg (PO) tid x 7 days	Dcrmatomal zoster or primary V in immunocompromised pt
	Val acyclovir	1 g (PO) qid x 7 days	Dermatomal zoster or primary V in immunocompromised pt
	Ganciclovir	5 mg/kg (IV) ql2h x 14-21 days	CMV, Herpes B virus
	Valganciclovir	900 mg (PO) bid x 21 days (induction), then 900 mg (PO) qd (maintenance)	CMV Retinitis
	Ribavirin	2 g (IV) x 1, then I g (IV) q6h x 4 days, then 0.5 g (IV) q8h x *6* days	Lassa fever
		20-35 mg/kg/day x 7 days	Measles virus
	Cytarabine	2 mg/kg (IV) x 5 days x 4 wks	PML
	Trifluridine	1 % ophthalmic solution	Herpetic keratoconjunctivitis
Pyrophosphate analogue	Pose a met	90 mg/kg (IV) ql2 x 14-21 days	Acyc 1 ovir-resistant HSV/VZV Ganciclovir-resistant CMV
Other	Amantadine	100 mg (PO) bid x 5 days	Influenza A
	Rimantidine	100 mg (PO) bid x 5 days	Influenza A
	Oscltamivir	75 mg (PO) bid x 5 days	Influenza A and R
	Zanamivir	10 mg (PO) bid x 5 days	Influenza A and R
Cytokine	Interferon-ct	3 million U/day (SC)	PML, acyelovir-resistant VZV, Hepatitis C
		10-^{5}-10^d U/m^2 body surface (intrathecal)	SSPE
Supplements	Vitamin A	400,000 IU (IM)	Acute measles in vitamin A deficiency

CNS = central nervous system; CMV = human cytomegalovirus; HSV = herpes simplex virus; PML ~ progrcssive multifocal panencephalitis; VZV = varicella zoster virus.

Tabic 59B.8: Immunotherapy of viral infections"

Immunotherapy class	*Immunotherapy*	*Dose or route*	*Indications*
Specific hyperimmune globulin (IG)	VZIG (Varicella Zoster)	One vial (125 U) per 10 kg of body weight (IM)	Postexposure prophylaxis in hypogammaglobulinemic pt
	RIG (rabies)	Human RIG, 20 IU/ kg (Inject as much as possible in area of wound and remainder IM at site distant from vaccine)	Postexposure prophylaxis
	Human cytomegalovirus h yperi mmu n ogl o b u lin	IV	Prophylaxis after bone marrow transplantation
	Central European encephalitis hy peri mmu noglo b u lin	IM	Postexposure prophylaxis following multiple tick bites in endemic area
	Mea si es hyp erim m uno gl o b ulin	IV	Treatment of measles inclusion body encephalitis in immunocompromised pt
Polyvalent immune globulin	IV1G	IV	Treatment of chronic enterovirus meningo-encephalitis in hypogamma-globulinemic pt
	IVIG	IV	Treatment of human T-cell leukemia virus I myelopathy
Cv to toxic T Cells	Epstein-Barr vims (EBV)-spccific cytotoxic T lymphocytes		Prophylaxis of KBV 1 ympho p r o life r ative d lsea s e in bone marrow transplant recipients

*Live vaccines include yellow fever, measles, mumps, rubella, smallpox, polio, and varicella zoster virus. Killed vaccines include polio, rabies, influenza, arboviruses (Japanese encephalitis, tick-borne encephalitis, Kyasanur Forest, Rift Valley, eastern equine encephalitis, wcii.cni equine eccepl minis, a:id Vcnc/ueliin equine encephalitis). Soluble protein includes hepatitis *V*>.

genital herpes, none with lesions concurrent with their most recent episodes of meningitis.

Varicella Zoster Virus (VZV)

Primary Infection. VZV can involve virtually every part of the CNS and PNS. Primary VZV may produce encephalitis in immunocompromised patients and, rarely, a progressive, fatal encephalitis in healthy children. A self-limited cerebellar ataxia is often seen in otherwise healthy children during or immediately following primary VZV infection (chickenpox). Meningitis, brainstem encephalitis, and myelitis due to VZV can also occur in immunocompetent hosts, VZV can also cause both granulomatous arteritis leading to stroke and/or multifocal infarcts and small vessel vasculopathy (leukoencephalitis) (Kieinschmidt-DeMasters and Gilden 2001). Postinfectious encephalomyelitis follows an estimated 1 in 2500 cases of primary VZV infection. Reye's syndrome (2.5 per 10,000 cases) has been associated with primary VZV infection, particularly in children who concomitantly received aspirin.

Antiviral treatment of acute VZV encephalitis and myelitis is intravenous acyclovir, at the high dose of a 20 nig/kg (or 500 mg/m^2 per dose) every 8 hours. Treatment of immunocompromised children with primary VZV infection (in the absence of CNS disease) with intravenous acyclovir should begin within the first 24-72 hours after onset of the rash and be continued for a minimum of 7 days, or until lesions have crusted over. Foscarnet may be used for acyclovir-resistant zoster infections. Corticosteroids are often used for sighr-threatening complications (optic neuritis, orbital apex syndrome) and postviral cerebral (large vessel) vasculitic complications, but when utilized, should be accompanied by antiviral therapy. Corticosteroids may also be used to limit inflammatory response in myelitis. Brief courses of corticosteroid are also used to treat the small and large vessel vasculopathy that accompanies persistent VZV encephalitis in immunocompromised patients, although no clinical trials demonstrating its efficacy are available. VZV immunoglobulin is used for prophylaxis of seronegative immunocompromised patients and pregnant women who have been exposed to VZV. VZV immunoglobulin, one vial (125 units) per 10 kg of body weight intramuscularly, should be given within 96 hours and preferably within 48 hours of exposure (Arvin 1996).

Herpes Zoster. Following primary infection, VZV becomes latent in cells of the dorsal root ganglia. Reactivation of endogenous latent virus produces herpes zoster, or shingles. The virus can reactivate after injury or trauma to the spine or nerve roots or in response to waning cell-mediated immunity to VZV caused by age or immunosuppression related to HIV infection, cancer, cytotoxic drugs, or systemic illness. Herpes zoster is

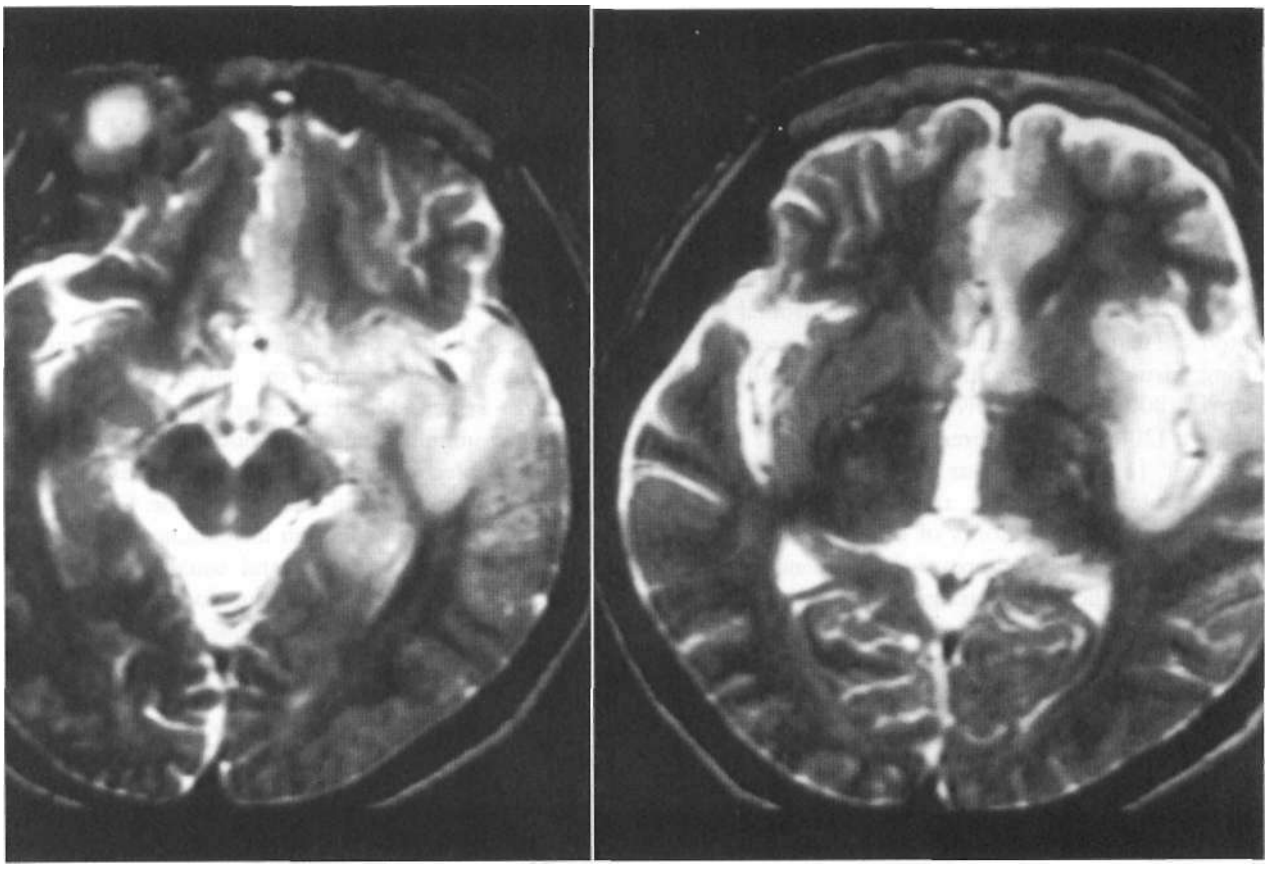


FIGURE 59B.1 Herpes simplex encephalitis. T2W-MRI showing increased signal in left media] temporal lobe, inferior frontal lobe, and insular cortex. (Courtesy J. Healy.)

frequently the first clinical presentation of underlying HIV infection, in which case it may he protracted and multidermatomal. In Africa, herpes zoster has a positive predictive value for HIV infection of *95%.*

Herpes zoster typically begins with pain and paresthesias in one or two adjacent spinal or cranial dermatomes. Pain is followed in 3-4 days by a painful pruritic vesicular eruption in the area supplied by the affected root. The eruption can last 10 days to 2 weeks. Occasionally, a few lesions appear outside the primary dermatome. Herpes /.oster most often involves the thoracic dermatomes, usually T5-T12. Fourteen to 20% of patients have disease in the distribution of a cranial nerve and 16% in lumbosacral dermatomes, usually LI or L2. Involvement of the first division of the trigeminal ganglion produces ophthalmic zoster and may be associated with conjunctivitis, keratitis, anterior uveitis, or iridocyclitis. Occasionally corneal transplantation may be required to correct visual impairment from corneal scarring. Vision loss following herpes zoster ophthalmicus is rare, however, and more commonly is caused by retrobulbar neuritis. Involvement of the geniculate ganglion produces otic zoster, or the Ramsay Hunt syndrome: painful facial paresis accompanied by tympanic membrane and external auditory canal vesicular rash. Older age and cranial nerve involvement are risk factors for zoster encephalitis, so all cases of ophthalmic zoster in older adults should be treated with antivirals. Herpes zoster involving cervical and thoracic levels may be associated with myelitis, and in the lumbosacral region may be accompanied by bladder dysfunction or ileus. The clinical variant, zoster *sine her pete,* refers to syndromes of prolonged radicular pain without zoster rash **but with** detectable VZV DNA in the CSF.

Herpes zoster should be considered in the differential diagnosis of new onset acute radicular pain. A CSF lymphocytic pleocytosis, with cell counts to several hundred cells per microliter, may precede the rash. Approximately 40% of healthy individuals with herpes zoster have elevated CSF cell counts and protein concentration, and VZV can frequently be isolated from the CSF of these patients. VZV DNA can be detected in the CSF by PCR techniques, and VZV may be cultured from vesicles or detected by microscopic examination of vesicular scrapings by direct fluorescent antibody testing.

Complications of zoster include postherpetic neuralgia, segmental motor atrophy in the affected dermatome, meningitis, myelitis, large vessel vasculitis (usually involving the carotid or its branches on the side of zoster ophthalmicus), and multi-focal leukoencephalitis or encephalitis with generalized cerebral vasculopathy. VZV

encephalitis with vasculopathy has been reported in AIDS and cancer patients and in individuals treated with cyclophosphamide or corticosteroids. The syndrome may occur without signs of cutaneous infection or may progress after cutaneous lesions have healed. Mixed ischemic and hemorrhagic infarcts in subcortical gray and white matter, plus ischemic, demyelinative, or both kinds of lesions in deep white matter, are noted radiologically and pathologically.

Risk factors for postherpetic neuralgia in patients with shingles include age over 50 years and prodromal sensory symptoms. Treatments are directed toward lessening pain, reducing virus shedding, and shortening healing time. Acyclovir (800 mg orally five times daily for 7 days), famciclovir (200 mg orally three times daily for 7 days), or valacyclovir (1 g orally four times daily for 7 days) accelerate cutaneous healing and decreases acute zoster pain if begun within 72 hours of onset of rash. Whether these agents significantly decrease the incidence, duration, or severity of postherpetic neuralgia is uncertain. In patients without contraindications, a short course of corticosreroids, such as 40 mg prednisolone per day, tapered over 3 weeks, may be added to antiviral therapy. Compared with acyclovir therapy alone, addition of corticosteroids has been shown to improve comfort levels (pain reduction during the acute phase) following herpes zoster, although its efficacy in reducing subsequent risk of postherpetic neuralgia remains uncertain. Intrathecal methylprednisolone and oral gabapentin have been studied as treatments for postherpetic neuralgia and have been efficacious in some studies. A live attenuated varicella vaccine boosts VZV immune responses in adults, raising hope that, in the future, it may be possible to prevent dermatomal zoster eruption (Jumaan 2001; Johnson 2002).

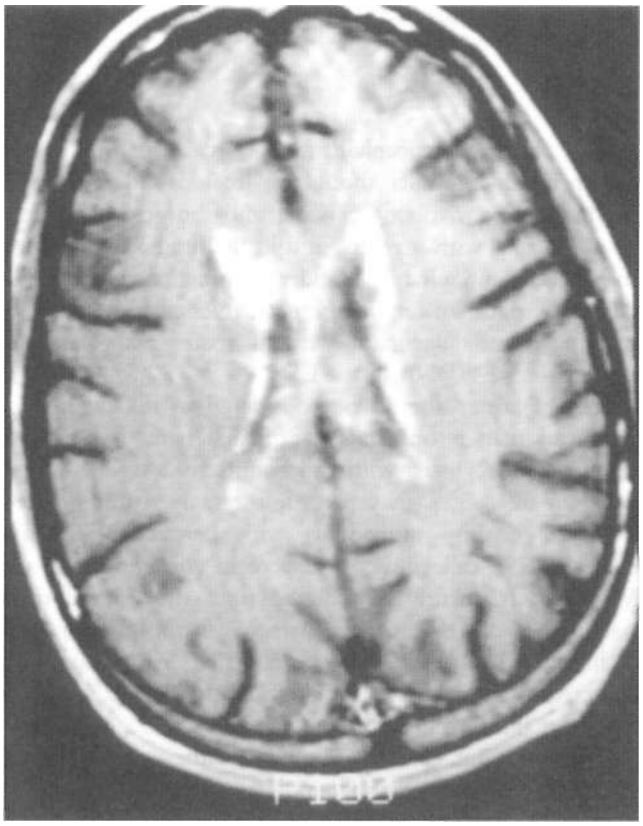


FIGURE 59B.2 Human cytomegalovirus ventriculitis. Axial gadolinium-enhanced 'I'lW-MRI showing contrast enhancement of ependyma of lateral ventricles. (Courtesy J. Hcaly.)

Cytomegalovirus (CMV)

CMV causes both acute and latent or persistent infections in humans. It is transmitted through saliva, milk, genital secretions, semen, blood transfusions, and organ transplants. In immunocompetent hosts, CMV may cause inapparent infection, a mononucleosis syndrome, aseptic meningitis, or the Guillain-Barrc syndrome. CMV encephalitis is exceedingly uncommon in immunocompetent hosts beyond the neonatal period and usually presents as an encephalopathy, with or without focal features, in the context of a subacute febrile illness. However, immunocompromised adults and developing fetuses are at high risk of developing CNS disease due to CMV. CMV may also infect the peripheral nerves, nerve roots, and spinal cord in patients with advanced HIV, presenting as an ascending myeloradiculitis.

Congenital CMV. CMV infection is the most common congenital infection affecting humans and can cause severe injury to the infected fetus. Up to 10% of infants born to mothers with primary CMV infection (the bulk of whom acquire CMV in the first trimester of pregnancy) are symptomatic at birth. 10% of symptomatic infants die, and 80% of survivors suffer severe neurological morbidity (9000 infants each year in the United States) (Ahlfors et al. 1999). Infection by passage through the birth canal or following breastfeeding in the perinatal period accounts for additional infantile cases. Persistent, high levels of viral replication in the eye and brain of the developing fetus produce encephalitis, ependymitis, and retinitis, a pattern similar to that seen in patients with opportunistic CMV infection in the setting of HIV infection. Pathologically, encephalitis occurs in a periventricular pattern and may cause polymicrogyria and hydrocephalus. (Figure 59B.2). CT scans characteristically show periventricular calcifications. Symptomatic infants usually have hepa to splenomegaly and thrombocytopenia in addition to CNS findings. Mild or subclinical congenital infections may also manifest later in childhood as sensorineuronal deafness or developmental delay. Congenital human CMV infection is the most common, nonhcritablc cause of hearing loss in the United States,

Although congenitally infected infants will excrete CMV in their urine throughout the first year of life, diagnosis of congenital CMV infection depends on the detection of virus by culture in urine, saliva, or CSF during the first 3 weeks of life. The clinical utility of CSF PCR for CMV

in the setting of congenital infection is being investigated, particularly with respect to correlating neurological outcome with CSF viral load. CMV inclusion-bearing cells are found in affected organs (Plate 59B.II) and in stained preparations of urinary sediment and saliva. Diagnosis of acute CMV infection in immunocompetent adults usually relies on serologic methods, specifically the detection of CMV IgM antibody because infected patients may intermittently excrete virus in their urine for years following infection, and CMV lgG persists for life following primary infection.

In a study evaluating the efficacy of intravenous ganciclovir therapy (4-6 mg/kg every 12 hours for 6 weeks) in neonates with symptomatic congenital CMV infection, quantitative excretion of CMV in the urine decreased initially, but returned to pretreatment levels after cessation of therapy. Hearing improvement or stabilization occurred in 16% of treated infants at *6* months or later posttreatment. However, a large proportion of treated infants developed cytopenias on prolonged ganciclovir therapy (Whitley et al. 1997).

CMV in Immunocompromised Adults. CMV encephalitis in the transplant patient (Tsclis and Lavi 2000) presents as a nonspecific febrile encephalopathy, with or without focal features. AIDS associated CMV encephalitis presents either as microglial nodular encephalitis wirh acute onset of confusion and delirium or as a more slowly progressive ventriculocncephalitis, characterized by confusion and cranial nerve palsies. There is a broad pathological spectrum of CMV infection of the brain in AIDS patients, ranging from scattered microglial nodules, to widespread necrotizing ependymitis and perivascular infiltrates, to necrotizing leukoencephalopathy. The broad spectrum of disease is likely related to variable degrees of immunosuppression resulting in wide ranges of viral load, as well as synergistic interactions between CMV and HIV.

Diagnosis of CMV encephalitis can be difficult, particularly by serological resting, because CMV antibody titers can fluctuate spontaneously. Serological and virus detection methods are currently being extended to focus on quantitation of viral burden (particularly in peripheral blood leukocytes) for patients with persistent infection, as well as to help predict which immunosuppressed patients might develop end-organ disease. CMV PCR has a reported sensitivity of 82% and specificity of *99%* in AIDS patients with CNS disease due to CMV (Cinque et al. 1997). Findings on brain imaging are poorly characterized in nonimmunocompromised and transplant patients. In AIDS patients, a wide spectrum of imaging results has been reported, ranging from normal to generalized atrophy, periventricular abnormalities, and focal, discrete lesions, often involving white matter. MRI is more sensitive than CT and most characteristically demonstrates periventricular increased signal on T2-weighted images and ependymal enhancement on TI-weighted images.

Ganciclovir, foscarnct, and cidofovir are all antiviral agents with efficacy against CMV, However, the clinical response of AIDS-associated CMV encephalitis to antiviral drugs appears to be poor. The response to peripheral nerve and nerve root infection with CMV appears to be better. Systemic and retinal CMV infections arc known to respond very well to ganciclovir and foscarnct, either alone or in combination. In immunocompromised patients with CMV retinitis, encephalitis, or myeloradiculitis, antiviral therapy should be instituted with intravenous ganciclovir, 5 mg/kg every 12 hours for 2 weeks of induction, followed by maintenance dosing of 5 mg/kg per day, 5 days per week. The addition of foscarnct should be considered. There is less clinical experience with cidofovir, which is currently licensed only for treatment of retinitis. Recently, valganciclovir, an orally administered prodrug that is rapidly hydrolyzed to ganciclovir, has been shown to be efficacious for the treatment of CMV retinitis (Martin et al. 2002). An extended discussion of CMV treatment in HIV-infected patients is presented in Chapter 59E. Because of the frequency of subclinical infection in the adult population, bone marrow transplant recipients should receive human CMV hyperimmune globulin as prophylaxis (see Table 59B.8).

Epstein-Barr Virus (EBV)

Primary EBV infection may be asympromatic, present as a nonspecific febrile illness, or classically, as the infectious mononucleosis syndrome with cervical lymphadenopathy, exudative pharyngitis, and splenomegaly. Nervous system disease occurs in less than 1% of EBV infectious mononucleosis cases and can manifest as meningitis, encephalitis, cerebellitis, transverse myelitis, optic neuritis, cranial neuropathy, Guillain-Barre syndrome, or as small fiber sensory or autonomic neuropathy syndromes. As a B-cell transforming virus, EBV is also associated with the development of CNS lymphomas. Detection of latent EBV nucleic acid has been demonstrated in the jaw, orbit, and CNS of patients with endemic and sporadic Burkitt's lymphoma, as well as in the CNS of patients with AIDS-associated CNS lymphoma.

The diagnosis of EBV is suggested by the presence of serum heterophile antibodies (monospot), although this is a nonspecific test that may be positive in other disease states such as hepatitis and lymphoma or in the presence of certain drugs. Specific diagnosis of CNS EBV disease requires the detection of serum and CSF EBV-specific antibodies. In serum, the presence of EBV Viral Capsid Antigen (VCA) IgM antibody is indicative of recently acquired, active infection. The presence of EBV VCA IgG antibody in the absence of VCA IgM and Epstein-Barr Nuclear Antigen (EBNA) antibodies is indicative of recent infection within the previous 2 months. The presence of EBNA antibodies indicates distant infection, and these antibodies remain positive for the lifetime of the infected individual.

CSF PCR for EBV is positive during the acute phase of illness in children with infectious mononucleosis and neurological complications such as transverse myelitis, meningoencephalitis, and aseptic meningitis. CSF PCR is negative in EBV-seropositive individuals in the absence of CNS infection. However, positive EBV PCR may be seen in patients with evidence of other viral or nonviral CNS infection, raising the possibility that these infections may trigger viral reactivation. EBV has been one of the most frequent agents associated with dual-positive CSF PCR testing and may not always correlate clinically with the presence of CNS infection known to be caused by this virus (Studahl et al. 2000). CSF PCR testing for EBV has been found to be nearly 100% sensitive as a tumor marker for EBV-related CNS lymphoma and has changed the way in which clinicians diagnose CMS lymphoma in immunocompromised individuals. EBV DNA may even be detectable in CSF before CNS lymphoma is clinically apparenr.

Immunomodulation with intravenous immunoglobulin may Improve EBV-associated small fiber sensory or autonomic neuropathies if treatment begins during acute disease. None of the currently available antiviral agents, including acyclovir, ganciclovir, and foscarnct, have significant activity against EBV. However, there are case reports describing successful treatment with ganciclovir of EBV meningoencephalitis following bone marrow transplantation. Vaccine and immune therapies are in development for treatment of these conditions, including the use of virus-specific cytotoxic T lymphocytes as prophylaxis for EBV lymphoproliferative disease in bone marrow transplant patients {Heslop and Rooney 1997).

Human Herpesvirus-Type 6 *(HHV-6)*

HHV-6 is a prevalent, E lymphotropic virus, causing a spectrum of diseases ranging from inapparent infection to disseminated, fatal disease. Exanthem subitum (or roseola) of infants or lymphadenopathy syndromes are the most common presentations of primary infection. HHV-6 genome has been demonstrated in CSF from children younger than 1 year of age who have febrile seizures and has also been seen in children with recurrent febrile convulsions with CNS involvement. However, primary infection may also rarely result in meningoencephalitis in immunocompetent children. Retrospective studies from Whitley's group indicated that approximately 6% of a series of children and adults with focal encephalitis had HHV-6 genome demonstrable in the CSF by PCR analysis. HHV-6 has increasingly been recognized as an opportunistic infection resulting in encephalitis in immunocompromised patients (Figure 59B.3), and can mimic HSV encephalitis. A possible role for HHV-6 in the etiology of multiple sclerosis (MS) has been suggested but remains unproven. (Caserta et al. 2001).

In a large study of immunocompromised (HIV-infected) patients, conducted to assess the diagnostic reliability of CSF PCR by comparison with biopsy or autopsy diagnoses, the most frequent false-positive herpesvirus detected was HHV-6. In another large study of mostly immunocompetent patients, detection of HHV-6 by CSF PCR did not always correlare clinically with the presence of a CNS infection known to be cause by that virus (Studahl et al. 2000). Additional large studies are necessary to determine

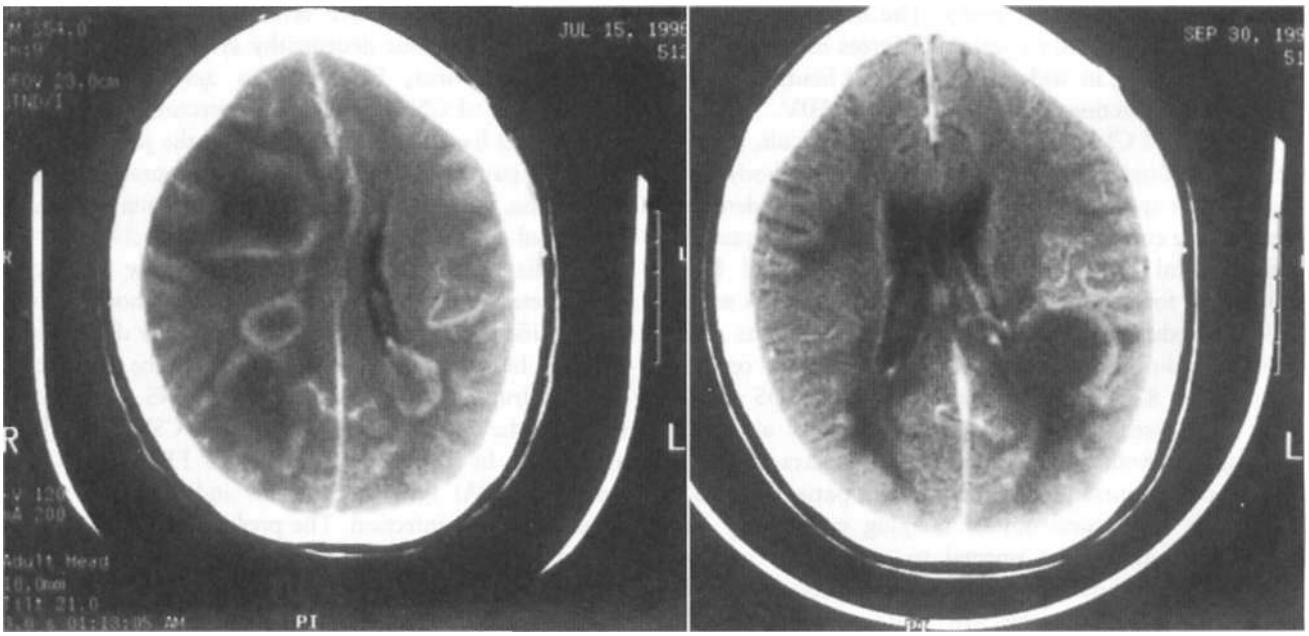


FIGURE 59B3 Concurrent human herpesvirus 6 and human immunodeficiency virus disease. Contrast CT scans showing multiple, ring-enhancing frontal, parietal, and occipital lesions. The second image shows parietal recurrence 3 months later. Pathology demonstrated perivascular lymphocytic infiltrates, demyehnation, and axonal sparing. (Courtesy S. Busono.)

PLATE 59B.I Hippocampal granule cell neurons in herpes simplex 1 encephalitis. Many of the nuclei contain acidophilic Cowdry type A intranuclear inclusions, which are surrounded by haloes and which marginate the nuclear chromatin. (Hematoxylin-eosin stain, x .350) (Courtesy R. Kim.)

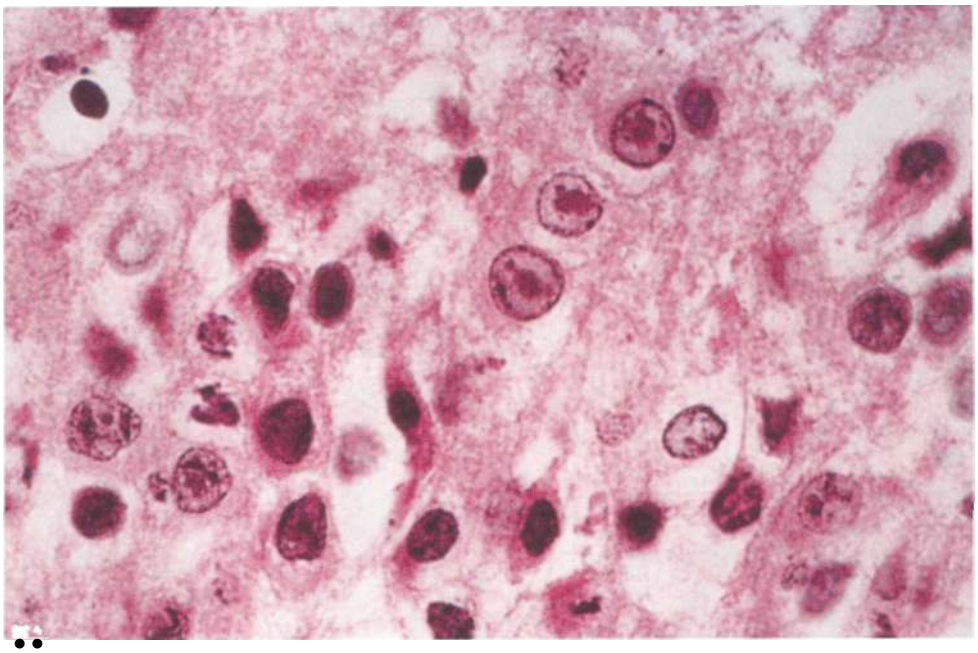
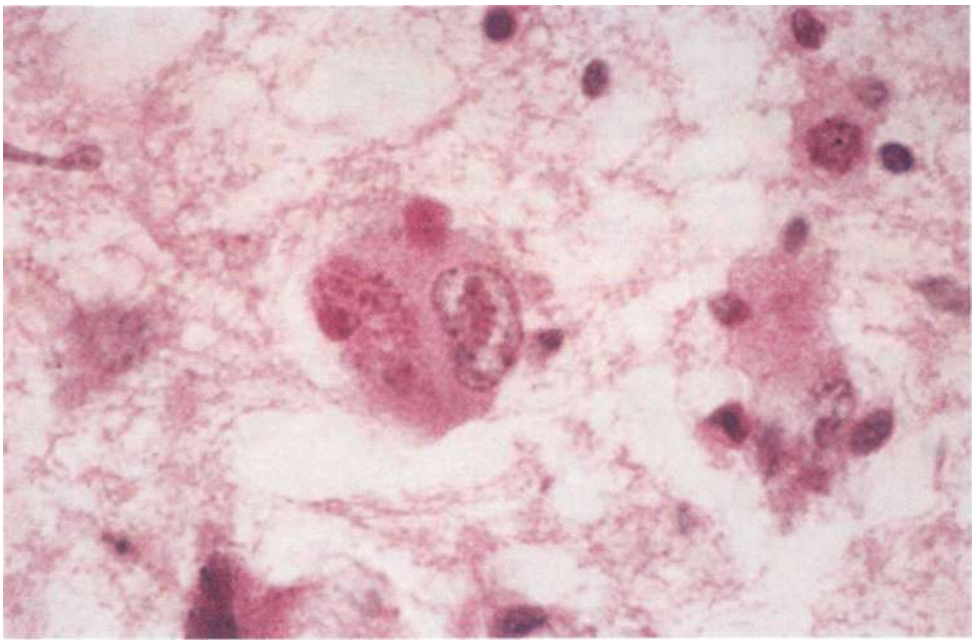


PLATE 59B.II Ballooned cell with eccentric nucleus in human cytomegalovirus encephalitis. An acidophilic Cowdry type A intranuclear inclusion body, with its surrounding halo, marginates the nuclear chromatin. The cytoplasm also contains granular inclusion material. (Hematoxylin-eosin stain, x 350) (Courtesy R.Kim.)



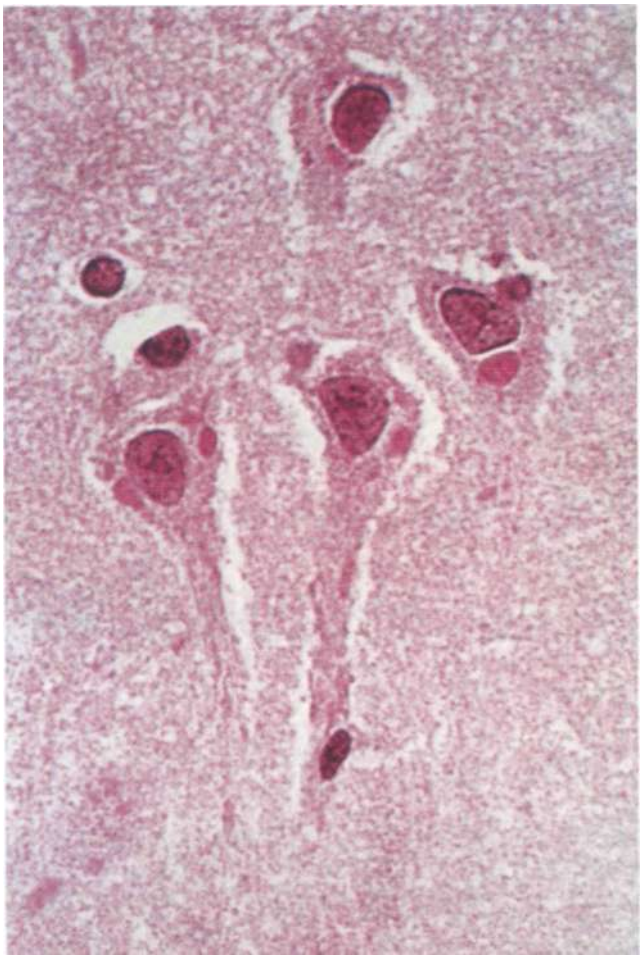


PLATE 59B.HI Hippocampal neurons in human rabies encephalitis. The cytoplasm of these neurons bears one or more rounded or oval Negri inclusion bodies. (Hematoxylin-eosin stain, x 350) (Courtesy R. Kim.)

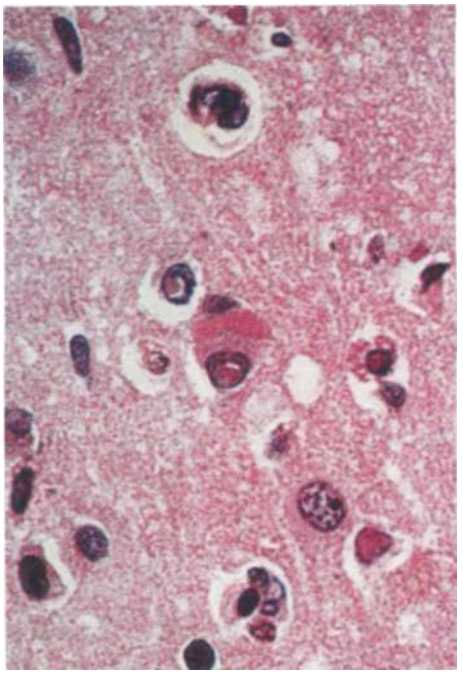


PLATE 59B.IV Cerebral cortex in subacute sclerosing panencephalitis. A pyramidal neuron contains both a Cowdry type A intranuclear inclusion and a cigar-shaped cytoplasmic inclusion, Cowdry A inclusions are present also in the nuclei of several nearby glia cells. (Hematoxylin-eosin stain, x 350) (Courtesy R. Kim.)

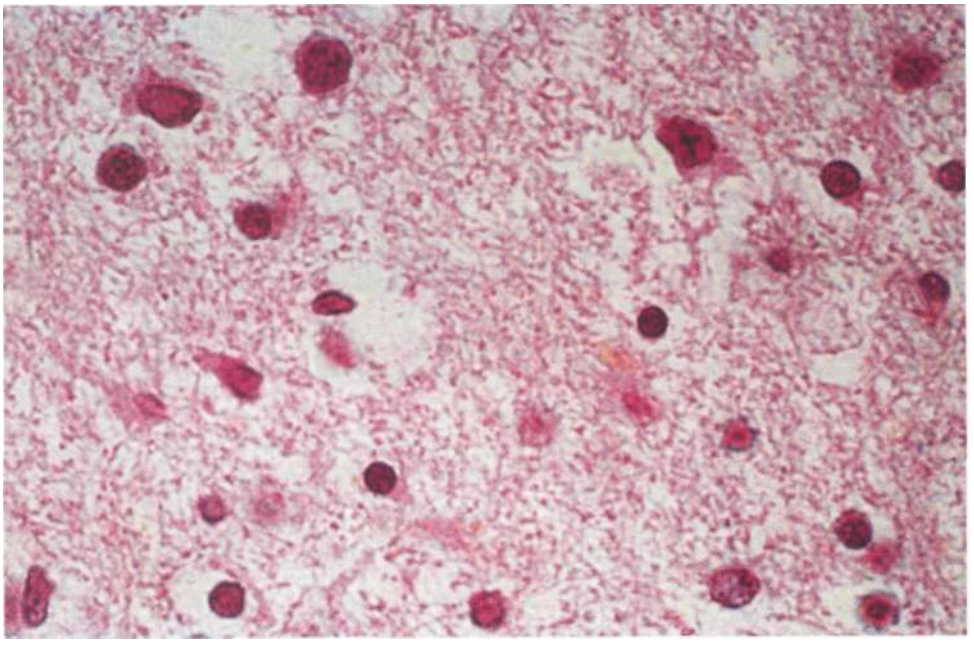


PLATE 59B.V Cerebral white matter in progressive multifocal leukoencephalopathy. Oligodendroglial cell nuclei are greatly enlarged and their nuclear chromatin replaced by glassy acidophilic material. (Hematoxylin-eosin stain, x 350) (Courtesy R. Kim.)

the reliability of positive CSF PCR results for HHV-6 in immunocompromised and immunocompetent hosts. The B variant of HHV-6, the variant most commonly isolated from immunocompromised patients, has a susceptibility to ganciclovir that is similar to the susceptibility of CMV in vitro.

Human Herpesviruses-7 and -8 (HHV-7 and HHV-S)

The role of HHV-7 in neurological disease is unclear, although detection of HHV-7 DNA in CSF and serum of children with roseola and encephalopathy has been reported. HHV-7 genome has also been detected by PCR in neoplastic brain tissue from patients with primary and metastatic brain tumors (Chan et al. 1999), but whether this represents reactivation from latency in an immunocompromised state, or contributes to the pathogenesis of tumor development is unknown. Encephalitis in immunocompromised individuals associated with HHV-8 has been described, but awaits additional confirmation (Said ct al. 1997). HHV-8 DNA has been detected in primary CNS lymphomas in some studies but not others.

Herpes B Virus (Cercopithecrine Herpes Virus 1)

Herpes B virus of Old World monkeys is highly pathogenic to humans, and infection is fatal in 70% of cases. Ocular, oral, and genital secretions of monkeys, as well as CNS tissues and CSE of monkeys, are potentially infectious. Disease is transmitted by direct contact with the virus, usually by animal bite or by virus-containing fomites. However, the first fatal case of B virus infection due to mucosal splash exposure was reported in 1998, leading to updated recommendations for prevention and treatment by the Centers for Disease Control (CDC) in 1999 (Cohen etal. 2002).

Fever, myalgia, herpctiform rash, meningismus, and early stage nystagmus or diplopia are followed by an ascending encephalomyelitis causing flaccid paralysis, urinary retention, and signs of CNS involvement, including seizures, progressive lethargy, and coma. Diagnosis is by wound or contact site culture and demonstration of increasing antibodies in paired acute and convalescent sera. Median nerve somatosensory evoked potential may identify early brainstem and cervical cord involvement and aid in differentiating R virus from HSV encephalitis.

Suggested preventative measures for primate workers include use of protective eyeware including side shields and a mask to protect from mucous membrane exposure. Should exposure occur, the most critical period for prevention of infection is within the first few minutes after exposure. Immediate cleansing of the affected skin surface should be undertaken by soaking or scrubbing the contact area with povidone-iodine, ehlorhexidine, or detergent soap for 15 minutes. Eyes or mucous membranes should be immediately irrigated with sterile saline solution or water for 15 minutes. Postexposure prophylaxis within 5 days of exposure can be considered using acyclovir, valacyclovir, or famciclovir. Based on animal studies, many experts prefer valacyclovir 1 g three times a day for 2 weeks. Symptomatic patients without CNS symptoms should be treated with either intravenous acyclovir, 15 mg/kg every 8 hours or intravenous ganciclovir 5 mg/kg every 12 hours, although some experts recommend ganciclovir for all symptomatic B virus infections due to the unpredictability of rapid and life-threatening brainstem involvement. When CNS symptoms are present, treatment should be initiated using intravenous ganciclovir 5 mg/kg every 12 hours. Treatment should be continued until symptoms resolve and the results of two sets of cultures are negative for B virus after being held for 10-14 days. Following IV therapy, most experts suggest that therapy should be switched to oral valacyclovir, famciclovir, or acyclovir in the dosages used for postexposure prophylaxis. Although no good data exist to aid in determination of when therapy should he discontinued, many experts recommend continuing trearmem for months to years, with regular cultures of the conjunctiva and oropharynx to assess for viral shedding.

Poliovirus and Other Nonpolio Enteroviruses

The enterovirus (EV) family comprises over 70 different serotypes, within the *Picornaviridae* family. They can be subgrouped into the polioviruscs, coxsackieviruses A and B, echoviruses, and the newer sequentially numbered enteroviruses. The most common forms of infecrion by any of the enteroviruses are subclinical or mild febrile illness. Collectively, the enteroviruses are the leading causes of viral meningitis for which a pathogen can be identified. However, severe neurological syndromes, including encephalitis and acute anterior poliomyelitis, are associated with several of these agents.

Poliovirus

Poliovirus, one of the most virulent members of the enterovirus group, is the agent of acute anterior poliomyelitis (infantile paralysis). The virus is worldwide in distribution (although wild-type poliovirus circulates only in six countries in Southeast Asia and Africa as of 2002), is more prevalent in temperate regions, and causes disease most commonly in late summer and early fall. Poliovirus is transmitted by fecal-oral contact and, during epidemics, also by pharyngeal spread. Three antigenically distinct types of poliovirus have been defined. All can cause paralytic disease through destruction of motor neurons in the spinal cord and brainstem.

Clinically apparent infection with poliovirus results in aseptic meningitis (8% of cases) or paralytic illness {1% of all cases). A 7- to 14-day incubation period is followed by

headache, fever, signs of meningeal irritation, drowsiness, and seizures in infants. Asymmetric flaccid weakness of limbs, diaphragm, or cranial nerve-innervated muscles develops within days and progresses, on average, for 3-5 days. Cercbellitis, transverse myelitis, and facial paresis also have been reported.

Diagnosis is suspected based on the clinical picture and presence of CSF pleocytosis and confirmed by serology, virus isolation, or PCR amplification of poliovirus RNA from CSF. In the CSF, polymorphonuclear cells predominate early, with a shift to lymphocytes after several days. CSF protein concentration is slightly elevated; levels of 100-300 mg/dL may accompany cases of severe paralysis. The differential diagnosis of nonparalytic polio includes viral meningitis caused by other pathogens. The differential diagnosis of an acute, pure motor neuronopathy with CSF pleocytosis is broad and includes West Nile virus, Japanese encephalitis virus infection, and carcinomatous meningitis. Bulbospinal disease with inflammatory spinal fluid is seen in the Russian spring and summer encephalitis variant of arbovirus infection and in rabies. The Guiilain-Barre syndrome is distinguished by antecedent rather than concurrent febrile illness, CSF albuminocytological dissociation, absent reflexes, more common facial nerve involvement, and nerve electrophysiological abnormalities consistent with proximal demyelination.

Approximately one quarter of polio patients develop progressive lower motor neuron weakness 30-40 years after acute polio ("the postpolio syndrome"). Atrophy, fasciculations, and electromyographic evidence of active denervation are found in previously involved muscle groups.

Treatment of poliomyelitis is supportive, with particular attention to ventilatory assistance. Mortality from paralytic poliomyelitis is less than 10%, but bulbar forms have a poorer prognosis, and mortality may approach 50%. Clinical and virologic improvement has been reported with pleconaril in several cases of wild-type and vaccine-associated paralytic polio (Rotbart et al. 2001).

The WHO has set 2005 as a goal for eradication of poliovirus from the globe. Great progress has been made toward this goal using aggressive vaccination campaigns. In 1988 there were 350,000 cases of wild-type polio occurring in 125 countries; as of 2002 there were approximarely 1400 cases of wild-type polio, with circulation restricted to only six countries in Southeast Asia and Africa. There have been no cases of circulating wild-type polio in the United States since 1979 and in the Western Hemisphere since 1991. Fot this reason, as of the year 2000, the Advisory Committee on Immunization Practices has recommended the use of inactivated (Salk, intramuscular) polio vaccine in the United States for the entire primary immunization series in the first year of life, as well as the booster dose prior to school entry. In areas of the world in which poliovirus is still endemic, primary immunization should be carried out with trivalcnt live attenuated (Sabin, oral) vaccine. The advantages of oral polio vaccine are ease of administration and induction of intestinal immunity. The disadvantage is the risk of reversion to neurovirulence and production of paralytic disease in vaccinees and contacts. Therefore, inactivated polio vaccine should always be used for vaccination of persons with immunodeficiency diseases, in which the risk of vaccine-associated paralytic polio from live attenuated vaccine strain is high. Vaccine-related cases of paralytic polio have included infants with unrecognized immunodeficiency who have received their first oral polio vaccine dose and immunocompromised patients who have been in contact with recipients of live attenuated oral polio vaccine.

Nonpolio Enteroviruses

The nonpolio enteroviruses may cause a wide spectrum of CNS and PNS disease, including aseptic meningitis, encephalitis, acute anterior poliomyelitis, acute cerebellar ataxia, peripheral and optic neuropathy, cranial polyneuritis, and epidemic myalgia. In neonates, encephalitis is generally part of an overwhelming sepsis-like illness, with up to 10% mortality. Congenital CNS defects are associated with infection acquired in utero. Infection of hypogammaglobulinemic patients commonly leads to progressive meningoencephalitis. Certain strains have also been associated with an acute motor neuron disease in association with epidemic hemotrhagic conjunctivitis.

Meningitis

Nonpolio enteroviruses are the most common cause of viral meningitis (Pallansch and Roos 2001). Over 75,000 cases of EV meningitis occut in the United States each year, and these also occur in a worldwide distribution. The strains most commonly isolated in aseptic meningitis are Coxsackie A9, B3-5, and echovirus 4, 6, 7, 8, 11, 18, and 30. Spread of infection is by fecal-oral and, rarely, respiratory routes. Outbreaks tend to cluster in the late summer and early fall and may be associated with pharyngitis and gastrointestinal symptoms, such as anorexia, vomiring, or diarrhea. Other findings suggestive of enteroviral infection include the cxanthem of herpangina or the rash of hand-foot-and-mouth diseases. Although EV is the most common cause of viral meningitis in the adult as well the pediatric population, children are epidemiologically over-represented as victims of enteroviral infection. Fortunately, EV meningitis occurring beyond the neonatal period in immunocompetent hosts is only rarely associated with severe disease or subsequent neurological deficits (Sawyer 2002).

Meningitis caused by coxsackievirus produces CSF cell counts typically up to 250 WBC per uL with 10-50% polymorphonuclear cells. Echovirus infections are associated with CSF pleocytosis from several hundred to greater than 1000 WBC per uL, 90% of which may be polymorphonuclcocytes in the first 24 hours of infection. Until

recently, recovery of enteroviruses was the primary means of establishing the diagnosis of CNS cntcroviral disease. Recovery of nonpolio EV from throat or rectal swabs is also suggestive, but not diagnostic, m .1 patient with viral meningitis because shedding from a previous, unrelated, F,V infection may be detectable for 1-3 weeks following infection in respiratory specimens and up to 6 weeks in stool specimens. The clinical utility of obtaining viral CSF culture is further limited by the amount of time required for EVs to grow (days to weeks), the relatively low sensitivity (65-75%), as well as the poor cultivability of some EV serotypes. The development of a reliable PCR for the detection of EV has been extremely useful in circumventing these problems (Ramcrs et al. 2000). PCR primers and probes are directed against the 5' nontranslatcd region of the viral genome, which is highly conserved among almost all cntcroviral strains. The newest generation of cntcroviral reverse transcriptase-polymerase chain reaction (RT-PCR) on CSF has >95% sensitivity and 100% specificity for known strains of EV. Conventional RT-PCR methods produce results within 24 hours, but more recently developed colorimetric assays, and real-time quantitative techniques can yield results in 4 hours. The availability of rapid turnaround EV RT-PCR should allow for more rapid diagnosis of this common illness and limit unnecessary hospitalizations, imaging procedures, and empiric antibacterial therapy.

Although treatment has been supportive to date, resolution of the atomic structure of EVs by x-ray crystallographic studies has led to the design of new antiviral therapy. These studies demonstrate a deep cleft or canyon in the center of each protomeric unit of the EV viral capsid, which engages specific cellular receptors on targer cells. The drug pleconanl was specifically designed to fit into this cleft and can block the cell/receptor interaction required for viral entry into the host. This drug may allow treatment of meningitis and encephalitis caused by EV and may be particularly useful in the case of more severe or overwhelming disease as in neonates and agammaglobulincmic patients. Clinical trials in childhood and adult meningitis demonstrated minimal improvement in symptoms, but the drug is available for compassionate release in more severe cases of EV disease, including vaccine-associated paralytic polio (Rotbart et al. 2001).

Meningoencephalitis

Although more commonly the etiologic agent in aseptic meningitis, EVs may also cause encephalitis, particularly in immunodeficient patients with hypogammaglobulinemia, and in neonates. Focal and generalized presentations of encephalitis have been reported. EV strain 70 has been implicated most frequently in instances of encephalitis. In neonates, meningoencephalitis is generally a component of an overwhelming sepsis-like illness, with up to 10% mortality. Infection of hypogammaglobulinemic patients leads to a chronic and progressive meningoencephalitis; these patients should be treated with IV inimnrniejolnilui therapy. Pleconaril, an antiviral therapy with activity against EVs (described earlier), has become available and can be used in neonates and immunodeficient patients on a compassionate use basis.

Epidemic Conjunctivitis and Acute Motor Neuron Disease

Enterovirus type 70 is the etiological agent of a syndrome of conjunctivitis and an acute motor neuron disease. Epidemic acute hemorrhagic conjunctivitis first appeared in Ghana, West Africa, in 1969 and spread across Africa, Asia, and Europe in 1970 and 1971 to involve tens of millions of people. The eye disease was characterized by severe eye pain, photophobia, blurred vision, and varying degrees of subconjunctival hemorrhage. In a minority of patients, usually young men, a neurological (polio-like) phase developed 2 weeks after the conjunctivitis as acute asymmetric hypotonic or flaccid weakness of the lower extremities. Isolated facial nerve palsy, upper limb weakness, radicular, myelopathic, dysautonomic syndromes, or multiple cranial neuropathies were also reported. Acute hemorrhagic conjunctivitis surfaced again in 1981 in many of the same countries, in French Polynesia, and in other Pacific Islands; was imported to the United States; and spread among household contacts. A similar disease caused by enterovirus type 71 has occurred in Bulgaria and moved around the world. The other agent of epidemic hemorrhagic conjunctivitis, coxsackie A24, has not been associated with an acute motor neuron disease. These are highly contagious viruses for which there is no specific antiviral treatment, underscoring the importance of surveillance, public health measures, and sanitation in limiting disease,

Enteroviruses and Amyotrophic Lateral Sclerosis

Viruses have been proposed to play a potential role in the pathogenesis of amyotrophic lateral sclerosis (AI.S) because of the predilection of viruses such as polioviruses for motor neurons and some climcopathological similarities between ALS and poliomyelitis. A report describing detection of echovirus 7 sequences by RT-PCR in formaldehyde-fixed spinal cord samples suggested a possible association between persistent enterovirus infection and ALS (Berger et al. 2000). However, subsequent studies have not confirmed this finding (Walker et al. 2001).

Arboviruses

The term *arbovirus* (ffrthropod-frorne *virus)* is a general term for viruses transmitted to humans by mosquito and

tick (arthropod) vectors. Arboviruses exist in nature in complex cycles involving birds and mammals, which serve as reservoirs of disease. When transmitted to humans, arboviruses can cause fever, headache, meningitis, and encephalitis. Arboviruses comprise a group of over 500 RNA viruses, of which > 100 are known ro infect humans. The three taxonomic families into which arboviruses are divided are togaviruses (subdivided into flaviviruses and alphaviruscs), reoviruses, and bunyaviruses. Considered l()j;e[her, .;rbovimsrs represent lhe li'.uliii;; , ausc of encephalitis worldwide (Lowry 1997). The salient features of arboviral infections occurring in North America are summarized in Table 59B.9.

St. Louis Encephalitis Virus (Flavivirus)

St. Louis encephalitis (SLE) virus is a cause of late summer encephalitis outbreaks in North America. In epidemic years, SLE accounts for a significant number of viral encephalitis cases reported in the United States. SLE virus cycles between *Cutex* mosquitoes and birds each summer. In the United States, there are an average of 135 endemic cases per year, although during epidemics there can be thousands of cases.

The illness is characterized by febrile headache only, aseptic meningitis, or encephalitis. Signs and symptoms of CNS infection progress over several days to a week. The incidence of encephalitis is higher in the elderly; in this population, case-fatality rates reach 30%. Season, place of residence, exposure, and presence of similar cases in the community are important considerations in the diagnosis. CSF cell counts are generally less than 200 WBC per uL, with lymphocytic predominance. CSF protein concentration is mildly elevated. Although the virus may be isolated from scrum or CSF, specific diagnosis usually relies on serological testing. IgM antibodies may be present in the CSF as early as day 3 of illness and are diagnostic. The slower evolution of neurological symptoms, the presence of generalised weakness and tremor, and the absence of focal findings and seizures favor a diagnosis of SLE over HSV encephalitis.

No specific antiviral treatment exists. Treatment, as for all the arboviral encephalitides, is supportive, with control of cerebral edema, hyperthermia, and seizures.

West Nile Virus {Flavivirus)

West Nile virus (WNV) was already one of the world's most widely distributed arboviruses, present in many parts of Africa, West Asia, the Middle East, Eastern Europe, and Australia, when it emerged in North America in 1999. l-'ili[1]. mm- people IVITI hospitalised with encephalitis or meningitis in late summer in the New York City metropolitan area, with seven resultant fatalities (Nash et al. 2001). Transmission occurs primarily by insect bite; however, person-to-person transmission through organ transplantation, blood and blood product transfusion, and intrauterine infection have been reported as of 2002. Mosquitoes of the genus *Culex* arc the principal maintenance vectors; wild birds served as the principal amplifying hosts for the New York epidemic. Concurrent epizootics with high mortality occurred in wild and exotic birds and horses. The rapid spread of the epidemic across the United States between 1999 and 2002 is causing concern that this virus has not only emerged, but also established itself as a major cause of viral meningitis and encephalitis in I he I iiiteJ States, with human cases reported in all but five states by the end of 2002. During the 2002 season, 4008 cases were reported, of which approximately 2500 cases presented as West Nile virus encephalitis (WNVF), resulting in 263 deaths. The 2002 WNV epidemic in the United States was the largest arboviral meningoencephalitis epidemic documented in the western hemisphere and the largest reported WNVE epidemic ever. West Nile should be included in the differential diagnosis of encephalitic illness in the summer and fall, particularly in patients with associated lower motot neuron weakness,

Most human infections are completely asymptomatic. Following an incubation period of 3-14 days, illness presents as a nonspecific febrile illness in approximately 20% of infected persons. One in 150 infected persons will develop encephalitis and/or meningitis, and the elderly (>50 years) are at most significant risk for severe neurological disease and death. The high frequency of associated motor weakness in patients with WNVE is a characteristic feature of nervous system involvement and has been reported in nearly 60% of cases. As illustrated by the New York epidemic, in which a large proportion of patients had some degree of associated weakness, patients may be flaccid, a reflex ic, or have milder weakness with diminished reflexes and cranial neuropathies (Tyler 2001). Nerve conduction studies show axonal or demyelinating neuropathy. More recently, it has been recognized that the bulk of cases preventing with weakness have a clinical and pathological picture more consistent with a poliomyelitis-like involvement of anterior horn cells, rather than Guillain-Barre type illness. The case fatality among hospitalized patients is approximately 12-14%.

Diagnosis is best achieved by detection of IgM antibodies in CSF and/or IgM and IgG antibodies in serum. CSF PCR is less sensitive than serological studies, although when positive, it is diagnostic, WNV may be isolated from serum, blood, and CSF early in the febrile stage and from brain tissue. Currently, commercial testing for WNV-spccific antibody is limited. Because of potential cross-reactions with antibodies to other flaviviruses (yellow fever, dengue, Japanese encephalitis antigen-complex members), experience in test interpretation is important, and positive tests should be confirmed by experienced laboratories such as the CDC and/or local public health departments (Marfan and Gulber 2001). Neuroimaging is often unremarkable, although meningeal and periventricular enhancement has been reported using MRI. CT scan is usually normal,

Table 59B.9: Details of North American arboviruses

Agent	*Geographic distribution*	*Reservoir*	*Vector*	*Season*	*Group affected*
Eastern equine	Atlantic and Gulf coasts, Great Lakes region	Birds	Mosquito	June-Aug	Children
\\ estern equi"t'	Western U.S. and Canada	Birds and small m a in in a Is	Mosquito	June-Sept	Infants, adults >50 ye
Venezuelan equine	Texas and Florida	Horses, small animals	Mosquito	Rainy season May-Sept	Adults
St. Louis	Throughout U.S.. but greatest prevalence in Texas, Florida, and Ohio-Mississippi River Valley	Birds	Mosquito	June-Aug	Adults >50 years
California (La Crosse)	Midwest and Northeast U.S., Southern Canada	Chipmunk, squirrel, small mammals	Mosquito	June-Sept	Children
West Nile virus	Throughout U.S.	Birds	Mosquito	June-October	All ages, adults >50 with severe disease
Powassan	North Central U.S., Eastern Canada	Squirrel, porcupine, groundhog	Tick	Spring /SuiniTU'r	
Colorado tick fever	U.S. and Canadian Rocky Mountains	Chipmunk, squirrel, rodent	Tick	March-Sept	Children and adulrs

Treatment of WNV encephalitis is supportive, but clinical response to intravenous immunoglobulin (1VIG) was reported after administration of an immunoglobulin preparation contained high titers (1:1600) of anti-WNV antibodies (Shimoni ct al. 2001), Unfortunately, the batches of IVIG currently available in the United States do not contain significant titers of WNV antibody and would therefore presumably be of limited benefit. Clinical trials are needed to determine optimal therapy for this disease.

laj'.uir-;f Encephalitis Virus Ehwirtrus) JEV)

JEV is widely distributed in Asia, through Japan, China, T:rv, .in, Korea, [he far Eastern former Soviet Union, Southeast Asia, and India. Worldwide, JEV infection is the most important cause of arboviral encephalitis and produces the greatest number of deaths worldwide each year. The virus cycles between *Culex, Aedes,* or *Anopheles* species of mosquitoes; pigs; and birds. Recently detected in Northern Australia, JE virus may soon become endemic on that continent as well (Mackenzie et al. 2001).

Following an incubation period of 6-16 days, patients may present with a febrile headache syndrome, aseptic meningitis, or encephalitis. The encephalitic form is characterized by a 2- to 4-day viremic prodrome of headache, fever, nausea, vomiting, dizziness, drowsiness, and abdominal symptoms in children, progressing to meningoencephalitis with signs of cortical, subcortical, extrapyramidal, bulbar, cerebellar, and spinal cord involvement. Excitability or delirium, seizures, hyperthermia, expressionless facies, axial rigidity, limb tremors and other involuntary movements, erratic eye movements, cranial nerve palsies, ataxia, limb paresis, including lower motor neuron type weakness in the arms, and segmental sensory disturbance are reported. Prolonged fever, seizures, coma, respiratory complications, and high CNS virus load arc all associated with a poorer prognosis. The case-fatality rate is 30-40%. Sequelae include parkinsonism, seizure disorders, paresis, mental retardation, and psychiatric diseirdci s,

In JEV encephalitis, there is a CSF pleocytosls with 10-500 (rarely up to 1000) WBC per LII„ with an early polymorphonuclear predominance later replaced by lymphocytes. CSF protein is elevated (50-100 mg/dE). Specific diagnosis is made by demonstrating a fourfold increase in IgG antibodies between acute and convalescent sera, or IgM antibodies in serum and CSF. Virus isolation from the blood is infrequent, but may be isolated from the CSF in one third of patients. MRI studies may show areas of abnormal signal in thalamus and basal ganglia.

No specific therapy is available for JEV encephalitis. A formalin-inactivated vaccine with excellent efficacy in prevention of disease is available for travelers to and residents of endemic areas. The risk of disease among travelers has been estimated to be between 1 in 5000 and 1 in 20,000 per week of travel. Primary immunization is with two doses, separated by 7-14 days and a single booster dose at 1 year. Revaccination is recommended at 3-year intervals.

California Serogroitp of Viruses (Family Bunyaviridae)

The California serogroup contains several viruses with mosquito vectors, small mammal or deer hosts, and limited geographic range. Among this group, La Crosse virus is an endemic cause of summer encephalitis in the mid western United States. Most cases are in children, who have seizures and polymorphonuclear or mononuclear pleocytosis on CSF examination. Children who recover may have sequelae including seizures (10%), cognitive dysfunction (2%), or weakness (<2%). Jamestown Canyon virus (Michigan, New York) and Snowshoe Hare virus (Alaska, Canada, and the northern United States) are other bunyavituses that can cause viral meningitis.

Equine Encephalitis Viruses (Family Aiphaviridae)

Eastern equine encephalitis (EEE) is the most severe of the arboviral encephalitidcs, with a mortality of 50-70%. There arc approximately five cases per year in the United States. Younger children are more susceptible to EEE than adults, as judged by higher case-infection ratios and more severe sequelae. EEE is a summertime epizootic encephalitis in the eastern United States. A prodrome of fever, headache, nausea, and vomiting progresses rapidly to delirium and coma. Meningeal signs and excessive salivation are common. Children show opisthotonus, generalized rigidity, or focal findings. The CSF may be under increased pressure, with a pleocytosis of 500-3000 WBC per pL, with polymorphonuclear leukocyte predominance and elevated protein concentration. The virus cycles in *Culex* mosquitoes and birds in the eastern United States. FEE-related horse or pheasant deaths in an area often precede human cases (sentinel infection). Diagnosis is made by virus isolation from sera or CSF or the documentation of seroconversion.

Western equine encephalitis (WF.F) is seen in mid-]Line through late September in the western United States. WEE is less virulent, with 5-10% mortality. Seizures, altered sensorium, rigidity, tremor, and other involuntary movements are noted during disease. CSF contains few to 500 WBC per pL, with monocytes being the predominant cell type. Moior or intellectual sequelae are common in infants. There are an average of five cases per year in the United States, although no documented cases have occurred in the United States the last several years. Highlands J virus, a WEE complex virus, cycles between bird- and riosquuoes :n freshwater swamp habitats ol the Atlantic coast and is a rare cause of encephalitis in the eastern United States.

Venezuelan equine encephalitis (VEE) virus causes a febrile illness with myalgias progressing to encephalitis and

coma in a small proportion of cases. Epilepsy, paralysis, tremor, hallucinations, and emotional lability may persist as permanent sequelae in children, and occasional cases of residual epilepsy or tremor have been reported in adults. Outbreaks have accompanied equine epidemics in Venezuela and other northern latitude areas of South America. Other favored ecological zones are tropical or subtropical forests of both Americas. Because the clinical presentation of Venezuelan equine encephalitis infection is rarely overtly encephalitic, the diagnosis may be missed unless recent travel in an area of disease activity in tropical America is taken into account. Both saliva and blood are infectious early in the disease.

A vaccine combining EEE, WEE, and VEE antigens has been used to protect laboratory workers or others in high-risk occupations, bin is nol general y offered In individuals not at high risk.

Colorado Tick Fever Virus (Orhi'virus)

Colorado tick fever virus causes a self-limited viral meningitis in persons exposed to wood ticks in the Rocky Mountains in spring and summer. The illness is classically biphasic, with an initial period of symptoms lasting 3 days, followed by a 3-day period of interim improvement, then relapse of symptoms for an additional 3-5 days. Diagnosis is made by serological detection of antibodies and, less commonly, virus isolation from blood.

Powassan Virus (Flavivirus)

Powassan encephalitis has been reported in Russia, Canada, and the United States. The virus cycles between ticks and small mammals. Powassan virus has been called the most herpes-like of the arboviruses because of the temporal lobe involvement noted in several cases. Neurological sequelae occur in an estimated 35% of survivors, ("Outbreak of Powassan encephalitis" 2001).

Modoc Virus (Flavivirus)

Modoc virus has caused viral meningitis in an individual exposed to deer mice in Modoc County, California. Virus has been isolated from the same rodent species in Oregon, Montana, and Alberta, Canada.

Murray Valley Encephalitis Virus (Australian X Disease; Flavivirus)

Murray Valley encephalitis virus has caused epidemics in Australia, primarily the Murray Valley region of New South Wales and Victoria, and sporadic cases in New Guinea. Outbreaks occur in summer months after years of heavy rainfall. The virus cycles between *Culex* and *Aedes* mosquito species and large water birds. Surveillance of virus activity in mosquitoes and birds, and targeted insect control efforts are practiced in areas of recurrent epidemics.

A 2- to 5-day viral prodrome is followed by rapid progression to ,u: eneephahtic illness, Most patients are in a coma when first examined. Treatment is supportive. Neurological sequelae are seen in 40% of milder cases and all patients who recover from coma. These include cognitive impairment, paraplegia, or ataxic gait.

Tick-Borne Encephalitis Virus (Flavivirus)

TBE occurs over a wide area of Europe and the former Soviet Union, corresponding to the distribution of ixodid tick vectors. Central European encephalitis virus and Russian spring-summer encephalitis virus, subtypes of the same virus, cycle between ticks and several wild rodent species and domestic livestock. Transmission also occurs by consumption of unpasteurized goat's milk.

The Central European form is a biphasic illness with systemic febrile illness followed by second-stage aseptic meningitis, encephalitis, myelitis, or radiculitis; there is a case-fatality rate of 1-2%, Russian spring-summer encephalitis is an indolent or more protracted febrile illness progressing to a meningoencephalitis, with a case-fatality rate of 20%. Neurological sequelae occur in 30-60% of survivors of Russian spring-summer encephalitis, particularly a bibrachial paresis. Serum antibodies arc usually present by the time neurological disease appears. Vaccines and TBE-immunoglobulin for preexposure or postexposure prophylaxis are available, Immunoglobulin should be given within 4 days of the tick bite. The TBE vaccine is also protective against Omsk hemorrhagic fever, a tick-borne hemorrhagic illness with geographical overlap to Russian spring-summer encephalitis.

Louping lit Virus (Flavivirus)

Louping ill was first recognized as a neurological disease in sheep in Scotland in the late 1800s. The virus is distributed among several domestic livestock species in the United Kingdom and spreads to humans by tick bites or to abattoir workers or veterinarians by direct exposure ro sick sheep. The human illness is biphasic, with an initial influenza-like illness followed by remission, and then a meningoencephalitis. Diagnosis is by CSF virus isolation or high antibody titers in the CSF. The western subtype TBE vaccine may confer cross-protection. Negtshi virus (flavivirus), antigenically related to louping ill, is a recognized cause of encephalitis in Japan and China.

Kyasanur Forest Disease Virus (Flavivirus)

Kyasanur Forest disease is a tick-borne biphasic illness in which an initial hemorrhagic fever is followed by remission and then meningoencephalitis. A formalin-inactivated

vaccine is in use in the Mysore state of India, its endemic area.

Rocio Vims (Flavivirus)

Rocio virus caused an encephalitis epidemic in the Sao Paulo state of Brazil in 1975-1976. The case-fatality rate was *4%.* Sequelae, including cerebellar, motor, and neuropsychiatry signs, were reported in 20% of survivors. The virus is presumed to cycle between *Aedes* mosquito species and wild birds.

Rift Valley Fever Virus (Bunyavirus)

Rift Valley fever is usually an influenza-like illness, but hemorrhage, hepatitis, meningoencephalitis, and retinitis are reported. Common complaints are of fever, headache, retto-orbital pain, and loss of vision. Macular and petimacular retinitis, with retinal hemorrhage and edema are seen. The virus cycles between a wide variety of mosquito species and large domestic animals. The disease is found in Egypt, Sudan, East Africa, southern Africa, and Mauritania, West Africa, at times of high mosquito density related to wet seasons or new dam constructions. Formalin-inactivated vaccines have been developed to protect laboratory and veterinary personnel working in disease areas.

Rabies

Rabies is a significant cause of encephalitis worldwide, with nearly 100% mortality. The disease is enzootic in all continents with the exception of Australia and Antarctica, as well as certain island states or nations: Great Britain, Ireland, Iceland, Japan, New Zealand, Hawaii, the Bahamas, and Bermuda. Reservoirs of infection are bats, wild carnivores (skunks, foxes, raccoons, coyotes, wolves), and nonimmunized dogs. In the United States, the bulk of human cases are related to bat exposure. Human rabies cases are frequently linked to bat exposures, often in rhe absence of a recognized or documented bite or scratch. Rare nonbite (aerosol) exposures have also been documented. liiles in [lie head and face carry the highest risk of mortality.

The incubation period is usually from 1-2 months, but may vary from 1 week to several years. A prodrome of headache, fever, paresthesias, and pain at the site of inoculation is followed by an acute neurological phase, then coma. Cases in which hyperactivity dominates have been called *furious* rabies. Characteristic neuropathologies! intraneuronal inclusions (Negri bodies) (Plate 59B.III) and inflammatory changes are maximal in the brainstem and limbic system. Up to 80% of patients exhibit hydrophobia or aerophobia: spasms of pharyngeal and nuchal muscles lasting from 1-5 minutes, triggered by swallow attempts or tactile, auditory, visual, and olfactory stimuli. The spasms arc thought to be an exaggerated respiratory rract protective reflex. As the disease progresses, attacks increase in frequency and are accompanied by agitation, hallucinations, autonomic hyperactivity, and seizures. Body temperature may reach 105" to 107° F. Paralytic, myelitic, or "dumb" rabies, accounting for 20% of patients, is characterized by paresthesias, weakness, and flaccid paralysis in rhe bitten extremity progressing to quadriplegia. Paralytic rabies is most often associated with bat rabies virus strains,

The diagnosis of rabies should be entertained in any patient with a history of exposure and clinical picture of agitated or paralytic encephalitic illness. When no history-can be obtained, rabies should be included in the differentia] diagnosis of any encephalitis progressing rapidly to coma, particularly if the patient has been to an endemic area. Othet differential diagnostic considerations include intoxications, postvaccination encephalitis, tetanus, which has a shorter (<2 week) incubation period and normal spinal fluid, or rabies phobia (a hysterical response to an animal bite).

Intracerebral inoculation of mice with patient saliva, examination of skin from the face or neck within the hairline (nuchal biopsy), and corneal smears for the presence of rabies antigen by immunofluorescence arc the most rapid methods of antemortem diagnosis. The presence of neutralizing antibodies in the scrum and CSF of an unimmunized patient is diagnostic, but are not highly sensitive methods. Active disease produces high diets (>1:5000), which may be helpful for diagnosing acute rabies in previously immunized individuals. High titers also distinguish acute rabies from postvaccination encephalomyelitis associated with vaccines detived from animal neural tissue. PCR protocols for detection of viral sequences in brain specimens have been established (Wacharapluesadee and Hemachudha 2001).

Transdermal bites or scratches and mucous membrane contact with saliva from known reservoir animal species constitute exposure. In addition, any history of bat exposure, with or without recognized bite, should be con si tiered .. significant exposure, (SF and other body fluids from rabies patients are highly infectious, and appropriate precautions should be taken. Postexposure treatment and prophylaxis of rabies includes wound care and the immediate administration of multiple doses of rabies vaccine and of antirabies immunoglobulin to nonimmune individuals. Wounds should be cleansed with soap and water, followed by povidone-iodine. Human diploid cell rabies vaccine (HDCV), rabies vaccine adsorbed (RVA), or purified chick-embryo vaccine (PCEC) should be administered intramuscularly on days 0, 3, 7, 14, and 28 into the deltoid or anterolareral thigh muscles ("Human rabies prevention" 1999). Previously immunized individuals are given vaccine on days 0 and 3. Human diploid ceil vaccines, in use in many areas of the world, are improvements over the biological products derived from animal (usually sheep) neural tissue, which have caused Guillain-Barre syndrome or acute disseminated

encephalomyelitis approximately once per 2000 vaccinations and other less-severe neurological complications as often as once in 120 vaccinations. Human rabies immunoglobulin, 20 IU/kg, should be administered once as soon .is possible after exposure (up to 7 days after the firsl dose of vaccine) at the beginning of prophylaxis to patients who have not been previously vaccinated. As much of the entire dose as possible should be administered in the area of the wound, and the remainder should be administered intramuscularly at a site distant from the vaccine administration. Because human rabies immunoglobulin may partially suppress active production of antibody, the recommended dose should not be exceeded.

Local pubhc health officials should be consulted before postexposure prophylaxis is started to avoid unnecessary vaccination and to assist in proper handling of the animal, from which infection is suspected, if confinement or testing is appropriate. A dog or cat immunized within the previous 3 years is considered an unlikely source of infection, hut should he confined and observed for 10 days. If ill, the animal should be euthanized, and the brain is examined at a regional health laboratory by iminunohistochemistry for rabies virus antigen. Wild animals belonging to known infected species, based on area health department data, should be considered as rabid until laboratory test results are negative. Treatment can he stopped if the animal remains healthy for the 10-day observation period or if the euthanized animal is confirmed antigen-negative.

Preexposure prophylaxis is available to veterinarians, animal handlers, laboratory workers, or travelers to endemic areas. One-milliliter injections of human diploid cell rabies vaccine administered intramuscularly or 0.1 mL intradermally is given on days 0, 7, and 21 or 28.

Novel Zoonotic Diseases of Oceana

Since 1995, the emergence of a number of zoonotic diseases in Southeast Asia and the western Pacific has lead to the detection of several new viruses of bats and livestock causing encephalitis in man (Mackenzie et al. 2001}.

Hendra virus

In 1994-1995 in Australia, Hendra, a new paramyxovirus originally called *Australian equine Morhillivirus,* was noted to cause fatal respiratory disease in racehorses and their trainer and fatal encephalitis in two horses and a farmer. Hendra virus has now been described as causing acute pneumonia, aseptic meningitis, and delayed encephalitis. Spread from horse to man is thought to occur through direct contact with secretions and body fluids of infected animals. Fruit bars (flying foxes) have been implicated as a reservoir host by the presence of anti-Hendra virus antibodies,

Nipah Virus

Nipah virus, another new paramyxovirus most closely related to Hendra virus, was discovered in 1999 during the investigation of an outbreak of encephalitis in Malaysia, A major outbreak of disease in pigs and man from September 1998-April 1999 resulted in 265 infected persons, 105 deaths, and the eventual destruction of 1.1 million pigs. Clinical signs and symptoms include fever, headache, myalgia, drowsiness, stupor, and coma. Most patients had a history of direct contact with pigs. A bat reservoir was again suspected, based on serologic testing.

Australia Bat Lyssavirus

Australia bat lyssavirus was isolated from fruit bats in 1996 during the investigation of the deaths of two bat handlers with clinical syndromes consistent with rabies encephalitis. Australia bat lyssavirus, closely related to rabies virus, possibly fills an ecologic niche that might otherwise be occupied by rabies, which is no longer found in Australia, due to effective vaccination and animal quarantine measures.

Measles

Despite the availability of an effective vaccine, measles, a highly contagious respiratory-borne disease, is still an important cause of childhood mortality and blindness in developing countries, as well as in sporadic outbreaks in industrialized nations. Measles causes four major CNS syndromes: acute encephalitis, postviral encephalomyelitis, measles inclusion body encephalitis, and SSPE.

Acute Encephalitis and Postviral Encephalomyelitis

Fever, maculopapular rash, cough, coryza, and Koplik's spots are characteristic of acute measles. CSF pleocytosis and EEG slowing may be documented in otherwise uncomplicated cases, but true encephalitis is infrequent. Keratitis and corneal ulceration accompany measles in children with preexisting malnutrition, particularly vitamin A deficiency. High-dose vitamin A supplementation, a single intramuscular dose of 400,000 1U for all ages, is recommended in regions with vitamin A deficiency or measles fatality rates greater than 1%. Postinfectious encephalomyelitis follows an estimated 1 in 1000 cases, usually within 2 weeks of the rash.

Measles Inclusion Body Encephalitis

Measles inclusion body encephalitis is a rapidly progressive dementing illness, with behavior changes, myoclonus, refractory focal or generalized seizures, delirium, oleoma developing 1-6 months after measles exposure in

individuals with deficiencies in cell-mediated immunity, Patients are afebrile, and CSF analysis is normal. Treatment consists of supportive care, the reduction in immunosuppression if possible, and passive immunoglobulin therapy.

Subacute Sclerosing Panencephalitis (SSPE)

SSPE is a rare late complication of measles, caused by persistent, nonproductive measles virus infection of neurons and glia. The pathogenesis of SSPE is related to defective measles virus maturation in neural cells. Aberrant M (matrix) protein as well as other envelope proteins interfere with assembly and budding of infectious virus. The virus remains in intracellular form and spreads by cell-to-ccll contact.

SSPE has an annual incidence from under 0.1 cases to 5 or 6 cases per million in nonimmunized populations. In areas of high early-life measle attack rates, SSPE accounts •'or ,1 nnipnnioTl <il' clrk: :KioJ iiei:i'o(.1q!,enei'ati'.\> conditions. Children infected in the first 2 years of life arc at greater risk, and case-series consistently show SSPE to be more frequent in boys. The median interval between acute measles infection and SSPE is 8 years, with a range from 2-12 years. The early stage is marked by behavioral or personality changes and declining school performance. Myoclonus, seizures, spasticity, choreoathetoid or ballistic movements, ataxia, and chorioretinitis follow in the second stage, Optii atrophy, quadripaivsis, autonomic bisuhiliiy, akinetic mutism, and coma are -ecu in the linal s'.agc. The majority of cases follow a progressive downhill course to death within a few years, some temporarily plateau or improve, and possibly 5% remit spontaneously (Garg 2002).

At the time neurological symptoms occur, neurons and glia contain nuclear and cytoplasmic viral inclusion bodies (Plate 59B.IV), and high titer antimeasles antibody is found in both serum and CSF. The CSF/serum antibody ratio is consistent with high levels of intrathecal synthesis of measles antibody. CSF pleocytosis is absent, glucose is normal, and total protein is normal or elevated. Acute symptoms, together with increased intracranial pressure, are poor prognostic signs. The earliest MRI findings are high-signal intensity on T2-weighted images of gray and subcortical white matter in posterior portions of the hemispheres. During the second stage of disease, the EEG shows a pattern of generalized slow-wave complexes with a regular periodicity (Figure 59B.4). The complexes may last up to 3 seconds and occur at regular intervals, between 4 and 14 seconds, against a background of depressed activity.

Some patients have improved or stabilized after one or several 6-week treatments with intraventricular interferon-a through an Ommaya reservoir, starting at 10 U/in^2 body surface area per day, with daily increments, up to 106 U/m per day on the fifth day, 5 days per week, combined with oral isopdnosine (Inosiplex), 100 mg/kg per day. There have also been reports of response to intravenous ribavirin in combination with intrathecal interferon-a (Tomoda et al. 200 i). The laboratory endpoint of treatment is the eradication of detectable measles antigen from the CSF. Systemic (subcutaneous) interferon-a, in daily doses of up to 5 million units, has been used with intrathecal interferon-a, to simultaneously tteat the peripheral reservoirs of measles virus, lymphoid, and glandular tissue. Prolonged or repeated treatments carry the risks of meningitis, interferon-a induced encephalopathy, and interferon-a upper and lower motor neuron toxicity.

Immunization with attenuated live measles vaccine is recommended for infants between 12 and 15 months of age; measles vaccine is one component of the trivalent measles-mumps-rubella (MMR) vaccine. In areas where measles circulates widely, immunization is performed early, at 6 or 9 months. Fata! infection has followed measles vaccine in severely immunocompromised children, but

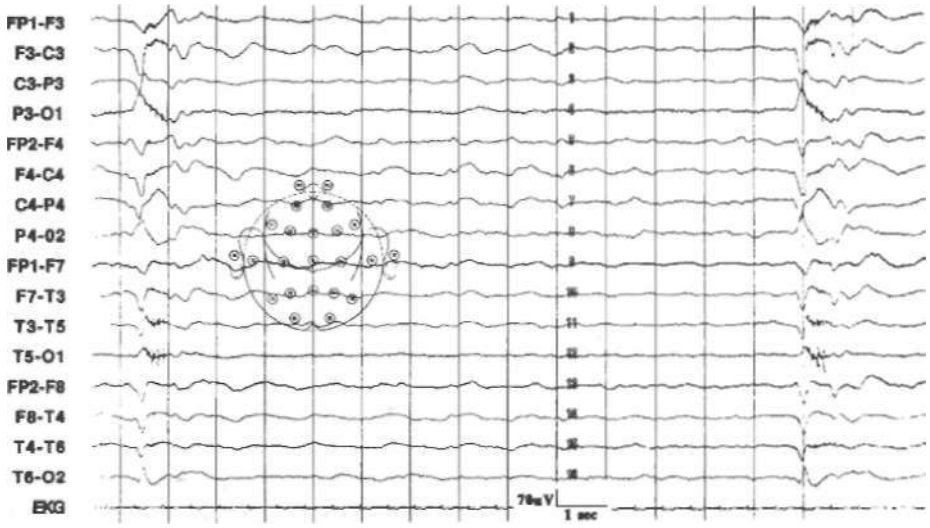


FIGURE 59B.4 Electroencephalogram of a 23-year-old man with subacute sclerosing panencephalitis showing generalized slow-wave complexes occurring approximately every 12 seconds. (Courtesy K. Nudleman.)

there is no epidemiological evidence that vaccination causes SSPE.

Rubella

Rubella virus infection in childhood or adult life is usually a mild illness. Maculopapular rash, fever, and lymphadenopathy characterize clinically apparent infection. Postinfectious encephalomyelitis is estimated to complicate 1 of 6000 cases, with onset 1-6 days after the appearance of the rash.

Gestational rubella, especially infection acquired during the first trimester, has serious consequences for the fetus. Eighty percent of children with a congenital rubella syndrome have some form of nervous system involvement. Signs in infancy include bulging fontancllc, lethargy, irritability, and abnormalities in muscle tone. CSF protein concentration is elevated, and the virus may be isolated from the CSF. Sequelae in survivors include mental retardation, sensorineural hearing loss, motor and posture abnormalities, cataracts, pigmentary retinopathy, and congenital heart disease. Congenital rubella syndrome has become rare in the United States since the institution of effective vaccination strategies in the 1960s (Reef et al. 2002).

An uncommon, late-onset rubella encephalitis, progressive rubella panencephalitis, may follow congenital rubella or natural childhood rubella. There is a prolonged asymptomatic period, followed by the onset of neurological deterioration during the second decade of life. Symptoms include behavioral changes, intellectual decline, ataxia, spasticity, and seizures. Although progressive rubella panencephalitis may exhibit some of the clinical features of SSPE, patients with progressive rubella panencephalitis tend to be older, have more protracted clinical courses, and lack generalized myoclonus or periodic burst-suppression IT(. patterns. Although .1 few spontaneous remissions have been reported, the typical course is one of progressive neurological decline, leading to death within 8 years. Sera and CSF from affected children contain antirubella IgG antibodies. Diffuse brain attophy may be found on MRI. Since institution of widespread administration of live attenuated rubella virus vaccine to preschool children (as a component of the MMR vaccine), the incidence of rubella and rubella-associated acute disseminated encephalomyelitis has drastically declined. Postexposure vaccination is not recommended,

Mumps

Mumps virus causes a mild childhood illness characterized by parotitis, but has the capacity for widespread invasion of visceral organs, the vestibular labyrinths, and the CNS. In unimmunized populations, mumps is a common cause of aseptic meningitis and encephalitis. Before introduction of widespread vaccination in the United States, mumps virus was the leading cause of viral meningoencephalitis in the United States, with over 200,000 cases reported in 1964. Since the introduction of effective vaccination strategies, there has been a steady decrease in the incidence of mumps virus infection, with an all-time low of 231 U.S. eases reported in 2001. The incidence of mumps meningitis and encephalitis varies with different epidemics from less than 1% to 70%. Mumps meningitis may precede parotitis and can occur without salivary gland enlargement in 40-50% of patients. In the remainder of cases, mumps meningitis or encephalitis develops approximately 5 days after the onset of parotitis. Postinfectious encephalomyelitis follows an estimated 1 in 6000 cases and develops 7-15 days after parotitis.

Seizures occur in 20-30% of patients with CNS symptoms, but follow-up EEGs are usually normal. Obtunded patients may have relatively mild EEC changes and recover with few sequelae. Complications include deafness from labyrinth membrane and sensory transducer damage, myelitis, or hydrocephalus following viral replication in choroidal and ependymal cells.

In mumps meningoencephalitis, there is a CSF pleocytosis of 25-500 WBC per |iL with lymphocytic predominance, although higher counts may occur occasionally, as high as 3000 WBC per ul„ CSF protein concentration is normal or moderately elevated and may include mumps-specific oligoclonal IgG; glucose concentration is depressed in 29% of cases. Mumps virus can be cultured from the CSF.

Mumps prevention is best achieved by vaccination with live attenuated virus at 12-15 months of age and an additional booster dose at 4-6 years of age; mumps vaccine is one component of the trivalent measles-mumps-rubella (MMR) vaccine. Infrequent reports of mumps meningitis had been reported from following vaccination with strains of mumps vaccine (Urabe strain) that are no longer in use in the United States. Recent studies evaluating the use of the current MMR vaccine (containing jeryl-Eynn strain) have not documented any association between vaccination and encephalitis, aseptic meningitis, or autism (Makcla et al. 2002).

Arenaviruses

Arenaviruses are rodent-borne viruses, with human infection originating primarily when humans come in contact with infected rodent excreta. The arenaviruses of neurological consequence are lymphocytic choriomeningitis virus (I.CMV), Lassa fever, and Argentine hemorrhagic fever viruses.

LGMV usually causes aseptic meningitis, but encephalitis has been diagnosed in 5-34% of serologically confirmed LCMV cases. CSF cell counts in excess of the 10-500 WBC

pi-r ul. range usually seen in viral meningitis may be present with LCMV. Ascending or transverse myelitis, bulbar syndromes, parkinsonism, and sensorineural bearing loss also have been reported. Hydrocephalus may arise as a sequelae of ependymitis or ventriculitis. LCMV infection of the fetus has produced hydrocephalus, diffuse parenchymal disease, mental retardation, and chorioretinitis.

Lassa fever, the West African viral hemorrhagic fever with high mortality, produces a multisystem disease with fevet, pharyngitis, hemorrhage, hepatic involvement, and shock plus neurological syndromes in 40% oi hospital ized patients. Imported cases have occurred in Europe, Israel, Canada, the United States, Japan, and Australia. Encephalitis with seizures, depressed consciousness, amnestic syndromes, dystonia or tremor, convalescent ataxic syndromes, and neuropsychiatry sequelae have been described. One third of all patients with Lassa fever develop hearing impairments, two thirds ot whom are left with significanl sensorineural hearing loss.

Ai:;cmme hemorrhagic fever may be accompanied b) acute ataxia. Arenaviral diagnosis is by viral culture and serology. lgM antibody to LCMV is present in serum, CSF, or both during acute meningitic disease. Ribavirin, a guanosine analogue, has proven efficacy in arenaviral hemorrhagic fever animal models. For the treatment of Lassa fever in humans, intravenous ribavirin is administered as a 2 g loading dose, followed by 1 g every *6* hours for 4 days, then 0.5 g thrice daily for 6 additional days. Anemia is the major side effect. Oral ribavirin is available through the CDC (Atlanta, Ceorgia) for the prophylaxis of contacts.

Other Hemorrhagic Fever Viruses

Arhoviral Agents of Hemorrhagic Fevers

Dengue (Flavivirus). In terms of size of epidemics and severity of disease, dengue fever and dengue hemorrhagic fever arc the most important arthropod-borne viral diseases of humans. Up to 100 million cases of dengue fever and 250,000 cases of dengue hemorrhagic fever occur each year in tropical Asia, Africa, Austtalia, and the Americas. Dengue virus cycles between humans and mosquitoes. *Aedes aegypti,* the most important vector, is a mosquito that has evolved to live in proximity to humans and breeds well in manufactured throwaway containers holding stagnant water. The expansion of *Aedes aegypti* throughout the Americas and the inadvertent import of another competent vector, *Aedes alboticus,* to the United States and Brazil from Asia, have established dengue on all continents with tropical and subtropical areas.

Dengue fever begins, after a 2- to 7-day incubation period, as a sudden febrile illness with headache, myalgias, arthtalgia, prostration, abdominal discomfort, and rash. Over the next 2-3 days the rash clears whereas the patient defervesces. A second, maculopapular rash appears, first on the trunk, and bleeding may follow. Dengue hemorrhagic fever is the severe form of disease, occurring in persons, usually children, previously sensitized by infection with a heterologous dengue serotype.

Neurological complications including encephalopathy, encephalitis, mononeuritis multiplex involving cranial and peripheral nerves, and Guillain-Barrc and Reye's syndromes have been associated with both self-limited (classic) dengue fever and dengue hemorrhagic fever (Solomon et al, 2000). Diagnosis depends on virus isolation from blood in the early stages or serological tests. The CSF may contain few (<30) or no WBC. The differential diagnosis of fever with rash, petechiac, or purpura includes malaria, typhoid fever, the viral exanthems (measles, rubella, enteroviruses), viral hemorrhagic fevers, syphilis, scarlet fever, meningococcemia, rickettsial diseases, gram-negative sepsis, drug reactions, and noninfectious causes of disseminated intravascular coagulation. Specific antiviral treatment has not been evaluated for dengue, and care is supportive. Salicylates are contra indicated because of the risk of hemorrhagic exacerbation and Reye's syndrome.

Yellow Fever (Flavivirus). Yellow fever occurs in tropical South America and sub-Saharan Africa. The risk of yellow fever returning to the Americas to produce large urban epidemics has increased due to the large numbers of susceptible people and successful expansion of the host range of the mosquito vector, *Aedes aegypti.* Vaccination with yellow fever 17kD, a live attenuated viral vaccine developed by the World Health Organization, has been associated with rare encephalitis cases in infants (within 30 days of immunization). Rare but severe cases of multisystemic illnesses and death following yellow-fever vaccination have recently been reported from Australia and the Americas. These events have caused revaluation of the vaccine's use. However, these reports should not deter visitors to endemic areas from being vaccinated (Monath and Cetron 2002). Because of the risk of encephalitis, the vaccine is con train dica ted for infants less than 4 months of age. A French vaccine, produced from infected mouse brains, was associated with a 1 % incidence of postvaccinal encephalitis and is no longer manufactured.

Filoviruses. Ebola and Marburg viruses are the two known members of the *Filoviridae.* Outbreaks of Ebolavirus occur in Africa, in regions of which the virus is endemic, and occurred most recently in Gabon (1996), Uganda (1998), Zaire (2000), and Uganda/Congo (2001) (Isaacson 2001). Both viruses are characterized by highly-efficient replication in liver, spleen, lymph nodes, GI tract, and lung, leading to fulminating hemorrhagic fever with severe shock and high mortality. Early headache and additional signs of a meningeal or encephalitic process are rapidly eclipsed by complications of hemorrhage, hypotension, hepatic failure, and disseminated intravascular

coagulopathy. Muscle necrosis caused by disseminated intravascular coagulopathy and intramuscular hemorrhage follows early myositis or muscle pain. A low-grade (<25 WBC) CSF pleocytosis has been reported in patients with Marburg virus early in their illnesses. The reservoir of Ebola virus is unknown. Treatment is supportive. No therapeutic role of convalescent sera or interferon has been established by controlled clinical trial. Blood and all body fluids are highly infectious.

Papovaviruscs and Progressive Multifocal Leukocnccphalopathy

Progressive multifocal lcukoencephalopathy (PML), a subacute, demyelinating disease of the CNS, is a result of infection of oligodendrocytes by an opportunistic papovavirus (Plate .59B.V). All well-documented cases have been caused byJC virus, though the JC virus, when contracted in early childhood, is not associated with illness. JC virus persists in the host and is reactivated in cases of diseases or medical treatments known to impair cell-mediated immunity: lymphoproliferative disorders, tuberculosis, sarcoidosis, prolonged immunosuppression, and inherited and acquired immunodeficiency diseases. Rare until the 1980s, **PML** is now encountered more frequently because of its association with AIDS. In a small number of cases, no underlying disease can be identified.

Onset is subacute, with signs and symptoms of multifocal, asymmetric white matter involvement. In non-AIDS-associated PML, early lesions tend to be in subcortical white matter of the occipital lobes, causing visual field deficits or cortical blindness. Motor weakness, behavior changes, cognitive impairment, cerebellar ataxia, dysarthria, and sensory abnormalities also are seen, whereas headache, seizures, and i:\itapyramidal syndromes are rarer. The disease progresses to dementia as the number of lesions increases.

CSF cell counts and protein levels are usually normal. Nenroimaging results help suggest the diagnosis. MR! studies show focal or multifocal lesions of subcortical white matter, sometimes involving the cerebellum, brainstem, and spinal cord, without mass effect or contrast enhancement. Fluid attenuation inversion recovery sequences, which remove CSF signals, are particularly good for demonstrating paraventricular disease (Figure 59B.5). White matter lesions are larger and more confluent than those of multifocal leukoencephalitis of VZV. Lack of CSF pleocytosis and an indolent course distinguish PML from paraviral and postviral encephalomyelitis. Brain biopsy establishes the diagnosis by showing characteristic changes, including oligonucleocytcs with enlarged nuclei that contain inclusion bodies, as well as viral particles and antigen or viral DNA. JC virus has never been cultured from CSF. *JC* virus DNA may be detected in CSF' using PCR amplification (Eggers et al. 1999). Finding JC virus DNA in CSF by PCR in the appropriate clinical setting is diagnostic of PML and obviates the need for bram biopsy. However, CSF PCR is less sensitive than biopsy, which may still be required to establish the diagnosis in PCR-negative cases.

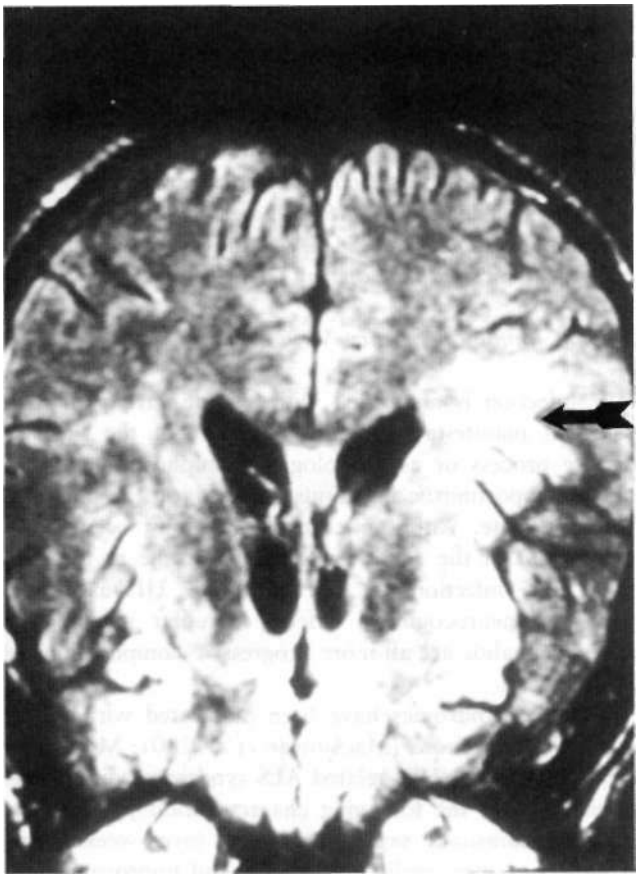


FIGURE 59B.S Progressive multifocal leukoencephalopathy. Coronal MRI fluid attenuation inversion recovery sequence, with arrow showing hypermtense temporal white matter. (Courtesy J. Hcaly.)

No specific therapy is available. Isolated reports of benefit from cytarabine were not confirmed in a randomized prospective clinical trial (Hall et al. 1998). Interferon-a has been reported to be of benefit in case reports but has not been tested in clinical trials. Cidofovir has also been suggested to be of benefit in patients with HIV-associated PML, although results in a recent prospective clinical trial were disappointing (Marra et al. 2002). Improvement of rhe immune deficiency with high intensity antiretroviral therapy has been reported to lead to regression of the PML. lesions.

Retroviruses: HIV and HT1.V-I and II

The *Retraviridae* is a large family of viruses, grouped initially by pathogenic features, but later revised on the

basis of nucleotide sequence and genome structure. Human T-cell lymphorropic virus (HTLV) types I and II belong to the HTLV-bovine leukemia group; HIV belongs to the lentivirus group. HTLV, the etiological agent of adult T-ce!l leukemia, was serologically linked to a progressive spastic paraparesis, known as *tropical spastic paraparesis fTSP),* in West Indies patients in 1985. Later, in Japan, a similar syndrome with elevated HTLV-I antibodies was named *HTLV-I associated myelopathy (HAM),*

Human Immunodeficiency Virus (HIV)

HIV infection is associated with a wide variety of neurological manifestations, either as part of the primary disease process or as neurological complications of secondary opportunistic infections occurring in the immunodeficient state. An aseptic meningitis may occur as a component of the acute retroviral syndrome at the time that HIV infection is first acquired. HlV-associated dementia, neurocognitive defects, vacuolar myelopathy, and encephalitis are all more progressive complications of HIV disease.

ALS-like syndromes have been associated with HIV-1 and H1V-2 infections (MacGowan et al. 2001; Moulignier et al. 2001). The HIV-related ALS syndromes differ from classic ALS in the following characteristics: younger age of onset, unusually rapid progression (over weeks), presentation as monomelic syndromes, and improvement or stabilization with highly active antitetroviral therapy. In most cases, ALS symptoms preceded the clinical diagnosis of acquired immunodeficiency syndrome (AIDS). Neurological manifestations of HIV infection ate discussed in detail in Chapters 59E and 59F,

Nonbuman Immunodeficiency Virus Retroviruses:

Human T-Cell Lymphocytotropic Viruses (HTLV-I and-Il)

HTLV-I is endemic in southern Japan, Taiwan, Okinawa, the Caribbean basin (including northeast South America), central and West Africa, southern India, and the Seychelles, In the United States and Western Europe, the incidence of HTLV infection is higher among intravenous drug users and homosexuals. Estimates show that 10-20 million people around the world are infected with HTLV-I. Most seropositive individuals are asymptomatic; less than 1% of infected patients develop spastic paraparesis. Spread of HTLV-I, as other retroviruses, is by sexual, parenteral, or vertical transmission. In the United States, all blood supplies have been screened for HTLV-I since **1988** (Osame et al. 1990).

With an incubation period of approximately 20 years, HAM is usually recognized in the fifth decade of life is .i progressive spastu paraparesis or myeloneiiroparhy. Occasionally, acute cases, resembling transverse myelitis, also occur. Neurological findings includi[1] lower iMivnmy weakness and spasticity that is usually symmetric, impotence, urinary and fecal incontinence, and generalized hyper-reflexia except in cases of concomitant sensory neuropathy. Inflammatory myosins, cerebellar ataxia, nystagmus, vertigo, deafness, optic neuritis, adult T-cell leukemia, uveitis (as vitreous opacities, iritis, retinal vasculitis), sicca syndrome, inflammatory arthropathy, and lymphocytic alveolitis may be present (Jacobson 2002), Conditions clinically similar to the subacute spastic paraparesis of HTLV-I include HIV-associated vacuolar myelopathy, idiopathic inflammatory conditions, hereditary spastic paraplegia, and toxic-metabolic disorders such as vitamin B_{12} deficiency, lathyrism (India), cycad poisoning (Pacific Islands), or konzo (Central Africa). HTLV-II is associated with atypical hairy cell Icukemias, mycosis fungoides, other lymphocytic or leukemoid malignancies, and a similar myelopathy.

Serological testing using an enzyme-linked immunosorbent assay, followed by Western blot confirmation, is used for diagnosis. False-positive serologic test results for syphilis and Lyme disease and antiphospholipid antibodies have been reported with HAM. The CSF contains mild elevations in lymphocytes and protein; elevated gamma-globulin fraction, oligoclonal bands, and CSF antibody levels, reflecting intrathecal synthesis. HTLV-I is usually not found in cells of the CSF, but has been detected in small populations of lymphocytes in the CSF by PCR, Spine MR] studies may show normal spinal cord, hyperintense signal abnormalities on T2-weighted images, or atrophy in late disease. The patterns of signal enhancement **tend to** be diffuse in HAM, in contrast to discreet or multifocal abnormalities seen in MS. Periventricular gray or white matter lesions may be seen also.

Treatments have been directed against the inflammatory components of disease. Primary therapy has been with initial intravenous injections of 1 g of methylprednisolone per day, followed by oral prednisone, 80 mg on alternate days for 2 months, then tapering by 10 mg each month for the next *6* months. Patients who fail prednisone therapy may receive intravenous immunoglobulin at 400 mg/kg per day for 5 days; repeated monthly for three or more cycles, intramuscular interferon-a, or plasmapheresis. The anabolic corticosteroid danazol, 400 mg thrice daily, has been reported to slow or reverse bladder symptoms. Because the progression of disease is most rapid during the first year, early treatment during this time has the best chance of improving outcome.

Influenza

Influenza virus has been associated with myositis, Reye's syndrome, acute cnccphalopathy/eneepbalitis, and post-influenzal encephalitis 2-3 weeks after recovery. The acute cncephalopa thy/encephalitis that has been reported

to occur within 1-3 days of onset of respiratory symptoms (associated with both influenza A and B) has a high rate of mortality/morbidity (Morishima et al. 2002). The postencephalitis syndrome, accompanied by an inflammatory spinal fluid, is transient, with full recovery in most cases. Oral amantadine or rimantadine are approved for use in treatment and prophylaxis of influenza A. Oseltamivir and zanamivir, two recently approved neuraminidase inhibitors, are effective against both influenza A and B and may have an additional advantage over amantadine and rimantadine, in that they rarely lead to selection of resistant isolates.

Thought to be a late sequelae of the 1917-1918 influenza pandemics, encephalitis lcthargica and postencephalitic parkinsonism have been historically linked to influenza. However, more recent studies using molecular biology techniques have failed to provide convincing evidence for this link. The postencephalitic parkinsonian syndrome was distinguished from idiopathic Parkinson's disease by its younger age of onset and the presence of hyperkinetic movements, oculogyric crises, respiratory tics, and behavior disorders.

Adenovirus

Adenoviruses cause acute respiratory disease in children and military recruits, conjunctivitis, hemorrhagic cystitis, and gastroenteritis. Meningoencephalitis or unilateral deafness Coincident with nasopharyngeal infection arc rare complications in normal hosts; fatal meningoencephalitis was reported in a bone marrow transplant patient. Diagnosis is by isolation of virus from extraneural sites or by serology.

Parvovirus

Acute infection with B19 parvovirus causes the febrile exanthema tons illness fifth disease (erythema infectiosum) in childhood, transient aplastic crises, particularly in immunocompromised and sickle-cell patients, and small joint chronic arthritis in adults. Chronic parvovirus infection has been found in patients with necrotizing vasculitis resembling polyarteritis or Wegener's granulomatosis. Neurological manifestations have included encephalitis with fifth disease, brachial plexitis, abnormal pupillary reflexes, and recurrent paresthesias. Immunocompromised patients should be treated with 1VIG to speed clearance of viremia.

Hepatitis Viruses

The viral causes of hepatitis are hepatitis A, B, C, D (delta), and E viruses. Hepatitis C and occasionally hepatitis B have been associated with a systemic vasculitic disease and mixed cryoglobulinemia, and hepatitis B has been associated with polyarteritis nodosa. Exrrahepatic manifestations of hepatitis C viral infection include cranial and peripheral neuropathies, mononeuritis multiplex, polymyositis, and anterior spinal artery stroke. A brain autopsy specimen of a patient with progressive encephalomyelitis with rigidity yielded hepatitis C viral ON A by RT-PCR, Interferon-a treats liver and renal involvement but has variable effects on the neuropathy. Plasma exchange may be of benefit for patients whose neuropathy is worsened by intcrferon-a.

Other Syndromes with Possible, but Unproven, Viral Etiologies

Viiiuisk Encephalomyelitis

Viliuisk encephalomyelitis is a biphasic illness of the lakut people of Siberia, in whom an acute meningoencephalitis is followed weeks or months later by a progressive dementia with pyramidal, extrapyramidal, or amyotrophic lateral sclerosis-like features. The acute febrile onset, CSF pleocytosis, epidemiology, geographical clusters, and inflammatory neuropathology have suggested an infectious etiology, but no agent has been identified.

Rasmtissen's Encephalitis

Rasmusscn's encephalitis is a rare inflammatory brain disease of unknown etiology that occurs predominantly in children and is characterized by subacute focal encephalitis of one hemisphere. Pathogenetic concepts have considered the role of viral infection, autoimmune antibodies, and autoimmune cytotoxic T lymphocytes as key factors contributing to this syndrome (Bien et al. 2002). Human CMV has been detected by PCR in brain biopsy specimens in some cases, and HSV-1 has been implicated in other cases, based on PCR and in situ hybridization studies. Nonetheless, a viral etiology for Rasmussen's remains unproven, and there are no appropriately designed and controlled studies establishing a benefit for antiviral therapy. Nonviral treatments have been directed toward the immunologic aspects of the disease, such as the presence of glutamatc receptor antibodies in some patients. Neurosurgical approaches, including hemisphcrectomy or subpial intracortical transection, may facilitate seizure control in some cases.

Progressive Encephalomyelitis with Rigidity

Progressive encephalomyelitis with rigidity is a syndrome of limb and trunk rigidity and stimulus-sensitive muscle spasms, cellular spinal fluid, and inflammatory pathology in cervical cord and brainstem. Early descriptions of

progressive encephalomyelitis with rigidity noted clinical and pathological similarities between this syndrome and spinal forms of encephalitis lcthargica described by von Kconomo. The pathology is consistent with either previous viral infection or an immunopathological process. Some cases are paraneoplastic or manifest antineuronal auto-antibodies and have been treated with plasmapheresis and prednisone. The differential diagnosis of progressive encephalomyelitis with rigidity includes other syndromes with involuntary motor symptoms: tetanus, stiff person syndrome, cramps, tetani, and hemifacial spasm. The electromyographic silent period is usually absent in patients with tetanus, but normal in progressive encephalomyelitis with rigidity.

Epidemic Neuromyasthenia (Benign Myalgic Encepbalo myelitis)

Descriptions of epidemic neuromyasthenia (benign myalgic encephalomyelitis) were of a syndrome of protracted fatigue, following an initial "viral'" syndrome that may include respiratory or gastrointestinal complaints, headache, muscle pain, and lethargy. Many of the described patients would meet modem diagnostic criteria for chronic fatigue syndrome. Several viruses have been suggested as etiological candidates, based largely on serological studies, including enteroviruses, herpesviruses, measles, and rubella viruses.

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Chapter 59
Infections of the Nervous System

C. FUNGAL INFECTIONS

Madhuri Behari, Manjari Tripathi, and Ashok Verma

There are over 20,000 fungal species identified in the world. They form an integral part of our ecosystem and have been harnessed to make bread, beer, and antibiotics. Among them, over 250 fungal species have been reported to be pathogenic. From the common *Candida* infections to the deadly mucormycosis, fungal infections influence all levels of clinical practice (Luna 2000).

Fungi differ from bacteria in that they have a nucleus that is bounded by an organized membrane, they divide by mitosis, and they usually have a chitinous cell wall. The cell wall and a lack of mobility differentiate fungi from protozoa (Davis 1999). The absence of chlorophyll distinguishes them from most plants. Most pathological fungi are dimorphic and can exist in yeast and filamentous states, depending on growth conditions and temperature. In the yeast state, they are unicellular, are round to elongated, and reproduce by budding or fission. In the filamentous or mold state, they grow by extension of their tips forming tubular structures called hyphae, which often have septae that divide them into many segments. Spores arc the reproductive elements of these hyphae. Spores develop into yeast when infecting humans or animals but remain in the filamentous form when grown in vitro.

Fungi have varying predilection for involvement of the central nervous system (CNS). In general, fungi found in the meninges and the cerebrospinal fluid (CSF) are in the yeast phase (e.g., Cry/)(ococci«), whereas those causing brain parenchymal infection are in filamentous stage (e.g., *Aspergillus).* CNS fungal diseases are often difficult to diagnose and, as a consequence, are misdiagnosed or undiagnosed during life. Although many therapeutic options have been developed to treat superficial fungal infections, invasive and deep CNS fungal infections often prove tenacious to therapy.

EPIDEMIOLOGY AND CURRENT TRENDS

The incidence of CNS fungal infections varies greatly with the geographic location. For example, histoplasmosis is common in areas infested with bats, and cryptococcosis and histoplasmosis are common in patients exposed to birds. Histoplasmosis is commonly seen in the central United States (Ohio River Valley) and in restricted areas of the tropics. *H. dubaisii* is frequently found in West Africa. Coccidioidomycosis is mainly found in the southwestern United States (San Joaquin Valley) and in Central America, where it resides in the soil. Blastomycosis is endemic in Ohio ,uul Mississippi IVIMIIS in IIIL- United Si.; us. Oihci" fungi such as *Cryptococcus, Aspergillus,* zygomycetes *(Mucor),* and *Candida* species are more universally distributed. With respect to clinically recognized fungal CNS illnesses, *Cryptococcus* and *Candida* infections arc the most common, followed by *Coccidioides, Aspergillus,* and the zygomycetes. Fortunately, other fungi involve the CNS rarely. *Candida* and the zygomycetes rarely invade the deep viscera or CNS in the normal host and are therefore considered to be opportunistic in nature in immunocompromised hosts.

Recently fungal disease of the CNS has become increasingly common as a consequence of the acquired immunodeficiency syndrome (AIDS) epidemic and the use of

aggressive immunosuppressive regimens for cancer, and for solid organ and bone marrow transplantations. A study from the San Francisco Bay area found that more than 75% of patients who had invasive mycoses had serious underlying medical conditions that affected their immune systems (Rees et al. 1998). Only 9% were thought to be healthy at the time of the systemic fungal infection. The authors reported an overall incidence of invasive mycotic infections at 178 per million per year in 1992 to 1993, but the rate climbed to 5000 per million per year in individuals who were infected with the human immunodeficiency virus (HIV). The study found that the rates of invasive fungal infections per million per year for individual fungi were highest for *Candida* followed by *Cryptococcus* {73% and 66%, respectively). In another study from Australia, the two most common strains of *Cryptococcus* had different epidemiological features. *C. neoformans, var. neoformans* primarily caused meningitis in immunosuppressed patients, whereas C. *neoformans, var. gatti* infected healthy hosts. The reason for this difference is unclear. There is no specific epidemiological data available from the developing countries (Bharucha et al. 1999).

PATHOGENESIS

fungi produce disease by direct invasion, allergic phenomenon, or liberating toxins (e.g., ergotism resulting from rye ergot, which thrives on cereals, especially groundnuts, and trichothecene mycotoxins, which are misused in aerosol form as "yellow rain" in biological warfare to produce an illness characterized by weakness, ataxia, hypothermia, and shock).

Fungi are generally not invasive unless there are predisposing factors. They gain entry into the body mainly by inhalation of spores. This causes a localized lung infection, which may be asymptomatic or produce mild respiratory symptoms and is usually successfully terminated by a functional immune system. Failing this, the infection reaches the bloodstream and produces fungemia. If the fungemia overcomes the liosi's reticuloi'iicnilidi.i!, cellular, and humoral defense systems and penetrates the blood-brain or blood-CSF harrier, it reaches the brain parenchyma or the meninges. Fortunately, in the healthy individual, this seldom happens. Indwelling arterial or venous catheters can also he infected *(Candida),* forming a direct source for fungemia. Less common routes of infection are from the skin (sporotrichosis), the mouth, the gastrointestinal tract *(Candida),* and the nasal sinuses *(Aspergillus* and zygomycetes). Finally, direct inoculation of fungi into skull fractures or during neurosurgical procedures that place indwelling devices such as intraventricular shunts also predisposes to CNS infection. Certain conditions predispose a patient to infection with a particular fungus (Table 59C.1).

CENTRAL NERVOUS SYSTEM FUNGAL SYNDROMES

Myriad clinical presentations of the CNS fungal infections occur. Meningitis, meningoencephalitis, cerebral abscess, CNS granuloma, rhinocerebral necrotic mass, and base of skull lesions are the common modes of presentation. Cerebrovascular accidents or epidural fungal abscess are rare. The manner in which fungal CNS disease manifests is largely determined by the growth characteristics of the particular fungal species during systemic invasion. Fungi that are true yeast when invasive (e.g., *Cryptococcus)* most often present as chronic meningitis. Fungi that are pseudohyphae (e.g., *Candida]* often present with encephalitis as a consequence of multiple intraparenchymal microabscesses. Those that are true hyphae {e.g., *Aspergillus)* can present as strokelike illness because of their propensity to invade blood vessels. Clinicians must remain aware that these presentations are not mutually exclusive and that it is not uncommon for the various forms of clinical illness to coexist (Miszkiel et al. 1996).

INDIVIDUAL FUNGAL PATHOGENS

The True Yeasts

Cryptococcus

Cryptococcus is by far the most common cause of fungal meningitis and meningocerebral syndromes. Cryptococcosis is a systemic infection caused by the encapsulated yeast fungus, C. *neoformans,* which has a ubiquitous distribution in soil and pigeon excreta. Infection occurs by inhalation. Occasionally a mild pulmonary clinical infection occurs at the time of invasion. Meningitis is the most common neurological presentation, though multiple small cryptococcomas or a single large granulomatous lesion and abscess may also occur, presenting with symptoms of a mass lesion, seizures, or focal neurological deficits. Cystic lesions or hydroecpb.ilus may develop in patients who survive. Rarely, chronic infection presents with a dementia-like syndrome. The progression of the disease depends on the degree of immunosuppression. A papular or ulcerative skin lesion, lytic bone lesions, prostatitis, pulmonary, and renal involvement occur in disseminated systemic cryptococcosis.

Histoplasma

Inhalation of infectious spores found in soil containing bird excreta causes histoplasmosis. The primary infection may be subclinical, and many cases are diagnosed by chest radiography done for another reason. Acute pulmonary histoplasmosis may result in an influenza-like illness that may be accompanied by erythematous skin eruptions. The disease, often mistaken for miliary tuberculosis, presents

Table S9C.1: Therapy for CNS fungal infections

		Ciinicopathological features			
Organism	*Predisposing cause*	*Meningitis*	*Abscess*	*Infarct*	*Therapy in immunocompetent host*
C. *netifomulns*	Inherited immunodeficiency (CGD, SCID, etc-l, HIV/AIDS, cytotoxic agents, corticosteroids	++++			AMP B, 0.5-1 mg/kg/d, p 100 mg/kg/d (in four d doses) for 6-10 wks or nation for 2 wks follow FLUCO 400 mg/d for Consolidation with FL *6* mo-1 year.
C. *hnrrtitis*	Inherited immunodeficiency [CGD, SCID, etc.), HIV/AIDS, cytotoxic agents, corticosteroids	+++			FLUCO 400-800 mg/d fo yrs or IV 0.25 to 1.5 m with or without IT AM rimes/wk for many w dual tapering to biwee then monthly, a cumul of 35-100 mg in conju with IV AMI[1] B 0.5 m to a total cumulative d 0.5-2.0 g for 1 year.
H. capsulatum	Inherited immunodeficiency (CGD, SCID, etc.), HIV/AIDS, cytotoxic agents, corticosteroids	++++			AMP B 0.7-1.0 mg/kg/d. Maintenance FTRA, 40 for 4-12 weeks for 6
C. *albicans*	Inherited immunodeficiency (CGD, SCID, etc.), HIV/AIDS, cytotoxic agents, corticosteroids, cancer, trauma, indwelling catheters, prematurity, alcoholism, intt a venous drug abuse, ma lnutririon, pregnancy	++	++	(Microabscesses)	AMP B, 0.5-1 mg/kg/d, w FLU, 100 mg/kg/d (in divided doses) for 4-6
Z. *rhizopus*	Diabetic ketoacidosis, intravenous drug abuse, iron chelation therapy		+++	++++	AMP B, 1-1.5 mg/kg/d u total dose of 3 g. Surg debridement.
A. fumigattts	Inherited immunodeficiency (CGD, SCID, etc.), HIV/AIDS, cytotoxic agents, corticosteroids		+—	++++	AMP B, 0.7-1.5 mg/kg/d up to a total dose of 3 followed by ITRA, 40 mg/d for extended per
B. dermatitidis		•+++			AMI' b, 2-3 g total until followed by ITRA, 40 for 6 mo.

AMP B, Amphotericin B; CGD, chronic granulomatous disease; d, day; FLU, Flucytosine; FLUCO, Fluconazole; IT, intrathecal; ITRA severe combined immunodeficiency; wks, weeks.

as an acute or chronic febrile illness with diffuse pulmonary infiltrate, abnormal liver function, mucosal ulceration, and less often with neurological involvement (10-20%) in the form of a basilar meningitis, focal cerebritis, or CNS granuloma. Headache, fever, and neck stiffness are seen in about half of the cases. Manifest disease may occur even after leaving an endemic /one indicating the importance of taking a travel history. Diffuse-disease is seen in immunocompromised hosts and at the extremes of age. Approximately 50% of patients who have a CNS infection develop subacute meningitis, whereas 40% have cerebral abscess. The meningitis usually occurs in the setting of disseminated infection but may occur by itself.

Blastomyces

Blastomycosis is a systemic disease caused by *B. dermatitidis,* which proliferates as a saprophyte in soil, and it typically infects healthy individuals. Inhalation of the mycelial form results in the disease. Both systemic and cutaneous forms of blastomycosis may follow pulmonary infection. Neurological involvement occurs in 6-35% of individuals with disseminated blastomycosis and is characterized by intracranial or spinal abscesses or meningitis. Meningitis is often accompanied by rapid deterioration. Infection of vertebrae may lead to osteolytic lesions, which are often painless and may spread to the contiguous soft tissue. For some reason, blastomycosis is not significantly more frequent in HIV/AIDS, and it is not identified as an AIDS-defining infection.

Coccidioides

Inhalation of airborne spores of C. *immttis* found in soil results in coccidioidomycosis. Although the majority of the cases are self-limiting, chronic pulmonary, skin or disseminated disease occurs in approximately 1% of patients. The male gender, extremes of age, non-Cauc.]-.i.iu MCC, pregnancy, and immunosuppressed state are known to predispose to disseminated coccidioidomycosis. Lytic skull and vertebral lesions are seen in approximately one third of patients with disseminated disease. The vertebral arch is most frequently involved initially. Involvement of the vertebral body and disc space classically seen in tuberculosis is uncommon. Meningitis may be the presenting feature and usually occurs within 6 months of symptomatic or asymptomatic primary infection. Nonspecific signs and symptoms of headache, fever, malaise, and weakness are common, but seizures, cranial nerve palsies, and focal neurological deficits may also occur. The meningitis, if present, is more intense than cryptococcal meningitis. Prominent basilar meningitis frequently leads to the development of obstructive hydrocephalus, and meningeal vasculitis may cause occlusions of arteries, leading to cerebral infarcts. If untreated, nunv ilian iO.'•<. (it p.ckiio, \utli coccidioidal meningitis die within 8 months.

Paracoccidioides

Paracoccidioidomycosis is endemic in Central and South America, particularly Brazil, where it resides in soil and chiefly affects laborers in rural areas. Pulmonary infection is usually self-limiting. Dissemination occurs in immunosuppressed patients. Progressive pulmonary disease and extrapulmonary involvement of skin, lymph nodes, and the CNS are common clinical manifestations. Cerebral and cerebellar masses are also seen.

The Pseudohyphae

Candida

The *Candida* species are normal commensals of the human respiratory, gastrointestinal, and genitourinary tracts. Although *Candida* is the fourth most common organism isolated from blood, CNS infection is uncommon in normal hosts. In the immunodeficient host it causes nosocomial and disseminated infection. C. *albicans* is the most important pathogenic species causing neurological involvement. Patients with malignancies, debilitation, those receiving corticosteroids or broad-spectrum antibiotics, transplant recipients, critically ill neonates, and post-operative neurosurgery patients are predisposed to *Candida* infection. Involvement of multiple organs, including the brain parenchyma, meninges, and eye is often seen in disseminated disease. Intracranial abscesses, small vessel thromboses, and microinfarcts occur in areas of vasculitis and tend to have a predilection for the middle cerebral artery. Hemorrhage may occur from rupture of a mycotic aneurysms. Coexistence of ophthalmological and dermatological infection provides a helpful clue to the diagnosis. Patients with endophthalmitis often report blurred vision, eye pain, or scotoma. White, cotton-like exudates ate seen in the retina on funduscopic examination.

] he 1 rue 1 lyphae

Aspergillus

Aspergillus has a predilection for growing on stored grain and decaying vegetation. It mainly affects the paranasal sinuses and causes a hypersensitivity pneumonitis. CNS disease results from direct extension and invasion or embolization. Dissemination from a primary pulmonary focus occurs in immunosuppressed patients, particularly transplant recipients. The posterior circulation is particularly vulnerable, resulting in vertebrobasilar strokes. A strokelike syndrome occurs from direct vessel wall invasion

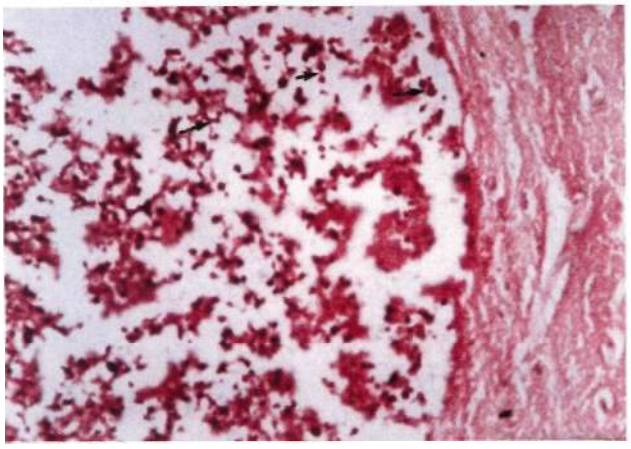

PLATE 59C.I Mucicarmine staining of cerebrospinal fluid sediment showing numerous cryptococci. (Courtesy Dr. C. Sarkar.)

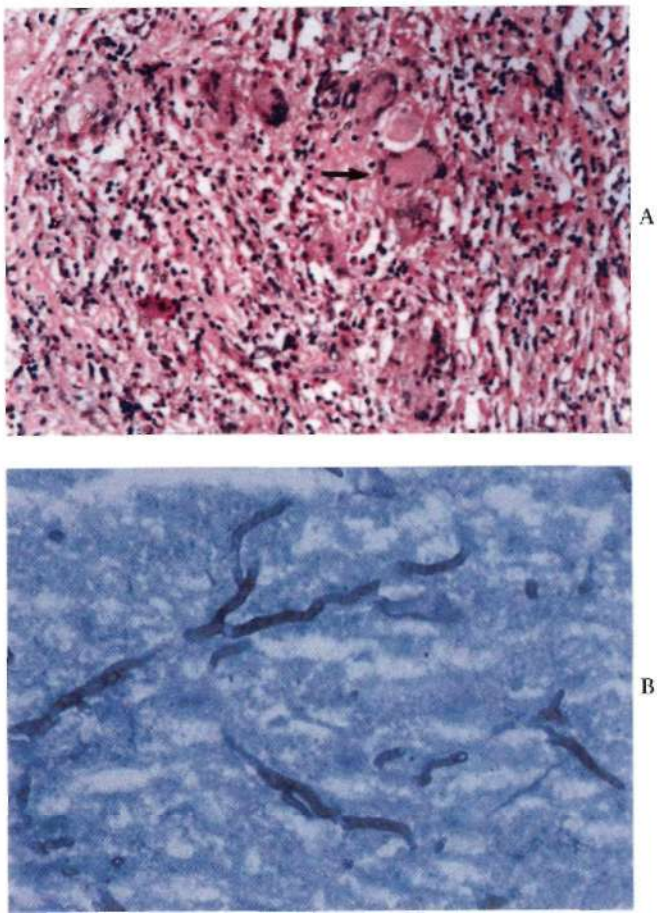

PLATE 59C.1I *Aspergillus* cerebral granuloma showing foreign body giant cell reaction {*arrow* in A, H&E x 200) and fungal hyphae of *Aspergillus* (B, silver methianaminc x 200). (Courtesy Dr. C. Sarkar.)

resulting in vasculitis or from rapidly progressing parenchymal granuloma or brain abscess. *Aspergillus* sinusitis may infiltrate intracranially causing a rhinocerebral syndrome. Pulmonary infection may invade the thoracic vertebrae and then the epidural space, causing spinal cord compression. Meningitis is generally rare, but may occur after transsphenoidal surgery and in intravenous drug abusers.

Zygomycetes (Mucormycosis)

The Zygomycetes belong to a group of saprophytic fungi growing on decaying vegetation or food of high sugar content. Infection is usually sporadic with a worldwide distribution. Diabetes and acidosis are the most frequent predisposing conditions; however, malignancies, high-dose corticosteroids, renal transplantation, and iron chelation therapy in hemochromatosis also predispose individuals to this infection. Mucormycosis causes pulmonary and cutaneous manifestations, Rhino-orbito-ecrebral invasion and cerebral mucormycosis occur after head or orbital trauma. *Mucor* invades through vascular channels producing occlusive ischemic lesions in single or several anatomically related sites. Within the CNS, /.ygomycosis causes an acute necrotizing tissue reaction and thrombosis of neighboring vessels. Cavernous sinus and internal carotid artery thromboses are common. A black regional discharge, such as from the nose, indicates necrosis of the underlying tissue and should suggest the diagnosis of mucormycosis, Ocular manifestations occur due to ischemia and present with loss of vision, optic nerve pallor, corneal ulcer, ocular gangrene, choroidal infarction, and central retinal or ophthalmic artery occlusion.

OTHER **FUNGAL** PATHOGENS

Sporotrichosis is caused by infection by *S. schenkti.* Cutaneous sporotrichosis presents as single or multiple chronic ulcers, spreading along regional lymphatics. Disseminated infecrion affects the CNS (meningitis), joints, and lungs. *Pseudallescheria boydii* is another uncommon opportunistic pathogen, it characteristically presents as neutrophilic meningitis or multiple brain abscesses. Factors predisposing to CNS infection by *I', boydii* include immunosuppression or aspiration of contaminated water (near drowning).

DIAGNOSIS

Fungal infections of CNS may challenge physicians' diagnostic skills. In order to diagnose them early, a physician must have a high index of suspicion in any case presenting as chronic meningitis. The chronic nature of fungal infections often results in patients being anemic with elevated total leucocyte counts and erythrocyte sedimentation rate. Renal involvement results in presence of red blood cells, white blood cells, casts, and protein in urine. Urinary sediment may demonstrate fungal hyphae or yeasts, depending on the load of infection. Culture of urine in fungal media often shows growth, especially in cryptococcosis. Chest x-ray may be useful in cases of concomitant lung infection. Patients with chest x-ray showing infiltrates or abscess should undergo sputum cultures and bronchoscopy and, if needed, a biopsy. Complaints of localized bone pain should always be subjected to bone scan because the lesion can be biopsied or aspirated. Joint radiographs are helpful if fungal arthritis is present.

Neuroimaging in the form of contrast-enhanced magnetic resonance imaging (MR!) or computerized tomography (CT) of the brain is important in identifying the involvement of ncuraxis, MR1 is superior to CT m its higher sensitivity and resolution. Meningeal enhancement, especially in the basal cisterns (Figure 59C.1), is commonly seen and suggests the presence of subacute or chronic meningitis. Infections such as cryptococcal meningitis may have multiple small cerebral abscesses due ro fungal invasion of the Virchow-Robin spaces around the meningeal vessels penetrating the brain parenchyma.

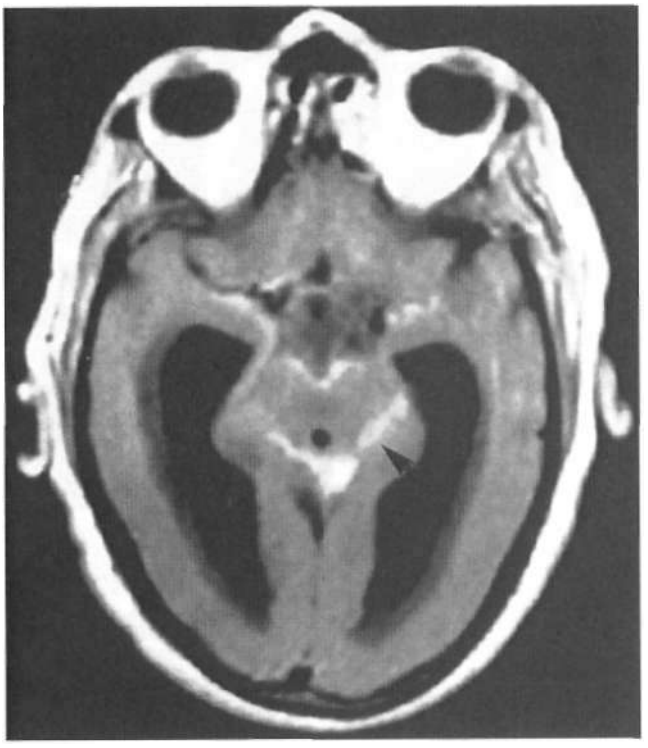

FIGURE 59C.1 Cryptococcal meningitis. Postgaddinium axia [[W-MKI shown is" . i: 111 c s 111! a' lept< IUICIUIIL;NII enhancement i>ee around midbrain *arrow]* and in suprasellar cistern) and ventricular dilatation from obstructive hydrocephalus Courtesy Dr. S. K. Gaekwad.)

Hydrocephalus resulting from blockage of CSF flow at the level of the basal cisterns ot at the outflow pathways from the fourth ventricle by arachnoiditis may also be observed. If the fungus directly invades the brain, neuroimaging often demonstrates an enhancing localized cerebral mass with variable surrounding edema (Figure 59C.2 and Figure 59C.3). Large space-occupying abscesses or granulomas are associated generally with *Aspergillus, Mucor, Blastomyces,* and *Vseudallescherla.* Bland or occasionally hemorrhagic cerebral infarcts may be seen if meningitis causes vasculitis with thrombosis of arteries or veins. In suspected rhinocerebral syndromes, sinus and orbit imaging must be reviewed. Mucosal thickening, air-fluid levels or erosion of bone in the walls of the sinus or orbit suggests rhinocerebral infection.

Lumbar puncture and analysis of the CSF is the most crucial test in establishing the diagnosis of fungal meningitis. The cerebrospinal pressure is often elevated. The fluid is

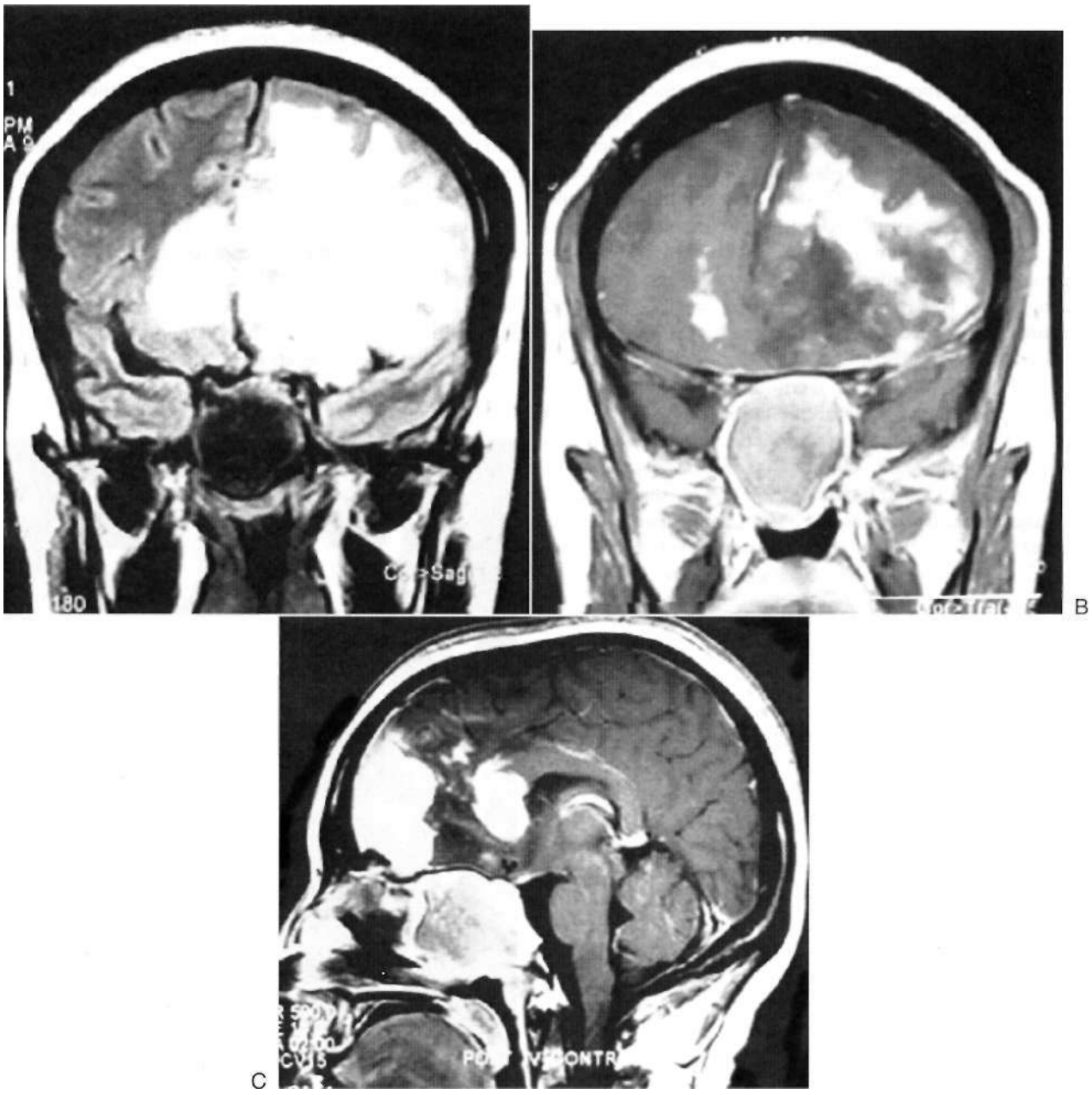

FIGURE 59C.2 Rhinocerebral aspergillosis. Coronal Tl MR1 showing sphenoid sinus mass extending to left frontal lobe and through corpus eallosum to the right frontal lobe (A), coronal FLAIR image showing left frontal mass (also extension to the right) of heterogeneous intense signals (B), and sagittal Tl postgadolinium image showing enhancing contiguous sphenoidal, frontal lobe and corpus eallosum mass (C). (Courtesy Dr. S. K. Gaekwad.)

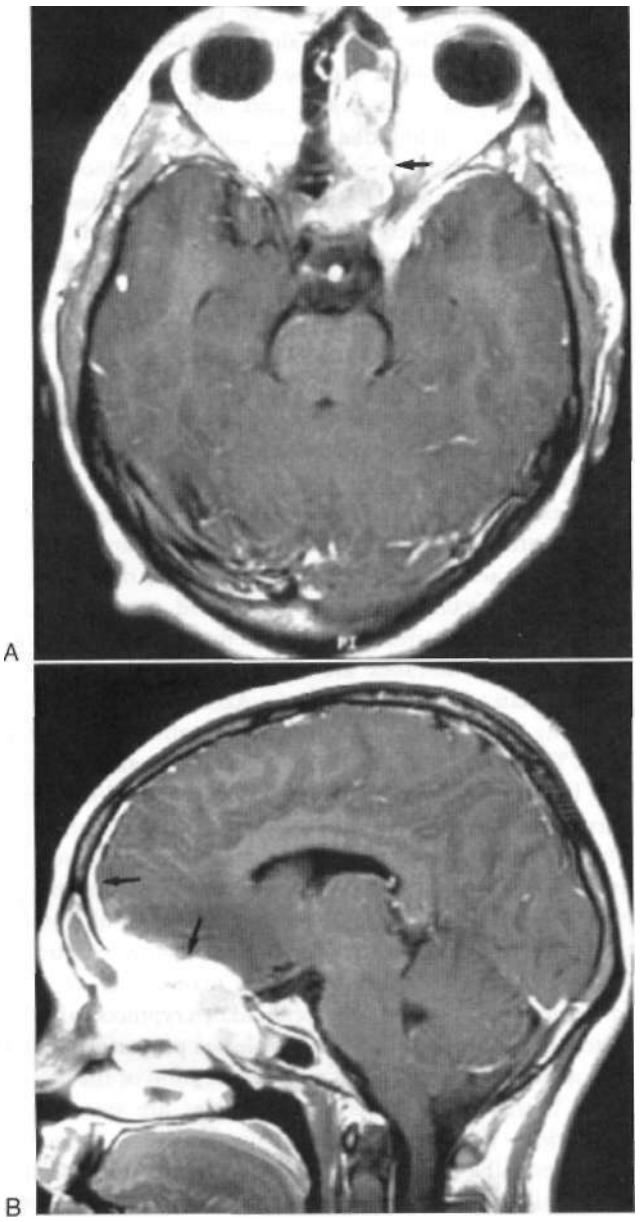

FIGURE 59C.3 Rhinocerebral mucormycosis. Posrgudolium axial T1W-MRI showing enhancing left ethmoid sinus mass (A) and sagittal image showing the (.-Financing mass in sphenoid, ethmoid, and frontal sinuses extending intracranially and producing frontal pachymeningitis (B). [Courtesy of Dr. S. K. Gaekwad.)

usually clear and colorless unless either the white blood cell (WBC) count or the protein concentration is significantly elevated due to other associated infection in an immuno-compromised host. The leucocyte count may range from 50 to 1000 cells/mm' with a lymphocytic predominance. A neutrophilic predominance should raise the suspicion of aspergillosis, mucormycosis or *Pseudallescheria* infection. An eosinophilic pleocytosis suggests coccidioidal infections. CSF glucose levels are usually, but not always, decreased and range from 10-39 mg/dL. Very low glucose levels (<1() mg/dL) are unusual and suggest the possibility of coexisting bacterial infection. CSF ptotein levels are elevated and range from 50-1000 mg/dL. A suspicion of a subarachnoid block must arise if the protein level is very high. Gram's stain of CSF is unhelpful unless concomitant bacterial infection exists. Rarely hyphae of *Aspergillus* and *caccidioides* may be seen on microscopic examination of the CSF sediment. India ink examination is useful for *Cryptococcus.* An identifiable capsule and budding yeasts may be seen (Figure 59C.4 and Plate 59C.I). A negative control of India ink should be examined to exclude the possibility of contamination of the ink with the fungus. CSF test fot cryptococcal antigen latex particle agglutination is more sensitive than the India ink preparation. Other tests arc still in the process of development for fungi (e.g., the polymerase chain reaction (PCR) to detect fungal nucleic acid in fluids). Fungal culture growth, except in crypto-coccal infection, is time consuming and does not always isolate the organism. Coccidioidomycosis, histoplasmosis, and blastomycosis yield a growth in only 50% of cases. The yield is even lower for other fungi. The sensitivity and specificity of CSF smear and cultute increase with repeated examinations of large volumes of CSF, centrifuging the CSF, and subjecting the sediment to cultute. The isolation of fungus is important because drug sensitivity patterns can be determined. However, one must also be aware of the possibility of contamination, especially in the case of *Candida* and *Aspergillus.*

Serologic tests can be carried out on blood and CSF. CSF serologic tests may be difficult to interpret. In the early stage, the ptesence of low titers could indicate an acute infection, an immunosuppressed state, or a past infection that is inactive. A high antibody titer suggests an active systemic infection.

If biopsy of a lesion is obtained, it should be subjected to culture in addition to the histopathologic a I investigations. Often a biopsy is the only way to identify infection due to

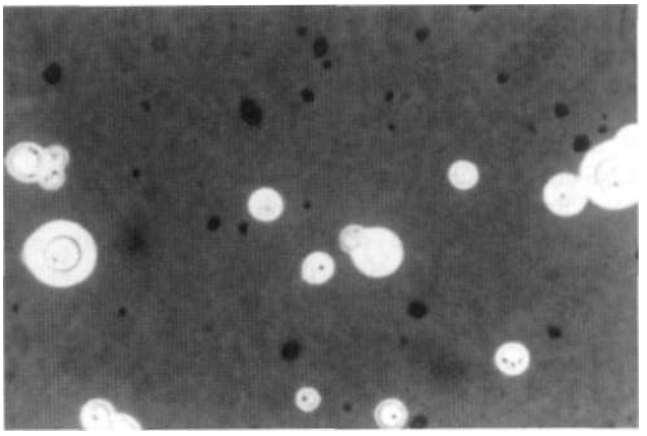

FIGURE 59C.4 India ink preparation of CSF revealing numerous cryptococd with wide, optically clear capsules

mucor and *Aspergillus* (Plates 59C.IIA and B}. Attempts to harvest fungi from other involved sites, such as skin, lung, lymph node, joint, paranasal, or bone marrow enhance the iv.K[1] t>1 deu-ain-i In 10- VS"„.

THERAPY OF FUNGAL INFECTIONS

Antifungal Agents

Amphotericin B is the treatment of choice for most fungal infections of the CNS (see Table 59C. 1). This agent is a polyene compound that binds to the ergosterol component of fungal cell membranes. It acts by increasing the permeability of the cell membrane resulting in the leakage of intracellular contents and lysis of the cells (Patel 1998). The serum half-life of amphotericin B is approximately 12 to 24 hours with peak serum levels lasting 6 to 8 hours. Excretion is chiefly in the urine. Depending on achievable concentrations, it is either fungistatic or fungicidal. It has no effect on other classes of pathogens.

Limitations of amphotericin B include its poor penetration of the blood-brain barrier, making it difficult to achieve effective fungicidal levels in brain. The drug also has renal toxicity (up to 80%), and it causes electrolyte wasting (K^+ and Mg^{++}), normochromic—normocytic anemia and a flulikc allergic reaction after intravenous (IV) use. CNS toxicity limits its intrathecal use. Occasionally life-threatening reactions such as anaphylaxis, acute hepatic failure, seizures, ventricular fibrillation, and cardiac arrest may occur. Premedication with diphenhydramine, hydrocortisone, and ihuprofen for the fever and chills, antiemetics for nausea, and oral potassium supplement to guard againsr hypokalemia reduce adverse effects. Renal toxicity of amphotericin B is related to its peak serum concentrations and the cumulative dose. Patients should be monitored by frequent urinalyses for detection of red blood cell (RBC) or WBC casts, serum creatinine levels, and creatinine clearance. Inability to use this dtug orally limits its use in therapy. Idiosyncratic reactions may fotce stoppage of medication. Amphotericin B should be avoided in patients who are hypersensitive to the drug unless it is the only possible therapy in the face of a life-threatening fungal disorder. In spite of all these limitations, it is the initial choice in induction therapy for most CNS infections, particularly those that are life threatening. New lipid formulations of amphotericin B (vide infra) have been developed to overcome the toxic it}', and though they are expensive, they are as effective as the original drug,

Flucytosine, which was initially developed as an antineoplastic agent, is commonly given as an adjunct to amphotericin B to patients with invasive infections by *Ci-yptnctiLLiis, Ciimi'uh,* and *Aspergillus.* The drug interferes with the metabolism of fungal nucleic acid and disrupts its genetic code. It is rapidly absorbed from the alimentary tract, has minimal protein binding, and is excreted unchanged in urine. CSF concentrations reach 75% of serum. The serum half-life is 3-5 hours. When given alone, flucytosine has few side effects, which include rash, cosinophilia, diarrhea, and hepatic dysfunction; however, in com hi nation with amphotericin B, bone marrow suppression is the major side effect. Blood levels exceeding 100 ug/ml, are associated with increased incidence of these complications. Existing renal failure calls for adjustment of dosage. A twice weekly leukocyte count and platelet count is mandatory in these cases. Flucytosine blood level estimations are done in reference mycology laboratories and are important in patients with azotemia. Blood levels for flucytosine should be drawn 2 hours after the last flucytosine dose and just before the next dose once or twice a week and should be between 50 and 100 (.tg/mL.

Fluconazole and itraconazole are synthetic broad-spectrum antifungal agents that belong to the triazole (azoles) class. They act by inhibition of the synthesis of ergosterol and cause accumulation of substituted sterols, which interfere with the permeability of the fungal cell membrane. Fungal cell membranes are far more sensitive to these agents than mammalian ones. Azole antifungals are generally considered to be fungistatic rarher than fungicidal. The advantage of these drugs is that they are less toxic, can be administered orally, and have good blood-brain barrier penetration. The disadvantage is a lower cure rate, The cure rate is low for cryptococcosis and still lower for aspergillosis with azoles alone. In vitro and animal studies have suggested that concomitant administration of amphotericin B and azole drugs may show antagonistic effects, The use of azoles is hence limited for maintenance therapy to prevent recurrences of coccidioidal, cryptococcal, and bistoplasmal meningitis. Itraconazole has properties similar to fluconazole except for its poor penetration of the blood-brain barrier. Adverse effects of azoles are uncommon but include nausea, abdominal pain, headache, dizziness, rash, reversible alopecia, pedal edema, and transiently increased liver enzymes. Physicians must watch for drug interactions of antifungal azoles with other drugs to prevent side effects or lack of effectiveness of the primary medication.

Newer Agents

Lipid amphotericin preparations (liposomal amphotericin B, amphotericin B cholesteryl, and amphotericin B lipid complex) have the advantage of lower toxicity and infusion-related side effects. The half-life of these preparations varies, and the larger particles are mostly cleared by the reticuloendothelial system faster. The disadvantages of lipid formulation are higher cost and lower CNS permeability compared to the original drug. The CSF/plasma concentration at steady state for amphotericin B is typically

less than 25% and lower for lipid formulations. Doses of lipid formulations range from 3-5 mg/kg per day. There seems to be no major difference in the overall efficacy between the two preparations. A favorable initial response of amphotericin B may permit a switch to a less toxic antifungal preparation after a period of time. Voriconazole, a new triazole derivative, has broad-spectrum antifungal activity and is especially useful for aspergillosis and candidiasis. Doses vary from 50-200 mg per day. SCH59562 is another triazole with apparently greater potency than voriconazole and is currently under investigation. Agents that boost the immune system, which is often deranged in patients with fungal infections, may help in treating invasive fungal infection. Cytokines and gamma interferon are being tried in CNS fungal infections and continue to remain experimental at this stage (Stevens 1998).

Surgery

Surgical procedure may be critical for CNS fungal treatment, especially in cases of invasive rhinocerebral fungal disease. Surgical biopsy may also be essential for establishing the diagnosis. Among the procedures of therapeutic relevance are exenteration of infected facial, nasal, and intracranial tissues in cases of mucormycosis and aspergillosis, extirpation or drainage of fungal cerebral abscess, repair of rare mycotic aneurysm, and surgical drainage of hydrocephalus complicating fungal meningitis. Hydrocephalus can occur in any fungal meningitis and is seen in as many as 15% of cases of cryptococcal meningitis. Acute hydrocephalus may require emergent ventricular drainage, and chronic hydrocephalus may require a ventriculopcritoneal shunt. Ventricular shunt in the face of active fungal meningitis may produce venrriculitis. In cryptococcal meningitis with communicating hydrocephalus, daily lumbar puncture may also alleviate symptoms. However, lumbar puncture is contraindicated in patients with intracranial mass lesions, such as fungal abscess and intracranial shifts on imaging studies. With elevated intracranial pressure, lumbar puncture should be performed cautiously, especially in patients with low-lying cerebellar tonsils, to avoid tonsillar herniation. The later has even been observed following lumbar puncture in the absence of focal mass brain lesion.

TREATMENT OF SPECIFIC INFECTIONS

Cryptococcal Central Nervous System Infection

Practice guidelines by the Infectious Diseases Society of the United States of America (Saag et al. 2000) have suggested therapy beginning with amphotericin B in the dose of 0.5-1 mg/kg per day plus flucytosine 100 mg/kg per day for 6-10 weeks in immunocompetent hosts with CNS cryptococcal disease. An alternative regimen is to use this combination for 2 weeks followed by fluconazole 400 mg per day for 10 weeks or more, especially if the patient develops amphotericin B toxicity. The consolidation therap\ with fluconazole mai be continued for d months to a year, depending on the clinical and CSF response. In patients with HIV infection, induction with amphotericin B (0.7-1 mg/kg per day) plus flucytosine (100 mg/kg per day) for 2 weeks followed by fluconazole 400 mg per day is recommended. The fluconazole dose can later be reduced to 200 mg per day but generally has to be continued for life in HIV/AIDS patients. An alternative regimen consists of amphotericin B in dosage of 0.5-1 mg/kg per day plus flucytosine 100 mg/kg per day for 6-10 weeks followed by fluconazole maintenance therapy. If the patient does not tolerate amphotericin B, fluconazole 400-800 mg per day with flucytosine 100-150 mg/kg per day for 6 weeks can be used. Renal function must be monitored, and serum flucytosine blood levels must be kept between 50 and 100 ug/mL. Neutropenia requires that the treatment be halted. Repeat lumbar puncture evaluation at 2 weeks of therapy to obtain CSF for antigen titers and fungal culture is needed to ensure the response to treatment. Relapse rates may be as high as 50%. An important predictor of final outcome in patients with HIV is the CSF culture sterility 14 days after the initiation of treatment. Patients likely to have poor response are those with a high cryptococcal antigen level, low CD4 count, and low serum albumin level. Mass lesions greater than 3 centimeters may require surgery. Prophylaxis with fluconazole in AIDS is important as about 5-10% of patients develop cryptococcal meningitis, especially when their CD4 count falls below 100 cells/mm (Van der Horst et al. 1997).

Coccidioidal Central Nervous System Infection

Prolonged treatment is usually required for coccidioidal CNS infections. Recent reports suggest that long-term oral fluconazole is as effective as amphotericin B and is now the treatment of choice. Its use in the dose of 400 mg per day orally for 4 years has been shown to result in improvement in 75% cases. Occasionally higher doses of 600-800 mg per day may be required. Signs of improvement may come only 4 to 8 months after beginning the treatment, Intrathecal administration of amphotericin B in the dose of 0.25-1.5 mg/dose 3 times per week for several weeks with a gradual tapering to biweekly and then monthly to a total cumulative dose of 35-100 mg may be given in difficult to control infections. Intrathecal drug is given in conjunction with IV amphotericin B 0.5 mg/kg per day, up to a total cumulative dose of 3 g. The duration of treatment may need to be extended to up to 1 year (Stevens 1995). As many as 78% cases may relapse when the therapy is discontinued. This is especially so in immunocompromised

patients. Hence, lifelong maintenance with fluconazole (200 mg per day) may be required.

Histoplasmal Central Nervous System Infection

IV Amphotericin B (0.7-1.0 mg/kg per day) for a total cumulative dose of at least 30 mg/kg or 1.5-2 g) is used in most cases. Intrathecal amphotericin B in a dose of 0.25—1.0 mg/dose on alternate days can be given if there is no contraindication. Four to 12 weeks of induction therapy is required. Maintenance therapy is required because many patients show relapse following induction therapy alone (Wheat et al. 1990).

Central Nervous System Mucormycosis

Mucormycosis generally occurs in rhino-orbito-cerebral form in patients with diabetic ketoacidosis or other associated illnesses (see Table 59C. 1). Surgical debridement is required, diabetes should be controlled, and in patients with hemochromatosis, desferoxamine should be discontinued. Amphotericin B should be administered in rapidly increasing doses of 1—1.5 mg/kg per day, with an anticipated dose of 2.5-3 g. Hyperbaric oxygenation has been suggested by some investigators. The prognosis is generally poor.

Therapy of other major CNS fungal diseases is summarized in Table 59C.1. Cure rate for cryptococcal meningitis is about 75%, coccidioidal meningitis 50%, *bistoplasyna* meningitis 40%, and for aspergillosis and zygomycetes approximately 25%. Outcome in immunosupprcsscd patients is less favorable, and many of these patients die due to concomitant infections. Shott- and long-term complications in CNS fungal infections are as high as 40-75%, and these include hydrocephalus, infarction, cranial nerve palsies, seizures, and dementia (del Brutto 2000).

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Chapter 59
Infections of the Nervous System

D. PARASITIC INFECTIONS

Madhuri Behari, Sumit Singh, and Ashok Verma

Parasites are a group of organisms that thrive on or in the body <ł other organisms, deriving protection and nutrition from them. Whereas protozoa arc microscopic single-celled organisms, helminths arc macroscopic, multicellular organisms ranging from few millimeters to several meters in size. i hanges ill social, technical, political, behavioral, and economical factors have resulted in a dramatic increase in the incidence of some human parasitic infections in recent decades. At least 10% of world population is infected by *Entamoeba histolytica,* a common gut pathogen. It is estimated that one third of the world population harbors helminthic infestations. *Plasmodium falciparum,* the species responsible for 40% to 60% of the 200 million annual cases of malaria and 95% of malarial deaths, remains one of the top infectious disease killers in the world. Of the 1 to 2 million annual deaths caused by malaria, most are the result of cerebral malaria (WHO 1999), Parasitic infections are not restricted to the tropical regions alone. Migrations of individuals across the continents and increasing travel have enabled them to spread all over the globe. Emergence of the pandemic of acquired immunodeficiency syndrome (AIDS) has caused an exponential inctease in the number of individuals affected by certain parasites {Lanjewar et al. 1998). Apart from an absolute increase in the incidence, altered immunity of patients with AIDS has resulted in atypical presentation of these diseases. Parasites that are well tolerated by the human body do not elicit inflammatory response. On the other hand, parasites that are not well tolerated develop intense inflammatory reaction around the larvae or the adult worms, resulting in a multitude of symptoms.

Protozoan infections are responsible for acute meningitis or meningoencephalitis *[Naegleria,* African trypanosomiasis), encephalopathy *(Plasmodium* spp.), chronic meningitis *(Acanthamoeba, Toxoplasma),* space-occupying lesions of the brain *(Toxoplasma, Entamoeba histolytica),* neuropathy (Chagas' disease, filariasis), myositis *[Trichinelia,* cysticercosis), and chorioretinitis *(Toxoplasma).* Helminths cause nervous system involvement due to their size, mobility, and challenge to the host immune response. Helminths can cause meningoencephalitis *(Taenia solium, Trichinelia, Angiostrongylus, Gnathostoma, Toxocara, Strongyhides, Schistosoma,* etc.), encephalopathy *(Trichinelia, Loa loa),* cerebral mass lesions *(Taenia, Echinococcus, Gnathostoma, Schistosoma),* and ocular involvement *(Taenia, Angiostrongylus, Gnathostoma, Eoa loa, Toxocara)* (Table 59D.1). Invasion through the foramina of skull and vertebral column and of tissues surrounding nerves can cause features of nerve or nerve root compression or compressive myelopathy *(Schistosoma).* Ectoparasites do not invade the tissues of the host but release toxins that may affect the nervous system.

It would hardly be possible within the confines of this chapter to discuss with any degree of completeness

Table 59D.1: Parasitic infections of the central nervous svstem

Parasite	*Range*	*Neurological ma infestations*	*Treatment of choice*
Protozoans			Guided by local resistance pattern (see text)
Plasmodium falciparum	Africa, South America, Southeast Asia, Pacific Islands, Haiti	E, Sz	Oral: Chloroquinc phosphate 600 mg base (1 g), then 300 mg base (500 mg) at *6*, 24, and 48 h (if resistance, quinine sulfate plus pyrimethamine-sulfadiazine, nr plus tetracycline, or plus clindamycin) Parenteral: Quinine dihydrochloride 20 mg/kg ioading (maximum 600 mg) over 1/2 hr followed by 10 mg/kg every 8 hour IM or PO for 7 days
Naegleria fowleri	Southern United States, Australia, Europe	ME	Amphotericin R 1 mg/kg/d IV for uncertain duration
Acantbamoeba spp.	Europe	ME, E, O	Amphotericin B 1 mg/kg/day TV plus vitampin for uncertain duration
Entamoeba histolytica	Tropics worldwide	M	Metronidazole 750 mg IV q8h for 10 days followed by iodoquinol 650 mg tid lor 20 days
Trypanosoma brucei rbodesiense	Africa	ME	Mclarsoprol 2-3.6 mg/kg/day IV for 3 days, after 1 week 3.6 mg/kg/day IV for 3 days, repeated after 10-21 days; or eflornithine 100 mg/kg qid for 14 days, then 300 mg/kg/day for 3-4 weeks
Trypanosoma brucei gambiense	Africa	ME	Mclarsoprol 2-3.6 mg/kg/day IV for 3 days, after 1 week 3.6 mg/kg/day IV for 3 days, repeated after 10-21 days; or eflornithine 100 mg/kg qjd for 14 days, then 300 mg/kg/day for 3^t weeks
Trypanosoma cmzi	Central and South America	ME, M, St	Nifurtimox 8-10 mg/kg/day in 4 doses for 120 days
Toxoplasma gondii	Worldwide	ME, Sz, M, O	Pyrimethamine 25-100 mg/day plus sulfadiazine 1-1.5 g qid plus folinic acid 10 mg/day for 3-4 weeks
Helminths			
Ccstodcs			
Taenia solium (cysticercosis)	Worldwide	ME, Sz, M, Sp.O	Albendazole 15 mg/kg/day in 2 doses for 8-28 days, or praziquantel 50 mg/kd/day in 3 doses for 14 days or repeated as necessary, with concurrent glucocorticoids for CNS disease

Echinococcus granulosus	Worldwide	Sz, M, Sp, O	Surgical excision if possible and albendazole 400 mg once; or albendazole 15 mg/kg/day for 40 days, repeated after 2 weeks	—
Echinococcus multilocularis	Arctic	Sz, M	Surgical excision	—
Taenia multiceps (Coenurosis)	Worldwide	M, O	Surgical excision	—
Spirometra spp. (Sparganosis)	Worldwide, mainly Asia, Africa	ME, Sz, M, St	Surgical excision	—
Diphyllobothrium latum	Worldwide	E, Sp, O, N (vitamin B_{12} deficiency)	Praziquantel 10 mg/kg 1 dose, vitamin B_{12}	—
Hymenolepis nana	Worldwide	E, Sz	Praziquantel 25 mg/kg 1 dose	—
Nematodes				
Trichinella spp.	Worldwide	ME, E, Sz, St	Glucocorticoids (for severe symptoms) plus mebendazole 200–400 mg tid for 3 days, then 400–500 mg tid for 10 days	—
Angiostrongylus cantonensis	Asia, Africa, Pacific, Caribbean	ME, Sz, O	Supportive therapy and glucocorticoids as needed	—
Gnathostoma spinigerum	Asia, Israel	ME, Sz, M, St, Sp, O	Surgical removal plus albendazole 400–800 mg/d for 21 days	—
Onchocerca volvulus	Africa, Central and South America, Yemen		Ivermectin 150 μg/kg/day once, repeated every 3–12 months	—
Loa loa	Africa	E, O	Diethylcarbamazine, day 1: 50 mg, day 2: 50 mg tid, day 3: 100 mg tid, days 4–21: 9 mg/kg/day in 3 doses	—
Toxocara spp.	Worldwide	ME, Sz, O	Thiabendazole 25 mg/kg bid for 5 days, supportive therapy and glucocorticoids	Diethylcarbamazine 2 mg/kg tid for 7–15 days, or mebendazole 100–200 mg bid for 5 days, or albendazole 400 mg bid for 3–5 days
Baylisascaris procyonis	Worldwide	ME, Sz	Thiabendazole 25 mg/kg bid for 5 days, supportive therapy and glucocorticoids	Mebendazole 100–200 mg bid for 5 days, or albendazole 400 mg bid for 3–5 days
Strongyloides stercoralis	Worldwide	ME, St	Thiabendazole 25 mg/kg bid for 3–7 days or longer if host is immunosuppressed	Ivermectin 200 μg/kg/day for 1–2 days, or albendazole 400 mg bid for 3 days
Ascaris lumbricoides	Worldwide	Sz	Mebendazole 100 mg bid for 3 days, or piperazine 75 mg/kg (max 3.5 g) for 2 days	Pyrental pamoate 11 mg/kg (max 1 g) or albendazole 400 mg once
Wuchereria bancrofti	Coastal areas in tropics and subtropics	N	Diethyl carbamazine 6 mg/kg/day in 3 divided doses for 12 days	Surgical resection

ME, meningoencephalitis; E, encephalitis; Sz, seizures; St, stroke; Sp, spinal cord; N, nerve.

the innumerable rare parasitic infections that affect the central nervous system (CNS). Rather, we will introduce some general clinical approaches to parasitic CNS infections and deal in greater detail with important or relatively common parasitic CNS diseases. A summary of patasitic CNS infections is given in Table 59D. 1. The interested reader is referred to a number of texts (Gorbach ct al. 1997; Scheld et al. 1997), comprehensive reviews, and references listed at the end of this chapter.

CLINICAL APPROACH TO PARASITIC CNS INFECTION

Because of the diversity of parasitic organisms that may infect the human CNS; a number of factors are important in the assessment of a possible parasitic etiology for a patient's complaints. These factors include issues related to the patient's work, travel and recreational history, immune sratus, and presenting neurological and orher systemic symptoms. The specific laboratory tests required, ranging from standard blood biochemical assays to brain imaging and cerebrospinal fluid (CSF) analysis, are dictated by the nature of the patient's illness.

Geographic, Travel, and Other Exposure History

The cornerstone for the diagnosis of parasitic infections is a thorough history of the patient's illness. Epidemiological aspects of the illness are particularly important because the risk of acquiring many parasites is closely related to occupation, recreation, or travel to areas of high endemicity. A history of travel to, residence or work in, or immigrarion from areas of the world in which various parasites occur offers a clue to the possible parasitic-etiology of a patient's disease. Some parasitic infections may become manifest early after a traveler's return to home; most important among them in terms of mortality is malaria. For patients with history of recent travel, the onset of gastrointestinal symptoms only after return suggests protozoan diseases. Diseases that may become manifest some years after an individual leaves an endemic region include schistosomiasis, some form of filatiasis, strongyloidiasis, echinococcosis, and cysticercosis. Consumption of contaminated or undercooked food may be associated with trichinosis, cysticercosis, Toxocariasis, or eosinophilic meningitis *{Angiostrongylus cantomnsis).* Other relevant exposure history includes blood transfusion (malaria, filanasis, Cliagas' disease) and wading or swimming in freshwater lake or pond *{Naegieria* meningitis, schistosomiasis), Residence in an institutional setting, in which fecal-oral hygiene may he lacking, raises the possibility of exposure to gut parasites, such as *Y.nlamoeba* and *Strongyloides.*

Immune Status

In patients infected with human immunodeficiency virus (HIV), especially those with low CD4(T cell counts, specific protozoan diseases, such as toxoplasmosis or trypanosomiasis, may develop opportunistically. Patients who are asplenic are ar risk not only for overwhelming infections due to encapsulated bacteria, but also for fulminant intra erythrocytic protozoa, including malaria. In patients developing symptoms of enterocolitis while receiving corticosteroids, the possibility of exacerbation of iri--,ii-|-ivi(r -,;ni-i,:.vloi..f,;-.h, •... .niiivlin ^ihiis should In-considered.

Laboratory Investigations

Most protozoa and helminths are excreted from the body in the feces. Stool samples, therefore, should be collected and examined for ova and parasites in appropriate clinical settings. Because of cyclic shedding of most parasites in rhe feces, a minimum of three samples collected on alternate days should be examined. Microscopic examination of feces is not complete until direct wet mounts have been evaluated.

Eosinophilia in blood may offer a hematologic clue to the presence of parasites. Protozoan infections restricted to the CNS, however, do not cause eosinophilia. Thus eosinophilia in the face of CNS parasitic infection mandates a consideration of the multicellular helminthic parasites that characteristically elicit this abnormality. Helminth-elicited eosinophilia, however, may be suppressed by glucocorticoid therapy or by intercurrent bacterial or viral infections. The magnitude of eosinophilia generally correlates with the extent of tissue invasion by the helminths. Marked eosinophilia (more than 2500 eosinophils per microliter) develops during early tissue migration of nematodes. Eosinophilia is also marked in the early stages of trematode infections, including schistosomiasis (Katayama fever), paragonimiasis, and fascioliasis; during the stage of muscle invasion (trichinosis); during tissue migration of adult worms {loiasis and gnathostomiasis); and with heavy infections in visceral larva migrans. Eosinophilia persisting for more than a year may be indicative of strongyloidiasis, visceral larva migrans, filarial infection, trematode infections, or cysricercosis. Leakage of fluid from echinococcus cysts can cause intermittent eosinophilia. Eosinophilia may be the only clue to the presence of helminthic infection, and it should prompt an evaluation for such infection.

Laboratory procedures may detect parasites in body fluids. The most common parasites detected in Gicmsa-stained blood smears are the *Plasmodium* spp., microfilariae, and African trypanosomes. The diagnosis of malaria and the critical distinction between the various *Plasmodium* spp. is made by the microscopic examination of stained thick and thin blood films.

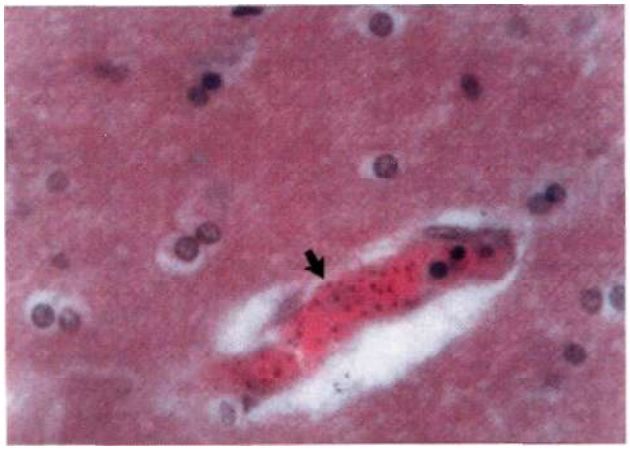

PLATE 59D.I A capillary in brain parenchyma showing RBCs filled with hemozoin pigmenr *(arrow)* in a case of cerebral malaria. (H & E x 100)

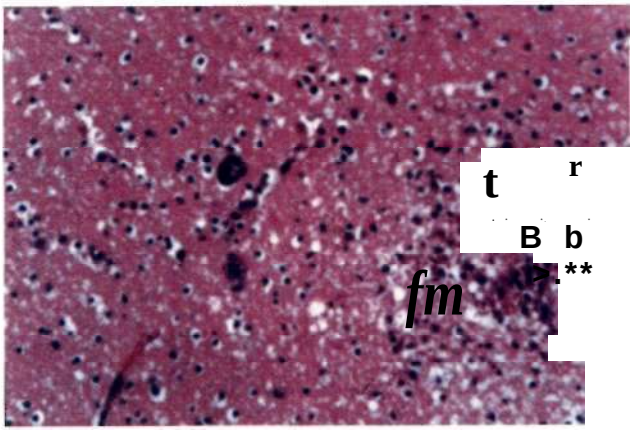

PLATE 59D.11 *F.ntamoeba histolytica* cysts *(arrow)* in a case of cerebral amoebic abscess. (H 6c E x 100)

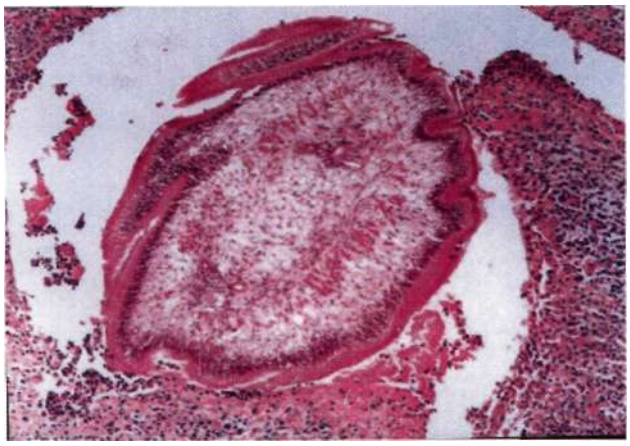

PLATE 59D.1I1 Cysticercus cyst showing scolex in a case with solitary cyst in brain parenchyma. (H & E x 100)

The value of serum antibody assays is generally limited in parasitic CNS infections. The detection of serum antibody to *Plasmodium* is primarily an epidemiologic tool and is of limited use for establishing the diagnosis of malaria in an individual patient. Filarial antigens cross react with those from other nematodes, and antibody assay cannot distinguish between past and current infections. Despite these specific limitations, the restricted geographical distribution of many of the tropical parasites increases rhe usefulness of antibody deteuinii as a means (it establishing diagnosis in travelers from industrialized countries who have returned from the tropics. The presence of a specific IgM antibody in CSr indicates active CNS disease, such as in CNS toxoplasmosis. Polymerase chain reaction (PCR) for the detection of *Plasmodium* DNA is now available.

Imaging Studies

Contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) studies of the brain and spinal cord can identify meningeal enhancement (parasitic meningitis), para meningeal infections (including parasitic granulomas), or inrraparenchymal lesions (cysticercosis, echinococcosis) (Chang and Han 1998). Imaging studies are also useful to localize areas of meningeal or parenchymal disease prior to meningeal or brain biopsy or lesion resection.

Cerebrospinal Fluid Analysis

Once the clinical syndrome is recognized as a potential manifestation of parasitic CNS infection, lumbar puncrure (LP) and CSF analysis are essential. However, if the possibility of raised intracranial pressure (ICP) exists, a brain imaging study should be performed before LP. In patients with communicating hydrocephalus caused by impaired absorption ol (.Sl', I I' is gcneralh safe and may lead ro temporary improvement. However, if ICP is elevated because ol a mass lesion or a blink in ventricular CSF ourflow (obstructive hydrocephalus), then LP carries the potential risk of brain herniation and death. Acute obstructive hydrocephalus usually requires direct venrricular drainage of CSF.

The CSF pressure should be measured and samples sent for cell count and differential, measurement of glucose and protein, microbial stain, and orher investigations. When eosinophils predominate or are present in limited numbers in a primary mononuclear cell response in the CSF, parasitic disease must be considered *(Angiostrongylus cantonensis, Gnathostoma spinigerum, Toxocara cants, Toxoplasma gondii,* cysticercosis, schistosomiasis, and echinococcal disease). Centrifugation of CSF and wet mount preparation with Giemsa stain may reveal parasites in African trypanosomiasis and *Naegleria fowl en.* IgM antibodies against T. *gondii* in blood or CSF suggest recent infection. Other specific CSF rests should be ordered as indicated on the basis of the clinical picture.

Meningeal or Brain Biopsy

A diagnostic brain biopsy should be considered in patients who are severely disabled, who need chronic ventricular decompression, or whose illness is progressing rapidly. Targeting regions rhar enhance with contrast on MRI or CT scan can increase rhe diagnostic yield of biopsy. Single symptomatic lesions *{Cysticercus, Echinococcus)* can be resected for both diagnosis and treatment. The activities of surgeon, pathologist, microbiologist, and cytologist should be coordinated so that adequate sample is obtained and appropriate histological and molecular srudies, including PCR, are performed.

PROTOZOAN INFECTION OF THE CNS

Cerebral Malaria

Malaria caused by genus *Plasmodium* is one of the oldest and most dreaded protozoan diseases affecring more rhan 500 million people throughout the world (WHO 1999). The endemic zones for malaria, sub-Saharan Africa, Asia, and Central and South America, account for the majority of cases. In hyperendemic areas most children acquire infection with *Plasmodium* before they reach 5 years of age. Infants under 6 months enjoy immunity inherited from their mothers. World Health Organization (WHO) defines cerebral malaria as unexplained unconsciousness lasting 30 minurcs or more in a patient with asexual forms of *Plasmodium falciparum* in rhe peripheral blood smear. It occurs in about 0.5-1% of infections with *Plasmodium falciparum.* Though a large majority of cases are due ro *P. falciparum,* few case reports of cerebral malaria due to *P. vivax* are recorded.

Natural transmission of all species of *Plasmodium* occurs by the female *Anopheles* mosquito. Accidental transmission occurs through blood transfusion, laboratory accidents, experimental infection, and zoonotic infection. The female *Anopheles* mosquitoes inject the sporozoites form of *Plasmodium* into the host body during a blood meal. Sporozoites undergo successive developmental stages of trophozoites, schizonts, and merozoites that are liberated into the circulation by rupture of erythrocytes, thus ending the asexual cycle.

Pathogenesis

Pathogenesis of cerebral malaria is ill understood. Evidence based on animal models suggests that the fundamental process in cerebral malaria is the increased cyroadhcrance

due to formation of knobs on parasitized red blood cells (pRBC) containing schizonts. Other endothelial factors such as leucocyte differentiation molecule (LD36), intercellular adhesion molecule-1 (ICAMi) and thrombospondin, ap extracellular matrix protein, may help in the process of cytoadherence (Lou et al. 2001). Additionally, immune mediated ptoinflaminatory response due to tumor necrosis factor-cc (TNF-r*), interleukin-1 and other cytokines may aggravate cytoadhesion, leading to cerebral microvascular occlusion, cerebral anoxia, and ischemic cerebral damage (Singh et al. 2000). Activation of nitric oxide synthetase and the complement cascade induced by prostaglandins and glycophosphatidil inositol, leading to inflammation, may also be contributory. Hypoglycemia and acidosis, common complications of cerebral malaria, produce or worsen encephalopathy and neurological deficit.

Pathology

Pathological description in cerebral malaria is necessarily based on severe cases, which are eventually fatal. Grossly, the brain is heavy, and the meningeal vessels are congested, giving a pink hue to the brain. Microscopically, engorged blood vessels containing pRBCs with asexual forms of parasite can be seen (Plate 59D.I). Petechial hemorrhages showing engorged blood vessel in the center and a surrounding ring of extravasated red blood cells (RBCs) are called ring hemorrhages and are a characteristic finding in cerebral malaria. "Durks nodules" are granulomas consisting of central dcmyelinated core with inflammatory cells in the ring hemorrhage. Immunohistoehemical staining shows amyloid precursor protein in ring hemorrhages indicative of axonal damage (Medana et al. 2002).

Clinical Features

The incubation period depends to a large extent on the immune status, species of *Plasmodium,* dose of inoculation, and prctrcatment with prophylactic drugs (Warrell 1997). In *P. falciparum* the mean incubation period is 12 days but may be 6-12 hours in children and if a massive dose is inoculated. The prodrome consisting of lassitude, myalgia, headache, and chills usually precedes the acute attack, High-grade fever (104= to 105°F), shaking chills, and rigors with diaphoresis announce the presence of malaria. Rarely, patients may have hypothermia due to shock and endotoxemia. The periodicity of fever in *P. falciparum* malaria is once every third day, but it may not be obvious because of multiple exposures and several cycles of parasitemia. Malaria being a systemic disease, symptoms such as nausea, vomiting, abdominal pain, cough, tachycardia, arthralgia, myalgia, and weakness occur commonly. Most patients have enlarged liver and spleen with chest rales and muscle tenderness.

Cerebral symptoms start with seizures (generalized or partial), acute onset delirium, or coma. In children, seizures are more common (70%) as compared to adults (20%), and one third of patients may present with status epilepticus. Other CNS manifestations include headache, meningismus, focal neurological deficits (aphasia, ataxia, hemiplegia, chorea, and tremor), ncuro-opbrhalmological signs (conjugate gaze disturbance, oculomotor palsies, ocular bobbing, and nystagmus), retinal hemorrhages (up to 15%), and rarely papilledema (<1%). In endemic areas, rhe presence of febrile encephalopathy with nearly normal CSF findings warrants a diagnosis of cerebral malaria. Systemic effects of severe malaria often complicate the clinical picture and **adversely iliecl '.hi-** prognosis I'he -.ystemic etlecls include severe anemia, renal complications with oliguria/anuria and azotemia, jaundice, pulmonary edema, adult respiratory distress syndrome, resistant hypoglycemia, secondary infections, and septicemia (Kochar et al. 2002).

Cerebral malaria carries a mortality of 20-50%, it being higher in children. Important prognostic factors are level of consciousness at the time of presentation and the presence of complications. Additionally, recurrent seizures, absent corneal reflex, decerebrate rigidity, retinal hemorrhage, age less than 3 years, high degree of parasitemia, peripheral schizontemia, red cell mass less than 20%, peripheral leucocytosis, lactic acidosis, elevated CSF lactate, elevated serum transferases, and low antithrombin III levels are associated with a poor prognosis. Though complete recovery occurs in the majority who survive, sequelae are reported in 10-18%, being higher in children. Ataxia, hemiparesis, memory disturbance, neuropsychological deficits, visual field defects, vertigo, cognitive impairment, behavioral abnormalities, and psychosis are common sequelae, which are mostly reversible in 4-8 weeks (Rozc et al. 2001). A postmalaria neurological syndrome characterized by acute onset confusion, seizures, ataxia, myoclonus, tremor, and aphasia is described in patients successfully treated for cerebral malaria in the absence of parasitemia. The pathogenesis of this syndrome is not understood, but immunologic mechanism seems to be involved as the condition is responsive to corticosteroids (Nguyen et al. 1996).

Diagnosis

Diagnosis and species identification tequire examination of thick and thin smear of peripheral blood stained with Giemsa or Field's stain for the presence of ring-shaped trophozoites. Cerebral malaria usually occurs when more than 10% of peripheral RBCs are parasitized. Absence of trophozoites in the peripheral smear may occur due to sequestration of RBC in the cerebral circulation or earlier treatment with antimalarial drugs, as it is a common practice in endemic areas to treat all fevers with antimalarial drugs. If the initial smear is negative, two or three smears 6-8 hours later should be repeated (at least three sine.its should he declared negative before **excluding llie** diagnosis of malaria).

CSF examination is necessary to exclude other causes of febrile encephalopathies (meningitis, encephalitis, enteric encephalopathy, yellow fever, viral hemorrhagic fever, relapsing fever, leptospirosis, and heat stroke). In cerebral malaria, the CSF is largely normal. However, mild lymphocytic pleocytosis (10-50 cells/a!.), and mildly elevated protein {up to 200 mg/dL) may be seen. Neuroimaging with CT and magnetic MRI in cerebral malaria is usually normal or it shows edema or cortical or subcortical infarcts in the watershed zones in a small number of cases (15-20%). Recently, a dipstick antigen capture assay for malarial antigen PfHRPi has shown 75-96% sensitivity and 87-100% specificity (Craig et al. 2002). However, its cost prohibits its use where it is maximally needed. Immunochromatographic tests and PCR for malarial parasite in the CSF and blood are also available (Craig et al. 2002). Electroencephalography (EEC) shows a number of abnormalities such as diffuse slowing of background, burst suppression or spike and wave discharges, but is nonspecific for diagnostic purpose (Crawley et al. 2001). Cerebral malaria may occur with negative blood smears. A high index of suspicion in endemic areas is the key to successful treatment in a case of high fever, rigors, encephalopathy, seizures, anemia, jaundice, diarrhea, hemorrhages, renal failure, and respiratory distress. In such cases with a history of malaria exposure, treatment with antimalarial drugs should be initiated even before evidence of parasitemia becomes available.

Treatment

Mortality in cerebral malaria is 20-50% and virtually I 00",) if untreated for 48 hours. In endemic areas if cerebral malaria is suspected, treatment should be started without waiting for laboratory confirmation.

In most tropical and endemic countries the parasite has developed resistance to chloroquine due to its widespread use. Quinine dihydrochloride is the drug of choice. Due to alteration in the pharmakinetics of quinine related to the volume of distribution and renal clearance in severe malaria, an intravenous loading dose of 20 mg/kg of quinine dihydrochloride in dextrose or saline over 30 minutes is advocated to achieve rapid therapeutic concentration in severe cases. The loading dose can be omitted if the patient has already received quinine. Maintenance dose is 10 mg/kg infused over 2-8 hours. The maximum daily dose is 1800 mg. This dose can be used for all age groups. Therapeutic minimal parasiticidai concentration after oral treatment is achieved in about 4 hours. Once patients regain consciousness oral treatment with quinine in 10 mg/kg, every 8 hours can be started. Total duration of treatment is 7 days. Alternatively, 600 mg of quinine can be given orally thrice a day in an adult. In patients who do not tolerate quinine due to scwiv •. oriiitmg, h\ pcrseiisitivin, <r hypoglycemia, quinidine gluconate in doses of 10 mg/kg base can be infused intravenously over one hour under cardiac monitoring, followed by continuous intravenous infusion at the rate of 0.02 mg/kg per hour for 7-10 days or longer. Concurrently or immediately following quinine dihydrochloride, tetracycline 250 mg every 6 hours or pyrimethamine (25 mg)-sulfadiazine (500 mg) every 8 hours should also be administered. In multi-drug-resistant malaria Artemisia derivatives (derived from traditional Chinese medicine *ginghaosu),* artcmether, and artesimate are used. The dose of artemether is 3.2 mg/kg intramuscularly as a loading dose followed by 1.6 mg/kg intramuscularly every day for 4 days plus mefloquine 750 mg orally on the last day of treatment; or artcsunatc 2.0 mg/kg intravenous loading dose, followed by 1 mg/kg intta-venously at 4 hours and 24 hours, then daily for *6* days (Faiz et al. 2001). In children, mefloquine solution given by nasogastric tube in a single dose of 25 mg/kg has been found to be as effective as intravenous quinine.

Treatment of Complications

Hypoglycemia, resulting from consumption of glucose by parasites, malabsorption, and increased pancreatic secretion of insulin induced by quinine, may be severe in young children and pregnant women and is an important prognostic factor. It should be suspected in patients who show deterioration despite adequate treatment and is treated by infusion of 50% dextrose. Anemia can be severe, with hematocrit falling by 8-10% in 48 hours in severe parasitemia. Blood transfusion sin mid be given to keep the hemoglobin at 7 g/dL. In children exchange transfusion is safe as it also clears the parasite load and does not alter hemodynamics. Raised ICP is also common in children and requires intracranial pressure monitoring. Use of corticosteroids has been reported to be associated with increased risk of seizures and gastrointestinal hemorrhages in patients with cerebral malaria. However, there is insufficient evidence to contra indicate the use of corticosteroids in cerebral malaria (Prasad and Garner 2000). Other complications such as renal failure, lactic acidosis, disseminated intravascular coagulation, shock, gastrointestinal hemorrhage, pulmonary edema, and gram-negative septicemia need to he managed as they appear. Adjuvant therapy with vitamin A, immunoglobulins, and monoclonal antibodies has been used without change in morbidity or mortality,

Prevention

Area-specific guidelines for malaria control can be obtained from the regional WHO centers. Chemoprophylaxis with adequate drugs can be used for prevention of transmission of the disease. It should be given to all individuals traveling to malaria endemic zones (Table 59D.2). Vector control is difficult due to resistance of mosquitoes to various insecticides. Recently, the entire genomes of P. *falciparum* and *Anopheles* mosquito have been decoded, and this may help in finding ways to better control malaria.

Table 59D.2: Prophylaxis of malaria

Sensitivity of malaria parasite	*Drug used for chernapropbylaxss*	*Doses*
Sensitive to chloroquine	Chloroquine	300 nig base/week Beginning 2 weeks before departure and up to *6* weeks after return
Resistant to chloroquine	Mefloquine	250 mg/week 2 weeks before departure and 4 weeks after return
	Chloroquine + proguanil or chlorproguanil	Chloroquine as described, proguanil 100-200 mg/day ehlorproguanil 20 mg/day as described above
	Chloroquine or amodiaquine -+ sulpha doxine pyrimethamine (Fansidar) combination, or 4- pyrimethamine alone	Chloroquine as above and Fansidar one tablet/ week, pyrimethamine 50 mg/week as described above

African Trypanosomiasis

African trypanosomiasis or sleeping sickness *(malaise du sommeil)* is caused by *Trypanosoma brucei gambietue* (Gambian trypanosomiasis) or *Trypanosoma brucei rhodesimse* (Rhodesian trypanosomiasis).

African trypanosomiasis occurs in a wide belt of African continent between latitude of 10° north to 25" south. Gambian trypanosomiasis is more widely distributed in western and central Africa, whereas Rhodesian trypanosomiasis is limited to cast and southeast Africa. The official incidence of about 20,000-50,000 cases per year is probably an underestimation, as a large number of cases are not reported due to nonavailability of medical facilities. In the wild, reservoir hosts arc pigs and dogs for *T. b. gambiense* and antelope, wild hogs, and cattle for T. *b. rhodesiense.* It is spread by tsetse fly of the genus *Glossina.* Humans contract the disease by the bite of tsetse fly when they go hunting or searching for water and food in areas in which the infected reservoirs and vector abound. About 25-50 million people in sub-Saharan Africa live in the endemic zone, wherein more than 200 hyperendemic /ones are recognized. Other causes of spread include laboratory accident, blood transfusion, transplacental spread, and perhaps by bites of other insect vectors (Enanga et al. 2002).

Pathogenesis and Pathology

The pathogenesis of CNS trypanosomiasis is poorly understood. Inoculation of the parasite by the tsetse fly is followed by formation of a nodule due to an inflammatory response and parasitic replication (stage 1). Recurrent bouts of parasitemia follow thereafter, resulting in the hemolynipliatic stage (stage 2). The parasites gain access to the brain and meninges through the choroid plexus and Virchow-Robin spaces (stage 3). African trypanosomes are densely coated with a glycoprotein called the variant surface glycoprotein (Magcz et al. 2002), which keeps changing its antigenic character with each new population of trypanosomes. This may result in letting the trypanosome escape immunological control even after the mounting of IgM antibodies against a large number of antigenic subtypes. Mechanism of damage to the host tissue is unknown.

The characteristic pathological finding of CNS trypanosomiasis is meningoencephalitis, with infiltration of perivascular and Virchow-Robin spaces by dense lymphocytic and plasmacytic inflammatory infiltrate, accompanied by glial proliferation. The meninges are covered by a milky white exudate, especially in the region of vertex where the meninges are adherent to each other and the skull. The choroid plexus shows inflammation, round cell infiltration, and edema. The brain is swollen with cerebral vascular congestion. Perivascular demyelination of the subcortical white matter is seen in most cases. Hemorrhagic leukoencephalopathy with fibrinoid necrosis of parenchymal vasculature may also occur.

Clinical Features

Characteristically the disease can be recognized as occurring in stages. The first stage is characterized by formation of chancre at the site of fly bite, second stage is hemolynipliatic stage, and the third stage is systemic stage with involvement of the CNS. A firm, tender nodule (chancre), 2-5 cms in size develops in 20-50% of patients 10-14 days after the bite of tsetse fly. This may ulcerate with enlargement of regional lymph nodes, lasting for 1-2 weeks. This is followed within 1-5 weeks by the hemolymphatic stage characterized b) high grade inter mittent fever, sweating, nausea, vomiting, general malaise, arthralgia, and generalized lymphadenopathy, often coinciding with bouts of parasitemia. Other symptoms are headache, dizziness, tachycardia, debility, amenorrhea, and sterility as parasitemia worsens. During this stage each bout of parasitemia is associated with the liberation of successive generation of parasites with slightly different surface antigens. Treatment, if commenced at this stage, is associated with good prognosis. The hemolymphatic stage can lead to the systemic stage with CNS involvement or several cycles of hemolymphatic stage may occur before the CNS is involved. The pace of disease is rapid in Rhodesian trypanosomiasis, whereas it is more chronic and indolent

in Gambian disease with easy identification of different clinical stages.

The systemic stage is also associated with liberation of a new generation of parasites lasting 1-6 days at several-week intervals. The systemic stage is characterized by serous effusions, pancarditis, deep hyperesthctic pain out of proportion to injury (Kerandel's sign), and lymphadenopathy particularly of the posterior cervical lymph nodes (Winterbottom's sign) in the Gambian form. CNS involvement is indicated by the presence of psychological and behavioral changes. Initial symptoms of lethargy, apathy, indifference, euphoria or depression give way to insomnia (10%), daytime hypcr-somnolence, disturbance of circadian thythm, chorea, rigidity, tremors, ataxia, and hemiplegia. Less commonly, seizures, cranial neuropathies, and altered mentation occut. Eventually patients develop increasing drowsiness and finally coma. Untreated patients with *T. rbodesiense* generally die in 6-9 months aftet the onset of the disease.

Diagnosis

Diagnosis is made by demonstration of parasites in the peripheral blood, lymph node aspirate, bone marrow, or CSF. Examination of wet peripheral smear of blood stained with Giemsa stain can demonstrate motile parasites. Repeated examination is necessary because parasitemia is intermittent. Using thick smear, microhematocrit ccntri-fugation, anion exchange, or huffy coat preparation can increase the chances of parasite detection. CNS involvement is confirmed by demonstration of the motile trypanosome in the CSF, though it occurs in only 17% of severe cases of sleeping sickness. CSF examination shows lymphocytic pleocytosis and elevated protein, IgM levels, oligoclonal bands, and morular or Mott's cells, which are modified plasma cells containing large eosinophilic inclusions. Although, these cells are not pathognomonic of trypanosomiasis, their presence in large numbers is fairly characteristic of the disease. Nenroimaging with CT scan shows meningeal, choroidal, or parenchymal enhancement, hut is not specific. EEC shows diffuse nonspecific generalized slowing of background activity, especially in the later stages.

The elevation of IgM in both serum and CSF can be used as a screening test in endemic regions. Serological techniques such as indirect hemagglutination and immunofluorescence to detect trypanosomal antigen is reported to be sensitive, but high antigenic variability of these parasites poses a major diagnostic problem. Enzyme-1inked immunosorbent assays and immunofluorescent antibody tests allow detection of antibodies in the CSF. Animal inoculation technique, though sensitive, is time consuming, expensive, and impractical in field conditions. The disease should be differentiated from febrile disorders with lymphadenopathy, headache, sleep disorders, malaria, infectious mononucleosis, arboviral cnccphalitides, leukemia, lymphoma, tuberculosis, syphilis, brucellosis, relapsing fever, toxoplasmosis, and onchocerciasis (Enanga et al. 2002).

Treatment

Before initiating therapy, confirmation of the diagnosis is essential because most of the drugs used fot the treatment of trypanosomiasis are highly toxic. T. *b. gambiense* in the hcmolymphatic stage is treated with intramuscular pentamidine at 3 mg/kg per day for 10 days. For *T. b. rbodesiense* in the hcmolymphatic stage, intravenous suramin in the dose of 20 mg/kg per day with a maximum o[I ;-,m per day is s;iven on days I, 3, , 14. and 21. A suramin test dose of 200-300 mg is essential because a severe idiosyncratic reaction presenting with shock is not uncommon. Suramin is nephrotoxic; hence, it cannot be given to patients with pre-existing renal disease. Prolonged use of suramin results in an axonal sensorimotor neuropathy. Both suramin and pentamidine do not cross the blood-brain barrier and therefore are not effective in the meningocncephalitic stage of the disease.

For meningocncephalitic trypanosomiasis cflornithine (difluromethyl ornithine, DFMO), a polyamine synthetase inhibitor has shown promise but is expensive. A 14-day course of DFMO in the dose 100 mg/kg intravenously every 6 hours for primary meningocncephalitic trypanosomiasis, and a 7-day course for treating relapses are recommended. Because the response of T. *b. gambiense* to DFMO is variable, organic arsenicals continue to be the mainstay in the treatment of Gambian trypanosomiasis {Enanga et al. 2002).

Melarsoprol {an organic arsenical) is given intravenously three to font times per day, 200-500 mg (maximum 3.6 mg/kg) per injection. The treatment is given for 3 days, and 3 such treatment cycles are given with an interval of 7 days in between two cycles. Arsenical encephalopathy is a dreaded complication, occurring in about 15-20% of cases. It is characterized by recurrent seizures, cognitive impaitment, and progressive coma, occurring between the first and fifteenth day of treatment. It is fatal in about 10% of cases. A high CSF pleocytosis and simultaneous use of thiabendazole increase the risk of arsenical encephalopathy. Premedication with corticosteroids, nutritional supplementation for malnourished patients, and prophylactic anticonvulsants are recommended before commencing melarsoprol therapy. MRI may assist ro distinguish arsenical encephalopathy from relapse. Focal bilateral high signal areas in white matter on T2- weigh red MRI indicate recurrence of infection or incomplete treatment [Burchmore et al. 2002).

Continuous surveillance for 2-3 years is essenrial as relapses are common. Relapses are indicated by headache, fever, worsening of neurological signs, seizures, and worsening of CSF profile. Relapses in T. *b, gambiense* are treated with eflornithine and in T. *b. rbodesiense* with melarsoprol. Eradication of infection is achieved in about 90% of cerebral cases. However, sequelae in the form of insomnia, irritability, and poor impulse control may occur.

Prevention

Preventive measures include eradication of the tsetse fly, use of protective clothes, reservoir control, regular medical surveillance, and treatment of early cases in endemic areas.

American Trypanosomiasis

Existing as an acute or chronic disease American trypanosomiasis or Chagas' disease is caused by the hemoflagellate protozoa, *Trypanosoma cruzi.* The disease occurs in Centra! and South America. Chagas' disease causes cardiac and gastrointestinal tract autonomic de-efferentation years aftet primary infection. CNS involvement, though tare, should snidest ctincunvnr I IIV infection.

Chagas' disease is a zoonotic disease, transmitted by reduvid bug of the genus *Triatoma.* The trypanosome inhabits the gut of the bug. The bug bites at night and defecates at the time of biting. The infection is transmitted by rubbing the fecal matter containing the metacyclic stage of the parasite into the tiny skin punctutc, other abrasions of the skin, or by rubbing the eyes or orher mucosal surface with infected fingers. The infection can also be transmitted transplacental^, by blood transfusion, or from organ transplant.

Clinical Features

Acute Chagas' disease, mostly in children, is a flulike illness occurring about 1 week after inoculation with fever, lymphadenitis, malaise, hcpatosplenomegaly, facial edema, tachycardia, and, rarely, meningoencephalitis. The portal of entry may show nodular or ulcerative swelling (chagoma) in about 25% of cases. In 50% of cases the primary site is the outer canthus of the eye, with unilateral palpebral edema and periauricular lymph node enlargement (Romana's sign). Early myocarditis, meningoencephalitis, or reactivated Chagas' disease suggest concurrent I IIV infection. CNS involvement manifests as seizures, tremors, rigidity, paralysis, and altered mentation. Death in the acute stage is caused by acute myocarditis, congestive cardiac failure, or meningoencephalitis.

Chronic Chagas' disease develops years or decades after initial infection with clinical features suggesting involvement of heart, gastrointestinal tract, and nervous systems. Cardiac involvement is commonest in chronic disease with congestive cardiomyopathy, syncopal attacks, and systemic and CNS embolization from mural thrombi of a left ventricular apical aneurysm. Destruction of autonomic ganglion in the heart tcsults in postural hypotension, dizziness, and rhythm disturbance, whereas similar involvement of the gastrointestinal tract results in megacolon and megaesophagus. CNS involvement in chronic Chagas' disease is due to embolization of cerebral vessels from intramural cardiac thrombi or from formation of mass lesions with seizures, hemiparesis, cerebellar ataxia, or other focal deficit.

Transplacental transmission of T, *cruzi* results in congenital Chagas' disease with premature birth and developmental delay in the survivors.

Diagnosis

In the acute stage the diagnosis can be established in about 90% of patients by the presence of parasites in thick or thin smears of peripheral blood or buffy coat during febrile episodes. Aspiration of spleen, liver, lymph nodes, and bone marrow may show the parasites in macrophages. Serological tests include hemagglutination, immunofluorescence and compliment fixation tests, which become positive after about 1 month and remain so for life. Chronic Chagas' disease is diagnosed serologically. False positive serology can occur in syphilis, leishmaniasis, malaria, leprosy, or collagen vascular disease.

Treatment

Treatment for Chagas' disease is unsatisfactory as it only reduces the duration of symptoms and mortality. As soon as infection with T. *cruzi* is suspected, treatment should be started without waiting for laboratory confirmation (Urbma 2001). In acute Chagas' disease, nifurtimox in a dose of 8-10 mg/kg for adults, 12.5-15 mg/kg for adolescents, and 15-20 mg/kg for children {1 to 10 years) is recommended in four divided doses for 90-120 days. Adverse effects include abdominal pain, anorexia, nausea, vomiting, weight loss, and neurological side effects (restlessness, disorientation, insomnia, neuritis, and seizures). Alternatively, benzimidazolc 5 mg/kg per day orally for fit) Jays may be used. Side effects include peripheral neuropathy, granulocytopenia, and rash.

Prevention

Vector control by spraying insecticides, improving housing, and screening of donated blood may check transmission of the parasite. Mosquito nets, insect repellents, and the use of protective clothing provide additional protection. Tourists traveling to endemic areas should avoid sleeping in dilapidated houses. Laboratory workers should wear gloves and eye protection.

Amoebic Infections of the CNS

Protozoan free-living amoebae are widely distributed in nature and are particularly found in moist soils and in warm fresh waters {Marshall et al. 1997). Amoebic infections of the brain are extremely rare, but they have a very high mortality. Two climcopathological syndromes are recognized: "primary amoebic meningoencephalitis"

(PAM) and "granulomatous amoebic encephalitis" (GAE). Amoebae from the genera *Naegleria* cause PAM, and those from the genera *Acanthamoeba* cause GAE. *Naegleria fowleri* exists in three forms: trophozoites, flagellates, and cysts. The trophozoite and flagellate forms are highly motile and transform into cystic form under nutritionally deprived conditions. The parasite excysts when the conditions become favorable through the pores in the cyst wall. The most potent stimulus for the excystment is the presence of molecular carbon dioxide in the environment. *Acanthamoeba* lacks the flagellate stage, and the trophozoites are larger than *Naegleria,* The cysts are stellate and have a small opening at one end from which the excystment occurs. *Leptomyxida,* another free-living amoeba, has been recently identified as a cerebral pathogen, and the genus *Balamuthta mandrillaris* is a rare cause of GAE.

N. *fowleri* has been isolated from puddles, pools, mud, rivers, and sewage disposals. They have also been isolated from air conditioners and thermal effluents from factories. Children acquire PAM as they swim or play in water com miniated h) thes< free living amoebae. I'lie disease has a male:female ratio of 2:f for *Naegleria* and 5:1 for *Acanthamoeba.* PAM is more common in children. Granulomatous amebic meningitis can be seen at any age. *Acanthamoeba* causes GAE in immunocompromised hosts, such as patients with AIDS, those on long-term antibiotics or corticosteroids, or transplant recipients on immunosuppression. CNS invasion is generally through the nasopharynx or respiratory tract. The incubation period of the disease is not known hut is probably long.

Pathogenesis and Pathology

The parasites enter the brain by passing through the cribriform plate along the fila of the olfactory nerve to enter the frontal lobes and cause a necrotizing inflammation with extensive destruction. *Acanthamoeba* can also invade the CNS through this route, through the bloodstream, or through a primary corneal infection acquired by using contact lenses stored in contaminated saline solution. A large number of proteolytic enzymes are produced by the amoebae, which destroy the tissues around the area of invasion (Marciano-Cabral et al. 2000).

The meninges in PAM are hypcremic with diffuse superficial hemorrhages and are ensheathed in purulent basal exudates, most intense around the olfactory bulbs. There is extensive necrotizing destruction of the cerebral parenchyma, more so in frontal and temporal lobes. Histopathology reveals polymorphonuclear inflammatory infiltrate with interspersed trophozoites in and around the subarachnoid space. The inflammatory infiltrate is devoid of cysts and flagellate forms. Extracerebral tissues are usually spared but pulmonary and myocardial infiltration has been reported. GAK is characterized by formation of small necrotic abscesses.

Clinical Features

PAM presents with acute onset of fever, headache, vomiting, and photophobia with altered mentation. In the acute phase, the disease closely resembles acure pyogenic meningitis; however, seizures and focal neurological deficits are more common in PAM. Patients may complain of anosmia or cacosmia as the olfactory bulbs are involved early in rhe course of the disease. Rapid deterioration occurs, as patients do not respond to antibiotics, which are often given for the suspected bacterial meningitis. The common preterminal event is raised intracranial pressure and consequent cerebral herniation.

GAE has a slow and insidious course suggestive of an intracranial space-occupying lesion and, rarely, as insidiously progressive meningoencephalitis. The lesions in GAE are most commonly localized in the posterior fossa. The patients gradually deteriorate and eventually die after two to three weeks. *Acanthamoeba* keratitis has been reported in patients who use soft contact lenses kept in contaminated saline solutions. Rarely the corneal infection spreads intracranially (Marciano-Carbal et al. 2000). *Balamuthia* meningitis affects the cortex more frequently, especially the temporal lobes.

Diagnosis

CSF examination reveals polymorphonuclear leukocytosis, with hypoglycorrhachia, and increased protein, but the Gram's stain and the culture are negative. Rarely, their typical sluglike movements in a wet drop preparation of fresh CSF can identify the actively motile trophozoites. I hi (.SI- picture <>l patients with GA1 *i*--. suggestive oJ granulomatous infection, with moderately raised protein, a near normal or slightly low CSF glucose, lymphocytic CSF pleocytosis, and absence of motile trophozoites.

The majority of patients with PAM has normal CT and MRI scans of the brain. In GAE cerebral lesions resembling spaec-occupyiug lesions are seen (Kidney and Kim 1998). PAM needs to be differentiated from acute bacterial meningitis or brain abscess rupturing into the subarachnoid space. The differential diagnosis of GAE is chronic meningitis of fungal or tuberculous origin, brain abscess, neoplastic lesions, and encephalitis. A similar clinical syndrome may occur in CNS vasculitis, PAM and GAE are so rare and with so high mortality that these ate usually-diagnosed postmortem, unless diagnosed and treated very early.

Treatment

Diagnosis is usually delayed in amoebic CNS infections, and the therapeutic response is poor to available drugs. Many drugs, including amphotericin B, misonidazole, rifampin, trimethoprim, phenothiazines, and ginghousu, have been tried. *Acanthamoeba* is more resistant to

treatment than *Naeglena.* As there are no established guidelines for treatment due to the rarity of the disease, the treatment is individualized. The best response has been observed with a combination of chemothcrapeutic agents, which includes amphotericin B given by intrathecal and intravenous routes, in maximal possible doses.

Cerebral Amoebiasis

Entamoeba histolytica, the commonest intestinal parasite colonizing the large bowel in man, causes local ulceration of the wall of the colon and presents as amoebic dysentery. It is endemic in Southeast Asia, India, and South America. Man is the primary host and gets infected by consuming water and food contaminated with infected feces. The amoebae entet the bloodstream and colonize in distant organs causing metastatic abscesses. Liver is affected in about 10%, resulting in amoebic liver abscess. Cerebral involvement is seen in about 0.1% of all cases. Cerebral abscess is almost always associated with hepatic abscess.

Pathogenesis and Pathology

The abscesses are located at the junction of gray and white matter in the cerebrum or cerebellum. Proteolytic enzymes of the amoebae cause tissue destruction locally with gtanulomatous inflammatory infiltrate. The brain appears edematous, with patchy meningeal exudates. The cut surface reveals a necrotic and hemorrhagic center surrounded by poorly differentiated rim with perifocal edema. The rim consists of dense inflammatory infiltrate comprising of mononuclear cells and RBCs. Amebae or tissue cysts can be identified in the tissue sections (Plate 59D.II).

Clinical Features

The disease affects predominantly young adults, with male: female ratio of 10:1, Clinical features are not specific. Intestinal complaints usually predominate initially. Febrile encephalopathy and focal neurological signs should raise the possibility of this disease. Cerebral abscesses have been reported in patients without clinical amebic colitis. An invasive amoebiasis is usually evident in other organs like **ihr** li\ ;**! ,'nul** Inn;--,, l-'ot.il iii-Lin Mimical sie.ns, lever, lethargy, seizures, and varying degree of altered mental status are common symptoms.

Diagnosis

Isolated cerebral abscesses arc rare. Imaging of liver and brain are helpful. CT scans show single or multiple abscesses especially in frontal lobes or basal ganglia, which appear as low attenuating, ring-enhancing lesions with marked perifocal edema. Tl-weighted MRI shows the abscess as a central hypointensity surrounded by an isointense rim, enhancing on gadolinium. On T2-weighted images they are hypcrintensc with a hypointense rim. Antiamebic antibodies are detected in most cases.

Treatment

Medical therapy consists of metronidazole 1 g, followed by 500 mg 6 hourly intravenously or 750 mg intravenously three times a day for 10 days, followed by iodoquinol 650 mg three times a day for 20 days. In children the dose of metronidazole is 30-50 mg/kg per day in divided doses. Emetine in dosage of I mg/kg per day to a maximum of 60 mg per day can also be used. Chloroquine has also been tiled in do',.t!.v u: iiOO iiisJ, per **day** tor 2 days lol owed by 300 mg per day for 2-3 weeks. The result of medical treatment is universally poor. Combining surgical resection of the abscess with antiamoebic therapy may improve survival (Shah et al. 1994). The results of all forms of treatment are poor, and the mortality is 90%,

Toxoplasmosis

Toxoplasmosis is caused by *Toxoplasma gondii,* an intracellular protozoa first described by Janku in 1923 in the retina of a child. Common manifestations of toxoplasmosis are chorioretinitis and meningoencephalitis. After the pandemic of HIV/AIDS beginning in the 1980s, toxoplasmosis has acquired the dubious distinction of being the commonest cause of cerebral mass lesion in AIDS patients. Cerebral toxoplasmosis in HIV/AIDS is covered in Chapter 59E.

The only definitive hosts for T. *gondii* are domestic cats, which are infected by eating infected rodents, ot oocysts passed in the feces of cats that harbor the parasite in their intestines. The tissue cysts of the patasite in these animals infect the intestinal epithelial cells and develop into merozoites. The sexual cycles starts when some of the merozoites develop into gametocytcs, which fuse and form diploid oocysts, which are excreted in the feces. Under favorable conditions (i.e., warm and humid climate) sporogony occurs in the oocysts. Sporulated oocysts are infective *A\K* if ingested by rodents, cats, or other small animals, they release large numbers of sporozoites in the small ir.iestiiie. Spurn/ones penetrate the gui wall, replicate, and spread hematogenously to most mammalian tissues. Once in a cell, spotozoitcs undergo fission until the host cell ruptures and liberates sporozoites that infect the surrounding cells. Over time, tissue cysts are formed containing a large number of parasites, which arc now called bradyzoites as they divide slowly. The tissue cysts are immunologically inert and remain so for years, failing to elicit an inflammatory response. Reactivation of tissue cysts occuts if cell-mediated immunity wanes as occurs in patients with cancer, organ transplant, chronic corticosteroid use, and AIDS. Most human infections are acquired by ingesting

oocysts contaminating food, hands, or soil or tissue cysts contained in raw or undercooked meat. Transplacental transmission is also common. Rarely, organ transplantation and blood transfusion may the routes of entry of the parasite.

Pathogenesis and Pathology

The toxoplasma gains entry into the host macrophages and occupies a "parasitophorous vacuole." Whereas, activated macrophages destroy the parasite with clearance of parasitemia, resting macrophages allow intracellular replication of patasite. The mechanism by which toxoplasma survive the tissue macrophages is not known. As the disease is mild and not fatal in the immunocompetent host, pathological reports are scanty. The lesions are found in eyes, brain, and other organs. In the brain they are present in both gray and white matter and appear as moth-eaten, necrotic honeycombed areas, infiltrated with inflammatory cells, especially in the perivascular area with pyknotic nuclei. In congenital toxoplasmosis the lesions are most intense in cortex, basal ganglion, and periventricular area (Figure 59D.1). Calcification within the areas of necrosis is common. Hydrocephalus occurs as a result of obstruction of aqueduct of Sylvius or foramen of Monroe by active ependymitis or deposition of necrotic debris in the ventricles. Periventricular and periaqueductal vasculitis and necrosis are almost pathognomonic of congenital toxoplasmosis {Kristennson et al, 2002).

Clinical Features

Primary infection in an immunocompetent host is usually asymptomatic. Acute infection is associated with fever and lymphadenitis in 10-20% of patients, 1-2 weeks after ingestion of cysts. A maculopapular rash similar to infectious mononucleosis occurs in a small number of patients. Rarely, immunocompetent hosts develop disseminated toxoplasmosis with CNS involvement, Meningoencephalitis, seizures, drowsiness, confusion, and coma are often the presenting symptoms. The CSF in CNS toxoplasmosis shows lymphocytic pleocytosis, mildly elevated protein with normal sugar. Acute chorioretinitis may precede or follow CNS toxoplasmosis.

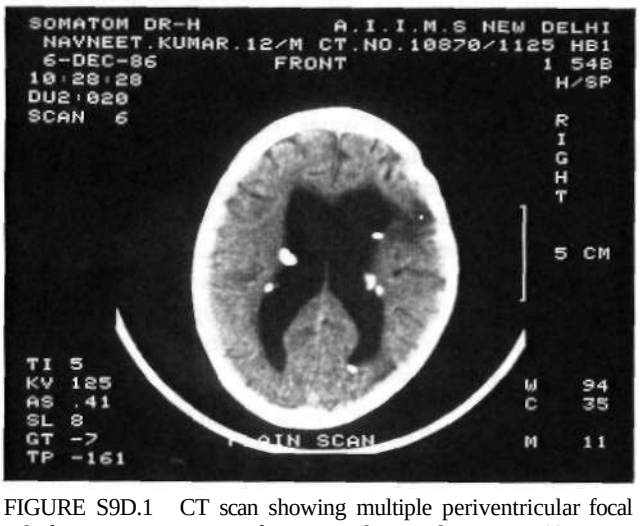

FIGURE S9D.1 CT scan showing multiple periventricular focal calcifications in a case of congenital toxoplasmosis. (Courtesy Dr. S. K. Gaekwad.)

Congenital toxoplasmosis is transmitted transplacentally when a woman acquires *Toxoplasma* infection during pregnancy (Wallon et al. 1999). The infant may be born with bilateral chorioretinitis (blindness and strabismus), CNS involvement (epilepsy, psychomotor retardation, microcephaly, periventricular calcification, hydrocephalus, pituitaty insufficiency), or systemic effects (jaundice, hepatosplcnomegaly, anemia, low birth weight, lymphadenitis, and pneumonitis) (Lowichik and Siegel 1995).

Ocular toxoplasmosis occurs during primary infection, when it is usually unilateral, during congenital infection, when it is usually bilateral, and during reactivation of previous infection in an adult, *'toxoplasma* chorioretinitis usually involves the posterior pole near the macula. Pain in the eye, photophobia, and diminution of vision occur in the acute stage. Focal yellow-white patches of necrotizing retinitis along with retinal edema and exudates give way to darkly pigmented scars after healing. Uveitis, scotoma, defect in central vision, photophobia, glaucoma, cataract, microphthalmia, and strabismus may be associated. Papilledema may occur due to CNS involvement.

Diagnosis

Serodiagnostic tests for toxoplasmosis are available. Antitoxoplasma IgG antibody detection done by Sabin-Fieldman dye test is useful in *Toxoplasma* encephalitis up to 8 weeks as the titers decline slowly after that. Titers above 1:1024 are indicative of acute infection. The test is 93% sensitive but lacks specificity. IgM antibody detection by double sandwich enzyme linked immunosorbent assay (EL1SA) is sensitive and indicates infection in the p.iM 2 .; months. Acute congenital toxoplasmosis is diagnosed by finding high or rising IgG titers or positive IgM titers. Negative IgG in an immunocompetent host with chorioretinitis almost excludes toxoplasmosis. CSF examination in a patient with encephalitis shows monocytic pleocytosis, raised protein and DNA sequences of *T. gondii,* which can be detected by PCR (Montoya 2002). Plain x-rays of skull may show characteristic spotty intracranial calcifications, which are localized in the periventricular area on CT scan (sec Figure 59D.1). In acute stage *Toxoplasma* abscesses are seen as multiple round, nodular, or ring-enhancing lesions with intense edema in the immunocompetent hosts. MRI is mote sensitive (than CT) in detecting these lesions. Differential diagnoses of such lesions on neutoimaging arc tuberculomas, lymphoma, metastases, and pyogenic

abscesses (Kornbluth and Destian 2000). Tissue diagnosis by biopsy of the intracranial lesion is the gold standard but is seldom indicated. It is indicated only if the condition worsens after initiation of therapy, if there is a solitary, large lesion on MR I, or if a patient develops these lesions while on prophylaxis of *Pneumocystis carinii* pneumonia. Differential diagnosis of neonatal toxoplasmosis includes human cytomegalovirus, herpes, rubella, and syphilis or *Escherichia colt* meningitis, sepsis, and erythroblastosis fetalis.

Treatment

A combination of pyrimethamine (a dihydrofolate reductase inhibitor) in a loading dose of 200 mg followed by 50-75 mg per day (or 1 mg/kg per day up to maximum of 100 mg per day) in three divided doses and sulfadiazine (a dihydrofolate synthetase inhibitor) 4-6 g per day (or 100 mg/kg per day, up to maximum 8 g per day) for 3–4 weeks is recommended. Immunocompromised hosts require lifelong prophylaxis. Supplement of folinic acid (10 mg per day) prevents hematological complications. The drug is effective against tachyzoir.es (in active macrophages) but ineffective on the cystic stage. Alternatively, clindamycin 600 mg orally or parenteral ly every *6* hours is recommended. It has poor CSF penetration, and side effects include neutropenia, rash, pseudomembranous enterocolitis, myositis, and elevated CK levels. Another drug atovaquone, a hydroxynephthaquinone derivative, in doses of 750 mg four times a day has shown promise. Patients that cannot tolerate standard therapy may be treated with azithromycin, roxithromycin, or clarithromycin (Derouin, 2001).

Immunologically competent adults and children with only h mphadenopathy do noi require specific Lhcrapv unless the symptoms are severe. Ocular toxoplasmosis should be treated with pyrimethamine plus either sulfonamide or clindamycin for 1 month. Congenital toxoplasmosis is treated with pyrimethamine (0.5-1 mg/kg) and sulfadiazine (100 mg/kg) orally for 1 year. Additionally, spiramycin (100 mg/kg) plus prednisolone (1 mg/kg per day) has shown good results. The choice of antiparasitic agent for its safety and efficacy profile for congenital toxoplasmosis remains unsettled.

Prevention

Prevention requires clean habits while handling pet cats and dogs. Stray dogs and cats should be avoided, and meat should be properly cooked and stored at -20°C. Immunocompromised hosts, especially those with AIDS, require lifelong prophylaxis with 25-50 mg pyrimerhamine and 1-2 grams of sulfadiazine per day after recovery from toxoplasmic encephalitis. Patients intolerant to sulfadiazine should receive clindamycin 1200 mg per day in three divided doses.

HELMINTHIC INFECTIONS OF THE CNS

Twenty different species of the helminths affect the CNS in man. Of these, cystieereosis and echinococcosis arc by far the commonest.

CESTODES

Cystieereosis

Cystieereosis is invasion of tissues by the larval stage of pork tapeworm, *Taenia solium.* Neurocysticercosis (NCC) by larvae is an important public health problem particularly in developing countries. NCC has worldwide distribution and is endemic in Latin America, the Indian subcontinent, China, and most of the African and Asian countries. It is absent in Israel and certain Asian countries in which pig rearing is unacceptable for religious reasons. In the United States and European countries, NCC is becoming more common due to infected immigrants. Seroprevalcnce in villages of Mexico, Guatemala, Bolivia, Peru, and Ecuador is between 4.9-24%. In India it is between 2-3% in the general population. The high incidence of epilepsy in Latin America is attributed to rampant NCC. According to the Commission on Tropical Diseases of International League Against Epilepsy, age-adjusted prevalence of epilepsy in tropical countries is 10-15 per 1000 population and is largely due to NCC. Seizures in people above 25 years of age in endemic areas are due to NCC in 50-70% of cases. Globally, it causes about 50,000 deaths annually. In India 40% of focal seizures arc due to NCC, calcified NCC and granuloma, or single-enhancing CT lesion consistent with cysticercal granuloma (Padma et al. 1994; Pal et al. 2000).

The disease is most common where there is close contact with pigs and where poor sanitation and personal hygiene exist. Man, the definitive host, harbors the adult tapeworm in the intestines. Gravid proglomds containing highly infective fertile eggs are shed in the feces. NCC is acquired iIn ongh the feco-oral route by consuming contaminated food (raw vegetables or water) or even through infected fingers of self or food handlers. On the other hand, tapeworms are acquired by eating raw or undercooked infected pork. After ingestion, the eggs hatch into invasive larvae, which penetrate the gut wall and lodge in various tissues, including brain, muscles, subcutaneous tissue, liver, eyes, and spinal cord, through hematogenous spread. In tissues they mature into the larval form, the cysticercus, with an invaginated scolex.

Pathogenesis and Pathology

By necessity the survival of cysticerci in pigs depends on absence of significant inflammatory response on the part of the host. Cysticerci appear as ihir.-wnLed oval cysts, aboui

1 cm m diameter, with an in vagina ted scolex, which appears as a white nodule, attached to one side of the cyst, The cyst wall consists of an outer smooth white eosinophilic layer, an inner cellular layer, and an innermost layer of loose connective tissue (Plate 59D.IH). The parasite escapes the host's immune surveillance mechanisms by secreting a serine protease inhibitor called teniastatin, which inhibits complement activation, lymphocytic migration, and cytokine formation. The presence of cysts is not always associated with symptoms. Approximately 3-8% of individuals dying of other causes show viable cysticerci in their brains on autopsy in endemic areas. It is only when the cysticerci undergo degeneration that the inflammatory response starts and symptoms like seizures occur. This is especially true for patients with single-enhancing CT lesions. On the other hand, when the infection load is high, patients present with features of raised intracranial pressure and deteriorating mental status.

Different stages of natural evolution of cysticerci are described. Viable cysts have minimal associated inflammatory response (vesicular stage). Inflammation, especially by the mononuclear cells around the cyst, results in the colloidal stage, which i^ followed bj gradual replacement by fibrotic tissue and collapse of cyst wall (granular nodular stage). Finally, replacement by fibrotic tissue and mineralization of the parasite results in the calcific stage. Whereas, parenchymal cysts are small (about 1 cm diameter) in the enrticosuhorned area, larger IMI,I|\I-renchymal cysts may be present in the ventricles or the Mili;ir:u-hiioid space, ['.irenchvinal cysts are generally associated with seizures, raised intracranial pressure, and deteriorating mental status. When parasite load is high, inflammation around the cysts gives rise ro a fulminant meningoencephalitis picture. Subarachnoid cysts generally attain large size with lobulations (grapelike appearance, the racemose variety), lose the scolices, and are usually seen at the base of brain or Sylvian fissure. Intraventricular *NCC.* results in persistent or intermittent raised intracranial pressure due to blockage of aqueduct of Sylvius or foramina of Lushka and Magendie. Inflammation of these cysts results in cpendymitis and arachnoiditis with resultant meningitis, communicating hydrocephalus, or vasculitis with stroke.

Clinical Features

The clinical symptoms occur 1-35 years after exposure and several years after CNS infestation by cysticerci. NCC has protean clinical manifestations depending on number, site, stage, duration of the cysts, and whether inflammatory response is present or not. Seizures, both generalized and partial, are the commonest symptoms, occurring in about 92% of patients with parenchymal NCX; in the active (colloidal and nodular-granular) and inactive (calcific) stages. The acute encephalitic form, common in children, is associated with rapid deterioration in neuropsychological status, recurrent seizures, intracranial hypertension, and coma. This form of presentation is usually seen in patients with high infection load with inflammatory response. Focal neurological signs, such as hemiplegia and cerebellar ataxia, usually occur following the inflammatory reaction (meningoencephalitis), vasculitis, and stroke due to NCC in the subarachnoid space. NCC is a common cause of stroke in young patients in Latin American countries. The infarcts may be small (lacunar) or large involving middle cerebral artery. The clinical picture of raised intracranial pressure with headache, vomiting, cognitive dysfunction, neuropsy-**JualriL. deeiine. j:kl papilledema** liiairs **with** multiple parenchymal NCC, with or without acute meningoencephalitis, with intraventricular cysts causing obstructive hydrocephalus, or with subarachnoid cysts causing severe meningitis and CSF outflow obstruction. Patients harboring cysts in the brainstem present with corresponding focal neurological deficit. Involvement of spinal cord is associated with compressive myelopathy. Downward migration of subarachnoid cyst from the posterior fossa may cause extramedullary compression, whereas intramedullary cysticercosis occurs from hematogenous spread. Root pain occurs in about 1-5% of patients. Ocular cysts occur in about 1 % of cases with retro-orbital pain similar to migraine, proptosis, ptosis, and diplopia. Retinal, vitreous, or subconjunctival cysts present with visual loss, scotoma, floaters, orbital abscess, and panophthalmitis, which occur spontaneously or after initiating specific cysticidal therapy. Patients with cysticerci in muscles can present with painful muscular hypertrophy and weakness, especially of the proximal group of muscles. Subcutaneous nodules may provide a clue to the etiology of epilepsy {Figure 59D.2A).

Diagnosis

In endemic areas, diagnosis of NCC should be considered in almost all cases with neurological or psychiatric complaints. Presence of nodules in subcutaneous or subconjunctival tissue helps in the diagnosis. Definite diagnosis depends on demonstration of latval forms of T. *solium.* Del Bruno et al, have proposed diagnostic criteria of NCC based on clinical, neuroimaging, serological, histopathological, and epidemiological criteria. Absolute criteria include histopathological demonstration of parasite in brain or spinal cord lesion, neuroimaging consistent with NCC (cystic lesion showing scolex), or direct visualization of subretinal parasite by funduscopy. Major criteria include neuroimaging highly suggestive of NCC (cystic lesion without scolex, enhancing lesion, or typical parenchymal brain calcification), resolution of intracranial cystic lesions after cysticidal therapy, or spontaneous resolution of small, single-enhancing lesion. Minor criteria include lesions compatible with NCC on neuroimaging (hydrocephalus, abnormal leptomeningeal enhancement, myelogram showing multiple filling defect in the column of contrast medium), clinical manifestations suggestive of NCC,

positive CSF ELISA for detection of anticysticercal antibodies or cysticercal antigens, and cysticercosis outside CNS (histological diagnosis of subcutaneous or muscle nodule, x-ray films showing "cigar-shaped" soft tissue calcification, direct visualization of cysticerci in the anterior chamber of eye). Epidemiological criteria are evidence of household contact with T. *solium* infection, individuals living in or coming from endemic area, and history of frequent travel to disease-endemic area. The presence of one absolute criterion or two major, one minor, and one epidemiological criterion is required for definitive diagnosis. On the other hand, one major plus two minor, one major plus one minor plus one epidemiological or three minor plus one epidemiological criteria constitute probable diagnosis (Carpio et al. 1994; Del Brutto et al. 2001).

Among the serological tests, more widely used ELISA shows 50% sensitivity and 65% specificity in CSF. More recently, enzyme-linked immuno-electrotransfer blot (F.ITB) assay has been shown to be 98% sensitive and *\00%* specific. This test is, however, positive in only 28% with single-enhancing lesion. Patients with calcified lesions and single-enhancing CT lesions are often serologically negative. A monoclonal antibody-based antigen detection assay is highly specific for viable and degenerating cysticerci (Sako et al. 2001).

Plain radiography of soft tissue may show classical cigar-shaped calcifications (Figure 59D.2B). NcLiroimaging with CT scan is more sensitive in detecting calcified lesions. When there are numerous calcified lesions, it gives the appearance of "starry night" (Figure 59D.2C). Vesicular

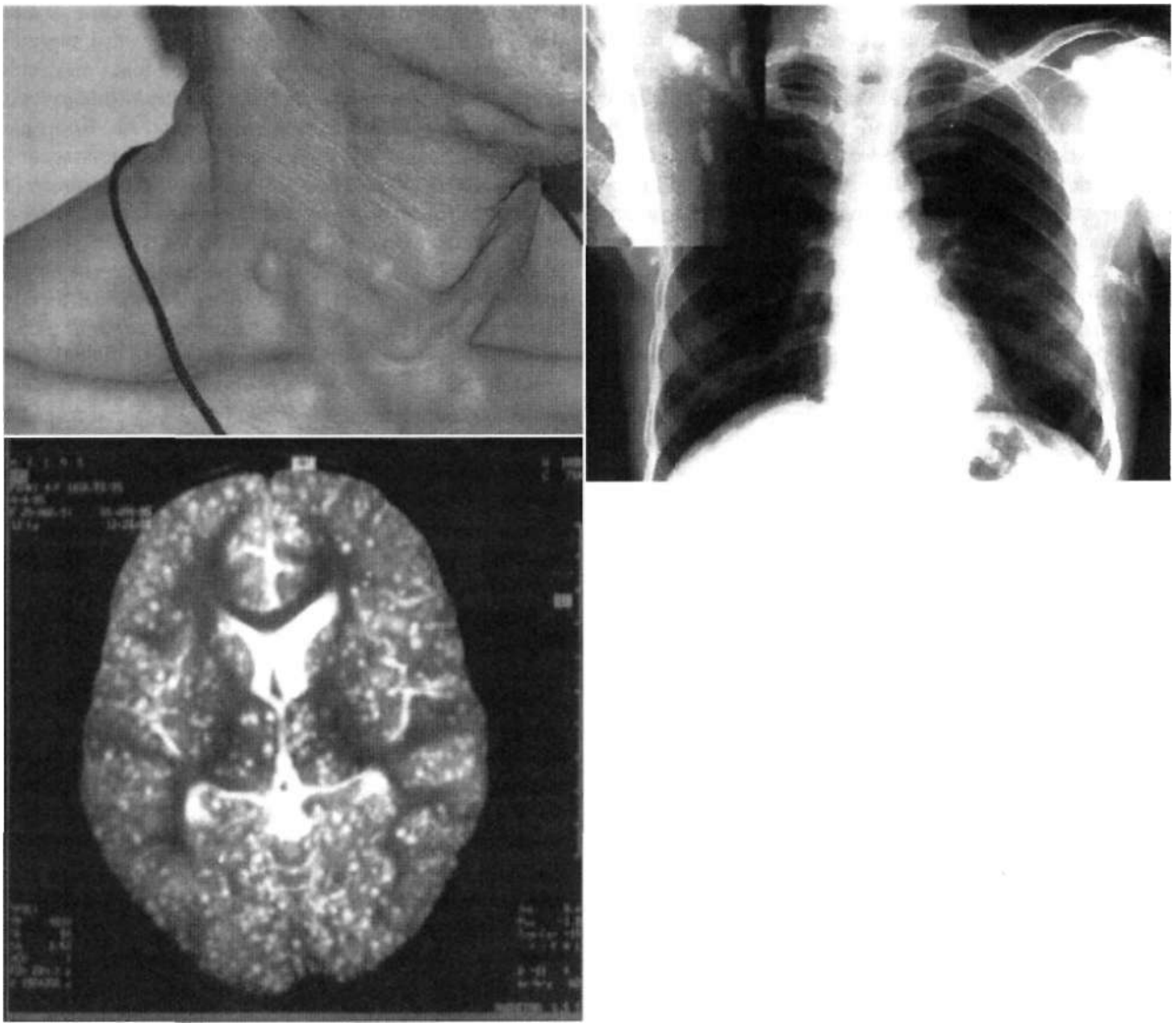

FIGURE 59D.2 Patients with neuroeysticereosis and seizures presenting with multiple subcutaneous nodules (A) and asymptomatic cigar-shaped calcifications in soft tissue (B), and CT brain showing innumerable cystieerci (starry-night appearance, C). (Courtesy Dr. S. K. Gaekwad.)

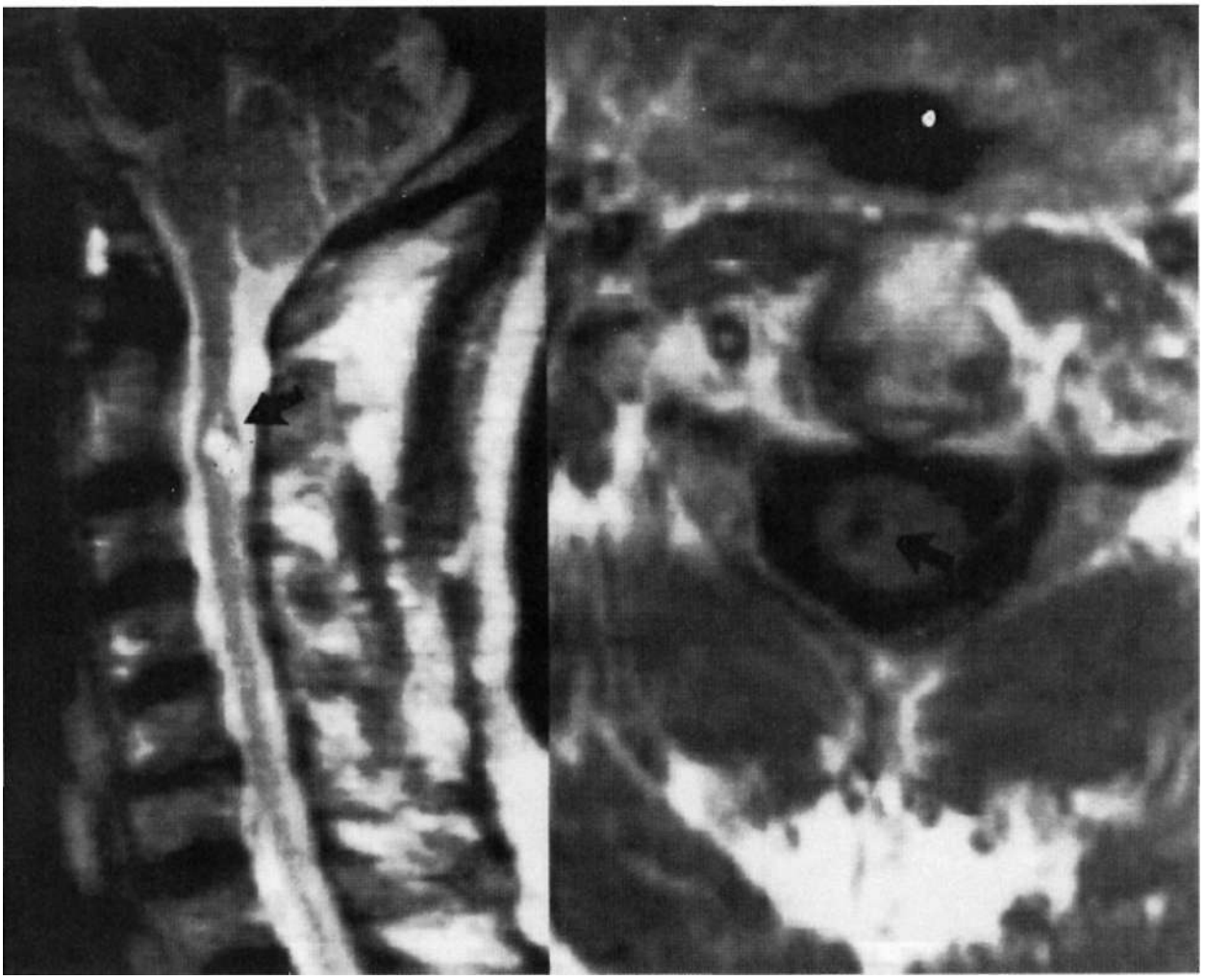

FIGURE 59D.3 MRI scans in cases with neurocysticercosis showing cysricercus cysts in the cervical spinal cord (A, *arrow)* midbrain (B), cerebellum (C), and intraconal compartment of the right orbit (D). (Courtesy Dr. S. K. Gaekwad.)

cysts appear as hypointense lesions with an eccentric intramural nodule representing the scolex in MRI scan. In the colloidal stage the cysts show ring enhancement with edema, whereas in the granular-nodular stage they show disc-enhancing lesion with perilesional edema (Figure 59D.3). The racemose form of the neurocysticerci appears as bunch of grapes in the MRI.

CSF examination is usually nonspecific and shows mononuclear, lymphocytic, or eosinophilic pleocyrosis and positive cysticercal antibody titers. Differential diagnosis includes tuberculosis, echinococcosis, paragonimiasis, sparganosis {Kudesia et al. 1998), cryptococcosis, and cysiic .istnicyloin.i for parenchymal N((and ixhinocoe cosis, coenurosis, CNS tumors, epidermoids, and arachnoid and colloid cysts for extra-axial cysts.

Treatment

NCC is treated with antiparasitic drugs along with symptomatic therapy. Patients with inactive parenchymal NCC with evidence of calcified lesions or degenerating parasites on neuroimaging do not require antiparasitic treatment. As seizures are common symptoms in these patients, chronic anticonvulsant therapy is required. Patients with inactive disease and hydrocephalus due to prior subarachnoid or ventricular infection also do not require antiparasitic treatment, but vcntriculoperitoneal shunt may be required. Shunt failure is uncommon in this group.

Patients with active parenchymal disease are treated with albendazole, a benzimidazole anthelminthic agent, or praziquantel (Garcia et al, 2002). Albendazole is preferred because it is cheaper, has better penetration into subarachnoid cysts, and is unlikely to have pharmacological interference with corticosteroids and other anticonvulsant agents (Salinas et al. 2000). The dose of albendazole is 15 mg/kg per day divided in two oral doses for 8 to 28 days along with dexamethasone. Recent reports of treatment with praziquantel in three oral doses of 25 mg/kg separated by 2 hours, followed 5 hours later by dexamethasone 10 mg

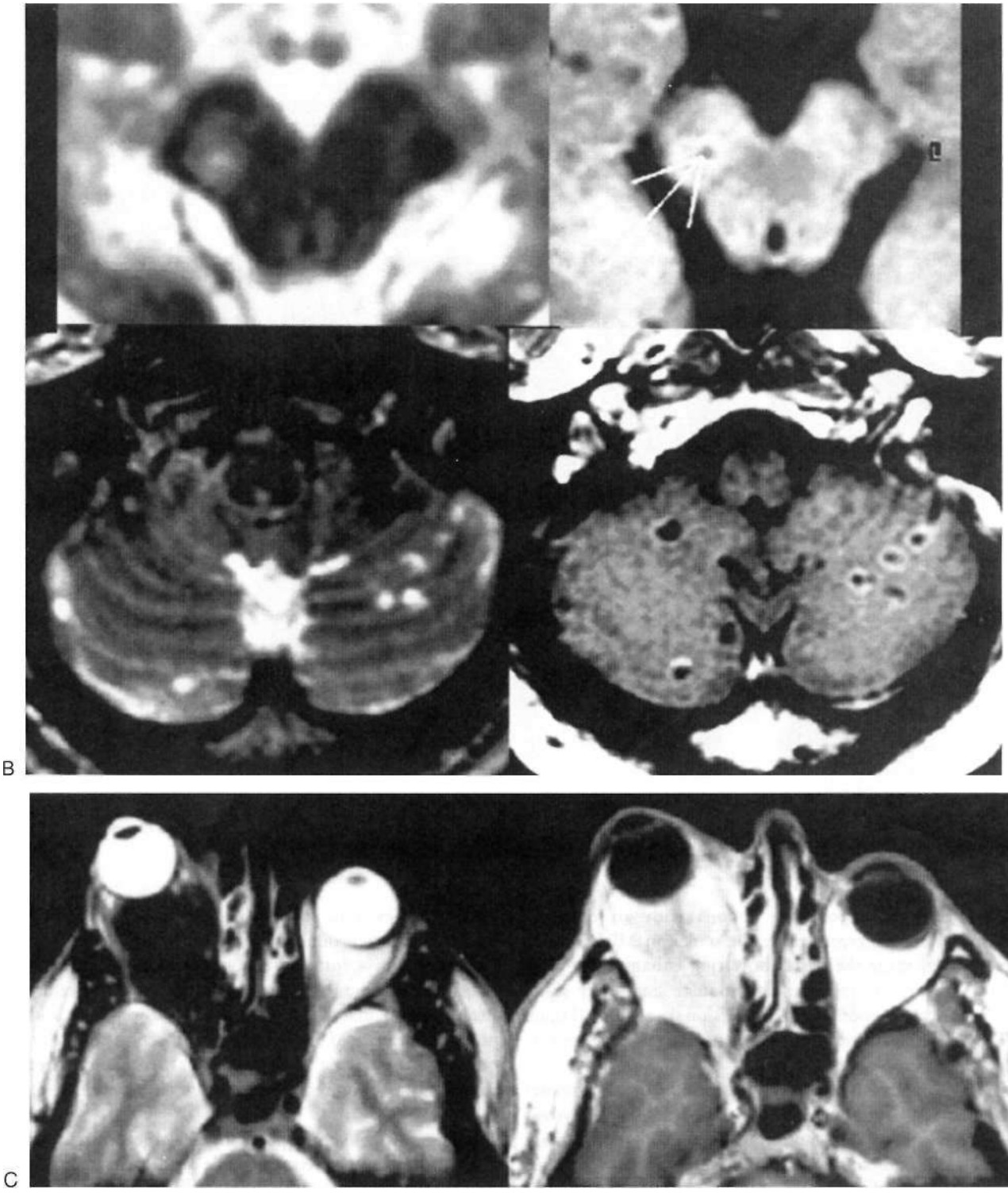

FIGURE 59D.3, cont'd.

intramuscularly, then 10 mg intramuscularly on next 2 days, has also shown good results. Administration of dexamethasone a few hours after praziquantel allows uptake of the drug hy the cyst. Earlier, praziquantel was given otally in doses of 50 mg/kg per day in three divided doses for 14 days. Adverse effects of antiparasitic drugs are worsening of neurological status (headache, vomiting, di/.ziness, seizures, coma, and increased ICP) and are believed to be due to host inflammatory response to dying parasites. Many cysts resolve spontaneously over

time. There is no consensus regarding treatment of active extraparenchymal NCC. Until recently, surgical removal of intraventricular NCC was done with or without ventriculoperitoncal shunt. Ventriculopcritoneal shunt in this group is complicated with frequent shunt failures. Neuroendoscopic removal of intraventricular NCC as an alternative method is less invasive. In patients with single-ring-enhancing CT lesions presenting with epilepsy, treatment with anticonvulsant drugs alone is advocated as most of these resolve spontaneously. Treating them with anthelmintic agents does not improve the resolution of these lesions.

Prevention

Improving sanitation, elimination of intestinal tapeworms, improving sewage disposal system, surveillance of pork farming, preventing pigs from entering human dwellings, and eating properly cooked clean vegetables and pork are some of the methods to prevent the occurrence of NCC.

Echinococcosis

Hydatid disease is caused by the cestode of genus *Echinococcus,* found in the intestines of canines. The disease is common in people who live in close contact with dogs and cats. The highest incidence of echinococcal disease is seen in Greece, Lebanon, and Turkey. It is also reported from Australia, South Africa, East Africa, Canada, North America, Asia, and parts of Russia. The larval cysts of the parasite, the metacestodes, cause the hydatid disease in the intermediate hosts. Common sites are liver (.50-70%), lungs (20-30%), bones, heart, and the spleen. CNS involvement is seen in less than 2% of cases and involves brain parenchyma and intraventricular and subarachnoid spaces.

Human hydatidosis can be caused by four different species, causing different types of cysts. E. *granulosus* infection is the commonest, and it causes simple hydatid cyst. Dogs, cats, and other canines are the definitive hosts. The eggs, containing the *Echinococcus* larvae, are excreted in the feces of the host, which are accidentally ingested by the intermediate hosts (humans). The larvae penetrate the intestinal wall and are spread hematogenous I y to liver, brain and other sites where they develop into the hydatid cysts.

Clinical features

The latent period is 2-20 years. Involvement of liver and lungs causes abdominal pain, hepatosplenomegaly, or cough. Rupture of cyst causes an acute abdomen syndrome, dyspnea, hemoptysis, or hypersensitivity reaction (60-70%). In the brain, cysts grow at a rate of about 1 cm per year. Patients with CNS cysts generally present with focal neurological deficits, seizures, or signs of raised KT. T:ic rupture of the cysts can cause an acute allergic response (Khalidi et al. 2000). Rarely, involvement of basal ganglia, cerebellum, cavernous sinus, and intrasellar and intra-orbital spaces can be seen. Other sites of involvement are intraventricular, subdural, or spinal canal. Cord compression also occurs due to vertebral collapse caused by hydatid bone disease (hydatid Pott's disease).

Diagnosis

The first clue to the diagnosis comes from plain x-ray abdomen showing a calcified lesion or peripheral or CSF eosmophilia. X-ray of the skull is normal, or it shows evidence of bone erosion due to a large cyst. Neuroimaging with CT and MRI reveals a large spherical, smooth cystic lesion filled with fluid of CSF intensity with ventricular distortion and midline shift (Figure 59D.4). The cyst wall is isodense or hyperdense to the brain tissue and does not show contrast enhancement unless ruptured or infected. On MRI, the cyst appears hypointense on Tl-wcighted images with a slightly byperintense rim. On T2-weighted images the cyst wall appears hypointense and the fluid hyperintense. Daughter cysts usually accompany the main cyst (Kornbluth ct al. 2000). E, *granulosus* gives rise to single solitary cyst, whereas *E. multilocularis* is associated with multichambered complex cysts. The Casoni's test is now obsolete, hut the serological tests such as hemagglutination test and ELISA using arc-5 antigen of the parasite are more sensitive.

Treatment

The treatment of choice is surgical resection of the cyst. During the resection, care must be taken to not to spill the contents of the cyst because this causes anaphylaxis and the formation of innumerable daughter cysts in the surrounding tissues. Intracystic instillation of 20% saline, formalin, cetrimide or silver nitrate, and topical applications of 20% saline or silver nitrate to the surrounding tissues avoid this complication. The size of the cyst can he shrunk hy prctrearment with albendazole (1.5 mg/kg per day for 40 days) or mebendazole (50 mg/kg) for 3 months. In those patients where only partial resection of the cyst is possible, lifelong treatment is required.

NEMATODES

Angiostrongyliasis

Angiostrongylus, or the rat lung worm, can cause eosinophilic inciungiris or meningoencephalitis in humans. The parasite is widespread in distribution and has been reported from practically every part of the world including Asia, the Pacific region, Africa, and the Caribbean.

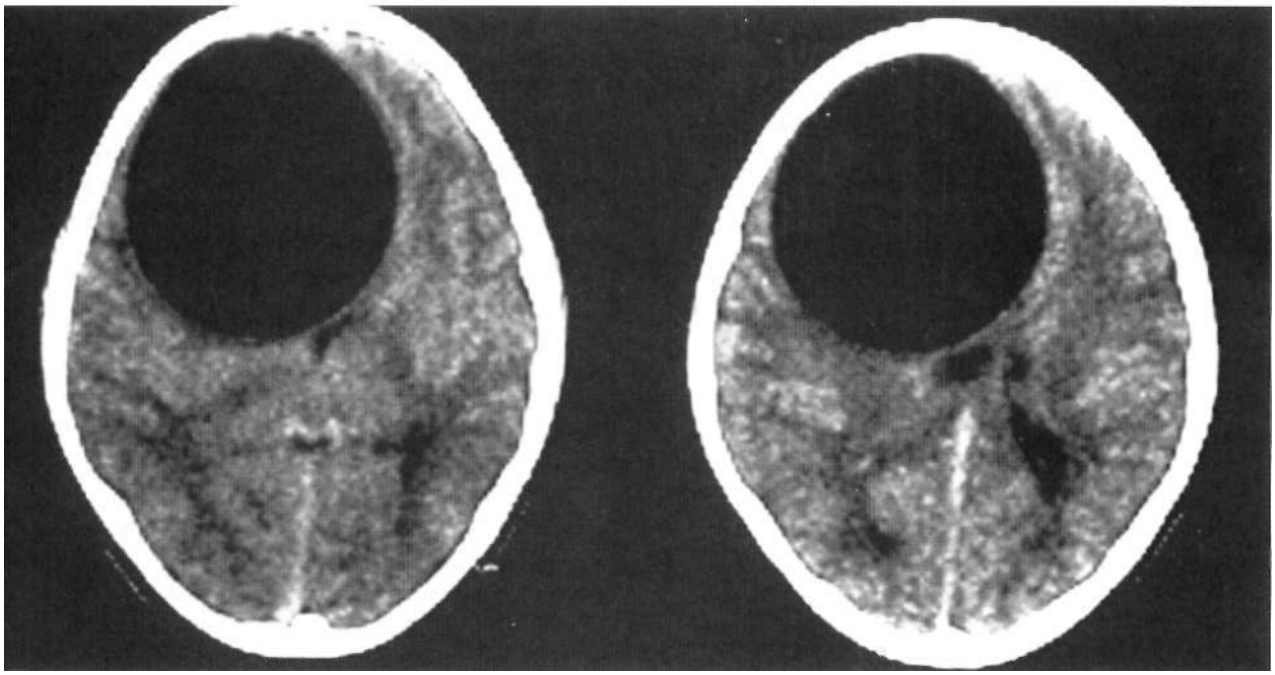

FIGURE 59D.4 CT scan in a patient with raised intracranial pressure and epilepsy showing large well-defined hypodense mass in right frontal lobe (Hydatid cyst). (Courtesy Dr. S. K. Gaekwad.)

Transmission and Pathogenesis

Rats arc the definitive hosts for the parasite *Angiostrongyius cantonensis,* and the parasite is present in their pulmonary circulation. The intermediate hosts are freshwater snails including grand African snail *(Achatina julica),* prawns, and crabs. Humans become infected if they consume molluscs containing the third-stage larvae. Once the larvae gain entry into the human brain, spinal cord, meninges, eyes, and other tissues, the parasites die and result in eosinophilic meningitis. The leptomeninges are more intensely affected with dense eosinophilic infiltrates along with mononuclear cells and neutrophils.

Clinical Features

The latent period is 1-36 days. Severe headache, neck rigidity, varying degrees of altered mentation with vomiting, papilledema, optic neuritis, cranial nerve deficits, brisk reflexes, and seizures are common clinical features, Paresthesia, impaired vision, and generalized weakness are other common symptoms.

Diagnosis

Hie (ST ;s liclptul ir. ;li.i;',i!i-.-,is ami roi'.tls r.ux'il IC l\ pleocytosis between 150-2000/uL with predominantly eosinophilic leucocytosis, raised protein, and near-normal sugar levels. Rarely, larvae can be seen on CSF examination. Ncuroimaging findings on MR images include prominence of Virchow-Robin spaces,'Subcortical enhancing lesions, and abnormally high T2 signal lesions in the periventricular regions.

Treatment

Treatment is generally supportive and analgesic and anti-inflammatory drugs are used. Corticosteroids have no significant role. Larvicidal drugs are generally avoided because they exaggerate CNS symptoms (Chotmongkol and Sawanyawisuth 2002).

Gnathostomiasis

Gnathostomiasis (Yangtze river edema, Shanghai's rheumatism, nodular eosinophilic panniculitis, consular disease, woodhury bug) is caused by *Gnathostoma spinigerum,* a nematode found in the gul oi dogs and cats, li usual!) causes cutaneous larva migrans and orbital masses, hut rarely, CNS involvement in the form of eosinophilic meningitis and radiculomyelopathy can occur (Lo Re and Gluckman 2002). Larva migrans refers to a condition of protracted migration of larvae in tissues. The disease is common in Southeast Asia, Japan, Thailand, and Israel.

Dogs and cats are the primary hosts, and freshwater fish and cyclops arc the intermediate hosts. The eggs passed in the feces contaminate fresh water whete cyclops and other aquatic animals ingest them. Consuming an undercooked intermediate host infects humans. The larvae migrate actively through various tissues producing symptoms.

Clinical Features

Patients present with firm, red, itchy subcutaneous nodules or urticarial rash, fever, and eosinophilia about 3 weeks after exposure. At times the parasite pierces the skin and appears externally on the skin surface where it can be removed for diagnosis and treatment. CNS involvement is the most serious complication and presents with meningoencephalitis, headache, cranial nerve palsy, depressed consciousness, subarachnoid and intracerebral hemorrhage, focal neurological deficits, and spinal cord involvement. Painful myeloradiculopathy with segmental pain and paraparesis is one of the most characteristic presentations. The CNS involvement may occur in isolation without concomitant skin involvement. Eosinophilic meningitis occurring in gnatbostomiasis has a more serious course than that caused by *Angiostrongylus,* Orbital involvement results in uveitis, retinal hemorrhage, and detachment.

Diagnosis

The diagnosis is based on the typical clinical picture, CSF findings, and history of exposure. CSF is hemorrhagic or xanthochromic with eosinophilic pleocytosis. CT and V1RI reveal ring or disc-enhancing lesions and evidence of intracerebral or subarachnoid hemorrhage. Serological tests are unreliable. Hemorrhagic CSF, painful radiculomyelopatby, and diffuse neurological involvement help differentiation from angiostrongyliasis.

Treatment

The treatment is symptomatic with analgesics forming the mainstay of treatment. Albendazole in doses of 400-800 mg per day for 21 days has been tried with variable results. Recently ivermectin is used in single dose as an effective alternative. Systemic corticosteroids can be given in severe cases. The prognosis is not good, and mortality is between 8-25%. About one third are left with permanent neurological deficits. Surgical removal of the worm is possible if it migrates to accessible locations.

Trichinosis

Trichinosis or trichinellosis is caused by the nematode *Tricbinella spiralis.* Other species known to cause the disease are T. *nativa* (of Arctic bears) and T. *nelson* (of scavengers of Africa). Trichinosis is seen all over the world except Australia. *Tricbinella* cysts have been found in Egyptian mummies from 1200 BC.

The adult worm is an intestinal inhabitant, but the larvae localize in the skeletal muscles eliciting an eosinophilic inflammatory response, and they transform there into cysts. Eating undercooked pork (T. *spiralis),* bear, or walrus in Arctic regions and "bush meat" in the tropics causes trichinosis. CNS involvement results in intense inflammatory reaction by the parasite. The meninges in the fatal cases are intensely hyperemic with dense eosinophilic infiltrate in the perivascular regions. The CSF remains free of significant inflammatory response. Inflammation of the vessels causes endarteritis and infarctions or hemorrhages in the involved regions of brain.

Clinical Features

Gastrointestinal symptoms with fever are the first symptoms occurring 1-2 days after ingestion of infected pork. Dissemination of the larvae by the hematogenous route causes fever, muscle pain, conjunctival chemosis, periorbital edema, subconjunctival hemorrhage, and eosinophilia about 5 days after infection. Localization of larvae in muscles leads to pain, swelling, and weakness of extraocular, neck, diaphragmatic, intercostal, limb, and paraspinal muscles. The larvae can invade heart, lungs, brain, and meninges. Involvement of brain occurs in about 10% of patients with eosinophilic meningitis, meningoencephalitis, seizures, delirium, coma, brain infarction, hemorrhage, and venous thrombosis. Peripheral neuropathy, necrotizing arteritis with mononeuritis multiplex are reported in less severe cases. Death is rare and occurs due to respiratory failure or massive involvement of myocardium with cardiac failure.

Diagnosis

In the appropriate clinical setting, eosinophilia, raised muscle enzymes, and raised serum IgG levels clinch the diagnosis. Muscle biopsy is diagnostic, and a fresh muscle sample can reveal the larvae. Serological tests are available. The differential diagnosis includes inflammatory myopathies, eosinophilic myalgia syndrome, and systemic vasculitis.

Treatment

Oral mebendazole 20 mg/kg given in 6 hourly doses is the treatment for the intestinal nematode, which also prevents the larval stage. The efficacy of this drug against tissue invasive form is not established. The allergic symptoms secondary to tissue invasion can be managed by corticosteroids, analgesics, and antipyretics.

Strongyloidiasis

S. stercoralis is a free-living nematode found in warm and moist climates all over the world. Adult worms are passed in human feces and are found in soil where they lay eggs, which hatch to liberate rhabditiform larvae. In the indirect cycle, the rhabditiform larvae, under favorable conditions,

transform into infective filiform larvae, pierce the skin of the host, and gain access to lungs by the hematogenous route. Adult worms develop in the lungs, travel to the trachea from where they make their way into the gastrointestinal tract. Occasionally rhabditiform larvae transform into infective filiform larvae and gain entry into the systemic circulation. The parasite lodges in the lungs, lymph nodes, spleen, muscle, heart, and brain. J ligh-risk individuals are (1) residents and immigrants from countries where strongyloidiasis is common, (2) residents of the Appalachian region of the United States, and (3) institutionalized individuals. The parasite has capacity of multiplying in the host, especially by an auto infection cycle. This is called hypcrinfection,

Clinical Features

Gastrointestinal symptoms include epigastric pain, tender-ness, anorexia, nausea, vomiting, diarrhea, and malab-sorption. Lungs are affected in the migratory phase and result in bronchospasm, cough, and hemoptysis. Inflammatory reaction at the site of skin penetration causes cutaneous larva migrans. Gram-negative septicemia and disseminated strongyloidiasis arc serious manifesta-tions. CNS involvement is in the form of polybacterial pyogenic meningitis and meningoencephalitis caused by gram-negative enteric bacteria, which ensheathe the sur-face of the parasite during its transit from the gastro-intestinal tract. The commonest organisms involved in these cases are *Klebsiella, E. colt,* and *Serratia.* Other manifestations arc eosinophilic meningitis, encephalitis, vasculitis, and infarcts. The worms are identified in the CSF only on rare occasions.

Diagnosis

The disease is difficult to diagnose antemortem but should be suspected in immunocompromised individuals wirh features of sudden febrile encephalopathy or frank poly microbial meningitis. Rarely, patients have eosinophilic meningitis. The CSF shows polymorphonuclear or eosino-philic pleocytosis with hypoglycorrhachia and raised protein. Diagnosis is based on finding adult worm, larvae, or eggs in stool.

Treatment

If diagnosed in time, treatment for immunocompetent host is with albendazole 400 mg once or twice daily for three days, ivermectin in a single dose of 200 mg/kg or thiabendazole 25 mg/kg twice a day for 3 days. Bacterial meningitis and septicemia associated with the disease should be managed with appropriate antibiotics. In the immunocompromised host treatment with thiabendazole 50 mg/kg twice a day for 2-4 weeks is recommended (Zaha et al. 2000).

Toxocariasis

Toxocariasis is caused by larvae of T. *cams* (dogs), T. *catis* (cats), and *Baylisascaris procyonis* (raccoons). Larva migrans (K.vurs in skip., \iscer..i, and neural tissue.

Ingestion of food contaminated by eggs from the feces of cats and dogs results in human infection. It is common in children with history of pica and geophagia. It is also contacted on beaches where cats and dogs deposit their feces. The larvae hatch from the eggs in the small intestine, penetrate the intestinal wall, and migrate to various tissues.

Clinical Features

Cutaneous larvae migrans show serpiginous creeping tracts, which are itchy and get secondarily infected. Visceral larva migransischaracterizedbypronouncedeosinophilia(100%), hepatomegaly (85%), pulmonary symptoms (50%), and fever. Involvement of the nervous system causes encephalitis, meningoencephalitis, and spinal cord compression resulting in headache, disturbance of consciousness, seizures, child-hood dementing v\ minim s, lri.nvl^ n oin \ .IMILII :-., c< iv.nu phil ic granuloma, and paraplegia or quadriplegia. Ocular larva migrans rcsulrs in retinal inflammatory mass.

Diagnosis

Diagnosis of neural larva migrans is suspected by history of exposure to dogs or cats and peripheral eosmophilia in a child with an encephalitic or a dementing illness. CSF shows eosinophilic pleocytosis, normal sugar, and protein. HI ISA and Western blot technique to detect IgG against larval secretory and excretory antigen can confirm the diagnosis. The differential diagnosis of neural larva migrans includes loiasis, gnathostomiasis, and strongyloi-diasis. Ocular larvae migrans must be differentiated from retinoblastoma, toxoplasmosis, histoplasmosis, optic neuritis, and Coat's disease.

Treatment

Anthelminthic agents, including thiabendazole (25 mg/kg twice daily for 5 days), mebendazole (100 mg three times a day for 7 days), or albendazole (15 mg/kg per day for 5 days) are useful, Diethylcarbamazine also shows good results. Laser photocoagulation to kill the larvae can be used if they are away from the macula or disc in the retina.

TREMATODES

Schistosomiasis

Schistosomiasis, caused by the trematode *Schistosoma mansoni,* is seen in Africa, Brazil, and the West Indies. The adult worm infects humans. Ova of different

schistosomes are passed in urine *(S. hematobium)* or feces *(S. japonicum* and *S. mansoni)* of the infected mammals. They gain access to fresh water, hatch, and penetrate freshwater snails and Cyclops. The larvae pierce the infected host and are liberated into the water. Humans are infected by bathing in or wading through the infected water. After entering the human body, larvae reach the circulation where they develop into adult worms that produce eggs. Oviposition takes place in the urinary venous plexus in 5. *hematobium* and in the mesenteric and hepatic venous system in *S. japonicum* and *S. mansoni.*

Clinical Features

A pruritic papniar rash or swimmer's itch develops after exposure, and signs of acute toxemic schistosomiasis in the form of fever, myalgia, headache, urticaria, and lymphadenopathy (Katayama fever) develops I 1-50 days later. At this stage a mild transient meningoencephalitis or generalized vasculitis may occur in infection with *S. mansoni.*

The chronic stage of disease occurs when the worms complete intravascular migration and settle in the venules of mesentery, portal system, and bladder, depending on the species. At this stage symptoms are related to portal hypertension, hepatic cirrhosis, hcpatosplenomegaly, variceal bleeding, intestinal polyps, diarrhea, cystitis, and hematuria.

Involvement of spinal cord, cauda equina, and conus medullaris, resulting in cord infarction, transverse myelitis and granulomatous cauda equina compression is associated with *S. mansoni* and *S. haematobium.* These are thought to be due to ectopic eggs or worms in the spinal canal or cord parenchyma via arterial egg embolization or through the valveless intra vertebral venous plexus causing cord infarction or inflammatory granuloma. Cerebral involvement commonly occurs with S. *japonicum* (60%), and it may be in the form of cerebral inflammatory masses or vasculitis resulting in seizures, confusion, coma, focal neurological signs (hemianopic field defects, hemiplegia, ataxia, etc.), and papilledema.

Diagnosis

In endemic areas or in individuals with a history of travel to endemic areas schistosomiasis should be considered in the differential diagnosis of painful cauda equina or spinal cord syndromes. Examination of stool and urine for ova and peripheral cosinophilia are not helpful. Liver or rectal biopsy may show granuloma with a centrally located ovum. CSF examination may show eosinophilic pleocytosis with CNS involvement. CT and MR! scans may demonstrate granuloma with edema in the brain and enlargement of the spinal cord with granulomatous cord disease. Multiple serological tests ate described to detect antibodies to eggs, larvae, or adult worm, but they lack sensitivity and specificity. ELISA using keyhole limpet hemocyanin is helpful to distinguish acute from chrome antibody responses.

Treatment

Praziquantel is effective against all species of schistosomes. A single oral dose of 40 mg/kg is sufficient for 5. *japonicum, S. mansoni,* and *.S. hematobium. S. mckongt* requires three doses of 20 mg/kg separated by 4 hours. Corticosteroids are needed during the treatment with antiparasitic therapy to reduce reaction and edema. Metrifonate and oxamniquine arc effective against *S. hematobium* and *S. mansoni,* respectively. Neurological involvement during the acute phase is self-limiting and does not require treatment. Masses in Lite brain ami spinal cord require surgical decompression.

Paragonimiasis

The causative agent is the oriental lung fluke of the *Paragonimus* spp. The adult worms inhabit lungs but rarely do the larvae gain entry into ectopic sites, of which the brain is the most common leading to meningoencephalitis, seizures, and focal neurological syndromes.

The parasite is found in the Southeast Asian countries (Japan, Taiwan, Philippines, India, and China), America, and West Africa. The most common etiological agents arc *P. westermant. P. mexicanus,* and /'. *miyazakii.* The intermediate hosts are freshwater fishes, snails, and crabs. Humans get infected by consuming infected and partially cooked crabs and fishes, contaminated water, or contaminated water plants. Adult worms migrate from the gastrointestinal tract to the lungs. The brain is affected when the parasite passes through the sheaths around the jugular veins, internal carotid arteries, or the nerve trunks.

Clinical Features

Acute infection is characterized by cough, fever, pleural effusion, and hcpatosplenomegaly. The chronic stage is associated w'ith a cough productive of brown sputum, chest discomfort, recurrent hemoptysis, and night sweats. Migrating larvae and worms localize in the brain or spinal cord and present as a space-occupying lesion, taiscd intracranial pressure, epilepsy, meningitis, subacute encephalitis, infarction, headache, cranial nerve paresis, focal neurological deficits, papilledema, optic atrophy, mental retardation, and depressed consciousness.

Diagnosis

Diagnosis is made by examination for eggs in the sputum, ELISA, intradermal test, chest x-rays and peripheral cosinophilia. CSF findings are nonspecific. CT or MRI scans reveal characteristic conglomerate, multiple ring-shaped contrast enhancing lesions, 1-3 cm diameter located most commonly in temporal or occipital lobes

(Nomura et al. 1999). In chronic stages the CT and the plain radiographs of the skull may show evidence of characteristic soap bubble appearance and dilated ventricles.

Treatment

The most widely used drug for the treatment of paragonimiasis is praziquantel in doses of 25 mg/kg thrice daily for 2 days. Longer treatment may be required in resistant cases. Niclofalan in a single dose of 2 mg/kg is an alternative. Cerebral and spinal masses require surgical decompression, Corticosteroids or ventriculo peritonea I shunt maybe indicated in some cases.

Diseases Caused by Ectoparasites

Tick paralysis is an ascending flaccid paralysis caused by a large number of species (Greensrein 2002). These are *Dermacentor andersoni* {Korrh American wood tick), *D. variabilis* (dog tick), *Amblyomma macttlatum* in North America, *Omithodoros laborensis* in the Russian Republic, *Otobius megnini, Ixodes rubicundus,* and *Kbipicephalus simus* in South Africa; *Ixodes tancitarus* in Mexico, *Ambiyomma cyprium aeratipes* in the Philippines, and *Ixodes holocyclns* in eastern Australia. The tick is removed by pulling it out from the point of attachment with the help of forceps; it is induced to release its hold by paralyzing it with chloroform or lighter fluid. Tick paralysis may be severe and fatal. The agent injected by the tic that produces paralysis has yet to be fully characterized. Paralysis resolves within a few hours of removing the tic.

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Chapter 59
Infections of the Nervous System

E. NEUROLOGICAL MANIFESTATIONS OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN ADULTS

Ashok Verma

EPIDEMIOLOGY AND CURRENT TRENDS

Acquired immunodeficiency syndrome (AIDS) was first recognized in the United States in the summer of 1981 when unexplained occurrences of *Pneumocystis carom* **and** Kaposi's sarcoma were reported in cohorts of previously-healthy homosexual men. Within months, the disease became recognized in intravenous drug users (IDUs) and soon thereafter in recipients of blood transfusions and blood product including hemophiliacs. As the epidemiological pattern unfolded, it became clear that a microbe transmitted by sexual (homosexual and heterosexual) contact and through blood and blood products was the most likely etiologic agent of the epidemic. In 1983, human immuno-deficiency virus type-1 {HIV-1, henceforth called HIV) was isolated, and in the following year it was demonstrated clearly that it was the causative agent of AIDS. In 1985, a sensitive enzyme-linked immunosorbent assay (ELISA) test was developed, which led to the recognition of the scope of HIV infection among cohorts of individuals in the United States and elsewhere. As the disease spread, scro-prevalence studies revealed the enormity of the global pandemic, with cases reported ftom virtually every country.

According to **the Joint** United Nations Program on HIV/AIDS (http://www.mednav.com), as of the end of 2002, 42 million people were living with HIV/AIDS worldwide. Of these, 38.6 million are adults, 19.2 million are women, and 3.2 million are children under 15. An estimated 5 million people acquired the HIV infection in 2002, including 2 million women and 800,000 children under 15. During the year 2002, AIDS caused the deaths of an estimated 3.1 million people, including 1.2 million women and 610,000 children under 15, Three fourths of the world's AIDS population is currently in sub-Saharan Africa and Asia; 45% of cases are women. In certain sub-Saharan African countries, such as Zimbabwe and Botswana, available seroprcvalence data indicate >25% of adult population aged between 15 and 49 is HIV infected. The epidemic in Asian countries, particularly India and Thailand, has lagged temporarily behind that in Africa; however, the number of new cases in these countries is accelerating rapidly (Anonymous 2002).

In the United States, the cumulative number of AIDS cases reported to the Centers for Disease Control and Prevention (CDC) as of December 2001 was 816,149. Adult and adolescent AIDS cases were at 807,075, with 666,026 males and 141,048 females, and 9074 were children under age 15. The total number of AIDS deaths reported during this period is 467,910, including 462,653 adults and adolescents, 5257 children under age 15, and 388 persons whose age at death is unknown. It is estimated that between 650,000 and 900,000 adults and adolescents in the United States are living with HIV infection, including 120,000 to 160,000 women. This estimate results in an overall nationwide prevalence of HIV infection of approxi-mately 0.3%. The number of new infections per year is estimated to be approximately 40,000, and this number has remained stable for several years (Fauci 1999). Following the use of the highly active anti retroviral therapy (HAART), the death rate from AIDS declined 40% from 1996 to 1998, and it has further declined over the subsequent years. It is currently the fifth leading cause of

death among Americans aged 25 and 44, having dropped from first within the past six years.

The high prevalence and striking diversity of neurological disorders complicating AIDS were recognized early in the epidemic (Snider et al. 1983). Neurological opportunistic infections (OIs} and malignancies predominated in early reports, but it became also clear that AIDS was associated with distinct neurological syndromes, such as dementia, myelopathy, and painful neuropathy, that appeared to result from the HIV itself. It also became recognized that the risk of neurological complications increased with the progression of the HIV infection and decline of the CD4" T cell counts. Clinically apparent neurological disease develops in approximately one half of HIV-infected patients. Neuropathological abnormalities arc nearly universal in patients dying with AIDS, suggesting subclinical disease, underdiagnosis, or both. Neurological disorders cause significant morbidity and mortality, and they may be the AIDS-defining illnesses in previously asymptomatic HIV disease or, occasionally, hetald unrecognized HIV infection. Nervous system complications may directly lineal en life, as well as impair ability to comply with complex HA ART regimens necessary to manage HIV disease optimally. These disorders affect every level of the neuraxis, and a given patient may suffer more than one HIV-associated neurological disease. Familiarity with the common HlV-telated neurological syndromes (Tables 59E.1 and Tables 59E.2) facilitates their recognition, even in the medically complex patient with several medical and neurological diagnoses.

Table S9E.1: Major HIV-associated CNS disorders classified by neuroanatomical localization

Meninges
Aseptic HIV meningitis
C) ry p toeocca l meningitis
Tuberculous meningitis
Syphilitic meningitis
Listeria monocytogenes meningitis
Lymphomatous meningitis (metastatic!
15 rain
Predominantly nonfocal
HIV-associated dementia (HAD)
HIV-associated minor cognitive motor dysfunction (MCMD)
Toxoplasmic encephalitis
Cytomegalovirus (CMV) encephalitis
Aspergillus encephalitis
Herpes encephalitis
Metabolic encephalopathy (alone or concomitantly)
Predominantly focal
O r e bra I toxoplasmosis
Primary CNS lymphoma (PCNSL)
['in;,;;;-.\i>. ▪▪ multifocal leukoenceplia lopa tlii I'M I i
Cryptococcoma
Tuberculoma
Varied la-zoster virus (VZV) encephalitis
Stroke
Spinal cord
Vacuolar myelopathy (VM)
Cytomegalovirus (CMV) myeloradiculopathy
VZV myelitis
Spinal epidural or intradural lymphoma (metastatic)
HTI.V-1-associated myelopathy

The stage of systemic HIV infection influences both the risk of neurological disease, .is well as likely ecologies, and hence $CD4^+$ T cell count provides critical information that helps guide the evaluation (Figure 59E.1). In early infection, corresponding to $CD4^+$ T cells greater than 500/jiL, autoimmune disorders, such as demyelinating neuropathies, may develop. During midstagc infection, or $CD4^+$ T cell levels of 200-500/uL, ptimary HIV-reiated disorders, such as dementia, may become symptomatic, as may some infections such as varicella-zoster virus (VZV) radiculitis (shingles). In advanced HIV infection, defined as CD4' T cell count less than 200/uL, the risk of dementia, myelopathy, and painful neuropathy increases further, and patients become vulnerable to major OIs such as cerebral toxoplasmosis, progressive multifocal leukoencephalopathy (PML), and cryptococcal meningitis, as well as to neoplasms such as primary central nervous system lymphoma (PCNSL).

NATURAL HISTORY OF HIV INFECTION AND NEURO-HW DISEASE

The clinical consequences of HIV infection encompasses a spectrum ranging from an acute syndrome associated with primary infection to a prolonged asymptomatic state to advanced disease. It is best to regard HIV disease as beginning at the time of primary infection and progressing through various stages. In most patients active viral replication and progressive immunological impairment occur throughout the course of HIV infection. With some exceptions, HIV disease in untreated patients inexorably progresses, even during the clinically latent stage. Accumulating clinical and laboratory observations clarify that the brain is infected early at the time of primary HrV infections, the infection and low-grade inflammation of brain continue through the latent phase of HIV infection, and significant central nervous system (CNS) morbidity and mortality are due to the continued CNS infection in the late stages of the HIV disease. In this context, the CNS serves as a parallel compartment to the systemic HIV disease. The CNS manifestations relate principally to the continued infection in the CNS compartment, the interaction of the virus with the systemic immune system, and the consequent failure of the immune defense system,

The Acute **HIV** Syndrome

It is estimated that 50-70 % of individuals with HIV infection experience an acute clinical syndtome

Tabic 59E.2: Classification of HIV-associated neuromuscular disorders

Peripheral neuropathies
Early stages (immune dysregulation)
- Acute inflammatory demyclinating polyradiculoneuropathy (AIDP)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Vasculitic neuropathy
- Brachial plexopathy
- Lumbosacral plexopathy
- Cranial mononeuropathy
- Multiple mononeuropathies

Mid- and late stages (HlV-rcplieation driven)
- Distal sensory polyneuropathy
- Autonomic neuropathy

Late stages (opportunistic infection, malignancy)
- CMV poiyradiculomyelitis
- Syphilitic poiyradiculomyelitis
- Tuberculous poiyradiculomyelitis
- Lymphomatouspoly radiculopathy
- Zoster ganglionitis
- CMV mononeuritis multiplex
- Nutritional neuropathy (vitamin Bij, BJ
- ?AlDS-cachexia neuropathy
- ?AI.S-like motor neuronopathy

AH stages (toxic neuropathy)
- Nucleoside reverse transcriptase inhibitors (ddl, ddC, d_4T)
- **Other drugs (vincristine, INH, ethambutol, thalidomide)**

Myopathics
- Polymyositis
- Pyomyositis
- PInclusion body myositis
- **Toxic (Zidovudine) myopathy**
- AlDS-cachexia myopathy

approximately 1-6 weeks after the primary infection. The syndrome is typical of an acute viral syndrome and has been likened to acute infectious mononucleosis. Fever, erythematous or maculopapular rash, headache, nausea, anorexia, lethargy, arthralgia, sore throat, and lymphade-QOpathy occur in different combinations in this syndrome.

Neurological manifestations occur in approximately 10 % of cases at the time of initial HIV infection. Several general principles of this early interaction are apparent. First, the neurological complication, as also the seroconversion syndrome, usually occurs 1-6 weeks after the exposure and primary infection. Second, the neurological presentation frequently involves multiple parts of the nervous system, although one part is usually dominant. Third, the illness is monophasic, with the majority of patients recovering within weeks. Meningitis, meningoencephalitis of varying severity, seizures, myelopathy, and cranial and peripheral neuropathies have all been linked to the primary HIV infection or seroconversion. Occasionally, opportunistic CNS infections have been reported during this stage of infection, reflecting the temporary immunodeficiency that results from the reduced number and the likely-dysfunction of CD4"""" T cells. In a review of 139 published cases of primary HIV infection, encephalopathy and neuropathy were each reported in 8% of the cases (Clark ct al. 1991). Meningitis and less severe symptoms, such as headache, have been reported in up to 30-45% of patients. Laboratory analysis at this stage (with or without neurological disease) reveals cerebrospinal fluid (CSF) abnormality with mild mononuclear pleocytosis and moderate rise in protein. Imaging of the brain is usually normal, whereas the electroencephalogram (EEC) may be diffusely or focally slow in brain-symptomatic cases. The diagnosis of these neurological syndromes can be difficult because they are indistinguishable from other acute vital or postinfectious syndromes, most of which are self-limiting and never achieve specific diagnoses.

Most patients recover spontaneously from these acute systemic and neurological HIV syndromes in one to several weeks and are left with only a mildly depressed $CD4^h$ T cell count that remains stable for a variable period of time. In most cases, primary infection with or without the acute HIV syndrome is followed by a prolonged period of clinical latency.

The Asymptomatic or Latent Stage

Although the length of time from initial infection to the development of clinical AIDS varies greatly, the median time for untreated patients is approximately 10 years. During this asymptomatic phase the virus is actively replicating, and the disease is gradually progressing. The rate of disease progression is directly correlated with HIV RNA levels (viral load). Patients with high vital load in the plasma progress to symptomatic disease faster than do patients with a low viral load. During asymptomatic HIV infection, the average rate of $CD4^+$ T cell decline is approximately 50/uL per year. When the CD4~ T cell count falls to <200/uL, the resulting state of immunodeficiency is severe enough to place the patient at high risk of OIs and neoplasms.

Evidence indicates that the CNS continues to harbor and mount a host reaction to the HIV through the asymptomatic or latent stage, yet without apparent immediate clinical sequelae. The CSF in patients with latent HIV infection generally shows abnormalities, including abnormal cell count, protein and immunoglobulin, and local synthesis of anti-HIV antibodies within the CNS compartment; the intact virus can be recovered from the CSF (Price 1 996). Pathological studies have shown evidence of inflammatory reactions in the CNS, with perivascular mononuclear cell infiltrations, although the HIV RNA burden, as evident by polymerase chain reaction (PCR) from CSF and brain samples, appears to be negligible at this stage. Neither overt nor subclinical cognitive or motor dysfunction appears to be common in the early latent stage. From a practical standpoint, the risk of isolated cognitive decline in asymptomatic individuals is sufficiently small as to provide no

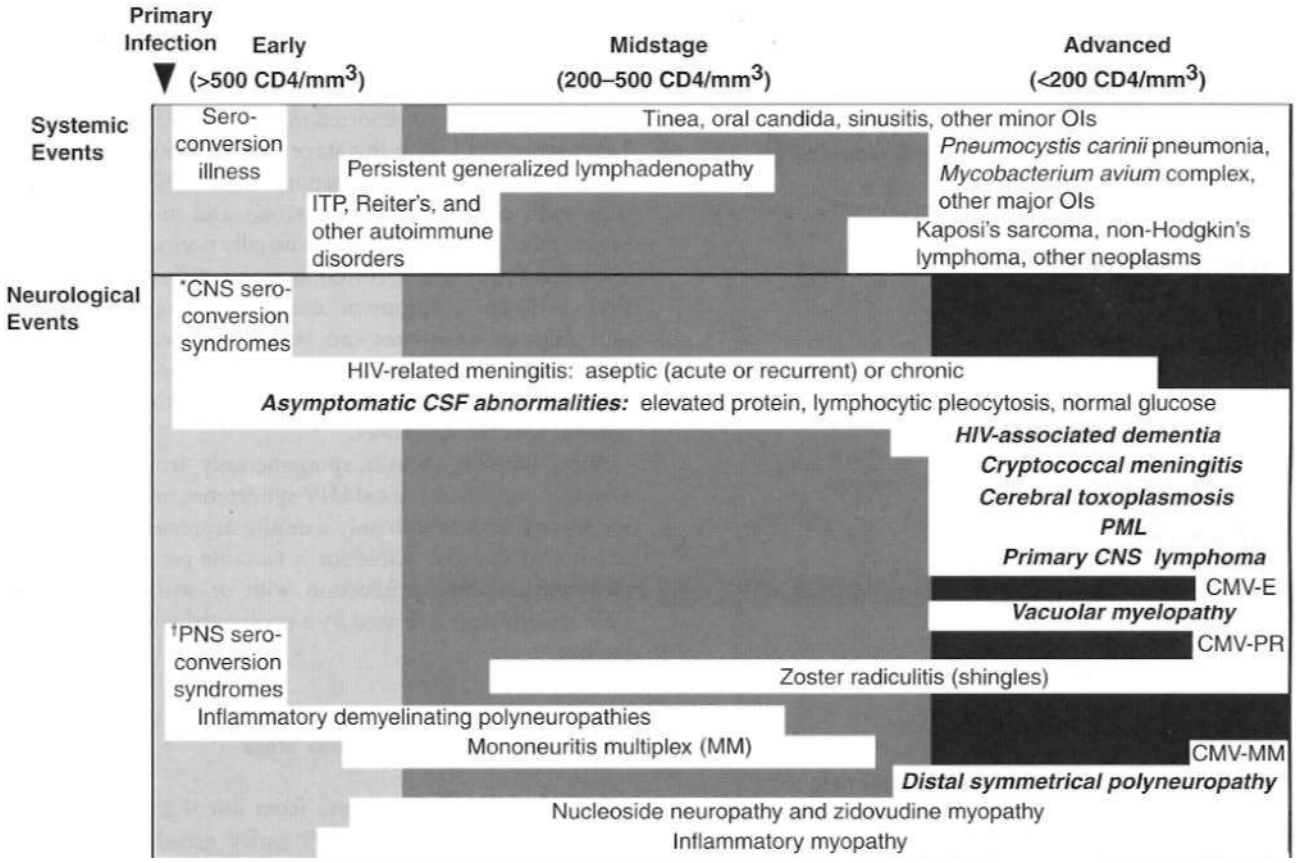

FIGURE 59E.1 Systemic and neurological events in human immunodeficiency virus (HIV) infection. Temporal sequence is ^ppni^iin.iv: ;md indicates the increasing risk oi systemic and neurological complications as HIV infection advances. [CMYT — Cytomegalovirus encephalitis; CMV-PR = CMV polyradiculitis; CNS = central nervous system; CSF = cerebrospinal fluid; ITP = idiopathic thrombocytopenic purpura; Ols = opportunistic infections; PML = progressive multifocal leukoencepbalopathy; PNS — peripheral nervous system.) 'Includes, in addition to HIV-related meningitis and asymptomatic cerebrospinal fluid abnormalities, meningoencephalitis, acute demyelinating syndromes, myelopathy. Includes, in addition to acute inflammatory demyelinating polyneuropathies, sensory ganglioneuritis, brachial plexitis, and rhabdomyo lysis. Common neurological syndromes are in bold italics.

basis for disability or disqualification from work based simply on HIV-positive status.

Some patients who are termed "long-term nonprogressors" show little if an\ decline in (1)-1 ! I cell comic-, over a prolonged period of time (Samson et al. 1996). These patients generally have extremely low levels of HIV RNA, Certain other patients remain entirely asymptomatic despite the fact that their CD4 h T cell counts show *a* progressive decline to extremely low levels. In these patients, the appearance of a systemic or CNS opportunistic infection may be the first manifestation of HIV disease. The length of asymptomatic stage is determined by the viral and host factors.

Symptomatic Stage

Following the initial burst of viremia during primary infection, HIV-infected individuals generally mount a robust immune response that usually curtails the level of viremia and likely contributes to delaying the ultimate clinically apparent disease. The host immune response is directed against multiple antigenic determinants of the HIV virion as well as against viral proteins expressed on the surface of infected cells. Ironically, those $CD4^+$ T cells with T cell receptors specific for HIV are the cells most likely to bind to the virus, be infected, and themselves be destroyed. Thus, the early consequence of HIV infection may be dysimmune in the face of persistent high antigenemia, and the late consequence is an immunocompromised state, through the elimination of HIV-spccific $CD4^+$ T lymphocytes.

HIV-associated neurological complications in late-stage HIV infection include primary manifestations, secondary complications related to the Ols and neoplasia, and complications arising from antiretroviral or prophylactic therapy. The primary neurological complications include HIV-associated dementia (HAD) or its less severe form,

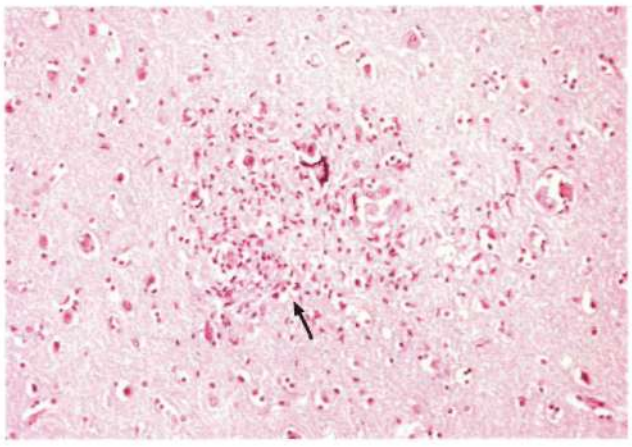

PLATE 59E.1 HIV encephalitis. Microglial nodule (*arrow*) containing multinucleated giant cells. (H & E × 200)

minor cognitive motor dysfunction (MCMD), vacuolar myelopathy (VM), and distal sensory polyneuropathy (DSP). Generally, the nature and severity of illnesses (systemic and neurological) that one observes change as the $CD4^+$ T cell count progressively declines. The frequent and life-threatening complications of HIV infection occur in patients with $CD4^+$ T cell count <200/uL. Although the causative agents of the secondary infection are characteristically opportunistic organisms such as cryptococcus, cytomegalovirus (CMV), and other microorganisms that do not ordinarily cause disease in the absence of a compromised immune system, they also include common bacterial and micobacteriai pathogens. Secondary complications (systemic and neurological) are of great importance because they are rather common. Timely and appropriate therapy is critical and potentially Ufesaviug in many of them. Approximately 80% of deaths among AIDS patients are as a direct result of an infection other than HIV.

PATHOGENESIS OF NEURO-H1V DISEASE

HIV-infected individuals can experience a variety of neurological abnormalities due cither to direct effects of the HIV or its products or to opportunistic infections or neoplasms. With regard to the direct effects of HIV, the main cell types infected in the brain in vivo are those of the monocyte/macrophage iineage. These include monocytes that have migrated into the brain from the peripheral blood, as well as resident microglial cells (Sabri et al. 2003). Although there have been reports of infrequent HIV infection of astrocytes and neurons, there is no convincing evidence that brain cells other than those of monocyte/macrophage lineage can be productively infected in vivo. Nevertheless, in vitro infection of a neural cell line can occur (Klein et al. 1999), and it appears that galactosyl ceramide on neuronal surface is an essential component of the HIV gpl20 receptor, and that antibodies to galactosyl ceramide inhibit the entry of HIV into the neural cell lines.

HIV enters the brain during viremia of primary infection and remains there for the life of the HIV-infected individuals. The viral entry is due, in part, to the ability of virus-infected and immune-activated macrophages to induce adhesion molecules such as vascular adhesion molecule-1 (VCAM-1) on brain endothelium. Other studies have demonstrated that HIV gpl20 enhances the expression of intercellular adhesion molecule-1 (1CAM-1) in glial cells; this effect may facilitate entry of HIV-infected cells into the CNS and may promote syncytia formation (Plate 59E.1). HIV isolated from the brain is preferentially of the R5 strain, as opposed to other strains; in this regard, HIV-infected individuals who are heterozygous for CCR5delta32 {a mutation of HIV $GD4^+$ T cell receptor) appear to be relatively protected against the development of HIV encephalitis (Weiss et al. 1999). Distinct HIV envelope sequences are also linked with the clinical manifestation of HAD.

HIV-infected individuals may manifest white matter changes as well as neuronal loss. Given the relative absence of evidence of HIV infection of neurons either in vivo or in vitro, it is unlikely that direct infection of these cells account for this cell loss. Rather, the HIV-mediatcd effects on brain tissue arc thought to be due to a combination of direct effects, either toxic or function-inhibitory, of virus or viral antigens on neuronal cells and effects of a variety of neurotoxins released from the infiltrating monocytes, resident microglial cells, and astrocytes. In this regard, it has been demonstrated that HIV-1 antigens, for example, Nef and Tat (viral core antigens), can induce chemotaxis of leukocytes, including monocytes, into the GNS. Neurotoxins can be released from monocytes as a consequence of other HIV-associated infections or immune activation. Activated monocyte-derived neurotoxic factors have been reported to injure neurons via the N-methyl-D-aspartate (NMDA) receptor. Additionally, HIV gp!20 shed by virus-infected monocytes, and a variety of cytokines, including tumor necrosis factor-alpha (TNF-tx), IL-1, IL-6, rnterferon-a (IFN-a), and endothelin, can contribute directly or indirectly to the neurotoxic effects in HIV infection. Further, infection or activation of monocyte-lineage cells can result in increased production of cicosanoids, nitric oxide, and quinolinic acid, which may also contribute to the neurotoxicity.

Astrocytes may play diverse roles in HIV neuropathogenesis, Astrocytosis and reactive gliosis occur in brains of HIV-infected individuals, and TNF-ur and II.-6 have been shown to induce astrocyte proliferation. In addition, astrocyto-derived IL-6 can induce HIV expression in infected cells in vitro. Furthermore, it has been reported that HIV-infected older individuals and individuals with the E4 allele for apo-lipoprotein E (Apo E) are at increased risk of HIV encephalitis and polyneuropathy (Gordcr et al. 1998). The fact that neuropsychiatric abnormal ides may undergo remarkable and rapid improvement on the initiation of antiretroviral therapy, particularly in HIV-infected children, indicates that it is virus driven, that the 111V or its products are involved in the neuropathogenesis of primary HIV neurological disorders, and that the dominant changes are either structural or functional at the synapses.

ANTIRETROVIRAL THERAPY AND ITS IMPACT ON NEURO-HIV DISEASE

Combination antirctroviral therapy or HAART is the cornerstone of management of patients with HIV infection (Fauci 1999; Arendt and von Giesen 2002). Following the widespread use of HAART in the United States from 1996, dramarie declines have been noted in the incidences of most AIDS-defining conditions, including neurological

diseases (see earlier). Successful HA ART with rcconsritution of immune defense can even enable some patients to discontinue secondary prophylaxis against certain CNS pathogens, which had not been possible in the pre-HAART era. It appears also that certain primary neurological diseases, where the disease processes are driven by the HIV burden, can be prevented or delayed by successful HAART (Geraci and Simpson 2001), although the evolution of drug-resistant viral strains may eventually limit the sustained benefits of HAART (Power et al. 2002; Samuel ct al. 2002). It is currently unknown if in the future, as patients develop increasing drug-resistant HIV mutations, the incidence of neuro-HIV diseases would begin to rise (Anonymous 2002; Sacktor 2002; Kandaneararchi et al. 200.'5). Moreover, some anriretroviral drugs have significant neurological side effects. Additionally, there are numerous drug-drug interactions that one must take into consideration when using these drugs. It is desirable that neurologists caring for HIV-infected patients have a broad understanding of the principles and practical guidelines of modern antirettovirai therapy.

Treatment decisions must take into account the fact that one is dealing with chronic infection that can only be controlled; eradication of HIV infection has not yet been possible. Although early therapy is generally the rule in infectious diseases, immediate treatment of every HIV-infected individual on diagnosis may not he prudent, and the decision to treat must balance risks and benefits. Early use of antiretroviral drugs in the latent stage, for example, may select resistant HIV strains and preclude theit use in later stages when viral suppression is even more important. Unfortunately, some of the most impottant questions related to the treatment of HIV disease currently lack definitive answers. Among them are the questions of when should the HAART be started, what is the best initial regimen, and when should a given regimen he changed. Notwithstanding these difficulties, the physician and patient must come to a mutually agreeable plan based on the best available data. Given the complexity of this field, decisions regarding antiretroviral therapy are best made in consultation with experts. At present, a reasonable course of action is to initiate therapy in anyone with the acute HIV syndrome; HIV meningitis or meningoencephalitis; patients with asymptomatic disease with $CD4^+$ T cell counts <400/uL or with >20,000 copies of viral RNA per milliliter; and patients with HAD, VM, or DSP. In addition, one may wish to administer a 6-week course of therapy to uninfected individuals immediately following a high-risk exposure. Currently licensed drugs for the treatmenr of HIV infection are summarized in Table 59EJ.

Once the decision has been made to initiate therapy, the physician must decide which drugs to use as the first therapeutic regimen. Initial choice of drugs will determine the immediate response to therapy, and it will have implications regarding options for future therapeutic regimens. The two options for initial therapy most commonly in use today are a three-drug regimen from two different antiretroviral classes (see Table 59E.3). The first regimen utilizes two nucleoside analogues (one of which is ptefetably 1 amivudine) and a protease inhibitor. The second regimen utilizes two nucleoside analogues and a non-nucleoside reverse transcriptase inhibitor. Unfortunately there are no clear data at present on which to base a distinction between these two approaches.

For HIV-associatcd brain disease, one must use drugs tli at have good blood-bra in barrier penetration (sec Table 59E.3). Following the initiation of therapy, one should monitor virological (HIV RNA levels) and immunological ($CD4^{"1"}$ T cell counts) responses periodically. The HIV RNA levels in serum generally reflect viral levels in CSF, at least until late stages of the HIV disease. In terminal stages, the CNS compartment may harbor slightly different and divergent HIV strains, with different degrees of drug susceptibility (Antinori et al. 2002). In an attempt to determine an optimal therapeutic regimen, antitetroviral drug susceptibility through genotyping or phenotyping of HIV quasi species has been attempted, although its practicality[7] for general use is questionable. Maximal suppression of viral replication is the goal of therapy, not just to prevent the disease progression but also to prevent the appearance of drug-resistant HIV quasi species. The principles of thetapy for HrV infection arc well articulated in publications of the U.S. Department of Health and Human Services (CDC 1998, see updates at www. hivatis.otg). There are a scries of excellent sites on the V/orld Wide Web that are frequently updated, and they provide the most recent information on a variety of topics, including epidemiological data (www.cdcnpin.org) and consensus panel reports on treatment of HIV infection (www. cc.nih.gov/phar/hiv-mgt).

MAJOR HIV-ASSOCIATED NEUROLOGICAL SYNDROMES

The neurological complications of HIV infection are both common and varied, and they occur at all stages of the HIV disease {Price 1996; Simpson and Berger 1996; McArthur 1997). Disorders of both the CNS and peripheral nervous system (PNS) can complicate HIV infection from the period after initial infection through the end stages of the severe immunosuppression. These neurological complications can be classified in a number of ways. A classification based on the underlying pathophysiology and HIV disease stages is summarized in Figure 59E.1. At the time of initial HIV infection or soon after seroconversion, when the immune defense mechanism is generally robust, dysimmune diseases of the CNS and PNS are encountered. In later stages of HIV disease, when HIV RNA burden is high and the immune system is compromised, primary neurological diseases, OIs, and neoplasia are frequently encounteted. Tables 59L. I and Tables 59E.2 present classification based

Tahle 59E.3: Currently approved antiretroviral drugs tor HIV infection

Drug	*Duse*	*i • i.v/iV/i*	*Ri-injrki*
NRTIs			
Abacavir (Ziagen)	300 mg bid	Rash, CI, LA	Abacavir-resistant HIV strains are typically also resistant to 3Tc, ddl and ddC
Cornbivir (Zidovudin f Lamivudine)	Zidovudine 300 mg + lamivudine 150 mg, bid	GI, HA, P, LA, BM, rash	May cause myopathy, pancytopenia
Didanosinc (ddl, Videx)	200 nig bid or 400 nig qd	PN, GI, P	Pancreatitis can be fatal
'] anm ndiiiL- ⋮ 1'c. hpivin	150 mg bid	HA, GI, P, LA	May cause hepatic steatosis
*Stavudine (d_4T, Zerit)	20^t0 mg bid	PN, HA, GI, LA, rash	May cause fatal lactic acidosis
*Trizivir (Zidovudin + Lamivudine + Abacavir}	Zidovudine 300 mg + Lamivudine 150 mg + Abacavir 300 mg, bid	GI, HA, P, BM, LA, rash	May cause myopathy, pancytopenia
Zalcitabin (ddC, Hivid)	0.75 mg tid	PN, GI, P, oral ulcers	Low potency, rarely used
'Zidovudine (Retrovir)	300 mg bid	CI, FIA, BM, rash	May cause myopathy, pancytopenia
NtRTIs			
Tinofovir (Viread)	300 mg qd	P, LA	
NNRTls			
Delavirdine (Rescriptor)	400 mg bid	Rash, (J, fatigue	
'Efavircnz (Sustiva)	600 mg qd	K isli, sli .p J:-.: .:rb:i-\ • . CNS symptoms	
*Ncvirapinc (Viramune)	200 mg qd *x2* wk then 200 mg bid	Rash, GI	Close monitoring first 2 weeks (severe rash, hepatic steatosis)
Pis			
Amprenavir (Agenerase)	1200 mg bid	Rash, HA, GI, metabolic changes	Contra indicated in pregnancy, <4 yr age
'Indinavir (Crixivan)	800 mgtid	Nephrolithiasis, diabetes, GI	
Kaletra (Lopinavir + Ritonavir)	Lopinavir 133..3 mg + Ritonavir 33.3 mg, (400/100 mg, 3 capsules) bid	GI, perioral paresthesia, metabolic changes	Lower dose blocks metabolism of ritonavir
Neifinavir (Viracept)	750 mg tid	Rash, GI, diarrhea	
Ritonavir (Norvir)	600 mg bid	GI, perioral paresthesia	Lower dose blocks metabolism of other Pis
Saquinavir (Invirase)	1200 mg tid	GI	

'Indicates good CNS penetration

NRTIs = nucleoside reverse transcriptase inhibitors; NtRTIs = nucleotide reverse transcriptase inhibitors; NNRIs = nonnucleosidc reverse transcriptase inhibitors; Pis = protease inhibitors; BM = bone marrow suppression; CNS = central nervous system toxicity; GI = gastrointestinal toxicity; HA = headache; LA = lactic acidosis; I^1 — pancreatitis; PN = peripheral neuropathy,

on neuroanatomical localization, following the classic proven methods of the neurologist. Clinicians must be aware that more than one site of neural axis can be involved in the same HIV-infected patient at the same time. Further, the clinical deficits from one site may be masked by another lesion higher in the neuraxis; appropriate investigations may be necessary to delineate the complete clinical diagnosis. One example is peripheral neuropathy in the face of HIV-associated VM. The clinician must be vigilant also for common conditions that are not necessarily associated with the HIV or AIDS.

Experience in large HIV clinics indicates that the diagnosis of the neurological complications of HIV infection and AIDS is far from an academic exercise. Rather, precise diagnosis is critical, and it frequently leads to specific therapy with resultant reduction in morbidity, mortality, and preservation of meaningful function and quality of life.

Diffuse Disorders of the Meninges and Brain

Aseptic HIV Meningitis

Diverse clinical forms of meningitis, without other evident cause, may develop during HIV infection. Although the seroconversion-rclatcd illness may be accompanied by headache and meningeal irritation, this clinical syndrome, in less severe and protracted form, is more frequent in the later course of HIV infection. It occurs more commonly in patients undergoing progressive HIV disease with decline in CD4'" T cell counts and clinical manifestations of HAD. Isolated persistent headache is common in HIV-infected patients and often occurs in the same setting as aseptic meningitis. The headache can be severe and intractable. In some patients, it may be precipitated or aggravated by a concomitant systemic infection, such as *Pneumocystis carinii* pneumonia (PGP) and hence may be

related in part to the systemic release of vasoactive cytokines.

Included among HlV-rclatcd mcningitidcs is acute aseptic meningitis, which occasionally accompanies or follows the flulike, febrile illness frequently associated with I1IV seroconversion (Price 1996). By definition, preserved alertness and cognition accompany headache and other symptoms of meningeal inflammation. A similar illness with signs and symptoms of parenchymal cerebral dysfunction suggests meningoencephalitis related to the HIV, a relatively rare seroconversion syndrome. The typical CSF profile consists of elevated protein (<100 mg/dl.) and lymphocytic plcocytosis (<25/uL), with normal glucose. Meningeal exposure to HIV can occur early in systemic infection, as inferred by recovery of HIV from CSF and evidence of intrathecal anti-1 NV IgG synthesis. The practical consequence of the CSF abnormalities routinely observed in HFV infection is that they can complicate interpretation of CSF obtained to diagnose other neurological disorders.

HIV-related meningitis is principally a diagnosis of exclusion, and hence evaluation for other causes of aseptic or chronic meningitis, such as parameningeal infection, other infections (syphilis, tuberculosis, *Listeria,* fungi, among others), lymphomatous or carcinomatous meningitis, other noninfectious etiologies (sarcoid, Behcet's syndrome, among others) or medications (nonsteroidal antiinflammatory agents, among othets) is usually undertaken (Marinac 1992). Patients suspected of having acute HIV meningitis with an initially negative HIV test result tequire repeat testing in Mveral months, because HIV antibodies may not be detectable in early infection. The prognosis in acute HIV meningitis is generally good, and it requires no specific therapy.

HIV-Associated Dementia and Minor Cognitive Motor Dysfunction

HAD, called also AIDS dementia complex (ADC) or HIV encephalitis, is characterized by cognitive, motor, and behavioral dysfunction, usually developing later in the course of infection. HAD and its less severe form, MCMD, are the most common complications of late untreated HIV disease. An alternative terminology, HIV-assoeiated cognitive/motor complex, has also been proposed to encompass the full constellation of this syndrome. Characteristically, this syndrome manifests after patients have developed AIDS-dehning systemic illnesses. However, a small number of patients present with HAD at a time when they do not yet fulfill formal diagnostic criteria of AIDS, although they show significant immunosuppression by laboratory criteria. Recognition of this early presentation was instrumental in the addition of HAD to the diagnostic criteria of AIDS.

Clinical Features. Patients' early symptoms usually consist of difficulties with attention and concentration. Manv complain of slowness of thinking. Complex tasks become more difficult and take longer to complete, and forgetfulness and difficulty in concentration lead to missed appointments and the need to keep detailed lists outlining each day's plan. The HAD is recognized early if patients require a high level of concentration and organization in their occupation or at home, because impaired performance becomes obvious in such situations. In many instances, an employee, friend, or family member may be the first to notice subtle cognitive and personality changes as the patient begins to withdraw socially and appears apathetic and uncharacteristically quiet and forgetful. An agitated organic psychosis and dysphoria are rare as presenting or predominant aspects of this illness. Psychological depression and fatigue are not uncommon in HIV-infected individuals and require differentiation from early HAD.

The second major component of HAD syndrome is psychomotor dysfunction. Although cognitive dysfunction usually appears earlier than motor symptoms and continues to predominate, motor manifestations in the form of poor balance and incoordination may be an initial presentation. Fine and skilled hand movements are affected early, resulting in deterioration of handwriting. Cait incoordination may result in frequent tripping or falling or a need for extra caution in walking. The later may impart a slow and somewhat rigid character to the gait. Usually, these patients also have VM pathologically. Even if not symptomatic, motor abnormalities can usually he detected on examination early in the course of the disease.

Initially, formal mental staus testing may be normal. As the disease progresses, patients begin to perform poorly on tasks requiring concentration and attention, such as digit and word reversals and serial sevens. Later, a large array of mental status tests becomes abnormal, affecting multidomains of cognitive function. However, mental slowing continues to remain a prominent feature, and afflicted individuals often appear apathetic with poor insight, and even indifferent to their illness. Parallel to cognitive deterioration, ataxia, which at first affects only rapid tutns ot tandem gait, may become disabling. Associated HIV VM causes worsening of leg weakness, and paraparesis limits walking. Postural tremors are common, and on occasion, patients may exhibit choreiform movements and myoclonic jerks (Cardoso 2002). Bowel and bladder disturbances are common in the latet stages of the disease. In the end stage, patients become almost vegetative, lying in bed mute with vacant stare, unable to ambulate, and incontinent. Characteristically, the course is notable for the absence of focal or lateralizing neurological deficit, such as hemiparesis or aphasia.

Laboratory Investigations

Neuropsychological Tests. Formal neuropsychological testing can be useful in diagnosis, management, and clinical monitoring of individual patients and in clinical research

studies. Appropriately chosen neuropsychological tests that target the same cardinal cognitive dysfunction delineated by the AIDS-directed clinical assessment provide a formal, quantitivc means of monitoring patients serially. These assessments focus chiefly on motor speed, concentration, and motor manipulation. However, the neuropsychological test findings are not disease specific and should always be interpreted in the clinical context. Nor do the neuropsychological tests substitute for the clinical neurological examination. Clinicians should be vigilant because some patients with MCMD perform within the population norms, and some without HAD/HMCD perform poorly on testing for other reasons.

Neuroimagmg. Neuroimaging procedures arc often essential in i-valuaLon ot *ihc* AIDS patients with cognitive dysfunction. Hirst, neuroimagitig is particularly helpful in ruling out other conditions such as primary CNS lymphoma. Second, neuroimaging often reveals abnormalities that are characteristic, although not pathognomonic, of HAD. Diffuse cerebral atrophy on cither CT or MRl is an almost universal finding in HAD (Figure 59F.2). In some patients, MRI shows abnormalities in the hemispheric white matter and, less commonly, in basal ganglia and thalamus, with patchy or diffusely abnormal signals, most apparent on FLAIR images. Children with AIDS-related dementia often have basal ganglia calcification in addition to atrophy. Results of metabolic imaging, such as single-photon emission computed tomography (SPECT) and MRI spectroscopy have also been reported, although their utility in clinical diagnosis remains undefined.

Cerebrospinal Fluid Analysis. CSV examination is used chiefly to exclude other diagnoses. The results need to be considered in the context of the nonspecific changes found in clinically normal HIV-infected individuals (discussed earlier). Routine examination of CSF in patients with HAD reveals nonspecific findings of mild mononuclear pleocytosis and mildly elevated protein in approximately 60% of the cases. Specialized CSF examination may also reveal abnormalities in immunoglobulin, including evidence of intrathecal IgC synthesis and the presence ol oligoelonal bands, but because these abnormalities are also detected in patients who do not have HAD, their diagnostic utility is uncertain. HIV can be isolated directly or HIV DNA be amplified from the CSF sample in many of these patients, but this finding is common also in infected patients who are asymptomatic or who have HIV meningitis. Similarly, detection of HIV antigens in CSF is of limited practical utility.

Several surrogate markers of virological and immune-eel 1 activation in CSF have been investigated in patients with HAD. Quantitative HIV PCR to assess the CSF viral burden is perhaps the best parameter that relates to HAD; effective suppression of HIV in the CNS compartment is demonstrated to improve the clinical status in HAD (Antinori et al. 2002). However, there is no absolute correlation of the CSF HIV burden with the clinical severity of HAD among all patients. Other CSF surrogate immune-activation markers, including ^-microglobulin, neopterin, quinolinic acid, and cytokines, have been reported but their practical utility is currently uncertain (Letendre et al. 1999).

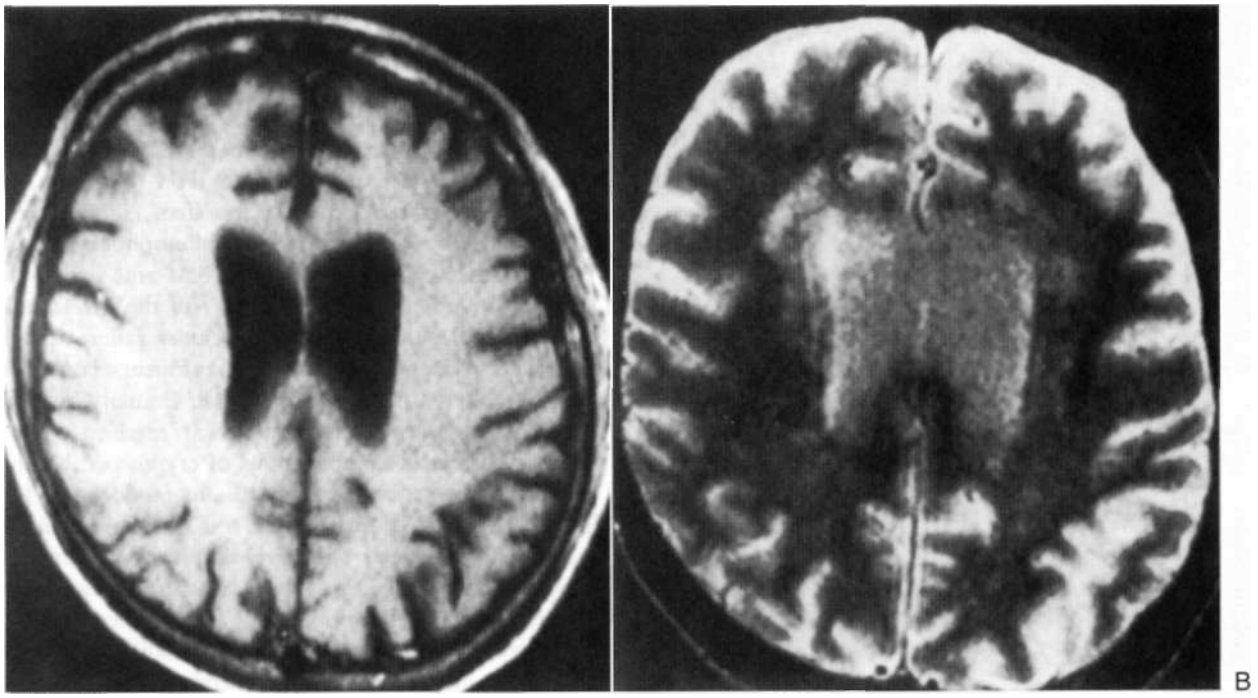

FIGURE 59E.2 Human immunodeficiency virus-associated dementia. Gadolinium-enhanced (A) Tl and (Bl T2 magnetic resonance images, obtained from a patient with acquired immunodeficiency syndrome and progressive cognitive impairment, show marked cerebral atrophy and diffuse white matter abnormalities.

Neuropathology. Histopathological abnormalities in HAD include white matter pallor, multinucleated-cell encephalitis (Plate 59E.1), and vacuolar myelopathy. Other findings include vacuolar changes in the brain, focal necrosis, and neuronal loss. These abnormalities are most common in the subcortical structures: the hemispheric white matter, basal ganglia, thalamus, brainstem, and the spinal cord. The cerebral cortex is relatively spared, at least on routine examination. There is good clinicopathological correlation in the sense that these pathological findings relate to the subcortical character of dementia in AIDS patients.

Management. Accumulating evidence indicates that HAD can be treated and even prevented, at least to some extent, by effective antiretroviral therapy (Clifford 2002; Arendt and von Giesen 2002). Initial case reports and small case series have been supplemented by controlled studies showing that HAART improves neuropsychological performance in patients with HAD. With a growing list of HIV therapies in several classes of drugs (described previously; sec Table 59E.3), many combination regimens are potentially availabc.

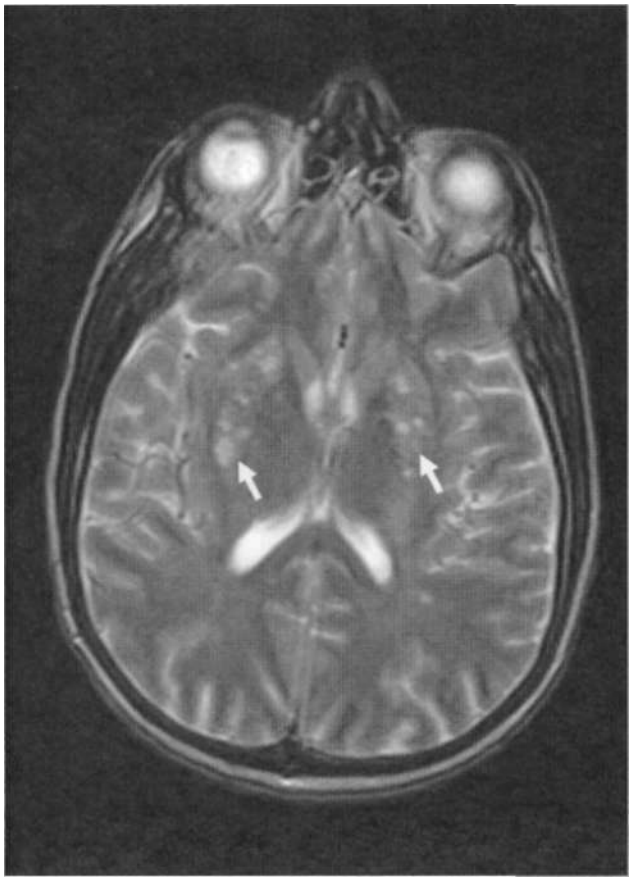

FIGURE 59E.3 Cryptococcai meningitis in AIDS. Axial T2-W-MR1 showing multiple small gelatinous pseudocysts in basal ganglia *{arrows).* [Courtesy Dr. S. Ouanouuou.)

For successful management of patients with HAD, HAART should be designed to enhance the probability of a patient's adherance to the therapy, fly the nature of the disorder, adherance to complicated treatment schemes might be particularly difficult. Simpler regimens with the least number of drug side effects arc important to enhance the adherance to therapy. For example, a once daily dose of cfavirenz is possible, and a combination formulation {combivir or kaletra; see Table 59E.3) may be easier for patient compliance. Adherence may also be enhanced by the patient entering a living facility with greater assistance and supervision, active support of family and close friends, and careful organization of medications (timers, pill boxes, etc.). Directly observed treatment is desirable in later stages of HAD.

Although the data are scanty, selecting retroviral drugs that enter the CSF and brain optimally can be an advantage in patients with HAD (Aminoh et al. 2002). The relative CNS penetranon of different antiretroviral drugs is summarized in Table 59E.3. The possible neurotoxic role of viral antigens, cytokins, and other substances in HAD and strategies to counteract these neurotoxicities are currently under active reasearch, Patients must be encouraged to participate in clinical trial research that may provide the patient the best available therapy and also assist future development of therapy. Treatment trials and a listing of health providers with expertise in this area may be accessed through the Neurological AIDS Research Consortium Web site at http://www.ncuro.wustl.edu/narc.

Cryptococcai Meningitis

Cryptococcai meningitis is covered in Chapter 59C. Approximately 10% of patients with AIDS develop cryptococcai meningitis, a neurological OI by the encapsulated yeast *Cryptococcas neoformans* {Zeind et al. 1996). This complication of advanced HIV infection, with CD4~ T cell counts generally less than 200/uE, presents as headache, fever, stiff neck, and photophobia (Powderly 1996). However, meningeal symptoms and signs may be minimal or absent in over one half of the cases, and the rather broad clinical spectrum includes failure to thrive, personality change, cognitive impairment, cranial neuropathy, altered mentation, or coma. Cranial CT or MRI, typically obtained to exclude focal cerebral disorders, sometimes reveals complications of cryptococcai meningitis, such as hydrocephalus, gelatinous pseudocysts, infarction, or cryptococcoma (Figure 59E.3}. More commonly, neuroimaging reveals only cerebral atrophy related to the advanced HIV disease. The CSF profile ranges from striking protein elevation, mononuclear plcocytosis, and hypoglycorrhachia to minimal abnormalities that overlap with those attributable to HrV infection alone. Fungal CSF culture is the gold standard, but the weeks that may pass before a positive result is obtained limit its clinical utility. India ink smear is helpful when positive, but is too

insensitive to exclude the diagnosis if negative. Fortunately, CSF cryptococcal antigen (CrAg) testing is a rapid, specific test with a sensitivity exceeding 90%. The rather diverse clinical presentations of cryptococcal meningitis may indicate that CrAg be performed routinely in patients with AIDS undergoing diagnostic CSF examination.

A typical acute regimen for cryptococcal meningitis consists of amphotericin B (0.5-0.7 mg/kg per day} with or without flucytosine (75-150 mg/kg per day) for 2-3 weeks. Renal insufficiency, hypokalemia, and Hypomagnesemia may complicate amphotericin B therapy, and the hematological toxicity of flucytosine sometimes precludes its use in patients with AIDS, in whom pancytopenia is common. Patients who are doing well can be switched to fluconazole, 200 mg twice a day for 8-10 weeks (Simpson and Bergcr 1996; Apisarnthanarak and Powdcrly 2001), and then placed on maintenance therapy of 200 mg daily to prevent relapse. Although fluconazole therapy may be as effective as amphotericin B for acute therapy of cryptococcal meningitis, delayed CSF clearance of the fungus and a trend toward poorer outcomes among fluconazole-treated patients suggest this approach be reserved for patients with mild disease.

Poor prognostic features at presentation include altered level of consciousness, CSF cell count less than 20 cells/uL, and CSF CrAg greater than 1:1024, Acute mortality approaches 30% and is related to increased intracranial pressure (ICP) at presentation. Medical management with corticosteroids or acetazolamide and CSF drainage with repeated lumbar punctures or ventriculostomy can be used to lower ICP, although none of these interventions has been subjected to clinical trial (Zeind et al. 1996). Optic nerve sheath fenestration has been MI^.MUI as .m ..kfunu *u*> these measures when increased ICP threatens vision. Focal cerebral signs accompanying cryptococcal meningitis may suggest stroke from cryptococcoma or infectious vasculitis, Other complications include cranial neuropathies and obstructive or communicating hydrocephalus. Without chronic suppressive therapy, relapse rates exceed 50%. As noted, first-line maintenance therapy is fluconazole, 200 mg daily; second-line agents include weekly amphotericin B or itraconazole. In patients who escape early complications, cryptococcal meningitis is compatible with long-term survival in patients who tolerate and adhere to HAART.

Neurosyphilis

Neurosyhilis is covered in Chapter 59A. Diagnosis and management of neurosyphilis in I [IV-infectcd patients pose some complex challenges. Syphilis and HIV infection often coexist, as the disorders share risk factors. Moreover, both infections are characterized by diverse neurological syndromes affecting brain, meninges, spinal cord, and nerve roots. CNS invasion in early syphilis appears to occur at similar rates in patients with and without HIV infection (Rolfs et al. 1997; Pao et al. 2002). Individuals without HIV infection frequently clear *Treponema pallidum* from CSF even without antibiotic therapy. Whether the same is true in HIV-infected patients is less certain. Meningeal disorders characteristic of early neurosyphilis dominate case reports of HIV infection and neurosyphilis, perhaps implicating impaired CSF clearance of T, *pallidum* in HIV-infected patients, even with adequate therapy for early syphilis. Other clinical syndromes described in association with HIV infection include syphilitic eye disease, gumma, and myelopathy.

Several factors complicate the diagnosis of neurosyphilis, particularly asymptomatic forms, in the setting of HIV infection. Individuals coinfected with HIV and *Treponema pallidum* may demonstrate unusual serological responses. When clinical suspicion of neurosyphilis is high and syphilis serology results are negative, repeat testing to exclude the prozone effect and darkfield examination or immunofluorescence staining of the biopsied lesion may be necessary (Bergcr and Levy 1997). Assuming an atraumatic lumbar puncture, CSF Venereal Disease Research Laboratory test is quite specific, but not particularly sensitive, for diagnosing neurosyphilis (see Chapter 59A). Moreover, relying on CSF pleocytosis and protein elevation to make the diagnosis, as is done for HIV-negative individuals, is complicated by the high frequency of these CSF abnormalities caused by HIV infection alone. Treponerne-specific tests in CSF are quite sensitive, but not specific, for neurosyphilis. Hence negative CSF fluorescent treponemal antibody or microhemagglutination-7". *pallidum* excludes the diagnosis of neurosyphilis, but a positive result does not establish the diagnosis. The CDC recommends that HIV-infected patients with late latent syphilis or syphilis of unknown duration undergo CSF examination before therapy, regardless of whether there are associated ophthalmic, vestibular, or neurological symptoms (CDC] 199S).

Regardless of HIV status, recommended treatment for neurosyphilis consists of a 10- to 14-day course of either aqueous crystalline penicillin G, 3-4 million units intravenously every 4 hours, or procaine penicillin, 2.4 million units intramuscularly daily, with oral probenecid, 500 mg four times a day. Because alternative agents, such as doxycycline and tetracycline, are of uncertain efficacy in neurosyphilis, desensitization should be considered in patients allergic to penicillin. The CDC recommends CSF examination every 6 months after therapy for all patients with neurosyphilis, regardless of HIV status, until pleocytosis, if initially present, resolves. Whether this is appropriate for patients with HIV infection and neurosyphilis remains uncertain. Treatment failures may occur more commonly in the serting of HIV infection, and neurological status and serum serologies should be carefully monitored as well.

Cytomegalovirus Encephalitis and Ventriculaenccphalitis

Unusual causes of global cerebral dysfunction in advanced AIDS ($CD4^{P}$ T cell <50/pL), CMV encephalitis and

ventriculoencephalitis often cause death within weeks to months (McCutchan 1995; Williams 19991. Prior or active disseminated CMV disease, such as retinitis, esophagitis, or colitis, may provide important clues to the neurological diagnosis. CMV encephalitis typically presents as a confusional state evolving over weeks and can resemble HAD. In addition to a course that is more subacute than chronic, focal cerebral signs, hyponatremia, and cranial MR1 showing periventricular enhancement are other factors that favor a diagnosis of CMV encephalitis over HAD. CSF abnormalities are typically nonspecific, and CMV PCR is positive in less than one half of cases. Pathological findings include microglial nodules and cytomegalic cells in cortical and subcortical gray matter, thought to be consistent with hematogenous spread of CMV to brain. By contrast, CMV ventriculoencephalitis may reflect dissemination from CSF and presents more acutely than CMV encephalitis, often on a background of CMV retinitis or concurrently with polyradiculomyelopathy. Brainstem signs and neuroimaging studies revealing dilated ventricles also suggest the diagnosis. CSF abnormalities tend to be more striking than CMV encephalitis, revealing elevated protein, polymorphonuclear or lymphocytic plcocytosls, and normal or low glucose. Identifying CMV DNA in CSF by PCR helps confirm the diagnosis. Pathological features include epei:dym.i! uci:(isi.s ,i:ul M ; K peiu:\ in.'il : M O V , V. nil cytomegalic cells, but no microglial nodules. CMV viremia is quite common in late-stage AIDS, and hence detection in this setting by culture, antigen testing, or PCR from blood does not help establish the diagnosis of CMV-related neurological syndromes. Prospective data are needed to confirm the impression that CSF PCR for CMV DNA is specific and reasonably sensitive for these and other CMV-related neurological disorders. Clinical trial data for the efficacy of ganciclovir, foscarnet, cidofovir, or combination therapy for CMV encephalitis and ventriculoencephalitis are lacking, though a trial of empiric therapy is probably appropriate given the poor prognosis (Table 59F..4).

Other Meningitis and Meningoencephalitis Syndromes

Odier causes of meningitis complicating HIV infection include neoplasm, other rare infections, and meilic.itions. Patients with AIDS are at increased risk for systemic lymphoma, which can cause lymphoma tons meningitis. Additional infectious causes of meningitis include bacteria *{Salmonella typhi, Pneumococcus pneumonae, Mycobacterium tuberculosis,* syphilis, *No card ia aster aides, Listeria monocytogenes, Bartonella henselae)* and fungi *[Htstoplasma capsulatum* and *Coccidioides immitis* in individuals who have lived in endemic regions, *Candida albicans, Blastomyces dermatidis, Sporothrix schenckii).* Medications are often overlooked as a cause of meningitis; implicated agents in common use for HIV infection include nonsteroidal anti-inflammatory drugs, trimethoprim/sulfamethoxazole (TMP/SMX), and intravenous immunoglobulin. Causes of meningoencephalitic syndromes include VZV and the parasites *Toxoplasma gondii, Trypanosoma cruzi,* and *Acanthamoeba* spp. (Ambroise-Thomas 2001).

Focal CNS Disorders

Four disorders account for most HlV-related focal CNS dysfunction: cerebral toxoplasmosis, PCNSL, PML, and VM. All are disorders of advanced HIV infection, when $CD4^+$ T counts decrease below 200/uL. Although they share focal hemisphcral and, less commonly, brainstem and cerebellar or spinal cord symptoms as a prominent clinical feature, other aspects of the history, supplemented by neuroimaging studies, response to therapeutic trial, and occasionally brain biopsy, usually allow each to be diagnosed quickly and accurately (Skiest 2002).

Cerebral Toxoplasmosis

CNS toxoplasmosis is described in Chapter 59D. Toxoplasmic encephalitis (TE) is the most frequent of the CNS OIs in AIDS (Porter and Sande 1992; Hill and Dubey 2002); it complicates the course of 10% patients or more, depending on the geographic origin. The varying incidence relates principally to the likelihood of earlier environmental exposure to the etiological parasite, T. *gondii.* It is most common in patients from the Caribbean and from France. Cerebral toxoplasmosis in AIDS almost always occurs from recrudescence of previously acquired infection and relates to the loss of the immune defenses that maintain *T. gondii* in an inactive, encysted form. It is 10 times more common in patients with antibodies to the organism than in patients who are seronegative. It is generally a late complication of HIV infection and usually occurs in patients with $CD4^1$ T cell counts <200/uL. The incidence has declined where TMP/SMX has been used as prophylaxis for PCP, because this regimen is also effective in reducing the development of TH. More recently, incidence of cerebral toxoplasmosis is further decreasing in the HAART era.

The most common clinical presentation in TF is headache and focal neurological deficit with or without fever. Patients may present with seizure, hemiparesis, or aphasia as a manifestation of these focal lesions or with a picture more influenced by the accompanying cerebral edema characterized by confusion, mental torpor, and lethargy, which can progress to coma. Diagnosis is usually suspected on t:ie basis ot (. T or MR! findings ol nuiltipie icsk>rs in multiple locations, although in some cases only a single lesion is seen. Pathologically, these lesions generally exhibit inflammation and central necrosis and, as a result. demonstrate ring enhancement on contrast CT or MR1 (Figure 59E.4). There is usually surrounding edema. In addition to toxoplasmosis, the differential diagnosis of multiple mass lesions in the HIV-infected patient include primary CNS lymphoma (see following) and, less

Table *59EA:* Selected therapies of HIV-associated neurological complications

E tio logy idiso rder	*Therapy*	*Major side effects*	*Primary prophylaxis*
Qryptococcus neoforma ns (meningitis, meningoencephalitis, abscess)	Amphotericin B (0.7 mg/kg/day IV) for >3 wk; adjust for renal status, plus Flucytocin (induction: 25 mg/kg/day po q6h for x3 wk Or Fluconazole 400 mg po qd x3 wk, then 200 mg po qd	Renal toxicity, chills, hepatic toxiciry (amphotericin B) IUme inarrow suppression (flucytocin) Hepatotoxicity (fluconazole)	(If prior documented disease elsewhere and CD4* Tcell <100VuJL) Fluconazole 200 mg po qd
Toxoplasma gondii (encephalitis, abscess)	Sulfadiazine (induction: 1.5 g po q6h *x6* wk; maintenance: 0.5 g po qid), plus Pyrimethamine (200 mg po one day, then 75 mg po qd), plus Folinic acid 10 mg po qd, or Clindamycin (induction: 600 mg/day IV or po qd; maintenance up to 450 mg po qid)	Rash, bone marrow suppression, crystalluria (sulfadiazine) Rash, leukopenia (pyrimethamine) Rash, diarrhea, pseudomembranous colitis (clindamycin)	(If IgG antibody seropositive and CD4+T cell <100/ul.) Trimethoprim/ Su 1 fa methox a zo 1 e DS po qd, or Trimethoprim/ Sulfamethoxazole SS po qd, or Atovoquone 1.5 g po qd, ot Dapsone 50 mg po qd, plus pyrimethamine 50 mg po weekly, plus lciieoYonii 25 mg po weekly
I ytomeg.llovirus (encephalitis, polyradiculomyclitis, tnononcl.inipathy multiplex)	Ganciclovir (induction: 5 mg/kg/day IV qSh x2 wk; maintenance: 5 mg/kg/day IV 5 days/wk) Foscamet (induction: 60 mg/kg IV q8h x2 wk, adjust for renal function; maintenance: SO mg/kg/day IV) Cidofovir (5 mg/kg IV! weekly *x2* wk, then every 2 wk	Bone marrow toxicity (ganciclovir) Renal toxiciry, hypocalcemia (foscamet) Renal failure, neutropenia, iriris, uveitis, ocular hypo tony (cidofovir)	(If prior cytomegalovirus retinitis) Ganciclovir 5 mg/kg/day IV 5 days/wk, or Foscamet 90 mg/kg/d IV, or Cidofovir 5 mg/kg IV every other wk
JC virus (progressive mulrifocal leukoencephalopathy)	Inter feron-ur (3 million U/day sc) Cidofovir (.5 mg/kg IV wkly x2 wk, then every 2 wk	Flulike syndrome (interfere n-nr) Renal failure, neutropenia, iritis, uveitis, ocular hypotony (cidofovit)	
AIDP	IVIG 0.4 g/kg/day IV x5 days	Flulike syndrome, renal failure, headache	
Q DP	IVIG 0.4 g/kg/day IV *x5* days for relapse Prednisone 1 mg/kg/day until improvement, then titrate downwards	Flulike syndrome, renal failure, headache (IVIG) GI, hypertension, weight gain, infection	
Polymyositis	Prednisone 1 mg/kg/day until improvement, then titrate downwards	Gl, hypertension, weight gain, infection	

AIDP = acute inflammatoty demyelinating polyradiculoneuropathy; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy[1]; PS double strength; * .1 -.islioiiHesiin.il; SS -,i11;:.!.• si n.••.-.:'.:; *w* \v.rk.

commonly, tubercular, fungal or bacterial abscesses (Minamoto and Rosenberg 1997). Resolution of lesions on antitoxoplasma therapy confirms the clinical diagnosis. The definitive diagnostic procedure is brain biopsy, but it carries morbidity and therefore is reserved for the patient who has failed 2—4 weeks of empirical antitoxoplasma therapy.

Standard therapy in TE is sulfadiazine (0.5-1.5 g by mouth every 6 hours) and pyrimethamine (200 mg loading day 1, then 75 mg by mouth every day). Folinic acid 10 mg a day is given to counteract pyrimethamine bone marrow toxicity. Clindamycin (600 mg intravenously or by mouth every day) can be substituted for sulfadiazine in sulfa-allergic patients. Long-term suppressive therapy is generally

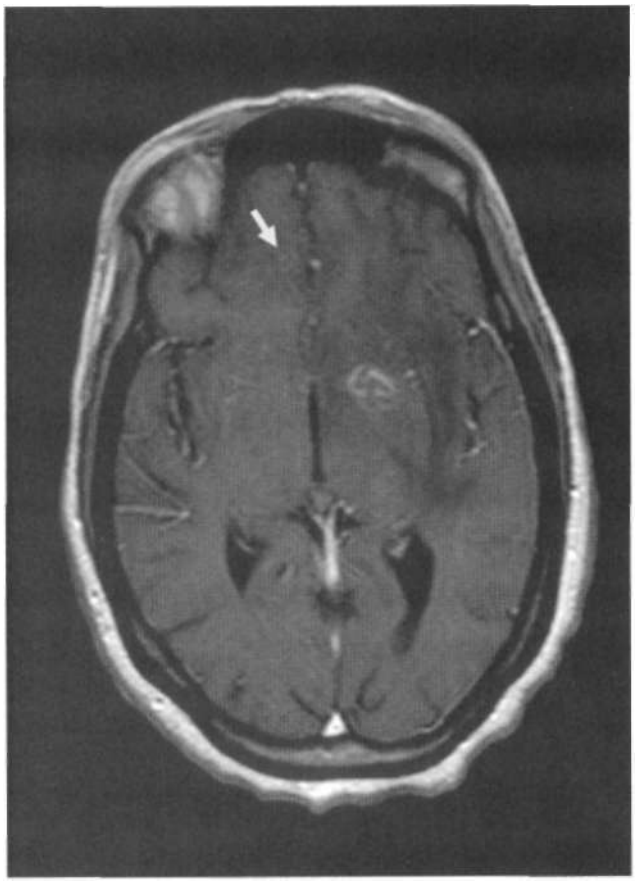

FIGURE 59H.4 Cerebral toxoplasmosis in AIDS. Post-gadolinium axial Tl-W-MRI demonstrating ring-enhancing lesions in tlie left basal ganglia and right parasagittal frontal region *(arrow).* Courtesy Dr. S. Ouanounou

required, but doses may be tapered to pyrimethamine 2.5 mg per day and sulfadiazine 2 g per day. Relapses are common, and it is recommended that patients with a history of TE receive lifelong maintenance therapy with sulfadiazine, pyrimethamine, and folinic acid. In patients who do not tolerate sulfa drugs, clindamycin (300-450 mg three or four times daily po) can be substituted. The patients who show immune reconstitution on successful HAART with CD4~ T cell counts >100/uL may not require continued prophylaxis after 3-6 months prophylactic therapy. Rarely, toxoplasmosis manifests as acute meningoencephalitis, variably accompanied by muscle involvement (Gherardi et al. 1992), In the even more unusual circumstance in which the diagnosis is made premortem, antiroxoplasma therapy may be lifesaving.

Patients with $CD4^1$ T cell counts <100/uL and IgG antibodies to *Toxoplasma* should receive primary prophylaxis against toxoplasmosis. HIV-infected patients who are seronegative for *Toxoplasma* should be counseled about ways to minimize the risk of primary infection, including avoiding consumption of undercooked food and careful liaiul w:i~li::ii', after contact with **soil** or chansiinj; **ifc oil** litter box.

Primary CNS Lymphoma

Primary CNS lymphomas (PCNSL) of B-cell origin arc considered opportunistic neoplasms that complicate the course of AIDS in up to 5% of patients. The incidence of PCNSL in HIV-infected individuals appears to be incteasing because of their increased longevity following the efficacy of both prophylactic and therapeutic measures against OIs and HAART. Patients with PCNSL present with progressive focal or multifocal neurological deficits similar to those seen with toxoplasmosis and PML (DeAngclis 2001). The tempo of disease evolution in PCNSL is generally slower than in toxoplasmosis and faster than in PML, with patients presenting after several days or a few weeks after the onset of symptoms. These symptoms may include headache, hemiparesis, aphasia, ataxia, behavioral changes, and altered mentation. Fever and constitutional symptoms arc absent except in patients with associated systemic infection.

The diagnosis of PCNSL is generally considered following review of neuroimaging in appropriate clinical setting. MRI is more sensitive than CT scan, and it characteristically shows one or more lesions (Thurnher et al. 2001); PCNSL microscopically is multicentric. The location is typically deep in the brain, adjacent to the lateral ventricles and often in white rather than gray matter; MRI may show characteristic subependymal extension (Figure 59E.5). Mass effect may be present, but there is usually little contrast enhancement or surrounding edema. CSF cytology is frequently unhelpful, although the presence of monoclonal B-lymphocyres by flocytometry, if demonstrated, indicates PCNSL. PCR amplification of Epstcin-Barr virus DNA in CSF corroborates the diagnosis of PCNSL (Cinque et al. 1997). The definitive diagnosis of PCNSL generally requires brain biopsy. Most often, brain biopsy is undertaken after a therapeutic trial for cerebral toxoplasmosis. Thallium-201 SPECT may be useful in supporting the diagnosis of PCNSL and prompting early biopsy. The use of stereotactic biopsy techniques has increased the access to these tumors and reduced the morbidity of biopsy.

Before HAART era, the outcome of AIDS-associated PCNSL had been dismal, with medial survival of approximately 80 days. As with PML, the prognosis in PCNSL is improved by successful HAART and immune reconstitution, and vigrous attempts to supress HIV replication are recommended in all patients. Mass effect is treated by high-dose corticosteroid therapy. Palliative whole brain irradiation therapy is reasonable, at least to buy time for HAART regimen to work. Use of chemotherapy remains controversial outside a clinical trial setting (Forsyth and DeAngelis 1996).

Progressive Multifocal Leukoencephalopatby

JC virus, a human papilloma virus that is the etiological agent for PML, is an important opportunistic pathogen in

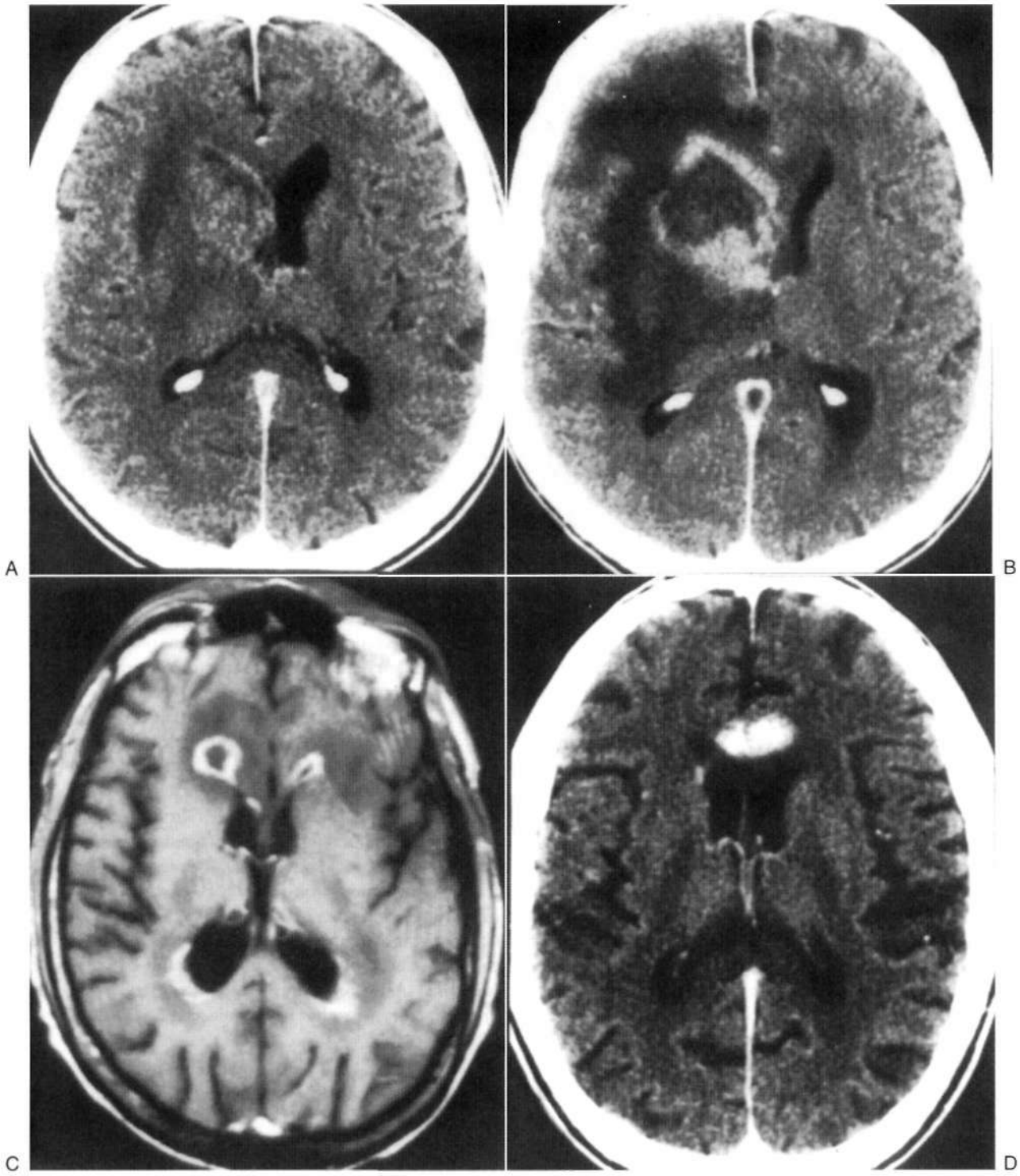

FIGURE 59E.5 Primary central nervous system lymphoma. (A) Contrast-enhanced computed Tomographic scan shows a solitary, enhancing lesion adjacent to the right frontal horn with edema and mass effect. (Bl Repeat contrast-enhanced computed tomographic scan after empiric antitoxoplasma therapy shows increased lesion size, enhancement, edema, and mass effect, consistent with lymphoma. Images train two additional patients show involvement of subependymal regions on (C) gadolinium-enhanced Tl magnetic resonance imaging and (D) corpus callosum on contrast-enhanced computed tomographic scan. (Courtesy Dr. Alisa D. Gean.)

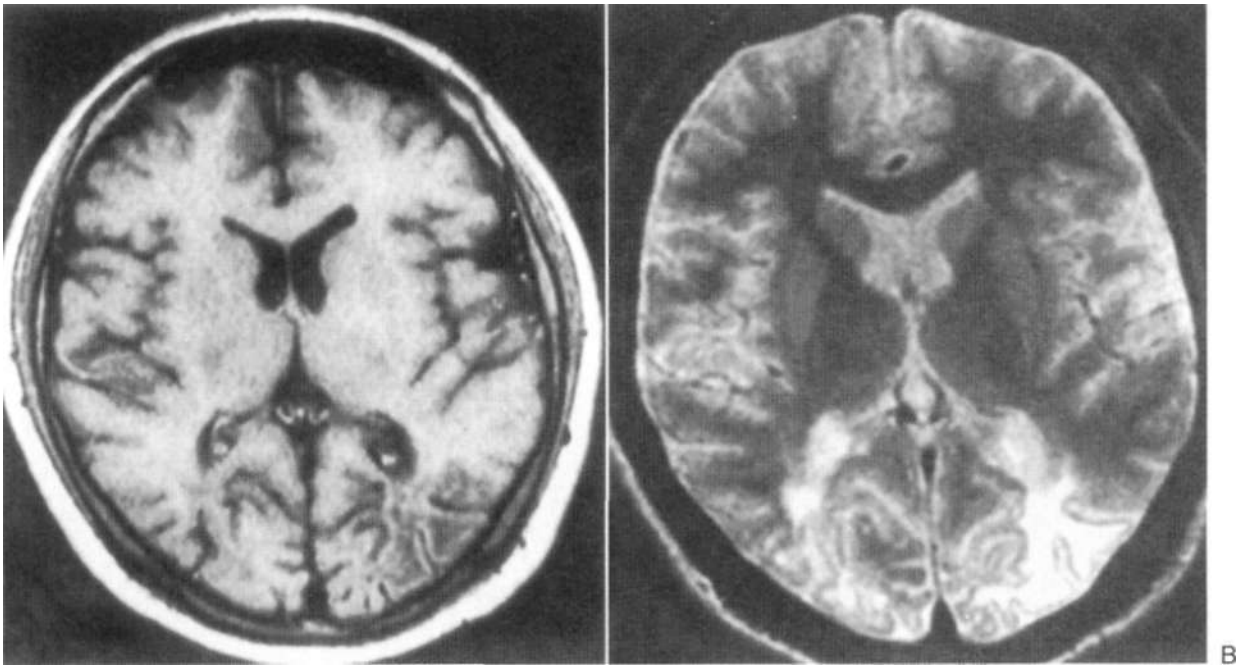

FIGURE 59E.6 Progressive multifocal leukoeiiecphalopathy. (A) TL and (B) T2 cranial magnetic resonance images show bilateral lesions in occipital white matter without mass effect.

patients with AIDS (Dworkin 2002). Approximately 70% of the general population has antibodies to JC virus, indicative of prior infection, hut less than 10% of healthy persons show any evidence of ongoing viral replication. PML is the only known complication of JC virus infection. It is a late manifestation of AIDS and is seen in approximately 4% of patients with AIDS. The lesions of PML begin as small foci of demyelination in subcortical white matter, often in the parietooccipital area, that eventually coalesce. The cerebellum, the brainstem, and very rarely the spinal cord can be involved in PML. Patients typically have a protracted course with focal neurological deficit, with or without changes in mental status. Visual field defects, hemiparesis, aphasia, sensoty defects, and ataxia may occur. MRI typically reveals multiple, nonenhancing white mattet lesions that may coalesce and have a predilection for occipital or parietal lobes (Figure 59E.6). CSF is usually normal or shows nonspecific changes, hut the viral DNA can be amplified from the CSF sample. CSF PCR for JC virus DNA appears to be more specific than sensitive for the diagnosis of PML, but eventually may decrease the need for brain biopsy {in positive cases) in practice and in clinical trials. In cases in which viral DNA is not detected in CSF, a brain biopsy is necessary to confirm the diagnosis. Brain biopsy reveals bizarre giant astrocytes with pleomorphic hyperchromatte nuclei, altered oligodendrocytes with enlarged nuclei that contain viral inclusions, and myelin loss.

There is no specific therapy for PML. Mean survival is 2^1 months; approximately 8% of patients experience spontaneous remission (Simpson and Berger 1996). Despite anecdotal evidence describing benefit from intrathecal or intravenous cytosine arabinoside therapy, a controlled study showed no benefit. Regression of the lesion and prolonged survival for more than 2.5 years have been recently reported in patients with **PML** treated successfully with HAART for their HIV disease (Clifford et al. 1999). Factors influencing a favorable outcome include CD4' T cell counts >100/uL at baseline and the ability to maintain an HIV viral load of less than .500 copies per milliliter. Baseline viral load docs not seem to have independent predictive value of survival. Unfortunately, immune reconstitution takes considerable time, in some cases longer than the survival expectation from PML and, hence, the necessity to develop therapy directed against the JC virus. Cidofovir, a drug used for cytomelovirus in AIDS patients, topotecan, a topoisomerase inhibitor, and IFN-a have been tried in AIDS-related PML with varying, generally unsatisfactory, results (Gasnault et al. 2001; Dworkin 2002).

HIV-associated Vacuolar Myelopathy

VM is the most common cause of spinal cord dysfunction in patients with AIDS, apparent pathologically in 25-55% of AIDS autopsy series (Dal Pan et al. 1994; Dt Rocco and Simpson 1998). VM complicates late HIV infection and frequently coexists with HAD and DSP. Affected patients develop gait difficulty, caused by spasticity, leg weakness, and impaired proprioception, often accompanied by sphincter dysfunction, evolving over several months. Back pain is not a prominent feature. Examination reveals spastic paraparesis with Babinski's signs and hyper-reflexia, unless concomitant neuropathy is severe. Sensation in the legs,

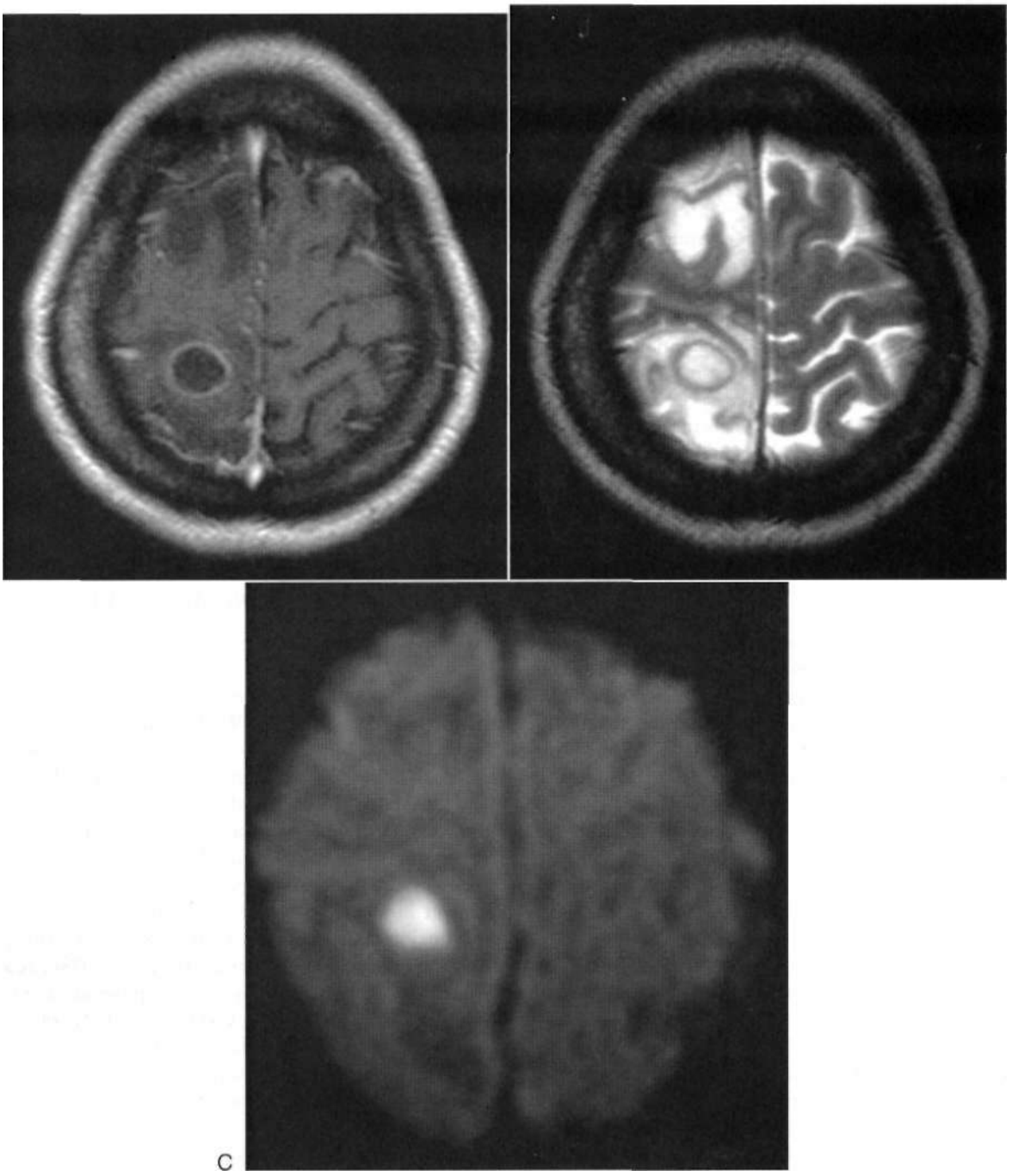

FIGURE 59E.7 Pyogenic brain abscess in AIDS. Postgadolinium axial T'l-W-MRI showing ring-enhancing lesion (A) with surrounding edema best seen in T2-W sequence (B) and with associated intralesional diffusion restriction (DW-MRI, C). (Courtesy Dr. S. Ouanounou.)

particularly proprioception and vibratory sense, is usually impaired, but a clear sensory level on the trunk is unusual. The arms are typically spared until VM is advanced. MRI may occasionally reveal cord atrophy, but usually is unremarkable. Pathological findings are most striking in the dorsolateral thoracic cord and include vacuolar changes in myelin sheaths with relative preservation of axons. Despite the clinical and pathological resemblance to combined systems degeneration, vitamin Bi_2 levels are typically normal in affected patients. HIV-induced release of neurotoxic cytokines or abnormalities in vitamin B12 utilization may contribute to the development of VM.

Evidence that viral control can result in unproved neurological function is not well documented in VM, but there are such reports, making the effort to control the infection important. Additionally, VM is often associated with HAD, in which improvement following HA ART and virus control is better documented. One should construct a

potent and toletahle regimen individualized to the patient's virus and medical history (discussed previously, principles of antiretroviral therapy). Patients with myelopathy and paraplegia require considerable assistance, comparable with that fot multiple sclerosis patients with severe spinal cord demyelination. Care of the neurogenic bladder, bladder infection, management of limb spasticity, prevention of skin breakdown and dccubiti, and assist devices to improve mobility are the issues that tequire individualized attention,

Numerous other infectious, neoplastic, and metabolic disorders occasionally cause myelopathy in patients with HIV infection, and they need to be differentiated from VM. Compared with VM, these disorders may progress more rapidly, often with associated back or radicular pain. CMV, VZV, and herpes simplex virus may cause myelitis. Helpful diagnostic tests include spinal MRI, which may teveal cord swelling with intramedullary enhancement and T2 signal changes, and CSF PCR testing for viral DNA. Because HIV shares risk factors with human T-cell lymphotropic virus I and II, cotnfection with these retroviruses ;iko may cause myelopathy ill the HIV-infected patient. Othet causes of myeloneuropathy complicating HIV infection include neurosyphilis and vitamin B_{12} deficiency. HIV-infected parenteral drug users may develop spinal epidural abscess, a neurosurgical emergency whose clinical manifestations do not appear to be significantly modified by HIV infection (Heary et al. 1994). Rarer infectious causes of myelopathy include M. *tuberculosis* and *T. sioiulii.* Patients with AIDS arc susceptible to systemic lymphoma, which can cause myelopathy ftom epidural metastases.

Stroke

Cerebrovascular disease also causes focal brain dysfunction in HIV infection. Ischemic and hemorrhagic stroke have been reported in up to 4% of clinical series and up to 34% of autopsy series (Pinto 1996). Whether HIV infection itself elevates stroke risk remains uncertain. Thrombocytopenia, coagulopathy related to liver disease or disseminated intravascular coagulation, PCNSL, metastatic Kaposi's sarcoma, and rarely, toxoplasmosis, may be associated with cerebral hemorrhage. Causes of ischemic stroke include bacterial endocarditis, particularly in IDUs, as well as nonbacterial thrombotic endocarditis, vasculitis, and procoagulant states. Granulomatous angiitis of the nervous system has been reported in AIDS. VZV, tuberculous meningitis, and meningovascular syphilis can cause infectious vasculitis, as can the angioinvasivc fungi *Aspergillus* and *Mucar.*

Other Focal CNS Disorders

Numerous other infections have been reported to cause focal cerebral dysfunction in HIV-infected patients. Bacteremia from indwelling catheters needed to manage other aspects of HIV infection or from parenreral drug use predisposes to bacterial brain abscess (Figure 59E.7). Other bacterial causes of focal cerebral dysfunction include *Mycobacterium tuberculosis* abscess, syphilitic gumma, *Bartotiella henselae* (Marra 1995), and *Nocardia asteroides.* Fungal causes of focal brain disease, in addition to the angioinvasive fungi discussed previously, include cryptococcoma, *Blastomyces dermatitidis,* and *Histoplasma capsulatum* (Minamoto and Rosenberg 1997}. Among parasites, relevant diagnostic considerations in patients who have lived in or traveled through endemic areas arc cysticercosis and intracerebral Chagas' disease *{Trypanosoma cruzii)* (Gluckstein et al. 1992). VZV can cause a demyclinating syndrome with lateralmng fearures (Gray et al. 1994), and CMV has been reported to cause mass lesions (Moulignier et al. 1996). Interestingly, HIV infection docs not appear to increase significantly the risk for herpes simplex virus encephalitis.

H1V-ASSOCIATED NEUROMUSCULAR DISORDERS

Neuropathies

Peripheral neuropathies are common in HIV infection (Sadler and Nelson 1997; Wulff et al. 2000; Verma 2001; Sacktor 2002). Peripheral neuropathies complicate all stages of the HIV disease and cause considerable morbidity and disability in HIV-infected individuals and AIDS patients. Although symptomatic neuropathy occurs in approximately 10 to 15% of HIV-infected patients overall, pathological evidence of peripheral nerve involvement is present in virtually all end-stage AIDS patients. There are five major clinical types of HIV-associatcd neuropathies that are regularly seen in large HIV clinics: DSP, acute and chronic inflammatory demyelination polyradiculoneuropathies (AIDP and CIDP), CMV-associated polyradiculomyelopathy, and nucleoside-associated toxic neuropathies. A vasculitic neuropathy is less common but often responds well to corticosteroid treatment.

Distal Sensory Polyneuropathy

Of the various peripheral nerve syndromes that complicate HIV infection, the most common is DSP, also called HIV-associated neuropathy or AIDS neuropathy. This axonal, predominantly sensory, length-dependent polyneuropathy develops in approximately one third of patients with AIDS, becoming more prevalent as the CD4~ T cell count decreases (Sadler and Nelson 1997; Childs et al. 1999). Depressed or absent ankle jerks and mild pain, Temperature, and vibratory sensory loss in the feet, with or without associated foot parcsthesiae and numbness, may be the only evidence of the disorder, and probably make up the more common clinical syndrome. Less frequently, severe burning

pain and parcsthesiae develop in the feet, often disrupting sleep in a manner reminiscent of diabetic or nutritional sensory polyneuropathies. Symmetrical involvement is a characteristic clinical feature, and the hands are usually spared until the disorder is advanced. F.ven though DSP typically spares motor function and proprioception, walking may be impaired because of severe pain. The pathogenesis of DSP is not well understood. Cytokine upregulation in advanced infection has been proposed, as have dorsal root ganglion toxicity of HIV antigens and the effects of chronic, multisystemic illnesses.

The rather typical clinical features usually obviate the need for electromyography and nerve conduction studies. Exposures to neurotoxins, including ethanol, should be reviewed. Neurotoxic drugs commonly used to manage HIV infection include the nucleoside analogs didanosine, zalcitabine, and stavudine (see Table 59H.3), in addition to isoniazid, pyridoxine, dapsone, metronidazole, and vincristine. Screening for vitamin B_{12} deficiency and diabetes mellitus is important. Goals of treatment include minimizing neurotoxic exposures, virus suppression by HAART, and management of pain. Tricyclic antidepressants and anticonvulsants ameliorate neuropathic pain in DSP. When there is coexisting dementia or other cerebral disease, the anticholinergic effects of amitriptylinc may be poorly tolerated. Using very low doses or switching to a less anticholinergic tricyclic antidepressant such as nortriptyline, plus addition of a selective serotonin reuptake inhibitor, may facilitate tolerance. With regard to anticonvulsants, the high rate of adverse reactions and drug interactions with carbamazepine in patients with AIDS limits its utility for the management of neuropathic pain, The favorable side effect and drug interaction profile of gabapentin makes it the treatment of choice for managing neuropathic pain in AIDS. Mexiletine, selective serotonin reuptake inhibitors and topiramate have been tried with variable success, A recent trial with nerve growth factors failed to show clinically significant improvement. Topical capsaicin is an appealing choice for select patients with DSP. but is rarely dramatically beneficial. Other occasionally useful adjuncts include nonsteroidal anti-inflammatory drugs, transcutaneous electrical nerve stimulator units, and acupuncture, but some patients may require chronic narcotic therapy.

Nucleoside Analogue-Associated Toxic Neuropathy

A painful polyneuropathy that closely resembles DSP is the major dose-limiting toxicity of the nucleoside analogue antiretroviral agents didanosine, zalcitabine, and stavudine (Verma 2001; Sacktor 2002). Two clinical features can help distinguish nucleoside neuropathy from DSP. First, nucleoside neuropathy typically evolves over weeks following initiation of therapy, in contrast to DSP, which progresses over months or even years. Second, stopping the offending agent eventually leads to regression of nucleoside neuropathy over several months, although *coasting,* in which symptoms worsen for several weeks before improvement, may complicate the evaluation of this strategy for diagnosis. Although pre-existing DSP increases the risk for nucleoside neuropathy, many patients with DSP tolerate neurotoxic anciretrovirals, particularly if the dose is kept low. Similarly, many patients who develop nucleoside neuropathy can resume therapy at a lower dose or may tolerate a different neurotoxic drug. Other aspects of the evaluation and treatment are similar to DSP.

inflammatory Demyel'mating Polyradiath>!u-itrojhHk'w<,

Less common than the painful neuropathies related to HIV or nucleoside antiretrovirals are the inflammatory demye-Imaring polyradiculoneuropathies (IDP), AIDP, and CIDP {Wulff et al. 2000). These disorders resemble the syndromes seen in individuals without HIV infection with regard to pathogencsi* and men cluneal features. 1 he precise prevalence is unknown, but case series from the United States and Africa suggest that the IDP often develops during early HIV infection, sometimes around the time of seroconversion. Before the frank immunosuppression of AIDS, viral antigenemia and immune dysregulation are presumed to cause autoimmune disorders, such as the IDI[J], in early HIV infection. AIDP or the Guillain-Barre syndrome typically presents as rapidly progressive ascending weakness with areflexia, variably accompanied by respiratory failure and dysautonomia. The Miller-Fisher variant, in which cranial nerve dysfunction, areflexia, and ataxia are more prominent than limb or respiratory weakness, also has been described during HIV infection. In CIDP, neuropathic weakness and sensory loss occurs in a more indolent and episodic manner than in AIDP. Cranial nerves may be involved in CIDP, but respiratory failure or autonomic dysfunction are unusual. In both AIDP and CIDP, electrophysiological studies reveal slowed conduction, temporal dispersion, multifocal block, and ptolonged F waves, indicating demyelination. CSF from seronegative patients with IDP typically reveals only elevated protein, sometimes with oligoclonal bauds on Immunoelectrophoresis, without associated pleocytosis. In HIV-infected patients with IDP there is often lymphocytic pleocytosis (10-50 cclls/nl.) in addition to increased protein. Clinical experience suggests that intravenous immunoglobulin, plasmapheresis, and corticosteroids {only CIDP) are beneficial.

Lumbosacral Folyradiculomyelitis

Subacute lumbosacral polyradiculomyelitis is an uncommon HIV-relatcd syndrome that results from a variety of infectious agents, most notably CMV, Clinical manifestations suggest a cauda equina syndrome, with leg weakness and later paralysis, sphincter dysfunction, sacral and leg paresthesiae and sensory loss, and areflexia, typically

evolving over several days. When such a syndrome develops in a patient with a CD4' T cell count less than 50/|iL, and CSF reveals marked polymorphonuclear pleocytosis, elevated protein, and low to normal glucose, CMV infection of the nerve roots, with subsequent inflammation and necrosis, is the likely cause. CMV PCR or branched DNA assay in CSF is a helpful confirmatory test, but treatment should not be delayed pending these results. Intravenous ganciclovir (see Table 59F.4) can arrest and reverse the deficit in CMV polyradiculomyelitis, which is fatal without treatment (McCutchan 1995; Wulff et al. 2000). Polyradiculomyelitis caused by ganciclovir-rcsistant CMV has been reported and may respond to foscarnet, either alone or with cidofovir. Other causes of polyradieulomyelopathy in AIDS include tuberculosis, neurosyphilis, and lymphomatous meningitis.

Other Neuropathies and Neuronopathies

Mononeuritis multiplex (MM) is a relatively rare peripheral nerve syndrome of HIV infection that manifests clinically as multifocal, asymmetrical peripheral nerve lesions that may include cranial nerves. When the syndrome develops in early or mid-stage HIV infection, it often responds well to corticosteroid therapy, though it may be self-limited, not requiring immunosuppressive therapy (Bradley and Verma 1996). MM complicating advanced HIV infection, with $CD4^+$ T cell count less than 50/uL, may be caused by CMV and responds to intravenous ganciclovir. An ALS-like syndrome (Moulignier et al. 2001) and brachial plexus and lumbosacral plexus (Benatar and Eastman 2000) neuropathies have also been reported in HIV disease.

Myopathics

Myopathic symptoms in HIV-infected individuals can arise from toxic (zidovudine) or dysimmune (polymyositis) causes or from AIDS cachexia (muscle wasting syndrome) (Lange 1994; Sheikh et al, 1999). In HIV-associated polymyositis, patients develop proximal weakness and, less commonly, myalgia, both of which are ascribed to a dysimmune response following 1IIV infection. On occasion it may occur with immune restoration following HAART (Sellier et al. 2000). Serum creatine kinase is elevated in most cases, and electrophysiological studies often reveal myopathic motor units and increased insertional activity and spontaneous activity typical of an inflammatory myopathy. Muscle biopsy reveals fiber size variability, fiber degeneration, and endomysial infiltrates. Cytoplasmic bodies and nemaline rod bodies are other common histological features. HIV does not appear to directly infect muscle fibers, but rather induces them to express major histocompatibility complex I, triggering cell-mediated muscle fiber injury. Even so, inflammatory myopathy is among the few HIV-related neurological disorders that develop at any time during HIV infection. Despite the potential risks of corticosteroid therapy in the setting of HIV infection, such treatment is often well tolerated. Prednisone has helped in motor recovery and pain improvement in HIV-associated polymyositis. Starting with dose of 1 mg/kg per day, the dose is titrated downward as strength improves. Inclusion body myositis also has been reported in association with HIV infection (Cupler et al. 1996).

Zidovudine myopathy is a toxic mitochondrial disorder that presents with the insidious onset of proximal weakness and myalgia, making it difficult to distinguish clinically this condition from HrV-associated inflammatory myopathy (Grau et al. 1993). Though first described in patients raking zidovudine in doses of 1000 mg per day or more (Dalakas et al. 1990), zidovudine myopathy also develops on lower dose regimens in current HAART regimen. Affected patients typically have taken zidovudine for at least *6* months. Serum creatine kinase may be normal or elevated, .uul iiiusclr :iiojv-\ slunv, hivolniuV,!! leanre[1]. v.ii',i',iMmi>, mitochondrial dysfunction, with no or scanty inflammation, Clinical response to a drug holiday or reduction in zidovudine dose often obviates the need for muscle biopsy.

Pyomyositis, a focal suppurative bacterial muscle infection, was more common in the tropics but rare in developed nations, before the AIDS epidemic (Medina et al. 1995; Hossain et al. 2000). Clinical features include fever accompanied by local muscle pain and swelling evolving over several weeks. A source of bacteremia may be evident by history or general examination. Typically, the affected area is swollen, hot, and indurated, but not fluctuant, Peripheral white count and serum creatine kinase are usually normal, prompting consideration of cellulitis or deep venous thrombosis as the initial diagnosis. Ultrasound, CT, or MRI of the affected area establishes the diagnosis. Blood cultures may reveal the causative organism, usually *Staphylococcus aureus* or, less commonly, *Salmonella typhi* or other gram-negative bacilli (Medina et al. 1995). Empirical intravenous antibiotic therapy should be given to cover these pathogens. Surgical drainage may be required. Intravenous therapy for 1-2 weeks is usually followed by oral antibiotic therapy for up to 8 weeks. Disseminated infection with C. *twoformans*, *T. gondii*, M. *tuberculosis*, *Mycobacterium avium-intracellulare*, and Microsporidia occasionally may involve muscle also. HIV infection has also been associated with adult-onset nemaline rod body myopathy. Rhabdomyolysis may occasionally occur at the time of seroconversion.

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Chapter 59
Infections of the Nervous System

F. NEUROLOGICAL MANIFESTATIONS OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN CHILDREN

Ashok Verma and Anita L. Belman

EPIDEMIOLOGY AND CURRENT TRENDS

Epidemiology of human immunodeficiency virus type-1 (HIV-1, called henceforth HIV) infection and acquired immunodeficiency syndrome (AIDS) in adults is covered in Chapter 59E. The epidemiological consideration of pediatric HIV infection must take into account HIV-infected women and children together because the worldwide increase in the number of children with vertically acquired HIV infection parallels the increase in number of HIV-infected women of childbearing age. The exact number of HIV-infected children is unknown because surveillance systems in the past have relied on identification of children younger than age 15 years who had clinical manifestations of AIDS. According to the United Nations Program on HIV/AIDS, as of the end of 2002 out of 42 million people estimated to be living with HIV infection, 19.2 million arc women and 3.2 million are children under 15. An estimated 5 million people acquired HPV in 2002, including 2 million women and 800,000 children under 15. During 2002, AIDS caused the deaths of an estimated 3.1 million people, including 1,2 million women and 610,000 children under 15 (United Nations: www.unaids.org/epidemic update),

The cumulative number of AIDS cases in the United States reported to the Center for Disease Control and Prevention (CDC) is 816,149, and children under age 15 account for a total of 9074 AIDS cases {CDC: www.hivatis.org). Total deaths of persons reported with AIDS reported to the CDC are 467,910, including 5257 children under age 15. The incidence of perinatally acquired AIDS peaked in the United States in 1992 and then decreased in the ensuing years (Figure 59F.1). In April 1994, the United States Public Health Setvice released guidelines for the use of zidovudine (ZDV) to reduce perinatal HTV transmission, and in 1995 recommendations for HIV counseling and voluntary testing for pregnant women were published. Highly active antiretroviral therapy (HAART) was introduced in 1996. Since then, the percentage of perinatally HIV-exposed or HIV-infected children who received antiretroviral therapy (postnatally) and whose mothers received IIAART (parapartum) has increased steadily and significantly. As a tcsult, in 2000 only 196 children were reported to CDC with AIDS, a decrease from 263 in 1999. Over 90% of HIV-positive children acquire the infection pctinatally, that is, from their mothers before or during the birth or from breastfeeding.

The prevalence of neurodevelopmental abnotmalities in children with HIV is high. Approximately 50% of HIV-infected children who have not received antiretroviral therapy have abnormal neurodevelopmental findings: abnormal motor function, reflexes, and cognition. The frequency with which HIV-rclated progressive encephalopathy (HPE) is reported as an initial AIDS-defining illness is much higher in children (12-67%) than is reported in adults. Particularly noteworthy is the finding that more than half of these children are not severely immunosuppressed at the time of the HPE diagnosis: 26% of the children do not demonstrate CD4+ T cell depletion at all;

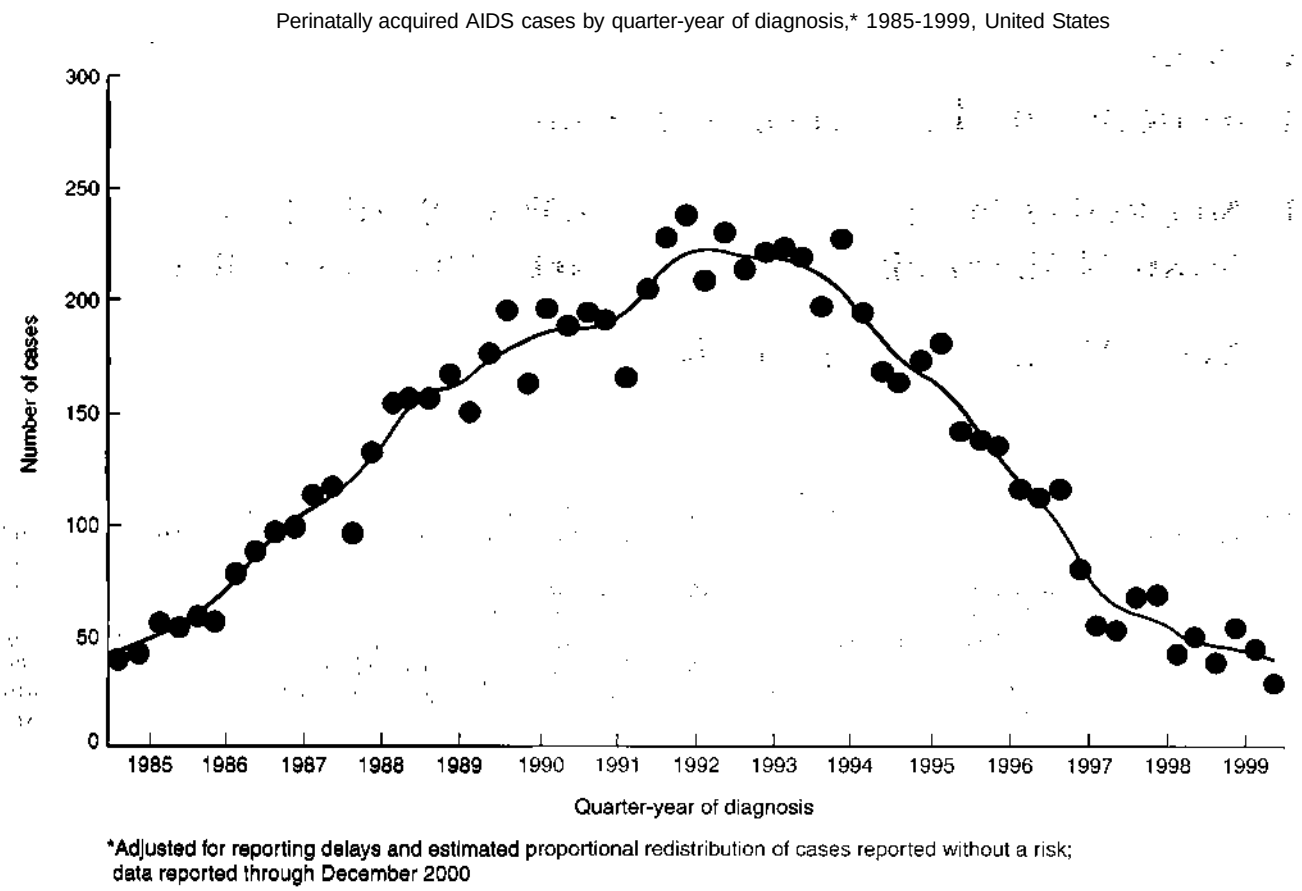

FIGURE 59F.1 Notified cases of pediatric AIDS in the USA from 1985 to 1999. Source: CDC Atlanta (http://phil.cdc.gov/phil/).

approximately 30% have moderate suppression; and only 44% are severely immunosuppressed.

TIMING AND MODE OF HIV INFECTION IN CHILDREN

Vertical Transmission

Most mother-to-child transmissions of I NV occur in utcro in intrapartum, or in postpartum period via breastfeeding The true frequency of in utero versus peripartum transmis sion is not known. A healthy placenta generally protects the fetus in utero from HIV in the maternal blood for most of the gestation. The integrity of the placental protection against HIV may rarely be breached by infections and drugs (e.g., *Toxoplasma).* In a nonbreastfeeding population, modeling backwards from the earliest detection of HIV DNA by polymerase chain reaction (PCR) in the infant's blood in the first days or weeks of life has suggested that the majority of transmissions occur around the time of delivery, with the remainder mostly late in the third trimester. For breastfeeding, the risk of transmission extends beyond delivery and throughout the breastfeeding period. The overall risk of transmission of HIV from the untreated mother to child is about 20-30% for nonbreastfeeding mothers and 30-45% for breastfeeding mothers.

Although infection during or near the time of birth has become rare in industrialized countries following the use of antirctroviral therapy, it continues to be rampant in the underdeveloped nations. It is estimated to be 19-24% in Thailand and 25-45% in Africa. Factors associated with increased transmission risk include low maternal CD4+ T cell count, high viral load, advanced HIV disease or AIDS, low vitamin A level, placental membrane inflammation, premature rupture of membranes, increased infant exposure to maternal blood, premature delivery, and breastfeeding.

Parenterally Acquired Infection

Before routine blood donor screening for HIV, recipients of HlV-contaminated blood or blood products included children with hemophilia or other coagulation defects and children with illnesses that required blood transfusions

(e.g., children with leukemia, sick neonates). Virus transmission also occurred through the use of contaminated injection equipment. Although hlood screening and preventive medical practices have significantly improved the risk of contracting HIV infection through blood transfusion, the risk of contact with unsterile skin-piercing instruments still remains for children, particularly for children living in areas where blood supplies are not properly screened and universal preventive precautions are not observed.

Sexually Transmitted Infection

Sexual abuse during childhood and adolescence in the home or community or by exploitation is a well-documented problem that affects all societies. Sexual abuse of children takes two forms: (1) commercial sexual exploitation (a clandestine trade in certain parts of the world) and (2} sexual abuse in the home and community. Most sex industry children are girls aged 13-18 years. Although not a new phenomenon, childhood sexual abuse has recently been recognized by the World Health Organization as a major worldwide concern. Ir is unknown how many child sex workers exist in the world and how frequent is the sexual transmission of HIV in these young individuals.

CLINICAL APPROACH TO CHILDREN WITH HIV DISEASE

The diagnosis of pediatric HIV infection and the associated neurological disorder requires experience, clinical skills, and major neurodiagnostic investigative tools. A careful medical and developmental history, HIV systemic disease history (see following), current immunological and virological status, neurological examination, neuropsychological assessment, and neuroimaging studies arc often required to diagnose accurately the HIV-associated neurological diseases in children.

The diagnosis is straightforward if a previously known seropositive child is found to have cognitive and motor impairment and the clinical assessment documents the new onset of, or progression of, these deficits. Serial assessments of untreated children with HPE reveal progressive neurological deficits (other causes excluded). The diagnosis of opportunistic infections (OIs), neoplasia and Hl'K is often straightforward if the child has been followed prospectively. The infant may show impaired head control, speech deterioration, axial hypotonia, or upper motor neuron signs. The toddler or older child may have a change in gait, become hyperreflexic, refuse to walk, and over time may develop progressive corticospinal tract (CST) signs.

Diagnostic difficulties arise when the youngster who has not been followed prospectively is found to have a neurological deficit. Because of the relatively high frequency of neurological and developmental impairments in this population, it is often difficult for the clinician to ascribe these findings to ! NV-associatcd central nervous system (CNS) disease. A careful history is paramount. If no other risk factors are identified, the diagnosis of HIV-associated disease is likely. Neuroimaging studies are critical. If calcification of basal ganglia is present (see following), it is probable that the child's neurological deficits arc related to HIV infection. If cerebral atrophy is present in the absence of documented perinatal complications or other known causes of atrophy, the diagnosis is also very likely. Head circumference measurements are invaluable (Belman 1990). A careful review of medical records will document at least one or two past head circumference measurements, allowing serial measurements to be plotted. If a pattern of downward deviation and acquired microcephaly is present, the diagnosis is likely. Thus neuroimaging evidence of atrophy accompanied by acquired microcephaly clearly strengthens the diagnosis 01 Hl'K. 1 ol;ow-Lip neimi'oL'.ival, pv> chonu-tric, and neuroimaging studies help confirm the clinical diagnosis.

Laboratory Monitoring of HIV Infection in Infants and Children

Plasma viral load data from prospective cohorts followed from birth demonstrate the difference in response to infection in infants and young children compared to adults. Within 4-8 weeks of birth a peak viremia is reached in perinatally HIV-infected infants, and this may take many years to decline to a baseline. The HIV RN'A copies at the peak are higher and the subsequent decline is much slower in children than that seen in newly infected adults (Abrams ct al. 1998; Dickover et al. 1998). In one cohort *[n* - 106), HIV was not detected in most infants at birth, consistent with very recent intrapartum infection, and the median viral load at one month was 318,000 copies/uL. The median base line level of 34,000 copies/ul. was not reached until around 24 months of age. Infants with rapidly progressive disease generally have higher levels of viremia in the first days of life and during the first 2 months.

The HIV plasma viral load has also been measured in cohorts of children presenting with symptoms of disease and who had not been followed from birth. The relative risk of death during follow-up increased if the HIV RNA load was higher. In a time-independent model, the relative risk of death was 2,8 per $h>g_m$ increase in HIV RNA copy number. HIV RNA viral loads were highest in the young infants, and the greatest decline in viral bad occurred by *2-4* years, giving an average yearly decline of approximately 0.29 logio/year, unrelated to any interventions. Similar findings were demonstrated in a retrospective analysis of HIV RNA load in 70 children

(median age 3.5 years) entered in a study of immediate versus deferred ZDV monotherapy. The majority of these children (76%) were asymptomatic (stage N, see following) at enrollment, and the HIV RNA load was significantly higher in those <3 yrs (median 5.23 logio), and it fell to a nadir of 4,25 logio at 6 years; the decline was most rapid in the first 2 years of life. The predictive value of baseline viral load and its relation to the age of the infant/child was also demonstrated in another cohort. The risk of progression with elevation of viral load in the older children in these cohorts was similar to that seen in adults (CDC 1998).

A recent meta-analysis of more than 3000 untreated children from cohorts in the United States and Europe demonstrated that for children over 6 months of age progression to AIDS or death increased sharply for viral loads over 10" copies/uL, and at 2 years of age the risk of progressing ro AIDS was 5% with a viral load $<10^5$ copies/uL, 24% at 10^6 copies/uL, and 66% at 10^7 copies/uL (Lyall 2002).

CD4+ T cell Count and Progression of HIV Disease in Infants and Children

Assessment of a CD4+- T cell count in a child must be in relation to the appropriate count for age, the 50th percentile CD44- T cell count at age 6 months being 3000/pL, compared to 1,000/uL for a 6-year-old, by which time the CD4+ T cell count range approaches that of adults (Comans-Bitter et al. 1997). Further, for an individual child the CD4+ T cell count varies and is often depressed with intercurrent infections. Therefore, this parameter should be measured when the child is in a stable clinical condition. The CD4+ T cell percentage varies less with age and other factors than the absolute count and may be a more useful measure of immune function in children.

Although CD4+ T cell count may be less helpful in infants, overall the baseline CD4+ T cell count along with the plasma viral load are predictive of progression of HIV disease in children. Fot example, in one cohott, if the CD4+ T cell count dropped to < 15% the relative risk of death was 2,8 (95% CI 1.6-4.9). In a time-in dependent model the relative risk of death per 5-point decrease in CD4+ T cell percentage was *13 (95%* CI 1.2-1.5). In this cohort both HIV RNA levels and CD4-I- T cell counts were significantly and independently associated with mortality in the follow-up period.

In a recently reported meta-analysis, in children over 2 years of age the 12-month risk of developing AIDS was 6% for a CD4+T cell count of >20%, increased to 18% with a CD4+ T cell count of 10%, and 34% with a CD4+ T cell count of 5%. The CD4+ T cell count was less predictive of progression of disease in infants than that in older children in this meta-analysis.

CLINICAL FEATURES OF HIV INFECTION IN CHILDREN

Clinical features of HIV infection in a pediatric population differ from those in adults in a number of ways. First, up to 20% of children with HIV present with severe symptoms or they die in infancy (fast progressors). Whether their poor prognosis is related to a greater inoculum of HIV, earlier infection in the face of an immature immune system, the acquisition of immune escape HIV mutants from the mother, or a combination thereof is not completely known. Second, mononucleosis-like seroconversion illness with or without acute aseptic meningitis or meningoencephalitis described in some adults does not occur in infants. Third, the spectrum of neurological and non-neurological manifestations m I llV-infected children is somewhat different from adults. For example, hepatosplenomegaly and bone marrow failure, lymphocytic interstitial pneumonia (LIP), chronic diarrhea and failure to thrive, acquired microcephaly, cerebral vasculopathy and basal ganglia calcification are unique to or occur more frequently in children. Fourth, OIs that represent recrudescence of previously acquired infections in adults (e.g., cerebral toxoplasmosis, ptogressive multifocal leukoenceph.ilopathy) are obviously rare in infants. Fifth, absolute CD4+ T cell counts as a parameter of disease stage is less helpful in infants and young children as previously described. A high number of CD4+ T cells can be associated with a higher HIV load in infants and children than in adults, and infant fast progressors usually harbor higher plasma HIV RNA levels. Sixth, in an infant anti-HIV antibody in the serum may be of maternal (transplacental) origin and therefore is not diagnostic of infection (Blanche et al. 19fi^{L}>). The current gold standard test for HIV infection in infancy is HIV-DNA PCR on peripheral blood lymphocytes. Because most infants are infected intrapartum and circulating HIV levels may still be very low, HIV DNA cannot be amplified from the plasma in all infected infants at birth. Indeed a positive HIV-DNA PCR result within 48 hours of birth has been taken as evidence of intrauterine transmission. Finally, 1 iPE, clinical equivalent of HIV-associated dementia (HAD) in adults, is more frequent in children and is generally more amenable to treatment with HAART.

The current classification system of infection used for children was revised in 1994 prior to the availability of measurements of HIV plasma viremia. This classification is based on clinical signs and symptoms, giving a clinical score (Table 59F.1), as well as age-related CD4+ T cell count, giving an immunological score (Table 59F.2). Clinical signs and symptoms are allocated to four categories: N (none), A (mild), B (moderate), and C (severe). OIs and other conditions associated with an AIDS diagnosis are all category C. Originally, LIP was an AlDS-defining diagnosis, despite its good prognosis, but it is now listed as a category B condition (see Table 59F.1).

Table 59F.1: Symptom categories of HIV disease in children

Category N: Not symptomatic
No signs or symptoms considered to be the result of HIV-1 infection or only one of the conditions listed in category A.

Category A: Mild symptomatic
Two or more conditions listed following, but none of the conditions listed in categories B and C:
Lymphadenopathy (0.5 cm or greater at more than two sites; bilateral = one site)
Hepatomegaly
Splenomegaly
Dermatitis
Parotitis
Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

Category B: Moderately symptomatic
Symptomatic conditions other than those listed for categories A or C that are attributed to HIV infection. Including:
Anemia (<8 g/dL), neutropenia (< 1,000/uL), or thrombocytopenia (< 100,000/uL) persisting at least 30 days
Bacterial meningitis, pneumonia, or sepsis (single episode)
Candidiasis, oropharyngeal (i.e., thrush) persisting for >2 months
Cardiomyopathy
Cytomegalovirus infection with onset before age I month
Diarrhea, recurrent or chronic
Hepatitis
Herpes simplex virus stomatitis, recurrent (i.e., *>2* episodes within I yr)
Herpes simplex vims bronchitis, pneumonitis, or esophagitis with onset before age 1 mo
Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome
I i-iomj nsarcoma
Lymphocytic interstitial pneumonia or pulmonary lymphoid hyperplasia coinpleN
Nephropathy
Nocardiosis
Fever lasting > 1 month
Toxoplasmosis with onset before age 1 month
Varicella, disseminated (i.e., complicated chickenpox)

Category C: Severely symptomatic
Any condition listed in the 1987 surveillance case definition of AIDS, with the exception of lymphocytic interstitial pneumonia (which is a category B condition).

Adapted from Centers for Disease Control and Prevention. 1994, "Revised classification system for human immunodeficiency virus infection in children less than 13 years of age," MMWR, vol. 43, no. 12, pp. 1-10.

AIDS-RELATED NEUROLOGICAL DISORDERS

Neurological disorders associated with HIV may be divided into two major categories: (1) HIV-associated primary neurological diseases (e.g., HPE, a syndrome complex with cognitive, motor, and hehavioral features related to primary HIV CNS infection), and (2) HIV-associated secondary neurological complications (e.g., disorders related to immunosuppression). The secondary complications include CNS neoplasms, CNS infections caused hy pathogens other than HIV, and strokes. The child's nervous system may also be adversely affected by complications related to systemic HIV disease and its therapy and metabolic and toxic complications associated with and retro viral therapy. These conditions are not mutually exclusive, and coexisting pathological conditions are common at the same or different anatomical levels of the nervous system in HIV-infected children. Ncurodevelopmental status may also be affected by non-HIV-related comorbid conditions. Some of these conditions relate to maternal high risk factors during pregnancy (malnutrition, drug abuse), complications in the perinatal period (premature birth), as well as postnatal psychosocial stressors. OIs, neoplasia, neuromuscular i:i.im\-.uiiiiM.v and antircu-m iral i:ui\ip\ ivhuo compli cations associated with HIV infection arc described in Chapter 59E.

HIV-ASSOCIATED PROGRESSIVE ENCEPHALOPATHY (HPE)

Neurological involvement associated with pediatric AIDS was reported early in the AIDS epidemic. Longitudinal follow-up of HIV-infected children showed several patterns

Table 59F.2: Immune categories of 1 IIV disease in children

	CD4+- *T ceil: No./fiL(%)*		
Immune category	*< 12 months*	J-5 *years*	*6-12 years*
Category L(no suppression, Nl)	> 1,500 (>25)	> 1,000 {> 25)	>500(>25)
Category 2:(modcrate suppression, N2)	750-1499 (15-24)	500-999 (15-24)	200-499 (15-24)
Category 3:(severc suppression, N3)	<750 (<15)	<500 (<15)	<200 (< 15)

Source: Centers for Disease Control and Prevention. 1994, "Revised classification system for human immunodeficiency virus infection in children less than 13 years of age," *MMWR,* vol. 43, no. 12, pp. 1-10.

of neurological dysfunction and deterioration, now known under the rubric of **HPE.** It was also observed that by the time HIV infection had advanced to "full-blown" AIDS, HPE was extremely common, and in the majority of cases (in contrast to adult cases) there was no evidence of concomitant CNS OIs or neoplasms. Furthermote, clinical and research studies documented that the CNS was infected by HIV in the early stage. Morphological and generic similarities were documented between HIV and *visna* virus, an ovine retrovirus with well-known neurotropic properties in the developing brain. The clinical syndrome of HPE in children is similar to the adult counterpart, HAD, and is related to the primary HIV CNS infection. Following its recognition, HPE in infants and children was added to the CDC's list of pediatric AIDS-defining conditions.

Cognitive impairment, poor brain growth (acquired microcephaly), and progressive CST signs are the frequent manifestations of HPE (Belman 1990). Disorders of movement, usually superimposed on spasticity, and cerebellar signs are less frequent. Mood and behavioral problems are common. Rate and pattern of disease progression show variations. Neurological deterioration is rapidly progressive in some infants and young children (rapid processors). Within a few months they develop severe and progressive CNS dysfunction resulting in quadriparesis and mental deficiency. In a subset of children, neurological deterioration occurs over a period of months, followed by a relatively stable period, which then is followed by further deterioration. Cognitive and motor impairment can also be discordant. Some children develop progressive and disabling motor deficits yet maintain relatively stable (albeit impaired) cognitive function. In contrast, other children have more impaired cognitive function than motor function. Finally, some children have relatively minor and stable motor and cognitive deficiencies over a prolonged period of time (slow progrcssors). Clinical HPE syndrome is described according to the age of onset of the clinically apparent disease.

Neonates

HIV-infected newborns are usually well and have generally no recognizable neurological features of HIV-associated CNS disease at birth. Some HIV-infected neonates, however, have or will develop coexisting neurological problems in rhc neonatal period. The developing nervous system in HIV-infected infants, as in non-HIV-infected infants, may be adversely affected by maternal conditions during pregnancy (e.g., inadequate prenatal care and nutrition, AIDS-associated and non-AIDS-associatcd illnesses, premature delivery). Premature delivery is often interlinked with these high-risk conditions, and in turn, the prematurely born HIV-infected infant (as the uninfected prematurely born infant) is at risk for developing perinatal CNS complications.

Infants

The most severe and clearly recognized syndrome in HPE of childhood is rhc "severe infantile" form. Age of onset is usually in the first year of life but may begin in the second to third year. Neurological deterioration results in mental deficiency and spastic quadriparesis, usually by 2-3 years of age. Characteristic features include decline in intellectual and motor milestones, CST signs, and acquired microcephaly. The children look aloof and often have "masklike" facies. They appear alert and wide-eyed but have a paucity of spontaneous facial expression (manifestations of the basal ganglia and subcortical pathology). Pseudobulbar signs with feeding difficulties are frequent. Neuroimaging studies show progressive atrophy, white matter abnormalities, and frequently, calcification ol [he basal ganglia (Figure 59F.2). Magnetic resonance imaging (MRI) is more sensitive for demonstrating the white matter abnormalities, maturational changes of myelination, and structural abnormalities in the CNS. Computed tomography (CT) is more sensitive for demonstrating calcification. Both CT and MRI demonstrate cerebral atrophy. The end-stage picture is an apathetic, withdrawn, often irritable, quadriparetic child with markedly impaired higher cortical functions.

Young Children

A change of gait is often the first sign of HIV-associated CNS disease in toddlers. Children begin to toe walk. They develop hypcr-reflexia and increased tone in the lower extremities. The rate of progression varies. Progression may be rapid in some children who will become wheelchair bound within months; some will progress gradually to quadriparesis. Cognitive decline becomes evident over time. Although the child may gain additional skills, the rate of acquisition of these new skills deviates not onlv from the norm, but also from the child's previous rate of developmental progress. Poor brain growth is common. Some children maintain independent ambulation for years, although they have a spastic gait. Associated impairment of fine motor ability and dexterity is common. Cognitive deficits, although frequent, are not invariable. The degree of impairment ranges from low-average or "borderline" intelligence to mild mental retardation. A subset of children will have a prolonged stable course.

Older Children and Adolescents

Cognitive decline, impaited attention, decreased linguistic and scholastic performance, psychomotor slowing, emotional lability, and social withdrawal are common in older children with HPE, HPE in adolescents is reminiscent of HAD in adults. Hyperreflexia, clumsy and poor fine motor ability, and poor dexterity are noted initially. Progressive

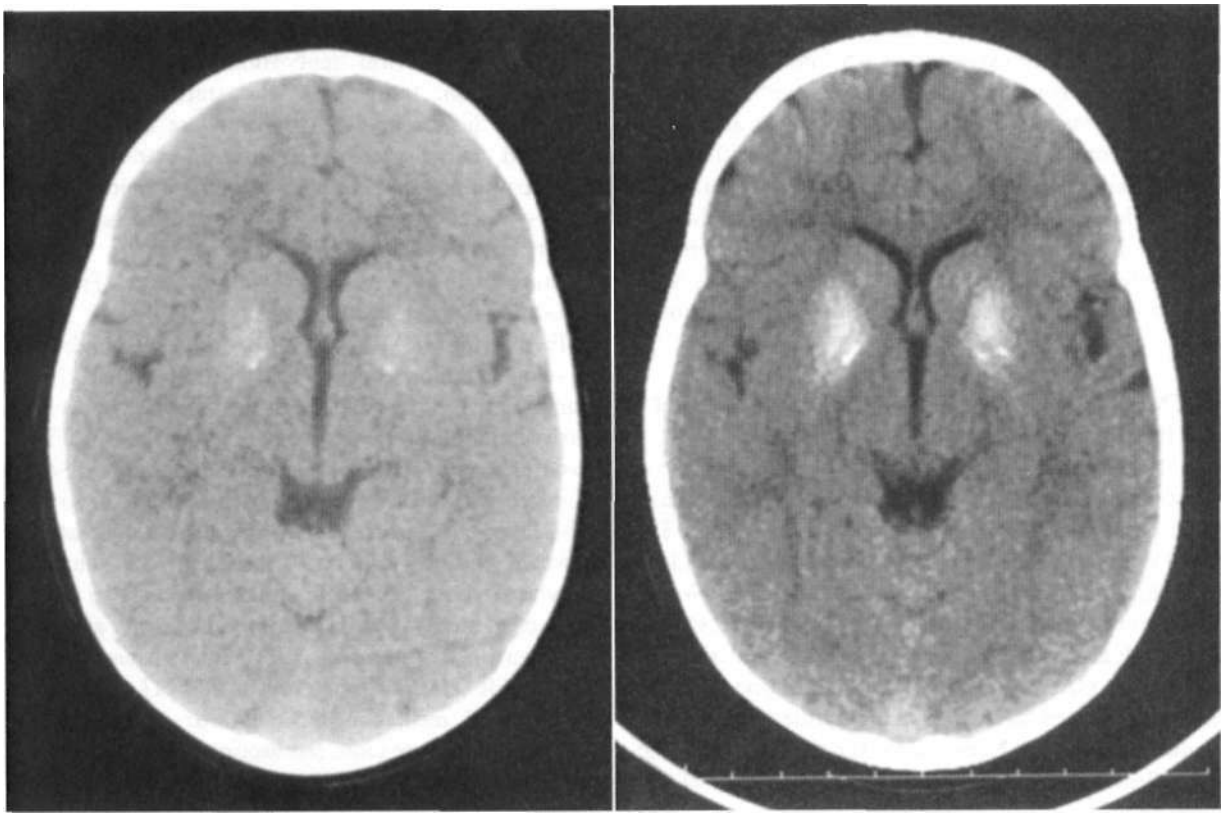

FIGURE 59F.2 (A,B) Serial studies show progressive calcification of the basal ganglia in a child with HIV infection. (From Devita, V. T., Jr., Hellman, S., & Rosenberg, S. A. (eds). 1997, *AIDS: Biology, Diagnosis, Treatment, and Prevention,* 4th ed, Lippincott-Raven, Philadelphia.)

long-tract signs, movement disorders, cerebellar signs, and myelopathy may develop as the disease advances, Progressive cerebral atrophy and white matter abnormalities are commonly seen on neuroimaging, and some children have basal ganglia calcification.

Cerebrospinal fluid (CSF) may be normal or may show mild pleocytosis with or without protein elevation. Presence of HIV antigens, intrathecal anti-HIV antibody production, oligoclonal bands, and cytokines in CSF are also reported. These data come ftom a small numbet of cross-sectional studies of small cohott size; thus, their prognostic significance is uncertain. As with adults, howevet, the data suggest that HIV CNS invasion occurs in the early stage of infection. CSF viral RNA levels have been studied in children and are reported to correlate with cognitive impairment. Electroencephalography shows diffuse mild to moderate slowing of the background rhythms.

STROKE IN HIY-INI ICIED CHILDREN

Acute strokes are the second most common cause of large lesions demonstrated by imaging studies in HIV-infected children (after primary and secondary CNS lymphoma). A 4-10% estimated incidence of stroke (hemorrhagic and ischemic) was reported from clinical series conducted during the early years of the AIDS epidemic, with an even higher rate noted at autopsy. A stroke incidence of 1% per yeat was estimated in children with AIDS. Clinical presentation includes the new onset of focal neurological deficits, most commonly hemiparesis, with or without seizures.

Intracerebral hemorrhage usually occurs in the setting of immune-mediated thrombocytopenia. Hemorrhage into a minor may also occur, as may subarachnoid hemorrhage associated with aneurysmal arteriopathy of major cerebral arteries. Clinical presentation is variable, reflecting the location and severity of the hemorrhage.

Nonbemnrrhagic infarctions are most often associated with pathological changes of cerebral blood vessels, meningeal infections, or cardiomyopathy. Cerebral vascular ectasia, aneurysmal arteriopathy of major cerebral arteries, and thrombosis of these arteries or of small cortical vessels are reported. Aneurysmal dilation of the branch vessels of the circle of Willis is increasingly recognized in HIV-infected children. It may be diffuse and fusiform or focal and saccular. The mechanism by which HIV causes CNS arterial damage is unclear. Possibilities include direct HIV endothelial invasion and exposure to toxic cytokines. Varicella zoster virus (VZV) infection can cause cerebral vasculitis and consequently an ischemic stroke. A fibrosing

inflammatory vasculopathy is also described and is thought to be related to the primary HIV CNS infection.

A subacute necrotizing encephalopathy with cystic encephalomalacia was reported in 8% of cases in an autopsy series. This entity appears to be associated with dilated cardiomyopathy and may be related to an acquired mitochondrial cytopathy or hypoxic-ischemic damage. Multiple ischemic infarcts may also result from leptomeningitis associated with infectious etiologies such as VZV, *Mycobacterium tuberculosis,* and *Treponema pallidum.*

TREATMENT AND PROGNOSIS FOR CHILDREN WITH HIV INFECTION

Treatment and prognosis of HIV-associated OIs, neoplasia, and neuromuscular disorders is described in Chapter 59E. Children with HPE generally harbor a high HIV RNA load, and the encephalopathy illness is related to the vircmia. Effective antiretroviral therapy and viral suppression is therefore a logical strategy in HPE. Recommendations for when to start HAART and which combination to use in infants and children have been made by the United States, the Pediatric European Network for the treatment of AIDS, and the British HIV Association. All children in clinical stage C should receive IIAART. Therapy may be considered in stage B if CD4+ T cell count is low or viral load is high. Treatment is deferred in stage A and N diseases. One circumstance in which it might theoretically be appropriate to treat an asymptomatic infant is where HIV infection is detected within a few weeks, akin to treatment of an adult in acute seroconversion. The HAART regimen for children is similar to that in adults and typically consists of either two nucleoside reverse transcriptase inhibitors (NRTIs) and one protease inhibitor (PI) or two NRTI and one nonnucleoside reverse transcriptase inhibitor (NNRI) (see Chapter 59E, Table 59E.3). Three NRTI can also be considered as a part of HAART if NNRTI or PI cannot be used because of drug intolerance or resistant viral strains. Ideally, drugs with high CNS penetrance should be included in HAART regimen for pediatric neuro-HIV disease (Chapter 59E, Table 59E.3).

To date, most published reports of HAART in children have demonstrated poor maintenance of viral load suppression, with up to half of the children showing viral rebound within a yeat of treatment (Spector et al. 2000; Krogstad ct al. 2002), This is most likely related to the difficulties with adherence to unpalatable liquid formulations, very high viral loads at the base line, and insufficient dosing regimens due to less known pharmacokinetics in infants and children. However, with increasing awareness of these problems, treatment of children is improving with active adherence support, therapeutic drug monitoring, and careful planning and education for families prior ro starting the therapy.

Survival on HAART depends on the fact that effective suppression of viral replication would allow immune reconstitution. Individuals who start treatment in later stages of infection, when the immune system is severely depleted, may have less effective immune reconstitution with continued susceptibility to OIs, despite elevation in CD4+ T cell counts. Children appear to have a greater ability to reconstitute the immune system than adults because of their persistent thymic function (Franco et al. 2000; Gibb et al. 2000).

In the pre-HAART era, up to 50% of children in the developed countries were surviving into later childhood, compared to most children in the African cohort dying in early childhood. Since the beginning of HAART in 1996, progressions to AIDS or death have become rare events in children with HIV in resource-rich settings (Figure 59F. 1). The long-term survival of the currently treated HIV-infected children cannot be predicted, but most should survive at least into their adult years. It also seems that long-term survival on HAART would come at some cost; children on long-term HAART regimen may have cumulative side effects from NRTI, NNRTI, PI, and other HIV-related medications. Long-term effects of HAART in children require close monitoring.

PREVENTION OF HTV INFECTION IN CHILDREN

Pediatric HIV infection is a preventable disease if pregnant women are able to receive interventions to stop transmission of the virus to their children. This, of course, depends on the availability of routine antenatal screening for HIV and availability of antiretroviral therapy. The landmark PACTG 076 study in 1994 demonstrated that use of ZDV monotherapy could reduce vertical HIV transmission by nearly 70%, and this rapidly became standard of care for pregnant women with HIV (Connor er al. 1994). It has since been further documented that the most important factor in terms of an individual woman's risk of transmission is her plasma viral load, hence the importance of the combination HAART (Garcia et al. 1999). In recent years, where women have delivered while on HAART with complete viral suppression, the HIV transmission has been very rare.

As most transmission of HIV occurs around the time of labor and delivery, avoidance of the labor, vaginal delivery, and birth canal exposure with planned prelabor caesarean section also reduces the risk of HIV transmission for woman at all levels of vircmia. Whether planned prelabor caesarean section can have an added effect where there is undetectable plasma viral level is not known. Finally, as the risk of transmission may be doubled for breastfeeding mothers, women should be advised to formula feed their seronegative infants.

Women who are found to be HIV-infected on screening in pregnancy and who commence HAART for their own

health will concomitantly greatly reduce the risk of infant infection. Women who do not yet require treatment for their own health may take a short course of therapy during the third trimester and intrapartum period, with their newborns receiving a postnatal short-term oral prophylaxis. No specific teratogenic effects of antenatal exposure to combination antiretrovira! therapy have been reported to date (Antiretroviral Pregnancy Registry 2000).

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Chapter 59
Infections of the Nervous System

G. PRION DISEASES

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in accordance with contemporary practice, prion diseases, also called the transmissible spongiform encephalopathies (TSE) or prionoses, are included for discussion with the infectious diseases of the nervous system. It is now clear that the cause of these slow infections is neither a virus nor any nucleic acid-containing particle. During the past 20 years, a comprehensive body of research led by Prusiner and colleagues has presented compelling evidence that the transmissible pathogen for these diseases is a proteinaceous infectious particle, which Prusiner termed *prion,* derived from "proteinaceous and infectious" (Prusiner 1982, 2001). The prion protein (PrP) is encoded by a gene (designated as *PRNP)* on the short arm of chromosome 20. The discovery of mutations in *PRNP* and its linkage to prion diseases in patients with familial Creutzfeldt-Jakob disease (fCJD) and the reports of accidental transmission of CJD (iatrogenic, iCJD) in humans attest to the fact that prion diseases can be genetic, infectious, or spontaneously acquired; in this respect prions are unique among all infectious agents.

The prion diseases affect both human and nonhuman mammalian species (Table 59G.1). All prion diseases result from a conformational alteration of the same host-derived, membrane protein PrP^{c} (C for cellular). The first recognized and documented prion disorder was scrapie affecting sheep flocks about 250 years ago. The word *scrapie* was used as a vivid descriptive term of ataxic sheep that scrape against fences to prevent falls. The first reports of prion diseases affecting humans came from Creutzfeldt in 1920 and Jakob in 192i (Jakob 1921), who independently reported cases of a progressive dementing neurological illness with prominent spongiform changes in the grey matter, although Creutzfeldt's original case does not correspond to what is currently classified as a CJD, In 1928 Gerstmann (Gerstmann ct al. 19.36) described purely familial disease with a clinical course dominated by slowly progressive ataxia, with minimal spongiform changes but extensive amyloid deposits. As the new cases were described and studied, the term Gerstmann-Straussler-.Scheinkcr syndrome (GSS) emerged and the syndrome was found to be caused by mutation in the *PRNP* gene. It has been recognized subsequently that fCJD related to different mutations of this same *PRNP* gene exists as well.

The infectious nature of the prion disorders was first recognized in 1936 by Cuille and Chcllc, who transmitted the disease by intraocular inoculation of scrapie-infected spinal cord (Cuille and Chellc 1939). First transmission of human prion disorder was demonstrated by the Gajdusek group, who transmitted kuru into chimpanzees (Gajdusek et al. 1966). Success of these experiments was followed by successful transmission of sporadic Creutzfeldt-Jakob disease (sCJD) from man to chimpanzee. It was recognized from the beginning that the prion diseases have a very long incubation followed by a relatively short symptomatic period preceding death. This long incubation time, extending up to 24 months for intracerebrally inoculated laboratory animals, explains why these illnesses are sometimes called slow infections. Prusiner demonstrated that the major component of the infectious agent is a protease-resistant 27 to 30 kDa prion protein, PrP^{c} (sc-scrapie, because prions were first isolated as a scrapie infectious agent). PrP^ is a conformcr of PrP with an identical

Table 59G.1: Prion diseases in humans and nonhuman mammalian species

Pathomechattism	*Human prion diseases*	*Animal prion diseases*
Sporadic Resulting from spontaneous conversion of PrP^{c} to PrP^{SL}, or somatic mutation	Sporadic Crcutzfeldt-Jakob disease (sCJD) Sporadic fatal insomnia (sFI)	Scrapie of sheep and goats Chronic wasring disease (CWD) of mule and white-tailed deer and elk Transgenic mice expressing normal human $PrP^{1"}$
Genetic Dominantly inherited with almost 100% penetrance	Familial CJD (fCJD) Gerstmann-Strauss ler-Schc inker (GSS) syndrome Fatal familial insomnia (FFI)	Scrapie in sheep and goats spread vertically from ewes to lambs Transgenic mice expressing mutated human PrP
Transmissible	Kuru Iatrogenic CJD (iCJD) New variant CJD (nvCJD)	Scrapie among flocks of sheep in the field Bovine spongiform encephalopathy (RSF) Chronic wasting disease (CWD) of mule and white-tailed deer and elk Transmissible mink encephalopathy (TME) Feline spongiform encephalopathy Fxotic ungulate encephalopathy (nyala, oryx, kudu) TSF transmitted to laboratory animals: mice, sheep, goats, monkeys

amino-acid sequence but has an increased j9-sheet content. PrP has the ability to bind to PrP^{c} and induce its conformational change. Therefore PrP uses endogenously produced host PrP^{L} as a template for its own replication. The increase in /?-sheet content is associated with a dramatic change of physical-chemical properties of PrP^{c} resulting in increased proteinase resistance, decreased water •ioluHliu. and *::r.* MK iv.iscd tendency to polymerize, .ill of which ultimately leads co neuronal death.

Although PrP^ has an increased resistance to proteolytic digestion and denaturating agents, the infectivity of prion diseases remains very low. Human-to-human transmissions (iatrogenic or iCJD) have been described in a limited number of cases worldwide. So far these have been related to surgical operations using contaminated instruments, contaminated EEG electrodes, corneal transplantation, contaminated **dura** mater grafts and the use of contaminated cadaver-derived human growth and gonadottophic hormones (P. Brown et al. 2000). Although $PrP^{1"}$ is a phylogenetically conserved protein, slight variations in ammo-acid sequence exist between species. These differences arc responsible for the species barrier limiting spread of this disease from one species to another; however, such spread can occur. Accidental transmission of scrapie to cattle receiving feed containing ground bones contaminated with central nervous system (CNS) tissue from serapie-infected sheep resulted in an outbreak of bovine spongiform encephalopathy (BSE) in the United Kingdom. BSE, in turn, led to the emergence of new variant CJD (nvCJD) {Collinge and Rossor 1996). Although, no effective treatment for the prion disease yet exists, two major approaches are under development focused on vaccination against the prionoses and the development of agents able to inhibit or revert the conformational change from PrP^{c} to $PrP^{5""}$ (Brown 2002; Wisniewski and Sigurdsson 2002).

EPIDEMIOLOGY

The incidence of sporadic CJD is estimated as 1 per million in the general population. The risk of disease is age-related but does not indefinitely increase with age. In populations younger than 50 years the incidence is 1 per 10 million and after the age of 50 years it sharply rises, reaching a peak in the population between 65 and 74 years, with an average of about 5.7 per million. The incidence in the population older than 75 years slowly decreases to less than I per million in subjects older than *85* years.

fCJD is about nine rimes less common than sCJD. There are two ethnic groups, Slovaks from Orava and descendants of Sephardic Jews originally living in territory of current Libya (Gabizon et al, 1991; Hsiao et al. 1991), that have a significantly increased occurrence of *PRNP* mutations resulting in an incidence of CJD 60-100 times greater than in other populations. GSS remains an extremely rare disorder with a yearly incidence of 2-5 cases per 100 million. The most common mutation related to GSS is P102L. This mutation has been found in *M* kindreds living today in nine countries: Austria, United Kingdom, Canada, France, United States, Germany, Italy, Israel, and Japan. Fatal familial insomnia (FFI) has been described in two large kindreds and in several sporadic cases.

There is no significant sex difference among patients with CJD. Cumulative data gathered by the Centers for Disease Control and Prevention (CDC) indicated a slight preponderance for sCJD in women younger than 60 years and in men older than 60 years. An exception is kuru, in which mainly women and children were affected; this is related to this group eating body parts with a higher prion concentration such as the brain, whereas males ate more muscular portions.

To date about 250 cases of iCJD have been described, both among older and younger subjects. The biggest

clusters were related to the use of contaminated dural grafts in Germany (about 60 cases) and contaminated cadaver-dcHved human growth hormone therapy in France *(55* cases). Rare sporadic cases of kuru arc still described in New Guinea, and these are linked to its extremely long incubation time, which can extend to 40 years.

Since the original report in 1995 a total of 139 confirmed cases of nvCJD have been diagnosed, 128 in the Great Britain, six in France, and one each in Italy, Ireland, Hong Kong, Canada, and the United States. The patients from Canada, Ireland, Hong Kong, and the United States resided in the United Kingdom during a key exposure period of the UK population to the BSE agent. It has been difficult to predict the expected future numbers of nvC]D. Mathematical analysis has given a range from 5 thousand to about 136 thousand individuals who will eventually develop the disease. This broad range reflects a lack of knowledge regarding the time of incubation and the number of patients who could be infected from a given dosage of BSE agent. Because the nvCJD agent is present at high levels in the lymphatic tissue, screening for $Pr?^{Sl\eta}$ was performed on sections from lymph nodes, tonsils, and appendices archives in the United Kingdom. One out of 8300 randomly selected cases showed evidence of subclinical infection, leading to a prediction that the total 55 million population of the United Kingdom will ultimately have about 8000 nvCJD cases. However, because this predication is based only on one report, it should he viewed with caution. The initially predicted epidemic of nvCJD does not seem to be materializing, as the number of cases in the United Kingdom has declined from a peak of 28 in 2000 to 17 in 2002 (Tvler 2003). The estimated risk for new cases of nvCJD in other European countries looks more optimistic. In the United Kingdom, 200,000 cases of BSE were reported (it is estimated that four times this number entered the food chain), compared to about 500 BSE cases in other European countries. This suggests a significantly lower exposure of these populations to BSE prions. A few cases of BSE have also been reported in other parts of the world, such as japan and Canada.

PATHOGENESIS OF PRION DISEASES

Genetics

The gene *PRNP* coding for the prion protein has been mapped to the short arm of the human chromosome 20 (murine *PrP* gene is located on chromosome 2) (Spnrkcs etal. 1986; Westaway, Cooper etal. 1994). The whole gene is translated within a single-reading frame (Plate 59G.IA). Human *PRNP* shows limited nonpathogenic polymorphism of *PRNP,* which includes an octapeptide deletion from the repeat region, methionine/valine polymorphism at codon 129 and a glutamine/lysine polymorphism at codon 219 (Table 59G.2). The methionine/valine 129 polymorphism is of special importance because 129 homozygotes are more susceptible to prion infection than hetcrozygotes. The 129 codon M/M, V/V, and M/V allelic frequency in Caucasian populations is 37%, 12%, 51%, respectively (Collinge et al. 1991). The incidence of the M/M allele is significantly increased among patients who died from sCJD, being 72% (V/V—17%, M/V—12%) (Palmer etal. 1991; Parchi etal. 1996; Parchi, Giese et al. 1999). All genotyped patients who died with nvCJD so far were M/M homozygotes. Of subjects with iCJD related to hC.H, 50% were V/V homozygotes and 31% were homozygotes for M/M (Collinge et al. 1991).

Of interest ovine *PRNP* shows more extensive polymorphism than the human gene, having nine allelic variants. Of these, A/V136, R/H154, and QH/R171 arc linked to susceptibility to disease. Increased susceptibility is associated with the presence V136, R154, and Q171; VRQ/VRQ homozygotes being the most susceptible (Westaway, Zulani et al. 1994). In contrast, arginine in the position 171 seems to increase resistance to scrapie infection, and no disease has been detected in carriers of the ARR/ARR allele (Eaplanche et al. 1993; Belt et al. 1995; Clouscard et al. 1995; Bosscrs et al. 1996; Hunter et al. 1996).

Pathogenic *PRNP* mutations are autosomal dominant with near 100% penetration (sec Table 59G.2). Great variability in clinical phenotype, age of onset, and the length of disease course related to different mutations of this same gene is one of the most astonishing aspects of inherited prion disorder. The fCJD phenotype is linked to either octapeptide repeat insertions equal to or less than 168 base pair (Owen et al. 1989), or missense mutations located mainly in regions of a-helices B or C (Gabizon et al. 1991; Hsiao ct al. 1991). The GSS-phcnotype is associated with either longer octapeptide repeat insertions (192 or 216 bp) or missense mutations in the region preceding oc-helix A (Hsiao, Baker et al. 1989; Hsiao, Doh-ura et al. 1989). - Three other missense mutations, namely, at 145 codon resulting in a stop codon and truncation of the *PRNP* product (Dlouhy et al. 1992), F189S (Piccardo et al. 1996), and Q217R also result in a GSS phenotype. The rare FFI phenotype is a result of the coexistence of a D178N mutation and methionine at the polymorphic position 129 (Gambetti et al. 1992; Medori et al. 1992). Coexistence of the same D178N mutation and valine in position 129 produces a picture of fCJD (Goldfarb et al. 1992; Gambetti etal. 1995).

Biology of Prion Protein

PrP ' is expressed in many types of cells; however, the highest level of expression is found in the CNS neurons (Kretzsehmar ct al. 1986; jendroska ct al. 1991). The molecular anatomy of PrP is crucial for understanding its malfunction in prion diseases. The whole protein is located on the outer surface of the cell anchored to the cell

Table S9G.2: Genetic forms of prion diseases

Disease phenotype	*Mutations*	*Comments*
Nonpathogenic *PRNP* polymorphism	Octapcptidc deletion from the repeat region (— 8)	
	MTV 129	Increased susceptibility for nvCJD and iCJD in homozygotes
	E7K219	
Mutations producing fCJD phenotype	Octapcptidc repeat insertions of 168 or base pair (24, 48, 96, 120, 144, 168)	Protracted clinical course (4-13y)
	D178N (V129)	The same mutation associated with M at 129 produces FFI
	VI801	
	T183A	
	E200K	fCJD associated with peripheral neuropathy
	H20SK	50% penetrance
	V210I	50% penetrance
	M232R	
Mutations producing GSS phenotype	Octapeptide repeat insertions of 192 or 21 6 base pair	
	P102L	The most common ataxic form with NFTs
	P105L	
	A117V	Symptoms of parkinsonism as a result of severe neuronal loss in the basal ganglia and the substantia nigra
	Y145stop codon	Associated with CAA and NFTs; clinical course over 20 y
	F198S	Associated with the greatest number of NFTs
	Q2.17R	
Mutations producing PHI phenotype	D17SN (M129)	Pathology targeting primarily autonomic centers

CAA = cerebral amyloid angiopathy; NFTs = neurofibrillary tangles; y = years.

membrane by phosphatidylinositol glycolipid (GPI) attached to its C-terminus. The C-terminus contains two ot-helical domains B and C, which are interconnected by a disulfide bond between serines at residues 179 and 214. Two oligosaccharide chains attached to the ot-helical regions additionally stabilize the structure of the C-terminus. The C-terminus is the site of binding protein-X (see following), which plays a role in maintaining oc-helical structure and preventing transmissibility of the disease. The central portion of the peptide contains one short oc-helical segment (ct-hdix A) flanked by two short ^-strands. The N-tcrminns is unstructured and extends into the intracellular space. Positively charged arginine and lysine residue at the N-tcrminns give it a potential to interact with negatively charged moieties on the cellular surface or with sialic acid residues in the two asparagines—linked oligosaccharides. This allows for significant mobility and possibly for a certain degree of conformational plasticity. The N-terminus harbors five octapeptide repeats. 1 listidincs located within the octapeptides bind copper ions (Brown et al. 1997). It has been postulated teceiuly that the possible function of PrP^c is in capture, storage, and presentation of copper to the neuron (Brown et al. 1997; Qin et al. 2000, 2002). The exact function of PrP^c remains yet to be elucidated. The protein is not essential because *PRNP* knockout mice (Bueler et al. 1992) did not show a significant disease phenotype. Minor abnormalities in synaptic physiology (Collinge et al, 1994) and in circadian rhythm (Tobler et al. 1996) using more detailed methods have been described in these knockout mice.

The prion diseases belong to a broader category of conformational diseases. The etiology of each of the conformational IKIMM'S IS ivi.ued (o a specific protein thai can exist in at least two distinct forms associated with either health or disease. The most common conformational disorder is Alzheimer's disease (AD), in which the disease state is associated with the accumulation of an endogenously expressed peptide, the amyloid-/8 peptide, in a ,8-shcet structure within neuritic plaques. The pathological conformer of PrP ' is PrP* , which due to its increased ,8-shect content demonstrates increased resistance to proteolysis and the abilin to aggregate and polymerize isec Plate .590,1). Although the insolubility of PrP has prevented performing crystallographic conformational studies, less exact structural methods such as circular dichroism and Fourier transform infrared spectroscopy indicate a *0*-sheet content as high as 45% (compared with 3% in PrP) and oc-hclix content of 30% (40% in PrP^c) (Aucouturier et al. 1999). Understanding the mechanism that convetts PtP into PrP""- is another intriguing aspect of the prion disease. This conversion may happen spontaneously in sCJD, be induced by the introduction of exogenous PrP in

transmissible forms, or be induced by *PRNP* mutations (Gabizon et al. 1996). The spontaneous conversion of PrP^{1} into PrP^ has been demonstrated in sheep and probably is the major cause of scrapie and sCJD. A high rate of spontaneous conversion has been also shown in transgenic mice ove rex pressing human $PrP^{(}$ on a murine PrP knockout background (Westaway, DeArmond et al. 1994). It has been postulated that the PrP molecule exists in two forms, PrP*' and PrP^, able to change conformation between these two by spontaneously unfolding and refolding. Neuronal PrP has a half-life of approximately 3 hours. The mechanisms that maintain the PrP molecules in $PrP^{1,}$ state have not been fully elucidated. Protein X has been hypothesized to exist, having the role of binding to PrP and increasing the energy threshold needed for the conformational shift to PrP^{s}\ It has been also demonstrated thai binding copper to tile \-termmus significantly change-; tin: seeondan structure of PrP^{c}, increasing its /S-sheet content and resistance to proteinase K (Qin et al. 2000). Furthermore, a copper imbalance has been implicated in early stages of the disease.

One of the most crucial features of PrP^{v} allowing for the mmsmissibility of prion diseases is the ability of PrP^{c} to bind to PrP , initiating a self-perpetuating vicious cycle (Prusincr et al. 1998). It has been demonstrated in cellular models that the PrP is transported to the membrane in $PrP^{1'}$ form and that the conversion of PrP^{c} to PrP^ occurs at the cell surface. Neurons produce native PrP (Krctzschmar et al. 1986) and transport it to the cellular surface where it can encounter PrP^{s}\ leading to its conformational change into a high fi-shcer content state. During progression of the disease, the amount of PrP produced remains stable, whereas the amount of $PrP^{K,:}$ increases. Homozygosity of PrP^{c} facilitates prion replication. This has been observed in humans with respect to the codon 129 polymorphism, as well as in sheep with respect to the VRQ/VRQ polymorphisms. Evidence from transgenic animals expressing various segments of PrP indicates that residues 90-150 are required for the interaction with PrP^{s}^ leading to conversion of $PrP^{(}$ into PrP^{Sc}.

Mechanisms of prion-related toxicity require both the conversion of PrP to PrP^{St} and the subsequent accumulation of proteinase resistant, /J-sheet rich $PrP^{Si:}$ (jendroska et al. 1991; Kret/schmar et al. 1997). Animals infected with prion strains demonstrated that accumulation of PrP^ preceded dendritic and synaptic degeneration, which was followed by gliosis and neuronal dropout (Plate 59G.II) (Jeffrey et al. 2000). Two cellular compartments—cell membranes and the endosomal/lysosomal system—show the highest concentration of PrP , and dysfunction of these two compartments is thought to be two separate phenomena responsible for breaking down neuronal homeostasis and subsequent degeneration. The highest cellular concentration of PrP^{St} was demonstrated in caveole-likc domains (CLD) associated with the plasma membrane, which are involved in metabolism of glycolipid-anchorcd proteins. The most commonly accepted scenario assumes that initial accumulation of $PrP^{Si:}$ in the membrane results in early alteration of membrane properties required for synaptic transmission, signal transduction and generation of second messenger, maintenance of ion and water balance, and the responsiveness of neurons to trophic factors necessary for neuronal viability. 1 he appearance ol so-called spongiform changes (see following) is a result of swelling of dendritic processes mainly in the vicinities of synaptic contacts. Accumulation of PrP^{Sc} in the endosomal/lysosomal system follows its accumulation on the cell surface and leads to dysfunction of the cell disposal system. Although PrP is present in many cell lines, symptoms of the disease derive mainly from neuronal degeneration. This probably occurs because of the significantly higher expression of PrP in neurons compared with glial or endothelial cells and the greater sensitivity of neurons to membrane perturbations.

Another aspect of prion-related pathology is amyloidosis characteristic for some but not all prion diseases (see Plates 59G.ID, 59G.III, and 59G.IVB) (Ghetti, Piccardo, Frangione et al. 1996). PrP^{St} purified from diseased brains using proteinase K, which cuts off the N-terminus leaving 143 amino-acid fragment called PrP 27-30 (Ocseh ct al. 1985) and treated with detergents, readily polymerizes in vitro into amyloid. The mechanisms of prion-reiated amyloidosis in vivo and reasons for its occurrence only in certain clinical variants are elusive. sCJD amyloid deposits are only demonstrated in 10% of cases, whereas florid amyloidosis is a hallmark of nvCJD. It has been postulated that this feature is determined at lea si partially by host responses because neither scrapie in sheep nor BSE in cattle is associated with amyloid, whereas significant amyloidosis is found in transgenic mice infected with scrapie or BSE that express either human $PrP^{<}$ alone or a chimeric combination oi human and murine $PrP^{c'}$. The heavy amyloid deposits in GSS consist of truncated 8-11 kDa peptides (Tagliavini ct al. 1991) containing the central portion of the peptide. Recently, a distinct mechanism of amyloidosis has been demonstrated for some, but not all, GSS-related *PRNP* mutations (see Plate 59G.IVB). These mutations result in a specific form oi PrP where the N-terminus is located intracellularly, and the C-tcrminus remains outside the cell, anchored by GPL The central transmembrane PrP^{c} domain is designated ^{Ltm}PrP '. It is postulated that peptidases cut both sides of the transmembrane section of $^{ctl,1}PrP^{c}$, and the remaining short central segment of the PrP protein is endocytosed and then secreted to the extracellular space, where its aggregation and polymerization into amyloid occurs.

Infectivity, Species Barrier, and the Immune System

Despite commonly expressed concerns, the infcctivity of the TSE is relatively low even within the same species. Transmission between species is much less efficient due to species harrier, which is in part explained by differences

in the amino acid sequence of PrP . The gene sequence is highly conserved among mammals with only 28 differing amino acids between human and mouse and two between human and chimpanzee. The exogenous Prl'V has to he similar enough to the host PrP ' to bind and use it as a template for further replication. Moreover, numerous lines of evidence suggest that the propagation of PrP^{L} also involves interactions with prion-associated proteins, such as protein X, which differ among species (Telling et al. 1995). Mice are susceptible to hamster and sheep PrP strains but not to human PrP^. CJD can be transmitted only to the transgenic mouse expressing human PrP (Telling et al. 1994), Transmission of all human forms of prionoses including GSS and FFI (Tateishi et al. 1995) to these transgenic mice strains has been documented (Masters et al. 1981).

Although the existence ot scrapie :us Ixvi documented in Great Britain since the early eighteenth century, no nans-mission to humans has been demonstrated. However, the species barrier between sheep and cows is more limited, resulting in the epidemics of the BSE, also called mad cow disease, once these animals received feed enriched with sera pie-contaminated sheep bone meal. Transmissibiliry of scrapie to cows has been confirmed by transfusion of sheep blood into cattle. The spatial and temporal relationship between the outbreak of BSE and nvCJD, as well as the biochemical and neuropathological similarities between these strains when they are transmitted to transgenic mice expressing bovine PrP' in the absence of mouse PrP, indicates that the species barrier between humans and nonhumans has also been breached.

There is an increasing incidence of the chronic wasting disease (CWD) of mule and white-tailed deer and elks in the Midwestern and Rocky Mountain states. Occurrence of the CJD among three young deer hunters from this same region raised the speculation of transmission of the CWD into humans {Belay er al. 2001). Like BSE, CWD is transmissible to the transgenic mouse expressing human PrP^{c} (Raymond et al. 2000). However, autopsy of these three subjects did not show the extensive amyloidosis characteristic of the nvCJD and CWD (Liherski et al. 2001).

The pathophysiology of prion disease also depends on the distinct isolates or strains of prion. The strains are defined by the production of distinct patterns of incubation time, distribution of CNS lesions, and resistance to proteolytic digestion. PrP^{L} from different strains have variable proportions of monoglyeosylated, diglycosylated, and nonglycosylated PrP^{1m} and a variable length of $PrP^{c,}$ residues following proteinase K digestion. Although, a given strain may show different behavior when first trans-mitted into mice compared to the original species, once a pattern is established the strain can be stably passaged among inbreed mice of the same genotype (Baron 2002). At least 14 different sheep scrapie strains and two human strains PrP-19 and PrP-21 (Parchi et al. 1996) (19 and 21 kDa-main nonglycosylated peptide cleaved either at residue 97 or 82 of PrP ', respectively) have been isolated and passaged into mice. However, the possible number of human strains is higher (Parchi ct al. 1996; Aucouturicr et al. 1999). Because all strains originating from one species have the same amino-acid sequence, according to the Prusmcr protein only theory, it has been hypothesized that PrP^{bc} is able to adopt multiple, distinct pathological con-formations that result in the existence of multiple strains {Telling et al. 1996; Scott et al. 1999).

ReeenlH . recognition *n*\ the role oi tile immune system in the pathomechanism of prion diseases has been steadily growing. This is particularly important for BSE, nvCJD, and iCJD. PrP molecules introduced to the bloodstream or to the alimentary tract ultimately uudctgo endocyrosis by dendritic cells. The proteinase resistance of PrP^{Sc} renders it impossible for the dendritic cells to digest it. Furthermore, PrP^{L} is able to replicate inside dendritic cells. Lymphatic organs like spleen, tonsil, lymph nodes, or lymphatic tissue in the digestive tract mucosa contain high concentration of PrP^{Sc} long before PrP^{Sc} starts replicating in the brain (K. I.. Brown et al. 2000; Hcggebo et al. 2002). Dendritic cells from infected animals are capable to spread the disease (Aucouturier et al. 2001). Splenectomy in infected animals, probably by decreasing the PrP burden, has been shown to increase the incubation period (Fraser and DiDario 1978). The presence of high levels of $PrP^{"c}$ in the lymphatic tissue, such as the tonsil and Peyer's patches, is typical for nvCJD, iCJD, BSE, and CWD, but not for other forms of the disease such as sCJD.

How the prions reach the CNS remains an unanswered question. In light of the important tolc of the lymphatic system, especially dendritic cells, spread from the blood has been considered as the most likely route of CNS invasion. The supportive role of B lymphocytes in hematogenic ncuroinvasion has also been suggested (Klein et al. 1997). An alternative and not mutually exclusive hypothesis suggests that ption invasion of the CNS occurs via the peripheral nervous system (PNS). This has been proposed based on serial observations of intraperitoneal!}' infected animals, the $PrP^{1"}$ entering via the vagus nerve (Beekes et al. 1998) and then spinal cord, brainstem, and eventually the brain. The highest accumu-lations of spongiform changes in BSF cattle and scrapie sheep have been found in the brainstem, including the cuneate nucleus and the dorsal nucleus of the vagal nerve. Following intraperitoneal delivery of prions, disease can be delayed by sympathectomy or accelerated by sympa-thetic hyperinnervation of lymphoreticular organs (Glatzel et al. 2001).

Neuropathology

The gross examination of the brain in prion disease is variable and not specific. The spectrum extends from a lack of recognizable abnormalities to marked atrophy of

cortex, basal ganglia, and/or the cerebellum. The term *transmissible spongiform encephalopathy* (TSE) was coined to emphasize the most characteristic aspect of the microscopic picture of these diseases: vacuolar changes observed in the grey matter neuropil and sometimes within neurons, Intrancuronal vacuoles are typical for **kuru and** sheep scrapie and are also sometimes seen in CJD (Beck et al. 1964), The vacuolar changes seen in the neuropil, are round or oval, arc 5 to 25 urn in diameter, and represent cross sections of swollen dendritic and axonal processes. Most of the vacuoles appear to he in the region of synaptic elements. There is significant degeneration and loss of both axons and synapses (Jeffrey et al. 2000}. Occasionally neuropil vacuoles ma\ he as hig .is 100 jmi in diameta and be surrounded by a meshwork of reactive astrocytes. This picture bears the name of the status spongiosis (Masters and Richardson 1978). In the end stage of certain forms of prion diseases vacuolar changes may disappear from the neuropil, following very extensive neuronal loss. Other typical features of the microscopic picture of prionoses are neuronal loss and astrocytosis (see Plate 59G.I1IB and C) (Dormont et al. 1981). Little inflammatory response or activation of microglia cells is observed. Spongiform degeneration, neuronal loss, and astrocytosis are typical features for all variants of prion diseases. These changes in some types of prion disease may be associated with amyloid deposition (sec Plate 59G.M1B). Differences between particular subtypes include relative intensity of these lesions, their anatomical distribution, presence and type of amyloid deposits, as well as the occasional presence of neurofibrillary tangles (NFTs). A summary of pathological variations found in specific forms of human prionoses is provided in Table 59G.3.

Sporadic, Iatrogenic, and familial Creutzfeldt-Jakob Disease

The histopathological picture of sporadic, iatrogenic, and familial CJD is similar. The spongiform encephalopathy is found mainly in the cerebral cortex, putamen, caudate nucleus, thalamus, and the molecular layer of the cerebellar cortex. Unlike the putamen and caudate, the globus pallidus is usually spared. The brainstem and the spinal cord are affected to a lesser degree. Severe involvement is often found in the suhiculum, hut interestingly the cornu ammonis and the dentate gyrus arc usually spared. Vacuoles can be diffusely distributed throughout the whole thickness of the cortical neuropil or have pseudolaminar distribution, especially in deeper layers. There are variants of sCJD described with more focal intensity of pathology. These are the *Heidenhain variant* with involvement of the visual cortex out of proportion to rest of the brain, the *Broumell-Oppenheimer variant* characterized by predominantly cerebellar involvement, and the *Stern-Garcin variant* demonstrating prominent involvement of the basal ganglia and thalamus. Only 5-10% of CJD cases of sporadic or inherited forms demonstrate cortical amyloid plaques in the cerebrum or cerebellum (Snow et al. 1989, 1990). They are either kuru type or primitive amyloid deposits (see below) (Klatzo et al. 1959; Pearlman et al. 1988). Prion pathology affects mainly the grey matter, however in rare sCJD cases vacuolar myelopathy has been observed. These vacuoles are present wirhin the myelin sheath and are occasionally intra-axonal.

Nv Creutzfeldt-Jakob Disease

The highest intensity of spongiform degeneration and neuronal loss is found in the basal ganglia and thalamus followed by the cerebral and cerebellar cortices. Of interest in BSE and sheep scrapie cerebral cortex, basal ganglia, and thalamus are relatively spared and the highest density of lesions is found in the brainstem, cerebellum, and hypothalamus. Also neuronal vacuoles are much more frequent in scrapie and BSE than in nvCJD.

The most characteristic ncuropathological feature of nvCJD are numerous amyloid plaques consisting of protcinase-resistant prion protein (Collee and Bradley 1997; Will et al. 1997). The amount of these deposits is higher than in other forms of CJD and can be compared only with GSS. Two types of plaques in nvCJD can be distinguished: primitive plaques, which can be stained with specific anti-PrP antibodies but do not show properties of amyloid, and mature amyloid plaques. The latter in addition to reacting with anti-PrP antibodies show the classical properties of all amyloid, such as positive staining with thioflavin, and an appie-green birefringence under polarized light when stained with Congo red. These physical properties reflect a high /J-sheet content. Some of the plaques are found in the center of a vacuole and beat the name of florid plaques. Another charactcrisin. feature is clustering oi primitive and classical plaques. Plaques are distributed throughout the whole cerebral cortex, usually with a predilection for the occipital lobes and the cerebellum. Unlike nvCJD, neither cattle with BSE nor sheep with scrapie develop plaques. Transgenic mice expressing bovine PrP on a murine *PRhiP* knockout background also do not develop plaques when infected with scrapie, but they do when inoculated with BSE or nvCJD. This indicates that each specific histopathological picture results from a combination of the strain of the agent and the host background.

Fatal Familial Insomnia and Sporadic Fatal Insomnia

Fatal familial insomnia (FEI) is a result of a D178N missense mutation in the *PRNP* gene in association with a methionine at position 129 (D178N M129). Interestingly, the same missense mutation, D178N, when associated with a valine at position 129, produces a picture of fCJD. In FFI there is severe neuronal loss and atrophy of the antcroventral and mediodorsal thalamic nuclei not associated

Table 59G.3: Comparison of the most characteristic clinical and pathological features of human prion diseases

Characteristic	*sCJD*	*twCJD*	*fCJD*	*iCJD*	*FFI/SFI*
Average age at onset (yr)	67	28	Variable among kindreds 23-55	All ages	50
Average duration of disease (mo)	7	14	Variable among kindreds 8-96	12	18
Most prominent early signs	Cognitive dysfunction	Psychiatric abnormalities, sensory symptoms	Cognitive dysfunction	Cognitive dysfunction	Insomnia, autonomi instability
Cerebellar dysfunction (%)	40	100	40	40	No
PSW on EEG	Yes in 79%	No	Yes	Yes	No
Amyloidosis	Sparse plaques in 10%	Severe in all cases	Sporadically seen	Sporadically seen	No
Presence of $PrP^{\sim c}$ in the lymphoreticular system	No	Yes	No	Yes	No

CJD = Creutzfeldt-Jakob disease; EEG = electroencephalogram; FFI = familial fatal insomnia; SF1 = sporadic fatal insomnia mo = months; N/A = not available; PSW = positive sharp waves; yr = years,

with spongiosis, along with mild to moderate spongiosis of the cerebral cortex. The neuropathologies! features of sporadic fatal insomnia (SFI) are indistinguishable from FFI (Parchi, Capcllari et al. 1999). Inoculation of transgenic mice expressing human PrP^{c} with brain extracts from either FFI or SFI patients gave the same pathological picture (Mastrianni et al. 1999).

Gerstmann-Straussler-Scbeinker Syndrome

Severe amyloidosis is a hallmark of GSS (Piccardo et al. 1995). Three types of plaques are found: multicentric amyloid plaques (i.e., consist of a large central deposit surrounded by smaller satellite amyloid plaques) (see Plate 59G.IVB), primitive plaques, and kuru-type plaques. GSS plaques are composed of a highly truncated form of the PrP peptide (8-1 lkD) (Ghetti, Piccardo, Frangione et al. 1996). Plaques an abundant in the cerebellar cortex and are also present in the cerebral cortex and in the basal ganglia. Unlike the amyloidosis, spongiform degeneration in many GSS kindreds may be minimal. Some GSS pedigrees show additional histo pathological features. Those with the most common P102L mutation demonstrate severe white matter degeneration resembling that of Friedreich's ataxia. Neuronal loss is scattered throughout brain and cerebellum. In GSS A117V there is severe neuronal loss in the putamen, globus pallidus, and thalamus and somewhat less in the substantia nigra. These lesions in the basal ganglia correlate with parkinsonian symptoms observed frequently in probands expressing this mutation. The F198S mutation is associated with abundant neutofibrillary pathology including intraneuronal tangles composed of paired helical filaments and neuntic plaques (Ghetti et al. 1995; Ghetti, Piccardo, Farlow et al. 1996). As in AD, they show immunoreactivity for abnormally phosphorylated lai: rvn;.: r (Ghetti et al. 1994). Neuronal loss is prominent in the cerebral and cerebellar cortex, substantia nigra, red nucleus, inferior olivary nucleus, and the dentate nucleus. NFTs are also a feature associated with P105L, Q217R, and Y145Stop mutations (Hsiao et al. 1992; Ghetti et al. 1994, 1995). The Y145Stop mutation is unique in that PrP^{St} deposits are present in the vessel wall producing a picture of cerebral amyloid angiopathy (CAA) (Ghetti, Piccardo, Spillantini et al. 1996).

Kuril

In kuru the highest neuronal dropout affects the cerebellum, followed by the medial temporal lobe, basal ganglia, and the medial and anterior nuclei of the thalamus, Isocortical areas show usually mild to moderate spongiform degeneration in the neuropil. Amyloid deposits classical kuru plaques—are found in 75% of cases (Klatzo et al. 1965). These are on average 15—20 pm in diameter and consist of spherical deposits with radiating spicules at their periphery—sometimes called spiked ball plaques. The greatest number of plaques is usually found in the cerebellar granule cell layer.

PrP-relatcd abnormalities might not only be confined to the CNS. The prion protein has been identified in the common age-related myopathy and in inclusion body myositis (Askanas et al. 1998). Overex press ion of PrP in transgenic mice causes age-related necrotizing myopathy (Westaway, DeArmond et al. 1994). Myopathy may also be associated with scrapie in sheep and CWD in mule deer and elk.

CLINICAL FLATURFS

Sporadic Crcutzfeldt-Jakob Disease

The classic sCJD patient is between 50 and 75 yeats with a mean age of 67 years (see Table 59G.3). Subjects as young as 17 years and as old as 83 years have been reported. The disease is characterized by a rapid development of Kyuipioitis and progression to dearh. The clinical course averages 7 months but may vary from 2 months to 2 years. In 15% of cases a subacute course over several days or in rare cases even acute presentations have been described. There is, however, a subgroup of patients (less than 10%) with pathologically confirmed disease, who lived more than 2 years from initial presentation. In rare cases patients in whom the diagnosis was confirmed by the transmission of disease to primates have survived as long as 15 years.

Three stages can be distinguished in typical cases. The first stage is characterised by discrete neurological and psychiatric symptoms. Retrospective questioning can reveal prodromal symptoms weeks to months prior to diagnosis in some patients. These can include asthenia, altered sleep pattern, decreased or increased appetite, and loss of libido. Difficulties with memory, concentration, and problem solving are the usually first symptoms that bring the patient to medical attention. Fpisodes of disorientation also have been described. A variety of personality and behavioral changes are often present in the initial phase of CJD, and these may include apathy, self-neglect, irresponsibility, emotional liability, and inappropriate behavior. The second stage evolves over a period of weeks to months and is characterised by a rapid deterioration of the global cognitive deficit, which in 29% is associated with significant behavioral disturbances. Frank psychiatric symptoms such as hallucinations, paranoia, psychosis, uncontrolled outburst of aggression, or conversely depression also may be present. These symptoms are typically associated with the presence of myoclonus. Cerebellar dysfunction in CJD is present at this stage in one third of cases and develops in roughly 70% of cases during the course of the disease. These symptoms include truncal and limb ataxia, dysarthria, and nystagmus. Prominent visual and/or oculomotor complains are present in 19%,

and these include blurred or distorted vision, altered color perception, held defects, visual agnosia, diplopia, and supranuclear patsies. The second stage of the disease usually has a rapid course; however, either periods of stabilization of symptoms or a slowing of the progression after an acute onset have been reported. In the final stage the cognitive, cerebellar, and visual symptoms progress, resulting in severe dementia. Most patients become bedridden. Myoclonus, choreiform, and/or athetotic movements are ultimately observed in 90% of cases. Other infrequent symptoms include seizure, vestibular dysfunction, lower motor neuron, or pseudobulbar symptoms. The final stage is characterized by akinetic mutism followed by death frequently preceded by a period of autonomic dysfunction. The clinical picture of sCJD is influenced by the anion 12^{L}) genotype and its classification based on the Western blot appearance of the PrP^{L} after PK digestion. In type 1 CJD the molecular mass of the unglycosylated $PrP^{Sl_{m}}$ band is approximately 21 kDa, whereas in type 2 CJD it is approximately 19 kDa. Individuals with an M/M genotype at codon 129 are more likely to show a type 1 Western blot appearance and have a classical clinical presentation as described earlier. Patients with an M/V or V/V genotype are more likely to shovv a type 2 Western blot appearance, which is associated with a younger age at onset and ataxia as a more prominent clinical feature.

The differential diagnosis may be challenging due to variation in the initial presentation; however, as the disease evolves the diagnosis typically becomes obvious. A good history taken from family members and documenting the rate of progression is extremely important. There is no noninvasive biomarker that would definitively diagnose CJD (Plate 59G.V). Abnormalities are observed in several clinical tests (see following), but none of these shows specificity or sensitivity allowing them to be used in isolation. The diagnosis is made by a sum of clinical symptoms, course of the disease, abnormalities on adjunctive tests, and ruling out other dementing illnesses. The diagnosis is confirmed by a brain biopsy.

The speed of progression of the memory disorder m CJD typically allows differentiation from AD. The frontotemporal dementia (FTD) spectrum, including corticobasalganglionic degeneration and dementia lacking distinctive hismpathological features, especially presenting in lobar form associated with occipital predominance, and dementia with Lewy bodies may be more problematic in early stages. Thyroid studies, antithyroid antibodies, syphilis serology, and cyanocobalamin/methylmaloiuc levels should be checked to rule out treatable causes of dementing illnesses. In the differential diagnosis of rapidly progressive neurological disorders, the paraneoplastic syndromes, especially those producing limbic encephalitis, cerebellar syndrome, or myoclonus, have to be taken into account. In such instances evaluation for the presence in the serum of anti-Yo and anti-flu antibodies should be performed. Antithyroid antibodies should be checked when Hashimoto thyroiditis with dementia is suspected (Scipelt ct al. 1999). A spinal tap especially combined with magnetic resonance imaging (MRI) using gadolinium as intravenous contrast is helpful in ruling out brain lymphoma, neoplastic or infectious meningitis, as well as encephalitis, especially caused by herpes simplex,

Iatrogenic Crcutzfeldt-Jakob Disease

Because sCJD before age 50 is extremely rare, the occurrence of this disease in *55* patients between ages 10 and 41 years who received human growth hormone (hGH) strongly suggested an iatrogenic etiology. All the patients received two to three injections per week of cadaver-derived hGH over many years. Similarly, the occurrence of CJD in two young patients with intractable epilepsy, in whom intracerebral electrodes were surgically implanted, suggested an iatrogenic etiology. One case occurred after repair of a perforated eardrum with pericardial graft. Five cases were reported among women receiving human pituitary gonadotropin. Three cases were related to corneal transplantation. The incubation time can vary depending on the route of infection: corneal transplant, '16-20 months; deep brain electrodes, 1 6-20 months; neurosurgical procedure, 15-28 months; dura marer graft, 1.5-16 years; intravenous gonadotropin preparation, 12-16 years; and intravenous growth hormone preparation, 5-30 years. Eighty-one percent of iCJD cases were homozygotes at codon 129. The course of the disease ranged from fi to 18 months. The clinical presentation can be dominated by a primary dementia, cerebellar symptoms, or visual symptoms; however, the course ultimately leads to dementia and death. The differential diagnosis remains the same as for sCJD.

Familial Creutzfeldt-Jakob Disease

I'RNP mutations linked to fCJD are inherited in an autosomal dominant fashion but they do not always show 100% penetrance. The rate of penetrance depends on the mutation and increases with age. The most frequent mutations at codons 208 and 210 have only 50% penetrance. Kindred with the E200K missense mutation have a 1% penetrance at age 40 years, which increases up to almost 100% by the age of 80 years. The onset of disease in fCJD is usually earlier and the course longer than in sCJD. These also greatly depend on the specific mutation. The E200K kindred has an onset at 55 ±8 years, with an average course of 8 months, whereas kindred D178N, V129 has an onset at 46±7 years of age with death occurring in an average of 22 months. Kindreds with octapeptide insertion present at the age 23-25 years and have a protracted course of 4—13 years.

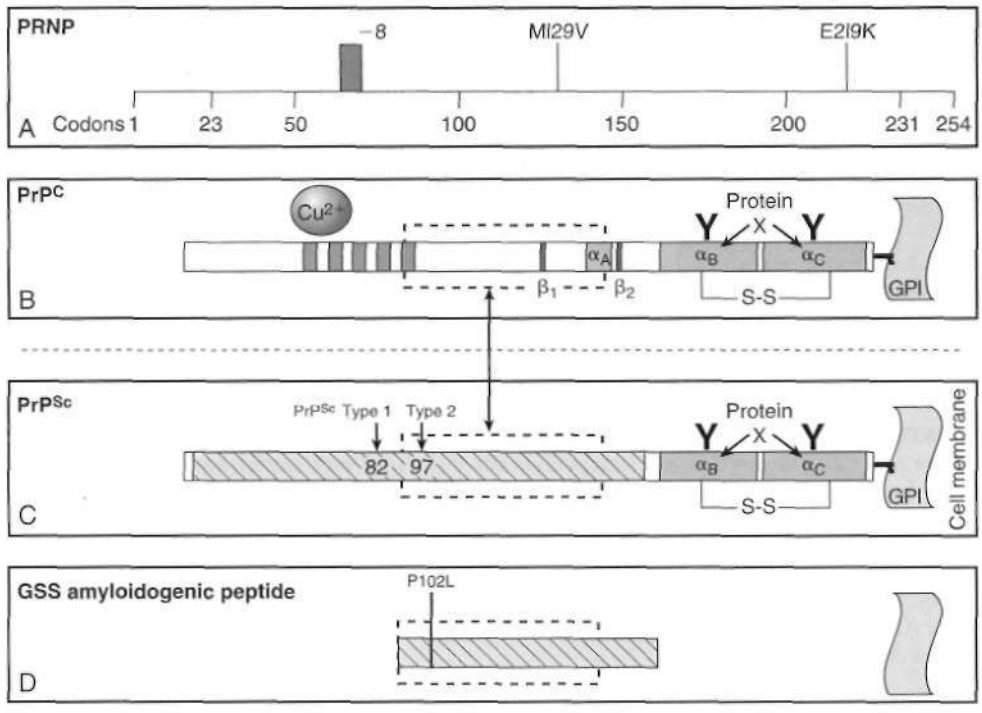


PLATE 59G.1 The Prion protein. (**A**) The prion protein gene *(PRNP)* is located on the short arm of the human chromosome 20. The nonpathogenic polymorphism includes deletion of one of octarepeat segments, methionine/valine polymorphism at the position 129, and glutamine/lysine polymorphism at the position 219. (**B**) Posttranslational modification truncates the cellular prion protein (PrP^C) at positions 23 and 231 and glycosylates (*Y*) at positions 181 and 197. The phosphatidylinositol glycolipid (*GPI*) attached to serine at the position 231 anchors the C-terminus to the cellular membrane. The intracellular N-terminus contains five octarepeat segments P(Q/H)GGG(G/-)WGQ (*blue blocks*) that can bind copper ions. The central part of the protein contains one short ∝-helical segment (∝-helix A encompassing residues 144-157 [*green block*]), flanked by two short β-strands (*red block*): β_1(129-131) and β_2(161-163). The secondary structure of the C-terminus is dominated by two long ∝-helical domains: ∝-helix B (residues 172-193) and ∝-helix C (residues 200-227), which are connected by a disulfide bond. The blue arrows indicate binding sites of the protein X within ∝-helices B and C. The purple, dotted frame marks a segment between positions 90–150 which is crucial for the binding of PrP^C to PrP^{Sc}. (**C**) PrP^{Sc} has increased β-sheet content (*red dashed block*). (**D**) Unlike PrP^{Sc}, which is anchored to the membrane, Gerstmann-Straussler-Scheinker (*GSS*) amyloidogenic peptides are truncated and excreted into the cellular space where they aggregate and fibrilize into GSS amyloid deposits. This example is an 8 kDa PrP fragment associated with the most common GSS/P102L mutation. A synthetic form of this peptide (90–150 residues), exposed to acetonitrile treatment to increase β-sheet content, is the only synthetically generated peptide, which when injected intracerebrally into P102L transgenic mice is able to induce the GSS disease.

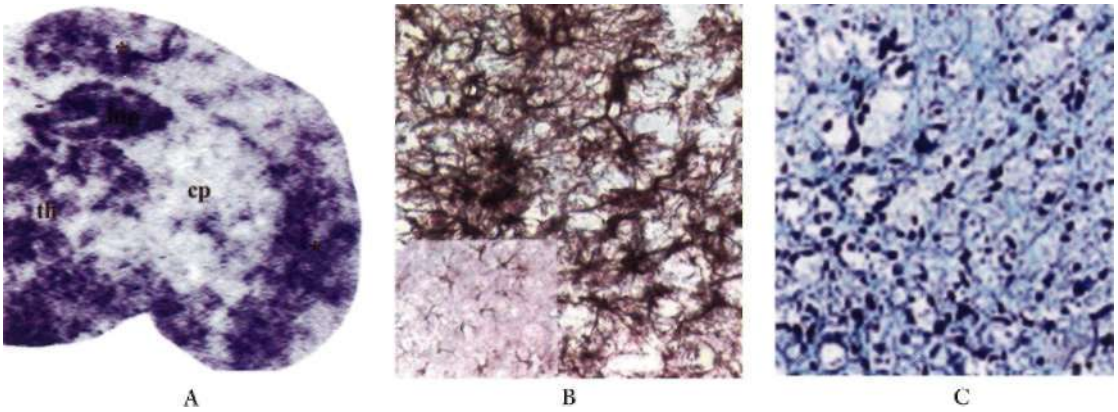


PLATE S9G.II Brain pathology associated with prion diseases. (A) Distribution of PrP^{St} in the brain of a CD-I mouse that was intraperitoneal!)' inoculated with murine-adapted scrapie strain and developed symptoms of disease f 50 days later. The picture shows an imprint of histological section on a nitrocellulose membrane that was treated with proteinase K and immunostamed with anti-PrP antibodies. The highest concentration of PrP^{St} is in the hippocampus (hip), followed by the cortex (*) and the thalamus (th). (B) Marked astrogliosis is associated with prion infection of CNS. Insert shows a control brain. Section was immunostained against glial-fibrillary acidic protein (GFAP). (C) Cresyl violet stained sections demonstrate advanced spongiform state and neuronal dropout.

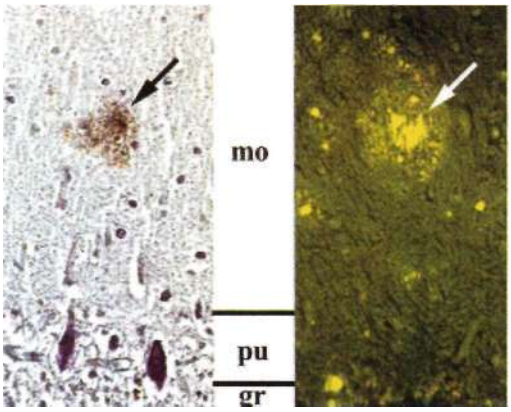
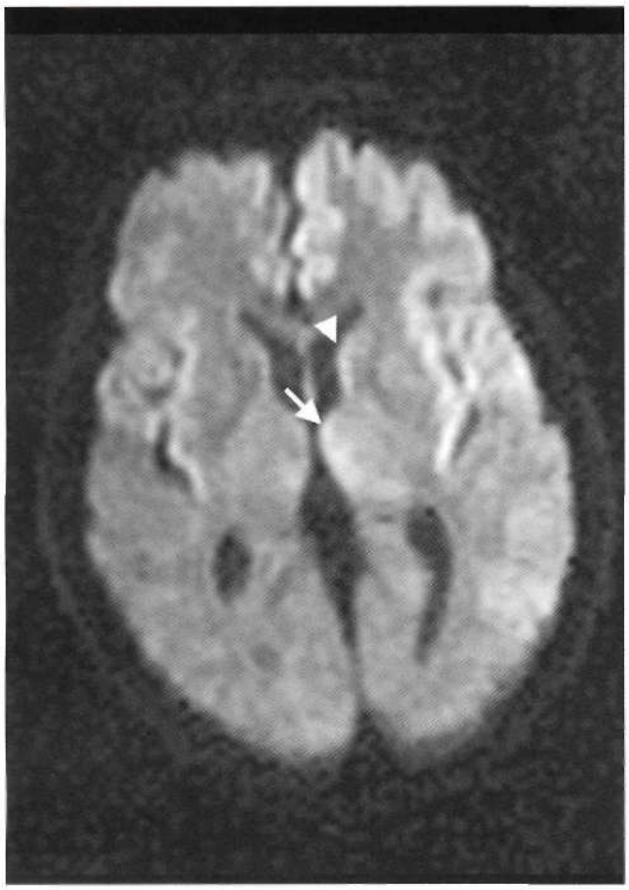
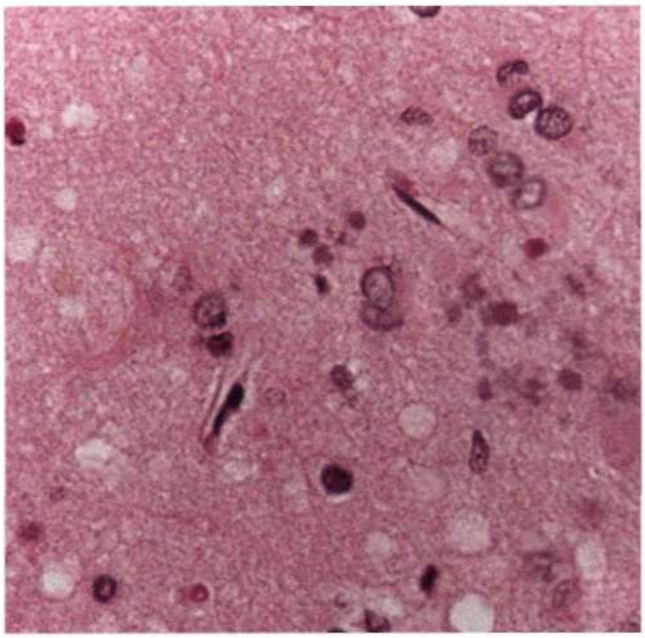


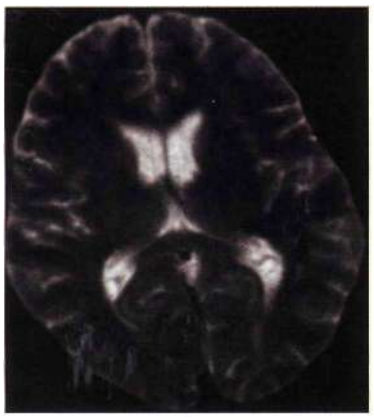
PLATE .S9G.III Amyloidosis associated with GSS. Two section through the cerebellum demonstrating amyloid deposits in the molecular layer (mo). (A) Imrminostaming with anti-PrP antibodies shows a plaque *(black arrow).* (B) Staining with Thioflavin-S, which selectively binds to pS-plcated sheet of PrP^{Sc} and can be detected on fluorescence microscopy *(white arrow).* gr = granular layer; mo = molecular layer; pu = Purkinje cell layer).

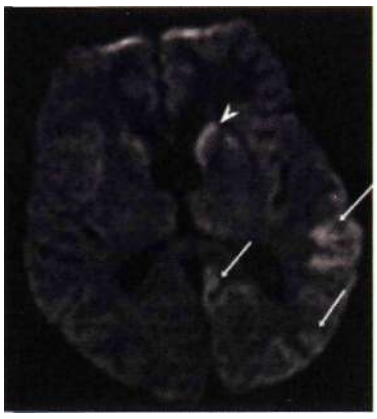


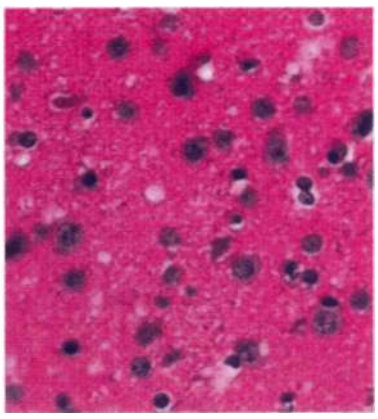


B

PLATE 59G.IV Gerstmann-Straussler-Scheinker syndrome. Axial diffusion weighted imaging showing abnormal signal intensity in cerebral cortex ribbon sign, head of caudate nucleus (*arrowhead*) and thalamus (*arrow*) (A), and multicentric plaques and spongiform changes in brain biopsy (B). (Courtesy Dr. P. Gambetti.)







A B C

PLATE 59G.V A case of sporadic CJD showing normal post-gadolinium Tf- and T2-weighted MR images (A) and mildly increased signal in die cortex *(arrows)* and basal ganglia *(arrowhead)* on diffusion-weighted images (DWI, B). The diagnosis was confirmed by a brain biopsy, which demonstrated spongiform changes, neuronal loss and gliosis (C).

Once a patient is evaluated in the light of an identified familial mutation, the diagnosis is not problematic, unless there is a suggestion of another inflammatory or malignant process. The differential diagnosis for unrecognized families must include familial forms of AD (especially related to presenilin mutations) or FTD. Of interest is the fact that fCJD associated with the E200K mutation has, in addition to a classical rapidly ptogressive dementia, features of a peripheral neuropathy.

Gerstmann-Straussler-Scbeinker Syndrome

This inherited form of ptionoses demonstrates a broad spectrum of clinical symptoms related to diffcrcnr mutation subtypes (Ghetti et al. 1995). Symptoms become apparent usually in the third or fourth decade. The clinical course is the slowest among human TSE and may progress over several years (3-8 year range with an average of 5 years). The largest number of cases has the P102L mutation. This mutation was causative in the original family described by Gerstmann in 1929. The clinical picture is dominated by cerebellar ataxia and dysarthria followed by dementia in the advanced disease stage. Unlike ataxia in P102L mutation, beatcts of A117V mutation ptescut with dementia, associated with dysarthria, rigidity, tremor, and hyper-reflexia. Parkinsonian features including masked face, tremor, and rigidity may be also present. Probands with F198S mutation initially present wirh short-term memory loss and clumsiness, which further progresses to global dementia and ataxia, associated with parkinsonism (Ghetti et al. 1994). The Yl45Stop mutation has the longest clinical course. A Japanese patient, cartying this mutation, presented initially with short-memory disturbance and disorientation at the age of 38 years (Ghetti, Piccardo, Spillantini et al. 1996). Ovet 21 years symptoms progressed toward global dementia. She was initially wrongly diagnosed with AD. Other features associated with GSS include gaze palsies, deafness, cortical blindness, extensor plantar response, or loss of deep tendon reflexes in lower extremities. Unlike CJD, myoclonus is relatively infrequent. The disease, especially in the early stage, may be confused with spinocerebellar ataxias, olivopontocerebellar atrophy, early onset Parkinson's disease, or dystonia. Because many of these conditions can also be inherited, the definitive diagnosis of GSS requires analysis for mutations in the *PKNP* gene.

Fatal Familial Insomnia and Sporadic Familial Insomnia

FFI was first described by Medori and colleagues in 1992 (Manetto et al. 1992; Medori, Montagna et al. *1992;* Medori, Tnschler et al. 1992). The age of onset is between 35 and 61 years and the course ranges from 6 months to 3 years. It is distinct from other prionoses by a progressive intractable insomnia and symptoms of sympathetic system hyperactivity such as hypertension, tachycatdia, hypetthermia, and hyperhidrosis. These may be accompanied by tremor, ataxia, hyper-reflexia, and myoclonus. Mild cognitive symptoms, rather than frank progressive dementia are present. They include decreased attention span and memoty deficit. Disorientation, confusion, or complex hallucinations may also be present. There are endocrine abnormalities consisting of loss of circadian rhythm for the secretion of melatonin, prolactin, and growth hormone. Decrease in adrenocorticotropic hormone secretion and increase in Cortisol secretion were noted. Clinical and pathological data on FFI is derived from two kindteds. Recently sporadic cases fitting this phenotype have been reported (Parchi, Capellari et al. 1999). Clinical features of SFI are indistinguishable from those of FFI; however, no *PRNP* mutation has been found in affected individuals.

Insomnia associated with autonomic instability presents a anique picture. The differential diagnosis is limited, but includes multiple system atrophy with Shy-Draget syndrome or hypothalamic lesions.

Kuru

Kuru is the Fore language word, which connotes trembling associated with feat or cold and describes the major clinical sign of the disease. Once a common cause of death among the Fore women, kuru is being viewed from the historical perspective since etadication of cannibalistic tituals eliminated this disease. Rare cases are still occurring and can be attributed to an incubation period that extends up to 40 years. Clinical symptoms of kutu differ from othei human prionoses. Its course is dominated by ptogressive cerebellar ataxia. Three clinical phases of this disease have been described: (1) an initial phase when affected individuals are able to ambulate with minimal to moderate ataxia. The ataxia is mainly truncal associated with dysarthria and Tremor. (2) A sedentary phase where ambulation become impossible due to progression of ataxia and associated choreoathetosis. There is worsening of tremor and mood instability. (3) A terminal phase characterized by general hyper-reflexia and progression of dysarthria and dysphagia. Muscle strength and the sensorium are usually preserved. Usually the downhill course of the disease takes 12 months from presentation to death. The disease affected mainly women and children, who consumed preferentially the brains of deceased tribal members during cannibalistic rituals.

DIAGNOSTIC **TESTS**

Unfortunately there is currently no single test that with high specificity and sensitivity can diagnose human prion disease, other than brain biopsy. The clinical diagnosis is made based on clinical course, ruling out other

diseases, and the combined results of diagnostic tests. Brain biopsy histology combined with Western blot analysis of proteinase K (PK)-treated brain homogenate still is the diagnostic gold standard.

Cerebrospinal Fluid Evaluation Including Assays of 14-3-3 and Tau Proteins

In the majority of cases routine examination of cerebrospinal fluid (CSF) including measuring opening pressure, glucose, protein, and cell count is normal. In a small fraction of patients, elevated protein and elevated rg/protein ratio, sometimes with oligoclonal hands, have been reported. Performing a spinal tap, however, helps to rule out other causes of dcrncntia. It is recommended to measure the levels of 14-3-3 and tau proteins in the CSF while evaluating for CJD (Green 2002a, 2002b; Van Everbrocek et al. 2002). The 14-3-3 protein is ubiquitously present in the cytoplasm of central nervous system neurons and is thought to play a chaperoning function in a number of phospborylation-dcpcndent intracellular signal transduction pathways. The sensitivity and specificity of the 14-3-3 protein assay has been reported to be up to 94% and 93%, respectively, in patients with sCJD. The assay was found to be less sensitive in nvCJD with a sensitivity of 77% (Green et al. 2002). The 14-3-3 protein is also elevated in most familial forms of CJD but not in FFI and rarely in GSS. The 14-3-3 protein may be elevated after acute stroke, exacerbation of multiple sclerosis, and encephalitis (Zerr and Poser 2002). Some false positive results of the 14-3-3 test can be related to blood contamination of CSF because some anti-14-3-3 protein antibodies can cross react with the light chain of immunoglobulins. Positive assays have also been sporadically reported (in less than 10% of cases) in end stages of slowly progressing dementing illnesses such as AD, FTD, or AIDS dementia. Therefore, the 14-3-3 protein assay is useful for the work-up of rapidly progressive dementias and this clinical setting has been recommended by both the World Health Organization and the American Academy of Neurology (Knopman et al. 2001), but the results need to be closely correlated with the clinical setting. Similarly, the tau protein level is elevated in the CJD. Its elevation may precede elevation of 14-3-3 (Olio ct al, 2002). Unfortunately, testing tor tin: ran protein has similar limitations as testing for 14-3-3. Its level is transiently elevated after acute stroke (Bitsch et al. 2002) and permanently in AD and FTD. Otto and colleagues (Otto et al. 2002) reported that using a cutoff value of 1300 pg/ml, of tau in the CSF allows for a diagnostic sensitivity of 94% and a specificity of 90% because tau protein elevations in FTD and in most AD cases arc below this limit. The level of tau, like the 14-3-3 protein, increases iliirmti the course of the discs;c; hence, repeated testing can lie useful in iiutully negative cases (Brandel el al. 2001; Otto et al. 2002).

Electroencephalogram

Electroencephalogram (KEG) is the oldest clinical test demonstrating some specificity for CJD. Classical recordings demonstrate theta and delta waves with occasional burst-suppression in the background, in association with rhythmical, paroxysmal sharp waves (PSW). They are present in up to 79% of sporadic CJD cases but not in nvCJD. A similar EEG pattern may be associated with lithium toxicity or other toxic encephalopathies; however, PSWs in these conditions typically do not show rhythmic - ity. Rhythmic PSW are also seen in the subacute sclerosing panencephalitis, but with much longer interbursr intervals.

Neuroimaging

There is a growing interest in using MRI to detect CJD. Besides evident atrophy and ventricular enlargement, increased signal on proton density, T2-weigh ted and fluid attenuated inversion recovery images (FLAIR) has been reported in moderately advanced patients in the brain cortex, thalamus, caudate, and putamen nuclei, but not in the globus pallidus (sec distribution of pathology) (Demaerel et al. 1999; Collie et al. 2001; Mirtal et al. 2002). Changes arc frequently asymmetric, and their intensity increases along the course of the disease on serial scans. It has been demonstrated that increased T2 and FLAIR signal may be preceded by increased intensity on diffusion-weighted images (DWI) with colocalizing dropout on the apparent diffusion coefficient (ADC) map (see Plates 59G.TVA and 59G.VA and B) (Murata et al. 2002). The characteristic cortical ribbon sign on DWI (see Plate 59G.IVA} and signal dropout on ADC that extends beyond the two-week period allows its distinction from acute stroke. Bilateral signal increase in the thalami, especially in their posterior parts (the pulvinar complex), is statistically more frequently found in nvCJD (Collie et al. 2001). This so-called pulvinar sign has been described in up to 60% of nvCJD patients. In contrast, abnormalities in the caudate/ putamen are more frequent in sCJD (Murata et al. 2002). The term *hockey stick sign* refers to an axial section through the head of the caudate nucleus and the putamen where increased signal in a distribution resembling a field hockey stick (the putamen) and a ball (the head of the caudate nucleus). Increased signal correlates with accumulation of $PrP^{Sl\text{''}}$ protein in the tissue (Maik et al. 2002). Unlike the grey matter, the white matter usually demonstrates normal signal, which helps to differentiate from vasculitis, encephalitis, lymphoma, demyelinating disease, parasite, or fungal infections. Lesions associated with CJD do not enhance after intravenous administration of gadolinium. Functional imaging has limited utility in TSE. Single-photon emission spectroscopy CT and positron emission tomography (PET) studies have demonstrated a nonspecific pattern of regional hypomerabolism.

Brain, Tonsillar, and Olfactory Mucosal Biopsy

In unresolved cases where the sum of clinical observations and diagnostic test results is inconclusive, a brain biopsy is needed for definitive diagnosis (sec Plate 59G.V}. The area of greatest EEC or MR1 abnormalities can guide the site of the biopsy. The finding of spongiform change is indicative of prion infection. If amyloid plaques are found, they should be confirmed to consist of PrP by immunostaining. A lack of amyloid plaques speaks against but does not rule out the nvCJD. Amyloid deposits are found only in approximately 10% of sCJD patients. In all cases it is advisable to confirm the diagnosis by Western blot analysis of fresh tissue to establish the presence of PK-resistant prion protein. The sensitivity of brain biopsy, comparing to postmortem diagnosis, and perioperative morbidity greatly varies even between academic centers. In a National Institutes of Health series, 52 out of 55 (95%) autopsy-verified cases biopsies were diagnostic for CJD. A report of positive immunostaining for PrP^{c} in the cytoplasm and dendrites of olfactory receptor neurons in postmortem specimens of olfactory mucosa in sCJD (Zanusso et al. 2003), if confirmed, may provide extra-cerebral tissue for definitive diagnosis. If nvCJD is suspected, a tonsillar, lymph node, or rectal mucosa biopsy can be performed, rather than a brain biopsy. The yield and sensitivity is close to 100% in nvCJD patients. However, the level of PrP^ is too low for detection in sCJD; hence, a lymphoid tissue biopsy is only useful for the diagnosis of nvCJD and not sCJD.

I'RI VI NTION

Prevention of prion diseases starred with breeding sheep about 1000 years ago by Moorish Berbers to maintain healthy flocks. By the 1950s extinction of cannibalism among New Guinea Fore people eradicated kuru, Recognition of the routes of prion transmission in iCJD decreased the potential for new cases. These included introducrion of recombinant growth hormone in place of cadaver-derived hypophyseal homogenatc, use of disposable I'IXT electrodes and neurosurgical instruments used to biopsy suspected CJD cases, and the use only of synthetic dura or lyophilized human dura after a special decontamination process. The epidemic of BSE and nvCJD in the United Kingdom resulted in the slaughtering of 4.5 million asymptomatic cattle. No cattle older than 30 months are allowed to enter the food chain in the United Kingdom, and in other European countries they are tested for PK-resistant PrP^{L} prior to slaughtering. In 1996 in the United Kingdom mammalian meat and bone meal residue produced by rendering was prohibited from all animal feed and from fertilizers. To prevent spreading of BSE to humans, the British government introduced in 1989 a ban on specified bovine offal for human consumption, and in 1992 use of head meat collected after the skull was opened was banned. In 1996 production of mechanically recovered meat from the spine (homogenizarion of bones with remnants of meat) w;v; prohibited. In the United States the Eood and Drug Administration restricted bovine source materials for pharmaceutical, dietary supplements, and cosmetic products to BSE-free countries. Because blood can be a potential source of prion infection, currently in the United States all subjects who resided in Great Britain for more than 6 months between 19S0 and 1996 are deferred as blood donors. In the United Kingdom Ieukodepletion of the whole blood is mandated. Restrictions concerning donations of dura, corneas, hematopoietic stem cells, bone marrow, liver, and kidney are debated in the United Kingdom.

Although infectivity of TSE is low, prions are unaffected by routine antiseptic practice. Therefore special measures should be taken when handling infected matetial. All instruments used for spinal tap, brain biopsy, or processing of the histological specimen should be disposable, or if not possible these instruments should undergo prolonged steam autoclaving for 1 hour at 132"C (Budka ct al. 1995; Ironside and Bell 1996). Unautoclavablc instruments can be decontaminated by immersion for 1 hour in 1 M sodium hydroxide (NaOH) or undiluted bleach. All contaminated surfaces should be cleaned with 1 M NaOH or undiluted bleach and during specimen shipment special precautions should be maintained. Brain tissue is the most contagious specimen even after fixation in formalin. Eor complete disinfection, it should be immersed in 100% formic acid for 1 hour (Brown et al. 1990). Direct contact with the patient's skin or mucosa and exposure to body fluids other than blood do not pose any additional risk of infection.

There is no epidemiological evidence that medical personnel are at incfeased risk of developing CJD as the result of direct patient care, performing an invasive procedure, including brain biopsy, or handling a patient's tissue obtained during biopsy or autopsy. On the contrary, the incidence of CJD among health care personnel including neurosurgeons and pathology technicians remains the same as in the general population (Brown et al. 1992). There is one reported case of CJD in a spouse (Brown et al. 1998), and the incidence of CJD among other family members and friends remains similar to that in the general population. Therefore there is no justified reason to keep patients in contact isolation.

In the United States and in Europe, surveillance of patients with CJD is performed. Therefore reporting the diagnosis to these surveillance organizations may be necessary. In particular, any suspected case of nvCJD should be reported. The incubation period of prionoscs is very long. During this clinically silent period, material from the patient, such as blood, is potentially infectious; therefore whether the patient donated blood or other body tissues in the past should be appropriately investigated.

TREATMENT APPROACHES

Currently there is no treatment that would arrest and/or reverse progression of the disease. All forms of prion diseases are ultimately fatal. Patients and their caregivers may, however, benefit from symptomatic treatment. Agitation and outbursts of violence may require antipsychotic agents, especially atypical antipsychotics with a lower incidence of extrapyramidal side effects, and benzodiazepines. Benzodiazepines and other antiepileptic agents can be used for the treatment of seizures and myoclonus. Parkinsonian symptoms can be alleviated by [.-dopa preparations and D_z receptor agonists. Prolonged survival of patients with GSS when treated with antiparkinsonian medications has been demonstrated. This seems to be related to increasing mobility and reducing risk of fatal comorbidities, rather than slowing down the course of the disease. Amantadine has been used with limited efficacy for symptomatic treatment of ataxia associated with spinocerebellar degeneration and CJD with prominent cerebellar syndrome.

The quest for treatment specifically arresting and reversing symptoms of the prion diseases is underway. Several compounds have been proven to be effective at delaying development of prion diseases when given to sera pie-infected hamsters. These included Congo red (Caspi et al. 1998; Demaimay et al. 1998), anthracyclines (Tagliavini et al. 1997), amphotericin B (Adjou et al. 1996, 1999), and sulfated polyanions (Earquhar et al. 1999). Unfortunately, these agents are toxic or have unfavorable pharmacokinetic properties when used in humans. Derivatives of acridinc (Quinacrine) and phenothiazine ((hlorpromazine), commonly used in humans as antimalarial and antipsychotic agents, have been shown in tissue culture to inhibit the conversion of PrP^c into PrP^{Sc} (Korth et al. 2001). Unfortunately, recent reports of anecdotal use of these agents in a limited number of sCJD and nvCJD patients are not encouraging.

Treatment approaches aimed to arrest or reverse the detrimental secondary structure of proteins are under investigation for many conformational disorders including prionoses and AD (Sigurdsson et al. 2000). The sequence between amino acid residues 90 and 150 is critical for PrP^{Sc} binding to PrP^c and the conformational shift. Synthetic peptides corresponding to PrP^c residues 109-141 can reproduce some of PrP^{Sc} properties in vitro, including high jS-sheet content and aggregation to form amyloid-like fibrils (Dc Gioia et al. 1994; Zhang et al. 1995). Short-peptide homologues to PrP^c have been designed to interact with PrP^{Sc} and act as /3-sheet breakers (Wisniewski et al. 1998, 2001). They have been tested and shown to inhibit the murine $PrP^{5'}$ conversion (Soto et al. 2000), demonstrating their therapeutic potential in prion diseases.

Another approach, which may be beneficial for prion diseases, is immunological. Splenectomy has been shown to prolong the period of TSE incubation. Recently some reports have shown that immunization with nontoxic recombinant PrP or amyloid-^ homologous peptides is beneficial for prion diseases and AD animal models, respectively (Sigurdsson et al. 2001). Vaccination of mice with recombinant PrP delayed the onset of disease (Sigurdsson et al. 2002). The delay was longer when mice were vaccinated before exposure, and it correlated with the antibody titer. Similar beneficial effect was reproduced after passive immunization. Reduction in PrP^{St} level without affecting PrP^c level with immunization has been reported in a sera pie-infected mouse model. It is speculated that antibodies binding to PrP^c interfere with the PrP^{St}-mediated conversion of PrP^c into PrP^{Sc} and thereby delay the onset of disease. Epitope mapping of the anti-PrP antibodies produced by immunization is under way to establish which portion of PrP^{St} is essential for prion replications. The ultimate goal of these vaccination studies is either to develop a vaccine or a compound, using peptidomimetic technology, which would interact with PrP^{Sc} molecule to prevent its multiplication. It is hoped that some of these strategies will produce a successful therapeutic approach.

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Chapter 60
Multiple Sclerosis and Other Inflammatory Demyelinating Diseases of the Central Nervous System

Michael J. Olek and David M. Dawson

Diseases affecting central nervous system (CNS) myelin can be classified on the basis of whether a primary biochemical abnormality of myelin exists (dysmyelinating) or whether some other process damages the myelin or oligodendroglial cell (demyelinating), Demyelinating diseases in which normal myelin is disrupted include autoimmune, infectious, toxic and metabolic, and vascular processes (Table 60,1). Dysmyelinating diseases in which a primary abnormality of the formation of myelin exists include several hereditary-disorders (see Table 60.1; Chapter 68). Infectious demyelinating disease (progressive multifocal leukoencephalopathy) is discussed in Chapter 59B, toxic and metabolic demyelinating diseases in Chapter 62, and vascular demyelinating disease (Binswanger's disease) in Chapter 57, The present chapter concentrates on multiple sclerosis and "tiicr mllanimalon demyelinating diseases ol myelin (acute disseminated encephalomyelitis [ADEMJ and acute hemotrhagic leukoencephalopathy), as well as other CNS diseases that are presumably immune-mediated (see Table 60.1). The paraneoplastic disorders are discussed in Chapter 58.

Multiple sclerosis (MS) is the most common disease caused by an inflammatory demyelinating process in the CNS, MS is a leading cause of disability in young adults. In the United States the total lifetime cost per patient, including services, alterations to home and vehicle, medications, purchase of special equipment, and loss of earnings, was $2.5 million in 1994 dollars. In 2002 average annual insurance expenditures for MS patients were 1.9 to 3.2 times higher than the average for three different third-party payers, and 1% of the MS patients accounted for 20% of the total costs.

Pathologically, MS is characterized by multifocal areas of demyelination with relative preservation of axons, loss

Tabic 60.1: Diseases of myelin

Autoimmune
Acute disseminated encephalomyelitis
Acute hemorrhagic leukoencephalopathy
Multiple sclerosis
Infectious
Progressive multifocal leukoencephalopathy
Toxic/metabolic
Carbon monoxide
Vitamin B,; deficiency
Mercury intoxication (Minamata disease)
Alcohol/rob a ceo amblyopia
Central pontine myclinolysis
Marchiafava-Bignami syndrome
1 lypi ixiii
Radiation
Vascular
Binswangcr's disease
Hereditary disorders of myelin metabolism
AdrL'iiDk-iikiidj'si'i'iiphy
Metachromatic leukodystrophy
Krabhc's disease
Alexander's disease
Canavan-van Bogaert-Bertrand disease
Pelizaeus-Merzbacher disease
Phenylketonuria
Multiple sclerosis

of oligodendrocytes, and astroglial scarring. Certain clinical features are typical of MS, but the disease has a highly variable pace and many atypical forms. Investigative studies are often needed to confirm the diagnosis and exclude other possibilities. Advances in disease monitoring and treatment hold promise of slowing the progression of disability. Our understanding of the basic nature of the disease remains limited, and true control of the disease and repair of damaged myelin remain as goals for the future.

PATHOPHYSIOLOGY

The symptoms and signs of MS must be the manifestations of the pathological lesions seen in the CNS, namely demyelination with, in general, axonal preservation. However, detailed pathological and magnetic resonance (MR) spectroscopy studies indicate axonal loss of a moderate degree can occur in MS plaques (Trapp et al. 1998). A comparison of the physiological properties of normally myelinated axons and of dcmyclinated axons provides insight into the basis for the symptoms and signs characteristic of MS,

Compacted myelin is the lipid-rich plasma membrane of oligodendrocytes that provides insulation tor electric impulses traveling along axons. Myelinated axons propagate nerve impulses rapidly in a saltatory fashion with a high safety factor for transmission (five to seven times above threshold) (Waxman and Ritchie 1993). Current is induced by the opening of voltage-gated $Na^{\wedge}$ channels found at the nodes of Ranvier. The resultant Na^{+} influx creates a current that then moves toward the *next* node of Ranvier, as current cannot flow outward in myelinated internodal segments (Figure 60.1). K^{l} channel opening terminates current flow and leads to repolarization. Several types of K^{ch} channels exist in the axon. Fast $K^{:}$ channels sensitive to 4-aminopyridine arc located in internodal axonal membrane and contribute to repolarization of demyel mated axons. Slow K channels .-re found a: the nodes of Ranvier and have a role in modulating repetitive firing. The Na^{+}, K^{+}-adenosinetriphosphatase (ATPase) in the axon membrane restores ionic balance following high-frequency firing.

Demyelination interrupts current flow by removing the insulator of internodal axon current flow. For short segments (one or two internodes) demyelination is not critical because of a high safety factor for transmission. However, longer segments of demyelination can result in interruption of current flow, because current must flow by continuous propagation. The low density of internodal Na^{+} channels, at least in the early stages of demyelination, inhibits impulse propagation. If conduction does occur, it is at a much-reduced speed (5-10% of normal). The refractory period of dcmyclinated axons is prolonged, and repetitive volleys may be blocked when encountering an axon segment in a refractory period. Persistent neurological deficits or negative symptoms of MS are caused by regions in which conduction block persists, such as in regions of large plaques, whereas transient worsening of function teflccts a drop below the safety threshold for conduction because of physiological changes involving the partially dcmyclinated axon (Uhthoffs phenomenon, worsening with increased body temperature).

Mechanical stimulation of demyeliuated axons can generate *de novo* action potentials in the axon and may explain Lhermitte's phenomenon, electric shocklike sensations on flexing the neck. Spontaneous action potentials have been recorded from dcmyclinated axons and, if present in the CNS, could explain paroxysmal positive-symptoms of MS such as trigeminal neuralgia, myokymia, and visual phosphencs.

In addition to structural changes, one must consider functional impairment of nerve transmission caused by edema or factors liberated by immunocompetent cells (cytokines, adhesion molecules) in the plaque and peri-plaque regions that may be toxic to cells or axons. Rapid recovery of function may be caused by resolution of edema, pH changes, and reduction of cellular infiltrates, whereas more delayed recovery may reflect use of alternate axonal pathways or an increase of internodal Na^{+} channels.

PATHOLOGY

The pathological hallmark of MS is the cerebral or spinal plaque, which consists of a discrete region of demyelination

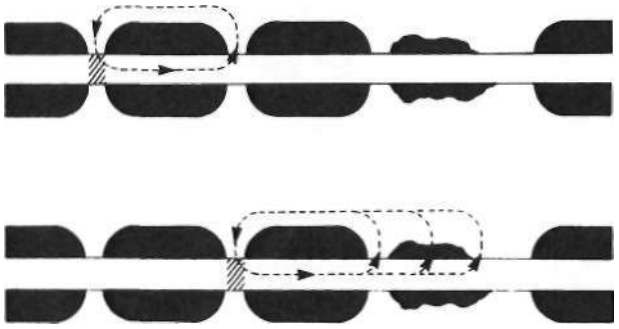


FIGURE 60.1 Schematic diagram of impulse conduction in normal (upper panel) and demyelinated (lower panel) regions of a nerve fiber. The solid arrow indicates the direction of impulse conduction; the shaded area indicates the region occupied by the impulse. Current flow is indicated by the broken atrows. In normally myelinated regions (top), the high resistance, low capacitance directs the majority of action cutrent to the next node of Ranvier. In contrast, in demyelinated regions (bottom), action current is short-circuited Through the damaged myelin sheath or denuded regions of the axon, and hence further propagation of the action potential is blocked. (Reprinted with permission from Waxman, S. G. 1982, "Membranes, myelin, and the pathophysiology of multiple sclerosis," *N Engl J Med*, vol. 306, pp. 1529-1533.)

with relative preservation of axons, although spectroscopic and pathological studies suggest some axonal loss may be an integral part of the demyelinating process.

Gross examination of the brain in MS often reveals variable degrees of atrophy and ventricular dilatation. Plaques may be visible on the surface of the spinal cord on inspection. The cut surface of the brain reveals the plaques, which, when active, appear whitish yellow or pink, with somewhat indistinct borders. Older plaques appear translucent with a blue-gray discoloration and sharply demarcated margins. These plaques often have a hard or rubbery consistency. Individual lesions are generally small (1-2 cm), but may become confluent, generating large plaques. Plaques develop in a perivcnular distribution and are seen most frequently in the periventricular white matter, brainstem, and spinal cord (Figures 60.2 and 60.3), a finding confirmed with magnetic resonance imaging (MRI) studies. However, large numbers of small plaques, often detected only by microscopy, are found in cortical regions affecting intracortical myelinated fibers.

One of the earliest features of acute MS lesions is a disruption of the blood-brain barrier (BBB) as detected by MRI studies. Disruption of the BBB appears to be a critical early step in lesion pathogenesis. The BBB depends on tight junctions between brain endothelial cells. These junctions are not disrupted; rather, a rransendothelial cell vesicular transport system will become active. It can carry water, proteins, antibodies, and cytokines (and gadolinium) into the brain.

Histological examination of active plaques reveals perivascular infiltration of lymphocytes (predominantly T cells) and macrophages with occasional plasma cells. In the plaque, myelin is disrupted, resulting in myelin debris found in clumps or within lipid-laden macrophages. Macrophages, most prominent in the plaque center, appear to have an integral tole in stripping myelin lamellae from axons. Reactive astrocytes ate prominent in plaques. Immunohistochemical studies have found increased levels of cytokines in active plaques indicative of ongoing immimoreactivity.

The fate of oligodendroglia in MS lesions is disputed; consensus opinion is that oligodendroglia number is reduced proportionate to myelin loss in the plaque center, whereas at the plaque edge oligodendroglia are preserved or even increased, suggesting an attempt at remyelination. Remyelination has previously been considered improbable in the CNS (as opposed to the peripheral nervous system [PNS]), yet the finding of shadow plaques (areas of thinly myelinated axons) supports the concept of central rcmyclination (Prineas ct al. 2001). Remyelination may involve either oligodendrocytes that previously produced myelin or maturation of progenitor cells. Such remyelination may explain the clinical finding of slow and delayed tccovcry from an acute attack, whereas rapid clinical recovery presumably reflects the resolution of edema, inflammation, and removal of toxic factots associated with acute plaques in which myelin destruction is minimal.

Studies of plaques with tecurrent demyehnation provide insights into a possible mechanism whereby permanent demyehnation occurs. Evidence of recurrence of activity in old plaques may be demonstrated by gadolinium-enhanced MRI. Chronic demyelinated plaques could thus result not from a single severe episode of demyelination, but rather from recurrent bouts of demyelination at the same site

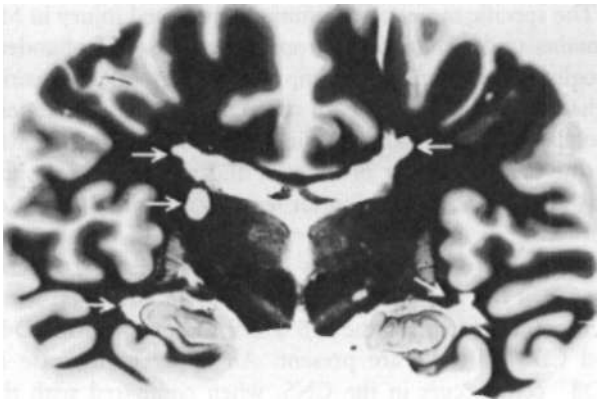


FIGURE 60,2 Coronal section of brain showing large plaques adjacent to lateral ventricles and temporal horns. A plaque is seen also in the left internal capsule *[arrows)* (stain, Heidenhain's myelin). (Courtesy Dr. S. Carpenter.)

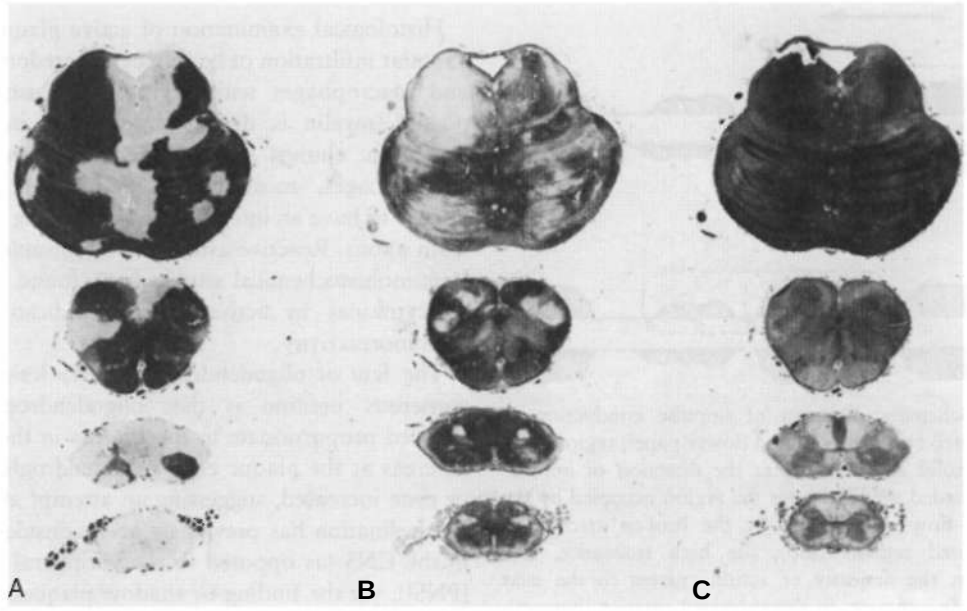


FIGURE 60.? Brainstem and spinal cord sections from patient with multiple sclerosis stained with (A) Hcidcnhain's myelin stain; (B) Holzer's stain for gliosis; and (C) Bodian's stain for axons. Note mirror image of myelin and Holzer's stains in the pons. Also note dramatic demyelination of sacral cord with preserved myelin in nerve roots (A, bottom). (Courtesy Dr. S. Carpenter.)

(Prineas et al. 2001). This could eventually exceed the ability of oligodendroglia to remyelinate or result in tissue changes that eventually prevent remyelination,

Data derived from biopsy as well as autopsy material (I.uccmerti et al. 1999, 2000) has emphasized the heterogeneity of the MS lesion. Some lesions appear to be chiefly inflammatory with retention of active oligodendrocytes, derived from identifiable precursor cells, and evidence of remyelination. In other patients extensive destruction of oligodendrocytes, little replacement, and closer resemblance to a viral or toxic cell apoptosis was found. Because all active lesions from an individual patient were of the same type, the tissue response must clearly be genetically controlled.

The specific target of the immune-mediated injury in MS remains undetermined. A proportionate loss of oligodendroglia and myelin would imply a primary attack against cither oligodendroglia or an antigen present on oligodendroglial cell bodies and myelin. Alternatively, myelin may be the primary target of disease, and the oligodendroglia may survive demyelination, at least in the initial stages of disease.

The active lesions contain T lymphocytes and macrophages in the perivascular regions and parenchyma. Most of the T cells express the *tx/fi* T-cell receptor. Both $CD4^+$ ami I l)N T cells arc present. An apparent increase in $CD8^+$ cells occurs in the CNS, when compared with the prevail me of this subset in the peripheral blood. C D4' cells extend from the periphery of active plaques into adjacent white matter, whereas $CD8^+$ cells predominate in the perivascular regions. Some MS lesions also have an accumulation of T cells expressing the *y/S* T-cell receptor, which may mediate cytolysis of CNS cells expressing heat shock proteins.

Among the lymphocytes are cells specifically sensitized to myelin antigens. **Reports** vary **with** regard to the extent of restriction and the precise profile of the T-cell receptor repertoire of CNS T cells. T-cell sensitization could occur via direct exposure to myelin antigens within the CNS or within cervical lymph nodes, a site to which CNS antigens are transported, or via exposure to exogenous agents sharing antigenic determinants with myelin. The latter has been termed *molecular mimicry.* Microglial cells, endothelial cells, and possibly astrocytes can be induced to express major histocompatibility complex antigens and function as antigen-presenting cells, thus potentially promoting myelin antigen interaction with immune-mediating cells.

Activated T cells and the microglia-macrophages can contribute to tissue injury via nonantigen-restricted mechanisms. Each of these cell types releases an array of soluble factors that can contribute to tissue injury including oligodendroglia. Cytokines characteristic of T cells include imerleukin-2 (I1.-2), interferon-^, and tumor necrosis factor-/* (TNF-£) (lyinphotoxin), A shift toward Th 1 cells expressing IFN-gamma, TNF, and IL-2 and away from Th 2 cells, expressing IL-4, IL-5, IL-10, and IL-13, may be characteristic. Soluble factors released by macrophages **and microglia include** TNF-or, leukotrienes, thromboxanes, proteases, and complement components. Many of these immunologically active substances can result in uprcgulation of adhesion molecules, which can promote or facilitate

nonspecific lymphocyte-macrophage migration to the site of immune injury and immune effector-target cell interactions.

B cells and immunoglobulin are also found in MS lesions. To date, no specific myelinotoxic antibody is identified in MS. Antimyelin antibodies are shown, however, to enhance the disease seventy in the experimental allergic encephalomyelitis (EAE) model, suggesting that both cellular and humoral mechanisms may be needed for full expression of immune injury.

Chronic, inactive plaques display sharp demarcation from surrounding brain and are hypocellular (Figures 60.4 and 60.5). The plaques show astrocytic proliferation with denuded axons and an absence of oligodendroglia. Axonal shrinkage or loss also may be noted to a variable extent. Microglia and macrophages, occasionally with a foamy appearance, are scattered throughout the lesion. The edge of chronic plaques may still exhibit hypercellularity, suggesting continued disease activity.

Pathological differences are described between classical MS and disorders considered as variants of the disease. Balo's concentric sclerosis is characterized by alternating bands of myelinated and demyelinatcd fibers in white matter. Clinically, the illness is more fulminant in onset and course than typical MS and has a more inflammatory cerebrospinal fluid (CSF). Transitional forms exist with typical MS. The affected CNS structures in Devic's neuromyelitis optica show more necrosis, cyst formation, and vascular proliferation than is seen in the usual MS case (Mandler et al. 1993). Large tumor-like plaques, found in the variant of MS known as Marburg variant, may show extensive areas of inflammation and edema.

An important area of investigation, now underway in a number of centers, is to correlate recent concepts of pathological heterogeneity with the pace of the illness and tendency toward recovery, ongoing disability, or axon loss and other clinical features. So far little information in this area is available. With time, different pathological processes may predominate. In secondary progressive MS (defined later), ongoing low-grade demyelination was found at the borders of plaques, associated with C3D, an opsonin coupled with complement activation, and this profile may explain the slow expansion of plaques leading to progressive loss of function (Prineas 2001).

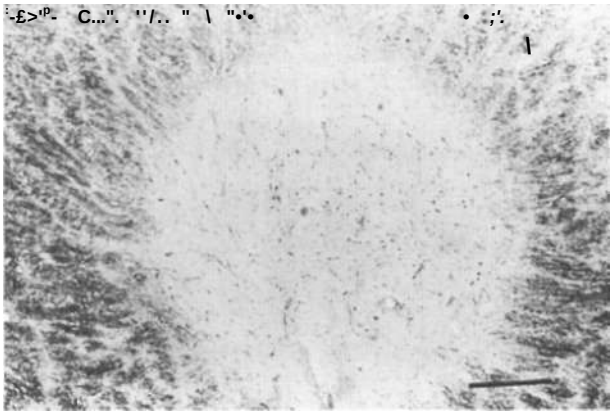


FIGURE 60.4 Punched-out appearance of old multiple sclerosis plaque surrounded by regions with varying amounts of myelin preservation (periodic acid-Schi£f Luxol fast blue; bar = 100 (im). (Courtesy Dr. S. Carpenter.)

FIGURE 60.5 Plaque edge of old plaque with sharply demarcated zone of demyelinarion with normal myelin above (periodic acid-Schiff Luxol fast blue; bar — 50 u.m). (Courtesy Dr. S. Carpenter.)

ETIOLOGY

Autoimmunity

Low levels of autoreactive T cells and B cells are present in normal individuals. Presumably they have escaped from clonal depletion during the process of immune development and arc now tolerant of their antigens. Autoimmunity develops when these cells lose tolerance and a complex process of immune reactivity in target tissues begins. One potential way in which tolerance can be broken is by means of molecular mimicry between self-antigens and foreign antigens, for example, viral components. Several viral and bacterial peptides share structural similarities with important proteins of myelin, and a few of them are able to

activate specific T-cell clones derived from patients with MS. Another way in which tolerance can be broken is by CNS infection, causing tissue damage and releasing antigens into the peripheral circulation where they may encounter corresponding autoreactive T cells.

Myelin basic protein (MBP) has long been considered one of the primary candidates for an autoimmune attack. T cells that respond to MBP are found in the peripheral blood in normal persons and those with MS, possibly at higher levels in patients with MS with active disease. MBP can be an antigen for EAE, the primary animal model of MS. MBP accounts for 30% of the protein of myelin.

Several other proteins characteristic of myelin are also candidates for an autoimmune attack. Proteolipid protein accounts for 50% of CNS myelin protein and is an integral membrane protein of the myelin leaflets. In the PNS P0 protein fulfills this role. Myelin-associated glycoprotein, myelin oligodendrocyte glycoprotein, and cyclic nucleotide phosphodiesterase are proteins that account for a few percent of myelin. Myelin oligodendrocyte glycoprotein and cyclic nucleotide phosphodiesterase are not found in peripheral nerve myelin and arc therefore of interest because MS is a disease affecting only central myelin.

Infection

A possible role for viral infection in the causation of MS has been a matter of ongoing debate for decades. The epidemiology of MS (see Epidemiology, later in this chapter) suggests an exogenous or environmental factor of some type. Beyond epidemiology, and much speculation, there is little to support the concept of a role for viral infection. Innumerable efforts to culture a sir LIS from autopsy-derived or biopsy material have yielded no consistent result. Serological data are difficult to interpret because titers may reflect only a nonspecific tendency toward increased immune reactivity. Specific efforts to recover a known viral genome (e.g., that of human T-cell lymphotropic virus type 1 [HTEV-1|) have proven negative. Retrovirus infection is unlikely because reverse transcriptase is absent from the CSF, despite the use of sensitive assay techniques.

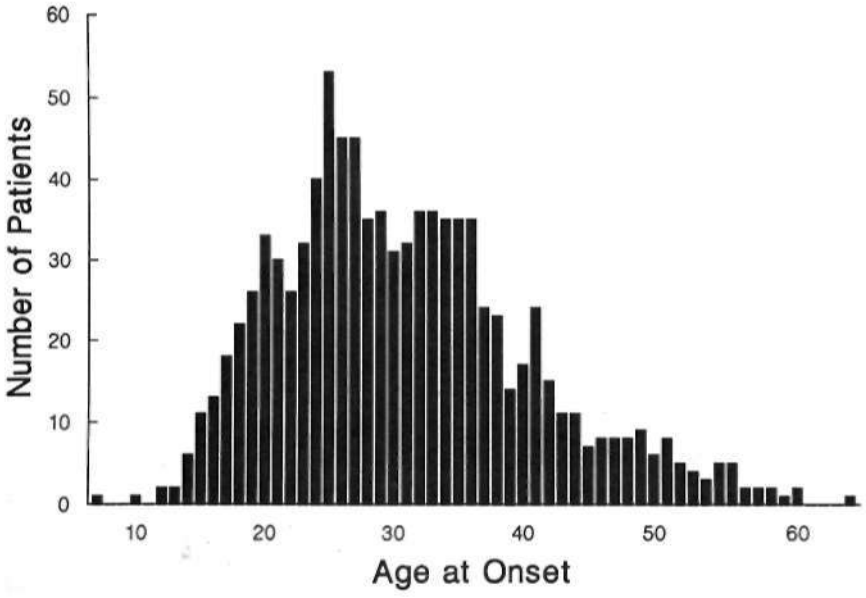
Recently, human hcrpcsvirus-6 (HHV-6), Epstcin-Barr virus (EBV), and Chlamydia pneumoniae have been the focus of intetcst as potential triggers for MS. Several studies of serum and CSF samples have yielded varying results. For example, one early study showed 47% of MS brains were positive for HHV-6, and *H0%* showed elevation in the serum. A more recent study found no HHV-6 DNA in any CSF sample, and the serum antibody titers were comparable to the general population. As has been stated before about viruses and MS, the final word is pending.

Epidemiology

The epidemiology (see Chapter 43) and genetics of MS are complex topics. The interested reader is referred to the articles of Sadovnick and Ebers (1993) and Ebers and Sadovnick (1994).

Age of Onset

Most studies agree that the median age of onset is 23.5 years of age (Figure 60.6). The peak age of onset is approximately 5 years earlier for women than for men. The mean age of onset is 30. Relapsing-remitting MS tends to have an earlier onset, averaging 25-29 years,



KK ;UR1 6!).6 \ge at i inset of (ympti *ns of multiple sclerosis in 940 patients followed at the multiple sclerosis clinic of the Montreal Neurological Institute. Mean age of onset is 30.6 years, median is 27 years, and peak incidence is 25 years.

compared with the relapsing-remirting progressive type with an average of onset of 25-29 years, and a mean age of conversion to progressive MS of 4CM14 years. Primary progressive MS has a mean age of onset of 35-39 years. The onset of MS can occur as late as the seventh decade, although it rarely occurs.

Sex Distribution

Autoimmune diseases in general and MS in particular affect more women than men. In a summary of 30 incidence and prevalence studies, a cumulative ratio of female to male subjects was 1.77 to 1.00.

Mortality

Mortality caused by MS is difficult to ascertain because of poor data collection and reporting. The U.S. Department of Health and Human Services report of deaths in the year 1992 indicates that 1900 U.S. citizens died of MS in that year, giving MS a U.S. mortality of 0.7 per 100,000. The mean age of death of all patients with MS was 58.1 years, compared with a national average of 70.5 for all causes of death. The life expectancy of patients with MS was therefore calculated to he 82.5% of the normal life span, In Denmark, in an exceptionally complete survey of the country, median survival after diagnosis for men was 28 years and for women 33 years, compared with matched population death rates of 37 and 42 years, respectively.

In another study, MS mortality figures were calculated for England and Wales for the years 1963-1990. Over this span of years there was a steady and consistent decline in the death rate attributable to MS compared with the overall death rate. Patients with MS tended to live longer, and other diseases were more likely to be the cause of death. Current estimates indicate that about half of the deaths in MS patients arc directly due to the disease, slightly more than half if accidents and suicide are included as uu'ireci causes.

Geographic and Racial Distribution

More than 250 prevalence surveys have been carried out, serving as the basis for the delineation of geographic risk for MS that is depicted in Figure 60.7. High-frequency

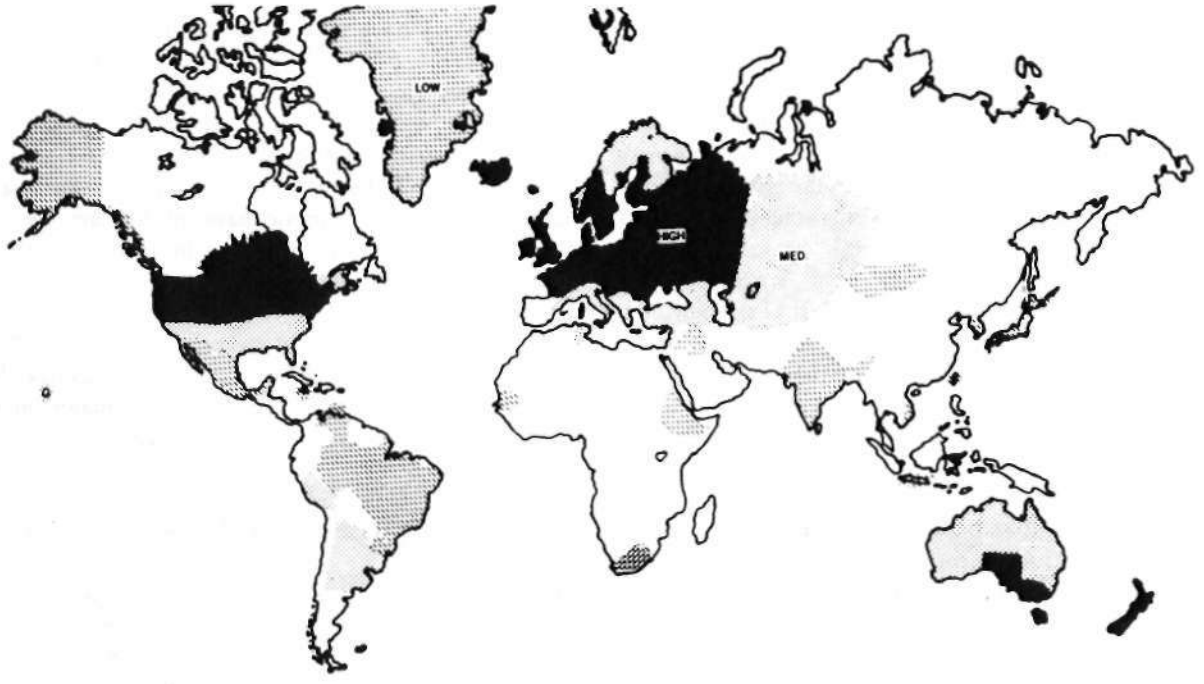


FIGURE 60.7 Worldwide distribution of multiple sclerosis as of 1980. High-frequency areas (>30 per 100,000 population) are indicated in black, medium-frequency areas (5-25 per 100,000) with dots, and low-frequency areas (<5 per 100,000) with diagonal dashes. Open areas are regions without data. South American frequencies are tentative, ['lie low frequency in South Africa is for native South Africans, with medium frequency for persons of European stock native to South Africa. (Reprinted with permission from Kurtzke, J. F. 1980, "The geographical distribution of multiple sclerosis—an update with special reference to Europe and the Mediterranean region," *Acta Neurol Scand,* vol. 62, pp. 65-80. Copyright 1980, Munskgard International Publishers Ltd., Copenhagen, Denmark.)

areas of the world, with current prevalence of 60 per 100,000 or more, include all of Europe including Russia, southern Canada, the northern United States, New Zealand, and the southeastern portion of Australia. In many of these areas the prevalence is more than 100 per 100,000, with the highest reported rate of .500 per 100,000 occurring in the Orkney Islands. In the United States, the prevalence is 0.1 %, or a total of 250,000 persons with MS.

Medium frequency areas comprise most of Australia, the southern United States, the Mediterranean basin (other than Italy), the Asian parts of the former Soviet Union, parrs of South America, and the white population of South Africa.

Low-risk areas include most of South America, Mexico, most of Asia, and all of Africa. One possible conclusion is that MS is a place-related illness, with a latitude gradient. However, notable exceptions then need to be explained. Japan, situated at the same latitude as areas of high prevalence in Europe, is a low-risk area. Second-gene rat ion Japanese in the United States retain their parents' low risk of MS. The white population of South Africa, of medium prevalence of MS, is surrounded by a black population in which the disease is very uncommon. Native North Americans, especially of pure Amerindian background, have a very low prevalence, but are surrounded by a white population with a medium or high risk for VIS.

It seems plausible that race is a determinant of MS risk, with populations of white extraction, especially from Northern Europe being the most susceptible. People of \si;n, African, or Anic'imlian origin have rhc IOWCM v.sk, whereas other groups are variably intermediate.

Migration data have often been used to support the view that a transmissible agent is involved in the pathogenesis of MS. The data indicate that persons migrating from an area of high risk ro an area of low risk after the age of puberty carry their former high risk with them. With migration during childhood, the risk seems to be that of the new area to which the person has migrated. The data are not always clear-cut. Japanese in Japan are at low risk for MS. People of Japanese extraction living in the United States have a higher risk, although less than their neighbors of Northern European extraction. However, those Japanese who migrate to this country do not seem to acquire the risk of their new area. Comparable data are available for persons moving to Israel from Europe (high risk) compared with those arriving from countries in the Middle East.

Genetic and Racial Distribution

The frequency of familial occurrence of MS has varied from 3-23% in different studies. The studies with the higher percentages are those in which ascertainment was more intense; that is, the more one looks, the more one finds. An overall risk in first-, second-, and third-degree relatives of at least *15%* seems a reasonable estimate. The risk is highest for siblings and decreases progressively for children, aunts, uncles, and cousins (Table 60,2). for genetic counseling purposes, it may be stated that the sibling risk is 3-5%, approximately 30-50 times the background risk for this same population. In some studies unaffected family members may have been found to have abnormalities on MRI, implying that the risk may be even higher. The risk applies to blood relatives; only a few studies of adopted children have been done, but they show no increased risk, One unexplained finding is rhe marked deficiency of transmission from father to son.

Table 60.2: Risk of developing MS in family members

Parent with MS	Son	Daughter
Mother	3.8%	3.7%
father	0.8%	2.0%
Sibling with MS	Sister	Brother
Female	5.6%	2.2%
Male	*3,5%*	4.1%
Twin with MS	either sex	
Identical	25-40%	
Nonklentical	4%	

The 95% confidence numbers for these figures range from 0.86 to 1.5.

Source: Modified from Sadovnick, A. D., Baird, P. A., Ward, R. H., et al. 1988, "Multiple sclerosis: Updated risks for relatives," *Am) Med Genet,* vol. 29, pp. 533-541.

Twin studies have shown the familial nature of MS in dramatic fashion. The risk for dizygotic twin pairs is the same as that for siblings, that is, 3-5%. The risk for monozygotic twins is at least 20%, and if the subjects are followed for long periods of time and if various nonclinical data are included, the risk may reach 38.5%. Because the highest rates for the genetic basis of MS are less than 50%, there must be a contribution by nongenetic factors. There arc several candidate genes for MS, including human leukocyte antigen, T-cell receptor, MBP, portions of the immunoglobulin chain, and mitochondrial genes. Three entire genomic scans for MS susceptibility genes have been reported, without an identifiable region of major interest. The data argue for non-Mcndelian polygenic inheritance.

CLINICAL SYMPTOMS AND PHYSICAL FINDINGS

Although the clinical syndrome of MS is classically described as a relapsing-remitting disorder that affects multiple white matter tracts within the CNS, with usual onset in young adults, the disorder displays marked clinical heterogeneity. This variability includes age of onset, mode of initial manifestation, frequency, severity and sequelae of relapses, extent of progression, and cumulative deficit ovet the course of time. The varied clinical features reflect the multifocal areas of CNS myelin destruction (MS plaques), although discrepancies occur between the extent of clinical and pathological findings.

Cognitive Impairment

Data from formal neuropsychological studies indicates that cognitive involvement has been underreported in MS. Neuropsychological test results have shown that 34-65% of patients with MS have cognitive impairment. The most frequent abnormalities are with abstract conceptualization, recent memory, attention, and speed of information processing. Patients refer to memory loss or frustration. The abnormalities are usually not apparent during a routine office visit. In a fast-paced environment with multiple stimuli the cognitive deficit of the MS patient is most obvious. Aphasia, neglect syndrome, cortical blindness, or marked behavioral problems are rare.

Two kinds of recent data have added urgency to the need to assess cognitive deficits: the demonstration by Trapp and colleagues of ongoing axon loss in central white matter beginning at the earliest stages of MS and the demonstration that thinning of the corpus callosum, enlargement of the ventricular system, and other evidences of brain atrophy can be measured accurately by MRI and also begin earlier than previously believed.

Cross-sectional studies have shown some degree of affective disturbance in up to two thirds of patients with MS (Rao et al. 1993). Depression is the most common manifestation and is in part secondary to the burden of having to cope with a chronic, incurable disease. Some data suggest that depression is more common in patients with MS than in others with chronic medical conditions. The lifetime risk of depression a study of 221 patients with MS was 34%, compared with 12.9% in patients' chronic medical conditions in another study. Some data indicate a comorbid association, presumably genetic, between bipolar illness and MS. brontal or subcortical white matter disease may also be a contributory causative factor. Euphoria is usually associated with moderate or severe mental impairment. Patients may manifest a dysphoric state with swings from depression to elation.

On occasion, acute cerebral lesions can manifest as a confusional state. Epilepsy is more common in patients with MS than in the general population, with a cited figure of 3%. Convulsions may be either tonic-clonic in nature or partial complex. They generally respond well to anticonvulsants.

Cranial Nerve Dysfunction

impairment of the Visual Pathways

Optic neuritis (ON) is the most frequent type of involvement of the visual pathways, usually presenting as an acute or subacute unilateral syndrome characterized commonly by pain in the eye accentuated by ocular movements, which is then followed by a variable degree of vision loss (scotoma) affecting mainly central vision. Bilateral ON may occur, but one needs to distinguish whether it is truly simultaneous or sequential. Bilateral simultaneous ON is rare in MS and its occurrence in isolation may suggest another diagnosis such as Leber's hereditary optic atrophy or toxic optic neuropathy (see Chapter 14). In bilateral ON in MS cases, the impairment begins asymmetrically and is usually more severe in one eye. Recurrence is highly variable. In a large ON treatment trial, 15% of placebo-treated patients developed recurrent (ipsilateral or contralateral eye) ON within 6-24 months following the initial bout of ON. Mapping of visual fields teveals a central or cecocentral saiumi.i (antral scotoma involving the physiological blind spot). The finding of a bitemporal hemianopia is rare in MS; if present, it should raise the suspicion of a mass lesion compressing the optic chiasm. Although uncommon, homonymous field defects can be seen in MS caused by involvement of the optic radiations (see Chapters 14 and 40).

Patients with ON have a relative afferent pupillary defect (Marcus Gunn pupil) {see Chapter 40). The afferent pupillary defect is tested by shining a bright light alternately in each eye (the swinging flashlight test), and in the case of unilateral optic nerve dysfunction, the abnormal pupil paradoxically dilates when the light is shifted from the normal to the affected eye. The interpretation of this sign becomes difficult when the degree of optic nerve impairment is similar in the two eyes. When the acute ON lesion involves the head of the optic nerve, one observes disc edema (papillitis), a finding more commonly seen in children than in adults. More often, the lesion of the optic nerve is retrobulbar, and funduscopic examination is normal in the acute stage. Later the optic disc becomes pale as a result of retrograde axonal loss and resultant gliosis. This pallor predominates in the temporal segment of the disc (temporal pallor). After an attack of acute ON, 90% of patients regain normal vision, typically over a period of 2-6 months. Desaturation of bright colors, particularly red, is often reported by recovered patients; some also report a mild nonspecific dimming of vision in the affected eye.

Uhthoffs phenomenon refers to a decrease in visual acuity following an increase in body temperature. This can occur following exercise, a hot bath, or fever. This phenomenon, which reflects subclinical demyclination or pre-existent injury to the optic nerve, may occur without a history of clinical involvement of the optic nerve. A similar phenomenon can occur at other sites of CNS dysfunction with an increase in body temperature.

Impairment of the Ocuiar Motor Pathways

Impairment of individual ocular motor nerves is infrequent in MS. When present, the involved nerves are, in decreasing order of frequency, cranial nerves VI, III, and, rarely, IV. More frequent findings are those that reflect lesions of vestibuloocular connections and internuclear connections. Nystagmus is a common finding in MS (see Chapters 14

and 39), One form of nystagmus particularly characteristic of MS is acquired pendular nystagmus, in which there are rapid, small amplitude pendular oscillations of the eyes in the primary position resembling quivering jelly. Patients frequently complain of oscillopsia (subjective oscillation of objects in the field of vision). This type of nystagmus usually is seen in the presence of marked loss of visual acuity.

Internuciear ophthalmoplegia, defined as abnormal horizontal ocular movements with lost or delayed adduction and horizontal nystagmus of the abducting eye, is secondary to a lesion of the medial longitudinal fasciculus on the side of diminished adduction. Convergence is preserved. When present bilaterally, it is usually coupled with vertical nystagmus on upward gaze. Although most suggestive of MS, a bilateral internuciear ophthalmoplegia can be observed with other intra-axial brainstem lesions, including brainstem glioma, vascular lesions, Arnold-Chiari malformations, and Wernicke's encephalopathy.

Ocular pursuit movements are frequently saccadic rather than smooth. Ocular dysmetria may coexist with other signs of cerebellar dysfunction and other ocular oscillations, such as intrusive saccadic movements (square wave jerks), though these are more common with spinocerebellar degenerations.

Impairment of Other Crantai Nerves

Impairment of facial sensation, subjective or objective, is a relatively common finding in MS, The occurrence of trigeminal neuralgia in a young adult is frequently an early sign of MS. Facial myokymia, a fine undulating wave!ike facial twitching, and hemifacial spasm can be caused by MS, but other causes of a focal brainstem lesion must be excluded. Unilateral facial paresis can occur, but taste sensation is almost never affected. In these syndromes, as with acute oculomotor palsy, the nerve is affected in its course within the neuraxis, rather than peripherally. Vertigo is a reported symptom in 30-50% of patients with MS and is commonly associated with dysfunction of adjacent cranial nerves. Resulting symptoms include hyperacusis or hypoacusis, facial numbness, and diplopia. Complete hearing loss, usually unilateral, is an infrequent complaint. Malfunction of the lower cranial nerves is usually of the upper motor neuron type (pseudobulbar syndrome).

Impairment of the Sensory Pathways

Sensory manifestations are a frequent initial feature of MS and are present in almost every patient at some time during the course of disease. The sensory features can reflect spinothalamic, posterior column, or dorsal root entry zone lesions. The sensory symproms are commonly described as numbness, tingling, pins and needles, tightness, coldness, or swelling of limbs or trunk. Radicular pains, unilateral or bilateral, can be present, partieulatly in the low thoracic and abdominal regions, or a bandlike abdominal sensation may be described. An intensely itching sensation, especially in the cervical dermatomes, usually unilateral, suggests MS.

The most frequent sensory abnormalities on clinical examination are the following: varying degrees of impairment of vibration and joint position sense, decrease of pain and light touch in a distal distribution in the four extremities, and patchy areas of reduced pain and light touch perception in the limbs and trunk. A bilateral sensory level is a more frequent finding than a hemisensory (Brown-Sequard) syndrome. Patients commonly report that the feeling of pinprick is increased or feels like a mild electric shock or that the stimulus spreads in a ripple fashion from the point at which it is applied. The sensory useless hand (the numb clumsy hand syndrome) is a characteristic but uncommon feature, consisting of an impairment of function secondary to a pronounced alteration of proprioception, without loss of power, A lesion of the relevant root cutty zones or posterior columns in the spinal cord is postulated in such cases.

Impairment of Motor Pathways

Corticospinal tract dysfunction is common in MS. Paraparesis, or paraplegia, is a much more common occurrence rhan is significant weakness in the upper extremities. With severe spasticity, extensor or flexor spasms of the legs and sometimes the trunk may be provoked by active or passive attempts to rise from a bed or wheelchair. The physical findings include spasticity, usually more marked in the legs than in the arms. The deep tendon reflexes are exaggerated, sustained clonus may be elicited, and extensor plantar responses are observed. All of these in....tcsiaiions are coin monk asymmetrical. Occasionally, deep tendon reflexes may be decreased because of lesions interrupting the reflex arc at a segmental level, and one may observe an inverted reflex wherein one reflex, such as the triceps, is lost, and the efferent component is represented by a contraction of a muscle below the lesion, such as the triceps muscle. The Achilles reflex can be absent in lesions of the sacral segments of the spinal cord with or without concomitant sphincter and sexual problems. Occasionally, reduced reflexes reflect hypotonia resulting from cerebellar pathway lesions. Amyotrophy, when observed, most frequently affects the small muscles of the hand; lesions of the motor root exit /.ones may produce muscle denervation caused by axon loss. Secondary entrapment neuropathies are also a cause of muscle atrophy in patients with MS.

A common pattern of disease evolution seen in the spinal fotm of MS is an ascending pattern of weakness that begins with involvement of the lower extremities and spreads to involve first one upper extremity and then the other, beginning in rhe intrinsic hand muscles. Often there is an

associated weakness of the trunk muscles with abnormal posture and involvement of respiratory muscles.

Impairment of Cerebellar Pathways

Cerebellar pathway impairment results in gait imbalance, difficulty in performing coordinated actions with the arms, and slurred speech. Examination reveals the usual features of cerebellar dysfunction, such as dysmetria, decomposition of complex movements, and hypotonia, most often observed in the upper extremities. An intention tremor TI 1;y he noted m the limbs and head. Walking is impaired by truncal ataxia. Ocular findings of nystagmus, ocular dysmetria, and frequent refixation saccades suggest cerebellar or cerebellovestibular connection dysfunction. Speech can be scanning or explosive in character. In severe cases there is complete astasia (inability to stand), inability to use the arms because of a violent intention tremor, and virtually incomprehensible speech. Cerebellar signs are usually mixed with pyramidal (corticospinal) tract signs.

Impairment of Bladder, Bowel, and Sexual Functions

The extent of sphincter and sexual dysfunction often parallels rhe degree of motor impairment in the lower extremities. The most common complaint related to urinary bladder dysfunction is urgency, usually the result of uninhibited detrusor contraction, reflecting a suprasegmental lesion. As the disease progresses, urinary incontinence becomes more frequent. With involvement of sacral segments of the spinal cord, symptoms of bladder hypoactivity may evolve, such as decreased urinary flow, interrupted micturition, and incomplete bladder emptying. An atonic dilatatcd bladder that empties by overflow results from loss of perception of bladder fullness and is usually associated with urethral as well as anal and genital hypoesthesia, and sensory deficits in the sacral dermatomes. A dyssynergie voluntary sphincter, interrupting bladder emptying, will lead to frequent small-volume urinations, combined with a large postvoiding residual. When evaluating bladder incontinence or urgency in patients with MS, one must exclude other causes, particularly in multiparous women. Urinary tract infections are common in MS, especially in women. These infections may not cause fever and back pain, but may increase the extent of bladder and other neurological dysfunction.

Constipation is more common than fecal incontinence and is mainly due to decreased general mobility. Almost all patients with paraplegia require special measures to maintain regular bowel movements.

Sexual dysfunction, although frequently overlooked, is a common occurrence in MS. Approximately 50% of patients become completely sexually inactive secondary to their disease, and an additional 20% become sexually less active. Men experience various degrees of erectile dysfunction, often with rapid loss of erection at attempted intercourse, whereas loss of ejacuLition is less common. Most women preserve their orgasmic capabilities, sometimes even in the presence of complete loss of bladder and bowel function. Sexual dysfunction can be the result of multiple problems, including the direct effects of lesions of the motor and sensory pathways within the spinal cord in addition to psychological factors involved with self-image, self-esteem, and fear of rejection from the sexual partner. Mechanical problems created by spasticity, paraparesis, and incontinence further aggravate the problem.

Clinical Features Distinctive of Multiple Sclerosis

Although there are no clinical phenomena that are unique to MS, some are highly characteristic of the disease (Table 60.3). Bilateral internuclear ophthalmoplegia has been mentioned previously. Lhermitte's phenomenon is a transient sensory symptom described as an electric shock radiating down the spine or into the limbs on flexion of the neck. It may be infrequent or occur with the least movement of the head or neck. Although most frequently encountered in MS, this symptom can be seen with other lesions of the cervical cord, including tumors, cervical disc herniation, postradiation myelopathy, and following trauma.

Paroxysmal attacks of motor or sensory phenomena may arise as a manifestation of demyelinating lesions. Within the brainstem, lesions can cause paroxysmal diplopia,

Table 60,3; Common clinical features of multiple sclerosis

Clinical features suggestive of multiple sclerosis	*Clinical features not suggestive of multiple sclerosis*
Onset between ages 1 5 and 50	Onset before age 10 or after 60
Relapses and remissions	Steady progression
Optic neuritis	Early dementia
Lhermitte's sign	Rigidity, sustained dystonia
Internuclear ophthalmoplegia	Cortical deficits such as aphasia, apraxia, alexia, neglect
Fatigue	Deficit developing within minutes
Worsening with elevated body temperature	

facial paresthesia, trigeminal neuralgia, ataxia, and dysarthria. Motor system involvement results in painful tonic contractions of muscles of one or two (homolateral) limhs, trunk, and occasionally the face, but these only rarely occur in all four limhs or the trunk. These paroxysmal attacks usually respond to low doses of carbamazepine and frequently remit after several weeks to months, usually without recurrence.

Heat sensitivity is a well-known occurrence in MS (llhthoff's phenomenon; see discussion under Impairment of the Visual Pathways, earlier in this chapter); small increases in the body temperature can temporarily worsen current or pre-existing signs and symptoms. This phenomenon is encountered in other neurological diseases, but to a lesser extent, and is presumably the result of conduction block developing in nerves as the body temperature increases. Normally, the nerve conduction safety factor decreases with increasing temperature until a point is reached at which conduction block occurs; this point of conduction block is reached at a much lower temperature in demyelinated nerves.

Fatigue is a characteristic finding in MS, usually described as physical exhaustion that is unrelated to the amount of activity performed. Many patients complain of feeling exhausted on waking, even if they have slept soundly. Fatigue can appear also during the day but may be partially or completely relieved by rest. There is a poor correlation between fatigue and the overall severity of disease or with the presence of any particular symptom or sign. Unlike cognitive deficit, no MRI findings correlate with fatigue or with depression. Fatigue is often seen in association with an acute attack and may precede the focal neurological features of the attack and persist long after the attack has subsided.

DIAGNOSTIC CRITERIA

The cornerstone of the diagnosis of MS remains the neurological history and physical examination. To improve the homogeneity of MS patient groups being studied, the Schumacher Committee on Diagnostic Criteria for MS elaborated six items required to diagnose clinically definite MS: (1) objective CNS dysfunction, (2) involvement of white matter structures, (3) two or more sites of CNS involvement, (4) relapsing-remitting or chronic (more than 6 months) progressive course, (5) age 10-50 years at onset, and (6) no better explanation of symptoms as assessed by a competent neurologist. These criteria made no use of laboratory studies. Such stringent criteria would exclude some patients with MS; for example, they were fulfilled in only 95% of a group of patients who came to autopsy study. The criteria were modified for diagnosis in 1983 by Poser et al., expanding the age at onset to 59 years and using data derived from laboratory studies, including analysis of **the** CSF, evoked potentials (FT[1]), and neuroimaging These criteria were developed to ensure that only patients with MS were included in research studies. Recently, McDonald et al. have proposed new diagnostic criteria that include stringent guidelines for MRI and timing intervals to determine possible or definite MS (Fable 60.4). The outcome of a diagnostic evaluation is either MS, possible MS, or not MS.

There remains the clinical problem, distinct from research criteria, of the patient early in the course who does not meet diagnostic criteria. In the setting of a monophasic neurological illness that is clinically consistent with MS and in the presence of multifocal white matter lesions on MRI consistent with demyelinating plaques, the diagnosis of MS is almost certain. In the long-term

Table 60.4: McDonald et al. (2001) diagnostic criteria for multi] le sclerosis

Clinical pre$e?itatior!	*Additional data needed for MS diagnosis*
Two or more attacks; objective clinical evidence of 2 or more lesions	Num.
Two or more attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by MR] OR two or more MRI-detected lesions consistent with MS Plus positive CSF OR await further clinical attack implicating a different site
One attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by MRI OR second clinical attack
One attack; objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space, demonstrated by MRI OR second clinical attack OR two or more MRI-detected lesions consistent with MS Plus positive CIS!-" AND dissemination in time. demonsttated by MRI
Insidious neurological progression suggestive of MS	Positive CSF AND dissemination in space, demonstrated by (1) nine or more T2 lesions in brain or (2) 2 or more lesions in spinal cord or (3) 4-8 brain lesions plus one spinal cord lesion OR abnormal VF.P associated with 4-8 brain lesions, or with fewer than 4 brain lesions plus 1 spinal cord lesion demonstrated by MRI AND dissemination in rime, demonstrated by MRI OR continued progression for 1 year

Positive CSF-oligoclonal bands (detected preferably by isoelectric f lsing) of raised IgG index. MRI parameters as listed in Table 60.4.1 and Table 60.4.2.

Table 60.4.1: MRI demonstration of space dissemination for McDonald et al. (2001) diagnostic criteria for multiple sclerosis

Three or four of the following:
1. One gadolinium-enhancing lesion OR nine T2-hyperintense lesions if there is no gadolinium enhancing lesion
2. At least one infratentorial lesion
3. At least one juxtacortical lesion
4. At least three periventricular lesions

(Adapted from Barkhof et al. [1997] and Tintore et al. (20001.)

study of Brex ct al. (2002), which followed patients with initial demyelinating episodes for up to 14 years, in practical terms no diagnoses were encountered other than MS or suspected MS. Rarely, cases of postinfectious encephalomyelitis, ADFM. or vasculitis may present in a similar fashion. In addition, follow-up studies have shown that a significant percentage of patients with MRI lesions detected at onset do not progress to clinically symptomatic MS, even after many years of follow-up. The issue of the monophasic demyelinating disease is discussed in the next section. Such patients may be classed as suspected MS; they may, in fact, represent particularly benign forms of the disease.

Differential Diagnosis

The differential diagnosis of MS (Table 60.5) is quite limited in the setting of a young adult with two or more clinically distinct episodes of CNS dysfunction with at least partial resolution. 1' rob I ems arise with atypical presentations, monophasic episodes, or progressive illness. The unusual nature of some sensory symptoms and the difficulty patients experience in describing such symptoms may result in a misdiagnosis of hysteria. The retrospective nature of inquiries also blurs details of prior events, making clear ascertainment of prior attacks difficult in some cases, A monophasic illness with symptoms attributable to one site of the CNS creates a large differential diagnosis that includes neoplasms, vascular events, or infections.

Table 60.5: Differential diagnosis in multiple sclerosis

Inflammatory diseases
Granulomatous angiitis
Systemic lupus erythematosus
Sjogren's disease
Behcet's disease
Polyarteritis nodosa
Paraneoplastic encephalomyelopathies
Acute disseminated encephalomyelitis, postinfectious encephalomyelitis
Infectious diseases
Lyme neuroborreliosis
Human T-cell lymphotropic virus type 1 infection'
Human immunodeficiency virus infection
Progressive multifocal leukoencephalopathy*
Neurosyphilis*
Granulomatous diseases
Sarcoidosis
Wegener's granulomatosis
Lymphomatoid granulomatosis
Diseases of myelin
Metachromatic leukodystrophy (juvenile and adult)*
Adrenomyeloleukodystrophy*
Miscellaneous
Spinocerebellar disorders"[1]
Arnold-Chiari malformation
Vitamin B|2 deficiency*

"Indicates disorders that are predominantly important to differentiate in the setting of progressive disease.

Appropriate imaging studies may help clarify the situation, depending on the site of involvement and clinical progression. The most trouble arises with progressive CNS dysfunction, in which great care must be taken to exclude treatable etiologies (e.g., vitamin B_{12} deficiency, compressive spinal cord lesions, arteriovenous malformations, cavernous angiomas, Arnold-Chiari malformation), infectious causes (syphilis, HTLV-1, human immunodeficiency virus), or hereditary disorders (adult metachromatic leukodystrophy, adrenomyeloleukodystrophy, spinocerebellar disorders).

Table 60.4.2: MRI demonstration of time dissemination for McDonald et al. (2001) diagnostic criteria for multiple sclerosis

If a first scan occurs 3 months or more after the onset of the clinical event, the presence of a gadolinium-enhancing lesion is sufficient to demonstrate dissemination in time, provided that it is not at the site implicated in the original clinical event. If there is no enhancing lesion at this time, a follow-up scan is required. The timing of this scan is not crucial, but 3 months is recommended. A new T2 or gadolinium-enhancing lesion at this rime then fulfills the criteria for dissemination in time.

If the first scan is performed less than 3 months after the onset of the clinical event, a second scan done 3 months or more after the clinical event showing a new gadolinium-enhancing lesion provides sufficient evidence for dissemination in time. However, if no enhancing lesion is seen ar this second scan, a further scan not less than 3 months after the first scan that shows a new T2 lesion or an enhancing lesion will suffice,

The new criteria have advantages. The former categories of possible, probable, and definite MS have become obsolete. The MRI criteria are based on extensive data of Barkof et al. (1997) and Tintore ct al. (2000) and are designed ro retain sensitivity while enhancing specificity. They will have liulc usefulness in patients with clear-cut demyelinating syndromes such as optic neuritis or a brainstem syndrome: in such cases many clinicians will be satisfied with less stringent MRI criteria. In patients with obscure symptoms the criteria will help avoid premature or erroneous diagnosis and treatment. In addition, criteria for primary progressive MS are proposed.

Revisions to the McDonald criteria have been proposed. For example, the role of spinal cord lesions needs to be evaluated and expanded, It may take some time before the final crircrm are decided on and accepted as the standard for diagnosis.

A common error is to overinterpret multiple hypei intense lesions on MR1 as equivalent to MS. Clinical symptoms must be consistent with MS. A few white matter lesions in T2-weighted MRI scans are not infrequent, particularly in the elderly, and do not indicate a diagnosis of MS. CNS vasculitidcs such as systemic lupus erythematosus (SLE), Sjogren's disease, polyarteritis nodosa, syphilis, retroviral diseases, and Behcet's disease may all produce multifocal lesions with or without a relapsing-remitting course. SLE can present as a recurrent neurological syndrome before the systemic manifestations of this disease declare themselves. Behcet's syndrome is characterized by bucco-genital ulcerations in addition to the multifocal neurological findings, CNS sarcoidosis can be mistaken for MS with multifocal neurological and MRI lesions. Although rare, ADEM must be considered in the. differential diagnosis (sec Acute Disseminated Fivephalomyelitis, later in this chapter). An MS-like phenotype associated with mitochondrial gene defects has been described; it is of note that when there arc multiple MS cases in *a* family, maternal transmission is more frequent than paternal transmission.

More important than features characteristic for MS are features that should prompt the clinician to reconsider the diagnosis oi MS-red flags indicating that another diagnosis is more likely. Many physicians fail to pursue further diagnostic steps when a patient is labeled as having .MS. Features that should alert the clinician to the possibility of other diseases include (1) family history of neurological disease, (2) a well-demarcated spinal level in the absence of disease above the foramen magnum, (3) prominent back pain that persists, (4) symptoms and signs that can be attributed to one anatomical site, (5) patients who are over 60 years of age or less than 15 years at onset, and (6) progressive disease (see Table 60,3). None of these features excludes the diagnosis of MS, but in these situations one should seek other etiologies before accepting the diagnosis of MS.

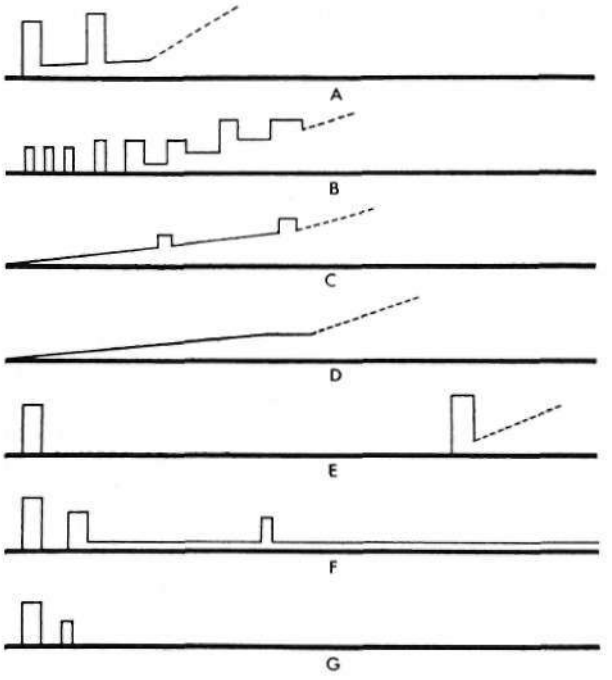


FIGURE 60.8 The course of multiple sclerosis. (A) Severe relapses, increasing disability, and early death. (B) Many short attacks, tending to increase in duration and severity. (C) Slow progression from onset, superimposed relapses, and increasing disability. (D) Slow progression from onset without relapses. (E) Abrupt onset with good remission followed by long latent phase. (F) Relapses ot diminishing frequency and severity, slight residual disability only. (G) Abrupt onset, few if any relapses after first year, no residual disability. (Reprinted with permission from McAlpine, D., Compston, A., Fbers, G., et at. 1VVK, AIIVW/JW'S *Multiple Sclerosis*, 3rd ed, Churchill Livingstone, London, p. 32.)

Course

The most characteristic clinical course of MS is the occurrence of relapses (Figure 60.8), which can be defined as the acute or subacute onset of clinical dysfunction that usually reaches its peak from days to several weeks followed by a remission during which the symptoms and signs resolve partially or completely. The minimum duration for a relapse has been arbitrarily established at 24 hours. Clinical symptoms of shorter duration arc less likely to represent what is considered as a true relapse (i.e., new lesion formation or extension of previous lesion size). Worsening of previous clinical dysfunction can occur concurrently with fever, infection, physical activity, or metabolic upset and last for hours to a day or more. Such worsening is thought to reflect conduction block in previously demyelinated axons. Relapses of MS vary markedly with regard to the CNS site involved; the frequency of attacks (the free interval between relapses ranges from weeks to years); the mode of onset (from quite sudden to subacute); and the duration, severity, and quality of remission. The frequency of relapses is highly variable and depends on the population studied and the closeness of observation and recording by patients and physicians. Summaries of many studies provide an average figure of 0.4-0.6 relapses per year. Patients followed closely in clinical trials have higher relapse rates, probably reflecting self-selection and closer reporting and examinations in such studies. The attack rate in the placebo group in clinical studies ranges from 0.8-1.2 attacks per year. In general, relapses arc more frequent during the first years of the disease and tend to wane in later years. A course marked by relapses, interspersed by periods during which the disease seems relatively dormant, is termed relapsing-remitting.

Approximately 15% of patients never experience a second relapse. The exact frequency of such benign MS is unknown, however, because many such individuals never come to medical attention. Autopsy studies found a significant numbers of cases with CNS pathology consistent with MS and yet no documented clinical evidence of

such disease. Similarly, MRI studies have shown MS-like plaques in T2- weigh ted scans in patients who have never-had a neurological episode. Asymptomatic relatives of patients with MS have MRI lesions consistent with dcmyelination in up to 15% of these relatives (Sadovnick et al. 1993). The use of MRI may expand the specttum of MS by detecting milder cases that previously were not included in prognosis studies.

A standardization of terms has been agreed on to determine the pattern and course of the illness (Lublin and Reingold 1996). Four categories of disease are described:

1. Relapsing-remitting MS: Clearly defined relapses with full recovery or with sequelae and residual deficit on recovery. The periods between disease relapses are characterized by a lack of disease progression.
2. Primary-progressive MS: Disease progression from onset with occasional plateaus and temporary minor improvements allowed.
3. Secondary-progressive MS: Initial relapsing-remitting diseast course followed hy progression with or without occasional relapses, minor remissions, and plateaus.
4. Progressive-relapsing MS: Progressive disease from onset, with clear acute relapses, with or without full recovery. The periods between relapses are characterized by continuing progression.

Two severity outcomes are also described: (1) Benign MS is disease in which the patient remains fully functional in all neurological systems 15 years after the disease onset; and (2) malignant MS is disease with a rapid progressive course, leading to significant disability in multiple neurological systems or death in a relatively short time after disease onset.

Data from a clinic-based study of 1100 patients who represented the population of the region found that 66% of patients at onset had relapsing and remitting disease, 15% had relapsing-progressive, and 19% had progressive disease from the onset. Patients evolved from a relapsing-remitting course to a progressive course; 85% of patients began with a relapsing course, but the proportion continuing as relapsing disease decreased steadily, so that by 9 years from onset, only one half were still relapsing. Likewise, the probability of reaching 6 on the Kurtzke disability score was 50% 16-17 years after onset. The course of MS with onset after the age of 40 was progressive in over 60% of patients.

The rate of clinical progression of MS is variable. The commonly used index of clinical disability, the Kurtzke disability status score (DSS), or the expanded version called the expanded disability status score (EDSS), uses numbers ranging from 0 for normal examination and function, to 10 for death caused by MS. This scale is nonlinear, with great emphasis on ambulation capabilities with scores above 4. Most MS populations have bimodal distributions of EDSS scores, with peaks at values of 1 and 6 (ambulation with unilateral assistance). The time spent by a patient at a given level of disability varies with the score. Thus, for patients with DSS scores of 4 or 5, median time spent at these levels was 1.2 years, whereas for those at DSS 1, median time to stay at that level was 4 years, and at DSS 6, it was 3 years. These results have powerful implications for the conduct of clinical studies with respect to patient selection, stratification, and duration of follow-up: If many patients of DSS 1 or *6* are included, little movement is seen in a group followed for a year or two. The rate of progression with chronic progressive disease in the placebo groups of three clinical trials ranged from 0.5-0.7 points per year on the DSS scale.

In a cohort of patients followed for *25* years, the following data emerged (Runmakcr and Andersen 1993): 80% of the patients had reached the progressive phase by 25 years, 15% of the patients had died, *65%* of the patients had reached EDSS 6 (requiring aids for walking), and 50% of the patients reached EDSS 6 within 16 years of onset.

The HDSS, although universally used m clinical trials, has a number of serious limitations. Even with special training and examiner blinding, interrater and intrarater variations in scoring are common. EDSS scores of 4 and higher depend almost entirely on the ability to walk, and developing dementia, vision loss, or weakness of hands may pass undetected by the scoring. An obvious implication of these facts is that other outcome measures should be used as well and that minor changes in EDSS alone should not be ovcrinterpreted.

The Multiple Sclerosis Functional Composite Scale (MSEC) is a clinical tool designed to avoid the problems encountered with the EDSS. The MSFC consists of three parts: (1) Paced Auditory Serial Addition Test (PASAT) (2) 9-Hole Peg Test (9HPT) and (3) Timed 25-Foot Walk (T25FW), These three measures take into account cognition, upper extremity, and lower extremity functions, A z-score is obtained for each measure and a combined z-score is then derived. The MSFC has been validated in several clinical trials. The tests can be performed by a nonphysician and are highly reproducible and predictable.

Effect of Exogenous Factors on the Course

The role of a variety of exogenous factors cither influencing the development of MS or inducing disease exacerbations has been examined using epidemiological techniques. A disproportionately high number of relapses occur in patients with MS who have suffered recently from viral infections, and a high number of infections are followed by acute attacks. Increased interferon-)' and TNF-a produced by cells of the immune system during viral infections may play a role in this increased relapse rate by increasing expression of ma]or histocompatibility complex class II antigens and adhesion molecules on cells of the immune

system and CNS, with a resultant increase in the number of activated T cells being attracted to the CNS.

Controversy exists about a link between occurrence of stressful events and exacerbation of MS. Trauma appears not to be implicated in disease induction or relapse, although in the experimental animal model EAE, lesions are most prominent at sites of pre-existent traumatic lesions. Performance of neurological diagnostic procedures such as myelography and lumbar puncture has not been linked with aggravation of the MS disease coutse, nor has administration of local or general anesthetics. Recent data do not establish a link between vaccination and disease exacerbations, and few clinicians withhold immunization programs, for example, for influenza or hepatitis.

Effect of Pregnancy on the Course

MS is a disease that predominantly affects women and has a maximum incidence during child bearing years. The influence of pregnancy on MS has been repeatedly examined, with evidence that relapses are reduced late in pregnancy and are more frequent than expected in the 3-monrh postpartum period. However, this is not the finding in all studies. There is general agreement that the overall prognosis is no different in women who have been pregnant, compared with those who have not. Studies of women with MS reveal no increase in stillbirths, ectopic pregnancies, or spontaneous abortions. These data would suggest that pregnancy has no ill effect on MS and that MS has no negative effect on the fetus or the course of pregnancy. In a study of postmenopausal women, there was no difference in disease severity in multiparous or nulliparous women. An important issue in the pregnant woman with MS is to avoid exposing the fetus to toxic drugs (Table 60.6).

Tabic 60.6: Safety in pregnancy of drugs used in the treatment of multiple sclerosis

Category B: Animal data showing no harm to the fetus; no human data available
Glatiramer acetate [Copaxone)
Pemoline
Oxybutymn
Fluoxetine (and other selective serotonin reuptake inhibitors)
Desmopressin
Category C; Animal data shows harm to the fetus; no human data available
Corticosteroids
Interferon-^,
Interferon-^]$_b$
Baclofen
Amantadine
Tizanidinc
Carbamazepine
Category D: Known to cause fetal harm when administered to pregnant women
Azathioprine
Cladribine
Cyclophosphamide
Category X: Contraindicated for use during pregnancy
Methottexate

Source: Modified from Damek, D. M. & Sinister, *E.* A. 1997, "Pregnancy and multiple sclerosis," *Mayo Clin Proc,* vol. 72, pp. 977-989.

PROGNOSIS

Although great individual variability exists with regard to disease prognosis, a variety of factors have been identified as possible prognostic indicators.

Sex: MS appears to follow a more benign course in wumui il'i.ii: in men.

Age at onset: The average age at onset of MS is 29 years. Onset at an eatly age is seemingly a favorable factor, whereas onset at a later age carries a less favorable prognosis. As previously stated, the pattern of disease varies in different age groups, with the re lapsing-remitting form being more common in younger patients and the progressive form being more common in the older age group. Data arc lacking as to whether prognosis differs as a function of age in patients with similar patterns of disease.

Initial disease course: The relapsing form of the disease is associated with a better prognosis than progressive disease. A high rate of relapses early in the course of illness may correlate with shorter time to reach EDSS 6, as docs a short first interval between attacks.

Initial complaints: Among initial symptoms, impairment of sensory pathways or cranial nerve dysfunction, particularly ON, is found in several studies to be ;• favorable prognostic feature, whereas pyramidal and particularly brainstem and cerebellar symptoms carry a poor prognosis.

Both benign and fulminant forms of MS arc recognized. There is no agreement among workers in the field as to the meaning of these terms, ft is the general experience that a patient whose disease has had a benign course for 15 years only rarely develops a more severe course. Patients with mild disease (KDSS score O-.i) 5 years after diagnosis only uncommonly progress to severe disease (EDSS score 6) by 10 years (7.5% of patients) and 15 years (11.5% of patients). The term *malignant MS* is variably used by different workers; some use it to imply a rapid course, others a clinical course in which there are frequent severe relapses with little tecovery. Clues to etiology, susceptibility, and resistance factors must be present in such extremes of the clinical spectrum but they remain elusive at present. Entities such as Devic's disease, Balo's concentric sclerosis, and particularly Marburg disease are more fulminant variants of MS with early disability and even death (Tabic 60.7).

Table 60.7: Risk of multiple sclerosis after monosymptomark episodes

Investigator	*Followf-uf)*	*Patients*	*MR! lesions*	*Conversion rate to CDMS*	*EDSS >3*	*F.DSS >S.S*
Morrissey 1993	5 years	32	0	6%	0	
		6	1	17%	0	
		18	2-3	67%	17%	
		13	4-10	92%	30%	
		1ft	>10	80%	*56%*	
O'Riordan 1998	10 years	27	0	1 1%	0	4%
		3	1	33%	0	0
		16	2-3	87%	31%	13%
		15	4-10	87%	27%	20%
		20	>10	85%	75%	35%
Brex 2002	14.1 years	21	0	19%	0	0
		18	1-3	89%	11".	12.5%
		15	4-10	87%	53%	38%
		17	>10	88%	80%	73%

Conversion rate to clinically definire MS (CDMS) indicates that the patient had second clinical episode,

Optic Neuritis

The incidence of MRI abnormalities in children with ON is less than that in adults, and this factor, coupled with clinical experience, siii'.i'.i^f. tiui ihe r.iu- ;>' |ir(«-;vssuin i<> MS in children with isolated ON may well be less than that in adults. Five-year data from the original Optic Neuritis Treatment Trial revealed that the 5-year cumulative probability of developing clinically definite MS was 30% and did not differ by treatment group (oral prednisone, intravenous methylprednisolonc, placebo). However, MRI was a strong predictor; the 5-ycar risk of developing clinically definite MS was 16% in patients with no brain MRI lesions and 51% in patients with three or more lesions.

Myelopathic Syndromes

Acute Myelopathy

Patients presenting with acute complete transverse myelitis have a cited risk of MS of only 5-10%. However, partial or incomplete myelitis is a much more common clinical entity and bears more relevance to MS. Studies examining the issue of acute partial myelitis as an initial presentation of MS found that 57-72% of such patients had cranial MRI abnormalities consistent with MS. Follow-up from *i-5* years found that 60-90% of these patients developed MS, whereas 10-30% of those with normal MRI developed MS (Morrissey et al. 1993). CSF studies suggest that patients with monosymptom a tic disease with positive oligoclonal bands (OCBs) have a higher risk of evolution ro MS than those without OCBs, although CSF results do not help further in prognosis when compared with MRI alone. CSF analysis would be most useful in a situation in which MRI is not available.

Chronic Myelopathy

In patients with chronic progressive myelopathy, 60-70% have cranial MRI abnormalities consistent with MS in the absence of clinical evidence of disease above the level of the spinal cord. What remains unclear is whether the remaining 30% have a disease other than MS or whether MS can manifest as a purely spinal disorder. Probably both situations apply; improved spinal neuroimaging should help resolve this issue.

Diagnostic Studies

Although the diagnosis of MS remains clinical, a number of ancillary laboratory tests can aid in the diagnosis of MS. The tests used most often are neuroimaging, particularly MRI, analysis of CSF, and to a lesser extent, EP studies.

Neuroimaging

Magnetic Resonance imaging

MRI has changed significantly the approach to MS and is now the modality of choice as an aid to the diagnosis. MS pi a (.pies are typically found in the periventricular region, corpus callosum, centrum semiovale, and to a lesser extent, deep white matter structures and basal ganglia. Features typical of MS plaques have an ovoid appearance; lesions are arranged at right angles to the corpus callosum as if radiating from it ("Dawson's fingers"). The plaques appear hyperintense on proton density and T2-weightcd studies (Figure 60.9), whereas the plaques appear (if visible at all) hypointense on Tl-wcighted images. Such hypointense lesions on Tl-weighted scans ("black holes") are associated with evidence of axonal loss in addition to demyelination.

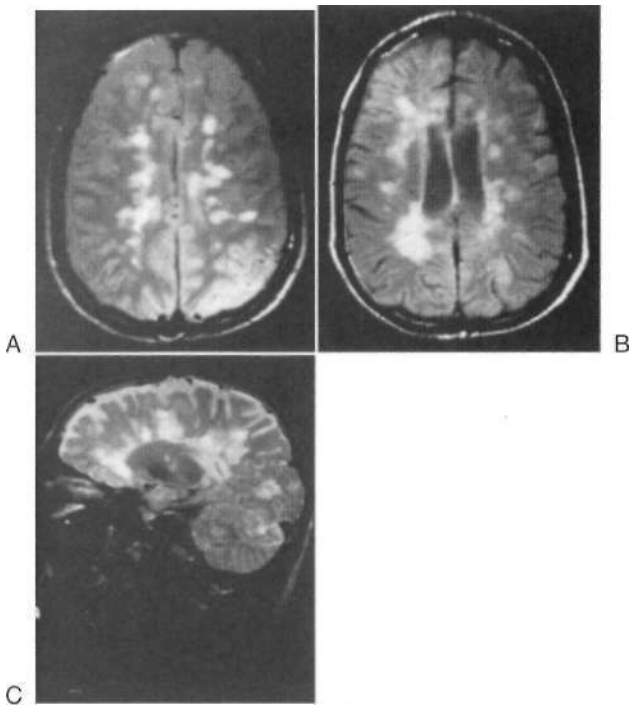


FIGURE 60.9 Magnetic resonance imaging studies in a 29-year-old man. (A) Multifocal lesions in the centrum semiovale (proton density image). (B) Multiple, at times confluent, white matter lesiims abutting the lateral ventricles (proton density image). (C) Lesions distributed in a radiating fashion from the corpus callosum ("Dawson's fingers"). Significant cerebral atrophy with vcntriculomcgaly and cortical atrophy is also noted (T2-wcightcd image).

The earliest studies of cranial MRI in MS rapidly established that MRI detected many more lesions than did computed tomographic (CT) scanning. Furthermore, plaques were readily detected in regions that were rarely abnormal on CT, such as the brainstem, cerebellum, and spinal cord. Most lesions seen on MRI correlate with lesions seen on pathology. However, some lesions that arc quite extensive on MRI show only small plaques on pathological examination, suggesting that much of the abnormal MRI signal may be a result of increased water content of the brain around such plaques caused by presumed BBB disruption. This would be consistent with the finding of reduction of size of plaques in serial studies of MS using MRI.

The major effect of MRI technology has been on diagnosis. Patients with clinically definite MS have white matter lesions typical of MS in over 90% of cases. One mnsl keep ::i mind lh.it other t. !NS diseases (e.g., ischemia, SLE, Behcet's disease, other vasculitides, HTLV-1, sarcoidosis) may have lesions on MRI that appear similar to MS. This is particularly true for ischemic lesions, which make MRI criteria much less reliable for the diagnosis of MS in patients over the age of 50 (Offenbacher et al. 1993). Several sets of criteria have been proposed for determining whether lesions seen on MRI arc caused by MS. The criteria take into account the typical sites of MS plaques and also consider the relatively frequent finding of scattered hyperintense signals on T2-weightcd images seen in the more elderly population and thought to he caused by vascular disease. Patients with at least three lesions, lesions abutting the ventricles, lesions in the posterior fossa, and lesions of greater than 5 mm are likely to have MS. If at least two of these thtee criteria were met in an initial group of patients with MS and elderly controls, these ctiteria had a sensitivity of 88% and specificity of 100%. Testing of a target, more diverse patient population indicated that these criteria had a sensitivity of 81% and a specificity of 96% (Offenbacher et al. 1993).

MRI scanning is both mote sensitive and more specific for predicting evolution to clinically definite MS than other paraelmieal investigations such as CT **scans,** CSF, or EP. Two-year follow-up of 200 patients tefetred for suspected MS showed that 30% {50% of those under age 50) bad developed clinically definite MS, of whom 84% had initial MRI scans thai were strongly suggestive <:. MS. Subsequent studies have shown even higher rates of progression to MS (Morrisscy et al. 1993) and that total MRI lesion number and load correlated with subsequent development of MS, degree of disability, and lesion load at follow-up (FUippi et al. 1994).

Efforts continue to delineate differences in the **MRI** appearance of acute or active lesions and chronic lesions. Acute lesions tend to be larger, with somewhat ill-defined margins when acute and become smaller with sharper margins as resolution occurs. This presumably reflects resolution of edema and inflammation present at the time of acute plaque formation, leaving only residual areas of demyelination, gliosis, and enlarged extracellular space with lesion evolution. The MRI appearance of primary progressive MS shows a smaller total disease burden, a greater preponderance of small lesions, fewer gadolinium-enhancing new lesions, and acquisition of fewer lesions per unit time than the secondary progressive form of MS.

Gadolinium-diethylcnetriaminepentaacetic acid, a para-magnetic contrast agent that can cross only disrupted BBB, has been used to assess plaque activity. Gadolinium increases signal intensity on T1-weighted images. The accumulation of gadolinium in plaques is associated with new or newly active plaques and has been associated with pathologically confirmed acute inflammation in MS. Gadolinium enhancement usually persists for less than 4 weeks but may persist up to 8 weeks in acute plaques, Gadolinium enhancement diminishes or disappears after treatment with corticosteroids, a therapy thought to restore the integrity of BBB permeability.

Allied to the concept of using MRI data as outcome measures of MS therapeutic studies is the notion of following disease burden, which is the total volume of brain affected by plaques as detected on MRI scans. This can be done by measuring the surface area of all plaques and multiplying by the slice thickness. This is most

reliable for thin-slice techniques and preferably with three-dimensional acquisition. A number of studies have examined the ability to detect lesion burden changes over time and have found that it is possible to detect changes that may not be clinically apparent (Figure 60.10).

The extent of cranial MRI abnormalities (and even pathology) does not necessarily correlate with the degree of clinical disability. Patients with small numbers of lesions may be quite disabled, whereas others may function well despite a large burden of disease as detected by MRI. Several possible explanations exist for this. Lesions may occur in areas that are clinically silent; small lesions in the spinal **cord** can cause major disability. MRI may miss lesions that are clinically relevant such as those in cortex, basal ganglia, and brainstem; and large plaques detected by MRI may not have functional correlates but reflect increased tissue water without impairment of neural function.

Several studies have shown that the amount of ongoing MR] activity (new or enlarging lesions, gadolinium-enhancing lesions, or both) exceeds the observed clinical activity by a factor of 2-10. This may reflect not only the factors discussed previously, but also may partly reflect under-re porting of minor symptoms and under-rccogninon of minor signs in patients with MS. It docs, however, suggest that MS is a much more dynamic and active disease, both in progressive and relapsing MS, than is clinically apparent and that MRI is essential to studies of therapy in MS.

The utility of cranial MRI in relation to spinal myelopathies was addressed previously in the section on monosymptomatic disease. Spinal MRI is an evolving technology that can detect lesions consistent with demycliuation in some but not all patients. In part, this may be caused by technical limitations of spinal MRI, but also may reflect involvement of small tracts in a relatively small anatomical structure. Many of the pathological lesions extend vertically in the affected tract, and such lesions may be best detected by transverse imaging. Newer technology detects lesions in 75% of patients with definite MS (Kidd et al. 1993). The frequency of abnormal signals in normal individuals is only 3%, as the non-MS hyperintense T2-weightcd signal seen m older patients mi cranial MRI appears not to occur in the spinal cord.

Conventional MRI technology provides excellent images, but makes it difficult to distinguish edema of an acute plaque from gliosis and demyelination of a chronic plaque. Using phosphorus MR specttoscopy, information on phospholipid metabolism can be obtained, whereas proton MR spectroscopy can generate information about other metabolic components, such as N-acetylaspartate (NAA), an exclusively neuronal marker, creatine phosphate

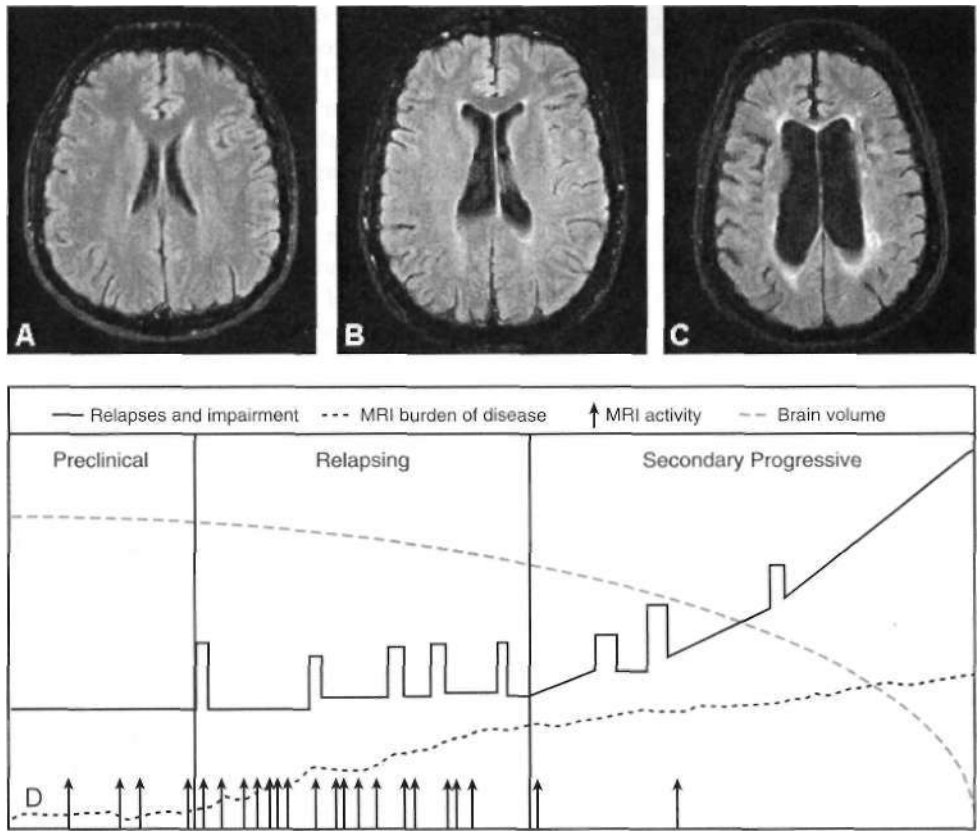


FIGURE 60.10 Changes in MRI scans with duration of disease. The first panels compare three scans from patients with different disease duration, indicating the appearance of atrophy and ventricular dilatation with time. The second panel indicates that as brain atrophy appears it is common to observe that the number of gadolinium-enhancing lesions declines.

(Cr) (energy marker), choline (membrane component), and lactic acid. Brains of patients with chronic MS have a reduced amount of NAA in comparison with choline and Cr; a reduced NAA to Cr ratio is the common means of expressing such a reduction. This reduced ratio implies loss of neurons or axons, which is consistent with pathological studies and appears to parallel disability in MS {Arnold et a I. 1994) (Figure 60.11). In acute MS lesions studied by MR spectroscopic imaging, the NAA to Cr ratio may be transiently reduced, whereas the levels of choline and lactic iicid i:i;i> lv He" ;iicd, pL.rli;'.ps retaied to myelin membrane disruption and tissue acidosis associated with acute plaque fotmation. Some investigators have found abnormal lipid peaks on MR spectroscopy, suggesting acute demyelination (Davie et al. 1994). The use of these metabolic parameters may both lead to a better understanding of the evolution of plaques in vivo and be useful as further adjunct measures of disease progression that antedates clinical disability. A number of new technological advances appear likely to enhance yet further the ability to understand the pathogenesis of the disease process.

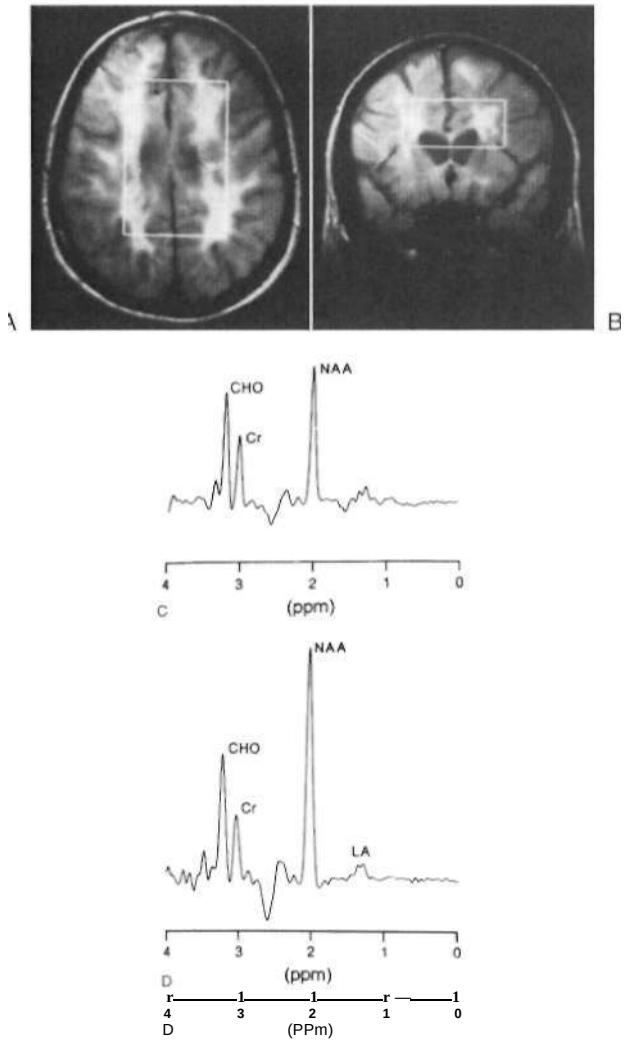


FIGURE 60.11 (A, B) Areas of confluent demyelination in a severely affected progressive multiple sclerosis patient. Outlines show volume of interest selected for spectroscopy study. (C) Spectra obtained with proton spectroscopy in this patient (I)) Spectra of normal brain. Note the reduced height of the N-acety I aspartate (NAA} peak with resultant reduction in the ratio of NAA to creatine (Cr). (CHO = choline; LA = lactic acid.)

Computed Tomography

The current utility of CT scans in the evaluation of patients with MS is largely to exclude other treatable or ominous etiologies as the cause of symptoms. Findings on CT of patients with MS include nonspecific atrophy, hypodense lesions often in a periventricular distribution, and contrast-enhancing lesions presumed to be active plaques with disruption of the BBB (see Figure 60.10).

Cerebrospinal Fluid

CSF findings alone cannot make or exclude the diagnosis of MS, but they can be useful adjuncts to clinical criteria. The CSF is grossly normal in MS, being clear, colorless, and under normal pressure. Total leukocyte count is normal in two thirds of patients, exceeding 15 cclls/uL in less than 5% of patients and only rarely exceeding 50 cells/uL (a finding that should raise suspicion of another etiology). The predominant cell type is the lymphocyte, the vast majority of which are T cells.

CSF protein (or albumin) level is normal in the majority of patients with MS. Albumin determinations are preferable because albumin is not synthesized in the CNS and thus gives a better indication of BBR disruption than does total protein, some of which may be synthesized within the CNS (i.e., immunoglobulin). Albumin levels are elevated in 20-30% of patients, although less than 1% of patients have a level twice that of normal (Table 60,8). A common finding in MS is an elevation of CSF immunoglobulin level relative to other protein components, implying intrathecal synthesis. The immunoglobulin increase is predominantly IgC, but the synthesis of IgM and IgA is increased also. The IgG shows an excess of IgGl and • light chains. The IgG level may be expressed as a percentage of total protein (normal <11%), as a percentage of albumin (normal <27%), by use of the IgG index (normal value <0.66), or by use of a formula for intra-BBB synthesis of IgG. An abnormality of CSF IgG production as measured by the IgG index or IgG synthesis rate is found in more than 90% of patients with clinically definite MS, and different formulas appear to have differing sensitivity and specificity. The sensitivity of IgG as a percentage of protein or albumin is slightly lower (see Table 60.8).

Linked to the elevation of IgG is the finding of OCRs in the cathodal region of an electrophoretic analysis of CSF. When normal CSF is electrophoresed, the cathodal region shows only a homogeneous blur of immunoglobulin. In MS and

Tabic 60.8: Cerebrospinal fluid abnormalities in multiple sclerosis

	Albumin	*IgG/TP*	*IgG/albumin*	*IgG index*	*Otigoclonal banding of Ig*
Clinically definite multiple sclerosis	23%	67%	60-73%	70-90%	85-95%
Normal controls	3%		36%	3%	7%*

IgG/TP = IgG value/total protein.
'"Other neurological diseases.

other conditions usually associated with inflammation or an immune response, electrophoretic analysis reveals a number of disctete bands distinct from the background; these bands represent excess antibody produced by one or more clones of plasma cells. In subacute sclerosing panencephalitis, the majority of these OCBs represent antibody directed against the causative agent, measles virus. However, in MS, there is no disease-specific antigen yet identified against which the majority of bands are directed. The pattern of banding remains relatively consistent in individual patients during the disease course, although bands may be added over time. Occasionally, patients with definite autopsy-proved MS do not have OCBs.

A common method for electrophoresis uses agarose gels, but a more sensitive assay is the use of isoelectric focusing on polyacrylamide gels. OCBs are found in 85-95% of patients with clinically definite MS (Table 60.9). Up to 8% of CSF samples from non-MS patients show OCBs; most are from cases of chronic CNS infections, viral syndromes, and autoimmune neuropathies. The presence of OCBs in monosymptomatic patients predicts a significantly higher rate of progression to MS than the absence of bands: 25% versus 9% at 3 years' follow-up. However, one must not assume that the presence of OCBs is equivalent to a diagnosis of MS, given the number of false-positive results that can occur and the variability in technique and interpretation in different laboratories.

The presence of myelin components and antimyelin antibodies in CSI' and other body fluids has been used to a limited extent as a measure of CNS myelin destruction and presumed demyelinating activity in the CNS (Whitaker et al. 1993).

Evoked Potentials

EPs arc the CNS electrical events generated by peripheral stimulation of a sensory organ (see Chapter 37A). The utility of EPs is the detection of a CNS abnormality of function that may be clinically undetectable. In the case of MS, detection of a subclinical lesion in a site remote from the region of clinical dysfunction supports a diagnosis of multifocal disease. The EPs also may help define the anatomical site of the lesion in tracts not easily visualized In imaging inpiu nerves, dorsal columns). The i h w niosi frequently used EPs are somatosensory (SSEP), visual (VER), and brainstem auditory-evoked responses. MRI technology has largely eliminated the utility of EPs, given the much greater anatomical information obtained and the much higher sensitivity of MRI in the diagnosis of MS (see Table 60.9).

SSEPs have abnormal results in 65-80% of patients with MS, including approximately one half of patients with MS who do not have sensory signs or symptoms. Some patients with clinical evidence of posterior column dysfunction may have normal SSEPs. Using pattern shift VERs, abnormalities are detected in over 90% of patients with a history of ON, even when visual acuity has returned to normal. Patients with clinically definite MS have abnormal VERs with a t're(|Lu-;icy <>• S.S'.',,. 11K- V ! K ıs parlieularh useful in those patients lacking clear clinical evidence of dysfunction above the level of the foramen magnum, such as those with a chronic progressive myelopathy. Ocular or retinal disorders must he excluded before attributing abnormal VERs to demyelination in the optic pathways. Brainstem auditory evoked response abnormalities are less frequent in MS than are VER or SSEP abnormalities, being present in 50-65% of patients with MS.

VARIANTS OF MULTIPLE SCLEROSIS

MS is a condition with many variable forms, but in most cases the common signs and symptoms described previously are readily apparent, and with proper laboratory confirmation the diagnosis is not difficult. However, there are several inflammatory demyelinating disotders that bear an unknown relationship to MS. They are listed here as

Tabic 60,9: Comparison of sensitivity of laboratory testing in multiple sclerosis

	VER	*BAER*	.....	*OCB*	*MRI*
Clinically definite multiple sclerosis	80-85%*	50-65%	65-80%	85-95%	90-97%

BAER = brainstem auditory evoked response; MRI = magnetic resonance imaging; OCB = oligoclonal bands; SSEP = somatosensory evoked potentials; VER = visual evoked response.
'Numbers show the percentage of patients with abnormal study results.

variants of MS, rather than as separate illnesses, because it is often found, after long follow-up, that the disease has reverted to a more standard variety of MS.

Recurrent Optic Neuropathy

There arc patients whose entire clinical illness is confined to the optic nerves. They may have sequential affection of one nerve, then the other, or they may have simultaneous bilateral vision loss, a state that is quite uncommon in classic MS. In some iriM.nuvs VI Is I <t IIK- head shows (in addition to lesions of the optic nerves) scattered intracerebral lesions, or a CSF examination shows OCBs, attesting to some degree of dissemination of the lesions. Children and prcadolescent patients are more likely than adults to have recurrent or simultaneous optic neuropathy. Rarely there is slowly progressive optic neuropathy, similar to that seen with optic nerve sheath tumors, such as meningioma. The distinction from an MS variant can be quite challenging. In bilateral ON, sarcoidosis is commonly a diagnostic consideration.

Devic's Disease (Neuromyelitis Optica)

A combination of bilateral optic neuropathy and cervical myelopathy make up this condition, which most authorities now classify as a variant of MS. Reported cases indicate that the myelopathy tends to be more severe, with less likelihood of recovery, and that the neuropathological features at autopsy are those of a much more severe necrotic lesion of the cord rather than incomplete dcmyelination. In some patients the optic neuropathy and the myelopathy occur at (In same time, in others on. or the other component is delayed. The longer the interval, the more like typical MS is the pathology. Because the optic nerve and the cervical spinal cord are two of the locations in the nervous system in which the lesions of MS are typically found, many patients could be classified as having Devic's disease, or syndrome. Little is to be gained by this nomenclature, because Devic's syndrome can be a manifestation of ADEM (see Acute Disseminated Encephalomyelitis, later in this chapter), or rarely of other autoimmune disease, such as SLE. This seems to be especially true of patients with relapsing Devic's syndrome, making up approximately one half the patients. In a few patients the distinction between an MS variant and SLE (so-called lupoid sclerosis) is essentially impossible to make, and some of these are patients with neuromyelitis optica.

Slowly Progressive Myelopathy

A syndrome of slowly progressive spinal cord dysfunction can present a major diagnostic challenge. If there are no sensory signs or symptoms, the entity known as primary lateral sclerosis, one ot the group of motor neuron diseases, may be the cause. HTLV-1 infection, vitamin B_{12} deficiency, and human immunodeficiency virus infection all can be excluded by appropriate tesring. Spinal dural arteriovenous fistula can cause a steadily or stepwise progressive myelopathy, usually in the lower spinal segments. Adrenomyeloneuropathy should be considered.

A number of patients remain do not fit into these categories, and their spinal MRI results arc repeatedly negative. VERs, CSF OCBs, and MRI of the head show no sign of demyelination elsewhere. No firm diagnosis is possible. Minor clues that MS is present may be furnished by a Lhermitte's sign that has come and gone or by undue sensitivity to elevated temperature. The degree of compression of the cervical cord by intervertebral disc disease is often an issue in the middle-aged patient, because a majority of persons have some degtee of disc disease, and following trauma there may be a T2 bright signal within the cord due to contusion. There is little doubt that some laminectomies have been carried out for cervical spondylosis where MS was the final correct diagnosis.

Progressive myelopathy caused by MS is part of the primary progressive MS group and carries the poor prognosis typical of that group. The choice of therapy is difficult. Some patients do better for a time with monthly intravenous corticosteroid therapy.

Acute Tumor-like Multiple Sclerosis (Marburg Variant)

Some patients with demyelinating disease present with a large acute lesion of one hemisphere (Figure 60.12) or rarely other locations, such as the spinal cord. Mass effect may occur, with compression of the lateral ventricle and shift across the midline. The clinical abnormalities in such patients are variable: They may be slight even in a patient with a massive lesion, whereas confusion, hemiparesis, or neglect syndrome may be seen in another patient with a lesion that appears no different. Much of the T2 bright lesion volume is often caused by edema and may be rapidly responsive to corticosteroids. {This change with corticosteroids also may occur with glioma or CNS lymphoma and is therefore not a useful diagnostic criterion.) Biopsy is often required.

In one series of 31 patients, the prognosis was good, most patients recovered well clinically, and their lesion volume rapidly cleared. In 24 of the patients the demyelinating lesion was solitary, whereas in the others one or more satellite nodules existed. Six of the patients were older than 57. In follow-up, 28 of the patients did not develop additional evidence of demyelinating activity during a period of 9 months to 12 years. Other authorities have reported a higher rate of recurrent disease, in particular a conversion to more ordinary types of MS, both clinically and by MRI scan criteria.

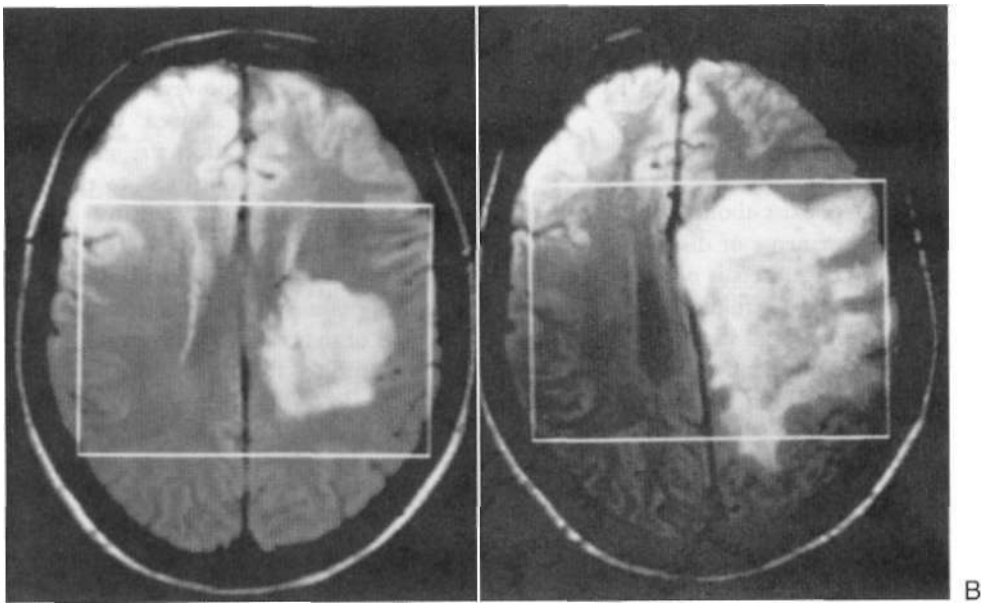


FIGURE 60.12 (A) Magnetic resonance sain showing a large white matter lesion initially without mass effect in a young woman with right hemiplegia developing over 5 days. (B) Marked increase in size of lesion with associated edema and mass effect 1 month later while on corticosteroids and at a time when clinical deficits wen- improving. Biopsy showed evidence of demyelination.

TREATMENT AND MANAGEMENT

In prior decades, treatment of this often progressive disease of young adults was judged to be ineffective, and many clinicians and patients adopted a nihilistic and pessimistic attitude. The advent of more effective symptomatic therapy, and the widely publicized U.S. Food and Drug Administration (FDA) approval of five agents capable of modifying the disease course have drastically changed that view. There remain many problems, particulatly the treatment of progressive MS, yet there arc clearly reasons for hope.

Treatment of MS should be directed toward these basic goals:

1. Relief or modification of symptoms
2. Shortening the duration or limiting the residual effects of an acute relapse
3. Preventing progression or slowing its pace
4. Supporting family and patient, alleviating social and economic effects, and advocating fot the disabled ot handicapped

Monitoring Disease Activity

Magnetic Resonance Imaging

A surrogate marker fot disease activity in MS is badly-needed. It is now clear from several of the completed interferon therapy trials that there is far more activity in MRI scans of patients than is apparent clinically. Some authors estimate a ratio of new MRI lesions to clinical events as 10 to 1 in patients with active telapsing-remitting MS. New MR! lesions may be measured by change in total T2 visible lesion load, by new or enlarging lesions, or by gadolinium enhancement. All three criteria have been used with success in one trial or another.

Several therapies are known to reduce the accumulation of MRI lesions in clinical trials; these include intetfeton-^i_a, interferon-/fit,, and mitoxantrone. Unpublished data suggest that cyclophosphamide blocks the appearance of new gadolinium-positive lesions. The MRI data have been strong indicators of clinical effectiveness in clinical trials and are clearly now a cornerstone of therapeutic investigations in MS. Nevertheless, problems exist. In the care of patients who ate not enrolled in large-scale trials, **MRI** plays only a doubtful role in monitoring the progress of treatment. Data from the National Institutes ot Health ttials of relapsing MS demonstrate that frequent scanning of an individual patient is required to obtain reliable information, possibly as often as once a month. Infrequent scans can miss lesions that have come and gone. In patients with progressive MS, the lesion load in the head MRI scans can remain unchanged while the patient steadily worsens. Often this state of affaits is caused by ptogressive spinal disease, which cannot be imaged well. A minority of patients with MS, possibly as many as 5%, have no MRI lesion characteristic of MS at all.

Advantages exist in some instances for single or relatively infrequent scans. In the eatly stages of illness, aftet a monosymptomatic relapse, many patients wish to know their risk of developing MS, which can often be defined hy MRI (see previous sections). In patients under rreatment in

whom disease activity develops and a change of therapy-is contemplated, additional evidence, for or against the change, can sometimes be derived from an MRI scan.

Immunological Data

Thus far, little relevant data exist about levels of cytokines or T-ccll subsets as measurements of disease activity. The expression of different T-cell subsets is not relevant. Levels in blood of the inflammatory cytokine 11,-12 appear to correlate \\ ith activin of relapsing MS and ma] functioE as a surrogate marker. Interferon-)', a cytokine that can itself provoke relapses in patients with MS, may decrease in blood levels when MS is treated successfully. Many investigators are in the process of measuring IL-2, TNF-D, IL-10, and other cytokines (see Chapter 46 for more details).

Clinical Examination

The eventual gold standard of success in MS treatments is the clinical condition of the patient. Every clinical trial includes these data as a primary or secondary outcome. Yet the difficulties of clinical measurement are exemplified by the number of scales and indices that are used. The problems of the EDSS were noted previously. A one-point increase or decrease in the EDSS is often taken as an endpoint; this may require special training of observers, and even rhen variability of observations occurs. The Air.bufuiun liiiKx, :i direct a^essrneiu ol walk MIL;„ is useful in most patients. MRI is increasingly considered as the primary endpoint.

Relief or Modification of Symptoms

Spasticity

Spasticity slows voluntary movement, impairs balance and gait, and may cause painful flexor or extensor spasms. Partial control is often possible, although recovery of motor power is rare.

Baclofen is a *y*- amino butyric acid agonist that can effectively relieve spasms and has modest effects in improving performance. Daily divided doses of 20-120 mg and occasionally more are used. Too large a dose may produce drowsiness or sufficient hypotonicity as to increase the degree of weakness. Intrathecal baclofen via an implanted pump can be effective against spasticity in suitable patients. The pump can be electronically regulated to deliver small doses of baclofen in pulses or a varied dose at different times over 24 hours to increase efficacy and decrease side effects. Its effectiveness has been demonstrated in several controlled trials, and the side effects are few.

Tizanidinc (Zanaflcx), a centrally active ^-noradrenergic agonist, may be used alone or in combination with baclofen because the mechanism of action is different. The medication, available in 4-mg tablets, must be gradually increased starting with 2 mg at bedtime. The side effects are similar to baclofen; however, a blind prospective trial in patients with MS showed that although it relieved spasticity, it did not affect strength.

Benzodiazepines contribute to the control of spasticity, although sedation and possible drug dependency are limiting factors.

Dantrolene sodium (Dantrium), an agent that acts within muscles on excitation-contraction coupling, is rarely used because of the risk of liver damage. If used, the medication must be titrated from 25 mg daily up to 100 mg three times a day.

4-Aminopyridinc and 3,4-diaminopyridine (3,4-DAP) are compounds that block potassium channels in the axolemma, and a double-blind trial showed improvement in motor strength. The risk of seizure and hepatitis has limited the use of these compounds.

Botulinum toxin type A (Botox) also has been shown to be effective in selective cases.

Tremor

One of the most disabling and hard to treat symptoms in MS is tremor. Appendicular tremors are usually seen in action or intention and may limit activities of daily living.

Weighted wrist bracelets and specially adapted utensils are a nonpharmaccutical option.

lsoniazid, 800-1200 mg per day, with pyridoxine, 100 mg per day, may have marginal success.

Anticonvulsants also have been reported to be helpful with tremor. Primidone (Mysoline), 125-250 mg two to three times per day, is recommended. Dizziness, somnolence, and nausea are the primary side effects. Carbamazepinc (Tegretol) in divided doses up to 800 nig per day has been used also. Gabapentin (Neurontin) in daily divided doses up to 3600 mg has shown some benefit.

Clonazepam (Klonopin), 0.5-2.0 mg one to four times daily, is effective. However the side effects, including ataxia, behavioral changes, confusion, and respiratory depression, must be kept in mind when treating patients.

Propranolol (Inderal), 20-40 mg two to three times daily, is another option. Caution must be taken in patients with concomitant cardiac, circulatory, or respiratory disorders.

Ondansetron (Zofran), 4-8 mg once or twice daily, has been reported effective in case studies of patients with MS. Side effects include diarrhea, headache, and elevated liver enzymes.

Surgical thalamotomy or deep brain stimulation may be used in patients with refractory disease.

Fatigue

Fatigue is seen in as many as 78% of patients and interferes with daily activities. Fatigue must be separated from

depression, medication side effects, or physical exhaustion from gait alterations.

Amantadine (Symmetrel), 100 mg twice a day, has relatively few side effects and is well tolerated by most patients. Caution must be taken in patients with renal insufficiency or seizure disorders. Studies have found an efficacy rate of 40%.

Modafinil (Provigil) is a wake fulness-promoting agent that is chemically and pharmacologically distinct from CNS stimulants, although the precise mechanism of action is unknown. Modafinil was recently approved for use in narcolepsy. There are open-labeled studies showing that Modafinil is effective for fatigue in MS patients. Oral dosage srarts at 200 mg in the morning and can be increased to 400 mg.

Pemoline (Cylcrt) is an alternative medication if no response to amantadine is seen. The starting dose is 18.75 mg twice daily and can be increased to a maximum of six tablets per day. The risk of hepatic failure is an obstacle to using this drug as first-line therapy. Some patients also may respond to methylphenidate (Ritalin), 10-60 mg per day in two to three divided doses.

Selective serotonin reuptake inhibitors, in addition to treating the depressive symptoms associared with MS, have been used to treat fatigue. Fluoxetine (Prozac), 10-20 mg once or twice daily, has a side effect profile including nausea, headache, extrapyramidal effects, hypotension, and mania. There is now a once weekly oral dosage of fluoxetine available.

Bladder Dysfunction

Symptomatic bladder dysfunction can be identified at some time during the course of MS in 50-80% of patients. The severity of bladder symptoms is unrelated to the duration of the disease but parallels the severity of othet neurological symptoms. Differentiating between bladder spasticity and hypotonia is important before initiating therapy because different medications are employed for each condition. Common disorders such as urinary tract infections, prostate and bladder cancer, and benign prostatic hypertrophy may mimic symptoms of neurological dysfunction and should be excluded.

Initial steps in managing bladder dysfunction include fluid management, timed voiding, and bedside commode.

Oxybutynin (Ditropan) is a first-line medication for l:vpi.T ivlli'\ii bladder without outlet obstruction. Dosage ranges from 2.5-5.0 mg one to three times daily. An extended release formulation is now available. General precautions and side-effect profiles of the anticholinergics must be observed.

Propantheline (Pro-Banthine), 15 mg three to four times per day, is another anticholinergic option for bypcr-reflcxic bladders without outlet obstruction.

Imipramine (Tofranil), a tricyclic antidepressant, 50-300 mg in divided daily doses, is also helpful, especially with enuresis. Side effects are similar to the anticholinergics. This medication has the dual effect of treating concomitant depression.

Desmopressin is also effective with hyper-re flex ic bladder without outlet obstruction. Doses of 20-40 ug daily are suggested. Adverse effects include nausea, flushing, and headache.

Toltcrodine (Detrol) is a muscarinic receptor antagonist with fewer side effects than anticholinergic medications. This medicine, given at 2 mg twice daily, was shown to reduce bladder frequency and urgency as well as urge incontinence. A long-acting formulation is now available.

Detrusor hypcr-reflexia with outlet obstruction may respond to Crede's maneuvers, antispasticity medications, or anticholinergics in combination with alpha-sympathetic blocking agents such as terazosin hydrochloride (Hytrin). The maintenance dose is 2-10 mg daily. Adverse effects include tachycardia, dizziness, syncope, headache, and asthenia.

Detrusor areflexia may respond to Crede's maneuvers, alpha-sympathetic blocking agents, or bethanecbo! chloride (Urecholine). The usual dose is 10-50 mg three to four times a day with a side-effect profile including diarrhea, excessive lacrimation, and flushing of the skin. This medication is also contra indicated in many common medical conditions.

Catheterization may be employed if the previously mentioned measures are ineffective; however, the long-term effects of catheterization must be considered. Squamous metaplasia of the bladder was significantly greater in patients who had been catheterized for more than 10 years (80%) in comparison with those catheterized for less than 10 years (42%) and those without catheters (20%).

Surgical correction, such as augmentation of bladder capacity with an exteriorized loop of bowel, for appropriate **patients** is **another** alternative.

Depression

Prevalence rates for depression in patients with MS range from 14-57% as compared with 1.3-3.7% in the general population. The lite time prevalence of depression in a group of patients with chronic medical disorders was 12.9%. The nature of a chronic debilitating neurological disorder contributes to depressive symptoms and coping problems. Patients taking multiple medications arc prone to depression, and the side-effect profile of the interferon-/) medications includes depression.

Selective serotonin reuptake inhibitors are the medication of choice for depressive symptoms in patients with MS. In addition to the previously mentioned fluoxetine, any of the other medications in this class may be used.

Amitriptyline (Elavil), 25-100 mg daily (or other tricyclic antidepressants in equivalent dosage), is a second-line

choice because of anticholinergic side effects. However, anticholinergic properties may be helpful to patients with symptoms of bladder spasticity or chronic pain, thus avoiding polypharmacy.

Sexual Dysfunction

Studies suggest that 45-74% of women with MS experience sexual dysfunction. These symptoms have been associated with depression, bowel dysfunction, fatigue, spasticity, and pelvic floor weakness. There was no association between duration of disease, type of disease, recent exacerbations, or disability scores. Erectile dysfunction in men is common, especially in patients with spinal cord involvement. Symptoms also may be caused by medications or psvchnio;;ie;i] issues.

Sildenafil (Viagra) has supplanted traditional approaches to erectile dysfunction in men, which used to include intracavernous papaverine, prostaglandin E, phentolamine, vacuum devices, and penile prostheses. Doses of 25-100 mg 1 hour before sexual intercourse arc used with minimal side effects, which include headache, flushing, dyspepsia, and musculoskeletal pain. Reports suggest caution in patients with cardiovascular disease. Sildenafil is probably also effective in women.

Cognitive Impairment

Problems with cognition are increasingly being recognized as an important deficit affecting patients with MS. Studies have found a correlation between dementia and lesion burden on MR1 as well as atrophy of the corpus callosum. In a study of patients with chronic progressive MS who underwent MRI scans and a neuropsychological screening battery, those who were impaired according to the neuropsychological screening battery had significantly more cerebral lesions than those who were judged unimpaired. Treatment of cognitive deficits consists of support, improvement of coping strategies, and treatment of depression.

Paroxysmal Symptoms

A variety of paroxysmal symptoms consist of brief, almost stereotypical, events occurring frequently and often triggered by movement or sensory stimuli. They are likely caused by ephaptic transmission of nerve impulses at sites ot previous dise.ise activity. These symptoms include, but are not limited to, trigeminal neuralgia, pain, paresthesia, weakness, tonic seizures, dysarthria and ataxia, pruritus, diplopia, akinesia, and hemifacial spasm and dystonia.

Anticonvulsants, especially carbamazepine and valproate (Depakote], have been used in their usual doses with some benefit. Newer anticonvulsants, such as gabapentin, have been used in small case studies.

Benzodiazepines also have been effective in some patients.

Baclofen, acetazolamide (Diamox), ibuprofen, and bromocriptine are cited as potentially beneficial with these paroxysmal symptoms.

Treatment Strategies

For some patients MS is a disease with one or two acute neurological episodes with no further evidence of disease activity. In others it is a chronic, relapsing, or progressive-disease with an unpredictable clinical course that generally spans 10-20 years, during which time neurological disability accumulates. Treatment of MS, as with diseases in other branches of medicine, has come to rely on prospective clinical trials. Most such trials have been designed to establish efficacy but do not last longer than 2 or 3 years and give only hints about long-term results of treatment. Patients may differ markedly from those who have been treated in clinical trials, yet therapeutic decisions must be made. Table 60.10 outlines the treatment paradigm used at our institutions.

Class I—Prospective, randomized, controlled clinical trial with masked outcome assessment and requires the following:
Primary outcomes are clearly defined.
Inclusion/exclusion criteria are clearly defined.
Adequate accounting of dropouts and crossovers wirh numbers sufficiently low to have minimal potential for bias.
Relevant baseline characteristics are presented and substantially equivalent between groups or there is appropriate statistical adjustment.
Class II—Prospective matched group cohort study with masked outcome assessment that meets a-d or a randomized controlled trial that lacks one criteria a-d.
Class III—A11 other controlled trials where outcome assessment is independent of patient treatment.
Class IV—Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Treatment of Acute Attacks

Acute attacks are typically treated with corticosteroids. Indications for treatment of a relapse include functionally disabling symptoms with objective evidence of neurological impairment such as loss of vision and motor, cerebellar, or both kinds of symptoms. Thus mild sensory attacks arc typically not treated. In the past, adrenocorticotropic hormone and oral prednisone were primarily used. More recently, treatment with short courses of intravenous methylprednisolone, 500-1000 mg daily for 3-7 days, with or without a shorr prednisone taper is commonly used. ON may occur anytime during the course of MS or be one of

Tabic 60.10: Multiple sclerosis treatment strategies

Disease course/stage	*Treatment options*	*Evidence*
Monosymptomatic (e.g., optic neuritis)—Acute attack	IV methylprednisoione, 1000 mg for .5 days, without oral taper	Class I evidence
Rciapsing-remitting, no disease activity for so , T.I I VIM:-,. a ml/or no activitj on MR]	IV corticosteroids if acute attack occurs	Class I evidence
Relapsing-remitting, current disease at tl\ llv :llki (PI .Kill llv •••• \1U!	IV corticosteroids for acute attacks, plus for prevention (1) interferon iS-lb (Avonex), 30 pg 1M weekly; or (2) interferon *p-lb* (Betaseron), 1 ml SC qod; or (3) interferon /?-1a (Rebif), 22 or 44 micrograms SC three times/week; or (4) glatiramer acetate (Copaxone), 20 ug SC daily	Class I evidence for Avonex, Betaseron Rebif and Copaxone, All four are FDA approved
Relapsing-remitting, disease activity while on interferon or Copaxone	Add monthly bolus of IV methylprednisoione OR oral immunosuppressants	Class I and 11 evidence
Relapsing-remitting, accumulating disability (interferoii/Copaxoric/corticostcroid nonresponders)	IV monthly cyclophosphamide and pulse therapy OR IV mitoxantrone (Novantrone)	Class I evidence for Novantrone, which is FDA approved
Rapidly progressing disability	IV cyclophosphamide and corticosteroid 8-day induction, followed by pulse maintenance	Class III evidence
Very rapidly progressing disabiliry	Plasma exchange	Empiric
Secondary progressive	IV corticosteroid monthly pulses	Empiric
	IV cyclophosphamide/corticosteroid monthly pulses	Class 111 e\ ideuce
	Methotrexate, oral or SC, 7.5-20 mg/wk, with or without monthly corticosteroid pulses	Class I evidence
Primary progressive	IV corticosteroid monthly pulses	I'.nipiric
	Methotrexate, oral or SC, 7.520 mg/wk, with or without monthly corticosteroid pulses	]:.m pi vie
	Clcidribine, IV or SC	F.mpiric
	Consider mitoxantrone	Empiric

the initial symptoms. A randomized therapeutic trial in ON demonstrated that patients treated with oral prednisone alone were more likely to suffer recurrent episodes of ON as compared with those treated with intravenous methylprednisoione followed by oral prednisone (Beck et at. 1993). Furthermore, definite MS developed in 7.5% of the intravenous methylprednisoione group, 14.7% of the oral prednisone group, and 16.7% of the placebo group over a 2-year period (Beck et al. 1993). Five-year data from the same study showed that CDMS developed in 16% of patients with no MRI lesions at baseline and 51% in patients with 3 or more MRI lesions at baseline. Development of disability, even when the diagnosis of MS had been made, was very rare, reemphasizing the need for follow-up periods of decades and the benign nature of MS presenting with ON. These data support the use of high-dose intravenous methylprednisoione for acute MS attacks. High-dose intravenous methylprednisoione appears to be accompanied by relatively few side effects in most patients, although mental changes, unmasking of infections, gastric disturbance'., and an increased incidence of fractures have been reported. Baseline and yearly bone density scans are recommended for patients undergoing repeated courses of corticosteroid therapy. Anaphylactoid reactions and arrhythmias are rare, but may also occur. The immunological mechanisms of high-dose corticosteroids include reduction ot CI)4" cells, decrease in cytokine release from lymphocytes and cytokines including TNF, inter feron-y, and decreased class II expression (Kupersmith 1994). Corticosteroids have been shown to decrease IgG synthesis in the CNS and reduce CSF antibodies to MBP and OCBs. Intravenous methylprednisoione may decrease the entry of cells into the brain and may affect cytokine patterns also.

Two other trials have focused on oral corticosteroid use. A double-blind, ptacebo-controlled trial of oral methylprednisoione use in acute attacks involving 51 patients followed over *8* weeks showed a statistically significant beneficial effect of oral corticosteroids. Patients received a total of 3676 mg of oral methylprednisoione over 15 days with no serious adverse events. A second randomized trial of 80 patients evaluated oral versus intravenous methylprednisoione in acute relapses. The results showed no statistical difference between the treatment groups.

Disease-Modifying Treatments

The first meditation approved by the FDA for use in MS was recombinant interferon /t-lb (Betaseron), which has been shown in a double blind, placebo-controlled trial of 372 patients to decrease the frequency of relapses by 34% after 2 years in relapsing-remitting patients receiving 8 mlU every other day (IFNB MS Study Group 1993). In treated patients, the MRI T2 lesion burden went up only 3.6% over 5 years, compared with 30.2% in the placebo group (Paty ct al. 1993). No significant change in disease progression was seen over 5 years. Bclasm>n is administered every other day under the skin by self-injection. Side effects include influenza-like symptoms, depression, and reaaions at the injection site, but these tend to diminish with time. Elevated liver enzymes, leukopenia, and anemia were seen, and blood monitoring is suggested every 3 months. Also 34% of patients developed neutralizing antibodies that may reduce the clinical efficacy of the drug. The mechanism of action of interferon ,8-1 b is currently unknown.

A second double-blind, placebo-controlled study in 301 patients with relapsing-remitting disease investigated the efficacy of weekly intramuscular injections of 6 million U (30 ug) of interferon /J-la (Avonex), a glycosylated recombinant interferon-/* (Jacobs et al. 1996). Over 2 years the annual exacerbation rate decreased 29%. After 2 years the MRI data revealed a lesion volume of 122.4 (mean) in the placebo group compared with 74.1 (mean) in the Avonex group. The number of enhancing lesions on MRI over 2 years was 1.65 (mean) in the placebo group and 0.80 (mean) in the Avonex group. The proportion of patients progressing by the end of 104 weeks of the trial was 34.9% in the placebo group and 21.9% in the Avonex group representing a 37% reduction. Adverse events included mild influenza-like symptoms and mild anemia. No skin reactions occurred. Laboratory monitoring is suggested, but not mandatory because no serious liver toxicities occurred. Also, 22% of patients on treatment developed neutralizing antibodies.

Glatiramer acetatc/copolymer 1 (Copaxone) is a daily subcutaneous injectable synthetic polymer. In a large double-blind trial in relapsing-remitting MS involving 251 randomized patients (Johnson et al. 1998), the patients receiving Copaxone bad a 29% reduction in the relapse rate over 2 years. Extension data shows that over 140 weeks 41% of patients receiving placebos experienced worsening of their disability by greater than or equal to 1.5 HDSS steps, whereas only 21.6% of Copaxone-treated patients had worsening (Johnson et al. 1998). Side effects included local injection site reactions and transient systemic postinjection reactions including chest pain, flushing, dyspnea, palpitations, and anxiety. No laboratory monitoring is necessary. No neutralizing antibodies were detected in the study. The mechanism by which copolymer 1 may work in humans is unknown.

A randomized, double-blind, placebo-controlled study of interferon *fi-&* in higher doses was conducted in Europe (European Study Group 1998). This involved 560 patients with relapsing-remitting disease given subcutaneous interferon *fi-a* (Rebif). Patients were randomized to placebo, 22 pg, or 44 ug of Rebif three times a week for 2 years. There was a 27% reduction in the relapse rate in the group receiving 66 ug per week and a 33% reduction in the group receiving 132 ug per week. The MRI lesion burden showed a decrease of 1.2% in the group receiving 66 pg per week, a decrease of 3.8% in the group receiving 132 ug per week, and an increase of 10.9% in the group receiving a placebo. The side-effect profile was similar to the other interferons. Of note, 23.8% of the group receiving 66 pg per week and 12.5% of the group receiving 132 pg per week were positive for neutralizing antibodies. Rased on this data and a recent comparison trial of Avonex versus Rebif (EVIDENCE), Rebif was approved by rhe FDA in March 2002.

Both the EVIDENCE trial and a trial in Europe comparing high- and low-dose interferon (INCOMIN) were short-term trials and do not address the important question of which of these agents, if any, truly suppress the development of long-term disability. It docs appear that there is a detectable dose-response in the use of beta interferons.

Another factor to consider is that all four medications (Betaseron, Avonex, Copaxone, Rebif) are contraindicated in pregnancy. With al! three agents, when pregnancy occurs, treatment should be discontinued, and if relapses occur during pregnancy they are treated with intravenous corticosteroids. In addition, the safety of symptomatic medications for pregnancy must be kept in mind when managing these patients (see Table 60.6).

Much controversy has arisen since the introduction of the four approved medications for RR-MS. Analysis and comparison of these trials has been difficult because each trial used slightly different statistical, clinical, laboratory, and MRI measures. No direct comparison can be made because in each of the pivotal trials the drug was tested only against placebo. The neutralizing antibody issue is another point of contention. Current consensus does not recommend the routine testing of neutralizing antibody and does not recommend switching between interferons if neutralizing antibodies are in the high titer range.

As a general rule, all patients with relapsing forms of MS should be receiving one ol the immunonujJulamry agents indefinitely.

Treatment of Progressive Disease

Treatment directed at the progressive phase is the most difficult because the disease may be harder to affect once the progressive stage has been initiated. Immunosuppressive agents such as total lymphoid radiation, cyclosporinc, methotrexate, 2-chlorodeoxyadenosinc, cyclophosphamide

(Cytoxan), mitoxantrone, and azathioprine have shown some positive clinical effects in progressive disease. All of these nonspecific immunosuppressive agents suffer from the same basic defect: They may temporarily halt a rapidly progressive downhill course, but it is difficult, or dangerous, to employ them for more than a few months. MS is an illness of decades, not months. Therefore nonspecific immunosuppression often is a temporary solution, even if effective.

Total lymphoid irradiation has potent immunosuppressive effects, and a double-blind study of lymphoid irradiation reported benefit in patients with progressive MS. The ahsolute lymphocyte count appeared to be an indicator of therapeutic efficacy, with greater efficacy in patients with lower counts. Many patients began progressing again after initial therapy, and a major limitation of the use of total lymphoid radiation is that it may preclude the use of other treatments that affect the immune system at a subsequent time.

Large multicenter trials of cyclosporine indicate that cyclosporine has a beneficial, albeit modest, effect in ameliorating clinical disease progression, but it has not found clinical use because of the narrow benefit-to-risk ratio.

Weekly low-dose oral methotrexate (7.5 mg) was studied in a randomized, double-blind, placebo-controlled trial in 60 patients with chronic progressive disease and has been reported to positively affect measures of upper extremity function in progressive MS. Lower extremity function was not affected (Goodkin et al. *1995).*

Cyclophosphamide (Cytoxan) has been in use for treatment of patients with MS, despite conflicting data, since the early 1980s. When used, the drug is now given in monthly bolus injections and maintained over a year or more, usually with intravenous cotticostcroids. Effects often can be observed in patients younger than age 40 and especially in those who have been in the progressive phase for less than a year. The drug appears to be ineffective for primary progressive MS. Duration of treatment is limited by the risk of bladder cancer, which appears to increase with time and may depend on total accumulated drug dose.

A trial of mitoxantrone in 42 patients with active MS was published (Edan et al. 1997), in which patients were treated monthly with cither intravenous mcthytprednisolone plus intravenous mitoxantrone or intravenous methylprcdnisolone alone over 6 months. Although the numbers were small, a statistically significant reduction occurred in the number of relapses and an increase in the number of patients tree of attack. Also, 90% of the group receiving intravenous methyl prednisolone/intra venous mitoxantrone showed no new enhancing lesions on MRI versus only 31% in the group receiving intravenous methylprcduisolone. The risk of cardiotoxicity prevents prolonged usage.

Azathioprine has been studied in both relapsing-remitting and chronic progressive MS since 1971. A metaanalysis of the results of five double-blind and two single-blind, randomized, controlled trials of azathioprine use in MS showed only a small difference in favor of azathioprine after 2 years.

Interferon *fl-b* was studied in patients with secondary progressive MS in 32 centers in Europe. In this study 358 patients received placebo and 360 patients received interferon *fi-b* every other day subcutaneously for up to 3 years (European Study Group 1998). In the group receiving interferon *fi-b* a relative reduction of 21.7% occurred in the proportion of patients with progression. The rime to becoming wheelchair-bound was also significantly delayed, equivalent to 12 months *(p* < 0.01). The mean relapse rate was reduced overall by approximately 30% in the treatment group. In terms of MRI lesion volume, the group receiving placebo showed a mean increase of 8% compared with the group receiving interferon *fi-b,* which showed a mean decrease ot 5%. This study has major implications for the treatment of the largest single category of MS, and the effects on the cost of medical care and the search for other treatments arc obvious.

Monthly bolus intravenous corticosteroids, typically 1000 mg of methylprednisolone, arc used at many institutions for treatment of primary or secondary progressive MS. This use remains empiric because no relevant studies have been reported.

Immune globulin may help a number of autoimmune diseases and has been tried in MS. A randomized, placebo-controlled trial of monthly intravenous immunoglobulin in relapsing-remitting MS involved 150 patients over 2 years (Fazekas et al. 1997). In the group receiving placebo there were 11 6 relapses compared with 62 in the group receiving intravenous immunoglobulin, and 36% of the group receiving placebo were relapse-free compared with 53% of the group receiving intravenous immunoglobulin, with a significant *p* value of 0.03.

Other therapeutic strategies that are in [he process of trial are antibodies against inregrin, which block entry of immune cells into the CNS, antibodies against 11-2 receptor, T-cell vaccination, and other interferons. Accepting the limitations of monothetapy with the interferons or glatiramet, many investigators are attempting combinations with other agents, such as corticosteroids or chemotherapeutic drugs.

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

History

ADEM is a monophasic demyelinating syndrome that occurs in association with an immunization or vaccination (postvaccination encephalomyelitis) or systemic viral infection (parainfectious encephalomyelitis). It is characterized pathologically by perivascular inflammation, edema, and demyelination within the CNS and clinically by rapid development of focal or multifocal neurological

Table 60.11: Acute disseminated encephalomyelitis and related disui di'i's

Acute disseminated encephalomyelitis
Uniphasic parainfectious or postvaccination inflammatory demyelmating disorder of the central nervous system
Acute hemorrhagic leukoencephalitis
Hyperacute form of acute disseminated encephalomyelitis, usually occurring after upper respiratory infections, with more tissue-destructive pathology
Site-restricted forms of monophasic acute inflammatory demyelinating disorders that ma}[1] occur after viral illness or vaccination
Transverse myelitis
Optic neuritis
Cerebellitis
Brainstem encephalitis
Chronic or recurrent forms of parainfectious or post vaccination encephalomyelitis
Relationship with multiple sclerosis?
Combined peripheral and central nervous system inflammatory demyelinating disorders
Post vaccination: rabies, influenza?
Postinfectious: measles

dysfunction. The most precise clinical and pathological observations regarding ADEM are derived from case studies in which there has been a close link between the specific virus infection or vaccine and the syndrome. The syndromes arising after acute measles infection or rabies vaccine administration can be considered the prototypes of the illness. When cases with the clinical features of the syndrome occur with viral infections or vaccine administration linked by weak epidemiological data, problems arise (Table 60.11).

Postvaccination Acute Disseminated Encephalomyelitis

The occurrence of neuroparalytic accidents as a consequence of the Pasteur rabies vaccine prepared from spinal cords of rabbits inoculated with fixed rabies virus was recorded soon after introduction of the treatment. Similar neurological complications were observed as a consequence of the Jenner vaccine used for the prevention of smallpox.

The concern regarding the presence of neural tissue in vaccines as the majot factor in predisposing to neuroparalytic accidents has led to attempts to develop vaccines devoid of CNS tissue in the case of rabies and to the discontinuation of routine smallpox vaccination because the natural disease has been eradicated. The incidence of encephalomyelitis associated with the original Pasteur rabies vaccine prepared in rabbit brain has been estimated at 1 per 3000-35,000 vaccinations. An incidence rate of 1 per 25,000 vaccinations occurred with duck embryo rabies vaccine, a preparation containing minimal amounts of neural tissue; many of the complications with this vaccine involved the PNS. Introduction of the non-neural, human diploid cell vaccine has virtually eliminated neuroparalytic complications of rabies vaccinations.

Reports have associated ADEM with other vaccines, including pertussis, rubella, diphtheria, and measles. The association of influenza vaccination, particularly the swine influenza vaccine, with ADEM has been the subject of medicolegal conti nvei s\ . In i..i, (, Al 'I'M is not known in In-associated with any vaccine currently used in the United States, and the administration of influenza vaccine to people with MS does not induce relapse. ADEM developing after drug administration has been reported with sulfonamides and para-aminosalicylic acid/streptomycin. The aforementioned associations can only be substantiated by strong epidemiological evidence or by the development of a pathognomonic laboratory finding for ADEM, neither of which yet exists.

Measles-induced Acute Disseminated Encephalomyelitis

Descriptions of cerebral and cerebellar abnormalities after measles appeared in the mid- to late nineteenth century. By 1928, Ford summarized more than 100 cases and delineated subgroups of cases including those with diffuse cerebral features, focal ot multifocal cerebral findings, cerebellar dysfunction, and spinal cord abnormalities. The overall experience suggests that neurological sequelae complicate 1 in 400 to 1 in 1000 cases of measles infection, and that patients do not develop peripheral nerve damage, nor do relapses occur. The introduction of measles vaccination has greatly reduced the incidence of measles and its neurological complications, but the disease continues to occur in large epidemics in specific geographic areas with at-risk populations.

Idiopathic Acute Disseminated Encephalomyelitis

Cases of acute encephalomyelitis occurring in the setting of nonspecific viral illness arc difficult to diagnose with certainty and to distinguish from episodes of MS. Cases occurring in children at an age too young to overlap with MS are perhaps the most readily delineated. Features deemed characteristic of ADEM include simultaneous bilateral ON, loss of consciousness, meningismus, loss of deep tendon reflexes and retained abdominal reflexes in the presence of Babinski's reflexes, central body temperature of greater than 100"F, and severe shooting limb pains, Recovery from ADEM is more rapid compared with MS (days versus weeks) and usually more complete. Tentative associations with ADEM have been made with a wide array of viral and bacterial infections: rubella, mumps, herpes zoster, herpes simplex, influenza, Epstein-Barr virus, coxsackievirus, *Borrelia burgdorferi. Mycoplasma,* and *Leptospira.*

IAtvpl III children, an ia'i.il .ruck •I MS is ruin hundreds of times nunc common than is ADEM.

The hallmark clinical feature of the disorder is the development of a focal or multifocal neurological disorder following exposure to virus or receipt of vaccine. In some, but not all, cases, a prodromal phase of several days of fever, malaise, and myalgias occurs. The onset of the CNS disorder is usually rapid (abrupt or up to several hours), with peak dysfunction within several days. Initial features include encephalopathy ranging from lethargy to coma, seizures, and focal and multifocal signs reflecting cerebral (hemiparesis), brainstem (cranial nerve palsies), and spinal cord (paraparesis) involvement. Other reported findings include movement disorders and ataxia. Each of these findings may occur as an isolated feature or in various combinations.

Recovery can begin within days, with complete resolution noted on occasion within a few days, but more often over the course of weeks or months. The mortality varies between 10% and 30%, with complete recovery in 50%. Poor prognosis is correlated with severity and abruptness of onset of the clinical syndrome. In the postrabies vaccine case series, a mortality of 18% was recorded. At a mean follow up of 17 months, 68% "1 survivors were complexly recovered, and 32% were partially recovered, most with minimal deficits. In three patients in the series, a relapse of neurological deficits occurred during the recovery period. No patients were recorded as having relapses after complete recovery had occurred.

Measles virus-associated ADEM may carry a worse prognosis than vaccine-associated disease. In earlier series, the occurrence of acute hemiplegia, which was intetprctcd as vascular occlusion and akin to the syndrome of acute hemiplegia of childhood, carried a particularly unfavorable prognosis with respect to recovery. Relapses are rare.

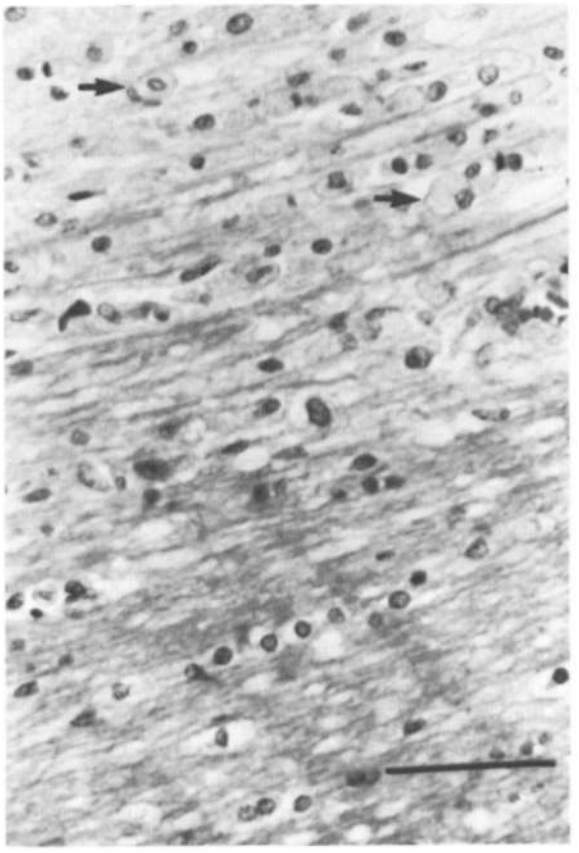


FIGURE 60.13 Lesion of acute disseminated encephalomyelitis showing dcmyelination and macrophage infiltration *{arrows)* (hematoxylin and eosin; bar = 50 |im). (Courtesy Dr. S. Carpenter.)

Laboratory Features

The hallmark lesions of ADEM are perivascular inflammation and surrounding demyclination within the CNS (Figures 60,13 and 60.14). Vessel necrosis is frequently observed. The demyclinating aspect may be minimal or widespread, with coalescence of the multiple lesions. Some meningeal reaction may be apparent also. Reports of MRI studies, largely from apparent sporadic cases of ADEM, describe multifocal CNS lesions initially indistinguishable from those observed in MS. In ADEM, after several weeks lesions show at least partial resolution without the appearance of new lesions; this is unlike MS. In some cases lesions ean [HTSIM, MKI in ADF.M. .is with MS, is more sensitive than CT scanning, which may in some cases show enhancing lesions. The usual CSF formula is normal pressure, little or no increase in cell count (<100 cells/uL) and a modest increase in protein. Well-documented cases exist with totally normal CSF. Cases with high cell counts, including some polymorphonuclear cells and high protein values, occur and seemingly reflect a more necrotizing disease process. The high counts usually return to normal within a few days. The CSF immunoglobulin content is not usually increased, and **OCB** patterns ate not usually observed. In many patients with postrabies vaccination and postmeasles ADEM, one can show some systemic blood lymphocyte sensitivity to MBP in vitro. Although technically difficult to assess, CSF lymphocyte sensitivity to MBP may be even more marked than is systemic lymphocyte sensitivity. The occurrence of cases without MBP sensitivity indicates that this assay is insufficiently sensitive to establish or exclude the diagnosis of ADEM.

The diagnosis ol ADEM can usually be made with confidence ;n tlu setting of .1 clear-cul antccedenl evcnl sttongly associated with the disorder, such as measles infection or vaccination. The occurrence of an acute focal or multifocal CNS syndrome subsequent to a more nonspecific viral illness or vaccination in which the epidemiological link with ADEM is weak does create a wider differential diagnosis, particularly depending on the age of the patient and the clinical manifestations of the disease. The following would be included in this differential diagnosis: (1) an initial episode of what will prove to be MS; the presence of increased levels of IgG in the CSF may favor the diagnosis of MS; follow-up MRI may be needed, because initial MR]

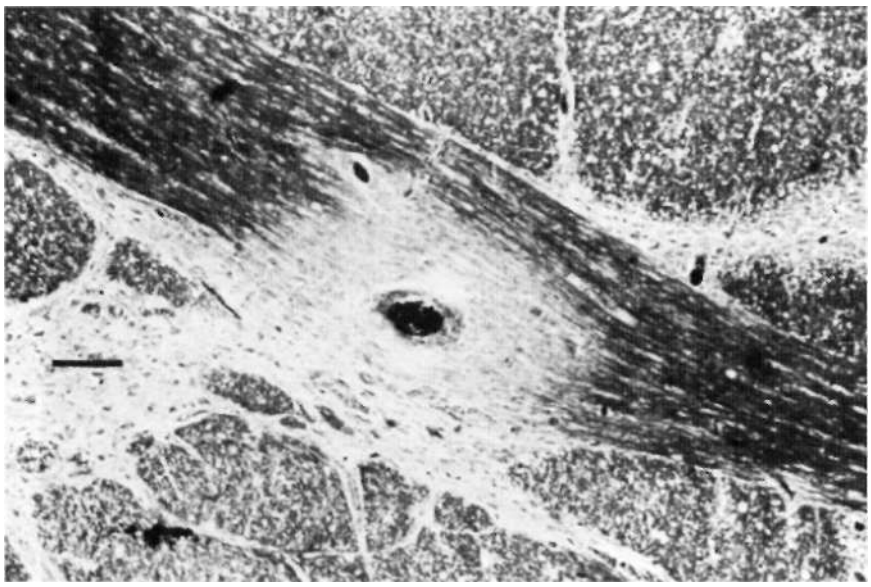


FIGURE 60.14 Penvenular zone of (linui'liii.iriou in brainstem of patient with acute disseminated encephalomyelitis (Heidcnhain Woclkc stain; bar — I 00 p i).

scans may appear similar in the two diseases; the occurrence of a nonspecific viral illness before the onset of the clinical neurological syndrome does noi di->ungmsh between MS and ADEM, because the incidence of exacerbations of MS is increased following such infections; (2) CNS vasculitis with or without systemic features {such as disseminated intravascular coagulation or serum sickness); (3) multiple cerebral infarcts, particularly embolic from infected cardiac valves; and (4) chronic meningitis or granulomatous disease (sarcoidosis). If the main clinical feature is unifocal, encephalitis, abscess, or rumor needs to be excluded.

Treatment

The current favored therapy for ADF.M is corticosteroids, based to some extent on their efficacy in EAE, although no clinical controlled studies have been conducted. Immunosuppressants such as cyclophosphamide have been used in refractory cases, as well as plasmapheresis. Data on the various other immunotherapies described in the section on MS are lacking.

OTHER INFLAMMATORY DEMYELINATING DISEASES OF THE CENTRAL NERVOUS SYSTEM

Acute Hemorrhagic Leukoencephalitis

Acute hemorrhagic leukoencephalitis is a rare entity that represents a hypetacute form of ADEM, in a parallel fashion to the hyperacute forms of EAE. The most frequent antecedent history is that of an upper respiratory infection. Given the nonspecific nature of the antecedent event and the lack of a specific diagnostic clinical laboratory rest, the exact incidence and lull clinical spectrum ot the disorder can only be estimated and are based largely on descriptions of autopsy-proved cases. The clinical manifestations mimic ADEM, but arc more abrupt in their development and more severe. They include focal or multifocal signs, seizures, and obtundation. Relapse following initial recovery has been described. Fever is common. The CSF usually demonstrates increased pressure, protein, and both white and red cells. The peripheral white blood cell count also is usually increased. CT scans in suspected clinical cases show an initially normal scan followed by low-density white matter lesions developing within 72 hours of the first symptoms. With improvement, the lesions on CT may largely resolve. MRI may yield additional information on lesion evolution.

The differential diagnosis of this syndrome includes entities that presenr as rapidly evolving focal cerebral disorders with fever and obtundation. These include brain abscess and encephalitis, particularly caused by herpes simplex, in addition to those syndromes considered in the section on ADEM.

Pathology

This disorder represents a more severe and destructive form of ADEM. The CNS white matter shows necrotizing vasculitis involving venules and capillaries. There are perivascular accumulations of polymorphonuclear cells and red blood cells. The perivascular dcinyehnatmg lesions frequently coalesce to form large lesions.

Treatment

Corticosteroids arc frequently used in suspected cases, with no firm data yet available regarding efficacy.

Chronic or Recurrent Forms of Postinfectious and l'o s t v acci n a tio n En ccp halo myelitis

As previously stated, the clinical hallmark of ADEM occurring after measles infection or rabies vaccination is its course. Relapses occurring during the recovery phase could well represent physiological conduction blocks rather than true reactivation of immune-mediated mechanisms. Recurrent encephalomyelitis cases are described, however, particularly in the pediatric age groups. Recurrent cases in adults, if they occur, would be difficult to distinguish from MS. The existence of chronic or recurrent encephalomyelitis cases might be considered as a parallel of the peripheral neuritis syndromes, of which acute nonrelapsing Guillain-Barre syndrome is the prototype, but in which chronic and recurrent cases are reported. The basis of these latter syndromes and their relation to classic Guillain-Barre syndrome remain unresolved. The animal models of encephalomyelitis (EAE) and peripheral neuritis (experimental allergic neuritis) can both be induced in relapsing form, if one selects animals of critical age and specific genetic background,

Combined Central and Peripheral Demyelinating Disease

The existence of combined central and peripheral demyelinating disease as a postinfectious disorder or as a complication following administration of vaccines not known to contain PNS, and CNS tissue remains highly questionable based on available epidemiological evidence. Cases of combined PNS and CNS involvement following swine influenza vaccination were reported, but some of these cases had subacute progressive courses. To date, no convincing in vitro immune sensitization to cither viral or neural antigens has been shown in such cases. Reports of combined centtal and peripheral demyelination syndromes do exist in which onion bulb formation in the PNS is demonstrated, indicating recurrent demyelination and remyelination. Some, although not ail, of these patients have clinical features consisrent with MS. Whether such combined demyelination represents a chance occurrence of two processes or a distinct disease is unresolved.

Site-Res trie ted Forms of Postinfectious Demyelinating Disorders

Acute and Subacute Transverse Myelitis

Acute and subacute transverse myelitis is defined as the development of isolated spinal cord dysfunction over hours or days in patients in whom no evidence exists of a compressive lesion. In the combined experience of several series reviewing complete transverse myelitis, 37% of patients reported a preceding febrile illness. The initial symptoms are paresthesias, back pain, or leg weakness; 37% of patients had the maximal deficit within I day, 45% in 1-10 days, and 18% in more than 10 days. Outcome was rated as good in 42%, fair in 38%, and poor in 20%. The prognosis may be worse in the rapid-onset group of patients. Only approximarely 7% of patients develop MS by clinical criteria. Whether these cases represent a homogeneous entity remains speculative and doubtful, particularly because the ages of reported cases range from 4-83 years. In addition, acute transverse myelitis is known to occur on a background of systemic vasculitis, such as SLE and that associated with heroin abuse. One must distinguish complete transverse myelitis from the partial or incomplete syndromes that more frequently predict evolution to MS in 50-90% of patients.

Optic Neuritis

The clinical features of ON are described in the previous section on MS. In ON associated with MS, the majority of clinical episodes are unilateral, although VERs also may indicate involvement of the contralateral eye. Simultaneous bilateral ON is rare in MS, although somewhat more frequent in Dcvic's disease. The estimated incidence of subsequent development of MS following an initial episode of ON varies widely among different series (from less than 20% to more than 70%). The issue remains whether some cases of isolated ON do represent formes frustes of ADEM. In this regard, cases of ON occurring after childhood exanthems would represent the best example of parainfectious ON, Cases are reported following measles, rubella, mumps, and varicella. Most patients had bilateral optic-nerve involvement; additional neurological abnormalities occurred in only a minority of patients. The young age of the patients further suggests that these events arc not the initial manifestations of MS. The prognosis for recovery of vision is good in most cases, perhaps less so in postvaricella cases.

Cerebetlilis

Acute, isolated ataxia has been observed after many different viral illnesses but most frequently in association with varicella infections. Cerebellar araxia accounts for 50% of the postvaricella neurological syndromes, which overall occur in 1 in 1000 cases of childhood varicella. The prognosis for recovery is excellent, although the duration of symptoms varies from a few days up to 3-4 weeks. The fact that most cases remit spontaneously and that the etiology (direct invasion versus autoimmune) is unresolved leaves the issue of corticosteroid therapy unsettled.

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Chapter 61
Hypoxic/Anoxic and Ischemic Encephalopathies

Bruce D. Snyder and Robert B. Daroff

Hypoxic/anoxic and ischemic central nervous system (CNS) injuries may result from a number of conditions, such as cardiac arrest, carbon monoxide intoxication, or septic shock. Corrective action aimed at the underlying disorders must be instituted immediately to ensure survival and minimize residual CNS damage. Hypoxic states have been subdivided into four categories: (1) insufficient cerebral blood flow, (2) reduced oxygen availability, (3) reduced oxygen carriage by rhe blood, and (4) metabolic interference with the use of available oxygen. Clinically, these mechanisms often coexist, causing an anoxic-ischemic encephalopathy (AIE), and can result in a wide spectrum of CNS dysfunction (Table 61.1).

SYNCOPE AND CONFUSIONAL STATES

Syncopal attacks {see Chapter 2) are brief episodes of global cerebral ischemic anoxia. The brief loss of consciousness is followed by an almost immediate return of full awareness. If the drop in cardiac output is prolonged beyond a few seconds, a few clonic movements or an actual generalized tonic-clonic seizure may occur. Distinguishing a syncopal attack from a primary convulsive disorder can at times be difficult; a prodrome of tight-headcdness, the prompt cessation of ictal activity after circulation is restored, and the usually brief or absent postictal state after syncopal attacks are helpful.

More prolonged but still brief episodes of global hypoxia may be followed by minutes to hours of confusion (see Chapter 4) and potentially the appearance of an amnestic syndrome resembling Korsakoff's psychosis (see Chapter 63). The predominantly anterograde amnesia may persist for weeks and occasionally is permanent. The persistent anterograde amnesia, with otherwise preserved cognition, presumably reflects the selective vulnerability of hippocampal neurons to anoxic insult.

Certain agents, such as carbon monoxide and cyanide, or pharmaceuticals such as nitroprusside (Curry and Arnold-Capelt 1991) (see Chapter 64) can produce states of histotoxic hypoxia. These types of poisons disrupt cellular mechanisms for carrying and using oxygen. Nervous system damage is virtually identical to lesions resulting from ischemic or anoxic hypoxia.

Prolonged states of marginal cerebral perfusion or reduced oxygen availability (e.g., respiratory failure, high-altitude exposure, or profound hypotension) initially result in mild cognitive deficits that may ptogress to frank confusion. If such conditions are more severe and prolonged, a typical delirium is seen with fluctuating levels of alertness, hallucinations, and delusions. Sensitivity to given levels of arterial blood pressure, oxygen, and carbon dioxide varies significantly among patients. Delirium in the critically ill patient may, of course, be multifactorial, and hypoxia may be one of many factors to consider (see Chapter 4).

Acute mountain sickness (see Chapter 64E) is common among nonacclimatized persons who ascend higher than 6500 feet. Headache, malaise, anorexia, and nausea occur and are due to the development of mild cerebral edema. Factors that suppress ventilatory drive, such as sedation (e.g., ethanol ingestion), worsen the condition. Symptoms of headache with nausea, vomiting, and especially obtundation require immediate descent and treatment with acerazolamide, corticosteroids, and oxygen (Ikv,ruehka 1992). Stroke-prone individuals are at greater risk at high altitudes, and previously asymptomatic intracranial masses may declare themselves.

Tabic 61.1: Clinical syndromes of central nervous system hypoxia and ischemia

"Mild" sustained hypoxia
  Cognitive impairment
    Confusional states
    Delirium
Brief anoxic-ischemic events
    Syncope
    Abortive or actual generalized seizure activity
Sustained severe hypoxia
    Coma with residual neurological deficits
      Dementia
      Vegetative state
      Brain death
    Seizure activity
    "Watershed" infarction of cerebrum, cerebellum, spinal cord
    Infarction distal to a pre-existing arterial stenosis or occlusion
    Postanoxic demyelination

Source: Adapted from Caronna, J, J. & Finklestein, S. 1978, "Neurological syndrome after cardiac arrest," *Stroke,* vol, 9, pp. 517-520.

FOCAL CEREBRAL ISCHEMIA

Prolonged hypotensive episodes associated with delirium or impaired levels of consciousness may result in cerebral infarction. Focal neurological deficits may then coexist with diffuse dysfunction due to generalized neuronal injury. Several mechanisms of infarction (hemodynamic, embolic, and thrombotic) may be involved. Failure of perfusion pressure can result in areas of infarction in the arterial watershed zones, the end-arreriolar territories lying at the boundary of brain areas supplied by a single major intracranial artery, such as the middle cerebral artery. These border-zone areas are last in line for blood supply when cerebral perfusion pressure is reduced. Watershed zones extend high over the cortical convexity to involve the visual cortex, visual association areas, and superior parietal lobules. Further anteriorly, the upward extent of the primary motor and sensory cortices, including interhemispheric structures, may be damaged. Cortical areas surrounding the primary speech areas are within these vulnetable zones, as are sectors of cerebellar cortex, the basal ganglia, and the thoracic spinal cord.

infarction in watershed areas can cause characteristic clinical signs, including transcortical aphasias, cortical blindness (with varying degrees of anosognosia), bibrachial paresis with possibly some gait dysfunction (man-in-a-barrel syndrome), cerebellar dysmetria, and anterolateral spinal cord infarction (usually midthoracic}. Rarely, extensive and selective loss of central spina! cord gray matter can result in a diffuse amyotrophic picture. Although watershed infarctions are generally symmetrical, underlying pre-existing cervical atherosclerotic disease (e.g., unilateral carotid occlusion or high-grade stenosis) may lead to strictly unilateral or predominantly unilateral infarction. In these circumstances, the infarct is in the central area of perfusion of the stenotic vessel; hence, the distribution of the lesions is the inverse of watershed infarcts (see Chaptet 57A).

Cardiogenic embolization may complicate myocardial infarction, cardiac arrhythmias, valvular heart disease, or cardiopulmonary arrest. Resultant cerebral or brainstem infarctions may occur. Hypotensive crises due to sepsis or hypovolemia can be associated with cerebral venous thrombosis with parasagittal or mesodiencephalic infarction (see Chapter 57A). Parasagittal venous cortical infarctions are generally hemorrhagic and often heralded by prominent focal seizure activity. Thrombosis of the cerebral venous system can propagate ro the cerebral venous sinuses, resulting in impaired cerebrospinal fluid absorption and the development of hydrocephalus with gradually declining alertness. Thrombotic propagation to the straight sinus and vein of Galen can cause high midbrain infarction with an itreversible comatose state.

POSTANOXIC COMA

The specific duration of anoxia necessary to produce prolonged loss of consciousness and profound cerebral damage is unknown. Individual variation may be significant. Factors such as prcarrcst blood glucose levels, preischemic medications (e.g., aspirin or calcium-channel blockers), and associated hypothermia (as in cold-water drownings and avalanche victims) may be important. (Mullner et al. 1998). Young children are somewhat more resistant to anoxic damage. Generally, at least 4 or 5 minutes of circulatory arrest is considered sufficient to cause serious brain injury, but the duration of anoxia is rarely well defined in clinical settings.

After resuscitation, the severely anoxic patient is in deep coma, often transiently without even the most resilient brainstem response, the pupillary light reflex. Survivors regain brainstem functions over the first 1-3 hours but generally require supported ventilation. Initially flaccid, the patient subsequently manifests decerebrate or decorticate posturing. Seizure activity of various kinds appears in almost one of every three patients within the first few days (Snyder et al. 1980; Snyder et al. 1980). Axial myoclonus can be so violent that mechanical ventilation is disrupted. Asynchronous distal limb myoclonus also may be seen. Generalized tonic-clonic seizures occasionally occur, due to a variety of toxic or metabolic factors. The increased cardiovascular strain due to seizure activity may be dangerous to the patient; additionally, hyperthermia and increased cerebral metabolic demand due to seizures may reduce the chances of cerebral recovery.

Later, after some degree of cerebral recovery, parrial simple and partial complex seizures may develop. Partial complex status epilepticus can appear as simply a prolongation of the patient's postanoxic stupor or

confusional state. The clinician should consider the diagnosis of nonconvulsivc status epilepticus in patients who plateau in a stuporous state or secondarily decline in level of alertness. The only clinical sign may be gaze deviation with nystagmus.

Recovery rates vary among these patients. With time, initial flaccidity is replaced by reflex motor posturing. This, in turn, is succeeded by avoidance movements, reflex grasping, eye opening, and finally, arousal, as manifested by complex interaction with the environment. As patients emerge from postanoxic coma, several clinical patterns are seen. The patient arousing early (within 24 hours) is frequently agitated and confused for a period of hours to days but ultimately recovers most cognitive functions. The patient's combativeness may necessitate the use of neuroleptics and poses difficulties for nursing care and cardiopulmonary stability. Hainpcr.dnl, ri^peridnl, or similar, less sedating, nonanticholmergic dopaminergic blocking agents may provide good control without further clouding the sensorium. The use of sedatives, anticonvulsants, and the like will tend to delay arousal and make clinical assessment more difficult. The clinician must weigh this against the requirements of patient care and safety.

As awareness is regained, the clinician can begin to assess cognitive and sensorimotor deficits. The effects of focal or multifocal infarction become apparent. Patients with more diffuse cortical damage display affective shallowness and lability[7], inattention, impaired logical flow of thought, hallucinations, and delusions. These gradually clear at varying rates and to varying degrees. Involvement of the basal ganglia, either because of watershed infarction or diffuse neuronal loss (particularly after carbon monoxide intoxication), can result in prominent movement disorders that may be cboreoathetoid or even strikingly parkinsonian. Similarly, cerebellar signs, such as limb dysmetria or truncal ataxia, may appear. Most typically, in patients with residual motor dysfunction, combinations of these signs are seen.

Memory acquisition seems particularly sensitive to hypoxia. After a significant hypoxic episode, anterograde amnesia with deficits in acquiring and retaining new information may be permanent. Some patients whose coma persists beyond 4 or *5* days slowly become responsive to the environment, if only in a limited fashion. These patients remain cognitively impaired, although recovery proceeds to some extent for up to a year. Structured environments, neuroleptic medication, bladder and bowel programs, and rehabilitative therapy may help optimize functioning.

Persistent Vegetative State

Sniiir |io>M:ioxic voituimse patients develop a vegetative state. They begin to open their eyes within a few days but make no apparent contact with the environment. Motor responses continue to be decorticated or decerebrate posturing. Triple-flexion leg withdrawal may be seen, along with spontaneous clonus, flexor or extensor thrusting of the legs, or shivering, Brainstem reflexes recover quickly; sleep-wake cycles appear. With eye opening, other behaviors emerge such as yawning, bruxism, spontaneous smiling or crying, sneezing, and blinking to threat. Absolutely no consistent nonreflexive response to stimulation can be established with the patient. These patients do not consistently follow moving people or objects with their gaze. They meet the criteria for being called *vegetative.* If this condition persists for a month after resuscitation, it is considered a persistent vegetative state (PVS) (Ashwal et al. 1995). Pathologically, there is virtually complete forebrain necrosis with preservation of the brainstem. The electroencephalogram (EEG) is diffusely abnormal. Arousal changes may be seen in the EEG record with stimulation of the patient but normal reactive alpha activity is absent. Serial brain scans demonstrate diffuse and multifocal cerebral damage; severe cerebral atrophy develops during ensuing months of survival. These patients must be distinguished from those with central pontine infarctions, who are "locked in" or de-efferented but have normal cognition with preserved awareness. Other comalike states should be distinguished from TVS (American Neurological Association Committee on Ethical Affairs 1993) as well (see Chapter 5).

Cerebral Edema

The mechanisms for the development of cerebral edema in hypoxia are discussed in Chapter *65,* but the role of edema in A1E remains uncertain. Patients with AIE do not develop papilledema, although ischemic papillopathy may be observed rarely. Measurements of intracranial pressure (ICP) yield equivocal results. In small reported series, some—but not all—postresuscitation patients have had either elevated ICP or evidence of diffuse cerebral edema on imaging studies. Intracranial hypertension may be more likely to occur after cardiac arrest due to respiratory failure. The effects of prearrest hypercapnia and acidosis are unclear.

Autopsies of patients in coma due to AIE have revealed the presence of gross brain edema and cerebral liquefaction when there had been both a deep level of coma and prolonged survival (5 days or more). Patients who died within 24 hours of cardiopulmonary arrest (CPA) in deep coma do not show cerebral edema or liquefaction, suggesting that brain swelling is a postnecrotic phenomenon in these patients. In the setting of global anoxic ischemia, the presence of high ICP may portend a poor prognosis related to antecedent widesptead tissue death. There is no established indication for the use

of corticosteroids, osmotic diuretics, barbiturate-induced coma, hyperventilation, or ventriculostomy.

Delayed Postanoxic Deterioration

Occasionally, patients seem to arouse early and begin to recover well from anoxic coma, only to relapse with the appearance of apathy, confusion, gait disturbance, spasticity, incontinence, movement disorders, and dysarthria. Pathologically, there are varying degrees of demyclination in the centrum semiovale, bilateral pallidal necrosis, and patchy cortical necrosis, especially in the hippocampi. With supportive care, these patients may recover but are often left with residua] deficits. This unusual disorder is most often seen after carbon monoxide poisoning, in which the clinical picture is frequently that of parkinsonism. Indu ulimls older than 50 years are at greater risk !ur delayed deterioration. The overall frequency of delayed neurological degeneration in several series of cases of carbon monoxide intoxication approximates 2.75% (Gottfried ct al. 1997). An oligodendroglial injury resulting in delayed demyelination is a speculation.

Other Sequelae

Recovery of cognitive functions generally proceeds rapidly during the first several weeks after anoxic injury and seems to plateau by 3 months. Moderate to severe biparietal dysfunction (acalculia, apraxia) occurs in one of every three survivors. Almost one half of patients are left with moderate to severe memory impairment. Problems with planning and organizational skills, as well as depression, arc common. It remains unclear whether these patients may show some continued cognitive recovery in the first several years after their AIE.

Movement disorders frequently emerge during recovery from severe hypoxic events. Bilateral hemiparesis, pseudobulbar palsy, parkinsonism, tremor, choreoathetosis, and dystonia may appear as the patient awakens from coma or may develop weeks to months later (Govaerts et al. 1998). Features of different disorders may coexist in a given patient. Treatment is often unsatisfactory, and medications that seem to benefit one problem may well worsen others.

Epilepsy is uncommon in surviving postanoxic patients, although one syndrome deserves mention: delayed-onset action sensitive myoclonus (Lance-Adams syndrome) can be extremely disabling and may occur in patients who have made good cognitive recoveries from AIE, Intractable stimulus- and action-sensitive, asynchronous, distal limb myoclonus occasionally emerges days to weeks after recovery from anoxic coma. These patients often improve over the course of years after onset of myoclonus (Werhahn et al. 1997). Clonazepam and valproic acid may be therapeutically effective.

Prognosis of Anoxic Coma after Cardiopulmonary Arrest

("PA is associated with a high rate of morbidity and mortality and is rhe most common cause of severe anoxic injury. Of patients who survive until hospital admission, in-hospital mortality rates range from 54% to 88%. Of those surviving to hospital discharge, 20% die in 1 year, and 40% within 3 years; of the remaining patients, 75% have severe neurological impairment (Mullner et al. 1998), often with severe memory deficits (Mecklinger et al. 1998).

Statistics describing the outcome for patients in anoxic coma have varied somewhat in different clinical scries, largely because of patient selection criteria. Some investigators reported series of consecutively tcsuscitated patients, whereas others have selected those who remain in deep coma for some specified period. The clinician must be aware of the differences in selection criteria when attempting to apply a specific set of published statistics to a given patient. The use of sedatives, analgesics, muscle relaxants, or anticonvulsants may weaken the applicability of published statistics to a specific case.

Survival after CPA is closely correlated with the duration of coma. Individuals who are either arousablc or fully alert within 12 hours of resuscitation tend to do well neurologically, although they still experience a 25% mortality rate, related primarily to their underlying cardiac disease. In a series of consecutive patients with an overall 40% survival rate, the presence of initial postanoxic unarousability was a negative prognostic sign, with only 28% of that group surviving. The level of consciousness or motor responsiveness to stimulation may fluctuate after resuscitation; a decline within 48 hours is generally associated with a fatal outcome. A declining level of consciousness at any time during hospitalization also is associated with a reduced survival rate and poorer outcome. Prognosis in the first few hours of resuscitation remains uncertain. Patients making reflex responses to pain (decorticate or decerebrate posturing) within 1-3 hours of CPA still have a 20-30% possibility of survival with good outcome. Patients who achieve arousal within 72 hours of resuscitation may do well. Such arousal, however, does not guarantee either survival or independent functioning. The clinician should be cautiously optimistic while continuing vigorous life support in such situations. Occasional patients do not achieve full alertness for up to 10 days after CPA (Snyder et al. 1980; Snyder et al. 1980). The delay may relate to some superimposed or associated metabolic factor, in which case outcome may still be quite good.

A meta-analysis of published work rating prognosis after CPA led to the following conclusions: when evaluated 3 days after CPA, the absence of pupil light reflexes, the absence of any motor response to pain, and the absence of cortical evoked responses (SSEP) to median nerve stimulation were each 100% predictive of a poor outcome or death (Zandbergen et al. 1998).

Table 61,2: Cranial nerve reflex abnormalities and survival after cardiopulmonary arrest

Time after cardiopulmonary arrest	*Number of cranial nerve reflex abnormalities**	*Survivors (%)*
<3 hrs	0	so
	1	46
	2	29
	3	0
<6 hr	0	80
	1	37
	2	27
	3	n
<24 hrs	0	HI
	I	58
	:	21
	3	0
24-48 hrs	0	76
	I	21
	2	0
	3	0

* Absent pupillary light reflex, absent corneal responses, absent spontaneous conjugate roving gaze; each count as one abnormal finding.
Source: Adapted from Snyder, B. D., Gumnit, R. J., Leppik, I. E., et al. 1981, "Neurologic prognosis after cardiopulmonary arrest: IV. Brainstem reflexes," *Neurology,* vol. 31, pp. 1092-1097.

Cranial nerve (brainstem) reflexes correlate in a highly significant fashion with outcome (Table 61.2). When these reflexes are lost after having been initially present (e.g., the recurrent loss of pupillary reactions}, survival is extremely unlikely. Whereas the absence of brainstem reflexes is highly predictive of poor outcome and death, the presence of intact reflexes is not a clear indicator of good outcome (Snyder ct.nl. 1981).

Persistent early onset myoclonus (myoclonic status epilepticus) is a negative prognostic finding (Krumholz and Berg 2002). Guidelines for predicting very good and very poor prognosis appear in Table 61.3.

This sort of prognostic information is used to guide the clinician and family in decisions related to life support and the aggressiveness of clinical management. A discussion of the complex ethical issues behind these decisions is beyond the scope of this chapter. Medicolegal considerations are evolving and vary from state to state and country to country. In the United States, the sanctioned termination of life support is restricted to situations of brain death and medical futility, including PVS. Prognosis for life and function in postanoxic PVS patients is virtually nil; there are very rare reported cases of recovery of awareness after 1 to 2 years of survival but with ptofound sensorimotor disability.

We will not review clinical data for the prediction of outcome from anoxic injury in infants and children (see Kriel et al. 1994), but the combination of magnetic resonance imaging and spectroscopy may provide the best prognostic information (Dubowitz et al. 1998), Outcome assessments in children must be based on more prolonged follow-up, with recognition of the difficulty of judging intellectual capabilities in the developing child. Young mammals seem to be more resistant to anoxic injury than their ciders, which suggests that data collected in adult clinical series are not directly applicable to children. Further discussion of the assessment of the critically ill child is presented in Chapter 7.

BRAIN DEATH

Guidelines for determining death in the adult are well established (see Chapter 5). The rwo principal categories are irreversible cessation of cardiopulmonary function and irreversible cessation of CNS function. In the former group, clinical examination is all that is necessary to determine death. In the CNS group, a patient with ongoing circulatory function who is being artificially ventilated presents a more difficult issue. The diagnosis of brain death is based on

Tabic 61.3: Guidelines that identify patients wirh poor or good prognosis after cardiopulmonary arrest

Time after cardiac arrest clinical sign	*Patients with virtually no chance of regaining independence*	*Patients with best chance of regaining independence*
Initial examination	No pupillary light reflex"	Pupillary light reflexes present; motor response decorticate posturing or decerebrate posturing; spontaneous eye movements conjugately roving or orienting
1 day	1-day motor response no better than decorticate posturing; spontaneous eye movements neither orienting nor conjugate; roving	1-day motor response withdrawal or better; I-day eye opening to noise or spontaneously
i days	3-day motor response no better than decorticate posturing	Motor response withdrawal or better; spontaneous eye movements normal
I wk	Xot obeying commands; spontaneous eye movements neither orienting nor conjugate	Obeying commands

"In the absence of some other cause.
Source: Adapted from Levy, D. E., Caronna, J. J., Singer, B. H., et al. 1985, "Predicting outcome from hypoxic-ischemic *corns." JAMA,* vol. 253, pp. 1420-1426.

absence of all cerebral and brainstem functions persisting over a period of observation sufficient to exclude any possibility of recovery. Once a patient has met brain-death criteria, a repeat evaluation 6 hours later is advised Wijdicks [L·9v.. Twenty four hours ol observation is recommended in states of postanoxic damage. Periods of observation may be reduced if suitable techniques, such as a nuclear medicine cerebral blood flow study, establish beyond a doubt that no blood flow exists to the brain. Electrocerebral silence on EEG is considered a desirable but not necessary confirmatory feature; in any event, EEG recordings to establish cerebral death require a high level of technical and interpretive expertise.

Complicating conditions, such as hypothermia, neuromuscular blockade, severe peripheral neuropathies, lower motor neuron disorders, and comalike states (e.g., loekcdin syndrome, the presence of sedative or analgesic drugs, or reversible metabolic abnormalities), must all be considered and ruled out before making a diagnosis of brain death.

Guidelines for determining brain death in children must deal specifically with the age group from full-term newborn to the 5-year-old. Features unique to the childhood criteria are primarily the changing periods of recommended observation relative to the patient's age. For children of age 7 days to 2 months, two examinations and two EEGs 48 hours apart are required. For those of age 2 months to I year, a 24-hour interval is adequate. After 1 year of age, laboratory testing need not be performed, and a 12-hour interval is adequate for most cases.

ELECTRODI AGNOSTIC STUDIES

Electroencephalography

Cardiac arrest results in a stereotyped sequence of EEG changes (see Chapter 36A). In the first 6-9 seconds after a CPA, there is no change in ongoing EEG activities. At 7-9 seconds, thctc is a transition from normal frequencies to generalized, frontal-dominant 100- to 200-uV delta activity. By 14-18 seconds aftet CPA, there is generalized voltage attenuation with no recognizable EEG activity. If the cardiac arrest is brief, EEG activities recover in 5-12 seconds after a reverse sequence.

Normothermic individuals incurring a hypoxic-ischemic insult develop varying degrees of cerebral damage. A wide variety of abnormal EEG patterns appear, some of which have prognostic significance for neurological outcome. Burst-suppression activity and other periodic generalized phenomena denote severe cerebral dysfunction (Young ct al. 1994).

The term *alpha coma* refers to an F,FG pattern comprising widespread alpha-frequency activity that is not reactive to eye opening or other stimulation, recorded from a patient in coma. It occurs in patients after anoxic-ischemic insults and drug intoxication. Because continuous fT< i recording b.is nn: been widi\\ UM\I in monitoring comatose individuals, the actual frequency and significance of alpha coma is unclear, but its persistence is usually associated with a fatal outcome.

The absence of detectable EEG activity in individuals studied after CPA is ominous, although one must consider how long after CPA the tracing was taken. Proper interpretation of EEGs demonstrating no detectable cortical activity requires ascertaining conditions capable of causing temporary reversible loss ol [K(, activity (e.g., anesthesia, hypothermia). Occasional patients with no detectable EEG activity for up to 8 hours after resuscitation have subsequently regained consciousness.

There are several detailed systems of grading the conventional EEG in adults to aid in determining prognosis after CPA (Yamashila el al. 19951. ITGs showing normal or near-normal frequency, activity, topography, and reactivity arc assigned low grades; those with delta activity, intermittent voltage attenuation, electrocerebral silence, or the patterns mentioned in the preceding paragraphs are assigned higher grades. Patients with grade 1 EEGs (normal or near normal) have a good prognosis for neurological recovery. Patients with grade 4 or 5 EEGs (e.g., alpha-coma, intermittent voltage attention, or electrocerebral silence) die, usually without regaining consciousness. Patients with grade 2 or 3 FF.Gs (mild or moderate abnormalities) experience variable outcomes not accurately predicted by a single post-CPA EEG. In these patients, sequential EEGs may be of some prognostic assistance.

Evoked Potential Studies

The absence of the early cortical complex (N20-P27) of somatosensory-evoked potentials (SSEPs) (see Chapter 36A) in comatose patients (excluding those with brain disease, drug intoxication, major medical abnormalities other than acidosis, or coma of unknown origin) makes it unlikely that the patient will ever regain consciousness. Combining the results of the clinical examination, EEG, and SSFPs improves the sensitivity for predicting prognosis (Chen et al. 1996).

A practical clinical approach to the electrophysiological study of individuals {Figure 61.1) with AIE may begin with a conventional bedside EEG and SSEP recorded S-24 hours after resuscitation. If clinically required, repeat recordings, made on days 3 and 7 after resuscitation allow detection of specific EEG and SSFP patterns that denote a poor neurological prognosis. In addition, the rate and direction of changes in electrocortical activity can be established, with attendant short-term and long-term prognostic implications.

fin. proper **use** ni (ke-.e electrophysiological **techniques** requires technical and interpretive experience and expertise, Minimal technical standards and guidelines are available to assist the clinician (American Electroencephalographic

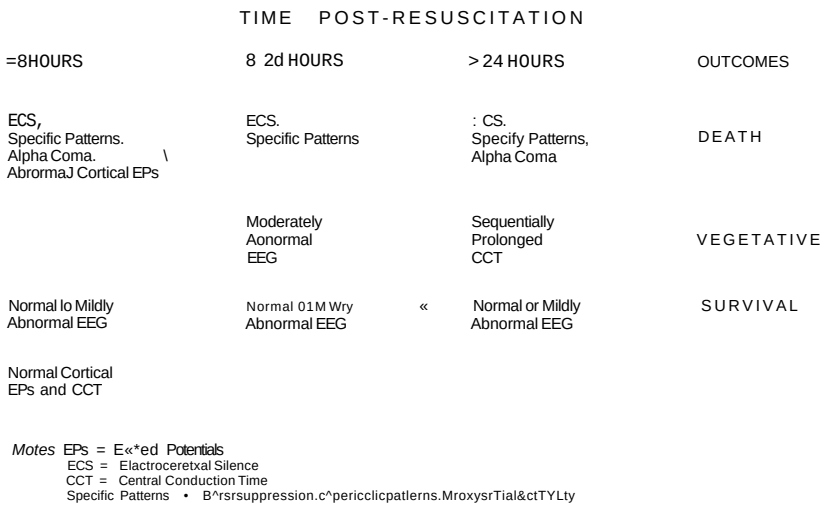

FIGURE 61.1 Time course and neurological implications of eiecrro-eneeplialograpfiie (KEG) and evoked potentials in hypoxic-ischemic coma.

Society 1994). Most of these patients are studied in the intensive care unit, where sources of artifact are legion and often difficult to eliminate. Recognizing artifact is essential.

Other Laboratory Aids in Assessing Prognosis

In addition to the electrophysiological techniques reviewed here, investigators have explored other laboratory techniques for predicting outcome after CPA. Neuroimaging and radionuclide studies have been useful in establishing cerebral nonperfusion and brain death. The concentrations of potassium and lactate in the CSF correlate with the severity of CNS insults in clinical series of patients with a variety of disorders. There are no established correlations, however, for patients with AIE alone. Large elevations of CSL creatine kinase-BB levels are closely correlated with poor outcome but are no more accurate than EEGs and SSEPs in outcome prognostication. Levels of S-100 protein are increased in patients with poor prognosis (Rosen et al. 1998). Magnetic resonance spectroscopy in vivo is also prognostically useful (Berek et al. 1997).

MANAGEMENT **OF COMA** DUE **TO** ANOXIC-ISCHEMIC ENCEPHALOPATHY

The patient who is confused, delirious, or comatose during or after an anoxic injury presents difficult diagnostic and treatment issues.

AIE after CPA is a metabolic coma with static or improving course that is often complicated by seizure activity. Diagnostic difficulty is increased because new factors, such as sepsis and drug effects, may intervene during the p.mer.v's prolonged ilhirv,. Primary intracranial disease can resemble anoxic states and may coexist with them, and care must he taken to rule out other relevant factors. Patients presenting with cardiac arrhythmias may have sustained a primary intracranial insult, such as a subarachnoid or intracerebral hemorrhage. The optic fundi should be inspected for papilledema, peripapillary nerve fiber layer hemorrhages, or subhyaloid hemorrhages. findings such as these or unilateral third cranial nerve-palsies should lead to a search for other intracranial pathology.

Continued monitoring of the neurological status serves to warn of deteriorating medical status, to establish the neurological prognosis (as outlined earlier), and to identify neurological complications, such as status epilepticus. Cerebral imaging studies, lumbar puncture, and EEG techniques may assist in ruling out other diagnoses.

Complications of anoxic coma may involve virtually every organ system. Blood pressure and pulmonary function usually require support. Fluid and electrolyte management may he complex. Hyperglycemic hyperosmolar crises may result from combinations of endogenous and exogenous catecholamines, corticosteroids, osmotic diuretics, and glucose infusions, particularly in the diabetic patient.

Two recent studies (Bernard et al. 2002; Hypothermia after Cardiac Arrest Study Group 2002) suggest that patients may benefit from the induction of mild hypothermia for 12 to 24 hours postarrest. The investigators began externa! cooling within 100 minutes after resuscitation from out-of-hospital cardiac arrest and suppressed shivering with deep sedation and neuromuscular blockade. Cooling seemed quite safe with no documented complications. Cooled patients were 16-23% more likely to achieve fair to good outcomes than controls.

Anticonvulsant therapy is indicated if seizure activity-does not respond promptly to the correction of metabolic factors. Axial myoclonus can be very difficult to control. Benzodiazepines (clonazepam, lorazepam) or valproic acid may be effective, but neuromuscular blockade or deep sedation with midazolam will more likely be required to prevent distuption of ventilation and interference with nursing care.

As noted previously, current evidence suggests that post-CPA brain swelling is a postnecrotic event. There is no indication for the active treatment of brain edema in this setting. Glucocorticoids and calcium-channel blockers are of no value in treating All[1]..

The patient with emerging focal neurological deficits may have sustained one or more cerebral infarctions. Diagnostic studies can rule out other intracranial structural lesions. Anticoagulation may be indicated in patients at high risk for recurrent infarction (e.g., those with atrial fibrillation, intracardiac thrombus), but routine anticoagulation after CPA is not indicated.

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Chapter 62
Toxic and Metabolic Encephalopathies

Alan H. Lockwood

Toxic and metabolic encephalopathies are a group of neurological disorders characterized by an altered mental status. Typically, they are caused by the failure of organs other than the nervous system or the presence of an endogenous or exogenous toxin or drug. Although the brain is isolated from the rest of the body by the blood-brain barrier (BBB), the nervous system often is affected severely by organ failure that may lead to the buildup of toxic substances normally removed from the body. This is encountered in patients with hepatic and renal failure, Damage to homeostatic mechanisms affecting the internal milieu of the brain, such as the abnotmalities of electrolyte and water metabolism associated with renal failure or the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, also affect brain function. In some cases, deficiency of a critical substrate after the catastrophic failure of an organ, such as hypoglycemia caused by fulminating hepatic failure, is the precipitating factor. Frequently, the history and physical examination provide information that defines the affected organ system. In other cases, the cause is evident only after laboratory data are examined.

CLINICAL MANIFESTATIONS

Encephalopathy that develops insidiously may be difficult to detect. The slowness with which abnormalities evolve and replace normal cerebral functions makes it difficult for patients and families to recognize deficits. When examining patients with diseases of organs that are commonly associated with encephalopathy, neurologists should include encephalopathy in the differential diagnosis.

Mental status abnormalities are always present and may range from subtle abnormalities, detected by neuropsychological testing, to deep coma. The level and content of consciousness reflect involvement of the reticular activating system and the cerebral cortex. Deficits in the spheres of selective attention and the ability to process information appear to underlie many metabolic encephalopathies and affect performance on many tasks. These deficits are manifested as disorders of orientation, cognition, memory, affect, perception, judgment, and the ability to concentrate on a specific task. Evidence ftom studio of patients with cirrhosis (sec Hepatic Encephalopathy, later in this chapter) suggests that metabolic encephalopathies are the result of a multifocal cortical disorder rather than uniform involvement of all brain regions. Among patients with coma of unknown cause, nearly two thirds ultimately are found to have a metabolic causal agent. A complete discussion of coma is found in Chapter 5.

The ueuro-ophthalmological examination is extremely important in the differentiation of patients with metabolic disorders from those with structural lesions. The pupillary light reflex and vestibular responses are almost always present, even in patients with deep coma. However, it is common for these reflexes to be blunted. Exceptions include severe hypoxia; ingestion of large amounts of atropine or scopolamine; and deep barbiturate coma, which is usually associated with circulatory collapse and an isoelectric electroencephalogram (EEG). The pupils arc usually slightly smaller than normal and may be somewhat irregular. The eyes may be aligned normally in patients with mild encephalopathy. With more severe encephalopathy, dysconjugate roving movements may occur. Other cranial nerve abnormalities may be present, but are less useful in formulating a differential diagnosis.

Motor system abnormalities, particularly slight increases in tone, are common. Other signs and symptoms of metabolic disorders may include spasticity with extensor plantar signs (in patients with liver disease}, multifocal myoclonus (in patients with uremia), cramps (in patients with electrolyte disorders), Trousseau's sign (in patients with hypocalcemia), tremors, and weakness.

Asterixis, a sudden loss of postural tone, is common. To elicit this sign, the patient should extend the arms and

elbows while dorsiflexing the wrists and spreading the fingers. Small lateral movements of the fingers may be the earliest manifestation. More characteristically, there is a sudden flexion of the wrist with rapid resumption of the extended position, the so-called flapping tremor. Asterixis also may be evident during forced extrusion of the tongue, forced eye closure, or at the knee in prone patients asked to sustain flexion of the knee. Electrophysiological studies have shown the sudden onset of complete electrical silence of muscles that coincides with the lapse of posture. This sign, once thought to be pathognomonic of hepatic encephalopathy (HE), occurs in a variety of conditions, including uremia, other metabolic encephalopathies, and drug intoxication. Asterixis may be present in patients with structural brain lesions.

Generalized seizures occur in patients with water intoxication, hypoxia, uremia, and hypoglycemia, but only rarely as a manifestation of liver failure. Focal seizures, including epilepsia partialis continua, may be seen in patients with hyperglycemia. Multifocal myoclonic seizures may occur in patients with uremia, after hypoxic brain injury, and in other disorders (see Chapters 24 and 77).

TOXIC ENCEPHALOPATHIES

Hepatic Encephalopathy

Disorders of the liver are a common cause of death resulting from disease. Among the poor, the incidence of cirrhosis may be as much as 10 times higher than the national average, and accounts for almost 20% of their excess mortality. As patients with chronic liver disease enter the terminal phases of their illness, encephalopathy becomes an increasingly important cause of morbidity and mortality. However, it is important to stress that mild encephalopathy is common in patients with cirrhosis. This treatahle problem is commonly overlooked. The unfortunate term *subclinical encephalopathy* has been used by some to describe a mild form of encephalopathy.

A clinical concensus statement seeks to minimize the substantial confusion in the literature and in clinical practice concerning the diagnosis of HE (Eerenci et al. 2002). A multi-axial system was proposed. The initial categorization addresses the presence of hepatocellular disease and portacaval shunting. Patients with acute liver disease or fulminating hepatk failure, a disorder occurring in patients with previously normal livers who exhibit neurological signs within 8 weeks of developing liver disease, form the first group. A second group consists of a small number of patients who are free of hepatocellular disease, but who have portacaval shunting of blood. The largest number of patients have hepatocellular disease with shunts. Further subdivisions address temporal aspects—whether HE is episodic, persistent, or minimal. Causal considerations are then applied to separate patients with precipitated HE from those with recurrent and ideopathic encephalopathy, and to identify the severity of the syndrome.

The features that differentiate patients with fulminant hepatic failure from those with the much more common portal systemic encephalopathy are shown in Table 62.1. The clinical criteria that are useful in defining the severity of HE are shown in Table 62.2.

An episode of HE may be precipitated by one or more factors, some of which are iatrogenic. In one series, the use of sedatives accounted for almost 25% of all cases. A gastrointestinal (GI) hemorrhage was the next most common event (18%), followed by drug-induced azotemia and other causes of azotemia (15% each). Excessive dietary

Table 62.1: Features distinguishing fulminating hepatic failure from chronic hepatic encephalopathy or portal systemic encephalopathy

Feature	*Fulminating hepatic failure*	*Portal systemic encephalopathy*
History		
Onset	! Ml.lib ;u ..If	Varies; may be insidious or subacute
Mental state	Mania may evolve to deep coma	Blunted consciousness progresses to coma
Precipitating factor	Viral infection or hepatotoxin	Gastrointestinal hemorrhage, exogenous protein, drugs, uremia
History of liver disease	No	Usually yes
Symptoms		
Nausea, vomiting	Common	i iiusual
AkInrniiiiil --•:iin	Common	Unusual
Signs		
Liver	Small, soft, tender	Usually large, firm, no pain
Nuiritiiiii;i! -1.111•	Normal	Cachectic
Collateral circulation	Absent	Present
Ascites	ı ····..··ıı	May be present
Laboratory Tests		
Transaminases	Very high	Normal or slightly high
Coagulopathy	['[•L'HL'lll	Often present

Table 62.2: Neuropsychiatry abnormalities associated with cirrhosis severity of encephalopathy*

	Grade 1 (mild)	*Grade 2 (moderate)*	*Grade 3 (severe)*
Consciousness	Alert, trivial Lick of awareness, short attention span	Slight blunting	Lethargic, somnolent
Behavior	Personalis change, fatigue, abnormal sleep pattern	Slight lethargy, disinhibition	Bizarre, paranoia
Affect	Irritable, depressed	Anxious, angry	Blunted
Cognition	Selective visuospatial abnormalities	Impaired	Too impaired to test reliably
Neurological examination	Tremor, asterixis, hypetactive reflexes, Babinski's reflex	Blunted consciousness, slurred speech	Dilation of pupils, nystagmus

*Grade 0: Overtly normal in all spheres. Grade 4: Coma, intact oculocephalic and pupillary light reflexes, no appropriate response to noxious stimuli,

protein accounted for 10% of episodes; hypokalemia, constipation, infections, and other causes accounted for the remaining cases. As liver disease progresses, patients appear to become more susceptible to the effects of precipitants. Ilir, phcilnmenim lias been iTlenvd i<> as M\iii h\ petsensi tivity. Other data that show older patients are more likely to develop HE after the transpigular intrahepatic portosystemic shunts suggest that age-related changes in the brain affect the susceptibility to the agents that cause HE.

The diagnosis of HE is based on the signs and symptoms of cerebral dysfunction in a setting of hepatic failure. Usually, standard laboratory test results, including serum bilirubin and hepatic enzymes, are abnormal. Products of normal hepatic function, including serum albumin and clotting factors, often are low, leading to prolongation of the prothrombin time. Measurements of the arterial ammonia level may be helpful in diagnosing HE. When obtaining blood samples for an ammonia determination, care must be taken to be certain that the sample is of arterial origin (venous ammonia levels may be artificially high, especially after the outpouring of ammonia by muscle made ischemic by applying a tourniquet). The sample should be placed on ice and carried by hand to the laboratory for immediate analysis. Delays can result in ammonia production in the specimen, producing a spuriously elevated result. Normal or minimally elevated blood ammonia values in a comatose patient with long-standing disease should be interpreted with some caution because of the possibility of an altered dose-response relationship between the arterial ammonia concentration and blood flow and oxygen metabolism, discussed elsewhete in this section.

The EEG may be the most useful of the commonly used laboratory diagnostic tests. Bursts of mode rate-to-high-amplitude (100-500 pV), low-frequency (1.5- to 2.5-Hz) waves are the most characteristic abnormality. There are three stages in the EEGs evolution: a theta stage with diffuse 4- to 7-Hz waves; a triphasic phase with surface-positive maximum deflections; and a delta stage, characterized by random, arrhythmic slowing with little bilateral synchrony. Computerized analysis of the EEG, designed to identify abnormalities in the spectra, may become a valuable means to identify patients with minimal encephalopathy.

Neuropsychological tests are an underused and valuable means to diagnose encephalopathy and monitor the response to therapy. Sixty percent or more of all patients with cirrhosis with no overt evidence of encephalopathy exhibit significant abnormalities when given a battery of neuropsychological tests. Tests of attention, concentration, and visuospatial perception arc the most likely to be abnormal. Specific tests that are useful include Trailmaking A and B, the digit symbol and the block design subtests of the Wechsler Adult Intelligence Scale (Revised), and the Purdue Pegboard, These abnormalities appear regardless of the cause of the cirrhosis. Patients with alcoholic cirrhosis typically have more difficulty with memory deficits than patients with nonalcoholic cirrhosis. Even though these patients appear to be normal, the degree of impairment, particularly in the visual-spatial sphere, may be severe enough to interfere with the safe operation of an automobile or other dangerous equipment, especially if visual-spatial performance is required. Language functions are usually normal. Treatment with lactulose lessens the severity of the test score abnormalities in many cases. These data, combined with other studies showing that the quality of life is affected by these abnormalities, suggest that neuropsychological tests should be used more extensively for the routine evaluation of all patients with cirrhosis, particularly those without overt evidence of HE.

Abnormal event-related potentials, characterized by prolonged latencies and altered waveforms characterize visual event-related potentials may be abnormal in patients with minimal encephalopathy. Although there has been less experience with auditory P300 potential recordings, in which the subject is asked to discriminate between a rare and common tone, differences in latencies and waveforms also have been associated with encephalopathy. A combination of visual-evoked potentials, auditory P300s, and selected neuropsychological tests (such as Trailmaking A and B) may be useful in detecting minimal encephalopathy in cirrhotic subjects. It is uncettain whether this less complex approach to detecting minimal encephalopathy

will prove to be more reliable and cost-effective than a focused neuropsychological test battery.

Neuroimaging

Although the diagnosis of HK is typically made on the basis of clinical ctiteria, neuroimaging techniques are commonly employed to exclude structural lesions. Magnetic resonance imaging (MRI) and spectroscopic^ studies have revealed new insights into the pathophysiology of HE (Lockwood ct al. 1997). On Tl-weighted images, it is common to find abnormally high signals arising in the pallidum. These arc seen as whiter than normal areas in this portion of the brain, as shown in Figure 62.1. In addition to these more obvious abnormalities, a systematic analysis of MRI images shows that the Tl signal abnormality is quite widespread and is found in the limbic and extrapyramidal systems, and generally throughout the white matter. A generalized shortening of the T2 signal occurs also. This abnotmality is less evident on visual inspection of the images because of the generally short duration of T2 signals. These abnormalities have been linked to an increase in the cerebral manganese content. The abnormalities become more prominent with time and regress after successful liver transplantation. The unexpected finding of high Tl signals in the pallidum should suggest the possibility of liver disease.

Proton magnetic tesonance (MR) spectroscopical techniques also have been applied to the study of patients with citrhosis. In the absence of absolute measures that are referable to concentrations, the signal of specific compounds is usually teferenced to creatine and expressed as a compound-to-creatinc ratio. There is genera! agreement among studies that an inctease in the intensity of the signal occurs at approximately 2.5 ppm that is attributed to glutamine plus glutamatc. With high-field-strength magnets, this peak can he resolved into its components. Results show that the increase is attributable to glutamine, as expected on the basis of animal investigations. Correlations between the glutamine concenttation, generally considered to be a reflection of exposure of the brain to ammonia, and the severity of the encephalopathy, have led some to propose that MR spectroscopy may be useful in the diagnosis of HE.

Myoinositol and choline signals decrease, whereas N-acety (aspartate rL-.on.mci-, ;.i nciircm:il scirkcr are am sistently normal. MR spectroscopic studies are difficult and expensive to perform. Because they show no clear advantage over less costly and readily accessible psychometric tests, they are not likely to he used clinically. Neuroimaging studies are not generally required in patients with HE. They may be useful in the diagnosis of coexisting structural lesions of the brain, such as subdural hematomas or other evidence of cerebral trauma, or complications of alcohol abuse and thiamine deficiency, such as midline cerebellar atropin, third ventricular dilatation and mamillary body atrophy.

Pathophysiology

The pathophysiological basis for the development of HF is still not completely known. However, treatment strategies for the disorder are all founded on theoretical pathophysiological mechanisms. A number of hypotheses have* been advanced to explain the development of the disorder, Suspected factors include hyperammonemia; altered amino acids and neurotransmitters, especially those related to the y-aminobutyric acid (GAIiAl-beii/odiazepinL- complex; mcrcaptans; and short-chain fatty acids. Although none of the current hypotheses is completely capable of explaining the development of HE, it is likely that ammonia plays a central role. Because of the complexity of the metabolic derangements that attend liver disease, other factors may contribute synergistically to the development of this complex disotder.

Cerebral Blood Flow and Glucose Metabolism. Whole-brain measurements of cerebral blood flow (CBE) and metabolism are norma! in patients with grade 0-1 HE, but reductions occur in more severely affected patients. The positron-emission tomography (PET) data show clearly that minimal forms of HE are caused by the selective impairment of specific neural systems rather than global cerebral dysfunction. This is a novel concept, because more traditional thinking suggests that brain regions are affected more uniformly by the action of toxins. Sophisticated statistical techniques designed to analyze images have made it possible to identify specific brain regions in which glucose metabolism is abnotmal in patients with low-grade encephalopathy and abnormal neuropsychological test scores (Lockwood ct al. 2002). Reductions occur in the cmgulare gvrus, an important element m the attentional system of the brain and in frontal and parietal association cortices. These PF7T data are in accord with cottical localizations based on the results of neuropsychological tests. Figure 62.2 shows the results of correlation analyses between scores on selected neuropsychological tests and sites of reduced cerebral glucose metabolism.

Role of Ammonia. HE is linked to hyperammonemia. Patients with encephalopathy have elevated blood ammonia levels that correlate to a degree with the severity of the encephalopathy. Metabolic products formed from ammonia—most notably glutamine and its transamination product, ketoglutaramic acid—also are present in excess cerebrospinal fluid (CSF) in patients with liver disease. Treatment strategies that lower blood ammonia levels are the cornerstone of thctapy.

Tracer studies performed with ' N-ammonia have helped clarify the role of this toxin in the pathophysiology of HE. Ammonia and other toxins arc formed in the GI tract and carried to the liver by the hepatic portal vein, whetc toxification reactions take place. Portal systemic shunts cause ammonia to bypass the liver and enter the system

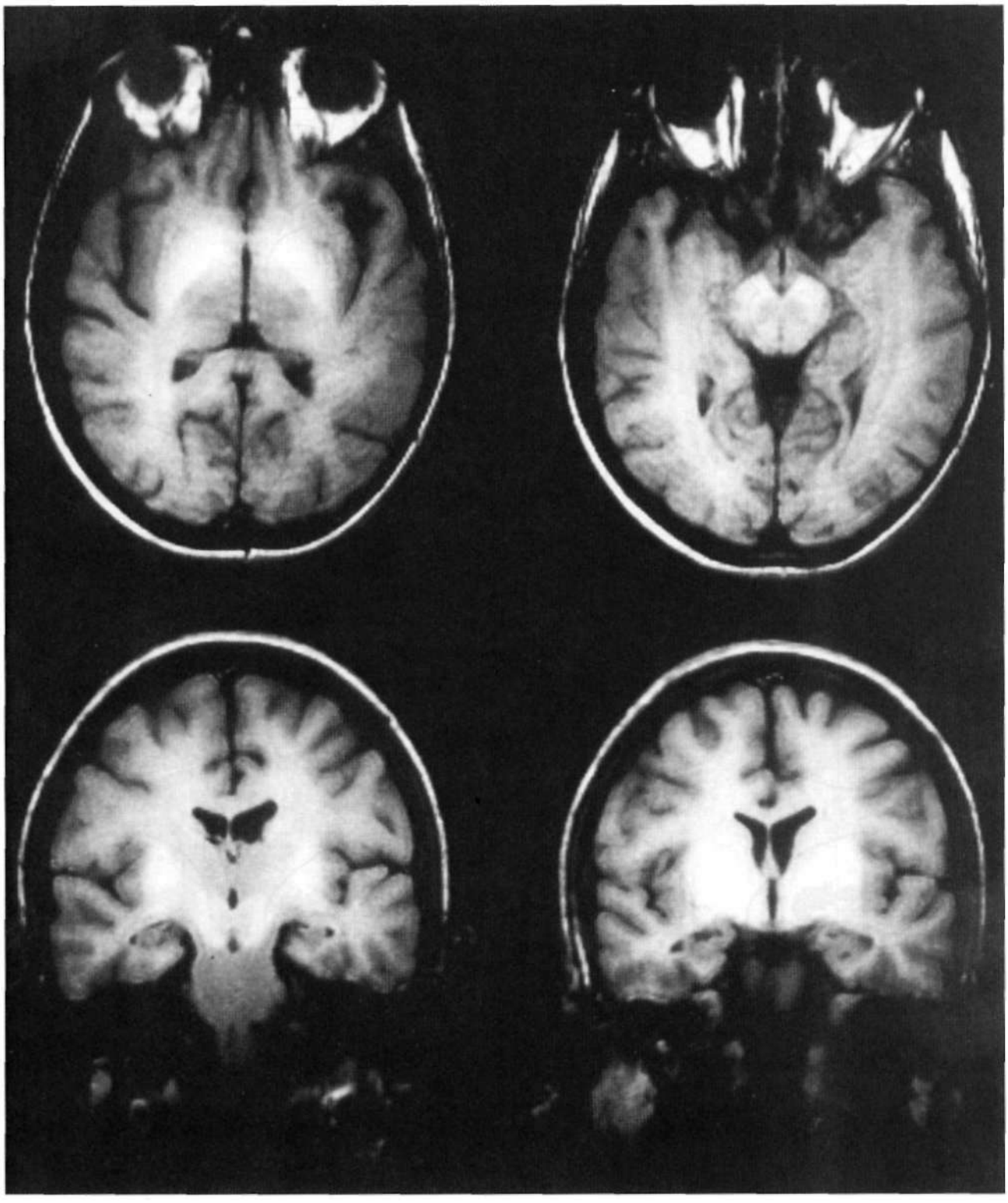

FIGURE 62.1 Tl-weighted magnetic resonance images from a patient with cirrhosis of the liver. Note high signal in basal ganglia, cerebral peduncles, and substantia nigra.

circulation, where it is transported to the various organs as determined by their blood flow. The liver is the most importaiil uri;;ni for ;hc delii\ii'v.uii>[i of ./nnmonia. However, in patients with portacaval shunting of blood, because of the formation of varices, transcutaneous intrahepatic portacaval shunts or surgically created shunts, skeletal muscle becomes more nupnn.iiir as [lie fraction of blood bypassing the liver increases. Under the

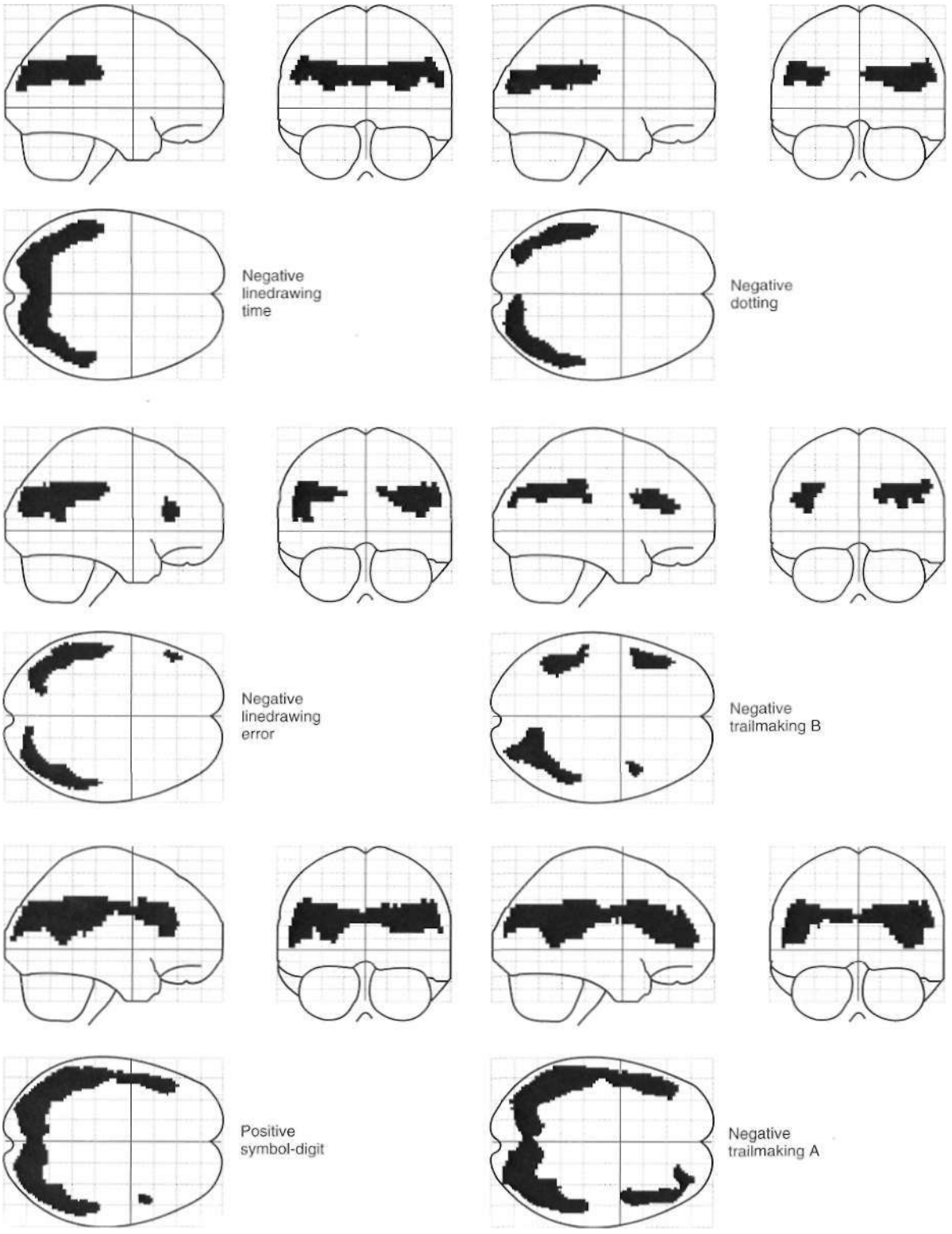

FIGURE 62.2 Correlations between performance, as measured by age-corrected *z* scores, **and metabolism for** various subtests in the composite battery. Only those subjects able to complete the test arc included in the analyses. The SPM Z image projections arc as in other figures. They all show significant correlations with bilateral parietal associative cortcxt with increasing correlations with frontal regions. The disparity of these results, particularly with regard to the correlations with frontal lobe metabolism, like the factor loading scores, suggests that the different tests appear to make different demands on cerebral resources. [Used with permission from I.ockwood, A. **H., Weissenborn, K.,** Bokeineyer, M., Tietge, et al. 2002, "Correlations between cerebral glucose metabolism and neuropsychological test performance in nonalcoholic cirrhotics," *Metabo Brain Dis,* vol. 17, pp. 29-40.)

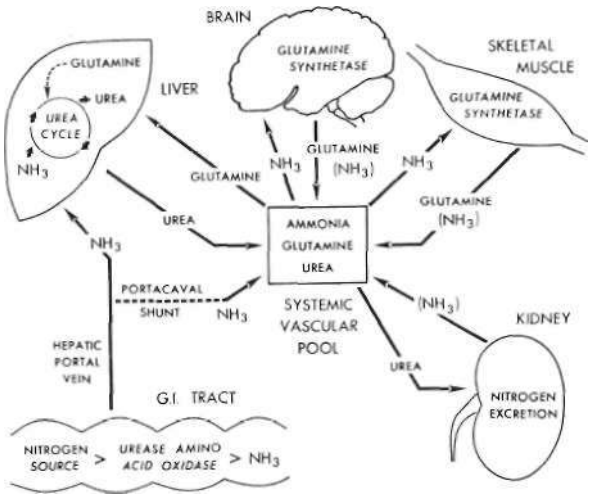

FIGURE 62..1 Human ammonia metabolism. The brain becomes more sensitive to ammonia as time progresses. Although the reasons for this are largely unknown, studies of cerebral ammonia metabolism have shown that the blood-brain barrier is more permeable to ammonia in patients with liver disease than in controls. Thus at a given arterial ammonia concentration, more ammonia enters the brain of a patient with cirrhosis than a patient without cirrhosis. This observation may explain the presence of encephalopathy in patients with near-normal arterial ammonia levels. In addition, ammonia may cause anorexia by stimulating hypothalamic centers, leading to reductions in muscle mass and an impaired ability of muscle to detoxify ammonia. CI —gastrointestinal. (Adapted from Lock wood, A. H., McDonald, J. M., Reiman, R. E., et al. 1979, "The dynamics of ammonia metabolism in man: Effects of liver disease and hyperammonemia,"/ *Clin Invest*, vol. 6"5, pp. 449-460.

most extreme conditions, muscle becomes the most important organ for ammonia detoxification. It is partly for this reason that nutritional therapy for patients should be designed to prevent development of a catabolic state.

Ammonia is always extracted by the brain as arterial blood passes through the cerebral capillaries. When ammonia enters the brain, metabolic trapping reactions convert free ammonia into metabolites (Kgure 62.3). The adenosine triphosphate (ATP(-catalyzed glutaminc synthetase reaction is the most important of these reactions. The BBB is approximately 200 times more permeable to uncharged ammonia gas (NH3) than it is to the ammonium ion (NH4+); however, because the ionic form is much more abundant than the gas at physiological pH values, substantial amounts of both species appear to cross the BBB in humans. Because of this permeability difference and because ammonia is a weak base, relatively small changes in the pH of blood relative to the brain have a significant effect on brain ammonia extraction. As blood becomes more alkalotic, more ammonia is present as the gas and cerebral ammonia extraction increases; however, the role this has in the production of HE is not known.

Other Pathophysiological Mechanisms

Abnormalities of Neurotransmission. Since the early 1970s, a variety of hypotheses have suggested that HE is caused by disordered neurotransmission. Although early hypotheses related to putative false neurotransmitters were disproved, there is still a substantial effort in this direction.

As a result of the false neurotransmitter hypothesis, it was shown that the ratio of plasma amino acids (valine + leucine + isoleucine) to (phenylalanine + tyrosine) was abnormal in encephalopathy patients, leading to the development of amino acid solutions designed to normalize this ratio, which arc now commercially available. Although infusion of the solutions normalizes the ratio and patients improve, the results of several controlled clinical trials arc inconclusive; it is not clear whether the amino acids or the associated supportive care measures caused the improvement noted.

Substantial effort has been focused on potential abnormalities of the GABA-benzodiazepine complex. Initial attention was directed at GAB A itself. Early reports that GABA concentrations were elevated in patients with encephalopathy have been disproved, and attention has shifted toward the presence of benzodiazepines or benzodiazepine-like compounds. A number of anecdotal reports have described dramatic improvements in patients who were refractory to more conventional therapy after they were given flumazenil. Some of the patients in the reports had been given benzodiazepines during the course of their care; however, whether a patient has been given benzodiazepines is not always clearly the case, and very low concentrations of benzodiazepines and their metabolites may be found in blood and CSF of patients with encephalopathy. Typically, these concentrations are substantially lower than concentrations that relieve anxiety, and appeal to be too low In produce coma. In controlled studies, patients given flumazenil are more likely to improve than those given placebo, but it is not clear that benzodiazepine displacement is the mechanism, because these patients do not have benzodiazepines in their systems. This raises the possibility that any of flumazenii's beneficial actions may be related to some other action of the drug. More recent theories have linked the presence of a increased expression of peripheral types of benzodiazepine receptors to HE. These receptors are found on mitochondrial membranes and are implicated in intermediary metabolism and neurosteroid synthesis. Hyperammonemia causes an increase in peripheral types of benzodiazepine receptors and creates a potential for an increase ill inhibitory tone in the brain, hi add in 011, there arc significant alterations in cerebral serotonin and dopamine metabolism, and a reduction in postsynaptic glutamate receptors of the N-methyl-D-aspartate type. Thus there is a substantial interest in the potential role of neurotransmitters in the pathogenesis of HE. As of yet, there is no unifying hypothesis and no rational thetapcutic approach based on altering neurotransmission.

Fatty Acids. Short-chain fatty acids affect a variety of metabolic processes, including uncoupling oxidative phosphorylation, alteting the mitochondrial respiratory state and state control mechanisms, and inhibiting the urea cycle that may, in turn, lead to hyperammonemia. They work synergistically with ammonia to produce coma in experimental animals.

Medium-chain fatty acid dehydrogenase activity deficiency may lead to the development of a clinical syndrome similar (o Rcy.'-, syndrome (see Chapter f.SR}. Indeed, many early cases of Reye's syndrome may have been caused by this metabolic deficiency.

Mercaptans. Mercaptans are thio-alcohols. In this class of compounds, the -Ol 1 group is replaced by an -SH group. Methanethiol is the principal mercaptan in humans, is formed by the cataholism of methionine, and occurs in measurable amounts in blood and exhaled air. Injecting or inhaling mercaptans produces coma in animals, and there were early teports of correlations between the concentration of mercaptans in the blood and the severity of encephalopathy in individual patients. An improved methodology for measuring mercaptans has confirmed their presence in elevated amounts in encephalopathy patients, but the correlation between the concentration and the neurological status is poor. Because mercaptans work synergistically with short-chain fatty acids, ammonia, or both to produce coma, synergistic effects may be of importance in humans.

Neuropathology

The Alzheimer's type II astrocyte is the neuropathological hallmark of hepatic coma. An account of the original descriptions of this change was provided in translation by Adams and Foley in 1953. In this report, they presented their own findings of this astrocyte change in the cerebral cortex and the lenticular, lateral thalamic, dentate, and red nuclei, offering the tentative proposal that the severity of these changes might be correlated with the length of coma, The cause of the astrocyte change was established by studies that reproduced the clinical and pathological characteristics of HE in primates by continuous infusions of ammonia. In studies of rats with portacaval shunts, astrocyte changes become evident after the fifth week, Before coma develops, there is an increase in astrocytic protoplasm and a proliferation of endoplasmic reticulum and mitochondria, suggesting that these are metabolieally activated cells. After the production of coma, the more typical signs of the Alzheimer's type II change became evident as mitochondrial and nuclear degeneration appeared. Norenbcrg (1998) suggested that HE is an astrocytic disease, although oligodendroglial cells arc affected as well,

The neuroparhological-neurochemical link between astrocytes and the production of hyperammonemic coma is strengthened by immunohistochemical studies that localized glutamine synthetase to astrocytes and their end-feet. Similar findings for glutamate dehydrogenase have been described. Long-standing or recurrent HE may lead to the degenerative changes in the brain characteristic of i ion - Wilson i a n hepatocerebral degeneration. Brains of these patients have polymicrocavitary degenerative changes in layers five and six of the cortex, underlying white matter, basal ganglia, and cerebellum. Intranuclear inclusions that are test positive by periodic acid-Schiff also are seen, as are abnormalities in tracts of the spinal cord.

Treatment

Ideally, the management of patients with cirrhosis should involve a cooperative effort be I ween he pa tologists. surgeons, neurologists, and psychologists with additional input from nurses and dieticians. Practice guidelines published by the American College of Gastroenterology identify four goals: (1) Provide supportive care, (2) identify and treat precipitating factors, (3) reduce the nitrogenous load from the gut, and (4) assess need for long-term therapy (Rlci and Cordoba 2001; Ferenci et al. 2002).

Initial diagnostic and therapeutic efforts should be directed at the identification and mitigation of precipitating factors and reducing the nitrogenous load arising from the GI tract. This is accomplished by a brief withdraw! of protein from the diet and the administration of cleansing enemas, followed by the use of lactulose. Antibiotics maybe used as an alternative to lactulose. After the acute phase of HE, patients should receive the maximum amount of protein that is tolerated. Prolonged periods of protein restriction should be avoided. Protein is required for the regeneration of hepatocytcs and prevention of a catabolic state and muscle wasting.

In patients who have cirrhosis without overt encephalopathy, diagnostic efforts should be directed toward identifying patients with minimal encephalopathy and monitoring the effects of treatment. The inappropriate terms *subclinical* or *latent HE* have been too commonly applied to patients with minimal encephalopathy. Patients with minimal encephalopathy have a diminished quality of life and benefit from therapy, typically lactulose. Although rigorous criteria have not been developed to establish this diagnosis, deficits on neuropsychological test scores are usually used as the criterion. Some have advocated the use of computerized EEG analysis for this purpose with a focus on abnormal slowing seen on an analysis of the spectrum, Follow-up testing is needed to monitor treatment.

Lactulose. Lactulose is a mainstay for the treatment of both acute and chronic forms of HE. It is a synthetic disaccharide metabolized by colonic bacteria to produce acid and causes an osmotic diarrhea.

A widely held but incorrect theory concerning the mechanism of action of lactulose centers on its ability to acidify the colon. Acidification presumably trapped ammonia as the charged and nonabsorbable ammonium

ion, thereby preventing ammonia absorption. This theory has been questioned because lactulose treatment does not increase the fecal ammonia concentration or the total amount of ammonia excreted. The effect of lactulose is attributable to its role as a substrate in bacterial metabolism, leading to an assimilation of ammonia by bacteria or reducing deamination of nitrogenous compounds. It is probably the single most important agent in the treatment of acute and chronic encephalopathy. The usual dose of lactulose is 20-30 g three or four times a day, or an amount sufficient to produce two or three stools per day. Lactulose also can be given as an enema. Lactitol, another synthetic disaccharide, is also effective. Although it is nt>i yet available in the United States, it may have some advantages over lactulose because it can be prepared in a crystalline form that may make it more acceptable to patients who' may object to the taste of lactulose preparations.

Amino Acids. The hypothesis that altered plasma amino acid ratios (discussed earlier), especially the (valine + leucine + isoleucine) to (phenylalanine + tyrosine) ratio, affect brain neurotransmitter pools has led to attempts to treat encephalopathy by normalizing the blood-amino acid profile with branched-chain amino acids. After preliminary open trials suggested a possible therapeutic benefit, a number of controlled trials were undertaken. Although they failed to show a clear beneficial effect, amino acid solutions (oral and parenteral) are still used.

Complications and Prognosis

The incidence of HE is probably underestimated, mainly because n on-neurologists are usually the primary physicians of these patients and may miss early, subtle signs of cerebral dysfunction. It is important to establish the diagnosis of Lib promptly and proceed with vigorous treatment. Although HE is potentially completely reversible, prolonged or repeated episodes risk transforming this reversible condition into non-Wilsonian hepatocerebral degeneration, a severe disease with fixed or progressive neurological deficits, including dementia, dysatthria, gait ataxia with intention tremor, and chorcoathetosis. Other patients may develop evidence of spinal cord damage, usually manifested by a spastic paraplegia. This complication may be a part of the spectrum of hepatocerebral degeneration. Differentiating correctly between early myelopathy or hepatocerebral degeneration and the motor abnormalities that characterize reversible encephalopathy may not always be possible. Because of the high sensitivity of MRI, M -.]io-.-.iNr i i.ii rhi-n recln:<)1o;Ly will aid in this difficult task. Patients with HE may develop toxin hypersensitivity, wherein previously, innocuous levels of toxins caused symptoms. This concept implies that there may be a steadily increasing risk for developing permanent neurological damage as toxin hypersensitivity evolves.

Severe hepatic coma carries a substantial risk of death. Fulminant hepatic failure is usually the result of massive necrosis of hepatocytcs and is defined as a syndrome in which the signs of encephalopathy develop within 8 weeks of the onset of the symptoms of liver disease in a patient with a previously normal liver. This condition has been desctibed as "metabolic chaos," because of coexisting acid-base, renal, electrolyte, cardiac, and hematological abnotmalities, usually culminating in GI bleeding, ascites, sepsis, and death frequently caused by cerebral edema. In spite of intensive treatment, patients who become comatose have an 80-85% mortality. Improvements in liver transplantation have led to better treatment and improved survival for these patients. Transplantation is associated with its own spectrum of neurological problems (see Chapter 55A).

Uremic Encephalopathy

Neurological disorders in patients with renal failure may present more problems for the neurologist than are found in patients with failure of other organ systems. This is primarily because of the complexity of the clinical status of many of these patients. Many of the disorders that lead to the development of renal failure, such as hypertension, systemic lupus erythematosus, diabetes melhtus, and others, are frequently associated with disorders of the nervous system. Thus it may be difficult to determine whether new neurological problems are caused by the primary disease or by secondary effects of uremia. Similarly, it is frequently difficult to determine whether neurological problems are the consequence of the progression of renal disease and progressive azotemia, the treatment of renal failure by measures such as dialysis and its associated disequilibrium and dementia syndromes, or a complication of transplantation and immunosuppression. With increasing numbers of renal transplants and improved treatment designed to prevent rejection, it is likely that the complexity of these issues will continue to increase. For these reasons, good cooperation and communication between neurologists and the nephrologists and transplant teams who care for these patients arc important,

Patbophysio logy

Clinically, patients with uremic encephalopathy exhibit many of the signs and symptoms described earlier in this chapter. Perhaps the most notable difference between these patients and those with otbet forms of metabolic encephalopathy is the frequent coexistence of signs of obtundation (suggesting nervous system depression) and twitching, myoclonus, agitation, and occasionally seizures (suggesting neural excitation). Little is known of the pathophysiology of uremic encephalopathy. As in HE, the complexity of the normal kidney's functions makes it likely that failure of the

organ leads to a variety of abnormalities that exert -.ynr !;i.-,lu JL'lekTi<ni\ **:.'kvls 0:1 ibr hi LI in.**

As in other metabolic encephalopathies and other conditions associated with a depression of consciousness, CEF and metabolism are reduced.

Water, Electrolyte, and Acid-Base Balance. Although derangements in electrolyte, water, and acid-base balance are common in patients with renal failure, they usually do nol ntaki a substantial com nbutu >n In t:ic dcvL-liipruciil of uremic encephalopathy. Disordered water balance is, however, a major factor in the syndrome of dialysis disequilibrium (see Syndromes Related to Dialysis, later in this chapter). Many patients complain of headache, fatigue, and other relatively nonspecific symptoms at the time of dialysis that are attributable to the removal of free water and solutes from the vascular compartment and a lag in re-establishing a new steady-state osmotic equilibrium with the brain. More severe forms of dialysis disequilibrium arc now rare. Before the current level of sophistication in equipment, membranes, and schedules for dialysis was developed, severe abnormalities of the EEG, epileptic seizures, coma, and even death occurred as the result of this syndrome.

Calcium and Parathyroid Hormone. Abnormal calcium metabolism and abnormal control of the parathyroid glands are common in uremic patients, including those receiving dialysis. Experimental studies have shown a doubling of the brain calcium content and serum parathyroid hormone levels within days of the onset of acute renal failure. EEG slowing correlates with elevations in the plasma content of the N-terminal fragment of parathormone. Treatment with 1,25 dihydroxyvitamin D leads to improvements in the KEG and reductions in N-reniniial fragment parathyroid hormone concentrations. Brain calcium concentrations may be related to the activity of an ATP-dependent sodium-calcium transporter protein.

Neurotransmitters, Disorders of plasma amino acids, most notably glutaminc, glycine, aromatic and branched-chain amino acids, and potential relationships to GABA, dopamine, and serotonin, have led to speculations that neurotransmitter function may be abnormal in patients with uremic encephalopathy. Others have suggested that brain calcium abnormalities may exert an effect on neurotransmitter release. These hypotheses remain unproven.

Treatment and Its Complications

Dialysis is the primary treatment for uremic encephalopathy. This may be preceeded by a period of peritoneal dialysis, which can be administered ro ambulatory patients. Many patients ultimately require transplantation.

Epileptic seizures occur in up to one third of all uremic patients. In evaluating patients with seizures, it is essential to determine whether the seizure is the result of uremia or the consequence of some other coexisting or causative illness, such as malignant hypertension with encephalopathy, intercurrent infection, dialysis disequilibrium syndrome, or cerebral infarction. Usually, the seizures caused by uncomplicated uremia arc generalized, but focal motor seizures and epilepsia partialis continua occur.

Treatment of uremic seizures is complicated by abnormalities of anticonvulsant metabolism and plasma binding encountered in patients with renal failure; phenytoin, a mainstay in seizure treatment, is affected particularly. Regardless of the route of phenytoin administration, uremic patients have lower drug levels than do normal controls, and plasma levels ot the metabolite 5-phenyl-5-para-hydroxylphenylhydantoin are higher. The half-life of phenytoin is shortened in uremia and unrelated to the binding of phenytoin to plasma proteins or to the volume of distribution. Plasma protein binding studies of phenytoin in normal and uremic patients show that normal people have approximately 8% unbound, or free, whereas uremic patients have between 8% and 25% in the unbound state. The unbound fraction correlates well with both the blood urea nitrogen and the creatinine concentration in Moo J, will[1] Ix'lui cnnylaiion with ovar.niiic :h.in blond urea nitrogen. In regulating phenytoin doses in uremic patients, it is critical to use the free drug level rather than the more commonly used total drug level. As a general rule, the free level should be kept between 1 and 2 ug/ml,, roughly 10% of the therapeutic level for total phenytoin. Phenytoin toxicity is difficult to manage in uremic patients because the drug is not removed by dialysis.

Phcnobarbital is also a useful drug for treating seizures in uremic patients in spite of the fact that it is excreted by the kidneys. Plasma phcnobarbital levels are unaffected by uremia and may be used to monitor therapy.

Orher abnormalities detected on examination of uremic patients include asterixis, tremor (which may appear before asterixis), and myoclonus. These signs do not require specific therapy and usually clear as the mental status responds to dialysis or transplantation. Tetany and spontaneous carpopedat spasms also may occur.

Treating renal failure by dialysis and transplantation has given rise to a number of neurological syndromes. Because of the large number of patients being treated by these modalities, especially dialysis, it is important to recognize currently described complications and to be alert to the possibility that new syndromes will emerge as treatment modalities evolve.

Although dialysis is clearly an important life-sustaining treatment modality for patients with renal failure, two important neurological syndromes related to this modality are recognized: dialysis disequilibrium syndrome and dialysis dementia syndrome. The former is an acute syndrome that may be seen during or after a single dialysis treatment; the latter is a chronic condition that emerges subacutely or chronically after prolonged treatment by

dialysis. The treatment and prophylaxis of these syndromes have become much more successful as our understanding of their pathophysiology has improved.

Dialysis disequilibrium syndrome occurs during or immediately after treatment by either hemodialysis or peritoneal dialysis. Symptoms range from subtle signs to death, and include seizures (usually grand mal, although focal seizure's may occur), coma, and death. Other symptoms that may be encountered include disorientation, headache (often associated with nausea, restlessness, or fatigue), muscle cramps, and tremulousness. During the acute syndrome, disorganization and KEG slowing may be seen, and CSF pressure is elevated. EEGs recorded during chronic maintenance hemodialysis show that there is usually some abnormality during the treatment of stable patients, with the most significant abnormalities seen in patients reporting symptoms such as fatigue.

The symptoms of dialysis disequilibrium are probably caused by the development of cerebral edema. Uremic patients have increased serum and brain osmolality because of the accumulation of urea and idiogenic osmoles. When rapid hemodialysis is compared with slow hemodialysis, the water and osmole content of brains of the animals treated by rapid dialysis is found to be greater than in those treated by slow dialysis. Urea concentration in the CSF and the brain exceeds the plasma urea concentration in both treatments. Rapid hemodialysis also is associated with the development of CSF acidosis and a significant osmotic gradient between blood and brain not explained by sodium, potassium, chloride, or urea concentration. These conditions result in the obligatory water retention by the brain relative to blood, which causes the brain to swell. Idiogenic osmoles are probably of critical importance in the development of this syndrome. Presumably under conditions of slower dialysis, the brain has an opportunity to rid itself of idiogenic osmoles and is less susceptible to the development of edema during dialysis. The presence of acidosis in the central nervous system also may be important. Recognizing these mechanisms has led ro a rcducuoii in the severity and incidence of this potentially fatal disorder.

Dialysis dementia syndrome is now rare and is a more serious syndrome. It is a subacute syndrome of impaired memory with personality changes, apractic dysarthric speech, myoclonus, seizures {usually multifocal), and an abnormal EEG characterized by slowing with multifocal bursts of more profound slowing and spikes. Aluminum levels in the brains of patients with the syndrome are higher than the levels in controls, in uremic patients not receiving dialysis, and in uremic patients on dialysis but without the syndrome. Epidemiological studies of the relationship of the syndrome to the aluminum content of dialysate fluid have established the latter as the probable source of rhe aluminum and the most likely cause of the syndrome. In general, all areas with large numbers of cases of the dialysis dementia syndrome had high aluminum concentrations in dialysis fluid (100-500 pg/liter). Cases occurred most frequently in areas with a high aluminum content in the municipal water supply; removal of aluminum from dialysis baths, preferably by deioni/ation, has markedly reduced the incidence of the syndrome. Although it seems clear that the majority of cases of dialysis dementia can be related to aluminum in the dialysate, there are unexplained sporadic cases occurring in centers with low aluminum levels. In these patients, blood aluminum levels appear to be high, suggesting that CI aluminum absorption may be of occasional importance in the pathogenesis of the disorder,

Treatment of the syndrome has been difficult, and link-success has been reported.

METABOLIC DISTURBANCES

Disorders of Glucose Metabolism

Under normal conditions, glucose is the exclusive fuel for the brain. The brain, unlike other organs such as rhe liver and skeletal muscle, is able to store only trivial quantities of glucose as glycogen. Because brain glucose concentrations are normally low, approximately 25% of the plasma concentration, and the cerebral metabolic rate for glucose is high, [he brain is highly vulnerable in interruptions in the supply of glucose. Hyperglycemia is tolerated by the brain better than hypoglycemia, but it, too, produces neurological symptoms, largely because of osmotic effects.

Physiology

Glucose Homeostasis. After ingesting food, blood glucose levels begin to climb, wbich, in concert with a number of complex factors, leads to the release of insulin from the pancreas. Insulin has the combined effects of suppressing hepatic glucose production and fostering the storage of glucose, particularly as glycogen in the liver. After carbohydrate absorption is complete, homeostasis is maintained by hepatic glveogeunlysis. Normally, the liver contains sufficient glycogen stores to maintain the blood glucose concentration at 80-90 mg/dE for 24-36 hours. After this time, glue oncogene sis becomes the principal mechanism for maintaining adequate plasma glucose levels. Alanine and glutamine are the amino acids that, along with lactate and pyruvate, are the most important glucose precursors. Initially, most glue oncogenes is takes place in the liver, but with extended starvation, the kidney begins to produce glucose, accounting for roughly one half of the glucose produced. Approximately one half of the glucose produced in the postabsorptive state is metabolized by the brain. Because the metabolic processes of glucose homeostasis, including insulin release, glycogen break down, and gluconeogenesis, arc complex and involve the pancreas, liver, and other organs, it is not surprising that an extensive list of conditions may present as hypoglycemia.

Cerebral Glucose Metabolism. Under normal conditions with a mean CBF of 50 mL/100 g of brain per minute and a glucose concentration of approximately 5 mmol/liter, large amounts of glucose are presented to the brain at all times. Approximately 10% of this total is transported across the BBB by a glucose transporter enzyme that exhibits Michaelis-Mentcn kinetics. Once in the brain, the majority of the glucose is metabolized by the glycolytic pathway and then by the tricarboxylic acid cycle to generate the ATP needed to maintain brain function. Normally, approximately 85% of the glucose that enters the brain is metabolized in this fashion. The remaining glucose is metabolized by the hexose monophosphate shunt and converted to glycogen. After the administration of uniformly labeled glucose, label appears in carbon dioxide in the venous blood in less than 1 minute and eventually appears in a variety of amino acids, proteins, and other compounds.

Measuring cerebral glucose metabolism was revolutionized by the development of PET using an 18F-labcled glucose analogue, fluorodeoxyglucose (FDG). FDG PET scans of the brain are an important aspect in the preoperative investigations of patients with intractable seizure disorders.

Clinical Aspects of Hypoglycemia

Diagnosing hypoglycemia on the basis of clinical symptoms is ftaught with hazards. Although the majority of symptoms are attributable to nervous system dysfunction, they are extremely varied, nonspecific, and not always present, even when blood glucose levels are very low. Because of the close link between the symptoms of hypoglycemia and the brain, some authors use the term neuroglycopenia to refer to symptomatic hypoglycemia. There arc three syndromes: acute, subacute, and chronic.

The acute syndrome most commonly develops as the result of the action of short-acting insulin preparations or oral and hyperglycemics and begins with vague symptoms of malaise, feeling detached from the environment, restlessness associated with hunger, nervousness that may lead to panic, sweating, and ataxia. Patients may recogni/.e these symptoms. The symptoms respond quickly to oral or parenteral glucose. An EEG during this period may reveal nonspecific abnormalities. Attacks may end spontaneously or proceed rapidly to generalized seizures and coma, with the attendant risk of permanent brain injury. These patients may arrive in the emergency department m coma with no history.

The subacute syndrome is the most common form and occurs in the fasting state. Most of the symptoms listed for the acute syndrome are absent. In their place is a slowing of thought processes and a gradual blunting of consciousness with a retention of awareness, although amnesia for the episode is common. The diagnosis may be difficult to establish until the possibility of hypoglycemia is considctcd or routine testing uncovers the abnormality. Hypothermia is encountered frequently in this form of the disorder, and unexplained low body temperatures always should be followed by a blood glucose measurement.

Chronic hypoglycemia is rare and, if confirmed, suggests a probable insulin-secreting tumor or obsessively good control by a diabetic. Plasma hemoglobin A_{1t}. levels arc helpful in making this differential diagnosis. This syndrome is characterized by insidious changes in personality, memory, and behavior that may be misconstrued as dementia. Unlike those of the acute and subacute forms of hypoglycemia, these symptoms are not relieved by administering glucose, suggesting the presence of neuronal injury. Clinical improvement after removal of the source of the exogenous insulin is gradual, extending over periods as long as a year.

The symptoms of sweating, tremor, and the sensation of warmth may be attributed to activity of the autonomic nervous system. The inability to concentrate, weakness, and drowsiness arc attributable to neuroglycopenia. Hunger, blurred vision, and other symptoms are of uncertain cause.

Diabetics may develop hypoglycemia without being aware of the usual warning symptoms, a condition known as *hypoglycemia unawareness,* which may occur in a complete or partial form in up to 17% of all episodes in patients with type 1 diabetes (MacLeod et al. 1993). The underlying mechanisms appear to be related to the occurrence of prior episodes of hypoglycemia, altered neuroendocrine responses that regulate blood glucose levels, and central nervous system dysfunction that may interfere with symptom detection and analysis (Lingenfclser et al, 1993).

There are special problems associated with detecting hypoglycemia in neonates and children that center on the various nonspecific symptoms {e.g., pallor, irritability, and feeding difficulties) and on the variable sensitivities of individual children to a given plasma glucose concentration. As with adults, the diagnosis is most likely to be made when the physician consciously keeps his or her index of suspicion high and when glucose measurement is done routinely when there is any doubt about a diagnosis. The risk of missing the diagnosis and having irreversible neuronal injury develop in the patient justifies liberal use of screening measures and, in some cases, presumptive treatment with parenteral glucose.

Because of the complexity of glucose homeostasis, the causes of hypoglycemia arc many and varied, and a detailed discussion is beyond the scope of this chapter. In general, most authors present a physiological classification as shown in Table 62.3.

Drugs are frequently cited as an important cause of hypoglycemia. In some cases the effect of a drug may be pnk'ruiak'i.: by .i lvsnvtinn of food intake. Ai;i'-v;iyving causes have been found and should aid in the diagnosis of the disorder. In the newborn period, administration of sulfonylureas to the mother dominated as a cause of

Table 62.3: Causes of hypoglycemia

Postprandial hypoglycemia (reactive)
Postoperative rapid gastric emptying (alimentary hyperinsulinism)
Fructose in tolerance
Galactosemia
I rlkIli:- intolerance
Idiopathic
Fasting hypoglycemia
Overuse of glucose
Elevated insulin levels
Exogenous insulin (therapeutic, factitious)
Oral hypoglycemic (therapeutic, factitious)
Islet cell disorders (adenoma, nesidioblastosis, cancer)
Excessive islet cell function (prediabetes, obesity)
Antibodies to endogenous insulin
Normal to low insulin levels
Kctotic hypoglycemia
Hypermetabolie state (sepsis)
Rare extra pancreatic tumors
Carnitine deficiency
Antibodies to endogenous insulin
Underproduction of glucose
Hormone deficiencies (growth hormone, glucagon, hypoad renal ism)
Enzyme disorders
Glycogen metabolism (glycogen phosphorylase, glycogen synthetase)
Hexosc metabolism (glucose-6-phosphatase, fructose-1,6-bi phosphatase)
Glycolysis, Krebs cycle (phosphoenolpyruvate carboxykinase, pyruvate carboxylase, malate dehydrogenase)
Alcohol and probably other drugs
Liver disease (cirrhosis, fulminant hepatic failure)
Severe malnutrition

hypoglycemia. From 0-2 years, salicylate ingestion dominates. Surprisingly, alcohol predominated as a cause in the 2- to 7-year age group. Alcohol-containing cough syrups **and** alcoholic beverages were responsible. Sulfonylureas again dominate in the 11- to 30-ycat and 50 and older age groups. Alcohol predominated between the ages of 30 and 50 years. Significant numbets of patients in most age groups were encountered in whom beta blockade with propranolol was a factor in masking the symptoms of developing hypoglycemia. The use of beta blockers in patients receiving insulin or oral hypoglycemic agents therefore should be avoided. A number of risk factors have been recognized that predispose to the development of hypoglycemia. These include (in addition to diabetes) decreased caloric intake (usually related to severity of some illness or disruption of dietary routines), uremia, livet disease, infection, shock, pregnancy, neoplasia, and burns.

Hypoglycemia is associated with a substantial morbidity. A study of 600 patients with diabetes showed that the frequency of severe hypoglycemia was 1.60 episodes pet patient per year and that it occurred twice as often in patients with the type 1 form of the disorder (MacLeod et al. 1993). Among patients with severe episodes of hypoglycemia, injuries and convulsions occurred at rates of 0.04 and 0.02 episodes per patient per year. Five patients had automobile accidents caused by hypoglycemia. Patients with episodes of severe hypoglycemia were more likely to have had priot sevete episodes, were on insulin longer, and had lower hemoglobin $A]_c$ concentrations. A southern California medical examiner found 123 deaths caused by hypoglycemia in a series of 54.S.50 autopsies. The risk of death is highest in patients with the most sevete hypoglycemia and the largest number of risk factors. Among hospitalized patients, whites have the lowest mortality (approximately 6%), whereas black and Hispanic patients have mortalities of 30% and 46%, respectively.

Hypoglycemia is a medical emergency, and all patients suspected of being hypoglycemic, including all patients with coma of unknown cause, should be treated with parentetal glucose after adequate blood samples ate obtained fot laboratory testing. It is prudent to dtaw extra blood so that insulin and hemoglobin $A|_e$ levels can be measured if indicated by the patient's subsequent coutse. These measures are particularly important in patients with obscure histories and in whom factitious hypoglycemia may be present. The total amount of glucose administeied may be of little consequence if the patient is found to have a notmal or elevated plasma glucose concenttation. Exogenous glucose is harmful to the brain during hypoxia or ischemia, and caution must be exercised in administering glucose to this group of patients.

Clinical Aspects of Hyperglycemia

Although thetc ate many causes of hyperglycemia, diabetic ketoacidosis (DKA), nonketotic hyperosmolar coma, and iatrogenic factors, such as parenteral hyperalimentation, are the most important. DKA is a relatively common disorder affecting patients with type 1 diabetes. It is frequently precipitated by an infectious process in a patient who has been otherwise stable, develops ovet sevetal days, and is heralded by polyuria and polydipsia caused by the osmotic diuresis produced by glucosuria. These symptoms ate followed by anorexia, nausea, disorientation, and coma. On physical examination, sustained hyperventilation is common, especially in patients with severe acidosis. The diagnosis is frequently suspected on the basis ot clinical findings, but labotatory data, including the plasma glucose, arterial blood gases, electrolytes, and an appropriate test for ketone bodies, ate essential fot confirming the diagnosis and management.

Nonketotic hyperosmolar coma, by contrast, is a feature of type 2 diabetes and is thus encountered in older patients, commonly as the first manifestation of the disease. This syndiome evolves more slowly than DKA, and the period of polyuria is more prolonged, leading to much mote severe dehydration. Because glucose is a less effective dipsogen than other solutes, watet-sceking behavior is not as strong in this group of patients as it is in patients with

hypematremic hyperosmolality, thus promoting the development of dehydration. Suppressed water-seeking behavior, combined with the inhibitory effect of hypertonicity on insulin release, can lead to severe dehydration and hyperglycemia that can be in excess of 2000 mg/dL. The disorder's signs and symptoms are those of hyperosmolality, hypovolemia, and cerebral dysfunction, with epileptic si'i/LLivs inYiirnns! in MUHC individuals. Precipitating factors include infection, gastroenteritis, pancreatitis, and, occasionally, treatment with glucocorticoids or phenytoin. Because many total parenteral nutrition protocols use solutions with high glucose contents, hyperglycemia is a potential complication of their use.

DKA is an insulin-deficient state, and insulin is the cornerstone of therapy. In the absence of insulin, peripheral glucose uptake and glycogen formation are reduced, and glycogenosis and lipblysis are accelerated, leading to the formation of acidic ketone bodies and hyperglycemia. When plasma glucose levels exceed the renal threshold (usually approximately 180 mg/dL), glucosuria and a forced osmotic diuresis ensue. The treatment of DKA is designed to reverse these pathophysiological abnormalities and consists of administering insulin to enhance glucose uptake, enhance glycogen formation by nonccrchral tissues, and reduce the rate of ketone body formation that occurs during low-insulin, high-glucagon states that promotes the entry of fatty acids into mitochondria, where they are converted to ketones. Replacing fluid and electrolytes also is required, as is treatment of precipitating factors. It is important to remember that overly vigorous treatment with rapid restoration of plasma osmolality to normal levels can lead to the development of cerebral edema (see Complications of Treatment, later in this chapter).

Neurologists may become involved in the diagnosis and management of patients with nonketotic hyperosmolar coma when a patient has no prior history of diabetes and is brought to the emergency department with unexplained coma or seizures. Because hyperosmolality and the associated hypovolemia are usually much more severe in this condition than in DKA, maintaining an adequate blood pressure and cardiac output are the first priorities in treatment. One or two liters of normal saline should be given rapidly to restore blood volume and to begin to reduce plasma osmolality. Additional fluid and insulin therapy then can be initiated as indicated by laboratory and clinical data. These patients may require intensive monitoring with arterial and Swan-Ganz catheters to monitor the circulatory system status and avoid inducing a volume overload; at the same time, adequate amounts of fluid should be given to restore osmolality to normal levels. The exact mechanisms leading to the development of the syndrome, particularly the absence of ketosis, are not fully explained.

ComplicationsofTreatment. AlthoughtreatmentofDKA has improved, the mortality rate is still appreciable. The majority of patients who succumb do so because of cardiovascular collapse or from complications of the precipitating factor. A small number of patients die unexpectedly when laboratory and clinical indicators all show initial improvement,

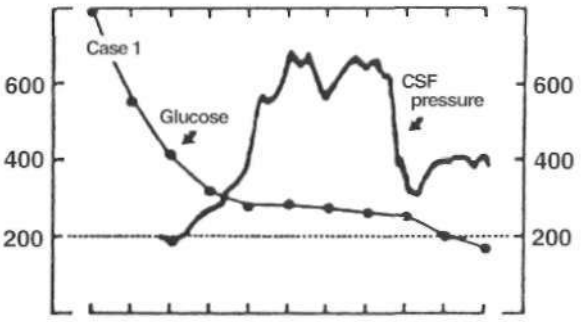

FIGURE 62.4 Blood glucose and intracranial pressure during treatment of diabetic ketoacidosis. The untreated hyperosmolar state leads to the intracerebral accumulation of idiogenic osmoles. As blood glucose and osmolality levels decrease during treatment, free water niters the brain more rapidly than idiogenic osmoles arc shed, leading to an increase in intracranial pressure from the swollen brain. This mechanism presumably operates in all cases in which hyperosmolality is corrected rapidly. CSF = cerebrospinal fluid. (Reprinted with permission from Clements, R. S. Jr, Blumenthal, S. A., Morrison, A. D., et al. 1971, "Increased cerebrospinal fluid pressure during treatment of diabetic kcroses," *Lancet,* vol. 2, pp. 671-675.)

Clinically, patients with DKA who die experience rapid neurological then cardiovascular deterioration. Postmortem examinations of the brains show lesions similar to those seen in acute asphyxia, including capillary dilation with perivascular and pericellular edema. Death is heralded by a rapid evolution of signs and symptoms indicating an increase in intracranial pressure. Approximately one half of patients die during the initial episode of DKA. The rate and degree to which the plasma glucose level is lowered is not a major risk factor for death.

Some degree of cerebral edema attends the treatment of most patients with DKA, occasionally to the high level of 600 mm CSF pressure, as shown in Figure 62.4.

The data suggest that at least mild, clinically silent cerebral swelling may be much more common than is realized in cases of DKA. Rare, unknown factors appear to trigger a malignant increase in intracranial pressure in a small number of patients, producing a syndrome characterized by rapid neurological deterioration and death caused by neurological and circulatory collapse. Published experience suggests that if this diagnosis is made, prompt, aggressive treatment of cerebral edema is indicated, preferably using intracranial pressure monitoring as a guide to therapy. Nevertheless, there is still a high mortality.

Glucose and Cardiopulmonary Resuscitation. A number of studies suggest that hyperglycemia is associated with an

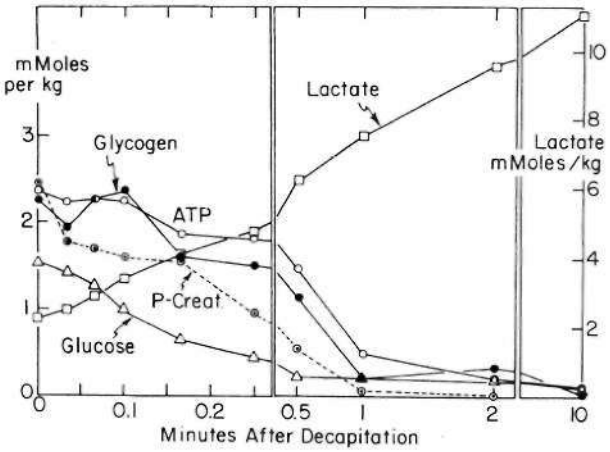

FIGURE 62.S Neurochemical consequences of decapitation. Experimental animals were decapitated and then frozen at various times thereafter. Brains were assayed for metabolites, as shown in the figure. As can lie seen, high-energy phosphates are depleted rapidly. Glucose and glycogen also are consumed, generating lactate, as metabolism changes from the normal aerobic condition to an anaerobic state. The changes shown in this figure are analogous to those following acute hypoxia or cerebral infarction. ATP = adenosine triphosphate; P-Crcat = phosphocreatine. (Reprinted with permission from Lowry, O. H. & Pasonneau, J, V. 1964, "The relationships between substrates and enzymes of glycolysis in brain," / *Biol Chem*, vol. 239, pp. 31-42.)

increase in the severity of complications of cerebral ischemia and hypoxia. The presumption is that blood, and hence brain, glucose levels are higher in hyperglycemic individuals and that this glucose produces more lactate during the hypoxic-ischemic insult. This sequence is shown in Figure 62.5, in which the metabolic consequences of decapitation in animals are shown. Glucose is metabolized anaerobically to lactate, which, with the hydrolysis of ATP, causes acidosis. A large number of experimental studies suggest that cerebral acidosis is an important determinant of brain injury, including acidosis associated with lactate production during ischemia. The results of these studies have been extended to humans, in whom a less favorable outcome was suggested for stroke patients with diabetes and hyperglycemia compared with euglycemic diabetic stroke patients.

A number of animal studies have shown that the risk of neurological injury during resuscitation from cardiopulmonary arrest increases if exogenous glucose is administered. This issue has been investigated in humans by Longstretch et al. (1993), who randomly administered 5% dextrose in water or half-normal saline while treating out-of-hospital cardiopulmonary arrest. These treatments did not produce significant differences among three measures of outcome: awakening, survival to admission to the hospital, or discharge from the hospital. However, because patients with ventricular fibrillation or asystole with high blood glucose levels at the time of admission to the hospital were less likely to awaken than patients with lower blood glucose levels, they concluded that it is appropriate to restrict the amount of glucose administered during cardiopulmonary resuscitation.

Disorders of Water and Electrolyte Metabolism

Patients with abnormalities of water and electrolyte metabolism frequently exhibit signs and symptoms of cerebral dysfunction. Typically, these patients have altered states of consciousness or epileptic seizures that herald the onset of the abnormality. The vulnerability of the nervous system to abnormalities of water and electrolyte balance arises from changes in brain volume, especially the brain swelling that may be associated with water intoxication; the abnormalities are symptomatic almost immediately because the brain is enclosed by the rigid skull. The role played by electrolytes is also important in maintaining transmembrane potentials, neurotransmission, and a variety of metabolic reactions, such as those involving the role of calcium and calmodulin. Although most clinicians are aware of the importance of water and electrolyte disturbances as a cause of brain dysfunction, the importance of the brain in the control of water and electrolytes is less well appreciated.

Disordered Osmolality

Osmotic Homeostasis. The serum, and hence whole-body osmolality, are regulated by complex neuroendocrine and renal interactions that control thirst and water and electrolyte balance. When serum osmolality increases, the brain loses volume; when osmolality falls, the brain swells, Events related to water loss are illustrated in Figure 62.6. The brain has little protection in terms of volume changes when an osmotic stress is acute. Examples of acme osmotic stress may be found in patients with heat stroke, inadvertent solute ingestion (particularly in infants), massive ingestion of water (which may be psychogenic), hemodialysis, and diabetics with nonketotic coma. When osmotic stress is applied more slowly over a longer period, the predicted volume changes arc smaller than would be expected. The mechanisms that underlie these protective adaptations are not known completely but involve the gain of amino acids in the case of the hyperosmolar state and the loss of potassium in the hypo-osmolar state. Experimental studies have failed to identify all of the osmotically active particles that must exist in the brain after a given osmotic stress is applied. These unidentified molecules are called *idiogenic osmoies.*

Hypo-osmolality and Hyponatremia. Hypo-osmolality almost always is associated with hyponatremia. The diagnosis usually is made by laboratory testing. Conditions associated with hyponatremia are shown in

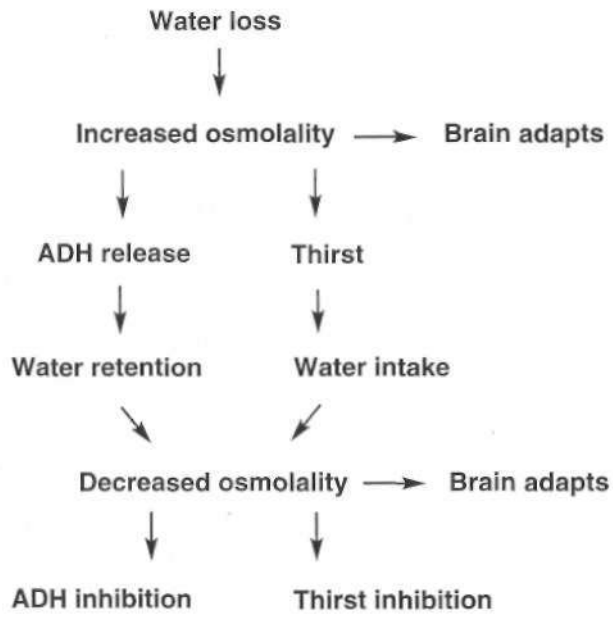

FIGURE 62.6 Water balance and tlie brain. A reduction in water (or an increase in water loss or solute gain) stimulates tbirst and vasopressin release, leading to increased water conservation and intake, which in turn reduces vasopressin levels and ends thirst. Excessive water intake or excessive water loss leads to hypo-osmolality or hyperosmolality and the loss or gain of osmotically active particles in the brain, respectively. Excessively rapid treatment of these conditions may lead to the development of neurological symptoms. ADH = antidiuretic hormone,

Table 62.4. When hyponatremia is encountered, a measurement of serum osmolality should be performed to differentiate true from pscudo hypo-osmolaliry, which may be encountered in patients with lipemic serum or in neurological patients treated with mannitol.

A large and diverse group of neurological conditions is associated with hyponatremia as a result of SIADH,

Table 62,4: Causes of hyponatremia

Combined water and sodium depletion (hypovolemia)
Renal loss
Primary renal disease
Osmotic diuresis (glucose, mannitol)
Adrenal insufficiency
Nonrenal loss
Gastrointesfinal (diarrhea, suction, vomiting)
Transcutaneous (sweating, burns)
Sequestration (ascites, peritonitis)
Hyponatremia without water loss
Edema with water and sodium retention
Dilutional (iatrogenic, psychogenic)
SILA .ell ss ndrome
Hyperosmotic (hyperglycemia or mannitol administration)
Syndrome of inappropriate antidiuretic hormone secretion (see Table 62,5)
Artifact (laboratory error, hyperlipemia)

Table 62.5: Causes of the syndrome of inappropriate antidiuretic hormone secretion

Malignant neoplasms
Small cell carcinoma of lung
Pancreas
Thymoma
Mesothelioma
Lymphoma (lymphosarcoma, reticulum cell sarcoma, Hodgkin's disease)
Bladder, ureter, prostate
Duodenum
Ewing's sarcoma
Central nervous system disorders
Infections (meningitis, encephalitis, abscess, Rocky Mountain spotted fever)
Trauma
Subarachnoid hemorrhage
Infarction
Guillain-Barre syndrome
Acute intermittent porphyria
Hydrocephalus
Neonatal hypoxia
Shy-Drager syndrome
Delirium tremens
Systemit lupus erythematosus
Drugs
Vasopressin
Oxytocin
Vine a *alkaloids*
Thiazides
Chlorpropamide
Phcnothia zincs
Carbamazepine
Clofihratc
Nicotine
Monoamine oxidase inhibitors
Tricyclic antidepressants
Cyclophosphamide
Narcotics
Pulmonary diseases
Tuberculosis
Other pneumonias
Abscess or cavity
Empyema
Cystic fibrosis
Obstructive airway disease
Pneumothorax
Asthma
Positive pressure ventilation
Miscellaneous causes
Hypothyroidism
Acute psychosis
Postoperative state
Idiopathic

as shown in Table 62.5. SIADH is characterized by hyponatremia in the face of normal or increased blood volume, normal renal function, and the absence of factors that normally operate to produce antidiuretic hormone

release. The syndrome may be relatively asymptomatic, in which case water restriction is the treatment of choice. In more severe cases, hypertonic saline combined with a diuretic may be required. Overly zealous treatment may produce central pontine myclinolysis (sec Therapy, later in this chapter). Chronic syndromes have been treated successfully with a variety of drugs, including the tetracycline dcmeclocycliue, which interferes with the action of antidiuretic hormone on the renal tubules.

Great care must be taken when considering the diagnosis of SIADH in patients with subarachnoid hemorrhage. Patients with subarachnoid hemorrhage, hyponatremia, and reduced blood volume may not have true SIADH. In these patients fluid restriction may lead to further volume reduction and cerebral infarcts during the period of the highcsi risk for vasospasm, The mechanisms underlying this phenomenon are not clear, but may be related to the complexity of the peptidergic neurotransmitter systems in the vicinity of the third ventricle and to the possibility that they are damaged by the ruptured aneurysm. Damage is especially likely with an aneurysm on the anterior communicating artery. Hyponatremia occurs in approximately 1 % of patients with recent surgical procedures. Because the symptoms are frequently mild or attributed to the surgery itself, this diagnosis may be missed. Typically, these patients seem to do well in the immediate postoperative period and then develop symptoms and signs of encephalopathy. Men and postmenopausal women are less likely to develop postoperative hyponatremia than women who are still menstruating. Complications, such as respiratory arrest, are particularly likely to occur in menstruating women and occur at higher serum sodium concentrations than in men or menopausal women. Thus it is important to be particularly vigilant when evaluating younger women with postoperative encephalopathy.

Therapy. The treatment of hyponatremia always has been controversial and has become more so since the link between hyponatremia and the subsequent development of central pontine myclinolysis was recognized and experimental replication of the syndrome achieved. Harris et al. *(1993)* reviewed this problem. They were not able to identify rite rue a I which sera m sodium was con,.., led, the absolute magnitude of the correction, or the type of solution infused as a factor that predisposed to the development of central pontine myelinolysis. They noted that there are undoubtedly thousands of patients with symptomatic hyponatremia who have been treated successfully using a large number of protocols but who have not been reported. This makes it impossible to estimate the risk of central pontine myclinolysis associated with any given treatment regimen. However, because they were unable ro identify any cases of central pontine myelinolysis among the 185 published examples of symptomatic hyponatremia (published since 1954) in which patients were allowed to "self-correct" during a period of water restriction (as opposed to the infusion of saline solutions of varied concentrations), they suggested that the preferred therapy of hyponatremia might be water restriction and discontinuing diuretics. Fraser and Arieff (1997) recommend the use of hypertonic sodium chloride for the treatment of symptomatic hyponatremia. Infusions should be adjusted to increase the plasma sodium concentration at a rate of 1 mmol/liter per hour. Complicating factors such as evidence for cerebral edema or seizures require more rapid correction of the deficit. A rate of 4-5 mmol/liter per hour was suggested. Hypertonic saline therapy may he discontinued when patients become asymptomatic, when the serum sodium reaches 120-125 mmol/liter, or when the plasma sodium has increased by a total of 20 mmol/liter. Protection of the airway and ventilatory support may he required. Diuretics acting at the loop of Henle, such as furosemide, may be required. It is important to monitor electrolytes at frequent intervals (every 2 hours) and to avoid the administration of excessive amounts of sodium and the production of hypemarremia.

Hyperosinoiality. Hyperosmolality is less common than hypo-osmolality but may present with similar symptoms or evidence of intracranial bleeding caused by the tearing of veins that bridge the space between the brain and dural sinuses. Usually, hyperosmolality is diagnosed by laboratory findings of an elevated scrum sodium or, perhaps more commonly, hyperglycemia in diabetics. The syndrome frequently is caused by dehydration, especially in hot climates; by uncontrolled diabetes with or without ketosis; and, less frequently, by central lesions that reset the osmotically sensitive regions of the brain. As with hypo-osmolality, cautious correction of the defect is important. Replacement should be given orally, if possible. The first half of the deficit can be given rapidly, but the second half must be given with much more caution to avoid producing iatrogenic brain swelling as the whole-body osmotic pressure decreases.

Chronic hyperosmolality is associated with relative brain volume preservation as a result of the production of idiogenic osmoles, as described earlier. Administering free water at a rate that exceeds the rate at which the brain is able to rid itself of idiogenic osmoles is associated with the development of paradoxical brain edema that occurs at a time when serum glucose and electrolyte concentrations are normalized. This is illustrated by the data in Figure 62.4, in which the CSF pressure was measured continuously as hyperglycemia caused by diabetes mellitus was corrected. The increase in intracranial pressure is undoubtedly caused by adapted brain cells imbibing free water as serum osmolality decreases in response to therapy. If patients undergoing treatment for hyperosmolar states develop new neurological signs, including altered consciousness and seizures, rhe diagnosis of brain swelling should be considered, Mannitof treatment to restore osmolality to the

prior elevated level may be required to prevent death caused by brain swelling.

Disorders of Calcium

Hypercalcemia and hypocalcemia both have diverse causes associated with disordered parathyroid gland function and a variety of oilier conditions. Under normal circumstances, approximately one half of the total serum calcium is bound to proteins, mainly albumin, and one half is in the ionized form, the only form in which it is active. When there is doubt about the ionized calcium concentration, as in patients with hypoalbuminemia, direct measurement of ionized calcium with ion-sensitive electrodes may be required.

Hypercalcemia is associated with hyperparathyroidism; granulomatous diseases, especially sarcoidosis; treatment with drugs including thiazide diuretics; vitamin D; calcium itself; tumors that have metastasized to bone; and thyroid disease. Many cases are idiopathic. The symptoms and signs of hypercalcemia may be protean. Severe hypercalcemia affects the brain directly, causing coma in extreme cases. In this group of patients, metastatic tumors are common, especially multiple myeloma and tumors of the breast and lung. Cancer patients seem to be particularly vulnerable to developing hypcrcaleemia after a change in therapy. Less severe hypercalcemia may cause altered consciousness with a pseudodementia syndrome and weakness. GI, renal, and cardiovascular abnormalities also may be present.

Severe hypercalcemia is life threatening. Initial treatment consists of a forced diuresis using saline and diuretics. Because the volumes ol saline thai are required ma\ he large, a central venous or Swan-Ganz catheter may be needed lo monitor thcrap-.. OIKC the initial phase ol treatment is accomplished, further management is determined by the cause of the hypcrcaleemia.

f lypocalcemia usualh is associated with hypoparathyroidism. The neurological symptoms are caused by the enhanced excitability of the nervous system. Symptoms include paresthesias around the mouth and fingers, cramps caused by tetanic muscle contraction, and, in more extteme cases, epileptic seizures. In more chronic hypocalcemia, headache caused by increased intracranial pressure may occur, and extrapyramidal signs and symptoms such as chorea or parkinsonism may be encountered. These patients may have calcification of the basal ganglia, evident on computed tomographic scans of the brain. The physical examination should include attempts to elicit Chvostek's and Trousseau's signs. Cataracts and papilledema may be seen.

Severe hypocalcemia should be treated with infusions of calcium to treat or prevent epileptic seizures or laryngeal spasms, both of which are life-threatening but unusual complications. Chronic therapy usually involves the administration of calcium and vitamin D. Care must be taken to avoid hypercalcemia and hypercalciuria. Consultation with an endocrinologist is prudent, but continued neurological care may be necessary, especially in patients with extrapyramidal syndromes, who may require specific treatment.

Disorders of Magnesium

Hypermagnesemia is an unusual condition because ol unease with which normal kidneys act to preserve magnesium homeostasis. The most frequent cause of hypermagnesemia is infusions given to treat symptoms of eclampsia, in which its effect to lower blood pressure and inhibit the nervous system is desirable. Care must be observed in administering magnesium to patients with renal failure. This group of patients is the most vulnerable and the most likely to develop hypermagnesemia because the kidneys' homeostatic function is impaired. Hypocalcemia potentiates the effects of excess magnesium. Severe hypermagnesemia is life threatening, and concentrations in excess of 10 mEq/liter must be treated. Discontinuation of magnesium preparations usually suffices. When cardiac arrhythmias are present or circulatory collapse is possible, calcium must be infused, especially when hypocalcemia is present.

Isolated Hypomagnesemia is unusual. Magnesium deficiency usually occurs in patients with deficiencies of other electrolytes. Hypomagnesemia may result from a diet deficient in magnesium, including prolonged parenteral alimentation with insufficient or no magnesium replacement, malabsorption, and alcoholism. Excess magnesium loss from the GI tract or the kidneys also can lead to calcium deficiency. Magnesium deficiency is usually part of a complex electrolyte imbalance, and accurate diagnosis and management of all aspects of the state are necessary to ensure recovery.

Pure magnesium deficiency has been produced experimentally and is expressed primarily through secondary reductions in serum calcium levels in spite of adequate dietary calcium intake. Ultimately, anorexia, nausea, a positive Trousseau's sign, weakness, lethargy, and tremor develop but are rapidly abolished by magnesium repletion. Balance studies indicate that magnesium deficiency causes a positive sodium and calcium balance and a negative potassium balance. Magnesium is necessary for proper mobilization and homeostasis of calcium and the intracellular retention of potassium. Some of the effects of magnesium depletion are secondary to abnormalities of potassium and calcium metabolism.

Disorders of Manganese

Manganese poisoning occurs primarily in manganese ore miners and causes parkinsonism. As presented in the section on HE, there is increasing evidence rhat accumulation of this metal in the brain causes the Tl MR! hyperintensities and may be associated with disorders of dopaminergic neurotransmission.

DRUG OVERDOSE AND TOXIC EXPOSURES

The tentative diagnosis of intentional or accidental drug overdose must be considered during the course of the evaluation of almost all emergency department patients with altered behavior (see Chapter 64B). Most overdoses are attributable to drugs in one of six groups that account for more than 80% of all positive laboratory results. They are, in order of decreasing frequency, ethanol, benzodiazepines, salicylates, acetaminophen, barbiturates, and tricyclic antidepressants. Table 62.6 classifies dtugs into four groups based on the usefulness of toxicotogieal information and the relationships between drug levels and symptomatology. Regional poison control centers usually are staffed by well-informed, helpful personnel and should be consulted when further information is needed or there is uncertainty about the contents of specific products. Reported patterns of drug overdoses vary among communities and with time. Illicit drug availability varies substantially by region and evolves constantly. So-called designer drugs arc unpredictable. As benzodiazepine use has increased and replaced barbiturates used as sleeping pills, barbiturate intoxications have declined. The prevalence of overdose varies as a function of the numbet of prescriptions written.

Miscellaneous Disorders

Neurologists may be asked to evaluate patients with vague complaints such as headache, poor concentration and memory, and other symptoms to determine whether toxin exposure is a contributing factor. These requests may occur during the coutsc of ordinary patient care, litigation, or more systematic population-based investigations, hi some instances, the doctor-patient relationship is clouded by political or legal ramifications of the questions asked and the possible answers. Concerns about Gulf War syndrome typify this dilemma. Many veterans of the Persian Gulf conflict contend that a variety of problems ranging from the complaints outlined previously to more definitive problems, such as amyotrophic lateral sclerosis, a variety of cancers, birth defects among their children, and others, are the consequence of exposure to chemicals, including insecticides, pytidostigmine bromide, and nerve agents. This anxiety was heightened by the revelation in the summer of 1997 that the destruction of a munitions depot in Khamisiyah, Iraq, in March 1991 released a cloud of sarin that exposed almost 100,000 troops to this nerve agent. Kven though there were no documented acute effects of sarin on the exposed combatants, suspicion and distrust of the federal authorities charged with evaluating the Gulf War veterans were heightened by the chatges of cover-up that were inevitable because of the delay in acknowledging the exposure. In spite of investigations that have failed to show excess mortality in Gulf War veterans, increases in birth defects in their children, or more frequent hospitalizations, this issue is far from settled. The findings of a Presidential Advisory Council and an independently chartered commirtce appointed by the National Academy of Sciences Institute of Medicine also have failed to satisfy those who believe that Gulf War syndrome is a real entity.

Tahlc 62.6: Characteristics of drug overdose

1. Toxicity predicted by drug level—specific therapy determined by toxicology
   Acetaminophen, digoxin, ethylene glycol (not detected by most systems), lithium, salicylates, theophylline
2. Toxicity parallels drug level—supportive care required
   Barbiturates, ethanol, phenytoin
3. Toxicology confirms only clinical impression—clinical decisions determined by direct patient evaluation
   Cyanide, narcotics, organophosphates, tricyclic antidepressants
4. Toxicity correlates poorly with drug level—clinical decisions determined by direct patient evaluation
   Amphetamines, benzodiazepines, cocaine, hallucinogens, neuroleptics, phencyclidine, phenylpropanolamine

Source: Based on Mahoney, J. D., Gross, P. L., Stern, T. A., et al. 1930, "Quantitative scrum toxic screening in the management of suspected drug overdose," *Am} Emer Med,* vol. 8, pp. 16-22.

A similar and parallel situation has arisen among some who complain that pesticide exposure has affected their health. Because many pesticides are organophospbate cholinesterase inhibitors (OPCIs; differing from nerve agents in potency), links between exposure and a variety of complaints have been claimed or sought. "Worldwide, OPCIs are a common cause of death in agricultural workers, particularly in underdeveloped nations. In Western countries, death is less common, but accidental or intentional exposure may occur (ingestion by children, overdose among adults and agricultural workers). OPCIs may cause peripheral neuropathy, as described in Chapter 64B, and a subacute condition characterized by proximal weakness and respiratory failure known as intermediate syndrome. Comparisons among control populations and OPCI-exposed subjects have shown differences in performance on certain neuropsychological tests, buttressing claims of disability and distress among exposed individuals. Epidemiological, case control, and animal model studies all suggest that pesticide exposure may be related to the subsequent development of Parkinson's disease (Lockwood 2000). Efforts to redefine pesticide tolerances, the maximal permissible concentration of pesticides in food, arc complicated by predictable disagreements between pesticide manufacturers and public lie,l till groups. Recently [he pesticide industry has sponsored experiments that appear to be designed to raise tolerances. In these studies, pesticides have been administered to volunteers who are monitored for adverse effects. Ethical challenges to these studies arc unresolved.

The clinical neuroscience community faces a major challenge in aiding regulatory bodies as they develop

rules that govern exposure to potential toxins that respect the boundaries of science while providing adequate protection for the public and social accountability.

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Chapter 63
Deficiency Diseases of the Nervous System

Yuen T. So and Roger P. Simon

Undernutrition causes a wide spectrum of neurological disorders. Although deficiency of almost any nutrient can lead to some kind of neurological symptoms, the B vitamins (thiamine, pyridoxine, nicotinic acid, and vitamin B12), vitamin E, and perhaps folic acid are the most important to the nervous system. Despite great advances since the turn of the twentieth century, nutritional deficiency is still a serious worldwide problem. Kwashiorkor and marasmus arc endemic in many underdeveloped countries. The problem in Western countries is usually the result of dietary insufficiency from chronic alcoholism or malabsorption states from gastrointestinal (GI) diseases. Drugs such as isoniazid and hydralazine also interfere by altering vitamin metabolism.

Most causes of nutritional deficiency, whether dietary or malabsorptive, do not selectively deplete a single vitamin. This is especially true among the malnourished populations in underdeveloped countries, in which the diet may lack more than one vitamin, and overlapping neurological syndromes are the result. One exception is pernicious anemia, in which malabsorption is restricted to vitamin Bu-

Individual vitamin requirements are influenced by many factors. The daily need of thiamine and nicotinic acid, important compounds in energy metabolism, increases proportionally with increasing caloric intake and energy need. For example, symptoms of thiamine deficiency often occur in at-risk patients during periods of vigorous exercise and high carbohydrate intake. Other factors, such as growth, infection, and pregnancy, may worsen deficiency states, although the relationship is not precisely known. Vitamin requirement is genetically determined in some cases, as in some infants dependent on unusually large doses of pyridoxine to prevent seizures. Low scrum levels of vitamins in many individuals do not necessarily correlate with the occurrence of symptoms, and laboratory data should always be interpreted in light of clinical findings.

The most frequent neurological deficits fall into several categories (Table 63.1). Peripheral neuropathy, the most common, occurs with the deficiency of many vitamins. Cerebral dysfunction, ranging from mental dullness to acute encephalopathy, may occur with deficiency of vitamin $B]_2$ or in Wernicke-Korsakoff syndtome. Myelopathy usually suggests a deficiency of vitamin ii_{l2}, although vitamin E

Tabic 63.1: Neurological manifestations in deficiency diseases

Neurological manifestations	*Associated nutritional deficiencies*
Peripheral neuropathy	Thiamine, vitamin $B_{1;}$, vitamin E, pyridoxine, folate
Dementia, encephalopathy	Vitamin B|>, nicotinic acid, thiamine, folate
Seizures	Pyridoxine
Myelopathy	Vitamin B_{12}, vitamin E, folate
Myopathy	Vitamin D, vitamin E
Optic neuropathy	Vitamin B12, thiamine, folate, and probably others
Spinocerebellar degeneration	Vitamin ¥.

and folate have been implicated in rare instances. A spinocerebellar degeneration may occur with severe vitamin E deficiency.

VITAMIN B_{12} DEFICIENCY

The terms *vitamin B\2* and *cobalamin* are used interchangeably in the literature. Cobalamins are abundant in meat, fish, and most animal by-products. Although vegetables are generally devoid of the vitamin, strict vegcranu:^ alnu.M ik'\cr develop a clinical deficiency, because only 1 ug of vitamin $B|_2$ is needed per day, and an adequate amount is available in legumes. Intestinal absorption of vitamin R_{12} requires the presence of intrinsic factor, a binding protein secreted by gastric parietal cells; inadequate availability[7] of intrinsic factor is probably the most common cause of vitamin Bi_2 malabsorption. The transport protein transcobalamin II binds Bj_2 and is important in transporting it to the liver. Deficiencies may also occur with derangement of this transport process.

Clinical Features

The onset of symptoms is insidious, with paresthesias in the hands or feet in the majority of patients. Weakness **and** unsteadiness of gait are the next most frequent complaints. Lhermitte's sign may be present, and a myelopathy may develop. Cerebral symptoms, such as mental slowing, depression, confusion, delusions, and hallucinations, are quite common, and occasionally patients present with only cognitive or psychiatric symptoms. Many patients also complain of dyspepsia, flatulence, altered bowel habits, or other GI symptoms.

On examination, most patients show signs of both peripheral nerve and spinal cord involvement, although either can be affected first in the early stage of the disorder. Loss of vibration or joinr position sense in the legs is the most consistent abnormality. If impaired position sense is severe, Romberg's sign may be present. Tendon reflexes **often** are decreased or absent in the legs, although the effect on reflexes is quite variable. Motor impairment, if present, results from pyramidal tract dysfunction and is most sevete in the legs, ranging from mild clumsiness and byper-reflexia to spastic paraplegia and extensor plantar responses. Visual impairment occasionally is encountered and may antedate other manifestations of vitamin deficiency; ophthalmological examination reveals bilateral visual loss, optic atrophy, and centrocecal scotomata. Brainstem or cerebellar signs, or even reversible coma, may occur.

Laboratory Studies

As most patients present with clinical features suggesting a myelopathy or encephalopathy, imaging studies are necessary to exclude structural causes. Magnetic resonance imaging (MRI) abnormalities may be seen in tin- lateral or posterior columns in patients with subacute combined degeneration (Figure **63.1).** Both treatment-reversible T2

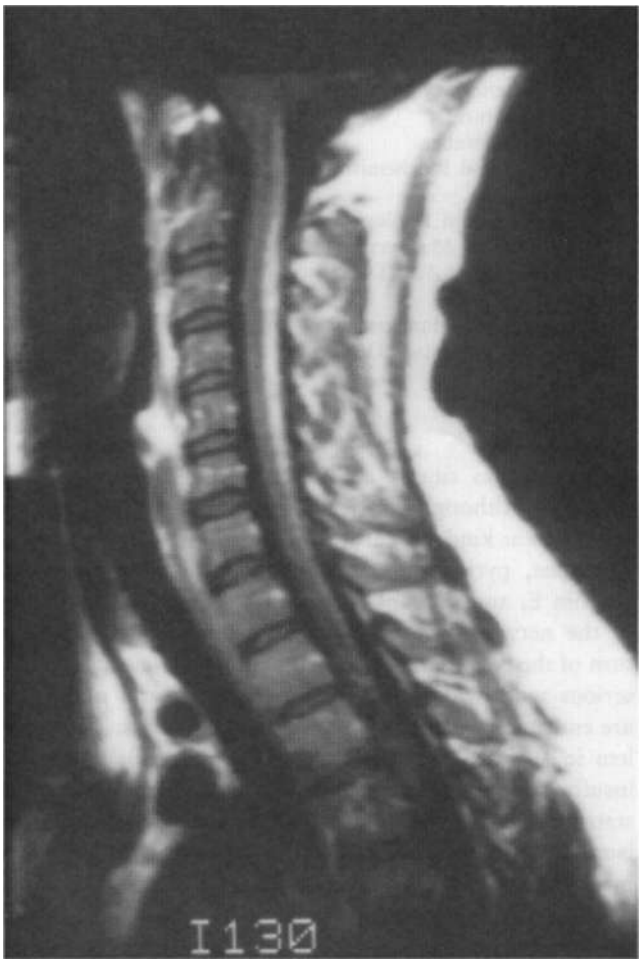

FIGURE 63.1 Vitamin $B|_2$ deficiency myelopathy. Gadolinium enhanced, Tl-weighted cervical and upper thoracic MRI image •Jiriv-.Ty. iin:ki'd ailiancc-mc-nt ol pnstcrioi i><;,: o! .:. ill yen nld African-American woman wheelchair bound due to an 18-month history of progressive myelopathy; B12 level: 60 pg/mL. (Courtesy R. Laurcno.)

enhancement and spinal cord swelling have been described (Locatelli et al. *1999).* Based on case reports (reviewed by Locatelli), symptoms or signs may precede MRl changes by at least 2 weeks, are most prominent at 3-5 months, and can normalize over as few as 10 weeks with treatment. Residual imaging abnormalities may persist after treatment, and MRl resolution may be greater than clinical normalization. Radiographically, myelopathy and encephalopathy seem distinct. The encephalopathy may be accompanied by multiple deep white matter lesions seen on T2-wcighted images, which become confluent with disease progression. Radiographical improvement is seen within a few months, and clinical normalization occurs over a few years of treatment (Stojsavljevic et al. 1997),

Nonspecific electroencephalographic abnormalities may be present, and follow-up electroencephalography in selected cases can provide one of the earliest physiological responses to vitamin B12 therapy. Visual and somatosensory responses are frequently abnormal; nerve conduction studies show abnormally small or absent sural nerve sensory potentials in approximately 80% of patients, providing evidence for an axonal polyneuropathy.

Serum assay of cobalamin provides a direct assessment of its bioavailability, although it is important to recognize certain limitations. Most of the cobalamins present in serum are bound to several transport proteins, trauscobalamin (TC) II and haptocorrins (formerly TC I and III). The cobalamin bound to TC TI is the most important physiological fraction, but it accounts for only 10-30% of the serum level measured by standard laboratory methods. Serum levels are influenced by conditions that affect rranscobalamin concentrations. Myeloproliferative and hepatic disorders may raise the concentration of haptocorrins and cause a falsely normal serum level. A misleadingly high serum level also may result from the presence of an abnormal cobalamin-binding protein. In contrast, pregnancy and contraceptives may give falsely low measurements in the absence of deficiency. Folate deficiency also causes falsely low cobalamin serum level that corrects after folate replacement.

The classic hematological manifestation of pernicious anemia is a macrocytic anemia. Erythrocyte or bone marrow macrocytosis or hypersegmentation of polymorphonuclear cells may be present without anemia. Hematological abnormalities may be absent at the time of neurological presentation and are thus insufficiently sensitive for use in diagnosis, particularly true if the patient is taking folate supplements.

Homocysteine and methylmalonic acid are precursors of vitamin Bji-dependent pathways. Because norma! hematological studies and serum cobalamin level do not exclude a deficiency state (Savage et al. 1994), assay of serum levels of these metabolites is important in any patient with suspected deficiency. This is especially true in those with scrum vitamin B,i levels in the range of 200-350 pg/mL, even though these levels may be above the "lower limit of normal" reported by many reference laboratories. Testing of metabolites is also necessary in those with neurological deficits secondary to nitrous oxide abuse and some inherited metabolic disorders (see Pathogenesis and Etiology, later in this chapter). Homocysteine level should be measured either at fasting or aftct an oral methionine load. The blood sample should be refrigerated immediately after collection because levels increase if whole blood is left at room temperature for several hours. The concentration of either lioiiu icvstc:i.- or rutl". in;ilocic .ice is c'cviiled in over 90% of patients with cobalamin deficiency. The specificity of the finding is less clear because there are many other causes of increase of these metabolite levels (Table 63.2).

Tabic 63.2: Causes of elevated serum levels of homocysteine and methylmalonic acid

Elevated methylmalonic **acid**
Cokil.iinin ccHeiiTivv
Renal insufficiency
Inherited metabolic disorders
Hypovolemia
HI c vn 1 cd h o 111 ocy s tci nc
Cobalamin deficiency
Folate deficiency
Pyridoxine deficiency
Renal insufficiency
Hypothyroidism
Psoriasis
Inherited metabolic disorders
Hypovolemia

Abnormally low serum vitamin R,j or elevated metabolite levels provides confirmatory evidence of deficiency in the presence of an appropriate neurological picture. A dietary history is helpful occasionally, though inadequate dietary intake is seldom a sole cause of cobalamin deficiency. Schilling's test should be considered to further document the underlying cause of malabsorption. Further evaluation should include measurement of antibodies against parietal cell and against intrinsic factor (IF), either of which may be elevated in 60-90% of patients with autoimmune gastritis and intrinsic factor deficiency. Antiparietal cell antibodies are nonspecific and arc present in autoimmune endocrinopathies as well as occasional normal individuals. In comparison to antiparietal cell antibodies, anti-IF antibodies are less sensitive and more specific.

In cases of uncertain diagnosis, it is useful to institute a therapeutic trial of parenteral cobalamin while monitoring serum levels of homocysteine and methylmalonic acid both before and after treatment. In cobalamin-deficient patients, homocysteine and methylmalonic acid levels typically normalize within 7 to 10 days after treatment.

Physiology

Dietaty vitamin B_{12} binds readily to intrinsic factor, and the complex is transported to the terminal ileum, where

it is absorbed into the circulation via specific receptors on ileal mucosal cells. Once absorbed, vitamin $B]_2$ binds to transcobalamin II for transport to tissues. As much as 90% of total body vitamin Bi_2 (1-10 mg) is stored in the liver. Even when vitamin absorption is severely impaired, many years arc needed to deplete the body store. A clinical relapse in pernicious anemia after interrupting vitamin $B_{!2}$ therapy takes an average of 5 years to be recognized.

Biochemistry

Two biochemical reactions depend on vitamin B_{12}. One involves methylmalonic acid as precursor in the conversion of mcthylmalonyl coenzyme A (CoA) to succinyl CoA. The importance of this to the nervous system is unclear. The other is a folate-depcndent reaction in which the methyl group of methyltctrahydrofolate is transferred to homocysteine to yield methionine and tetrahydrofolate. The reaction depends on the enzyme methionine synthase that uses cobalamin as a cofactor. Methionine is converted to S-adenosylmethionine (SAM), which is used for methylation reactions in the nervous system, including DNA symbols in dividing cells (Snow 1999).

Pathology

The term *subacute combined degeneration of the spinal cord* describes the pathological process seen in vitamin B_{12} deficiency. Microscopically, spongiform changes and foci of myelin and axon destruction are seen in the white matter of the spinal cord. The most severely affected regions are the posterior columns at the cervical and upper thoracic levels (Figure 63.2); pathological changes also are seen commonly in the lateral columns, whereas the anterior columns are involved in only a small number of the advanced cases. The pathological findings of the peripheral nervous system are those of axonal degeneration, but in some cases there is evidence of demyelination. Involvement of the optic nerve and cerebral white matter also occur.

Pathogenesis and Etiology

Pernicious anemia caused by defective intrinsic factor production by parietal cells accounts for many cases of vitamin h_{J2} deficiency. These patients may have demonstrable circulating antibodies to parietal cells or lymphocytic infiltrations of the gastric mucosa, suggesting an underlying autoimmune disorder. Another cause of intrinsic factor deficiency is gastrectomy, although it rarely leads to symptomatic deficiency in isolation. Other cases of malabsorption are surgical resection of the terminal ileum and the blind loop syndrome. Prolonged use of drugs such as colchicine, neomycin, and omeprazole may cause vitamin deficiency by their interference with intestinal absorption. Dietary insufficiency in strict vegetarians occurs only rarely. Low serum level of vitamin $[i,_{\pm}$ also occurs in patients with acquited immunodeficiency syndrome (AIDS), though the significance is unknown; serum homocysteine and methylmalonic acid levels are within the normal range in most of these patients, and cobalamin supplement often fails to induce clinical improvement. The vacuolar myelopathy seen in AIDS patients resembles subacute combined degeneration both clinically and

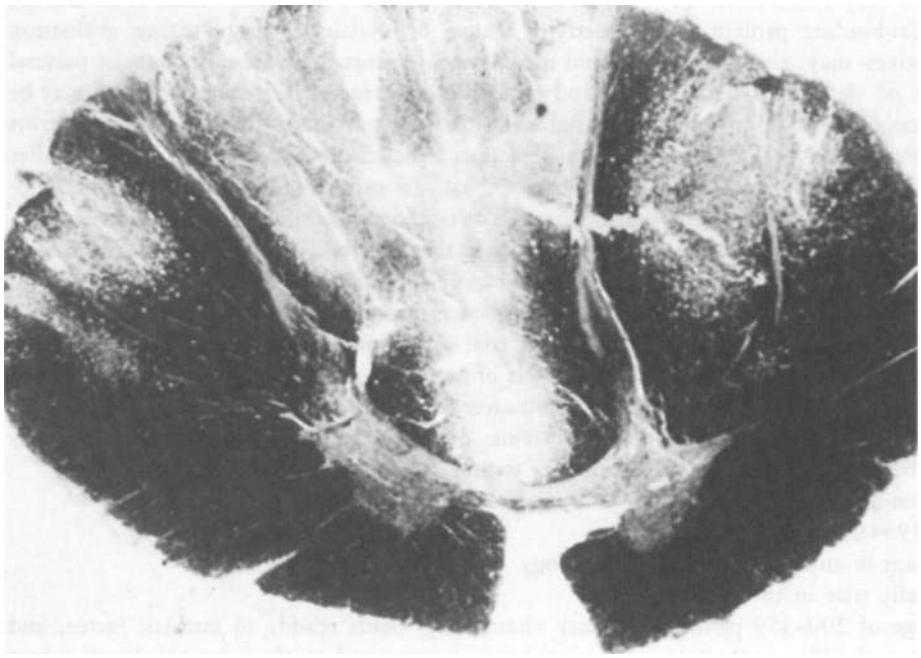

FIGURE 63.2 Subacute combined degeneration of the spinal cord in vitamin B_{tl} deficiency. Demyelination and loss of axons are more widespread in posterior than in lateral columns (Weigert's stain). (Courtesy Dr. Michael F. Gonzales.)

pathologically. It is hypothesized that immune mediated mechanisms may limit the availability of S-adenosylmethionine (Di Rocco et al. 2002).

After heavy abuse of nitrous oxide, subjects may develop a clinical syndrome of myeloneuropathy indistinguishable from that of vitamin B_{12} deficiency. Symptoms include numbness, paresthesia, Lhermitte's sign, gait ataxia, and leg weakness. Subjects improve slowly when nitrous oxide is stopped, but the myelopathy may not recover completely. Serum vitamin B_{12} level and Schilling's test result are normal, and hematological derangements arc usually inconspicuous. The mechanism appears to be an interference with the vitamin B_{12}-dependent conversion of homocysteine to methionine. The other pathway, conversion of methylmalonyl coenzyme A to succinyl coenzyme A, is unaffected by . nitrous oxide. Prolonged exposure to nitrous oxide is necessary to produce neurological symptoms in normal individuals. By contrast, patients who are already vitamin B_{12} deficient may experience neurological deficits after brief exposures to nitrous oxide during general anesthesia. Symptoms typically appear 2-6 weeks after surgery and resolve quickly with vitamin B_{12} treatment (Marie et al. 2000).

Course and Prognosis

With proper treatment, at least partial improvement can be expected. Most of the symptomatic improvement occurs during the first 6 months of therapy, although it may not be complete for a year or more. The need for early diagnosis and treatment is underscored by the observation that remission correlates inversely with the time lapse between onset of symptoms and initiation of therapy. The myelopathy is least likely to make a complete recovery.

Treatment and Management

Any patient with clinically overt vitamin B_{12} deficiency should be treated with parenteral vitamin therapy aimed at replenishing the total body pool. The usual regimen uses intramuscular injections of 100 ug daily or 1000 ug twice weekly for 2 weeks. This is followed by weekly injections of 1000 ug for another 2-3 months. If Schilling's test demonstrates malabsorption of vitamin Bi_2, the patient should be placed on lifelong maintenance therapy, usually in the form of monthly 1000 ug injections. The parenteral dose of vitamin B_{12} recommended here provides quantities considerably higher than the body's requirement. Although there is no evidence that overdosing can speed neurological recovery, adverse reactions to these doses of vitamin B_{12} are unknown.

Oral preparations of intrinsic factor are available but are not reliable for clinical use. Antibodies to intrinsic factor may nullify its effectiveness in the intestinal lumen, and many patients eventually become refractory to intrinsic factor therapy.

FOLATE DEFICIENCY AND HOMOCYSTEINE

Theoretically, folate deficiency should produce the same neurological deficits as those seen in vitamin B_{12} deficiency because of its importance in the production of methionine, S-adcnosy I methionine, and tetra hydro folate (see Biochemistry under vitamin B_{12} Deficiency). However, overt neurological manifestations like those seen in vitamin Bi_2 deficiency are rare in folate deficiency. This is probably due to alternative cellular mechanisms that are available to preserve S-adenosylmcthionine levels in times of folate scarcity. In contrast, accumulating evidence in recent years suggests that chronic folate deficiency is likely to manifest in a subtle manner. Folate deficiency may result in mild cognitive impairment or increased stroke risk in adults and increased frequency of neural tube defects in babies bom to folate-deficient mothers (Diaz-Arrastia 2000). Since 1998, the U.S. Food and Drug Administration has mandated fortification of grain products with folate. The level of supplement on the average increases the dietary folate intake of adults by 100 ug per day. The impact of this policy remains to be seen.

Clinical Features

Folate deficiency may rarely produce a syndrome indistinguishable from subacute combined degeneration of vitamin Bi_2 deficiency. The majority of patients with laboratory evidence of folate deficiency do not have overt neurological findings or have mild cognitive impairment.

Serum homocysteine is an important surrogate marker for folate metabolism (sec Laboratory Studies under vitamin B_{12} Deficiency). Though deficiency of vitamin B_{12} or B_{fi} as well as several other factors can raise scrum homocysteine, most cases of elevated homocysteine level are due to folate deficiency. Numerous studies over the past 30 years have identified hyperhomocystinemia as an independent risk factor for cerebrovascular disease, coronary artery disease, peripheral vascular disease, and venous thrombosis. For cerebrovascular disease, the association is strongest for multi-infarct dementia and white matter microangiopathy, but there is little or no association with cardioembolie or large artery disease. Even a modest increase in scrum level, in the range of 15 to 20 umol/I., engenders a recognizable increase in risk.

Although a low folate level is present in many elderly asymptomatic people, the prevalence is much higher in the psychiatric and Al/.hcimer's disease populations (Reynolds 2002). Moreover, a low folate level appears ro correlate with depression and cognitive impairment. Even in healthy older adults, a low folate level is associated with subtle but

significant deficits in neuropsychological test performance. The relationship is stronger when serum homocysteine is used as a surrogate marker. This connection cannot he explained simply by an increased risk of multi-infarct dementia or other cerebrovascular diseases.

Clinical observations in two inborn errors of metabolism reinforce our understanding of the role of homocysteine in neurological diseases. Hereditary deficiency of cystathionine ^-synthase leads to hypcrhomocystinemia and hyperhomocysteinuria. The homozygous form presents with markedly elevated homocysteine levels, mental retardation, premature atherosclerosis, and seizures. The heterozygous individuals have milder elevations of homocysteine and also have increased risk of vascular disease. A much more common condition is a C-to-T substitution at codon 677 in the gene coding for N^5,N^{11}-methylenetetrahydrofolatc reductase (MTHFR). Homozygotes for this C677T mutation comprise about 5-10% of the white population. These individuals have mildly elevated homocysteine levels and increased risk of vascular disease.

Laboratory Studies

Plasma and erythrocyte folate levels may be measured directly. Erythrocyte level is generally more reliable than plasma level because it is less affected by short-term fluctuation in intake. Serum homocysteine measurement is discussed in Laboratory Studies under Vitamin Bi_2 Deficiency.

Pathogenesis and Etiology

Absorption of folate occurs in the jejunum and, to a lesser extent, the ileum. Chronic alcoholism is an important cause of folate deficiency. Folate deficiency also may complicate small bowel disease (e.g., sprue, Crohn's disease, and ulcerative colitis). Other populations at risk are pregnant women and patients receiving anticonvulsant drugs that interfere with folate metabolism. Sulfasalazine, methotrexate, triamterene, and oral contraceptives also may cause folate deficiency, although the mechanism is often unclear. Intrathecal methotrexate, in particular, causes a leukoencephalopathy associated with marked elevation of homocysteine levels in the cerebrospinal fluid.

Treatment and Management

Prospective studies on the use of folate in the prevention of vascular disease are under way. Results from these trials will greatly enhance our knowledge of the role of folate in human diseases. In women of childbearing potential with epilepsy, daily folate supplement of 0.4 mg or more is recommended as prophylaxis against neural tube defect. In patients with documented folate deficiency, the initial dose is usually 1 mg of folate three times per day, followed by a maintenance dost- of 1 mg per day. For acutely ill patients, parenteral doses of 1-5 mg may be given. Even with oral doses as high as 15 mg per day, there is no substantiated report of toxicity. It is important to keep in mind that large doses of folate can cotrcct the megaloblastic anemia of vitamin Bi_2 deficiency without altering the neurological abnormalities. A hematological response to folate, therefore, does not preclude the diagnosis of pernicious anemia.

VITAMIN E DEFICIENCY

Vitamin E is a free radical scavenger and an antioxidant and has attracted considerable attention for its potential use in the prevention and treatment of vascular diseases and neurodegenerative diseases such as Alzheimer's disease and amyotrophic lateral sclerosis. The pharmacological use of vitamin E in these conditions has yet to be unproven. We will limit the following discussion to the neurological manifestations of vitamin E deficiency.

Clinical I'eaiiircs

Vitamin E is a fat-soluble vitamin that is normally stored to a massive degree in the body. Clinical symptoms typically do not begin until many years of malabsorption deplete the vitamin reserves. This takes 15-20 years in adults, but clinical onset as early as 2-3 years of age may occur in children, presumably because of their small vitamin reserves.

The usual presenting symptoms are weakness or gait unsteadiness. Neurological examination reveals a syndrome of spinocerebellar degeneration, often accompanied by a varying degree of peripheral nerve involvement. Some patients are diagnosed erroneously with Friedreich's ataxia. The most consistent abnormalities arc limb ataxia, areflexia, and severe loss of vibration and position sense. Cutaneous sensation usually is spared or affected to a lesser degree. Approximately one half of the patients have nystagmus, ptosis, or partial external ophthalmoplegia. Mild to moderate proximal weakness is common, although weakness can be diffuse or predominantly distal. Babinski's sign may be present.

Laboratory Studies

The diagnosis is not difficult when the appropriate neurological syndrome and a low serum vitamin E level are both present. Serum level should be interpreted in light of the clinical findings. Some patients with low levels do not have demonstrable neurological deficits. Moreover, plasma vitamin K is largely incorporated into chylomicrons and is

highly dependent on the concentrations of total plasma lipids, cholesterol, and very low density lipoproteins,

Other laboratory abnormalities, despite their nonspecific nature, help to clarify the diagnosis. Stool fat is increased in many patients with malabsorption syndromes causing hypovitaminosis E, and serum carotene concentration is often abnormally low, both reflecting a generalized state of fat malabsorption. Cerebrospinal fluid should be normal, Nerve conduction studies usually reveal a mild axonal neuropathy, with small or absent sural nerve action potentials and normal or slightly slow motor nerve conduction. Somatosensory and visual evoked responses are frequently abnormal. High signal lesions in the posterior columns on T2-weighted MRI images have been reported (Vorgerd etal. 1996).

Physiology and Biochemistry

By reacting with free radicals and perhaps with other oxidative intermediates, vitamin E functions as an antioxidant capable of Stabilizing polyunsaturated membrane lipids. It is potentially important in maintaining the integrity of cellular membranes. Whether this action bears any relationship to the development of neurological deficits in the deficiency state is uncertain.

Pathology

Few cases of proven vitamin E deficiency have come to autopsy. Degeneration of large myelinated fibers may be present in the peripheral nerves, posterior columns, and sensory roots. Accumulations of lipopigments are seen in both neurons and endothelial cells, especially prominent in tile spinal cord and the cerebellum.

Pathogenesis and Etiology

Like other fat-soluble compounds, vitamin K depends on the presence of pancreatic esterases and bile salts for its solubilization and absorption in the intestinal lumen. Neurological symptoms of deficiency occur most commonly in patients with significant fat malabsorption (Table 63.3). A reduced bile salt pool may be caused either by reduced hepatic excretion, as in congenital cholestasis, or by interruption of the enterohepatic rcabsorption of bile, as in patients with extensive small bowel resection. Other settings for malabsorption include cystic fibrosis, adult celiac disease, and abnormalities of specific vitamin E receptors, such as in abetalipoproteinemia.

A rare familial form of fat malabsorption is abetalipoproteinemia (Bassen-Kornzweig syndrome), a disorder in which impaired chylomicron and lipoprotein synthesis is partly responsible for the impaired fat absorption

Table 63.3: Causes of vitamin E deficiency

Gastrointestinal diseases
Biliary atresia, chronic cholestasis
Intestinal resection
Crohn's disease
Pancreatic insufficiency (e.g., cystic fibrosis)
Blind loop syndrome and bacterial overgrowth
Bowel irradiation
Celiac disease
Other causes of steatorrhea
I lereditary diseases
Abetalipoproteinemia
Alpha-tocopherol transfet protein mutation

(Kayden 1993). In addition to a neurological syndrome similar to that seen in other vitamin E-deficient states, spiky red blood cells (acanthocytes) and retinal pigment changes are characteristic. Another hereditary cause of vitamin E deficiency may be due to a genetic defect in the assembly or secretion of chylomicrons, leading to a chylomicron retention disease that is demonstrable in the intestinal mucosa (Aguglia et al. 2000).

A syndrome of ataxia with isolated vitamin E deficiency (AVED) occurs in patients without gastrointestinal disease or generalized fat malabsorption. Mutations in the a-tocopherol transfer protein gene on chromosome 8ql3 are responsible (Cavalier et al. 1998). This condition is inherited in an autosomal recessive manner. The defect appears to be impaired incorporation of the vitamin into hepatic lipoproteins that are necessary for delivery to tissues.

Treatment and Management

The recommended daily requirement of vitamin E in normal adults is 10 mg (equivalent to 10 IU) of d,l-alpha-tocopherol acetate, a commonly available form of the vitamin. In the deficiency state, a wide range of doses has been used, ranging from 200 mg per day to 100 mg per kg per day. Although there is little consensus on the optimal therapeutic dosage, there is also no evidence of toxicity from overdose. A reasonable approach is to begin therapy with a preparation of water-miscible tocopherol at a dose of 200-600 mg per day. The clinical picture and serum level should be followed; if no improvement occurs, higher oral dosages or even parenteral administration should be tried. Supplementation of bile salts may be ol value in Mime patients.

PELLAGRA (NICOTINIC ACID DEFICIENCY)

Nicotinic acid *(niacin,* another term for nicotinic acid, was introduced to avoid confusion with the alkaloid nicotine) is converted in the body to two important coenzymes in

carbohydrate metabolism; nicotinamide adenine dinucleotide and nicotinamide adenine dinucleoridc phosphate. Dietary deficiency of nicotinic acid produces *pellagra* (from the Italian *pelle agra,* meaning *rough skin).* Pellagra classically occurs in populations who consume primarily corn as their carbohydrate staple. Corn lacks nicotinic acid as well as tryptophan, a precursor that can be converted in the body to nicotinic acid. In underdeveloped countries, pellagra is still a common health problem. Even in the United States, pellagra was endemic until approximately 1940 in the South and in alcoholic populations, it has now largely disappeared, credited to the widespread consumption of bread enriched with niacin.

Clinical Features

Pellagra affects three organ systems in the body: the gastrointestinal tract, skin, and nervous system (hence the mnemonic of the three Ds; diarrhea, dermatitis, and dementia). The chief gastrointestinal symptoms are anorexia, diarrhea, stomatitis, and abdominal discomfort. Skin changes range from erythema to a reddish-brown hypcrkeratotic rash distributed ovet much of the body, with the face, chest, and dorsal surfaces of the hands and feet being most involved.

The neurological syndrome of pellagra is not well defined. Reported cases, especially of patients with alcoholic pellagra, frequently are confounded by other coexisting central nervous system disorders. The primary early symptoms are neuropsychiatric (e.g., irritability, apathy, depressed mood, inattentiveness, memory loss) and may progress to stupor or coma. In addition to the confusional state, spasticity, Babinski's sign, gegenhalten, and startle myoclonus may be prominent on neurological examination.

Nonendemic pellagra occurs rarely in patients with alcoholism or malabsorption secondary to gastrointestinal disease. The diagnosis of nonendemic pellagra can be made only on clinical grounds because there is no available blood niacin level determination, and diagnosis is frequently difficult because diarrhea and dermatological changes may be absent. Unexplained ptogressivc encephalopathy in alcoholic patients not responsive to thiamine therapy (see Wernicke-Korsakoff Syndrome, later in this chapter) should raise the possibility of pellagra.

Treatment and Management

The recommended daily allowance for nicotinic acid is *6.6* mg/1000 kcal dietary intake. Oral nicorinic acid in doses of 50 mg three times a day is usually sufficient to treat symptomatic patients. Alternatively, parenteral doses of 25 mg can be given two to three times a day. Nicotinamide has a similar therapeutic efficacy in pellagra, but it does not have the vasodilatory and cholesterol-lowering activities of niacin.

VITAMIN B_t, (PYRIDOXINS) DEFICIENCY

Although the term *pyridoxine* often is used synonymously with vitamin Bg, two other naturally occurring compounds—pyridoxal and pyridoxamine—possess biological activities similar to pyridoxine. All three compounds are readily converted to pyridoxal phosphate, the coenzyme form important for the metabolism of many amino acids.

History

The original recognition of one of the complications of pyridoxine deficiency provides a useful lesson in nutrition. (a the early 1950s, physicians in the United States riKoimk'ivd cases nt an LIIIIIIMI.II sri/uiv ilisordci in inunls at the age of several weeks to a few months. These seizures were difficult to control with the usual anticonvulsants. In contrast, the response was often dramatic when vitamin B_f, was given. As more patients were identified, it became clear that the symptomatic infants had been fed a commercially prepared formula that contained only 60 mg/liter of vitamin $B_{(„}$ or approximately one third the amount found in other infant formulas. The underlying cause eventually was traced to a manufacturing process that apparently reduced the formula's pyridoxine content.

Clinical Features

Even with better awareness of the problem, sporadic cases of infantile seizures from dietary vitamin B_f, deficiency still occur, most commonly as a result of breastfeeding by malnourished mothers from poor socioeconomic backgrounds or in underdeveloped countries. The typical patients have a normal birth history and are entirely healthy until the development of hyperirritability and an exaggerated auditory stattle. Recurrent convulsions often occur abruptly, as may status epilepticus. Once the dietary insufficiency is corrected, patients become free of seizures and develop normally.

Another form of pyridoxine-responsive seizure occurs in infants with a congenital dependency on pyridoxine. They develop symptoms despite a normal dietary supply of pyridoxine. In contrast to infants with dietary deficiency, most of these children manifest seizures earlier in life (within days of birth) and require much larger doses of pyridoxine (5-100 mg) to control their convulsions. Long-term administration of large amounts of pyridoxine is needed, generally in the range of 10 mg per day. Even after several years of successful treatment, seizures often reappear within days of pyridoxine withdrawal.

Pyridoxine dependency should be considered in infants with undiagnosed seizures, especially in those with a poor response to anticonvulsants.

Adults are much more tolerant of vitamin B_A deficiency. Not only are most adult diets adequate in pyridoxine and related compounds, but also symptoms are rare even when there is demonstrable low vitamin level, Isoniazid and a few other drugs, such as hydralazine and penicillamine, are responsible for many adult cases. This is especially a problem in slow inactivators of isoniazid, among whom as many as 50% may develop peripheral neuropathy when treated with the drug. Sensory symptoms generally appear first, consisting of numbness, tingling, and occasionally burning pain in the distal portions of the feet. If the drug is continued, symptoms may spread prox.im.ally to the knees and hands, burning pain is disabling in some instances. On examination, there is distal weakness, depressed tendon reflexes, and impaired distal sensation,

Use of high doses of pyridoxine (1000 mg per day or more) for several months causes a distal sensory length-dcpciulrilt .'VHi.i'i r.i'Uiopatln 1:1 .1 tinsc dependem mar.:KT. Reported patients ingesting such a high dose for a prolonged period had a syndrome of sensory ataxia, with impaired cutaneous and deep sensation, areflexia, and Romberg's sign, Many years of taking doses as low as 200 mg per day may also cause a mild, predominantly sensory polyneuropathy. Hence, in therapeutic use of pyridoxine, it seems prudent to limit the dosage to 100 mg per day or less.

Treatment and Management

Treatment of pyridoxine-relatcd seizures in infants was discussed earlier. The neurotoxicity of isoniazid and hydralazine is dose dependent. Even with high doses of isoniazid, pyridoxine supplements of 50 mg per day can prevent the development of neuropathy in nearly all patients,

BERIBERI (THIAMINE DEFICIENCY POLYNEUROPATHY)

Beriberi literally means extreme weakness. It affects the heart and peripheral nerves, producing congestive cardiomyopathy, sensorimotor polyneuropathy, or both. The classical wet and dry forms refer to **the** presence or absence of edema.

Clinical Features

The neuropathy generally progresses over several weeks or months. Affected patients characteristically complain of paresthesias or pain of the feet. Walking becomes difficult. Distal muscle weakness with foot drop appears as the neuropathy worsens. Muscle tenderness and cramps, especially of the calves, are prominent in some patients, When cardiac dysfunction is present, patients also experience tachycardia, palpitations, dyspnea, fatigue, and ankle-edema.

The most common finding is a stocking-glove distribution of cutaneous sensory loss and distal weakness. Deep tendon reflexes of the ankles are losr in the majority of patients. Cranial nerve deficits are unusual, although there may be laryngeal nerve paralysis producing hoarseness and voice weakness. A subacute optic neuropathy may occur rarely in thiamine-deficient patients secondary to a ketogenic diet used to control epilepsy.

Laboratory Studies

Diagnosis of beriberi is based on recognizing the appropriate clinical features in a background of nutritional deficiency. Thiamine levels in scrum and urine may be decreased, though the levels do not reliably reflect tissue concentrations. Erythrocyte transketolase activity level is dependent on thiamine and provides an assay of functional status. Pyruvate accumulates during thiamine deficiency, and elevated serum level provides additional confirmation. A blood sample should be drawn before initiation of treatment because these laboratory abnormalities normalize quickly.

Dectrodiagnostic studies show an axonal neuropathy with reduced amplitude of sensory and motor responses, normal or mildly reduced conduction velocity, and neurogenic changes on electromyography. Lumbar puncture sometimes shows a mildly elevated opening pressure, a finding probably related to the presence of congestive heart failure. Cerebrospinal fluid examination is otherwise unremarkable. If cardiac impairment is present, electrocardiographic abnormalities or cardiac enlargement on chest roentgenography may occur.

Physiology and Biochemistry

Thiamine is the precursor for the coenzyme thiamine pyrophosphate, which catalyzes the oxidative decarboxylation of pyruvate and alpha-ketoglutarate, with the eventual production of coenzyme A. Thiamine pyrophosphate also serves as a cofactor for the transketolase reaction in the hexose monophosphate shunt, A corollary of the biochemistry is the dependence of the thiamine requirement on the body's metabolic rate, with the requirement being greatest during periods of high metabolic demand or high glucose intake. This explains the clinical observation that symptoms of thiamine deficiency frequently occur during periods of refceding or intravenous administration of glucose.

Pathology

Ultrastructural and morphomctric analysis of sural nerve biopsy reveals axonal loss of wallenan type. Segmental demyelination is infrequent and is probably secondary to axonal degeneration.

Epidemiology

Beriberi is rare in most industrialized nations. Even in Japan, where beriberi once accounted for over 20,000 deaths a year, the disease has ail but disappeared. An exceptional outbreak occurred in the 1970s in young people with a history of an unbalanced diet high in instant food, unfortified rice, and other carbohydrates and deficient in protein and vegetables. The symptoms typically appeared acutely or subacutely after a period of strenuous athletic training or heavy work. Exercise precipitated the condition by raising the metabolic requirement for thiamine. Other causes of increased metabolic demands such as pregnancy, malignancy, and systemic infection may rarely precipitate symptoms, especially in people with marginal nutritional status. In developed countries, many cases are probably related to alcoholism, but ir is difficult to distinguish beriberi from alcoholic neuropathy.

Course and Prognosis

Cradual return of sensory and motor function can be expected after thiamine replenishment. Mildly affected patients experience considerable improvement after a few weeks of treatment; in severe cases, improvement may take many months and may be incomplete.

Treatment and Management

The major goal is to initiate a balanced diet with supplements of thiamine and other vitamins. Thiamine is water soluble and usually supplied as thiamine hydrochloride, either in crystalline form or as a 100-mg/mL solution. The minimum daily requirement is 0.3 mg/1000 kcal dietary intake in normal subjects, but the requirement is higher during pregnancy and old age. For therapeutic purposes, 50-100 mg per day is used. The parenteral form of thiamine should be considered whenever there is doubt about adequate gastrointestinal absorption.

Infantile Beriberi

\n ,ui;li' \> iuln>i:n- "I i':i: • mi:u- drl k::.no in miauls iii i .its in the rice-eating populations of Asia, most frequently in breastfed infants less than I year of age; thiamine is often deficient in breast milk from mothers who eat primarily polished rice. Although the disorder is called *infantile beriberi,* it bears little resemblance to the adult form, Acute cardiac symptoms arc common, often preceded by a prodrome of anorexia, vomiting, deficient weight gain, and restlessness. Dyspnea, cyanosis, and signs of heart failure follow and can lead rapidly to death. Arytenoid edema and recurrent laryngeal neuropathy give rise to hoarseness, dysphonia, and eventually aphonia. Early warning signs of coughing and choking may be mistaken for respiratory tract infections. Central nervous system manifestations include drowsiness, ophthalmoplegia, and convulsions. These symptoms often begin abruptly and carry a grave prognosis. Parenteral administration of 5—20 mg of thiamine can be hfesaving and should never be delayed.

WERNICKE-KORSAKOFF SYNDROME

Wernicke's Encephalopathy

History

Although there were earlier descriptions of patients with probably the same form of encephalopathy, Carl Wernicke is credited with recognizing the disease in 1881. He described an acute syndrome of mental confusion, ophthalmoplegia, and gait ataxia in three patients, two of whom were alcoholics. At autopsy, multiple small hemorrhages were seen in the periventricular gray matter, primarily around the aqueduct and the third and fourth ventricles.

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Although the most common clinical setting for Wernicke's encephalopathy is chronic alcoholism, a large number of cases occurs in other conditions, with the only prerequisite being a poor nutritional state, either from inadequate intake, malabsorption, or increased metabolic requirement (Table 63.4). Wernicke's encephalopathy may be

Table 63.4: Associated conditions in nonalcoholic patients with Wernicke's encephalopathy

I lypercmesis of pregnancy
Systemic malignancy
Gastrointestinal surgery
Hemodialysis or peritoneal dialysis
Prolonged intravenous feeding
Rcfccding after prolonged fasting or starvation
Anorexia nervosa
Dieting and gastric plication
Acquired immunodeficiency syndrome

precipitated acutely in at-risk patients by intravenous glucose administration or carbohydrate loading,

Wernicke's original description of the clinical triad of confusion, ophthalmoplegia, and ataxia is still valid. The confusion.il state develops over days or weeks and is characterized by inattention, apathy, disorientation, and memory loss. Stupor or coma is rare. Ophthalmoplegia, when present, commonly involves both lateral recti, either in isolation or together with palsies of other extraocular muscles. Patients may have horizontal nystagmus on lateral gaze, and many also have vertical nystagmus on upgaze. Sluggish reaction to light, light-near dissociation, or other pupillary abnormalities are sometimes seen. Truncal ataxia is common, but limb ataxia is not, findings similar to those seen in alcoholic cerebellar degeneration.

Other frequent, findings include hypothermia and postural hypotension, reflecting involvement of hypothalamic and brainstem autonomic pathways. Signs of nutritional deficiency and complications of alcoholism are common. These include peripheral neuropathy, tongue redness, skin changes, and liver abnormalities.

Laboratory Studies

Wernicke's encephalopathy is a clinical diagnosis, though brain MRI can be very helpful. MRI may show signal abnormalities on T2-wcighted, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted images in the periaqueductal regions, medial thalami, and bilateral mamillary bodies (Doherty et al. 2002). The lesions sometimes show contrast enhancement. The signal abnormalities typically resolve completely with prompt treatment, but shrunken mamillary bodies may be seen as a late residual finding. The cerebrospinal fluid is either normal or shows a mild elevation in protein. Serum thiamine level and erythrocyte transketolase activity may be depressed, and there also may be an elevation of serum pyruvate. Treatment should not be withheld while the clinician waits for laboratory results because a delay may lessen the likelihood of recovery.

Physiology

The clinical findings reflect the localization of pathological abnormalities in this disease, namely, the prominent involvement of periventricular structures at the level of the third and fourth ventricles. Lesions of the nuclei of the III, VI, and vestibular nerves are responsible for the eye findings. The truncal ataxia is probably caused by the vestibular dysfunction and involvement of the superior cerebellar vermis.

Biochemistry

Biochemistry is discussed in the section on beriberi.

Pathology

The pathological process depends on the age of the lesions. Macroscopically, varying degrees of congestion, petechial hemorrhages, shrinkage, and discoloration may be present (Figure 63.3). Chronic lesions are characterized by foci of glial proliferation and myelin pallor primarily affecting the aforementioned locations. In acute lesions, dilatation and hyperplasia of small blood vessels occur, with punctate hemorrhages in the subependymal gray matter.

Epidemiology

The frequency of "Wernicke's encephalopathy as estimated from various autopsy studies is approximately 0.8-2.8%, a figure far greater than that expected from clinical studies. Only 20% of the cases in one scries were diagnosed during life. This is disturbing because Wernicke's encephalopathy is readily preventable and treatable. One reason for undcr-recognition is that some patients do not have the classic triad of ataxia, ophthalmoparesis. and encephalopathy. Misdiagnosis also may result from an overemphasis on alcoholism as a cause (see Table 63.4). Wernicke's encephalopathy

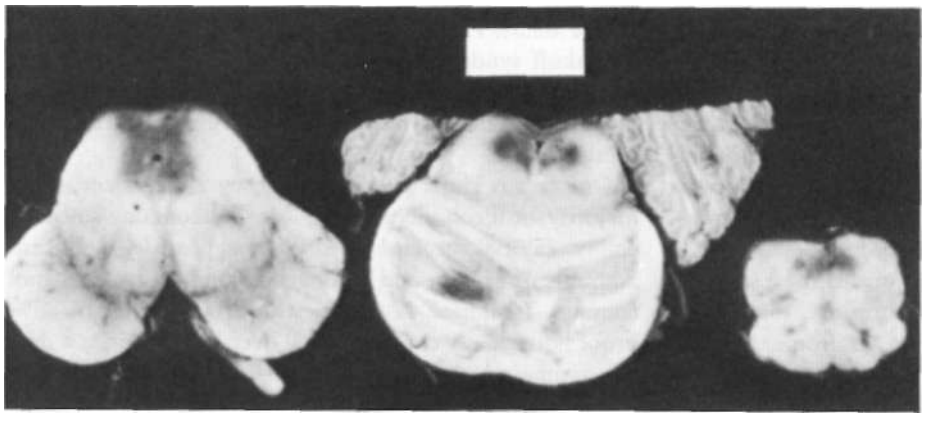

FIGURE 63.3 Acute Wernicke's disease. Hemorrhagic areas are seen adjacent to the fourth ventricle and aqueduct in the *{from right to left)* medulla, pons, and midbrain. (Courtesy Dr. Michael F. Gonzales.}

occurring under other settings may be mistaken for encephalopathy of uremia, dialysis, sepsis, or other systemic diseases.

Course and Prognosis

If left untreated, Wernicke's encephalopathy is progressive. The mortality, even with thiamine treatment, is 10-20%. With treatment, the majority- of ocular signs resolves within hours, although a fine horizontal nystagmus persists in approximately 60% of patients. Apathy and lethargy improve over days or weeks. The gait disturbance resolves much more slowly, and in one third or more of cases, gait may be abnormal even months after treatment. As the global confusional state recedes, some patients are left with a Korsakoff's syndrome—a disorder of impaired memory and learning.

Treatment and Management

Patients suspected of Wernicke's encephalopathy should receive thiamine before administration of glucose to avoid precipitation of acute symptom worsening. Thiamine is the only treatment known to alter the outcome. Thiamine of 50-100 mg should be given parenterally in the acute stage because intestinal absorption is unreliable in debilitated and alcoholic patients. Thiamine can then be continued daily through the acute period.

Korsakoff's Syndrome

Like Wernicke's encephalopathy, Korsakoff's syndrome is historically defined in chronic alcoholism. Shortly after Wernicke's original treatise, Korsakoff, a Russian psychiatrist, described this amnesia syndrome in 20 alcoholic men. At the time, however, neither Wernicke nor Korsakoff recognized the relationship between the encephalopathy and impaired memory. The clinical connection and the pathological similarity between the two conditions were not appreciated until 10 years later by other investigators.

Korsakoff's syndrome and Wernicke's encephalopathy do not represent separate diseases but arc different stages of one disease process (Wernicke-Korsakoff syndrome). Korsakoff's syndrome typically follows Wernicke's encephalopathy, emerging as ocular symptoms and encephalopathy subside. In *Korsakoff's syndrome,* memory is impaired out of proportion to other cognitive functions. This is due to the selective localization of the lesions in the diencephalon and temporal lobes. Injury to these regions, regardless :?t cause (e.g., infarction, trauma, tumors, or herpes encephalitis), can produce a syndrome indistinguishable from the amnesia syndrome seen in alcoholic patients.

Clinical Features

The memory impairment is characterized by the presence of both anterograde and retrograde amnesia. Affected patients have severe difficulty establishing a new memory, always coupled with a limited ability to recall events that antedate the onset of illness by several years. Most patients are disoriented as to place and time. Alertness, attention, social behavior, and most other aspects of cognitive functions are relatively preserved. Confabulation can be a prominent feature, especially in the early stages, although it may be absent m some patients.

Pathology

The histopathoJogieal changes in patients with Korsakoff's syndrome are similar to those in patients with predominantly Wernicke's encephalopathy. Patients with Korsakoff's syndrome have, in addition, involvement of the dorsal medial nucleus of the thalamus.

Course and Prognosis

Despite treatment with thiamine, improvement in memory function is slow and usually incomplete, and those who improve usually do so after a 1-month delay or longer. Occasionally, patients may not achieve maximal improvement for more than a year.

Treatment and Management

Except for the initial thiamine administration, treatment usually is limited to social support. Many patients **require** at least some form of supervision, either at home or in a chronic care facility.

OTHER NUTRITIONAL DISEASES ASSOCIATED WITH ALCOHOLISM

The neurological consequences of alcohol abuse have been recognized for centuries, but little is known about their pathogenesis. A nutritional cause is often invoked (Table *63.5).* However, with the exception of Wernicke-Korsakoff syndrome and rare cases of pellagra, no single nutritional factor has been defined conclusively. Many investigators instead have proposed a direct neurotoxicity of alcohol.

One fact is clear: Dietary deficiency is prevalent in the majority of alcoholic patients. Alcohol contains so-called empty calories because it docs not provide significant amounts of protein and vitamins. A gram of pure ethanol contains 7 calories. A person who drinks a pint of 86% proof liquor daily consumes well over 1000 calories a day, approximately one half of the daily caloric requirement. The alcohol consumption inevitably results in reduced

Table <i3,,S: Neurological complications associated with alcohol abuse

Nutritional deficiency
  Wernicke's encephalopathy
  Korsakoff's syndrome
  Pellagra
Direct effects of alcohol
  Acute intoxication
  Fetal alcohol syndrome
Abnormalities of serum electrolytes and osmolality
  Central pontine myelinolysis
Alcohol withdrawal
  Delirium tremens
Diseases of uncertain pathogenesis
  Alcoholic polyneuropathy
  Alcoholic myopathy
  Amblyopia
  Cerebellar degeneration
  Marchiafava-Bignnmi disease

intake of other foods. The problem is compounded further by malabsorption and abnormal metabolism of vitamins, both of which are common in alcoholics.

Alcoholic Neuropathy

Neuropathy is the most frequent neurological complication of alcoholism. Depending on the method of ascertainment, it may be diagnosed in 10-75% of alcoholic patients. Most affected patients are between 40 and 60 years of age, and in essentially all cases, there is a history of chronic and heavy alcohol intake.

Clinical Features

Alcoholic neuropathy is a mixed sensory and motor disorder. The onset of symptoms is usually insidious, beginning in the feet and progressing proximally and symmetrically. Paresthesia is the most common presenting complaint. Many patients also complain of pain, either an aching discomfort in the calves or a burning sensation over the soles. Dysesthesias at times become so severe that a light touch or gentle rubbing over the skin is interpreted as intensely unpleasant (Koike et al. 2001). Interestingly, pain is more often a problem in those with milder neuropathy.

On examination, signs of a distal symmetrical polyneuropathy are invariably present. Both deep and superficial sensations are affected. Ankle tendon reflexes and sometimes knee reflexes arc absent. Weakness and wasting are limited to the distal feet in mild cases but can 11)volvi' the distal upper extremities in more severe cases. Rarely, there may be vagus-recurrent laryngeal nerve involvement, with prominent hoarseness and weakness of voice.

Other manifestations of chronic alcoholism are often evident. Liver cirrhosis, hepatic encephalopathy, Wernicke-Korsakoff syndrome, alcoholic cerebellar degeneration, and alcohol withdrawal symptoms all occur frequently at the time of evaluation. Trophic skin changes in the form of hypcrpigmentation, edema, ulcers, and cellulitis in the distal part of the feet may also occut. There may be radiological suggestions of a distal neuropathic arthropathy (Charcot's forefeet, acrodysrrophic neuropathy), with phalangeal atrophy, bony resorption, and subluxation of small joints in the feet. Repeated ttauma and infections to insensitive parts of the feet are probably responsible; this syndrome is prevalent in the south of France and Spain, where the term *TbcvenanVs syndrome* is applied.

Laboratory Studies and Pathology

The pathology of alcoholic neuropathy is predominantly axonal loss. Nerve conduction studies show reduced amplitude of sensory nerve responses with normal or mildly reduced conduction velocities. Electromyography may reveal signs of denervation and reinnervation in distal muscles of the lower extremities. Axonal degeneration of both myelinated and unmyelinated fibers is present on sural nerve biopsy. In approximately one fourth of patients, autonomic dysfunction may be demonstrated by abnormalities in heart rate variation to deep breathing, Valsalva maneuver, and postural change (Mouforte et al. 1995).

l'<.itboi>cnesis

Both alcohol neurotoxicity and thiamine deficiency may play major roles in the pathogenesis of alcoholic neuropathy. Many patients with alcoholic neuropathy have no evidence of nutritional deficiency but there are also reports that a balanced diet and supplemental vitamins occasionally produce improvement in neuropathy in those patients who continued to drink heavily.

Treatment and Management

It seems prudent to treat most affected patients with supplemental multivitamins and a balanced diet. Most patients probably do not respond to vitamin supplements alone, and abstinence from alcohol is paramount for treatment success. Even under ideal conditions, recovery is slow and incomplete.

Tobacco-Alcohol or Nutritional Amblyopia

Tobacco-alcohol amblyopia is a syndrome of vision loss caused by a selective lesion of the optic nerves. In Western countries, most affected patients ate chronic and severe alcoholics, often with a history of poor dietary intake or marked weight loss. Vision loss occurs insidiously and

painlessly, progressing in both eyes over a period of several weeks. The mosi common deficit* arc unpaired visual acuity and the presence of central or centrocecal scotomata. Even in severely affected subjects, the optic discs may show only mild pallor.

Although it is commonly called tobacco-alcohol amblyopia, neither agent has been proved to be directly responsible for the vision loss. The underlying cause is probably a nutritional deficiency. The disease is essentially identical to the amblyopia seen in prisoners of war and malnourished individuals who have no access to either alcohol or tobacco. Moreover, treatment with a combination of an adequate diet and B vitamins, despite the continuation of drinking and smoking, results in visual recovery. Dietary deficiencies of vitamin B_{12}, thiamine, folate, and riboflavin, all of which have been linked to optic neuropathy, may individually or together be responsible.

Marchiafava-ISignami Disease

In 1903, Marchiafava and bignami, two Italian pathologists, described a curious syndrome of selective demyelination of the corpus callosum in alcoholic Italians who indulged in large quantities of red wine. The disease seems to affect severe and chronic alcoholics in their middle or late adult life, with a peak frequency between 40 and 60 years of age. It is not restricted to any one ethnic group and consumption of red wine is not an invariable feature. Because of the background history of alcohol abuse, a nutritional cause has been invoked, but no nutritional factor has been identified. A toxic cause, such as direct toxicity of ethanol or other constituents, seems equally plausible.

A clinical diagnosis is often difficult, because neurological presentations vary considerably. Mental and motor slowing, other personality and behavior changes, incontinence, dysarthria, seizures, and hemiparesis occur to a varying extent. Occasional patients present with *a* coma. The most common picture on neurological evaluation is that of a frontal lobe or dementing syndrome. Sucking, grasping, and ;;e;;erih.iin.'ii may be prominent. 'I hese symptoms have a tendency to remit, and many patients survive and later die of an unrelated cause.

Pathologically, selective involvement of the central portion of the corpus callosum occurs; the anterior and posterior portions are spared or affected to a much lesser degree. There also may be symmetrical involvement of other white matter tracts. Magnetic resonance imaging is valuable for premortem visualization of these white matter lesions.

Treatment should be directed at nutritional support and rehabilitation from alcoholism. In those patients who recovered, it is not clear whether improvement was a result of vitamin supplementation or merely a tcflection of the disease's natural history.

Alcoholic-Nutritional Cerebellar Degeneration

Although the prevalence of this disorder is not known, alcoholic cerebellar degeneration is likely the most common of the acquired degenerations of the cerebellum. Men arc affected more frequently than women, and the incidence peaks in the middle decades of life. Alcohol abuse is long-standing in all patients, and alcoholic polyneuropathy occurs in most patients. The clinical syndrome is usually quite stereotyped. The presentation is a progressive unsteadiness in walking that evolves over weeks or months. Less commonly, a mild gait difficulty may be present for some time, only to worsen acutely during binge drinking or an intercurrent illness. On examination, the most obvious finding is a truncal ataxia, readily demonstrated by a wide-based gait and difficulty with tandem walking. Limb ataxia, if present, is much milder than the truncal ataxia and more severe in the legs than in the arms. In contrast to Wernicke's encephalopathy, nystagmus and ocular dysmetria arc uncommon. Dysarthria, tremor, and hypotonia are rare findings. With abstinence I. . . .; alcohol JI:J niiirilional supplement.'), improvement in cerebellar symptoms occurs slowly but may be incomplete.

The pathological changes consist of selective atrophy of the anterior and superior parts of the cerebellar vermis, with the cerebellar hemispheres involved to a lesser extent, lirain imaging is useful in demonstrating the atrophy during life. Histologically, cell loss involves all neuronal types in the cerebellum, although Purkinje's cells are the most severely affected. A mild secondary loss of neurons is common in the deep cerebellar nuclei and the inferior olivary nuclei. In some patients, concomitant pathological changes of Wernicke's encephalopathy may be present.

MISCELLANEOUS DEFICIENCY DISEASES

Strachan's Syndrome and Related Disorders

In 1887, Strachan, a medical officer in the West Indies, described a syndrome of severe painful polyneuropathy, sensory ataxia, vision loss, and mucocutaneous excoriations. Although it was originally known as *jdimncan neuritis,* hundreds of cases were quickly recognized around the world. More recent cases are seen primarily in underdeveloped countries and in prisoners of war. Nutritional deficiency plays a leading role in the pathogenesis of this disorder, but specific vitamins have not been identified. The majority of patients likely had deficiencies of multiple vitamins, especially that of thiamine.

The clinical picture varies from patient to patient. The essential features are (1) a polyneuropathy that is often sufficiently severe to produce sensory ataxia; (2) amblyopia with optic atrophy; (3) tinnitus, hearing

loss, and sometimes vertigo; and (4) a varying combination of stomatoglossitis, genital soreness and excoriation, and corneal degeneration. Gait ataxia and loss of sensation to vibration and joint position are prominent findings.

In the absence of a distinctive cause, there seems to be little value in distinguishing Strachan's syndrome from nutritional amblyopia and polyneuropathy. As in other deficiency diseases, treatment is directed toward establishing adequate diet and replenishing vitamins. Some degree of improvement can be expected, especially in the polyneuropathy.

An outbreak of optic and peripheral neuropathy in Cuba provides further insight into the etiology of this nutritional condition (Roman 1994). The Cuban outbreak occurred in 1992-1993, coinciding with a period of food shortage and rationing. Clinical manifestations included a varying combination of retrobulbar optic neuropathy, peripheral neuropathy, sensorineural deafness, spasticity, position and vibration sense loss, dysphonia, and dysphagia. Increased risk was associated with poor dietary intake, smoking, heavy alcohol drinking, weight loss, and excessive sugar consumption. No toxic etiological agent was identified. Supplementation of multivitamins to the entire Cuban population coincided with abatement of the epidemic. A dependence on cane sugar and a relative deficiency of meat and vegetables (and hence the B vitamins) seemed responsible for the outbreak.

Vitamin A

Dietary deficiency of vitamin A is uncommon in Europe and the United States. Deficiency may occur rarely in fat malabsorption syndromes, such as sprue, biliary atresia, and cystic fibrosis. A few cases occurred in infants put on nondairy formula free of vitamin A.

The earliest sign of deficiency is reduced ability to see in dim light (night blindness). Rctinol, an aldehyde form of vitamin A, binds with the protein opsin to form rhodopsin, which is responsible for vision at low light levels. Xerosis, or keratinization, of the conjunctiva and cornea often accompanies the night blindness. Some patients have the characteristic Bitot's spots, which are white, foamlike spots appearing at the side of the cornea. These eye findings are caused by metaplasia of epithelial cells and, if severe, can lead to permanent blindness. Rarely, infants may manifest a syndrome of raised intracranial pressure, bulging fontanelles, and lethargy.

Patients with signs of vitamin A toxicity or overdose are also likely to see a neurologist. The classic syndrome of toxicity is that of pseudotumor cerebri with headache and papilledema. The skin is often dry and pruritic, and patients may complain of generalized joint or bone pain. Especially in children, joint swelling and hyperostoses are often evident on roentgenography. Chronic daily consumption of more than 25,000 IU may produce toxicity, although most reported patients consumed much higher doses over a shorter period of time. Unusual foods, such as polar bear liver and halibut liver, contain high concentrations of vitamin A and have caused acute toxicity. Serum retinol level is useful in the diagnosis. The generally accepted lower limit of normal is 20 mg/dL, whereas concentrations in excess of 100 mg/dL are suggestive of toxicity.

Vitamin D

Derangement in vitamin D and calcium metabolism is responsible for a syndrome of proximal weakness that often occurs in the setting of vitamin D deficiency and osteomalacia. Although the pathogenesis of the disorder is not fully elucidated, patients recover partially or completely with vitamin D treatment. The disorder may be caused by a diversity of systemic conditions, including hyperparathyroidism, hypophosphatemia, chronic renal failure, anticonvulsant use, malabsorption, dietary deficiency, and inadequate exposure to sunlight.

A waddling gait and proximal weakness of the pelvic girdle is the most prominent finding on examination. Neck muscles also may be weak, but bulbar and ocular weakness is not present. Tendon reflexes and sensation are normal. Aside from the manifestations of myopathy, accompanying clinical features include a long history of multiple bone fractures, vertebral collapse, and disabling bone pain. Bone pain mainly affects the pelvic girdle, and the muscles are usually not painful. The pain may make the actual weakness difficult to assess. When vitamin D therapy is instituted, the pain disappears quickly, and true muscular weakness is unmasked.

Serum creatine kinase level is usually normal or mildly elevated. Nonspecific type II muscle fiber atrophy is seen on biopsy. Electromyography typically shows short-duration, low-amplitude, and polyphasic motor unit potentials without spontaneous activities, features similar to those of other metabolic myopathies. Other laboratory abnormalities of deranged bone metabolism are present. Osteomalacia is evident by roentgenography. Serum alkaline phosphatase almost always is abnormally high, and serum calcium and phosphorus may be normal or mildly decreased. These laboratory studies return to normal after a short period of vitamin D therapy. Muscle weakness, however, recovers much more slowly over a period of several months.

Vitamin D deficiency and compensatory increase of parathyroid hormone are common in hospitalized or immobilized patients (Thomas et al. 1998). Some of the contributing factors include insufficient exposure to sunlight, anticonvulsant drug therapy, renal dialysis, and Parkinson's disease. The deficiency poses a risk for bone loss and fracture. Its effect on neuromuscular function in this population is uncertain.

Protein-Calorie Malnutrition

Millions of infants and children in underdeveloped countries suffet ftom varying degrees of protein and calotie deficiencies and manifest two interrelated syndromes, marasmus and kwashiorkor. Marasmus is primarily a result of caloric insufficiency and is characterized by extreme emaciation and growth failure in early infancy. These infants usually have never been breast fed or were weaned before the age of 1 year. Kwashiorkor is seen most commonly in children weaned between 2 and 3 years of age, and its primary underlying cause is protein deficiency. The signs of kwashiorkor are edema, ascites, hepatomegaly, sparse hair, and skin depigmentation.

The earliest and most consistent neurological signs in these children are apathy to the environment and extreme irritability. In addition, weakness, generalized muscle wasting, hypotonia, and hvporeflexia occur frequently. Cognitive deficits may be permanent despite improvement in nutrition. It is difficult to separate the effects of malnutrition from those of socioeconomic deprivation, but comparison studies in siblings show persistent impairment of intelligence attributable to malnutrition. Autopsy and imaging studies show the brain to be slightly atrophic and neutonal development less mature in these patients.

A mild encephalopathy, usually no more than transient dtowsiness, sometimes occurs during the first week of dietary treatment. Occasionally, children develop asterixis or coma or even die as a result of their treatment. Other children manifest a transient syndrome of rigidity, coarse tremors, myoclonus, and exaggerated tendon reflexes during the first few weeks of recovery from malnutrition.

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Chapter 64
Effects of Toxins and Physical Agents on the Nervous System

A. EFFECTS OF OCCUPATIONAL TOXINS ON THE NERVOUS SYSTEM

Michael J. Aminoff

Neurotoxic disorders, especially those with an iatrogenic basis, arc well described. Hence any neurological condition, such as a peripheral neuropathy, may be thought to be caused by a neurotoxin and may be the subject of potential litigation. Nevertheless, neurotoxic disorders are occurring increasingly as a result of occupational or environmental exposure to chemical agents and often go unrecognized.

RECOGNITION OF NEUROTOXIC DISORDERS

Exposure to neurotoxins may lead to dysfunction of any part of the central, peripheral, or autonomic nervous system and the neuromuscular apparatus. Neurotoxic diMirJirs .:,i..- nvotuii/id iv.ulily il n Jusr temporal relationship exists between the clinical onset and prior exposure to a chemical agent, especially one known to be neurotoxic. Known neurotoxins produce stereotyped or characteristic neurological disturbances that generally cease to progress soon after exposure is discontinued and ultimately improve to a variable extent. Recognition of a neurotoxic disorder is more difficult when exposure is chronic or symptoms are nonspecific. Diagnosis may be clouded by concerns about possible litigation, and the problem is compounded when the exposure history is unclear. Patients often attribute symptoms of an idiopathic disorder to chemical exposure when no other cause can be found. Such patients have often been exposed to several chemical agents or are known to abuse alcohol or other dtugs, thereby further confounding the issue.

Single case reports that an agent is neurotoxic arc unreliable, especially when the neurological symptoms are frequent in the general population. Epidemiological studies may be helpful in establishing a neurotoxic basis for symptoms. However, many of the published studies are inadequate because of methodologic problems such as the selection of appropriate control subjects. Recognition of a neurotoxic basis for neurobchavioral disorders, for example, requires matching of exposed subjects and unexposed controls, not only for age, gender, and race but also for premorbid cognitive ability; educational, social, and cultural background; and alcohol, recreational drug, and medication use. Laboratory test results are often unhelpful in confirming that the neurological syndrome is caused by a specific agent, either because the putative neurotoxin

cannot be measured in body tissues or because the interval since exposure makes such measurements meaningless.

The part of the central, peripheral, or autonomic nervous system and of the neuromuscular apparatus that is damaged by exposure to neurotoxins depends on the responsible agent. The pathophysiological basis of neurotoxicity is often unknown. In considering the possibility of a neurotoxic disorder, it is important to obtain a detailed account of all chemicals to which exposure has occurred, including derails of the duration and severity of exposure, any protective measures taken, and the context in which exposure occurred. Then it must be determined whether any of these chemicals are known to be neurotoxic and whether symptoms are compatible with the known toxicity of the suspected compound. Many neurotoxins can produce clinical disorders thai resemble well-known metabolic, nutritional, or degenerative neurological disorders, and it is therefore important to consider these and any other relevant disease processes in the differential diagnosis. Neurotoxins cause diffuse rather than focal or lateralized neurological dysfunction. In recognizing new neurotoxic disorders, a clustering of cases is often important, but this may not be evident until patients are referred for specialist evaluation.

The neurological disorder is typically monophasic. Although progression may occur for several weeks after exposure has been discontinued (coasting), it is eventually arrested and improvement may then follow, depending on the severity of the original disorder. Prolonged or progressive deterioration long after exposure has been discontinued, or the development of neurological symptoms months to years after exposure, suggests that a neurotoxic disorder is not responsible.

This section reviews the neurotoxicity of some occupational and environmental agents, in alphabetical order.

ORGANIC: CHEMICALS

Acrylamide

Acrylamide polymers are used as flocculators and are constituents of certain adhesives and products such as cardboard or molded parts. They also are used as grouting agents for mines and tunnels, a solution of the monomer being pumped into the ground where polymerization is allowed to occur. The monomer is neurotoxic, and exposure may occur during irs manufacture or in the polymerization process. Most cases of acrylamide toxicity occur by inhalation or cutaneous absorption. The acrylamide is distributed widely throughout the body and is excreted primarily through the kidneys. The mechanism responsible for its neurotoxicity is unknown. Studies in animals have shown early abnormalities in axonal transport, and this ma\ accomn tor ihe lusloparhological changes discussed here.

Clinical manifestations of acrylamide toxicity depend on the severity of exposure. Acute high-dose exposure results in confusion, hallucinations, reduced attention span, drowsiness, and other encephalopathy changes. A peripheral neuropathy of variable severity may occur after acute high-dose or prolonged low-level exposure. The neuropathy is a length-dependent axonopathy involving both sensory and motor fibers; some studies suggest that terminal degeneration precedes axonopathy and is the primary site of involvement (LoPachin, Ross, and Lehning 2002), Hyperhidrosis and dermatitis may develop before the neuropathy is evident clinically in those with repeated skin exposure. Ataxia from cerebellar dysfunction also occurs and relates to degeneration of afferent and efferent cerebellar fibers and Purkinje cells. Neurological examination reveals disral sensorimotor deficits and early loss of all tendon reflexes rather than simply the Achilles reflex, which is usually affected first in most length-dependent neuropathies. Autonomic abnormalities other than hyperhidrosis are uncommon. Gait and limb ataxia are usually greater than can be accounted for by the sensory loss. With discontinuation of exposure, the neuropathy coasts, arrests, and may then slowly reverse, but residual neurological deficirs are common. These consist particularly of spasticity and cerebellar ataxia; the peripheral neuropathy usually remits because regeneration occurs in the peripheral nervous system. No specific treatment exists.

Klectrodiagnostic studies provide evidence of an axonal sensorimotor polyneuropathy. Workers exposed to acrylamide may be monitored electrophysiological!)' by recording sensory nerve action potentials, which arc attenuated early in the course of the disorder, or by measuring the vibration threshold. Histopathological studies show accumulation of neurofilaments in axons, especially distally, and distal degeneration of peripheral and central axons. The role of neurofilament accumulation in the generation of axonal degeneration has been questioned (Stone ct a!. 2001). The large myelinated axons are involved first. The affected central pathways include the ascending sensory fibers in the posterior columns, the spinocerebellar tracts, and the descending corticospinal pathways. Involvement of postganglionic sympathetic efferent nerve fibers accounts for the sudomotor dysfunction. Measurement of hemoglobin-acrylamidc adducts may be useful in predicting the development of peripheral neuropathy.

Allyl Chloride

Ally I chloride is used for manufacturing cpoxy resins, certain insecticides, and polyacrylonitrile. Exposure leads to a mixed sensorimotor distal axonopathy. Cessation of exposure is followed by recovery of variable degree. Intra-axonal accumulation of neurofilaments occurs multifocally before axonal degeneration in animals exposed to this

compound. Similar changes may occur also in the postero-lateral columns of the spinal cord.

Carbon Disulfide

Carbon disulfide is used as a solvent or soil fumigant, in perfume production, in certain varnishes and insecticides, in the cold vulcanization of rubber, and in manutacniring viscose rayon and cellophane films. Toxicity occurs primarily from inhalation or ingestion but also may occur transdermally. The pathogenetic mechanism is uncertain but may involve a chelating effect of carbon disulfide metabolites, direct inhibition of certain en/ymes, or the release of free radicals following cleavage of the carbon-sulfur bond. Most reported cases have been from Europe and Japan.

Acute inhalation of concentrations exceeding 300-400 ppm leads to an encephalopathy, with symptoms that vary from mild behavioral disturbances to drowsiness and, ultimately, to respiratory failure. Behavioral disturbances may include explosive behavior, mood swings, mania or depression, confusion, and other psychiatric disturbances. Long-term exposure to concentrations between 40 and 50 ppm may produce similar disturbances. Minor affective or cognitive disturbances may be revealed only by neuro-psychological testing.

Long-term exposure to carbon disulfide may lead also to extrapyramidal or pyramidal deficits, impaired vision (Gobba 2000), absent pupillary and corneal reflexes, optic neuropathy, and a characteristic retinopathy, A small-vessel vaseulopathy may be responsible (Huang et al. 2001). A clinical or subclinical polyneuropathy develops after exposure to levels of 100-150 ppm for several months or to lesser levels for longer periods and is characterized histologically by focal axonal swellings and ncurofilamen-tary accumulations.

No specific treatment exists other than the avoidance of further exposure. Recovery from the peripheral neuropathy generally follows the discontinuation of exposure, but some central deficits may persist.

Carbon Monoxide

Occupational exposure to carbon monoxide occurs mainly in miners, gas workers, and garage employees. Other modes of exposure include poorly ventilated home-heating stoves and suicide attempts. The neurotoxic effects of carbon monoxide relate to intracellular hypoxia. Carbon monoxide binds to hemoglobin with high affinity to form carboxyhcmoglobin; it also limits the dissociation of (i\ylieinoL;lobir ami binds ro various enzymes. Acute toxicity leads to headache (Hampson and Hampson 2002), disturbances of consciousness, and a variety of other behavioral changes. Motor abnormalities include the development of pyramidal and extrapyramidal deficits. Seizures may occur, and focal cortical deficits sometimes develop. Treatment involves prevention of further exposure to carbon monoxide and administration of pure or hyperbaric oxygen (Hawkins, Harrosin, and Charters 2000). Neurological deterioration may occur sevetal weeks after partial or apparently full recovery from the acute effects of carbon monoxide exposure, with recurrence of motor and behavioral abnormalities. The degree of recovery from this delayed deterioration is limited, and some patients lapse into a persistent vegetative state.

Pathological examination shows hypoxic and ischemic damage in the cerebral cortex as well as in the hippocam-pus, cerebellar cortex, and basal ganglia. Lesions are also present diffusely in the cerebral white matter. The delayed deterioration has been related to a diffuse subcortical leukoencephalopathy, but its pathogenesis is uncertain.

Ethylene Oxide

Ethylene oxide is used to sterilize heat-sensitive medical equipment and as an alkylating agent in industrial chemical synthesis. A by-product, ethylene chlorohydrin, is highly toxic. Operators of sterilization equipment should wear protective ventilatoty apparatus to prevent occupational exposure. Acute exposure to high levels produces headache, nausea, and a severe, reversible encephalopathy. Long-term exposure to ethylene oxide or ethylene chlorohydrin may lead to a petipheral sensorimotor axonopathy and mild cognitive changes, for example, in operating-room nurses and sterilizer workers. Recovery generally follows cessation of exposure. Neuropathy may be produced in rats by exposure to ethylene oxide, and the residual ethylene oxide in sterilised dialysis tubing may contribute to the poly-neuropathy occurring in patients undergoing chronic hemodial; sis.

Hex a carbon Solvents

The hexacarbon solvents w-hexane and methyl «-butyl ketone ate both metabolized to 2,5-hexanedione, which targets proteins required for the maintenance of neuronal integrity (Spencer, Kim, and Sabri 2002) and is responsible in large part for their neurotoxicity. This neurotoxicity is potentiated by methyl ethyl ketone, which is used in paints, lacquers, printer's ink, and certain glues. «-Hexane is used as a solvent in paints, lacquers, and printing inks and is used especially in the rubber industry and in certain glues. Workers involved in the manufacturing of footwear, laminating processes, and cabinetry, especially in confined, unventilated spaces, may be exposed to excessive concen-trations. Methyl H-butyl ketone is used in the manufacture of vinyl and acrylic coatings and adhesives and in the printing industry. Exposure to either of these chemicals by

inhalation or skin contact leads to a progressive distal sensorimotor axonal polyneuropathy. Optic neuropathy or maculopathy and facial numbness also have followed w-hexane exposure. The neuropathy is related to a disturbance of axonal transport, and histopathological studies reveal giant multifocal axonal swelling and accumulation of axonal neurofilaments, with distal degeneration in peripheral and central axons. Myelin retraction and focal demyelination are found at the giant axonal swellings.

Acute inhalation exposure may produce feelings of euphoria associated with hallucinations, headache, unsteadiness, and mild narcosis. This has led to the inhalation of certain glues for recreational purposes, which causes pleasurable feelings of euphoria in the short tetm but may lead to a progressive, predominantly motor neuropathy and symptoms of dysautonomia after high-dose exposure and a more insidious sensorimotor polyneuropathy following chronic use.

Electrophysiological findings include increased distal motor latency and marked slowing of maximal motor conduction velocity as well as small or absent sensory nerve action potential[1], and electromyographic signs of denervation in affected muscles. The conduction slowing relates to demyelinative changes and is unusual in other toxic neuropathies. A reduction in the it/e or sensory nerve action potentials may occur in the absence of clinical or other electrophysiological evidence of nerve involvement. Central involvement may result in abnormalities of sensory evoked potentials. The cerebrospinal fluid is usually normal, but a mildly elevated protein concentration is sometimes found. Despite cessation of exposure, progression of the neutological deficit may continue for several weeks or months (coasting) before the downhill course is arrested and tecovery begins. Severe involvement is followed by incomplete recovery of the peripheral neuropathy. When the polyneuropathy does resolve, previously masked signs of central dysfunction, such as spasticity, may become evident.

Methyl Bromide

Methyl bromide has been used as a refrigerant, insecticide, fumigant, and fire extinguisher. Its high volatility may lead to work-area concentrations sufficient to cause neurotoxicity[7] from inhalation. Following acute high-level exposure, an interval of several hours or more may elapse before the onset of symptoms. Because methyl bromide is odorless and colorless, subjects may not even be aware that exposure has occurred. Hence chloropicrin, a conjunctival and mucosal NTH nit, > aimmonl) added to warn ot mhalatinn exposure. Acute methyl bromide intoxication leads to an encephalopathy with convulsions, delirium, hyperpyrexia, coma, pulmonary edema, and death. Acute exposure to lower concentrations may result in conspicuous mental changes including confusion, psychosis, or affective distutbances; headache; nausea; dysarthria; tremulousness; myoclonus; ataxia; visual disturbances; and seizures.

Long-term low-level exposure may lead to a polyneuropathy in the absence of systemic symptoms. Distal paresthesias are followed by sensory and motor deficits, loss of tendon reflexes, and an ataxic gait. Visual disturbances, optic atrophy, and upper motor neuron deficirs may occur also. Calf tenderness is sometimes conspicuous. The cerebrospinal fluid is unremarkable, although clectrodiagnostic study results reveal both sensory and motor involvement. Gradual improvement occurs with cessation of exposure.

Treatment is symptomatic and supportive. Hemodialysis may also be helpful in removing bromide from the blood (Yamano et al. 2001). Chelating agents have been used in the past but are of uncertain utility.

Org an o chlorine Pesticides

The organochlorinc pesticides include aldrin, dieldrin, and lindane as well as the once popular insecticide dichlorodiphenyltrichloroethylene, commonly called *DD'i.* Tremor and convulsions may follow acute high-level exposure, but the effects of chronic low-level exposure are uncertain. Chlordecone, which belongs to this group, may produce a neurological disorder characterized by "nervousness," tremor, clumsiness of the hands, gait ataxia, and opsoclonus. Minor cognitive changes and benign intracranial hypertension may occur. The pathophysiology of the disorder has not been established.

Organophosphates

Organophosphates are used mainly as pesticides and herbicides bur are also used as petroleum additives, lubricants, antioxidants, flame retardants, and plastic modifiers. Most cases of organophosphate toxicity result from exposure in an agricultural setting, not only among those mixing or spraying the pesticide or herbicide but also among workers returning prematurely to sprayed fields. Absorption may occur through the skin, by inhalation, or through the gastrointestinal tract. Organophosphates inhibit acetylcholinesterase by phosphorylation, with resultant acute cholinergic toxicity. This has both central and neuromuscular manifestations. Symptoms include nausea, salivation, lacrimation, headache, weakness, and bronchospasm in mild instances and bradycardia, tremor, chest pain, diarrhea, pulmonary edema, cyanosis, convulsions, and even coma in more severe cases. Death may result from respiratory or heart failure. Treatment involves intravenous administration of pralidoxime (1 g) together with atropine (1 mg) subcutaneously every 30 minutes until sweating and salivation are controlled. I'ralidoxime accelerates reactivation of the inhibited acetylcholinesterase, and atropine is

effective in counteracting muscarinic effects, although it has no effect on the nicotinic effects such as weakness or respiratory depression. It is important to ensure adequate ventilatory support before atropine is given. The dose of pralidoximc can be repeated if no obvious benefit occurs, but in refractory cases it may need to be given by intravenous infusion, the dose being titrated against clinical response. Functional recovery may take approximately 1 week, although acetylcholinesterase levels take longer to reach normal levels.

Carbamate insecticides also inhibit cholines re rases but have a shorter duration of action than organophosphate compounds. The symptoms of toxicity are similar to those described for organophosphates but are generally milder. Treatment with atropine is usually sufficient.

Certain orga no phosphates cause a delayed polyneuropathy that occurs approximately 2-3 weeks after acute exposure. In the past, contamination of illicit alcohol with triorthocresyl phosphate ("Jake") led to large numbers of such cases. There is no evidence that peripheral nerve dysfunction follows prolonged low-level exposure to organophosphates (Lotti 2002). Paresthesias in the feet and cramps in the calf muscles are followed by progressive weakness that typically begins distally in the limbs and then spreads to involve more proximal muscles. The maximal deficit usually develops within 2 weeks. Quadriplegia occurs in severe cases. Although sensory complaints are typically inconspicuous, clinical examination shows sensory deficits. The Achilles reflex is typically lost, and other tendon reflexes may be depressed also; however, in some instances evidence of central involvement is manifest by brisk tendon reflexes. Cranial nerve function is spared typically. With time, there may be improvement in the peripheral neuropathy, but upper motor neuron involvement then becomes unmasked and often determines the prognosis for functional recovery. There is no specific treatment to arrest progression or hasten recovery. Electro diagnostic studies reveal an axonopathy with partial denervation of affected muscles and small compound muscle action potentials but normal or only minimally reduced maximal motor conduction velocity.

The delayed syndrome follows exposure only to certain organophosphates such as triorthocresyl phosphate, leptophos, trichlorfon, and mi pa fox. The neurological disturbance relates m some way to phosphorylation and inhibition of the enzyme neuropathy target esterase (NIT"), which is present in essentially all neurons and has an uncertain role in the nervous system (Glynn ct al. 1998). In addition, *aging* of the inhibited NTF (loss of a group attached to the phosphorus, leaving a negatively charged phosphoryl group attached to the protein) must occur for the neuropathy to develop. The precise cause of the neuropathy is uncertain, however. No specific treatment exists to ptevent occurrence of the neuropathy following exposure, but measurement of lymphocyte NTE has been used to monitor occupational exposure and predict the occurrence of neuropathy. Moreover, the ability of any particular organophosphate to inhibit NTE in hens may predict its neurotoxicity in humans.

Three other syndromes related to organophosphates require brief comment. The intermediate syndrome occurs in the interval between the acute cholinergic crisis and the development of delayed neuropathy, typically becoming manifest within 4 days of exposure and resolving in 2-3 weeks (Guadarrama-Naveda, de Cabrere, and Matos-Bastidas 2001). It reflects excessive cholinergic stimulation of nicotinic receptors and is characterized clinically by respiratory, bulbar, and proximal limb weakness. It relates to the severity of poisoning and to prolonged inhibition of acetylcholinesterase activity but not to the development of delayed neuropathy. The syndrome of clipper's flu refers to the development of transient symptoms such as headache, rhinitis, pharyngitis, myalgia, and other flulike symptoms in farmers exposed to organophosphate sheep dips. Vague sensory complaints (but no objective abnormalities on sensory threshold tests) may also occur (Pilkington et al. 2001). Whether these complaints relate to mild organophosphate toxicity is uncertain. Similarly uncertain is whether chronic effects (persisting behavioral and neurological dysfunction) may follow acute exposure to organophosphates. The occutrencc of chronic symptoms in the absence of any episode of acute toxicity is unlikely. Evaluation of reports is hampered by incomplete documentation and the variety of agents to which exposure has often occurred. Carefully controlled studies may clarify this issue in the future.

Pyrethroids

Pyrethroids are synrhetic insecticides. Occupational exposure has led to paresthesias that have been attributed to repetitive activity in sensory fibers as a result of abnormal prolongation of the sodium current during membrane excitation. Treatment is purely supportive.

Solvent Mixtures

In the 1970s a number of reports from Scandinavia suggested that house paintets, in particular, developed a disturbance of cognitive function that related to exposure to mixtures of organic solvents. However, further studies (including cases previously diagnosed with the disorder) have failed to validate the earlier reports, which in many instances were methodologically flawed. Furthermore, workers performing the same basic tasks in different companies have highly variable levels of solvent exposure, complicating the interpretation of published studies (Horstman et al. 2001). Because of these factors, the existence of so-called "painter's encephalopathy" in those

exposed to low levels of organic solvents for a prolonged period remains uncertain.

Styrene

Styrene is used for manufacturing reinforced plastic and certain resins. Occupational exposure occurs by the dermal or inhalation routes and is typically associated with exposure to a variety of other chemicals, thereby making it difficult to define the syndrome that occurs from styrene exposure itself. Acute exposure to high concentrations of styrene has led to cognitive, behavioral, and attentional disturbances. Less clear are the consequences of exposure to chronic low levels of styrene. Abnormalities in psychomotor performance have been reported, but there is little compelling evidence of persisting neurological sequelae in this circumstance. Visual abnormalities (impaired color vision and reduced contrast sensitivity) have also been described (Castillo et al. 2001).

Toluene

Toluene is used in a variety of occupational settings. It is a solvent for paints and glues and is used to synthesize benzene, nitrotoluene, and other compounds. Exposure occurs among workers laying linoleum, spraying paint, and working in the printing industry, particularly in poorly ventilated locations. Chronic high exposure may lead to cognitive disturbances and to central neurological deficits with upper motor neuron, cerebellar, brainstem, and cranial nerve findings and tremor. An optic neuropathy may occur, as may ocular dysmetria and opsoclonus. Disturbances of memory and attention characterize the cognitive abnormalities, and subjects may exhibit a flattened affect. M,I::IH'IK K-MJIUIKV ::ii;i;;i:u:. :MRI) shows cerebral atrophy and diffuse abnormalities of the cerebral white matter; symmetrical lesions may be present in the basal ganglia and thalamus and the cingulate gyri. Thalamotomy may ameliorate the tremor (Miyagi et al. 1999). Lower levels of exposure lead to minor neurobeksvior.il disUirhina-..

Tricliloro ethylene

Trichloroethylene is an industrial solvent and degrcaser that is used in dry cleaning and the manufacture of rubber. It also has anesthetic properties. Recreational abuse has occurred because it may induce feelings of euphoria. Acute low-level exposure may lead to headache and nausea, but claims that an encephalopathy follows chronic low-level exposure are unsubstantiated. Higher levels of exposure lead to dysfunction of the trigeminal nerve, with progressive impairment of sensation that starts in the snout area and then spreads outward. This has been particularly associated with rebreathing anesthetic circuits where the trichlorcthylcnc is heated by the carbon dioxide absorbent. With increasing exposure, facial and buccal numbness is followed by weakness of the muscles of mastication and facial expression. Ptosis, extraocular palsies, vocal cord paralysis, and dysphagia may occur also, as may an encephalopathy, but occurrence of a peripheral neuropathy is uncertain. The clinical deficit relates to neuronal loss in the cranial nerve nuclei and degeneration in related tracts. With discontinuation of exposure, the clinical deficit generally resolves, sometimes over 1-2 years, bur occasional patients are left with residual facial numbness or dysphagia.

Vacor

Vacor, *a* rodenticide, has led to severe autonomic dysfunction accompanied by a usually milder sensorimotor axonopathy following its ingestion. The mechanism by which this develops is unclear, but it may relate to an impairment of fast anterograde axonal transport. Acute diabetes mellitus also resulrs from necrosis of the beta islet cells of the pancreas.

METALS

Aluminum

Aluminum exposure is responsible for dialysis encephalopathy, which is characterized by speech disturbances, cognitive decline, seizures, and myoclonus.

Arsenic

Arsenic poisoning can result from ingestion of the trivalent arsenite in murder or suicide attempts. Large numbers of persons in areas of India, Pakistan, and certain other countries are chronically poisoned from naturally occurring arsenic in ground water (Hall 2002). Traditional Chinese medicinal herbal preparations may contain arsenic sulfide and mercury and arc a source of chronic poisoning. Uncommon sources of accidental exposure include burning preservative-impregnated wood and storing food in antique copper kettles. Exposure to inorganic arsenic occurs in workers involved in smelting copper and lead ores.

With acute or subacute exposure, nausea, vomiting, abdominal pain, diarrhea, hypotension, tachycardia, and vasomotor collapse occur and may lead to death. Obtundation is common, and an acute confusion a 1 state may develop. Arsenic neuropathy takes the form of a distal axonopathy, although a demyelinating neuropathy is found soon after acute exposure. The neuropathy usually

develops within 2-3 weeks of acute or subacute exposure, although the latent period may be as long as 1-2 months. Symptoms may worsen over a few weeks despite lack of further exposure, but eventually stabilize. With low-dose chronic exposure, the latent period is more difficult to determine. In either circumstance, systemic symptoms arc also conspicuous. With chronic exposure, similar but less severe gastrointestinal disturbances develop, as may skin changes such as melanosis, keratoses, and malignancies. Mees' lines are white transverse striations of the nails (striate leukonychiae) that appear 3-6 weeks after exposure **(Figure** 64A.1). As a nonspecific manifestation of nail matrix injury, Mees' lines can be seen in a number of other conditions, including thallium poisoning, chemotherapy, and a variety of systemic disorders.

The neuropathy involves both large- and small-diameter fibers. Initial symptoms are typically of distal, painful dysesthesias and are followed by distal weakness. Proprioceptive loss may be severe, leading to marked ataxia. The severity of weakness depends on the extent of exposure. The respiratory muscles are sometimes affected, and the disorder may simulate Guillain-Barre syndrome both clinically and electrophysiologically. Elcctrodi a gnostic studies may initially suggest a demyelinating polyradiculo-neuropathy, but the changes of an axonal neuropathy subsequently develop. Arsenic levels in hair, nail clippings, or urine may be increased, especially in cases of chronic exposure.

Detection of arsenic in urine is diagnostically useful within 6 weeks of a single large-dose exposure or during ongoing low-level exposure. Inorganic arsenic values over 25 ug per 24 hours are abnormal. Methods are available in reference laboratories to distinguish between inorganic (toxic) and organic (sea food-derived) arsenic compounds. Arsenic bound to keratin can be detected in hair or nails months to years after exposure. Pubic hair is preferable to scalp hair for examination because it is less liable to environmental contamination. Levels exceeding 10 ug/g of tissue arc abnormal. Other abnormal laboratory features include aplastic anemia with pancytopenia and moderate cerebrospinal fluid protein elevation. Nerve conduction studies in chronic arsenic neuropathy reflect the changes of distal axonopatby with low-amplitude or unelicitable sensory and motor evoked responses and preserved conduction velocities. Electromyography typically shows denervation in distal extremity muscles. In the subacute stages, however. Mime clectropl'.\ siolnejcil v.mnv-., such .is partial motor conduction block, absent F responses, and slowing of motor conduction velocities are suggestive of demyelinating polyradiculoneuropathy. Progressive slowing of motor conduction velocities sufficient to invoke consideration of segmental demyelination has been reported in the first three months after massive exposure. Biopsies of peripheral nerves show axonal degeneration in chronic cases. Arsenite compounds react with protein sulfhydryl groups, interfere with formation of coenzyme A and several steps in glycolysis, and are potent uncouplers of oxidative phosphorylation. These biochemical reactions are responsible for the impaired neuronal energy metabolism, which in turn results in distal axonal degeneration.

Chelation therapy with either water-soluble derivatives of dimercaprol (DMSA or DMPS) or penicillamine is effective m controlling the systemic effects of acute arsenic poisoning and may prevent the development of neuropathy if it is started within hours of ingestion (Graeme and Pollack 1998). There is little evidence that chelation in the **later** stages of arsenic neuropathy promotes clinical recovery. The neuropathy itself often improves gradually over the course of many months, but depending on the

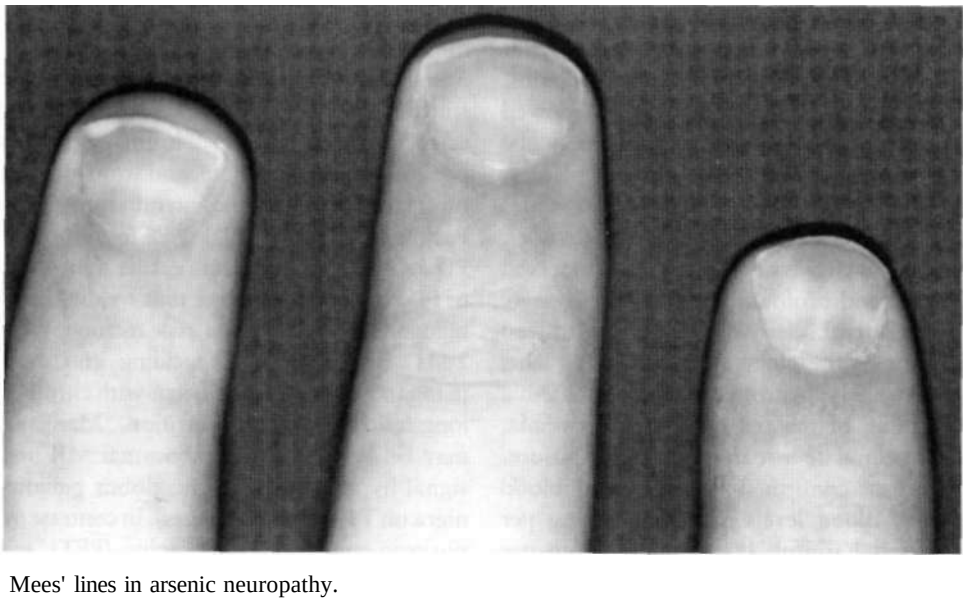

FIGURE 64A.1 Mees' lines in arsenic neuropathy.

severity of the deficit when exposure is discontinued, a substantial residual neurological deficit is common.

Lead

Occupational exposure to lead occurs in workers in smelting factories and metal foundries and those involved in demolition, ship breaking, manufacturing of batteries or paint pigments, and construction or repair of storage tanks. Occupational exposure also occurs in the manufacture of ammunition, bearings, pipes, solder, and cables. Non-industrial sources of lead poisoning are home-distilled whiskey, Asian folk remedies, earthenware pottery, indoor firing ranges, and retained bullets. Lead neuropathy reached epidemic proportions at the end of the nineteenth century because of unfcontrolled occupational exposure but now is rare because of strict industrial regulations. Exposure also may result from ingestion of old paint in children with pica and consumption of illicit spirits by adults. Absorption is commonly by ingestion or inhalation but occasionally occurs through the skin.

The toxic effects of inorganic lead salts on the nervous system commonly differ with age, producing acute encephalopathy in children and polyneuropathy in adults. Children typically develop an acure gastrointestinal illness followed by behavioral changes, ^HIIUMHM. drowsiness, reduced alertness, focal or generalized seizures, and {in severe cases) coma with intracranial hypertension. At autopsy, the brain is swollen, with vascular congestion, perivascular exudates, edema of the white matter, and scattered areas of neuronal loss and gliosis. In adults, an encephalopathy is less common, but behavioral and cognitive changes are sometimes noted. In adults, lead produces a predominantly motor neuropathy, sometimes accompanied by gastrointestinal disturbances and a microcytic, hypochromic anemia. The neuropathy is manifest primarily by a bilateral wrist drop sometimes accompanied by bilateral footdrop or by more generalized weakness that may be associated with distal atrophy and fascieulations. Sensory complaints are usually minor and overshadowed by the motor deficit. The tendon reflexes may be diminished or absent. Older reports describe a painless motor neuropathy with few or no sensory abnormalities and distinct patterns of weakness affecting wrist extensors, finger extensors, and intrinsic hand muscles. Preserved reflexes, fascieulations, and profound muscle atrophy may simulate amyotrophic lateral sclerosis. A rare sign of lead exposure is a blue line at the gingival margin in patients with poor oral hygiene. Hypochromic microcytic anemia with basophilic stippling of the red cells, hyperuricemia, and azotemia should stimulate a search for lead exposure.

Lead intoxication is confirmed by c lev a red blood and urine lead levels. Blood levels exceeding 70 j.iu, pet 100 mL are considered harmful, but even levels greater than 40 tig per 100 mL have been correlated with minor nerve-conduction abnormalities. Lead inhibits erythrocyte ^-aminolevulinic acid dehydratase and other enzymatic steps in the biosynthctic pathway of porphyrins. Consequently, increased red cell protoporphyrin levels emerge together with increased urinary excretion of 5-aminolevulinie acid and coproporphyria Excess body lead burden, confirming past exposure, can be documented by increased urinary lead excretion aftet a provocative chelation challenge with calcium ethylenediaminetetraaceric acid. Only a few electrophysiological studies have been reported in patients with overt lead neuropathy. These investigations indicate a distal axonopathy affecting both motor and sensory fibers. These observations corroborate changes of axonal degeneration seen in human nerve biopsies, Contrary to the findings in humans, lead produces segmental demye11nation in animals. Lead is known to cause early mitochondrial changes in cell-culture systems, but the biochemical mechanisms leading to neurotoxicity remain unknown.

Lead encephalopathy is managed supportively, but corticosteroids arc given to treat cerebral edema, and chelating agents (dimercaprol or 2,3-dimercaptopropane sulfonate) are prescribed also. No specific treatment exists for lead neuropathy other than prevention of further exposure to lead. Chelation therapy does not hasten recovery.

Manganese

Manganese miners may develop neurotoxicity following inhalation for prolonged periods (months or years) of dust containing manganese. Headache, behavioral changes, and cognitive disturbances ("manganese madness") are followed by the development of motot symptoms such as dystonia, parkinsonism, retropulsion, and a characteristic gait called "cock-walk" manifested by walking on the toes with elbows flexed and the spine erect. There is usually no tremor and the motor deficits rarely improve with l.-dopa therapy. Manganese intoxication has been reported in miners, smelters, welders, and workers involved in the manufacture of dry batteries; after chronic accidental ingestion of potassium permanganate, and from incorrect concenttation of manganese in parenteral nutrition. Welders with Parkinson's disease (PD) were found to have their onset of PD an average of 17 years earlier than a control population of PD patients, suggesting that welding, possibly by causing manganese toxicity, is a risk factor for PD (Racette et al. 2001). In addition to welding and manganese mining, manganese toxicity may occur with chronic liver disease and long-term parenteral nutrition. Manganese intoxication may be associated with abnormal MR imaging (abnormal signal hyperintensity in the globus pallidus and substantia nigra on'11-weighted images). In contrast to PD, fluorodopa positron-emission tomography (PET) scans arc usually normal in patients with manganese-induced parkinsonism,

and raclopride (D2 receptor) binding is only slightly reduced in the caudate and normal in the putamen. Neuronal loss occurs in the globus pallidus and substantia nigra pars reticularisj as well as in the subthalamic nucleus and striatum. There is little response to L-dopa of the extrapyramidal syndrome, which may progress over several years (Huang et al. 1998). Myoclonic jerking may occur, sometimes without extrapyramidal accompaniments (Ono, Komai, and Yamada 2002),

Mercury

The toxic effects of elemental mercury (mercury vapor), inorganic salts, and short-chain alkyl-mercury compounds predominantly involve the central nervous system and dorsal root ganglion sensory neurons. Inorganic mercury toxicity may result from inhalation during industrial exposure, as in thermometer and battery factories, mercury processing plants, and electronic applications factories. In the past, exposure occurred particularly in the hat-making industry. No evidence exists that the mercury contained in dental amalgam imposes any significant health hazard. Differences in health and cognitive function between dentists and control subjects cannot be attributed directly to mercury (Ritchie et al. 2002), Clinical consequences of exposure include cutaneous erythema, hyperhidrosis, anemia, proteinuria, glycosuria, personality changes, intention tremor ("hatter's shakes"), and muscle weakness. The personality changes ("mad as a hatter") consist of irritability; euphoria; anxiety; emotional lability; insomnia; and disturbances of attention, with dtowsiness, confusion, and, ultimately, stupor. A variety of other central neurological deficits may occur but are more conspicuous in patients with organic mercury poisoning,

The effects of methyl mercury (organic mercury) poisoning have come to be widely recognized since the outbreak that occurted in Minamata Bay (Japan) in the 1950s when industrial waste dischatged into the bay led to contamination of fish that were then consumed by humans. Outbreaks have occurred also following the use of methyl mercury as a fungicide, because intoxication occurs if treated seed, intended for planting, is eaten instead. Methyl and ethyl mercury compounds have been used as fungicides in agriculture and in the paper industry. Methyl mercury and elemental mercury are potent neurotoxins that cause neuronal degeneration in the cerebellar granular layer, calcarine cortex, and dorsal root ganglion neurons. The primary molecular target of methyl mercury is probably sulfhydryi ligands in enzyme complexes or critical membrane sites.

The characteristic features of chronic methyl mercury poisoning are sensory disturbances, constriction of visual fields, progressive ataxia, tremot, and cognitive impairment. Electrophysiological studies have shown that these symptoms relate to central dysfunction. Sensory disturbances result from dysfunction of sensory cortex or dorsal root ganglia rather than petipheral nerves, and rhe visual complaints also relate to cortical involvement. Pathological studies reveal neuronal loss in the cerebral cortex, including the parietal and occipital regions, as well as in the cerebellum. A few cases presenting with peripheral neuropathy or a predominantly motor neuronopathy resembling amyotrophic lateral sclerosis have been described in association with intense exposure to elemental mercury vapors.

The diagnosis of elemental or inorganic mercury intoxication usually can be confirmed by assaying mercury in urine. Monitoring blood levels is recommended for suspected organic mercury poisoning.

Chelating agents increase urinary excretion of mercury, but insufficient evidence exists to substantiate the claim that chelation increases the rate or extent of recovery.

Tellurium

Tellurium is used in the manufacture of various alloys; the coloring of glass, ceramics, and metalware; the production of rubber; and the manufacture of thermoelectric devices. Inhalation of volatile tellurium compounds may lead to headache, drowsiness, a metallic taste, hypohidrosis, skin rashes and discoloration, and a curious odor resembling garlic on the breath. Recovery generally occurs spontaneously.

Thallium

Thallium salts cause severe neuropathy and central nervous system degeneration that has led to their discontinued use as rodenticides and depilatories. Most intoxications result from accidental ingestion, attempted suicide, or homicide. After consumption of massive doses, vomiting, diarrhea, or both occur within hours. Neuropathic symptoms, heralded by limb pain and severe distal paresthesia, are followed by progressive limb weakness within seven days. Cranial nerves, including optic nerves, may be involved. Ptosis is common. In severe cases, ataxia, chorea, confusion, and coma as well as ventilatory and cardiac failure may ensue. Alopecia, which appears 2-4 weeks after exposure, provides only rerrospective evidence of acute intoxication. A chtonic progressive, mainly sensory neuropathy develops in patients with chronic low-level exposure. In this form, hair loss is a helpful clue.

Electrocardiographic findings of sums tachycardia, U waves, and T-wave changes of the type seen in potassium depletion are related to the interaction of thallium and potassium ions. Electrophysiological findings are characteristic of distal axonal degeneration. Autopsy study results confirm a distal axonopathy of peripheral and cranial nerves. Studies in animals show accumulation of swollen mitochondria in distal axons before wallcrian degeneration of nerve fibers. The diagnosis is confirmed by the

demonstration of thallium in urine or bodily tissues. High levels are found m central nervous system gray matter and myocardium. The toxic effects of thallium may be related to binding of sulfhydryl groups or displacement of potassium ions from biologic membrane systems.

With acute ingestion, gastric lavage and cathartics art-given to remove unabsorbed thallium from the gastro-intestinal tract. Oral potassium ferric ferrocyanide (Prussian blue), which blocks intestinal absorption, together with intravenous potassium chloride, forced diuresis, and hemodialysis, has been used successfully in acute thallium intoxication.

Tin

Although ingested inorganic tin usually produces little or no systemic and neurological complications, organic tin compounds used in various industrial processes have definite neurotoxicity. Intoxication with trimethyl tin leads to multifocal central dysfunction with conspicuous behavioral disturbances, emotional lability, confusion, disorientation, cognitive disturbances, sleep dysfunction, headaches, and visual disturbances. Triethyl tin may lead to severe cerebral edema with headache, papilledema, and behavioral abnormalities that generally resolve some weeks after discontinuation of exposure.

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Chapter 64
Effects of Toxins and Physical Agents on the Nervous System

B. EFFECTS OF DRUG ABUSE ON THE NERVOUS SYSTEM

Yuen T. So

Drug abuse occurs in several different forms. The use of drugs such as heroin or cocaine may be termed abuse simply because they are illegalal or are obtained illegally. Legal prescription drugs, such as the opioid analgesics and benzodiazepines, also may be abused if taken in excessive amounts or used solely for recreational purposes. *Drug dependence* refers to either a psychological dependence or a physical dependence. In the former, drug-craving or drug-seeking behavior emerges when the drug is not available. Physical dependence, on the other hand, implies the appearance of physiological symptoms and signs during drug withdrawal. *Drug tolerance* is defined as a diminished response to the same dosage of a drug and reflects either increased metabolism of the drug or reduced physiological response to the drug at its normal cellular target.

Of the abused drugs that result in emergency room visits, cocaine is the most commonly encountered. This is followed in frequency by heroin, marijuana, and methamphctamine. The so-called *club drugs* have risen in popularity in recent years. They are frequently used in dance clubs and include GHB (gamma hydroxybutyrate), kern mine, MDMA (3,4-rnethyleiiedioxymcthamphcraminc or *ecstasy),* LSD (lysergic acid diethylamide), and methamphetamine. All these drugs have been implicated in causing deaths in one way or another. Aside from the biological effects to be discussed in this chapter, forensic data link these drugs to many vehicular accidents, blunt trauma, and gunshot and other penetrating injuries and deaths.

All the substances of abuse have potent acute and chronic .•tlirr- (in t'le nervous -.ystern. h i– helpt.k l‹> divide flic neurological consequences of drug abuse into three broad categories according to the mechanism of action (Table 64B.1). First, acute intoxication or overdose often leads to delirium, stupor, or coma, sometimes accompanied by myoclonus, seizures, or serious systemic consequences such as respiratory depression and cardiovascular collapse. Second, chronic use of most of these agents often leads to drug tolerance or dependence. With abrupt abstinence of a habitually used drug, a patient may present for emergency care with an acute withdrawal syndrome. Third, drug abuse may affect the nervous system indirectly via infectious and embolic consequences of intravenous drug use, hypersensitivity ot immunological mechanisms, or some other manner that is not yet understood.

Urine screening of drugs of abuse is widely used in the diagnostic evaluation of patients (Table 64B.2).

The detection times listed in Table 64B.2 are rough estimates at best, as detection is dependent on the time, dose, and route of administration, a subject's metabolism, and the characteristics of the screening assay. Negative test results are difficult to interpret, and detection is particularly problematic for the designer amphetamines (see MDMA, latet in this chapter). Positive results may be confirmed by an alternative method such as gas chromatography and mass spectroscopy. The urine test provides only qualitative information of recent drug use. Because urinary levels are dependent on time and clearance, they often do not correlate with toxic symptoms,

The first part of the following discussion reviews the pharmacological effects of commonly abused drugs, wirh emphasis on the acute effects and the withdrawal syndromes. The second part discusses the indirect effects of drug abuse on the nervous system.

Tabic 64B.1: Neurological complications of drug abuse

Acute intoxication and overdose
Drug withdrawal syndrome
Indirect complications of drug abuse
  Infectious endocarditis
    Cerebral or spinal cord abscess
    Meningitis or encephalitis
    Myelopathy
  Strokes
    Cerebral or spinal cord infarct
    Postanoxic encephalopathy
    Hemorrhage
Brachial plexitis
Nerve compression
Rhabdomyolysis

PHARMACOLOGICAL EFFECTS

Opioid Analgesics

The name *opium* came from the Greek word for *juice* because the drug was derived from the juice of the poppy. Its medicinal uses were discovered as early as the third century BC. Opium contains more than 20 alkaloids. Morphine was the first to be isolated, in 1806, and was named after Morpheus, the Greek god of dreams. Other alkaloids, such as codeine, were discovered soon afterward. By the middle of the nineteenth century, the use of these compounds was widespread in medicine.

Pharmacology

Opiates refer only to those drugs derived from opium and include the naturally occurring alkaloids as well as semi-synthetic derivatives. Kndorphins are endogenous opioid peptides and encompass the enkephalins, dynorphins, and jS-endorphins. The term *opioid* is more inclusive and is used for all agonists and antagonists with morphine-like activities as well as the naturally occurring and synthetic opioid peptides. These compounds act on the three opioid receptor subtypes, /*, *S,* and *K,* and have a wide spectrum of activities as analgesics, psychotomimetics, miotics, and suppressants of respiration, cough, and gastric motility.

Development of drug tolerance and dependence is an almost unavoidable physiological consequence of repeated use of opioids. For example, when used in prolonged treatment of pain, increasingly higher doses of opioids are often required to maintain the same degree of pain control. The pharmacological basis of this phenomenon is poorly understood, although the N-methyl-d-aspartatc (NMDA) receptor may play an important role. Neither tolerance nor dependence predicts drug abuse; thus the fear that tolerance may develop should not interfere with the appropriate use of opioids.

Table 64B.2: Common drugs of abuse: maximum time interval after last drug use when drugs and their metabolites are still detectable by enzyme immunoassay of urine

Drug	*Maximum detection time after last use*
Amphetamine	48 hrs
Cocaine	48 hrs
Benzodiazepines*	5 to 7 days
Barbiturates, long-acting	7 days
Barbiturates, short- or intermediate-acting	1 to 2 days
Heroin*	4 ro 5 days
Methadone	3 days
Morphine	48 hrs
Phencyclidine*	2 wks
Propoxyphene	48 hrs

'Maximum detection times given for chronic users. Single dose in nonhabitual users is cleared considerably more rapidly.

Drug Abuse

A prescription opioid analgesic may be abused. A typical patient may seek multiple physicians for prescription, present with exaggerated complaints, or engage in other drug-seeking behavior. A second group of abusers are the street addicts, typified by use of the illegal drug heroin. Heroin crosses the blood-brain barrier rapidly. Heroin's effect on the brain is identical to that of morphine. Three milligrams of heroin is roughly equivalent to 10 mg of morphine. Heroin may be snorted (sniffed up the nose), smoked, injected subcutaneously {"skin-popping"), or administered intravenously ("mainlining"). Heroin is sold in the streets in varying degrees of purity, and it is sometimes combined with cocaine ("spcedball").

Acute Effects

Aside from the analgesic effects, morphine and heroin acutely produce a sense of rush, accompanied by either euphoria or dysphoria. Hallucinations may occur also. Other effects include pruritus, dry mouth, nausea and vomiting, constipation, and urinary retention. Examination may show pupillary constriction so marked that it may be difficult to discern the light reflex. Overdose of heroin leads to coma and respiratory suppression. Hypotension and hypothermia also occur, but seizures are rare.

Acute treatment of opioid overdose should include close monitoring of vital signs and, if necessary, support of blood pressure and respiration. Naloxone is a safe and effective opioid antagonist and should be used immediately in any suspected opioid overdose. Naloxone is also useful for diagnosis, because it induces immediate reversal of coma and respiratory depression in a patient with opioid over-dose. For treatment of respiratory depression, 2 mg of naloxone is given parenterally, and the dose is repeated as needed up to a total of 10-20 mg. Because the half-life of

naloxone (1—4 hours) is shorter than most opioid agonists, it should be given in repeat boluses and the patient should be monitored closely through the at-risk period, With careful titration of the dose, respiratory depression can be reversed without precipitating acute opioid withdrawal.

Drug Dependence and Withdrawal

With development of drug dependence, symptoms and signs of withdrawal appear hours after the last opioid use. Drug craving appears first, followed by restlessness and irritability. Autonomic symptoms such as sweating, Inclination, and rhinorrhea then emerge. Still later, piloerection, aching, nausea, abdominal cramps, diarrhea, and coughing develop. Tin- time ol tile appearance of withdrawal symptoms depends on the duration of action of the drugs. With morphine and heroin, withdrawal symptoms appear within *6-9* hours of rhe last dose, peak at 24-72 hours, and last approximately 10 days. With methadone, symptoms appear within approximately 12-24 hours, peak at 6 days, and last approximately 3 weeks.

Opioid withdrawal in adults, although unpleasant, is usually not life threatening. In contrast, opioid withdrawal in neonates is sometimes accompanied by myoclonus, seizures, or even status epilepticus. This occurs typically in newborns of opioid-dependenr mothers. Naloxone used during the treatment of respiratory depression sometimes precipitates withdrawal reactions. Acute administration of paregoric or methadone is an effective treatment. Phcnobarbital may be used if there has been prenatal exposure to other drugs such as barbiturates and alcohol.

Oral methadone, a long-acting opiate, is used to relieve opioid withdrawal symptoms. A dose of 10 to 20 mg once or twice a day is sufficient in most patients. The dose is then gradually reduced, win the hope of eventually achieving detoxification. Clonidine, an a_2-adrenergic agonist, suppresses the autonomic disturbances of opioid withdrawal and is useful when combined with methadone. Methadone is becoming a primary drug of addiction.

Sedatives and Hypnotics

Sedatives and hypnotics as a group have calming effects and are capable of inducing sleep when taken in sufficient dti.vigev The group includes die bcn/.odia/.cpincs. barhitu rates, and various less commonly used agents. As with opioid analgesics, manifestations of abuse include excessive use of prescription drugs, recreational use, drug overdose, drug dependence, and withdrawal symptoms. The benzodiazepines are among the most frequently prescribed medications in Western countries and account for over one-half of the overdoses in the United States. Addicts often use benzodiazepines and barbiturates in conjunction with heroin. Alcoholics also sometimes use them to alleviate symptoms of alcohol withdrawal.

Benzodiazepin es

All the benzodiazepines share similar effects on the central nervous system, and the differences among individual drugs are largely those of dosage and duration of action. The benzodiazepines with rapid onset of action, such as diazepam, are among the most likely to be abused.

Acutely, the recipient experiences varying degrees of lassitude, drowsiness, confusion, amnesia, euphoria, and impairment of other psychomotor functions. Even in conventional dosages, these neurological effects are potentially dangerous, especially in elderly people. Falls, for example, may result from drowsiness and motor incoordination. Sufficiently severe overdose leads to coma, although benzodiazepines arc less likely than barbiturates and opioids to cause respiratory or cardiovascular depression. Thus benzodiazepine overdose is rarely fatal unless other drugs are used concurrently. Still, treatment of comatose patients should be directed to immediate assessment and management of cardiovascular and respiratory functions. Flumazenil is a specific antagonist for benzodiazepines. It reverses rapidly the stupor or coma of overdose, although its usefulness is limited by its short action of only 30-60 minutes. A dose of 0.2-5.0 mg given intravenously over 2-10 minutes is sufficient to reverse benzodiazepine overdose. A lack of response is strong evidence that another drug is involved.

Chronic use of benzodiazepines may lead to tolerance and physical dependence. Withdrawal symptoms typically occur within 24 hours of cessation of use of a short-acting benzodiazepine and approximately 3-7 days after stopping a long-acting agent. Withdrawal symptoms include irritability, increased sensitivity to light and sound, sweating, tremor, tachycardia, headache, and sleep disturbances. In more severe withdrawal states, delirium, hallucinations, and seizures may occur. Withdrawal symptoms may last several weeks. Reinstituting the benzodiazepine, followed by gradual tapering of the dosage, is usually sufficient to treat these withdrawal symptoms.

Barbiturates

The acute symptoms of barbiturate use are **similar to those** of alcohol and include euphoria, sedation, slurred speech, and gait ataxia. Severe intoxication leads to coma, hypotension, and hypothermia. Breathing may be slow or rapid and shallow. Cheyne-Stokes breathing, respiratory depression, and eventually apnea occur with sufficient intoxication. Treatment is primarily supportive. The lethal dose varies, but as a general rule, ingestion of more than 10 tunes the hypnotic dose is likely to be dangerous. Gastric lavage may be useful within 24 hours because barbiturates

may reduce gastric motility. Hemodialysis or hemoperfusion is rarely necessary.

Withdrawal symptoms are similar to those seen with alcohol withdrawal. Insomnia, irritability, tremor, tachycardia, nausea, and vomiting are common. With short-acting barbiturates, symptoms usually begin within 36 hours; the long-acting barbiturates are associated with a longci delay of several days. In sevcte cases, delirium tremens and seizures may occur. Treatment of withdrawal consists of reinstitution of the batbiturates, followed by gradual tapeting.

Other Sedatives and Hypnotics

Othet sedatives and hypnotics are abused much less frequently than barbiturates and benzodiazepines. Mctha-qualone was popular in the 1970s. Overdose is characterized b; delirium, myoclonus, and seizures, sometimes followed by coma and acute congestive heart failure. Glurcthimide overdose leads to coma, hypotension, and, less frequently, respiratory depression. Abuse of this agent is recognized by its anticholinergic effects, which produce dilated unteactive pupils. Other uncommonly abused drugs include paraldehyde, chloral hydrate, meprobamate, and ethchlorvynol. Ethchlorvynol overdose is characterized by its long duration of action, which may last many days. Treatment includes diuresis, perironeal dialysis or hemodialysis, or hemoperfusion with activated charcoal or resin.

Psychomotor Stimulants

Psychomotot stimulants all share sympathomimetic effects on the central nervous system. Cocaine is the most commonly abused. It may be administered intranasal!}' or parcntcrally or may be smoked (crack). Amphetamine, dextroamphetamine, methamphetamine, and methylphenidate also have significant abuse potential. Another drug in this group is MDMA or *ecstasy,* as ir has hallucinogenic effects in addition to its stimulant properties. Other agents such as fenflutamine, phentermine, ephedtinc, and phenylpropanolamine have less liability for abuse.

Acute Effects

In modetate doses, stimulants produce mood elevation, increased alertness, reduced fatigue, dectcased appetite, and enhanced performance in various tasks. There arc individual differences in the psychic effects of these stimulants. Some patients develop paranoia, delusions, hallucinations, agitation, and violence. Other patients may be depressed or lethargic. Systemic symptoms include palpitation, pupillary dilation, tachycatdia, and hypertension. For patients presenting to the emergency room, systemic complications such as hyperthermia, dehydration, and rhabdomyolysis are sometimes encountered. An increased risk of myocardial infarction is also especially well documented with cocaine use,

Of the neurological symptoms seen in the emergency room, headache is probably the most common and ftequcntly accompanies other more serious symptoms. Some patients may present with encephalopathy, myoclo'-nus, or seizures. Seizures are usually self-limiting, although status epilepticus is an uncommon but well-recognized complication of overdose.

Of the abused stimulants, cocaine is the most likely to cause seizures (Zagnoni and Albano 2002). Seizures are more likely when cocaine is smoked (crack) or given intravenously than with other modes of administration. The estimate of seizure frequency varies widely from 1^40%, depending on the study population. Typically, seizures occur within 1-2 hours of cocaine use. Other drugs, such as methamphctamine, amphetamine, MDMA (ecstasy), methylphenidate, ephedrine, and phenylpropanolamine also cause seizures. MDMA in particular has been linked to the development of hyponattcmia with resultant seizures and encephalopathy. The mechanism may involve inappropriate secretion of antidiuretic hormone (Hartung et al. 2002).

Both acute ischemic and hemorrhagic strokes have been reported in association with stimulant use. This is especially true for cocaine and amphetamine, although other stimulants may also be responsible. Stroke is discussed further later in this chapter (see Indirect Neurological Complications). Movement disorders are sometimes seen after stimulant use (Catdoso and jankovic *199i).* Hyperkinetic movement disorders may be exacerbated or may develop *de novo* in cocaine users. These include vocal and motot tics, chorea, dystonia, and acute dystonic reaction to neuroleptics. Rarely, dyskinesias may persist months after abstinence (Weiner et al. 2001). Otomandibular stereotypies such as teeth-grinding and tongue protrusion are common among amphetamine users.

Treatment of overdose should include supportive measures such as oxygen, cardiac monitoring, cooling for hyperthermia, antihypertensives, and blood pressure and ventilatory support as necessary, Sedarives may be used judiciously to treat agitation. Seizures arc managed with benzodiazepines and phenytoin. Forced diuresis and urine acidification promote drug excretion bur should be avoided if myoglobinuria is present.

Drug Dependence and Withdrawal

Aftet repeated use of cocaine or amphetamines, tolerance develops to the euphoric and anorexic effects of these agents. A wide range of psychiattic symptoms have been described in chronic active users. Functional imaging studies have shown altetations of dopamine and serotonin transporters in the brain, although the clinical significance of these findings is unknown. Acute abstinence aftet

chronic use manifests primarily as fatigue and depression. The withdrawal syndrome is seldom life-threatening, with the exception of those who develop suicidal ideations. Treatment with imipramine or other antidepressant drags may be helpful.

Other Substances of Abuse

MDMA (1,4-methylenedioxymethampketamine) or Ecstasy

MDMA merits a special mention as it has become a very popular club drug internationally, and there is a widely held misconception among users that it is safe. The drug is used commonly on college campuses and at all-night dance parties. As its name implies, MDMA is a derivative of methamphctamine, and it has properties of both a stimulant and a hallucinogen (Kalant 2001). The hallucinogenic effects result from its structural resemblance to mescaline.

Complications from MDMA's acute stimulant effects were discussed in the previous section (see Psychomotor Stimulants). Although the incidence of serious complications with MDMA use is low, the unpredictability of these serious and sometimes fatal complications is of great health concern. Adding to the unpredictability is the fact that the street name *ecstasy* has also been applied by vendors and users to other related compounds: 3,4-merhylenedioxyamphetamine (MDA), N-ethyl-3,4-methylcncdioxyamphetamine (MDF.A), and paramethoxyamphetamine (PMA). These compounds share the biological effects of MDMA and have also been linked to serious complications. These drugs are often referred to as "designer-drugs" or "designer-amphetamines," because they were created by illicit attempts to achieve a blend of amphetamine-like and mcscaline-like pharmacological properties.

MDMA has been linked to death from hyperthermia, hyponatremia, seizures, rhabdomyolysis, hepatic failure, coagulopathy, and cardiac arrhythmias. Recent studies also suggest long-term neurotoxicity with MDMA use. MDMA acutely causes massive central serotonergic discharge that is the physiological basis for its pleasurable psychic effects. By contrast, habitual users often report depression or lethargy during the time period between drug binges. Neuropsychological testing reveals impairment in verbal and visual memory in abstinent MDMA users compared to controls. Autopsy study in one patient demonstrated depletion of serotonin level in the striatum (Kish ct al. 2000). Functional imaging studies also suggest a long-lasting alteration of brain function.

Marijuana

Tetrahydrocannabinol is the primary active ingredient of marijuana and has effects on mood, memory, judgment, and sense of time. A sense of relaxation, subjective slowing of time, euphoria, and depersonalization can occur during its use. Variable degrees of anxiety, paranoia, sedation, and sleepiness may occur also. High doses of tetrahydrocannabinol produce hallucinations, paranoia, or a frank panic reaction. Treatment of such cases generally requires only calm reassurance. Tolerance develops with chronic use. Irritability, restlessness, and insomnia are typical after abrupt discontinuation.

Pbencyclidine and Ketamine

Phencyclidine and ketamine were developed as anesthetics. At progressively increasing dosages, analgesia, anesthesia, stupor, and coma develop. At moderate doses, phencyclidine and ketamine produce variable degrees of euphoria, dysphoria, relaxation, paranoia, and hallucinations. Psychosis, agitation, bizarre behavior, and catatonia arc common. These may be accompanied by physical signs of fever, hypertension, sweating, miosis, and horizontal as well as vertical nystagmus. Treatment is largely supportive. Violent behavior may require restraint. Rhabdomyolysis is common with overdose, and myoglobinuria should be looked for and treated if discovered.

Anticholinergics

The recreational use of anticholinergics includes abuse of prescription drugs as well as use of plants that contain the belladonna alkaloids atropine and scopolamine. These agents are abused for their pharmacological ability to induce delirium and hallucinations. The psychoactive effects are accompanied by mydriasis, dry and flushed skin, tachycardia, urinary retention, and fever. Severe overdose may lead to myoclonus, seizures, coma, and death. Acute treatment employs intramuscular or intravenous injection of 1 mg of physostigmine. This is followed by titrating doses of 0.5-2.0 mg of physostigmine every 30 minutes to 2 hours.

inhalants

1'his group ol compounds comprises a wide range ol volatile compounds, including various hydrocarbons, nitrites, and nitrous oxide. Many are present in common household and industrial products. Despite the diversity of chemicals, the acute effects are similar. At low to moderate doses, these chemicals induce a sense of euphoria, relaxation, incoordination, and slurred speech. These effects resemble alcohol intoxication for most practical purposes. Higher doses produce psychosis, hallucinations, and seizures. The duration of action is typically only 15-30 minutes, but the effects may be sustained by continual use. Various complications such as cardiac arrhythmia; suffocation from the use of plastic bags, vomiting, and aspirations; and, rarely, sudden death have been reported.

Aside from die acute neuropsychological effects, different systemic and neurological complications may result from chronic abuse of individual agents. Lead intoxication may result from sniffing leaded gasoline. A peripheral neuropathy with disabling weakness and slow nerve-conduction velocities may result from the chronic use of M-hcxane. Nitrous oxide abuse leads to a syndrome of subacute combined defeneration similar to that seen in vitamin]>L' deficiency. Cerebral and cerebellar dysfunctions are seen after chronic toluene abuse. Mild cognitive dysfunction has been associated with chronic exposures to many volatile hydrocarbons. Systemic complications include renal, hepatic, and bone marrow abnormalities after exposure to benzene and methemoglobinemia after use of alkyl nitrite,

Hallucinogens

The hallucinogens as a group cause alteration of mood, perception, and thought processes without significantly changing alertness, memory, and orientation. The synthetic ergot LSD is the best-known example and is still popular among drug abusers. In addition, a wide range of plants and mushrooms are known to be hallucinogenic. Acute ingestion leads to rapid onset of dizziness, blurred vision, nausea, and weakness followed by hallucinations that are often visual and complex. There may be depersonalization and a distortion of time. Sometimes the experience is terrifying (the so-called 'Lbad trips"), resulting in injuries to self or others. Physical signs include fever, tachycardia, hypertension, mydriasis, seizures, and coma.

INDIRECT NEUROLOGICAL COMPLICATIONS

Stroke

Drug abuse increases the risk of strokes. In retrospective studies of stroke patients between 15 and 44 years of age, drug abusers accounted for 12-31% (Sloan et al. 1998). Drug abuse was the most important risk factor for stroke in those younger than 35 years of age. The relative risk of stroke was 6.5 after controlling for other stroke risk factors. The possible mechanisms are diverse (Table 64B.3) and arc dependent on the route of drug administration and the agents involved. The risk increase does not take into consideration the abuse of alcohol and tobacco, both of which, though legal, also increase stroke risk.

The evaluation of patients with drug-related strokes should include a careful search for endocarditis or other source of embolization, a full cardiac evaluation, erythrocyte sedimentation rate, and antiphospholipid antibody assay. Cerebral angiography may be necessary, especially when vasculitis, aneurysms, or vascular malformations are suspected.

Table 64B.3: Probable mechanisms of strokes associated with drug abuse

Intravenous drug abuse
Endocardins, infectious or marantic
Embolization of foreign materials
Right-tO-left shunt in pulmonary vasculature
Mycotic aneurysm
Direct effects of drugs
Vascular injury: hypertensive changes, arterial dissection
Acute severe hypertension
Vasoconstriction or vasospasm
Impaired auto regulation
Indirect effects of drugs
Vasculitis
Pre-existing vascular malformation or aneurysm
Cardiomyopathy and arrhythmia
Antiphospholipid antibodies
Nephropathy and secondary hypertension
Hypotension or hypoxia from overdose
Acquired immunodeficiency syndrome or HIV iiiUvnon

Embolism

The sources of embolism include valvular disease secondary to infective or marantic endocarditis, mural thrombi of cardiomyopathy, right-to-left shunt, aortic or other arterial dissection, and foreign materials injected during intravenous drug abuse. Strokes occur in approximately 20% of cases of infective endocarditis; many of them are due to intravenous drug abuse. Early recognition is important because prompt antibiotic therapy can markedly reduce the risk of stroke. Mycotic aneurysm complicates 1-3% of cases of endocarditis and may cause intracerebral hemorrhage, Angiography should be considered when mycotic aneurysm is suspected, although the role and timing of surgery are controversial.

Kmboli of particulate materials often occur because of the poorly controlled sale and manufacture of these injected drugs. Some intravenous preparations of methyl ph en idate, meperidine, and pentazocine are made by crushing or dissolving drug tablets. Other intravenous preparations may contain insoluble fillers such as talc. Undissolved particles, if injected intravenously, become lodged in the lungs and may cause pulmonary hypertension and arteriovenous fistulae. This in turn provides a path for emboli materials to reach the cerebrovascular circulation.

Vasculitis and Other Vasculopathies

Vasospasm is associated with many drugs of abuse, most notably the psychostimulants such as cocaine, amphetamines, methylphenidatc, and phenylpropanolamine, for poorly understood reasons, some drugs of abuse also lead to the development of vasculitis. This has been best documented in some patients with amphetamine abuse and less convincingly in a few patients who abused

phenylpropanolamine, cocaine, or heroin. The diagnosis of vasculitis without histological verification is difficult, because the classic angiographic findings of segmental narrowing and beading of intracerebral arteries do not distinguish among vasculitis, vasospasm, arteriosclerosis, and other vasculopathics. Abstinence should be the first step in treatment of patients suspected to have vasculitis. The role of immunosuppressive therapy is undefined. It is not clear if the clinical course and response to treatment of drug-induced vasculitis are different from those of other vasculitis of the nervous system.

Hypotension and Anoxia

Anoxic brain injury often follows drug overdose, most notably overdose from heroin and other opiates. An autopsy series of heroin addicts observed that 2% had ischemic injury to the globus pa Hid us. Delayed postanoxic encephalopathy also rarely occurs. The clinical manifestations are similar to those described after prolonged cardiac arrest, respiratory failure, and carbon monoxide poisoning.

Cocaine

Cocaine is without question the most important cause of drug-related stroke and accounts for approximately 50% of all cases. Neurological symptoms typically develop within hours of cocaine use, although rarely symptoms may progress gradually for up to a week. Seizures sometimes accompany the strokes. There are reports of transient ischemic attacks or ischemic infarctions of almost any area of the brain or spinal cord. In most series, over half of the ischemic infarcts involve die middle cerebral artery territory. Asymptomatic subcortical white matter lesions are also more prevalent in cocaine users when compared to normal controls. The difference is especially apparent in older subjects, irrespective of the years of cocaine use (Bartzokis et al. 1999). Intraparenchymal or subarachnoid hemorrhage is another common mode of presentation (Aggarwal et al. 1996; Noltc, Brass, and Fletterick 1996).

There arc several porential pathophysiologic mechanisms of cocaine-induced stroke. Acute hypertension, vasospasm, and vasoconstriction probably play an important role (Kaufman et al. 1998). Under experimental conditions in cocaine users, modest intravenous doses of 40 mg or less can induce vasospasm of large arteries and reduce cerebral Hood flow by 25 oO'V I'hese doses .ire lower than those habitually consumed by many chronic cocaine users. Preexisting vascular pathology may be a key factor in some patients. Among those who present with intracranial hemorrhages, approximately one-half have underlying cerebral aneurysms or vascular malformations. Endocarditis, myocardial infarction, cardiac arrhythmias, aortic dissection, and anticardiolipin antibodies arc other observed associations.

Myelopathy

An acute myelopathy may develop rarely after drug abuse. The association is best documented in heroin abuse and rarely in cocaine use. For rhe most part, the syndrome resembles an anterior spinal artery syndrome. Paraparesis, urinary retention, and a segmental sensory level appear acutely. On examination, posterior column function is often relatively spared. Myelography, magnetic resonance imaging (MRI), and cerebrospinal fluid findings are usually normal, although mild elevation of cerebrospinal fluid protein may be present. There are several possible causes. Watershed infarct secondary to hypotension may be responsible. Embolic infarct from injected particulate material may account for other cases, as may hypersensitivity or vasculitis.

Rhabdomyolysis and Myopathy

It is unclear whether any of the commonly abused drugs are directly toxic to muscles. Evidence of muscle injury ranges from asymptomatic elevation of serum creatine kinase to frank myoglobinuria and renal failure. The observations are made most commonly in the abuse of heroin, cocaine, amphetamine, MDMA, and phencyclidinc. The patients were typically severely intoxicated. Possible mechanisms include trauma, crush :njur>, hypotension, hypertension, fever, seizures, and excessive muscular activities,

Repeated intramuscular injections of meperidine, pentazocine, or heroin sometimes lead to focal fibrosis and weakness of the injected muscles. Contractures develop slowly. The affected muscles have a woody and firm quality. Weakness is mild and is limited to the injected muscles. Flccrronv. ogniphic elimination ot affected areas demonstrates reduced insertional activity (suggesting extensive fihrotic replacement of the muscle), short duration, and small-amplitude motor-unit action potentials.

Ncuroparhy and Plexopathy

Compressive or stretch injuries ro peripheral nerves and plexuses result from drug abuse of any kind. Focal neuropathies may also develop as a result of compartment syndrome and secondary nerve ischemia. The most commonly affected sites are the brachial plexus, the radial nerve at the upper arm, the ulnar nerve at the elbow, the sciatic nerve in the gluteal region, and the peroneal nerve at the fibular head. Some cases of idiopathic brachial or lumbosacral plexitis have been attributed to heroin use. A potential though tin proven cause is a hypersensitivity reaction to heroin or the accompanying adulterant.

Many drug abusers have physical signs of a distal sensory or sensorimotor polyneuropathy, but a causal

relationship to the ahused drugs is difficult to establish because confounding factors such as alcohol abuse and systemic diseases are often present. An exceptional example is in the chronic use of hydrocarbon inhalants (Smith and Albers 1997), in which the neuropathy is similar to that observed during industrial outbreaks caused by exposure to ji-hexane or methyl w-butyl ketone. Distal paresthesias and numbness appear first, followed by development oi distal weakness. Weakness worsens with continuing abuse and may progress to involve proximal muscles of both upper and lower limbs.

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Chapter 64
Effects of Toxins and Physical Agents on the Nervous System

C. NEUROTOXINS OF ANIMALS AND PLANTS

Neil E. Schwartz and Yuen T. So

Naturally occurring neurotoxins of animals, plants, and fungi are of great scientific interest in addition to their obvious clinical concern. Many of them serve as important tools used by investigators to probe the workings of the nervous system. One of the oldest and best-known examples is curare, a plant toxin used in Claude Bernard's classical experiments on neuromuscular transmission over 100 years ago, a-Bungarotoxin, from the venom of the banded krait, is a competitive blocker of the acetylcholine receptor that has proven to be invaluable for studies of the neuromuscular junction and myasthenia gravis. Our understanding of the mechanisms of neurotransmitter release has been enhanced by toxins such as a-latrotoxin, from the black widow spider. Likewise, the toxins from a multitude of plants and fungi have helped advance our knowledge of many aspects of cellular neurophysiology. This chapter highlights some of the more common and clinically relevant neurotoxins that might be encountered by the neurologist in the United States.

NEUROTOXINS OF ANIMALS

The neurotoxins of animals serve several essential functions in nature. Reptiles and arthropods use venoms to defend against predators and to immobilize prey. Some venom may contain enzymes that aid in the digestion of consumed food. Many of these agents are among the most potent neurotoxins known to humankind {Table 64C.1) (Markland 1997). Major components of snake and insect venoms are disulfide-rich small molecules that exhibit phospholipase A_2 activity (Schiavo, Matteoli, and Montecucco 2000). Despite their biological potency, mortality caused by these agents is uncommon. The rarity is in part a result of the healthy respect most people have for snakes, spiders, and scorpions. Moreover, most bites result in a relatively small amount of envenomation that is well below lethal dosage. Mortality tends to occur at the extremes of age.

Snakes

The overwhelming majority of venomous snakebites in the United States are inflicted by the pit vipers (subfamily *Crotalidac),* a group that includes rattlesnakes (genera *Crotalus* and *Sistrurus),* fer-dc-lances (genus *Bothrops),* and the bushmaster *(Lachesis muta).* Moccasins (genus *Agkistrodon),* including cottonmouths and copperheads, account for up to half of pit viper envenomations in the United Stares (Litovitz et al, 2002). Pit vipers are so named because of an identifiable heat-sensing foramen "pit" between each eye and nostril; they have a triangular head with elliptical pupils and retractable, canalized fangs (Gold, Dart, and Barish 2002). All but one species of rattlesnake has a characteristic rattle on the tip of its tail. Coral snakes (family *Eiapidae)* such as *Micrurus fulvius tenere* (Texas coral snake) and *Micrurus fulvius fulvius* (eastern coral snake) are the only native venomous snakes that are not pit vipers; they account for less than *5%* of envenomations in the United States. Important venomous snakes in other

Table 64C.1: Neurotoxins of snakes and arthropods

Source	*Toxins*	*Physiological site of action*
Snake (various species)	a-Bungaroroxin, cobrotoxin	Postsynaptic: competitive blockade of AChR
Snake (various species)	*0* Bungarotoxin, crotoxin, notexin, taiposin	Presynaptic: inhibition of ACh release
Black widow spider *(Latrodectus mactans)*	cr-Latrotoxin	Presynaptic: facilitation of ACh release, followed by (lerlerion •••• Ac h
Scorpion *(Tityus serrulatus)*	Tityustoxin	Presynaptic: facilitation of ACh release Postsynaptic: inhibition of Na^{+1} channel inactivation
Scorpion *(Centrtiroides* sp.)	At least two groups of toxins	Presynaptic: membrane depolarization

Ach = acetylcholine; AchR = acetylcholine receptor; Na^+ = sodium.

parts of the world include Elapidae such as cobras, mambas, kraits, coral snakes *(Maticora* sp.), and most Australian venomous snakes. Bites from these non-native species among zoo petsonncl and amateur snake keepers are not unusual. Viperidae (true vipers) include the puff adder, daboon viper, rhinoceros-horned viper, and Russell's viper, *Hydrophiidae* (pelagic sea snakes) are highly neurotoxic but rarely bite humans.

As many as 25% of pit viper bites and half of coral snake bites are "dry" and do not result in envenomation. Signs and symptoms of envenomation may vary. Morbidity and mortality depend on the venom composition of the local snakes and the availability and sophistication of emergency medical care. In the United States, approximately 6400 snake bites were reported in 2001 (about one-fifth of which were from rattlesnakes). Mortality, fortunately, is uncommon (averaging *5.5* deaths/year) and is due mostly to diamondback rattlesnake bites. By contrast, over 10,000 deaths are reported yearly from the Nigerian savannas and apptoximatcly 23,000 from West Africa. Up to 110,000 deaths per year worldwide have been reported, with many more individuals experiencing permanent morbidity. Young male adults are bitten most commonly, with about half of all bites in persons aged 18—28. In many cases of snakebite, the subject is intoxicated with alcohol.

Snake venoms are composed of a complex mixture of peptides, many of which have enzymatic activity. Low-molecular-weight polypeptides in the venom have neurological activities on both presynaptic and postsynaptic elements of the neuromuscular junction (see Table 64C.1). Diverse effects on platelets, endothelial cells, and the coagulation cascade, as well as almost every organ system, are responsible for much of the morbidity and mortality of envenomation. Some of the toxins may be directly myotonic; rhabdomyolysis and compartment syndrome are sometimes seen after envenomation. Considerable species and geographic variations occur in the spectrum of biological activities. For example, snakebites may cause primarily neuromuscular paralysis in one region, whereas bites by the same species in another region may result mainly in coagulopathy and hemorrhage. In general, when weakness is present, the pattern of involvement resembles myasthenia gravis, with predilection of the neck flexors and ocular, bulbar, and proximal limb muscles. Respiratory paralysis, if severe and untreated, may lead to death,

At the time of patient presentation, fear and panic are common symptoms; the accompanying autonomic reactions should not be mistaken for systemic symptoms of envenomation. The cardinal signs of pit viper envenomation are local pain, swelling, and erythema. Early signs of envenomation include tender regional lymph nodes; nausea; and a metallic, rubbery, or minty taste in the mouth. Systemic symptoms appear over the ensuing 12-24 hours and consist of a variable combination of perioral or limb paresthesias, muscle fasciculations, weakness, hypotension, and shock. Ptosis is common following envenomation by some Mojave rattlesnakes. In contrast to pit viper envenomation, little pain or swelling accompanies coral snake bites. After a delay of up to 24 hours, cranial nerve palsies, dysphagia, diffuse weakness, areflexia, and respiratory suppression may develop. Initial laboratory evaluation should include complete blood cell and platelet counts, coagulation panel, fibrinogen, fibrin split products, serum chemistries, creatine kinase, and urinalysis. In patients with significant weakness, nerve-conduction studies with repetitive stimulation testing may reveal a pattern of either presynaptic or postsynaptic blockade. The observed changes consist of reduced amplitude of the compound muscle action potentials, decremental response to low-frequency repetitive stimulation, and postexercise and post-tetanic facilitation. Treatment includes calming and supportive measures. Even in the absence of life-threatening symptoms, a patient should be monitored for at least 6 hours if bitten by a pit viper and 12 hours if bitten by a coral snake. Appropriate antivenin should be administered as soon as it is certain that significant envenomation has occurred.

Spiders

Of the commonly encountered spiders, few produce significant symptoms in humans. Venom is injected via fangs (chelicerae). The female widow spider *(Latrodectus* sp.)

is the most important worldwide in terms of morbidity and is the only one commonly found in the United States with significant neurological morbidity. Over 2600 widow spider bites were reported in the United States in 2001,16 of which had major health consequences; there were no fatalities if.mn it/. et .{.. 2l>iUj, In fact, no deaths have bt.rn reported to the Ametican Association of Poison Control Centers since 1983. *Vboneutria* (banana spiders) from South America and *Atrax* (funnel web spiders) from Australia also cause neurotoxic lesions. Black widow spider *[Latrodectus mactans mactans)* venom contains a-larroxin, a neurotoxin capable of inducing neurotransmitter release from presynaptic cholinergic, noradrenergic, and aminergic nerve endings. Re-uptake is hindered as well.

Although the toxin itself is fat mote potent than those found in snake venom, most spider bites do not cause many symptoms because only a small volume of venom is injected. Sometimes a characteristic erythematous ring surrounding a paler center (target or halo lesion) develops around the site of the spider bite. Within 30-60 minutes of black widow envenomation, intense pain and involuntary muscle spasms may appear in abdominal muscles, with spread to limb musculature (lactrodeemm); this can be seen as many as 6-12 houts after the spider bite. Dysautonomia, piloerection, and unique sweating patterns may be present. Respiratory arrest can result from diaphragmatic muscle involvement. Other associated symptoms include priapism, salivation, sweating, bronchospasm,and bronchorrhea. Hypertension is a nearly universal finding in affected individuals (Woestman et al. 1996). Serum creatine kinase may be elevated, Treatment begins with careful monitoring of respiration and vital signs and intensive-care support if necessary, Antivenin shortens the duration of symptoms if administered early but should be reserved primarily for severe disease. Muscle spasms may be treated with slow infusion of calcium gluconate or methocarbamol. Benzodiazepines and opioids are useful for the control of anxiety and pain.

Scorpions

Although only a few of the approximately 1400 scorpion species are of neurological importance, bites by poisonous scorpions are generally more dangerous than spider bites. Scorpion envenomation is a public health problem in warm climates. In Mexico alone, there are 100,000-200,000 scorpion bites annually, resulting in 400-1000 fatalities. Small children in particular are prone to developing neurological sequelae; as many as 80% of bites to children are symptomatic. More than 14,500 scotpion bites were reported in the United States in 2001, with no mortality (Litovitz et al. 2002). All potential lethal scorpions ate **members** of the family *Butbtdae,* with the exception of *Hemiscorpious* (family *Scorpionidae).* They are characterized by a triangular sternal plate, to be distinguished from the pentagonal plate seen in less dangerous species. *Buthntus tamulus* of India, *Leiurus quinquestriatus* of North Africa and the Middle East, *Tityus serrulatus* of Brazil, *Centmroides suffusus* of Mexico and *Androctonus a us tralis* of Africa and Asia are among the most toxic species. The Arizona bark scorpion *{Centmroides exilicauda)* is found in southwestern United States and Mexico. Venom from C. *exilicauda* is relatively low in toxicity, with only one death reported in the United States since 1964 (Boyer et al. 2001). Other species of medical importance include *Butbus, Mesobuthus, Parabutbus,* and *Nebo.* The venoms of these scorpions contain a wide range of polypeptides that have a net excitatory effect on autonomic and skeletal neuromuscular systems. Effects are exerted through alteratior. ol voluj^- g.m-d ion uunnu's, panicu larly sodium ionophores (see Table 64C.1).

Venom is delivered from glands located on the lateral tip of the scorpion's tail stinger. Presenting symptoms are highly variable, from local pain (which may be secondary to serotonin found in scorpion stings) to a general state of intoxication. Paresthesias are common and are usually experienced around the site of bite but also may be felt diffusely. Autonomic symptoms of sympathetic overdrive (tachycardia, hypertension, and hyperthermia) are often present, but parasympathetic symptoms, including the SLUD syndrome (salivation, /acrimation, wrination, and defecation), may be present as well. Muscle fasciculations, spasms, dysphagia, and other cranial nerve signs arc sometimes seen, as well as dy scon jugate roving or rotary ocular movements (Bond 1999). With severe envenomation, encephalopathy may result from direct central nervous system (CNS) toxicity or secondary to uncontrolled hypertension. The constellation of symptoms has led to the misdiagnosis of seizures, particularly in infant victims of scorpion stings; although seizutes can occur, they have never been proven in *Centruroides* envenomation. Treatment is often limited to symptomatic control. Severe cases should be monitored and treated in an intensive care setting, with attention to a secure airway. Use of scorpion antivenin is controversial, but the consensus is that it should be used for significant envenomations.

NEUROTOXINS OP PLANTS **AND** MUSHROOMS

Pharmacologically active agents arc present in thousands of plants and mushtooms species. Many of these have been known since antiquity. Although fatal poisoning is relatively rare, some of the commonly encountered species are capable of inducing serious neurological symptoms. In the United States, 105,560 cases of plant poisoning and 8483 cases of mushroom poisoning were reported in 2001; only two fatalities occurred (Litovitz et al. 2002). Clinically significant toxicity happens under several circumstances. Approximately 75% of cases occur in children under the age of six, most as a result of accidental ingestion. Adult poisoning may occur when toxic plants or mushrooms are

mistaken for edible species. Undoubtedly an under-reported category is the intentional consumption among some adolescents and young adults who attempt to get "high" from so-called "natural" botanical sources.

Common names of plants are entirely inadequate for their identification; botanical names should be used whenever possible. Identification is neither easy nor accurate, even with the aid of current computer software (Lawrence 1998). Naming the plant or mushroom involved in a botanical exposure should be left to a trained botanist or mycologist. Even without a definitive identification, the history of exposure and the recognition of a characteristic syndrome are often sufficient to establish a tentative diagnosis. The best treatment is usually empiric, including gastric lavage or catharsis, supportive measures, and control of symptoms. With the exception of anticholinergic poisoning, there are few specific antidotes.

Several of the important neurological syndromes are discussed in the following sections. A comprehensive review of the many botanical toxins is impossible, and only a small selection is presented. Table 64C.2 lists several major categories and the commonly associated plants in each category. Omitted are plants that do not have direct toxicity on the nervous system, such as those containing cardiac glycosides, cournarin, oxalates, taxines, andromedotoxin, colchicine, and phytotoxins. Secondary neurological disturbances may result from these toxins because some can cause severe electrolyte abnormalities, cardiovascular dysfunction, or coagulopathy.

Jimson Weed *(Datura stramonium)*

Jimson weed, first grown by early settlers in Jamestown from seeds brought from England, was initially used to treat asthma. It is now found throughout the United States. Intoxication is not uncommon, especially among young recreational users in rural areas. The chief active ingredient is the alkaloid hyoscyamine, with lesser amounts of atropine and scopolamine. Among the 1144 intoxications by anticholinergic drugs reported in 2001, the single fatality was attributed to *Datura* ingestion (Litovitz ct al. 2002). Symptoms of anticholinergic toxicity appear within 30-60 minutes after ingestion and often continue for 24-48 hours because of delayed gastric motility (Centers for Disease Control 1995). The clinical picture can include hyperthermia, delirium, hallucinations, seizures, and coma. Autonomic disturbances such as mydriasis, cycloplegia, tachycardia, dry mouth, and urinary retention are often present. Treatment includes gastrointestinal decontamination with or without the induction of emesis. Supportive measures and symptom relief should be provided, and physostigmine should be reserved for severe or life-threatening intoxications.

Tabic 64C.2: Neurotoxicity of plants

Principal Toxins	*Plants (representative examples)*	*Main Clinical Features*
Tropane alkaloids (belladonna)	Jimson weed *(Datura stramonium),* Deadly nightshade (belladonna, *Atropa belladonna),* Matrimony vine (Lycium halimifolium), Henbane *(Hyoscyamus niger),* Mandrake *(Mandragoran officinarum),* Jasmine *[Cestrum* sp.)	Mydriasis, cycloplegia, tachycatdia, dry mouth, hyperpyrexia, delirium, hallucinations, seizures, coma
Solanine alkaloids	Woody nightshade (bittersweet, *Solanum dulcamara),* Black nightshade *{Solanum nigrum),* Jerusalem cherry *(Solanum pseudocapsicum),* Wild tomato *{Solanum gracile),* Leaves and roots of the common potato *{Solanum tuberosum)*	Mydriasis, cycloplegia, tachycardia, dry mouth, hyperpyrexia, delirium, hallucinations, seizures, coma
Nicotine-like alkaloids (e.g., Cytisine)	Tobacco *(Nkotiana* sp.}, Golden chain *{Laburnum anagyroides),* Mescal bean *(Sophora* sp.), Scotch broom (CyrisHs sp.), Poison hemlock *(Conium maculatum)*	Variable sympathetic and parasympathetic hyperactivity, hypotension, drowsiness, weakness, hallucinations, seizures
Cicu toxin	Water hemlock *(Cicuta maculata)*	Diarrhea, abdominal pain, salivation, seizures, coma
Triterpenc	China berry *{Melia azedarach)*	Confusion, ataxia, dizziness, stupor, paralysis, seizures
Anthracenones	Buckthorn *{Karwinskia humboldtiana)*	Ascending paralysis; polyneuropathy
Excitatory amino acid agonists	Chickling pea and others *[Lathyrus* sp.), Cycad *(Cycas rumpbii),* False sago palm *(Cycas circinalis)*	Neurodegenerative diseases

Poison Hemlock *(Cortiutn maculata)*

The dangers of poison hemlock have been known since ancient times. It was reportedly used to execute Socrates. The Old Testament describes rhabdomyolysis in Israelites who ate quail fed on hemlock (coturnism). The highest concentration of toxin is in the root of this ubiquitous plant, which may be mistaken for wild carrots. Alkaloid toxins structurally similar to nicotine initially cause CNS activation and general autonomic stimulation. In severe cases, a depressant phase may then ensue, presumably secondary to acetylcholine receptor tachyphylaxis. Death is usually secondary to respiratory paralysis.

Water Hemlock *{Cicuta maculata)*

Water hemlock is a highly toxic plant found primarily in wet, swampy areas and sometimes mistakenly ingested as wild parsnips or artichokes. Although related to poison hemlock, its clinical toxidrome is quite different. The principal toxin, the long-chained aliphatic alcohol cicutoxin, is a highly potent, noncompetitive GABA receptor antagonist (Uwai et al. 2000). Symptoms consist of initial gastrointestinal effects (abdominal pain, salivation, and diarrhea) followed by generalized convulsions, obtundation, and coma. Mortality is secondary to refractory status epileptieus; seizures are treated with standard protocols.

Peyote *(Lapbapbora williamsii)*

Peyote is a small cactus native to the southwestern United States and Mexico, but it can be cultivated anywhere. The principal agent is mescaline, which has actions similat to those of the hallucinogenic indoles. A peyote button, the top portion of the cactus, contains about 45 mg of mescaline; 6 to 9 buttons (5 mg/kg) are sufficient to be hallucinogenic. Dizziness, drowsiness, ataxia, paresthesias, sympathomimetic symptoms, nausea, and vomiting are frequent accompanying clinical features. Ingestions are rarely life-threatening.

Morning Glory *(Ipomoea tricolor)*

The active agents in morning glory seeds are various amides of lysergic acid. The seeds are consumed for purposes of abuse. The neuropsychological effects are similar to those of lysergic acid diethylamide (LSD) and consist of hallucinations, anxiety, mood changes, depersonalization, and drowsiness. Acute clinical effects may also include mydriasis, nausea, vomiting, and diarrhea.

Medicinal Herbs

Treatment of illness with herbal remedies, either purchased over-the-counter at health food stotes or procured from practitioners of traditional medicine, has become increasingly popular in the United States. Potentially harmful ingredients may be included in products as contaminants or intentionally added to increase a desired effect. The labels, if present, often do not fully represent the myriad of compounds contained within. Many of these can have potential GNS effects of varying severity. Gomamination of products with *Atropa belladonna* (deadly nightshade), *Datura* sp., and Mandragora officinarum (mandrake) have been reported. Common herbal preparations such as kava-kava *(Piper methysticum)* and St. John's wort *(Hypericum perforatum)* have neurotoxic potential, particularly if combined with other herbal or standard pharmaceuticals. *Podophyllum peltatum* (mayapplc), widely used in Ghinese herbal medicine, is potentially neurotoxic.

Excitatory Amino Acids

Various *Latbyrus* species, including *L. sativus* (chickling pea), L. *clymenum* (Spanish vetch), and *L. cicera* (flat-podded pea) are responsible for lathyrism (Spencer 1995). These hardy plants are an important part of the diet of people in the India subcontinent, Africa, China, and some parts of Europe. Epidemics of lathyrism often coincide with periods of famine or war, probably a result of excessive dietary dependency on these legumes. The disease, know[r]n since antiquity, is still endemic in many underdeveloped countries; astounding prevalence rates as high as 66% have been reported during famines. The putative toxin is beta-N-oxalylamino-L-alanine (L-BOAA), an amino acid with potent agonist activity at the (R.S)-a-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) subclass of glutamate receptors. L-BOAA is capable of inducing ncurolathyrism in several animal models.

Clinically, the affected patients present with subacute or insidious onset of spastic paraparesis, upper motoneuron signs, and gait instability. Muscle aching and paresthesias may be present, but the sensory examination is largely normal. Cognition ami tv:vbella: lumtioiis are \(\nvd. Partial recovery after discontinuation of *i.athyrus* intake is possible, but interestingly, there are reports of deterioration without further exposure many years later.

Historically the Chamorro people of Guam have had a high incidence of parkinsonism, amyotrophic lateral sclerosis, and dementia; however, the occurrence has now markedly decreased in the younger population. The etiology of this complex is uncertain; many have speculated that it is due to unique aspects of their diet, especially the consumption of flour made from the seeds of the cycad *(Cycas rumpbii).* Among other compounds, cycads contain

a toxic amino acid, ^-N-methylamino-L-alanine. (BMAA) that has heen shown to damage motoneurons in primates and cause parkinsonian and behavioral changes. [Neurodegenerative diseases in other populations have also suggested a possible link to plant-detived neurotoxins. Causal relationships are often difficult to prove in these instances.

Mushroom Poisoning

Of the more than 5000 varieties of mushrooms, approximately 100 are known to be toxic to humans. Ingestion by children comprises the majority of cases teported to poison centers. These exposures arc generally not serious, because usually only small amounts are ingested and most "lawn" mushrooms are harmless. Adults mote frequently consume mushrooms in larger quantities and more likely develop toxic symptoms. Aside from accidental ingestion, mushrooms such as *Psihcybe* sp,, *Panaeolus* sp., *Amanita mu scar la,* and *Amanita panthcrma* are popular among drug users for their psychoactive effects. Many ate used also in tribal ceremonies as an intoxicant.

The classification system most commonly adopted by clinicians divides poisonous mushrooms into groups according to clinical symptomatology. The gtoups associated with significant neurological morbidity are listed in Table 64C.3. The most lethal mushrooms belong to the *Amanita* genus and contain various cyclic polypeptides, including the amatoxins, phallotoxins, and virotoxins. Amatoxins have potent hep a to toxicity and nephrotoxicity. In significant intoxications, severe gastrointestinal symptoms appeat initially, after a characteristic latency period of 6-24 hours, followed by fulminant hepatic and renal failute *3-5* days later. Seizures, encephalopathy, and coma often accompany systemic organ failure. With the exception of poisoning by some monomethylhydrazine-containing genera (gyromitrin), toxicities ate rarely life threatening. In 2001, nearly 8500 mushroom ingestions wete reported in emergency rooms in rhe United States; thcte were no fatalities, but 38 were classified as having significant medical outcomes (Litovitz 2002),

Poisonous mushrooms often closely resemble edible varieties. A specimen may be distorted during transport or after cooking. The task of taxonomy is best left to a mycologist. Even in the absence of a positive identification, the nature of the symptoms and the time of their onset after ingestion are valuable guides to diagnosis and management. Supportive care and decontamination are the mainstays

Table 64C.3; Poisonous Mushrooms

Principal toxins	*Mushrooms {representative examples)*	*Mode of action*	*Time of onset/main clinical features*
Cyclic polypeptides (especially amatoxins)	*Amanita pballoides* ("death cap"), *Amanita mrosa, Amanita bisporigera, Amanita verria,* and others	Inhibition of mRNA synthesis; lie pa to toxicity and nephrotoxicity	6-24 hr: GI symptoms; 3-5 days: hepatotoxicity and renal failure
Monomethylhydrazines (Gyromitrin)	*Gyromitra* sp, ("false morels")	Functional pyridoxine deficiency; GABA deficiency (through decreased GAD activity)	6-10 hr: GI symptoms, hemolysis; seizures respond to pyridoxine
Coprine	*Coprinus atrame.ntarms* ("inky cap") and other Coprinaceae	Inhibition of aldehyde dehydrogenase (disulfiram-Iike)	20-120 min: flushing, palpitations, and headache after alcohol ingestion
M11.i.!	*C.lilotybc* and *btocybe* genera	Cholinergic agonist	15-120 min: cholinergic hyperactii it;
Isoxazoles (Muscimol, ibotenic acid)	*Amanita muscatia* ("fly agaric"), *Amanita gemmata, Amanita pantbenna* ("the panther"), *Amanita cotburnata*	GABA receptor agonist; glutamate receptor agonist; anticholinergic	30-90 min: ethanol-like intoxication; euphoria, hallucinations, dysarthria, ataxia, myoclonic jerks, seizures, and coma
Indoles (psilocybin, psilocin)	*Psilocybe caerullpes, Psliocybe cubensis, Panaeolus foenisecii, Gymnopbilus speclabilis, Psathyrella foenisecii*	Structural analogue of serotonin (5-HT); actions resemble LSD	30-60 min: euphoria, hallucinations, mydriasis, tachycardia, seizures (in children)

GABA = y-aminobutyric acid; GAD = glutamic acid decarboxylase; GI = gastrointestinal; 5-HT 5-hydroxytrypta mine; LSD lysergic acid diethylamide.

of treatment. This can be further supplemented by specific treatments, such as infusion of pyridoxine (gyromitrin poisoning), atropine (muscarine poisoning), or physostigmine (ibotenic acid and muscimol poisoning), as needed.

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Chapter 64
Effects of Toxins and Physical Agents on the Nervous System

D. MARINE TOXINS

Neil E. Schwartz and Yuen T. So

Seafood is a vital component of the human diet worldwide and is essential fot the economic stability of many regions. Various toxic syndromes have occurred from the consumption of contaminated fish and shellfish, some of which have neurological consequences. Descriptions of marine food poisoning date back to ancient times. A carving on the tomb of the Egyptian Pharaoh Ti *(circa* 2700 KC) depicts the dangers of the toxic puffcrfish, and the Old Testament warning that forbids the eating of fish that "hath not fins and scales" may have carried the same truth. Galen claimed that moray eels, possible vectors of various marine toxins, were dangerous to eat. Ciguatera intoxication was known in China during the T'ang Dynasty (618-907 AD); it was later described by early Spanish explorers and in the journals of Captain Cook's expedition in 1774. George Vancouver recognized paralytic shellfish poisoning in the Pacific Northwest toward the end of the eighteenth century. Periodic outbreaks of marine intoxications affecting humans or wildlife continue to make news headlines. In addition to their obvious clinical concern, many of these toxins have been essential in our quest to understand cellular neurophysiology, in particular, ionic fluxes through excitable membranes. Some toxins have been exploited for other human purposes, such as tetrodotoxin-tipped darts and arrows used in the Americas for hunting purposes.

Most marine toxins originate from micro-organisms, typically unicellular flagellated algae (dinoflagellates). During periods of intense algal proliferation (blooms), high concentrations of toxins accumulate in fish or shellfish, which then act as transvectors for human disease. Typically, the toxins do not adversely affect the transvector; in fact, there is often bio-concentration of the toxin as it is consumed by larger animals further up the food chain. This chapter highlights some of the more common intoxications that occur from ingestion of contaminated seafood (Table 64D. 1), Other marine-associated intoxications, such as those that occur from venomous fish, cchinoderms, sponges, red whelks, cyanobactcria, and coelenterate stings are not covered here. Likewise, envenomation with conotoxins (predatory mollusks from the superfamily Conidac), although of tremendous interest to the research neuroscientist, is less relevant for the clinical neurologist.

The proliferation of toxin-producing microalgae depends on poorly understood interactions of a number of environmental and seasonal factors. Outbreaks of shellfish poisoning are associated with so-called "red tides," which refer to algal blooms and tile subsequent reddish-brown discoloration of the water. Red tides have great economic effects on coastal communities dependent on both tourism and fisheries; blooms can cause massive fish kills, wiping out entire fish farms within hours. Not all red tides are toxic, and shellfish contaminations do not necessarily follow red tides (Whittle and Ga Mac her 2000). Moreover, ciguatera poisoning {see Ciguatera Fish Poisoning in next section) is not associated with blooms or any other reliable forewarning.

The marine toxins arc generally colorless, tasteless, and odorless. Normal food screening and preparation procedures do not typically prevent intoxication. This heat and acid stability renders marine toxins particularly dangerous to unsuspecting consumers of contaminated seafood and poses difficulty in formulating public health strategies for prevention. Globalization of the food industry, with its efficient methods of transportation, raises the possibility of intoxication with imported fish and shellfish not typically found in the United States. The American Association of

Tabic 64D.1: Fish and shellfish poisoning

Syndrome	*'Principal toxins*	*Toxin source*	*Transvector*	*Path op hysio logy*
Ciguatera fish poisoning	Ciguatoxins; ma i to toxin; others	Dinoflagdlates *(Gambwrdiscus toxicus* and others)	Fish (multiple species of reef fish)	Na^{+} and Ca^{++} channel activation
J'uil. Irtish poisoning	Tetrodotoxins	Presumed bactetial *[}Vibrios* spp., *IPseudomonas* spp.)	Various {puffcrfish, salamanders, newt, and others)	Na^{T} channel blockade
Scombroid fish poisoning	I listamme	Presumed bacterial *[}Vibrios* spp,)	Scombroid fish (tuna, mackerel, skipjack, ere.) and non-scombroid fish (mahi-mahi, sardines, etc.)	H i stain in ergic i-l'n i ·
Paralytic shellfish poisoning (PSP)	S.iximxin and derivatives	[dinoflagdlates *{Alexandrium* spp., ***Gymnodium catena turn,*** *Pyrodinium bahamense)*	Shellfish	Na^{+} channel blockade
Neurotoxic shellfish poisoning (NSP)	Brcveioxms	Dinoflageltates *[Gymnodinuim breve)*	Shellfish	Transforms fast Na^{-t} channels into slower ones
Amnestic shellfish poisoning (ASP)	Domoic acid and its cogencrs	Diatoms *{Pseudo-nitzscbia* spp., *Nitzscbia actydrapbila, Amphora coffeifornus)*	Shellfish; fish (?)	Glutamate receptor activation
Diari hetit shellfish poisoning (DSP)	Okadaic acid and derivatives; dinophysistoxins	I (uniflagellates *{Dinophysis* sp., *Prorocentrum* spp., *Proceratium reticulatttm, Coolia* sp.)	Shellfish	Serine/threonine protein phosphatase nhibirion

Poison Control Centers (AAPCC) logged over 67,000 incidents of food poisoning in the United States in 2001; exposure data for marine intoxications, however, are not reported separately (Litovjtz et al. 2002). Physicians who treat any suspected cases should report them to public health agencies, as any index case may be the beginning of a wider outbreak. Whenever possible, the contamman d food should be retrieved and tested, and many toxin assays are currently available. Diagnosis is dependent on the history of ingestion and the recognition of the appropriate clinical features. Treatment, unfortunately, is mostly symptomatic. Although marine toxins can cause significant morbidity, most illnesses are short-lived and mortality is rare.

CIGUATERA FISH POISONING

Ciguatera is a marine food poisoning endemic to the tropics, but it is also the most common nonbacterial fish borne poisoning in the United States. The ciguatera toxins are produced by algae that thrive in the tropical or subtropical coral reef ecosystem, extending between *iS'* North and 35" South. The epiphytic dinoflagellate *Gambierdiscus toxicm* has been implicated in ciguatera, but other organisms may also play a role. The algae are consumed by small herbivorous fish that in turn arc eaten by carnivorous ones. As such, larger and older fish such as barracuda, eel, sea bass, grouper, red snapper, and amber-jack are more toxic. Practically any reef fish eaten in significant quantity, however, may cause ciguatera; more than 400 species have been implicated. Outbreaks can also occur in residents of temperate areas after travel or consumption of imported fish.

Accurate disease incidence is not available because of unavoidable undcr-rceognition and under-reporting. One estimate puts the annual number of cases between 20,000 and S0,000 among people in endemic areas, predominantly Australia, the Caribbean, and the islands of the South Pacific. A telephone survey estimated that 7% of Puerto Rico's residents might have suffered at least one episode of ciguatera in their lifetime. In the United States, most cases are encountered in Hawaii, Rhode Island, and Florida. Even in Canada, there arc an estimated 1000 cases per year from tourism and imported fish. Mortality has been reported at less than 0,5%. No deaths from ciguatera have been documented in the United States.

A number of toxins are responsible for ciguatera, including ciguatoxins and maitotoxin. Ciguatoxins are a group of lipid-solublc, highly oxygenated cyclic poly-ethyl molecules similar in structure to the brevetoxins (see Neurotoxic Shellfish Poisoning, later in this chapter). Ciguatoxins act on tetrodo toxin-sensitive voltage-gated

sodium channels in nerves and muscles, leading to increased sodium permeability at rest and membrane depolarization. This results in spontaneous neuronal firing that presumably underlies the neurological symptoms. Maitotoxin is a water-soluble bisulfated compound that increases calcium ion influx through voltage independent calcium channels; it is the most potent nonproteinaceous toxin known (LD50 = 50 ng/kg, i.p.; Yasumoto 2001). Gambierol and palytoxin, lipid- and water-soluble toxins, respectively, have also been implicated in ciguatera (Daranas, Norte, and Fernandez 2001).

Clinical Features

Symptoms of abdoiiiin.il pain, nausea, vomiting, and diarrhea are usually the first to appear and may last 1-2 days. Neurological symptoms are almost invariably present in ciguatera and arc the dominant feature in poisoning that occurs from Pacific Ocean fish (Lewis 2001). Patients develop centrifugal spread of paresthesias involving the oral cavity, pharynx, limbs, trunk, and, most disagreeably, genitalia and perineum. Particularly characteristic is a paradoxic temperature reversal; patients perceive cold as burning, tingling, or unbearable heat. A smaller proportion may sense warm objects as cold. 1 leadache, weakness, fatigue, arthralgia, myalgia, metallic taste, and pruritus are common. Bizarre symptoms such as a sensation of loose teeth are occasionally described; referrals to psychiatrists have been made by clinicians unacquainted with the disease. Curiously, symptoms are worsened by alcohol consumption, exercise, sexual intercourse, or dietary factors. The severity of symptoms is typically dose-dependent, with more severe poisonings tending to occur after consumption of the toxin-rich head, liver, and viscera of contaminated fish. Paralysis and death have occurred. Rare cases of polymyositis and peripheral neuropathy have also been reported. Irritability may be the only neurological symptoms in children, but life-threatening cases occur more frequently in this age group. Acute transient cardiovascular abnormalities are sometimes seen, and there tends to be an increase in parasympathetic tone. Most neurological symptoms remit in approximately one week, although some-degree of paresthesias, asthenia, weakness, and head-ache may persist for months to years. The long-lasting symptoms, which are often accompanied by depression, may ultimately resemble chronic fatigue syndrome. Lipid storage and slow release of toxin may underlie the prolonged nature of some symptoms (Pearn 2001).

Diagnosis

Although a commercially available immunoassay exists for ciguatoxiu detection in fresh fish, it is often impossible to find what remains of the offending species. Diagnosis is largely based on the characteristic gastrointestinal, neurological, and cardiovascular disturbances. Clustering of cases in people who consumed the same fish helps confirm the diagnosis. However, there is significant variation in individual susceptibility, even when two persons eat a similar quantity. Nerve-conduction studies may show slowing of both sensory and motor nerve-conduction velocities, with prolongation of the absolute refractory, relative refractory, and supernormal periods. These findings are consistent with prolonged opening of sodium channels in the axonal cell membranes.

Treatment

Decontamination of the gastrointestinal tract with charcoal may be beneficial if the patient presents soon after ingestion. Intravenous mannitol (20%; 1.0 g/kg at 500 mlVhour) is a specific treatment for acute ciguatera. The mechanism of action may be related to the reduction of edema in Schwann cells, but this is a matter of debate. Neurological improvement can be dramatic in over 60% of patients, especially if mannitol is given soon after symptom onset; gastrointestinal symptoms, however, are resistant to this therapy. Repeat dosages may be helpful. Fluid and electrolyte status should be assessed and corrected if necessary, because mannitol may induce severe dehydration and electrolyte derangements. Supportive care during acute disease may include fluid supplementation, control of bradycardia, and symptomatic treatment of anxiety, headache, and pain. Calcium gluconate, anticonvulsants, and corticosteroids have been tried wir'i varying results. The chronic symptoms of ciguatera arc difficult to treat. Amitriptyline or other tricyclic antidepressants may provide partial relief.

PUFFERFISH POISONING

Tetrodotoxin (TTX) is the causative agent in pufferfish poisoning. Pufferfish (family *Tetraodontidae)* have a worldwide distribution in both freshwater and saltwater but are most commonly found in the waters around Japan and China. Over 100 species are identified, known variously as pufferfish, tarn bores, porcupine fish, jugfish, and blowfish. Other sources of TTX include the ocean sun fish, toad fish, parrotfish, Australian blue-ringed octopus, gastropod mollusk, horseshoe crab (eggs), *Atelopid* frogs (skin), newts (genus *Taricba),* and some salamanders. The source of pufferfish TTX is debatable. It is thought to be marine bacteria, possibly *Vibrio,* thai colonize the fish and allow the TTX to be sequestered. Concentrations are especially IneJ'- m the skin, liver, roe, and gonads and relatively low in the muscles, *hugu* refers to a preparation of pufferfish in Japan that is considered a delicacy. Specially trained *fugu* chefs certified by the government fillet the fish

in a way that avoids contamination by the deadly viscera. A handful of these chefs prepare pufferfish in the United States. Despite these precautions, *fugu* poisoning accounts for approximately half the fatal food poisonings in Japan, with up to 50 deaths each year. Toxicity is seasonal, and pufferfish is served only from Octobet to March.

TTX is a heat-stable, water-soluble heterocyclic small organic molecule that selectively blocks voltage-gated sodium channels in excitable membranes. It interferes with the inward (excitatory) flow of sodium current that occurs during an acrion potential, 'lerrtnloroxin blocks in pulse conduction in somatic and autonomic nerve fibers, reduces the excitability of skeletal and cardiac muscles, and has profound effects on vasomotor tone and central mechanisms involved in respiration. A dose of 1-2 mg of purified TTX can be lethal. Toxicity has been documented with the consumption of as little as 1.4 ounces of *fugu.*

The clinical symptoms of TTX poisoning are similar to those of saxitoxin (STX)-induced paralytic shellfish poisoning (sec Paralytic Shellfish Poisoning, later in this chapter). Lip and tongue paresthesias appear within minutes of ingestion. Gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain are common. Progressive ascending weakness is apparent in moderately severe cases. Reflexes may be preserved early in the course of paralysis. Dysphoria, dysphagia, hypoventilation, and profound hypotension develop in more severe intoxications. Coma and seizures may be seen. Fatality rates are high, with estimates at 50-80%, mostly due to respiratory insufficiency, cardiac dysfunction, and hypotension. Treatment is supportive. Gastric lavage and charcoal are indicated if presentation is early. Anticholinesterases have variable success. Patients who survive the acute period of intoxication (approximately the first 24 hours) tend to recover without neurological sequelae, while those who succumb tend to do so within the first several hours. Fluorescent spectrometry can detect TTX, and the mouse bioassay for STX detection is also positive for TTX.

SCOMBROID FISH POISONING

Scombroid fish poisoning—also known as histamine fish poisoning, pseudoallele fish poisoning, or "mahi-mahi flush"—is among the most common causes of fish toxicity worldwide. The AAPCC does not maintain specific data on scombroid fish poisoning, but it represents 5% of food-borne disease outbreaks reported to the Centers for Disease Control and Prevention. Poisoning can occur after eating improperly stored fatty, dark-fleshed scombroid fish (family Scombri da e; e.g., tuna, mackerel, skipjack) or non-scombroid fish (e.g., mahi-mahi, marlin, sardines, .iiu hi ivies . Alleued fish typical [\ have a peppery, inei.il lie, or bitter flavor. The pathophysiology is incompletely inhk IMIIOJ, lull poisoning is believed to be caused lij bacterial decarboxylation of histidme to biogenic amines such as histamine. This occurs at temperatures above 15°G Histamine is heat-stable, so once it is formed by improper storage it cannot be inactivated by proper cooking. It is typically present at levels below 0.1 mg/100 g in normal fish but can be higher than 20-50 mg/100 g in toxic fish. Oral consumption of similar quantities of histamine does not cause symptoms to the same degree, raising the possibility that another mechanism is at play in scombroid toxicity.

The syndrome is distinctive; it closely resembles an acute allergic reaction and is often misdiagnosed as such. Clinical features include pruritus, throbbing headache, skin flushing, urticaria, oral burning or paresthesias, palpitations, and gastrointestinal disturbances. Symptoms occur within minutes after fish ingestion and are self-limited to 3-6 hours. Patients at the extremes of age and those with asthma are most vulnerable. Persons taking isoniazid or monoamine oxidase inhibitors may have more severe symptoms because of blockade of histaminasc.

Diagnosis is made by a careful history and examination. Histamine levels can be measured in fish, and urinary levels of histamine and N-methylhistidine may be elevated in affected patients, but these studies are not typically used clinically. Intravenous histamine receptor types 1 and 2 (Hj and H_2) blockers should be given promptly, as their administration often provides rapid symptomatic relief. Treatment is otherwise supportive. Epinephrine is sometimes given under the assumption that an allergic reaction is taking place; it should typically be reserved for cases with symptomatic bronchospasm.

SHELLFISH POISONING

Food poisoning caused by shellfish is more likely to be from infectious agents than toxins. Hepatitis A, Norwalk virus, and various *Vibrio* species can be transmitted through the ingestion of shellfish. Classically, four syndromes may result from consumption of shellfish contaminated by-toxins: patalytic shellfish poisoning, neurotoxic shellfish poisoning, amnestic shellfish poisoning, and diarrhetic shellfish poisoning. All arc primarily associated with bivalve mollusks (clams, mussels, scallops, oysters), filter feeders that can accumulate toxic microalgae at high levels. Outbreaks are common during the summer months, especially during periods of red tides. The World Wide Web is a good source for up-to-date information on harmful algal blooms. Although the teaching in North America and Britain is that shellfish arc safe in mouths that contain the letter "r." toxic contamination may occur in any month and in the absence of red tides. The incidence of shellfish poisoning has been on the decline in the United States, even as the incidence of harmful algal blooms is on the rise. This is probably due to greater public awareness and governmental safety measures such as forced beach closures and shellfish analysis.

Paralytic Shellfish Poisoning

Paralytic shellfish poisoning (PSP) occurs in the United States along the coast of New England, in the Pacific Northwest, and in Alaska. It is the most severe of the shellfish intoxications, with mortality rates of 1-12%>, with higher rates being in areas without advanced life support capabilities. Children appear to be more sensitive than adults. Dinoflagellates of the species *Alexandrmm* are the primary source of the saxitoxins, the agents responsible for the neurological symptoms of PSP. Blooms occur between April and October, with shellfish remaining toxic for several weeks after the bloom subsides. Saxitoxin (STX) is a heat-stable toxin that acts primarily on the peripheral nervous system, where it binds reversibly to voltage-gated sodium channels in nerve and muscle membrane. Its action is similar to TTX (see Pufferfish Poisoning, earlier in this chapter). In comparison with TTX, STX has a greater potency to cause skeletal muscle weakness but has a lesser propensity to induce severe hypotension. It also has a shorter duration of action.

Symptoms typically appear within 5-30 minutes of ingestion of contaminated shellfish. Paresthesias develop in almost all patients and initially involve the perioral areas, oral cavity, face, and neck. These symptoms spread to the limbs and trunk in severe cases. Some patients complain of an unusual floating sensation. Brainstem symptoms and signs are sometimes present; these include dysarthtia, dysphagia, dysphonia, ophthalmoplegia, nystagmus, and dilated pupils. Other neurological symptoms include headache, gait ataxia, and limb incoordination. Gastrointestinal symptoms are less common. Despite the name of this syndrome, muscle paralysis does not develop in every patient. If present, weakness may involve muscles of the face, jaw, swallowing, respiration, and upper and lower limbs. In severe cases, respiratory paralysis appears within 2-12 hours of ingestion; the incidence of required respiratory support is 3-6%. Untreated respiratory paralysis is responsible for the deaths seen in PSP. Spontaneous recovery begins to appear after 12 hours and is usually complete within a few days. Weakness, however, may persist for weeks. There is no antidote, and treatment is supportive.

Initial diagnosis is largely dependent on recognition of the history and clinical features. An enzyme-linked immunosorbent assay (El.ISA) is available for STX, but its utility is limited by the variability of toxin constituents in each outbreak. If the contaminated shellfish is available, a useful test is the mouse bioassay. A mouse unit is defined as the minimum amount necessary to induce death of a mouse in 15 minutes. The lethal dose for humans is approximately 5000-20,000 mouse units. The mouse assay is employed to monitor commercial shellfish production in many parts of the world. Nerve-conduction studies may show reduced amplitude of the sensory and motor responses and prolonged latencies with slowed nerve-conduction velocities. Unlike acute demyelinating neuropathies, in which electrophysiological abnormalities lag behind clinical findings, the electrophysiological abnormalities in PSP are most prominent at symptom onset and improve over a few days as clinical symptoms resolve.

Neurotoxic Shellfish Poisoning

Neurotoxic shellfish poisoning (NSP) is caused by the di no flagellate *Gymnodinium breve,* which is found primarily in the Gulf of Mexico, the Caribbean Sea, and the waters around New Zealand. These microalgae are known for causing the infamous Florida red tides. They elaborate a group of lipophilic polyether toxins called brevetoxins, which cause depolarization of excitable membranes, persistent activation, and repetitive firing of nerves and muscles by transforming fast voltage-gated sodium channels into slower ones. Brevetoxins are probably more toxic to wildlife than humans, and red tides from blooms of G. *breve* are typically associated with massive fish, invertebrate, and seabird kills.

Clinical presentation is characterized by the simultaneous onset of gastrointestinal and neurological symptoms within minutes to hours after ingestion. Nausea, diarrhea, rectal burning, myalgia, circumoral paresthesias, dizziness, and ataxia are common. Less common signs and symptoms include tremor, dysphagia, mydriasis, and hyporeflexia. In general, the neurological symptoms are milder than those of PSP. Temperature reversal similar to that seen in ciguatera may be reported. A separate respiratory syndrome has been attributed to inhalation of brevetoxin aerosolized by the surf. A response consisting of conjunctival irritation, rhinorrhea, cough, and bronchoconstriction can be seen in sensitive individuals. No human deaths have been associated with NSP. There is a mouse bioassay for the detection of brevetoxin; radioimmunoassay (RIA) and ELISA are also available.

Amnestic Shellfish Poisoning

In November iyS7, 107 Canadians were stricken by a novel illness after eating mussels harvested off the Prince Edward Island coast. Gastrointestinal symptoms were followed by cognitive dysfunction and headache. The syndrome, referred to as amnestic shellfish poisoning (ASP), was found to be microalgae toxin-mediated. The toxin was later identified as domoic acid, an analogue of kainic acid. It functions as a potent agonist at excitatory ionotropic glutamate receptors. A pennare diatom, *Psetidonitzschia pungens,* was the probable source of the domoic acid. Very high concentrations of the excitotoxin were found in the digestive glands of uneaten mussels and those sampled from three river estuaries in Prince Edward Island. Since the initial epidemic, domoic acid has been found in

anchovies in Monterey Bay, California; in razor clams and Dungeness crabs in the Pacific Northwest; and in the marine food web along the Texas coast (Morris 1999). Massive killing of seabirds and mammals in the waters around Baja, California, have been attributed to domoic acid (Sierra-Beltran et al. 1998).

Domoic acid acts as an excitatory neurotransmitter in animal models; it is approximately three times more potent than kainic acid and over 30 times more potent than glutamic acid. Neurological disease results from its excitotoxic actions, especially on the limbic system. Symptoms usually appear within a few hours of ingestion. Almost all patients have diarrhea, vomiting, or abdominal cramps, although the severity varies. Roughly one-half of patients have headache, and approximately 25% present with anterograde memory . loss. In those with neurological dysfunction, the findings are quite varied. They include disorientation, mutism, seizures, myoclonus, and altered state of consciousness (ranging from somnolence to coma). Reflexes may be depressed or hyperactive, and some patients may have Babinski's signs. Two patients were reported to have a unique alternating hemiparesis and complete external ophthalmoplegia.

After ASP, gradual improvement occurs over a three-month period. Those with residual deficits often have anterograde amnesia with relative preservation of intellect and other higher cortical functions. Some patients develop temporal lohe epilepsy. There also may be coexisting distal limb weakness and atrophy, and electrophysiological testing suggests a picture of either a pure motor neuronopathy or a sensorimotor axonopathy. In a few patients who have died, autopsy revealed astrocytosis and selective neuronal loss in the amygdala and hippocampus (Cendes et al. 1995). These lesions are reminiscent of those seen in the rat model of kainate-induced seizures. In the one reported outbreak, the mortality rate was 3%, all of which occurred in elderly patients.

Treatment is primarily symptomatic. Previous experience suggests that diazepam and phenobarbital, but not phenytoin, are the drugs of choice in the control of seizures. Diagnosis may be established with high-per forma nee liquid chromatography (HPLC); the mouse bioassay was deemed too insensitive. A surveillance program now exists in Canada to monitor commercial shellfish operations, with mussels and clams being analyzed regularly for domoic acid.

Diarrhctic Shellfish Poisoning

Diarrhetic shellfish poisoning (DSP) is a self-limiting gastrointestinal illness without clinical evidence of neurotoxicity. It is most common in Japan but has also been desctibed in Europe, South America, Canada, and New Zealand; there have been no confirmed cases in the United States. Okadaic acid, a polycthcr toxin that is a highly selective inhibitor of protein phosphatase type 1 (PP1) and 2A (PP2A), is responsible for the pathophysiological features. Diarrhea, nausea, and vomiting are almost universal symptoms. A mouse bioassay is available for analysis of shellfish. Complete recovery is expected within 3 days. No deaths have been reported from DSP.

OTHERS

New marine intoxications with neurological consequences continue to be described. Neurocognitive deficits have been reported in the so-called P/sesteria-associated syndrome, a recently described constellation of symptoms linked to the dinoflagellate *Pfiesteria piscicida* {the "fish killer"). Deficiencies in learning and memory, headaches, and acute confusional state have been seen. Exposure is probably mediated by aerosoli/ation or skin contact with an undetermined toxin and not shellfish consumption (Morris 1999).

An outbreak of an illness reminiscent of DSP in several people who ate mussels cultivated in Ireland led to the identification of azaspiracid. When injected into mice, the toxin causes paralysis and convulsions prior to death. The source is thought to be a dinoflagellate. Many other marine microalgae toxins found in shellfish have been characterized; the dangers and utilities of these compounds are still under investigation (Daranas, Norte, and Fernandez 2001).

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Chapter 64
Effects of Toxins and Physical Agents on the Nervous System

E. EFFECT OF PHYSICAL AGENTS ON THE NERVOUS SYSTEM

Michael J. Aminoff

The nervous system may be damaged by physical agents such as kmi/.iiu; .siul nonionizing "ulialinn, r';rl nary, extreme heat or cold, and vibration. The extent of damage depends on the intensit) aiul duration ol exposure.

IONIZING RADIATION

Electromagnetic and particulate radiation may lead to cell damage and death. Radiation therapy affects the nervous system by causing damage to cells (particularly their nuclei) in the exposed regions; these cells include neurons, glia, and the blood vessels supplying neural structures. As a late carcinogenic effect, radiation therapy may also produce tumors, particularly sarcomas, that lead to neurological deficits. Neurological injury is proportional to both the total dose and the daily fraction of radiation received.

Encephalopathy

Radiation encephalopathy is best considered according to its time of onset after exposure (De Angelis et al. 2001). *Acute radiation encephalopathy* occurs within a few days of exposure and is characterized by headache, nausea, and a change in mental status. It may be related to increased intracranial pressure from breakdown of the blood-brain barrier due to the immediate effects of the energy dispersal in the nervous tissue. Treatment with high-dose corticosteroids usually provides relief.

Early delayed radiation encephalopathy is probably caused by dcmyelination and occurs between 2 weeks and 3 or 4 months after irradiation. Headache and drowsiness are features, as is an enhancement of previous focal neurological deficits. Symptoms resolve after several weeks without specific treatment. A brainstem encephalopathy, manifest by ataxia, nystagmus, diplopia, and dysarthria, also may develop if the brainstem was included in the irradiated field. Spontaneous recovery over a few weeks is usual, hut the disorder sometimes progresses to obtundation, coma, or death.

Delayed radiation encephalopathy occurs several months or longer after cranial irradiation. It may be characterized by diffuse cerebral injury (atrophy) or focal neurological deficits with signs of increased intracranial pressure. The disorder may result from focal cerebral necrosis caused by direct radiation damage or by vascular changes. Immunological mechanisms also may be involved. Occasionally patients develop a progressive disabling disorder, with cognitive and affective disturbances and a disorder of gait, approximately 6-18 months after whole-brain irradiation. Pathological examination in some instances has shown demyelinating lesions.

Myelopathy

A myelopathy may result from irradiation involving the spinal cord. *Transient radiation myelopathy* usually occurs within the first year or so after incidental spinal cord irradiation in patients treated for lymphoma and neck and thoracic neoplasms. Paresthesias and Lhermitte's phenomenon characterize the syndrome, which is self-limiting and probably relates to demyelination of the posterior columns. A *delayed severe radiation myelopathy* may occur approximately one year after completion of radiotherapy. Patients present with a focal spinal cord deficit that progresses over weeks or months to paraplegia or quadriplegia. This may

simulate a compressive myelopathy or paraneoplastic subacute necrotizing myelopathy, but the changes on magnetic resonance imaging (MRI) are usually those of a focal increased T2-weighted myelomalacia with cord atrophy. The cerebrospinal fluid is usually normal, although the protein concentration is sometimes elevated. Corticosteroids may lead to temporary improvement, but no specific treatment exists. The disorder is caused by necrosis and atrophy of the cord, with an associated vasculopathy (Okada and Okeda 2001). Occasional patients develop sudden back pain and leg weakness several years after irradiation, with MRI revealing hematomyelia; symptoms usually improve with time.

In some instances, inadvertent spinal cord involvement, usually by irradiation directed at the para-aortic nodes in cases of seminoma, leads to a focal lower-limb lower motor neuron syndrome. The neurological deficit may progress over several months or years hut eventually stabilizes, leaving a flaccid, asymmetrical paraparesis. Recovery does nor occur.

Plexopathy

A radiation-induced plexopathy may rarely occur soon after radiation treatment for neoplasms, particularly of the breast and pelvis, and must be distinguished from direct neoplastic involvement of the plexus. Paresthesias, weakness, and atrophy typify the disorder, which tends to plateau after progressing for several months. The plexopathy may develop 1-3 years or longer after irradiation that involves the brachial or lumbosacral plexus. In this regard, doses of radiation exceeding 6000 cGy, use of large daily fractions, involvement of tbc upper part of the brachial plexus, lymphedema, induration of the supraclavicular fossa, and the presence of myokymic discharges on electromyography all favor a radiation-induced plexopathy. Although radiation plexopathy is often painless, a point favoring this diagnosis rather than direct infiltration by neoplasm, pain is conspicuous in some patients. Symptoms progress at a variable rate (Fathers et al. 2002). The plexopathy is associated with small-vessel damage (endarteritis obliterans) and fibrosis around the nerve trunks (Johansson et al. 2001).

NONIONIZING RADIATION

Nonionizing radiation that strikes matter is transformed to heat, which may lead to tissue damage. Ultraviolet radiation is produced by the sun, incandescent and fluorescent light sources, welding torches, electrical arc furnaces, and germicidal lamps. Ultraviolet radiation is absorbed primarily by proteins and nucleic acids. Susceptibility to it is increased by certain drugs, such as chlorpromazine and tolbutamide, and by certain plants, such as figs, lemon and lime rinds, celery, and parsnips, which contain furocoumanns and psoralens. Short-term exposure to ultraviolet light can damage the rerina and optic nerve fibers. A severe central scotoma may result from macular injury. Prevention requires the use of goggles and face masks in work environments where exposure to high-intensity ultraviolet radiation is likely to occur.

Exposures to laser radiation can induce ocular damage. This is particularly a problem when the wavelength of the laser beam is not in the visible portion of the electromagnetic spectrum, because the patient may not be aware of the exposure.

Concern has been raised that occupational or environmental exposure to high-voltage electrical power lines may lead to neurological damage from exposure to high-intensity electromagnetic fields. However, the effects of such exposure are uncertain and require further study. Nonionizing radiation at the radio frequency used by cellular telephones has been reported to cause sleep disturbances, headache, and other nonspecific neurological symptoms. Several studies have raised concerns that such radiation may cause brain tumors or accelerate their growth, although any heating of cerebral tissue by cellular telephones is minimal, and a clear theoretical basis for such an association with brain tumors is lacking. In any event, a recent case-control study failed to identify any major increased risk associated with the use of cellular telephones, at least in the short term (Inskip et al. 2001). The neurological implications of long-term use of cellular telephones or changes in telephone technology are unknown.

High-intensin noise m the acme senmg IKLV 1CL'J lo tinnitus, vertigo, pain in the ear, and hearing impairment. Chronic exposure to high-intensity noise of any frequency leads to focal cochlear damage and impaired hearing.

ELECTRICAL CURRENT AND LIGHTNING

Electrical injuries (whether from manufactured or naturally occurring sources) are common. Their severity depends on the strength and duration of the current and the path in which it flows. Electricity travels along the shortest path to ground. Its passage through humans can often be determined by identifying entry and exit bum wounds. When its path involves the nervous system, direct neurological damage is likely among survivors. With the passage of current through tissues, heat is produced that is responsible, at least in part, for any damage, but nonthermal mechanisms may contribute also (Winkelman 2001). In addition, neurological damage may result from circulatory arrest and from trauma related to falling or a shock pressure wave.

A large current that passes through the head leads to immediate unconsciousness, sometimes associated with ventricular fibrillation and respiratory arrest. Confusion, disorientation, seizures, and transient focal deficits are common in survivors (Duff and McCaffrey 2001), but

recovery generally occurs within a few days. Some survivors develop a cerebral infarct after several days or weeks, attributed to thrombotic occlusion of cerebral blood vessels. Residual memory and other cognitive disturbances are also common. Weaker current leads only to headache or other mild symptoms for a brief period.

When the path of the current involves the spinal cord, a transverse myelopathy may occur immediately or within 7 days or so and may progress for several days. The disorder eventually stabilizes, after which partial or full recovery occurs in many instances. Upper and lower motor neuron Jetu iti .nul ii'iiMin J-.Muriuuuvs are a minion. Inn ilic sphincters are often spared. Unlike traumatic myelopathy, pain is not a feature. Autopsy studies show di-myclination of long tracts, loss of anterior horn cells, and areas of necrosis in the spinal cord.

Segmental muscle atrophy may occur also within a few days or weeks of electrical injury of the spinal cord. Whether this relates to focal neuronal damage or has an ischemic basis is uncertain. The current pathway is typically across the cervical cord from one arm to the other, and the resulting muscle atrophy in the arms may be accompanied by an upper motor neuron deficit in the legs. Sensory disturbances (in upper or lower limbs) and sphincter dysfunction also occur. Occasional reports have suggested the occurrence of a progressive disorder simulating amyotrophic lateral sclerosis after electrical injury.

Peripheral or cranial nerve injury in the region of an electrical burn is often reversible, except when high-tension current is responsible, in which case thermal coagulation necrosis is likely. Care must be taken to distinguish such neuropathies from compartment or entrapment neuropathies, which are suggested by severe pain and a delay between injury and development of the neuropathy. Compartment syndromes develop because of muscle swelling and necrosis, and entrapment syndromes because of swelling of tissues in confined anatomical spaces. Immediate decompression of the compartment is indicated in these cases.

Occasional patients have developed hemorrhagic or thrombotic stroke after electrical injuries, for uncertain reasons. Venous sinus thrombosis has also been described. Suggested mechanisms include coagulation necrosis of part of the vascular wall with aneurysmal distention and rupture ot intramural thrombosis. Intense vasospasm, acute hypertension, intramural dissections, or transient circulatory arrest may also contribute.

VI Li RATION

Exposure to vibrating tools such as pneumatic drills has been associated with both focal peripheral nerve injuries, such as carpal tunnel syndrome (Herbert et al. 2001), and vascular abnormalities, such as Raynaud's phenomenon (Byhind et al. 2001). The mechanism of production is uncertain but presumably reflects focal damage to nerve fibers.

HYPERTHERMIA

Exposure to high external temperatures may lead to heat stress disorders. *Heat stroke*, the most severe, sometimes has an exertional basis, and disturbances of thermoregulatory sweating may be contributory. Classic heat stroke occurs especially in older persons with chronic disorders such as diabetes or obesity and in hypermetabolic states such as thyrotoxicosis. Anticholinergic or diuretic drugs and dehydration predispose to heat stroke because they impair sweating and thereby limit heat dissipation.

Hyperthermia leads to thirst, fatigue, nausea, weakness, and muscle cramps and eventually to confusion, delirium, obtundation, or coma, bur coma can develop without any prodrome. Seizures are frequent, focal neurological deficits are sometimes present, and papilledema may occur. With recovery, symptoms and signs generally clear completely, but cognitive changes or focal neurological deficits may persist. Cataracts have been attributed to dehydration. Cardiac output is reduced, pulmonary edema may occur, and adult respiratory distress syndrome is sometimes conspicuous.

Other systemic manifestations include a respiratory alkalosis and often a metabolic acidosis, hypokalemia or hyperkalemia, hypoglycemia, other electrolyte disturbances, and various coagulopathies. Rhabdomyolysis is common, and acute renal failure may occur in exertional heat stroke.

The prognosis depends on the severity of hyperthermia and its duration before initiation of treatment. With proper management, the mortality rate is probably about 5%, Treatment involve control of the body temperature by cooling, rehydration of the patient, correction of the underlying cause of the hyperthermia, and prevention of complications. When excessive muscle activity is responsible, neuromuscular blockade may be necessary.

In the *malignant hyperthermia syndrome*, the responsible anesthetic agent is discontinued, the patient is vigorously cooled, oxygenation is ensured, and intravenous dantrolene is administered. Thyrotoxic crisis is treated with thyroid-blocking drugs. Patients with pheocbromocytoma are treated with a-adrenergic antagonists.

Cooling is achieved by evaporation or by direct external cooling, as by immersion of the patient in cold water. The skin should be massaged vigorously to counteract the cutaneous vasoconstriction that results from external cooling and that impedes heat removal from the cure. Antipyretic agents are unhelpful. Hypotension is treated by fluid administration rather than vasoconstrictor agents, which should be avoided if possible. High doses of mannitol and use of diuretics may be required to promote urinary output. Electrolyte and glucose abnormalities also require treatment.

Hyperthermic limb perfusion with doxorubicin or mcphalan, two widely used chemotherapeutic agents in patients with melanomas or sarcomas, may lead to a variety

of neuromuscular abnormalities related to the perfusion temperature, but this is also influenced by any pre-existing changes and awaits further clarification (Bonifati et al. 2000).

HYPOTHERMIA

A core temperature below 35°C may occur in very young or elderly persons with environmental exposure, coma, hypothyroidism, malnutrition, severe dermatological disorders (because of excessive heat loss and inability to regulate cutaneous vasoconstriction), and alcoholism. Alcohol promotes heat loss by vasodilation and may lead to coma directly or from trauma with resultant environmental exposure to cold. Hypothermia also occurs in persons exposed to low temperatures in the working environment, such as divers, skiers, and cold-room workers.

The usual compensatory mechanism for cooling is shivering, but this fails at body temperatures below approximately .WC. As the temperature declines, respiratory requirements diminish, cardiac ourput falls, and significant hypotension and cardiac arrhythmias ultimately develop. Neurologically there is increasing confusion, psychomotor retardation, and obtundation until consciousness is eventually lost. The tendon reflexes are reduced and muscle tone increases, bill extensor plantai responses are not usually found. The electroencephalogram (EEG) slows and ultimately shows a burst-suppression pattern or becomes isoelectric with increasing hypothermia. At core temperatures below 32"C, the appearance of brain death ma) be simulated clinical!) and electroencephalograph] cally, but complete recovery may follow appropriate treatment. Management involves slow rewarming of patients and the prevention of complications such as aspiration pneumonia ar.d iiKtabolie. acidosis. 1 1) potecsmn may occur from dehydration but can usually be managed by fluid replacement. Plasma electrolyte concentrations must be monitored closely, especially because of the risk of developing cardiac arrhythmias, With recover)-, -.here *AW* usually no long-term sequelae.

Nerve damage may occur as a consequence of the tissues becoming frozen by the cold (frostbite). This involves the extremities and is usually irreversible.

BURNS

Following common usage, rhe term *thermal burn* refers to a burn caused by direct contact with heat or flames. Patients with severe burns may have associated disorders such as anoxic encephalopathy from carbon monoxide poisoning, head injury, or respiratory dysfunction from smoke inhalation. Central neurological disorders may occur later during hospitalization and are secondary to various systemic complications. Thus metabolic encephalopathies may relate ro anoxia, liver or kidney failure, and hyponatremia, and central pontine myelinolysis may occur also. Infections (meningitis or cerebral microabscesses) are common, especially in the second or third week after the burn. Vascular complications, including multiple strokes, may result from septic infarction, disseminated intravascular coagulation, venous thrombosis, hypotension, or intracranial hemorrhage. Imaging studies are therefore important in clan tying die underlying disorder.

Peripheral complications of burns are also important. Nerves may be damaged directly by hear, leading to coagulation necrosis from which recovery is unlikely. A compartment syndrome may arise from massive swelling of tissues and mandates urgent decompressive surgery. In other instances, neuropathies result from compression, angulation, or stretching as a result of incorrectly applied dressings or improper positioning of the patient. A critical illness polyneuropathy and myopathy is now well recognized in patients with multiorgan failure and sepsis, including patients with burns, and is discussed in Chapter 82.

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Chapter 65
Brain Edema and Disorders of Cerebrospinal Fluid Circulation

Gary A. Rosenberg

Brain cells depend on the constant delivery of oxygen and glucose by the cerebral circulation. Cerebral endothelial cells are metabolically active, selectively permeable, epithelial-like, secreting structures that are critical in maintaining a constant fluid and electrolyte environment. Adhesions between endothelial cells are tight, and only substances that are lipid soluble are able to easily cross them. These tight junctions separate brain cells from substances circulating in the blood. Brain cells are surrounded by interstitial fluid (TSF), which is contiguous with the cerebrospinal fluid (CSF). Enzymatic and osmotic processes continuously form CSF and ISF, the choroid plexuses being the main source for the CSF and cerebral capillaries and cellular metabolism the source of the ISF. Together the CSF-ISF serve the same function for brain cells that lymph provides for other cells in the body. Loss of either oxygen or glucose for even short periods causes cellular damage and may lead to cell death. Cell swelling is poorly tolerated because of the constraints imposed by the bony skull and the tough dural membranes.

The brain and spinal cord arc subject to different physical processes than other otgans in the body because they lie within the rigid bony compartments of the skull and spinal canal. The character of the CSF, with its constituents, pressure, and flow, are of great importance to the function of the central nervous system (CNS). Increased intracranial pressure results from increased tissue within the rigid bony box of the skull (space-occupying lesions, such as tumor, abscess, and hematoma}, increased fluid (cerebral edema of several types}, and impaired flow of CSF (hydrocephalus).

Brain edema is a life-threatening complication of many neurological conditions. Damaged cells swell, injured blood vessels leak, and blocked absorption pathways force fluid co enter brain tissues. F.ach of these mechanisms results in a potential increase in intracranial volume. Compensation for the potential increase occurs by displacement of CSF and venous blood from the skull. Further volume increases cause brain tissue to shift. Herniation of brain leads to a life-threatening situation, requiring rapid assessment of the cause and utgent treatment.

Because [he CSF and [SI .u/i ;>. mic 'Hid, : lumbar puncture to withdraw CSF provides insight into brain cell function that is critical in diagnosis and management of patients. The analysis of CSF gives important information on bleeding, inflammation, and infection in the brain that is not available by other methods. Proper use of the information obtained by lumbar puncture, which is central to neurological diagnosis and requires an understanding of normal CSF and ISF physiology. Cerebrospinal fluid studies show increased pressure, the presence of cells, indicating infection and inflammation, and elevated levels of protein, showing a breakdown of the normal barriers between the brain and the blood or the production of those proteins by the brain cells. Diagnosis depends on the findings of the CSF examinations in certain conditions, such as idiopathic increased intracranial hypertension, in which an elevated pressure is essential for the diagnosis. Other conditions in which the examination of the CSF is the major diagnostic test include meningitis, subarachnoid hemorrhage with a negative computed tomography (CT), and carcinomatous

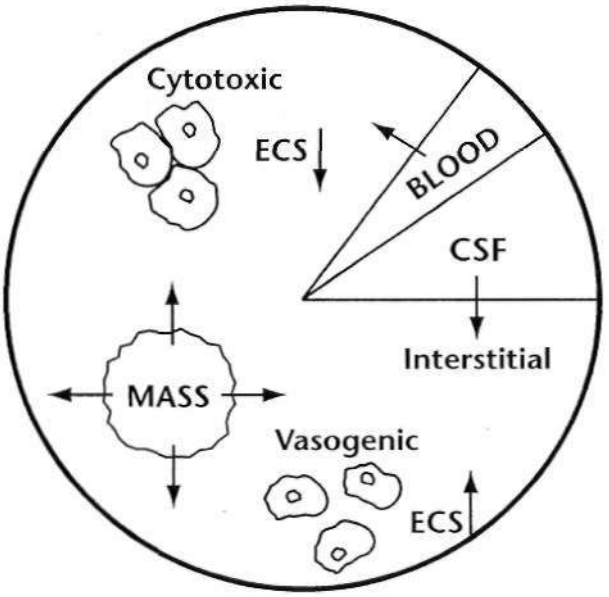

FIGURE 65.1 The rigid skull inhibits expansion of any brain compartments. An increase in blood or cerebrospinal fluid (CSF) volume directly affects CSF pressure. Masses, such as tumors, abscesses, or hematomas, increase brain tissue volume, thereby raising CSF pressure. Cell swelling causes loss of extracellular space (ECS) and cytotoxic edema. Blood-brain barrier damage increases extracellular space, particularly in the white matter with vasogenic edema.

meningitis. The examination of the CSF by lumbar puncture is one of the most cost-effective diagnostic tests, and when done properly it can provide unique information.

Brain swelling compresses the brain tissues. The recognition that the total volume of fluid and tissue contained in the rigid skull is constant is called the Monro-Kellie doctrine, which was formulated in the eighteenth century. Changes in volume of blood, CSF, or brain compartments produce compensatory changes in the others, with a resultant increase in CSF pressure (Figure 65.1). Obstruction of the CSF outflow pathways causes the enlargement of the ventricles. Hydrocephalus causes dysfunction by the movement of CSF into the tissues surrounding the ventricles, causing transependymal absorption. Masses, such as tumors or abscesses, cause an enlargement of the tissue space, compressing the CSF and blood volumes. Opening of the blood-brain barrier (BBB) due to disruption of the blood vessel wall leads to vasogenic edema with enlargement of the extracellular space by the extravasated fluid. On the contrary, damaged, swollen cells lead to cytotoxic edema with narrowing of the extracellular space. Finally, an increase in blood volume, as seen in hypercapnia and hypoxia, increases the intracranial pressure (Table 65.1).

The many surfaces in which brain tissue is exposed to the systemic circulation have evolved unique structural, metabolic, and enzymatic mechanisms to preserve the neuronal microenvironment. Fluid and electrolyte balance and

Tabic 65.1: Causes of increased intracranial pressure (ICP)

Site of increased ICP	*0jf<i.\t<(.'6*
Increased tissue volume	Tumor, abscess
Increased blood volume	Hypercapnia, hypoxia, venous sinus occlusion
Cytotoxic edema	Ischemia, trauma, toxins, metabolic diseases
Vasogenic edema	Infections, brain tumors, hyperosmolar states, inflammation
Interstitial edema	Hydrocephalus with transcpendymal (low

immunological protection are lost in the presence of ischemia, inflammation, infection, and tumors.

BLOOD-BRAIN INTERFACES

Cerebral Blood Vessels

Brain cells are separated from the general circulation by a complex series of interfaces that form the BBB. The large surface areas of the capillary endothelial cells form the major interface. Choroid plexuses and arachnoid granulations also have barrier surfaces that regulate the exchange of substrates between brain and blood (Table 65.2). At each of the BBB interfaces, bulk transport is restricted by high-resistance junctions (zona oceludens) between cells, which make the surface into an epithelium like structure. The epithelial sheets impede non-lipid-soluble substances, charged substances, or large molecules, whereas lipid-soluble substances, such as anesthetic gases, pass easily through the cells. Watet is unique in that it can pass through membranes with relatively little impedance.

Once substances ctoss the BBB, they have access to all brain regions through the ISF, which functions as a lymph fluid. The movement of CSF and ISF through the ventricles and brain tissues constitutes a "Third Circulation," which is analogous to the lymph fluids in other organs, Circulation of ISF begins with its fotmation at the capillaries. Flowing around cells, ISF brings nutrients, such as glucose and oxygen, to neurons and astrocytes and removes the products of metabolism. ISF is absorbed either into the blood via terminal capillaries and venules or into CSF for eventual absorption through the arachnoid granulations (Figure 65.2). A novel mechanism for ilu drainage of ISF into the cervical lymphatics has been shown in rats and rabbits, but its role in humans remains speculative.

Brain extracellular space comprises 15-20% of the total brain volume. Complex carbohydrates arc found in the extracellular space, including hyaluronic acid, chondroitin sulfate, and heparan sulfate. Hyaluronic acid forms large water domains. Othet glycosaminoglycans act as charge barriers and binding sites. A thin layer of basal lamina

Table 65.2: Characteristic features of the blood-brain interfaces

Interface	*Tight-junction location*	*Functional aspects*
Blood-CSF	Choroid plexus cell	Active secretion of CSF via ATPase and carbonic anhydrase
CSF-blood	Arachnoid membrane	Arachnoid granulations absorb CSF by one-way valve mechanism
Blood-brain	Capillary endothelial eel!	Active transport of ISF via ATPase; increased mitochondria and glucose transporters in die capillary

ATPase = adenosine triphosphatase; CSF = cerebrospinal fluid; ISF = interstitial fluid.

surrounds the cerebral capillaries. Type IV collagen, fibronectin, heparan sulfate, laminin, and entactin make up the various layers of the basal lamina. Entactin connects type IV collagen and laminin to add a structural element to the capillary. Fibronectin from the cells joins the basal lamina to the endothelium. Basal lamina provide structure through type IV collagen, charge barriers by heparan sulfate, and binding sites on the laminin and fibronectin molecules, but the role of the basal lamina in brain blood vessels is unclear.

During development, cerebral blood vessels acquire the characteristics that distinguish them from systemic capillaries. During embryonic life, vessels destined to form the BliB show increased expression of the cell surface protein, HT7. When quail embryonic brains are grafted into the coclomic cavity of chick embryos, chicken blood vessels growing into the grafted brain express HT7 protein, which is specific for chickens and not expressed in quails. Systemic blood vessels in the chick embryo at stages 17-20 can form a BBB when implanted into developing brain. The proximity of the astrocytic processes to the capillary cells suggests that the astrocytes provide essential substances to the capillary. A protein has been identified in the endothelial cell as the substrate for the tight junctions. Zona occludin-1 protein is anchored to the actin in the cytoskeleton, and damage to that protein leads to an increase in capillary permeability. Vascular endothelial growth factor (VF.GF), which is a factor in the increase in vascular permeability during hypoxia, alters ZO-1 protein (Fischer ct al. 2002).

Tight junctions between the endothelial cells create a high electrical resistance that limits transport of nonlipid soluble substances (Table 65.3). Carrier molecules that shuttle between the blood and brain sides of the capillaries selectively transport essential nutrients, such as glucose and amino acids. Glucose transporters are densely distributed in the capillaries. At low levels of blood glucose, the carriers function at high capacity, but at higher levels, they become saturated. Once they are saturated, any increase in uptake occurs by diffusion. Several isoforms of the glucose transporter molecule have been isolated and cloned. High concentration of one isoform, GLUT1, is found on cerebral blood vessels. GLUT3 is found on neurons and GLUT5 in microglia. GLUT2 is found predominantly in the liver, intestine, kidneys, and pancreas. Impairment of glucose transport due to lack of transporters has been described in patients with Alzheimer's disease and in other neurological disorders.

Amino acid carrier molecules are also toniul on cerebral capillaries. Substances that compete with essential amino acids for the carriers block their uptake and lead to deficiency states. For example, high-protein meals provide amino acids that compete for the carriers that transport [-dopa, which may interfere with i.-dopa uptake in the

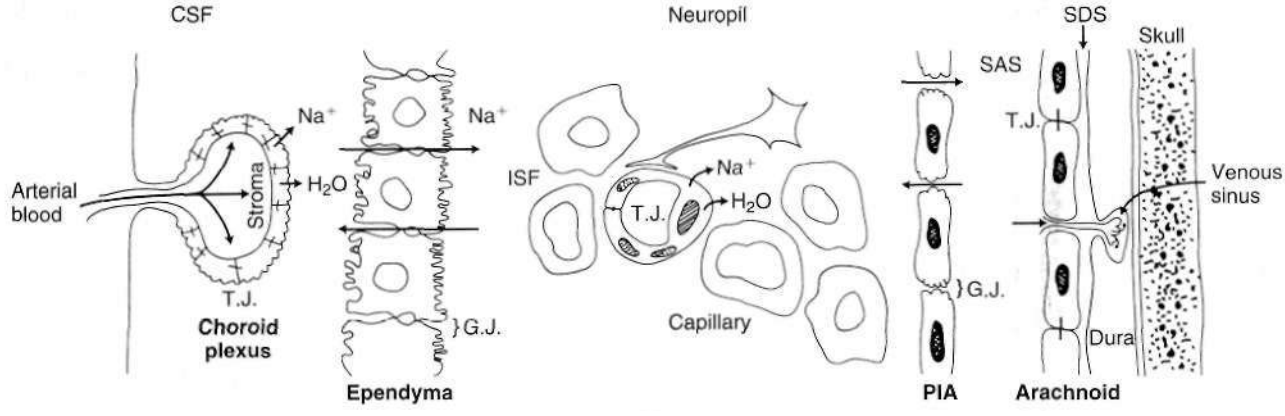

FIGURE. 65.2 Illustration of die third circulation. The cerebrospinal fluid [CSF) is formed by the choroid plexuses in the ventricles, and the interstitial fluid (ISF) is formed by cerebral capillaries. At both sites the action of the Na/K ATPase pump creates the osmotic gradient that pulls water from the blood. Tight junctions (T.J.) formed by the zona occludin-1 protein are found at each site where the blood and the brain interface. This includes the apical surface of the choroid plexus epithelial cells, the cerebral endothelial cells, and the arachnoid. Substances move between the brain and CSF across the gap junctions (G.J.) on the ependymal and pial surfaces. (Modified from Rosenberg, G, A. 1990, *Brain Fluids and Metabolism,* Oxford University Press, New York.)

Table 65.3: Unique features of cerebral capillaries

light junctions create high electrical resistance
Adenosine triphosphatase pumps on abluminal surfaces form interstitial tlnkl
Increased numbers of mitochondria for high-energy needs
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Basal lamina, pericytes, and astrocytes

treatment of Parkinson's disease. Serotonin uptake is decreased in patients with phenylketonuria.

Steady-state levels of brain electrolytes are preserved by-transport mechanisms at the BBB. Potassium is maintained at a constant level in the CSF and brain by the BBB. This prevents fluctuations of electrolyte levels in the blood from influencing brain levels. Calcium is similarly regulated. Glutamate, which is an excitotoxin, is excluded from the brain. High lipid solubility is needed for entry into the brain. Gases, such as carbon dioxide and oxygen, are rapidly exchanged across the capillary. Anesrhetic gases are effective because of rheir ease of entry into the brain. Water rapidly crosses rbe capillary wall, with only slight impedance found at faster blood flow rares.

Drugs acting on the CNS need to cross the BBB. Antibiotics, such as penicillin, have to be given in high doses because they enter the nervous system slowly. Newer generations of antibiotics, however, penetrate more readily, making them better agents for treatment of brain infections. Chemotherapy of brain tumors has been hampered by the agents' poor lipid solubility. The btain more readily takes up heroin than morphine because of its increased lipid solubility. Nicotine and alcohol are readily transported into brain, resulting in their addictive potential.

Paradoxical clinical siruations arise because of the limitations to transport across the BBB, causing different rates for equilibration of various substances between blood and brain. For example, patients with metabolic acidosis deplete bicarbonate from the brain. A compensatory respiratory alkalosis lowers carbon dioxide levels in the blood and the brain. Because of the limited transport of bicarbonate, correction of the metabolic acidosis with bicarbonate raises serum levels before those in the brain. As serum pH rises, respiratory rate falls, restoring carbon dioxide levels ro normal in brain and blood. Paradoxically, brain pH falls because the low brain bicarbonate levels fail to buffet the increased acidity due to the rise in carbon dioxide. Although treatment is necessary to correct the metabolic acidosis, patients may temporarily worsen as the treatment progresses due to brain acidosis (Figure 65.3).

Choroid Plexuses and Capillaries Produce Cerebrospinal Fluid and Interstitial Fluid

Choroid plexuses form an important interface between CSF and blood. These secretory structures protrude into the cerebral ventricles. Because the blood and the brain fluids are in contact, thctc are tight junctions. However, the tight junctions are at the apical surface of choroid plexus ependymal cells. Capillaries beneath the choroidal cells are fenestrated, and they permit substances to pass into the stroma that separate the blood vessels from the choroid plexus epithelial cells. Microvilli line the outer surface and contribute to the secretory function. The presence in the epithelial cells of many mitochondria, Golgi complexes, and endoplasmic reticulum suggests a high level of metabolic activity. The choroid plexus is the major source of CSF, with the capillaries contributing fSF at varying levels in different species. Production of CSF is constant across species when volume of fluid formed is divided by the weight of the choroid plexus. In humans, the rate of CSF production is approximately 0.35 ml. per minute. CSF production occurs at both choroidal and extrachoroidal sires, and estimates of the proportion of CSF from each site vary, depending on the species and the method of measurement. Choroidal production accounts for 60-70% of total CSF production in the cat, but it may be lower in the monkey, in which extrachoroidal sources are important. No measurements of the relative proportion of CSF produced at each source have been made in humans.

Higher levels of sodium, chloride, and magnesium and lower levels of potassium, calcium, bicarbonate, and

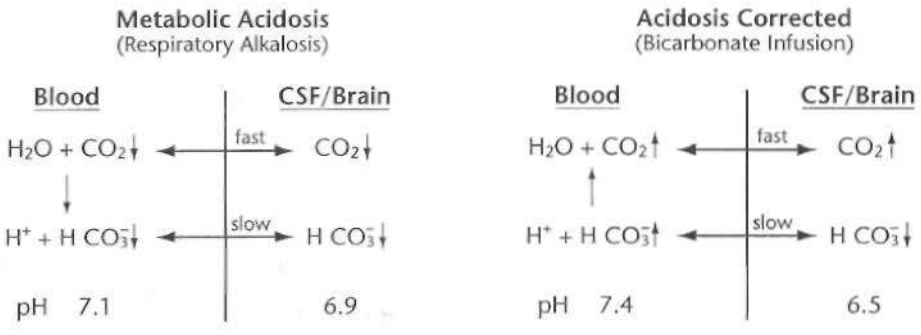


FIGURE 65.3 Illustration of the effects of metabolic acidosis with respiratory alkalosis on pH of blood and cerebrospinal fluid (CSF) and brain. Uncompensated, the blood bicarbonate and $C0_2$ are both low and art- mirrored by the levels in CSF and brain. Treatment with bicarbonate restores normal respiration, increasing CO2 levels in both compartments, but bicarbonare crosses the blood-brain barrier too slowly to compensate for the excess protons. CSF and brain pH paradoxically fall.

glucose are found in CSF than arc expected from a plasma ultrafiltrate, which suggests that the CSF is actively secreted. An adenosine triphosphatase (ATPase) pump on the apical surface of the choroidal cells secretes sodium-rich CSF that draws osmotic water into the ventricles. Carbonic ..inlndiasc enlivens cubon dioxide and water into hicar bonate, which is removed along with chloride to balance the sodium charge.

Although the steady production of CSF is difficult to decrease, several drugs have been found that reduce it. Acetazolamide, which inhibits carbonic anhydrase, reduces LSI production, as do hypothermia, hypocarbia, hypoxia, and hyperosmolality. Osmotic agents, such as mannitol and glycerol, increase serum osmolality, lowering CSI· production temporarily by about 50%. However, none of these measures is effective in the long-term reduction of CSF production. Agents that interfere with the action of ATPase reduce CSF production. Digitalis has an effect on rate of production of the CSF, but ouabain, which is a more effective agent experimentally, is too toxic for use in patients.

Capillaries, which have ATPase on the abluminal surface, are a source of extraehoroidal ISF production (Figure 65.4). Gray matter has a dense neuropil that restricts water flow, whereas white matter is more regularly arranged, making it a natural conduit for normal flow of ISF and for movement of edema in pathological conditions. Under the pressure gradient maintained by capillary ISF production, bulk flow of fluid occurs in the white matter.

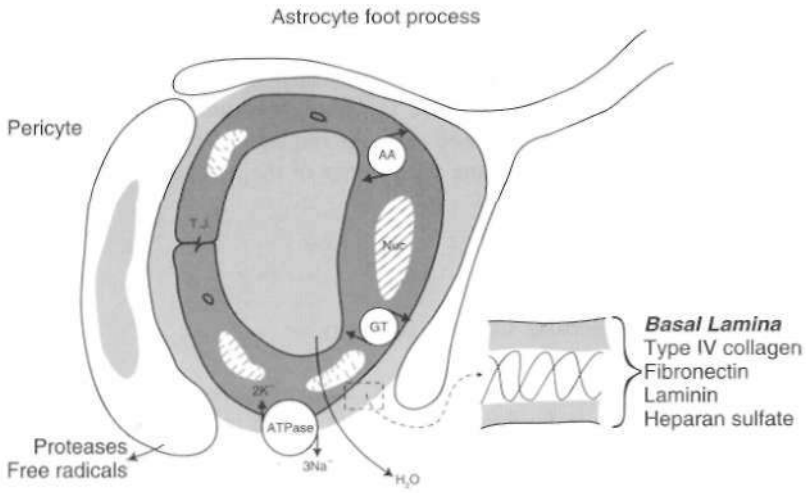
Advances in the speed of obtaining magnetic resonance images (MRI) have permitted the imaging of the diffusion of water. Normally there is a low level of water diffusion. When the cells swell and the movement of water molecules is slowed in the restricted extracellular space, the rate of water diffusion decreases. This appears as an abnormal region on the diffusion-weighted image (DWI). In cerebral ischemia, the DWI is abnormal very shortly after the onset of the ischemia, making this an excellent diagnostic test for the presence of cerebral ischemia. Another advance in nuclear magnetic resonance (NMR) technology is the development of proton NMR spectroscopy, which is a method to show biochemical abnormalities in the tissues. During an ischemic event, the signal from N-acetylaspartate falls and that from lactate increases. Combining DWI with NMR spectroscopy allows for identification of the damaged regions and increases the accuracy of spectroscopy (Carhuapoma et al. 2000).

Ependymal and Pial Surfaces

Lining the cerebral ventricles is a layer of ependymal cells with cilia. Pial cells line the surface of the brain, forming a limiting glial membrane. Cap junctions (zona adherens) are found between the ependymal cells that line the cerebral ventricles and the pial cells of the cortex. Fluid, electrolytes, and large protein molecules move through the gap junctions, allowing exchange between the CSF and ISF. Intrathecal administration of antibiotics and chemotherapeutic agents has been used to bypass the BBB. After injection into the CSF space, large proteins penetrate the perivascular spaces of Virchow-Robin, These perivascular routes may be important in the spread of infection into the brain from the subarachnoid space. Virchow-Robin spaces provide a conduit for substances in the subarachnoid space to enter brain.

Arachnoid Granulations and Absorption of Cerebrospinal Fluid

\raclrioid y,iin:i,i:inns pacchionian ;,;mnillations) are the major sites for the drainage of CSF into the blood. They protrude through the dura into the superior sagittal sinus and act as one-way valves. As CSF pressure increases, more fluid is absorbed. When CSF pressure falls below a threshold value, the absorption of CSF ceases (Figure 65.5). In this way, the CSF pressure is maintained at a constant level, with the rate of CSF production as one determining factor.



FIGURK (VS.4 The cerebral capillary is a fluid-secreting, epithelial-like cell with a high metabolic rate. The Na/K ATPase pump on the apical surface forms CSF. There are tight junctions between the endothelial cells that maintain the electrical resistance, A large number of mitochondria are seen in the capillary. Amino acid and glucose transporters are present. Around the cell is a basal lamina composed of type IV collagen, laminin, fibronectin, and heparan sulfate. Astrocytic end-feet form a glia limitans around the cells. Pericytes are maemph age-like cells that have microglia-type functions in the perivascular space.

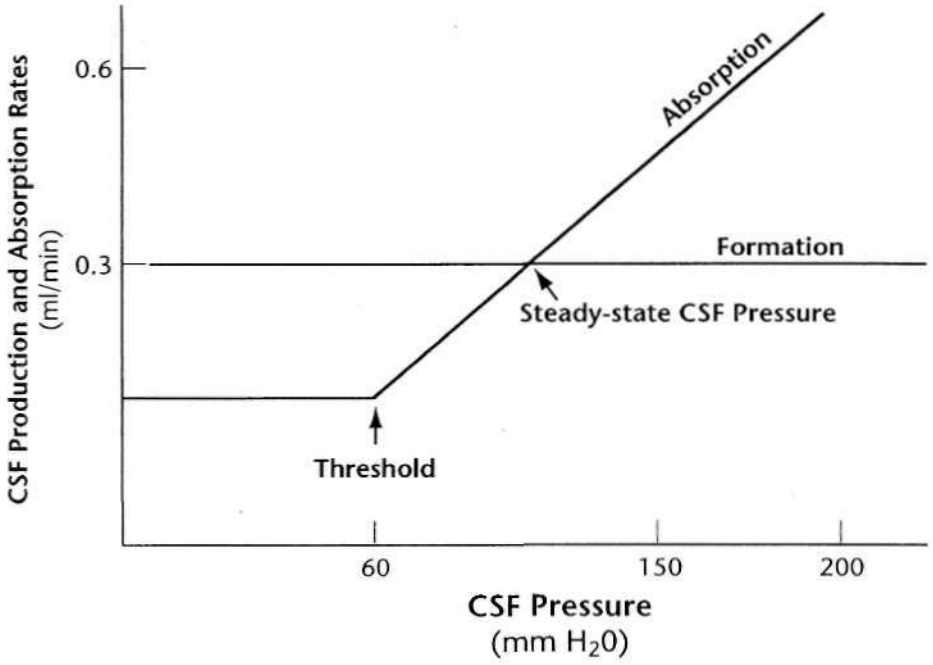


FIGURE 65.5 Schematic drawing of the relationship of cerebrospinal fluid (CSF) formation and absorption to pressure. CSF is formed at a constant rate of 0.35 mL per minute. Absorption begins above a threshold value that varies from person to person. Once CSF absorption begins, it is linear, as seen in a one-way valve. When formation tate equals absorption rate, the steady-state CSF pressure is determined. (Modified with permission from Cutler, R. W., Page, L, Galickh, J,, Waiters, G, V. 1968, "Formation and absorption of cerebrospinal fluid in man," *Brain,* vol. 91, pp. 707-720.)

Although channels are seen in the arachnoid granulations, actual valves are absent. The tissue appears to collapse around the channel as the pressure falls, and the channels enlarge as the pressure rises. Resistance to the outflow across the arachnoid granulations leads to elevation of the CSF pressure. Substances can clog outflow channels and increase resistance to CSF absorption. Blood cells are trapped in the arachnoid villi, and subarachnoid hemorrhage causes a transient increase in CSF pressure and can occasionally lead to hydrocephalus. Similarly, white blood cells from meningitis can increase CSF pressure.

Cerebrospinal Fluid Pressure

For more than 100 years, lumbar puncture has been used to measure CSF pressure, obtain CSF for diagnosis, and inject drugs. With the patient in the lateral recumbent position, a narrow-bore spinal needle is used to perform a lumbar puncture. An opening CSF pressure is measured with a manometer attached to the needle. Occasionally, the lumbar sac cannot be punctured, and the examination is done in the sitting position or under fluoroscopic guidance. Under those circumstances, the CSF pressure is difficult to measure. Normal CSF pressure is 80—I 80 mm H2O. Three components contribute to the measured pressure: volume of blood within the cranial cavity, amount of CSF, and the brain tissue. According to the Monro-Kellie doctrine, enlargement of any of these compartments causes an increase in CSF pressure due to the constraints imposed by the bony cavity of the skull.

The CS1 prewj-c recorded by [!u- manometer represents the venous pressure transmitted from the right side of the heart through the venous sinuses. Small fluctuations from the cardiac systolic pulse and larger fluctuations from respirations take place in the fluid in the manometer. Because veins are thin-walled structures, venous pulsations cause fluctuations in CSF pressure. Arteries with thick elastic walls dampen the pulsations from arterial pressures. Therefore, an increase in CSF outflow pressure at the sagittal sinuses, as occurs when pressure within the thoracic cavity increases, results in an increase in the CSF pressure. Deep respirations cause wide fluctuations in the CSF pressure, whereas changes in artetial pressure are barely visible. As intracranial pressure rises, tissue compliance falls, and reserve capacity of the intracranial contents is lost. At that point, small changes in fluid volume may lead to large increases in intracranial pressure. Patients with increased intracranial pressure have been continuously monitored with catheters placed in brain or into the cerebral ventricles or with bolts placed on the dura, Pathological elevations in intracranial pressure cause Lundberg A or B plateau waves that increase in steps to 50 mm Hg, where they persist for up to 20 minutes before returning to baseline. Treatment of patients with raised intracranial pressure is often monitored at the bedside. Monitoring is used to gauge response to the osmotic agents and to determine the severity of the head injury.

BRAIN EDEMA

Molecular Cascade in Injury

Cerebral edema occurs in many neurological diseases. Excess fluid can accumulate in the intracellular or extracellular spaces, A convenient classification separates brain edema into cytotoxic or vasogenic. Cytotoxic edema is

cellular swelling; vasogenic edema is blood vessel leakage. Another category has been proposed, namely, interstitial edema, which represents transcpcndymal flow of CSF in hydrocephalus. Rarely is the separation into distinct categories possible because there is often overlap between the various types of edema.

Vasogenic edema expands the extracellular space in the while matter. Cytotoxic edema, which results from pathological processes that damage cell membranes, constricts the extracellular spaces. Cellular and blood vessel damage follows activation of an injury cascade. The cascade begins with loss of energy ami glutamatc release into the extracellular space (Figure 65.6). This occurs during a hypoxic, ischemic, or traumatic injury and causes cytotoxic damage. Calcium and sodium entry channels on cell membranes are opened by glutamatc stimulation. Membrane ATPase pumps extrude one calcium ion in exchange for three sodium ions. Sodium builds up within the cell, creating an osmotic gradient and increasing cell volume by the entry of water. While the cell membrane is intact, the increase in water causes dysfunction but not necessarily permanent damage. Finally, hypoxia depletes the cell's energy stores, disabling the sodium-potassium ATPase pumps and reducing calcium removal from inside the cell by the sodium-calcium exchange channels. Accumulation of calcium ions within the cell activates intracellular cytotoxic processes, leading to cell death. An inflammatory response is initiated by the formation of immediate early genes, such as *c-fos* and *c-jun,* and cytokines, chemokines, and other intermediary substances. Microglial cells are activated and release free radicals and proteases, which contribute to the attack on cell membranes and capillaries. Irreversible damage to the cell occurs when the integrity of the membrane is lost. Free radicals are pluripotential substances that are produced in the ischemic brain and after traumatic injury. The arachidonic acid cascade produces reactive oxygen species, such as superoxide ion, hydrogen peroxide, and hydroxyl ion. Release of fatty acids, such as arachidonic acid, provides a supply of damaging molecules. Superoxide dismutase-1 and catalasc are the major enzymes that catalyze the breakdown of reactive oxygen species. Other defenses include glutathione, ascorbic acid, vitamin E, and iron chelators, such as the 21-amino steroids. Transgenic mice that overexpress the superoxide dismutase-1 gene have smaller ischemic lesions than controls (Gasche et al. 2001).

Nitric oxide (NO) is also a source of free radicals. NO synthetase (NOS) has three forms: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible or immunological NOS (iNOS). Macrophages and activated microglial cells form NO through the action of iNOS in response to ischemia, injury, and inflammatory stimuli. NO acts both as a normal vasodilator of blood vessels, by release of cyclic guanosine monophosphate in smooth muscle, and as a toxic compound in pathological conditions. Peroxynitrite anions (ONOO~) are formed from the reaction of NO with superoxide anions. Manipulation of the NOS gene has helped reveal the action of the enzyme. The free radical nNOS produces toxic free radicals early in ischemic injury. Deletion of the nNOS gene in transgenic mice results in smaller infarcts from middle cerebral artery occlusion. On the other hand, eNOS causes vasodilatation and increases cerebral blood flow. Removing the eNOS genes leads to increased infarct size. Inflammation induces iNOS, which reaches a maximum at 24 hours,

Vasogenic Edema and the Ncuroinflammatory Response

Capillary injury results in opening of the BBB, with leakage of protein and fluids into brain tissue. Vasogenic edema moves through the white matter. Opening of the BBB could occur by loosening of tight junctions, development of pinocytotic vesicles in the endothelial cell, or an alteration

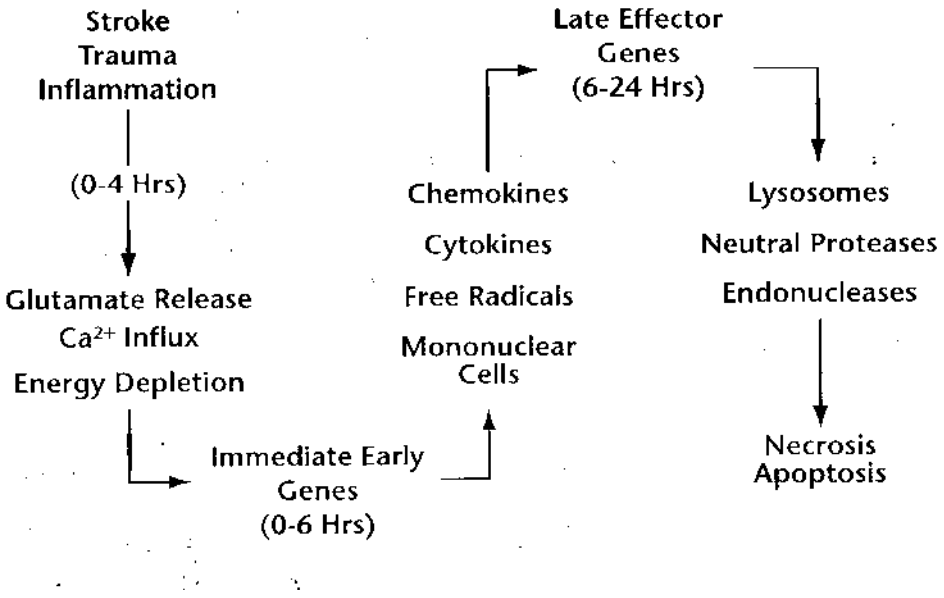


FIGURE 65.6 Mechanisms of ischemic-hypoxic injury leading to cell swelling and death. The chart shows the time course of the early events involving glutamatc release, immediate early gene production, and energy failure. This, leads to changes in electrolytes and initiation of the inflammatory response. Cytokines continue the damage that results in opening of the blood-brain barrier. Chemokines attract white blood cells to the injury site, where they release free radicals and proteases and enhance the injury. Finally, the proteases attack structural components, leading to membrane damage and cell death.

in the substrates surrounding the capillaries. Opening of tight junctions between cells has been observed after the infusion of hyperosmotic solutions. There is little evidence to support enhanced pinocytosis. Potentially toxic substances that may injure the capillary and the extracellular matrix include free radicals, cytokines, and proteases. Ftee radicals from oxygen and nitrogen can increase the permeability of the capillary. Cytokines have also been shown to have toxic effects on blood vessels, particularly tumor necrosis factor-a (TNF-a}. Several proteases damage the capillary.

Late effector genes arc activated by immediate early genes, such as *c-fos* and *c-jun,* free radicals, and cytokines. Proteases are produced that can attack substrates in the capillary and in the extracellular matrix around it. Neutrophils and macrophages enter the injury site through the blood vessel in response to a variety of injuries. The invading cells release proteases contained in the white blood cells, such as the matrix mctalloproteinases. The en/Miirs in;iK;- tlie wink[1] Mood tells In [vn-tr.ik- the capillary wall. Neutrophils release free radicals in the respiratory burst. Elastases and cathepsin are also released by neutrophils.

Astrocytic foot processes are attached by integrins to the basal lamina surround cerebral capillaries. Beneath and next to the astrocytes ate pericytes, which arc macrophage-like cells. Neutral proteases, such as serine proteases and matrix metalloprotcinascs, attack the extracellular matrix around capillaries. Brain cells make proteases. Astrocytes constitutively secrete the matrix metalioproteinase, gelatinase A or 72-kD type IV collagenase. Microglia secrete the inflammatory matrix metalioproteinase gelatinase B or 92-kD type IV collagenase. Proteases are secreted in latent forms and require activation. Free radicals and other proteases have been implicated in the activation of the gelatinases. Other proteases that may be released during the inflammatory process include elastases, plasmin, and cathepsin. Elastases are released from microglia cells and from invading neutrophils. Plasmin is generated in glia cells by plasminogen activators,

When an activated form of the 72-kD type IV collagenase is injected i ntra cere bra lly into rat brain, the BBB is opened. This reaction can be blocked by the tissue inhibitor ot metal loproteinase-2 and by synthetic metatloptoteinase inhibitors. During an ischemic injury produced by permanent occlusion of the middle cerebral artery, increased levels of gelatinase B are found around 24 hours after the occlusion. Gelatinase A increases approximately 5 days later, when the urokinase-type plasminogen activator is also elevated (Yong et al. 2001). Because of the highly disruptive properties of these hydrolytic enzymes, they arc tightly regulated by tissue inhibitors of metalioprotein-ases and plasminogen activator inhibitors (Cuzner and Opdenakker 1999). Hemorrhagic transformation occurs commonly after a stroke, particularly when ischemic tissue is reperfused. Proteolytic enzymes active in vessel regrowth, and extracellular matrix remodeling may be involved. Free radicals and proteases can damage cell membranes independently or can act in concert. Nitric oxide activates latent gelatinase B (Gu et al. 2002). Reactive oxygen species affect the production of the inflammatory matrix metallo-proteinases, whereas peroxynitrate activates gelatinase A. Because both free radicals and proteases are induced in injured brain tissue, separation of their individual effects in vivo has not been done.

Infection, Ischemia, and Inflammation

Bacterial meningitis initiates an inflammatory response in the meninges caused by the invading organisms and by the secondary release of cytokines and chemokines. The secondary, inflammatory response may aggravate the infection. Cytokines, including TNF-o and interleukin-6, are elevated in the CSF of patients with bacterial meningitis and contribute to the secondary (issue damage. Matrix metalloproteinases are increased in bacteria! meningitis, and matrix metalioproteinase inhibitors block the damage secondary to injection {Leib et al. 2001). Diagnosis of infections of the CNS has been aided by polymerase chain reaction (PCR) to detect messenger RNA from infectious agents. Herpes simplex encephalitis can be rapidly diagnosed by PCR. Patients with acquired immunodeficiency syndrome frequently have opportunistic CNS infections. Use of PCR assays helps to separate various causes, including toxoplasmosis, Epstein-Barr virus, and JC virus.

Cytotoxic Brain Edema

Cytotoxic edema is induced by stroke, trauma, and toxins. After a stroke, brain water increases rapidly due to energy failure and loss of ATP. Cytotoxic edema worsens for 24 to 48 hours, raising the danger of brain herniation (Figure 65.7). Capillary injury also takes place as part of the inflammatory phase. Vasogenic edema develops because of opening of the BBB. Reperfusion of brain after an ischemic insult increases brain edema. In animal studies of reperfusion injury after a stroke, there is a biphasic opening of the BBB. The first opening occurs several hours after reperfusion. This could be due to hyperemia, the activation of proteases, or the producrion of free radicals. The barrier then closes for an extended period before a second opening of the BBB occurs around the second day. This delayed opening is associated with activation of microglia and influx of inflammatory cells; multiple proteolytic enzymes and free radicals arc active at that time (Rosenberg et al. 1998). When oxygen is reintroduced into the tissue by reperfusion, brain edema occurs more rapidly, with a greater increase in water content. The effect of reperfusion on the capillary depends on multiple factors, including the time of occlusion and of reperfusion.

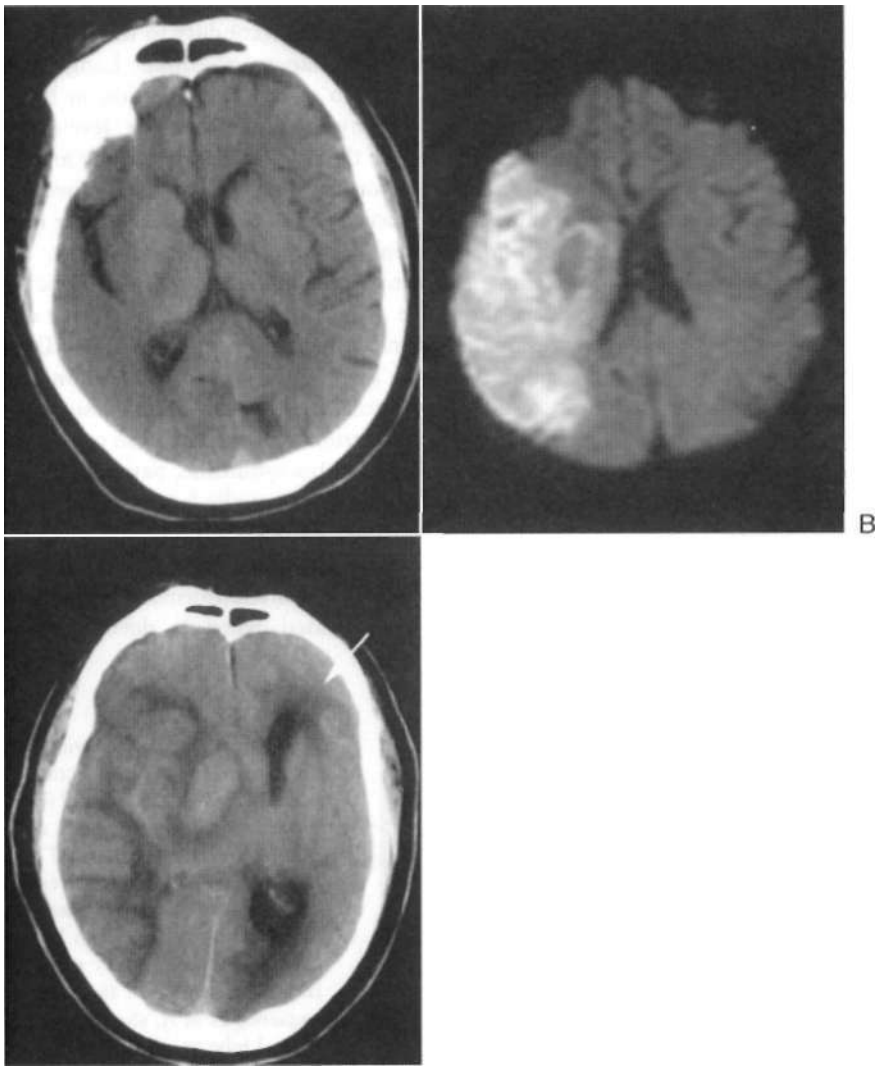


FIGURE 65.7 A patient with cytotoxic edema secondary to massive middle cerebral artery stroke. (A) The CT shows the early stages of the infarction with loss of the definition of the insular stripe, which is an early sign of infarction. (B) A diffusion-weighted image (DWI) shows restricted diffusion in the large region of rhe infarct. (C) One week after admission a CT scan shows mass effect with hydrocephalus on the contralateral side *{arrow)* due to obstruction ot tin- foramen ot Monro. (Courtesy Blaine Mart, MD.)

Intracerebral hemorrhage causes brain edema around the hemorrhagic mass. The edema is both cytotoxic due to the direct damage to the cells and vasogenic secondary to the inflammatory response induced by the toxic blood products. Growth of the hematoma has been seen in 38% of patients that were imaged shortly after the onset of hemorrhage and again within 24 hours. The injury that leads to the hemorrhagic mass goes through several stages. The initial stage is the disruption of the blood vessels with extravasation of the red blood cells into the brain. Upon lysis of the red blood cells, the second stage begins during which toxins are released into the surrounding tissues, amplifying the inflammatory response. Thrombin and plasminogen activators are major causes of tissue damage by rhe lysed red blood cells (Xi et al. 2001). The final stage is one of tissue compression by the fully formed mass lesion. The rate of progression through the various stages is variable and depends on the underlying pathology.

Stroke is the major cause of btain edema in the adult due lu the high incidence nl cerebral ischemia in the I'IIIITIV. Other causes include acute hepatic failure, hypoosmolality, exposure to toxins, and high altitude. In acute hepatic failure, the cerebral edema may cause death. Patients with hepatic failure are ofren young and have an acute cause for the liver failure. They may have overdosed on a drug that is toxic to the liver, such as acetaminophen, or they may have infectious hepatitis. Long-standing liver disease with cirrhosis and hepatic encephalopathy shows changes of astrocytes in the brain, but it is generally not complicated by cerebral edema. Reye's syndrome, which is seen primarily in children after an influenza infection, particularly when they are treated with aspirin, has a high incidence of brain swelling. Because of the restriction on use of aspirin in children, the number of cases of postinfluen/.a hepatic encephalopathy has dramatically declined. The mechanisms involved in the production of cerebral edema with acute hepatic disease are poorly understood (Rao and Norenberg 2001).

Rapid elevation of blood pressure causes hypertensive encephalopathy. In experimental animals, hyperemia is

present, suggesting that the blood vessels are dilated and have increased permeability. Confusion, focal findings, seizures with papilledema, and increased CSF protein are present in some patients with hypertensive encephalopathy. MRI has shown a vasogenic edema in the posterior white matter of the brain (Figure 65.8). Rapid elevations of blood pressure can occur with kidney disease and in eclampsia. The changes are transient unless hemorrhage or infarction occurs, which can be distinguished by the combination of TV weighted abnormalities on MRI with the presence of a lesion on diffusion-weighted MRI (Covarrubias et al. 2002). Rapid reduction in blood pressure is necessary. The reason for the involvement of the posterior circulation in this syndrome is uncertain. Eclamptic patients may have visual disturbances. In the rare autopsied patients, petechial hemorrhages may be seen in the occipital lobes, explaining the visual symptoms.

Another cause of cerebral edema is a rapid change in scrum osmolality. For example, parients treated for diabetic ketoacidosis, with rapid reduction of plasma glucose and sodium, are at risk for edema secondary to water shifts into the brain (Bohn and Dancmau 2002). Long-standing hyperosmolality leads to solute accumulation in brain to compensate for the hyperosmolar plasma levels. These idiogenic osmoles are thought to include taurine and other amino acids. Once formed, they are slowly removed from the brain. When blood osmolality is reduced, water follows the osmotic gradient, resulting in cerebral edema. Rapid reduction of serum hyperosmolality, as in diabetic ketoacidosis, should be avoided to prevent brain edema due to the residual idiogenic osmoles (Edge et al. 2001). Dialysis disequilibrium may also be due to an osmotic imbalance that results from urea buildup in brain tissue. Rapid correction of chronic serum hyponatremia can cause central pontine myelinolysis. In this syndrome, patients have very low sodium levels, which are usually less than 120 mEq/L, secondary to a variety of causes, including excessive water drinking, anorexia nervosa, alcohol withdrawal, and inappropriate secretion of antidiuretic hormone. Low sodium can sometimes be tolerated when it develops slowly,

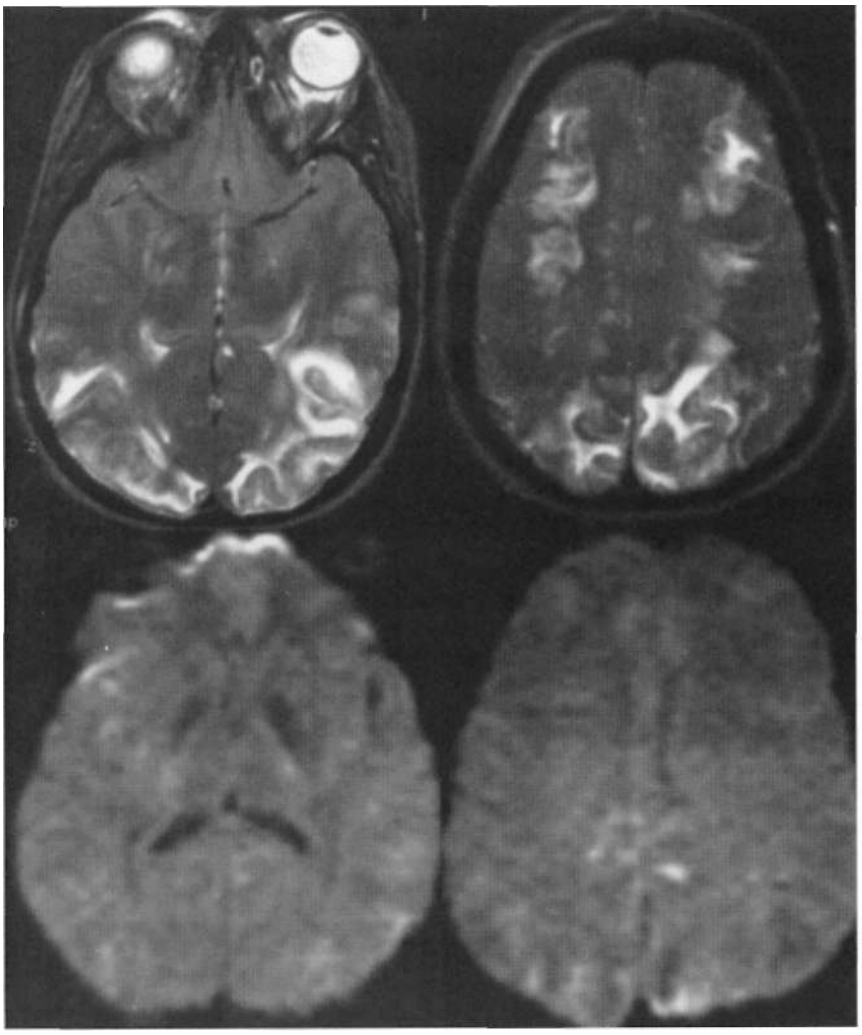


FIGURE 65.8 Patient with hypertensive encephalopathy secondary to eclampsia with the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. (A) A T2-weighted MRI showing the extensive cerebral edema in the posterior white matter regions with less involvement of the gray matter. (B) A higher level of the same scan sequence as in A, showing some frontal lobe involvement. (C and D) Diffusion-weighted images (DW1) with only one small area of involvement. The lack of DWI dianges is consistent with this being a vasogenic type of edema, and the patient had a good recovery without residual deficits. (Courtesy Blaine Hart, MD.)

but in the acute situation, coma may develop. As the sodium is corrected, water accumulates in the brain white matter tracts. The pontine white matter tracts are involved, and occasionally the involvement can extend into the internal capsule regions to cause a more diffuse myelinolysis.

Cerebral edema is a complication of acute mountain sickness, which in rare circumstances may be life threatening (Hackett and Roach 2001). Cerebral symptoms are prominent, and there is an increase in cerebral blood volume related to the hypoxia. Raised intracranial pressure causes headaches, ataxia, and confusion. Papilledema has been seen in people with high-altitude cerebral edema. MRI shows changes in the white matter, particularly the corpus callosum with involvement of the splenium, which may accompany high-altitude pulmonary edema. When hypoxia occurs along with extreme exertion, hyperventilation may lead to a drastic reduction in carbon dioxide, resulting in reduced blood flow and the possibility of cerebral ischemia due to vasoconstriction. Paradoxically, rebreathing carbon dioxide was shown to improve symptoms and cerebral blood flow.

Occlusion of the venous sinuses draining the brain can cause increased intracranial pressure and venous hemorrhagic infarction. When the superior sagittal sinus is involved, there may be extensive infarction in both hemispheres (Figure *65.9).* Dehydration and hypercoagulable states are often found in such patients. The early symptoms may be subtle with headache secondary to increased intracranial pressure. As the infarction develops, however, other symptoms, such as seizure, develop, leading to hemorrhagic conversion of the infarction, herniation, and death. There may be negative CT scan in the early stages thar will confound diagnosis. Some patients will recanalize the superior sagittal sinus and may have an excellent outcome (Figure 65.10).

Treatment of Brain Edema

Treatment of brain edema has not kept up with the advances in understanding the mechanisms producing the edema. Reduction of volume in one of the three compartments may be helpful. Blood volume can be reduced with hyperventilation, which lowers carbon dioxide. However, excessive hyperventilation, which can be dangerous, should be avoided. Reduction of CSF volume can he done mechanically by placing a drainage catheter into one of the ventricles. This can he difficult when the cerebral edema has compressed the ventricular system. Intraventricular drainage is mainly used in patients with head injuries, acute hydrocephalus, or postsurgically. Agents that reduce the production of CSF, such as acetazolamide or diuretics, may be used, but are of marginal benefit.

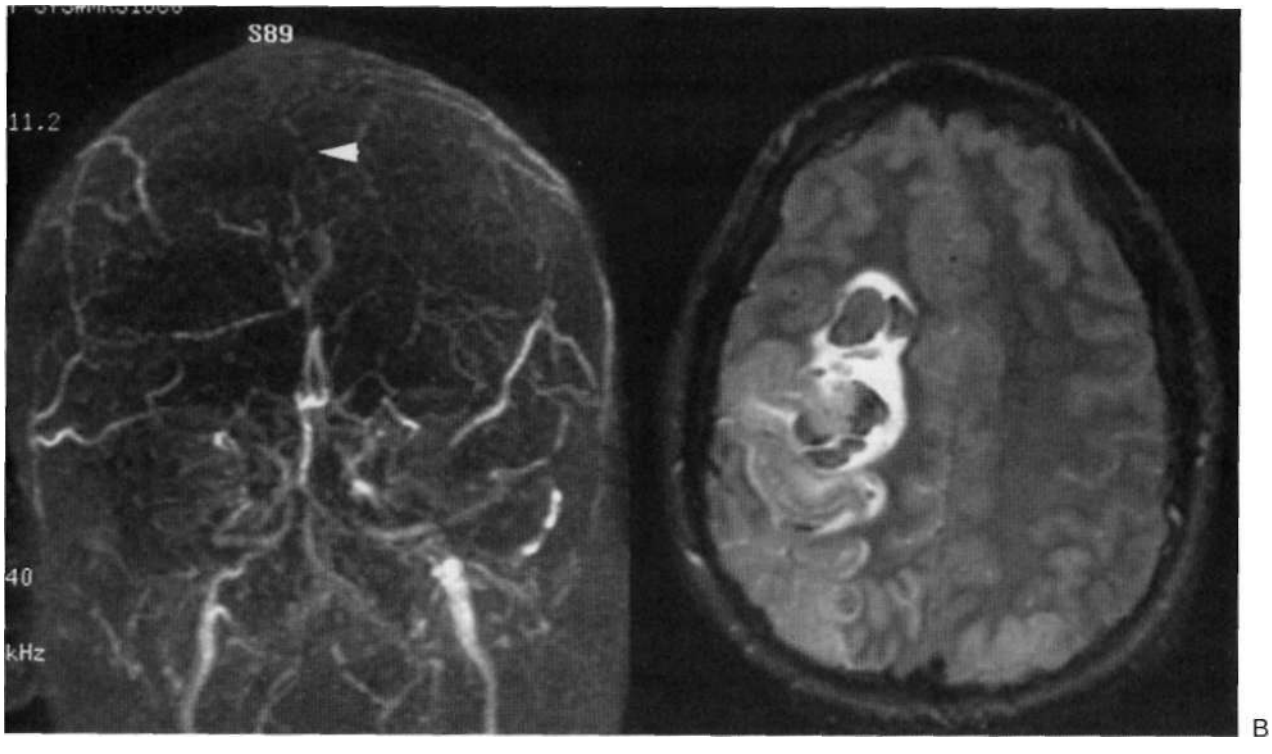


FIGURE 65.9 Sagittal sinus occlusion in 17-year-old boy with severe dehydration, (A) A MR venogram showing rhe absence of the sagittal sinus on the coronal view *(arrowhead).* (B} T_2-weighted image shows the extensive venous hemorrhagic infarction. (Courtesy Blaine Hart, MD.)

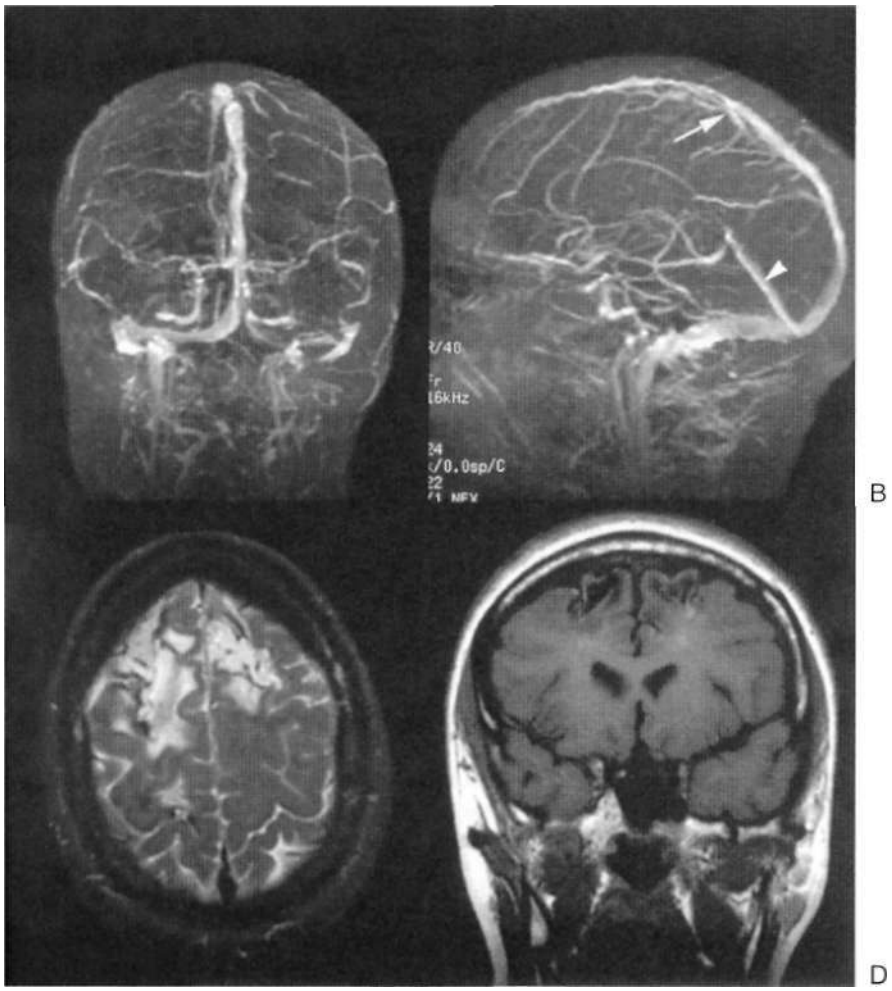


FIGURE 65.10 A patient with sagittal sinus occlusion that developed after pregnancy. The images shown were obtained several months after the event and demonstrate the ability ro recover. At onset of the illness, there was papilledema and increased intracranial pressure. ; A I he •-.i:-.iii.-il • mis is in< n.i in this coronal view from an MR venogram. (B) A lateral view from the venogram, showing flow in the sagirtal sinus *[arrow)* and straight sinus *(arrowhead),* (C) The region of prior venous infarction is shown on the axial Tj-weighted MR image, *(D)* The same region as in C on the coronal T^-weighted image. (Courtesy Blaine Hart, MD.)

For many years osmotic therapy has been the treatment of choice to temporarily lower intracranial pressure. Initially, urea was used, but the small molecule entered the brain, causing rebound edema. Current osmotic treatment is done primarily with mannitol, which reduces brain volume, lowers CSF production, and improves cerebral blood flow. Osmotherapy with low doses of mannitol infused ovet several days lowers intracranial pressure. Earlier studies employed 3 g/kg of mannitol, which had a dtastic effect on the serum electrolytes and permitted only one or two doses to be given. More recently, it was found that low doses of mannitol (0.25-1.0 g/kg) are as effective as the higher doses without affecting the electrolytes. The lower doses taised the serum osmolality slightly, suggesting that the agent had several mechanisms of action. The effect of the small change in the osmolality is to reduce the brain tissue volume; the effect is more prominent in the noninfarcted than in the infarcted hemisphere (Videcn ct al. 2001). Other effects are that mannitol reduces CSF and ISF secretion by 50%, which may contribute to its action. Some investigators have proposed that mannitol hyperosmolality alters the theological properties of blood, whereas others have noted an antioxidant effect. Prolonged administration of mannitol results in an electrolyte imbalance that may override its benefit and that must be carefully monitored. Although mannitol is often used in acute stroke, its efficacy has not been proven.

Corticosteroids lower intracranial pressure primarily in vasogenic edema because of their beneficial effect on blood vessel permeability. They have been less effective in cytotoxic edema, howevet, and are not recommended in the treatment of edema secondary ro stroke or hemorrhage, hi fact, systemic complications of corticosteroids can worsen the patient's condition in the treatment of patients with intracerebral hemorrhage. Edema surrounding brain tumors, particularly metastatic brain tumors, responds dramatically to treatment with high doses of dexamethasonc. The corticosteroid closes the BBB rapidly. Hence, it is important to obtain contrast-enhanced MRl or CT scans before treatment with cotticosteroids; otherwise, enhancement of the lesion may be missed. High doses of corticosteroids have been shown to be effective in brain edema secondary to inflammation in multiple sclerosis.

Opening of the BBB is frequently seen on MRI with gadolinium contrast in patients with multiple sclerosis (Noseworthy ct al. 2000). The opening of the BBB is associated with elevated levels of the proinflammatory cytokine, TNF-or. Inflammatory lesions, such as those that occur in acute attacks of multiple sclerosis, respond well to high-dose methylprednisolone. Treatment with 1 gram per day of methylprednisolone for 3-5 days reduces the inflammatory changes in the blood vessels during an acute exacerbation. Dramatic reduction in enhancement on MRI may he seen after treatment. However, the effect is lost after several months.

IDIOPATHIC INTRACRANIAL HYPERTENSION

Before the advent of CT scanners, the complaint of headache and the finding of papilledema raised the suspicion of hydrocephalus or tumor. When tests were negative for either of these conditions, the condition was called otitic hydrocephalus or pseudotumor cerebri. The latter term has remained in use along with benign intracranial hypertension. None of these terms is satis-factory, and the descriptive term, idiopathic intracranial hypertension (OH) is preferred,

Clinical features

Patients with IIH have headaches that are diffuse, worse at night, and often wake them from sleep in the early hours of the morning. Sudden movements, such as coughing, aggravate headache. Headaches may be present for several months before a diagnosis is made. Some patients complain of dizziness. Transient loss of vision (transient obscuration) may occur with change of position. Visual fields may show an enlarged blind spot due to the encroachment of the swollen nerve head into the region of the macula. Prolonged papilledema may lead to sector scotomas and, rarely, vision loss. Damage to one or both sixth cranial nerves may occur as an effect of shifts of cerebral tissue; because the sixth cranial nerve is remote from the site of the process producing intracranial hypertension, the cranial neuropathy is a false localizing sign.

Diagnosis requires ruling out other causes of increased intracranial pressure. All patients require a CT or MRI scan to look for hydrocephalus and mass lesions. After a mass lesion is ruled out, lumbar puncture is needed with careful attention to accurately measuring the CSF pressure, which must be elevated by definition. Characteristic findings in the CSF include normal or low protein, normal glucose, no cells, and elevated CSE pressure. The upper limit for normal CSF pressure is above 180 mm H_20, and most IIH patients will have readings well above 200 mm H_20. Measurement of CSF pressure should be done with legs extended and neck straight. Movements of the fluid column with respiration should be seen to confirm proper placement of the needle. It is important to obtain an accurate pressure reading at the time of the initial lumbar puncture because die diagnosis is made by the presence of increased CSF pressure. Measurements of pressure in subsequent lumbar punctures may be influenced by the loss of fluid during the first puncture.

IIH occurs more frequently in women than in men. Obesity and menstrual irregularities, with excessive pre-menstrual weight gain, are often present. Headache, often worse in the morning, is the main complaint. Because many illnesses are associated with IIH, a search for an underlying cause is essential before the diagnosis is made by exclusion. MR] has rekindled interest in conditions that cause occlusions of the venous sinuses. When the sinuses draining blood Irniv. the brain are obstructed, absorption oi CS1 is reduced, causing the pressure of the CSF to increase. MR venography is better for showing the thrombosis of the sinuses than conventional MRI. The role of venous sinus obstruction in III I, although important to rule out, may be limited. Hypercoagulable states should be looked for in patients with venous sinus obstruction.

Obesity is often found in women with IIH. Endocrine abnormalities have been extensively investigated in both obese and nonobese subjects, but none has been identified. Drugs associated with the syndrome include tctracycline-type antibiotics, nalidixic acid, nitrofurantoin, sulfon-amides, and trimethoprim-sulfamethoxazole (Table 65.4). Paradoxically, the withdrawal of corticosteroids, which are used to treat increased intracranial pressure, can cause an increase in intracranial pressure. Large doses of vitamin A, which are used in the treatment of various skin conditions, may cause the syndrome. Hypcrcapnia leads to retention of carbon dioxide and increase in blood volume. Sleep apnea and lung diseases may cause headaches and papilledema due to this mechanism. Less frequent causes include Guillain-Barrc syndrome, in which IIH may be due to an increase in CSF protein or an inflammatory response. Uremic patients have an increased incidence of papilledema with IIH. Patients with renal failure have increased levels

Tabic 65.4: Drugs frequency associated with idiopathic intracranial hypertension

Minocycline
Isotretinoin
Nalidixic acid
Tetracycline
Trimethoprim-sulfamethoxazole
Cimetidinc
Prednisolone
Methylprednisolone
Tamoxifen
tSeclomctfiasone

Source: Schutta, H. S. 8c Corbett, J. J. 1997, "Intracranial hypertension syndromes,"in *Clinical Neurology,* 12th ed,eds R. J. Joynt & R. C. Griggs, Lippincon, Philadelphia.

of vitamin A, use corticosteroids, and take cyclosporine, which have all been linked to 11H.

Cerebral edema was seen in one patient with early I1H, who had a brain biopsy at the time of subtemporal decompression, .1 treatment that is no longer used. However, two IIH patients who came to postmortem examination had no histological evidence of cerebral edema. Blood volume is increased and cerebral blood flow decreased. CSF circulation is impaired. Diseases that chronically raise cerebral venous pressure often produce increased intracranial pressure without increased ventricular size. The primary sites of obstruction may be the superior vena cava, jugular veins, or large cerebral veins. Increased superior sagittal sinus or transverse sinus pressure has been reported in IIH. Many investigators favor an elevation of dural venous sums pressure as a reasonable mechanism.

Treatment

Treatment involves reducing intracranial pressure. Acetazolamide is an inhibitor of carbonic anhydrase that lowers CSF production and pressure. It is given in a dose of 250 mg twice daily, which may be increased to 1 g per day. Occasionally, higher doses may be needed. Electrolytes must be monitored to look for metabolic acidosis. Distal paresthesias are reported to occur in up to 25% of patients. The hyperosmolar agent, glycerol (0.25-1.00 g/kg two or three times daily), and the diuretic, furosemide (20-60 mg daily), have also been used to lower intracranial pressure. Corticosteroids reduce increased intracranial pressure, but the pressure may increase when they are tapered. Drug effects are often transient, and when the syndrome does not resolve spontaneously, other treatments are needed. Although the relationship of obesity to IIH is uncertain, loss of weight can lead to resolution of the syndrome, and some patients have undergone surgical stomach size reduction to control the obesity.

Visual fields should be measured and the size of the blind spot plotted. When the papilledema spreads into the region of the macula, visual acuity falls, and in extreme cases, blindness may occur. Although most patients with IIH retain normal vision, a small percentage of patients develop impairment of vision. When vision is threatened, and drugs and lumbar punctures do not lower the CSF pressure, surgical intervention is necessary. Lumboperitoneal shunting has a reportedly high success rate. However, shunt malfunction is c 01111:1011 in lui:ibopci':lnii;\il •.hmils. Fenestration of the optic nerve sheath to drain CSF into the orbital region reduces the intracranial pressure, and some consider it the treatment method of choice in medically refractory patients. In the obese patients with IIH, weight loss is an important adjunct treatment, and some authors argue that it is as important as acctazolamide.

HYDROCEPHALUS

Obstruction of drainage of the CSF causes hydrocephalus, which is defined as enlargement of the ventricles. Although detection of enlarged ventricles has been greatly aided by CT and MRI, the separation of ventricular enlargement due to hydrocephalus from that due to loss of brain tissue remains .1 challenge. In carls life, obstruction oi the ventricular outflow most commonly occurs in the aqueduct, leading to noncommunieating hydrocephalus, while in the elderly, resistance to drainage of the CSF after the exit into the subarachnoid space results in a communicating hydrocephalus. Enlargement of the cerebral ventricles in children younger than 2 years produces enlargement of the head circumference because the skull sutures are still open. Children with bead growth that is more rapid than expected for age are suspected of having hydrocephalus and are imaged. In the elderly, the onset of symptoms may be gradual, beginning with problems of gait and intellect, which can suggest many different diagnoses. Obstruction prior to the outflow of CSF at the foramina of Luschka and Magendie results in a noncommunieating type of hydrocephalus, whereas in the communicating type of hydrocephalus, enlargement of the ventricles takes place with preserved flow of CSF between the ventricles and the subarachnoid space. Obstruction of CSF circulation may result in increased CSF pressure as the cerebral ventricles enlarge.

Acute, noncommunieating hydrocephalus develops rapidly, reaching 80% of maximal ventricular enlargement within 6 hours. A slower phase of enlargement follows the initial rapid expansion, and ventricular enlargement plus continual production of CSF causes fluid accumulation in the petiventricular white matter interstitial space. When the hydrocephalus stabilizes and enters a chronic phase, the CSF pressure may decrease, resulting in normal pressure recordings on random measurements. Atrophy may occur in the chronically hydrocephalic white matter. When the rate of ventricular enlargement stabilizes in patients with incomplete ventricular obstruction, CSF production is balanced by absorption at alternate sites. This time course is unpredictable, and occasionally, patients assumed to have arrested hydrocephalus can undergo acute decompensation after many years of apparent stability.

Hydrocephalus in Children

Hydrocephalus in children is often due to a structural abnormality, such as Chiari I or II malformation, congenital aqueducts I stenosis, aqueductal stenosis due to intrauterine infection or other congenital causes, such as anoxic injury, intraventricular hemorrhage, and obstruction of the CSF pathways after bacterial meningitis. Bulging of the anterior fontancllc may be seen, along with thinning of the skull and separation of the sutures. If the diagnosis is

delayed, abnormal eye movements and optic atrophy may develop. Spasticity[7] of the lower limbs may be observed at any stage. Acute enlargement of the ventricles is associated with nausea and vomiting.

During the neonatal and early childhood period, irritability is the most common symptom of hydrocephalus. The child feeds poorly, appears fretful, and may be lethargic. In the older child, headache may be a complaint. Vomiting due to increased intracranial pressure may be present in the morning. Remote effects of the increased pressure may affect the sixth cranial nerves on one or both sides, leading to the complaint of diplopia. The enlarged ventricles affect gait. A wide-based ataxic gait may be present due to the stretching of the white matter tracts from the frontal leg regions around the ventricles.

Premature infants weighing less than 1500 g at birth have a high risk of intraventricular hemorrhage, and approximately 2.5% of these infants develop progressive ventricular enlargement, as shown by CT or ultrasound scans. Ventricular size in the neonate may be followed at the bedside with B-mode ultrasound through the open fontanellc. Long-term follow-up studies of children with intraventricular hemorrhage due to prematurity show that 5% require shunting for hydrocephalus. The survivors of a large germinal plate hemorrhage often have multiple disabilities.

Before the widespread availability of antibiotics and vaccinations, meningitis was a frequent cause of hydrocephalus in children. Often, there was concurrent cerebral infarction, resulting in brain atrophy with ventricular enlargement. Separation of the atrophy from the obstructive hydrocephalus may be difficult.

Once the sutures are closed, which generally occurs by the age of 3, hydrocephalus causes signs of increased intracranial pressure rather than head enlargement. Meningitis, aqueductal stenosis, Chiari malformations, and mass lesions may be the cause of hydrocephalus in these young children. Tumors originating from the cerebellum and from the brainstem produce acute symptomatology, including headaches with vomiting, diplopia, visual blurring, and ataxia. Symptoms are due to the acute hydrocephalus secondary to obstruction of the aqueduct of Sylvius and to pressure on brainstem structures.

Examination shows papilledema, possible sixth cranial nerve palsy, and spasticity of the lower limbs. When the hydrocephalus is more long-standing, endocrine dysfunction may occur, involving short stature, menstrual irregularities, and diabetes insipidus. Excessively rapid growth of the head is the hallmark of hydrocephalus in the child before closure of the sutures. Charts are available to plot head growth and to compare it with the standardized curves for normal children. Bulging of the anterior fontanellc is found even with the child relaxed and upright. After 1 year, the firmness of the fontanellc cannot be used because the sutures have closed. Other findings include the "cracked-pot" sound on percussion of the skull (McEwen sign), engorged scalp veins, and abnormalities of eye movements. As spasticity develops, the deep tendon reflexes are increased.

Treatment involves shunting CSE from the ventricles to drain fluid into another body cavity. In very young children, the shunt is often placed in the peritoneal cavity. hi the older child, i ventriculoperitoneal shunt is generally-used. Complications of shunt placement include malfunction and shunt infection.

Adult-Onset Hydrocephalus

In the adult, symptoms of hydrocephalus include headaches, papilledema, diplopia, and mental status changes. Sudden death may occur with severe increases in pressure. Rarely, hydrocephalus causes an akinetic mutism due to pressure on the structures around the third ventricle. Other symptoms include temporal lobe seizures, CSF rhinorrhea, endocrine dysfunction {e.g., amenorrhea, polydipsia, and polyuria), and obesity, which suggest third ventricle dysfunction. Gait disturbances are reported in patients with aqueductal stenosis, but hyper-reflexia with Babinski's sign is infrequent.

Adult-onset hydrocephalus has similar causes to those in children, but the frequencies differ. As in children, acute obstruction of the ventricles results in rapidly progressive hydrocephalus with symptoms of raised intracranial pressure. Adults are more likely than children to present with an acute blockage of CSF flow by intraventricular masses, such as a colloid cyst of the third ventricle or an ependymoma of the fourth ventricle. These tumors cause sudden headaches, ataxia, and loss of consciousness with symptoms that may be intermittent due to the ball-valve effect of the masses. CT or MRI, which reveals the structural lesion in the ventricular system, can make the diagnosis.

Cerebellar hemorrhage and cerebellar infarction with edema cause an acute hydrocephalus by compression of the brainstem, occluding the aqueduct of Sylvius and fourth ventricle outflow pathways and causing noncommunicating hydrocephalus, which can be seen on CT and results in acute elevation in intraventricular pressure. Patients with cerebellar hemorrhage usually have a history of hypertension. Increasing drowsiness and difficult)' walking often follow the acute onset of headache. Hemiparesis and brainstem findings evolve after the ataxia, providing a clue that the origin of the problem is in the posterior fossa. The expanding hemorrhagic mass in the posterior fossa, if it is encroaching on the brainstem, requires urgent neurosurgical attention, with placement of a ventricular catheter to decompress the lateral and third ventricles, followed by posterior fossa craniectomy to remove the mass effect and pressure on the brainstem. In patients with cerebellar infarction, the progression is generally slower because the maximum swelling takes place in 24-48 hours, but the consequences of the enlarging posterior fossa mass are

the same as with hemorrhage, and surgery may he necessary to remove the necrotic tissues and restore the normal flow of CSF. CT is needed in the acute setting, particularly when MRI is not readily available, but visualization of the cerebellar infarction, which may be missed on the CT, is clearly seen on the diffusion-weighted scan (Figure 65.1 1).

Treatment of hydrocephalus involves an operation to insert a tube to shunt CSF from the ventricles to another body cavity, such as peritoneum (ventriculoperitoneal shunt). These devices have one-way valves that respond to pressure. In an emergency, hydrocephalic ventricles can be assessed readily due to the increase in their size. Shunt malfunction may cause abrupt decompensation. Symptoms of acute increased intracranial pressure from a shunt malfunction resemble those seen with onset of the hydrocephalic process.

Adult-onset hydrocephalus that is communicating may be due to a tumor in the basal cisterns, subarachnoid bleeding, or infection or inflammation of the meninges, but only a small percentage of these patients require insertion of a shunt. In the preantibiotic era, syphilis, tuberculosis, and fungal infections more commonly caused chronic obstruction of the subarachnoid pathways and hydrocephalus. Cultures of the CSF are indicated in the elderly patient with enlarged ventricles, and searching for other sources of infection in lungs and other organs may be helpful in establishing the type of infection.

Normal-Pressure Hydrocephalus

Chronic hydrocephalus in the adult can produce symptoms of gait disturbance, incontinence, and memory loss, with or without symptoms and signs of raised intracranial pressure, including headache, papilledema, and false localizing signs. Causes of chronic hydrocephalus include subarachnoid hemorrhage, chronic meningeal infections, and slow-growing tumors blocking the CSF pathways.

Normal-pressure hydrocephalus (NPH) is a term commonly used to describe chronic, communicating adult-onset hydrocephalus. Typically, patients with NPH have the triad of mental impairment, gait disturbance, and incontinence.

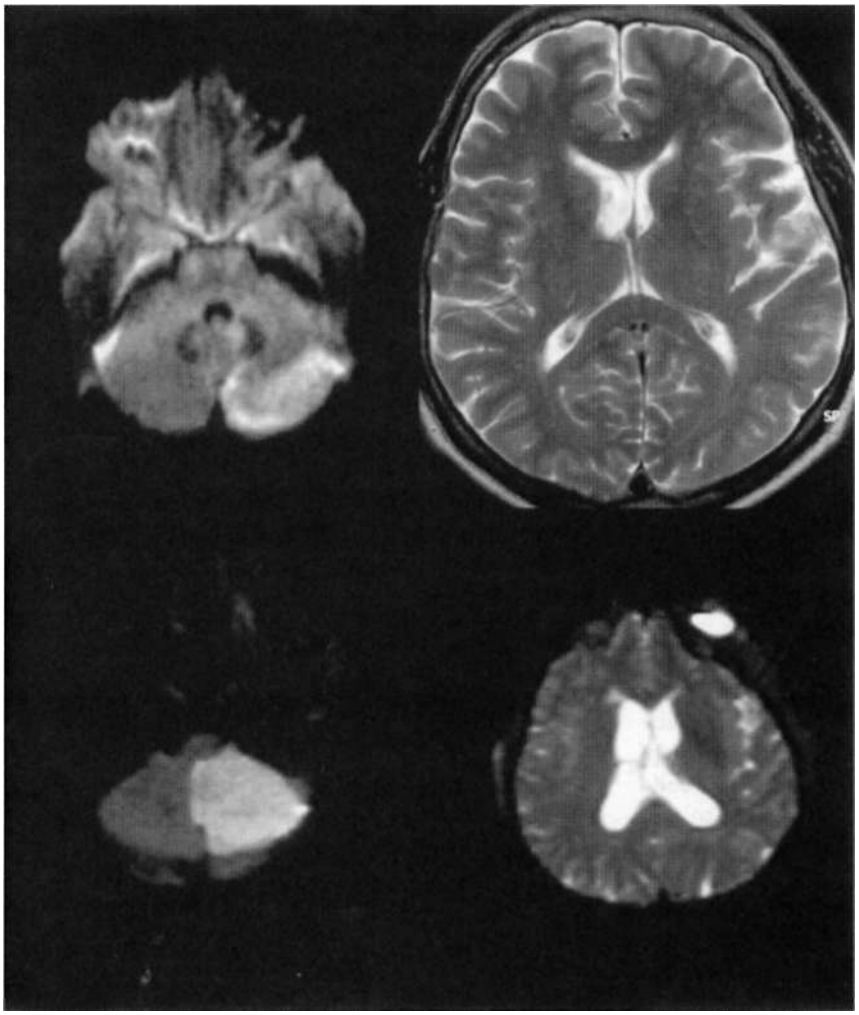


FIGURE 65.11 Cerebellar infarct with secondary hydrocephalus. (A) Initial diffusion-weighted image with cerebellar infarct in the territory of the left posterior inferior cerebellar artery. (B) Initial axial T^-weighted MR image shows n.....nil VL'iitrii ii'..ii si/.c. *C.)*] >\\ 1 3 days larer, showing swelling of the infarction in the cerebellum. ;D l.diu planar] _> .ixi.il imagu shows enlargement of the ventricles prior to surgery for hydrocephalus. (Courtesy Blaine Hart, MD.)

NPH can develop secondary to trauma, infection, or subarachnoid hemorrhage, but in about one third, no etiology is found. Enlarged ventricles ore seen on CT or MRI. By definition, lumbar puncture generally reveals a normal CSF pressure. Normal pressure is an unfortunate term because patients who have undergone long-term monitoring with this syndrome have intermittently elevated pressures, often during the night.

The presenting symptoms may be related to gait or to mental function. When gait is the presenting factor, the prognosis for treatment is better. NPH causes an apraxic gait, which is an inability to lift the legs as if they wete stuck to the floor. The motor strength is intact, reflexes are usually normal, and liabinski's sign is absent. Patients may be misdiagnosed as having Parkinson's disease because the gait disorder is similar in the two syndromes, suggesting that the etiology of the problem in the hydrocephalic patient lies in the basal ganglia. Because many of these patients also have hypertension, and some have small or large strokes, such patients may have other neurological findings, including spasticity and hyper-reflexia with Bahinski's signs. The combination of cerebrovascular disease and hydrocephalus is a poor prognostic sign for treatment with shunts.

NPH leads to a reduction in intellect, which at times may he subtle. The dementia is of the subcortical type, and involves slowing of vetbal and motot responses with preservation of cottical functions, such as language and spatial resolution. Neuropsychological testing quantitates the decline in intellect and the degree of dementia. Patients are apathetic and may appear depressed. Incontinence of urine may occur early in the coutse, particularly in patients with prominent gait disturbance. In the early stages of the illness, presumably as the ventricles are undergoing enlargement, patients can experience drop attacks ot btief loss of consciousness. Headache and papilledema are not a part of the syndrome.

Diagnosis of adult-onset NPH and selection of patients for placement of a ventriculoperitoneal shunt has been difficult (Boon ct al. 2000). Many of these patients have hypertensive vascular disease with lacunar infarcts. Featutcs of Parkinson's disease were noted in earlier reports of the syndrome, and it is now recommended that all patients with Parkinson's disease have scans to rule out hydrocephalus. CT and MRI have aided in separating Parkinson's disease, lacunar state, and NPH, although NPH may occasionally coexist with these diseases. Patients diagnosed with vascular diseases, such as lacunar state or subcortical arteriosclerotic encephalopathy (Binswanger's disease), along with the hydrocephalus respond poorly to shunting, and if there is a positive response, it may be transient as the underlying disease progresses. Selection of patients for shunting requires a combination of clinical findings and diagnostic test results, because no test can totally predict whether a patient will likely benefit from an operation.

There may be a correlation between improvement in gait after removal of CSF and improvement after shunting. Cisternography is a useful procedure that involves the injection of a radiolabeled tracer into the CSF with monitoring of its absorption for 3 days. Normally, the radiolabeled material fails to enter the ventricles, moving over the convexity of the brain and leaving the CSF space within 12-24 hours. In patients with large ventricles due to atrophy, there may be a delay in circulation time, with some isotope being seen in the ventricles during the first 24 hours. Communicating hydrocephalus with abnormal CSF circulation shows pctsistent ventricular filling for more than 48 hours. In patients with NPH, there is reflux of the tracer into the cetebral ventricles by 24 hours and retention in the ventticles for 48-72 hours. This suggests that transependymal absorption is occurring and that pcriventricular white matter has become an alternate route of CSF absorption. A positive cisteruogram is seen in some patients with hypertensive cerebrovascular disease and Binswanger's encephalopathy because of the overlap in the three syndromes.

CI and MRI in Nll'l I -hov. thai the temporal horns i>i' the lateral ventricles are enlarged and that cortical atrophy- is less than anticipated fot age. This is in contrast to patients with hydrocephalus ex vacuo due to a degenerative disease, such as Alzheimer's disease, in which there is atrophy of the cerebral gyri and enlargement of the ventricles. Another useful finding on proton density MRI is the presence of presumed transependymal fluid in the frontal and occipital periventricular regions. Quantitative cisternography using single-photon emission CT has been successfully used to predict the results of a shunt. Other proposed diagnostic methods, including measuring rate of absorption of CSF by infusion of saline or artificial CSF into the thecal sac, clinical improvement after CSF removal, or the prolonged monitoring of intracranial pressure, have been used with some success to select patients for surgery. Decreased cerebral blood flow has been reported in NPH; regional cerebral blood flow is reduced in both cortical and subcortical regions. Patients who show clinical improvement with shunting have a concomitant increase in cerebral blood flow. Removal of CSF may result in an increase in cerebral blood flow in patients in whom NPH is likely to respond to shunt therapy.

The number of patients undergoing shunt operations at most centers has fallen as the initial enthusiasm, which resulted in many shunts and a low success fate, has waned. None of the currently available tests by themselves identifies the patients that will benefit from shunting. Most helpful is a combination of clinical signs and judiciously chosen laboratory tests.

Success rates vary between investigators, with some reports describing improvement in approximately 80% of treated patients and others reporting lower rates. Shunts for presumed NPH fail about one third of the time, and as

many as one fourth of the patients may have major complications, including a high rate of infection and subdural hematomas after shunt placement. Clearly, more information is needed to aid in the management of patients with this uncommon, but treatable, syndrome.

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Chapter *66*
Developmental Disorders of the Nervous System

Harvey B. Sarnat and Laura Flores-Sarnat

EMBRYOLOGICAL AND FETAL **DEVELOPMENT OF THE** NERVOUS **SYSTEM**

Congenital malformations of the nervous system are best understood in the context of embryology. The scope of modern embryology now encompasses not only classical descriptive morphogenesis, but also the molecular genetic programming of development. *Maturation* refers both to *growth,* a measurement of physical characteristics over time, and *development,* the acquisition of metabolic functions, reflexes, sensory awareness, motor skills, language, and intellect. Molecular development is the maturation of cellular function. In the case of neurons, it includes the development of an energy production system to actively maintain a resting membrane potential, the synthesis of secretory molecules as neurotransmitters, and the formation of membrane receptors. Membrane receptors respond to various transmitters at synapses, to a variety of trophic and adhesion molecules, and during development, to substances that attract or repel growing axons in their intermediate and final trajectories. The role of homeobox genes in the differentiation of neural structures is an aspect of development recognized relatively recently. Molecular genetic data are rapidly becoming available because of intense interest in this key to understanding neuroembryology in general and neural induction in particular (Sarnat and Menkes 2000). Other aspects of current investigative interest include the roles of neurotrophic factors, hormones, ion channels, and neurotransmitter systems in fetal brain development. Many genetic models of human cerebral malformations have been created by genetic manipulation in animals, and these contribute greatly to our understanding of human dysgeneses and provide insights also into the pathogenesis of epilepsy and other functional results of dysgeneses (Chcvassus-au-Louis et al. 1999).

Maturation progresses in a predictable sequence with precise timing. Insults that adversely affect maturation influence events occurring at a particular time. Some insults are brief (e.g., a single exposure to a toxin), whereas others act over many weeks or throughout gestation, such as some congenital infections, diabetes mellitus, and genetic or chromosomal defects. Even brief insults may have profound influences on later development, by interfering with processes essential to initiate the next stage of development, so that the timing of an adverse event often is difficult.

The anatomical and physiological correlates of neurological maturation reflect the growth and development of the individual neuron and its synaptic relations with other neurons. The mature neuron is a secretory cell with an electrically polarized membrane. Though endocrine and exocrine cells are secretory, and muscle cells possess excitable membranes, only neurons embrace both functions. The precursors of neurons arc neither secretory nor excitable. The cytological maturation of neurons is an

aspect of ontogenesis that is as important as their spatial relations with other cells for future function and also for the pathogenesis of some functional neurological disorders of infancy, such as neonatal seizures. Neuroblasts are defined as postmitotic neuroepithelial tells committed to neuronal lineage. These cells have not yet achieved all functions of mature neurons such as membrane polarity, secretion, and synaptic relations with other neurons, and often they are still migratory. The term *blast* thus is used differently for neural development than for hematopoieses, in which blast cells are still in the mitotic cycle.

The events of neural maturation after initial induction and formation of the neural tube are each predictive of specific types of malformation of the brain and of later abnormal neurological function. These are (1) mitotic proliferation of neuroblasts, (2) programmed death of excess neuroblasts, (3) neuroblast migration, {4) growth of axons and dendtites, (5) electrical polarity of the cell membrane, *(6)* synaptogencsis, (7) biosynthesis of neurotransmitters, and (8) myelinstion of axons.

Malformations of the nervous system are unique. No two individual cases are identical, even if they can both be categorized as similar, such as alobar holoprosencephaly, agenesis of the corpus callosum, or type 2 lissencephaly. Functional expression of anatomically similar cases also may vary widely. For example, two cases of holoprosencephaly with nearly identical imaging findings and similar histological patterns of cortical architecture and subcortical heterotopia at autopsy may differ in that one infant may have epilepsy refractory to pharmacological control, whereas the other may have no clinical seizures at all. The difference may be at the level of synaptic organization and the relative maturation of afferent input and neuronal maturation (Sarnat and Born 1999).

NEURAL MATURATION

Mitotic Proliferation of Neuroblasts (Neuronogenesis)

After formation of the neural tube, neurons and glial cells are generated by proliferation of neuroepithelial cells in the ventricular zone with mitoses at the ventricular surface. The rate of division is greatest during the early first trimester in the spinal cord and brainstem and during the late first and early second trimester in the forebrain. "Within the ventricular zone of the human fetal telencephalon, 33 mitotic cycles provide the total number of neurons required for the mature cetebral cortex. Most mitotic activity in the ncuroepithelium occurs at the ventricular surface, and the orientation of the mitotic spindle determines the subsequent immediate fate of the daughter cells. If the cleavage plane is perpendicular to the ventricular surface, the two daughter cells become equal neuroepithelial cells preparing for further mitosis. If, however, the cleavage is parallel to the ventricular surface, the two daughter cells are unequal (asymmetrical cleavage). In that case, the one at the ventricular surface becomes another neuroepithelial cell, whereas the one away from the ventricular surface separates from its ventricular attachment and becomes a postmitotic neuroblast ready to migrate to the cortical plate. Furthermore, the products of two genes that determine cell fate, called *numb* and *notch,* are on different sides of the neuroepithelial cell. Therefore, with symmetrical cleavages, both daughter cells receive the same amount of each, but with asymmetrical cleavage, the cells receive unequal ratios of each, which also influences their subsequent development (Mione et al. *1997).* The orientation of the mitotic spindle requires centractin.

Active mitoses cease well before the time of birth in most parts of the human nervous system, but a few sites retain a potential for postnatal mitoses of neuroblasts. One recognized site is the periventricular region of the cerebral hemispheres (Kendler and Golden 1996). The best-documented site is the external granular layer of the cerebellar cortex, where occasional mitoses persist until I year of age. Postnatal regeneration of these neurons after most are destroyed by irradiation or cytotoxic drugs is demonstrated in animals and may occur in humans as well. Primary olfactory receptor neurons also retain a potential for regeneration. In fact, if a constant turnover of these neurons did not occur throughout life, the individual would become anosmic after a few upper respiratory infections, which transiently denude the intranasal epithelium. Recently, a population of "stem cells'[1] with mitotic potential has been demonstrated in the suliventncular /.one anil hippocampa! dentate gyrus (Johansson etal. 1999). These have generated a great deal of interest because of a potential for regeneration of the damaged adult brain and because they may be induced to mature as neurons (Schuldiner et al. 2001).

Disorders of Neuronogenesis

Destructive processes may destroy so many neuroblasts that regeneration of the full complement of cells is impossible. This happens when the insult petsists for a long time or is repetitive, destroying each subsequent generation of dividing cells. Inadequate mitotic proliferation of neuroblasts results in hypoplasia of the brain (Figure 66.1). Such brains are small and grossly malformed because neuroblast migration is affected directly or by destruction of the glial cells with radial processes that guide migrating nerve cells. The entire brain may be affected, or portions may be selectively involved. Cerebellar hypoplasia is often a selective interference with proliferation of the external granular layer. In some cases, cerebral hypoplasia and microcephaly are the result of precocious development of the ependyma before all mitotic cycles of the neuroepirhelium are complete because ependymal differentiation arrests mitotic activity at the ventricular surface (Sarnat 1992). The mutation of a gene that programs neuronogenesis may

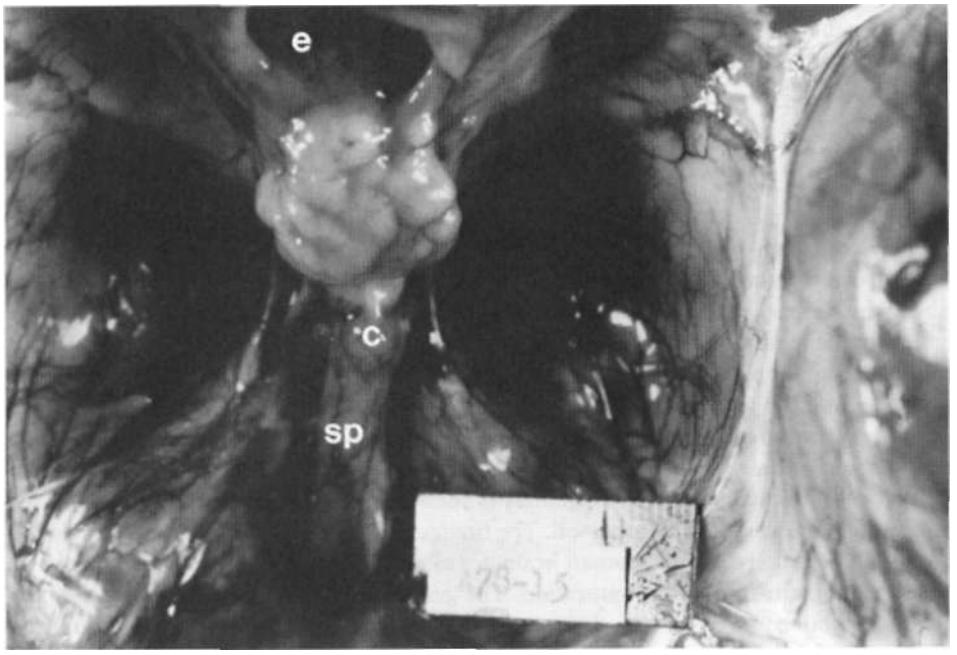

FIGURE 66.1 Severe cerebral hypnphsi;!. The brain of this term neonate weighed only 12.6 g (normal mean is 350 g), although the cranium was closed and mainly filled with fluid, The dysplasia architecture of the telencephalon. incluJ-iu', dysplasia cerebellar tissue, extended into a frontal encephalocele (e) and was not that of a neural tube defect or fetal infarction. The spinal cord (sp) is well formed except for the absence of descending tracts. The cerebellum (e) is small but normally laminated. This brain probably represents lack of neuronal proliferation. Note the well-formed fossae at rhe base of the skull, despite the absence of cerebri I development. (Reproduced with permission from Sarnat, H. B., de Mello, D. E., Blair, J. D., ct al. J 9S2, "Heterotopic growth of dysplastic cerebellum in frontal encephalocele in an infant of a diabetic mother," *Can j Neurol* So, vol. 9, pp. 31-35.)

he another explanation for generating insufficient neuroepithelial cells, although this pathogenesis remains hypothetical in humans.

Programmed Cell Death (Apoptosis)

Excessive neuroblasts are formed in every part of the nervous system by normal mitotic proliferation. This abundance is reduced by a programmed process of cell death until the definitive number of immature neurons is achieved. The factors that arrest the process of programmed cell death in the fetus are multiple and are in part genetically determined. Cells that do not match with targets are more vulnerable to degeneration than are those that achieve synaptic contact with other cells. Kndocrine hormones and neuropeptides modulate apoptosis. Some homeotic genes, such as *c-fos* arc important in the regulation of programmed cell death in the nervous system, and other suppressor genes stop the expression of apoptotic genes.

Two phases of apoptosis are distinguished. One involves yet undifferentiated neuroepithelial cells or neuroblasts with incomplete differentiation; another phase involves fully differentiated neurons of the fetal brain.

Disorders of Programmed Cell Death

Spinal muscular atrophy (see Chapter 79) is an example of a human disease caused by programmed cell death not stopping at the proper time. In this disorder, continued loss of spinal motor neurons (SMN) after all surplus embryonic neuroblasts are deleted is expressed as a progressive denervating process. Genetic factors are crucial in determining the arrest of cell death, which accounts for the hereditary character of spinal muscular atrophy. The SMN defective gene at the chromosome 5ql3.1 locus has now been isolated and is normally responsible for arresting apoptosis in motor neuroblasts (Roy et al. 1995),

Other neurodegenerative diseases of fetal life and infancy arc more widespread within the central nervous system (CNS) rather than limited to one type of neuron, such as the motor neuron. They also are characterized by progressive neuronal loss that is apoptotic rather than necrotic in character: There is no inflammatory or glial reaction, and the features of the DNA degradation differ from ischemic necrosis. An example is pontocerebellar hypoplasia, a group of progressive degenerative diseases that begin prenatally and continue postnatally. Despite the name, they involve much more than the cerebellar system. These diseases are associated with extensive cerebral cortical and basal ganglionic abnormalities, even in motor neurons, which cause a clinical presentation at birth resembling spinal muscular atrophy. This autosomal recessive group of diseases, all genetically distinct from olivopontocerebellar atrophy, exemplifies a semantic difficulty: If an atrophic process begins before development is complete, it results in both hypoplasia and superimposed atrophy.

In the CNS, glial cells also undergo programmed cell death. Glial necrosis is intimately linked to the interhemispheric passage of commissural fibers in the corpus

callosum. In a murine model of callosal agenesis, glial cells that do not degenerate act as a barrier to crossing axons and prevent the corpus callosum from forming.

Neuroblast Migration

No neurons of the mature human brain occupy the site in which they were generated from the neuroepithelium. They migrate to their mature site to establish the proper synaptic connections with appropriate neighboring neurons and to send their axons in short or long trajectories to targets. The subependymal germinal matrix (Figure 66.2) is the subventricular zone of the embryonic concentric layers and consists of postmitotic, premigratory neuroblasts and glioblasts. In general, the movement of maturing nerve cells is centrifugal, radiating toward the surface of the brain. The cerebellar cortex is exceptional in that external granule eel Is first spread over the surface of the cerebellum and then migrate into the folia. Migration of neuroblasts begins at about 6 weeks' gestation in the human cerebrum and is not completed until at least 34 weeks of fetal life, although the majority of germinal matrix cells after midgestation are glioblasts. Glioblasts continue to migrate until early in the postnatal period. Within the brainstem, neuroblast migration is complete by 2 months' gestation. Cerebellar external granule cells continue migrating throughout the first year of life.

Neuroblast migration permits a three-dimensional spatial relation to develop between neurons, which facilitates the formation of complex synaptic circuits. The timing and sequence of successive waves of migrating neuroblasts are precise. In the cerebral cortex, immature nerve cells reach the pial surface and then form deeper layers as more recent arrivals replace their position at the surface. Neurons forming the most superficial layers of neocortex are thus the last to have migrated, although in the three-layered hippocampus, the most superficial neurons represent the earliest migratory wave.

The laminated arrangement of the mammalian cerebral cortex requires a large cortical surface area to accommodate increasing numbers of migrating neuroblasts and glioblasts, Convolutions provide this large surface area without incurring a concomitant increase in cerebral volume. The formation of gyri and sulci is thus a direct result of migration (Figure 66.3). Most gyri form in the second half of gestation, which is a period of predominant gliogenesis and glial cell migration. Therefore, the proliferation of glia in the cortex and subcortical white matter may be more important than neuroblast migrations in the formation of convolutions, but the growth of dendrites and synaptogenesis also may influence gyration by contributing mass to the neuropil. The timing and sequence of gyral formation in the human brain arc as predictable as other aspects of cerebral maturation. The gestational age of a premature infant may be determined to within a 2-week period or less from the convolutional pattern of the brain at autopsy.

THE MAJOR MECHANISM OF NEUROBLAST MIGRATION: RADIAL GLIAL FIBER GUIDES

The majority of neuroblasts arriving at the cortical plate do so by means of radial glial guides from the subventricular zone. A second route, that of tangential migration, uses axons as the guides for the migratory neuroblasts. The genetically determined programming of neuroblast migration begins when cells are still undifferentiated neuroepithelial cells and even before all their mitotic cycles are complete. Neuroepithelial cells express the gene products of the lissencephaly gene (LIS1), as do ependymal cells and

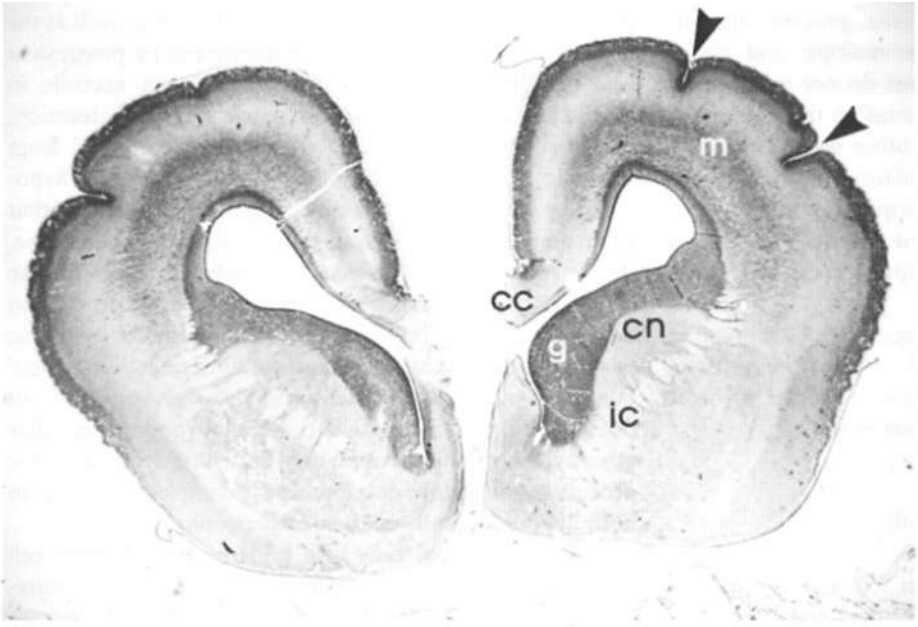

FIGURE 66.2 Coronal section of forebrain of 16-week normal fetus, showing extensive subependymal germinal matrix (g) of neuroblasts and glial precursors that have not yet migrated. The surface of the brain is just beginning to develop sulci *(arrowheads).* Migrating neuroblasts (m) are seen in the subcortical white matter. The corpus callosum (ce) is artifaetually ruptured and the two hemispheres should be closely approximated. (en = caudate nucleus; ic = anterior limb of internal capsule.) (Hematoxylin-eosin stain.)

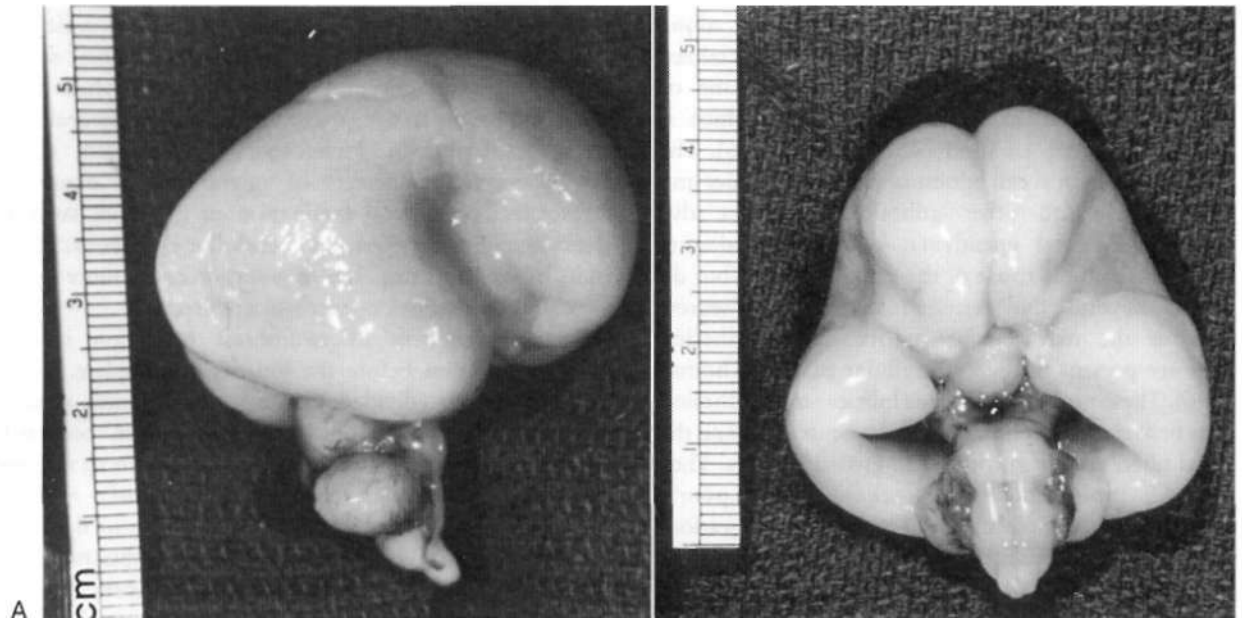

FIGURE 66.3 Lateral (A) and ventral (B) views of a normal brain of a 16-week ferus. The primary sulci, such as the sylvian fissure, calcarine fissure, and central sulcus, are forming, hut secondary and Tertiary sulci and gyri are not yet developed, and the Surface of the brain is smooth.

Cajat-Retzius cells of the molecular layer of cerebral cortex, This gene is defective in type 1 tissencephaly (Miller-Dieker syndrome), a severe disorder of neuroblast migration (Clark et al. 1997). How it functions in migration is not fully understood. Most neurons of the forcbrain are guided to their predetermined site from the germinal matrix (embryonic subventricular /one) by long, radiating fibers of specialized fetal astrocytes (Figure 66.4). The entire wall of the fetal cerebral hemisphere is spanned by the elongated processes of these glial cells, whose cell bodies are in the periventricular region and terminate as end-feet on the limiting pial membrane at the surface of the brain (see Figure 66.4), Radial glial cells are the first astroglial cells of the human nervous system converted into a mature fibrillary astrocyte of the subcortical white matter; some are still present at birth. Mature astrocytes are present throughout the CNS by 15 weeks' gestation, and gliogenesis continues throughout fetal and postnatal life. Several types of glial cells are recognized between 20 and 36 weeks' gestation.

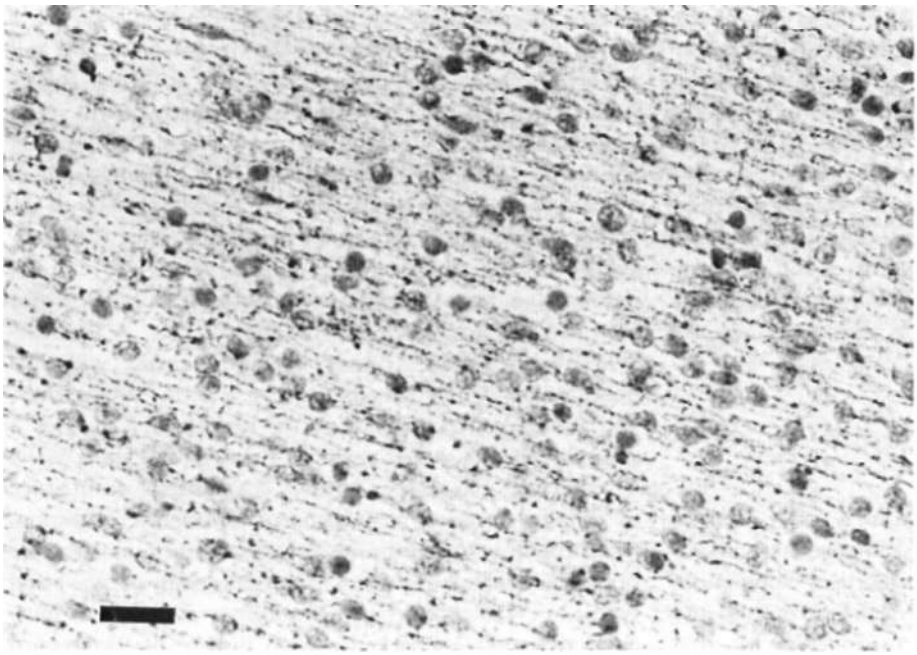

FIGURE 66.4 Radial glial fibers extending from subependymal region (*right*) toward cerebral cortex (*left*), guiding migrating neuroblasts in a 16-week fetus. (Glial fibrillary acidic protein reaction. Bar = 10 μm.)

The mechanical process of neuroblasts gliding along a radial glial fiber is facilitated by a number of specialized proteins at the radial glial fiber surface membrane or extracellular space. An example is astrotactin, which is secreted by the neuroblast itself (Zheng et al. 1996). The glial cell (e.g., LI neural cell adhesion molecules [Jouet and Kenwrick 1995| and orhc" adhesion molecules also facilitate gliding. Fetal ependymal cells have radiating processes that resemble those of the radial glial cell but do not extend beyond the germinal matrix and secrete molecules in the extracellular matrix. Some adhesion molecules are present in the extracellular matrix (Thomas et al. 1996). These molecules serve as lubricants, as adhesion molecules between the membranes of the neuroblast and the radial glial fiber, and as nutritive and growth factors. They stimulate cell movement by a mechanism still poorly understood. Deficient molecules lead to defective migration, For example, the abnormality of the LI adhesion molecule is the defective genetic program in X-linked hydrocephalus accompanied by poly microgyria and pachygyria.

The process of transformation of radial glial cells into astrocytes and ependymal cells begins during the first half of gestation and is completed postnatal ly. During mid-gestation, when neuronal migration is at a peak, many radial glial cells remain attached to the ventricular and pial surfaces, increasing in length and curving with the expansion and convolution of the cerebral wall. From 28 weeks' gestation to 6 years of age, astrocytes of the frontal lobe shift from the periventricular to the subcortical region. The centrifugal movement of this band of normal gliosis marks the end of neuronal migration in the cetebral mantle. Ependyma does not completely line the lateral ventricles until 22 weeks' gestation (Sarnat 1992}.

In addition to the radial migration to the cerebral cortex, tangential migration also occurs, but the number of neuroblasts is far smaller (Rakic 1995). These migrations perpendicular ro the radial fibers probably use axons rather than glial processes as guides for migratory neuroblasts, which explains why all cells in a given region of cortex are not from the same clone or vertical column. Most of the tangentially migrating neuroblasts in the cerebral cortical plate are generated in the fetal *gangltonic eminence,* a deep relecephalic structure that later becomes the basel ganglia. Tangential migrations occur in the brainstem and olfactory bulb as well as in the cerebrum. The subpial region is another site of neuroblast migration that docs not use radial glial cells.

Disorders of Neuroblast Migration

Nearly all malformations of the brain are a direct result of fauln- neuroblast migration or at least involve a secondary impairment of migration. Imperfect cortical lamination, abnormal gyral development, subcortical heterotopia, and other focal dysplasias are related to some factor that interferes with neuronal migration, whether vascular, traumatic, metabolic, or infectious. The most severe migrational defects occur in early gestation, often associated with events in the gross formation of the neural tube and cerebral vesicles. Heterotopia of brainstem nuclei also occurs. Later defects of migration are expressed as disorders of cortical lamination or gyration, such as lissencephaly, pachygyria, and cerebellar dysplasias. These insults of the third trimester of gestation cause more subtle or focal abnormalities of cerebral architecture.

Most disturbances of neuroblast migration involve arrested migration before the journey is complete. These disorders may be divided into three anatomical phases, depending on where the migratory arrest occurred. An example of neuroblasts never having begun to migrate from the periventricular region is *periventricular nodular heterotopia* an X-linked genetic disorder due to defective expression of the gene *Filamin-A.* If neuroblasts began migrating, but became arrested in the subcortical white matter and did not reach the cortical plate, *subcortical laminar* heterotopia may result, another X-linked recessive trait, but due to a different gene called *Dnublecortin (DCX).* If the neuroblasts reached the cortical plate but did not arrange themselves with correct lamination, this abnormal architecture of the cortical plate often is accompanied by abnormalities of gyration, such as lissencephaly or pachygyria. Several different genes, including *LIS!* and *Reelin* (RTN), are important in cortical plate organization (Curran and D'Arcangelo 1998) and are mutated in malformations of the terminal phase of neuroblast migration.

Lissencephaly is a condition of a smooth cerebral cortex without convolutions. At midgestation, the brain is essentially smooth; only the interhemispheric, sylvian, and calcarine fissures are formed. Gyri and sulci develop between 20 and 36 weeks' gestation, and the mature pattern of gyration is evident at term, although some parts of the cerebral cortex, such as the frontal lobes, are still relatively small. In lissencephaly type 1 (Miller-Dieker syndrome), the cerebral cortex remains smooth. The histopathological pattern is that of a four-layer cortex in which the outermost layer (1) is the molecular layer, as in normal six-layered neocortex. La yet 2 corresponds ro layers 2 through 6 of normal neocortex, layer J3 is cell-sparse as a persistent fetal subplate zone, and layer 4 consists of incompletely migrated neurons in the subcortical intermediate zone. In lissencephaly type 2 (Walker-Warburg syndrome), poorly laminated cortex with disorganized and disoriented neurons is seen histologically, and the gross appearance of the cerebrum is one of a smooth brain or a few poorly formed sulci (Figure *66.5),* The cerebral mantle may be thin, suggesting a disturbance of cell proliferation as well as of neuroblast migration, Malformations of the brainstem and cerebellum often are present as well (see Figure *66.5).* Lissencephaly of type 1 and type 2 (Walker-Warburg syndrome, Fukuyama muscular dystrophy, muscle-eye-bra in disease of Santavuori)

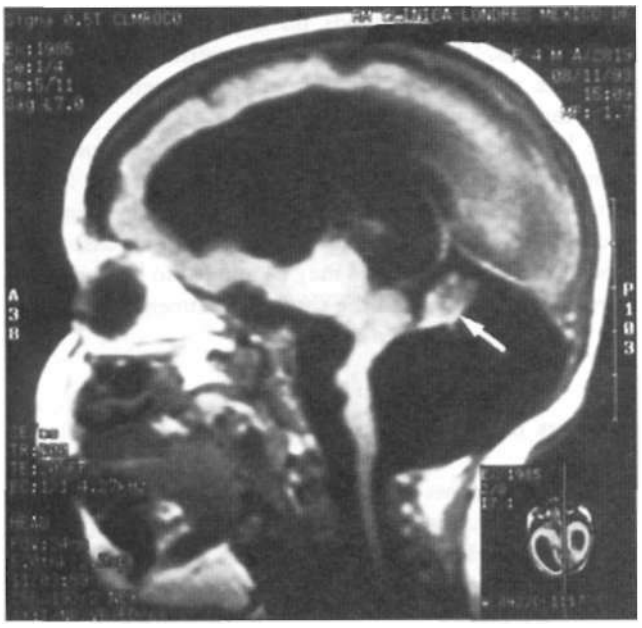

FIGURE 66.5 Sagittal Tl-weighted magnetic resonance image of a 10-month-old girl with lissencephaly type 2 and Dandy-Walker malformation. The cerebral mantle is thin, and the latetal ventricle is greatly enlarged. A few abnormal shallow fissures at the cerebral surface may indicate abortive gyration or pachygyria. The cerebellum is severely hypoplastic {*arrow* indicates anterior vermis), and the posterior fossa contains a large, fluid-filled cyst. The brainstem also is hypoplastic, and the basis pontis is nearly absent. A differential diagnosis of this image is pontocerebellar hypoplasia, but the high position of the toreula indicates a Dandy-Walker malformation.

are genetic diseases, but lissencephaly also may occur secondary to nongeneric disturbances of neuroepithelial proliferation or neuroblast migration, including destructive encephaloclastic processes, such as congenital infections during fetal life.

Other abnormal patterns of gross gyration of the cerebral cortex also occur secondary to neuroblast migratory disorders. *Pachygyria* signifies abnormally large, poorly formed gyri and may be present in some regions of cerebral cortex with lissencephaly in other regions. *Poly microgyria* refers to excessively mi men HIS and abnormally small gyri that similarly may coexist with pachygyria; it docs not necessarily denote a primary migratory disorder of genetic origin. Small, poorly formed gyri may occur in zones of fetal ischemia, and they regularly surround porencephalic cysts due to middle cerebral artery occlusion in fetal life. Schizencephaly is a unilateral or bilateral deep cleft usually in the general position of the sylvian fissure but is not a sylvian fissure: This cleft is the full thickness of the hemispheric wall, and no cerebral tissue remains between the meninges and the lateral ventricle (the pial-ependymal seam). If the cerebral cortical walls on either side of the deep cleft are in contact, the condition is called *closed lips,* and if a wide subarachnoid space separates the two walls, it is known as *open lips,* but these two variants do not provide a clue to pathogenesis. Schizencephaly occurs both as a genetic trait (the defective gene is *EMX2)* and sporadically; in some cases, it is a form of porencephaly due to fetal cerebral infarction.

In the cerebral hemisphere, most germinal matrix cells become neurons during the first half of gestation, and most form glia during the second half of gestation. Nonetheless, j small ium::KT o: gerir.sual matrix cells arc neuronal precursors, migrating into the cerebral cortex in late gestation. Because the migration of the external granular layer in the cerebellar cortex is not completed until 1 year of age, a potential for acquired insults to interfere with late migrations persists throughout the perinatal period. Anatomical lesions, such as periventricular leukomalacia, intracerebral hemorrhages and abscesses, hydrocephalus, and traumatic injuries, may disrupt the delicate radial glial guide fibers and prevent normal migration, even though the migrating cell itself may escape tin- focal destructive lesion.

Damaged radial glial cells tend to retract their processes from the pial surface. The migrating neuron travels only as far as its retracted glial fibers carry it. If this fiber is retracted into the subcortical white matter, the neuroblast stops there and matures, becoming an isolated hetcroropic nodule composed of several nerve cells that were migrating at the same time in the same place. In these nodules, neurons of various cortical types differentiate without laminar organization and with haphazard orientations of their processes, but a few extrinsic axons may prevent total synaptic isolation of the nodule.

Interference with the glial guide fibers in the cerebral cortex itself results in neurons cithet not reaching the pial surface or not being able to reverse direction and then descending to a deeper layer. The consequence is imperfect cortical lamination, which interferes with the development of synaptic circuits. These distutbances of late neuroblast migration do not ptoducc the gross malformations of early gestation and may not be detected by imaging techniques. They may account for many neurological sequelae after the perinatal period, including seizures, perceptual disorders, impaired coordination of gross or fine motor function, learning disabilities, and mental retardation.

In sum, disorders of neuroblast migration may be due either to defective genetic programming or may be acquired secondary to lesions in the fetal brain that destroy or interrupt radial glial fibers. Cells may not migrate at all and become manire neurons in the periventricular region, as occurs in X-linked periventricular nodular heterotopia (Eksioglu et al. 1996) and in some cases of congenital cytomegalovirus infection. Cells may become arrested along their course as heterotopic neurons in deep subcortical **white matter,** as occurs in many genetic syndromes of Iissencephaly-pachygyria and in many metabolic diseases, including cerebrohepatorcnal Zellweger syndrome and in many aminoacidurias and organic acidurias. The same aberration may occur in acquired insults to the radial glial cell during ontogenesis. Cells may overmigrate beyond

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the limits of the pial membrane into the meninges as ectopic neurons, either singly or in clusters known as *marginal glkmeurnnal heterotopia* or *brain warts.* Rarely, herniation of the germinal matrix into the lateral ventricle may occur through gaps in the ependyma; those cells mature as neurons, forming a nonneoplastic intraventricular mass that may or may not obstruct cerebrospinal fluid (CSF) flow. Whether disoriented radial glial fibers actually guide neuroblasts to an intraventricular site or are physically pushed into a direction of less resistance is uncertain.

Growth of Axons and Dendrites

During the course of neuroblast migration, neurons remain largely undifferentiated cells, and the embryonic cerebral cortex at midgestation consists of vertical columns of tightly packed cells between radial blood vessels and extensive extracellular spaces. Cytodifferentiation begins with a proliferation of **organelles,** mainly endoplasmic reticulum and mitochondria in the cytoplasm, and clumping of condensed nuclear chromatin at **the** inner margin of the nuclear membrane. Rough endoplasmic reticulum becomes swollen, and ribosomes proliferate,

The outgrowth of the axon always precedes the development of dendrites, and the axon forms connections before the differentiation of dendrites begins. The projection of the axon toward its destination was first recognized by Ramon y Cajal, who named this growing process the *cone d'accroissetnent* (growth cone). The tropic **factors** that guide the growth cone to its specific terminal synapse, whether chemical, endocrine, or electrotaxic, have been a focus of controversy for many years. However, it is now well demonstrated that growth cones are guided during their long trajectories by diffusible molecules secreted along their pathway by the processes of fetal ependyma! cells and perhaps some glial cells. Some molecules, such as brain-denved neurotrophic growth factor, netrin and -100 protein, attract growing axons, whereas others, such as the glycosaminoglycan *keratan sulfate* (not to be confused with the protein *keratin),* strongly repel them and thus prevent aberrant decussations and other deviations. Matrix proteins, such as laminin and fibronectin, also provide a substrate for axona! guidance. Cell-to-cell attractions operate as the axon approaches its final target. Despite the long delay between the migration of an immature nerve cell and the beginning of dendritic growth, the branching of dendrites eventually accounrs for more than 90% of the synaptic surface of the mature neuron. The pattern of dendritic ramification is specific for' each type oi neuron. Spines form on the dendrites as short protrusions with expanded tips, providing sites of synaptic membrane Jitii-i-nliation.

The Golgi method of impregnation of neurons and their processes with heavy metals, such as silver or mercury, has been used for more than a century and continues to be one of the most useful methods for demonstrating dendritic arborizations. Among the many contributions of this technique to the study of the nervous system, beginning with the elegant pioneering work of Ramon y Cajal, none has surpassed its demonstration of the sequence of normal dendritic branching in the human fetus. Newer immunocytochemieal techniques for demonstrating dendrites also are now available, such as microtubule-associated protein 2. These techniques may be applied to human tissue resected surgically, as in rhc surgical treatment of epilepsy, and to the tissue secured at autopsy.

Disorders of Neurile Growth

If a neuron becomes disoriented during migration and faces the wrong direction in its final site, its axon is capable of reorienting itself as much as 180 degrees after emerging from the neuronal cell body. Dendrites, by contrast, conform strictly to the orientation of the cell body and do not change their axis. The dendritic tree becomes stunted if axodendritic synapses are not established.

Because so much dendritic differentiation and growth occurs during the last third of gestation and the first months of the postnatal period, the preterm infant is particularly vulnerable to noxious influences that interfere wirh maturation of dendrites. Extraordinarily long dendrites of dentate granule cells and prominent basal dendrites of pyramidal cells have been described in term infants on life-support systems. Retardation of neuronal maturation in terms of dendrite development and spine morphology has been described in premature infants, compared with term infants of the same conceptional age, possibly as a result of asphyxia. Infants with fetal alcohol syndrome also have a reduced number and abnormal geometry of dcmlnric opines oi conical neurons.

Traditional histological examination of the brains of mentally retarded children often shows remarkably few alterations to account for a profound intellectual deficit. The study of dendritic morphology by the Golgi technique has revealed striking abnormalities in some of these cases. The alterations are best documented in chromosomal diseases, such as trisomy 13 and Down syndrome. Long, thin, tortuous dendritic spines and the absence of small, stubby spines are a common finding. Children with unclassified mental retardation but normal chromosomal numbers and morphology also show defects in the number, length, and spatial arrangement of dendrites and synapses.

Abnormalities of cerebellar Purkinje's cell dendrites occur in cerebellar dysplasias and hypoplasias. They consist of cactus-like thickenings and loss of brauchlet spines. Abnormal development of the dendritic tree is also a common finding in many metabolic encephalopathies, including Krabbe's disease and other leukodystrophies, Menkes' kinky hair disease, gangliosidoses, ceroid lipofuscinosis, and Sanfilippo's syndrome. Among genetically

determined cerebral dysgeneses, aberrations in the structure and number of dendrites and spines are reported in cerebrohepatorenal (Zellweger) syndrome and in tuberous sclerosis.

Electrical I'olariu of llic Cell Membrane

The development of membrane excitability is one of the important markers of neuronal maturation, but little is known about the exact timing and duration of this development. Membrane polarity is established before synaptogenesis and before the synthesis of neurotransmitters begins. Because the maintenance of a resting membrane pfiriT.ri.il rviiuin"-. considerable energ\ expenditure to fuel the sodium-potassium pump, the undifferentiated neuroblast would be incapable of maintaining such a dynamic condition as a resting membrane potential. The development of ion channels within the neural membrane is another important factor in the maturation of excitable membranes and the maintenance of resting membrane potentials.

Disorders of Membrane Polarity

Epileptic phenomena are largely due to inappropriate membrane depolarizations. They represent a complex interaction of excitatory and inhibitory synapses that modulate the resting membrane potential, metabolic alterations, and many unknown factors that also contribute to the discharge threshold of neural membranes. Cerebral malformations ate often associated with seizures because of abnormal synaptic circuitry, and the role of abnormal resting membrane potentials in development is largely speculative at this time. Electrolyte imbalances in the serum certainly influence the depolarization threshold, and hypothalamic disturbances may alter endocrine function and electrolyte balance.

Synaptogenesis

Synapse formation follows the development of dendritic spines and the polarization of the cell membrane. The relation of synaptogenesis to neuroblast migration differs in different parts of the nervous system. In the cerebral cortex, synaptogenesis always follows neuroblast migration. In the cerebellar cortex, however, the external granule cells develop axonal processes that become the long parallel fibers of the molecular layer and make synaptic contact with Purkinje cell dendrites before migrating through the molecular and Purkinje cell layer to their mature internal position within the folium.

Afferent nerve fibers reach the neocortex early, before lamination occurs in the cortical plate. The first synapses are axodendritic and occur both external to and beneath the cortical plare in the future layers I and VI, which contain the first neurons that have migrated.

An excessive number of synapses form on each neuron, with subsequent elimination of those that are not required. Outside the CNS, muscle fibers also begin their relation with the nefvous system by receiving multiple sources of innervation from multiple motor neurons, later retaining only one. Transitory synapses also form at sites on neurons where they are not found in the matute condition. The spinal motor neurons of newborn kittens display prominent synapses on theit initial axonal segment, where they are never found in adult cats. Somatic spines are an important synaptic site on the embryonic Purkinje cell, bur these spines and their synapses disappear as the dendritic tree develops.

A structure-function correlation may be made in the developing visual cottex. In preterm infants of 24-25 weeks' gestation, the visual evoked potentials (VEPs) recorded at the occiput exhibit an initial long-latency negativity, but by 28 weeks' gestation, a small positive wave precedes this negativity. The change in this initial component of the VEP corresponds to dendritic arborization and the formation of dendritic spines that occurs at that time.

The electroencephalogram (KEG) of the premature infant follows a predictable and time-linked progression in maturation that has been extensively studied. The EEC reflects synaptogenesis more closely than any other feature of cerebral maturation and thereby provides a noninvasive and clinically useful measure of neurological maturation in the preterm infant. Fetal EEC may even detect neurological disease and seizures in utero.

Disorders of Synaptogenesis

Because the formation of dendritic spines and the formation of synapses are so closely related, the same spectrum of diseases already discussed is equally appropriate for consideration in this section. The rate of maturation of the EECi is often slow in preterm infants, who are generally unwell, even if they do not have specific neurological disease, which may reflect an impairment of synapse formation. Chronic hypoxemia particularly delays neurological maturation.

Biosynthesis of Neurotransmitters

The synthesis of neurotransmitters and ncuromodulating chemicals is based on the secretory character of the neuron, without which synaptic transmission is impossible. Several types of substances serve as transmitters: (1) acetylcholine (ACh); (2) monoamines, including dopamine, norepinephrine, epinephrine, and serotonin; (3) neuropeptides, including substance P, somatostatin, and opioid-conraining

peptide chains, such as the enkephalins; and (4) simple amino acids, including glutamic acid, aspartic acid, *y*-aminobutyric acid (GABA), and glycine. Some transmitters are characteristically inhibitory (such as glycine, GABA, and ACh in the CNS). Each neuronal type produces a characteristic transmitter (motor neurons produce ACh, cerebellar Purkinje cells produce GABA, and granule cells produce glutamic acid in the adult). Neuropeptides may coexist with other types of transmitters in some neurons.

In some parts of the brain, transitory fetal transmitters may appear during development and then disappear. Substance 1' and somatostatin are present in the fetal cerebellum at midgestation, but these neuropeptides are never found in the mature cerebellum. In the cerebral cortex of the frontal lobe, there is laminar distribution of cholinergic muscarinic receptors of the mature brain that is the inverse of the pattern in the fetus. The functions of these transitory transmitter systems are unknown. Some serve as trophic molecules rather than transmitters in early development. Even amino acid transmitters, such as GABA, may serve mainly a trophic function at an early stage in development. In situ hybridization and new immunocytochemical Technique cki nor. M:\IIY r.eiirorransir-trci^ in neurons of the developing brain of experimental animals and may be applied to human tissue under some circumstances (Dupuy and Houser 1997).

The ontogeny of neurotransmitter systems depends not only on the mechanisms of synthesis of chemical transmitters, but also on the development of highly specific receptors of these chemical signals and the ability of these receptors to modify excitability of neuronal membranes and to trigger action potentials after the recognition of specific molecules (Rho and Storey 2001; Simeone et al. 2003).

Disorders of Neurotransmitter Synthesis

Ischemic and hypoxic insults impair RNA transcription and result in arrest of the synthesis of secretory products. Many of the clinical neurological deficits observed in neonates who underwent birth asphyxia are probably the result of neurotransmitter depletion and functional synaptic block. Some amino acid neurotransmitters, by contrast, arc neurotoxic when released in large quantities. The excitatory amino acids glutamic acid and aspartic acid induce transsynaptic degeneration when released in this way, as might occur with hypoxic stresses, and may be a major source of irreversible brain damage in asphyxiated neonates,

Developmental disorders due to inborn errors of metabolism that block the chemical pathway of transmitter synthesis may hypothetically occur bur are probably incompatible with survival if they interfere with the synthesis of a major transmitter, such as ACh, monoamines, or an essential peptide. Defects in the metabolic pathways of particular amino acids are known, and many of these are associated with mental retardation, epilepsy, spastic diplegia, and other chronic neurological handicaps. Phenylketonuria (a disorder of phenylalanine metabolism) and maple syrup urine disease (a disorder of the metabolism of the branched-chain amino acids leucine, isoleucine, and valine) are we 11-documented examples. However, it is not cettain whether absence of the product of the deficient enzyme or toxicity of high levels of precursors upstream from the enzyme deficiency is the principal insult to the nervous system,

Myelination

Myelin insulates individual axons and provides greatly increased speed ot conduction. It is not essential in all nerves, and many autonomic fibers of the peripheral nervous system remain unmyelinated throughout life. Conduction velocity in central pathways is important in coordinating time-related impulses from different centers that converge on a distant target and in ensuring that action potentials arc not lost by synaptic block. The nervous system functions on the basis of temporal summation of impulses to relay messages across synapses.

Myelination of pathways in the CNS occurs in a predictable spatial and temporal sequence. Some tracts myelinate as early as 14 weeks' gestation and complete their myelination cycle in a few weeks. Examples include the spinal roots, medial longitudinal fasciculus, dorsal columns of the spinal cord, and most cranial nerves. Between 22 and 24 weeks' gestation, myelination progresses in the olivary and cerebellar connections, the ansa lenticularis of the globus pallidus, the sensory trigeminal nerve, the auditory pathways, and the acoustic nerve as well as the trapezoid body, lateral lemniscus, and brachium of rhe inferior collicuius. By contrast, the optic nerve and the geniculocalcarine tract (i.e., optic radiations) do not begin to acquire myelin until near term.

Some pathways are late in myelinating and have myelination cycles measured in years. The corpus callosum begins myelinating at 4 months postnatally and is not complete until midadolescence. Some ipsilateral association fibers connecting the frontal with the temporal and parietal lobes do not achieve full myelination until about 32 years ol age.

Myelination can now be accurately measured in specific central pathways of the living patient by using T2-weigh ted magnetic resonance imaging sequences, but the time at which myelination can be detected is somewhat later than with traditional myelin stains of brain tissue sections, such as Luxol fast blue. Newer neuropathologies! methods, using gallocyanin and immunoreactiviry to myelin basic protein, may detect myelination even earlier than the traditional strains. Electron microscopy remains the most sensitive method of demonstrating the earliest myelination in tissue sections.

Disorders of Myclination

Many metabolic diseases impede the rate of myelination. Hypothyroidism is a classic example. Menkes kinky hair disease, a disorder of copper absorption and metabolism, is another example. Many aminoacidurias, including phenylketonuria, are also associated with delayed myelination. Cerebrohepatorcnal (Zellweger) syndrome is well documented with neuropathological findings that include disorders of neuroblast migration and of myelination. Some leukodystrophies, such as Krabbc disease and perinatal sudanophilic leukodystrophy, are already expressed in fetal life with defective myelination.

Chronic hypoxia in premature infants is probably the most common cause of delayed myelination and contributes to the delay found in clinical neurological maturation, Myelination depends on fatty acids that must be supplied by the maternal and infant diet; nutritional deficiencies during gestation or in postnatal life may result in delayed myelination and are clinically expressed as developmental delay. Unlike disorders of neuronal migration, delay in myelination is not necessarily irreversible if **the** insult is removed; myelination may catch up to reach the appropriate level of maturity.

Cajal-Retzius Neurons of the Fetal Brain

Cajal-Retzius cells arc large, mature, stellate neurons in the marginal (outermost) zone of the fetal cerebral cortex. They are the first cells to appear at the surface of the embryonic cerebrum, preceding the first wave of radial migration from the subventricular zone and forming a plexus in the marginal (later the molecular) zone. They migrate to the surface either lrom the ganglionic cmiiiciKV or from the midbrain neuromere (Sarnat and Flores-Sarnat 2002). The first afferent processes to enter the marginal layer are dendrites of pyramidal cells of layer VI; synapses between Cajal-Retzius and pyramidal neurons of layer VI form the first intrinsic cortical circuits (Marin-Padilla 1998). They eventually have synaptic contacts with cortical neurons in all layers.

Cajal-Retzius cells contain acetylcholinesterase and oxidative enzymes and secrete GABA and probably also ACh as neurotransmitters. Their long axons extend parallel to the surface of the brain, plunging short branches into layer II (Figure 66.6). Cajal-Retzius neurons are sparse by term but persist even in the adult, though their function after maturity is uncertain. Cajal-Retzius neurons strongly express the transcription product of the I .IS I gene, which is defective in X-linkcd hydrocephalus associated with polymicrogyria and defective neuroblast migration, and they also **strongly** express Reelin (RLN), another gene essential for radial neuroblast migration {Clark et al. 1997; Sarnat and Flores-Sarnat 2002). No other specific diseases involving Cajal-Retzius neurons are yet described.

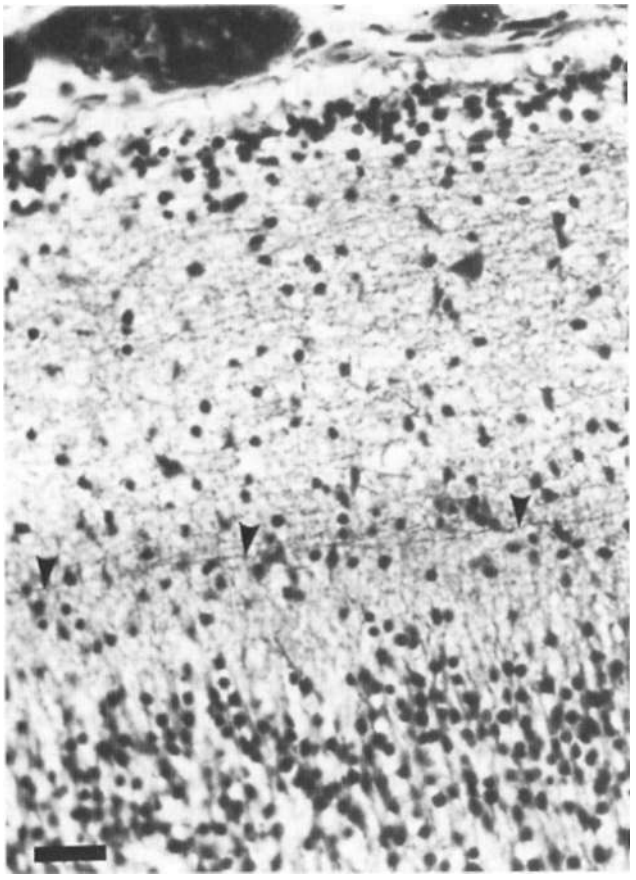

FIGURE 66.6 Silver stain of molecular layer of motor cortex in a 20-wcek fetus. The long fibers *[arrowheads]* extending parallel to the surface of the brain are axons of Cajal-Retzius neurons. They disappear with further cerebral maturation. (Bielschowsky stain. Bar= 10 urn.)

The fetal cerebral cortex has a subpial or external granular layer that histologically resembles that of the cerebellum but is of quite a different character. Cells of the cerebral cortex rise in columns from the germinal matrix of the hippocampus to form a thin layer on the surface of the archicortex at 12 weeks' gestation. They rapidly spread over the neocortex in a predictable sequence to cover the entire convexity by the sixteenth to eighteenth week, with the layer reaching the greatest thickness by 22 weeks' gestation. Subsequent involution of the external granular layer results from migration of these cells into the cerebral cortex, where they can no longer be distinguished. Only remnants of this once-prominent layer persist at term, confined to the inferior temporal and orbital surfaces. These surfaces are the last sites from which they finally disappear from the neocortex, although a few may persist over the paleocortex even into adult life. Their fate within the cerebral cortex is unknown, but it is speculated that they mature into glial cells because they lack ultra structural features of neurons, and they stain immunocytochemically for glial fibrillary acidic protein but not for vimentin.

The subpial granular layer of the cerebral hemispheres is partially or totally absent in most cases of holoproscn-ccphaly, even at the gestational period when it is expected to be most prominent; this absence may contribute to the marginal glioncural heterotopia found in the meningeal spaces and superficial cortical layers. The layer of the subpial granule cells may serve as a barrier to reverse the direction of migration in neuroblasts reaching the surface. In the Fukuyama type of congenital muscular dystrophy associated with cerebral cortical dysplasia, a heterotopic layer of stellate glial cells forms at the surface of the cerebral cortex, into which migrating neurons accumulate as they reach the surface rather than reversing direction and entering deeper layers of the cortex.

Suprasegmental Influences on Muscle Maturation

The motor unit is capable of developing normally in the absence of suprasegmental modification, as in infants with severe hypoplasias of the brain (see Figure 66.1). Malformations of the brainstem and cerebellar hypoplasia in particular are associated with a variety of aberrations in histochemical differentiation. These aberrations include (1) delayed maturation; (2) more than 80% predominance of type 1 or type 2 myofibers, with or without uniform hypoplasia of one or the other type {Figure 66.7); and (3) classic congenital muscle fiber-type disproportion. Malformations limited to the cerebral cortex do not cause fiber-type predominance. Muscle biopsy of children with cerebral palsy from birth asphyxia or other perinatal insults shows only nonspecific type 2 muscle fibct atrophy, with preservation of the normal ratios of fiber types, similar to the changes that follow disuse or immobili/ation of muscle.

It is speculated that many of the small bulbospinal "subcorticospinal" tracts (i.e., vestibulospinal, reticulo-spinal, olivospinal, tectospinal, and rubrospinal) are more important than is the larger corticospinal tract during the stage of histochemical differentiation of muscle between 20 and 28 weeks' gestation. These small descending pathways are generally well myelinated and functional at that time, whereas the corticospinal tract does not even begin its inyelination cycle or proliferation of axonal terminals until after muscle development is complete.

Etiologies of CNS Malformations

The causes of cerebral malformations generally fall into one of two categories. The first category is genetic and chromosomal disease in which there is defective program-ming of cerebral development. This genetic category also includes many inborn metabolic diseases, in which cerebral dysgenesis may be due to biochemical insults during devel-opment rather than, or in addition to, primary errors in molecular genetic codes for neural programming. The second category includes all induced malformations in which a teratogenic influence acts at a particular time in ontogenesis; the malformation depends on the timing of the insult in relation to brain development at that moment. The timing may be brief, as with a single exposure to a toxic drug, a dose of radiation, or a traumatic injury of the fetal lira in. It may be repeated two or more times or may

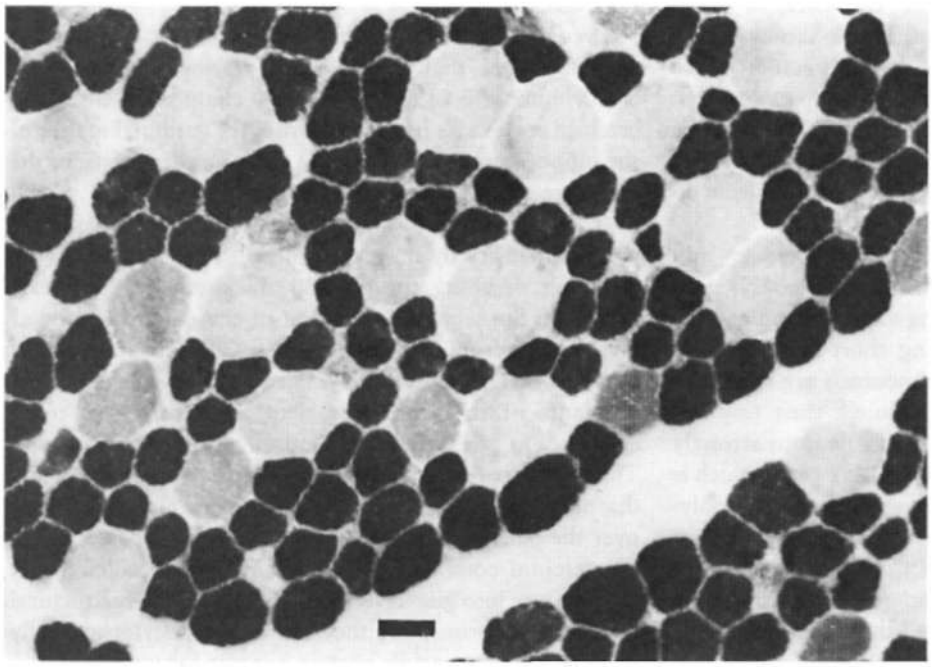

FIGURE *66.7* Histochemical type 2 myofiber numerical predominance and relative smallness of type 2 fibers. Type I fibers are stained lightly; type 2 fibers are dark. The small type 2 fibers do not show the angular contour characteristic of denervated muscle fibers in the adult or of those atrophic secondary to disuse. This muscle biopsy was taken from a 3-year-old boy with generalized hypotonia and cerebellar hypoplasia. (Myosin ATPase stain preincubated at pH 10.4. Bar=15 urn.)

be prolonged and involve the fetus at several stages of development. Examples of die latter include certain congenital infections, such as toxoplasmosis and cytomegalovirus disease, which may be active throughout most of gestation, even into the postnatal period. Genetic factors are the most frequent causes of malformations during the first half of gestation; environmental factors are more important in late gestation and may cause disturbances of late neuroblast migrations, particularly in premature infants. In some cases, no definite inductive factor is identified despite intensive clinical investigations during life and meticulous postmortem studies.

Ischemic Encephalopathy in the Fetus

Among the environmental factors that may interfere with the developmental process in utero or postnatally, cither briefly or more chronically, none is more important as a cause of morbidity than ischemic or hypoxic encephalopathy, Circulatory insufficiency or hypoxemia may interfere with migrations by causing infarction, which interrupts glial guide fibers.

Ischemia also affects the fetal cerebrum by producing watershed infarcts between zones of artetial supply because of poorer collateral circulation compared with the mature brain. Thin-walled vessels radiate perpendicular to the surface of the brain. The precursors of these radial vessels originate from leptomeningeal arteries and are evident at 15 weeks' gestation in the human embryo; horizontal branches appear in deep cortical layers at 20 weeks' gestation and increase to supply the superficial cortex by 27 weeks' gestation. The capillary network of the cortex proliferates mainly in the postnatal period, as radial arterioles dectease in number. Severe ischemia of the immature brain may result in cuffs of surviving nerve cells surrounding the radial arterioles, with vertical columns of necrotic tissue between these zones related to immaturity of the vascular bed, Alternating radial zones of viable cerebral tissue and infarctcd tissue thus occur in the cerebral cortex. Infarcts not only destroy maturing nerve cells that have already completed their migration hut also interfere with continuing and future migrations into those regions. The zones of infarction eventually become gliotic, and the geometric architecture of the cortex is disrupted.

The existence of fetal watershed zones of the cortical vascular bed is important in the pathogenesis of ulcgyria an atrophy of gyri that grossly resembles polymicrogyria. Focal areas of cortical atrophy and gliotic scarring after perinatal ischemic or hypoxic encephalopathy have been known for many years. The four-layered cortex of polymicrogyria is traditionally consideted quite a different lesion than ulegyria, resulting from a primary disturbance of neuroblast migration. Some authors question this interpretation, however, and provide evidence of postmigratory laminar necrosis of the cortex. Polymicrogyria is frequently distributed in vascular territories of fetal brain and often forms a rim surrounding a porencephalic cyst in the territoty of the middle cerebral artery. Multicystic encephalomalacia and hydranencephaly arc end-stage sequelae of massive cerebral infarction in the developing brain. Watershed zones also exist in the brainstem, between the territories supplied by paramedian penetrating, short circumferential, and long circumferential arteries, which all originate from the basilar artery. Transient hypoperfusion in the basilar artery in fetal life may produce watershed infarcts in the tegmentum of the pons and medullar oblongata. This is a probable pathogenesis of Mobius' syndrome and probably also of "failure of central respiratory drive" in neonates with hypoventilation not due to pulmonary or neuromuscular disorders. The cause is involvement of the tractus solitarius, which receives afferents from chemoreceptors, such as the carotid body, and provides efferent axons to motor neurons that innervate the diaphragm and intercostal muscles.

MOLECULAR GENETIC CLASSIFICATION Of MALFORMATIONS OF **THE** NERVOUS SYSTEM

Classification is a fundamental human thought process, allowing us to organize data in a systematic manner and understand relations. The classification of the malformations of the CNS traditionally is based on descriptive morphogenesis, but the new insight into the molecular genetic programming of neural development **in the last** decade (Simeonc 2002) requires that rhese new data be integrated with anatomical criteria to be etiological!)' relevant and clinically useful. For example, lissencephaly and holoprosencephaly are two important malformations, each formerly thought to be distinctive dysgeneses, but we now recognize many different genetic defects that cause each; hence they are end stages of ontogenetic errors with diverse etiologies (see following). A pure genetic classification to replace anatomical criteria, by contrast, would not be useful to clinicians, radiologists, ot pathologists and would be incomplete because many genetic mutations remain imkr.owr. A ;<impn imise (h;ii addresses the deficiencies of both pure analoinic.il and pure genetic schemes of classification is one based upon *patterns of genetic expression* in which the precise generic mutation may or may not be known but is stated while preserving anatomical criteria (Sarnat 2000; Sarnat and Flores-Sarnat 2001b), The upregulation or down regulation of a dorsalizing or ventraliziug gene thus may be recognized by its anatomical effect on neural tube development, even if the precise gene is not yet identified.

The traditional categories of CNS development that allow categoties of ontogenetic processes, such as ncuronogenesis, neuroblast migration, and synaptogenesis, and their disturbances in malformations, may -be preserved in the proposed new scheme of classification, bur are

Table 66.1: Summary of clinical features of major malformations of the brain

	Microcephaly	*Cephahicele*	*Dysmorphic faciei*	*Hydrocephalus*	*Seizures*	*Visual ttn[/airrrient*	*Mental retardation*	*Myoton*
} loloprosencepKaly, a lobar, semi lobar*"	+++	++	+++	+	++	+	++++	+++
I loloprosencephaly, lobar, middle intern cmispheric variant*	+	0	+	++	++	0	+++	....
Septo-optic-pit, dysplasia	+	0	+	+	++	+++	+++	++
Callosal agenesis, complete or partial	0	0	++	+	+++	+	+++	1
Callosal agenesis, Aicardi's syndrome	++	0	++	0	++++	+	++++	+++
Callosal agenesis lipoma	0	0	+	+	++++	0	+	++
Colpoeephaly, primary	—	0	++	+	++	++	++	++
Liss€ncephaly or pachygyria i Miller-Dieker)	+	0	++++	0	+++	+	++++	+++
Lissencephaly or pachygyria (Walker-Warburg)	+++	++	++++	++	+++	+++	++++	+++
Pachygyria (Fukuyama)	+++	0	++	0	+++	+	++++	++++
Cere b ro h ep a tore na 1 disease (Zellweger)	++	0	++++	+	[illegible]	++	++++	++++
Tuberous sclerosis (Bournevilie's disease)	+	0	++++	- +	++++	+	++++	++
Hem i mega lence p ha 1 y	+	0	++	+	++ +	+	+++	+
Chian malformations	+	+	0	++++	+	0	++++	0
Da.idy-Walker malformation	0	+	0	+++	+	0	+++	+++
Aqueductal srenosis/atresia	0	0	+	++++	+	0	++	+
Cerebellar hypoplasias	0	0	0	0	+	0	++	++++

0 = 0% of patients; + = 5-25%; ++ = 26-50%; +++ = 51-75%; ++++ = >75% of patients involved.

"•In holoprosencephaly, anatomical varieties do not correspond to genetic defect and correlate poorly with midfacial hypoplasia.

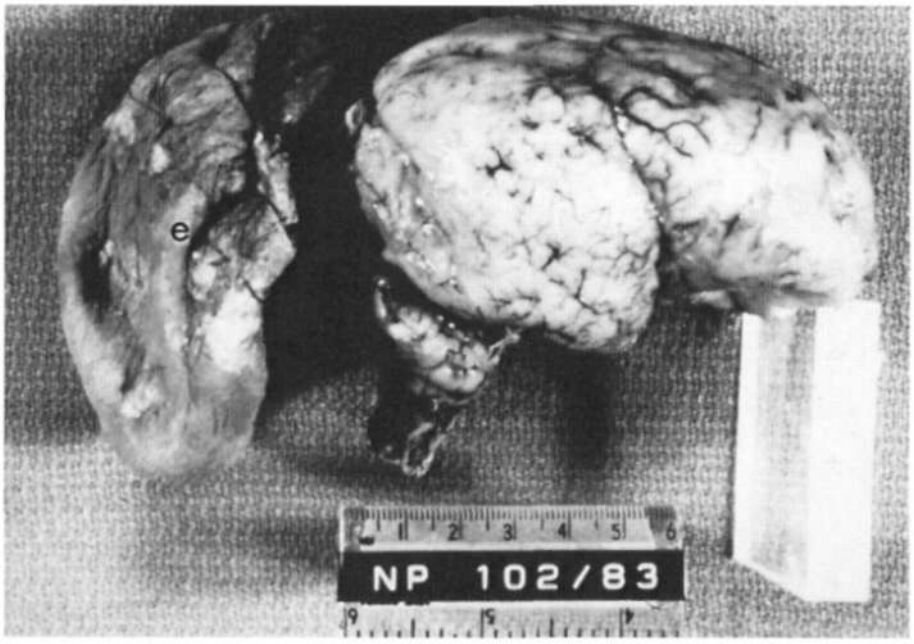

FIGURE 66.8 Lateral view of the brain of a term neonate with Meckel-Gruber syndrome. This dysplasia is a large occipital encephalocele (e) and lissencephaly. The brain is smooth and shows only a sylvian fissure and a few shallow abnormal sulci near the vertex. The encephalocele contains disorganized neural tissue, angiomatous malformations, focal hemorrhages, and zones of infarction.

surrounding countries. They nearly always include olfactory tissue.

The cerebral tissue in the encephalocele sac is usually extremely hamartomatous without recognized architecture. It may include heterotopia from an unexpected site, such as cerebellar tissue in a frontal encephalocele. Zones of infarction, hemorrhage, calcifications, and extensive proliferations of thin-walled vascular channels are common, approaching the disorganized tissue of the area cerebrovasculosa of atelencephaly. The remaining intracranial brain is often dysplastie as well. The ventricular system may be partially herniated into the encephalocele sac, at which point hydrocephalus ensues.

Kncephaloceles may be completely covered with skin, or lln:i, diMorlcd im rim;',„•.!I membranes may he expired. Leaking CSh' rapidly becomes infected. Some encephalocclcs, particularly those of the occipital midline, may become so large that they exceed the size of the infant's head. Nasopharyngeal encephaloccles arc rare but may be a source of meningitis from CSF leak through the nose. Malformations of the visceral organs often coexist with encephaloceles, and other congenital anomalies of the eyes and face, cleft palate, and Polydactyly also are common. The entire brain may be severely hypoplastic {see Figure 66.1).

Clinical neurological handicaps may be severe because even if the herniated tissue within the encephalocele is small and easily excised, concomitant intracranial malformations of the brain often result in epilepsy, mental retardation, motor impairment, and often cortical blindness in the case of occipital encephaloccles. The treatment of choice of small encephaloccles is surgical excision and closure of overlying cutaneous defects. Seizures and hydrocephalus are common but treatable complications.

Meningomyelocele (Spinal Dysrapbism, Rachiscbisis, Spina Bifida Cystica)

Spinal dysraphism involving the caudal end of the neural tube results from the posterior neuropore not closing at 26 days postnatal. The hypothesis that meningomyelocele .iiul .ik-lnvcplia'\ arc due to increased pressure and volume of fluid within the primordial ventricular system of the developing neural tube, which causes rupture at one end and prevents reclosure, has not been widely embraced. This is true because the choroid plexuses are not yet formed at the time of neural tube closure, and embryological evidence of hydrocephalus at that stage in experimental animals is lacking. Although many theories have been proposed, and several teratogenic drugs, hypervitaminosis A, and genetic models are able to produce neural tube defects and hydrocephalus in experimental animals, none explains the pathogenesis of faulty neurulation in humans.

The spina bifida syndromes are classified on one of two bases: the bony vertebral deformity or the neurological lesion and associated clinical deficit. The latter can cause a range of problems, including no deficit in the case of spina bifida occulta without herniation of tissue or mild spina bifida cystica with herniation of meninges alone. Deficits resulting from herniation of nerve roots and consequent motor, sensory, and autonomic neuropathy (meningomyelocele) also occur, as do extensive defects that also involve the parenchyma of the spinal cord (myelodysplasia). Most lesions are lumbosacral in location, but meningomyelocele also may occur in the thoracic or even the cervical region, usually as an extension rostrally of lumbosacral lesions. The level of involvement determines much of the clinical deficit. Type II Chiari malformation is consistently

present, and aqueductal stenosis coexists in 50% of cases. Hydrocephalus is a common complication, involving most patients with meningomyelocele and causing neurological deficit.

The tteatment of meningomyelocele is controversial and enters the arena of medical ethics. Small defects are easily closed surgically in the neonatal period, but large defects that cause complete paraplegia and flaccid neurogenic bladder, often accompanied by hydronephrosis, severe hydrocephalus, and other cerebral malformations, are associated with poor quality of life. A decision not to treat such infants or not to prolong survival poses a moral question to be addressed by the physicians in consultation with parents, hospital ethics committees, and other individuals whom the parents may identify.

The most important immediate complications of large meningomyeloceles are hydrocephalus and infection from leaking CSF. Long-term complications include chronic urinary tract infections, decubiti, hydrocephalus, paraplegia, and other neurological deficits. Mental retardation is common but may be mild.

Midline Malformations of the Forebrain (4-8 Weeks' Gestation)

A series of developmental malformations of the prosencephalon are embryologically related to the lamina tcrminalis not differentiating into telencephalie structures. The lamina terminalis is the rostral membrane of the primitive neural tube that forms with closure of the anterior neuropore. Disorders of the lamina terminalis are expressed mainly as midline defects, not only because of its location in the midline but also because lateral growth of the cerebral hemispheres is affected due to deficient or abnormal cellular migration centrifugally to form the cerebral cortex. The series of midline prosencephala malformations is related to the cmbryological time of the beginning of each and includes alobar, semilobar, and lobar hi^(prosencephaly, arhinencephaly, septo-optic dysplasia, colpocephaly, and agenesis ol [lie corpus , illnsum.

The lamina terminalis itself, after differentiating the forebrain structures, becomes the anterior wall of the third ventricle in the mature btain, extending between the optic chiasm ventrally and the rostrum of the corpus callosum dorsally. Some authors contend that a defective cephalic notochord induces midline forebrain defects. The complex embryological relationships of neuroectoderm and mesoderm in early ontogenesis arc incompletely understood.

Ho loprosencephaly

Holoprosencephaly is a malformation in which the two cerebral hemispheres appear to be fused in the midline, but is really a failure of cleavage in the midsagittal plane of the embryonic cerebral vesicle at 33 days" gestation and thus a paramedian hypoplasia of the forebrain. Holoprosencephaly (HPF.) has a frequency of 1:16,000 live births, but 1:250 spontaneously aborted fetuses in the first trimester, hence is among the most common of the major cerebral malformations.

HPF. was traditionally thought to be a single malformation, and four variants were defined: alobar, semilobar, lobar, supplemented more recently by the middle interhemisphcric varianta) (Hahn and Pinter 2002; Simon ct al, 2002). Recent molecular genetic data redefines HPF. as a common end-stage malformation with six known different genetic iiint.Hions Jrmnnsl r.iiiil in various cases iflnklcii 1998), and 12 other chromosomal defects also are known in which the specific genetic mutation is not yet identified (Table 66.2).

All six known defective genes together account for only about 20% of cases studied, so that many more genetic etiologies are undiscovered. Furthermore, each of the traditional anatomical variants ol holoprosencephaly is demonstrated in each of the six known genetic forms, signifying that these merely represent degrees of severity without etiological implication.

A defect in the ZIC-2 gene is associated with chromosome 13q deletions, and holoprosencephaly is frequent in infants with trisomy 13 (Brown et al. 1998}. One of the most studied of the genetic mutations is the strong vcntralizing gene, Sonic hedgehog (SI II I); the lack of expression of this gene in the ptechordal mesoderm ventral to the rostral end of the neural tube results in no neural induction (Roessler et al. 1996). Abnormal SHH expression also may be altered in metabolic diseases with impaired cholesterol synthesis and high serum levels of the cholesterol precursor molecule 7-dehydrocholcsterol, as in the Smith-Lemli-Opitz syndrome, associated with holoprosencephaly (Kelley et al. 1996).

After chromosomal defects, the most common association of holoprosencephaly is maternal diabetes mellitus;

Table 66.2: Known genetic mutations in holoprosencephaly

Chromosomal locus	*Defective gene*	*Vertical gradient effect*
2p21	SIX 3 Dors	o ventral
7q36	SHH	Ventrodorsal
13q32	ZIC-2	Dorsoventral
18q] 1.3	TGIE	Ventrodorsal
yq22.3	PTCH	Ventrodorsal
10qll.2	DKK	Ventrodorsal
3p26	?	
4	?	
5	?	
6	?	
14ql3	?	
14q21.1-q21.2	?	
20	?	
21q22.3	?	

sacral agenesis is another common malformation in infants •;il di ilx'tk mothers. hoth involve dowuregulation <•I SI li I. A defect at the same chromosome 7p36.2 locus associated with an autosomal dominant form of HPE also affects SHH at the posterior, rather than the anterior, end of the neural tube and results in sacral agenesis (Lynch et al. 1995). Disturbed insulin metabolism may affect SHH in programmi ng the neural tube.

Olfactory bulbs and tubercles differentiate a few days after forebrain cleavage, but olfactory agenesis almost always accompanies all but the mildest forms of holoprosencephaly; therefore the term *arb'mencephaly* has often been used interchangeably (and incorrectly). Callosal agenesis also is a uniform feature except in the mildest forms, and the cerebral mantle is grossly disorganized, with multiple heterotopia, poorly laminated cortical gray matter, and heterotopic neurons and glial cells in the overlying meninges. Extensions of germinal matrix into the lateral ventricles through gaps in the ependyma are common. Thus, although holoprosencephaly can be dated to about 33 days' gestation at onset, the pathological process extends throughout most of fetal life.

The anatomical variants of holoprosencephaly have been classified into four types, reflecting different degrees ol abnormal cerebral architecture. Alobar holoprosencephaly is characterized by a brain with a single midline telencephalic ventricle, rather than paired lateral ventricles, and continuity of the cerebral cortex across the midline frontally. The roof of the monoventriele balloons into a dorsal cyst. The corpus sttiatum and thalamus of the two sides are uncleaved, and the third ventricle may be obliterated, with rudiments of ependymal tosettes in its place. In semilobar holoprosencephaly, an incomplete intcrhemispheric fissure is formed posteriorly, and the occipital lobes, including the occipital horns of the ventricular system, may approach a normal configuration, despite noncleavage of the frontal lobes across the midline. Lobar holoprosencephaly is a less severe dysgenesis; the hemispheres are well formed but are in continuity through a band of cortex at the frontal pole or the orbital surface, and the indusium griscum and cingulate gyri overlying the corpus callosum are in continuity. The corpus callosum is incompletely formed but not totally absent, as in alobar and semilobar holoprosencephaly. The middle inrerhemispheric variant consists of hypoplasia of the middle part ol the corpus callosum and associated structures of the medial side of the hemispheres. In the more severe forms of holoprosencephaly, the optic nerves are hypoplastic or fused to enter a single median eye. Midline cerebellar defects, absent pyramidal tracts, and malformed brainstem structures accompany the more severe form-, ol [his malformation. Meningeal heterotopia or marginal gtioneuronal nodules commonly result from overmigration, perhaps associated with absence of the transitory external granular layer of rhe fetal brain in HPE.

Holoprosencephaly often is diagnosed at the time of delivery because 93% of patients exhibit midline facial dysplasias. Midfacial hypoplasia is present in most patients with I IPE, but others have a normal face. The facial dysmorphism ranges from mild hyporelorism and vomer bones to severe forms, including cebocephaly with a single nare, severe hypotelorism and absence of the premaxilla and vomer bones to produce a midline cleft lip and palate, or cyclopia with a midline proboscis dorsal to the single median eye, The severity of the facial dysmorphism does not correlate as well with the anatomical variant as originally thought, expressed in the often-cued statement, "The face predicts the brain," Midfacial hypoplasia does correlate, however, with the rostrocaudal extent of the defective genetic expression. If the gradient extends to the embryonic mesencephalic neuromerc and causes hypoplasia of the midbrain, neural crest formation and migration are affected (Sarnat and Flores-Sarnat 2001a). The mesencephalic neural crest is the most rostral origin of neural crest and this tissue forms not only peripheral neural structures such as the ciliary ganglion, but also most of the membranous bones of the face, globe of the eye (except the retina and choroid), and much of the facial connective tissue.

The various forms of holoprosencephaly are well demonstrated h\ must imaging tei ;i:ui[ik -s [figure d(i.[l]>), including prenatal ultrasound. The imaging features of each anatomical variant are distinctive (Halm and Pinter 2002) and correspond well ro the gross neuropathological findings (Golden 1998). The anterior cerebral artery is usually a single azygous vessel coursing just beneath the inner table of the skull, a pathognomonic finding. The sagittal sinuses are deformed or replaced by a network of large abnormal veins that resembles the early embryonic pattern of venous drainage.

The EEG in holoprosencephaly shows multifocal spikes that often evolve into hypsarrhythmia. In the neonatal period, the waking EEG is characterized by almost continuous high-voltage alpha-thcta monorhythmic activity, becoming discontinuous in sleep. VEPs also arc abnormal or altogether absent,

The clinical cotttse of holoprosencephaly is characterized by severe developmental delay and mental retardation and by a mixed pattern of seizures that often are refractory ro anticonvulsant medications. The presence or absence of seizures docs not correlate with the anatomical severity or variant of the defective forebrain and also correlates poorly with the genetic mutation (Hahn and Pinter 2002). A better correlation may be with the degree of mediolateral extension of genetic expression in disrupting the histological architecture of the cortex, or may relate to an abnormal sequence of maturation of axosomattc (inhibitory) and axodendritic (excitatory: synapses in relation to the maturation of the neuron innervated by these axonal terminations (Sarnat and Elores-Sarnat 2001a).

Some patients develop hydrocephalus and require shunting, and this condition is paradoxically more common in

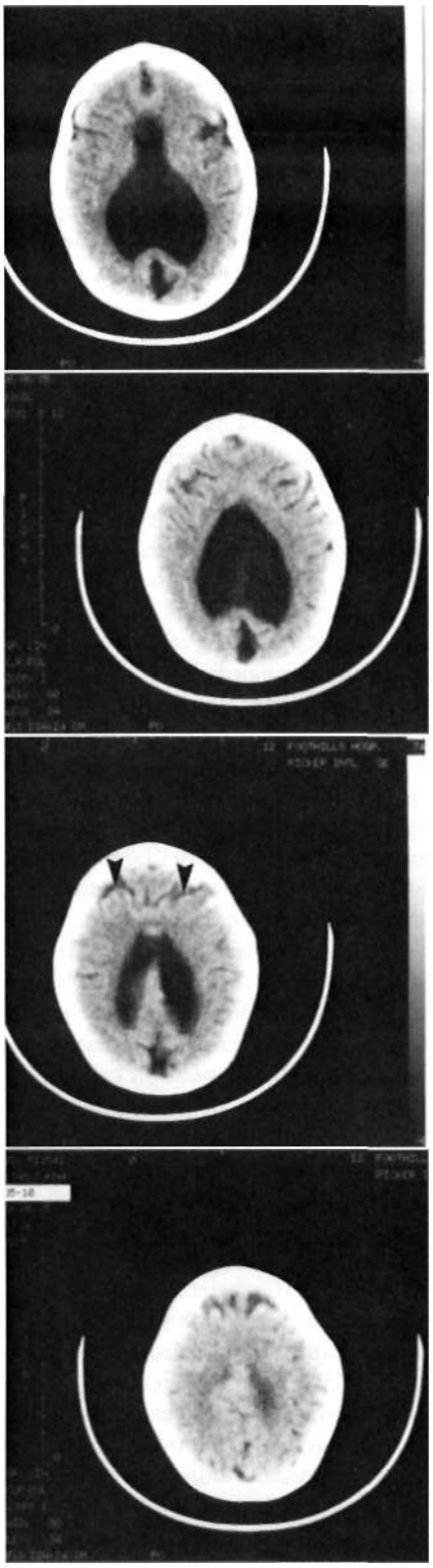

FIGURE 66.9 Unenlianced computed tomographic scan of a 6-year-old boy with semilobar holoprosencephaly. The lateral ventricles are fused, particularly frontally, but show some division into two occipital horns. A deep abnormal sulcus is seen across the fused frontal lobes *(arrowheads).* This is one of several radiological variants of holoprosencephaly.

the less severe anatomical forms of the malformation. In the severe, alobar form, a "dorsal cyst" occupies the entire posterior half to two thirds of the intracranial space and occasionally even protrudes through the anterior fontanelle as a unique encephaloeele that may be larger than the rest of the head. No other type of encephalocele is found at the anterior fontanelle. The dorsal cyst seems to originate from a dilated suprapineal recess of the third ventricle and later is a dorsal membrane that includes the roof of the forebrain, extending from the hippocampi (Sarnat and Flores-Sarnat 2001a).

Hndocrine dysfunction may be present, associated with hypothalamic or pituitary involvement, and vasopressin-sensitive diabetes insipidus occurs in about K6% of cases, other hypothalamic-pituitary dysfunction being much less frequent (Plawner et al. 20021. The basis of this specific involvement of the paraventricular and supraoptic hypothalamic nuclei may be hypoplasia in some cases in which the midline hypoplasia involves the diencephalon as well as the forebrain (most patients), hut also occurs in some children without hypothalamic noncleavage. One hypothesis is that the expression of the gene Orthopcdia (OTP) is secondarily suppressed by the primary genetic defect; OTP and downstream genes, such as SIM1 and BRN2, are essential for terminal differentiation of neuroendocrine cells of these hypothalamic nuclei (Sarnat and Flores-Sarnat 2001a).

The treatment of HPF is directed toward the complications, such as seizures, hydrocephalus, and endocrine disturbances. Educational potential and needs depend on the degree of mental retardation, speech, and visual impairment.

Isolated Arhinencepkaly and Kallmann's Syndrome

Absence of olfactory bulbs, tracts, and tubercles commonly accompanies more extensive malformations, such as holoprosencephaly and septo-optic dysplasia, but may occur with callosal agenesis or as an isolated cerebral anomaly. Kallmann's syndrome is an X-linkcd or autosomal dominant condition limited to males, in which anosmia secondary to arhinencephaly without other forebrain malformations is associated with lack of secretion of gonadotropic hormones. The genetic defect is KALI at the chromosome Xp22..'? locus, but the FMX2 gene also is implicated, though schizencephaly does not occur with Kallmann's syndrome (Taylor et al. 1999). Olfactory reflexes may he elicited in the neonate consistently after 32 weeks' gestation and provide a useful supplement to the neurological examination of newborns suspected of cerebral dysgenesis.

Septo-Optic-Pituitary Dysplasia

The association of a rudimentary or absent septum pellucidum with hypoplasia of the optic nerves and

chiasm was first recognized hy De Mosier in 1956. Underdevelopment of the corpus callosum and anterior commissure and detachment of the fornix from the ventral surface of the corpus callosum are additional features. Patients with this combination of anomalies overlap others with semilobar holoprosencephaly, and some children with septo-optic dysplasia also have arhinencephaly.

Disturbances of the hypothalamic-pituitary axis often occur in septo-optic dysplasia, ranging from isolated growth hormone deficiency to panhypopituitarism and deficient secretion of antidiuretic hormone. Hypothalamic hamartomas, gliosis, and the absence of some hypothalamic nuclei may he associated with a histologically normal pituitary. Absence of the neurohypophysis is demonstrated at autopsy in some cases.

Midline cerebellar defects and hydrocephalus occur inconsistently in septo-optic dysplasia. One cerebellar lesion, called *rhombencephalosynapsis* is aplasia of the vermis and midline fusion of the cerebellar hemispheres and of the dentate nuclei, probably the downrcgulation of a dorsalizing gene at the level of rhombomere 1 (Samat 2000).

Clinical manifestations relate mainly to the endocrine deficiencies and vision impairment. Ataxia may be compensated if the cerebellar vermis is mildly involved. Seizures are uncommon. Intellectual development usually is normal. Hypertelorism is nor a constant finding. Chromosomes are invariably normal. The gene HESX1 is defective in at least some cases (Dattani et al. 1998). Familial cases are not reported. There is, however, a high incidence of teenage pregnancy and drug abuse in early gestation in mothers of affected infants. Septo-optic-pituitary dysplasia has been described in an infant of a diabetic mother.

Rbmnbmneiic Deletions and Ectopic Genetic Expression

Rare patients with absence of certain parts of the brain have long been known, but only recently, with the understanding of the families of genes responsible for neural tube segmentation (e.g., HOX, WNT, PAX), have these medical curiosities been understood at the level of molecular embryology. Agenesis of the midbrain and upper pons (metencephalon) with cerebellar hypoplasia is attributed to the FN2 gene, which produces an almost identical malformation in the knockout mouse model (Sarnat ct al. 2002). EN1 and WNT1 genes also are essential for development of the mesencephalic and rhombomere 1, but the annual models of these genetic defects produce rotal agenesis of the cerebellum. Absence of the corpus striatum might be due to mutation of the EMX1 gene, which is essential in the programming of the basal telencephalon but not the cerebral cortex (Sarnat and Flores-Sarnat 2001a). The Chiari malformations, particularly type II, are traditionally but incompletely explained by mechanical theories of pathogenesis, but a molecular genetic hypothesis of ectopic expression provides a more complete and reasonable explanation (see following; Sarnat and Flores-Sarnat 2001). Whereas many of these genetic malformations are well demonstrated in experimental animal models, none are yet definitively confirmed in humans.

Agenesis of the Corpus Callosum

A commissural plate differentiates within the lamina terminalis at day 39 of embryonic life. The plate acts as a bridge for axonal passage and provides a preformed glial pathway to guide decussating growth cones of commissural axons. The inter hemispheric projection of the first axons is preceded by microcystis- degeneration m the commissural plate and physiological death of astrocytes. The earliest callosal axons appear at 74 days in the human embryo, the genu and the splenium are recognized at 84 days, and the adult morphology is achieved by 115 days.

The pathogenesis of callosal agenesis is related to two aspects of the commissural plate. If this plate is not available to guide axons across, the corpus callosum does not develop. However, failure of physiological degeneration of a portion of the plate results in a glial barrier to axonat passage, and primordial callosal fibers are deflected posteriorly to some other destination within their hemisphere of origin (bundle of Probst) or disappear.

Agenesis of rhe corpus callosum is a common malformation, having a 2..'!% prevalence m computed tomographic (CT) scans in North America and 7-9% prevalence in Japan. Most cases are isolated malformations, hut callosal agenesis is an additional feature of many other prosencephala dysplasias; it also occurs with aplasia of the cerebellar vermis and anomalous pyramidal tract. Simple callosal agenesis may involve the entire commissure or may be partial, usually affecting only the posterior fibers. Hypoplasia or partial agenesis of the commissure is much more common than total agenesis. In callosal agenesis, the anterior and hippocampal commissures are always well formed or large.

A rare genetic form of callosal agenesis is associated with defective neural crest migration causing aganghonic megacolon (Hirschsprung's disease) is due to a defective human gene, Smad-interacting protein-1 (SMAD1), at the chromosome 2q22-q23 locus (Cachcux ct al. 2001).

In the absence of a corpus callosum, the lateral ventricles are displaced laterally and the third ventricle rises between them (Figure 66.10). The ventricles also are often mildly dilated, but intraventricular pressure is normal. The anomaly may be demonstrated by most imaging techniques. The varying degrees of partial callosal agenesis produce several radiographic variants,

Clinical symptoms of callosal agenesis may be minimal and unrecognized in children of normal intelligence, although detailed neurological examination discloses deficits in the intcrhemispheric transfer of perceptual information for verbal expression. Mental retardation or learning disabilities arc found in some cases. Epilepsy is common, particularly in patients who are diagnosed early in life.

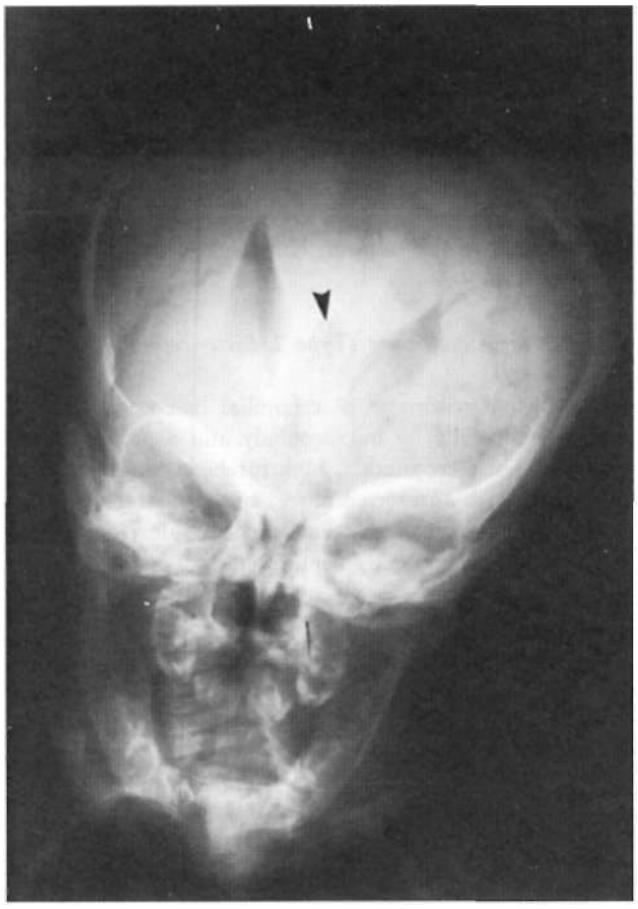

FIGURE 66.10 Pneumoencephalogram, from the pre-imaging period, of an lH-month-old boy with agenesis of the corpus callosum associated with an inter hemispheric arachnoidal cyst, a complication of some cases of callosal agenesis. The lateral ventricles are widely separated from the medial side of each hemisphere by the bundle of Probst; the third ventricle rises between them. The brainstem, cerebellum, and cerebral cortical convolutions appear normal. The patient has mental retardation and epilepsy.

Seizures may relate more to minor focal cortical dysplasias than to the callosal agenesis itself. Hypertelorism is present in many but not all cases and often is associated with exotropia and inability to converge.

The EEG characteristically shows interhemispheric asynchrony or poor organization, with or without multifocal spikes, but is not specific enough to establish the diagnosis. Asynchronous sleep spindles after 18 mouths of age arc a good clue.

Several hereditary forms of callosal agenesis are described besides its occurrence as an additional anomaly in some cases of tuberous sclerosis and various genetic syndromes. An autosomal recessive syndrome of callosal agenesis, mental deficiency, and peripheral neuropathy is known as Andermann's syndrome. Aicardt's syndrome consists of.agenesis of the corpus callosum, chorioretinal lacunae, vertebral anomalies, mental retardation, and myoclonic epilepsy. This disorder is found almost exclusively in girls and is thought to be X-linked dominant (chromosomal locus is Xp22) and generally lethal in the male fetus. The EEG shows a typical asymmetrical and asynchronous burst-suppression pattern. Neuropathologies! findings in Aicardi's syndrome include a variety of minor dysplasias in addition to agenesis of the corpus callosum and anterior commissure and nonlaminated polymicrogyric cortex with abnormally oriented neurons. I inllosal agenesis is a common compouail m main . limnm somal disorders, particularly trisomies 8, 11, and 13. Lipoma replacing part of the corpus callosum is associated with a high incidence of epilepsy.

Colpocephaly

Colpocephaly is a selective dilatation of the occipital horns, not due to increased intraventricular pressure but rather due to loss of white matter. Three conditions may cause colpocephaly: (1) it may appear as a primary malformation, histologically associated with poorly laminated striate cortex, subcortical heterotopia, and defective ependymn lining the occipital horns; (2) it is common in many cases of agenesis of the corpus callosum because of absence of the splenium and hypoplasia of white matter; and (3) it may be the acquired result of periventricular leukomalacia, especially in premature infants, because of loss of periventricular white matter in the posterior half of the cerebral hemispheres.

Clinical findings are usually those of mental retardation, spastic diplegia, epilepsy, and vision loss, but it does not always cause complete blindness. Most cases have been demonstrated by CT in the neonatal period or early infancy. Isotope cisternography shows normal CSF dynamics in most cases. Colpocephaly is associated with a number of syndromes and systemic disorders, including cerebro-hepato-renal (Zellweger) disease, hemimcgalcnccphaly, and several chromosomal disorders.

The EEG in colpocephaly ranges from normal in mild cases to near-hypsarrhythmia in infants who develop myoclonic epilepsy. Bilateral posterior slowing of low voltage with occipital spikes is common.

Colpocephaly also develops late in fetal life because of infarction and cystic degeneration of the deep white matter of the posterior third of the cerebral hemispheres, rather than as a developmental disorder of neuroblast migration. It should not be confused with hydrocephalus.

Disorders of Early Neuroblast Migration (8-20 Weeks' Gestation)

Lissencephaly (Agyria)

Lisscncephaly is a failure of development of convolutions in the cerebral cortex because of defective neuroblast

migration. The cortex remains smooth, as in the embryonic brain (see Figure 66.8). The migrations of the cerebellum and the brainstem also are usually involved, but the embryonic corpus gangliothalamicus pathway is not distutbed, so the thalamus and basal ganglia are well formed. Structural and metabolic abnormalities of the fetal ependyma may be important factors in disturbing the normal development of radial glial cells.

The cytoarchitecture of the neocortex in lissencephaly takes one of two forms. In the first, a four-layered sequence develops. The outermost layer is a widened molecular zone; layer 2 contains neurons corresponding to those of normal laminae III, V, and VI; layer 3 is cell-sparse; and layer 4 contains heterotopic neurons that have migrated incompletely. Decreased brain size leads to microcephaly, with widened ventricles representing a fetal stage rather than pressure hydrocephalus and an uncovered sylvian fossa representing a lack of opcrculation. The second form of cortical architectural abnormality- in lissencephaly is disorganized clusters of neurons with haphazard orientation, forming no definite layers or predictable pattern. Type 2 lissencephaly is associated with several closely related genetic syndromes: Walker-Warburg syndrome, Fukuyama muscular dystrophy, muscle-eye-brain disease of Santavuori, and Meckcl-Gruber syndrome. Encephalocele may be associated with some cases of lissencephaly (see Figure 66.8}.

Miller-Dieker Syndrome (Type 1 Lissencephaly)

Miller-Dieker syndrome is a familial lissencephaly characterized clinically by microcephaly and a peculiar facics that includes micrognathia, high forehead, thin upper lip, short nose with antevcrtcd nares, and low-set ears (Figure 66.11). Neurologically, the children are developmentally delayed in infancy and mentally retarded, lack normal

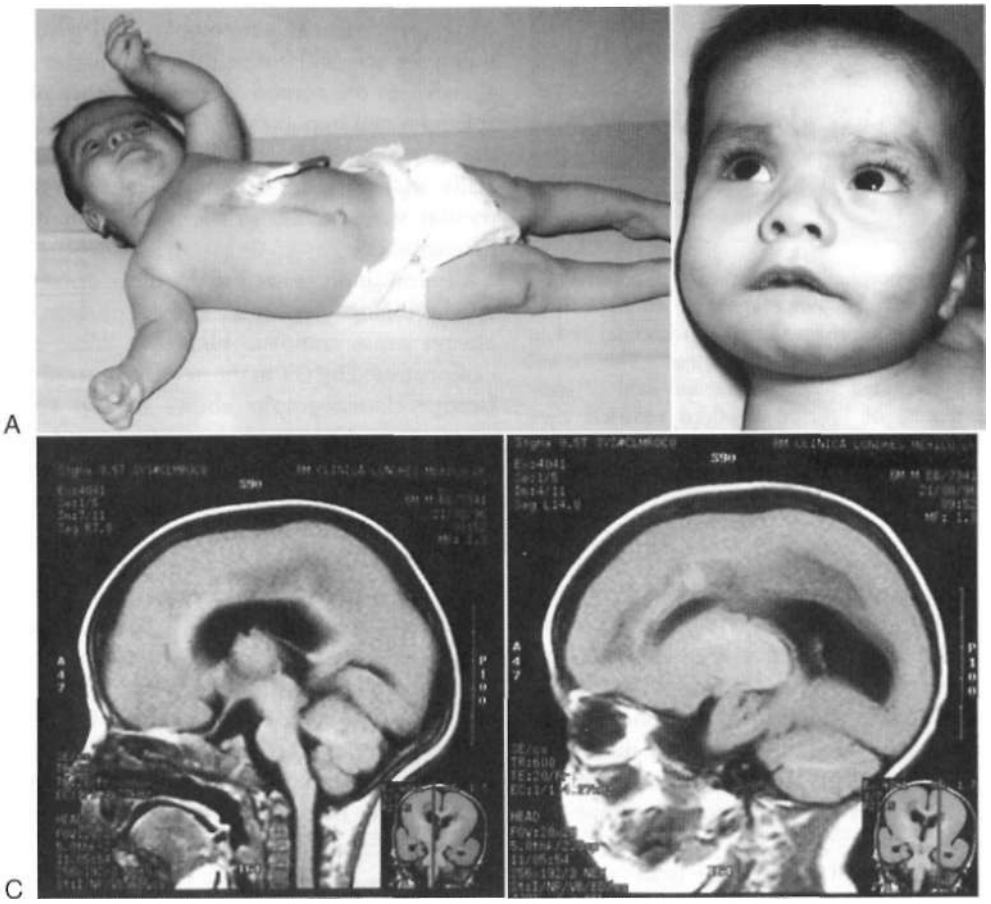

FIGURE 66.11 (A) This 7-month-old boy has Miller-Dieker syndrome. He has unusual postures of the extremities and opisthotonus, which are not seen in all patients with this genetic disorder. Note the gastrostomy that he required. (B] He has the typical facies of this genetic syndrome, with a high brow, upturned nares, and long phiitrum (upper lip). His gaze is dysconjugate, but there is no paresis of extraocular muscles. (C) Sagittal and (D) parasagittal views of Tl-weightcd magnetic resonance images, showing type I lissencephaly with only mild ventriculomegaly. The cerebellum and brainstem, including the basis pontis, are grossly well formed. The corpus callosum is very thin. Kxtra-fixial (i.e., subarachnoid) spaces are wide over rhe convexities of the cerebral hemispheres and in the cisterns surrounding the brainstem.

responsiveness to stimuli, initially exhibit muscular hypotonia that later evolves into spasticity and opisthotonos, and develop intractable seizures. Death before 1 year of age is common. The EEC often shows focal or multifocal spike-wave discharges that later become bisynchronous bursts of diffuse paroxysmal activity and extremely high-voltage diffuse rhythmic theta and beta activity.

At autopsy, the original cases showed lack of gyral development in the cerebral cortex, but later patients were found with the typical craniofacial features and clinical course but with gyral development, although the convolution-. were almoin:,il ;.rij pachygyria predominated. I he term *Miller-Dieker syndrome* was proposed to distinguish this syndrome from other cases of lissenccphaly without the clinical and dysmorphic facial features. A microdcletion at the chromosome 17pl3.3 locus is demonstrated by high-rcsolution studies in most patients with Miller-Dieker syndrome, and family members of the original patients also show the defect (Chong et al. 1997). The responsible gene is LIS1. Histological examination of the brain in Miller-Dieker syndrome confirms the presence of a severe disorder of neuroblast migration, as in other cases of lissencephaly.

Walker-Warburg and Related Syndromes (Type 2 Lissencephaly)

Type 2 lissencephaly/pachygyria includes several distinctive disorders of different genetic origin, but all of which involve the terminal organization and architecture of the cortical plate and most of which include a dystrophic myopathy. In Fukuyama muscular dystrophy, a congenital muscular dystrophy is associated with cerebral dysgenesis of this type, due to mutation in the gene Fukutin. Though common in Japan, where it is the second most common muscular dystrophy (after Duchenne type dystrophy), it is rare in othet ethnic populations. The muscle-eyc-brain disease of Santavuori is most common in Finland, but also exists in other northern European ethnic groups. Walker-Warburg is another congenital muscular dystrophy found in diverse ethnic groups. An autosomal recessive type 2 lissencephaly associated with cerebellar hypoplasia is due to defective expression of Reel in, and X-l inked congenital hydrocephalus (usually due to aqueductal atresia) is associated with pachygyria and mutation of the cell adhesion gene *L1CAM.*

Subcortical Laminar Heterotopia (Band Heterotopia, Double Cortex) and Bilateral Periventricular Nodular Heterotopia

Subcortical laminar heterotopia and bilateral periventricular nodular heterotopia both result from X-l inked recessive traits that occur almost exclusively in females. Both disorders present clinically as severe seizure disorders in childhood, although they arc often associated also with mental retardation and other neurological deficits. In subcortical laminar heterotopia, a band of gray matter heterotopia within the subcortical white matter lies parallel to the overlying cerebral cortex but separated from it by white matter. Histologically, it is not laminated, as is the normal cortex, and consists of disoriented neurons and glial cells and fibers with poorly organized architecture. The few male fetuses that have not spontaneously aborted have been born with lissencephaly in addition and even more severe neurological deficits. The defective gene and its transcription product in subcortical laminar heterotopia have been identified; the latter is called *dotiblecortin* ((ileeson et al. 1999). In bilateral periventricular nodular heterotopia, islands of neurons and glial cells occur in the subependymal regions around the lateral ventricles and are neuroepithelial cells that have matured in their site of origin without migrating (Eksioglu et al. 1996). The gene responsible is Filamin-1. Both conditions are best demonstrated by MRI, but also are detected by CT,

Scbizencephaly

Deep or shallow clefts in the region of the Sylvian fissure, with open or closed lips, is a configuration termed *scbizencephaly.* Schizencephaly is associated with defective expression of the gene EMX2 (Granata et al. 1997). It may be associated with a variable degree of lissencephaly/pachygyria and may be bilaterally symmetrical or asymmerrical, more severe on one side or even unilateral.

llemtm egalen cephaly

This is one of the most enigmatic cerebral malformations because it is a severe dysgenesis limited to one cerebral hemisphere or, less commonly, includes the ipsilatcral cerebellar hemisphere and brainstem ("total hemimegalencephaly"). Though traditionally regarded as another disorder of neuroblast migration, this feature is probably only secondary to involvement of radial glial cells and perhaps the neuroblasts themselves, and the primary process is a disturbance of cellular lineage and also involvement of genes of symmetry expressed as early as gastrulation (Flores-Sarnat 2002a; Elores-Sarnat et al. 2003). Individual neural cells exhibit both glial and neuronal proteins and have abnormal growth and morphology. Some cases of hem lm egalen cephaly are isolated malformations, but others are syndromic, particularly associated with epidermal nevus syndrome, Proteus syndrome and Klippel-Trenaunay-Wcber syndrome. Clinical features and neuropathological findings are virtually identical in isolated and syndromic forms. The principal clinical manifestation is severe partial epilepsy, often refractory to medical treatment and abolished only by hcmisphcrcctomy or other surgical resections. Other less constant features include variable mental retardation and contralateral motor deficit. Mild as well as severe forms

occur. Syndromic forms additionally include the features of the particular syndrome, such as lipoma formation in the ipsilatcral face in epidermal nevus syndrome.

Disturbances of Late Neuroblast Migration (after 20 Weeks' Gestation)

Although major neuronal migrations in the developing human brain occur in the first half of gestation, late migrations of immature nerve cells continue. A few neuronal precursors continue to migrate to the cerebral cortex after 20 weeks' gestation. Perinatal disorders of cerebral perfusion, small intraparenchymal hemorrhages in premature infants, intracranial infections, and hydrocephalus are examples of common perinatal complications that may interfere with the late neuronal migrations, either by destroying migrating neuroblasts or by disrupting their radial glial fiber guides. Reactive gliosis is detected as early as 20 weeks' gestation in the fetal brain, and proliferation of astrocytes is already evident 4 days after an insult. Neurons may be blocked from traversing a gliotie plaque.

Disorders of Cerebellar Development (32 Days' Gestation to 1 Year Postnatally)

The cerebellum has the longest period of cmbryological development of any major structure of the brain. Neuroblast differentiation in the cerebellar plates (rhombic lips of His) of the dorsolateral future medulla oblongata and lateral recesses of the future fourth ventricle are recognized at 32 days. Neuroblast migration from the external granular layer is nol complete until 1 year postnatally. As a result of this extended ontogenesis, the cerebellum is vulnerable to teratogenic insults longer than arc most parts of the nervous system. Malformations of the cerebellum may be focal, confined to the cerebellum, or associated with other brainstem or cerebral dysplasias. The cerebellar cortex is especially susceptible to toxic effects of many drugs, chemicals, viral infections, and ischemic-hypoxic insults.

Selective Vermal Aplasia

Selective hypoplasia or aplasia of the vermis, with intact lateral hemispheres, occurs in some genetic disorders, in association with other midline defects involving the forebrain, as in some cases of hoioprosencephaly and of callosal agenesis. A specific autosomal recessive disease, Joubert's syndrome, is characterized clinically by episodic hyperpnea, abnormal eye movements, ataxia, and mental retardation and has a variable but often progressively worsening course, with improvement in some cases. Anomalies of visceral organs and Polydactyly may be associated.

Selective Cerebellar Hemispheric Aplasia

Selective agenesis of the cerebellar hemispheres is much less common than aplasia of the vermis alone. Other components of the cerebellar system, such as the dentate and inferior olivary nuclei, may also be dysplastic. The lateral hemispheres and the inferior olivary and pontine nuclei more commonly arc selectively involved in certain degenerative diseases of genetic origin, such as olivopontocerebellar alropin and nllli-i spirincciYJvllar' degenerations.

Dandy-Walker Malformation

The Dandy-Walker malformation consists of a ballooning of the posterior half of the fourth ventricle, often but not always associated with nonopening of the foramen of Magcndie. In addition, the posterior cerebellar vermis is aplastic, and there may be heterotopia of the inferior olivary nuclei, pachygyria of the cerebral cortex, and other cerebral and sometimes visceral anomalies. Hydrocephalus from obstruction almost always develops, but if it is treated promptly, the prognosis may be good. Neurological handicaps, such as spastic diplegia and mental retardation, probably relate more to the associated malformations of the brain than to the hydrocephalus.

Chiari Malformations

The Chiari malformation is a displacement of the tonsils and posterior vermis of the cerebellum through the foramen magnum, compressing the spinomedullary junction. This simple form is termed *Chiari type I malformation.* Type II involves an additional downward displacement of a distorted lower medulla and dysplasia of medullary nuclei and is a constant feature of lumbosacral meningomyelocele. Chiari type III malformation is actually a cervical spina bifida with cerebellar encephalocele. Chiari originally identified a type IV in 1896, but this type is now recognized as cerebellar hypoplasia having no relation to the other types, and the term *Chiari malformation type IV* should now be used only in its historical context. Hydrocephalus is commonly associated with Chiari malformations.

The pathogenesis has been a matter of controversy for many years. Mechanical theories have dominated since the time of Chiari: (1) the traction theory, a result of a tethered spinal cord with traction as the vertebral column grows; (2) the pulsion theory of fetal hydrocephalus pushing the cerebellum and brainstem from above; and (3} the crowding theory in which a small posterior fossa provides insufficient room for the growth of neural structures and causes a "toothpaste tube effect." The torcula is indeed too low and the volume of the posterior fossa small, so that this latter explanation is probably a true contributory factor, but only in late gestation as a superimposed secondary

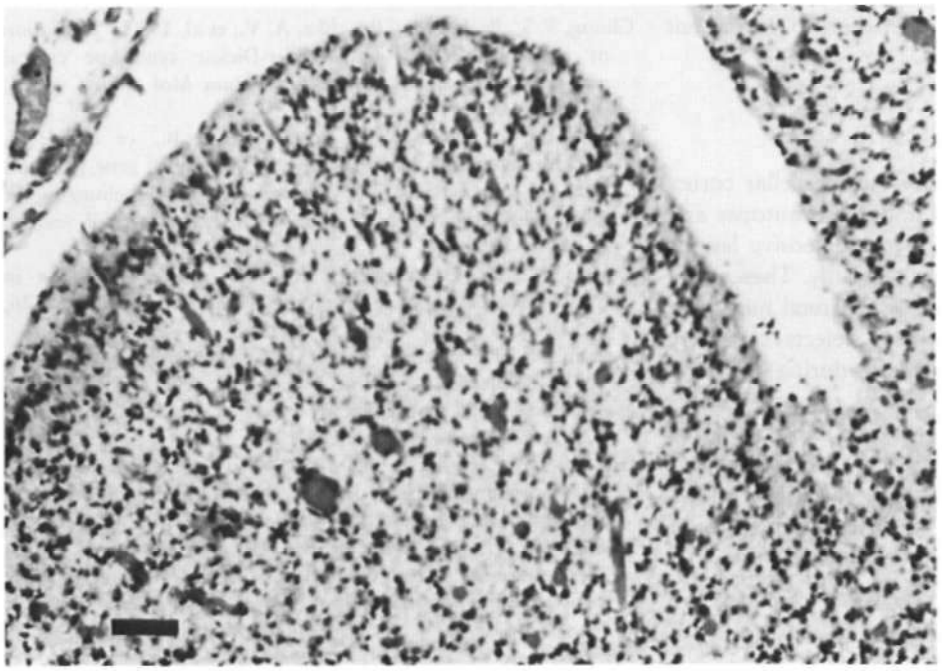

FIGURE 66.12 Cerebellar cortex of infant with cerebellar hypoplasia shows extensive gliosis and loss of ill neuronal elements. This histological appearance resembles that of cerebellar sclerosis secondary to acquired injury, but in the latter condition there arc usually a few neurons still surviving. Some cases of cerebellar hypoplasia show selective loss of granule cells and preservation of l'urkinje's cells. (Hcmatoxylin-eosin stain. liar = 100 urn.)

influence. A molecular generic hypothesis of ectopic expression of a segmentation gene in the rhombomcrcs explains not only the Chiari malformation, but also the brainstem anomalies, the myelodysplasia, and the defective basioccipital and suptaoccipital bone formation that tcsults in a too small posterior fossa (Sarnat 2001a, 2003).

Global Cerebellar Hypoplasia

Global cerebellar hypoplasia has diverse causes, which include chromosomal and genetically detennincd diseases, Tay-Sachs disease, Menkes' kinky hait disease, some cases of spinal muscular atrophy, and sporadic cases of unknown cause. Histologically, there may be a selective depiction of granule cells or a loss of Purkinje cells and other neuronal elements in addition to granule cells (Figure 66.12). In selective granule cell depletion, the axons and dendtites of Purkinje cells are deformed.

Clinically, the most constant features of cerebellar hypoplasia in infancy are developmental delay and generalized muscular hypotonia. Truncal titubation and ataxia become evident after several months, and nystagmus and intention tremor may appear in severe cases. Tendon stretch reflexes usually are diminished but may be

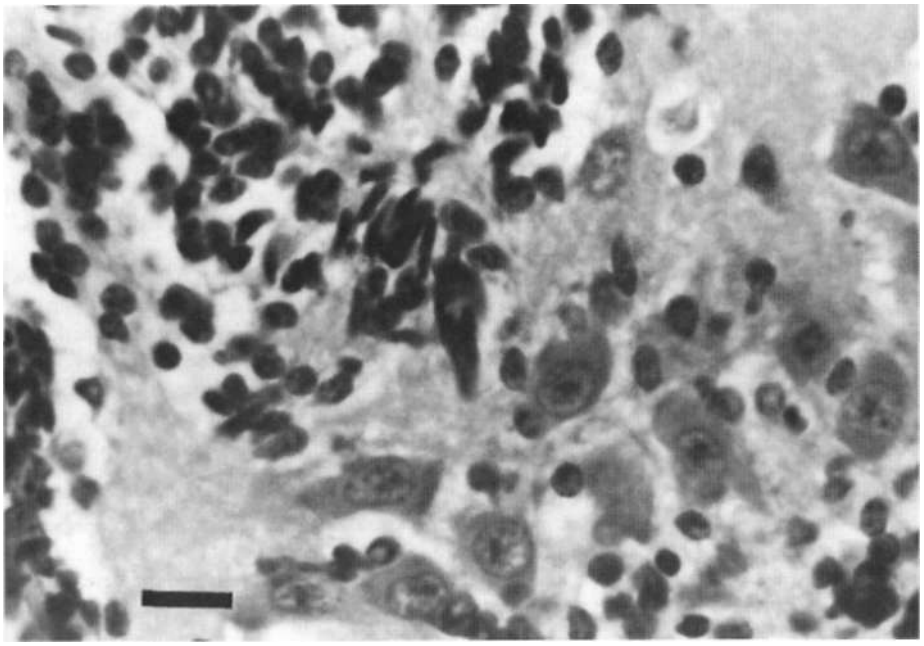

FIGURE 66.13 Focal dysplasia of cerebellar eorrcx. The normal laminar architecture is disrupted, and •IMI'IIK- .liul I'uikinjf cells show .L haphazard orientation and array. Some granule ceils arc spindle shaped, resembling the shape assumed during transit from the external granular layer in normal development. This dysplasia is due to faulty neuronal migration and probably occurred at midgestation. (Hematoxylin-eosin stain. Rar= 15 urn.)

hyperactive if corticospinal tract deficit also is present because of cerebral involvement.

Focal Cerebellar Dysplasias

Focal dysplasias and hamartomas of the cerebellar cortex (Figure 66.13} are often incidental findings at autopsy and are often clinically asymptomatic. More extensive lesions present abnormal cerebellar findings clinically. These small **focal** malformations are a disorder of neuronal migration that may be programmed as genetic defects or, more commonly, acquired from brief insults during the long period of cerebellar development. Focal ischemic insults and exposure to cytotoxic drugs or viruses are among the more common causes. The granule cells of the cerebellar cortex retain a regenerative capacity lost early in gestation by most other neurons, but the regenetative pattern of lamination in the cerebellar cortex may be imperfect.

Craniosynostosis

The development of the cranium and sutures is now recognized as closely related to neuromeric formation in the neural tube. More than 100 syndromes that include a component of craniosynostosis have been identified. Several have a genetic basis, including the syndromes of Apert, Crouzon, Pfeiffer, and Saethre-Chotzen; these are related to fibroblast growth factor receptor defects and, in some, specific causative genes such as TWIST are recognized (Flores-Sarnat 2002b). The genetic basis of the mure coniiiuin isolated craniostenoses "1 the coronal and sagittal sutures are not yet known. Once thought to be only a cosmetic defect, it is now known that neurological impairment may result in untreated cases. Advances in imaging have enhanced both prenatal and postnatal diagnosis, and parallel advances in craniofacial surgery makes treatment more effective from both a neurological and cosmetic perspective. True craniosynostosis must be distinguished from positional deformities of the head resulting from abnormal prenatal compression by the maternal pelvis and postnatal effects of head position, particularly in premature infants.

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Chapter 67
Developmental Disabilities

Ruth Nass

CEREBRAL PALSY

Diagnosis

Cerebral palsy (CP) is a static encephalopathy of prenatal or perinatal origin that affects motor function and tone. Spasticity, hypotonia, ataxia, and/or dyskinesias are the possible motor outcomes. A history of delayed motor milestones and the clinical features are the basis of diagnosis. CP occurs in approximately 2 per 1000 children. Low birth weight/pre term infants currently comprise more than 50% of children with CP. The prevalence is about 60 per 1000 among children weighing less than 1000 grams at birth. In a population-based study of births in the 1990s, the types of CP encountered were hemiplegia (33%), diplegic (44%), quadriplegic (6%), dyskinetic (12%), and ataxic (4%) syndtomes. Diplegic CP is the most common type in the preterm infant. Children with CP may or may not have intellectual problems, and seizures are a concurrent problem in about 40%. The likelihood of each is directly proportional to the severity of the motor impairment and the degree of brain damage.

Etiology

The National Perinatal Collaborative Project monitoring more than 50,000 pregnancies documented the following important risk factors among the 200 children with CP; maternal mental retardation (MR), birth weight less than 2000 grams, a malformation of any organ system, and breech presentation or delivery. Commonly used signs of perinatal hypoxic ischemic insults, such as an abnormal fetal heart rate, the presence of meconium, and low Apgar scores, did not predict CP and were relatively common in infants who were ultimately normal. Even when the Apgar score is low, the risk of CP appears to be minimal unless the infant continues to have neurological problems (e.g., lethargy, hypotonia, poor suck, seizures) in the newbotn nursery. Moreover, almost *95%* of infants with 5-minute Apgar scores of 3 do not have CP. In a population-based study of births in the early 1990s (Hagberg et al. 2001), the etiology of CP was established in 75% of preterm newborns and in about 85% of term infants. Most were due to perinatal problems. Among term babies with a known etiology of the CP, half were prenatal and half were perinatal. In addition to intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) in premature infants and perinatal hypoxic ischemic encephalopathy (HIE) in term newborns, documented causes of CP include brain malformations, small size for gestational age, congenital infections, maternal infection during pregnancy and labor, and genetic and metabolic disorders. Twin gestation is a risk factor, and a vanishing twin is a proven risk factor for CP in the survivor. Although most metabolic and genetic disorders ultimately cause progressive disability, some may be static for years and have a phenotype that suggests CP. Atypical features of CP and a history of other affected family members should indicate the need for further evaluation. Genetic disorders are the most common

cause of "ataxic CP syndromes." Dopamine-responsive dystonia, .111 r.ir-,;l\ diagnosed **arid :i\-;.ik'd** disorder, **mimics** CP. Other genetic or metabolic disorders that potentially mimic CP include metachromatic leukodystrophy, Krabbe's disease (spastic diplegia CP), Lesch-Nyhan syndrome, glutarie aciduria 1 (dyskinetic CP), ataxia telangiectasia, Leigh disease, and subacute sclerosing panencephalitis (ataxic CP).

Brain imaging is extremely useful in determining the etiology and prognosis of cerebral palsy. Brain malformations are relatively common in term infants with CP, whereas PVL is the most common cause of CP in preterm infants (Barkovich 2002). PVL is associated with even more severe disability in term-born children (Krageloh-Mann et al. 1999). HIE is associated with bilateral cerebral infarctions, whereas most unilateral infarctions arc prenatal, not perinatal, in origin (Volpe 2000). Ultrasound abnormalities are different in preterm newborns that develop disabling rather than nondisabling CP (Paneth 2001). Hypothyroidism of prematurity has twice the risk of echolucencies on ultrasound as compared to euthyroid newborns and has an increased risk of cerebral palsy (Leviton et al. 1999). Recent outcome studies of children and adolescents born prematurely suggest a correlation between the presence of magnetic resonance imaging (MRI) abnormalities and greater cognitive difficulties (Rushe et al. 2001). A reduction in cortical and cerebellar volumes among newborns with CP may result from enhanced apoptosis or excitotoxic damage to highly susceptible immature neurons (Bhurta and Anand 2001).

Treatment

The prevention of prematurity, respiratory management of preterm infants during the perinatal period, and the development of neuroprotective agents is the focus of CP prevention. Cesarean section and rapid initiation of supportive care may decrease the frequency of CP in the preterm newborn. Most IVH occurs within the first 6 hours after birth and possibly during labor and delivery. Infections during pregnancy as well as chorioamnionitis at delivery appear to be risk factors for CP. Elevated cytokines are the presumed agent toxic to the brain (Gilstrap and Ramin 2000).

Rehabilitative therapy influences outcome. The main goals of treatment are to improve motor function and to modify the environment to improve mobility. Orthopedic surgery is sometimes required. Dorsal rhizotomy has been used to decrease spasticity and improve gait or make children who are wheelchair-confined more comfortable. Botulinum toxin has had an important role in the treatment of spasticity. The factors that shorten life expectancy are immobility, profound retardation, and feeding difficulty (Hutton et al. 2000). Children with CP may otherwise live well into adulthood.

MENTAL RETARDATION

Mental retardation (MR) is not an absolute condition, but a construct that assists in educational planning and determining activities of daily living needs. The diagnosis therefore requires both low 1Q (less than 70) and difficulties in at least two areas of adaptive functioning: communication, self-care, home living, social skills, community use, self-direction, health and safety, functional academics, leisure, and work. The definition of mental retardation (American Association of Mental Retardation) links degree of severity to the degree of community support required to achieve optimal independence. In this context, mild retardation means intermittent support, moderate retardation indicates limited support, severe retardation indicates extensive support, and profound retardation indicates pervasive support. When IQ defines mental retardation, 100 is the mean and 15 is the standard deviation. Subdivided by severity, an 10 *55-70* is mild, an IQ of 40-55 is moderate, an IQ of 25—40 is severe, and below 25 is profound. A significant variability exists in the level of functioning among children with an IQ around 70; about half require special education and half attend regular school. Those in special schools are more likely to have a personal or family history of language delay. Such differences in functional level of children with the same IQ highlight the need to examine the specific cognitive profile of those with MR (Table 67.1).

In industrialized countries, the prevalence of MR is 1-3%. Mild MR represents the majority (75%). In general, individuals with severe retardation are more likely to have a definable biological cause, whereas those with mild retardation tend to come from socially disadvantaged backgrounds and often have a family history of borderline IQ or mild retardation (Opitz 2000; Stromme and Magnus 2000). Recent genetic studies demonstrate submicroscopic deletions in the subtclomcric chromosomal regions in about 3.5% of previously undiagnosed cases of MR (Leonard and Wen 2002).

Environmental factors play a role. For example, smoking during pregnancy is associated with more than a 50% increase in the prevalence of MR. The risk of recurrence of severe MR is 3-10% and of mild MR is 5-40%. The diagnosis of MR is more common in hoys than in girls (1.4:1). Male excess is present m those with autism, those with undiagnosed nonsyndromic mental retardation, and those with X-linked monogenic disorders. X-linkcd inheritance is responsible for more than 150 known mental retardation syndromes (Partington et al. 2000). Within the last 5 years specific X-linkcd gene abnormalities have been identified in 15 syndromes causing severe MR and in eight causing moderate MR (Leonard and Wen 2002), Fragile X syndrome has been considered the most frequent known X-linked disorder among the moderately handicapped and has been thought to occur with even greater frequency in mild MR. The prevalence of nonspecific (genetic etiology

Table 67.1: Psycho pathology and behavioral problems associated with genetically defined mental retardation syndromes

	1Q	*I WlglUZt!*	*Spatial skills*	*Executive*	*Social skills*
Down trisomy 21	Range 30-70, usually moderate, dementia in adulthood	Good vocabulary and conversation, weaker grammar, impaired verbal short-term m; trior y	Commensurate with 1Q	Perseverative impulsive	Relative strengt reported
Williams deletion 7q11	Mild-moderate	Expressive language and conversation a strength, loquacious	Weak visuospatial 6c global processing, face recognition spared, visuospatial short-term memory deficit	Inattentive, distractible, MiilHriMM.llit	Social perceptio emotional ex cognition im overly social
Prader-Willi deletion 15q11-q13	Mean 70, range profound MR to average	Oromotor dysfunction	Visuospatial strength, jigsaw puzzles a special interest	Obsessive	Internalizing an problems ca social functi
Fragile X males	Moderate to severe, decline after puberty, fully methylated patients more decline	Poor articulation, cluttering, verbal dyspraxia, weak word finding, pragmatics and conversational skills	Sporadic weakness of visuomotor skills	Weak attention planning, shifting sets	Strength in ada until puberty recognition autistic featu
Fragile X females	Normal to miId to moderate	Generally intact	Nonverbal memory problems	Relatively weak, ADHD	Very shy, anxi
VCF 22q11 haploin-suffkiency (reduced gene dosage)	Borderline to mild	Speak in single words despite their ability to converse, but verbal skills stronger than nonverbal	Impairments in visuoperceptual ability, NVLD	Weak problem solving, planning, abstraction, ADHD	Poor social int prevalence o bipolar diso

VCFS = velocardiofacial syndrome; NVI.D = nonverbal learning disability; PWS = Prader-Willi syndrome; ADHD = attention de
Modified from Nass and Ross, in press; Burack et al. 1998; Dykens 2000; Tager-Flusberg 1999; Howlin and Udwin 2002.

as yet unknown) X-linked MR (XLMR) (2.5/10,000), however, is three times greater. But diagnosis may be difficult because most males with XLMR have no specifiable phcnorypical, neurological, or biochemical features as yet identified. Advances in genetic technology will clearly change this.

Several iH'in-f)l(i;n'ail and neuropsyehianic problems *M'v* associated with MR. Epidemiological studies (Airaksinen et al. 2000) suggest that one fifth of children with MR are epileptic by 10 years of age. The probability of developing epilepsy is fivefold higher in severely MR children *(35%)* than in children with mild MR (7%). Cerebral palsy is a concurrent disorder in 6-8% of the mildly retarded and in *MV'A,* of the severely retarded. Blindness or deafness occurs in 2% of the mildly retarded and 11% of the severely retarded. An increased prevalence of psychopathology and maladaptive behavior occurs in children with MR, and almost 40% have a psychiatric disorder (Stromme and Disedi 2000). The most common diagnoses are hyperactivity and autistic spectrum disorders. Overall, autistic features are reported in 9-15% of the mildly retarded and 12-20% of the severely retarded. Table 67.1 details specific psychopathology and behavioral problems in several genetically defined MR syndromes.

Treatment

Treatment focuses on finding the appropriate educational setting and vocational training for the mildly and moderately retarded and determining home or institutional placement for the severely and profoundly retarded.

AUTISTIC SPECTRUM DISORDERS

Diagnosis

The triad of impaired sociability, impaired verbal and nonverbal communication skills, and restricted activities and interests, all of early onset, are the diagnostic features of autistic spectrum disorders (ASD) (Rapin 2002) (Figure 67.1). The presence or absence of social disabilities distinguishes *developmental language disorders* (DLD) from ASD. IQ, language, and social normalcy distinguish *nonautistic mental retardation* (NAMR) from DLD and ASD (figure 67.2). The range of disabilities seen among children in the spectrum is considerable. Asperger's disorder (Table 67,2) probably represents the high-functioning end of the ASD spectrum. Paralinguistic[1] rather than linguistic problems are characteristic. The iivideiice ol ASD varices from 0.4 to 70.0 per 10,000 children, depending on how the

'Paralinguistic skills include pragmatics—communicarive intent rather than content; prosody - tone of voice to express emotions, for example; understanding humor, sarcasm, and irony.

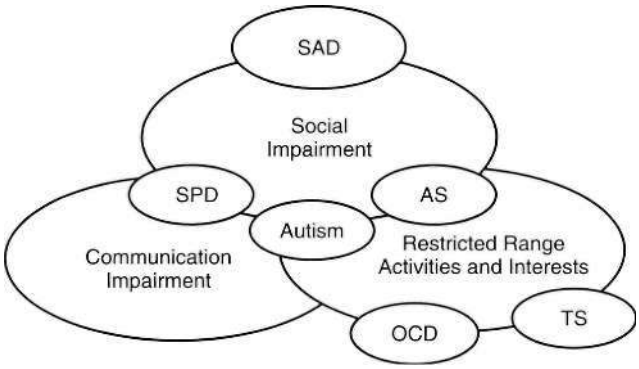

FIGURE 67.1 This Venn diagram shows the overlap of all three symptom areas in autism, of two areas in AS, and of disorders involving a single symptom often reported in ASD families. TS = Tourette syndrome; OCD = obsessive-compulsive disorder; AS = Asperger's disorder; SAD = social anxiety disorder; SPD = semantic pragmatic disorder. (Modified from N'ass and Leventhal, in press.)

term is used (Gillberg and Coleman 2000). A hereditary basis is probable in many cases because of (1) a high concordance in monozygotic twins (90%), (2) a 4.5% increased risk for dizygotic twins and siblings, (3) a broader autistic phenotype in families (Piven and Palmer 1999), and (4) an association with several genetic disorders (Spencer 2001). The dramatically diminished risk in relatives who share 50% versus 100% of their DNA is most consistent with an oligogenic inheritance pattern, where more than two and as many as 100 genetic variants may contribute to susceptibility to developing autism. Each gene may make a different contribution to the disorder, with gene A more important for the development of repetitive stereotyped behaviors and gene B mote important for language acquisition (Alarcon et al. 2002; Veenstra-Vanderweele and Cook 2003). Chromosomal abnormalities have been reported on chromosomes 2q37, 7q, and 22ql3,13q among others. Both fragile X and the Rett syndrome mutation can

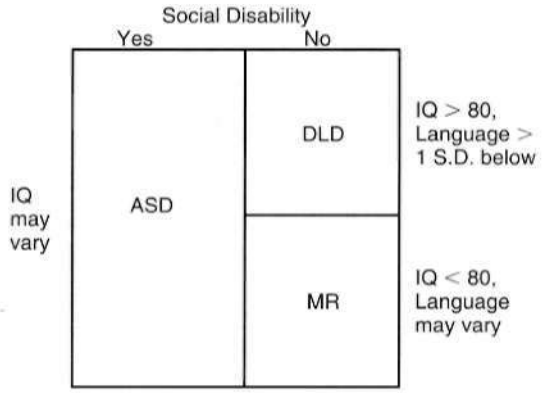

FIGURE 67.2 'The presence or absence of social disabilities distinguishes developmental language disorders (DLD) from ASD. IQ, language, and social normalcy distinguish nonautistic mental retardation (\'AMR) from DLD and ASD.

Tabic 67.2: Asperger's disorder diagnostic criteria

A. Qualitative impairment in social interaction, manifested by at least two of the following:
   1. Impairment in use of nonverbal behaviors to regulate social interaction
   2. Failure to develop peer relationships
   3. Lack of spontaneous seeking to share enjoyments and interests
   4. Lack of social or emotional reciprocity
B. Restricted repetitive and stereotyped behavior, interests, and activities, manifested by at least one of the following:
   1. Encompassing preoccupation
   2. Inflexible adherence to nonfunctional routines
   3. Stereotyped and repetitive motor mannerisms
   4. Persistent preoccupation with parts of objects
C. Disturbance causes significant impairment in functioning
D. No clinically significant language delay
E. No clinically significant cognitive deficit
F. Criteria not met for diagnosis of another pervasive developmental disorder or schizophrenia

Source: Modified from *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Washington, D.C.: American Psychiatric Association, 1994.

present with an autistic spectrum phenotype. However, the most common specific cause of autism appears to be maternally inherited duplications of chromosome 15qll-13, accounting for 1% to 3% of cases {Vcenstra-Vanderweele and Cook 2003).

The symptoms of ASD, like other developmental disorders, often change with age. Approximately one third of autistic children regress between the ages of 1 and 3 years. Conversely, some toddlers and preschoolers, with typical symptoms of autism, may not appear autistic by school age, but may seem a bit odd, have peculiarities of language prosody and pragmatics, and show tenuous social skills. Nonverbal learning disabilities (NVLD) or attention-deficit hyperactivity disorder (ADHD) is often the school-age diagnosis. Most retain the typical features of autism, particularly those who are mentally retarded. The natural history of Asperger's disorder is less well documented, and the diagnosis is often delayed until late childhood, adolescence, or even adult life because by definition early language development is normal. Nonverbal learning disabilities (LD) or ADI ID may be the apparent presenting complaint (Klin et a I. 2000). The characteristic overfocus in a particular, or sometimes peculiar, interest area may escalate with time, but may be the key to a special form of adult success.

Outcome studies suggest that among children with ASD, ovetall improvement occurs in approximately 40% during adolescence and deterioration occurs in as many as one third (Cillberg and Coleman 2000). The onset of seizures or mood disorders (depression and bipolar disorder) usually underlies the deterioration. Some adolescents may even become catatonic. A minority of children, usually the higher functioning group, improves significantly during adolescence, reaching adulthood with no significant problems. Approximately two thirds of adults with autism show poor social adjustment (limited independence in social relations), and one half require institutional care. Autistic individuals who are not retarded tend to improve more than those who are. Higher functioning people with autism and Asperger's disorder have the best outcome. Although fair-to-good outcomes are reported in 15-30%, only 5-15% become competitively employed, lead independent lives, marry, and raise families. Psychiatric problems are common even in this group. Some adults with Asperger disorder are probably undiagnosed in childhood and adolescence; therefore the percentage of adults with ASD that ultimately functions in the mainstream may be higher than reported. Some adults with ASD are highly productive and original in their work. Bartok, the composer, and Wittgenstein, the philosopher, are believed to have had ASD (Cillberg 2002).

Specific Clinical Features

Intelligence and Cognition

The presence of language and social deficits defines ASD, nor the IQ level (see Figure 67.2). Although 70-85% of children with ASD are mentally retarded, some have average or even superior intellectual ability. IQ is a key-predictor of long-term outcome in autism, especially when the IQ is less than 50 (Stevens et al. 2000). Those with low IQ generally fare poorly. If Asperger disorder is included as an autism spectrum disorder, the rate of mental retardation in ASD drops considerably. Some consider the core cognitive deficit of ASD to be an inability to grasp other people's thoughts or a failure to develop a theory of mind (Baron Cohen et al. 2001). "Mindblindness" manifests differently at different stages of development (Table 67.3).

Language

Communication difficulties are a cardinal feature of ASD. The extent of the language deficit generally parallels IQ. In lower functioning ASD children, language if present is echolalic; repetitive and stereotyped phrases are common. Some children fail to process language and despite normal hearing can appear deaf (verbal auditory *agnosia).* Higher functioning children sometimes talk too much; they talk to talk (semantic and pragmatic deficits). These children are often extremely literal and concrete. Prosody is frequently impaired as evidenced by mechanical, excessively rapid, monotonic, high pitched, or poorly modulated speech. Language skills at age 5 to 6 years are predictive of long-term prognosis. Children with conversational language will do significantly better than children who have little or no language.

Abnormalities of play are part of the autistic child's communication disorder. The range of play includes

Tabic 67.3: Theory of mind (TOM): Stages of development

14-18 mo	joint attention: adult and child look at a toy together
	Pi nlodi . l.: rule, : |H)i:l !-;;: i.'ild e.ll -, .id::':'-- ;IIIfIII ii ill ((> desired (>h|ea
18-24 mo	Symbolic play
2-3 yr	Beginnings of primitive TOM: seeing leads to knowing; understanding desire, pretending, intention to joke
i-4 ; i-	First-order TOM: knowing what another person is thinking, understand that another person may not know what you know (false beliefs]; seeing leads to knowing (e.g. looking up and away means thinking), knows someone's choice by eye gaze direction
4-5 yr	Advanced First-Order TOM: counter factual reasoning enhanced by pretense (e.g. "pretend" preparation for countcrfactual syllogism task)
6-7 yr	Second-Order TOM: knowing what another person thinks another person is thinking; belief about beliefs; false belief measures: jokes, lies
9-11 yr	Y\ i ii id Older I ike !vl:ei measure: faux pas, son in me s.n s something they should not have said, not knowing that they should not have said it
Around I 0 yr	Third-Order I OM: belief about belief about belief, knowing what another person thinks another person thinks he knows (e.g., lying about lying)
Adult	Third-Order TOM: belief about belief about belief: strange stories, awkward moments

Modified from Baron Cohen ct ai. 2001; Nass and Leventhat, in press,

repetitive Stereotypic and indiscriminate sensory use of objects (mouthing, rubbing, etc.); functional object use and imitation, mechanical play with puzzles and the like; interactive play with adults like running, catching, and tickling games; and activities involving their circumscribed areas of interest (e.g., board games, computers, electronic games, or high-level word and number tasks). These activities, when engaged, may provide pleasure. Pretend play is often rudimentary even in higher functioning children, involving, for example, simple role taking (Whitehouse et al. 1996).

Social Skills

The hallmark of ASD is social dysfunction. The *aloof* child most resembles the popular notion of autism. Such children do not follow their parents around, run to greet them, or seek their comfort. Such children tend to have low intelligence, have poor verbal and nonverbal communication skills, and show little symbolic play. *Passive* children are generally somewhat higher functioning overall. They do not make social approaches, but will accept them when made by others. They engage in some pretend play and join in games, but take a passive role (e.g., the baby in the game of mothers and fathers). Children who are *interactive but odd* make spontaneous social approaches to others, but do it in a peculiar way. They tend to talk at other people, and their persistence may become annoying. Pragmatic language skills are impaired. Conversation is started with a question. Many persons on the autistic spectrum are relatively unaware of their social ineptitude except to the extent that others tease them, but some are not (Whitehouse et al. 1996). Several books written by high functioning people with ASI) highlight this lack of awareness (Willey 1999).

Restricted Range of Behaviors, Interests, and Activities

A restricted range of behaviors, interests, and activities is the third cardinal feature of autism. In lower functioning children, these consist of repetitive, stereotyped behaviors like twirling, rocking, flapping, licking, and opening and closing doors. Overlap and comorbidity with tic disorders and obsessive-compulsive disorders are seen in higher functioning children (Gillberg and Coleman 2000; Nass and Leventhal, in press) (see Figure 67.1, Venn diagram). Many of these children have great difficulties with transitions. Not only do they not focus, but they also become overfocused. Some individuals with exceptional artistic, musical, or mathematical talents may meet other criteria for a diagnosis of an ASH or Asperger's disorder. Some of these children grow up to be single-minded, perhaps peculiar, nunsocial chess or mathematics geniuses.

Evaluation and Etiology

The standard neurological examination is generally normal. The skin must be careful examined for evidence of tuberous sclerosis, the most common diagnosable disease associated with autism (Gillberg and Coleman 2000). Formal audiological assessment is required to exclude a hearing impairment. An electroencephalogram (EEG), including a sleep record or overnight video-EEG monitoring, is appropriate to exclude subclinical seizures, especially when language comprehension is impaired or developmental regression has occurred. Mild-to-severe epilepsy, partial and generalized, occurs in up to one third of patients with autism *h* early adulthood, Ir.l.ino uniantile spasinsi .ind puberty are particularly vulnerable periods. The onset of

seizures may play a role in adolescent deterioration. Those who arc retarded are at higher risk, hut epilepsy occurs in high-functioning children as well. Epileptiform patterns on EEG and early epilepsy occur more frequently in children who show early regression. Studies using magnetoencephalography suggest that diffuse epileptiform activity is common in children with autistic regression (Rumsey and Ernst 2000).

Three major types of neuropathology have been reported in autism (Rumsey and Ernst 2000): (1) decreased development of forebrain limbic system structures {e.g., cingulate, hippocampus, amygdala), substrates for memory and emotion; (2) a decreased number of Purkinje cells in the cerebellum; and (3) age-related differences in cell size and number in cerebellar and brain stem nuclei, suggestive of a dynamic developmental process. Structural abnormalities reported in autism based on imaging studies include increased brain volume (especially males), increased ventricular volume, increased white matter volume, thin splcnium of corpus callosum, hypoplastic cerebellum (vermian lobules VI and VII), hyperplastic cerebellum (10%), and hypoplastic parietal lobes (Sparks et al. 2002). Recent imaging findings suggest that there may be differential effects driving white matter to be larger and cerebral cortex and hippocampus-amygdala to be relatively smaller (Herbert et al. 2003). Brain imaging is rarely productive in clinical practice. However, a recent meta-analysis of imaging in children with developmental delay, including autism, does demonstrate that MRI may show abnormalities in one third, especially when the neurological examination is abnormal (Shevell et al. 2003}. Most metabolic imaging studies show hypometabolism in the frontal lobes and to a lesser extent in the temporal lobes and cerebellum. Activation studies suggest an altered localization of language and cognition (theory of mind). Positron emission tomography (PET) studies suggest abnormalities of both serotonergic and dopaminergic function. Overall, the extent of metabolic workup depends on the clinical suspicions and the relevance to family counseling. Table 67.4 lists some specific causes of ASD/PDD (pervasive developmental disorder).

Table 67.4: Double syndromes: Medical disorders associated with ASD

Angel man
Anorexia nervosa
CHARGE association
Cohen syndrome
De Lange syndrome
Down syndrome
Ehlers-Danlos
Fragile X
Goldcnhar
Hypomelanosis
hull-: : :
Kleine Levin
Ltijan-Fryns
Mob ins
Mucopolysaccharidosis
Neurofibromatosis
Norman
Peroxisomal disorders
PKU
Rett complex
Smith Magenis
Steincrr myotonic dystrophy-
Tuberous sclerosis
Unilateral cerebellar hypoplasia
Velocardiofacial syndrome
Williams
Fndocrine disorders: hypothyroidism, hypopituitarism
Infections: rubella, herpes, CMV
Toxins: FAS, Fetal cocaine, thalidomide

Modified from Gillberg and Coleman 2000.

Treatment

Preschool children with ASD should receive special education in a therapeutic nutsery or in a home-based behavioral modification piogram. Table 67.5 lists medications that have proven helpful in some cases (Towbin 2003).

LEARNING DISABILITIES

Approximately 10% of school-aged children have learning disabilities (LD), and these can affect one or more cognitive skills. The common LDs involve reading (dyslexia), motor function (dysgraphia and dyspraxia), the spectrum of specific nonverbal LDs (mathematics, written composition, visuospatial skills, socioemotional abilities, paralinguistic communication, executive function), and attention deficit disorder (ADD) with or without hyperactivity (ADHD).

Dyslexia

Ditignosis

Dyslexia is the best studied and probably the most common of the learning disabilities, occurring in as many as l()% of school-aged children. This disability often has a genetic basis, and several different chromosomal loci are suspect (Fisher and DeFries 2002). The definition of *developmental dyslexia,* an unexpected difficulty in learning to read, has both exclusive and inclusive criteria. As with other I D, the dyslexic child should not have majot neurological abnormalities. The detection of minor abnormalities (soft signs) on examination is usual (Table 67.6). Although majot sensory function must be normal, studies of disturbed cortical visual functioning in children with reading disability are ongoing. Processing by a slow lateral geniculate magnocellular system (impottant for monitoring motion,

Table 67.5: Medications for autism

Hyperactivity and inattention	Psychostimulants (methylphemdate; dextroamphetamine); clonidine (Catapres)
Obsessive-compulsive behaviors	Tricyclics—Clomipramine (Anafranil); SSRI—fluoxetine (Prozac), sertraline (ZoloftJ, paroxetine (Paxil), fluvoxamine (Luvox); atypical neuroleptics—risperidone (Risperdal), olanzapine (Zyprexa), ziprasidone (Geodon)
Aggressive and impulsive behaviors	Mood stabilizers—carbamazepine (Tegretol), divalproex sodium (Depakote), gabapenten (Neurontin), topiramide (Topamax), lithium; clonidine; Beta blockers—propranolol (Inderal); anxiolytics—huspirone (BuSpar)
Ties/stereotypies	Clonidine, clonazepam (Klonipin), pimizide (Orap), haloperidol (Haldol), risperidone (Risperdol), baclofan (Liorisol)
Self-mutilation	Naloxone (Narean), propranolol, fluoxetine, clomipramine, lithium
Psychosis	Neutoleptics: haloperidol decanoate (Haldol), risperidone (Risperdal), chlorpromazine (Thorazine), olanzapine (Zyprexa), ziprasidone (Geodon), quetiapine (Seroquel), aripipra/ole (Ability), clozapine (Clozaril)
Seizures	Valproate (Depakote): adrenocorticotropic hormone (ACTH)

stereopsis, spatial localization, depth, and figure-ground perception) may not appropriately modify the information received from the fast parvoccllular system (crucial for color perception, object recognition, and high-resolution form perception) (Amity et aI. 2002; Angelique et aI. 2002). Normal intelligence and exposure to a social and educational environment conducive to learning to read is required for diagnosis. Studies ot iiuicr-city eleinemary school children show that enrichment programs can help some nonteaders become readers.

With respect to inclusive criteria, reading two grades behind actual or expected grade level is generally required for a diagnosis of dyslexia by educational institutions. The *two-grades-behind criterion* does not take into account the fact that different reading tests yield different reading levels and may be more or less reliable measures and predictors of reading ability at different ages and grade levels because of ilu complex dynamics of reading acquisition. Hie agi of the child affects the inclusive criteria. Because we do not expect children to read until first grade, the strict definition makes a diagnosis of dyslexia impossible before the third grade. Yet a history of language delay or a family history of reading disabilities is often predictive of dyslexia, and strict adherence to the definition should not preempt consideration of early intervention. In addition, a 2-year discrepancy reflects n greater disability for the younger than for the older child. Whether or not to factor intelligence into the diagnosis of teading disability is debatable. Spelling difficulties may be a mild form of dyslexia that persists into adulthood or that are present In good readers in dyslexic families *(forme fruste).*

Table 67.6: Common soft signs associated with learning disabilities

Cranial nerves	Head turns with eyes
	Month opens when eyes open
	Difficulty with grimace
Motor	Excess upper extremity posturing mi sin sseil giiil
	Excess overflow during finger tapping and sequencing
	Unsustained one-foot stand
	Difficulty with hopping
	Excess choreiform movements with arms extended
Cerebellar	Dysrhythmic rapid alternating movements
	Excess overflow during rapid alternating movements
	Ballistic finger-nose-ringer test
	Difficulty with tandem gait
Sensory	Extinction on double simultaneous stimulipoor finger localization
DTK	Minor reflex asymmetries

Evaluation and Etiology

Children with dyslexia deserve a formal neuropsychological evaluation to determine their cognitive strengths and weaknesses and to identify comorbid problems that might affect treatment. For example, dyslexia and ADHD can coexist. Deficits in phonological awareness frequently underlie reading difficulties and may petsist into adolescence (Shaywitz *\999).* Measures that assess phonological functioning best differentiate dyslexic from normal readers (e.g., segmenting words, saying cowboy without the boy, saying smack without the *m,* word and nonword blending, and sound matching of first and last syllables). Few children fail to read because of visual perceptual difficulties. The standard neurological examination is generally normal. Routine imaging is tarely abnormal and generally unnecessary, except perhaps in children with atypical features (Table 67.7). Pathological studies suggest that those with dyslexia have both atypical planum temporale asymmetries and areas of cortical dysplasia, particularly in the left hemisphere. Specialized imaging has corroborated the macroscopic pathological findings. In about two thirds of normal adults, the left planum temporale is larger than the right. By contrast, only 10-50% of dyslcxics show a left greater than right posterior asymmetry (Eckert and Leonard 2000). Dyslexics with atypical asymmetry patterns tend to have more sevete language and/or reading deficits. Theoretically, fluent reading requires the functional

Table 67.7: Atypical features in dyslexia

Female gender
Left-handed without family history
Strongly left-handed, early declaration
Dyslexic without family history
No history of developmental language problems
Large discrepancy between verbal and spatial skills
Neurological abnormalities or seizures

integrity of two left-hemisphere posterior systems: a tem-pt)[•(jp;iru-taI system .slid a ventral occipitotemporal system, Developmental^', the temporoparietal system predominates initially and is required for learning to integrate the printed word with its phonological and semantic features. The occipitotemporal system constitutes a hue-developing rapid sight-word identification system that underlies word recognition in skilled readers. In developmental dyslexia, both posterior systems may be disrupted causing reliance on the left inferior frontal and right posterior regions of the cortex (Pugh et al. 2000). The corpus callosum, which has a role in inrerhemispheric information transfer, may he structurally different in normal versus dyslexic readers. Theoretically, the splenium is critical hecause it contains axons linking the planum temporale and angular gyrus. Metabolic imaging confirms that the left temporal lobe and the cerebellum, an area that other studies suggest is crucial for language functioning, are involved in reading (Fulbrigbt etal. 1999). Measures demanding phonological processing activate the left temporal tegion in normal conttols, but not in dyslcxics.

Treatment

Although dyslexia is permanent, most children with early reading problems, when identified by 8-9 years (third to fourth grade) and provided with evidence-based reading instruction, can learn to read at average to above average levels. Children diagnosed later, even when provided remediation, are likely to continue having reading problems. Seventy-five percent of children with reading problems at the end of third grade are still having trouble in seventh gtade. Dyslexic children, identified after third grade, never catch up to average or superior high school readers (Shaywitz ct al. 1999). Early identification and provision of evidence-based reading instruction reduces the percentage of children reading below grade level in fourth grade from 37% to 6%.

Nonverbal Learning Disabilities

Diagnosis

No generally accepted definition is available for the term *nonverbal learning disabilities* (NVLD), and although the diagnosis of NVLD does not yet appear in the *Diagyiostic and Statistical Manual,* anywhere from 1-10% of school-aged children are thought to have problems that fall under this rubric. Many children with Asperger's syndrome have difficulties in the nonverbal domain that may manifest as learning issues in school,

In contrast to children with dyslexia, children with NVLD generally have significantly higher verbal than performance IQ scores. Problem areas include:

1. Social-emotional functioning
2. Nonvcrbal/paralinguistic communication
3. Sensorimotor functioning
   - Tactile perceptual
   - Gross and/or fine motor (clumsy, dysgraphia, dyspraxia)
   - Slow processing speed
4. Visuospanal processing
   - Perceptual, motor, visual-spatial-organizational, visual-spatial working memory, visual imagery, getting gestalt

.5. Executive functioning
   - Problems in planning, organization, working memory, processing speed
   - Attention difficulties/attention deficit hyperactivity disorder
   - Deficits in problem solving, reasoning, concept formation, hypothesis testing, seeing the gestalt, guessing
   - Difficulty adapting to novel (inflexible) or complex situations
   - Motivation
6. Academics
   - Problems with handwriting, reading comprehension, written expression, math operations and concepts, science

further complicating the diagnosis of NVLD is a changing pattern of deficits with time as school demands escalate (Rourke et al. 2002). In the elementary school years, the predominant problems are social difficulties, inflexibility, writing disturbances, poor gross motor coordination, sensorimotor problems, and inattention. In junior and senior high school, academic problems become apparent in mathematics, reading comprehension, and written composition despite good verbal skills. Social skills issues continue, and problem-solving and organizational skills are relatively impaired. In young adults, emotional problems may become prominent.

Evaluation and Etiology

In general, NVLD reflect right hemisphere dysfunction, particularly the frontal and parietal regions. Based on children at high risk for NVLD (e.g., children with closed head injuries, those treated for leukemia, and those with

hydrocephalus), Rourke (Rourke et al. 2002) has suggested that NVLD result from white matter abnormalities, but imaging studies to confirm this hypothesis have yet to be done.

Treatment

The basic management strategy is the use of verbal strengths to compensate for the visuospatial disability. Because these children have difficulties dealing with novel or complex situations, the educational process emphasizes systematic learning and appropriate strategies for troublesome, frequently occurring situations. Generalization of learned strategies should be encouraged. Appropriate nomerba; behavior to facilitate peer' interactions is learned and not instinctual. Social groups are often helpful in this regard. Sensorimotor deficits can be managed by occupational therapy, early instruction in keyboarding and minimization of the written load in school.

Developmental Disorders of Motor Function

Diagnosis

Among 7-year-old children, moderate coordination disturbances occur in *9%* and severe disturbances in *5%* (Kadesjo and Gillberg 1999). Hadders-Algra's (2002) longitudinal study suggests that the frequency of developmental coordination disability (DCD) changes with age and is affected by the presence or absence of early neurological problems. ADHD (Landgrcn et al. 2000), visual perceptual problems, and reading comprehension problems are often comorbid conditions. Several discrete types of motor skill disorders may coexist. These include clumsiness, dyspraxia, dysgraphia, adventitious movements, and anomalous dominance or handedness. Clumsiness is defined as "a slowness and/or inefficiency in performing elementary fine motor and sometimes gross motor movements.[1'] Clumsiness is more common in children with learning disabilities (LD), and for this reason, the combination was inappropriately termed *minimal brain dysfunction.* Children with *developmental dyspraxia* have difficulty with motor learning and motor execution. Dyspraxia may be associated with clumsiness, alone or in combination with other l.D. Ideomotor and ideational dyspraxia occurs in children. Dysgraphia (difficulty with writing) can be a primary disturbance, a manifestation of clumsiness or dyspraxia, or be secondary to dyslexia as a higher order cognitive disorder (Table 67.8). Adventitious movements (i.e., synkinesis, chorea, tremor, and tic) occur normally on a developmental basis and are designated *developmental soft signs* when they persist beyond the age when they normally cease (Table 67.9). With regard to handedness (manual dominance), most ultimately right-handed children declare handedness after 1 year of age and before age 5 years. Strong dominance when

Table 67.8: The development of pencil grip

Ulnar/vertical—1 % to 3 yr
Radial-acceptable until 3% yr
Tripod (static) 50% by 3 yr, 80% by 4 yr
Tripod (dynamic) 5-6 yr

established belorv age 1 year should raise concern that handedness is pathological and indicates disturbed use of the other hand. Many infants may appear to be left-handed and then become right-handed. The percentage of right-handed children, and probably the strength of handedness, increases through age 5 years. Eventually, more than 90% of children are right-handed. Most right-handed people are strongly right-handed, whereas most left-handed people are ambidextrous. Dexterity in left-handed and right-handed people is equal. However, the frequency of LD is greater in left-handed than right-handed people, and the frequency of left-handed people is greater among the learning disabled.

Evaluation and Etiology

Developmental coordination disorders, because of their heterogeneity, can only be fully evaluated using a battery that taps the gamut of motor skills. In one study (Geuze et al. 2001) about 75% of children who were]udged to have DCD by a team of specialists (rehabilitation doctor, occupational therapist, and physical therapist), performed below the fifteenth percentile on a comprehensive motor battery. The remaining 25%, had handwriting problems or low muscle tone issues not measured by the particular battery used. Adventitious movements arc generally assessed separately. Synkinesia is best elicited by finger tapping, finger sequencing, and stressed gait testing. Choreiform movements are best elicited by having the child stand with eyes closed, tongue out and pronated arms extended with fingers spread.

Some investigators suggest that children with developmental coordination disorders have difficulty representing internally the visuospatial coordinates of intended movements. Such a deficit implicates parietal lobe dysfunction. The parietal lobe is involved in processing *feed-forward* information from downstream motor areas by comparing it with local visuospatial representations that specify the coordinates of the prospective actions (Wilson et al. 2002).

Treatment

Children with significant disorders of motor control may benefit from process-oriented occupational therapy, motor imagery intervention, and perceptual motor training (Wilson et al. 2002), Computers can facilitate output for those with poor graphomotor skills. Sometimes, these difficulties are sufficient to require a scribe in the classroom.

Tabic 67.9: Natural history of soft signs

Neurological system affected	*Soft sign*	*Age of appearance or disappearance (yr)*
Cranial nerves	Head does not move with eyes	6 to 7
	Sticks tongue out for 10 sec	6 to 7
Motor	Toe-heel walk	3
	Heel walk without associated movements	5
	Hop I 0 times	5
	Hops indefinitely	7
	One-foot stand for 30 sec	7
	No longer drifts up and down with pronated and supinated arms	3 to 4
	Rigid tripod	5
	Dynamic tripod	7 to 8
	Choreiform movements	7 to 10
	Athetoid movements	2 to 4
Cerebellar	Tandem	6
	Ki: : n IT lli :\\ (luriiii; r.r.'kl ;i I [IT infills: move men Is	7 to 8
Sensoi •	Stereoagnosis, graphesthesia	6
	No longer extinguishes on double simultaneous stimulation	

Visuospatial Disabilities

Diagnosis

Visuospatial disabilities (perceptual, organizational, memory, and motor) occur in the context of NVI.D and in isolation. They may be the underlying cause of academic difficulties in reading, writing, and mathematics. Visuospatial difficulties are usually apparent on traditional IQ testing as a large verbal performance split as several performance IQ subtests measure visual perceptual processing.

Evaluation and Etiology

Difficulties in the visuospatial domain that are suggested by a large verbal performance split can be corroborated by specific neuropsychological measures such as design copy and memory, picture memory, and mental rotation. Visuospatial abilities are easily assessed in the office by the simply administered "draw a person test" (Table 67.10).

Studies of visuospatial disabilities have not been as extensive as studies of specific academic disabilities. Visuospatial difficulties are, however, hallmark deficits in such genetically divergent syndromes as Turner syndrome, Williams syndrome (WS), velocardiofacial (VCF) syndrome, and neurofibromatosis (see Table 67.1). WS is perhaps the best studied by neuroimaging. Affected individuals have decreased overall brain volume, particularly in the cerebrum and brainstem with relative preservation of cerebellar and superior temporal gyrus volumes. The ratio of frontal to posterior (parietal + occipital) tissue is greater than in controls. WS has relative preservation of cerebral gray matter volume and disproportionate reduction in cerebral white matter volume. However, within the cerebral gray matter tissue compartment, the right occipital lobe shows excess volume loss, a feature that could underlie the visuospatial difficulties (Reiss et al. 2000).

Table 67.10: "Draw a person test" scale

Humpty-Dumpty or better 50% at 3 yr, 80% at *1*>\ yr
Intermediate man or better 50% at 4 yr, 80% at 4/4 yr
Mature man 50% at 4/4 yr
I 0 part person at 5 *A*_ yr

Treatment

The treatment of visuospatial disabilities emphasizes the use of verbal strategies to navigate situations demanding visuospatial solutions. It is important to realize that visuospatial disabilities may seriously impair one's perception of the world. Insignificant tasks, like navigating the hallways at school, become difficult. Visuospatial misperceptions may lead to serious social errors.

Dyscalculia

Diagnosis

Dyscalculia can involve any or all aspects of mathematics from computation to conceptualization. The prevalence of dyscalculia is approximately 6%, a figure similar to that of dyslexia and ADHD. Both genders are equally affected. Indeed, the only clear gender difference in mathematical skills is in the extremely superior range (scoring over 700 on

the math SAT in seventh grade); within this group, males out-number females by mure than 10 to 1. A developmental Gerstmann's syndrome (right-left disorientation, finger agnosia, dysgraphia, and dyscalculia) occurs in as many as 2% of school-aged children. The mean IQ of children with dyscalculia is generally normal; ADHD occurs in 25% and dyslexia in 20%. Dyscalculia is common in children with NVLD (Shalev and Gross-Tsur 2001).

Evaluation and Etiology

Children with neuropsychological evidence of either left- or right-hemisphere dysfunction can have dyscalculia. Both groups have similar problems on arithmetic batteries, but those with left-hemisphere dysfunction perform significantly worse in addition, subtraction, complex multiplication, and division and make more visuospatial errors (Shalev and Gross-Tsur 2001). Imaging studies in children with dyscalculia who had been born prematurely suggest that left-parietal abnormalities predominate (Grafman and Romero 2001).

Treatment

Math remediation is appropriate for the child with isolated dyscalculia or with math difficulties in combination with other learning difficulties.

Attention Deficit Hyperactivity Disorder (ADHD)

Diagnosis

The reported prevalence of ADHD in school-aged children ranges from 1% to 20%. This wide range reflect-, (h_L- lack of a biological marker for the disorder. The variation in prevalence is secondary to differing technique of ascertainment (parent, child, or teacher perspective), the diagnostic questionnaire used, age at ascertainment {standards are most clear-cut for the elementary school-aged child), and even the country of study (e.g., ADHD is more common in the United States than in the United Kingdom). Although complete recovery used to be thought the rule, it now appears that ADHD persists in *60-70%* of adults diagnosed with ADHD in childhood. Almost half of such adults show significant social-emotional difficulties, and 10% show serious psychiatric or anrisocial disabilities. Assuming a prevalence of childhood ADHD of 6-10%, the prevalence **of ADHD** in adults may be 2-7%. **ADHD** is diagnosable in toddlers and may be four to eight times more common in males than females. Females, when affected, have less hyperactivity and more severe general cognitive deficits. This suggests that females with ADHD may have a gteater genetic load. Other learning difficulties as well as psychiatric disorders are commonly comorbid with ADHD (Brown 2000).

Clinical Features

Practically speaking, the following symptoms define ADHD: inappropriate inattention, impulsivity, disttactibility, and hyperactivity for chronological and mental age. The current standard for diagnosis is the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (Table 67.11). Table 67.12 lists the characteristics of ADHD in preschoolers. The physical examination of **the ADHD** child is generally normal. Minor signs on neurological examination may include synkinesis and choreiform movements. The neuropsychological profile reveals normal IQ but low scores on the Wechsler IQ subtests that demand attention or rapid processing: digit span, coding, arithmetic, and symbol search. Also often compromised are executive-frontal lobe functions tapping the ability to initiate, inhibit, sustain, and shift attention.

Evaluation and Etiology

Although many medical causes of ADHD exist, ADHD has a substantial genetic component. Genetic factors may account for 70-90% of cases. Approximately one quarter of the first-degree relatives of a child proband with ADHD also have or have had ADHD, generally the father or a maternal uncle. As many as 10% of ADHD children probably carry the Tourette gene, but may not have tics at the time of diagnosis or indeed ever. Girls with the Tourette gene more often have obsessive-compulsive disorder, whereas the combination of ADHD and tics predominate in boys. Structural imaging studies suggest atypical asymmetry

['able (S7.1 1 : Criteria lor diagnosis t)l Lirrcnuoil deficit hyperactivity disorder (ADHD)

ADHD with hyperactivity, impulsiveness
Fidgets with hands or feet
I vavi's si[h]a[in classroom
Runs about ot climbs excessively
Has difficulty playing quietly
Often on the go
Talks excessively
lilnrls "IK .niswL'i -.
Difficulty awaiting turn
Interrupts others
ADHD with inattention, distractibility
Has difficulty sustaining attention
Does not give close attention to details
Docs not seem to listen
Docs not follow through
Has difficulty organizing tasks
Avoids engaging in tasks requiring sustained mental effort
Easily distracted
Forgetful in daily activities

Source: Modified with permission from *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Washington, D.C.: American Psychiatric Association, 1994,

Tabic 67.12: Signs of preschool attention deficit hyperactivity disordci

High activity
Poor persistence
Group instruction problems
Poor behavior modulation
Poor social interactions
Excessive aggression
Silliness
Mossiness
Impulsiveness
"Immature," not on task
Inappropriate lieli.ivior
Unproductive

patterns in the basal ganglia, whereas metabolic imaging studies suggest dysfunction of frontal lobes and the right sided prefrontal-striatal systems (Ernst and Rtimsey 2000). Dopaminergic dysfunction appears to be the biochemical basis of ADHD. Genetic studies have focused on candidate genes involved in dopaminergic transmission, dopamine transport, and dopamine receptors (Solanto 2002).

Treatment

Medication, in particular psychostimulants, is the mainstay of treatment (Table 67.13). Approximately 75% of children respond to stimulants. In .5-10%, side effects, such as weight loss, rebound depression or irritability, or flat affect limit treatment. Neither tics nor Tourette's syndrome are contraindications to stimulant use in ADHD (Nass and Bressman 2002). Comorbid mood or anxiety disorders influence medication choice (Brown 2000). Atomoxetine (Strattera) a nonstimulant medication has recently been marketed for treating ADHD and may prove effective (Ktatochvil et ah 2002) and useful especially in stimulant nonrespondcrs. Other factors requiring attention are parent skills training, educational accommodations (extended time, separate testing site), cognitive behavioral therapy, social skills training, and behavioral modification. Behavioral modification requires setting goals, defining progress, and determining the incentives.

DEVELOPMENTAL LANGUAGE DISORDERS

Developmental language disorder (DLD) is the failure to develop language in an age-appropriate fashion in a child with normal intelligence and heating. Most children have good receptive language by age 2 years, along with a 50- to 100-word {ot more) vocabulary and some two-word phrases. Keen children w nil S'LHHI receptive skills who speak late may be at risk for continuing subtle language difficulties and later reading and language-based academic difficulties (Rescotla et al. 1997). Lack of well-developed expressive language by age 3 years is definitely abnormal. Table 67.14 lists additional warning signs that suggest DID duni it; [he m si 3 wnrs. \rnjuur basis lor diagnosis is a discrepancy between nonverbal intelligence and language capabilities (Klcc et al. 2000). However, both over- and underdiagnosis occur even when the best available discrepancy criteria are used. The difficulty in applying criteria and the need for strict discrepancy-based diagnostic criteria reflect, in part, the large degree of individual variability in rate of language acquisition (Toppleberg and Shapiro 2000). It is sometimes difficult to distinguish DLD from miti.il idiosyncratic delay in acquisition with eventual catch-up and ultimately notmal language. This probably accounts in part for the wide range (1-25%) in the reported prevalence of DLD in preschool children.

Risk factors for DLD identified by the National Collaborative Perinatal Project include low birth weight or prematurity and parental mental retardation. Another risk factor is a family history of developmental language disorders. Increased monozygotic versus dizygoric twin concordance rates indicate that heredity, not just shared environment, is the cause of the familial clustering (Bartlett et al. 2002). A number of gene loci have been implicated including: 13q, 16q, 19q (SLI Consortium 2002). In the three-generation KE family, half the members are affected with a severe speech and language disorder that is transmitted as an autosomal dominant monogenic trait—the gene responsible is the FOXP2 forkhead-domain gene. The first description of the language deficit in the KE family was of a severe form of developmental verbal apraxia. However, most recently investigatots argue in favor of a core deficit in sequencing and learning of verbal and

Table 67.13: Treatment of attention deficit hyperactivity disorder

Stimulants	Mcthylphenidate (Ritalin), dextroamphetamine (Dexcdrinc, Adderal), pemoline (Cylert)
Alpha agonists	Clonidine (Catapres), guanfacine (Tenex)
Antidepressant	Selective serotonin re-uptake inhibitors; tricyclic antidepressants; bupropion (Wellbutrin); trazodone, vcnlafaxine (Effexor); monoamine oxidase, selegiline (Deprenyl)
Norepinephrine transport inhibirer	Atomoxetine (Strattera)
Anti manic	Lithium
Mood stabilizers	Carbamazepine (Tegretol), divalproex sodium (Depakote)
Beta blockers	Propranolol (Inderal), atenolol (Tenormin)
Antianxiolytic	Buspirone (BuSpar); clonazepam (Klonopin)
Neuroleptics	Haloperidol deeanoate (Haldol); risperidone (Rispirdal); phenorhiazines

Table 67.14: Warning Tigris of ;i developmental language disorder

Limitations in expressive language
Mas feeding problems related to sucking, swallowing, and chewing
Fails to vocalize to social stimuli and fails to vocalize two syllables at 8 months
Produces few or no creative utterances of three words ot mote by age 3
[.imitations in vocabulary
Has small repertoire of words understood or used and acquires new words slowly or with difficulty
Limitations in comprehending language-
Relies too much on comextual cues to understand language
Limitations in social interaction
Rately interacts socially, except to have needs met
Limitations in play
Has not developed symbolic, imaginative play by age 3
Does not play interactively with peers
Limitations in learning speech
Expressive speech contains numerous articulation errors or is unintelligible to unfamiliar listeners
Limitations in using strategics for language learning
'. U– iHinsii.il or i 11. ;> prop-1. ue MI.;U;;K-. :i>r .ls-.i- li-vcl, . .;•„, ••>• t i i r o iniLiuoii *ii*\ liohilia .
does not imitate verbalizations of others (dyspraxia), does not use questions for learning ("why" questions'
Limitations in attention for language activities
Shows little interest in book reading, talking, or communicating with peers

Source: Modified with permission from Nelson, N. W. *Childhood Language Disorders in Context: infancy through Adolescence.* New York: Macmillan, 1993; and Hall, N. "Developmental language disorders," *Semin Pediatr Neurol,* vol. 4, pp. 77-85.

nonverbal associations (Watkins et al. 2002a). A recent screening of 270 4-year-olds with DLD was negative for the FOXP2 mutation (Meaburn et al. 2002).

Erring on the side of overdiagnosis in the young child and initiating therapy is probably better than underdiagnosis. Hearing impairment should be ruled out by formal audiological assessment in most children presenting with language delay. The current availability of brainstem-evoked responses (in addition to behavioral audiometry) makes possible an assessment of even an uncooperative young child. In view of the frequent concurrence of language disorders and epilepsy, an KEG, including a sleep record, to rule out subclinical seizures {see Verbal Auditory Agnosia, later in this chapter) is often appropriate, especially for those with impaired language comprehension.

Subtypes of Developmental Language Disorders

Depending on subtype, DLD vary in their characteristic features, etiology, prognosis, and treatment response. The subtypes listed in Table 67.15 focus on psycholinguistic features that most closely approximate the adult aphasias (see Chapter 12).

Articulation and Expressive Fluency Disorders

Pure Articulation Disorders

Articulator)' skills improve with age and, as with language development, the normal range is considerable. Most children (70%) speak intelligibly by age 2 years. Unintelligible speech is the exception at age 3 years (15%). However, almost 50% of children at age 4 years still have articulation difficulties. A com moo problem is defective use of *th* or *r.* At kindergarten entry, one third of children still have minor to mild articulation defects, but speech is unintelligible in less than 5%.

Stuttering and Cluttering

Stuttering is a disorder in the rhythms of speech. The speaker knows what to say, but is unable to say it because of an involuntary, repetitive prolongation or cessation of a sound. Some degree of dysfluency is common as language skills evolve during the preschool years, particularly as mean length of utterance (MLU) reaches 6-8 words between ages 3 and 4 years. However, stuttering in contrast to developmental dysfluency is probably a linguistic disorder {errors occur at grammatically important points in the sentence). Sniftering is often a genetic trait. Although the cause of developmental stuttering is unknown, the main theories are anomalous dominance and abnormalities of iuterhemisphcric connections (Eoundas et al. 2001). Stuttering occurs more frequently in children with other DLD and with mental retardation. Cluttering, by contrast, as seen in fragile X syndrome, is characterized by incomplete sentences and short outbursts of two- to three-word phrases, along with echolalia, palilalia (compulsive repetition reiterated with increasing rapidity and decreasing volume), perseveration, poor articulation, and stuttering.

Phonological Programming Disorder

Children with the phonological programming disorder are fluent, and MLU approaches normal. Despite initial poor intelligibility, the achievement of serviceable speech is

Table 67.15: Subtypes of developmental language disorders

	Rzceptive expressive		*Expressive*		*Higher order*	
	Verbal auditory agnosia	*Phonological syntactic*	*Verbal dyspraxia*	*Phonological programming*	*Seman t it-pragmatic*	*Lexical syntactic*
[illegible]	W	*i* ṗ			44	*i*
Production-expressive						
Semantics (lexical)	44	4			44	Nl or 4
Syntax	44	4	ȷ	ˌ		4
Phonology		4		4		
Fluency	44	4	Nlor J.	Nlor 4.	Nl or 4 ot 1	4
Pragmatics	Nl or J.	Nl or 1			44	4

Nl = normal.
Source: Modified from Rap in, i. 1996, *Preschool Children with inadequate Communication.* London: Mackeith Press.

expected. Language comprehension is relatively preserved. Most such children show delayed rather than deviant phonology, with improvement at 1 and 7 years after preschool diagnosis. It is debatable whether this disorder is a severe articulation problem (see Pure Articulation Disorders, earlier in this chapter) or a mild form of verbal dyspraxia (see Verbal Dyspraxia, latet in this chapter). The fact that patients witli the phonological programming disorder have more trouble learning manual signs and Bliss symbols than controls supports an association with dyspraxia. A prcrcmediation paired associate learning task may help select the best remediation method for each child because some arc better with symbols and some with signs. An adult aphasia equivalent does not exist.

Verbal Dyspraxia

The speech of children with verbal dyspraxia, also called *dilapidated speech,* is extremely disfluent. Utterances are short and laboriously produced. Phonology is impaired and includes inconsistent omissions, substitutions, and distortions of speech sounds. Syntactic skills are difficult to assess in the face of dysfluency. Language comprehension is relatively preserved. Many require speech and language therapy fot prolonged periods. Children with vetbal dyspraxia who do not develop intelligible speech by age 6 years are unlikely to acquire it later. The frequency with which nonverbal praxis deficits—buccal-Ungual dyspraxia (e.g., positioning muscles of articulation) and generalized dyspraxia or clumsiness—coexist with verbal dyspraxia is unknown. The presence of a more diffuse disorder of praxis has significant therapeutic implications because children with verbal dyspraxia may depend on signing and writing skills for communication.

The etiology of verbal dyspraxia is unknown. The excess of males and a familial tendency support a genetic basis. Postmortem studies show either hypoplasia of the motot tract running from the Rolandic region to cranial nerve nuclei X and XII or bilateral opercular lesions. In a few patients studied decreased cerebral blood flow in the frontal regions and failure of verbal activation to increase profusion in Broca's area have been found. Although often accompanied by more neurological symptoms, verbal dyspraxia most resembles the adult aphasia called *aphemia* (see Chapter 12A}.

Disorders of Receptive and Expressive Language

Phonological Syntactic Syndrome

Phonological syntactic syndrome (also called *mixed receptive expressive disorder, expressive disorder,* and *nonspecific formulation-repetition deficit)* is probably the most common DLD. The phonological disturbances consist of omissions, substitutions, and distortions of consonants and consonant clusters in all word positions. The production of unpredictable and unrecognizable sounds makes speech impossible to understand. The syntactic impairment consists of a lack of small grammatical words (e.g., *and, but)* and an absence of appropriate inflected endings (e.g., *-ed, -ing).* The syntactic deficit is not just a developmental lag. Whereas a normal young child may say "baby cry" or "a baby crying," these children create deviant constructions, such as "the baby is cry." Telegraphic speech is common. The presence or absence of difficulties in other language areas is variable. Overall, comprehension is relatively, although not wholly, spared. Semantic skills tend to be intact. Repetition, pragmatics, and prosody may be normal. Autistic children with this DLD subtype produce a significant amount of jargon.

Neurological dysfunction is especially frequent in this developmental language disorder subtype. Feeding problems related to sucking, swallowing, and chewing difficulties are common, and drooling is often persistent. The neurological examination may reveal signs of pseudobulbar palsy,

oromotor apraxia, hypertonia, and incoordination. A single patient with the phonological syntactic syndrome and oromotor apraxia had an atypical asymmetry of the planum region and a dysplastie gyrus in the left frontal cortex. Bilateral anterior and posterior perisylvian hypoperfusion has been demonstrated in a few children with this disorder. This DLD most resembles Broca's aphasia in adults.

Verbal Auditory Agnosia

Despite intact hearing, meaningful language is not understandable in verbal auditory agnosia {VAA). VAA may occur on a developmental basis and as an acquired disorder, the Landau-Kleffner syndrome (sec Chapter 73). *Generalized low performance* and *global dysfunction* are other names tor die developmental form. VAA is common in low-functioning children with autism. VAA best supports the theory that DI.D result from difficulty with processing basic sensory information entering the nervous system in rapid succession.

The outcome from the developmental form of VAA is generally poor. *1* be outcome from tin- acquired disorder is better in approximately one third of patients. VAA is seen in adults with acquired bitemporal lesions.

Higher Order Language Disorders

Semantic Pragmatic Syndrome

Children with the semantic pragmatic syndrome (also called *repetition strength and comprehension deficit* and *language without cognition)* are fluent speakers, even verbose. The tetm *cocktail party syndrome* describes the semantic pragmatic syndrome in children with hydrocephalus. Vocabulary is often large and somewhat formal. Parents are often encouraged by the child's sizable vocabulary only to find later that the verbosity did not indicate superior cognitive skills. Such children fall short in basic semantic skills required for meaningful conversation and informative exchange of ideas. *They talk to talk.* Phonological and syntactic skills arc generally intact, but comprehension is impaired. Pragmatic skills arc lacking and the rules that govern the use of language in conversation arc never learned. Finally, children with semantic pragmatic syndrome often show deficits in prosody. Their speech has a monotonous, mechanical, or singsong quality. They cannot convey the additional pragmatic intentions that prosody affords, such as speaking with the proper emotion or indicating by tone of voice that they are asking a question. Semantic pragmatic syndrome is often seen in higher functioning autistic children.

The neuroanatomical basis of this disorder is unknown. It is reported in patients with agenesis of the corpus callosum and with hydrocephalus, which supports a possible localization in the subcortex and its connections or a disconnection effect. Repetition strength in the setting of fluent speech with impaired comprehension characterizes the adult aphasia syndrome of transcortical sensory aphasia. Difficulties with prosody and pragmatics suggest right hemisphere dysfunction in addition to left.

Lexical Syntactic Syndrome

The lexical syntactic syndrome is seen in approximately 15% of children with DLD. Speech is generally dysfluent, even to the point of stuttering, because of word-finding difficulties and poor syntactic skills, with many hesitancies and false starts. Both literal and semantic paraphasias are common. Syntax is immature, not deviant. Phonology is spared, and therefore speech is intelligible. Repetition is generally better than spontaneous speech. In conversation, idiom use is better than spontaneous speech. Pragmatics may be impaired, particularly when this syndrome occurs in autistic children. Comprehension is generally acceptable, although complex questions and other linguistic forms taxing higher level receptive syntactic skills are often deficient.

The neuroanatomical basis of this disorder is .llso unknown. No clear counterpart for the lexical syntactic syndrome exists among the acquired aphasias of adulthood, despite similarities with anomic aphasia, conduction aphasia, and transcortical aphasia.

Ncurobtological Basis of Developmental Language Disorders

Structural Anatomy

Adult aphasia data and neurobiological theory implicate the left perisylvian regions in the processing of phonemes and linguistic information. Very few group studies have used neuroimaging to assess language-impaired children per se, other than those originally ascertained because of dyslexia. Perisylvian abnormalities of varying degrees and associated with varyingly severe language disorders are reported. Complete opercular agenesis has been reported in association with suprabulbar palsy (Worster-Drought syndrome). Poly microgyria has also been reported in the perisylvian region. Patients with the most extensive disease have the greatest language impairments, whereas those with posterior parietal polymicrogyria have milder symptoms (Nevo et a I. 2001; Gucrreiro ct al. 2002). Some children and adults with DLD (as well as relatives of DLD probands) do not have the typical planum temporale asymmetry pattern. The absence of the typical planum asymmetry may be the result of aberrant neurogenesis, which leads to reduced cell development in the perisylvian regions or atypical patterns of cell death. Caliosal si/e may be decreased in some children with DLD (Prcis ct al. 2000). An extra sulcus in the inferior frontal gyrus was statistically associated with a history of DLD (Clark and Plante 199S)

in a group of 41 neurological!)' normal adults. In one recent series one third of 35 children with DLD had nonspecific MRI abnormalities including ventricular enlargement (5), central volume loss (3), and white matter abnormalities (4) (Trauner et al. 2000). Rare reports document right hemisphere abnormalities in the DLD child suggestive of a right-hemisphere contribution to language acquisition {Plante et al. 2001). In the KL; family (see earlier) the caudate nucleus and inferior frontal gyrus are reduced in size bilaterally, whereas the left frontal opercular region (pars triangularis and anterior insular cortex) and the putamen bilaterally have a greater volume of grey matter (Watkins et al. 2002b), An insufficient dosage of a critical forkhead transcription factors during embryogenesis, may lead to maldevelopment of brain speech and language regions of the brain (Lai et al. 2001). Despite these research results, there is no reason to image the typical DLD child in clinical practice.

Metabolic Anatomy

Lew studies have specifically assessed children with primary DLD (as opposed to dyslexia) (Table 67.16). In addition, the comorbidity of attention deficit hyperactivity disorder (ADHD) in many of the subjects makes interpreting the results more difficult. However, finding differences in the temporal regions may be specific for the DLD or dyslexic groups because most areas implicated in ADHD research involve the caudate, frontal, and rerrocallosal white-matter regions. Moreover, some of these metabolic studies suggest that different pathological systems may be involved, depending on the DLD subtype,

F.lectropbysto logy

In addition to the EEG studies mentioned in the discussion of the VAA DLD subtype, several investigators have assessed evoked responses and auditory processing speed as markers of language development, normal and abnormal. Atypical patterns of brain activity are documented in children with DLD. Lateralization patterns of electrophysiological activity may predict outcome in late talkers.

Outcome of Developmental Language Disorders

The occurrence of a DLD, even when it appears to resolve, may affect later social emotional adjustment, educational achievement, and vocational choices. Short- and long-term behavioral, social-emotional and psychiatric problems are associated with early language problems (Irwin et al. 2002; Jerome et al. 2002). In one group of 5-year-olds with speech and language problems, the frequency of ADHD

Table 67.16: Metabolic imaging in children with developmental language disordets

\illiii;	*Subjects*	*".-:<• ty*	*Results*
	6 ADHD only	7-15	No separate information for ADHD + DLD group.
	3 ADHD + MR		Hypoperfusion found in striatum, sensory and sensorimotor areas hyperperfused more pronounced central hypoperfusion in mixed group and less hypcrperfusion in sensory and sensorimotor areas.
	9 ADHD + DLD		
	9 controls		
	9 ADHD only	., I'.	ADI ID low striatal, posterior periventricular regions, high occipital ADHD, DLD low striatal, posterior periventricular regions, DLD low left temporal frontal regions.
	8 ADHD + PS DLD		
	7 DLD only		
	15 controls		
	7 E/R DLD	10 ± 1	E/R did not show activation during phonemic discrimination task compated with other two groups. All Dl.D groups showed absence of left inferior parietal region activation.
	7 E DLD	8 ± 1	
	6 ADHD	8 ± 1	
	12 E DLD	5-16	E Dl.D showed hypoperfusion in left inferior frontal convolution (including Broca's area), I7R DLD showed hypoperfusion in left temporoparietal tegion and upper and middle areas of right frontal lobe.
	2 E/R DLD		
	10 DLD	4-10 yrs	Hypoperfusion left temporal region

ADHD = a i tent ion-deficit hyperactivity disorder; DLD = developmental language disorder; K = expressive; E/R — expressive/receptive; MR = mental retardation; PS = phonological syntactic syndrome.

Source: Modified wirh permission from Semrud Clikeman, M. 1997, "Evidence from imaging on the relationship between brain structure and developmental language disorders," vol. 4, pp. 117-124; Lee et al. 2002.

was 30%, and the frequency of emotional problems was approximately 10%. In preschool children with DLD, nonverbal intelligence is the best single predictor of overall long-term outcome, and expressive syntactic abilities arc the best predictor of adolescent language skills. Preschool language skills are the best single predictor of later reading ability and disability. Thus both screening and follow-up studies of children with DLD is important. Persisting language problems at adolescence have been reported as high as 90% (Conti-Ramsden et al. 2001; Rcscorla 2002). Communication problems may continue into adult life in 50-70% (Young et al. 2002).

Remediation

Whether intensive early therapy changes the long-term outcome to \in appreciable degree remains to be determined. Different theoretical frameworks drive the various approaches to intervention. One approach involves identifying specific linguistic deficits and targeting them for remediation (Tyler 201)21. Another involves identifying specific DLD subtypes and addressing them in remediation (Forrest 2002). This approach means, for example, that selecting a strategy for improving language producrion must account for a child's level of comprehension. A third approach aims to detect and target a core cognitive processing deficit for intervention. A fourth approach emphasizes the neuropsychological profile. In contrast CO the other approaches, which focus on the deficit, the neuropsychological approach defines and uses children's strengths t:[1] remediate their weaknesses. 11 also takes mio account the child's temperament and neurodevelopmental status to determine learning styles and to develop optimal methods for remediating targeted deficits. To date, no formal study has compared the efficacy of these approaches.

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Chapter 68
Inborn Errors of Metabolism of the Nervous System

Gregory M. Pastores and Edwin H. Kolodny

Archibald Garrod developed and introduced the concept of inborn errors of metabolism (IEM) in the 1908 Croonian Lectures and a 1927 Huxley Lecture given at Charing Cross Hospital in London. The IEM are now recognized as a heterogeneous group of disorders resulting from abnormalities of the synthesis, transport, and turnover of dietary and cellular components. Although individually uncommon, collectively they represent a significant cause of morbidity and mortality. In aggregate, approximately 1 per 1000 individuals is born with a metabolic disorder. IEM are estimated to account for 20% of all deaths from genetic diseases; hereditary neurological or storage disorders account for 38% (Yang et al. 1997). The cost of care associated with the acute critical and chronic care of patients with IEM is substantial. Early diagnosis and intervention may influence patient quality of life and lead potentially to health care cost savings.

Defects of intermediary metabolic pathways cause disease either by the accumulation of a toxic metabolite or depletion of a metabolic by-product required to maintain proper cellular function. When an enzyme deficiency blocks normal catabolic routes, metabolism is diverted to alternative pathways that may disrupt cellular integrity. Deficient enzyme activity may arise from (1) mutations in the primary gene sequence for the protein, (2) abnormal processing {i.e., defects of posttranslational modification), or (3) mistaken intracellular localization or improper folding of the enzyme. Metabolic defects may also result from defects of a structural or transport protein.

Most IEM are multiorgan disorders that usually involve the nervous system. The clinical course can be acute, subacute, or chronic. Disorders characteti/ed by intoxication or energy depletion usually present acutely as altered mental status. Seizures and hypotonia may be associated. Other clinical features of acute intoxication are vomiting and hepatic and renal dysfunction. Some IEM follow an insidious course characterized by developmental delay or mental retardation, sensory-motor impairment, or dementia. From a pathophysiological perspective, it is helpful to categorize the various IEM into one of three diagnostic groups: (1) disorders involving complex molecules (e.g., *lysosomal storage disorders, peroxisomal diseases, congenital defects of glycosylation (CDG),* and *defects of cholesterol synthesis);* (2) disorders involving "small molecules" (e.g., *amino and organic acidurias, hyperammonemias,* and *lactic acidemias);* and (3) disorders associated with disruption of cellular energy metabolism (e.g., *mitochondrial respiratory-chain defects, disorders of carbohydrate metabolism, and disorders of fatty acid oxidation* [FAOJ). Metabolic defects involving complex molecules are usually progressive and not related to food intake, whereas those involving small molecules and cellular energy metabolism may be temporally related to food intake. The latter relationship accounts for the importance of dietary manipulation in the management of patients with certain IEM.

IEM are most often inherited as an autosomal recessive trait that results in the deficiency of an enzyme or its

cofactor. This may account for the absence of a family-history when the sibship size is small. A few IEM arc transmitted as autosomal dominant traits (e.g., acute intermittent porphyria, familial hypercholesterolemia), as X-linked traits (e.g., Fabry's disease, Lesch-Nyhan syndrome, ornithine transearbamylase deficiency, phosphorylase kinase deficiency), or segregate in a matrilincal fashion {e.g., mitochondrial DNA defects).

The early diagnosis of an IEM is important not only for prognostication and genetic counseling, hut also to provide treatment. A major goal of newborn screening is to reduce **the** burden of learning and functional impairment of affected children through early diagnosis and intervention. Most families may not be aware of their a priori risk, and early diagnosis of an affected child may enable consideration of prenatal diagnosis (.hiring future pregnancies. Therapeutic advances in recent years are considerable, and early diagnosis provides the best opportunity for a favorable outcome. Furthermore, treatment of secondary disabilities (e.g., seizures, sensory impairments, and behavioral, slccp-wake cycle or communication problems) has a positive impact on quality of life and helps address some sources of parental frustration.

This review covers the major IEM, except for the mitochondrial disorders. Most clinicians are neither metabolic specialists nor bi< >,hcir.val ;vr.oric:srs, and they are not expected to be knowledgeahle of the details of all biochemical pathways. The current chapter provides a general approach to diagnosis and management of IEM.

GENERAL CONSIDERATIONS

Diagnostic Approach

When an IEM is suspected, the clinical features help focus the approach to diagnosis. In the setting of acute illness, IEM should be considered in parallel with more common disorders even when the family history is not informative. The blood and urine of patients with acute neurological deterioration should be examined for signs of acidosis, ketosis, hypoglycemia, and hyperammonemia (Table 68,1 and Table 68.2). Screening tests for abnormalities of amino or organic acids should also he considered. Abnormal metabolites may not be present during stable periods or when samples are obtained after tile acute illness is over.

Analyses of cerebrospinal fluid (CSF) may be indicated in certain cases. For example, determination of CSF levels of biogenic monoamines and GABA may be diagnostic in severe neonatal/infantile epileptic encephalopathy due to neurotransmitter defects. Such defects should be suspected in infants and children with (fluctuating)

Table 68,1: Commonly requested tests for the evaluation of a patient suspected to have an IEM

Tests	*Clinical utility*
Ammonia	Urea cycle defects, organic acidemia
Carnitine, plasma or serum total and free (unesterified) urine levels	Deficiency may develop in carnitine transport defects, disorders of fatty acid oxidation and branched chain amino acid metabolism, and valproic acid treatment
Acy lea mi tine profile	Normal plasma acyl/frcc carnitine ratio: < 0.25
Ccruloplasmin	Decreased in Wilson's and Menkes' disease, a ce miopias mi nemia
Cholesterol	Low plasma levels in Smith-Lemli-Opitz syndrome, cerebrotendinous xanthomatosis; abnormal profile in the dyslipidemias
Free fatty acids (FFA); ketone bodies (KB): 3-OHbutyrati', acctoacetate	Disorders of fatty acid oxidation and kccolysis; supervised fasting and assessment of FFA/Kli ratio and glucose and ketone levels enable distinction of hypo- and hyperketotk disorder
Lactate[1,]	Defects of glycogen metabolism, gluconeogenesis and fatty acid oxidation (often seen with hypoglycemia); defects involving the electron transport chain, Krebs cycle, and pyruvate dehydrogenase (absence of hypoglycemic episodes) LactateVpyruvate ratio (Nl: <20:1) provides insight into oxidariomreductation status Normal Blood lactate <1.8 mmol/L Normal CSF lactate < 2.2 mmol/L
VLCFA (Very-long-chain fatty acid);	Disorders of peroxisomal metabolism
Phytanic acid	Elevated in Refsum disease and rhizomelic chondrodysplasia punctata
Uric acid	Elevated in Lesch-Nyhan syndrome and other defects of purine metabolism and glycogen storage disorders; Decreased in molybdenum cofactor deficiency and defects of pyrimidinc metabolism
CSF: Plasma ratio	
Glucose	<0.35 Glucose transport defect
Glycine	>0.6 Nonketotic hyperglycinemia
Serine	<0.2 Serine synthesis defects (3-phosphoglycerate dehydrogenase and phosphoseune phosphatase deficiency)

^Presence or absence of hypoglycemia can be a useful aid to differential diagnosis of disorders that lead to lactic acidemia,
'Hyperuricemia may lead to formation of nephrolithiasis, obstructive nephropathy and gout.

Table 68.2: Clinical findings characteristic of an IEM

Disorder	*Acute metabolic encephalopathy*	*Metabolic acidosis*	*Hyperammonemia*	*Hypoglycemia*
Aminoacidopathies	•/			
Organic acidemias*	-/-		+/-	
Urea cycle defects	+/-		+	
THAN[1:]			+	
Fatty acid oxidation defects'			+	1/
Defects of ketolysis				1/
Defects of pyruvate metabolism and respiratory chain*			+/-	
Glycogen storage disorders		+		
Defects of gluconeogenesis				

'Additional findings include increased anion gap and ketonuria.
[f]Usually associated with hypoketosis and may lead to secondary carnitine deficiency,
[1] Normal lactate/pyruvate ratio (< 25) found with defects of pyruvate dehydrogenase or gluconeogenesis; elevated ratio suggests pyruvate carboxylase deficiency or mitochondrial disorder.
Transient hyperammoncnia of the newborn.

extrapyramidal disorders, in particular parkinsonism-dystonia or more general "athetoid cerebral palsy", and vegetative disturbances.

Neurological deterioration is a characteristic feature of acute intoxication disorders (e.g., certain aminoacidopathies [MSUD], organic acidemias [MMA, PA, IVA, MCD] and the urea cycle defects). Abnormal urine odor is present in diseases associated with the excretion of volatile metabolites (maple syrup in maple syrup urine disease [MSUD]; sweaty feet in IVA and glutaric acidemia type II), Isolated seizures are often the initial features of vitamin-responsive disorders (e.g., defects of pyridoxinc and folinic acid metabolism, biotin-responsive multiple carboxylase deficiency), and \w ;i prominenl feature in nonketotic hyperglycinemia, sulfite oxidase deficiency, and congenital malabsorption of magnesium. Congenital lactic acidosis and central hypotonia are features of deficiencies of pyruvate carboxylase (PC) and pyruvate dehydrogenase (PD) and disorders of the Krebs cycle and mitochondrial respiratory chain. Recurrent hypoglycemia typically occurs in the glycogen storage disorders and defects of FAO, which are also associated with signs of cardiac involvement (cardiomyopathy, arrhythmias).

Ophthalmological examination often provides a clue to the diagnosis of 1KM. Evidence of coloboma (congenital malformation of the optic nerve head or iris) may suggest an underlying brain abnormality. Vertical supranuclear ophthalmoplegia is noted in Niemann-Pick C, and saccadic initiation failure and defective optokinetic nystagmus can be found in Gaucher's disease type III. Kayser-Fleisher rings (orange or greenish deposits around the lirnbus of the cornea due to copper deposition within the Descemet's membrane) are seen in Wilson's disease. Additional eye findings characteristic of IEM arc shown in Table 68.3.

Hepatosplenomegaly and other signs of storage (e.g., coarse facies, nonimmune hydrops fetalis, dysostosis multiplex) occur with the lysosomal disorders. Liver dysfunction and/or hepatomegaly usually occur in defects of carbohydrate metabolism (galactosemia and hereditary fructose intolerance) and bile acid synthesis and in tyrosinemia and CDG. Unconjugated hyperbilirubinemia associated with liver dysfunction and/or hemolysis in infancy may lead to permanent brain damage due to kernicterus.

Cardiomyopathy may develop in IEM associated with infiltrative (storage) disorders and defects of energy

Table 68.3: Ophthalmologic findings associated with IEM

CatLiratis	Cherry red spot	Lens dislocation
Cerebrotcndinous xanthomatosis	Galactosialidosis	Homocystinuria
Cholesterol synthesis defects	GM1-gangliosidosis	Molybdenum cofactor deficiency
Galactokinase deficiency	Niemann-Pick disease A	Sulfite oxidase deficiency
Galactosemia	Sandhoff disease	
Lowe syndrome	Sialidosis type 1	
Menkes' syndrome	Tay-Sachs disease	
Mucopolysaccharidoses		
Peroxisomal disorders	Optic atrophy	Retinopathy
Serine deficiency disorders	Vlivnnk-iiktidvstnipliy	Carbohydrate-deficient glycoprotein syndrome
Tyrosinemia type II	Canavan's disease	Neuronal ceroid lipofuscinosis
	Hyperomithinetnia with gyrate atrophy	Mitochondrial defects
	Lafora's disease	Peroxisomal disorders

metabolism (Schwartz et al. 1996). The presence of hepatomegaly and other signs of systemic involvement (e.g., cataracts, coarse facics, dysostosis multiplex) may suggest storage disorders of glycogen or glycosaminoglycans. Defects of energy metabolism may be associated with acute or chronic encephalopathy, hepatic dysfunction and several biochemical abnormalities (e.g., hypoglycemia, lactic acidosis ± ketosis, and elevated liver transaminase levels).

Some disorders may have a later age at onset or follow .111 aiypsca; course. 'I lie diagnosis ma; be delayed until adolescence or adulthood. Examples include acid maltase deficiency (muscle weakness and respiratory problems in the absence of cardiomyopathy), fatty acid oxidation defects (myoglobinuria and rhabdoinyolysis after extreme exercise), X-linked adrenomyeloncuropathy (spastic paraparesis secondary to demy duration of the spinal **cord and** peripheral nerves), glycogen brancher enzyme deficiency (adult polyglucosan body disease with progressive upper and lower motor neuron disease, sensory loss, neurogenic bladder, and dementia), and acute intermittent porphyria (abdominal pain, psychosis).

Tandem mass spectrometry (TMS) analysis of blood spots on filter paper is an effective means of screening for some defects of amino and organic acid metabolism and FAO defects (Table 68.4) (Scaglia and Longo 1999; Rashed 2001; Zytkovicz et al. 2001). The main advantages of TMS over previous methods of newborn screening are improved accuracy, sensitivity and specificity, and suitability for cost-effective multi-IEM screening. Furthermore, the need for potentially harmful procedures (i.e., fasting or substrate loading) is avoided.

Assessment of carnitine profile (total and csterified carnitine levels and urinary carnitine excretion patterns) may also prove useful, when a primary or secondary carnitine deficiency is suspected (Kerner and Hoppel 1998). Carnitine plays an essential tole in the transfer of long-chain fatty acids across the inner mitochondrial membrane, in the detoxification of acyl moieties and in the maintenance of free Coenzyme A levels. It is primarily derived from dietary sources. Primary carnitine deficiency due to defective transport leads to increased urinary loss and cardiac and skeletal muscle disease. Secondary carnitine deficiency occurs in several II'.M and may be partially responsive to oral carnitine supplementation. A differential diagnosis of disorders involving carnitine metabolism is shown in Table 68.5.

Brain magnetic resonance imaging (MRI) has significantly advanced the diagnosis and management of patients with DEM (Kaye 2001; Faerber and Poussaint 2002). MR] also allows visualization of structural brain anomalies in children with mental retardation and seizures. For example, MRI images of patients with adrenoleukodystrophy typically show symmetrical areas of hypomyelination in the occipital lobes that extend to the splcnium of the corpus

Table 68.4: Metabolic disorders detected through Tandem Mass Spectrometry (MS-MS)*

Disorder	*Enzyme deficiency*	*Primary metabolic indicator*
Amino audopalhy		
Phenylketonuria	Phenylalanine hydroxylase	Phe
Maple syrup urine disease	Branched chain oxo- (or keto) acid dehydrogenase	Leu/Ile, Val
Homocystinemia	Cystathionine /?-synthase	Met
Hypermethioninemia	Methioninc-S-Adenosyltransferase	Met
Citrullinemia	Argininosuecinate synthetase	Cit
Argiiiinosuccinic aciduria	Argininosuecinate lyase	(ll
Tyrosinemia type I	Fumarylacetoacetase	Tyr
Organic acidemia		
Glutaric acidemia type 1	Glutaryl-CoA dehydrogenase	C5DC
Propionic acidemia	Pro pinny]-(!oA carhnx; lase	C3
Methylmalonic acidemia	Methylmalonyl-CoA mutasc	C3
Isovaleric acidemia	Isovaleryl-CoA dehydrogenase	C5
3-OH-3-methylglutary! CloA lyase deficiency		(MHI
3-methylcromonylearboxylase deficiency		CSOH
Fatty acid oxidation defects		
Medium-chain-acyl-Co A dehydrogenase deficiency		C8, CIO, C10:l, C6
Very-long-chain acyl-CoA dehydrogenase deficiency-		**C14:1,C14,** C16
Short chain acyl-CoA dehydrogenase deficiency		C4
Multiple acyl-CoA dehydrogenase deficiency		C4, C5, C8, C12, C14, C16, C5DC
Carnitine palmitoyl transferase deficiency		CIS, C18:1,C18
C a rnitine/acy (carnitine translocase deficiency		C160H, C18:10H, C180H
Very-long-chain hydroxyacyl-CoA dehydrogenase deficiency		C160H, C18:10H, C180H
Tri functional protein deficiency		C160H, C18:10H, C180H

*MMWR: Recommendations and reports. April 13, 2001.

Table 68.5: Useful measures as an aid in the differential diagnosis of 1EM involving carnitine*

Disorder	*Plasma total (ftmoI/L)*	*Carnitine esterified (% of total)*	*Urinary carnitine*
Control	40 *M*	**<30**	Normal
Carnitine transporter deficiency (CTD)	<5	**<30**	Paradoxically high free
Carnitine palmitoyl transferase-! (CPT-1) deficiency	60-100	**<20**	Normal or high
Carnitine translocase deficiency	5-30	80-100	High ester
Carnitine palmitoyl transferase-2 (CPT-2) deficiency	10-40	40-80	Normal or high ester
Defects in ^-oxidation	**lo ;o**	30-60	High ester
3-OH-3-mcthylglutaryl-CoA-lyasc deficiency	10-30	30-60	High ester

**Atias of Metabolic Diseases* by Nyhan, W, L., and Ozand, P. T.

callosum. Disease progression is associated with extension of white matter involvement from central to peripheral and from posterior to anterior, contiguously within the centrum semiovale and internal and external capsule. Reversal of early changes has been observed following bone marrow transplantation (BMT). Abnormalities of both white and gray matter arc observed with mitochondrial disorders that affect the centra! nervous system (CN5).

Proton magnetic resonance spectroscopy (MRS) is a useful adjunct to brain MRI and allows the determination of specific metabolites (e.g., elevated levels of N-aceroacetate in Canavan's disease, and lactic acid in mitochondrial disorders, defects of gluconeogenesis, and biotin-responsive multiple carboxylase deficiency). MRS is also useful in monitoring response to treatment. Recently, MRS has enabled definition of the creatine deficiency syndromes (secondary to guanidinoaceiaie methyltransferase deficiency), a newly discovered group of disorders causing mental retardation and other neurological problems (i.e., extrapyramidal movement abnormalities, hypotonia) (Stockler-Ipsiroglu *1997).* The common feature is severe depletion of brown creatine/phosphocrcatine.

Histological examination of appropriate tissue samples can provide clues to the nature of the storage materials found in certain IEM (e.g., lysosomal disorders) (Warren and Alroy 2000). When a skin biopsy is performed, it is advisable to obtain samples for microscopic examination and for tissue culture, which can be used as a source material lor subsequent biochemical or molecul.;i :i;ciictic) testing. Disorders of amino and organic acid metabolism are not associated with deposition of storage material, although nonspecific histological changes may be found. For this group of disorders, skin fibroblasts are used for confirmatory diagnosis by enzymatic assays. For some disorders, biochemical testing is not accurate for carrier detection because residual enzyme activity in a significant proportion of carriers overlaps with values obtained from the general population. In certain IEM, molecular assays may be available for diagnostic purposes and carrier testing.

A listing of diagnostic laboratories that perform the specialized genetic tests can be found in the GeneTests Web site (www.genetests.otg). Careful attention to sample requirements and shipping/handling considerations is imperative. Clinical information must be sent along with the specimen to receive expert advice in the evaluation of patients. In cases where the diagnosis is established, detailed information may be obtained from several Web sites, including Mendcliau Inheritance in Man (OMIM), GeneClinics, and the National Organization for Rare Disorders (NORD). Several support and patient advocacy groups also provide information about community resources and ongoing clinical trials.

Mutation Analysis in the Diagnosis of IEM

Molecular genetic techniques offer an alternative means for the diagnostic confirmation of IEM (Hill 1993; Baric et al. 2001). This is particularly true for diseases associated with common mutations in which one or a few alleles account for a significant proportion of cases. When the causal mutation is known, testing of other family members permits accurate carrier identification. Furthermore, DNA analysis for prenatal diagnosis provides .1 more rapid it lean-, of diagnosis bec.i use n is performed on chorionic villi or amniocytes without the need for culture (although in practice, most laboratories insist on subsequent confirmatory testing of cultuted cells).

Examples of disorders for which DNA testing has proven useful include MCAD deficiency, myophosphorylase deficiency (McArdle's disease), and Gaucher's disease (Gregersen et al. 2000; Mairc 2001; Madonna et al. 2002). Among patients with MGAD of northwestern European descent, 80% are homozygous for a single mis sense mutation (A985G), and 17% carry this mutation in combination with another less common defect. This finding iias unproved tin reliahb ot Mt.Al) earner ideii; iiic.inoii and diagnosis, particularly of siblings who may be affected but asymptomatic at the time of family screening. In hereditary fructose intolerance, screening for the disease mutation in blood obviates the need for liver biopsy. However, in mitochondrial disorders that cause myopathy, muscle biopsy is still required because the mutant gene may not be expressed in blood or skin fibroblasts.

IEM Associated with Abnormal Brain Development and Encephaloclastic Lesions

Structural brain anomalies are often thought of as developmental anomalies, and IEM are not considered as causative. However, several metabolic disorders can cause a disruption of the normal sequence of brain development and lead to encephalocele, dysgenic corpus callosum, and neuronal migration defects (Tables 68.6 and 68.7) (Gelineau-van Waes and Finnell 2001; Jeng et al. 2001; Nissenkorn et al, 2001). For instance, cystic necrosis of white matter (± basal ganglia involvement) has been described in deficiencies of PDH, PC, and molybdenum cofactor. The mechanisms proposed to explain abnormal brain development and encephaloclastic lesions in IEM include the production of a toxic or energy-deficient intrauterine milieu, modification of the content and function of membranes, and disturbance of the normal expression of intrauterine genes responsible for morphogenesis.

Imminent Death Prior to Diagnosis in a Child with a Suspected IEM

Samples needed for diagnosis nuisi In- obtained when a child develops acute fatal metabolic decompensation. A correct diagnosis may help families as they cope with their loss and enables appropriate counseling and prenatal diagnosis for subsequent pregnancies. Plasma (separated from whole blood) and urine should be frozen (Chace et al. 2001; Chakrapani et al. 2001). A skin sample should be obtained under sterile technique (using alcohol swabs and not iodine, which can interfere with cell growth) and stored at room temperature in tissue culture medium. When a storage disorder is suspected, a small snip of skin should be obtained and placed in glutaraldehyde for subsequent electron microscopic studies.

Management Considerations

The appropriate management of a patient with an IEM is determined by the particular metabolic derangement. Therapeutic strategies may include one or more of the following approaches: (1) substrate reduction by dietary manipulation or precursor synthesis inhibition; (2} removal (or enhanced clearance) of the toxic metabolites; (3) replenishment of depleted metabolites and/or cofactor supplementation; (4) enzyme (replacement) therapy; and (5) cellular replacement (e.g., bone marrow, liver, or kidney transplantation) (Chakrapani and Wraith 2002; Ogier de Baulny 2002). Gene therapy had been actively explored but the recent unexpected death of a study subject with OTC deficiency has prompted reexamination of this approach, with greater caution demanded for future clinical trials (Hsich et al. 2002). Other approaches under consideration are liver repopulation, chaperon-mediated therapy for diseases associated with residual enzyme activity, and the transplantation of stem cells with directed differentiation along specific lines (Gregersen et al. 2001; Grompe 2001, 2002). These advances have changed the attitude toward patients with IEM away from nihilism and hopelessness.

Table 68.6: Developmental brain malformations associated with an IEM*

Disease	*Neural tube defects*	*Holoprosencephaly*	*Cerebellar malformations*	*Hypoplastic temporal lobes*
Mitochondrial disorders				
Respiratory chain enzyme deficiency			1	
Fatty acid oxidation			t	
Glutaric acidemia 2				
Folic acid metabolism				
Mcthylenetetrahydrofolatc reductase deficiency				
Organic aciduria				
Glutaric aciduria L*				
Ethylmalonic aciduria				
Cholesterol metabolism				
Smith-Lcmli-Opkz syndrome				
Glycoprotein metabolism				
Congenital disorder of glycosylation type 1			4	
Trace element metabolism			-	
Menkes' kinky hair disease				

"^Nissenkorn, A„ et al. 2001, *Neurology,* vol. 56, suppl. 10, pp. 1265-1272.
'Due to a defect of the mitochondrial electron transport chain at coenzyme Q. MRI I'2-wcighted images also reveal increased signal intensity in the basal ganglia, and proton MRS show high choline:creatine ratio (indicative of dysmyetinarion) and elevated lactate.
'"Due ro deficient activity of the mitochondrial enzyme glutaryl-CoA dehydrogenase. MRI T2-weighted images also reveal increased signal intensity m the basal ganglia, and atrophy with progression,

Table 68.7: Migration disorders and dysgenetic corpus callosum associated with IEM*"

Disease	*Pachygyria lissencephaly*	*Polymicrogyria*	*Cortical heterotopia*	*Cerebellar dysplasia*	*Olivary nuclei dysplasia*	*Dysgenetic corpus callosum*
Peroxisomal disorders						
Zellweger syndrome'						
infantile Refsnm						I
Neonatal Pseudo-ALD				+		t-
Bi functional enzyme deficiency						
Chondrodysplasia punctata						
Mitochondrial disorders						
!\ ruvutt: dehydrogenase deficiency	-			+	-	-
Fumarase deficiency				t		+
Fatly acid oxidation						
Carnitnine palmitoyl transferase deficiency	-		+			
Glutaric acidemia 2			+			
Amino aciduria						
Maternal PKU						
Nonketotic liypm-JycirHTtiia						I
Organic aciduria						
3-OHisobutyric aciduria						f
3-OHburyl-CoA deacylase deficiency						I
(1 in L.-,; in il :;u'i..il-i il -.in				I		
Smith-Lemli-Opitz syndrome				-		-
Glycoprotein metabolism				·i		I-
Congenital disorder of glycosylation type 1						
Trace clement metabolism						
Menkes kinky hair disease						

^Nissenkorn, A., et al. 2001, *bleurology,* vol. 56, suppl. 10, pp. 1265-1272.
[+]Pseudo-2ellwcger and pseudo-neonatal adrenoleukodystrophy have normal appearing cortcxes.
•The perirolandic distribution of pachygyria in Zellweger syndrome may help in the differential diagnosis of infants with hypotonia. Pattern is mainly occipital in congenital muscular dystrophy.

An individualized approach is needed for each patient; some disorders require more than one management option. The clinical response to most treatment plans may vary, and residual disturbances are common. Patients may remain at risk for metabolic decompensation when stressed by infection, trauma, or surgery. Reducing energy expenditure and promoting anabolism arc immediate management goals. Emergency measures may prevent further deterioration, but most measures are nutritionally incomplete and should not be extended beyond 48 hours without dietary review. In most situations, symptomatic treatment must be ptovided in specialized care units with expertise in the specific disease.

When using special diets, attention must be given to caloric requirements and balanced nutrition that includes needed minerals and supplements. Diseases managed with dietary restriction include the aminoacidopathics: PKU, MSUD, and homocystinuria. In classic Refsum disease, reduction in dietary phytanate results in normalization of the biochemical and clinical phenotype.

In some disorders alternative dietary sources may be necessary. Thus, medium-chain triglycerides are given to patients with VLCAD and LCHAD as a lipid source. In Smith-Lemli-Opitz syndrome (3^-hydroxysterol-A^7-reductase deficiency), the use of a high cholesterol diet (± bile acids) improves growth and neurodevelopmental status, although clinical response is variable. In children with glycogen storage disorders (GSD), carbohydrates are given to prevent hypoglycemia and suppress secondary metabolic derangements (i.e., hyperlipidcmia, hyperuricemia). In the urea cycle disorders, arginine or citrulline is given to make up for compounds that are not synthesized secondary to the metabolic block.

Methods in enhance excretion or detoxification ol toxic metabolites ate employed when theit accumulation cannot be corrected by dietary manipulation. In patients with hyperammonemia, sodium benzoate and sodium phenylbutyrate, which conjugate with glycine and glutamine, are given to facilitate nitrogen excretion (Figure 68.1). In isovaleric acidemia, oral glycine conjugates with the highly

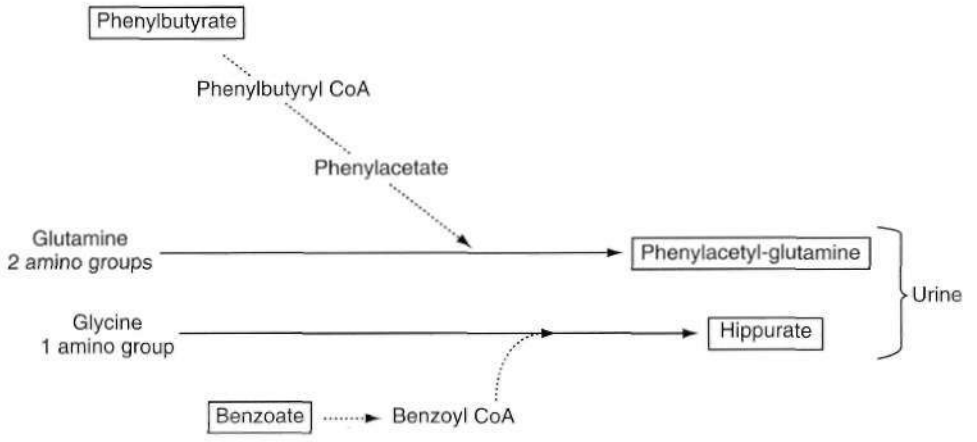

FIGURE 68.1 Alternative pathways to reduce accumulation of ammonia.

toxic isovaleric acid to form a harmless by-product excreted in the urine. Administration of cysteminc to patients with cystinosis promotes the formation of cysteine, which is subsequently excreted in the urine. Carnitine supplementation is given to patients with organic acidemia to prevent carnitine deficiency secondary to the formation and renal excretion of acylcamitinc compounds. During acute metabolic decompensation, dialysis and hcmofiltration may be used to facilitate rapid clearance of roxic metabolites. These techniques have been applied in the treatment of MSUD and carbamoylphosphate synthetase deficiency (Schaefer et al, 1999; Daschner and Schaefer 2002).

Novel therapeutic strategies for IEM are directed at blocking the production of toxic metabolites through the use of substrate synthesis inhibitors. In tyrosinemia type I (fumaroylacetoacetate hydrolase deficiency), NTBC (2-nitro-4-trifluoro-methylbenzoyl-l,3-cyclohexanedione) reduces the production of downstream metabolites of tyrosine degradation by inhibiting the enzyme 4-OH-pl'iLTi} jpyruvate citix^LiKisc. 'lit.- enzyme imolved in a

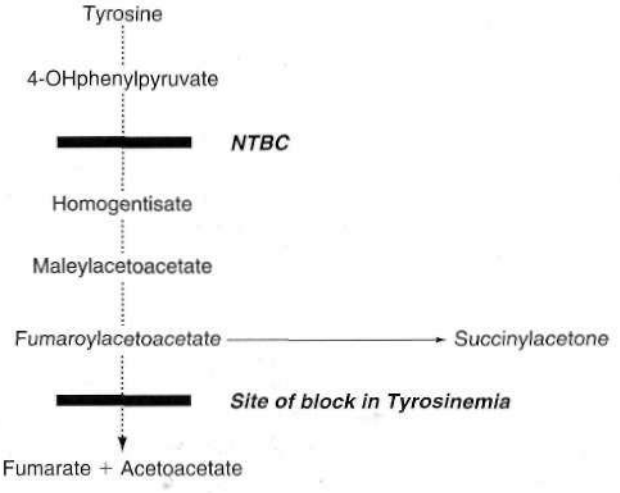

FIGURE 68.2 Substrate reduction therapy.

reaction preceding the block (Figure 68.2). In one study of NTBC in more than 300 patients with tyrosinemia type 1, 95% showed improvement of hepatic and kidney function (Grompe 2001). In Gaucher disease type I, NB-DNJ (N-butyldcoxynojirimycin) administration leads to decreased liver and spleen volumes and a gradual but significant improvement in hematological parameters with a decline in the levels of disease activity markers (Cox et al. 2000). NB-DNJ inhibits glucosyltransferase, the first enzymatic step in glycosphingolipid (GSL) biosynthesis. Metabolic homeostasis is achieved by limiting the accumulation of substrate to a level that can be sufficiently catabolized by a mutant but partially active enzyme. Given this mechanism of action, NB-DNJ may be potentially useful for other disorders of GSL metabolism (e.g., late-onset Tay-Sachs and Sandhoff disease).

The underlying defect in some IEM may be partially corrected by replenishing depleted substrates. In carnitine-transport defect, the use of carnitine results in the resolution of cardiomyopathy and prevention of further episodes of hypoketotic hypoglycemia. In other disorders, the production or binding affinity of a cofactor required for enzyme activity is impaired. These defects can be corrected by administration of pharmacological doses of the required supplement. Biotin given to children with biotinidase or holocarboxylase deficiency has led to good clinical outcomes, except in the most severe forms with neonatal-onset (Wolf 2002). Vitamin B12 given for late-onset forms of methylmalonic acidemia (MMA) caused by defects of adenosylcobalamin metabolism leads to a sustained decrease of toxic metabolites and a favorable developmental prognosis (Nicolaides et al. 1998). Suppression of gut microbial propionate production (through the use of metronidazole to inhibit anaerobic colonic flora) and dietary protein restriction are complementary approaches provided to children with MMA.

Additional examples of pharmacological correction include the use of tetrahydrobiopterin (BH_4) to treat disorders of biopterin synthesis, rare variants of the hyperphenylalaninemia. Although BH4 reduces elevated

Table 68.8: Cofactors used in the management of various IEM

Cofactor	*Dose (mgld)*	*Disorder*
Biotirj	10-20	Propionic aciduria Multiple carboxylase deficiency Hypcrlacticacidcmia due to pyruvate carboxylase deficiency
Carnitine	50-100 PO 400 rv	Branched-chain organic aciduria |MMA, PA, IVA) Primary hyperammonemia H y perl actica c id e m i a Fatty acid oxidation defects
• ..(III.I.. : 11 i 11 (B ₁ ₂)	1-2	Methylmalonic aciduria
Folinic acid	10-40	Folinic-responsive seizures
Pyridoxine (B_{fi})	50-100	Pyridoxine-responsive seizures, hyperoxaluria type 1, aromatic i.-amino acid decarboxylase Glutaric aciduria Homocysteincmia
Riboflavin (B_2)	20-40	Fatty acid oxidation defects
Thiamine (B])	10-50	Maple syrup urine disease Hyperlacticacidemia due ro pyruvate dehydrogenase deficiency

plasma phenylalanine levels by its action on liver phenylalanine hydroxylase, access to the CSE is minimal. Response has been observed in those with a peripheral type of defect. Tetrahydrofolate prevents demyelination in children with folate deficiency and dihydroptcridinc reductase deficiency (Steinfeld et al. 2002). Responsiveness to cofactor administration can be assessed by controlled enzyme assays involving the patient's cultured skin fibroblasts. A list of the cofactors used in various metabolic disorders and the recommended doses are shown in Table 68.8.

Enzyme replacement therapy (ERT) has been shown to reverse the hematological and visceral manifestations of Gaucher's disease. This approach has been considered for the treatment of lysosomal storage disorders (LSD) due to single enzyme deficiencies. The relevanl enzymes are produced from genetically manipulated mammalian cells in culture and subsequently modified to expose the appropriate sugar residues to facilitate targeted cell uptake. Once purified, the recombinant enzyme is given intravenously on a regular basis. Beneficial effects have been noted in patients with Fabry's disease, MPS type I (Hurler-Scheie syndrome), and GSD II (Pompe's disease) (Pastores and Thadhani 2002). Enzyme therapy is also being explored for other LSD including Niemann-Pick disease type B, MPS II (the mild variant of Hunter's syndrome), and MPSVI (Maroteaux-I.amy syndrome) (Schiffmann and Brady 2002).

Metabolic correction through cellular replacement by BMT has been performed in patients with LSD (e.g., MPS I, Gaucher's disease type III) (Krivit et al. 1999). In X-hnked adrcnoleukodystrophy, BMT has resulted in prolonged remission with reversal of MRI abnormalities and stabilization or improvement of motor function (Shapiro et al. 2000). Although BMT has altered the natural course of these diseases, donor limitation issues, procedural risks and long-term care considerations (e.g., immunosuppression) exist. Advances in the methods of conditioning (e.g., non-myeloablative procedures) prior to BMT and utilization of umbilical cord blood have addressed some of these concerns. Patients with IEM who may be suitable candidates for BMT should have serial follow-up visits incorporating neuropsychological and neuroradiological studies so that intervention can be timed prior to significant disease progression to allow an outcome with minimal neurological sequelae. BMT is not appropriate for disorders characterized by rapid neurodegeneration, such as MPS II (severe Hunter syndrome) and MPS III (Sanfilippo syndrome).

For disorders where the metabolic defect is confined to the liver (e.g., Crigler-Najjar syndrome, Hyperoxaluria type I) or leads to single organ failure (e.g., end-stage renal insufficiency in Fabry's disease and Hyperoxaluria type I, and liver failure in OTC deficiency, ryrosinemia, and GSD-IV), organ transplantation may be appropriate (Burdelski and Rogiers 1999; Khanna et al. 1999). In patients with tyrosinemia who do not respond ro NTBC therapy or have evidence of hepatic malignancy, orthotopic liver transplantation is the treatment of choice. Microchimerism (the migration of donor-derived cells from the allograft) has been reported in a few patients following livet transplantation. However, this phenomenon is probably not sufficient to correct the systemic metabolic defect.

Symptomatic treatment remains a vital component of patient care. Indeed, several palliative measures have been shown to improve quality of life and reduce the incidence and severity of disease-related complications. For instance, i-dopa improves motor function in patients with tyrosine hydroxylase deficieocv. DDAVP (dcamino-arginine-vasopression) has been used to reduce the tendency for abnormal bleeding during surgery of patients with GSD type 1A (von Gierke's disease). G-CSF (granulocyte colony-stimulating factor) has been administered to patients with GSD IB and neutropenia to minimize the risk of recurrent bacterial infection and gastrointestinal tract ulceration. Steroid and mineralocorncoid replacement is essential in patients with adrenoleukodystrophy and adrenal insufficiency.

In addition to dealing with the medical problems of an affected child, families should be provided with genetic counseling. Approximately 90% of the IEM are inherited

as autosomal recessive traits. Of the remaining 10%, approximately two thirds are X-linked and one third arc autosomal dominant traits. Prenatal diagnosis is available for most IEM. A tecent study that looked at teproductive decisions made by parents of children with IEM noted 56% were receptive to future prenatal diagnosis, and 41% would choose to take measures to prevent another affected pregnancy (Read 2002). The study also found that parents of children with IEM have higher scores on a stress index, lower scotcs on an adaptive behavior scale, and have fewer persons in their social support network. Furthermore, the parents expressed greater worry about their child's future and perceived difficulty in meeting the child's extra care needs. These observations underscore the importance of early intervention, supportive care and appropriate genetic counseling.

The Adolescent with an IEM and Transition to Adulthood

As a tcsult of early diagnosis and intetvention, many affected children have achieved longer survival. The overall prognosis and quality of life for these individuals in adolescence and adulthood is greatly influenced by the care they receive as children. An important goal is for societal integration and life-fulfillment, which may be possible in certain cases.

In most instances, patient care has been provided by pediatricians and metabolic specialists. Often, the majority of adult physicians are not ptepared to assume the management of these patients as they grow older. Familiarity with the natural history of the disease may lead to anticipatory guidance and appropriate monitoring, with early intervention at the first sign of trouble (Eons and Packman 2002). Several examples can be cited. Hepatic adenomas, which may become malignant, develop in the second and third decade of life in patients with GSD IA. Patients with tyrosinemia are also at risk for hepatocellular carcinoma, which can be monitored by serial <*-fetoprotein measurements and livct imaging.

Other complications to watch for include acute and chronic recurrent pancreatitis, which occurs in association with the hyperlipidemias, disorders of hranched-chain amino acid degradation, homocystinuria, and acute intermittent porphyria (Simon et al. 2001). Atherosclerosis and thromboembolism are potential causes of morbidity in homocystinuria and methylcnetctrahydrofolate reductase deficiency. LCHAD may be complicated by cardiomyopathy and retinopathy. Renal insufficiency/failure may develop in patients with cystinosis, Fabry's disease, GSD I, and MMA. Metabolic stroke with bilateral globus pallidus .ihi.iim.i In :;-S .in J i-xii,;pyramidal signs m.i\ Iv .i scqiu l.i oi metabolic decompensation in MMA.

As most IEM affect multiple systems, the involvement of a multidisciplinary team with central coordination by a primary physician is essential. Patients and family members usually appreciate being included in the decision-making process. These moments of interaction can also be used as an opportunity to assess the family's understanding of the disease and its management, and their coping mechanisms.

Efforts should be directed at ensuring the child reaches his/her maximum potential. Educational programs for the affected child must be adapted to developmental level and cognitive strengths to minimize frustration and associated behavioral problems. It is important to prepare for development of increasing handicap and take appropriate steps to facilitate individual performance during activities of daily living. Special attention should be given to self-care, communications skills, and mobility issues.

All individuals become increasingly self-conscious of their body image during puberty. Support may be needed to enhance self-esteem in adolescents who feel stigmatized by theit physical appearance, particularly when the IEM is associated with facial dysmorphic features and skeletal deformities. Dysarthria impedes communication, and disturbances of bowel and bladder continence undermine self-confidence and social interaction. Some disorders are associated with delayed puberty (GSD IA, galactosemia) and CDG-la or premature ovarian failure (hypergonadotropic hypogonadism). Osteoporosis is often under-recognized as an associated condition of IEM. It most often occurs in those conditions that cause poor mobility because of cognitive or neuromuscular impairment, or characterized by chronic acidosis and renal insufficiency. When dietary regimens are required for disease control, the adolescent should be expected to manage the diet without parental assistance. Peer pressure may lead to noncompliance, and the patient must understand the potential implications of this course of action.

Pregnancy is a critical time when measures are needed to ensure a good maternal-fetal outcome (Walter 2000), Women of childbearing age with an IEM must be well controlled before conception. Close follow-up is required during labor and delivery and postpartum. Children born to women with poorly controlled PKU are at risk for microcephaly (70%), attention deficit disorder and mental retardation (>90%), intrauterine growth retardation (40%), and congenital heart disease (12%). Risk to the fetus correlates with maternal p:ii.-iiy].il.minr k'vcls. Outcomes are optimal if maternal blood phenylalanine of < 10 mg/dL (600 uM) is achieved by 8-10 weeks of gestation and maintained throughout the pregnancy.

Women with liomocyslinisria **icvslalliioiniu ;> synthasr** deficiency) may have an increased risk for spontaneous abortion and preeclampsia. Pregnancy may exacerbate the cutaneous lesions of porphyria cutanea tarda during the first trimester. Women who are carriers of OTC deficiency may develop a hyperammonemia encephalopathy during the postpartum period. Postpartum metabolic decompensation also occurs in MSUD.

Psychiatric symptoms arc primary features of some disorders or may develop secondary to metabolic decompensation (Gray et al. 2000). For instance, behavioral changes are seen in individuals with X-linked adrenoleukodystrophy, late-onset GM2 gangliosidosis, and porphyria. Cognitive and behavioral problems also occur in children with PKU, especially in those who are not compliant with dietary restriction. Children subjected to BMT are at risk for neuropsychological complications secondary to chemotherapy and irradiation.

DISORDERS INVOLVING COMPLEX MOLECULES

The metabolism of complex molecules in lysosomes and peroxisomes involves different biochemical pathways than those responsible for the processing of dietary constituents. This explains why dietary manipulation and vitamin or cofactor supplementation are not effective. An overview of the distinctive characteristics of these organelles and the associated general features are summarized in Tables 68.9 and 68.10. LSDs involve tissues and organs that develop normally but later malfunction. In contrast, early-onset peroxisomal disorders arc often expressed as severe developmental malformations,

Lysosomal Storage Disorders

The lysosome is a membrane-hound intracytoplasmic vacuole that contains enzymes required for the degradation of complex lipids, proteins, and nucleotides. Its acidic milieu (pH-^5.4) is required for optimal activity of the contained hydrolytic enzymes and their cofactors/activators. More than 40 different LSDs are described (see Table 68.10).

H.G. Hers first proposed the LSD concept in 1963 based on the detection of glycogen-filled vesicles of lysosomal origin in cells obtained from a patient with Pompe's disease. Progressive lysosomal storage of incompletely metabolized substrates occurs either because of primary hydrolase deficiency, deficiency of a protective protein that aids in the lysosomal targeting and prevention of premature degradation of enzymes, or the absence of an "activator protein" necessary for enzyme-substrate interaction and degradation. Additional disease mechanisms include abnormal protein/enzyme processing, defects of posttranslational modification in the endoplasmic reticulum, failure to attach the appropriate targeting signals (e.g., mannose-6-phosphate) in the Golgi apparatus, and defective removal or transport of the substrate from lysosomes (e.g., Niemann-Pick type C and sialic acid storage disease) (Aula et al, 2002; Carver and Heidcnrcich 2002). Abnormalities in endocytosis, vesicle fusion, and the processing of autophagic elements are identified in Danon disease from defects of lysosomal associated membrane protein 2 (LAMP2). LAMP2 is an integral membrane protein of endosomes and lysosomes. Other syndromes of intracellular vesicle damage chat causes abnormal lysosomal formation and storage are Hermansky-Pudlak syndrome and Chediak-I Iigashi syndrome.

Clinically, the LSDs are a heterogeneous group of disorders involving multiple organ systems. The clinical features reflect the cellular sites of substrate storage and resultant organ dysfunction. In rapidly progressive forms, the onset of clinical features is in the newborn or in early infancy. With later-onset forms, the initial features are delayed until adolescence or adult life, and the course may be acure, subacute, or chronic. Acute and subacute courses are usually associated with primary CNS involvement, developmental delay, and mental retardation.

Unlike the small molecule diseases, the clinical features of LSD are often characterized by a subacute or chronic encephalopathy. Myoclonic seizures are seen in the following disorders: GMj-gangliosidosis, sialidosis type 1, Schidler's disease (a-N-aeetylgalactosaminidase deficiency), Gaucher's disease types IT and III, and fucosidosis. Some LSDs do not have primary CNS involvement (e.g., Fabry disease, Gaucher's disease type I, Niemann-Pick type B, MPS I-Scheie' syndrome, MPS IV-Morquio syndrome and mild MPS VI-Maroteaux-Lamy syndrome).

Tabic 68.9: Characteristic biochemical features of the major cellular organelles

Lysosome	*Peroxisome*	*Mitochondria*
Acidic compartment, actively maintained (proton ATPase)	Metabolic functions: ^-oxidation of fatty acids and derivatives, Ether phospholipid synthesis	Site of coupling of oxidation and phosphorylation, generation of ATP
Terminal compartment in en doc y tic pathway	Increased VI.CFA	Symptoms reflect tissue specificity for aerobic metabolism: Btain > Skeletal, Cardiac Muscle > Kidney > Eye
Rich in acid hydrolases (protease, glycosidase, sulphatase)	Disease often classified based on loss of single or multiple peroxisomal enzyme hi action	Has unique DNA, which replicates independently of nuclear DNA
Enzymes use M-6-P targeting into pre lysosome	Due ro defects of biogenesis and targeting thru PTS 1 and 2	Occur re 1 let- may be sporadic, matrilineal or autosomal (dominant or recessive) inheritance
Autosomal recessive, except Fabry's disease, Hunter's syndrome (MPD-II), and Danon disease which are X-linked traits	Autosomal recessive, except for X-l inked ad rem leukodystrophy	

Table 68.10: Classification of lysosomal storage diseases

Stored substrate	*Disease*	*Enzyme deficiency*	*Gene tocus*
Sphingolipids			
GMj -gangliosides, glycolipids	Tay-Sachs	ff-Suhunit ^-hexosaminidase	15q23-24
:_;Lr>11.:.i.!.• oligos iccharides	GMj-gangliosidosis (3 types)* Sandhoff	^-Subunit ^-hexosaminidase	5ql3
	GM_2-gangliosidosis GMi-gangliosulosis, AB variant	GM_Z activaror	5q32-33
GMt-gangliosides, oligosaccharides, keratan sulfate, glycol ip ids	GMi-gangliosidosis (3 types)*	/^-Galactosidase	3p21-3pter
Sulpha tides	Metachromatic leukodystrophy (MLD)	Arylsulphatase A (ga la ctose-3-sulpha ta se 1	22q1331-qter
GMi-ga ng! i os ides, sphingomyelin, glycol!pids, sulphatide	MLD variant	Saposiu B activator	10q21
Ga I actosy Ice ra m i d e s	Krabbc	Ga 1 actocerebros i dase	14q31
or-Gala ctosyl-sph i n golipids, oligosaccharides	Fabry	of-Galactosidase A	Xq22
GI ucos y leer am i de, globosides	Gaucher (3 types)*	/*-Clucosidase	lq21
Glucosylceramidc, globosides	Gaucher (variant)	Saposin C	10q21
Ceramidc	Faiber (7 types)	Acid ccramidase	X p22-21.2
Sphingomyelin	Niemann-Piek rypes A and B	Sphingomyelinase	llplS.1-15.4
Mucopolysaccharidoses (glycosamingoglycans)			
Dermatan sulphate and heparan sulfate	MPS I (Hurler Scheie)	a-l.-iduronidase	4pl6.3
	MPS II [Hunter)	Idu ron ate-2-sulphatase	Xq27.3-28
Heparan sulftc	MPS IMA (Sanfillippo A)	Sultainidase	17q25.3
	MPS 111B (Sanfillippo B)	tf-N-acetylglucosamindase	17q21,l
	MPSIIIC (Sanfillippo C)	Acetyl CoA:ff-glucosaminide-N-acerylrransferase	—
	MPS HID (Sanfillippo D)	N-acety lgl uco sa m i n e-<s-s u I ra ta s e	12ql4
Keratan sulphate	MPS IVA (Morquio A)	G a 1 actosa m i ne-6-su I ph a ta \e	1Sq24.3
	MI'S [VB (Morquio B)	/*-D-ga 1 actosid asc	3p21.33
Derma tan sulfate	MPS IV iMaroreaux-Lamy)	N-acetyl ga 1 actosa m i ne-4-s ul fa ta se	5ql3-14
Dermatan sulfate and heparan sulfate	MPS Vll (Sly)	/i-ll-glucoronidasr	7q21,1-22
Hyaluronan	MPS IX	Hyaluronidase	3p21.3
Glycogen			
Glycogen	Glycogen storage I1A (Pompe)	ff-D glucosidase	17q23
Glycogen	i 'l mon	Lysosomal associared membrane protein-2 (LAMP-2)	Xq24-25
Ol i gos acchari des/g lycopepti des			
ff-Mannoside	ur-Mannosidosis	a-Mannosidase	I9p13.2-q12
^•Mannosidc	£-Mannosidosis	^-Mannosidase	4q22-25
«-f ucosides, glycolipids	o-Fucosidosis	a-Fucosidase	lp34.1-36.1
a-N-acery tgalactosa m i nide	Schindler	of-N-acetylgalactosaminidase	22ql3.1-13,2
Sia lyloligosa ccha rides	Sialidosis	ff-Neuramin id a se	6p21.3
Aspartylglucosamine	Asparrylglucosaminuria	A-;V:II vl:[1].!-.. osamindasc	4q34-35
Multiple cmymc deficiencies			
Glycolipids, oligosaccharides	Mucolipidosis II (I-cell disease)	N-acetyl glucosamine^-phosphor raiiriH-Tiise	4q2l-q23
Sulphatides, glycolipids, gl ycosa in i nogl yc a n s	Mulrbk s-ulfatijcs		
Lipids			
Cholesterol esters	Cholesterol ester storage disease (Wolman disease)	V< id lipasi	10q23.2-q23.3
(' holesrerol, sphingomyelin	Xiemann-Pick tvpe C	NPC1; HE1	lSqll-12;14q24.3
Monosa ccra i des/ami no acid/mon om e rs			
Sialic acid, glucuronic acid	Infantile free sialic acid srorage (Salla)	Sialm	6qI4-15
Cystine	Cyst in os is	Cystinosin	17p12
Peptides			
Bone proteins	Pyc no dysostosis	Cathepsin K	lq21
S-aeylated proteins			
Palmitoylated proteins	Infantile neuronal ceroid-lipofuscinosis	Pa Imi toy]-protein thioesterase	l_P32
Pepstarin-inseusitive lysosomal peptidase	Late-infantile neuronal ceroid-Hpofusinosis	Pepstatin-insenstivie lysosomal peptidase	1 lpl.5

MLD = metachromatic leukodystrophy; MPS = mucopolysaccharidosis.
*Three types imply infanrile, childhood, and adulthood presentations.

Rare variants of some sphingolipid storage disorders are caused by defects in the enzyme cofactor/activator required for complete substrate hydrolysis instead of a primary-enzyme defect. Two categories of sphingolipid activators exist. One represents the GM_2-activator and the other a group of four molecules (saposin A, B, C, and D) derived by proteolytic cleavage of a common precursor, prosaposin. The gene localization for prosaposin is chromosome 10. Deficiency of the G_{M2}-activator results in the AB variant of GM2-gangliosidosis. Saposin B activates arylsulfatase A. Deficiency of saposin B gives rise to a variant of metachromatic leukodystrophy (MLD variant). Saposin C activates glucocercbrosidase and /i-galactocerebrosidasc; its deficiency leads to a clinical picture often referred to as an atypical form of Gaucher's disease (GD) because of the clinical overlap with the type 3 variant (subacute neuropathic GD). Disorders resulting from cofactor deficiencies are characterized by normal enzymatic activities in vitro when using the synthetic (artificial) substrate. Therefore the diagnosis can be missed by routine biochemical testing. Molecular analysis may reveal the presence of mutations in the relevant encoding genes.

LSDs are usually transmitted as autosomal recessive traits, except for Fabry's disease, Hunter's syndrome (MI'S-II), and Danon disease. These are inherited as X-linked recessive Traits. Biochemical assays are generally available for prenatal diagnosis. Care should be taken in the interpretation of certain enzyme assay results (e.g., arylsulfatase activity) because low values may be obtained in the presence of pseudo-deficiencies. Diagnostic confirmation is also available by molecular (DNA) testing. In families where the causal mutation is known, molecular testing enables accurate assignment of carrier or affected status. Prenatal diagnosis is possible for almost all LSD.

Neufeld and colleagues (1968) showed that an exchange of medium from fibroblasts with different disease gene mutations, MPS I (Hurler syndrome) and II (Hunter's syndrome), results in the clearance of intracellular storage material. The metabolic cross correction was due to secretion of the functional enzyme from one cell line followed by intracellular uptake by the deficient cells. These studies provided the rationale for treatment of the LSD by ERT. Today, cellular correction is achieved in certain clinical LSD subtypes through BMT and ERT. Other therapeutic strategies under consideration include the use of substrate synthesis inhibitors, chaperon-mediated agents, and gene therapy.

Peroxisomal Disorders

The peroxisome is an organelle involved in ^-oxidation of very-long-chain fatty acids (VLCFA), the synthesis of plasmalogen and bile acids, and oxidation of pipecolic, phytanic, and dicarboxylic acids. Peroxisomal disorders are generally classified according to the presence of single or multiple enzyme deficiencies (Table 68.11). Most peroxisomal matrix proteins are targeted using one of two targeting sequences in a unique system allowing the importation of oligomerized proteins through a specific shuttle involving a receptor and its cargo. Defects of these cellular mechanisms lead to disruption of peroxisomal metabolic functions (Baumgartner and Saudubray 2002).

The spectrum of clinical findings in peroxisomal disorders includes craniofacial abnormalities, encephalopathy. limb malfotmations, ocular abnormalities, and hepatic and intestinal dysfunction. In the late-onset types, the features are nonspecific and include behavioral changes and deterioration of intellectual function, Demyelination occurs in X-linked adrenoleukodystrophy, visual and hearing deficits in Refsum disease, and peripheral neuropathy and gait abnormality in the atypical peroxisomal biogenesis defects,

Screening for peroxisomal disorders is facilitated by demonstrating elevated plasma VLCEA levels and/or impaired erythrocyte plasmalogen synthesis. Increased phytanic acid levels are found in Refsum disease and rhizomelic chondrodysplasia punctata.

DISORDERS INVOLVING SMALL MOLECULES

Disorders of intermediary metabolism often result in the accumulation of compounds that cause acute progressive neurological disorders. The term "defects of small molecules" is used because the compounds that build up proximal to the metabolic block are often elevated in blood and CSF and may be excreted in the urine or potentially cleared by dialysis. Diagnosis is enabled by detection of these compounds in blood, CSF, and urine. Serin I measurements i a n lie used in monitor the eftccth etiess of disease control. Treatment often requires the elimination of the accumulating toxic compounds by dietary restriction and/or the provision of vitamins or cofactors. During episodes of acute decompensation, metabolic homeostasis may be rapidly achieved by exchange transfusion or by peritoneal or hemodialysis. Chronit control necessitates the use of compounds that bind with the toxic molecules and facilitate alternative pathways of clearance.

Included in this group are the aminoacidopathies, organic acidemias, and the urea cycle defects. Examples for each category and their estimated incidence are listed in Table 68.12.

Disorders of Amino and Organic Acid Metabolism

ll-.;' iii.iiii cluneal feature "I lliese c n:uli(inns i– .1 symptom free interval followed by an acute catastrophic event (e.g., vomiting, lethargy, and coma). The acute episodes arc characterized by metabolic acidosis, hypoglycemia, and/or hyperammonemia (Burlina et al. 1999; Ogier dc Baulny and Suadubray 2002). These metabolic disorders can lead

Table 68.11: Peroxisomal disorders

1. Defects of Biogenesis I	Craniofacial dysmorphic fearures: large anterior fontanel, high forehead
Spectrum:	Psychomotor retardation
Zellweger syndrome—severe	Hypotonia
Neonatal ALD	Neonatal seizures
Infantile Refsum disease—relatively milder	Cortical dysplasia, neuronal migration defects
	Hepatomegaly with liver dysfunction
	Chorioretinopathy
	Sensorineural hearing loss
	Calcific stippling of the epiphysis
	Renal cysts
2. Defects of Biogenesis II	Shortened proximal limbs
Rtnzomelie chondrodysplasia punctata	Facial dysmorphic features
	Cataracts
	Psychomotor retardation
	Calcific stippling of the epiphysis (may disappear after age 2 years) and extra skeletal tissues
	Ichthyosis
Single function deficiency	
Ad re no leu ko dy s tro ph y	Intellectual regression, behavioral problems, spastic paraparesis,
Adrenomyeloneuropathy	sphincter problems, adrenal insufficiency
Refsum disease	Retinitis pigmentosa, polyneuropathy, cerebellar ataxia
Pseudo-Zellweger syndrome	
Pseudo-Neonatal Al.D	
Pseudo-Infantile RD Bifurn.tioiii.il	
Protein deficiency	
Hyperpipecolic acidemia	Enzyme defect not definitively established
	Encephalopathy, seizures
	Hypocholestcrolemia
	Vitamin E deficiency

to progressive developmental regression and spasticity. A specific diagnosis relies on the pattern of abnormalities displayed on the amino and organic acid screening profile and by detection of the relevant acylcarnitine compounds in plasma and urine. These disorders are usually treated by dietary restriction, elimination of the toxic compounds, and adjunctive treatments using specific cofactor or vitamin supplements and carnitine as indicated.

Hyperammonemia

Blood ammonia is derived from protein catabolism and as a metabolic by-product of bacterial reactions in the gastrointestinal tract. It is a neurotoxic metabolite that promotes excessive glutamine production in the cytosol of astrocytes by its action on glutamine synthetase. Ammonia can promote cellular swelling and brain edema by its osmotic effect. Blood ammonia concentrations may be elevated from a primary defect of the urea cycle (UCD) or secondarily in disorders of amino and organic acid metabolism. In the organic acidemias, intraniitochondria) accumulation of acyl-CoA esters causes secondary inhibition of the urea cycle enzymes. The clinical diagnosis is made by assessment of the plasma amino acid and ammonia levels and analysis of urine organic acid profile. Measurement of orotic acid levels in urine is useful in the differential diagnosis (Table 68.13). Defects of the urea cycle are all inherited as autosomal recessive traits excepl for ornithine transcarbamylase deficiency, which is inherited as an X-linkcd trait.

The clinical features arc variable; newborns may exhibit rapidly progressive neurological deterioration, with

Tabic 68.12: Disorders of small molecule and energy metabolism

Disorder	*Incidence*
Aminoacidopathy	1:10,000
Phenylketonuria (PKU)	1:180,000
Maple syrup urine disease (MSUD)	1:300,000
1 lomocystinuria	
Tyrosinemia	
Organic acidemia	
Branched-chain (methylmalonic, propionic, isovaleric)	MMA 1:20,000
Urea cycle	
Ornithine transcarbamylase deficiency	1:70-100,000
Arginase	< 1:100,001)
Carbohydrate (sugar) intolerance	
Galactosemia	1:40,000
Glycogen storage disease type la (von Gierke's disease)	1:100,000
Fatty acid oxidation defects	
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	1:20,000

Table 6R.13: Defects of the urea cycle

Enzyme deficiency	*Plasma amino acid profile*	*Urine orotic acid*
Carbamoylphosphate synthase	AKi-m eiiniilnu-. JiviL-.iM.-d alanine: Increased glutamine, alanine	Normal or low
Ornithine Lranscarbamylase	Absent citrulline, decreased arginine; Increased glutamine, alanine, uracil	Increased
ArgininOSUCCinic synthase (Citrullinemia)	Markedly elevated citrulline; decreased arginine	Increased
Argininosuccinic lyase	Moderately elevated citrulline, argininosuccinic acid; decreased arginine	Increased
Arginasc	Increased glutamine, alanine	Increased

irritability or lethargy, seizures, coma, and respiratory arrest (Burton 2000; Stciner and Cederbaum 2001). Transitory hyperammonemia of the newborn (THAN) must also be considered. Neonates with THAN have significantly lower birth weights for gestational age, and chest radiographic findings are usually abnormal. Affected newborns are managed with exchange transfusion and peritoneal dialysis if necessary. Most THAN survivors have normal neurological and developmental examinations on follow-up and do not experience recurrent episodes of hyperammonemia.

Later-onset clinical UCD manifestations include developmental delay, behavioral problems, hepatomegaly, and gastrointestinal symptoms. Affected children and adults may show behavioral problems, confusion, irritability, and cyclic vomiting, with deterioration in mental status during metabolic stress. Of the UCD, arginasc deficiency is uniquely characterized by spastic diplegia, dystonia, ataxia, and seizures.

Two disorders of amino acid metabolism, lysinuric protein intolerance (I.SI) and hypcrainmoncmia-hyperormthinemia-homocitrLillinemia (HHH syndrome), are associated with hyperammonemia' encephalopathy. LSI presents with growth retardation, hepatic and renal dysfunction, and hematological and pulmonary abnormalities. It is caused by a defect in dibasic amino acid transport that leads to an increased urinary excretion of arginine, ornithine, and lysine. HHH syndrome is associated with an elevation of plasma ornithine and increased urinary excretion of homocitrulline {a derivative of lysine). The clinical features include intolerance to protein feeding, vomiting, seizures, and developmental delay. Ornithine administra-i-.nn improves urea cycle function m the Ml II I •»yndronie by providing the required precursor for uninterrupted completion of the sequential metabolic steps (Summar 200 1:•. Progressive spastic paraparesis is a late complication.

DISORDERS 01: ENERGY METABOLISM

The energy requirements of cellular metabolism are derived from carbohydrates in the nourished state and from glycogen and fatty acids stores during fasting. Cellular energy is stored in the form of ATP, generated in the cytoplasmic and mitochondrial compartments from glucose and fatty acid oxidation. The relevant metabolic pathways are to a great extent hormonally mediated. Tissues with high aerobic metabolic rates, in the brain, skeletal muscle, and cardiac muscle are most vulnerable to defects of energy metabolism.

Several clinical presentations suggest an underlying defect of energy metabolism (Sim et al. 2002). Acute or recurrent exercise intolerance and myoglobinuria, with or wirhout cramps, are features of the glycogen and fatty acid oxidation (FAO) disorders. Progressive neuromuscular weakness and hypotonia are features of the glycogenoses (acid maltase, debrancher enzyme, and brancher enzyme deficiencies), FAO defects, involving carnitine uptake and carnitine acylcarnitine translocasc detects, and mitochondrial disorders (cytochrome oxidase deficiency). Acute or chronic weakness occurs in long-chain or very long-chain acyl coenzyme A (CoA) dehydrogenase, short-chain 1-3-hydroxyacyl-CoA dehydrogenase, and trifunctional protein deficiencies.

Avoidance of fasting is an important consideration in the management of patients with disorders of carbohydrate metabolism (glycogenolysis), fatty acid oxidation, and ketogenesis. In some cases, the calories for energy metabolism must be maintained by nasogastric or gastrostomy tube feedings.

Glycogen Storage Diseases

The glycogen storage diseases (GSD) are caused by enzyme defects of glycogen degradation. The GSD are usually designated by a type number that reflects the historical sequence of their clinical characterization. Several subtypes are also designated in tecognition of the individual who called attention to the condition. For instance, Pompe's disease is the eponymous designation for GSD type II. GSD that result from liver enzyme defects are characterized by hepatomegaly and hypoglycemia. GSD that result from muscle enzyme defects are characterized by cramps on exertion and progressive weakness. Disorders of carbohydrate metabolism are inherited as autosomal recessive

traits, except for the X-linked form of phosphorylase kinase deficiency (GSD type VI).

Disorders of Gluconeogenesis

Defects of gtuconeogenesis result in recurrent hypoglycemia with lactic acidosis, with or without ketosis. Neurodegenerative features are found in deficiencies of pyruvate carboxylase (PC) and phosphoenolpyruvate carhoxykinasc (PEPCK).

batty Acid Oxidation Defects

The oxidation of fatty acids involves four components: the carnitine cycle, mitochondrial ^-oxidation, electron transfer, and the synthesis of ketone bodies (KB), Fatty acids and KB are used by some tissues as an alternative energy source to spare the consumption of glucose. In contrast to muscle, the brain is unable to fully oxidize fatty acids but can utilize KB synthesized by the liver. In early-onset cases, the clinical disease course is characterized by episodes of hypoketotic, hypoglycemic coma and periods of metabolic decompensation during prolonged fasting, operations, or infections K ioares 1998). Rhabdomyolysis, cardiomyopathy, and skeletal muscle weakness are features of chronic late-onset cases. Carrier women, hetcrozygoLis for a mutation associated with LCHAD deficiency and possibly other disorders of fatty acid oxidation, who arc pregnant with a homozygous (affected) fetus may be at risk for acute fatty liver.

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is the most common FAO defect. The initial crisis is fatal in up to 25% of cases. The diagnosis of MCAD is based on organic acid profile showing elevated levels of 5-OHhexanoate, 7-OHoctanoate, hexanoylglycine, suberylglycine, and phenylpropionylglycine.

Disorders of Ketogenesis and Ketolysis

Excess acetyl Co A, a by-product of FAO, is converted in the liver to ketones (3-OHbutyrate and aeetoaeetate) that are subsequently transported to and oxidized in the peripheral tissues. Ketone utilization by the brain spares other tissues, such as erythrocytes, which cannot meet their energy requirements from nonglucose substrates. Ketoacidosis is a prominent secondary feature of several defects of in tcrme di a r y mcta b ol i sm.

Primary disorders of ketogenesis and ketolysis are rare. Mitochondrial /i-ketothiolase deficiency leads to severe episodes of ketoacidosis and encephalopathy, which shows a rapid response to intravenous glucose administration. Urine organic acid analysis reveals the presence of 2-methyl-3-OH-butyrate, 2-methylacetoacetate, 2-butanone, and tiglyglycine (derived from the metabolism ul isok'uciiie). Cytosolic aceloncetyl-CoA ihiol.isc deficiency is a rare cause of psychomotor retardation and hypotonia, features that reflect the importance of the involved enzyme in sterol and isoprenoid synthesis.

MISCELLANEOUS METABOLIC DISORDERS

Dyslipidemias

Lipids arc transported in plasma on lipoproteins (consisting of a hydrophobic core of triglycerides and cholesterol esters), wrapped in an am phi phi lie coating of apolipoproteins, phospholipids, and unesterified cholesterol. Diseases associated with abnormal lipid absorption and metabolism can lead to low blood levels of the fat-soluble vitamins (A, D, E, and K). This is correctable by oral or parenteral supplementation.

Abetalipoproteinemia and Hypobetalipoproteinemia

Abctalipoproteinemia and hypobetalipoproteinemia are disorders of reduced low-density lipoprotein (LDL)-eholesterol metabolism. In abetalipoproteinemia, a rare autosomal recessive disorder also known as Bassen-Kornzweig syndrome, plasma apolipoprotein-B (apoB) levels are undetectable, and total cholesterol levels are low (usually <50 mg/dL). The defect is caused by absence of microsomal triglyceride transfer protein (MTP), and not by mutations in the apoB gene. MTP is a heterodimcric protein involved in the transfer of lipid to apoB. Patients with abetalipoproteinemia have fat malabsorption and neurological disturbances that include dysmctria, cerebellar ataxia, and spastic gait. Ocular disturbances are common and include retinitis pigmentosa, impaired night vision, nystagmus, and ophthalmoplegia. Failure to thrive and steatorrhea occurs in infancy, whereas the neurological complications appear during adolescence. Other features include anemia (acanthocytosis) and arrhythmia. Acantbocytosis is a consequence of reduced erythrocyte membrane fluidity. It is also seen in vitamin E deficiency and neuroacanthocytosis (Rampoldi et al. 2002).

Hypobetalipoproteinemia, due to mutations in the apoB gene, causes a clinical syndrome similar to Friedreich's ataxia (ataxia and peripheral neuropathy). It is transmitted as an autosomal dominant trait. Most patients have low LDL-cholesterol concentrations (usually < 60 mg/dL). Rare patients homozygous for the defect have clinical features indistinguishable from those of abetalipoproteinemia. Vitamin supplements (A and E) have a beneficial influence on the neurological and ocular symptoms. Care should be taken to avoid vitamin A toxicity by serial monitoring of vitamin levels.

Tangier Disease

Tangier disease is a rare autosomal recessive disorder caused by mutations in a cell-membrane protein called

ABCAl. ABCAl normally mediates the secretion of excess cholesterol from cells into the HDL metabolic pathway. It belongs to a family of ATP-binding cassette (ABC) transporters. These proteins are involved in the recognition of substrate and their transport across, into, and out of cell membranes. Cystic fibrosis, age-related macular degeneration, and X-linked adrenoleukodystrophy are othet disorders associated with defects of genes that encode this class of proteins. Tangier disease is characterized by severe deficiency of high-density lipoproteins (HDL) and tissue stotage of cholesterol estets. Clinical features include enlarged, orange-yellow tonsils (filled with foam cells representing deposits of ^-carotene cholesterol estets), splenomegaly, and a relapsing sensorimotor neuropathy. Patients may develop distal weakness, hyporeflexia, decreased pain, and temperature sensation with relative preservation of position and vibration sense.

Smith-Lemh-Opitz Syndrome

Smith-Lemli-Opitz syndrome is a disorder characterized by multiple malformations, growth and psychomotor retardation, and behavioral disturbances (Nowaczyk and Waye 2001). It is a disorder of cholesterol biosynthesis caused by mutations of the 7-dehydrocholestrel (DHQ-A -reductase gene, inherited as an autosomal recessive trait. Biochemical tests reveal low total cholesterol and elevated serum levels of 7DHC. Sterol abnormalities that result from deficiencies of cholesterol biosynthesis also explain other recently recognized disorders of morphogenesis (mevalonic aciduria [MVA], desmosterolosis, X-Hnked chondrodysplasia punctata, and CHILD syndrome). Sterol synthesis (SS) takes place partly in the peroxisome, and explains why SS defects show some overlap in clinical features with the peroxisomal biogenesis disorders. The diagnosis of MVA is based on determination of mevalonic acid in urine and the determination of residual enzyme (mevalonate kinase) activity. The diagnosis of other disorders secondary to distally located defects of cholesterol biosynthesis requires sterol analysis in blood or tissues by GC-MS.

Cerebrotendinous Xanthomatosis (Cholestanolosis)

Cholestanolosis is transmitted as an autosomal recessive trait. The condition is caused by mutations in the stetol 27-hydroxylase gene. The primary feature is the formation of xanthomatous lesions in the brain and tendons. Neurological impairments include mental retardation, progressive spasticity, pseudobulbar palsy, and cerebellar dysfunction (Moghadasian et al. 2002). Brain MRI shows hyperintense signals that involve the corticospinal tracts in the brainstem, the white matter of both internal capsules, and the peritrigonal white matter. Bilateral cataracts and chronic diarrhea may precede the neurological deterioration. Biochemical findings include elevated plasma and bile cholestanol levels and increased urinary excretion of bile alcohol glucuronides associated with diminished biliary chenodeoxycholic acid (CDCA). Therapy with CDCA reverses the neurological features. In one study of CDCA therapy in 17 patients, dementia cleared in 10, pyramidal and cerebellar signs resolved in 5 and improved in another 8. In addition, cerebral CT scans improved in 7 (Samenuk and Koffman 2001).

Lowe Oculocerebrorenal Syndrome

Lowe syndrome is transmitted as an X-linked trait and is characterized by bilateral congenital cataracts, mental retardation, and a renal ion-transport defect (Fanconi's syndrome) (Schneider et al. 2001). Disease results fiom mutations in the OCRL gene. This gene encodes a Golgi-associated protein (inositol polyphosphate-5-phosphatase) that regulates the cellular levels of a metabolite (phosphatidyl inositol 4,5-biphosphate) involved in vesicular transpon. female carriers ean be ulenlilieil by detrciion through slit-lamp examination of lens opacities. Symptomatic treatment with phosphate and vitamin D prevents the development of severe rickets. Patients are at risk for glaucoma and should have serial monitoring of intraocular pressure.

Nonketotic Hyperglycinemia (NKH)

Glycine encephalopathy is caused by a defect in the P-protein (glycine decarboxylase) gene, which encodes a component of the mitochondrial glycine cleavage system (Toone et al. 2002). NKH is clinically charactetized by a neonatal encephalopmlu . I'anenrs develop Iclhargy, hypo tonia, myoclonic seizures, and apnea. The electroencephalogram shows a burst suppression pattern. CSF glycine is elevated, and the ratio of CSK to plasma glycine concentration (normally below 0.4) is above 0.6. Brain MRI reveals a hypoplastic or absent corpus callosum and gyral malformations; cerebellar hypoplasia is an associated feature. The excitatory effects of glycine on the NMDA receptor may cause the neurological symptoms. Dextromethorphan and ketamine inhibit receptor excitation and are used fot tteatment. Prognosis is poor, and most affected children are mentally retarded.

Molybdenum Cefaclor Deficiency

Molybdenum cofactor is essential for xanthine oxidase, sulfite oxidase, and aldehyde oxidase activity. Deficiency of the cofactor causes refractory seizures, axial

hypotonia, and limb rigidity (Aukett et al. 1988), Urinary excretion of xanthine and sulfite is increased. Brain imaging shows multiple cystic cavities in the white matter. This autosomal recessive disorder should be considered in the differential diagnosis of ischemic/anoxic perinatal Icukomalacia.

Sulfite Oxidase Deficiency

Sulfite oxidase deficiency is transmitted as an autosomal recessive trait. SUOX, the gene encoding the enzyme that catalyzes the terminal reaction in the sulfur amino acid degradation pathway, is defective (Johnson et al. 2002). Clinical features include seizures and progressive neurological deterioration, features similar to that encountered with molybdenum cofactor deficiency. Dislocated ocular lens is characteristic.

Disorders of Copper Metabolism

Copper is an essential element for the activity of several enzymes (cytochrome c oxidase, Cu/Zn-su peroxide dismutasc, dopamines-hydroxylase). Menkes' disease and Wilson's disease result from mutations in highly homologous copper transportets (P-rype ATPases).

Menkes' syndrome: Menkes' syndrome is transmitted as an X-linked trait. The membrane copper transporter ATP7A is defective, causing a functional copper deficiency and low levels of serum copper and ceruloplasmin. Progressive neurodegcncration and marked connective tissue abnormalities are characteristic. The disease is usually lethal in infancy or childhood. Neuropathologies! findings include neovascularization and extreme reduplication of the cerebral arteries, in conjunction with cystic medial degeneration, bilateral cerebellar hypoplasia, focal cortical dysplasia, and cerebellar heterotopias (Strausak et al. 2001). Daily intravenous copper histidinc administration in Menkes' syndrome restores scrum copper and ceruloplasmin levels, and leads to favorable clinical results when started prior to neuro degeneration (Sarkar 1997). Occipital horn syndrome, formerly known as Ehlers-Danlos syndrome type IX or X-linked cutis laxa, is an allelic variant of Menkes' syndrome.

Wilson's disease: Wilson's disease is an autosomal recessive disorder caused by mutations in the copper transporter (ATP7B) gene. Excessive copper accumulates in the liver and brain. Neurological features include tremors, loss of fine motor control and poor coordination, rigid dystonia, dysarthria, and swallowing difficulties (Schilsky 2002). Diagnostic findings include the presence of Kayser-Fleischer rings, increased urine copper excretion, with low serum ceruloplasmin and increased liver tissue copper content. Basal ganglia degeneration is evident on MRI as increased T2 intensity in the caudate and putamen. The results of therapy by liver transplantation have been mixed.

Disorders of Purine and Pyrimidine Metabolism

Purine and pyrimidine nucleotides are essential cellular components involved in energy transfer and the regulation and synthesis of DNA and RNA. Defects of purine and pyrimidine metabolism can result from disruption of biosynthetic, catabolic, and salvage pathways.

Lesch-Nyhan syndrome is transmitted as an X-linked recessive rrait. Hypoxanthinc-guanine phosphoribosyltransferase (HGPRT), required in the purine salvage pathway, is deficient causing hyperuricemia. Clinical features include chorea and athetosis, dysarthria, hyperreflexia and hypertonia, cognitive impairment, and behavioral disturbances (including impulsive and self-injuring activity) (Schretlen et al. 2001). Dopamine concentrations in the basal ganglia and CSF are reduced and may account for some of the neurological features. Patients with partial HGPRT deficiency always have hyperuricemia and often have neurological abnormalities, but do not show self-injuring behavior and usually have normal intelligence.

Adenylosuccinate lyase deficiency is transmitted as an autosomal recessive trait. *De novo* purine and AMP synthesis are defective, and SAICA riboside and adenylosuccinate accumulate in cells and can be detected in CSF and urine. Severe developmental delay, seizures, and growth retardation are characteristic. Psychomotor retardation with autistic-like behavior occurs in about half of the cases (Ciardo et al. 2001).

Porphyrias

Porphyrins play an important role in the formation of metalloporphyrin complexes, including hemoglobin, myoglobin, cytochromes, peroxidases, oxidases, and catalases. The porphyrias are caused by deficiencies of specific enzymes involved in the heme biosynthctic pathway. This pathway occurs in bone marrow elements (85%) or in the liver. The porphyrias are characterized by the accumulation and excess excretion of by-products of intermediary heme metabolism and their oxidized products. A diagnosis of porphyria should be considered in patients with unexplained neuropsychiatry signs, visceral (gastrointestinal and hepatic) symptoms, or cutaneous photosensitivity (Ahmed 2002), Cutaneous manifestations are prominent in hereditary coptoporphyria and variegate porphyria, but the neurovisceral disturbances may be indistinguishabU from those of acuie :iuci'iniircill porphyria iAII'j. Porphyrias with neurological features have either a constant or an intermittent excretion of aminolevulinic acid and porphobilinogen. The elimination of precipitating

Table 68.14: Medications patients with porphyria should avoid and permissible alternatives

Contraindicated	*Alternative*
Sedatives, tranquilizers	Chloral hydrate
Barbiturates	Chlor promazine
Anticonvulsants (ethosuximide, clonazepam, sodium valproate, phenytoin, primidone)	
Anticoagulants	\spirin
Centrally acting agents (imipramine, nikethamide, metoclopramide, methyldopa)	Droperidol, methadone (physeptone), chlorproma/.inc, promethazine
Anaigesics/aiiti-infla matory (diclofenac, pentazocine, phcnylbutoazone, phenazone)	Morphine and derivatives

factors is an important method to reduce the frequency and intensity of acute exacerbations.

Acute intermittent porphyria: AIP is transmitted as an autosomal dominant trait. Mutations occur in the porphobilinogen deaminase (PBD) gene. Deficient activity of erythrocyte PBD activity is used to confirm the diagnosis. Bouts of abdominal pain, paresthesias, seizures, and peripheral neuropathy are prominent clinical features. Neurotic or psychotic behavior is also reported. Certain drugs can precipitate acute attacks and patients should be provided with a list of medications to avoid (Table 68.14). Carbohydrate loading and administration of heme analogues arc used to manage the acute crises.

Congenital Disorders of Giycosylation

The carbohydrate-deficient glycoprotein (CDG) syndromes are a heterogenous group of autosomal recessive disorders resulting from defects of the N-linked giycosylation pathway. Many proteins undergo giycosylation (a posttranslational modification step) to render them functional. The initial features of CDG syndromes may include ataxia, strabismus, unusual fat distribution, severe liver dysfunction, seizures, and strokelike episodes. All of these disorders, except for CDGTb (phosphomannose isomerase deficiency), show some degree of developmental and psychomotor retardation and many have gastrointestinal dysfunction (Freeze 2001). Severe brain involvement occurs in phosphomannomurase deficiency (CDG-Ia), which accounts for —80% of CDG cases, and *N*-acetylglucosaminyl ttansferase-H deficiency, a disorder with craniofacial abnormalities (Pearl and Krasnewich 2001), Testing for abnormal protein giycosylation is done by isoelectric focusing analysis of serum transferrin. Treatment is not available. Ota) mannose given to two children with CDG-Ib provided clinical improvement and normalization of blood glucose, aminotransferases, and coagulation factor levels in one child and resolution of gastrointestinal bleeding in another (Rush et al. 2000).

Canavan Disease (CD)

CD is transmitted as an autosomal recessive trait. It is caused by deficiency of aspartoacylase. N-acetyl-aspartic acid (NAA), a neurotoxic compound, accumulates in the brain and is excreted in urine, CD mainly occurs in Ashkenazi Jews (carrier frequency 1:37-58). Clinical features include hypotonia, delayed development, optic atrophy, and seizures (Matalon and Ma talon 2002). CD shares several features (e.g., progressive macrocephaly, demyelination) with Alexander's disease, a rare, progressive, leukoencephalopathy characterized by the widespread accumulation of Rosenthal fibers. However, Alexander's disease has a later onset and slower course. Missense mutations in the coding region of the glial fibrillary acidic protein (GFAP) gene occur in patients with Alexander's disease.

Neurotransmitter and Small Peptide Defects

Neurotransmitters are divided im« the following groups: inhibitory (GABA, glycine), excitatory (aspartate, glutamare), cholinergic (acetylcholine), monoaminergic (epinephrine, norepinephrine, dopamine, serotonin), and purinergic (adenosine, AMP, ADP, ATP), Inherited defects of neurotransmission may be caused by deficient synthesis, release, breakdown or re-uptake of neurotransmitters. In addition, disease may be caused by defects of receptors and failure of signaling pathways of glial cells to maintain an appropriate milieu. Clinical features vary from mild to severe and are characterized by psychomotor retardation, developmental delay, oculogyric crises, hypotonia, and ataxia.

Succinic semialdehyde dehydrogenase deficiency disrupts the normal metabolism of GABA, and y-OHbutyrate, a compound with neuromoclulatory properties, accumulates in plasma, CSF, and urine {Gibson et al. 1998). Vigahatrin inhibits GABA transaminase and causes variable improvement of the ataxia and behavioral disturbances.

Aromatic i -amino acid decarboxylase deficiency causes deficiency of serotonin and catecholamines. Pterin and phenylalanine metabolism are normal. The diagnosis is based on demonstrating low CSF homovanillic (HMV), 5-OHindoleacetic acid (.5HIAA), and 3-methoxy-4-OHphenyl-ethyleneglycol, associated with increased levels of i-dopa (Mailer et al. 1997). Combined treatment with pyridoxine {vitamin BJ, tranylcypromine (a MAO inhibitor), and bromocriptine promotes clinical improvement.

The 3-phosphoglycerate dehydrogenase deficiency, a disorder of i.-serinc biosynthesis, is characterized by

congenital microcephaly, intractable seizures, and severe psychomotor retardation (De Koning et al. 2002). Oral supplementation of the deficient amino acids reduces seizure frequency and can prevent psychomotor delay if given at an early age.

Defects in Leukotriene Synthesis

Leukotrienes are a group of highly active biological compounds that are synthesized by brain tissue and a limited number of other cells. Cysteinyl leukotrienes have neuromodulator functions apart from their role in the mediation of inflammation and host defense. Leukotriene synthesis defects results in severe muscular hypotonia, psychomotot retardation, failure to thrive, microcephaly, and the absence of cysteinyl leukotrienes in body fluids (Mayatepek 2000).

Animal Models of Human TEM

Several spontaneous animal models of human IEM exist; only a lew have been bred successfully. ()\ ••.-: the List decade, recombinant genetic techniques have enabled the generation of animal (primarily mice) models of disease. In a genotype-driven approach, mouse (knockout) models are generated by homologous recombination in embryonic stem cells incorporating a null allele. Alternatively, single-point mutations have been introduced, resulting in mice with partial rather than complete deficiencies. These animal models have proven useful in investigations of the natural history of the disease and in the preclinical testing of various drugs. In some cases, these investigations have provided the rationale for further clinical trials in humans. Although similarities exist between affected mice and men, species-specific differences in phenotypical expression result from alternative pathways of substrate processing. These considerations highlight the need for caution in carrying over observations made in the animal models to human trials.

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Volume II

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The Neurological Disorders

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presence of increased SWS after sleep deprivation. The critical role of REM sleep for CNS development in young organisms and increased protein synthesis in the brain during REM sleep may support the theory of restoration of hmin function by REM sleep. Although d/iu remain ^;im and controversial, studies of brain basal metabolism that suggest an enhanced synthesis of macromolccules during sleep, such as nucleic acids and proteins in the brain, provide an argument in favor of the restorative theory of sleep.

The energy conservation theory is somewhat inadequate. The fact that animals with a high metabolic rate sleep longer than those with slower metabolism has been cited in support of this theory. It should, however, be noted that during 8 hours of sleep, only 120 calories are conserved.

The adaptive theory suggests that sleep is an instinct that allows creatures to survive under a variety of environmental conditions.

The memory reinforcement and consolidation theory suggests that memory reinforcement and consolidation take place during REM sleep. This theory has been strengthened by the observation that, after REM and SWS sleep-deprivation experiments in six young adults, perceptual learning during REM deprivation was significantly less than it was with SWS deprivation. These data suggest that REM deprivation affected the consolidation of the recent perceptual experience.

The synaptic neuronal network integrity theory is an emerging thcor; proposing thai the primary tunciiun oi sleep is the maintenance of synaptic and neuronal network integrity. Intermittent stimulation of neural network synapses is necessary to preserve CNS function. The concept of dynamic stabilization (repetitive activation of brain synapses and neural circuitry) suggests that REM sleep maintains motor circuits, whereas NREM sleep maintains nonmotor activities.

The thermoregulatory function theory is based on the observation that thermoregulatory homeostasis is maintained during sleep, whereas severe thermoregulatory-abnormalities follow total sleep deprivation.

The preoptic anterior hypothalamic neurons participate in thermoregulation and NREM sleep. These two processes-are closely linked by preoptic anterior hypothalamic neurons but arc clearly separate. Thermoregulation is maintained during NREM sleep but suspended during REM sleep. Thermoregulatory responses such as shivering, piloerection, panting, and sweating are impaired during REM sleep. There is a loss of thermosensitivity in the preoptic anterior hypothalamic neurons during REM sleep,

PHYSIOLOGICAL CHANGES IN SLEEP

Various physiological changes occur during NREM and REM sleep that are different from those noted during wakefulness (Chokroverry 2002). These changes are observed in somatic and autonomic nervous systems and include respiratory, cardiovascular, and gastrointestinal systems; endocrine, renal, and sexual function; and thermoregulation (Table 74.6).

Table 74.6: Physiological changes during wakefulness, NREM sleep, and REM sleep

Physiology	*Wakefulness*	*NREM sleep*	*REM sleep*
Parasympathetic activity	++	+++	4-4-4-4-
Sympathetic activity	++	+	Decreases or variable (++)
Heart rate	Normal sinus rhythm	Bradycardia	Urady tachyarrhythmia
Blood pressure	Normal	Decreases	Variable
Cardiac output	**Normal**	Decreases	Decreases further
Peripheral vascular resistance	Normal	Normal or decreases slightly	Decreases further
Respiratory rate	Normal	Decreases	Variable; apneas may occur
Alveolar ventilation	Normal	Decreases	Decreases furthet
Upper airway muscle tone	++	+	**1)uir;hi> n[** absi'lll
Upper airway resistance	4-4-	++4-	4-+++
Hypoxic and hypercapnie ventilatory responses	Normal	Dcercases	1 :v, !V;LM-, further
Cerebral blond flow	++	++ or -H-+	4-4-4-4-
Thermoregulation	4-+	+	—
Gastric acid secretion	\i i-'iiial	Variable	Variable
Gastric motility	**Noi null**	1)t creases	Decreases
Swallowing	Normal	Decreases	Decreases
Salivary flow	Normal	1 (ecreases	Decreases
Migrating motor complex (a special type of intestinal motor activity)	Normal	Slow velocity	Slow velocity
Penile or clitoral tumescence	Normal	Normal	Markedly increased

NREM = non-rapid eye movement; REM = rapid eye movement; + = mild; ++ = moderate; +++ = marked; ++++ = very marked. - = absent.

Somatic Central Nervous System

Firing rates of many neurons in the CNS decrease during NREM sleep but increase during REM sleep.

Autonomic Nervous System

During sleep, the autonomic nervous system undergoes several changes that may have implications for the pathophysiology of autonomic failure and sleep disorders in humans. Most of the autonomic changes involve respiration, circulation, thermoregulation, and the pupils (e.g., pupilloconstriction during sleep). During NREM sleep, there is an overall tonic increase in parasympathetic activity, which increases further during tonic REM sleep. In addition, during phasic REM sleep, sympathetic activity decreases. Sympathetic activity during REM sleep, however, increases intermittently, which results in swings of blood pressure and heart rhythm, causing bradytachyarrhythmias.

Respiratory Changes

Two systems—metabolic (or automatic) and voluntary (or behavioral)—control respiration during sleep and wakefulness. Both metabolic and voluntary systems operate during wakefulness, whereas only the metabolic system operates during NREM sleep. The wakefulness stimuli that act through the ARAS also act as tonic stimuli to ventilation. Activity decreases in the respiratory neurons in the parabrachial and Kolliker-Fuse nuclei in the pons, the nucleus tractus solitarius, nucleus ambiguus, and nucleus retroambigualis in the medulla. Respiratory muscle activity decreases slightly during NREM sleep but markedly during REM sleep. A marked decrement or even temporary suppression of intercostal muscle tone occurs during REM sleep, whereas tonic activity of the diaphragm diminishes and phasic activity continues. Muscle tone in the upper airway decreases in NREM sleep and disappears in REM sleep, resulting in an increase in upper airway resistance. The decreased sensitivity of the respiratory neurons to carbon dioxide, inhibition of the reticular activating system, and alteration of metabolic control of respiratory neurons during sleep result in a decrement of tidal volume, minute ventilation, and alveolar ventilation, In normal individuals, diminished alveolar ventilation causes arterial carbon dioxide tension (Pco_2) to rise by 2-8 mm Hg, the arterial oxygen tension (P02) to decrease by 3-10 mm Hg, and oxygen saturation (So_2) to decrease by less than 2% during sleep. These blood -as changes are noted despite a fall in oxygen consumption and carbon dioxide production during sleep. Both hypercapnic and hypoxic ventilatory responses decrease during REM and NREM sleep, with a more marked decrease during REM sleep. These decrements result from a combination of factors: fewer functional medullary respiratory neurons during sleep, decreased sensitivity of the central chemorcccptors subserving medullary respiratory neurons, and increased resistance in the upper airway. Arousal responses also decrease, particularly during REM sleep. The voluntary respiratory control system may be active during some portion of REM sleep. Respiration is therefore vulnerable during sleep in normal individuals. Mild respiratory irregularity- with few apneic episodes (apnea index <5) may occur at sleep onset and during REM sleep. In disease states, however, apneas may become more frequent, prolonged, and pathologically significant.

Cardiovascular Changes

Heart rate, blood pressure, cardiac output, and peripheral vascular resistance decrease during NREM sleep and decrease still **tun her diLiiiie. REM** sleep. **Dunne,** phasic REM, blood pressure and heart rate are unstable because of phasic vagal inhibition and sympathetic activation caused by alterations in brainstem neural activity. Heart rate and blood pressure fluctuate during REM sleep. Cerebral blood flow and cerebral metabolic rate for glucose and oxygen decrease by 5-2.3% during stages 1 to IV of NREM sleep, whereas these values inctease by 10-41% above waking levels during REM sleep. These data indirectly suggest that NREM sleep is the state of resting brain, with reduced neuronal activity, decreased synaptic transmission, and depressed cerebral metabolism. The data also are consistent with the assumption that REM sleep represents an active brain state with increased neuronal activity and increased brain metabolism. The largest increases during REM sleep are noted in the hypothalamus and the brainstem structures, and the smallesl increases are in the cerebral cortex and white matter.

Because of all the hemodynamic and sympathetic alterations, REM sleep, which is prominent during the third part of the night's sleep, could initiate increased platelet aggregation, plaque rupture, and coronary artery spasm. These increases may act as triggering mechanisms tor thrombotic events, causing myocardial infarction, *vol* tricular arrhythmias, or even sudden cardiac death.

Gastrointestinal Changes

Gastric acid secretion shows a variable response during sleep in normal individuals, but patients with duodenal ulcers show a striking increase in acid secretion and no inhibition of secretion during the first 2 hours of sleep. Swallowing is suppressed during sleep, and there is prolonged acid clearance; these factors are important in the pathogenesis of esophagitis caused by nocturnal gastroesophageal reflux. Esophageal motility is also reduced during sleep. Results of studies of intestinal motility during sleep are contradictory. A special pattern of motor activity, called the migrating motor complex,

shows a circadian rhythm in its propagation with the slowest velocity during sleep.

Endocrine Function

Profound changes in neuroendocrine secretions are found during sleep (Figure 74,4), Growth hormone secretion exhibits a pulsatile increase during NREM sleep in the first i-.nc third of 'lie night. Prolactin secretion also rises 30-90 minutes after the onset of sleep. Sleep inhibits Cortisol secretion. Secretion of thyroid-stimulating hormone reaches a peak in the evening and then decreases throughout the night.

Testosterone levels in adult men continue to be highest during sleep, but no clear relationship has been demonstrated between levels of gonadotropic hormones and the sleep-wake cycle in children or adults. During puberty, gonadotropin levels increase in sleep. Melatonin, which is synthesized and released by the pineal gland and derived from serotonin, begins to rise in the evening, attaining maximal values between 3:00 AM and 5:00 AM, and decreases to low levels during the day.

Other endocrine changes include a maximum rise of aldosterone jusl before awakcnmi" in the carl; hours oi the morning and a marked decrease of plasma renin activity during REM sleep.

Sexual Function

The most striking finding is increased penile tumescence in men during REM sleep. In women, there is increased clitoral tumescence during REM sleep.

Them toregulatio n

iVuk rcMnuT.mnv has kvn linked intimately to the sleep-wake cycle, but it follows a circadian rhythm that is independent of the sleep-wake rhythm. At the onset of sleep, body temperature begins to fall. Body temperature reaches its lowest point during the third sleep cycle. Thermoregulation is maintained during NREM sleep but is nonexistent in REM sleep, and experimental animals become poikilothcrmic. Thus physiological responses (e.g., shivering, panting, sweating, and piloerection) to thermal stimuli are depressed or absent during REM sleep.

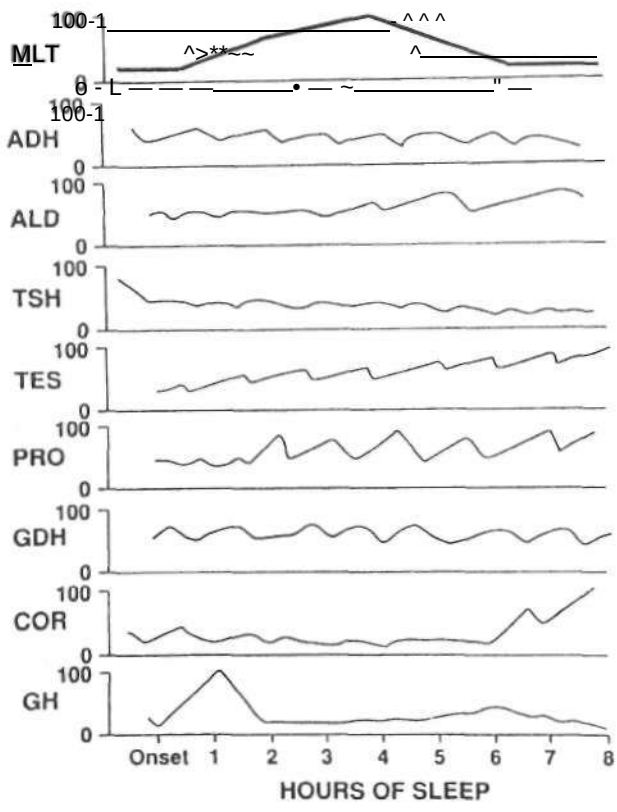

FIGURE 74.4 Schematic diagram to show plasma levels of hormones during 8 hours of sleep in an adult. {ADH = antidiuretic hormone; ALD = aldosterone; COR = Cortisol; GDI! = gonadotropic hormone; GH = growth hormone; MLT = melatonin; PRO = prolactin; TES = testosterone; TSH = thyroid-stimulating hormone. Zero indicates lowest secretory episode, and 100 indicates peak secretion.J (Reproduced with permission from Chokrovcrty, S. 1999, "Physiological changes in sleep," in *Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects,* ed S. Chokrovcrty, Butterworth-Heinemann, Boston.)

Sleep Deprivation and Sleepiness

Sleepiness is determined by both circadian and homcostatic factors. The circadian phase is determined by the supra-chiasmatic nuclei, and it works in a biphasic manner. There arc two phases when an individual has the maximal sleepiness propensity: One phase that is intense is around 3:00-5:00 AM, and the other, which is less intense, is around 3:00-5:00 PM. In addition, there are two forbidden or dead zones. The individual is wide awake and is unable to sleep, noted around late morning and early evening. Homeostasis refers to a balance between sleep and wakefulness. After prolonged wakefulness, there is an intense desire to sleep. REM sleep is influenced by the circadian rhythm, whereas SWS is influenced by homeostasis. Much is known about the physiology of circadian rhythm, but the neurobiology of the homeostatic influences remains largely unknown. Excessive sleepiness, therefore, may result from both circadian dysrhythmia and disruption of homeostasis of the body.

A large segment of the population working different shifts and having irregular sleep-wake schedules is chronically sleep deprived (Bonnet and Arand 1995). The at-risk groups include doctors, nurses, firefighters, interstate truck drivers, police officers, overnight train drivers, and high school and college students. Compared with a survey conducted in the beginning of the last century and another

toward the end of the century, modern America is sleep deprived by approximately 1.5 hours of sleep (Harrison and Home 1995). This does not necessarily mean that the sleep requirement is less today, but, simply, it means that people are sleep deprived. However, there may be a sampling error in these two surveys: for example, 2000 people were sampled in the earlier survey versus 311 in the later survey. Increased environmental light and sound, industrialization. increasing r, umber i of people work in L: in various shifts, and the advent of television and radio are cited as some of the factors responsible for this reduction of total sleep hours. Harrison and Home (1995), however, argued that most people are not chronically sleep deprived but have the capacity to take more sleep. In one epidemiological study, sleepiness in Western society was estimated to be found in *5-36%* of the total population.

Experiments have been conducted to study the consequences of total, partial, and selective sleep deprivation. These experiments have shown clearly that in animals sleep is necessary for survival, but studies of complete sleep deprivation for prolonged periods (e.g., weeks to months) cannot be conducted in humans from a practical point of view. Experiments in rats using a carousel device have provided evidence that sleep is essential for survival. All rats deprived of sleep for 10-30 days died after having lost weight despite increasing food intake. The rats also lost temperature control. It took longer for rats deprived of REM sleep to die than those deprived of SWS.

Total Sleep Deprivation

One of the earliest experiments in sleep deprivation in humans was in 1896 (Chokroverty 1999a). The effects of a 90-hour period of sleep deprivation were studied in three healthy young men. All subjects had difficulty staying awake, hut they felt totally refreshed and rested after they were allowed to sleep for 10 hours. One of them, however, had sensory illusions that disappeared completely after icon, LTV i>' sleep period, hi I Vfi.S, a spectacular experiment was conducted when a 17-year-old California college student named Randy Gardner (Chokroverty 1999a) tried to set a new world record for staying awake. He remained awake for 264 hours and 12 minutes and then slept for 14 hours and 14 minutes, after which he recovered fully. Thus the conclusion of the experiment was that it was possible to deprive people of sleep for a prolonged period without causing serious mental impairment. Other important observations include frequent occurrence of "microsleep[1]' episodes (i.e., brief episodes of NREM sleep) and loss of performance that may have been caused by the loss of molivation. Several order cvpcriiticnls Liter in humans showed no permanent adverse effects after sleep deprivation. However, sleep deprivation increases the daytime tendency to sleep as proven by multiple sleep latency tests in such subjects. The percentage of SWS increases considerably during the tccovery sleep period after sleep deprivation. The REM sleep percentages also increase during the recovery sleep after a prolonged period of sleep deprivation, but this increment of REM sleep percentage was not shown after short periods of sleep deprivation for 4 days. These facts might suggest that different mechanisms regulate NREM and REM sleep.

Partial and Selective Steep Deprivation

Measurements of mood and performance after partial sleep deprivation (e.g., restricting sleep to 4.5-5.5 hours for 2-3 months) showed minimal deficits in performance, which may have been related to decreased motivation. After selective REM deprivarion, PSC studies showed increased REM pressure (i.e., earlier and more common onset of REM sleep during successive nights) and REM rebound (i.e., quantitative increase of REM pcrcenrages during recovery sleep). The observation of a psychotic reaction after REM deprivation as noted by Dement was proved to be inaccurate in subsequent investigations. Similar ro REM deprivation, after stage IV NREM sleep deprivation for two consecutive nights, there is an increase in stage IV sleep during the recovery night. It is more difficult to deprive a person of stage IV NREM sleep than of REM sleep.

In summary, these experiments have proven conclusively that sleep deprivation causes sleepiness and impairment of performance, vigilance, attention, and concentration but does not cause permanent memory or other CNS changes,

Consequences of Excessive Daytime Sleepiness

Consequences of EDS (Table 74.7) are discussed under the following four headings: (1) performance and productivity ,u work and school; *;1* Imnur cerebral functions; (3) quality of life and social interactions; and (4) morbidity and mortality (Roth and Roehrs 1996).

Performance and Productivity at Work and School

Impaired performance and reduced productivity at work for shift workers, reduced performance in class for school and college students, and impaired job performance in patients with narcolepsy, sleep apnea, circadian rhythm disorders, and chronic insomnia are well-known adverse effects of sleep deprivation and sleepiness. Sleepiness and .issoi.-i.ilcd rn irhuiil v are worse- in niejit sliiti workers, older workers, and female shift workers.

Table 74,7: Consequences of excessive daytime sleepiness

Impaired performance and productivity
Impaired short-term memory, attention, conception, and cognition
Impaired quality of life
Psychological stress
Increased morbidity and mortality: i.e., increased likelihood of accidents

Higher Cerebral Functions

Sleepiness interferes with higher cerebral functions, causing impairment of short-term memory, concentration, attention, cognition, or intellectual performance. Psychometric tests document increased reaction time in patients with excessive sleepiness. These individuals make increasing numbers of errors, and they need increasing time to reach the target in reaction time tests (Dinges 1995). Sleepiness also can impair perceptual skills and new learning. Insufficient sleep and excessive sleepiness may cause irritability, anxiety, and depression. Learning disabilities and cognitive impairment due to impaired vigilance also have been described (Roth and Rochrs 1996).

Quality of Life and Social Interaction

People complaining of F.DS are often under severe psychological stress. They are often wrongly perceived as dull, lazy, and downright stupid. Excessive sleepiness may cause severe marital and social problems. Individuals with this problem have serious difficulty with interpersonal relationships. In a survey of 180 narcoleptic patients, one third thought that they were misunderstood because of their symptoms.

Shift workers constitute approximately 20-25% of the work force in America (i.e., approximately 20 million). A majority of them have difficulty with sleeping, and sleepiness as a result of insufficient sleep and circadian dysrhythmia. Many of them have an impaired quality of life, marital discord, and gastrointestinal problems.

Increased Morbidity and Mortality

Persistent daytime sleepiness causes individuals to have an increased likelihood of accidents. Estimates by the U.S. National Highway Traffic Safety Administration showed that approximately 56,000 police-reported crashes per year resulted from drivers who were "asleep at the wheel" (Knipling and Wang 1994). New York police estimate that 30% of all fatal crashes along the New York Thruway occur because the driver fell asleep at the wheel. Approximately 1 million crashes annually (one sixth of all crashes) are thought to be produced by driver inattention or lapses. Sleep deprivation and fatigue make such lapses more likely to occur. Truck drivers are especially susceptible to fatigue-related crashes (Lyznicki et al. 1998). Many truckers drive during the night while they are sleepiest. Truckers also may have a high prevalence ol sleep apnea. The I ".S. Department of Transportation estimates that 200,000 automobile accidents each year may be related to sleepiness. Nearly one third of all trucking accidents that are fatal to the driver are related to sleepiness and fatigue.

The presence of sleep disorders (see Primary Sleep Disorders Associated with Excessive Daytime Sleepiness, later in this chapter) increases the risk of crashes. Individuals with untreated insomnia, sleep apnea, and narcolepsy and shift workers, all of which cause excessive sleepiness, have more automobile crashes than other drivers (Costa de Silva et al. 1996). A 1991 Gallup organization national survey found that individuals with chronic insomnia report 2.5 times as many fatigue-re la ted automobile accidents than did those without insomnia. The same 1991 Gallup survey found serious morbidity associated with untreated sleep complaints as well as impaired ability to concentrate and accomplish daily tasks, impaired memory, and interpersonal difficulties.

A 1994 telephone survey of drivers by the New York State Task Force estimated that approximately 25% reported that they had fallen asleep at the wheel at some time. Young male drivers are especially susceptible to crashes caused by falling asleep as documented in a study in North Carolina in 1990, 1991, and 1992 (e.g., in 55% of the 4333 crashes, the drivers were predominantly male and 25 years of age or younger). In the October 1995 Gallup poll, 52% of all adults surveyed said that in the past year they had driven a car or other vehicle while feeling drowsy, 31% of adults admitted dozing off while at the wheel of a car or other vehicle, and 4% reported having had an automobile accident because of tiredness during driving. A number of national and international catastrophes involving industrial operations, nuclear power plants, and all modes of transportation have been related to sleepiness and fatigue (Dinges 1995): for example, the Exxon Valdez oil spill in Alaska; the nuclear disaster at Chernobyl in the former Soviet Union; the near-nuclear disaster at Three Mile Island in Pennsylvania; the gas leak disaster in Bhopal, India, resulting in 25,000 deaths; and the Challenger space shuttle disaster.

Causes of Excessive Daytime Sleepiness

Excessive sleepiness may result from both physiological and pathological causes (Table 74.8).

Physiological Causes of Sleepiness

Sleep deprivation and sleepiness because of lifestyle and habits of going to sleep and waking up at irregular hours can be considered to result from disruption of the normal circadian and homeostatic physiology. Groups who are excessively sleepy because of lifestyle and inadequate sleep include young adults and elderly individuals, workers at irregular shifts, health care professionals (e.g., doctors, particularly the house staff, and nurses), firefighters, police officers, train drivers, pilots and flight attendants, commercial truck drivers, and those individuals with competitive drives to move ahead in life, sacrificing hours of sleep and accumulating sleep debt. Among young adults, high school and college students are particularly at risk for sleep deprivation and sleepiness. The reasons for excessive

Table 74.8: Causes of excessive daytime sleepiness

- Physiological causes
  - Sleep deprivation and sleepiness related to lifestyle and irregular sleep-wake schedule
- Pathological causes
  - Primary sleep disorders
    - Obstructive sleep apnea syndrome
    - Central sleep apnea syndrome
    - Narcolepsy
    - Idiopathic hypersomnolence
    - Circadian rhythm sleep disorders
      - Jet lag
      - Delayed sleep phase syndrome
      - Irregular sleep-wake pattern
      - Shift work sleep disorder
      - Noii-24-hour sleep-wake disorders
    - Periodic limb movement disorder
    - Restless legs syndrome
    - Insufficient sleep syndrome
    - Inadequate sleep hygiene
    - Recurrent or periodic hypersomnia
      - Kleine-Levin syndrome
      - Idiopathic recurrent stupor
      - Catamenial hypersomnia
      - Seasonal affective depression
      - Occasionally due to insomnia
  - General medical disorders
    - Hepatic failure
    - Renal failure
    - Respiratory failure
    - Electrolyte disturbances
    - Cardiac failure
    - Severe anemia
    - Endocrine causes
      - I lypothyroidism
      - Acromegaly
      - Diabetes mcllitus
      - Hypoglycemia
      - Hyperglycemia
- Psychiatric or psychological causes
  - Depression
  - Psychogenic unresponsiveness or sleepiness
- Neurological causes
  - Brain tumors or vascular lesions affecting thalamus, hypothalamus, or brainstem
  - Post-traumatic hypersomnolence
  - Multiple sclerosis
  - Encephalitis Icthargica and other cnccphalitidcs and encephalopathies including Wernicke's encephalopathy
  - Cerebral trypanosomiasis (African sleeping sickness)
  - Neurodegenerative disorders
    - Alzheimer's disease
    - Parkinson's disease
    - Multiple system atrophy
  - Myotonic dystrophy and other neuromuscular disorders causing sleepiness secondary to sleep apnea
  - Medication-related hypersomnia
    - Benzodiazepines
    - Nonbcnzodiazepine hypnotics, e.g., phenobarbital, Zolpidem
    - Sedative antidepressants, e.g., tricyclics, trazodone
    - Antipsychotics
    - Nonbcnzodiazepine anxiolytics, e.g., buspirone
    - Antihistamines
    - Narcotic analgesics including tramadol (Ultram)
    - Beta blockers
    - Toxin and alcohol-induced hypersomnolence

sleepiness in adolescents and young adults include both biological and psychosocial factors. Some of the causes for later bedtimes in these groups include social interactions Willi peers, homework in the evening, sports, employment or other extracurricular activities, early wake-up times to start school, and academic obligations requiring additional school or college work at night. Biological factors may play a role but are not well studied. For example, teenagers may need extra hours of sleep. Also, the circadian timing system may change with sleep phase delay in teenagers. EDS associated with shift work is described (see Primary Sleep Disorders Associated with Excessive Daytime Sleepiness, later in this chapter).

Pathological Causes of Sleepiness

Neurological Causes of Excessive Sleepiness. Tumors and vascular lesions affecting the ascending reticulat activating arousal system and its projections to the posterior hypothalamus and thalamus lead to daytime sleepiness (Aldrich 1993). It should be noted that lesions of this system often cause coma rather than just sleepiness. Brain tumors (e.g., astrocytomas, suprasellar cysts, metastases, lymphomas and hamartomas affecting the posterior hypothalamus, pineal tumors, and astrocytomas of the upper brainstem) may produce excessive sleepiness. Prolonged hypersomnia may be associated with tumors in the region of the third ventricle. Symptomatic narcolepsy resulting from craniopharyngioma and other tumors of the hypothalamic and pituitary regions has been described (Aldrich 1993). Cataplexy associated with sleepiness, sleep paralysis, and hypnagogic hallucinations has been described in patients with rostral brainstem gliomas with or without infiltration of the walls of the third ventricle. Narcolepsy-cataplexy also has been described in a HLA DR2 antigen-negative patient with a pontine lesion documented by magnetic resonance imaging (MRI).

Other neurological causes of EDS include bilateral paramedian thalamic infarcts (Bassctti et al. 1996), post-traumatic hypersomnolence, and multiple sclerosis. Narcolepsy-cataplexy has been described in occasional patients with multiple sclerosis and arteriovenous malformations in the diencephalon (Calvelou ct al. 1995).

EDS has been described in association with encephalitis lethargica and other encephalitides as well as encephalopathies including Wernicke's encephalopathy. It was noted that the lesions of encephalitis Icthargica described by Von Economo in the beginning of this century, which severely affected the posterior hypothalamic region, were associated with the clinical manifestation of extreme somnolence.

These lesions apparently interrupted the ascending arousal systems projecting to the posterior hypothalamus. Encephalitis lerhargica is now extinct. Cerebral sarcoidosis involving the hypothalamus may cause symptomatic narcolepsy. Whipple's disease of the nervous system involving the hypothalamus may occasionally cause hypcrsomnolence.

Cerebral trypanosomiasis, or African sleeping sickness, is transmitted to humans by tsetse flies: *Trypanosoma gambiense* causes Gambian or West African sleeping sickness, and *Trypanosoma rbodesiense* causes East African sleeping sickness.

Certain neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple system atrophy also may cause EDS. The causes of EDS in Alzheimer's disease include degeneration of suprachiasmatic nucleus resulting in arcadian dysrhythmia, associated sleep apnea-hypopnea, and periodic limb movements in sleep, In Parkinson's disease, excessive sleepiness may be due to the associated periodic limb movements in sleep, sleep apnea, and depression. EDS in multiple system atrophy associated with cerebellar parkinsonism or parkinsonian-cerebellar syndrome and progressive autonomic deficit (Shy-Drager syndrome) may be caused by the frequent association with sleep-related respiratory dysrhythmias and possible degeneration of the reticular activating arousal systems (Chokrovcrty 1999b).

Sleep disorders are being increasingly recognized as a feature of Parkinson's disease and other parkinsonian disorders. Although some studies have attributed the excessive daytime drowsiness and irresistible sleep episodes ("sleep attacks") to anti-parkinsonian medications (Ondo et al. 2001), sleep disturbances are also an integral parr of Parkinson's disease (Arnulf et al. 2002). In one study of 303 patients with Parkinson's disease, 21% reported falling asleep while driving (Ondo et al. 2002). Several studies also reported a relatively high incidence (10-20%) of symptoms of restless legs syndrome in patients with Parkinson's disease (Ondo et al. 2002; Krishnan et al. 2003). There is also increasing awareness about the relationship between parkinsonian disorders and REM sleep behavior disorder (RBD), and RBD may be the presenting feature of Parkinson's disease, multiple system atrophy, and other parkinsonian disorders (Gagnon et a I. 2002).

These and other studies provide evidence supporting the notion that dopamine activity is normally influenced by circadian factors (Rye and Jankovic 2002). For example, tyrosine hydroxylase levels fall several hours before waking and their increase correlates with motor activity. The relationship between hypocretin and sleep disorders asso ciated with Parkinson's disease is currently being explored (Overeem et al. 2002).

Myotonic dystrophy and other neuromuscular disorders may cause EDS due to associated sleep apnea-hypopnea syndrome and hypoventilation. In addition, in myotonic dystrophy, there may be involvement of the ARAS as part of the multisystem membrane effects noted in this disease.

Excessive Daytime Sleepiness Associated with General Medical Disorders. Several systemic diseases such as hepatic, renal, or respiratory failure and electrolyte disturbances may cause metabolic encephalopathies that result in FDS. Patients with severe EDS drift into a coma. The other medical causes for EDS include congestive heart failure (CHE) and severe anemia. Hypothyroidism and acromegaly also may cause EDS due to the associated sleep apnea syndrome. Hypoglycemic episodes in diabetes mellitus and severe hyperglycemia arc additional causes of EDS.

Primary Steep Disorders Associated with Excessive Daytime Sleepiness. A number of primary sleep disorders cause excessive sleepiness (Tables 74.8 and 74.9). The most common cause of FJDS in the general population is insufficient sleep syndrome associated with sleep deprivation. The next most common cause is obstructive sleep apnea syndrome (OSAS); narcolepsy and idiopathic hypersomnolence are other common causes of EDS. Most patients with EDS referred to the sleep laboratory have OSAS. Other causes of EDS include circadian rhythm sleep disorders, periodic limb movement disorder, and restless legs syndrome, some cases of chronic insomnia, and inadequate sleep hygiene (sec later).

Many sedatives and hypnotics cause EDS. In addition to the benzodiazepine and nonbenzodiazepine hypnotics and sedative anti-depressants (e.g., tricyclic antidepressants and trazodone) as well as nonbenzodiazepine neuroleptics {e.g., buspirone), antihistamines, antipsychotics, and narcotic analgesics including tramadol (Ultram) cause EDS. Beta blockers for treatment of the hypertension also may cause excessive sleepiness.

Toxin and alcohol-related hyper somnolence can occur as well. Many industrial toxins such as heavy metals and organic toxins (e.g., mercury, lead, arsenic, and copper) may cause EDS. These may sometimes also cause insomnia. Individuals working in industrial settings using toxic chemicals routinely are ar risk. These toxins also may cause systemic disturbances such as alteration of renal, liver, and hematological function. There may be an impairment of nerve conduction. Chronic use of alcohol ar bedtime may produce alcohol-dependent sleep disorder. Usually, this causes insomnia, but sometimes the patients may have excessive sleepiness in the daytime. Many of these patients suffer from chronic alcoholism. Acute ingestion of alcohol causes transient sleepiness.

CLASSIFICATION OF SLEEP DISORDERS

The original diagnostic classification of sleep and arousal disorders by the Association of Sleep Disorder Centers categorized sleep-wake disorders into four classes: (1) disorders of initiating and maintaining sleep, (2) disorders of excessive somnolence, (3) disorders of sleep-wake schedule, and (4) dysfunctions associated with sleep,

Tabic 74.9: International classification of sleep disorders

- Dyssomnias
  - Intrinsic sleep disorders
    - Psychophysiological insomnia
    - Sleep-state mis perception
    - Idiopathic insomnia
    - Narcolepsy
    - Recurrent hypersomnia
    - Idiopathic hypersomnia
    - Obstructive sleep apnea syndrome
    - Central sleep apnea syndrome
    - Central alveolar hypoventilation syndrome
    - Periodic limb movement disorder
    - Restless legs syndrome
    - Intrinsic sleep disorders NOS
  - Extrinsic sleep disorders
    - Inadequate sleep hygiene
    - Environmental sleep disorder
    - Altitude insomnia
    - Adjustment sleep disorder
    - Insufficient sleep syndrome
    - Limit-setting sleep disorder
    - Sleep-onset association disorder
    - Food allergy insomnia
    - Nocturnal eating (drinking) syndrome
    - Hypnotic-dependent sleep disorder
    - Stimulant-dependent sleep disorder
    - Alcohol-dependent sleep disorder
    - Toxin-induced sleep disorder
    - Extrinsic sleep disorders NOS
  - Circadian rhythm sleep disorders
    - Time-zone (jet lag) syndrome
    - Shift work sleep disorder
    - Irregular sleep-wake pattern disorder
    - Delayed sleep-phase syndrome
    - Advanced sleep-phase syndrome
    - Non-24-hour sleep-wake disorder
    - Circadian rhythm sleep disorders NOS
- Parasomnias
  - Arousal disorders
    - Confusional arousals
    - Sleepwalking
    - Sleep terrors
  - Sleep-wake transition disorders
    - Rhythmic movement disorders
    - Sleep starts
    - Sleep talking
    - Nocturnal leg cramps
  - Parasomnias usually associated with REM sleep
    - Nightmares
    - Sleep paralysis
    - Impaired sleep-related penile erections
    - Sleep-related painful erections
    - REM sleep-related sinus arrest
    - REM sleep behavior disorder
  - Other parasomnias
    - Sleep bruxism
    - Sleep enuresis
    - Sleep-related abnormal swallowing syndrome
    - Nocturnal paroxysmal dystonia
    - Sudden unexplained nocturnal death syndrome
    - Primary snoring
    - Infant sleep apnea
    - Congenital central hypoventilation syndrome
    - Sudden infant death syndrome
    - lii'iiis'.ii **univ** II.**d .'.li :p** niyci. onus
    - Other parasomnias NOS
- Sleep disorders associated with medical or psychiatric disorders
  - Mental disorders
    - Psychoses
    - Mood disorders
    - Anxiety disorders
    - Panic disorders
    - Alcoholism
  - Neurological disorders
    - Cerebral degenerative disorders
    - Dementia
    - Parkinsonism
    - Fatal familial insomnia
    - Sleep-related epilepsy
    - Electrical status epilepticus of sleep
    - Sleep-related headaches
  - Other medical disorders
    - Sleeping sickness
    - Nocturnal cardiac ischemia
    - Chronic obstructive pulmonary disease
    - Sleep-related asthma
    - Sleep-related gastroesophageal reflux
    - Peptic ulcer disease
    - Fibromyalgia
- Proposed sleep disorders
  - Short sleeper
  - Long sleeper
  - Subwakefulness syndrome
  - Fragmentary myoclonus
  - Sleep hypcrhidrosis
  - Menstrua I-associated sleep disorder
  - Pregnancy-associated sleep disorder
  - Terrifying hypnagogic hallucinations
  - Sleep-related neurogenic tachypnea
  - Sleep-related laryngospasm
  - Sleep choking syndrome

NOS = not otherwise specified; REM = rapid eye movement.

sleep stages, or partial arousals (parasomnias). Tbis classification has been supplanted by the 1990 *International Classification of Sleep Disorders (ICSD),* which was revised slightly in 1997. The ICSD system is the one used by sleep specialists; it lists 84 sleep disorders in tour broad catcgories: dyssomnias, parasomnias, sleep disorders associated with medical or psychiatric disorders, and proposed sleep disorders (see Table 74.9).

Dyssomnias are subdivided into intrinsic, extrinsic, and circadian rhythm sleep disorders. Intrinsic disorders result from causes in the body, whereas extrinsic disorders are primarily caused by environmental factors. Circadian

rhythm disorders result from disruption of sleep-wake schedule changes.

Parasomnias arc characterized hy abnormal movements and behavior intruding into sleep without necessarily disturbing sleep architecture. These consist of arousal and sleep-wake transition disorders, REM-related parasomnias, and others.

Medical or psychiatric sleep disorders include those attributable to another condition; they are caused by mental (psychiatric), neurological, and other medical disorders.

Proposed sleep disorders include disorders for which inadequate or insufficient information is available to substantiate with certainty the existence of that particular disorder.

The *ICSD* includes descriptive details, specific diagnostic criteria, severity, and duration. There is also coding information for clinical and research purposes.

In addition to the *ICSD* two other systems are used: the *International Classification of Diseases (ICD),* ninth revision, clinical modification, and the *ICD,* tenth revision *[ICD-10).* The *1CD-10NA* is an expansion of *ICD-10* with alphanumeric codes for every neurological disease, including specific sleep disorders. There has been no study to assess the validity and reliability of any classification of sleep disorders.

Approach to a Patient with Sleep Complaints

The approach to a patient with a sleep complaint must begin with a clear understanding about sleep disorders as listed in the *ICSD.* Some common sleep complaints are trouble falling asleep and staying asleep (insomnia); falling asleep during the day (daytime hypersomnolence); and inability to sleep at the right time (circadian rhythm sleep disorders). Other common complaints are thrashing and moving about in bed with repeated leg jerking (parasomnias and other abnormal movements, including nocturnal seizures) and restless legs syndrome (RLS).

Cardinal manifestations in a patient complaining of insomnia include all or some of the following: difficulty falling asleep; frequent awakenings, including early-morning awakening; insufficient or total lack of sleep; daytime fatigue, tiredness, or sleepiness; lack of concentration, irritability, anxiety, and sometimes depression and forget fulness; and preoccupation with psychosomatic symptoms, such as aches and pains.

Cardinal manifestations of hypersomnia include EDS, falling asleep in an inappropriate place and under inappropriate circumstances, no relief of symptoms after additional sleep at night, daytime fatigue, inability to concentrate, and impairment of motor skills and cognition. Additional symptoms depend on the nature of the underlying sleep disorder (e.g., snoring and apneas during sleep witnessed by a bed partner in patients with OSAS; attacks of cataplexy, hypnagogic hallucinations, sleep paralysis, automatic behavior, and disturbed night sleep in patients with narcolepsy).

Sleeplessness and EDS are symptoms; therefore, every attempt should be made to find a cause for these complaints. Insomnia may be due to a variety of causes. The etiological differential diagnosis for EDS may include OSAS; central sleep apnea (C'SAt; narcolepsy; idiopathic hypersomnia; several psychiatric, neurological, and other medical illnesses; drug or alcohol abuse; and periodic hypersomnolence (e.g., Kleine-Levin syndrome, idiopathic recurrent stupor, and caramenial hypersomnolence). Sometimes a patient with RES may complain of f'.DS. Abnormal movements and behavior during sleep include REM and NREM sleep parasomnias and other abnormal movements (e.g., periodic limb movements in sleep [PLMS]), some daytime movement disorders that persist during sleep, and nocturnal seizures.

The physician must evaluate the patient first on the basis of the history and physical examination before undertaking laboratory tests, which must be determined by the clinical diagnosis (Chokroverty 1999a). The first step in the assessment of a sleep-wakcfulncss disturbance is careful evaluation of the sleep complaints. The history should include information on the patient's entire 24 hours and must include a detailed sleep history, with a sleep questionnaire as well as a sleep log or diary. It must also include psychiatric, neurological, medical, drug alcohol, and family and past histories. The history must be followed by a physical examination to uncover medical or neurological causes of insomnia, hypersomnia, and parasomnias. Physical examination of patients with OSAS may uncover upper airway anatomic abnormalities.

It is advisable to interview the bed partner, caregiver, or parents of children to get an adequate history, particularly the history during sleep at night, which may have an effect on daytime functioning. A sleep questionnaire containing a list of pertinent questions relating to sleep complaints; sleep hygiene; sleep patterns; medical, psychiatric, and neurological disorders; and drug and alcohol use may be filled out by the patient to save time during the history taking. A sleep log kept over a 2-weck period also is a valuable indicator of sleep hygiene. Such a log should include information on bedtime, arising time, daytime naps, amount of time needed to go to sleep, number of nighttime awakenings, total sleep time, and feelings on arousal. $0^{LlL,st}i^{o ll}s$ should be asked regarding the patient's mood and naps during the daytime, hi women, the relation of sleepiness to the menstrual cycle also should be ascertained.

Pertinent questions can help diagnose primary sleep disorders. For example, a history of snoring and apneas witnessed during sleep at night would suggest OSAS. Unusual movements during sleep at night may suggest periodic limb movement disorder. A history of short sleep attacks, cataplexy, hypnagogic hallucinations, sleep paralysis, and disturbed night sleep in a young adult suggests narcolepsy. Nonrefreshing sleep or no benefit from

additional sleep may suggest sleep apnea syndrome and idiopathic hypersomnolence. Identification of an irregular sleep-wake schedule and delayed sleep onset and awakening and inquiry into the patient's lifestyle to uncover sleep deprivation and insufficient sleep are important for the diagnosis of sleepiness. Paresthesias and uncontrollable limb movements at sleep onset or in the early evening may suggest RLS. A family history is important in primary sleep disorders such as narcolepsy, RLS, and OSAS, which may be responsible for EDS.

Subjective Measures of Sleepiness

A variety of scales have been developed to assess the subjective degree of sleepiness. The Stanford Sleepiness Scale (Table 74.10) is a seven-point scale to measure subjective sleepiness but may not be reliable in patients with persistent sleepiness (Robinson and Guilleminault 1999).

Another scale is the visual analogue scale of alertness and well-being. In this scale, subjects are asked to indicate their feelings on an arbitrary line. This scale has been used successfully in circadian rhythm disorders. The Epworth Sleepiness Scale evaluates general level of sleepiness (Johns 1998). The patient is rated on eight situations with a score of 0-3 (3 being the highest chance of dozing off). The maximum score is 24, and a score greater than 10 suggests the presence of excessive sleepiness (Table 74.11). This scale has been weakly correlated with the multiple sleep latency test (MSIT) scores.

CLINICAL PHENOMENOLOGY

In this section, the clinical characteristics of selected sleep disorders arc described.

Insomnia

Insomnia is a symptom rather than a disease and is characterized by an inadequate amount of sleep or impaired quality of sleep (Chesson et al. 2000; Satei et al. 2000).

Table 74.10: Stanford sleepiness scale

1. Wide awake, active, and alert
2. Awake and able to concentrate but not functioning at peak
3. Relaxed, awake, and responsive but not fully alert
4. Feeling a little foggy
5. Difficulty staying awake
6. Sleepy, prefer to lie down
7. Cannot stay awake; sleep onset is imminent

Source: Modified with permission from Hoddes, E., Zareone, V,, Smythe, H., et *a*\. 1973, "Quantification of sleepiness: A new approach," *Psychophysiology*, vol. 10, pp. 431-436.

Table 74.11: Epworth sleepiness scale

Eight situations	*Scores**
1. Sitting and reading	—
2. Watching television	—
3. Sitting in a public place (e.g., a theater or a meeting)	—
4. Sitting in car as a passenger for ;iu In iLLr v. iihtuii .i break	—
5. Lying down to rest in the afternoon	—
6. Sitting and talking to someone	
7. Sitting quietly after a lunch without alcohol	—
8. In a car, while stopped for a few minutes in traffic	—

*Scale to determine the total scores: 0 = would never doze; 1 = slight chance of dozing; 2 = moderate chance of dozing; 3 = high chance of dozing.
Source: Modified with permission from Johns, M. W. 1991, "A new method for measuring daytime sleepiness: The Epworth sleepiness scale," *Sleep*, vol, 14, pp. 540-545.

People with insomnia complain of difficulty initiating or maintaining sleep, which causes sleep that does not restore or refresh and impairment of daytime functioning. The National Institute of Mental Health (NIMH) consensus conference in 1984 divided insomnia (Chokroverty 2003b) into transient (1 week), short-term (1—3 weeks), and chronic (>3 weeks). The *ICSD* includes 14 categories that may have insomnia as a prominent complaint (included under the category of dyssomnias) and can occur in intrinsic, extrinsic, and circadian rhythm sleep disorders.

Insomnia is the most common sleep disorder in the population. In one survey, 35% of adults between the ages of 18 and 79 years complained of insomnia in the past year (Chokroverty 2003b). In the NIMH Epidemiological Catchment Area Study (1981-1985), 10% of the subjects responding to a sleep questionnaire had had problems sleeping for 2 weeks or more in the preceding 6 months; the problems were not related to neurological or psychological conditions. Other surveys have confirmed that insomnia affects about one third of the adult population in the United States at one time or another, and in 10%, it is a persistent problem {Leger et al. 2000; Ohayon and Guilleminault 1999). The prevalence of insomnia increases with age, and symptoms were more prevalent in women than in men. There is also a higher prevalence of insomnia among persons of lower socioeconomic status; in divorced, widowed, or separated individuals; and in those experiencing recent stress, depression, drug or alcohol abuse and anxiety disorder (Kirsti et al. 2003).

Clinical Manifestations of Insomnia

The symptoms of insomnia often interfere with interpersonal relationships or job performance. Decrements in daytime task performance and prolonged reaction times have been reported in patients complaining of insomnia (Chokroverty 2003b). Formal cognitive and motor skill

tests generally do not detect objective evidence of impairment. The NIMH Epidemiological Catchment Area Study, however, indicated an increased risk of major depression in those with chronic insomnia. A 1991 Gallup survey found that patients who report sleep deprivation due to chronic insomnia have 2.5 times as many automobile accidents as those who report fatigue from other causes. Some of these excessive risks may relate to the increasing proportion of drug or alcohol abuse with insomnia. Long-term detrimental health effects due to insomnia have not been documented, but one prospective study reported an increased chance of deaths from cancer, stroke, or heart disease among persons who reported sleeping for less than 4 hours or more than 10 hours per night (Chokroverty 1999a). These results have not been corroborated and may have been confounded by several factors. Objective tests for sleepiness (e.g., the MSI.T) document that people with insomnia are no more sleepy than age-matched normal control subjects; in fact, those with insomnia are less sleepy than normal control subjects, which suggests a hyperarousal state. These findings may also be due to an impaired perception of sleep. In one study, more than 70% of patients with chronic insomnia and more than 30% of normal subjects reported being awake if awakened from stage II NREM sleep (Mahowald et al. 1997) and patients wirh insomnia tend to overestimate sleep latency (the deviation of time between lights-out and the onset of sleep) after nocturnal awakenings. Patients with insomnia also tend to mispcrceive prior sleep as wake time, thus underestimating total sleep time (Mercer et al. 2002).

Causes of Insomnia

Insomnia is a heterogeneous condirion that may result from a wide variety of factors. Multiple causes may contribute to insomnia in an individual, and different causes may be responsible for different types of insomnia (transient, short-term, and chronic).

Transient and Short-Term Insomnia. Factors that can result in transient or short-term insomnia are similar, but the disturbances that produce short-term insomnia are of greater magnitude. Causes of transient and short-term insomnia arc listed in Table 74.12.

Tabic 74,12: Causes of transient and short-term insomnia

A change of sleeping environment (the most common cause of transient insomnia, the so-called first night effect)
Jet lag
Unpleasant room temperature
Stressful life events (e.g., loss of a loved one, divorce, loss of employment, preparing to take an examination)
Acute medical or surgical illnesses (including intensive care units)
Stimulant medications (e.g., theophylline, beta blockers, corticosteroids, thyroxine, bronchodilators, or withdrawal of central nervous system depressant medications)

Jet lag is experienced after travel through several time zones, which disrupts the synchronization between the body's inner clock and external cues (Bearpark 1994). Some of these sleep problems result from "jet" factors and others from "lag" factors. Jet factors that may be detrimental to sleep include long periods of travel with limited mobility, dryness of the eyes, headache, fatigue, gastrointestinal disturbances, and nasal congestion. Lag factots result in dyssynchrony berween the body's internal clock and the sleep schedule of the new environment. Symptoms are usually most pronounced when travel is from west to east and are more severe in elderly individuals. Readjustment and resynchronization occur at a rate of about 1 hour per day when one travels eastward and *1.5* hours per day when one travels westward (Bearpark 1994).

Shift work may affect up to 5 million workers in the United States; it can cause sleep disruption, chronic fatigue, gastrointestinal symptoms (including peptic ulcer), an increased chance of traffic accidents, and increased errors on the job. Drug-related insomnia includes rebound insomnia on discontinuation of short- and intermediate-acting hypnotics. Other drugs that may be responsible for insomnia are listed in Table 74,12.

Chronic Insomnia. Chronic insomnia can be caused by the chronic use of drugs or alcohol; various medical, neurological, or psychiatric disorders; or a variety of primary sleep disorders (Table 74.13).

Persistent insomnia can result directly from a medical illness (Table 74.14) or indirectly from the medications required for treatment of that illness. For example, sleep disruption may be caused by paroxysmal nocturnal dyspnea in patients with untreated CHF, whereas treatment with diuretics may disturb sleep by causing nocturia. Similar situations occur with nocturnal angina, chronic obstructive pulmonary disease (COPD), and bronchial asthma. Asthma may be exacerbated at night, with coughing and wheezing, which is related to several circadian factors {Chokroverty 1999c).

Table 74.13: Causes of chrome insomnia

General medical disorders
Neurological disorders, including fatal familial insomnia and post-traumatic insomnia
Psychiatric disorders
Drug- or alcohol-related insomnia
Primary sleep disorders
Primary or idiopathic (used to be called childhood-onset insomnia)
Psychophysiological insomnia
Circadian rhythm disorders associated with insomnia
Sleep-state misperceprion
Restless legs syndrome
Periodic timb movements in sleep
Inadequate sleep hygiene
Altitude insomnia
Insufficient sleep syndrome
Central sleep apnea-insomnia syndrome

Tabic 74.14: Medical causes of insomnia

Congestive heart failure
Ischemic heart disease
Nocturnal angina
Chronic obstructive pulmonary disease
Bronchial asthma including nocturnal asthma
Peptic ulcer disease
Reflux esophagitis
Rheumatic disorders, including fibromyalgia syndrome
Lyme disease
Acquired immunodeficiency syndrome
Chronic fatigue si ndrome

Neurological disorders causing insomnia are listed in Table 74.15. The pathogenesis of insomnia in neurological disorders may be related to direct or indirect mechanisms. For example, lesions of the hypnogenic neurons in the hypothalamic-preoptic nuclei and the lower brainstem area in the region of the nucleus tractus solitarius can alter the balance between waking and sleeping brain, causing sleeplessness. Other neurological conditions can produce pain, confusional episodes, changes in the sensorimotor system, or movement disorders that interfere with sleep. Insomnia in some neuromuscular diseases may be due to sleep-related hypoventilation with consequent sleep fragmentation. Insomnia may also be due lo medications used to treat neurological illnesses (e.g., anticonvulsants, dopaminergic agents, and anticholinergic drugs).

Insomnia commonly coexists with or precedes the development of a number of psychiatric illnesses. A large epidemiological study found that individuals with insomnia at baseline were about 34 rimes more likely than normal subjects to develop a new psychiatric disorder within a year compared with individuals without insomnia (Chokroverty 2003b). Those with insomnia are also about 40 times more likely than normal subjects to develop a new episode of major depression within 6 months. Individuals with insomnia that resolved within 1 year had a similar incidence of subsequent psychiatric disorders compared with normal individuals. Specific examples of psychiatric disorders that may be associated with insomnia include depression, anxiety disorders, and schizophrenia.

There is a high prevalence of depression among elderly individuals complaining of insomnia. Early morning awakening is considered to be the biological hallmark of depression. Adolescents and young adults with depression, in contrast, may report difficulty in initiating sleep. Characteristic findings in sleep disorders associated with depression are a short REM latency and maldistribution of REM cycle duration, with the longest nocturnal REM cycle occurring in the first one third of the night.

Table 74.15: Neurological disorders causing insomnia

Cerebral hemispheric and brainstem strokes
Neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease
Brain tumors
Traumatic brain injury causing post-trauma tie insomnia
Neuromuscular disorders, including painful peripheral neuropathies
Headache syndromes (migraine, cluster, hypnic headache, and exploding head syndromes)
Fatal familial insomnia, a rare prion disease

Anxiety disorders arc the most common psychiatric disorders and include panic, phobic, obsessive-compulsive, post-traumatic stress, and generalized anxiety disorders. Sleep may be disrupted by panic attacks, nightmares, or flashbacks, depending on the underlying anxiety disorder. Major depression coexists in many patients. In a recent telephone interview of a representative sample of the general population in several European countries Ohayon and Roth (2003) concluded that chronic insomnia can be a residual symptom of a previous mood or anxiety disorder, and subjects with these disorders have a higher risk of relapse.

In schizophrenia, the severity of sleep disturbances is related to the intensity of psychotic symptoms. There is often extremely prolonged sleep-onset latency during the acute illness, with a reduction of total sleep time.

Primary Sleep Disorders Associated with Chronic Insomnia

Some patients with chronic insomnia have either idiopathic or psychophysiological insomnia or insomnia as a symptom of another primary sleep disorder.

Idiopathic Insomnia. Idiopathic or primary insomnia, previously called childhood-onset insomnia, is defined as a life-long difficulty in initiating and maintaining sleep, resulting in poor daytime functioning. The cause of this syndrome is unknown, but a neurochemical imbalance, either in the arousal (hyperactivity) or sleep-promoting neurons (hypoactivity), has been suggested but not proved. Onset occurs in early childhood, and sometimes the syndrome rims in families. This condition should only he diiisMosi'd .ifrer •.•wln-ann of concomitant medical, neurn logical, and psychiatric or other psychological problems.

Psychophysiological Insomnia. Psychophysiological insomnia is defined as chronic insomnia resulting from learned, sleep-pre venting associations and increased tension or agitation. It is estimated that about 15% of all individual with insomnia attending sleep disorder centers have psychophysiological insomnia. Affected individuals are overly concerned and overly focused on the problem of sleep but do not have generalized anxiety, phobic, or other psychiatric disorders. Onset of these syndromes often occurs in young adulthood, and symptoms persist for decades. First-degree relatives may have similar sleep problems, suggesting a possible genetic component.

I be chanickTiNUc tenure i>' psychophysiological IKMIIII nia is development of conditioned responses that are

incompatible with sleep. The disorder begins in some patients during an initial period of stressful events, but the insomnia persists even after the inciting stressors have resolved. The combination of excessive worry, fear, and frustration about being unable to initiate and maintain sleep and the identification of the bedroom as a signal for arousal contribute to negative conditioning and sleeplessness. Affected patients tend to sleep poorly during PSG study, although occasional patients sleep better because they are removed from their usual sleep environment. This condition is distinguishable from generalized anxiety disorder because patients with psychophysiological insomnia have anxiety confined to issues relating to sleep. The condition tends to have a later onset than idiopathic insomnia, which typically begins in childhood.

Sleep-State Misperception. In this disorder, subjects complain of sleeplessness hut without objective evidence (e.g., PSG recording of a sleep disorder). Despite complaints of no sleep or poor sleep over many years, actigraphy (a technique that measures patient activity and permits an objective assessment of sleep time) or PSG recordings document a normal sleep pattern (Saadch et al. 1995).

Inadequate "Sleep Hygiene". Good sleep hygiene measures promote sleep. These include avoidance of caffeinated beverages, alcohol, and tobacco in the evening; avoidance of intense mental activities and vigorous exercise close to bedtime; avoidance of daytime naps and excessive time spent in bed; and adherence to a regular sleep-wake schedule.

Insufficient Sleep Syndrome. Insufficient sleep is probably the most common cause of sleepiness in the general population. The whole society appears to be sleep deprived (bonnet and Arand 1995), which results from various factors, such as lifestyle, competitive drive to perform that sacrifices sleep, and environmental light and sound. Chronic sleep deprivation may lead to daytime sleepiness, irritability, lack of concentration, decreased daytime performance, muscle aches and pains, or depression.

Altitude Insomnia, Altitude insomnia refers to sleeplessness that develops in some individuals on ascent to altitudes higher than 4000 m in conjunction with other features of acute mountain sickness, such as fatigue, headache, and loss of appetite (Coote 1994). The severity of the sleep disturbance is directly proportional to the height of ascent. Those who live at higher altitudes become acclimatized and tend to sleep normally, but in some, chronic mountain sickness may develop, causing sleep disturbance.

Affected patients have periodic breathing (Ghcync-Stokes asthma) due to the stimulation of peripheral chemoreceptors by hypobaric hypoxemia. This causes hyperventilation, hypocapnia, and a respiratory alkalosis that suppresses ventilation. The abnormal breathing pattern causes repeated awakenings and sleep fragmentation, which may be exacerbated by stress, an uncomfortable sleeping environment, and cold temperature. The best treatment for altitude insomnia is aceta/olamidc, which promotes a mild metabolic acidosis that compensates for the hypoxemia-driven respiratory alkalosis.

RLS, periodic limb movement disorder, and circadian rhythm disorders are some of the other causes of persistent insomnia. In some patients, CSA may cause insomnia.

Narcolepsy

In 1880, the French physician Gelineau coined the term *narcolepsy* and gave a classic description of irresistible sleep attacks (Bassetti 2003). He also described "astasia," which had all the clinical features of what was later termed *cataplexy.* Before Gelineau's description, however, there were isolated instances of hypersomnolence, many of which resembled narcolepsy (although some may have been EDS associated with sleep apnea). In the last century, reports of large series of patients brought the entity of narcolepsy to the attention of the medical profession (Bassetti 2003; Overeem et al. 2001). In 1957, Yoss and Daly listed the narcoleptic tetrad of sleep attacks, cataplexy, sleep paralysis, and hypnagogic hallucinations (Bassetti 2003). The modern era of narcolepsy research began in 1960 with Vogel's discovery of sleep-onset REMs (SOREMs) in the narcolepsy syndrome. The observation by Honda and coworkers of the presence of HLA DR2 and DQwl (now called DQwl5) antigens in 100% of Japanese narcoleptic patients brought narcolepsy research to the field of molecular neurobiology (Mignot 1998; Overeem et al. 2001).

Epidemiology, Genetics, and Family Studies in Narcolepsy

There is wide variation in the prevalence of narcolepsy throughout the world, and good epidemiological studies are lacking. In the United States, the prevalence is 3-6 per 10,000; in Japan, it is 1 per 600; and in Israel, it is only 1 per 500,000.

Both genetic and environmental factors contribute to the development of narcolepsy. About 1-2% of first-degree relatives of narcoleptic patients manifest the illness, compared with 0.02-0.18% of the general population (a difference of 10-40 times) (Mignot 1998; Overeem et al. 2001). Several reports of familial narcolepsy have appeared in the literature since the first report in 1877. A positive family history of hypersomnolence and, less commonly, of cataplexy was reported in up to 50% of relatives of narcoleptic patients in the early studies. Early reports were based on symptoms only and not on PSG studies; therefore, cases of sleep apnea causing EDS may have been misdiagnosed as narcolepsy. Reports show that 4.7% of first-degree relatives of people with narcolepsy-cataplexy

complain of F.DS (Billiard et al. 1994). In view of the fact that the prevalence of EDS in the general population may be **abonl 1 1%, M can he** concluded **tliat** IMOSI "slccp>'" **relatives** of patients with narcolepsy do not have narcolepsy.

The mode of inheritance is thought to be autosomal dominant in humans, recessive in Doberman pinschers *{canarc-1)* and Labrador retrievers, and multifactorial in poodles.

Narcolepsy lias been linked io dys:uiiclii'r: ol ;lie hypocretin (orexin) peptide system. Lin and colleagues (1999) found deletions in the transcripts of the hypocretin receptor 2 *{HcrtrZ)* gene in narcoleptic Doberman pinschers and Labrador retrievers. Chemelli and colleagues (1999) created a knockout of the orexin gene in mice, which exhibited a phenotype strikingly similar to that in human narcolepsy patients and *canarc-1* mutant dogs. Orexin-containing neurons are located exclusively in the lateral hypothalamus with projections throughout the CNS, including the major nuclei implicated in sleep regulation. These two studies implicate hypocretins as major sleep-modulating neurotransmitters, which are closelv linked to the pathophysiology of narcolepsy.

Twin studies in narcolepsy do not suggest a strong genetic influence. Approximately 25-31% of monozygotic twins are concordant, but the majority are discordant for narcolepsy, which suggests the influence of environmental factors in the etiology of narcolepsy. Because most monozygotic twin pairs are discordant for narcolepsy-cataplexy and three discordant dizygotic twins were identified in a sample of 11,354 twins in the Finnish study, there may be an interaction of environmental and genetic factors in the development of narcolepsy (Mignot 1998; Overeem et al. 2001).

Honda and co-workers first directed attention to an association between HLAs of the major histocompatibility complex for narcolepsy-cataplexy. The haplotypes DR15 subtype of DR2 and DQ6 subtype of DQ1 are closely associated with narcolepsy in 95-100% of white and Japanese patients (Mignot 1998; Overeem et al. 2001). In blacks with narcolepsy, the DR2 antigen is found in only *65%* of patients, but the DQ1 antigen is present in more than 90%. It has been established that the HLA allele DQB1*0602 is the narcolepsy subtype gene along with the allele DQA1*0102 located nearby on chromosome 6 in all ethnic groups (Mignot 1998; Overeem et al. 2001). However, cases of patients with narcolepsy not carrying HLA DR2 or DQ1 antigens have been reported (Mignot 1998; Overeem et al. 2001}. Also, 12-35% of the general population carry the same HLA alleles, but narcolepsy is present in only 0.02-0.18% of the population. Therefore, the alleles DQB1*0602 and DQAl'0102 are neither necessary nor sufficient for development of narcolepsy.

Clinical Manifestations

The syndrome of narcolepsy is a lifelong neurological condition that generally begins in an adolescent or young adult with EDS and sleep attacks. Peak incidence occurs during the teens and early 20s (mostly at ages 15-20 years); another peak is seen aftct the second decade. Rare occurrences have been described in patients younger than 5 years of age and older than age 50. In modern demographic studies, there is no difference in prevalence between men and women. Many precipitating factors have been described, but most of them are probably incidental. After a variable interval of mouths to years, at least 70% of patients develop the second characteristic feature, cataplexy, which is followed by other symptoms in a certain percentage of patients. Narcolepsy begins before age 10 in about 5-15% of patients and after age 50 in about 5% of patients. In about 10% of patients, cataplexy precedes EDS by a few months and rarely b>T as much as 28 years. Any of the other major symptoms may rarely he the first symptom before narcoleptic sleep attacks and cataplexy (Bassetti 2003; Overeem et al, 2001). Clinical manifestations of narcolepsy syndrome may be described under three headings; major, minor, and miscellaneous.

Major manifestations are narcoleptic sleep attacks and EDS, cataplexy, sleep paralysis, hypnagogic hallucinations, disturbed night sleep, and automatic behavior.

Narcoleptic Sleep Attacks. The patient complains of EDS and characteristic sleep attacks, which are manifested by an irresistible desire to fall asleep. The attacks may come under inappropriate circumstances *Mid* in inappropriate places: during driving, talking, eating, playing, walking, running, working, class time, sexual intercourse, watching television, sitting, and conditions of boredom and monotony. Attacks are generally brief, lasting for a few minutes to 15-30 minutes, and on awakening, the patient usually feels fresh, although occasionally, the patient feels tired and drowsy. The incidence of attacks varies widely from one or more attacks daily to attacks weekly or monthly. Sometimes they occur once every few weeks to months and, occasionally, once every year to every few years. The attacks persist throughout life, although there may be fluctuations and, rarely, temporary remissions. Because of these sleep attacks, EDS, and the common occurrence of microsleep episodes, performance at school and work declines, resulting in a variety of psychosocial and socioeconomic difficulties,

Cataplexy. Lowenfeld coined the term *cataplexy* (Bassetti 2003). Cataplexy is characterized by sudden loss of tone in the voluntary muscles, except for respiratory and ocular muscles. The cataplectic attacks are often *{>95%* of the time) triggered by emotional factors, such as laughter, rage, and anger. The attacks may be complete or partial and, rarely, unilateral (0.5-1.0% of patients). The patient completely loses tone in the limb muscles and falls to the ground. Knees may buckle, there may be head nodding, sagging of the jaw, dysarthria, or loss of voice, and in rare unilateral cases, there may be a loss of power in one arm

or leg. These attacks generally last for a few seconds to a minute and sometimes a few minutes. Consciousness is retained completely during the attacks, and there is never any jerking of the limbs or head. Physical examination during these brief spells reveals flaccidity of the muscles and absent or markedly diminished muscle stretch reflexes. The H-reflcx, which is the electrical counterpart of the muscle stretch reflex, and F responses arc decreased or absent.

Cataplexy is the second most important manifestation of narcolepsy syndrome and is present in 60-100% of patients with narcolepsy. In most patients, cataplexy appears months to years after onset of the sleep attacks, but occasionally, cataplexy may be the initial presentation, which causes diagnostic confusion. At the onset, the patient may have attacks daily or weekly; gradually, they occur less often and may even disappear in old age. Rarely, particularly after withdrawal of tricyclic medications, patients may develop status cataplecticus. The EEG recording shows wakefulness during the brief cataplectic spells, but if these arc prolonged to 1-2 minutes, shows REM sleep and all its manifestations.

Sleep Paralysis, Sleep paralysis is the third major manifestation of narcolepsy. It occurs months to years after onset of narcoleptic sleep attacks and is seen in about 25-50% of patients. There is sudden apparent unilateral or bilateral paralysis or paralysis of one limb, cither during sleep onset at night (hypnagogic) or while awakening (hypnopompic) in the morning. The patient is conscious during these paralytic attacks but is unable to move or speak and is often frightened and fearful. As the patient experiences more and more of these episodes, he or she overcomes the fear and anxiety.

Hypnagogic Hallucination. Hypnagogic hallucination is the fourth major manifestation of narcolepsy syndrome and may occur cither at the onset of sleep or during awakening early in the morning. The hallucination manifests as vivid, often fearful, visual imagery but sometimes has auditory, vestibular, or somesthetic hallucinatory phenomena. These hallucinations may occur years after the onset of sleep attacks in 20-40% of narcoleptic patients. Narcoleptic sleep attacks, cataplexy, and sleep paralysis or hypnagogic hallucination are seen in about 30% of patients; all four major features (narcoleptic tetrad) may occur together in about 10% of patients.

Disturbance of Night Sleep. Disturbance of night sleep, together with the four major manifestations, may be termed the *narcoleptic pentad.* PSG findings showing disturbed night sleep are seen in 72-H0% of patients (see Laboratory Assessment of Sleep Disorders, later in this chapter).

Automatic Behavior. Automatic behavior is included under major manifestation and is found in a large percentage of patients (20^0%). During these episodes, the patient performs the same function repetitively, speaks or writes in a meaningless manner, drives on the wrong side of the toad, or drives to a strange place and then forgets the episodes. The behavior resembles a fuguelikc state and may result from partial sleep episodes, frequent lapses, or microslccp episodes.

Minor Manifestations

In addition to major manifestations, many patients have other minor clinical featutes. These may include psychosocial disturbances, anxiety, depression, morning headache, impotence in men, frigidity and lack of orgasm in women, and recent memory impairment.

Miscellaneous Man ifes tat ions

Patients with narcolepsy syndrome may also have sleep apnea and PLMS, which often aggravate their sleep attacks. The incidence of associated sleep apnea in narcolepsy varies, but about 30% of narcoleptic patients may have sleep apnea, which is most commonly central but it may be obstructive or mixed. It is important to recognize obstructive sleep apnea (OSA) in narcoleptic patients because they may need additional treatment with continuous positive airway pressure (CPAP) for relief of apneas and EDS. The third important miscellaneous manifestation is RBD, which Schenck and Mahowald reported in 17 patients in whom the diagnosis was made by established criteria for narcolepsy and RBD. These patients ranged in age from 8 to 74 years, and 71% were men. Narcolepsy and RBD most commonly emerged in tandem. In three patients, treatment of narcolepsy-cataplexy with stimulants and tricyclic medications either induced or exacerbated RBD.

Differential Diagnosis

Narcoleptic sleep attacks should be differentiated from other causes of EDS. These include sleep deprivation and insufficient sleep syndrome; OSAS; alcohol- and drug-related hypcrsomnolcnce; other medical, neurological, and psychiatric disorders causing hypersomnolence; idiopathic hypersomnia; and circadian rhythm sleep disorders.

OSAS (see Sleep Apnea Syndrome, later in this chapter) is **the** most common cause of EDS in patients referred to a sleep laboratory for evaluation and is characterized by repeated episodes of obstructive and mixed apneas during NREM and REM sleep in overnight PSG recordings. These patients have prolonged daytime sleep episodes, followed by fatigue and drowsiness on awakening, which contrasts with a fresh feeling in narcoleptic patients on awakening from brief sleep attacks. All patients with hypersomnolence can he excluded after careful history and physical elimination and overnight PSG recording.

Idiopathic hypersomnia (see Idiopathic Hypersomnia, later in this chapter) closely resembles narcolepsy syndrome.

In contrast to narcolepsy, the sleep episodes in idiopathic hypersomnia arc prolonged, and the sleep is not refreshing. PSG recordings and MSLT scores do not show SORF.Vts but do show pathological sleepiness. There is no disturbance of REM-NREM organization on PSG recordings. Sun:-: patients with idiopathic hypersomnia ma) have a positive family history.

Cataplexy may be mistaken for partial complex seizure, absence spells, atonic seizures, drop attacks, and syncope. During partial complex seizure, there is an altered state of consciousness, but in cataplexy, patients retain consciousness. Patients with partial complex seizures may have secondary generalized tonic-clonk movements and postictal confusion, and EEG recordings may show characteristic epileptiform discharges in the anterior and midtemporal regions. Absence spells arc characterized by staring and vacant expression lasting for a few seconds to *30* seconds and an altered state of alertness accompanied by characteristic 3-Hz spike-and-wavc discharges on the EEG recording. Atonic seizures are accompanied by transient loss of consciousness, and the EEG findings may show slow spike-and-wavc or polyspike-and-wave discharges. Drop attacks may occur in vertebrobasilar insufficiency {transient ischemic attacks), and the patient may **have other** evidence of brainstem ischemia, such as vertigo, ataxia, or diplopia. Syncope results from Transient loss of consciousness and may have resulted from cardiogenic or other causes, **including** neurogenic orthostatic hypotension.

Sleep paralysis in narcolepsy should be differentiated from isolated and physiological sleep paralysis and familial sleep paralysis. In all these conditions, other manifestations of narcolepsy are absent,

Automatic behavior and fugue states should be differentiated from the automatism seen in partial complex seizure and psychogenic fugue. History, physical exanima tion, and the EEG findings are helpful in the differentiation.

Differential diagnosis should also include neurological conditions that were thought to be associated with secondary or symptomatic narcolepsy. Secondary narcolepsy has been controversial, and many cases of hypcrsom**nolence** resulting from CNS lesions have been described in the past as narcolepsy. Most of these are atypical sleep attacks and did not have the classic features of narcolepsy. Occasional cases of true narcoleptic sleep attacks and cataplexy have been described, however, in association with diencephalic and midbrain tumors. Multiple sclerosis and narcolepsy may occasionally be **seen** in **the** same individual and are associated with a 111.A DR2 antigen positi vity.

Pathophysiological Mechanisms

Physiological, neurochemical, genetic, and environmental factors all play distinct roles in the pathogenesis of narcolepsy syndrome. Physiological abnormalities in narcolepsy suggest a disturbance of REM-NREM sleep-wake state boundaries. The hallmark of physiological testing in narcolepsy is the presence of SOREMs (i.e., the onset of REM sleep at sleep onset or within 15 minutes of sleep onset). In most patients, this sign is found in two of four to five nap recordings in MSLT scores and in approximately 50% of PSG recordings. Other features point to dissociation of REM sleep and intrusion into wakefulness. During cataplexy, there is muscle atonia of REM sleep without other REM features during a wakeful electroencephalogram. If the episode is prolonged, however, the patient develops full REM sleep. Similarly, in sleep paralysis, **muscle** atonia is similar to the REM sleep atonia. **REM** sleep intrusion with dream imagery without other features of REM sleep is noted in hypnagogic hallucinations, In many of these episodes, the sleep state is intermediate between REM and NREM sleep. Many patients also have microsleep episodes during the daytime. The time -is o la tion laboratory experiments conducted by Pollak and coworkers showed strong evidence for circadian disorganization in narcoleptic patients. Although the total 24-hour sleep, as welt as the percentage of REM sleep, is norma! in narcoleptic patients, the intrusion of REM sleep atonia into wakefulness suggests the dissociation of REM sleep regulation. Occasional occurrence of RBD in some narcoleptic patients may be cited as evidence favoring an impairment of state boundary theory in narcolepsy.

Neurochemical Mechanisms

The neurochemical basis of narcolepsy is not well understood. Injection of cholinergic drugs (e.g., physostigmine) in narcoleptic dogs (Doberman pinschers are good models of narcoleptic dogs with an autosomal recessive inheritance) increases the cataplectic episodes, whereas atropine and scopolamine (muscarinic receptor-blocking agents) decrease cataplectic episodes (Guilleminault et al. 1998). M_2 subtypes of muscarinic cholinergic receptors are found to be upregulated in the pontine reticular formation of narcoleptic dogs {Guilleminault et al. 1998). Postmortem studies have also shown increased muscarinic Mj receptor binding in the basal ganglia and the amygdala. These findings, in conjunction with the pharmacological experiments, suggest hypersensitivity of the muscarinic cholinergic system in the cataplectic dog brain. There is also cvilli lice In suggest .1 deU\ I in ir.om >i i;ii[n-r;;ic t i.;;uLiUii!i oi the REM sleep mechanism contributing to narcoleptic symptoms. REM-off cells (serotonergic cells in the raphe and noradrenergic cells in the locus ceruleus) are completely inactive during REM sleep and appear to play a permissive role by modulating cholinergic activity. It has been postulated that an imbalance of the chemical regulation between the cholinergic and monoaminergic neurons may play a role in narcoleptic symptomatology. The stimulants (amphetamine and others) used for effective treatment of sleepiness in narcolepsy increase the synaptic availability of monoamines. Tricyclic antidepressants used in the

treatment of cataplexy decrease the reuptake of norepinephrine; fluoxetine decreases the reuptake of serotonin, thus increasing the availability of both of these monoamines. Modafinil, the wake-promoting agent used in the treatment of narcolepsy, may exert its effect by promoting dopaminergic transmission (Nishino and Mignot 1997; Wisor et al. 2001).

Documentation of an abnormality in the hypocretin (orexin) neurons in the lateral hypothalamus in patients with narcolepsy-cataplcxy is the most exciting recent development in its pathogenesis (Siegel 1999, 2002). This condition can be considered a hypocretin (orexin) deficiency syndrome. Such a hypothesis is supported by the following observations: induction of narcolepsy-like symptoms after preprohypocretin gene knockout in mice and mutation of the hypocretin receptor 2 gene in dogs (Chemelli etal. 1999; Lin etal. 1999); decreased hypocretin 1 levels in the cerebrospinal fluid of patients with narcolepsy-cataplexy (Nishino et al. 2000, 2001; Mignot et al. 2002); postmortem documentation of decreased numbers of hypocretin neurons in brains from narcoleptic individuals (Thannickal ct al. 2000); and identification of a prep ro hypocretin gene mutation in a child with severe narcolepsy and a generalized absence <t hypocretin peptides in the brain (Peyron et al. 2000).

Genetic and Environmental factors

Genetic and environmental factors in narcolepsy are described briefly under Epidemiology. Genetics, and family Studies in Narcolepsy, earlier in this chapter. The exact environmental factors in narcolepsy are unknown. The question of autoimmunity in narcolepsy is the subject of speculation, but no definite evidence has been uncovered (Overeem etal, 2001).

Idiopathic Hypersomnia

ICSD (1997) defines idiopathic hypersomnia as a disorder of excessive sleepiness of presumed (but not proved) CNS cause that is associated with normal or prolonged (1-2 hours) NREM sleep episodes. The syndrome has been described under a variety of labels, including NREM narcolepsy, idiopathic CNS hypersomnia, and functional, mixed, or harmonious hypersomnia. Idiopathic hypersomnia (Billiard and Dauvillicrs 2001) occurs insidiously, generally between the ages of 15 and 30 years. It closely resembles narcolepsy and sleep apnea. Although sometimes it is very difficult to distinguish from narcolepsy syndrome, the sleep pattern is different from that in narcolepsy or sleep apnea (Bassetti and Aldrich 1997). A patient with idiopathic hypersomnia generally sleeps for hours, and the sleep is not refreshing. The patient does not give a history of cataplexy, snoring, or repeated awakenings throughout the night. Sleep drunkenness (i.e., confusional arousal) is often seen in these patients, and they may have automatic behavior with amnesia tor the events. Physical examination uncovers no abnormal neurological or other findings. This is a very disabling and lifelong condition. The MSLT shows evidence of pathological sleepiness without SOREMs.

The differential diagnosis of idiopathic hypersomnia should include other causes of EDS, such as classic narcolepsy-cataplexy, upper airway OSAS, CSA syndrome, upper airway resistance syndrome (UARS), insufficient sleep, drug-induced hypersomnia, and other medical or psychiatric disorders, particularly mood disorders. Post-traumatic hypersomnia, chronic fatigue syndrome, delayed sleep-phase syndrome (DSPS), and long sleeper syndrome should also be included in the differential diagnosis. Based on a retrospective review of clinical and PSG features as well as questionnaire results derived from a database of 3618 patients evaluated between 1985 and 1993 at a sleep disorder center, Aldrich (1996) suggested that idiopathic hypersomnia is a heterogeneous syndrome. I le contradicted some of the previously reported findings, and in his analysis, these patients did not exhibit prolonged night sleep or sleep drunkenness. Aldrich also questioned the validity of using prolonged or "deep" sleep as a diagnostic criterion for idiopathic hypersomnia. He suggested that clinical heterogeneity may reflect differences in etiologies, such as reports of preceding Epstein-Barr viral infection, infectious mononucleosis, Guillain-Barre syndrome, or human immunodeficiency virus (HIV) infection. The author argued for revaluation of the diagnostic criteria for idiopathic disorders of sleepiness not associated with cataplexy. Some of these patients may have a positive family history, but the mode of inheritance is unknown. Unlike narcolepsy, there is no clear association between idiopathic hypersomnia and HLA antigens.

Sleep Apnea Syndrome

Sleep apnea syndrome encompasses both obstructive and central apneas as well as hypopnca. OSAS is very common but remains underdiagnosed, whereas CSA syndrome is uncommon in the general population. OSAS is the most common sleep disorder studied in the sleep laboratory by overnight PSG recording done to assess EDS, In the general population, however, sleep deprivation or insufficient sleep syndrome is the most common cause of EDS today. The reason for underdiagnosis of OSAS is inadequate awareness and insufficient knowledge about the serious consequences of this disorder among physicians and the public. OSAS causes significant morbidity and mortality, and it is important to diagnose the condition because effective treatment is available for most individuals who have it. To understand the condiiiuii, definition ol sever.:.! terms related to sleep disordered breathing (SDB) is necessary.

Sleep-Disordered Breathing: Terminology

Apnea (obstructive, central, or mixed), hypopnea, hypoventilation, paradoxical breathing, periodic breathing, increased upper airway resistance, dysrhyrhmic breathing, apneustic breathing, inspiratory gasps, and nocturnal stridor may all be grouped under SDB. Figure 74,5 shows some patterns of SDB. The term *sleep apnea* refers to temporary cessation or absence of breathing during sleep. Analysis of the breathing pattern has revealed the presence of three types of sleep apnea: upper airway obstructive, central, and mixed. Normal individuals may experience a few episodes of sleep apnea, particularly central apnea at the onset of NREM sleep and during REM sleep. To be of pathological significance, the sleep apnea should last at least 10 seconds, the apnea index (number of episodes of apnea per hour of sleep) should be at least 5, and the patient should have at least 30 episodes during 7 hours of all-night sleep,

Cessation of aitflow with no respiratory effort constitutes central apnea; diaphragmatic and intercostal muscle activities arc absent, as is air exchange through the nose or mouth. Upper airway OSA is characterized by cessation of airflow through the nose or mouth with persistence of diaphragmatic and intercostal muscle activities. Mixed apnea is manifested as an initial cessation of airflow with no respiratory effort {central apnea) followed by a period of upper airway OSA.

Sleep-related hypopnea is defined by the American Academy of Sleep Medicine Task Force (1999) as a reduction in the breathing signal to less than one half the volume measured during the preceding or following respiratory cycle with 3% or more oxygen desatitration or EEG arousal. The Sleep Heart Health Study reported by Shahar et al. (2001) defines hypopnea as a 30% or greater reduction in thoracoabdominal exertion or flow limitation associated with 4% or greater oxygen desaturation.

The respiratory disturbance index (RDI) or apnea-hypopnea index (AHI} is defined as the number of apneas and hypopneas per hour of sleep. A normal index is less than 5, but most investigators consider AHI or RDI of 10 or more significant.

Apneas and hypopneas are accompanied by oxygen desaturation and are terminated by an arousal, which is defined as transient (lasting 3-14 seconds) return of alpha activities in the EEG recording. Repeated arousals causing sleep fragmentation may be the main contributing cause to EDS. Arousals along with repeated hypoxemias are also the most important factors for long-term cardiovascular consequences of OSAS.

During paradoxical breathing, the thorax and abdomen move in opposite directions, thereby indicating increased upper airway resistance. This type of breathing may be noted in patients with OSAS as well as in some patients with UARS.

Periodic breathing includes Cheync-Stokes breathing and the Cheyne-Stokes variant pattern of breathing. Cheyne-Stokes breathing is a special type of central apnea manifested as cyclic changes in breathing, with a crescendo-dccrescendo sequence separated by central apneas. The Cheyne-Stokes variant pattern of breathing is distinguished by the substitution of hypopneas for apneas. Cheyne-Stokes breathing and the variant pattern arc most commonly noted in CHF and neurological disorders.

Dysrhythmic breathing is characterized by nonrhythmic respiration of irregular rate, rhythm, and amplitude that becomes worse during sleep. This type of breathing may

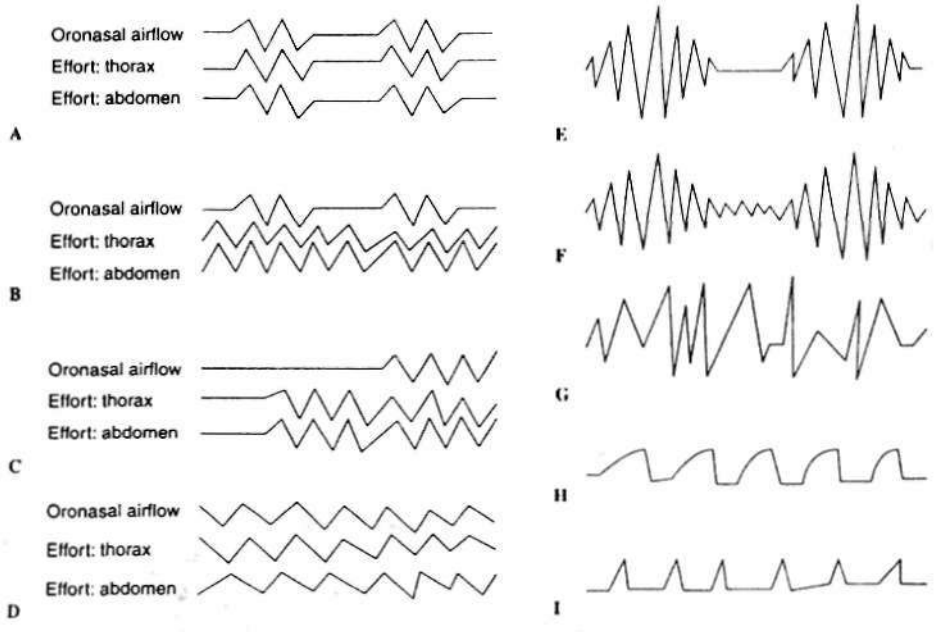

FIGURE 74.5 Patterns of sleep-disordered breathing: (A) central apnea; (B) upper airway obstructive apnea; (C) mixed apnea (initial central apnea followed by obstructive apnea); (D) paradoxical breathing; (E) Cheyne-Stokes bn.[1]:!tiling; (f) ('heytie-Stokes variant pattern; (G) dysrhythmic breathing; (H) apneustic breathing; (1) inspiratory gasp, (Reproduced with permission from Chokroverty, S. 1999, "Sleep, breathing, and neurological problems," in *Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects,* ed S. Chokroverty, Bu rter worth-I leinvituiiiri, Huston,)

result from an abnormality in the automatic respiratory pattern generator in the brainstem.

Apneustic breathing is characterized by prolonged inspiration with an increase in the ratio of inspiratory to expiratory time. This type of breathing may result from a neurological lesion in the caudal pons disconnecting the apneustic center in the lower pons from the pneumotaxic center in the upper pons.

Inspiratory gasp is characterized by short inspiratory time and a relatively prolonged expiration and has been noted after a lesion in the medulla.

Hypoventilation refers to a reduction of alveolar ventilation accompanied by hypoxemia and hypercapnia without any apnea or hypopnea; it may be noted in patients with neuromuscular disorders and kyphoscoliosis and those with underlying lung or chest wall abnormalities that impair gas exchange during wakefulness.

Upper Airway Resistance Syndrome

There is a general gradation from increasing upper airway resistance, which is found in normal individuals during sleep, to the limitation of airflow in subjects with loud snoring to a stage of UARS followed by the next stage of complete airway occlusion, seen in patients with OSAS. Patients with UARS show subtle airflow limitations due to increased upper airway resistance followed by repeated arousals during sleep at night. This subtle aitflow limitation cannot be identified by the usual recording of respiration using an oronasal thermistor or inductance plethysmography to register chest and abdominal wall motions. Nasal pressure monitoring with a nasal cannula is more sensitive than use of a thermocouple or thermistor in detecting airflow limitation and increased upper airway resistance (Ayappa et al. 2000), Intraesophageal balloon manometry, however, is the gold standard for detecting upper airway **resistance, and** this reveals increasing efforts, with increasing intraesophageal pressure, leading to arousal but without any apneas or hypopneas (Figure 74.6). These patients may or may not snore; they do have EDS and all its consequences, as seen in OSAS.

Epidemiology of Obstructive Sleep Apnea Syndrome

No study has been specifically designed to determine the incidence of OSAS in a previously healthy population. Based on a definition of at least five apneas or hypopneas per hour of sleep accompanied by EDS {Young et al. 1993), however, the prevalence of OSAS is 4% in men and 2% in women between 30 and 60 years of age. There is a strong

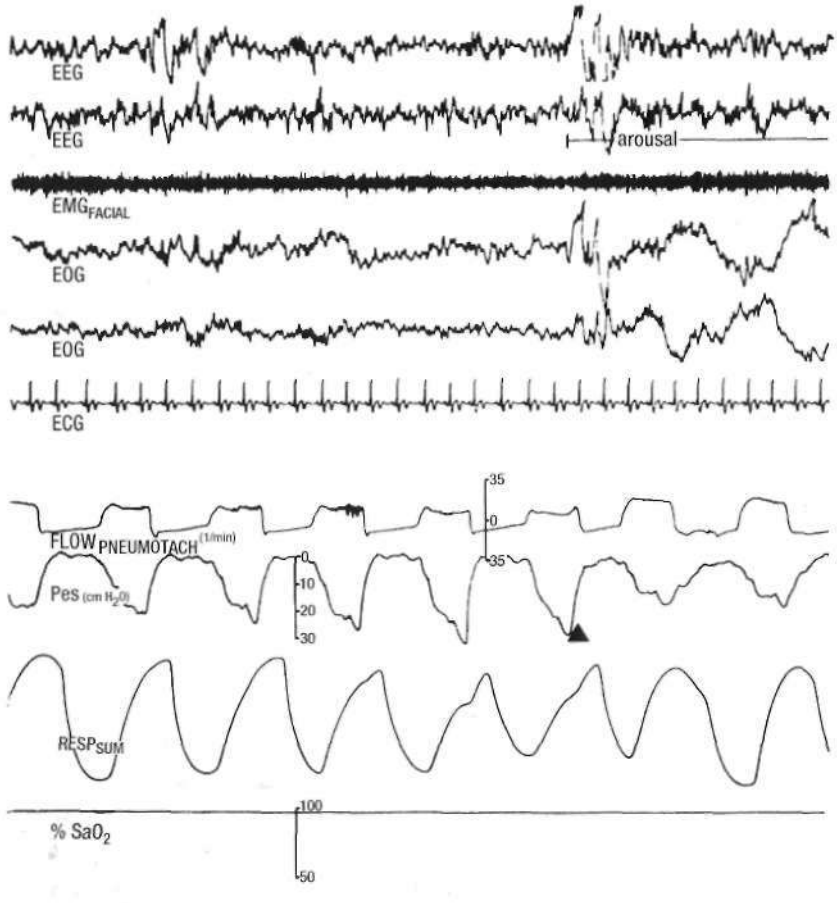

FIGURE 74.6 Polysomnography recording of a patient with upper airway resistance syndrome. Note that peak increase in effort *(solid arrow)* is associated with a small drop in peak flow and tidal volume causing a transient arousal on the electroencephalogram. ECG = electrocardiogram; EMGIJCJ;,] = facial muscle electromyogram; EOG = electrooculogram (right and left); FLOW = pneumotac ho meter to quantity airtli >>>; Pes = esophageal manometry to record esophageal pressure; $RESP_{mm}$=respiratory effort; Sao_2 = oxygen saturation. (Reproduced with permission from Robinson, A. & Guilleminault, C, 1999, in *Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects,* ed S. Chokroverty, Butte i worth-Hcinemann, Boston.)

association between OSAS and male gender, increasing age, and obesity. The condition is common in men older than 40 years of age, and among women the incidence of OSAS is greater after menopause. About 85% of patients with OSAS are men, and obesity is present in about 70% of OSAS patients. There is an increased prevalence of OSAS in those with a thick neck and large abdomen. Men with a neck circumference measuring more than 17 inches and women with a neck measuring more than 16 inches are at risk for OSAS.

Race may be a factor, given that a high ptevalence of SD13 is noted in Pacific Islanders, Mexican-Americans, and African-Americans. There are also family aggregates of OSAS. Other factors with a high association are alcohol, smoking, and drug use.

Consequences of Obstructive Sleep Apnea Syndrome

Short-term consequences of OSAS include impairment of the quality of life and increasing traffic accidents; long-term consequences include cardiovascular and neurological dysfunction. OSAS is associated with increased morbidity and mortality (Robinson and Guilleminault 1999; Flemons 2002).

Prevalence of hypertension in untreated OSAS exceeds 40%, whereas 30% of patients with idiopathic hypertension have OSA (Fletcher 2000; Robinson and Guilleminault 1999). Recent prospective and community-based studies have confirmed the previous suggestion of a clear relationship between hypertension and OSAS including mild OSAS (Peppatd et al. 2000; Nieto et al. 2000). Improvement of hypertension after treatment of OSA (Peppetell et al. 2002; Faceenda et al. 2001; Hla et al. 2002) further supports a causal relationship between OSAS and hypertension. A significant relationship between hypertension and the RD1 exists even after obesity and other confounding factors are eliminated. Factors responsible for hypertension in OSAS include repeated hypoxemia during sleep at night and increased sympathetic activity. Cardiac arrhythmias, pulmonary hypertension, and cor pulmonale, which are noted in patients with severe OSAS, may be related to severe hypoxemia during sleep. There is also a strong relationship between snoring, myocardial infarction, and stroke. The association of supratentorial infarction, mfratentonal infarction, and transient ischemic attacks with snoring and sleep apnea has been clearly documented (Basserti and Chervin 2000). Neuropsychological measurements document that cognitive dysfunction in patients with OSAS improves after treatment (Fugleman et al. 2000; Kim et al. 1997).

Pathogenesis of Obstructive Sleep Apnea Syndrome

The pathogenesis of OSAS includes local anatomical factors as well as neurological factors (Douglas and Polo 1994; Robinson and Guilleminault 1999). Collapse of the pharyngeal airway is the fundamental factor in OSA. During sleep, muscle tone decreases, including that of the upper airway dilator muscles, which maintain upper airway patency. As a result of this decreased tone, these muscles relax, causing increased upper airway resistance and narrowing of the upper airway space. This effect becomes more marked during REM sleep because of marked muscle hypotonia or atonia of muscles at this stage. This generates turbulent flow and vibration, causing snoring; in some individuals, there may be significant narrowing or occlusion, causing apnea. Episodes of upper airway narrowing causing apneas, hypopneas, or increased upper airway resistance that are terminated by arousals and sleep fragmentation, with repetition of the cycles numerous times throughout the night, are responsible for the daytime symptoms in OSAS. The site of narrowing in most individuals is at the level of the soft palate. Therefore, decreased tone in the palatal, genioglossal, and other upper airway muscles, causing increased upper airway resistance and decreased airway space, plays an important role in upper airway obstruction in OSAS. Obesity associated with increased fat deposition in the region of the pharynx and soft palate, abnormal facial features (e.g., rctrognathia or micrognathia), and other conditions (e.g., myxedema or acromegaly) that cause fatty tissue deposit in the pharyngeal region predispose individuals to upper airway narrowing and OSA. Imaging studies of the upper airway region have shown that in OSA, upper airway space is narrower than in those who do not have apnea or hypopnea.)n addition to the smaller airway space in OSAS, the activity of the genioglossus muscle is found to be higher than normal during wakefulness in these patients; this may be considered a compensatory mechanism to keep the upper airway patent. Other anatomical abnormalities include adenotonsillar enlargement in children and craniofacial dysostosis. Defective upper airway reflexes may also play a role in upper airway occlusion. In some family members, abnormal facial structures, a narrow upper airway, and long uvula have been found.

Neural factors responsible for OSAS include abnormalities of respiratory control in the medullary respiratory neurons. The output of sleep-related medullary respiratory neurons is thought to decrease in normal individuals during sleep. This reduction of the medullary respiratory neuronal activity in sleep causes a loss of tonic and phasic motor output to the upper airway dilator muscles, resulting in an increase in airway resistance. 1 [ypoxic and hypercapnic ventilatory responses, however, are found to be normal in OSAS, but in obesity-hypoventilation syndtomc (pickwickian syndrome), which may be considered a very advanced stage of OSAS in obese patients, these responses are depressed, causing hypercapnia and hypoxemia even during wakefulness. Thus a complex intetaction of peripheral upper airway and central neural factors combine to produce the full-blown syndrome of OSAS.

Symptoms

Symptoms of OSAS (Flemons 2002; Robinson and Guilleminault 1999) can be divided into two groups (Table 74.16): those occurring during sleep (nocturnal events) and those occurring during the daytime (diurnal events). Nocturnal sleep symptoms of OSAS include loud snoring (often with a long history), choking, cessation of breathing (apneas witnessed by the bed partner), sitting up fighting for breath, abnormal motor activities with thrashing about in bed, severe sleep disruption, gastroesophageal reflux, nocturia and nocturnal enuresis (seen mostly in children), and occasionally hyperhidrosis,

The major daytime symptom of OSAS is F.DS. Patients fall asleep during the day at inappropriate times and in inappropriate places and may be involved in driving accidents. They cannot function adequately during the day, and some patients may complain of morning headaches and forgetfulncss; men may report impotence. The prolonged duration and the unrefreshing nature of the EDS attacks differentiate them from narcoleptic sleep attacks.

Table 74.16: Symptoms and signs in obstructive sleep apnea syndrome

- Nocturnal symptoms during sleep
  - Loud snoring (often with a long history)
  - Choking during sleep
  - Cessation of breathing (apneas witnessed by bed partner)
  - Sitting up or fighting for breath
  - Abnormal motor activities (e.g., thrashing about in bed)
  - Severe sleep disruption
  - Gastroesophageal reflux causing heartburn
  - Nocturia and nocturnal enuresis (mostly in children)
  - Insomnia (in some patients}
  - Excessive nocturnal sweating (in some patients)
- Daytime symptoms
  - Excessive daytime somnolence
  - Forget fulness
  - Personality changes
  - Decreased libido and impotence in men
  - Dryness of mouth on awakening
  - Morning headache (in some patients)
  - Automatic behavior with retrograde amnesia
  - Hyperactivity in children
  - Hearing impairment (in some patients)
- Physical findings
  - Obesity in the majority of patients
  - Increased body mass index (body weight in kg/height in m^2) >25
  - Increased neck circumference (>17 in. in men and >16 in. in women)
  - In some patients:
    - Large edematous uvula
    - Low-hanging soft palate
    - Large tonsils and adenoids (especially in children)
    - Retrognathia
    - Micrognathia
    - Hypertension
    - Cardiac arrhythmias
    - Evidence of congestive heart failure

Snoring is present in most patients, and there is often a gradation from mild snoring for many years to very loud snoring for a period and then to the development of daytime symptoms. A histoty of apneas witnessed by a bed partner is a strong indicator of the presence of sleep apnea. Occasionally, patients may complain of difficulty falling asleep and numerous awakenings during the night. Excessive sweating in some patients may be related to the increased muscle activity related to abnormal motor activities during sleep at night. Increased release of atrial natriuretic peptide during sleep may be responsible for natriuresis, diuresis, and nocturnal enutcsis. Some patients may complain of hearing impairment related to a history of loud snoring for many years. Other complaints include memory impairment, automatic behavior with retrograde amnesia, dryness of mouth on awakening in the morning, decreased libido, personality changes, and hyperactivity in children. Factors that may aggravate symptoms of OSA include alcohol intake, CNS depressants, sleep deprivation, respiratory allergies, and .smoking.

Signs

Physical examination should include assessment of respiratory, oropharyngeal, neurological, hematological, and cardiovascular funcrions. Examination of the oropharyngeal region may detect redundant oropharyngeal tissues, such as large edematous uvula, redundant mucosal folds of the pharyngeal walls, low-hanging long soft palate, or large tonsils and adenoids, especially in children. Other findings may include microglossia, micrognathia, and rerrognarhin. Body weight and height measurements are important. Neck circumference correlates with SDB. Physical examination reveals obesity in about 70% of patients. Physical examination may also uncover the risk factors associated with repeated hypoxemia and apnea during sleep, such as hypertension, cardiac arrhythmias, and evidence of CHF,

Evaluation and Assessment

Evaluation and assessment are the same as those for other sleep disorders. Particular attention should be paid to the detailed sleep history as well as the daytime history, and careful physical examination should be focused on specific associated and risk factors. The laboratory assessment and management are described later in this chapter, under Laboratory Assessment of Sleep Disorders.

Restless Legs Syndrome

Clinical Manifestations

Thomas Willis gave a graphic clinical description of RLS more than 300 years ago. More than 50 years ago, Ekbom brought the entity to the attention of the medical

community (Chokroverty et al. 2003). RLS remains largely underdiagnosed or undiagnosed. The exact prevalence of RLS is not known because definitive population-based study has been inadequate. Ekbom gave a prevalence rate of 5%, but in several contemporary population surveys using the International Restless Legs Syndrome Study Group (IRLSSG) criteria (Walters et al. 1995; International Restless Legs Syndrome Study Group 2003) the prevalence of RLS has been estimated to be about 10% for all adult populations, particularly those of European descent (Chokroverty et al. 2003). In some surveys from \w„. • w i • • i -..i U: i. .• i-, < urciucb lew . suggesting .i possible ethnic and racial difference in prevalence of RLS. RLS is a lifelong condition that may begin at any age but is most severe in middle-aged and elderly persons, in whom it has a chronic progressive course. The fundamental problem in RLS is a complex sensorimotor disorder involving the legs predominantly (Allen ct al. 2001, 2003). The essential clinical diagnostic features as revised (Allen et al. 2003) from the previous IRLSSG criteria (Walters et al. 1995) are listed in Table 74.17. RLS is idiopathic in most patients, but it also may result from conditions such as iron deficiency, uremia, or polyneuropathy (Chokroverty and Jankovie 1999).

The hallmarks of idiopathic or primary RLS are intense, disagreeable, creeping sensations (paresthesia or dysesthesia) in the lower extremities that arc relieved by moving the legs (Allen et al. 2003). The symptoms are worse when the patient is lying down in bed in the evening and occur most commonly at sleep onset. The sensory manifestations include intense, disagreeable feelings that are generally different from the usual paresthesias or dysesthesias encountered in common polyneuropathies or radiculopathies. These creeping sensations occur mostly between the knees and the ankles, causing an intense urge to move the limbs, which relieves the feelings. Occasionally, patients complain of pain. Affected patients generally have severe difficulty in initiating sleep due to paresthesias and restlessness of the legs. Severely affected individuals may also have paresthesias during the day when resting or sitting quietly,

Motor manifestations of RLS can be divided into three groups: voluntary urge to move the legs causing restlessness, involuntary movements in wakefulness, and PLMS. The restlessness is seen mostly in the legs but occasionally also in the arms. The movements arc usually symmetrical but sometimes may be seen asymmetrically and asynchronously. Motor restlessness generally comprises tossing and turning in bed, floor pacing, leg stretching, leg flexion, foot rubbing, and occasionally marching in place and body rocking. The involuntary movements during relaxed wakefulness include myoclonic jerks and dystonic movements. These movements may be periodic, and these are called periodic limb movements in wakefulness (PLMW). The myoclonic jerks can also be aperiodic or may occur in clusters. The dystonic movements are more sustained and prolonged in duration than the myoclonic jerks. The salient features of PLMS (Table 74.18) are seen in at least 80% of patients with RLS. PLMS are mostly dystonic and rarely myoclonic, based on the EMG criteria of duration of the muscle bursts.

Neurological examination in the idiopathic form of RLS is generally normal because movements arc usually noted in the evening, when the patients are resting in bed. In sevctc cases, however, the movements may be noted during the day while subjects are sitting or lying down, and both voluntary and involuntary movements may be seen during neurological examination. In secondary forms of RLS, clinical signs of associated abnormality may be present. The course is gcnetally chronic and progressive, but remissions sometimes occur. The condition may be exacerbated during pregnancy or by caffeine or iron deficiency. Family history may be positive in 40-50% of the patients, which suggests a dominant mode of inheritance.

Table 74.17: Clinical diagnostic criteria for idiopathic restless legs syndrome

Essential criteria
An urge to move the legs usually accompanied or caused by uncomfortable sensations in the legs
The urge to move or unpleasant sensations beginning or worsening during periods of rest or inactivity such as lying or sitting
The urge to move or unpleasant sensations are partially or totally relieved by movements, MI eh as walking or stretching, at least as long as the activity continues
The urge to move or unpleasant sensations arc worse in the evening or night than during the day or only occur in the evening or night
Supportive features
Dopaminergic responsiveness
Presence of periodic limb movements in sleep or in wakefulness
Positive family histoty
Associated features
Usually progressive clinical course
Normal neurological examination in the idiopathic fotm
Sleep disturbance

['able 4, IK: Features of pcriodie limb movements in sleep

Repetitive, often stereotyped movements during NREM sleep
Usually noted in the legs and consisting of extension of the great toe, dorsiflexion of the ankle, and flexion of the knee and hip; sometimes seen in the arms
Periodic or quasi periodic at an average interval of 20-40 sec (range 4-90 sec) with a duration of 0.5-5.0 sec and as part of at least four consecutive movements
Occurs at any age but prevalence increases with age
May occur as an isolated condition or may be associated with a large number of other medical, neurological, or sleep disorders and medications
Seen in at least 80% of patients with restless legs syndrome

NREM = non—rapid eye movement.

Tabic 74.19: Causes of symptomatic or secondary restless legs syndrome

Neurological disorders
- Polyneuropathies
- Lumbosacral radiculopathies
- Amyotrophic lateral sclerosis
- Myelopathies
- Multiple sclerosis
- Parkinson's disease
- **Poliomyelitis**
- Isaac's syndrome
- Hyperexplexia (startle disease)

Medical disorders
- Anemia: iron and folate deficiency
- Diabetes mcllitus
- Amyloidosis
- Uremia
- Gastrectomy
- Cancer
- Chronic obstructive pulmonary disease
- Peripheral vascular (arterial or venous) disorder
- Rheumatoid arthritis
- Hypothyroidism

Drugs and chemicals
- Caffeine
- Neurolepsy
- Withdrawal from sedatives or narcotics
- Lithium
- **C.ikmm ..'vniivi** nir,u;nriiits e.g., nifedipine

Table 74.21: Pertinent features of akathisia that differentiate it from restless legs syndrome

Inner restlessness, fidgetiness with jittery feelings, or generalized restlessness
Common side effect of neuroleptic drugs
Can he acute, chronic, or tardive
Characteristic motor restlessness consists of swaying or rocking movements of the body; marching in place; crossing and uncrossing of the legs; shifting body positions in chair; inability to sit still; rhythmic or nonrhythmic, synchronous or asynchronous, symmetrical or asymmetrical limb movements; movements resemble chorea rather than the voluntary movements of restless legs syndrome
Motor restlessness present mostly during the day but may be worse when sitting or standing in one place for a long time
Polysomnography study shows no distinctive features and rarely may show evidence of mild sleep disturbance and periodic limb movements in sleep
No relevant family history
Neurological examination reveals evidence of akathisia and sometimes drug-induced extrapyramidal manifestations
Involuntary movements (e.g., myoclonic jerks) are uncommon and not a prominent feature
Best treated with anticholinergics or ^-adrenergic antagonists

Differential diagnosis of RLS may be considered under two categories: secondary RLS and the entities that may mimic RLS. In secondary or symptomatic RLS, several conditions may be associated with RLS or may cause symptomatic RLS (Table 74.19). The entities that mimic RLS are listed in Table 74.20. An important and often difficult condition to differentiate from RLS is akathisia. Essential features of akathisia that differentiate it from RLS are listed in Table 74.21.

Pathoph ysio logy

The physiological mechanism or the anatomical locus responsible for RLS-PLMS is unknown. Pathophysiological elms may be derived from electrophysiological and imaging studies as well as from state-dependent and circadian factors {Hening et al. 1999; Trenkwaldcr and Winkelmann 200.5; Chokrowrty el al. 200,51. Dopaminergic and peptidergic theories are based on pharmacological responses. On the basis of implications derived from secondary RLS, a vascular hypothesis, a peripheral neuropathy hypothesis, and deficient and toxic states have been suggested as etiologies, but none has been satisfactory. The most likely hypothesis is a functional alteration in the brainstem region, but the exact location is undetermined. Several studies have found inconsistent support for the presence of some hyperexcitable brainstem reflexes. Based on the absence of cortical prepofentials in a jerk-locked back averaging study, it is unlikely that the cortex is the generator of PLMS. Studies have shown that **RLS** was maximum during the falling phase of a body temperature curve, which suggests that there is a circadian factor that modulates severity of RLS, independent of activity state. A functional MR1 study showed increased activity in the contralateral thalamus and in the red nucleus, bilateral cerebellum, and brainstem reticular formation in patients with PLMS and sensory symptoms (Bucher et al. 1997). Two positron emission tomography (PF.T) studies (Turjanski et al. *1999*\ Ruottinen et al. 2000) and two single photon emission computed tomogtaphy (SPECT) studies (Staedt et al. 1995; Michaud et al. 2002) suggested small but significant striatal dopamine abnormalities. However, the small magnitude of these observations and reports of some negative dopamine system imaging studies (Trenkwalder et al. 1999; Eisensehr et al. 2001) raise some

Table 74.20: Entities that may mimic restless legs syndrome

NkamilqruL-n'.dikvU .lkaihsia
Syndrome of painful legs and moving toes
Muscular pain-fasciculation syndrome
Myokymia
Causalgia-dystonia syndrome
Painful nocturnal leg cramps
Myoclonus (essential myoclonus)
Hypnic jerks ("sleep starts")
Anxiety-depression
Growing pains

pertinent questions about whether these abnotmalities arc primary rather than epiphenomcna. The most exciting current development in RLS research is the hypothesis that brain iron depletion causes alteration of brain dopaminergic system thereby producing symptoms of RLS (Allen and Earley 2003).

Periodic Limb Movements hi Sleep

PI.MS is a PSG finding and is characterized by periodically recurring limb movements during NREM sleep; most commonly, patients dorsiflex the ankles and flex the knees and hips every 20-40 seconds (tange 4-90) seconds. ( )cc.iMOiiali\, I'l MS i- noted ill [lie np;vr li:r.;v,.]:, .,i least 80% of patients with RLS, PLMS is also seen, whereas RLS is found in about 30% of patients with PLMS. Additional criteria for PLMS are listed in Table 74.18. Limb movements may be accompanied by partial arousal, causing sleep fragmentation. A PLMS index fnumbci ul I[1]! MS per hour ol sleep) ol *S* is considered within normal range.

PLMS is seen most commonly in RLS but may also occur in a large number of othet medical, neurological, and sleep disorders (Montplaisir et al. 2000), and in association with medications (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, and r dopa . Whether PI MS occurs as a primary condition unassociated with RLS causing repeated awakenings and sleep fragmentation as described in the *ICSD* under the heading of PLMD remains controversial. There is a growing body of evidence that PLMS may not have a specific clinical significance and is simply a PSG observation seen in a wide variety of sleep disorders but is present in most patients with RLS (Montplaisir et al. 2000; Mahowald 2002).

(arcadian Rhythm Sleep Disorders

Orcadian rhythm sleep disorders result from a mismatch between the body's internal clock and the geophysical environment (Mahowald et al. 1997; Dagan 2002) either because of a malfunction in the biological clock (primary circadian rhythm disorders) or because the clock is out of phase due to a shift in environment (secondary circadian dysrhythmias). Jet lag and shift work are two common sources of secondary circadian dysrhythmias resulting from exogenous factors.

Delayed Sleep-Phase Syndrome

The *ICSD* defines DSPS as a condition in which the major sleep episode is delayed in relation to the desired clock time. This causes symptoms of sleep-onset insomnia or difficulty awakening at the desired time. Typically, the patient goes to sleep late (e.g., 2:00-6:00 AM) and awakens in the late morning or afternoon (e.g., 10:00-2:00 PM), Patients with this disorder have great difficulty in functioning adequately in the daytime if they have to wake up early in the morning to go to school or work. They have severe sleep-initiation difficulty and cannot function normally in society because of the disturbed sleep schedule. They often try a variety of hypnotic medications or alcohol in an attempt to initiate sleep sooner. Sleep architecture is generally normal if these individuals are allowed to follow their own uninterrupted sleep-wake schedule.

DSPS may represent 5-10% of complaints of insomnia in some sleep disorders centers. Onset occurs during childhood or adolescence. Sometimes there is a history of DSPS in other family membets. Some patients may have depression. Primary DSPS results from an unusually long intrinsic circadian period due to abnotmalities in • In- biological clock in the Si \. Aclii;rapliic recordings over several days document the charactetistic sleep schedule.

Advanced Sleep-Phase Syndrome

Advanced sleep-phase syndrome (ASPS) is the converse of DSPS: The patient goes to sleep in the early evening and wakes up earlier than desired in the morning (e.g., 2:00-4:00 AM). If these patients do not go to sleep at an early hour, they experience sleep disruption and daytime sleepiness. Occasional familial cases have been described.

ASPS is most commonly seen in elderly individuals. The basic mechanism is thought to be an inherent shortening of the endogenous circadian timing. The diagnosis is based on sleep logs and characteristic actigraphic recordings over several days. ASPS is easy to distinguish from the early morning awakening of depression because sleep architecture is normal and does not exhibit the shortened REM latency and other REM sleep abnormalities seen in depressed patients.

Hypernychthemeral Syndrome

Hypernychthenteral syndrome, also cailed non-24-hour sleep-wake disorder, is characterized by an inability to maintain a regular bedtime. Sleep onset wanders around the clock. Affected patients have a gradually increasing delay in sleep onset by about 1 hour per sleep-wake cycle, causing eventual progression of sleep onset through the daytime hours and into the evening. These individuals fail to be entrained or synchronized by usual time cues, such as sunlight or social activities.

Hypernychthemeral syndrome is an extremely uncommon disorder and is most often associated with blindness. Approximately one third of blind individuals are affected because of impairment of the retinohypothalamic pathway, which normally cues circadian patterns. The syndrome also may be associated with hypothalamic tumors. Sometimes depression and anxiety disorders are associated with this syndrome.

Neurological Disorders and Sleep Disturbance

Sleep disorders are very common in neurological illnesses, which ma; adversely affect punnus' •deep. llm.s (here is an interrelationship between sleep and neurological disorders. Sleep dysfunction may result from central or peripheral somatic and autonomic neurological disorders. Neurological diseases may cause insomnia or EDS as well as parasomnias. Neurological causes of excessive sleepiness have been described previously, and neurological disorders that cause insomnia are described under Insomnia, earlier in this chapter.

Sleep and Epilepsy

There is a distinct and reciprocal relationship between sleep and epilepsy (Chokroverry and Quinto 1999; Dinner 2002). Sleep affects epilepsy, and epilepsy affects sleep. In the beginning of the last century, before the availability of encephalography, several authors emphasized that many seizures are predominantly nocturnal and occur at certain times at night. The modern era of combining the clinical and EEC findings on sleep and seizures began with the observation of Gibbs and Gibbs in 1947 that EEG epileptiform discharges were seen more often during sleep than during wakefulness (Chokroverry and Quinto 1999). A basic understanding of the mechanism of epileptogenesis and sleep makes it clear why seizures are often triggered by sleep. The fundamental mechanism for epileptogenesis includes neuronal synchronization, neuronal hypcrexcitability, and a lack of inhibitory mechanism. During NREM sleep, there is an excessive diffuse cortical synchronization mediated by the thalamocortical input, whereas during REM sleep, there is inhibition of the thalamocortical synchronizing influence in addition to a tonic reduction in the interhemispheric impulse traffic through the corpus callosum. Factors that enhance synchronization are conducive to active ictal precipitation in susceptible individuals. NREM sleep thus acts as a convulsant by causing excessive synchronization and activation of seizures in an already hyperexeitable cortex. In contrast, during REM sleep, there is attenuation of epileptiform discharges and limitation of propagation of generalized epileptiform discharges to a focal area.

Sleep deprivation is another important seizure-triggering factor, and the value of sleep-deprived ERG studies in the diagnosis of seizures is well known. Sleep deprivation increases epileptiform discharges, mostly during the transition period between waking and light sleep. Sleep deprivation causes sleepiness, which is one factor for activation of seizures, but it probably also increases cortical excitability, which triggers seizures. However, in a recent report on 84 patients with medically refractory partial epilepsy with secondary generalization undergoing inpatient monitoring, Malow ct al. (2002) noted that acute sleep deprivation did not affect seizure incidence.

Biorhythmic classification of seizures has shown inconsistencies and contradictions. Seizures have been shown to occur predominantly during sleep (nocturnal seizures), predominantly in the daytime (diurnal seizures), or both during sleep at night and daytime (diffuse epilepsy). Taking into consideration different series, the incidence of sleep epilepsy has been quoted to be 22%, but most of these statistics were obtained before the advent of electroencephalography. The most likely figure for nocturnal seizures is aboul 10%. Because of inconsistencies in biorhythmic classification, modern epilcptologists use the International Classification of Epilepsy, which divides seizures into primarily generalized and partial seizures with or without secondary generalization.

Effect of Sleep on Epilepsy, True nocturnal seizures (Malow and Plazzi 2003; Chokroverry and Quinto 1999) may include tonic seizures, benign focal epilepsy of childhood with rolandic spikes or occipital paroxysms, juvenile myoclonic epilepsy, electrical status epilepticus during sleep or continuous spikes and waves during sleep, generalized tonic-clonic seizures on awakening, nocturnal frontal lobe epilepsy including nocturnal paroxysmal dystonia (NPD), and a subset of patients with temporal lobe epilepsy (nocturnal temporal lobe epilepsy). Many patients with generalized tonic-clonic and partial complex seizures also have predominantly nocturnal seizures, Nocturnal seizures may be mistaken for motor and behavioral parasomnias or other movement disorders that persist during sleep or reactivate during stage transition or awakenings in the middle of the night.

Tonic Seizure. Tonic seizures are characteristic of Lcnnox-Gastaut syndrome, which may also include other seizure types, such as myoclonic, generalized tonic-clonic, atonic, and atypical absence. Tonic seizures are typically activated by sleep, occur much more often during NREM sleep than during wakefulness, and are never seen during REM sleep. The typical EEG finding consists of slow spikes and waves intermixed with trains of fast spikes as intcrietal abnormalities during sleep.

Benign Rolandic Seizure. Benign rolandic seizure is a childhood seizure disorder seen mostly during drowsiness and NREM sleep and is characterized by focal clonic facial twitching, often preceded by perioral numbness. Many patients may have secondary generalized tonic-clonic seizures. The characteristic EEG finding consists of centrotemporal or rolandic spikes or sharp waves and sometimes occipital spikes. Seizures generally stop by the 15-20 years of age without any neurological sequela.

Juvenile Myoclonic Epilepsy. Onset of myoclonic epilepsy of Janz usually occurs between 13 and 19 years of age and

is manifested by massive bilaterally synchronous myoclonic jerks. The seizures increase shortly after awakening in the morning and occasionally on awakening in the middle of the night. A typical electroencephalogram shows synchronous and symmetrical polyspikes and spike-and-wave discharges. The intericta) discharges predominate at sleep onset and then on awakening but are virtually nonexistent during the rest of the sleep cycle.

Nocturnal Frontal Lobe Epilepsy. Nocturnal frontal lobe epilepsy includes (Provini et al. 1999; Malow and Plazzi 2003) nocturnal paroxysmal dystonia, paroxysmal arousals and awakenings, episodic nocturnal wanderings, and autosomal dominant nocturnal frontal lobe epilepsy. These disorders all share common features of abnormal paroxysmal motor activities during sleep and respond favorably to anticonvulsants. They most likely represent partial seizures arising from discharging foci in the deeper regions of the brain, particularly the frontal cortex, without any concomitant scalp EEC evidence of epileptiform activities. The relationship to seizures, particularly partial complex seizures of temporal or extratcmporal origin, however, remains controversial. Nonepilepric seizures or pseudoseizures are not common during sleep at night but sometimes can occur and be mistaken for true nocturnal seizures, and it is important to differentiate these from true seizures because of difference in management.

hive patients were originally described who had episodes of abnormal movements that were tonic and often violent during NREM sleep almost every night. Ictal and interictal EEG findings were normal. Later, 12 patients were described with NREM sleep-related choreoathetotic, dystonic, and ballismic movements each night, often occurring many times during the night for many years. The term *nocturnal paroxysmal dystonia {NPD)* was coined for this entity (Table 74.22). The disorder in all patients responded to carbamazepine therapy, and the spells lasted less than 1 minute. It was suggested that these spells were a type of unusual nocturnal seizure. Later, patients with NPD showed IT(. evidence ot epileptiform abnormalities arising from the frontal lobes. A study comparing groups of patients with NPD and those with undisputed frontal lobe seizures supported the contention that patients with NPD may have frontal lobe seizures. Therefore, short-duration NPD attacks may represent a form of frontal lobe seizures (Table 74.23) that arc evoked specifically during sleep at night. Provini and co-workers (1999) gave a comprehensive review of clinical and EEG features of 100 consecutive cases of nocturnal frontal lobe epilepsy.

Table 74.22: Features of nocturnal paroxysmal dystonia

Onset: infancy to fifth decade
Usually sporadic; rarely familial
Sudden onset from non-rapid eye movement sleep
Two clinical types: Common [ype is short-lasting (15 sec to <2 min)
Semiology: ballismic, choreoathetotic, or dystonic movements
Often occurs in clusters
Electroencephalogram: generally normal
Short-duration attacks arc most likely a tvpc of frontal lobe seizure
Treatment: carbamazepine effective in patients with short-lasting attacks

"Table 74.23: Features of frontal lobe seizures

Age of onset: infancy to middle age
Sporadic, occasionally familial (dominant)
lloth diurnal and nocturnal spells, sometimes exclusively nocturnal
Sudden onset in non-rapid eye movement sleep with sudden termination
Duration: mostly less than 1 min, sometimes 1-2 min with short postictal confusion
t Jr'ren occur in clusters
Semiology: tome, clonic, bipedal, bimanual, and bicycling movements; motor and sexual automatisms; contralateral dystonic posturing or arm abduction with or without eye deviation
lctal EEC! may be normal; interictal EEG may show spikes; sometimes depth recording is needed

EEG = electroencephalogram.

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy. An autosomal dominant form of frontal lobe epilepsy usually staffs in childhood and persists throughout adult life. Attacks are characterized by brief motor seizures in clusters during sleep. Neurological examination and ncuroimaging studies are normal. Videotelemetry during the attacks confirms their epileptic nature, and the response to carbamazepine treatment is excellent (Scheffer ct al. 1995).

Effect of Epilepsy on Sleep

Although the usefulness of sleep in the diagnosis of epilepsy has been established, the altered sleep characteristics in epileptic patients are not well known. Most studies have been conducted in patients who have been receiving anticonvulsants, thus adding the confounding factors of the effect of anticonvulsants on sleep architecture. Additionally, there is a dearth of longitudinal studies to determine the effect of epilepsy on sleep in the early stage versus the late stage of illness. A genetal consensus has been reached, however, on the effects of epilepsy on sleep and sleep structure. These effects can be summarized as follows: an increase of sleep-onset latency; an increase in waking aftet sleep onset; a teduction in REM sleep; increased instability of sleep states, such as unclassifiable sleep epochs; an increase in stages I and II NREM sleep; a decrease in stages III and IV NREM sleep; and a reduction in the density of sleep spindles.

Sleep Disorders Associated with Neuromuscular Disorders

Clinicians first became aware of sleep-related respiratory dysrhythmias in patients with neuromuscular diseases by observing hypoventilation in poliomyelitis. Sleep disturbances in neuromuscular diseases arc generally due to respiratory dysrhythmias associated with these diseases (Chokroverty 2001; Guilleminauit and Shergill 2002). In neuromuscular disorders, sleep disturbances are due to involvement of respiratory muscles, phrenic and intercostal nerves, or neuromuscular junctions of the respiratory and oropharyngeal muscles. The most common complaint is EDS resulting from transient nocturnal hypoxemia and hypoventilation, causing repeated arousals and sleep fragmentation. In addition to the sleep-related respiratory dysrhythmias, some patients, particularly those with painful polyneuropathies, muscle pain, muscle cramps, and immobility due to muscle weakness, may complain of insomnia. Patients with neuromuscular diseases often complain of breathlessness, particularly in the supine position.

Respiratory disturbances arc generally noted in the advanced stage of primary muscle disorders or myopathics, but respiratory failure may appear in an early stage. Sleep complaints and sleep-related respiratory dysrhythmias are common in Duchenne's and limb-girdle muscular dystrophies as well as in myopathies associated with acid maltase deficiency. They may also occur in other congenital or acquired myopathies, mitochondrial encephalomyopathy, and polymyositis.

Many patients with myotonic dystrophy have been described with central, mixed, and upper airway OSAS; alveolar hypoventilation; daytime fatigue; and hypersomnolence. Nocturnal oxygen desaturation accompanies alveolar hypoventilation and apneas and becomes worse during REM sleep. EDS in myotonic dystrophy often occurs in the absence of sleep apnea. An entity called *proximal myotonic myopathy* (PROMM) has been described. PROMM, also called DM 2, is a hereditary myotonic disorder that is differentiated from myotonic dystrophy by absence of the chromosome IV CTC trinucleotide repeat that is associated with classic myotonic dystrophy. A brief report (Chokroverty et al. 1997) describes sleep disturbances in two patients consisting of difficulty initiating sleep, EDS, snoring, and frequent awakenings and movement during sleep. An overnight PSG study showed decreased sleep efficiency, increased number of arousals, and sleep architectural abnormalities. One patient had absent REM sleep; the other had dissociated REM sleep characterized by phasic REM bursts associated with EEC patterns showing sleep spindles and alpha intrusions. These sleep abnormalities in PROMM suggested involvement of the REM- and NREM-generating neurons as part of a multisystem membrane disorder.

In polyneuropathies, involvement of the nerves supplying the diaphragm and the intercostal and accessory muscle of respiration may cause breathlessness on exertion and other respiratory dysrhythmias. These may worsen during sleep, causing sleep fragmentation and daytime hypersomnolence, In painful polyneuropathies, patients may have insomnia.

Neuromuscular junctional disorders (e.g., myasthenia gravis, myasthenic syndrome, botulism, and tic paralysis) are characterized by easy fatigability of the muscles, including the bulbar and other respiratory muscles, as a result of nerve impulses of the neuromuscular junctions not being transmitted. Patients with myasthenia gravis may have central, obstructive, and mixed apneas and hypopneas accompanied by oxygen desaturation. A sensation of breathlessness on awakening in the middle oi [he night and early morning hours may indicate respiratory dysfunction. Sleep-related hypoventilation and sleep apnea in neuromuscular junctional disorders may be severe enough to require assisted ventilation (Gonzalez, et al. 2002),

Sleep and Spinal Cord Diseases

Sleep disturbances related to respiratory dysfunction can occur in some patients with high cervical spinal cord lesions. Patients with poliomyelitis, amyotrophic lateral sclerosis (AES) affecting the phrenic and intercostal motor neurons in the spinal cord, spinal cord tumors, spinal trauma, spinal surgery (e.g., cervical cordotomy or anterior spinal surgery), and nonspecific or demyelinating myelitis may all have sleep distutbances. The most common symptom is hypersomnia due to sleep-related respiratory arrhythmias. Occasionally, patients with spinal cord diseases may complain of insomnia as a result of immobility, spasticity associated with flexor spasms, neck pain, and central pain syndrome.

Sleep Disturbances in Poliomyelitis and Postpolio Syndrome

Respiratory disturbances worsening during sleep may occur in many patients during the acute and convalescent stages of poliomyelitis. Some are left with the sequela of sleep-related apnea or hypoventilation requiring ventilatory support, especially at night. Another group of patients develops symptoms decades later that constitute postpolio syndrome, in which sleep disturbances and sleep apnea or hypoventilation have also been noted. Postpolio syndrome is manifested clinically by increasing weakness or wasting <>l UK- prvvioLisly affected muscles and b\ involvement oi previously unaffected regions of the body, fatigue, aches and pains, and sometimes symptoms secondary to sleep-related hypoventilation (e.g., EDS and tiredness).

Sleep and Headache Syndromes

In day-to-day practice, headaches and sleep complaints are common (Jennum and Jensen 2002; Poceta 2002).

Sleep disturbance in OSAS may cause headache, and headache irself may cause sleep disturbance. The *1CSD* (1997) includes cluster headache, chronic paroxysmal hemicrania, and migraine under the heading of sleep-related headaches. PSG recordings in patients with chronic migraine and cluster headaches show a clear relationship between REM sleep and attacks of headache, although sometimes migraine headaches with arousals may occur out of both slow-wave and REM sleep. Cluster headaches are thought to be related to REM, but cluster headaches may sometimes be triggered by NREM sleep. Chronic paroxysmal hemicrania, which is probably a variant of cluster headache, is most commonly associated with REM sleep. Significant sleep disruption in the form of decreased total and REM sleep time, accompanied by an increased number of awakenings during REM sleep, has been described in patients with chronic paroxysmal hemicrania. PSG recordings have documented sleep apnea in some patients with chronic recurring headache syndromes. The relationship between early morning headache and upper airway OSAS has been somewhat controversial, with conttadictory reports. There arc occasion;)I reports of the coexistence of OSAS and cluster headache with improvement of headache following CPAP titration (Zaliek and Cbervin *2000).*

A rare benign headache syndrome, called *bypnic headache syndrome,* is described in patients older than 60 years of age. The patients are awakened from sleep at a constant time each night. Hypnic headache syndrome is differentiated from chronic cluster headache by generalized distribution, age of onset, and lack of autonomic manifestation. This disorder often responds to lithium or indomethacin treatment.

Fxploding head syndrome is an unusual phenomenon that usually occurs in the transition from wake to sleep, abruptly arousing the patient with the sound of an explosion in the head, accompanied by bright light flashes. This is a benign condition and may represent a form of "sleep starts" (sec later).

Kleine-Levin Syndrome

Klcine in 1925 and Levin in 19.16 described an episodic disorder occurring mostly in adolescent boys (but also described later in girls) that was characterized by periodic hypersomnolcnce and bulimia. The episodes usually last for days to weeks. During sleep "attacks," the patient sleeps 16-18 hours a day or more and on awakening eats voraciously. Other behavioral disturbances during the episode may include hypersexuality, confusion, hallucination, inattention, and memory impairment. The condition is generally self-limited and disappears by adulthood. PSG study shows normal sleep cycling, and the MSLT shows pathological sleepiness without SOREMs. The cause of the condition remains undetermined, although a limbic-hypothalamic dysfunction is suspected but not proved. An autoimmune hypothesis has been suggested based on clinical and increased HLA DQBI0201 allele frequency (Dauvilliers et al. 2002). Lithium treatment is effective, and valproic acid may also be useful.

Fatal Familial Insomnia

Fatal familial insomnia (FFI) is a rare and rapidly progressive autosomal dominant prion disease with a missense mutation at codon 178 of the prion protein gene f/V/') (Montagna et al. 2003). FFI was originally described in a family with a progressive neurological illness characterized by insomnia and dysautonomia that terminated in death. Clinical manifestations are impaired control of the sleep-wake cycle, including arcadian rhythms; autonomic and neuroendocrine dysfunction; and somatic neurological, cognitive, and behavioral manifestations. Profound sleep disturbances and, in particular, severe insomnia are noted from the very beginning of the illness. PSG study shows almost total absence of sleep pattern and only short episodes of REM sleep, lasting for a few seconds or minutes, without muscle atonia. This abnormal sleep pattern is associated with dream-enacting behavior in the form of complex gestures and motions and myoclonus. The terminal stage of the illness is characterized by progressive slowing of the electroencephalogram, with the patient drifting into coma, \utonomic function t^rs reveal evidence of sympathetic hyperactivity with preserved parasympathetic activity. Neuroendocrine functions in FFI show a dysfunction of the pituitary-adrenal axis, as manifested by striking elevation of scrum Cortisol but normal adrenocorticotropic hormone, indicating abnormal feedback suppression of adrenocorticottopic hormone. Persistently elevated scrum catecholamine levels associated with abnormal secretory patterns of growth hormone, prolactin, and melatonin are noted. The nocturnal secretory peaks of growth hormone are absent. Plasma melatonin levels progressively decrease, and in the most advanced stage of the illness, there is a complete abolition of melatonin rhythm. Somatic neurological manifestations consist of ataxia, evidence of pyramidal tract dysfunction, myoclonus, tremor, and bizarre astasia-abasia. Neuropsychological studies reveal impairment of attention, vigilance, and memory. The disease progresses rapidly and ends in coma and death.

The neuropathological hallmark of ITl is severe atrophy of the thalamus, particularly the anterior ventral and dorsomedial thalamic nuclei associated with variable involvement of the inferior olive, striatum, and cerebellum. There are no spongiform changes, except in those with the longest duration of symptoms, who show mild-to-moderate spongiform degeneration of the cerebral cortex. Severe hypometaholism of the thalamus and mild hypometabolism of the cingulare cortex arc the main findings on PET study in FFI patients. Based on biochemical, genetic, and

transmission studies, it has been concluded that FFI is a transmissible prion disease resulting from a mutation at codon 178 of *PrP*, associated with substitution of aspartic acid with asparagine along with the presence of methionine codon at position 129 of the mutant allele. All human prion diseases (e.g., Creutzfeldt-Jakob disease and Gerstmann-Straussler-Scheinker disease) should be considered in the differential diagnosis. Approximately 30 unrelated families of patients with FFI have been identified so far. FFI has been transmitted to experimental animals. FFI is thus a transmissible prion disease and represents the third most common hereditary prion disease worldwide. Sporadic instances, however, have also been reported. The study of FFI has rekindled investigation of the role of the thalamus in sleep-wake regulation.

Stroke and Sleep Disturbances

Sleep disruption and sleep complaints resulting from sleep-related breathing dysrhythmias have been reported in many patients with cerebral hemispheric stroke (Bassetti and Chervin 2000). There is. however, a dearth of well-controlled studies establishing a relationship between sleep disorders and cerebrovascular disease. Sleep apnea, snoring, and stroke are intimately related. Sleep apnea may predispose patients to stroke, and stroke may predispose patients to sleep apnea (Shahar et al. 2001). Based on case-controlled, epidemiological, and laboratory studies, there is increasing evidence that snoring and sleep apnea are risk factors for stroke. Several confounding variables are common risk factors for snoring, sleep apnea, and stroke, however, and these should be considered when attempting to establish a relationship between snoring, sleep apnea, and stroke. These variables include hypertension, cardiac disease, age, body mass index, smoking, and alcohol consumption. There is an increased incidence of sleep apnea in patients with both infratentorial and supratentorial strokes (Basserti and Chervin 2000; lranzo et al. 2002). It is important to make a diagnosis of sleep apnea in patients with stroke because this may adversely affect short-term and long-term outcomes in these patients and because there is effective treatment for sleep apnea that can decrease the risk of future sttoke (Wessendorf et al. 2001). Other causes of sleep disruption causing insomnia may include associated depression, spasticity, and immobility.

1 ly per somnolence has been described after bilateral paramedian thalamic infarcts. Several authors have described sleep disturbances in brainstem infarction. PSG findings generally consist of increased wakefulness after sleep onset and decreased REM and SWS in these patients. EEG findings in several reports of patients with locked-in syndrome resulting from ventral pontine infarction generally showed teduced or absent REM sleep and variable changes in NREM sleep, including reduction of SWS and total sleep time (Chokroverty 1999b).

Brainstem infarction may cause the syndrome of primary failure of automatic respiration, or Ondine's curse. Voluntary breathing control is intact, but metabolic control, which is the only respiratory control during sleep, is impaired. Therefore the patients become apneic during sleep. Severinghaus and Mitchell named the condition. The syndrome of Ondine's curse is usually caused by bilateral lesions anywhere caudal to the fifth cranial nerve in the pons down to the upper cervical spinal cord in the ventrolateral region. Occasional patients with unilateral btainstem infarction have been described with loss of automatic respiratory control during sleep.

Traumatic Brain Injury and Sleep Disturbances

Traumatic brain injuries (TBIs) include concussion, contusion, laceration, hemorrhage, and cerebral edema. Insomnia, hypersomnia, and circadian rhythm sleep dysfunction may occur after TBIs, but objective sleep studies in such patients documenting sleep disturbances have not been adequately performed (Rao and Rollings 2002). After a severe TBI, brainstem function is compromised, and the patient becomes comatose. There have been many EFG studies in patients with coma after head trauma. However, no studies have adequately addressed the sleep-wake abnormalities in these patients after recovery from coma as well as in patients after minor brain injuries that did not result in coma. Many of these patients experience so-called postconcussion syndrome, which is characterized by a variety of behavioral disturbances, headache, and sleep-wake abnormalities. A few reports list subjective complaints of sleep disturbance but do not include formal sleep studies. In one report of patients with closed head injury, PSG studies documented sleep-maintenance insomnia with an increased number of awakenings and decreased night sleep. The mechanism of these sleep abnormalities is unknown. Post-traumatic hypersomnolence is listed in the *ICSD* (1997). TBIs may cause central and upper airway OSA by inflicting functional or structural alterations on the brainstem respiratory control system. Many of these patients may, however, have had sleep apnea syndrome

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Sleep and Multiple Sclerosis

Sleep-related breathing abnormalities and other sleep difficulties, including insomnia, EDS, and depression, have been described in patients with multiple sclerosis. Sleep disturbances in multiple sclerosis are thought to result from immobility, spasticity, urinary bladder sphincter disturbances, and sleep-related respiratory dysrhythmias

due to affected respiratory muscles or impaired central control of breathing.

Sleep Disturbances in Neurodegenerative and Movement 1 >isotdcrs

Neurodegenerative diseases are traditionally defined as a group of heterogeneous diseases of the CNS for which no causal agent can he identified. The disorders generally affect one or more systems symmetrically and run an inexorably progressive course.

Sleep-wake-promoting neurons are involved in the process of diffuse degeneration, causing a variety of sleep disorders in these illnesses (Chokroverry 1996; Hening et al. 1999). Neurodegenerative diseases can he considered under two broad categories: degeneration of the somatic neurons and degeneration of the autonomic neurons. Somatic neuronal degeneration can be predominantly cortical (e.g., Alzheimer's disease), predominantly basal ganglia, or basal ganglia-plus syndromes (e.g., Parkinson's disease, progressive supranuclear palsy, Huntington's chorea, torsion dystonia, and Tourette's syndrome. In contrast to other hyperkinetic movement disorders that are usually suppressed during sleep, motor and phonic tics may persist during all stages of sleep and, additionally, patients with Tourette's syndrome have disturbances of sleep such as increased sleep fragmentation, high co-incidence of arousals, decreased REM sleep, and enuresis (Hanna and Jankovic, 2003). Other neurological disorders with prominent sleep disturbances include cerebellar or cerebellar-plus syndromes (spinocerebellar ataxias (SCAs), such as olivopontocerebellar atrophy (OPCA), or those with degeneration of predominantly motor neurons of the cerebral cortex, brainstem, and spinal cord (ALS or motor neuron disease). Neurodegeneration of the autonomic neurons is responsible for multiple system atrophy (MSA) or Shy-Drager syndrome (Table 74.24) (see also Chapter 77).

Table 74.24: Salient clinical manifestations of multiple system atrophy

- Autonomic features
  - Cardiovascular
    - Orthostatic hypotension
    - Postprandial hypotension
    - Postural syncope
    - Postur'l dizziness, faint feelings, or blurring of vision
    - Orthostatic intolerance
  - Genitourinary
    - Urinary bladder dysfunction (incontinence, hesitancy, frequency, nocturia)
    - Impotence in men
  - Sudomotor
    - Hypoliidrosis or anhidrosis
  - Gastrointestinal
    - Gastroparcsis
    - Intermittent diarrhea or constipation (intestinal or colonic dysmotihty)
    - Abnormal swallowing (esophageal dysmotility)
  - Ocular
    - Horner's syndrome
    - Unequal pupils
- Nonautonomic manifestations
  - Parkinsonism
    - Rigidity'
    - Bradykinesia or akinesia
    - Postural instability
  - Cerebellar dysfunction
    - Ataxic gait
    - Scanning speech
    - Dysmetria
    - Dysdiadochokinesia
    - Intention tremor
  - Upper motor neuron signs
    - Extensor plantar responses
    - Hyper-reflexia
    - Spasticity
  - Lower motor neuron signs
    - Muscle wasting
    - Hasciculations
  - Respiratory
    - Sleep apnea-hypopnea
    - Other respiratory dysrhythmias
- Normal mentation
- Normal sensation

Alzheimer's Disease

Alzheimer's disease (AD) is the most common cerebral degenerative disordet causing dementia. Reports of sleep disturbances in AD have been contradictory. Sleep disorders may he related to the severity of dementia as well as to associated PLMS and sleep-telated respiratory dysrhythmias. In addition, the artificial environment of the hospital and laboratory where the sleep disturbance is evaluated may be partly responsible for confusional episodes, including "sundowning" in AD patients. Insomnia, inversion of the sleep rhythm, and in some cases, EDS are the presenting complaints. Sleep disturbances in AD should be differentiated irom ihosc (kvurnn;-, m depression, which is common in elderly subjects. A reduction in the amount of REM sleep and reduced REM density arc quite different from the reduced REM latency and increased REM density often seen in depressed patients. Sleep-related respiratory dysrhythmia has been estimated to be present in *i3-55%* of patients with AD. The questions of whether there is an increased prevalence of sleep apnea in Al) and whether sleep apnea increases with the seventy of the illness or more rapid progression of the disease remain somewhat controversial. Sundowning is a major problem in many patients with AD, causing nocturnal confusional episodes, often accompanied by partial or complete inversion of sleep schedule, with increased wakefulness at night and somnolence in the daytime. The exact relationship between sleep disruption, severe dementia, and sundowning is not clear. Several factors, singly or in combination, may be

responsible for sleep disturbances in AD. They are degeneration of the neurons of the SCN, of cholinergic neurons in the nucleus basalis of Meynert, of the pedunculopontine tegmental and laterodorsal tegmental nuclei, and of noradrenergic neurons of the btainstem, associated depression or PLMS, medication effects, associated general medical diseases, and environmental factors.

Parkinson's Disease

Sleep difficulties have been noted in 70-90% of patients with Parkinson's disease (PD) (Chokroverry 2000). Common complaints include difficulties in initiating and maintaining sleep, inability to turn over during the night or on awakening, and inability to get out of bed unaided. Leg cramps and jerks, dystonic spasms of the limbs or face, back pain, and excessive nocturia are also common. A clear relationship has been noted between sleep disruption and disease progression.

Motor abnormalities during sleep in PD include persistence of tremor in the lighter stages of sleep or its rccmergencc in the transition between sleep and wakefulness and on awakening as well as decreased body movements and positional shifts. Other motor abnormalities in PD during sleep include rapid blinking at sleep onset, blepharospasm during onset of REMs, and intrusion of REMs into NREM sleep. Sleep benefit (early morning improvement of parkinsonian motor features, lasting 1-3 hours) may be noted mostly in mild PD.

Sleep in PD may be secondarily affected because of associated depression, dementia, sleep-related respiratory dysrhythmias, RLS, Pl.MS, RBD, and other parasomnias (sleepwalking and sleep talking) as well as circadian rhythm disturbances. RBD is a common occurrence in I'D, (Gagnon et al. 2002; Ondo et al. 2002), and in some patients, this disorder appears even before parkinsonian symptoms are clinically evident. It is estimated that about 30% of patients with PD may have PLMS, and this proportion increases in elderly patients.

Sleep-related respiratory dysrhythmias may he mote common in patients with PD than in age-matched control subjects. Obstructive, central, or mixed apneas have been described in patients with PD, and such respiratory difficulties have been noted with increasing incidence in patients with autonomic dysfunction. Antiparkinsonian medications may cause respiratory and other dyskinesias, which could be peak-dose dyskinesia (mainly choreiform) or end-of-the-dosc dyskinesia (mostly dystonic). These dyskinesias may cause sleep disruption or fragmentation of sleep. Vivid or frightening dreams (nightmares) can occur after long-standing dopaminergic treatment, causing sleep maintenance problems and EDS.

A report of sudden sleep attacks (Frucht et al. 1999) heightened the awareness of excessive sleepiness and unintended sleep attacks in patients with PD. Excessive daytime sleepiness is very common and often undcrrecognized in PD and probably occurs in 10-50% of patients (Ondo et al. 2001). MSLTs document pathological sleepiness and sleep-onset REMs in many of these patients similar to those noted m patients with classic narcolepsy-cataplexy. Several studies have shown that sleep attacks and sleepiness in PD are class effects (related to all dopaminergic drugs) and are due to the pathology of PD, medications, and eomorbid conditions, e.g., depression, dementia, and OSAS (Homann et al, 2003; Rye 2003; Hobson et al. 2002; Arnulf et al. 2002; Chaudhuri et al. 2002).

Other Basal Ganglia Disorders

A variety of sleep disturbances have been observed in other basal ganglia disorders, such as 1 iuntmgton's chorea, progressive supranuclear palsy, and torsion dystonia, Insomnia with difficulty initiating and maintaining sleep is a common complaint in these conditions. Sleep disturbance is present in almost all patients with progressive supranuclear palsy, A particular L\pe o^{h} iKsioraa, called *hereditary progressive dystonia* with diurnal fluctuation, dopa-responsivc dystonia, or the Segawa variant, presents with parkinsonian-typc masked fades, rigidity, and flexed posture. Patients with this dystonia may obtain significant symptomatic relief from sleep and show dramatic improvement with small doses of L-dopa.

Predominantly Cerebellar or Cerebellar-Phis Syndromes

Sleep disturbances occur in many patients with OPCA and other types of SCAs. Central, obstructive, or mixed sleep apneas have been described in many patients with sporadic OPCA, also categorized as cerebellar form of MSA, but the apneas have occurred less often and have been less intense in this condition than in the parkinsonian variety of MSA. Typical features of RBD have been described in MSA and SCA3/Machado-Joseph disease (Syed et al, 2003). Other complaints in SCAs, particularly in SCA3, consist of sleep initiation and maintenance problems.

Degenerative Disease of the Motor Neurons

The classic example of degenerative disease of motor neurons is ALS, also called *motor neuron disease.* The most common sleep complaint in ALS is daytime hypetsomnolence as a result of repeated sleep-related apneas or hypopneas, hypoxemia, hypercapnia, and sleep fragmentation. Some patients may complain of insomnia. Sleep-related breathing disorders in ALS may result from weakness of upper airway, diaphragmatic, and intercostal muscles due to involvement of the bulbar, phrenic, and intercostal nerve nuclei. In addition, degeneration of the central respiratory neurons may occur, causing both CSA and OSA in this condition.

Sleep Disorders in Autonomic Diseases: Multiple System Atrophy (Sby-Drager Syndrome)

In a consensus statement (Consensus Statement 1996; Gilman et al. 1999), the term *MSA* was suggested to replace the term Shy-Drager syndrome (see Chapter 77). MSA defines a sporadic adult-onset progressive disorder of multiple systems characterized by autonomic dysfunction, parkinsonism, and ataxia in various combinations {see Table 74.24), *Striatonigral degeneration* is the name used when the predominant feature is parkinsonism, whereas *Ol'CA* is used when the cerebellar features are the predominant manifestations. The term *Sby-Drager syndrome* is still used when the autonomic feature is the predominant feature. Some patients complain of insomnia, and many patients manifest RBD, which may occasionally be the presenting feature, but the most common sleep disturbance in patients with MSA results from respiratory dysrhythmias associated with repeated arousals and hypoxemia. Sleep-related respiratory dysrhythmias in MSA may include obstructive, central, or mixed apneas and hypopneas as well as Chcyne-Stokes breathing or a variant oi Cheyne-Stokes breathing. ( )I]KT breathing disorders i:i sleep in MSA consist ni :nie:i.rn.il irispn.uorv stridor, apneustic breathing, inspiratory gasping, or dysrhythmit breathing. Hypersomnia often results from nocturnal sleep disruption. Sudden nocturnal death in patients with MSA, presumably from cardiorespiratory arrest, has been reported.

Both direct and indirect mechanisms are responsible for the pathogenesis of sleep disruption in MSA. These may include one or more of the following: degeneration of the sleep-wake-gene rating neurons in the brainstem and hypothalamus; degeneration of the respiratory neurons in the brainstem or direct involvement of projections from the hypothalamus and central nucleus of amygdala to the respiratory neurons in the nucleus tractus solitarius and nucleus ambiguus, interference with the vagal inputs from the peripheral respiratory receptors to the central respiratory neurons, sympathetic denervation of the nasal mucosa, and alteration of the neurochemical environment.

Sleep in Other Medical Disorders

A number of medical disorders other than neurological illnesses may cause severe disturbances of sleep and breathing that have important practical implications for diagnosis, prognosis, and treatment (Chokroverry 1999c). Sleep disturbances may have adverse effects on the course of a medical illness. A vicious cycle may result from the effect of sleep disturbance on the medical illness and the effect of the medical illness on sleep architecture. Sleep architecture, sleep continuity, and sleep organization may be affected by a variety of medical illnesses. Patients may present with either insomnia or hypersomnolence, but most medical disorders present with insomnia. Some patients may have a mixture of insomnia and hypersomnolence (e.g., those with COPD or nocturnal asthma). The general features of insomnia and medical disorders causing insomnia have been briefly described (see Insomnia, earlier in this chapter). The general features of hypersomnolence and medical conditions presenting with hypersomnolence have been briefly described earlier in this chapter, PSG findings in those presenting with insomnia include prolonged sleep latency, reduction of REM and SWS, more than 10 awakenings per night, frequent stage shifts, early-morning awakening, increased waking after sleep onset, and increased percentage of wakefulness and stage I NRKM sleep. PSG findings in those presenting with hypersomnolence may consist of SDB, repeated arousals with oxygen desatu ration at night, sleep fragmentation, sleep-stage shifts, reduced SWS, shortened sleep-onset latency in MSLTs, and sometimes REM sleep abnormalities. When a patient presents to a sleep specialist with a sleep disturbance, either with a complaint of insomnia or hypersomnia, an important step is to obtain a detailed medical history and other histories, followed by physical examination to uncover the cause of the sleep disturbance.

In an important epidemiological study by Gislason and Alinqvist involving a random sample of 320 I Swedish men, aged 30-69 years, difficulty initiating or maintaining sleep and too little sleep were the major sleep complaints, followed by EDS (Chokroverty 1999c). Sleep-maintenance problems occurred more often with increasing age. The following conditions were associated with sleep complaints: systemic hypertension, bronchitis and bronchial asthma, musculoskeletal disorders, obesity, and diabetes mcllirus. The authors suggested that the reported increased mortality among patients with sleep complaints might be related to the intercurrent somatic diseases.

Cardiovascular Disease and Sleep

Sleep disturbance is very common in patients with ischemic heart disease. Pain may awaken the patient often, thereby reducing sleep efficiency. Nocturnal angina is known to occur during both REM and NREM sleep. Epidemiologically, there is a clear relationship between increased cardiovascular morbidity and mortality and sleep disturbances associated with SDB. Shahar et al. (2001) reported on the cross-sectional data from the sleep Heart Health study cohort showing modest to moderate effects of sleep disordered breathing on various manifestations of cardiovascular disease (e.g., myocardial ischemia, heart failure, or stroke) within a range of apnea-hypopnea index values that are considered normal or mildly elevated. Patients with coronary artery disease and OSA may have an increased cardiac risk due to nocturnal myocardial ischemia triggered by apnea-associatcd oxygen desaturation. An important finding in several reports is circadian susceptibility to myocardial infarction (attacks are most likely between midnight and 6:00 AM).

In patients with CHF, sleep disturbances, periodic breathing, and hypoxemia at night have been described. Multiple factors, including associated SDB and nocturnal oxygen desaturation, are responsible for increased morbidity and mortality in CHF. Cheyne-Stokes respiration, which is commonly associated with CHF. may result in hypoxemia, hypercapnia, sleep disruption due to repeated arousals, daytime somnolence, and impaired cognitive function. Thus Chcyne-Stokes respiration and CHF may present as sleep apnea syndrome. Javaheri et al. (199.5) reported an AHI higher than 20 in 45% of patients with stable heart failure without other comorbid factors. After treatment with nocturnal oxygen administration, CPAP titration, and medications such as theophylline, the patients' conditions improved. However, the role of CPAP in the maintenance treatment of CHF remain's controversial.

A relationship between sleep and atrioventricular arrhythmia has been noted, but the reports are controversial. Contradictory results have also been noted in human studies of the effect of sleep on ventricular arrhythmia, but most studies show an antiarrhythmic effect of sleep on ventricular premature beats due to enhanced parasympathetic lone during sleep. \n .i:i,iK•-,]•-, nl the time of sudden cardiac death in 2023 individuals by Muller and associates revealed high incidence from 7:00 AM to 11:00 AM. Nonfatal myocardial infarction and myocardial ischemic episodes are also more likely to occur in the morning. It is known that sympathetic activity increases in the morning, causing increased myocardial electrical instability; thus sudden cardiac death may result from a primary fatal arrhythmia.

Several studies report an association between OSAS and systemic hypertension and some studies have confirmed that treatment of sleep apnea by nasal CPAP reduces blood pressure. (Sec section on Sleep Apnea Syndrome, earlier in this chapter.!

Sleep and Chronic Obstructive Pulmonary Disease

Disturbances in sleep architecture in patients with COPD have been teported by several authors and may be summari/.ed as follows: a reduction of sleep efficiency, delayed sleep onset, increased wake time after sleep onset, frequent stage shifts, and frequent arousals. Factors that may be responsible for sleep disturbance in COPD include the use of drugs that have a sleep-reducing effect (e.g., methylxanthine), increased nocturnal cough, resulting from accumulated bronchial secretions, and associated hypoxemia and hypercapnia. Severe noctutnal hypoxemia in many patients with COPD may or may not be accompanied by sleep-related apnea, hypopnea, or periodic breathing, and impairment of gas exchange. Repeated or prolonged oxygen desaturation at night may cause cardiac arrhythmias and may lead to pulmonary hypertension and cor pulmonale. Administration of supplemental oxygen at 2 liters per minute by nasal cannula during sleep is found to improve both oxygen saturation at night and sleep architecture by decreasing sleep latency and increasing all stages of sleep, including REM and SWS.

Sleep Disturbances in Bronchial Asthma

A variety of sleep disturbances have been noted in patients with asthma, including early-morning awakenings, difficulty maintaining sleep, and EDS. Sleep disturbances in general consist of a combination of insomnia and hypersomnia. PSG studies may reveal disruption of sleep architecture as well as sleep apnea in some patients. Nocturnal exacerbation of symptoms during sleep is a common finding in asthmatic patients. There is also evidence of progressive bronchoconstriction and hypoxemia during sleep in patients with asthma. Several pathogenic mechanisms, including circadian factors, have been suggested tor sleep disturbances and nocturnal exacerbation of asthma.

Gastrointestinal Diseases and Sleep

Sleep disturbances in peptic ulcer patients characteristically result from episodes of nocturnal epigastric pain. These symptoms cause arousals and repeated awakenings, thereby fragmenting and disturbing sleep considerably. With duodenal ulcers, there is increased nocturnal acid secretion, which can be abolished by vagotomy, thus improving healing of ulcers. Furthermore, patients with duodenal ulcers do not have inhibition of gastric acid secretion during the first 2 hours after sleep onset. In light of evidence about the role of *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drugs in the pathogenesis of gastroduodenal ulcers, the theory of hypersecretion of acid in peptic ulcer patients has been displaced.

Gastroesophageal reflux disease, which is preferable to the term *reflux esophagitis*% characteristically causes heartburn, which is described as retrosternal burning pain. This pain causes difficulty in initiating sleep, frequent awakenings, and fragmentation of sleep. Facilities for all-night PSG study and 24-hour esophageal pH monitoring have contributed to an understanding of the association between sleep and peptic ulcer diseases and esophageal reflux. Sleep adversely affects patients with gastroesophageal reflux disease by increasing the episodes of reflux and prolonging acid clearance time (Orr 2001). Furthermore, repeated spontaneous reflux episodes adversely affect sleep h\ causing arousals, frequent awakenings, and sleep fragmentation.

Sleep and Endocrine Diseases

In patients with myxedema, upper airway OS A and CSA that disappear after thyroxine replacement therapy have

been described. Mechanisms of SDH in this condition include deposition of mucopolysaccharides in the upper airway as well as impaired central respiratory drive, as evidenced by decreased hypercapnic and hypoxic ventilatory responses.

Patients with diabetes mellitus, particularly that associated with autonomic neuropathy, may have upper anway OSA and CSA. These sleep-related respiratory dysrhythmias may cause fragmentation of sleep, resulting in EDS.

CSA has been described in many patients with acromegaly. CSA has been generally associated with increased levels of growth hormone. The relationship between the growth hormone level and sleep apnea, however, has remained somewhat controversial. Octreotide, a long-acting somatostatin analogue, is an effective noninvasive treatment for sleep apnea in acromegaly.

Sleep Disturbances in Chronic Renal Failure

Sleep disturbances are common in patients with chronic renal failure with or without dialysis, particularly in those with end-stage renal disease. Sleep complaints include insomnia, EDS, and day-night reversal or disturbed nocturnal sleep. PSG findings include reduced sleep efficiency, increased sleep fragmentation, frequent awakenings with difficulty maintaining sleep, decreased SWS, and disorganization of sleep cycle. Many patients with chronic renal failure who are and are not receiving dialysis have sleep apnea syndrome, mainly upper airway OSAS, and may have PLMS. A PSG study to establish the diagnosis of OSA should be performed in any patient with a history of FDS mid disturbed night sleep because CPAP titration has been found to be an effective form of treatment in patients undergoing hemodialysis with OSA. Another important finding in patients with chronic renal failure is the presence of a secondary form of RLS. Uremic RLS and idiopathic RLS resemble each other and cannot be distinguished clinically. There has been a report of cure of this form of RLS after successful kidney transplantation.

Fibromyalgia Syndrome

Fibromyalgia syndrome is characterized by diffuse muscle aches and pains not related to diseases of the joints, bones, or connective tissues. Specific diagnostic criteria for fibromyalgia syndrome have been established. Sleep disturbance is very common in fibromyalgia. The characteristic PSG finding is intermirtenr alpha activity during NREM sleep, giving rise to the characteristic alpha-delta or alpha-NREM sleep pattern in the recording. Another important association is the presence of PLMS on PSG examination. Alpha-NREM sleep pattern is not specific for this condition and has been noted in patients with other rheumatic disorders and even in normal individuals, as well as some psychiatric patients. The most common complaints in patients with fibromyalgia include nonrestorative sleep associated with nonspecific PSG abnormalities of sleep fragmentation, increased awakenings, decreased sleep efficiency, and alpha-NREM sleep.

Chronic Fatigue Syndrome

This is an ill-defined medically unexplained heterogeneous condition with multiple causes (Evcngard and Klimas 2002). The condition is characterized by insidious onset of disabling fatigue present for at least 6 months without any causes despite intense laboratory investigations. Arthralgias, myalgias, sore throat, headache, and sleep disturbances are included as minor criteria. Orthostatic hypotension and orthostatic tachycardia syndrome on a tilt-table study may be present in some of these patients (Getrity et al. 2002). Sleep complaints include disturbed night sleep and excessive daytime sleepiness but adequate PSG studies have not been undertaken to characterize the precise sleep disturbance.

Sleep of Intensive Care Unit Patients

Patients in an intensive care unit (ICU) are generally admitted with acute medical, surgical, or neurological illnesses. All these conditions can be associated with sleep disturbances, e.g., insomnia, hypersomnia, and sleep-related respiratory dysrhythmia (Gabor et al. 2001; Richards et al. 2002), The ICU environment itself is deleterious to normal sleep and conducive to sleep deprivation, with attendant complications, such as ICU psychosis. Noise, bright light, and constant activity by ICU personnel for monitoring and drug administration play a significant role in disturbing the sleep of ICU patients. A variety of drugs in the ICU may aggravate sleep and sleep-related respiratory disturbances. ICU syndrome is a characteristic mental state defined as a tcvcrsiblc, confusional state developing 3-7 days after ICU admission; sleep deprivation has been cited as the major cause of ICU syndrome. ICU psychosis is more common in surgical than in medical ICOs. PSG findings to document disruption of sleep structure in the ICU consist of marked diminution of SWS and REM sleep, frequent awakenings, sleep fragmentation, and reduced total sleep time. ICU patients often have EDS because of disturbed night sleep. It is important to be aware of various ICU factors contributing to the problem of sleep disturbances so that correct diagnosis and management of secondary complications can be implemented promptly.

Acquired Immunodeficiency Syndrome

Acquired immunodeficiency syndrome (AIDS) is a multisystem disorder caused by infection with HIV. Sleep disturbances (insomnia, hypersomnia, and circadian dysrhythmia) have been reported in many patients with AIDS, but adequate systematic PSG studies to document sleep

disruption have not heen undertaken. The causes are multifactorial (Phillips *1999).* HIV infection can also cause SDB.

African Sleeping Sickness (Trypanosomiasis)

African sleeping sickness is caused hy T. *gambiense* or T. *rhodesiense* and is transmitted *to* humans by the bite of tsetse flics, CNS involvement is initially characterized by personality changes followed by delusions, hallucinations, and reversal of the sleep-wake rhythm. The patient remains somnolent in the daytime and progresses gradually into the stages of stupor and coma. PSG studies document disruption of the circadian sleep-wake rhythm, which is proportional to the severity of the illness. Circadian disruption of plasma Cortisol, prolactin, and sleep-wake rhyrhms is seen in the patients with the most advanced disease. These findings of circadian disruption suggest selective changes in the SCN. The diagnosis of trypanosomiasis is based on history as well as confirmation that the organism is in blood, bone marrow, cerebrospinal fluid, lymph node, aspirates, or a scraping from the chancre. The treatment of choice for patients in the meningoencephalitic stage is a rsen ica 1 mcl a rs o p r o 1.

Sleep Disturbances in Psychiatric Illness

In psychiatric disorders sleep disturbances are common and insomnia is present more often than hypersomnia (see Insomnia, earlier in this chapter, for a brief review). Specific examples of psychiatric conditions that are associated with insomnia include depression (including bipolar disorder), anxiety disorders, schizophrenia, and post-traumatic stress disorder. Hypersomnia is generally present in patients with seasonal affective disorder and may also be present in some patients with depression. Many patients with eating disorders, some of whom have associated major depression, may also have significant sleep complaints. Finally, antidepressant and neuroleptic drugs used to treat psychiatric illnesses may cause sleep disruption. Assessment of sleep disturbances in psychiatric patients should follow the genetal guidelines discussed earlier in the chapter. The primary treatment should be directed to the psychiatric illnesses causing sleep disruption.

Parasomnias. Parasomnias can be defined as abnormal movements or behavior intruding into sleep during the night intermittently or episodically without disturbing the sleep architecture. The *1CSD* classifies parasomnias into four groups (see Table 74.9): arousal disorders, sleep-wake transition disorders, REM sleep-related parasomnias, and other parasomnias. This classification lists 24 distinct entities, several of which are very rare. Major parasomnias can also be classified into motor and behavioral parasomnias. VI o tor parasomnias arc abnormal movements intruding into sleep and are classified into four categories: NREM sleep parasomnias; REM sleep parasomnias, sleep-wake transition disorders; and diffuse parasomnias (no stage preference). Several parasomnias occurring in NREM and REM sleep may be mistaken for seizures, particularly complex partial seizures. Somnambulism, night terror, confusional arousals, somniloquy, bruxism, head banging, nocturnal enuresis, RBD, and nightmares are some of the parasomnias that may be mistaken for seizures, RBD and nightmares are the only ones associated with REM sleep. Characteristic clinical features combined with EEC and PSG recordings are essential ro differentiate these conditions,

Somnambulism (Sleepwalking). Sleepwalking is common in children between 5 and 12 years of age {Table 74.25). Sometimes, it persists in adulthood or (rarely) begins in adults. Sleepwalking begins with abrupt motor activity arising out of SWS during the first one third of sleep. Episodes generally last less than 10 minutes. There is a high incidence of positive family history in sleepwalking. Injuries and violent actions have been reported during sleepwalking episodes, but generally, individuals can negotiate their way around the room. Sleep deprivation, fatigue, concurrent illness, and sedatives may act as precipitating factors.

Sleep Terrors, Sleep terrors, or pavor nocturnus, also occur during SWS (Table 74.26). Peak onser is between 5 and 7 years of age. As with sleepwalking, there is a high incidence of familial cases of sleep tenor. Episodes of sleep rerrors are characterized by intense autonomic and motor symptoms, including a loud, piercing scream. Patients appear highly confused and fearful. Many patients also have a history of sleepwalking episodes. Precipitating factors are similar to those described with sleepwalking.

Confusional Arousals, Confusional arousals occur mostly before 5 years of age. As in sleepwalking and sleep terrors, these episodes arise our of SWS with confusion. Patients may have some automatic and inappropriate behavior, but the majority of spells are benign, necessitating no treatment.

Hypnic Jerks, Hypnic jerks, or "sleep starts," occur at sleep onset in many normal individuals and are

Table 74.25: Features of sleepwalking (somnambulism)

Onset: common between ages 5 and 12 yr
1 ligh ineidence of positive family history
Abrupt onset of motor activity arising out of slow-wave sleep during the first one third of the night
Duration: less than L0 mm
Injuries and violent activity reported occasion ally
Precipitating factors: sleep deprivation, fatigue, concurrent illness, sedatives
Treatment: precaution, benzodiazepines, lmipramine

Table 74.26: Features of sleep terrors

Onset: peak is between ages 5 and 7 yt
High incidence of familial occurrences
Abrupt arousal from slow-wave sleep during the first one third of the night with a loud, piercing scream
Intense autonomic and motor components
Sleepwalking also seen in many patients
Precipitating factors: stress, sleep deprivation, fever
Treatment: psychotherapy, benzodiazepines, tricyclics

physiological phenomena without any pathological significance. The episodes are associated with sudden brief myoclonic jerks of the limbs or the whole body lasting for a few seconds. Sometimes these are accompanied by sensory phenomena, such as a sensation of falling. These may be triggered by stress, fatigue, or sleep deprivation. Sleep starts may occur in up to 70% of the general population.

Rhythmic Movement Disorder. Rhythmic movement disorder is noted mostly before 18 months of age and is occasionally associated with mental retardation. It is a sleep-wake transition disorder with three characteristic movements: head banging, head rolling, and body rocking. Rhythmic movement disorder is a benign condition, and the patient outgrows the episodes.

Nocturnal Leg Cramps. These are intensely painful sensations accompanied by muscle tightness that occur during sleep. The spasms usually lasl foi ,; lew MVIUVS bui sometimes persist for several minutes. Cramps during sleep are generally associated with awakening. Many normal individuals have nocturnal leg cramps; the cause remains unknown. Local massage or movement of the limbs usually relieves the cramps.

Nightmares (Dream Anxiety Attacks). Nightmares arc fearful, vivid, and often frightening dreams, mostly visual but sometimes auditory, seen during REM sleep. Night mares may accompany sleep ralking and body movements. These most commonly occur during the middle to late part of sleep at night. Nightmares are mostly a normal phenomenon. Up to 50% of children, perhaps even more, have nightmares beginning at age 3-5 years. The incidence of nightmares continues to decrease as the child grows older, and elderly individuals have very few or no nightma res. Very frightening and recurring nightmares (e.g., one or more per week) are not common and may occur in a very small percentage (<1%) of individuals. Nightmares can also occur as side effects of certain medications, such as antiparkinsonian drugs (pcrgolide and i.-dopa), anticholinergics, and antihypertensive drugs, particularly beta blockers. Nightmares are common after sudden withdrawal of REM sleep-suppressant drugs (e.g., tricyclic antidepressants and selective serotonin reuptake inhibitors). Benzodiazepines (e.g., diazepam and clonazepam) often suppress nightmares, but withdrawal from these drugs may precipitate nightmares. Nightmares have also been reported after alcohol ingestion or sudden withdrawal from barbiturates. Nightmares may sometimes be the initial manifestation of schizophreniform psychosis along with severe sleep disturbance. Many people with a certain personality type have nightmares throughout life. Nightmares generally do not require any treatment except reassurance. In patients with recurring and fearful nightmares, however, combined behavioral or psychotherapy and REM sleep-suppressant medications may be helpful.

Rapid Eye Movement Sleep Behavior Disorder. RBD is an important RIM sleep parasomnia commonly seen in elderly persons (Table 74.27). A characteristic feature of RBD is intermittent loss of REM sleep-related muscle hypotonia or atonia and the appearance of various abnormal motor activities during sleep. The patient experiences violent dream-enacting behavior during REM sleep, often causing self-injury or injury to the bed partner (Scheneck and Mahowald 2003; Olson et al. 2000). RBD may be idiopathic or secondary; most cases are now thought to be secondary and associated with neurodegenerative diseases. It is seen with increasing incidence in patients with PD, MSA, corticobasal degeneration, dementia with Lewy bodies disease, OPCA, and PSP. Many patients with narcolepsy, a probable degenerative disease of the hypocrerin-containing neurons in the hypothalamus, may also present with RBD. Some authors (Boeve ct al. 2001) proposed that RBD may he an or-synuclcinopathy disorder because a-synuclein inclusions have been observed in many of the associated neurodegenerative diseases (e.g., PD, MSA, and dementia with Lewy bodies disease). RBD may precede many of these degenerative diseases. RBD may sometimes be drug induced (e.g., sedative-hypnotics, tricyclic antidepressants and anticholingergics) or associated with alcoholism and structural brainstem lesions. RBD has been linked to dopamine cell dysfunction based on PET scan finding of reduced striatal presynaptic dopamine transporter and SPECT scan finding of reduced postsynaptic dopamine D_2 receptors. REM sleep without muscle atonia is the most important polysomnographic

Table 74.27: Features of rapid eye movement sleep behavior disorder

Onset: middle-aged or elderly men
Presents with violent dream-enacting behavior during sleep, causing injury to self ot bed pattner
Often misdiagnosed as a psychiatric disorder or nocturnal seizute (partial complex seizure}
Etiology: 50% idiopathic, 50% causal association with structural central nervous system lesion or related to alcohol or drugs (sedatives-hypnotics, tricyclics, anticholinergics)
Polysomnography: rapid eye movement sleep without muscle atonia
Expetimental model: bilateral peri-locus ceruieus lesions
Treatment: 90% response to clonazepam

finding. Experimentally similar behavior has been noted after bilateral perilocus cemleus lesions in cats.

Bruxism (Tooth Grinding). Bruxism often presents between 10 and 20 years of age, but it may persist throughout life, often leading to secondary problems such as temporomandibular joint syndrome. Both diurnal and nocturnal bruxism may be also associated with various movement and degenerative disorders such as oromandibular dystonia and Huntington's disease. It is also commonly noted in children with mental retardation or cerebral palsy. Nocturnal bruxism is noted most prominently during stages I and II NREM sleep and REM sleep. The episode is characterized by stereotypical tooth grinding and often precipitated by anxiety, stress, and dental disease. Occasionally, familial eases have been described. Local injections into masseter muscles may be used to prevent dental and temporomandibular joint complications (Tan and Jankovie, 2000).

Benign Neonatal Sleep Myoclonus. Benign neonatal sleep myoclonus occurs during the first few weeks of life and is generally seen in NREM sleep but sometimes during REM sleep. Episodes often occur in clusters involving arms, legs, and sometimes the trunk. The movements consist of jerky flexion, extension, abduction, and adduction. The condition is benign, needing no treatment.

Pediatric Sleep Disorders. The field of pediatric sleep disorders remains neglected despite a high incidence of sleep disturbance in children. Several recent surveys found that about 25% of children aged 1-5 years have some kind of sleep problem. Mentally handicapped children and those with attention-deficit/hyperactivity disorder and Tourerte's syndrome have higher rates of sleep disorders than normal children do. The common sleep problems in children include a variety of parasomnias, such as sleepwalking, nightmares, sleep talking, sleep enuresis, bruxism, sleep terrors, and rhythmic movement disorder; sleeplessness due to specific childhood-onset disorder or food allergy; EDS (e.g., narcolepsy or OSA); and DSPS or ASPS. Adjustment sleep disorder, limit-setting sleep disorder, sleep-onset association disorder, and nocturnal eating (or drinking) syndrome are some distinct sleep disorders causing insomnia in infants and children.

1CSD (1997) defines adjustment sleep disorder as a type of sleep disturbance temporally related to acute stress, conflict, or environmental change that causes emotional arousal. The disturbance in most cases is brief. Sleep-onset or maintenance insomnia or daytime sleepiness may be the presenting complaint, but insomnia is more common than sleepiness in children.

Limit-setting sleep disorder is exclusively a childhood sleep disorder eb.iracieii/.cd by the child's stalling or refusing to go to sleep at an appropriate time as a result of inadequate enforcement of bedtime by the caregiver. The condition usually resolves as the child grows older.

Sleep-onset association disorder is a childhood sleep disorder characterized by an impairment of sleep onset because of the absence of a certain object or set of circumstances (e.g., using a bottle, sucking on a pacifier, being rocked, watching television, or listening to the radio). Sleep is normal when the particular association is present.

ICSD (1997) defines nocturnal eating (drinking) syndrome as a condition characterized by recurrent awakenings with the inability to return to sleep without eating or drinking. This condition is common in infancy and early childhood. Treatment involves gradual withdrawal from eating or drinking behavior.

OSAS occurs in children, but there are certain differences from OSAS in adults. Children may present with EDS, but common symptoms include hyperactivity and behavioral problems during the daytime, impaired school performance, intellectual changes, increased motor activity, disturbed sleep at night, and nocturnal snoring for many months or years. An important cause in children is enlargement of tonsils anil adenoids. If OSAS is suspected, an overnight PSG study is indicated for documenting OSA. In contrast to adults, removal of the tonsils and adenoids in children promotes symptomatic improvement. Some occurrences of sudden infant death syndrome are thought to be related to OSA, but the relationship remains unproved and controversial. The most important factor in sudden infant death syndrome is sleeping in the prone position, and every attempt must be made to keep the infant in the supine position.

Primary enuresis is a condition of persistent bed-wetting after 5 years of age in the absence of urological, medical, psychiatric, or neurological disorders. Enuretic episodes occur during all stages of sleep but most commonly occur during the first one third of the night. Enuresis is particularly common in patients with attention deficit disorder and Tourette's syndrome.

Treatment includes behavioral modification and tricyclic antidepressants (e.g., imipraminc) and desmopressin (DDAVP), either as a nasal spray or tablets.

LABORATORY ASSESSMENT OF SLEEP DISORDERS

Laboratory investigation for sleep disorders should be considered an extension of the history and physical examination. First and foremost in the diagnosis of a sleep disorder is a detailed history, including sleep and other conditions, as outlined earlier, under Approach to a Patient with Sleep Complaints. This should be followed by a careful physical examination to uncover any underlying medical, neurological, or other causes of sleep dysfunction, Laboratory tests should include a diagnostic workup for the primary condition causing secondary sleep disturbance and a workup for the sleep disturbance itself. The two most important laboratory tests for diagnosis of sleep disturbance are polysomnography and the MSLT. Various other

rests art' also important lor asscssineiil ot a parienl willi sleep dysfunction.

Polysomnographic Study

An overnight PSG study is the single most important laboratory test for the diagnosis and treatment of patients with sleep disorders, particularly those associated with EDS. An all-night PSG study is required rather than a single-day nap study. A daytime single-nap study generally misses REM sleep, and the most severe apneic episodes are noted during REM sleep. Maximum oxygen desaturation also occurs at this stage; therefore, a daytime study cannot assess severity of symptoms. For CPAP titration, an all-11 iii.li l •deep Stud; is essentia!. In dtici :i nr i'i,- op;i:n.il level of pressure during CPAP titration, both REM and NREM sleep are required. In this section, the PSG study is described under three headings: technical considerations, indications for a PSG study, and characteristic PSG findings in various sleep disorders.

Technical Considerations

A PSG study includes simultaneous recording of various physiological characteristics, which allows assessment of sleep stages and wakefulness, tcspiration, cardiocirculatory functions, and body movements. Sleep staging is based on an electroencephalogram, electro-oculogram, and electromyogram of some skeletal muscles, especially chin muscles. Multiple EEG channels of recordings are preferable to one or two channels for documentation of focal and diffuse neurological lesions, accurately localization of epileptiform discharges in patients with seizure disorders, and more accurate determination of various sleep stages, awakenings, and transient events, such as microarousal episodes. The Reehtschaffen and Kales (1968) technique of sleep scoring, despite limitations, remains the standard for sleep staging. Ideally, sleep scoring should be performed manually; computerized scoring is not reliable. For newborns and infants, the technique recommended by Anders and co-workers is the standard. The following terms arc essential for sleep sraging and scoring (Mitler et al. 1999):

1. Total sleep period: Time from sleep onset to final awakening
2. Total sleep time: Total time spent between sleep onset and final awakening, excluding time spent awake
3. Sleep latency: Time from lights-out to sleep onset
4. REM sleep latency: Tune from sleep onset to the first REM sleep onset
5. Sleep efficiency; Ratio of total sleep time to total time in bed, expressed as a percentage
6. Sleep stages: Stages I to IV of NREM and REM sleep expressed as a percentage of total sleep time
7. Wake aftet sleep onset: Time spent awake during total sleep period
8. Sleep cycles: Number of sleep cycles, including REM cycles, during total sleep period
9. Stage shifts
10. Arousal index (based on guidelines proposed by the American Sleep Disorders Association): Number of arousals per hour of sleep

The PSG study should also include airflow, respiratory effort, an electrocardiogram (ECG), oximetry, and limb muscle activity, particularly EMG recordings of the tibialis anterior muscles bilaterally. It is advantageous to record snoring and body positions. Thermistors or thermocouples are generally used to record oronasai airflow qualitatively, but these are not reliable for accurate determination of hypopnea. Many laboratories, therefore, record nasal pressure using a nasal cannula-pressure transducer, which is more sensitive than a thermocouple or thermistor for detecting airflow limitation (Ayappa et al. 2000). Respiratory efforts can be recorded by use of si rain gauges or inductance plethysmography. Inductance plethysmography and a piezoelectric strain gauge are the **preferred** methods; they can be used in a qualitative or semiquantitative fashion to monitor chest and abdominal movements. Intraesophageal balloon recording, an invasive method, accurately determines intrathoracic pressure swings and is essential for documentation of UARS. EMG recordings of the intercostal muscles using surface electrodes may also be helpful in determining respiratory effort. SDB events are recorded as an AT IT or RDI score, as defined previously. PEMS are recorded from tibialis EMG recordings. The PLMS index is expressed as the number of PEMS per hour of sleep. The upper limit of the normal PLMS index is 5, Details on the technical aspects of PSG recording are beyond the scope of this chapter.

Indications for Polysomnography

Guidelines proposed by the American Sleep Disorders Association (1997) can be summarized as follows:

A PSG study is routinely indicated for the diagnosis of sleep-related breathing disorders.

A PSG study is indicated for **CPAP** titration in patients with sleep-related breathing disorders.

A PSG study is indicated to evaluate for the presence of OS A in patients before they undergo laser-assisted uvulopalatopharyngoplasty (UPP).

A PSG study is indicated for the assessment of treatment results after an oral appliance is used to push mandible and tongue forward and after surgical trearmenr of patienrs with moderately severe OS A, including those whose symptoms reappear despite an initial good response.

A follow-up PSG study is required when the clinical response is inadequate or when symptoms reappear despite a good initial response after treatment with CPAP. It is also necessary after substantial weight loss or weight gain has occurred in patients previously treated successfully with CPAP.

An overnight PSG study followed by MSLT on the next day is routinely indicated in patients suspected of having narcolepsy.

A PSG study is indicared in patients with parasomnias if these are unusual or atypical or the behaviors are violent or otherwise potentially injurious to the patient or others. A PSG study, however, is not routinely indicated in uncomplicated and typical parasomnias.

A PSG study is indicated in patients suspected of having nocturnal seizures,

An overnight PSG study is required in patients with suspected PLMS, but it is not performed routinely to diagnose RES.

A PSG study may be indicated for patients whose insomnia has not responded satisfactorily to a comprehensive behavioral or pharmacological treatment program for the management of insomnia. However, if the presence of a sleep-related breathing disorder or associated PI.MS is strongly suspected in a patient with insomnia, a PSG study is indicated.

Polysomnography Findings in Sleep Disorders

Characteristic PSG findings in OSAS include recurrent episodes of apneas and hypopneas, which are mostly obstructive (Figure 74.7) or mixed, and few episodes of central apneas accompanied by oxygen dcsaturation and followed by arousals with resumption of breathing. An Al II or RD] score of 5 or below is considered normal. An RDI score of more than 5-1 9 may be considered evidence of mild OSAS, 20-49 as evidence of moderate OSAS, and 50 or more as evidence of severe OSAS. Similarly, percentage oxygen saturation of 80-89 may be found in mild OSAS, whereas in moderate OSAS 70-79 is typical, and in severe OSAS, 69 and below is the usual findings. An arousal index of up to 10 is considered normal; 10-15 can be considered borderline. An arousal index above 15 is definitely abnormal. There are some sleep architectural changes in OSAS (reduction of slow-wave and RIM sleep); most of the sleep is spent in stage II NRKM sleep. Other findings include short latency, increased time spent awake after sleep onset, and excessive snoring. In patients with CSA syndrome, the apneas are all central.

Overnight PSG findings in patients with narcolepsy include short sleep latency, excessive disruption of sleep with frequent arousals, reduced total sleep time, excessive body movements, and reduced SWS and SOREMs (seen in 40-50% of patients). Some narcoleptic patients may have associated sleep apneas (Figure 74.8), particularly central apneas. In approximately *9-59%* of patients, PI.MS have been noted, and in about 12% of narcoleptic patients, RBD has been described.

PSG findings in MSA or Shy-Drager syndrome show a reduction of slow-wave, REM, and total sleep time; increased sleep latency; increased number of awakenings during sleep; absence of muscle atonia in REM sleep in those with RBD; and a variety of respiratory dysrhythmias, as described previously. Similar but less intense findings have been reported in patients with OPCA.

In Al), the essential features of sleep architectural alterations are reduced total sleep time, decreased REM and slow-wave sleep, reduction of sleep spindles and

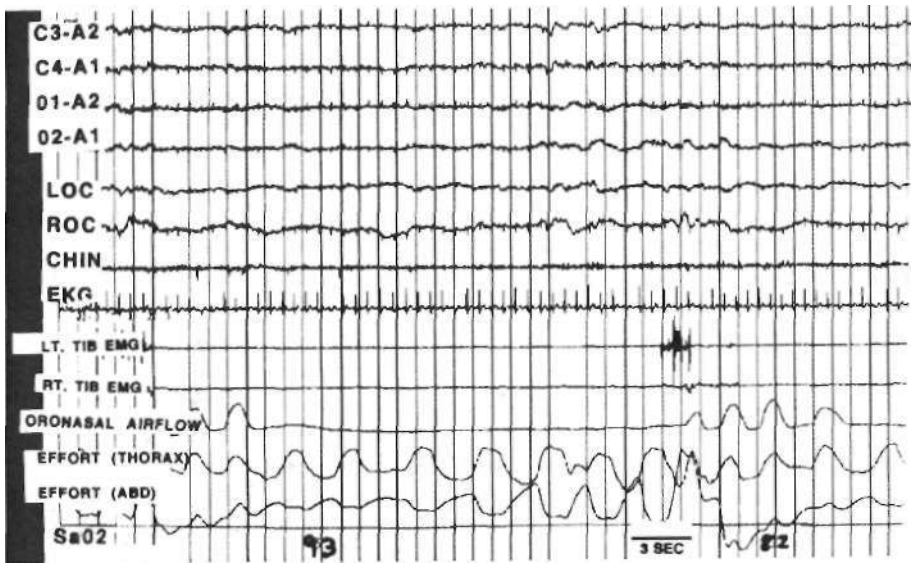

FIGURE 74.7 Polysomnography: recording of a patient with upper airway obstructive sleep apnea syndrome. Note absence of airflow for 23 seconds hut continued effort and oxygen desLituratioil from 93% to 82% in stage II non-rapid eye movement sleep, (Top four channels = electroencephalogram; ABD = abdomen; chin = electromyogram of chin muscle; EKG = electrocardiogram; LOC = lefr electro-oculogram; IT. TIB EMG = left tibialis electromyogram; ROC = right eleetro-oculogram; Sa02 = oxygen saturation; RT. TIB EMG = right tibialis electro myogram.)

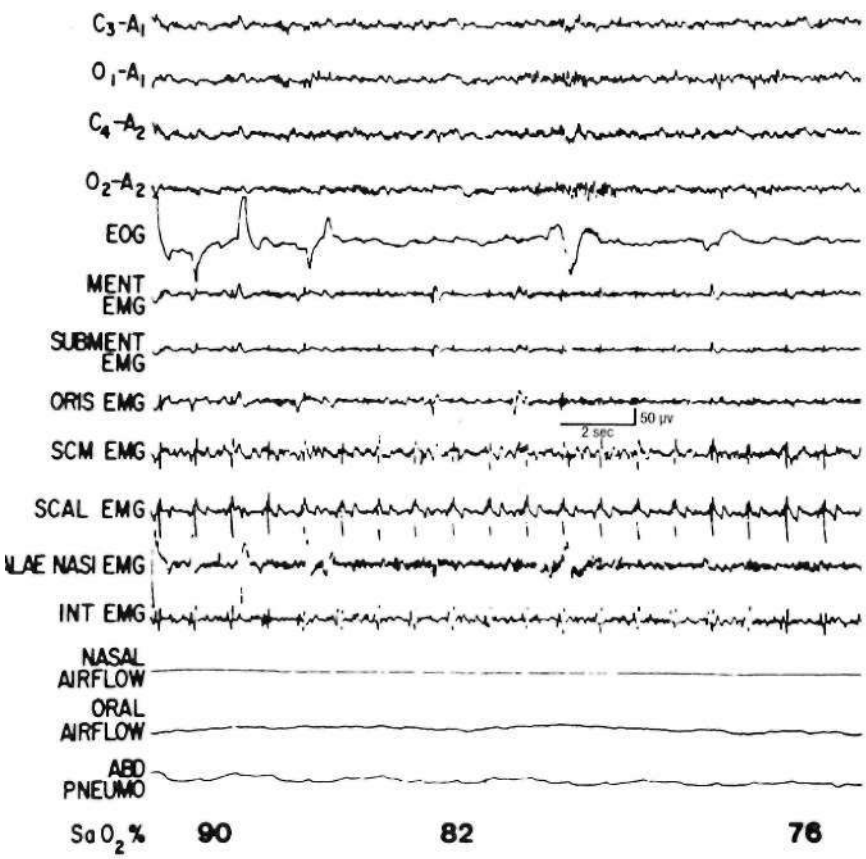

FIGURE 74.8 Polysomnography recording in ,i p;itiri;t with narcolepsy and sleep apnea. (Top four channels = electroencephalogram; EOG = electrooculogram; mentalis [MENT], submental |SUBMENT), orbicularis oris [ORIS], sternocleidomastoid muscle fSCM], scalenus amicus [SCAL], alae nasi, and intercostal [INT] electromyograms [EMG]; abdominal pneumogram [ABD PNEUMO].) Note central apnea during rapid eve movement sleep.

K complexes, increased nighttime awakenings, and sleep fragmentation. There is a high incidence of sleep apnea in those with AD compared with age-matched control subjects.

In PD, a PSG study shows a variety of sleep architectural changes: decreased sleep efficiency, increased awakenings, sleep fragmentation, decreased REM and slow-wave sleep, and sleep spindles, disruption of NREM-REM sleep cycling, absence of muscle atonia, and presence of increasing EMG activities in those presenting with RBD.

The characteristic PSG findings in RBD consist of absence of muscle atonia and presence of increased EMG activities in the upper and lower limbs (Figure 74.9) during REM sleep. It is important to record FMGs from both upper and lower limbs because in some patients with RBD, EMG activities are present in the upper limbs but not in the lower limbs.

In RES, PSG findings document sleep disturbance and PLMS (Figure 74.10), which is found in at least 80% of patients. Diagnosis of PLMD is based on the PLMS index (number of PLMS per hour of sleep); PLMS of up to 5 is considered normal. A high PLMS index with arousal is more significant than the index without arousal.

PSG findings in myopathies, including Duchenne's and other muscular dystrophies as well as myotonic dystrophy, may include sleep fragmentation and disorganization; increased number of awakenings; reduced total sleep time; central, mixed, and upper airway OSAs or hypopneas associated with oxygen desaturation; and nonapneic oxygen desaturation becoming worse during REM sleep. Similar findings may be noted in polyneuropathies or neuromuscular junctional disorders. In addition, in painful polyneuropathies and in neuromuscular conditions associated with muscular pain and cramps, a PSG study may show sleep-onset insomnia and reduced sleep efficiency.

Multiple Sleep Latency Test

The MSLT is an important test for documenting excessive sleepiness objectively. The test has been standardized and is performed after an overnight PSG study. The test consists of four to five daytime EEG, EMG, and electrooculographic recordings at 2-hour intervals with each recording lasting fot a maximum of 20 minutes. The test measures the average sleep-onset latency (timed to the first epoch of any sleep stage for the clinical purpose) and the presence of SOREMs (timed from sleep onset to the first REM sleep). A mean sleep latency of less than 5 minutes is consistent with pathological sleepiness. SOREMs in two or more of the four to five recordings during the MSLT suggest narcolepsy, although abnormalities of REM sleep-regulatory mechanism and circadian rhythm sleep disturbances also may lead to such findings. Pathological sleepiness is noted in all patients complaining of EDS.

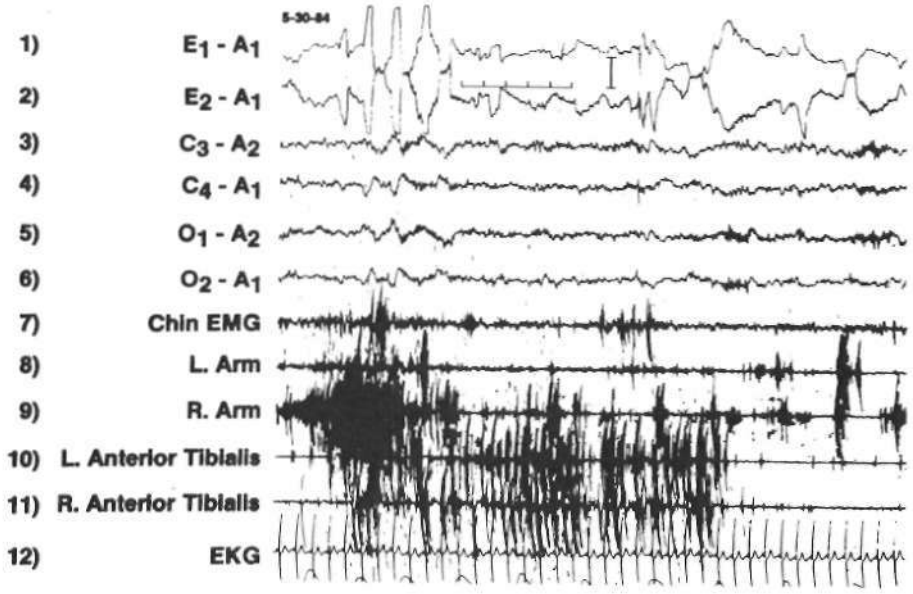

FIGURE 74.9 A portion of polysomnographic tracing in a 64-ycar-old man with rapid eye movement sleep behavior disorder. Electroencephalogram (C3-A2, C4-A1, 01-A2, 02-A1), shows mixed pattern with low-amplitude fast activities and thet.i activities. Chin clcctromyogram (EMG) as well as EMGs from left and right arms, left and right tibialis anterior muscles show tonic inctease in muscle tone with superimposed phasic increase. (EKG — electrocardiogram.) (Reproduced with permission from Broughton, R. "Behavioral parasomnias," in *Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects,* ed S. Chokroverty, Butterworth-Heinemann, Boston Courtesy Drs. Carlos Schenck and Mark Mahowald.)

In approximately 85% of patients with narcolepsy-cataplexy syndrome, a mean sleep latency of less than 5 minutes and two or more SOREMs are both noted. Aldrich and co-workers (1997) documented that both these findings are present in the initial MSLT in only 61% of narcoleptic patients. Occasionally, narcoleptic patients may have normal mean sleep latency with one or more SOREMs. Rarely, MSLT results may be entirely normal, particularly in narcoleptic patients who arc very anxious, A large percentage of patients presenting with EDS and two or more SOREMs have a condition other than narcolepsy.

Maintenance of Wakefulness Test

The maintenance of wakefulness test (MWT) is a variant of the MSLT that measures the patient's ability to stay awake. The MWT is performed at 2-hour intervals in a quiet, dark room; the patient adopts a semireclining position in a chair and is instructed to resist sleep. Four or five such tests are performed, each one lasting for 20 or 40 minutes. The MWT may be important for monitoring the effect of treatment in narcolepsy, but it is not as good as MSLT for measuring daytime sleepiness.

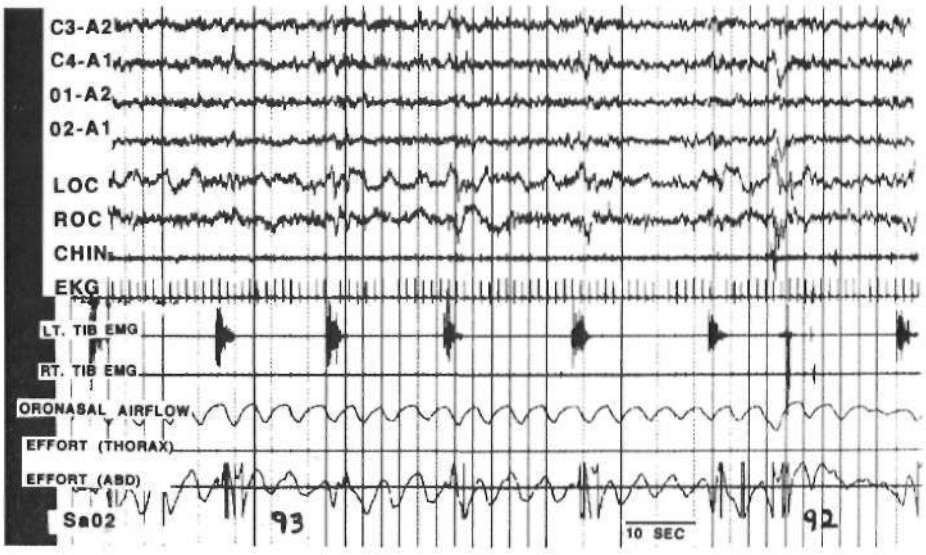

FIGURE 74.10 Polysomnography study of a patient with restless legs syndrome showing periodic limb movements in sleep in the left tibialis electromyogram (ET. TIB EMC). (Top four channels = electroencephalogram [EEG]jABD = abdomen; CHIN = electromyogram of the chin muscle, EKG = electrocardiogram; LOC= left electro-oculogram; RT. TIB FMG = right tibialis. I'kvtromvogmm; l<(>< right electro-oculogram.)

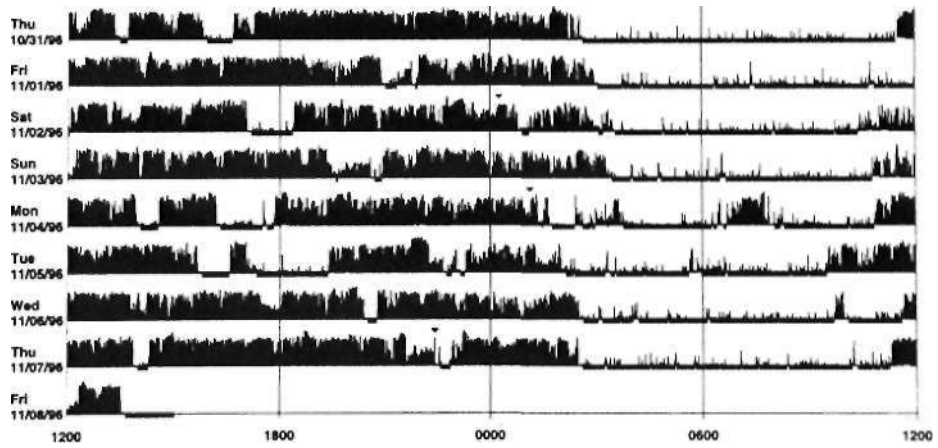

FIGURE 74.11 Acngraphic recording in a 29 year old man with delayed sleep-phase syndrome. The timing of the sleep period is delayed. Sleep typically occurs 3:00 AM to about 10:00-1 1:00 AM *(lighter areas).* The dark a teas represent the periods of activity.

Actigraphy

Actigraphy is a technique of motion detection that records activities during sleep and waking (Saadeh et al. 1995). It complements a sleep diary or sleep log data. The actigraphie instrument is a small device, slightly larger than a wristwatch, worn generally on the wrist but also on the ankle fot 1-2 weeks. It is a cost-effective method for assessing a sleep-wake pattern. Actigraphy is very useful in the diagnosis of circadian rhythm sleep disorders (Figure 74.11), sleep-state mis perception, and other types of insomnia. It can also be used to detect and quantify PLMS. It is not, however, suitable for assessment of SDB events.

Video-Polysomuographic Study

A video-PSG study is important for documenting abnormal movements and behavior during sleep at night in patients with parasomnias, including RBD, nocturnal seizures (Figure 74.12), and other unusual movements occurring during sleep. Parasomnias are generally diagnosed on the basis of the clinical history, but sometimes a video-PSG study is required to document the condition. For nocturnal epilepsy, a video-PSG study using multiple-channel electroencephalograms and multiple montages is required. Ideally, if sleep epilepsy is suspected, the video-PSG recording should be capable of EEG analysis at the standard EEG speed of 30 mm per second to identify epileptiform discharges.

Special Electroencephalographsc Studies in Nocturnal Seizure

In addition to standard EEG recording, 24-hour ambulatory EEG recording and long-term vidco-FEG monitoring may be needed for documentation of seizures. If the results of the EEG recording, including long-term monitoring and neuroimaging, are discordant in localizing the focus, the patient should be referred to a specialized epilepsy center for intracranial recordings.

Neuroimaging Studies

Neuroimaging studies include anatomical and functional (physiological) studies. These studies are essential when a neurological illness is susvvcicd of c.nism;; a sleep disturbance.

Cerebral angiography, including digital subtraction arteriography and magnetic resonance angiography, may be necessary in investigations for strokes in addition to computed tomography (GT) and MRI, which arc important in detection of structural lesions of the CNS (e.g., tumors, infarction, and vascular malformations). CT and MRI are also helpful in patients with demyelinating and degenerative neurological disorders that may be responsible for disturbed sleep and sleep-related breathing dysrhythmias.

A PET study dynamically measures cerebral blood flow, oxygen uptake, and glucose utilization and is helpful in the diagnosis of dementing, degenerative (e.g., PD and MSA), and seizure disorders. SPECT, which dynamically measures regional cerebral blood flow, may be useful for patients with cerebrovascular disease, AD, or seizure disorders. PET and SPEGT can also be performed to investigate dopamine D_2-rcceptor changes in RLS-PLMS as well as narcolepsy, Functional MRI can be useful to study the generators and areas of activation in RLS-PLMS. Doppler ultrasonography is an important test for investigation of stroke due to extracranial vascular disease. Myelography other than CT and MRI is important for diagnosis of spinal cord diseases.

In selected patients, fiberoptic endoscopy may be performed to locate the site of collapse of the upper airway and cephalometric radiographs of the cranial base and facial bones may be obtained to assess posterior airway space or maxillomandibular deficiency. These arc important when

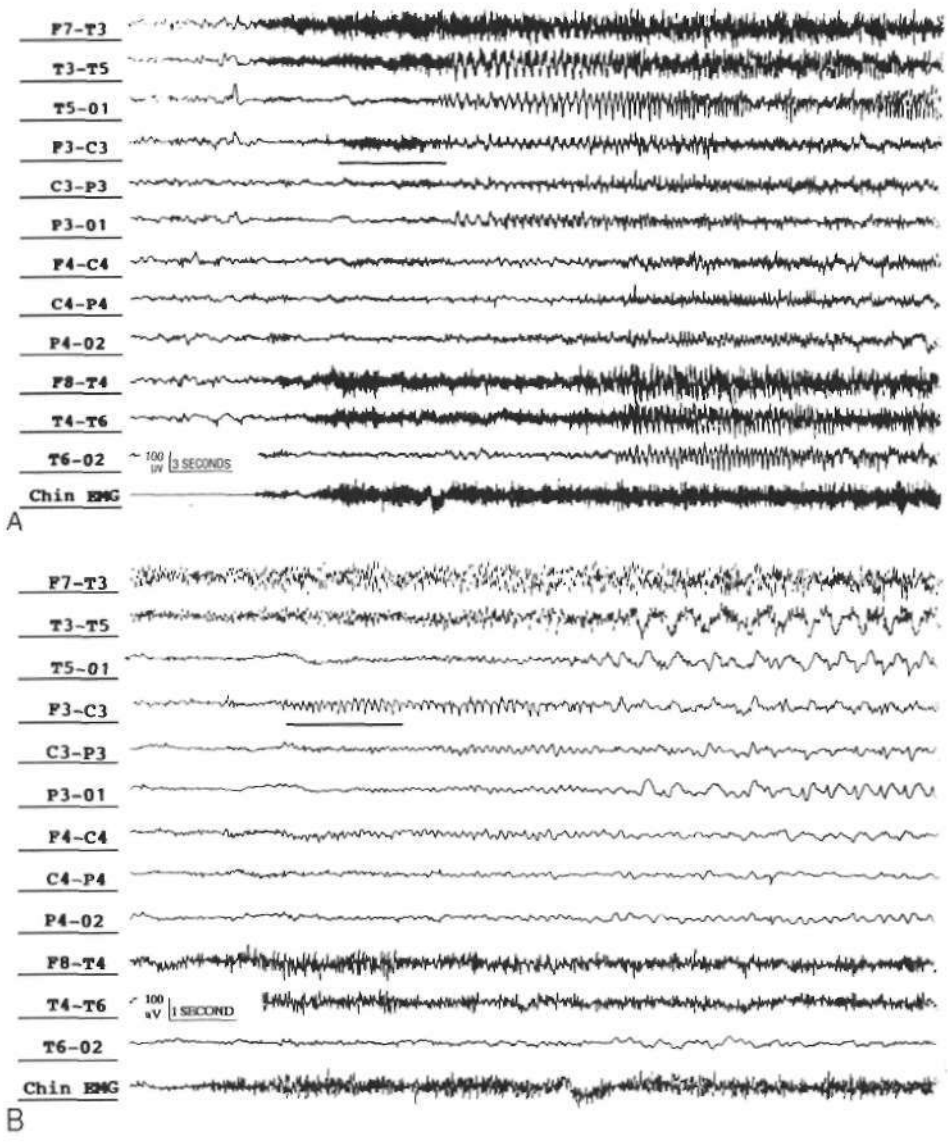

FIGURE 74.12 Portion of polysomnography recording showing the onset of a parrial seizure using (A) 10 mm per second and (B) 30 mm per second paper speed. Twelve channels of electroencephalogram (International Ten-Twenty electrode placement) and chin elccrromyogram arc shown. '. "ndcrlyint: activity represents rhythmic ictal discharges beginning at F3-C3 (left frontocentral) and spreading rapidly to the right hemisphere, and it is accompanied by clinical seizure. The underlying activity superficially resembles muscle artifacts at 10 mm per second paper speed (A) but it is obvious at 30 mm per second paper speed (B) that this activity is the beginning of the rhythmic epileptiform discharges in the electroencephalogram. (Reproduced with permission from Aldrieh, M. & Jahnke, B. 1991, "Diagnostic value of video - EEG po ly s omn ogra p hy," *Neurology,* vol. 41, p.1060.)

surgical treatment is planned. For research investigations, cross-sectional areas of the upper airway during wakefulness may be measured by CT and MRI (Robinson and Guillemmault 1999).

Pulmonary Function Tests

Pulmonary function tests exclude the presence of intrinsic bronchopulmonary disease, which may affect sleep-related lireathing disorders. Pulmonary function tests may include-assessment of ventilatory functions (forced expiratory volume in 1 second |FF.V; |, forced vital capacity [FVC], the FEVi to FVC ratio, peak expiratory flow rate, and forced expiratory flow rate), measurement of lung volumes (total lung capacity, residual volume, and functional residual capacity), gas distribution and gas transfer, and arterial blood gases (Po_2 and Pco>). Respiratory muscle function of individuals with neuromuscular disorders should be specifically assessed, and it is important to measure the maximal static inspiratory and expiratory pressures. Finally, chemical control of breathing (hypercapnic and hypoxic ventilatory responses) may be needed to assess respiratory functions and control systems in patients with various neurological disorders causing dysfunction of the metabolic respiratory controllers as well as in patients with obcsity-hypoventilation {pickwickian) syndrome.

Elcctrodiagnosis of the Respiratory Muscles

FMG recordings of the upper airway and diaphragmatic and intercostal muscles may detect affection of these muscles in various neurological diseases. A laryngeal EMG recording may detect laryngeal paresis in patients

with VISA with laryngeal stridor. A phrenic nerve and intercostal nerve conduction study may detect phrenic and intercostal neuropathy, which may cause diaphragmatic and intercostal muscle affections in some patients with neurological disorders.

Other Laboratory Tests

Appropriate laboratory tests should always be performed to exclude any suspected medical disorders that may be the cause of patients' insomnia or hypersomnia. These tests may include blood analysis and urinalysis, EGG, Holter ECG, chest radiography, and other investigations to rule out gastrointestinal, pulmonary, cardiovascular, endocrine, and renal disorders. In rare patients, when autonomic failure causes a sleep disturbance or sleep-related breathing disorder, autonomic function tests may he required for the diagnosis of the primary condition. In patients with narcolepsy, 1 1LA typing may be performed because most of the patients with narcolepsy show positivity for HLA DR2 DQ1, and DQB1*0602 antigens (Mignot 1998, 1999). Another important test is measurement of cerebrospinal fluid hypocretin 1 levels, which arc found to be low (below 110 pg/mL) in patients with narcolepsy-cataplexy who are HI.A DQBD0602 positive (Mignot et al. 2002). In selected patients suspected of having a psychiatric cause of EDS, neuropsychiatry testing (e.g., the Minnesota Multiphasic Personality Inventory) may be helpful.

In patients with RLS, EMG and nerve conduction studies are important to exclude polyneuropathies or lumbosacral radiculopathies and other lower motor neuron disorders that may be associated with RLS or cause symptoms resembling idiopathic RLS. Other important laboratory tests in patients with RLS include those necessary to exclude diabetes mellitus, uremia, anemia, and other associated conditions. It is particularly important to obtain levels of serum iron (including serum ferritin and transferrin), serum folate, fasting blood glucose, blood urea, and creatinine. The role of nerve biopsy remains controversial. In the vast majority of patients, a nerve biopsy is not necessary, but it may be obtained for research purposes and when there is a strong suspicion of polyneuropathy.

Management of Sleep Disorders

It is important to determine a cause for sleep disturbances so that the primary condition can be adequately treated. Treatment of secondary sleep disturbances is unlikely to be successful unless the primary cause is properly diagnosed and treated. Treatment of an underlying cause may resolve the sleep disturbance. If satisfactory treatment is not available for the primary condition or does not resolve the problem, however, treatment should be focused on specific sleep disturbance. Certain general principles of treatment should apply to treatment of any sleep disorders. It is beyond the scope of this chapter to discuss management of various medical, psychiatric, and neurological disorders. General sleep hygiene measures are listed in Table 74.28.

Steep Apnea Syndrome

The objective of management of sleep apnea syndrome is to improve the quality of life by improving the quality of sleep and to prevent life-threatening cardiac arrhythmias, pulmonary hypertension, CHF, and stroke, which arc related to SDK. Treatment of sleep apnea syndrome includes (Table 74.29) general measures, pharmacological agents, mechanical devices, and surgical treatment (Robinson and Guilleminault 1999).

Genera) measures include avoidance ot sedative-hypnotics and alcohol, which can aggravate sleep-related breathing disorders, and reduction of body weight in obese patients,

Pharmacological Treatment. Pharmacological treatment has not been very helpful in OSAS. The agents that have been partially successful in treatment of mild sleep apnea-hypopnea syndrome are protriptyline and acetazolamidc. There have been isolated reports of the use of selective serotonin reuptake inhibitors, theophylline and medroxyprogesterone acetate, without much benefit as well as topical nasal corticosteroids for OSAS in children with minimal benefit. Acetazolamide, a carbonic anhydrase inhibitor, produces metabolic acidosis, causing a shift in the CO2 apnea threshold, and has been used with some success to treat central apnea at high altitude. In a subset of patients with OSAS who were receiving CPAP treatment, modafinil, a novel wake-promoting agent, has been useful as adjunct treatment for residual daytime sleepiness.

Mechanical Devices. Nasal CPAP is an important therapy for treating OSAS. CPAP opens up the upper airway passage so that obstructive apneas and hypopneas,

Table 74,2H: Sleep hygiene measures

Sleep only as much as you need to feel rested
Keep a regular sleep schedule
Avoid forcing sleep
Exercise regularly for at least 20 min, preferably 4-5 hr before bedtime
Avoid caffeinated beverages after lunch
Avoid alcohol near bedtime: no nightcap
Avoid smoking, especially in the evening
Do not go to bed hungry
Adjust bedroom environment
Deal with your worries before bedtime

Table 74.29: Treatment of sleep apnea syndrome

General measures
Avoid alcohol, particularly in the evening
Avoid sedative-hypnotics
Reduce body weight
Pharmacological treatment (in mild cases)
Protnptyline
Acctazolamide (central apnea at high altitude)
Mechanical devices
Nasal continuous positive airway pressure for OSAS
Bilevel positive airway pressure for OSAS
Intermittent positive pressure ventilation for hypoventilation in neuromuscular disorders
Dental appliances in some mild to moderate OSAS
Tongue-retaining device for OSAS (unpredictable)
Surgical treatment
Uvulopalatopharyngoplasty (UPP), including laser-assisted and radiofrcquency UPP
Major maxillofacial surgical procedures
Tonsillectomy and adenoidectomy
Diaphragm pacing (central sleep apnea)
Tracheostomy (rarely performed nowadays)

OSAS = obstructive sleep apnea syndrome.

hypoxemias, snoring arousals, and sleep fragmentation are eliminated. The optimal (TAP pressure is first determined in the laboratory during overnight an PSG study, and the patient can purchase home units ro use nightly during sleep. Instead of CPAP, some patients may require bilevel positive airway pressure, which delivers a higher pressure during inspiration and a lower pressure during expiration. It is important to follow-up with such patients for the purpose of compliance and to identify patients who did not have adequate benefit and may require repeat titration. All patients do not comply with the CPAP regimen because of various problems, such as difficulty with the mask, claustrophobia, air leaks between the mask and face, and nasal congestion. The compliance vaties from 60% to 70% of patients. Further study is needed to determine the factors for compliance and noncompliance and to understand the long-term effect on the natural history of OSAS. The role of nasal CPAP in CSA syndrome is highly controversial. In a subgroup of patients with CSA who show narrowing or occlusion of the upper airway on fiberoptic scope, nasal CPAP may reverse the apneic episodes.

Surgical Treatment. In a few patients with severe OSAS in which CPAP therapy fails, UPP, including laser-assisted and radiofrequency UPP, and other upper airway surgical procedures have been tried with variable success (Sher 2002). Significant improvement is noted in approximately 50% of patients after UPP, and many of those who show improvement may still need (TAP for elimination of residual apneas. An overnight PSG study must always be performed before UPP is undertaken because it may eliminate snoring without adequately relieving OSAS. Other surgical approaches may be needed in patients with severe disease, including maxillofacial surgery, such as hyoid myotomy and suspension or mandibular osteotomy with genioglossus muscle advancement, although their role remains uncertain (Sher 2002). Tracheostomy may still be needed in an occasional patient as an emergency measure during severe respiratory compromise or severe apnea associated with dangerous cardiac arrhythmias causing a life-threatening situation. Tracheostomy for such severe cases of OSAS appears to be effective and well tolerated in the long term (Thatcher and Maisel 2003). Some patients may later be weaned from the tracheostomy and move to CPAP treatment, which has replaced tracheostomy for obstructive or mixed apneas. In patients with respiratory center involvement with CSA syndrome, diaphragm pacing or electrophrenic respiration has been used successfully, particularly for those who require ventilatory assistance during both day and night.

Other Ventilatory Supports. In patients with neuromuscular disorders, including those with AI.S, poliomyelitis, and postpolio syndrome, ventilatory support is often needed with either negative pressure or positive pressure ventilators ((^hokrovcrty 1999b; Guilleminault and Shergill 2002; Gonzalez et al. 2002). Intermittent positive pressure ventilation (IPPV) can be administered through a nasal mask. Negative pressure ventilation can be delivered from a tank respirator or from a cuirass. With ventilatory support, patients with neuromuscular disorders often obtain relief of daytime hypcrsomnolence and show improvement in sleep architecture. A combination of a nasal mask and positive pressure ventilation may be needed. When OSA complicates sleep hypoventilation, IPPV through a nasal mask during sleep may be a better treatment than negative pressure ventilation and may obviate the need for tracheostomy or diaphragm pacing. Negative-pressure ventilation may improve these patients' nocturnal ventilation during NREM sleep but can produce upper airway obstructive apnea during REM sleep, causing severe hypoxemia and hypercapnia. Patients with respiratory muscle weakness, including diaphragmatic muscle weakness, may require a combination of CPAP, cuirass ventilation, and later IPPV at night. Patients with motor neuron disease and associated sleep-related hypoventilation and apnea have been treated with cuirass ventilators, CPAP, and later IPPV at night with considerable symptomatic relief. Patients with poliomyelitis or postpolio syndrome who require ventilatory support to maintain respiratory homeostasis generally show improvement in sleep architecture and respiratory function after mechanical ventilation via nasal mask. Obstructive or mixed apneas respond to CPAP.

Other Treatment Modalities. Dental appliances can reduce snoring and help patients with mild sleep apnea, but at present, it is not possible to predict which patients will respond to such treatment. A tongue-retaining device is another unpredictable measure for treating sleep apnea.

Narcolepsy

The administration of stimulants, such as modafinil, NKilivlplH-r.ulaU'. pemoline, dextroamphetamine, or mcthamphetamine, is the treatment of choice (Table 74,30) for narcoleptic sleep attacks (Bassetti 2003). In 65-85% of patients, a significant improvement of EDS can be obtained. Modafinil, a novel wake-promoting agent, or methylphenidate is the drug most commonly used initially in patients with newly diagnosed narcolepsy. Because of hepatotoxicity pemoline is rarely used at present. The long-term efficacy and safety of modafinil fot the treatment of excessive sleepiness and sleep attacks associated with narcolepsy have been well established (Moldofsky et al. 2000; Mitlet et al. 2000). The starting dose is 100-200 mg daily and may be increased to 400 nig daily in two divided doses if needed. Methylphenidate treatment may be started with 5-10 mg two to three times daily. To avoid insomnia, the last dose should not be taken aftet 4:00 PM. In patients whose narcolepsy docs not respond to modafinil or methylphenidate, treatment with dextroamphetamine or mcthamphetamine can be administered, starting with 5-10 mg in the morning or twice a day. The maximum acceptable doses of stimulants for treatment of narcolepsy may include up to 50 mg daily (rarely 100 mg) for methylphenidate and 50 mg daily for both dextroamphetamine and methamphetamine. The most common side effects of the stimulants include nervousness, tremor, insomnia, irritability, palpitations, headache, and gastrointestinal symptoms. Another problem is tolerance, which may be noted in many patients, particularly with increasing doses.

The treatment of cataplexy and other auxiliaty symptoms of narcolepsy (see Table 74.30) consists of administration of tricyclic antidepressants, such as protriptyline (starting with 5 mg per day), imipramine (25-200 mg per day), and clomipramine (10-200 mg per day). Specific serotonin reuptake inhibitors, such as fluoxetine (20-80 mg per day), have been used with success. Recently sodium oxybatc (y-hydroxybutyrate) in two divided nightly doses of 3-9 g has been found to be an effective drug for treating cataplexy and narcoleptic sleep attacks (US Xyrctn Multicenter Study Group 2003).

Nonpharmacological treatment of narcolepsy includes general sleep hygiene measures, short daytime naps, and participation in narcolepsy support groups.

Table 74.30: Drug treatment for narcolepsy syndrome

For sleep attacks
- Modafini!: 200 mg/day
- Methylphenidate (Ritalin): 5 mg bid, 30 min before meals to a maximum of 30 mg, rarely 100 mg/day
- IV\m>nmphi'iamine (Dcxcdrine): 5 mg qd or hid, up to 50 mg/day
- YterriampriornmuH' : XI. • -11 L-L 31- i - . - • 5 NIL; qd nr hid, up r<> 50 mg/day
- Mazindol: 2 mg qd or bid, up to 8 mg/day

For cataplexy, sleep paralysis, and hypnagogic hallucinations
- Imipramine: 75-150 mg/day
- Clomipramine: 75-125 mg/day
- Fluoxetine: 20 mg qd, up to 80 mg/day
- Viloxazine: 150-200 mg/day
- Sodium oxybate: 3-9 g nightly

Idiopathic Hypersomnia

The treatment of idiopathic hypersomnia is generally unsatisfactory and is similar to the stimulant treatment for narcolepsy.

Parasomnias

No special treatment is needed for most ot the parasomnias. The subjects with partial arousal disorders (e.g., sleepwalking and sleep terrors) must he protected from injury to self or others by arranging furniture, using a padded mattress, and paying particular attention to doors and windows. If attacks of sleepwalking or sleep terrors are frequent, . realrr.eni v. uli ..u: aniulepirss.im e.g.. imipr.i mule or small doses of a benzodiazepine (e.g., clonazepam) may be tried for a short period.

Most RBDs respond dramatically to small doses of clonazepam (e.g., 1-2 mg at night). Occasional patients may need other drugs {e.g., melatonin).

Circadian Rhythm Sleep Disorders

Orcadian rhythm sleep disorders may be treated by the use of chronotherapy, phototherapy, or both. Chronotherapy refers to the intentional delay of sleep onset by *2-.y* hours on successive days until the desired bedtime has been achieved. After this, the patient strictly enforces the sleep-wake schedule. One study reported a high success rate among patients with DSPS even when the disorder had been present for many years. After several months, however, the patient generally becomes less adherent to the schedule and begins to lapse into his or her original sleep habits.

Exposure to bright light on awakening is effective in altering sleep onset and in synchronizing body temperature rhythm in patients with DSPS. The patient sits in front of a 10.000-lux light for 30^10 minutes on awakening; in addition, room lighting must be markedly reduced in the evening to achieve the desired results, A response is LU.Tiei,;lly (.vide:u Lillet 2-3 weeks- bin maintenance "l the response often requires indefinite treatment. This treatment is still evolving, and no large-scale study with adequate follow-up has been conducted to assess the long-term effect of phototherapy in DSPS. In patients with ASPS, bright light exposure in the evening has been successful in delaying sleep onset.

Melatonin (0,5-7,5 mg/day), taken orally in the evening or at bedtime, has been reported to be effective in some blind people with hypernychthemeral syndrome.

SiToml.m circuliau rhythm disorders (e.g., jet lag and effects of shift work) may be treated with benzodiazepine or /olpidem. Phototherapy has been tried, but its effectiveness has not been determined. Melatonin is being evaluated for treatment of arcadian rhythm disorders.

Restless Legs Syndrome and Periodic Limb Movements in Sleep

hour major groups of drugs have been used to treat RLS and PLMS (Table 74.31): dopaminergic agents, benzodiazepines, gabapentin, and opiates (Hcning et al. 1999). The typical dose for carbidopa/L-dopa (Sinemet) is 25/100 to 100/400 mg taken in divided doses before bedtime and during the night, Pergolide can be started at 0.05 mg and gradually increased to 0.2-0.5 mg taken in divided doses. One dose is taken 1 hour before bedtime and, depending on severity, another dose may be needed earlier in the evening or during the middle of the night on awakening. Another dopamine agonist, bromocriptine, may be tried, beginning with 2.5 mg and gradually increasing to a maximum of 15 mg per day. Bromocriptine has not been found to be as useful as pergolide or carbidopa/i.-dopa. Sometimes, a long-acting drug (e.g., Sincmct-CR) may be combined with short-acting carbidopa/L-dopa for maximum effect. Problems with the use of dopaminergic medications include abdominal pain, nausea, recurrence of RLS symptoms, poor sleep quality during the last part of the night, and the development of rebound or augmentation, consisting of symptoms of RLS-PLMS developing earlier in the day and more severely than before treatment. Nausea, vomiting, and headache also may occur after treatment with carbidopa/L-dopa, whereas nasal stuffiness, hypotension, and nightmares have been reported after treatment with pergolide.

Two new nonergot dopamine agonists, pramipexole and ropinirole, have been available in recent years. The safety and efficacy of these agonists in the treatment of RLS have been proven by several clinical trials. Most physicians now begin treating RLS with one of these agents. Pramipexole should be started at 0.125 mg I hour before bedtime and then gradually increased every 5-7 days as needed. The average dose is about 0.5-0.75 mg and may be increased up to 1.0-1.5 mg a day. Ropinirole should be started at 0.25 mg 1 hour before bedtime and gradually increased to an average dose of 1.5-2.5 mg. Side effects of these two drugs include nausea, sleepiness, dizziness, and peripheral edema. Another long-acting dopamine agonist, cabergolinc, has been used successfully to treat RLS, but this drug is very expensive and generally not used in the United States.

Clonazepam (0.5-2.0 mg per day at bedtime) or temazepam (15-30 mg at bedtime) may be useful in treating RLS-PLMS. Medications should be started with the lowest dose and gradually increased to obtain maximum benefit with minimal side effect. These agents may produce daytime sleepiness or confusional episodes, particularly in elderly patients.

Gabapentin is an anticonvulsant that has been found to be beneficial in mild-to-moderate RLS-PLMS. Divided doses of 300-1800 mg per day may be helpful but can produce somnolence, dizziness, ataxia, or fatigue in more than 10% of patients.

Opiates are effective for treating RLS-PLMS but are a less desirable alternative because of their proclivity to produce constipation and their potential fot addiction. Codeine, propoxyphene, oxycodone, and methadone have all been used for this purpose. Tramadol, a non-narcotic agent with activity at the opiate mu-receptor, also has been used with some success in patients with RLS-PLMS.

For mild RLS-PLMS, the physician may start with gabapentin. In moderate-to-severe conditions, most physicians start with pramipexole or ropinirole. In patients with refractory disease, one may have to use a combination of two to three drugs. In summary, the principle of treatment of RLS-PLMS is to start with the lowest possible dose and then increase by 1 tablet every 5-7 days until a maximum therapeutic benefit is reached or the side effects are noted. The dose can be divided and given 1-2 hours before bedtime. If necessary, for some patients with severe conditions, a daytime dose may be needed.

Other minor drugs (see Table 74,31) that have been helpful in occasional patients with RLS-PLMS include baclofen (10-60 mg daily), carbamazepine {200-600 mg daily), clonidine, an adrenergic agent (0.1-0.9 mg daily), and propranolol (80-120 mg daily).

In secondary RLS, the primary condition should be treated and the deficiency states, including the iron deficiency, should be corrected. The patient should also follow general sleep hygiene measures. Finally, the patients

Tabic 74.31: Drug treatment of restless legs syndrome

Major drugs
Dopaminergic agents
Carbidopa/L-dopa
Pergolide
Bromocriptine
Pramipexole
Ropinirole
Benzodiazepines
Clonazepam
Temazepam
Gabapenrin
(Ipiati-f,
Codeine
Propoxyphene
Oxycodone
Methadone
Minor drugs
Tramadol
Baclofen
Carbamazepine
Clonidine
Propranolol

should avoid certain medication and agents that might aggravate RLS, including neuroleptics, tricyclics, selective serotonin re-uptake inhibitors, other antidepressants, certain antinausea medications, calcium-channel blockers, caffeine, alcohol, and smoking.

Insomnia

Insomnia is a syndrome and not a specific disorder, and therefore treatment depends on the underlying cause of the syndrome. Treatment of secondary insomnia is unlikely to be successful unless the primary cause of the disturbance is diagnosed and properly treated. Both nonpharmacological and pharmacological therapies may be useful in the management of insomnia (Morin ct al. 1999, 2001; Espie ct al. 2001).

Nonpharmacological Treatment. The mainstay of treatment for patients with chronic insomnia is the use of nonpharmacologic.il measures in conjunction with the judicious, intermittent use of hypnotics. Nonpharmacological interventions include relaxation therapy and biofeedback; stimulus-control therapy; sleep restriction; and patient education about sleep hygiene, sleep habits, attitudes toward sleep, and the role of autonomic and cognitive arousals (Table 74.32). Sleep hygiene measures are listed in Table 74.28.

Relaxation therapy involves progressive muscle relaxation and biofeedback to reduce somatic arousal. One small study of several relaxation procedures found a 42% improvement in self-reported sleep complaints after 1 year of relaxation therapy. Stimulus-control therapy may also be useful in patients with chronic insomnia. Bootzin's stimulus-control technique is focused on discouraging the learned association between the bedroom and wakefulness and reestablishing the bedroom as the major stimulus for sleep. These techniques have been reported to lessen complaints of insomnia in approximately 50% of individuals after 1 year. Sleep-restriction therapy may improve sleep efficiency by restricting the total time in bed for sleep. Once this has occurred, gradually increasing the time allocated to sleep may improve the level of daytime functioning and the overall quality of sleep. Roughly one fourth of patients with insomnia may benefit from such a regimen. The relative efficacy of these various nonpharmacological approaches has not been well established. One metaanalysis involving 2102 patients in 59 trials found that sleep-restriction and stimulus-control therapies were more effective than relaxation techniques used alone (Smith et al. 2002). The use of sleep hygiene measures alone was not effective. The extent to which the concomitant use of nonpharmacological therapy augments the performance of pharmacological treatment is also unclear.

Tablt 74.32: Treatment of insomnia

- Nonpharmacological treatment
  - Relaxation therapy, including biofeedback
  - Stimulus-control therapy
  - Sleep-restriction therapy
  - Sleep hygiene measures
  - Chronotherapy (for circadian rhythm disorders)
  - Phototherapy (for circadian rhythm disorders)
- Pharmacological treatment
  - Benzodiazepines
    - Flurazepam: 15-30 mg
    - Estazolam: 1-2 mg
    - Clonazepam: 0.5-2.0 mg
    - Lorazepam: 1-2 mg
    - Temazepam: 15-30 mg
    - Triazolam: 0.125-0.250 mg
  - Nonbenzodiaiepines
    - Zolpidem: 5-10 mg
    - Zalcplon 5-10 mg
    - Antihistamines
    - Sedative antidepressants
    - Melatonin

Pharmacological Therapy. Hypnotic medications have generally not been the first choice of treatment for chronic insomnia (see Table 74.32). When they are prescribed, they should he used intermittently and always combined with nonpharmacological therapies.

Judicious use of hypnotics may be helpful in treating transient or short-term, idiopathic, and psychophysiological insomnia, but their use should be restricted to less than 4 weeks' duration. Intermittent use of hypnotic medications (e.g., 1-2 nights per week) may be necessary in some patients with chronic idiopathic or psychophysiological insomnia whose insomnia does not respond adequately to nonpharmacological treatment, although the drugs should not be the main component of therapy. Hypnotic medications are contraindicated in pregnancy because of data showing an increased risk of fetal malformations with diazepam or diazoxide if used during the first trimester. The drugs should also he avoided or used judiciously in patients with alcoholism or renal, hepatic, or pulmonary disease. A combination of alcohol and hypnotics is absolutely contraindicated. The drugs should also be avoided in patients with sleep apnea syndrome.

Benzodiazepine drugs (temazepam, flurazepam, triazolam, and estazolam) and two nonbenzodiazepine drugs (/olpidem and zalcplon) are commonly used as hypnotics; two other benzodiazepine drugs (lorazepam and clonazepam) are also often used for this indication (Morin et al. 2001; Walsh and Schweitzer, 1999; Walsh et al. 2000; Danjou et al. 1999). Triazolam is no longer available in Great Britain because of reports of serious side effects, such as amnesia, rebound insomnia, and anxiety. The selection of a specific hypnotic agent should be based primarily on the elimination half-life. Short-acting drugs, such as temazepam, estazolam, triazolam, and Zolpidem, are generally preferable because they produce less residual sleepiness the morning after use. However, these drugs,

particularly triazolam, may have a high incidence of amnesia and rebound insomnia and should be used cautiously in patients with anxiety disorders. Adjustment in dosage may be necessary in patients who have prolonged drug elimination half-lives due to age or impaired renal or hepatic function. Dependence and tolerance arc the major disadvantages of long-term use of hypnotics. The drugs should be discontinued gradually rather than abruptly to avoid precipitating symptoms of withdrawal.

Sedating antidepressants (e.g., amitriptyline and trazodone) are most useful in the management of patients in whom depression and insomnia coexist but are of limited usefulness in nondepressed patients because of rapidly developing tolerance to the sedative effects. Many over-the-counter sleep aids conrain the sedating antihistamine diphenhydramine or doxylaminc. These medications are generally not helpful in the management of chronic insomnia. Melatonin, a normal product of the pineal gland, is sold as a food supplement and an orphan drug in the United States, but over-the-counter sales are banned in the United Kingdom. Data on the efficacy and safety of melatonin are minimal, but the hormone does not appear to be a potent hypnotic for most patients with chronic insomnia. However, a subgroup of elderly patients with low melatonin levels have benefited from melatonin treatment, and it also is useful in some patients with jet lag, DSPS, and hypernychthcmeral syndrome.

Sleep Disturbances in Neurological llhess

Treatment of neurological illnesses causing sleep-related dysrhythmias have been described (see Sleep Apnea Syndrome, earlier in this chapter).

Nocturnal seizures should be treated with standard anticonvulsant medications. Sleep disturbances in these patients often resolve after effective therapy for seizures,

Trearment of acute confusional states associated with dementia should be focused on the precipitating or causal factors for such episodes. Often, episodes are precipitated when the patient is transferred from home to an institution. As much as possible, the home environment of such patients should be preserved. The darkness of night often precipitates episodes, so a night light is helpful. Medication that could have adverse effects on sleep and breathing should be teduced in dose or changed. Associated conditions that could interfere with sleep {e.g., pain due to arthritis and other causes) should be treated with analgesics. Depression is often an important feature in patients with AD, and a sedative antidepressant may be helpful. Frequency of urination in such patients may result from infection or an enlarged prostate gland and may disturb sleep at night. Appropriare treatment should be used for such conditions. Patients should be encouraged to develop good sleep habits. They should be discouraged from taking daytime haps and should be encouraged to exercise (e.g., walking) during the day. They should not drink caffeine in the evening before bedtime. For sleeplessness, a trial with intermediate-acting benzodiazepines, Zolpidem or zaleplon, should be tried for a short period. For extreme agitation, patients should be given small doses of high-potency antipsychotics, such as halopendol or thiothixene, or atypical antipsychotics (e.g., risperidone, olanzapine, quetiapine), which have less side effects than halopcridol or thiothixene. In some patients, appropriately timed exposure to bright light may be helpful.

Treatment of PD improves sleep inconsistently. In patients who have reactivation of parkinsonian symptoms during sleep at night, adjustment in the timing and choice of medication may be helpful. Some patients may benefit from an evening or bedtime dose. Longer-acting preparations of L-dopa also may help when taken near bedtime. Dopamine agonists (e.g., bromocriptine, pergolide, pramipexole, and ropinirole) with their sustained actions may benefit sleep in some patients. Antihistamines such as diphenhydramine may promote sleep in addition to giving a modest antiparkinsonian effect. A small dose of carbidopa/L-dopa, with a second dose later at night if the patient awakens, may sometimes help those with insomnia. In some patients, selegiline may improve sleep. Nocturnal dyskinesias related to i.-dopa and causing insomnia may respond to a reduction in the dose of dopamine agonists or by addition of a small dose of benzodiazepine. In patients with nocturnal hallucinations and nightmares, including nocturnal vocalizations and RBD, clonazepam (0.5-1.0 nag) at bedtime may be beneficial. Nocturnal hallucinations and psychosis in patients with PD have been treated successfully with clozapine or the newer drug olanzapine. During clozapine treatment, the usual precautions of monitoring blood count and testing liver function should be taken. Rivastigmine, a cholinesrerasc inhibitor, has been beneficial in improving sleep disturbance cognition and hallucinations in some patients with PD.

CONCLUSION

There has been an explosion of knowledge in our understanding of sleep and its disorders stretching from the gene to pathophysiology and phenomenology. The field of sleep medicine is beginning to take its rightful place as a distinct subspecialty in medicine. Sleep disorders affect multiple systems and result from dysfunction of almost every system in the body. It is therefore important to have a basic understanding of the physiological changes during sleep and the clinical phenomenology of sleep disorders. In this chapter, I briefly summarize the essential physiological changes during sleep, which are quite different from those during wakefulness as well as circadian rhythms, the function of sleep, and neurobiology of slcep-wakefulness. Clinical manifestations of many primary and secondary sleep disorders, methods of laboratory investigation, and management are also briefly reviewed. Sleep is a function of

the brain and patients with neurological disorders are particularly susceptible to disorders of sleep. Sleep adversely affects neurological illnesses, and neurological disorders in turn adversely affect the quality and quantity of sleep. Therefore, it is incumbent upon neurologists to have a basic understanding of disorders of sleep because sleep dysfunction encroaches on almost every aspect of neurology.

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Chapter 75
Headache and Other Craniofacial Pain

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Headache is one of humanity's most common afflictions. It has been estimated that one person in three experiences severe headaches at sonic stage of life. Most people with a mild recurrent or isolated headache do not consult a physician, and therefore the true prevalence is unknown. The lifetime prevalence for any type of headache as estimated from population-based studies is more than 90% for men and *95%* for women. A survey of a sample of 20,000 households in the United States revealed a prevalence rate of migraine of 18.2% in females and a 6.5% rate among males, resulting in an estimated 27.9 million migraineurs in the United States. Approximately 60% of patients with migraine experience 2 or more attacks per month, and more than 75% of migraineurs report severe or extremely severe pain during attacks. More than 90% of patients report an impaired ability to function during migraine attacks, and 53% report severe disability requiring bedrest. Approximately 31% of patients with migraine missed at least one day from work or school in the preceding 3 months due to migraine (Lipton et al. 2001). Indirect costs of migraine related to decteased productivity and lost days of work have been calculated to be $13 billion per year; it has been estimated that there are the equivalent of 112 million bedridden days per year due to migraine (Hu et al. 1999). Indeed, the World Health Organisation declared migraine to be among the most disabling medical conditions experienced worldwide.

PAIN TRANSMISSION AND MODULATION AS RELATED TO HEADACHE

An understanding of the pathophysiology of headache must first start with a knowledge of which intracranial structures are pain sensitive. Ray and Wolfe reported on the pain-sensitive structures in the head and mapped the pattern of pain referral based on the structure simulated from intracranial surgery performed during local anesthesia in the 1930s. The intracranial pain-sensitive structures include the arteries of the circle of Willis and the first few centimeters of their medium-sized branches, meningeal (dural) arteries, large veins and dural venous sinuses, and portions of the dura near blood vessels. Pain-sensitive structures that are external to the skull cavity include the external carotid artery and its branches, scalp and neck muscles, skin and cutaneous nerves, cervical nerves and nerve roots, mucosa of sinuses, and teeth. Pain from these structures is carried largely by cranial nerves V, VII, IX, and X.

Inflammation, traction, compression, malignant infiltration, and other disturbances of pain-sensitive structures lead to headache. Superficial structures tend to refer pain locally, whereas deeper-seated lesions may refer pain imprecisely to a distant part. A purulent maxillary sinus, for example, causes pain over the involved sinus, whereas within the cranial vault, nociceptive signals reach the central nervous system (CNS) largely by way of the first division of the trigeminal nerve, and therefore an occipital

lobe rumor may refer pain to the frontal head region. Infra tentorial lesions tend to refer pain posteriorly because this compartment is innervated by the second and third cervical nerve roots, which also supply the back of the head. This can change when posterior lesions or cervical spine pathological conditions produce frontal headache, which may occur because the caudal portion of the trigeminal nucleus extends down as far as the dorsal horn at the C3 level. Impulses arriving from C2-C3 converge on neurons within the trigeminal nucleus and may refer pain to the somatic distribution of cranial nerve VI.

Afferent pain impulses into the trigeminal nucleus are modified and modulated by descending facilitatory and inhibitory influences from critical brainstem structures, including the periaqueductal gray, rostral ventromedial medulla, locus ccrulcus, and dorsal raphe nuclei. Opioids diminish the perception of pain by activating the inhibitory systems, whereas fear, anxiety, and overuse of analgesics may activate the facilitatory systems thereby aggravating the pain.

CLASSIFICATION

In 198H, the I leadache Classification Committee of the International Headache Society introduced a detailed classification of headaches, which was revised in 2004. The 14 main headache types are shown in Table 75.1. bach In.\i J ulu- type ;•. furl her dclincd ;ind subclassified according to criteria agreed to by several international subcommittees. Careful definition of the many types of migraine and other primary headache disorders is expected to free future research and clinical publications from the confusing and often poorly defined terminology of earlier work. Until the actual pathogenesis of primary headache syndromes is determined, it will not be possible to develop a unitary classification of head pain.

Tabic 75.1: Classification of headache

The Primary Headaches
1. Migraine
2. Tension-type headache
3. Cluster headache and other trigeminal-autonomic cephalalgias
4. Other primary headache disorders

The Secondary Headaches
5. Headache attribured to head and/or neck trauma
6. Headache attributed to cranial and/or cervical vascular disorder
7. Headache attributed to nonvascular, noninfectious intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disturbance of homeostasis
11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
12. Headache attributed to psychiatric disorder
13. Cranial neuralgias and central causes of facial pain
14. Other headache, cranial neuralgia, central or primary facial pain

Source; Reprinted with permission from the International Headache Society Second Headache Classification Committee 2004. "The International Headache Classification, 2nd ed," *Cephalalgia,* vol. 24, suppl. 1, pp. 1-195.

Headache Attributed to Nonvascular, Noninfectious Intracranial Disorders

Intracranial lesions that occupy space, often referred to as *mass lesions,* produce head pain by traction on or compression of pain-sensitive structures. The nature, location, and temporal profile of headache produced by an intracranial mass depend on main [actor-., IIIJ-.KIIIH; tinlocation of the lesion, its rate of growth, its effect on the cerebrospinal fluid (CSF) pathways, and any associated cerebral edema. The intracranial mass lesion may be neoplastic, inflammatory, or cystic. Each type can result in either localized or generalized head pain. The type of headache is characteristic ᵬ(raised iiitracraniaI pressure (sec later) but is not diagnostic of a particular underlying disease.

Intracranial and nil r.iparcrk liyni,;' hematomas ate akn mass lesions and are responsible for traction headaches, but they are classified under vascular disorders causing headache.

Tumors

Approximately 50% of patients with brain rumors report headaches; in one third to one half of these patients headache is considered the primary complaint. The headache can be generalized, but in approximately one third of patients, it overlies the tumor and is referred to the scalp near the lesion. Rapidly growing tumors are more likely to produce headache than are indolent lesions, but slowly enlarging lesions can eventually produce pain by compromising the ventricular system or exerting direct pressure on a pain-sensitive structure, such as the trigeminal nerve. When the CSF circulation is partially obstructed, headache often becomes generalized and worse in the occipitonuchal area. This type of headache, which is a manifestation of raised intracranial pressure, is often worse on awakening, is aggravated by coughing and straining, and is often associated with nausea and vomiting. In children particularly, the vomiting may be precipitate and without nausea. This can lead to projectile vomiting because it occurs without warning. Projectile vomiting rarely occurs in adults.

Large parenchymal tumors and small tumors that interfere with the CSF pathways can be associated with periodic increases in inracranial pressure. Monitoring reveals periods of increased pressure (called the plateau waves of Lundberg), the beginning of which may be associated with increasing severity of headache and the peak of which may

be associated with vomiting or other ictal events, such as decreased consciousness or a change in respiration.

Supratentorial masses generally produce frontal or temporal head pain because of the trigeminal nerve supply to the anterior and middle cranial fossae. The superior surface of the tentorium cerebelli is supplied by the meningeal branches of the first division of the trigeminal cranial nerve, so an occipital lesion can cause pain referred to the fronto-orbital tegion. Mass lesions of the posterior fossa generally cause occipitonuchal pain because the meningeal nerve supply is largely through the upper cervical nerves, which also supply the occipital and cervical dermatomes. Some sensory innervation of the posterior fossa is also carried via cranial nerves VII, IX, and X, and therefore pain referral can be more widespread. Posterior fossa tumors result in headache earlier than their supratentorial counterparts because the greater likelihood of compromise of the ventricular system leads to rapidly developing hydrocephalus and raised intracranial pressure (Forsyth and Posner 1993).

Pituitary tumors and tumors around the optic chiasm commonly cause a frontotcmporal headache, but they can also cause referred pain near the vertex. However, patients with tumors of the sellar and parasellar regions do not often present with headache as the initial symptom because the visual and endocrine symptoms are typically noted first (Edmeads 1997).

Tumors growing in the ventricular system are rare, but they can present dramatically. The classic presentation of a colloid cyst of the third ventricle is a sudden headache of great severity, rapidly accompanied by nausea and vomiting and possibly by loss of consciousness. Intraventricular meningiomas, choroid plexus papillomas, and other intraventricular tumors can present in this manner if they suddenly obstruct the ventricular outflow pathways. A positional change may precipitate such an event; similarly, adoption of a different posture may rapidly relieve the headache and other symptoms. Colloid cysts of the third ventricle generally lead to slowly enlarging hydrocephalus that may result in a generalized, rather constant headache, superimposed on which may be episodes of catastrophic increases in headache. Obstruction of the egress of CSE from the ventricular system rapidly leads to increased intracranial pressure, which can exceed the capillary perfusion pressure of the brain and lead to loss of consciousness due to cerebral ischemia. Headaches that have a rapid onset and are associated with loss of consciousness, amaurosis, or vomiting are serious and should lead the examinet to consider conditions such as subarachnoid hemorrhage, brain tumor, or other mass lesions.

Headache, especially in the occipital region, that is precipitated by sudden Valsalva maneuvers (e.g., coughing, sneezing, ot lifting) or exertion should be taken seriously, A posterior fossa lesion, such as a cerebellar tumor or Chiari malformation, can lead to this clinical picture. In most patients with cough or exertional headache, however, no serious lesion is found.

Infiltrating tumors, such as gliomas, can reach considerable size without causing pain because they may not deform or stretch the pain-sensitive vessels and nerves. Such lesions are more likely to present as focal neurological deficits or with seizures than with headache. Sudden worsening of the neurological state due to hemorrhage into the tumor mass may present with sudden headache. The headache may initially appear in the part of the skull overlying the tumor and then become generalized if intracranial pressure rises. Infarction of a tumor can cause edema and swelling that result in a similar dramatic onset of head pain and neurological deficit.

Tumors that are intracranial but extraparenchymal, such as meningioma, acoustic neuroma, pinealoma, and craniopharyngioma, can all produce headaches, but, as with the parenchymal lesions, there are no specific headache patterns. The headaches can be near the lesion, referred to a more distant site in the cranium, or generalized when intracranial pressure increases. Meningiomas and meningeal sarcomas can invade the skull and can even cause a mass externally by direct tumor spread or by overlying hyperostosis. Such tumors arc often associated with localized head pain. Meningeal carcinomatosis (carcinomatous meningitis) produces a headache in most subjects, but the associated cranial nerve involvement and other neurological symptoms are generally more striking.

The headache associated with other intracranial mass lesions, such as cerebral abscess and intracranial granuloma, is no more specific than that due to a cerebral neoplasm.

In summary, the following features should serve as warnings that a patient's headaches may not be of benign origin and raise the possibility of an intracranial mass lesion (Purdy 2001):

1. Subacute and progressive in nature of headache
2. New onset in adult life (>40 years of age)
3. Change in headache pattern, such as incteascd intensity of pain, increased incidence of attacks, development of new features, or decreased response to treatment
4. Association with any of the following: nausea or vomiting not explained by migraine or systemic illness; nocturnal occurrence or morning awakening; precipitation or worsening by changes in posture or Valsalva maneuver; confusion, seizures, or weakness
5. Abnormalities on neurological examination

Arachnoid Cysts

Cystic spaces bounded by arachnoid membranes found with computed tomography (CT) or magnetic resonance imaging MRI scans IIUMIH-tin investigation ol headaches are rarely responsible for head pain. Uncommonly, an arachnoid cyst has a one-way valvelike structure in its wall, so that arterially induced pulsations of the CSF gradually pressurize

the cyst and cause it to enlarge. Compression of cranial nerves, such as the trigeminal nerve, or distortion of the midline structures causes headaches that may be either generalized or localized. Serial CT or MRI scans reveal the cyst to be increasing in size, and this finding should lead to operative intervention. Enlargement of normal subarachnoid spaces such as the cisterna magna and cisterna ambiens is not a cause for headache and should not lead to shunting or other surgical approaches.

Abnormalities of Cerebrospinal Fluid Circulation

Whether raised intracranial pressure, in the absence of a shift of intracranial structures, results in headache is uncertain. The rate at which the intracranial pressure is increased and the duration of the increase are probably factors that determine whether pain is produced.

Obstruction of the Cerebrospinal ¥luid Pathways

Lesions that prevent free egress of CSF from the ventricular system result in obstructive hydrocephalus. If this occurs before closure of the cranial sutures, enlargement of the skull occurs, usually without producing headache. Ventricular obstruction after closure of the sutures leads to raised intracranial pressure and often to headache. The pain is often worse on awakening, occipital in distribution, and associated with neck stiffness. Vomiting, blurred vision, and transient obscuration of vision due to papilledema may follow as well as failing vision due to optic atrophy.

Rapidly developing obstruction due to a posterior fossa mass lesion or a ball-valve tumor, such as a third ventricular colloid cyst, can lead to a rapidly increasing headache followed by vomiting, impaired consciousness, and iniTi'.isinj.'. nourological deterioration. S'.nwly developing hydrocephalus may result in massively dilated ventricles and may be associated with little or no headache.

Congenital obstruction of the foramina of l.usehk and Magendie—the Dandy-Walker syndrome—can lead to ballooning of the fourth ventricle and deformity of the cerebellum, Minor degrees of this malformation can remain asymptomatic until later in life and then present with obstructive hydrocephalus and headache. Similarly, the Chiari malformation in its various forms can obstruct the free circulation of CSF and lead to hydrocephalus and headache (Taylor and Larkins 2002). This malformation can result in an occipital-suboecipiral headache that is worsened or even initiated by Valsalva's maneuver during lifting, straining, or coughing. Thus, the Chiari malformation is one ol the causes of an exertional 01 Valsalva-induced headache.

In communicating hydrocephalus, there is free communication between the ventricular system and the subarachnoid space bill Mime impairment of CSI' circulation or absorption. Obstruction in the basal cisterns or at the arachnoid granulations may follow subarachnoid hemorrhage and meningitis. Venous sinus occlusion can impair absorption of C5F. Headache may be a prominent symptom of both obstructive and communicating hydrocephalus, except in the case of normal pressure hydrocephalus, which is generally painless (see Chapter 65).

Low Cerebrospinal Fluid Pressure Headache

The headache of lowered CSF pressure characteristically develops with the patient in the upright position and is rapidly relieved by recumbency. It most commonly occurs after a lumbar puncture, especially when this is performed as part of myelography. Loss of CSF volume, due in part to the removal of some CSF for diagnostic purposes and in part to later leakage through the hole in the arachnoid and dural layers, results in a traction headache. The brain normally floats in the intracranial CSF, loss of which allows the brain to sink and thereby exert traction on structures such as bridging veins and sensory nerves. Recumbency removes the effect of gravity, and the traction headache is relieved. The headache that occurs after a spinal tap usually resolves in a few days if the patient remains in bed with good hydration. Occasionally, the syndrome persists for days, weeks, or even months. Relict i.in usually be obtained by the application of a blood patch, in which 10-20 mL of the patient's own blood is injected into the epidural space close to the site of the original spinal tap. This technique prevents further leakage of CSF by exerting increased pressure in the epidural space and by coagulation of the blood, thereby relieving the headache in a few hours. The injection of blood is associated with a small risk of cauda equina compression or subarachnoid hemorrhage, but this is unlikely if the blood volume is small and the blood is injected gently.

An identical syndrome of headache due to low CSF prcssute can occur when there is a leak of fluid through the cribriform plate, through the petrous bones, or through any basal skull defect. CSF rhinorrhea and especially CSF otorrhea may not be obvious to the patient, whose complaint may be postoperative or post-traumatic headache. Leakage of CSF from the skull can occur spontaneously when inttacranial pressure is raised or a tumor erodes through the base of the skull. This occurs most often around the cribriform plate region, where the bone is especially thin. The CSF leak can be identified by radioisotope cisternography. Leakage of CSF through the nasal sinuses can be detected by placing numbered cotton pledgets in the nose next to the various ostia of the sinuses. Contamination of the pledgets by radioactivity enables the sinus, through which the fluid is leaking, to be identified. CSF otorrhea is not easy to identify if the fluid is draining down the eustachian tube when the eardrum is intact. Scanning with a gamma camera after instillation of a radioactive tracer by lumbar puncture may allow the leak

to be identified. Treatment is usually surgical repair of the bony and meningeal defect,

A similar low CSF pressure headache can occur when a tear develops in the spinal theca. This is usually in the midthoracic region and may result from lifting or coughing or, at times, spontaneously. It can also occur with a crush injury to the chest or abdomen and in patients with overdrawing CSF shunts. When it occurs without a significant history of trauma, it can be overlooked as a cause of daily headache. The history of a headache rapidly responding to recumbency should lead one to suspect the condition. However, in some patients whose headaches are longstanding, a persistent headache may be noted and the postural feature of the headache may become less prominent, Nausea or emesis, neck pain, dizziness, horizontal diplopia, changes in hearing, photophobia, upper limb paresthesias, vision blurring, and dysgeusia may also occur, particularly when the headache first develops.

The diagnosis first requires a clinical index of suspicion followed by an MRI scan with gadolinium. MRI has become an invaluable diagnostic tool in this syndrome, with the cardinal features being diffuse pachymeningeal thickening with gadolinium enhancement, subdural collections of fluid, and evidence of brain descent (Figures 75,1 through 75.3). This evidence includes cerebellar tonsillar descent (resembling a Chiari type I malformation); reduction in size or effaccment of the prcpontine, perichiasmatic, and subarachnoid cisterns; inferior displacement of the optic chiasm; and descent of the iter (the opening of the aqueduct of Sylvius as seen on a midsagittal MRI scan).

If the clinical and MRI findings are typical, determination of the CSF opening pressure may not be necessary. Measurement or the opening pressure is warranted in patients with normal MRI scans. However, in only 50% of patients is the CSF pressure less than 40 mm H_20. Because the opening pressure may be normal, the term *CSF volume depletion* identifies best the core of the problem in this disorder (Mokri 2000). These patients may have a variable pleocytosis with up to 40 or more mononuclear cells per ram[1] and a mild-to-modest increase in CSF protein (Mokri 1999).

In patients with the typical clinical and radiographic features of low CSF pressure headache, management may be conservative with bed rest and hydration for 1-2 weeks. If this is either not practical or not effective, options include empirical treatment with a blood patch or further studies to identify the site of the CSF leak. In patients with spontaneous leaks, the leak is often at the level of the thoracic spine or the cervicothoracic junction. Myelography with a CT scan of the spine is more sensitive than radioisotope cisternography or an MRI scan of the spine, but the latter procedures may serve as guides for obtaining multiple CT images at the appropriate levels. Most leaks are stopped with either conservative therapy or blood patches. Although an epidural blood patch is effective in the majority of patients, most requite more than one blood patch (Mokri 1999), and some require as many as four to six blood patches (Mokri 2001). For resistant leaks, surgical intervention with repair of the dural tear may be necessary. Even after a protracted duration, surgical repair of the causative dural tear can be quite effective (Schievink et al. 1998),

Idiopathic Intracranial Hypertension

Headache, transient visual obscuration, pulsatile tinnitus, and diplopia are the most common presenting symptoms of idiopathic intracranial hypertension (pseudotumor cerebri). The headache is rather nonspecific but tends to be worse on awakening and to be aggravated by activity. The blurring and obscuring of vision arc direct results of raised intracranial pressure leading to papilledema. Once it has been determined by MRI scans that there is no intracranial mass, obstruction of the ventricular system, or thrombosis of a dural venous sinus, the high CSF pressure can be confirmed by lumbar puncture manometry. Removal of CSF to achieve a normal closing pressure relieves the headache and temporarily prevents visual obscuration. Long-term management of idiopathic intracranial hypertension is discussed in Chapter 65.

Transient Syndrome of Headache with Neurological Deficits and Cerebrospinal Fluid Lymphocytosis

There is a transient syndrome characterized by recurrent episodes of headache accompanied by reversible neurological deficits and CSF pleocytosis, originally termed *migrainous syndrome with CSF pleocytosis* (Bartlcson ct al, 1981). Several reports of this syndrome used various terms, including headache with neurological deficits and CSF lymphocytosis (Berg and Williams 1995) and pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis (Gomez-Aranda et al. 1997). This self-limited syndrome consists of one to several episodes of variable neurological deficits accompanied by moderatc-to-severe headache and sometimes fever. Each episode lasts hours, with total duration of the syndrome being from 1-70 days. CSF abnormalities have included a lymphocytic pleocytosis varying from l() to more tha:i ,'UQ CL-lls/inm \ elevation of CSF protein, and in some patients, elevated opening pressure, MRI and CT scans are invariably normal, but an electroencephalogram often shows focal or diffuse slowing. Results of microbiological studies have been negative. The etiology of the syndrome is unclear, although it has been speculated to be due to an immune response to a viral infection. No treatment has been shown to alter the self-limited course of this disorder. In contrast to this syndrome, Mollaret's meningitis is characterized by recurrent episodes of aseptic meningitis with fever (see Chapters 59B and 79). The episodes are separated by months to years and are typically not accompanied by focal neurological symptoms. Classically, the CSF shows a

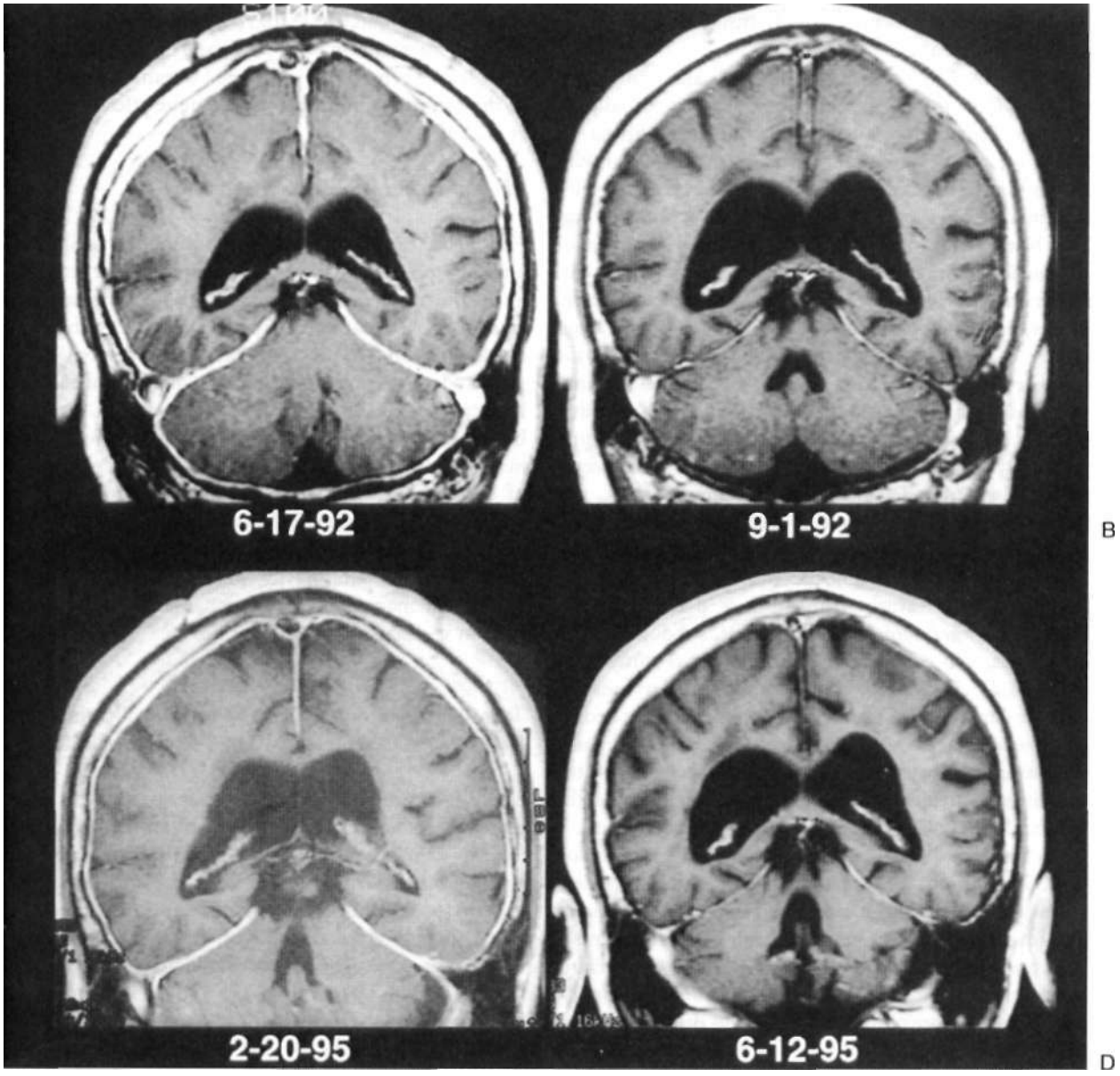

FIGURE 75.1 Coronal Tl-weighted magnetic resonance images with gadolinium in a patient with an overdrawing cerebrospinal fluid shunt and low-pressure headache demonstrate diffuse pachymeningeal thickening and enhancement (A) with resolution after shunt revision and resolution of headaches (B). Patient developed recurrent symptoms and imaging abnormalities after shunt revision (C) followed by resolution after another shunt revision (D). (Reprinted with permission from Mokri, B., Picpgras, D. G., *&C* Miller, G. M. 1997, "Syndrome of orthostatic headaches and diffuse pachvmeningeal gadolinium enhancement," *Maya Clin Proc,* vol. 72, pp. 400-413.)

pleocytosis and in the first 24 hours, neutrophils predominate, and large "endothelial cells" are present; these have been shown to represent monocytes.

Headache Attributed to Infection

Inflammation of any pain-sensitive structures in the cranial caviry can produce headache. Meningitis and meningoencephalitis both have headache as a major symptom. The eharactetistics of the head pain depend on whether the infection is acute or chronic. Acute meningitis produces a severe headache with neck stiffness and other signs of meningism, including photophobia and irritability. Pain is often tetro-orhital and worsened by moving the eyes. Chronic meningitis due to fungal or tuberculous infection can also lead to headache that may be severe and unrelenting. The headache of intracranial infection is nonspecific but

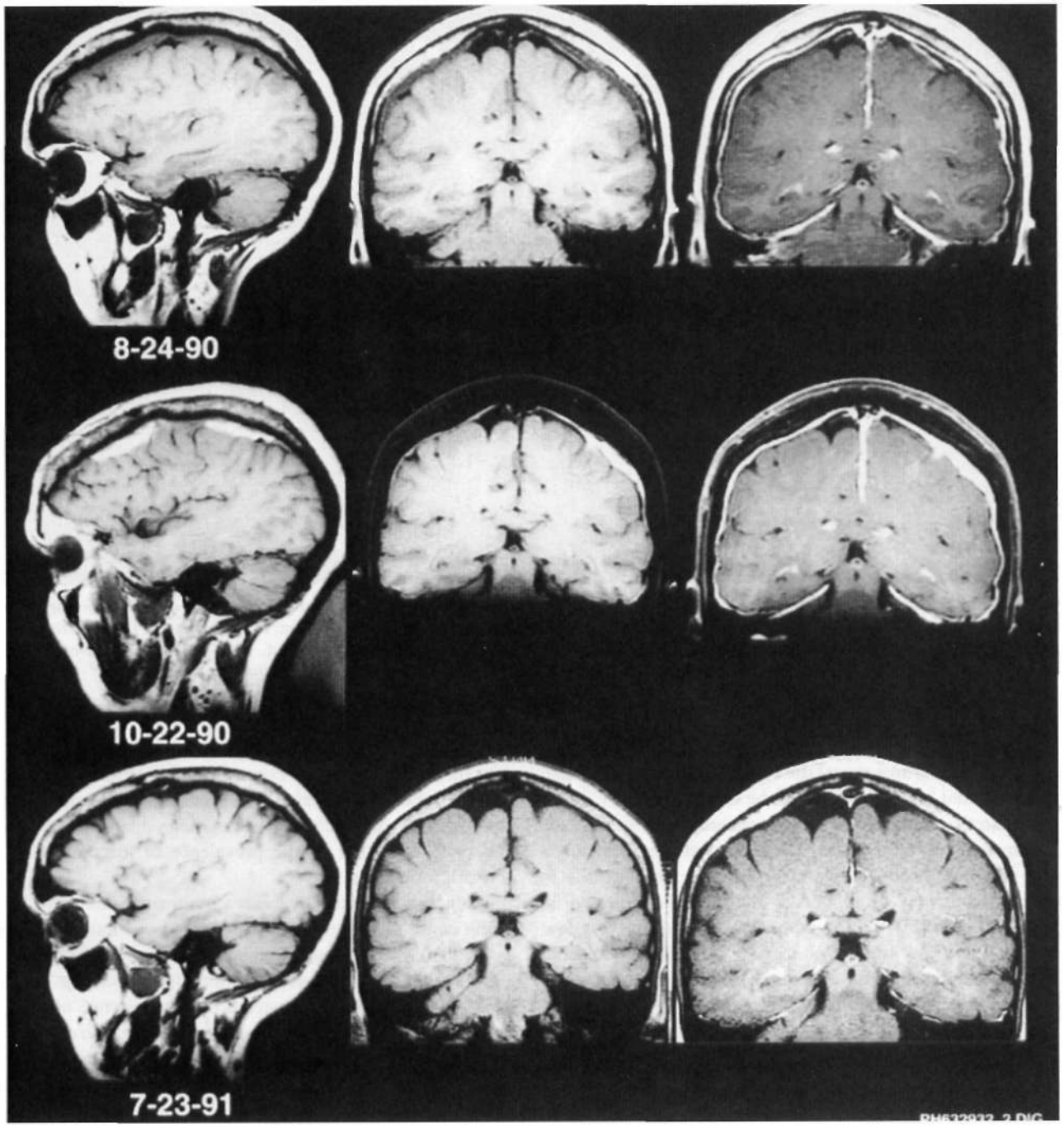

FIGURE 75.2 Sagittal and coronal Tl-weighted magnetic resonance images with gadolinium of a patient with spontaneous low cerebrospinal fluid (CSF)-p res sure headaches demonstrate subdural fluid collections and p achy meningeal enhancement *{top row)* with loculation and progression of subdural fluid collections *(middle row). Bottom row* demonstrates resolution of the fluid collections and meningeal enhancement after correction of the CSF leak and headache resolution. (Reprinted with permission from Mokri, B., Piepgras, D. G., & Miller, G. M. 1997, "Syndrome of orthostatic headaches and diffuse pachymeningeal gadolinium enhancement," *Mayo Clin Proc,* vol. 72, pp. 400-413.)

tinist be considered in the differential diagnosis, especially in patients with a compromised immune system. The diagnosis can be confirmed only by examination of the CSF. The chronic granulomatous meningitis of sarcoid may require biopsy of the basal meninges to confirm the diagnosis. Meningitis is discussed further in Chapter *59.*

Sinusitis, mastoiditis, epidural or intraparcnchymal abscess formation, and osteomyelitis of the skull can all cause focal and generalized headache. The diagnosis is usually suspected from the associated symptoms and signs. After craniotomy, increasing pain and swelling in the operative site may be due to osteomyelitis of the bone flap. Plain

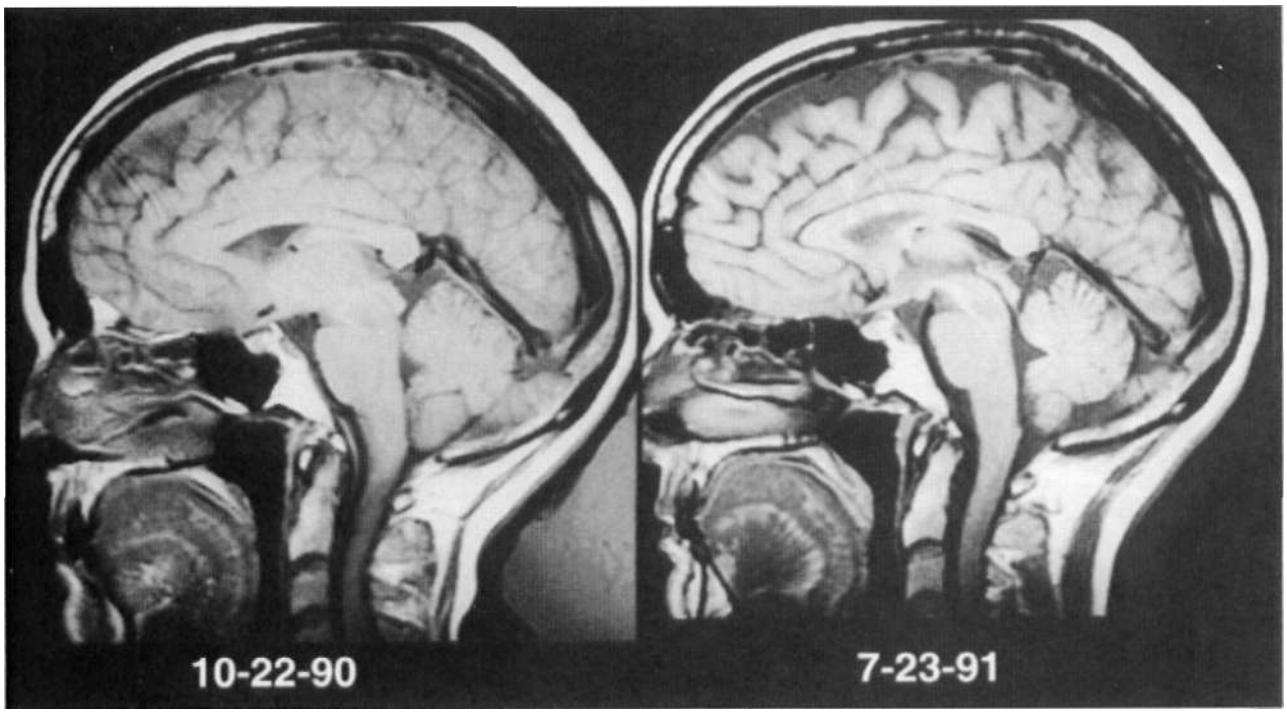

FIGURE 75.3 Sagittal Tl-weighted magnetic resonance images (MRIs) demonstrate cerebellar tonsillar descent and crowding of the posterior fossa in a patient witli spontaneous low-pressure headaches. After symptomatic resolution, the MR] scan of the posterior fossa returns to normal. (Reprinted with permission from Mokri, B., Piepgras, D. G., & Miller, G. M. 1997, "Syndrome of orrhosniric headaches and diffuse pachymeningeal gadolinium enhancement," *Mayo Clin Proc,* vol. 72, pp. 400-413.)

skull roentgenograms reveal the typical mottled appearance of the infected bone. Removal of the flap is necessary.

Mollaret's meningitis is tate, recurrent, and sterile (see Chapters 59B and 79). The CSF cellular response includes large epithelioid cells i Molhret's *a* lis). The pathogenesis is unknown but may be related to the herpes simplex virus (Jensenius et al. 1998). The condition may recur every few days or every few weeks for months or years. Headache, signs of meningism, and low-grade fever accompany each attack. Treatment is mainly symptomatic.

Headache Attributed to Cranial or Cervical Vascular Disorders

Aneurysms and Arteriovenous Malformations and Thunderclap Headache

Intracranial aneurysms are rarely responsible for headache unless the) rupture. K apid enlargement <i .11: aneurysm may produce local pain by pressure on a cranial nerve, especially the oculomotor nerve, or on other pain-sensitive structures. This is most common with aneurysms of the internal carotid and posterior communicating arteries. Enlargement of an aneurysm may occur shortly before rupture, and the local pain is therefore an important clinical sign. Cerebral aneurysms are not a cause of recurrent migraine-like headaches, even when the headache attacks are confined to one side. The prevalence of migraine in patients with subarachnoid hemorrhage due to a ruptured aneurysm is similar to the prevalence of migraine in the general population.

Parenchymal arteriovenous malformations (AVMs) rarely cause pain before rupture. Very large lesions can be associated with ipsilateral or bilateral throbbing cephalalgia, but they rarely cause a migraine-like syndrome. Large AVMs can usually be suspected by the presence of a cranial bruit or of the classic triad of migraine, seizures, and focal neurological deficits. The prevalence of headache in patients harboring AVMs is probably no higher than that in the general population.

The myth has developed that headaches of a migrainous type, if consistently on one side of the head, could be due to an aneurysm or an AVM. In the past, this belief led to many unnecessary arteriograms. The worry expressed by patients and physicians that a recurrent headache might be due to an aneurysm or AVM is now usually easily resolved by obtaining a cranial MRl scan or m.igneric resonance angiogram (MRA). Any aneurysm or AVM responsible tor a recurrent or persistent headache has a very high probability of being seen. Roth aneurysms and AVMs can bleed in a way that produces a less than catastrophic subarachnoid hemorrhage. These small warning leaks can result in one or more sentinel

headaches. 1'acli may be relatively mild Mid short-lived. They usually have a sudden, but not very dramatic, onset. Identification of the sentinel headache is important but is vety difficult.

Patients who do not usually have headaches should be examined whenever they report new onset of headaches or even a single episode if it was described as "the worst **headache** I've ever had" or if it was associated with neck stiffness or pain, transient neurological symptoms (e.g., extraocular nerve palsy), or fever. Patients in whom there is any suspicion of a sentinel bleeding episode or who describe a recent thunderclap headache should be examined with CT scanning to detect blood in the subarachnoid cisterns. If the scan is normal, the continuing suspicion of a warning bleeding episode should lead to an examination of the CSF. If the CSF is blood-stained or xanthochromic or if, despite the absence of positive findings on the lumbar puncture, there is still a suspicion of a sentinel hemorrhage, an MR A or cerebral angiogram may be advisable.

The term *thunderclap headache* describes a severe headache of instantaneous onset (within seconds)—abrupt and without warning like a "clap of thunder." A patient with a sudden, severe headache must be evaluated on an emergency basis for evidence of a subarachnoid hemorrhage as outlined above. Other conditions can present with thunderclap headache including cerebral venous sinus thrombosis, cervicocephalic arterial dissection, pituitary apoplexy, acute hypertensive crisis, and spontaneous intracranial hypotension (Dodick 2002). These entities are associated with significant neurological morbidity and may not be easily seen on the initial CT image, thus undctscoring the need for MRI in this group if results of the initial workup are negative,

The question as to whether an *unruptured* cerebral aneurysm can cause a thunderclap headache has been debated. The weight of evidence, based on several prospective studies of patients with normal neurological, CT, and CSF examinations, indicates that a symptomatic intracranial aneurysm will be rarely found in such patients. The issue of which patients need additional investigations in this setting depends on the clinical suspicion of an underlying disorder (Dodick 2002).

Several follow-up studies of patients with thunderclap headache and negative evaluations for subarachnoid hemorrhage and other underlying disorders have elucidated the often benign natural history of this peculiar headache disorder. Slivka and Philbrook (1995) reported four patients with thunderclap headache without subarachnoid hemorrhage, in three of whom angiography revealed diffuse segmental iir.iaccivlual .irieri.i! vasoconstriction. Resolution of the vasospasm was seen in the one patient in whom angiography was repeated. V/c have seen two similar patients, and through this collective experience, a characteristic profile has begun to emerge (Table 75.2).

Subarachnoid Hemorrhage

Rupture of an intracranial aneurysm or AVM results in a subarachnoid hemorrhage, with or without extension into the parenchyma of the brain. **The** headache of a subarachnoid hemorrhage is characteristically explosive in onset and of overwhelming intensity. Subjects who survive may relate that they thought they had been hit on the head. The headache rapidly generalizes and may quickly be accompanied by neck and back pain. Loss of consciousness may rapidly supervene, but many patients remain alert enough to complain of the excruciating headache. The patient is often vomiting, which aggtavates the head pain. Intraventricular blood, the distortion of the midline structures, and the heavy contamination of the basal cisterns by blood can each contribute to the rapid development of hydrocephalus, which worsens the headache.

Tabic 75.2: Diagnostic criteria for thunderclap headache

Idiopathic thunderclap headache
Very severe pain intensity
Hyperacute onset of pain (<30 sec)
Headache lasts 1 hour to 10 days (may last up to 4 wk)*
Headaches may recur over a 7-day period but do not recur regularly over subsequent weeks or month (may recur over subsequent months to years)*
Thunderclap headache associated with a normal cerebral vasculature or reversible segmental vasoconstriction
May be clinically iiulisiinguishahie from thunderclap head ache associated with intracranial disorder*
May occur spontaneously or be precipitated by Valsalva's maneuver, sexual activity, exercise, or exertion
Thunderclap headache with neurological signs or symptoms
Headache and angiographic features as described above
Neurological signs or symptoms transient or result in minimal residual deficits
Thunderclap headache associated with intracranial disorder
Associated conditions include subarachnoid hemorrhage (cerebral venous sinus thrombosis, pituitary apoplexy)*
May have associated neurological or systemic signs or symptoms, depending on underlying disorder

'"Modifications to diagnostic criteria.

Source; Adapted with permission from Dodick, D. w\. Brown, R. D., Britton, J. \V., & Huston, J, 1999, "Nonaneurysmal thunderclap headache with diffuse, multifocal, segmental, and reversible vasospasm," *Cephalalgia,* vol. 19, pp. 118-123.

The diagnosis is easily suspected and can he confirmed by an unenhanced CT scan that reveals blood in the subarachnoid cisterns or within the parenchyma. Early hydrocephalus may also be seen. When a CT scan unequivocally shows blood in the subarachnoid spaces, it is not necessary or advisable to perform a lumbar puncture because the resultant reduction of CSF pressure may cause herniation of the brain or may remotely induce-further bleeding from the aneurysm. Demonstration of subarachnoid hemorrhage generally indicates the need for cerebral angiography. The timing of this procedure and the subsequent mode of treatment are detailed in Chapter 57C.

Relief of the intense headache of subarachnoid hemorrhage generally requires parenteral administration of analgesics. The need to provide pain relief must be balanced against the need to interfere as little as possible with the level of consciousness, respiration, and physical signs, such as pupil size and reaction. Parenteral codeine is often used, but meperidine is also useful. Sedation with phenobarbital may also be required if the patient is restless because of pain. The headache that occurs after a subarachnoid hemorrhage may be persistent, lasting up to 7-10 days. Rarely, a chronic daily headache may persist for months to years.

The headache of subarachnoid hemorrhage is aggravated by movement and is associated with photophobia and phonophobia. Therefore, it is customary to nurse patients in a dark, quiet room and to disturb them as little as possible. Straining at stool, vomiting, and coughing should be minimized.

The hemorrhage and the headache that can result from a ruptured AVM have qualities and behavior that are essentially identical to those from a ruptured berry aneurysm of the circle of Willis.

Parenchymal Hemorrhage

Until the advent of CT scanning, it was widely believed that a stroke due to a cerebral hemorrhage was associated with severe headache and that an ischemic stroke was generally-painless. However, modern imaging techniques have shown that cerebral infarction is often painful and that cerebral hemorrhaae car v p..'" ;'ss. I best- caveats notwithstanding, a hemorrhage into the cerebral or cerebellar tissue is a potent source of headache of rapid onset and of increasing severity. The intra parenchymal mass causes a traction headache by deforming and shifting the pain-sensitive vascular and meningeal and neural structures. As the hematoma enlarges, it may obstruct the CSF circulation and lead to increases in intracranial pressure. Initially, the pain of a cerebral hemorrhage is often ipsilateral, but it may generalize if hydrocephalus and raised intracranial pressure occur. Rupture of the hematoma into the subarachnoid space or leakage of the blood into the basal cisterns through the CSF pathways causes the headache to intensify and be associated with neck stiffness and other signs of meningeal irritation,

Cerebral and cerebellar hemorrhage can be due to hypertension of any cause; to a bleeding diathesis, including the medical administration of anticoagulants; to an arteritis and amyloid angiopathy; or to an aneurysm or AVM, as discussed earlier (see Chapter 57B), Cerebral infarcts, primary and secondary brain tumors, and areas of cerebritis, such as those that occur in herpes simplex encephalitis, can each be complicated by hemorrhage into the lesion. Headache may signal the presence of the lesion or a worsening of the clinical condition. Almost without exception, the headache of intraparenchymal hemorrhage is ol acute o: subacute ousel and does nol indicate the exacl nature of the underlying disease. Headache associated with focal or generalized cerebral or cerebellar signs demands examination with an unenhanced CT scan.

Cerebellar hemorrhages, which account for about 10% of occurrences of intraparenchymal bleeding, can result in a catastrophic clinical picture. An enlarging hematoma in the cerebellum rapidly compresses vital brainstem structures and obstructs the outflow of CSF from the ventricular system. This leads to occipital headache, which is rapidly followed by vomiting; impaired consciousness; and various combinations of brainstem, cerebellar, and cranial nerve dysfunction. Cerebellar hemorrhage is a neurological and neurosurgical emergency. A CT scan should be obtained as soon as possible. Fvacuation of the hematoma with or without ventricular drainage may be the only chance to save the patient's life.

Treatment options for intracerebral hematomas are discussed in detail in Chapter 57B.

Cerebral Ischemia

Cerebral infarction, whether embolic or thrombotic, may cause head pain (Arboix er al. 1994). The location of the pain is a poor predictor of the vascular territory involved. Some studies indicate that cortical infarction is more likely to be associated with headache than deep cerebral hemisphere infarctions. It may be either steady or throbbing and is not as explosive or as severe as the headache of subarachnoid hemorrhage. The infarct responsible for the pain may be of a moderate size or very extensive. Even small ischemic events that resolve in 24 hours, by definition transient ischemic attacks (TIAs), may be associated with transient head pain in up to 40% of patients; however, the headaches arc rarely prominent. Some reports indicate that carotid distribution ischemia most commonly leads to frontotemporal head pain, whereas vertebrobasilar ischemia tends to lead to occipital headache.

The development of a new or different headache may be noted in about 10% of patients in the weeks and months before onset of ischemic stroke.

If a large cerebral or cerebellar infarct produces a significant mass effect as a result of edema, headache may

worsen. Obstruction of the ventricular system results in increasing hydrocephalus and further aggravation of the pain. The pain may be pulsatile and may be worsened by straining or by the head-low position. As the infarct decreases in size and the phase of hyperemia subsides, headache generally eases. Evolution of a bland infarct into a hemorrhagic infarct may be associated with worsening of headache.

Hashing lights, field defects, and other visual disturbances may represent symptoms ot cerebrovascular disease. Similarly, migraine with aura can produce many different visual symptoms before the headache develops. Hence it is not always possible to differentiate the visual disturbances of migraine from those of more serious cerebrovascular disease. The visual aura of migraine is usually an initially irritative phenomenon producing scintillating, often zigzag, visual hallucinations that can be seen with the eyes open or closed. This is described is .1 posit LM- so num.1. bavin.! tin-effect of spontaneously producing the sensation of light or color. Visual disturbances due to serious visual pathway ischemia or retinal ischemia usually results in vision loss or a negative scotoma, which cannot be recognized 111 the dark or with the eyes closed. Like many rules in medicine, this one is not absolute. An embolus to a retinal artery can result in showers of bright flashes, and calcarine ischemia can occasionally produce scintillating scotoma that resemble those of migraine. The migrainous aura tends to inarch across the visual field over the course of a few minutes and is generally followed by the headache after a latent interval, The headache of cerebrovascular insufficiency or occlusion has a more variable relationship to the visual disturbances.

Carotid and Vertebral Artery Occlusion and Dissection

Occlusion of the cervical portion of the carotid artery can result in headache in several ways. A consequent cerebral infarct may increase the intracranial pressure. Ipsilatcral headache may be due to vasodilatation of collateral vessels in and around the orbit. Headache due to carotid occlusion may be associated with a pattial ipsilatcral Horner's syndrome. The sympathetic hypofunction may be due to interference with the sympathetic fibers around the internal carotid artery as they ascend from the superior cervical ganglion to the intracranial structures. The combination of headache, ipsilatcral Horner's syndrome, and contralateral hcmiparesis is generally due to carotid occlusion.

Cervicocephalic arterial dissections result from penetration of the circulating blood through an intimal tear into the wall of an artery, usually penetrating the media, A variety of results may occur with dissection, including formation of an intramural hematoma that pushes the lumen to one side, resulting in an elongated narrowing of die vessel lumen. Other results arc compression of the lumen to cause an occlusion of the vessel; dissection of the intramural hematoma distally into the true lumen, with creation of two parallel channels; and expansion of the intramural hematoma toward the adventitia, resulting in an aneurysmal dilatation. The condition can result from intrinsic factors that predispose the aneurysm to dissection, including fibromuscular dysplasia, cystic medial necrosis, and association with Marfan's syndrome and Ehlers-Danlos syndrome. Extrinsic factors, such as trivial trauma, may play a pathogenic role when superimposed on structurally abnormal arteries. Severe head and neck trauma may occasionally be the proximate cause of dissection.

In most patients, the initial manifestation of internal carotid dissection is pain {headache, facial pain, or neck pain), which is typically ipsilatcral to the dissection; in a minority of patients, the pain may have a bilateral distribution. Cerebral or retinal ischemic symptoms are the initial manifestations in a lower percentage of patients. 1 lie , iMil 11:;HI el 1-real syndromes with which patients who have carotid dissection present include (I) hemicranial pain plus an ipsilatcral oculosymparbctic palsy, (2) hemicranial pain and delayed focal cerebral ischemic symptoms, or (3) lower cranial nerve palsies, usually with ipsilatcral headache or facial pain.

The most common symptom of vertebral dissection is headache and neck pain. The syndrome seen most often consists of headache, with or without neck pain, followed after a delay by focal CNS ischemic symptoms.

MRI or MRA usually confirms the diagnosis. At the level of involvement, the lumen of the artery appears as a dark circle of flow void of smaller caliber than the original vessel, and the intracranial clot appears as a hyperiutensc and bright crescent or circle (in both T1- and T2-weightcd images) surtounding the flow void (Figure 75.4). Catheter angiography may often be avoided (Mokri 2002).

I he pain .ISM:, ared with ccrvieoccphalk di.ssreiions is ol variable duration and may require treatment with potent analgesics. Patients are usually treated with either anti-platelet agents or, if evidence of distal embolization has occurred, anticoagulation.

Giant Cell Arteritis

tiiant cell arteritis is a vasculitis of elderly persons that has gone by many other names, including temporal arteritis, cranial arteritis, granulomatous arteritis, polymyalgia artcritica, and Horton's syndrome. It is one of the most ominous causes of headache in elderly persons. When unrecognized and untreated, it often leads to permanent blindness. The single most common reason patients with giant cell arteritis are seen by neurologists is headache of an unknown cause. *•

Clinical Symptoms. The clinical manifestations of giant cell arteritis result from inflammation of medium and large arteries. Table 75.3 summarizes clinical symptoms in 166 patients examined at the Mayo Clinic between

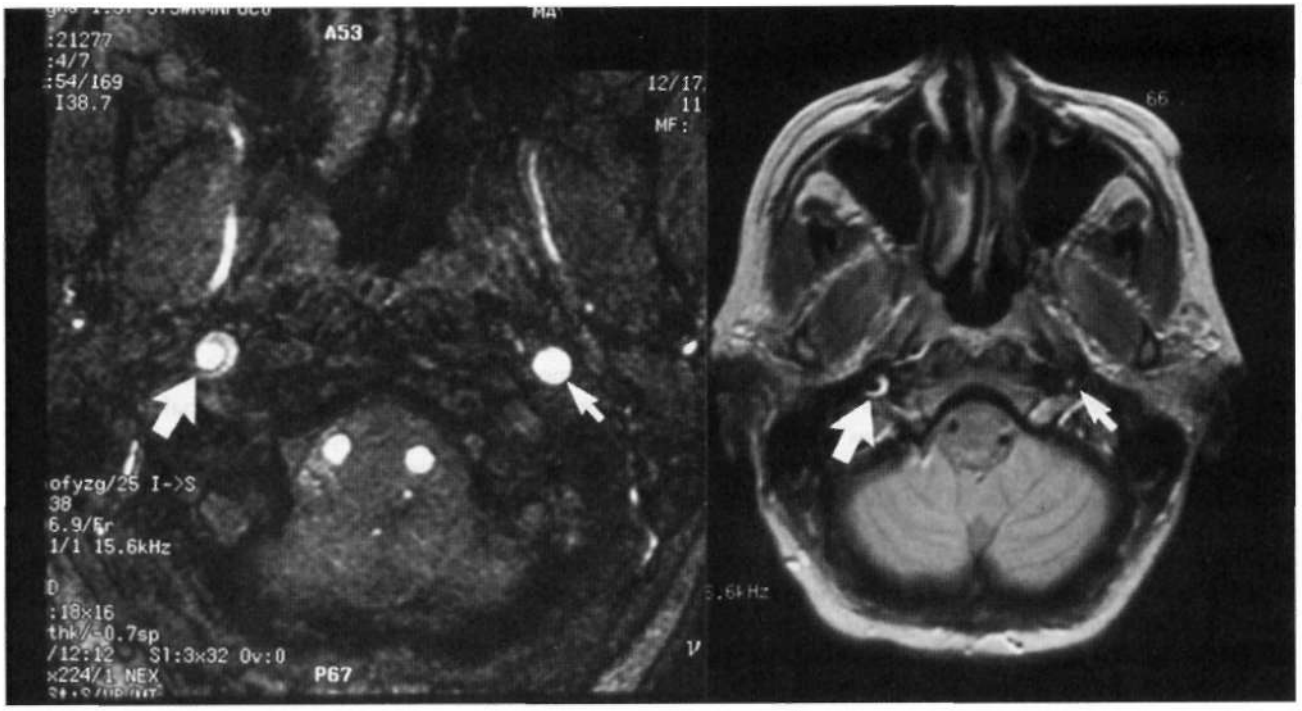

FIGURE 75,4 Magnetic resonance images of a patient with right internal carotid artery dissection. The *large arrow* in each figure points to the right internal carotid artery, which lias ,i smaller flow void than that of the left internal carotid artery *(small arrows),* reflecting the narrowed lumen of the vessel. The region of the flow void is surrounded by a hypcrintense crescent representing the intramural hematoma.

1981 and 1983. Headache was the most common symptom, experienced by 72% of patients at some time, and was the initial symptom in 33%. The headache is most often throbbing, and many patients report scalp tenderness on combing their hair. Headache, although often generalized, is associated with striking focal tenderness of the affected superficial temporal or, less often, occipital artery. One third of patients with headache may have no objective sign of superficial temporal artery inflammation.

More than one half of patients with giant cell arteritis experience polymyalgia rheumatica, and it is the initial symptom in one fourth of patients. Polymyalgia rheumatica consists of aching in proximal and axial joints, proximal myalgias, and often significant morning stiffness. Fatigue, malaise, and a general loss of energy occur in 56% of patients and are the initial symptoms in 20%.

Jaw claudication occurs commonly and is the initial symptom in 4% of patients. Tongue claudication occurs rarely. A nonproductive cough or a sore throat can be present.

One of the most ominous symptoms to occur in giant cell arteritis is amaurosis fugax because if it is untreated, 50% of affected patients subsequently become partially or totally blind. Ten percent of the patients in the Mayo Clinic series experienced amaurosis fugax, which was bilateral in 35%. Blindness occurred in 8% and was monocular in 86% but was preceded by amaurosis fugax in only 14%. In patients with untreated giant cell arteritis, the incidence of permanent vision loss is approximately 40%. Diplopia can occur and may be horizontal or vertical.

Fourteen percent of patients have a neuropathy, which is a peripheral polyneuropathy in 48%, multiple mononcuropathies in 39%, and isolated mononeuropathy in 13%. Limb claudication occurs in 8% of patients and usually involves the upper limbs. TIAs and strokes occur in 7% of patients, and the ratio of carotid to vertebral events is 2 to 1. Vertigo and unilateral hearing loss can occur. An acute myelopathy, acute confusional state, and subacute stepwise cognitive deterioration are rare manifestations.

Physical Findings. Signs on physical examination relate to involvement of various arteries and the end-organ damage-sustained from vasculitis-induced tissue infarction,

Forty-nine percent of patients with histologically verified giant cell arteritis have physical signs of superficial temporal artery inflammation, including erythema, pain on palpation, nodularity, thickening, or reduced pulsation on the affected side. Eighteen percent of patients with signs of superficial temporal artery inflammation do not complain of headache. Although it is rare, ischemic necrosis of the scalp and tongue can occur.

Almost one third of patients have large artery bruits or diminished pulses. The carotid artery is the vessel affected most often. The upper limb arteries are more commonly affected than are those in the lower limbs, and some

Table 75.3: Symptoms of giant cell arteritis in 166 patients*

Symptom	*Patients with symptom (%)*	*Patients in whom it was in it itil symptom (%)*
Headache	72	33
Polymyalgia rhcumatica	58	25
Malaise, fatigue	56	20
Jaw claudication	40	4
Fever	35	11
Cough	17	8
Neuropathy	14	0
Sore throat, dysphagia	11	2
Amaurosis fugax	10	2
Permanent vision loss	3	3
Claudication of limbs	8	0
Transient ischemic attack/stroke	7	0
Neuro-otological disorder	7	0
Scintillating scotoma	5	0
Tongue claudication	4	0
Depression	3	0.6
Diplopia	2	0
Tongue numbness	2	0
Myelopathy	0.6	0

*Some patients had coincident onset of more than one symptom.
Source: Data From Casclli, R. J., Hunder, C G. & Whisnant, J. P. 1998, "Neurologic disease in biopsy-proven giant cell (temporal) arteritis," *Neurology,* vol. 38, pp. 352-359.

patients have vasculitic involvement of the aorta or its major branches. Coronary arteritis with consequent myocardial infarction may also occur.

Ocular findings in giant cell arteritis may be striking. During amaurosis fugax, there is visible sludging of blood in the retinal arterioles. With infarction of the optic nerve, vision loss precedes the funduscoptc signs of an anterior ischemic optic neuritis by up to 36 hours. During the acute stage there is papilledema. The disc is pale, and the resulting visual field defect, when subtotal, tends to be altitudinal. Papilledema is followed by the gradual development of optic atrophy.

Extraocular muscle palsies show daily fluctuations in the severity of specific extraocular muscle involvement. Ocuiosympathetic paresis (partial Horner's syndrome) may occasionally occur.

Laboratory Studies. The laboratory abnormality most often recognized in giant cell arteritis is elevation of the erythrocyte sedimentation rate (ESR) (mean, 85 ± 32 mm in 1 hi nit with llu[1] Wcstergren mcthodi, alliouj'.h :l in.v. be normal *(<29* mm in I hour) in 3% of patients, C-reactivc protein levels may be more sensitive than the ESR in some patients and may be used to follow disease activity. Patients are usually anemic (mean hemoglobin **value, 11.7** ± 1.6 g/dL) and show a mild thrombocytosis (mean platelet count, 427 it 116 x IO'VUL). Mild elevation of plasma a_2-globulins, serum aspartate aminotransferase, and alkaline phosphatase concentrations may be present. All these findings are nonspecific, and the diagnosis rests on confirmatory temporal artery biopsy.

An angiogram of the cerebral circulation may fortuitously demonstrate a vasculitis of the superficial temporal, vertebral, or carotid artery, although it is too insensitive to be teliable. The temporal artery shows alternating stenosis and dilatation over several-centimeter segments, often more pronounced distally. An angiogram of the aortic arch vessels may show long segments of smoothly tapered stenosis and occlusions of subclavian, brachial, and axillary arteries,

Physiology. The symptoms and signs of giant cell arteritis result from systemic and local inflammatory processes leading to artetial stenosis and occlusion. End organs, such as the optic nerve, extraocular muscles, spinal cord, peripheral nerves, and brain, may be rendered transiently ischemic or infarcted. In amaurosis fugax, ischemia of the optic nerve and retina results from sludging of blood within the arterioles due to vasculitic involvement of the ophthalmic, posterior ciliary, and (less often) central retinal arteries.

Pathology. The histopathological features of the diagnostic arterial lesion include intimal proliferation with consequent luminal stenosis, disruption of the internal clastic membrane by a mononuclear cell infiltrate, invasion and necrosis of the media progressing to panartcritic involvement by mononuclear cells, giant cell fotmation with granulomata within the mononuclear cell infiltrate, and, variably, intravascular thrombosis (Figure 75.5). Involvement of an affected artery is patchy (skip lesions). Long segments of the notmal unaffected artery are flanked by vasculitic foci. Treatment with oral corticosteroids may change the histopathological findings within days, and a previously vasculitic focus may appear normal or show only intimal fibrosis. For these teasons, biopsy specimens of the superficial temporal artery should be generous (4- to 6-cm-long specimens), multiple histological sections should be taken, and the biopsy may be bilateral if necessary. If the first two conditions are satisfied, 86% of occurrences of giant cell arteritis arc correctly diagnosed by biopsy.

The term *temporal arteritis* can lead to a false sense of security that giant cell arteritis is largely a focal vasculitis affecting the relatively inconsequential superficial tempotal artery. Up to one thitd of patients, however, have clinically significant large artery disease. The most common causes of vasculitis-rclated death are cerebral and myocardial infarction. Rupture of the aorta occurs rarely. In fatal occurrences, vertebral, ophthalmic, and posterior ciliary arteries are involved as often and as severely as the superficial temporal arteries. Peripheral neuropathic syndromes occur, and in patients with acute mono neuropathies, ischemic infarction of peripheral nerves

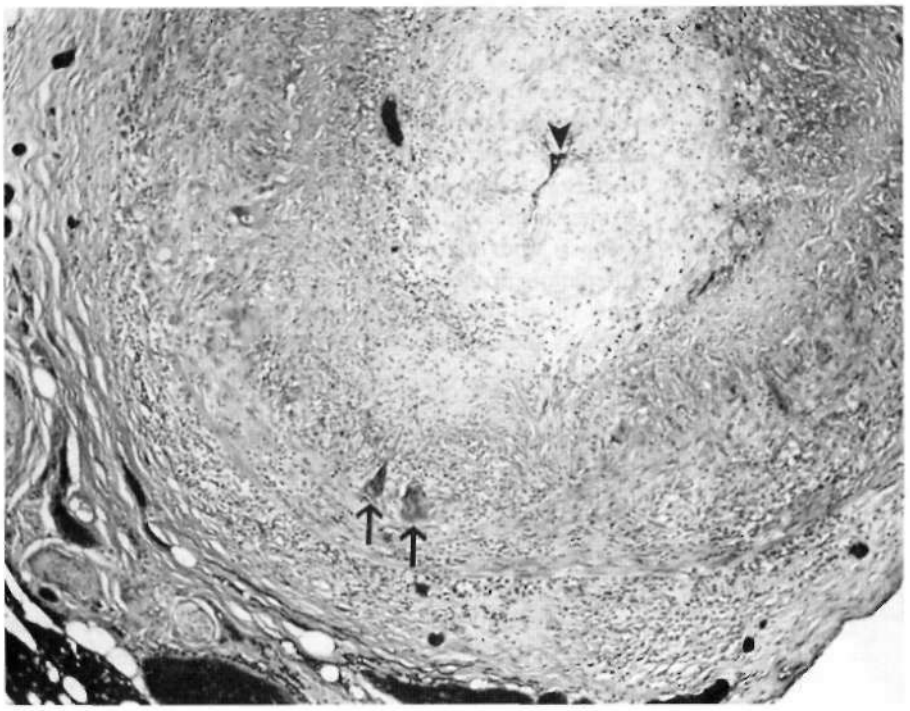

FIGURE 75.5 Transverse section of temporal artery showing narrowed lumen *{arrowhead)* and giant celb *{double arrows)* in relation to the elastic lamina (hematoxylin-cosin stain, xlOO). (Micrograph courtesy of R. jean Campbell, M.B.Ch.B.)

due to vasculitis has been demonstrated. Intracranial vascular involvement has been reported rarely.

Immunology, Etiology, and Pathogenesis. Giant cell arteritis is considered an autoimmune disease of unknown cause. Although it is often a systemic vasculitis, giant cell arteritis usually occurs much more focally than polyarteritis nodosa and is characterized by a mononuclear cell infiltrate with giant cell formation, suggesting differences in immunopathogencsis. No distinctive antigen has been identified to explain the particular tropism of giant cell arteritis, although the possibility that the immune reaction is directed against the internal elastic lamina, which is absent from cerebral vessels shortly after they pierce the dura, presumably explains the paucity of intracranial involvement. Lymphocytes sensitized to the purported antigen infiltrate the internal clastic lamina and release a host of lymphokines, which attract a mononuclear cell infiltrate. Activated macrophages release lysosomal proteases and may transform into epithelioid and multinucleate giant cells. T cells themselves, by antibody-dependent cell-mediated cytotoxicity or natural killer cell actions, may also be involved. Additionally, antibody and complement deposits have been demonstrated at the internal elastic lamina, which suggests that humoral mechanisms are involved.

Epidemiology. In a population-based study of Olmsted County, MN, the incidence of giant cell arteritis was found to increase over a 25-year period from 5,1 to 17.4 cases per 100,000 population per year in people aged 50 or older. This increase was attributed to greater clinical awareness and increased diagnosis. The prevalence was 133 cases per 100,000 population in people aged 50 or older on January 1, 1975. The femalc-to-male ratio was 3.7 to 1. The median age at onset was 75 years (range, 56-92 years).

Course and Prognosis. The clinical onset of giant cell arteritis may be acute (as in patients presenting with sudden transient or permanent vision loss), subacute, or chronic. The median duration of symptoms before diagnosis is I 1lu 'ii(l), Inil exceptional patients nay presenl with a history of up to several years of polymyalgia rheumatica.

On institution of corticosteroid treatment, reversible sympionis and the HSR normalize within days. With tapering doses, relapses may occur and may consist of prior symptoms or new symptoms. Neurological complications, including neuropathies and cerebrovascular events, are not always prevented by corticosteroid administration and have a median onset of 1 month after initiation of treatment. Similarly, large artery involvement can occur up to 7 months after initiation of treatment.

The occurrence of amaurosis fugax often brings a patient with undiagnosed giant cell arteritis to medical attention, but permanent loss of vision after initiation of treatment has been documented in rate instances. In patients with acute and incomplete loss of vision, some visual function may return with the immediate institution of corticosteroid therapy, but this is exceptional.

Treatment and Management. Once the diagnosis is suspected, histological confirmation should be obtained

and treatment started immediately. Treatment should not be withheld pending the result of temporal artery biopsy. Treatment consists of oral corticosteroids given initially in high doses and gradually tapered over months. Prednisone may be initiated at 40-60 mg per day and continued for 1 month, after which time a cautious taper of less than 10% of the daily dose per week may be started, If, at the time of presentation, ischemic complications are imminent or evolving, parenteral high-dose corticosteroids should be given until these complications stabilize. The adjunctive use of anticoagulants for patients with ischemia may be tried, hut their efficacy in this setting is unproved.

Disease activity must be monitored with both clinical assessment and determination of the ESR. A flare of symptoms accompanied by an increase in the ESR mandates increasing the corticosteroid dose at least to the last effective higher dose and, often, boosting it temporarily to a higher level. Relapses generally reflect too rapid a taper, and resumption of a more slowly tapering regimen is indicated after the relapse has stabilized. Some patients may require continuation of low-dose (7.5-10.0 mg per day) ptednisone for several years, although complete withdrawal remains the goal. There is evidence that treatment with methotrexate 10 mg per week may be an effective adjunctive treatment that allows for more rapid tapering of the prednisone dose (Jover et al. 2001).

Finally, the multitude of well-known adverse effects of exogenous corticosteroids necessarily influences management by prompting a more rapid taper and treatment of the side effects themselves. Three particularly alarming treatment complications are symptomatic vertebral body compression fractures (26% of patients), corticosteroid myopathy (11%), and corticostetoid-induced confusional state (3%). All may limit tteatment by necessitating a more aggressive taper thereby exposing the patient to the risks that accompany a relapse of the vasculitis.

Headache Caused by Disorder of the Cranium, Neck, Eyes, Ears, Nose, Sinuses, Teeth, Mouth, or Other Facial or Cranial Structures

Ocular Causes of Headache

In the absence of injection of the conjunctiva or other obvious signs of eye disease, headache and eye pain rarely have an ophthalmic cause. The maxim is that a white eye is not the cause of a monosymptomatie painful eye. Acute angle-closure glaucoma is a rare but often dramatic event, The patient may present with extreme eye and frontal head pain with associated vomiting and may be in the early stage of shock. The sclera is injected, the cornea is cloudy, the pupil is fixed in midposition, and the globe is stony hard. It is a true ophthalmological emergency.

Refractive errors, imbalance of external eye muscles, amblyopia, and (in the terminology used by many patients) eyestrain are not causes of headache in most instances. In children and teenagers, however, refractive errors, especially hyperopia, can produce dull frontal and orbital headaches from straining to achieve accommodation at school. Myopic children are unaffected.

Soon after initiation of miotic preparations such as pilocarpine, some patients with glaucoma complain of eye and frontal discomfort due to ciliary muscle spasm. This subsides with continued use of the drops.

Cluster headaches, migraine, dissection of the carotid artery, and many other varieties of headache cause orbital and retro-orbital pain. Each is discussed elsewhere in this chapter. Of particular interest is SUNCT (short-lasting, unilateral, neuralgiform, headache attacks with conjunctival injection, tearing, rhinorrhca, and forehead sweating) syndrome because of its specific localization to the orbit and associated conjunctival injection and marked tearing. Sharp jabs of pain through the eye lasting 1 second or longer can occur as part of an idiopathic stabbing headache that is considered to be responsive to indomethacin. This condition is of unknown pathogenesis but is most commonly seen in migraineurs. The sharp eye pain, known by various names, including *ophthalmodynia periodica* (or needlc-in-the-eye syndrome), is occasionally felt in the ipsilatcral occipital region simultaneously.

Nasal Causes of Headache and Facial Pain

Acute purulent rhinosinusitis causes local and referred pain. The distribution of the pain depends on the sinuses involved. Maxillary sinusitis causes pain and tenderness over the cheek. Frontal sinus disease produces frontal pain; sphenoid and ethmoidal sinusitis causes pain behind and between the eyes, and the pain may also be referred to the vertex. Acute rhinosinusitis is commonly associated with fever, putulent nasal discharge, and other constitutional symptoms. The pain is worse when the patient bends forward and is often relieved as soon as the infected material drains from the sinus. Currently, there is insufficient evidence to suggest that chrome rhinosinusitis is a cause for headache or facial pain unless associated with a relapse into an acute phase. Ftontal sinusitis that spreads through the posterior wall of the sinus to produce an epidural abscess is a serious cause of local head pain. If neglected, the abscess may pass through the meningeal layers to produce meningitis or a brain abscess. Similarly, an acute infection involving the sphenoid sinus can be particularly dangerous because of its close proximity to the cavernous sinus.

The occurrence of so-called "sinus headaches" without an underlying infection remains unsubstantiated. Commonly migraine headaches are erroneously diagnosed as sinus headaches either because they are associated with cranial autonomic symptoms, have prominent

facial involvement, ot are triggered (i.e., a change in altitude/weather, an exposure to pollens, or a seasonal predilection).

Rarely patients may suffer from mucus.il contact point headaches in which pain is localized to the periorbital, medial canthal, or temporozygomatic regions. Nasal endoscopy or CT imaging must reveal evidence of mucosal contact points to support this diagnosis.

Malignant tumors of the sinuses and nasopharynx can produce deep-seated facial and head pain befote involving ctanial nerves or otherwise becoming obvious. MKI scanning is the optimal technique for the detection of these cryptic lesions. Osteomyelitis, multiple myeloma, and Paget's disease in particular must be considered when bony invasion is present on a scan.

Temporomandibular Joint Disorders

In 1934, Costen first drew attention to the temporomandibular joint {TMJ) as a cause of facial and head pain. Until recently, Costen's syndrome was rarely diagnosed. During the past two decades, however, interest in disorders of the TMJ, the muscles of mastication, and the bite as they relate to headaches has been incteasing. Articles in the popular press and diagnoses by dentists have led many patients to believe that TMJ disorders are the most common cause of headache. Mechanical disorders of the joint, alterations in the way the upper and lower teeth relate, and congenital and acquired deformities of the jaw and mandible can all produce head and facial pain and are very occasionally responsible for the episodic and chronic pain syndromes seen by neurologists.

For the neurologist evaluating head or facial pain, the criteria for identification and localization of **TMJ** disorders listed in Table 75.4 should be helpful.

Bruxism, teeth clenching, and chronic gum chewing are important in the production of pain in the massetcr and temporalis muscles. Arthritis and degenerative changes in the TMJ, loss of teeth, ill-fitting dentures or lack of dentures, and other dental conditions can all lead to the TMJ or myofascial pain dysfunction syndrome that manifests as facial and masticatory muscle pain. Head pain and facial pain, even when associated with the criteria listed in Table 75.4, require full evaluation, which should include a detailed history and examination, appropriate radiographs, and laboratory studies to exclude other more serious causes. If TMJ dysfunction is thought to be the source of the pain, further evaluation and treatment are in the province of the appropriate dental specialist. Even when TMJ dysfunction is believed to be responsible for facial or head pain, conservative management with analgesics, anti-inflammatory agents, application ol local heat, and nonsurgical techniques to adjust the bite generally provide relief. Before surgical modalities are used on the TMJ or mandibles, the diagnosis must be secure and other causes of head and facial pain excluded by appropriate investigations,

Other Dental Causes of Craniofacial Pain

Pulpitis and root abscess generally produce dental pain that a patient can localize. The cracked tooth syndrome results from an incomplete tooth fracture, most commonly involving a lower molar. The initial pain is usually sharp and well localized, but thereafter the pain is often diffuse and hard to locate. After the initial fracture, the tooth is sensitive to cold. Pain may be felt in the head and face ipsilateral to the damaged tooth. With time, infection develops in the pulp, leading to extreme and well-localised pain. Confirmation of the diagnosis and treatment of the cracked tooth require the expertise of a dentist,

Headaches and the Cervical Spine

Degenerative joint disease and cervical disc herniation rarely produce headache in the absence of neck pain. Occipital headache and neck pain on awakening are not uncommon with arthritis of the cervical spine. With activity, the headache and associated stiffness of the neck subside. Similarly, holding the head in one position for hours while driving or working at a desk can cause an increase in neck and head pain in the presence of degenerative changes. The cervical myalgias can spread upward to produce a muscle contraction headache. Rclicl lolkiws rest or sirnpl\ adopt lor. ol ;i different position. For patients with severe degenerative changes in the cervical facet joints, exercise, heat, and the use of simple analgesics can help both the neck and the head pain. Surgical fusion or discccctomy should be performed only if there is bony instability or spinal cord or nerve root compression. A cervical fusion for relief of headache in the absence ot these indications is likely to be ineffective.

Table 75.4: Criteria for identification and localization of temporomandibular joint disorders

Temporomandibular pain	*Temporomandibular dysfu net ion*
Pnin should relate directly to jaw movements and mastication	Interference with mandibular movement (clicking, incoordination, and crepitus)
Tenderness in the masticatory muscles or over temporomandibular joint on palpation	Restriction of mandibular movement
Anesthetic blocking of tender structures should confirm presence and location of pain source	Sudden change in occlusal relationship of the teeth

Ccrvicogenic headache is an entity that is described as consisting of a strictly unilateral migraine-like head and facial pain with associated neck pain and stiffness. Attacks of pain arc often accompanied by ipsilateral autonomic phenomena, such as tearing and even erythema of the face, and can be precipitated by neck maneuvers. Tenderness on the side of the neck ipsilateral to the head pain is sometimes accompanied by triggering of the attacks by pressure over the C2 nerve root, the greater occipital nerve, or the transverse process of C4-C5. At present, the concept of cervicogenic headache remains controversial.

Other Primary Headaches

Cough Headache

Cough headache is a headache of sudden onset that is precipitated by a brief, nonsustained Valsalva's maneuvet, such as coughing, laughing, sneezing, and bending. Because transiently raised intrathoracic pressure is thought to be the trigger in this condition, use of the term *Vahalva-inditced headache* has rapidly gained momentum. The pain is usually described as bursting or explosive, lasting seconds to minutes. As a rule, the patient is free from pain between attacks, but benign cough headache with normal neuroimaging results has rarely been described as lasting up to 24 hours. The headache is usually bilateral and often occipital or suboccipital. The mean age at onset of this headache syndrome is approximately 55 years (range, 19-77 years) with a 4-to-l male predominance. The proportion of patients who have an underlying structural cause is difficult to detetmine because many of them were reported in the era before CT and MRI. However, a recent study suggested that more than 50% of patients have an underlying structural cause (Pascual et al. 1996). Chiari type I malformation is the most common structural abnormality found, but other entities have been described, such as carotid dissection, basilar invagination, platybasia, colloid cysts of the third ventricle, and other space-occupying lesions. All patients therefore require MRI scans before a diagnosis of benign cough headache is made. MRA should be obtained if there are features that raise the possibility of a carotid artery dissection. The treatment of choice is indomethacin, used similarly to the regimen used in the paroxysmal hemicranias. The response to indomethacin is not absolute nor does it confirm a benign etiology. Other reports suggest that benign cough headache may respond to propranolol, dihydroeigotamine, or lumbar puncture.

Exertional Headache

Exertional headache is a bilateral, throbbing headache that is precipitated by sustained physical exercise, such as weight-lifting, dancing, running, howling, and football. The headache is not explosive in onset but rather builds in intensity and lasts between 5 minutes and 24 hours, in contrast to the headache profile seen with cough headache. The headache can be ptevented by avoiding excessive exertion, particularly in hot weather or at high altitude. Similar to cough headache, this disorder can be benign or symptomatic of an underlying cause. Typically benign exertional headaches occur earlier in life compared with benign cough headache. In one series, 12 of 28 patients with exertional headache were found to have underlying causes (Pascual et al. 1996). These patients, however, were older (mean age 42 versus 24), developed acute, severe, bilateral headaches lasting I day to I month, and developed accompanying symptoms of nausea, vomiting, photophobia, or diplopia. Well-described causes of symptomatic exertional headache include subarachnoid hemorrhage, cerebral metastases, pansinusitis, and pheochromocytoma. *Cardiac cephalalgia* refers to a headache brought on by exertion in the setting of underlying coronary artery disease. Exercise-induced cardiac ischemia is thought to refer pain to the head and neck. Appropriate investigations are therefore mandatory in each patient. Indomethacin, either given shortly before exercise or on a regular basis, is effective in the majority of benign exertional headaches. Other medications that may be effective include ergotaminc or methysergide before exercise or the regular administration of a beta blocker, calcium-channel blocker, aceta/olamide, or aspirin.

Headache Associated with Sexual Activity

The onset of a severe headache, usually in the occipitonuchal region, during intercourse or at orgasm is usually benign. There are three types of benign headaches associated with sexual activity. The most common is a bilateral cervical and occipital headache that builds up through intetcourse and is believed to be due to sustained contraction of the cervical and scalp muscles. This headache rapidly resolves with rest. A mote acute and frightening headache develops al the height of orgasm and may be very severe. It usually subsides in minutes, although it may persist for hours and may cause tile subject to seek immediate medical attention. Such acute headaches associated with sexual activity arc typically benign, but careful consideration must be given to the possibility of a subarachnoid hemorrhage. A CT scan of the head should be obtained. If there is no sign of bleeding, a lumbar puncture should be undertaken to examine the CSF for the ptesence of erythrocytes or xanthochromia. If results of these examinations are negative, angiography may be necessary if the history and the physical examination suggest that a small subarachnoid hemorrhage or sentinel bleeding episode may have occurred. A third type of coital headache has been described. This headache type develops after orgasm and has a postural component resembling a low CSF pressure state. Benign coital headaches are more common in men than in women. They more commonly

occur as an isolated event with recurrence generally not the rule. If recurrent orgasmic headaches become problematic, they may be prevented in some patients by the use of indomethacin or ergotamine tartrate taken several hours before intercourse. Several case reports suggest that either daily propranolol or diltiazem may be effective as well.

Migraine

Migraine has afflicted humankind for centuries. Descriptions of acute migraine attacks appear as early as the second century AD in the writings of Aretaeus of Cappadocia. The term *migraine* is derived from the ancient Greek word *hemikranios* which means "half head," underscoring the unilateral distribution of head pain in many sufferers.

Definition and Classification

Because reliable biological markets for migraine currently do not exist, diagnostic classification is based on clinical features of the acute episode. Migraine is now classified according to the scheme devised by the Second Headache Classification Committee of the International Headache Society (Headache Classification Committee 2004), as shown in Table 75.5.

Clinical Aspects

Migraine can begin at almost any age; most commonly, the initial attack occurs during adolescence, and by 40 years of age, 90% of those with the condition have had their first attack. Although migraine can begin in older patients, it should be viewed with suspicion because the incidence of serious intracranial disorders that may mimic primary headaches is greater. After puberty, migraine is more common in females, whereas in children there is a small preponderance of males. A family history of migraine is present in up to 90% of patients. Although there has been some interpopulation variability, several large population-based studies in Europe and United States have shown the prevalence of migraine in women to be approximately 20% and in men approximately 6%. Once migraine has developed, it tends to tecur with varying frequency throughout much of a patient's life. Attacks have a tendency to get milder and occut less often in later yeats although this cerr.unl) is not .i universal finding.

Table 75.S: Migraine

1.1. Migraine without aura
1.2. Probable migraine without aura
1.3. Migraine with aura
1.3.1. Typical aura with migraine headache
1.3.2. Typical aura with non-migraine headache
1.3.3. Typical aura without headache
1.3.4. Familial hemiplegic migraine
1.3.5. Sporadic hemiplegic migraine
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Although migraine attacks have been separated into those that are and those that are not accompanied by transient focal neurological symptoms known as the aura, the two types are not mutually exclusive, and many patients have separate attacks of the two types. The headache phase of migraine with and without aura is similar and typically consists of episodes of unilateral throbbing head pain of modetate to severe intensity which, if untreated, persists fiom 4 hours up to 3 days and tends to worsen with routine levels of physical exertion. Migraine attacks tend to be accompanied by nausea, vomiting, and light or sound sensitivity although not every patient experiences all of these symptoms. It is important to realize that there is variability in the intensity and details of the headache from patient to patient and from attack to attack.

Migraine without Aura. Migraine without aura occurs episodically and is not preceded or accompanied by any easily identifiable aura due to focal cerebral or brainstem disturbances. Many patients with migraine report that their headaches are preceded by a prodromal phase that may consist of alterations in mood or energy level (either euphoria or depression), excessive yawning, thirst, or food cravings. After these premonitory warnings, the headache may occur within hours or during the next day. The attack may awaken the subject during the night, but more commonly the patient awakens near to the normal time to find that the attack has already started. At this stage, the pain may be unilateral and is usually supraorbital, but it may be holocephalic. An initially unilatetal headache may progress to generalized head pain, or it may switch to the conti a lateral side during the course of the attack. Headache arising frontally can radiate or migrate posteriorly or vice versa. Patients with migraine may have attacks that primarily affect the cheek, ear, nose, or neck. These attacks, sometimes called lower-half headache. should be considered in patients with facial pain accompanied by nausea, vomiting, and photophobia. Pain in the lateral portion of the neck with tenderness over the carotid artery may be found in lower-half headache.

The management of this condition is similar to that of the more common cephalic forms of migraine.

The quality of the pain of migraine is often described as throbbing (pulsatile) although in some patients the throbbing only occurs with more severe attacks. Many patients, however, describe the pain as steady while they remain still. It tends to pulsate or throb at the heart rate with exertion, after Valsalva's maneuver, or during the bead-low position. Strict insistence on obtaining a history of a throbbing pain **sii v/.Mijl.'ir** I'.e.ul.idles ie.uls **lo mum iiTiinmiis conclusions.** In general, during acute attacks migraineurs wish to remain as still as possible and prefer a dark quiet room, although with mild attacks some patients may be able to function at a reduced capacity.

Other symptoms are often associated with the pain of migraine. Photophobia and phonophobia are common and osmophobia (sensitivity to smells) may also occur. The onset of n.uisca and vomiting in migraine can occur almost as soon as the pain develops, but it is more commonly delayed until the attack has been in progress for 1 hour or longer, Anorexia, even intolerance to the smell of food, is even more common than nausea. The gastrointestinal symptoms can include diarrhea. Blurred vision is a common complaint during all types of migraine. Lightheadedness is also common and may progress to syncope in a small percentage. Subconjunctival hemorrhages, orbital ecchymoses, and epistaxis have all been reported to accompany migraine. Fever, tachycardia, and paroxysmal atrial tachycardia are rare migraine-related symptoms, possibly due to associated disturbances of the autonomic nervous system. Sacks' 1392 monograph on migraine has an extensive listing of the symptoms that have been described in migraine.

The pain of an attack of migraine tends to build up to a peak over 30 minutes to several hours. Rarely the onset is desctibed as being more explosive. The attack generally lasts several hours to a full day. Severe episodes can continue for several days and, if associated with vomiting, can lead to prostration and dehydration. Very prolonged attacks or a series of attacks with minimal relief between them is called *status migramosus,* and it often warrants admission to the hospital for pain relief and correction of fluid and electrolyte imbalance. More commonly, the attack subsides within a day or after a night's sleep. The day after the intense pain, the patient feels tired and listless. The head is still heavy and transient pain can occur with sudden movement, bending over, or Valsalva maneuvers.

The frequency and severity of episodes of migraine without aura (common migraine) are extremely variable both from patient to patient and over time within an individual patient. Recurrence of attacks one to four times per month is not uncommon, and attacks in relation to the menstrual cycle are a common pattern in women during the reproductive years. Attacks at less than weekly intervals are common in patients who attend neurology clinics and generally indicate that a chronic daily headache partem is evolving.

Migraine with Aura. In migriiii-e with anr.i. periodic headaches arc preceded or accompanied by an aura consisting of transient visual, sensory, motor, or language disturbance or other focal cerebral or brainstem symptoms. Aura occurs in about 15% of migraineurs and does not occur in every attack. Although each of the aura types may occur alone in a given attack, in some individuals they can occur sequentially. Classically, the visual disturbance is followed by sensory symptoms and then iti-turn by language or motor symptoms. When this occurs, the headache may overlap one or more of the later 'appearing aura symptoms. The head pain is identical to that of migraine without aura but is unilateral in a higher percentage of patients. Alterations in mood and other premonitory symptoms may precede the aura.

The most common aura is the disturbance of vision known as a scintillating scotoma (teichopsia). This generally begins as a shimmering arc of white or colored lights in rhe homonymous part of the left or right visual field. The arc of light gradually enlarges. It may have a definite zigzag pattern. It may be a single band of light or may have a much more complex pattern. It has a shimmering or flickering quality, similar to that seen when a fluorescent light fixture is close to failure or a strobe light is just short of the flicker fusion frequency. Gradually, over the course of a few minutes, the scintillating pattern expands from the point just lateral to the of fixation to involve a quadrant or hcmifield of vision in both eyes. Commonly, the positive scotoma is followed by a spreading zone of vision loss (negative scotoma). Even if there is no identifiable area of vision loss, the disturbance of vision produced by the scintillating scotoma makes it difficult to read or drive. The scotoma is believed to originate in the calcarinc cortex of one cerebral hemisphere and should therefore be an essentially congruent homonymous field defect; however, it is sometimes described as being seen in one eye only or' as being worse on one side than the other. Patients often describe the visual disturbance in vague terms, such as "blurry vision," "double vision," or "jumpy vision." Close questioning ot showing the patient an artist's teprescn-tation of a scintillating scotoma generally clarifies the complaint.

There are many variations of migrainous teichopsia (subjective visual images). The zigzag appearance may be so pronounced to justify the term *fortification spectrum* because of its fanciful resemblance to the ground plan of a fort. Occasionally, the scotoma is less complex and is simply described as a ball of light in the center of the visual fields. It may obscure vision to a significant degree. This type of teichopsia may represent a bilateral calcarine disturbance. The scintillating and positive (bright) scotomata can still be seen with the eyes closed or while in rhe dark. This is not a feature of the negative scotomata (areas of darkness), which disappear in the dark.

The teichopsia of migraine may be more complex and formed than the usual lines and geometric patterns. Rarely,

a complex scene is visible to the migraineur; it may be recognizable as an image from the patient's past experience, or it may be an unknown scene. Disturbances of this complex type may be due to dysfunction in the posterior HTiip-.r-:]l Ic-hc. Changes in the perception of [lie shape or form of viewed objects (mctamorphopsia) can lead to frightening and bizarre visuai hallucinations. The story of *Alice in Wonderland,* in which the heroine perceived herself shrinking, is believed to have been based on Lewis Carroll's own experience of migrainous mctamorphopsia.

Visual disturbances due to retinal dysfunction are relatively uncommon in migraine and nu\ lake the Innn of unilateral flashes of light (photopsia), scattered areas of vision loss, altitudinal defects, or even transient unilateral vision loss. When such monocular visual disturbances are followed by a headache, rhc term *retinal migraine* is appropriate. When the photopsia, teichopsia, and other disturbances are seen in both visual fields simultaneously, they probably originate from the calcarine cortex. A homonymous visual aura is generally followed by a headache on the contralateral side of the head, but exceptions are not uncommon. In such patients, the headache is ipsilateral to the visual disturbance, or it is bilateral.

Sensory aura, the second most common aura type is, like the visual aura, characterized by positive symptoms (paresthesias) followed by negative symptoms (numbness), which slow!\ spread or migrate. Paresthesias can occur, alone or in conjunction with one of the previously described visual symptoms. The numbness or tingling may be felt in almost any distribution, from a hemisensory disturbance to one that involves all four limbs or a much more restricted area, such as the lips, face, and tongue. The paresthesias can last from a few seconds to 20-30 minutes. The paresthesias of migraine aura seem to have a predilection for the face and hands. This may be due to the latge tepresentation of these structures in the sensory cortex or thalamus. The term *cbeiro-oral migraine* is sometimes applied to instances involving a sensoty disturbance of the fingers, lips, and tongue during the aura phase.

The rate of spread of a sensory aura is important to help distinguish it from a sensory seizure and rhe sensory disturbance of a TIA. Just as a visual aura spreads across the visual field slowly, taking as long as 20 minutes to reach maximum, the paresthesias may take 10-20 minutes to spread from the point at which they are first felt to reach their maximal distribution. This is slowet than the spread or march of a sensory seizure and much slower than the spread of sensory symptoms of a TIA. A migrainous sensory aura generally resolves over the course of 20-60 minutes. After the aura there is usually a latent period of a few minutes before the onset of the headache. In some subjects, the aura and the headache merge.

After sensory aura, the next most common type is the language aura. Dysphasia or aphasia can occur as the aura of migraine. The aphasia, which is usually mild and transient, can be either an expressive or a receptive type. Alexia and agraphia can also occur and can be associated with mild confusion and difficulty concentrating. The ensuing headache generally resembles headaches the patient has had in the past and that followed the more typical visual aura. *J*

Weakness of the limbs or facial muscles on one side'of the body occurs only rarely as a motor aura of migraine. Many patients describe a sense of heaviness in the limbs on one side before a headache, but examination during this phase rarely reveals any true weakness. If actual paresis docs occur, it is usually detected in the upper limb and may be accompanied by mild dysphasia if the dominant hemisphere is involved. The weakness genetally lasts 20-30 minutes, although in some patients the weakness may persist fot hours to weeks (see Complications of Migraine, later in this chapter).

A rare occurrence is for the motor aura of migraine apparently to precipitate a focal motor seizure. This may indicate an area of abnormal cortex that has a predisposition to act as a seizure focus. The seiztire appears to be triggered by the cortical abnormality that occurs in the aura of migraine.

Episodes of transient abdominal symptoms, periods of disturbed mentation, deja vu experiences, and other bizarre symptoms have all been thought to be the aura of migraine with aura at various times. The number of patients involved has generally been so small that the true nature of the experiences remains in doubt compared with the more commonly encountered visual, sensory, language, and motor auras already described.

Migraine Aura without Headache or Migraine Equivalents. When a visual, sensory, motor, or psychic disturbance characteristic of migraine aura is not followed by headache, the episode is termed *migraine aura without headache,* a *migraine equivalent,* or *acepkalic migraine.* Most commonly encountered in patients who have a past history of migraine with aura, the episodes can begin *de novo,* usually after 40 years of age, but they can occur at almost any age.

Migtaine equivalents are easily recognized when the attacks occur on a background of migraine with aura. In the absence of such a history, the transient disturbance may be difficult to distinguish from an episode of ttansient cerebral or brainstem ischemia. MRI/MRA, cerebral angiography, echocardiography, and tests of hemostasis may be needed to exclude the more serious causes. The typical scintillating scotoma, with its slow spread and zigzag appearance in both visual fields, is almost invariably migrainous, whether or not it is followed by a headache. Under these circumstances, it is rarely necessary to perform invasive investigations. A conttast-enhanced CT or MRi scan is a reasonable compromise when there is doubt about the migrainous nature of the event.

Acute episodes of confusion can occur with migraine, usually representing the aura stage. Acute confusional or

dysphrenic migraine occurs most often in children or adolescents, but it can occur later in life. In the absence of a long history of migraine with aura, the episodes arc rarely suspected of being migrainous at first. In an elderly patient, the diagnosis is considered only after exclusion of more serious conditions, including transient ischemic events. As a migraine equivalent, the acute confusional state may be unaccompanied by headache. The term *dysphrenic migraine* has been used to describe severe confusional states progressing to partial or generalized seizure activity or coma in young patients. The migrainous nature may be suspected from the past history of more typical migraine with aura.

Basilar Migraine. Basilar migraine is usually first encountered during childhood or the teenage years. It was initially thought to be primarily a disorder of women, but further case reports indicate that it occurs in men almost as commonly (Peatfield and Welch 2000). Basilar migraine is recognized only in the classic form because only the dramatic constellation of brainstem symptoms allows its recognition. The headache is usually occipital and severe. The aura, which lasts 10^45 minutes, usually begins with typical migrainous disturbances of vision, such as teichopsia, graying of vision, or actual temporary blindness. The visual symptoms are bilateral. Numbness and tingling of the lips, bands, and feet often occur bilaterally. Ataxia of gait and ataxic speech, vertigo, dysarthria, and tinnitus are also described in basilar migraine.

Involvement of the brainstem reticular formation can lead to impairment of consciousness, especially in young patients. This often occurs as the other symptoms of the aura are subsiding. The level of coma is never profound and can resemble sleep from which the patient can be temporarily aroused. Recovery usually coincides with onset of the severe throbbing occipital headache. The pain may generalize to the whole head and is often associated with prolonged vomiting. After sleep, the headache is usually gone. A basilar migraine equivalent occurs in which teenagers have the symptoms just described without the headache. This is a clinical picture that can be difficult to recognize. Certain investigations are needed for reassurance. MRI scans and an electroencephalogram usually suffice. Rarely, patients with otherwise typical basilar migraine can have seizures with the attacks of headache. Epileptiform electroencephalographic (EEG) abnormalities have been recorded under these circumstances.

With increasing maturity of the nervous system, attacks of basilar migraine become less common and are generally replaced by migraine without aura. Basilar migraine can occur in later life, but its onset at that age should be viewed with suspicion because arteriosclerotic vertebrobasilar artery insufficiency is more common and can produce almost identical symptoms.

Ophthalmoplegic Migraine. Ophthalmoplegic migraine is a very infrequent condition that almost always has its onset in childhood. Recurrent attacks are the usual pattern. Each episode begins with a unilateral orbital and retro-orbital headache, often accompanied by vomiting, that lasts 1-4 days. Either during the painful stage or occasionally as the headache subsides, ipsilateral ptosis occurs and, within a few hours, progresses to a complete paralysis of cranial nerve III. Rarely, cranial nerves TV or VI may be involved. The neural deficit can last from 1 hour to several months. The focal nature of the deficit has, in the past, often led to major investigations, including angiogtaphy to rule out the presence of an internal carotid or posterior communicating artery aneurysm, but usually no abnormality is found. MRI scans have shown thickening and contrast enhancement of the nerve as it exits the midbrain, which may persist after the third nerve palsy has disappeared (Daroff 2002). It has been speculated that this represents a recurrent demyelinating/inflammatory neuropathy although pathological evidence has not been available for confirmation [.ana and Zagnmi 2001}. In am case, this disordei is probably best considered a cranial neuropathy. The prognosis is favorable for recovery unless attacks occur very often.

Complications of Migraine

Attacks of migraine with associated hemiparesis can occur sporadically or, rarely, as a familial condition. Either form can occur singly or recurrently. The diagnosis can be considered only if the subject has a convincing past history of migraine with aura. The attack usually begins with a motor aura involving the limbs on one side, and facial involvement may be present. Unlike the common aura, however, this motor aura may involve quite profound weakness, which persists throughout the headache phase and for a variable period thereafter. The muscle weakness may last for hours, days, or even weeks in rare patients. Recovery is usually complete, except in patients in whom a dense hemiplegia develops and in whom a CT or MRI scan demonstrates an area of infarction. CSE pleocytosis can occur with hemiplegic migraine. The increased cell count is transient and is believed to occur in response to clinical or subclinical cerebral infarction. 1 he sporadic form of hemiplegic migraine, if it is recurrent, can alternate sides. In the familial form, the involved side tends to be the same with each attack. Inheritance of this condition may be a dominant trait and is discussed further under Migraine Genetics, later in this chapter.

A facioplegic form of complicated migraine with recurrent episodes of upper and lower motor neuron facial palsv also occurs. Whether this state is separate from hemiplegic migraine is unclear.

Usually on a background of migraine with visual aura, an occasional patient reports the persistence of visual symproms for long periods or even indefinitely. Most such patients are found to have a field defect. It can be

congruous and due to a cerebral lesion, or rarely it can be imiocular and due to a retinal abnormality. CT scans have shown small infarcts in the occipital lobes or along the course of the central visual pathways in some patients. In those with retinal involvement, occlusion or spasm of the retinal .lricri;^ has Kvn observed. A IH:L;.W.\ ;• senium.i can persist, and scintillating scotomata can persist for long periods. The association between migraine and stroke is also discussed in Chapter 57A.

Physical Findings

Between attacks, the migraineur generally has a normal physical examination. During an attack of migraine, rhe scalp vessels may be distended and tender. The blood pressure is likely to be raised due to the pain. Many patients are pale and clammy during the attack, especially if nauseated. The patient is likely to object to the lights of the examination room and try to avoid the glare of the ophthalmoscope during the eye examination. Occasionally, there is some inequality of the pupils, with the one ipsilateral in l:ie *ii*\\; .idle **timer .i'l**\ ln-ins; larger. A **lulK** developed "ophthalmoplegic migraine" reveals various degrees of a third cranial nerve deficit, with ptosis, a dilated pupil, and impaired medial and upward movement of the involved eye. Involvement of cranial nerve VI impairs lateral deviation of the globe.

Mild weakness, especially of the upper limbs, may be found during a motor aura, and various degrees of weakness up to hemiplegia may occur in complicated migraine.

Demonstration of impaired vision during the visual aura is difficult. Most often, a patient's visual complaints are purely subjective.

/ *abnnitory Findings*

No special investigation-, are useful for tin- JuiiL.il diagnosis of migraine. EEG, MRI, and CT scan abnormalities may be found during or shortly after an attack, but they are not specific for migraine and simply detect cortical or parenchymal changes that accompany the headache. The EEG changes can range from an area of focal slowing over the hemisphere ipsilateral to the headache to focal spikes, sharp waves, or the more generalized spike-wave discharges seen in idiopathic seizure disorders. Similar findings may be seen in basilar migraine.

Visual evoked potentials are slowed in some subjects with repeated attacks of migraine. This observation, although important for evaluation of the pathophysiology of the condition, is of little use clinically. CT and MRI scans can reveal large areas of decreased attenuation and signal changes over the hemisphere ipsilateral to the headache, especially if it is severe and prolonged. These changes, which are temporary and resolve in a few days, arc believed to represent edema of the affected region. Complicated migraine, especially that leading to a permanent deficit, such as a hemiparesis or a visual field defect, shows an appropriate area of cerebral infarction. The relationship of antiphospholipid antibodies to migrainous infarction is unclear, although the presence of such antibodies is considered a separate risk factor for stroke even in the absence of migraine. Detection of antiphospholipid antibodies in a migtaineur should lead to the administration of anticoagulants or antiplatelet agents.

CT and MRI scans are useful in the investigation of migraine only to the extent that they allow exclusion of other causes of recurrent headaches. If there is a question as to whether a vascular lesion such as an aneurysm or AVM is present, magnetic resonance angiography is often used as a screening tool, although standard angiography may in some instances be necessary when the diagnosis of migraine is doubtful and a vascular lesion is strongly suspected on clinical grounds. Finding a lesion such as an aneurysm does not always mean that the diagnosis of migraine was incorrect. It may simply mean that the patient has migraine and an incidental aneurysm as well. In other circumstances, the angiographic findings may negate the diagnosis of migraine entirely. The risk of angiography in migraineurs is probably no higher than that in other persons of the same age.

Migraine Genetics

The prevalence of a family history of migraine has been recognized since the seventeenth century. Although prior familial migraine studies have shown no clear Mendelian inheritance patterns, recent genetic epidemiological surveys, and a twin study using a polygenic, multifactorial model support the hypothesis of a genetic contribution. Perhaps the most striking evidence of a genetic basis for migraine has come to us over the past decade from investigation of familial hcmiplegic migraine.

Familial hcmiplegic migraine (FHM) is a rare autosomal dominant subtype of migraine with aura in which in the context of otherwise typical migraine attacks, patients experience hemiplegia. The hemiparesis of FHM in many patients is prolonged beyond the customary time limit of 1 hour usually associated with migraine aura. Ataxia, nystagmus, and coma have been described in the context of FHM. In 1993, FHM was mapped to chromosome 19p13 (Joutel 1993) in linkage studies that were inspired by the clinical association with migraine and cerebral autosomal dominant arrcnopathy with subcortical infarcts and leukoencephalopathy. About 50% of tested families have mutations in *C,AC,NA 1 A,* a gene located on chromosome I [L]Jp1 3 which codes for the ct^-subunit of a bra in-specific voltage-gated P/Q-type calcium channel (Ophoff et al. *1996).* Mutations in the same gene have been found in some pedigrees with hereditary paroxysmal cerebellar ataxia, indicating that these two disorders, which share several features, are allelic channelopathies (see Chapter 70). Four years later, Gardner and colleagues (1997) reported another

locus for FHM on chromosome 1 q 31 in a 39-member four-generation pedigree showing a clear FHM phenotype. This region on chromosome 1 is reported to contain a neuronal calcium-channel a_{1E}-subunit gene. Recent reports (Terwindt etal. 2001) indicate that *CACNA1A* is not only implicated in familial hemiplcgic migraine, but is over-represented in patients with migraine without hemiplegia.

Although FHM is a rare genetic subtype of migraine with aura, the clinical similarities (with typical migtaine, with and without aura) suggest at least the possibility of a shared pathophysiology. The discovery of a genetic locus for FHM has generated considerable interest and prompted a large effort in the field of molecular genetics to find the fundamental defect in the more common forms of migraine. However, studies testing the 19pl3 region for linkage to typical migraine have produced conflicting results. One study concluded that chromosome 19 mutations either in the *CACNL1A4* gene or in a closely linked gene are implicated in some pedigrees with familial typical migraine and that the disorder is genetically heterogeneous (Nyholt et al. 1998). Further invesngation will be necessary to determine the extent to which the more common types of migraine in the general population might be influenced by these FHM genes,

A recent study based on a genome-wide screen of 50 multigencrational, clinically well-defined Finnish families showing intergenerational transmission of migraine with visual aura yielded significant evidence of linkage between the migraine with aura phenotype and marker D4S1647 located on chromosome 4q24 (Wessman et al. 2002). The application of new genomic and proteomic techniques to migraine may then lead to the further unraveling of the precise molecular defects that underlie this highly prevalent and disabling condition.

Pathopbys iology

Genesis of the Migraine Syndrome. Clinical and experimental evidence supports the concept that there is abnormal intracranial and extracranial vascular reactivity in migraine and other vascular headaches. Dilatation of the scalp arteries causes incteased scalp blood flow and large-amplitude pulsations during attacks of migraine. Radioactive xenon cerebral blood flow studies show significantly reduced regional flow through the cortex during the aura stage of migraine with aura. At first sight, these studies seem to support the long-held theory of cerebral vasoconstriction during the aura and increased external carotid flow during the headache phase. However, the vasoconstriction-vasodilatation model has several difficulties. First, there is solid evidence from functional MR! studies that the phase of oligemia during the migraine aura is preceded by a phase of focal hyperemia {Hadjikhani et al. 2001). Second, headache may begin while cortical blood flow is still reduced, thereby rendering obsolete the theory that vasodilatation is the sole mechanism of the pain. The oligemia that spreads across the cerebral cortex at a rate of 2-3 mm per minute does not conform to discrete vascular territories, making unlikely the theory that vasospasm of individual cerebral arteries with subsequent cerebral ischemia is the source of the aura. The headache after an aura is often on the inappropriate side. In other words, a right-sided visual field or somatosensory aura can In- followed by an ipsilaieral headache, despite the f.ict thai the cerebral blood flow changes occurred in the opposite hemisphere. Finally, migraine is also associated with a premonitory phase in up to 60% of patients, which would be incompatible with a vascular or ischemic hypothesis. This premonitory phase consists of mood changes, thirst, food cravings, excessive yawning, and drowsiness. The brain location from which a migraine attack is initiated is still unclear, but brainstem and hypothalamic generators have been proposed (Weiller et al. 1995; Zurak 1997).

The observations on spreading oligemia led to a resurgence of the central or neuronal theories of migraine. Briefly, the phase of oligemia demonstrated during the aura of migraine by the tomographic blood flow techniques begins in one occipital pole and spreads forward over the ipsilateral hemisphere at a rate of about 3—4 mm per minute. The area of reduced cerebral blood flow does not correspond to the distribution of any particular cerebral artery but crosses the areas perfused by the middle and posterior cerebral arteries while advancing with a distinct wave front until some major change in cortical cellular architecture is reached (e.g., at the central sulcus). Recently, the description of a patient with migraine without aura who had an attack during positron emission tomography (PET) proved beyond a doubt the phenomenon of spreading oligemia (Woods et al. 1994). This study suggested the possibility that blood flow changes may occur in migraine with and without aura because this patient had only ttansient and mild visual blurring, a ubiquitous symptom in migraineurs. This slow, deliberate march of a wave of oligemia brings to mind two old observations. Lashlcy, in 1941, studying his own scintillating scotoma, postulated on purely theoretical grounds that it must have been due to a change spreading over his occipital cortex at about 3 mm per minute. In 1944, Leao, during his research on epilepsy, observed a wave of cortical electrical depression passing over the exposed brain of lower animals. Activating the posterior cortex of rats started a wave of electrical depression that moved out from the point of initiation at a rate of 3-4 mm per minute.

The spreading depression noted by Leao's and Lashley's observations led to the hypothesis th.it the aura of migraine is primarily a neuronal event that causes the cortical circulation to close down in response to decreased metabolic requirements. Although spreading depression has not been documented to occur in human cortex, functional MRI studies have been strongly supportive. There is also a body of evidence suggesting the presence of a disturbance in energy metabolism in both the brain and extraneural tissues

of patients with migraine. Based on abnormalities identified in the mitochondrial respiratory chain and matrix enzyme activities from the muscle and platelets of patients with migraine, it has been proposed that the defect in brain energy metabolism is due to abnormal mitochondrial oxidative phosphorylation (Welch and Ramadan 1995). In support of these findings, interictal phosphorus-31 magnetic resonance spectroscopy (MRS) studies have shown reduced phosphocreatine levels and phosphorylation potential and increased adenosine diphosphate levels in the occipital lobes of migraineurs. Phosphorus-31 MRS studies done during the ictal phase reveal depletion of high-energy phosphates without an accompanying change in intracellular pH, indicating that the energy failure results from defective aerobic metabolism rather than from vasospasm with ischemia.

In addition, there is increasing evidence to support the presence of both systemic and brain magnesium deficiency in migraineurs, particularly in the occipital lobes (Welch and Ramadan 1995). Magnesium normally maintains a strongly coupled state of mitochondrial oxidative phosphorylation. Magnesium also plays an important role in "gating" N-methyl-D-aspartate (NMDA) receptors. A magnesium deficit can therefore result in an abnormality of mitochondrial oxidative phosphorylation and lead to a gain in NMDA receptor function, thereby causing an instability of neuronal polarization because of a loss of ionic homeostasis, This would then lead to a state of neuronal hypcrcxcitability and a lower threshold for spontaneous depolarization.

Spreading depression might therefore be more aptly described as spreading activation, followed by a wave of spreading depression. This would support the clinical oils,.•!••..ilior nf "prisitiw" visual "scnltilhnnns" followed by a "negative" visual scotoma or by the march of positive sensory (paresthesia) symptoms. This theory may also explain why spreading oligemia may be preceded by focal hyperemia. These findings taken together suggest that the changes in blood vessel caliber and blood flow may be due to a primary neuronal event, triggered by enhanced neuronal excitability and susceptibility to spontaneous depolarization, resulting in prolonged hypometabolism because of an impairment in energy metabolism caused by mitochondrial dysfunction. This hypothesis has also been supported by the finding of increased interictal lactate levels in the occipital cortex of migraineurs using proton MRS (Watanabe et al. 1996).

The theory that the migraine aura is a primary neuronal event was further strengthened by a recent study, which demonstrated no change in the apparent diffusion coefficient on diffusion-weighted MRI despite a reduction of regional cerebral blood flow during spontaneous migraine aura. Because diffusion-weighted MRI is very sensitive to tissue ischemia, the authors concluded that the reduction in cerebral blood flow was not of sufficient magnitude to cause tissue ischemia (Cutrer et al. 1998).

Platelets and Serotonin. Platelets obtained from migraineurs are known to aggregate more readily than normal in response to exposure to several vasoactive amines, including serotonin (5-hydroxytryptamine), adenosine diphosphate, catecholamines, and tyramine. It is also known that platelets contain most of the serotonin normally present in blood and that at the onset of an attack of migraine there is a significant rise in plasma serotonin concentration followed by an increase in the concentration of urinary 5-hydroxyindoIcacetic acid, a breakdown product of the serotonin. Platelet aggregation is necessary for its release. The plarelets of migraineurs, even between attacks of migraine, contain less monoamine oxidase than normal, and a furthct decrease occurs with an attack of headache.

Although the platelet may not have a direct role in the biochemical changes that appear to underlie the basic pathogenesis of migraine, it has been extensively studied because of its similarities to serotonergic nerve terminals.

The role of serotonin in migraine has yet to be fully defined. It constricts large arteries and is a dilator of arterioles and capillaries; also, perhaps of more importance, it is a neurotransmitter. Serotonin-containing neurons are especially concentrated in the brainstem raphe, the projections of which have a widespread distribution to other neuronal centers and cerebral mierovessels. The importance of the brainstem in migraine is still uncertain. Its role is certainly highlighted by the presence of binding sites for specific antimigraine drugs and the demonstration of persistent brainstem activation during and after a migraine attack, as imaged by PET (Weiller et al. 1995). Moreover, recurrent migraine headaches were precipitated in a nonmigraincur after a stereotactic procedure produced a lesion in the dorsal raphe and periaqueductal gray matter, which is part of the endogenous antinociceptive system. Welch et al. (2001) have recently found evidence for simultaneous activation of red nucleus, substantia nigra, and occipital cortex during provoked attacks with a visual irinv.i..-.rior •-unuliizm. This was demonstrated using hood oxygen level-dependent functional MRI, which revealed hyperoxia in these regions. Furthermore, serotonergic circuits are believed to be involved in the modulation of sleep cycles, pain perception, and mood, all of which are important factors in migraine syndrome.

Interest in the role of serotonin in migraine and the recognition of multiple subtypes of serotonin receptors has led to the development of a number of agents having high affinities for specific receptors. This has revolutionized the field of migraine therapeutics (for more details, see Acute Menstrual Migraine Therapy, later in this chapter).

Mechanism of the Headache. Although the aforementioned data strongly suggest that the initiation of a migraine attack is centrally driven, this docs not adequately explain the mechanism of the head pain. Pain-sensitive intracranial structures, including large cerebral blood vessels, pial vessels, dura mater, and large venous sinuses, are

innervated by a plexus of largely unmyelinated fibers that arise from the ophthalmic branch of the trigeminal nerve. Once this trigeminal vascular system is activated, impulses are transmitted centrally toward the fitst synapse within lamina I and ITo of the trigeminal nucleus caudal is (TNC), which extends to the dorsal horn of C2-C3. Activation of neurons in the TNC is reflected in the increased expression of *c-fos* (an immediate early gene) activity. From this point, nerve impulses travel rostrally to the cortex via thalamic relay centers.

In addition to central transmission, there is evidence that neuropeptide transmitters are antidromically released from the widely branching perivascular trigeminal axon nerve terminals. These neuropeptides, including substance P, calcitonin gene-related polypeptide, and neurokinin A, mediate a neurogenic inflammatory process that can activate nociceptive afferents, tesulting in the central transmission of pain impulses. Neurogenic inflammation consists of vasodilatation, vasculat endothelial activation with formation of microvilli and vacuoles, increased leakage of plasma protein from dural vessels into sutrounding tissue, increased platelet aggregation, mast cell degranulation, and activation of the local cellulat immune response, A series of elegant experiments have suggested that the pain of migraine may be due to neurogenic inflammation, which would ako explain the changes in serotonin and platelet serotonin repotted in migraine (Moskowitz and Cutrer 1994).

The importance of neurogenic inflammation in the production of the pain of migraine is supported by the fact thai Il;.V:lL.;I u:is 1:1.11 block neurogenic inflammation and mediate vasoconstriction are successfully used to abort a migraine attack. Neurogenic plasma extravasation can be inhibited by the ergot alkaloids, indomethacin, acetylsalieylic acid, valproic acid, and the new highly selective serotonin (5-HT,) teceptor agonists, which are discussed under Symptomatic Treatment, later in this chapter. However, neurogenic inflammation by itself is probably not the sole mechanism of pain because treatment with selective inhibitors of neurogenic inflammation has uniformly failed in the clinic (May and Goadsby 2001).

Ergotamine compounds and the "triptans" also act centrally to inhibit the activity of neurons within the TNC, which may be important in the termination of an attack. Whether these drugs act on the postsynaptic neuron in the TNC is unclear.

Activation of the trigeminal sensory system is reflected by the development of cutaneous allodynia in most patients during migraine attacks. The underlying mechanism is sensitization of centra! trigeminal neurons (Burstein et al. 2001). Triptans can prevent, but not reverse, cutaneous allodynia in patients and central sensitization in animals, and the presence or absence of cutaneous allodynia can be used as a marker to predict whether triptans would be able to abort a given migraine attack (Burstein et al, 2002). Repeated quantitative sensory testing of patients with migraine was done (1) early in a migraine attack (triptans given before cutaneous allodynia) and (2) late in a migraine attack (triptans administered after cutaneous allodynia). In attacks without allodynia, triptans completely relieved the headache and blocked the development of allodynia. However, in 90% of attacks with established allodynia, triptans provided little or no headache relief and did not suppress allodynia. However, late triptan therapy abolished the throbbing quality of the pain and its worsening upon bending over (peripheral sensitization) in the 90% of attacks in which pain relief was not complete and allodynia was not suppressed.

A link between the migraine aura and headache has now established that cortical spreading depression (CSD), implicated in migraine visual aura, activates trigeminovascular afferents and evokes a series of cortical meningeal and brainstem events consistent with the development of headache (Bolay et al. 2002). By using laser speckle-contrast imaging, CSD was shown to cause long-lasting blood flow enhaiiccniem selective!) within the middle meningeal artery dependent upon trigeminal and parasympathetic activation. CSD has also been shown to lead to plasma protein leakage within the dura mater. This neuroinflammatory response to CSD may be in part due to an upregulation of inducible nitric oxide synthase and inflammation (Reiner et al. 2002). These findings provide a neural mechanism by which extracerebral cephalic blood flow and neurogenic inflammation are coupled to a cortical neuroelectric event.

Summary. A unified hypothesis for the pathogenesis of migraine is as yet unavailable. It appears that the susceptibility[7] to migraine is hereditary and that the migrainous brain is qualitatively and quantitatively different from the nonmigrainous brain. These differences produce a threshold of susceptibility governed by factors that lead to neuronal hyperexcitahility and a tendency for spontaneous depolarization. These laciors may include a deficit in mitochondrial oxidative phosphorylation, an alteration in neuronal voltage-gated calcium-channel function, an intracellular magnesium deficiency, or a combination thereof. Neuronal excitability may be responsible for the phenomena of spreading activation and depression, with subsequent changes in regional cerebral blood flow. In animal models, blockade of IVQ calcium-channel function within the periaqueductal grey leads to burst activity within the TNC. furthermore, spreading cortical depression can directly activate trigeminal vascular nociceptive afferents. These findings provide an anatomic and physiological explanation for how intrinsic brainstem dysfunction or a cortical neuroelectric event can produce trigeminal activation. Once activated, trigeminal nociceptive afferents can generate neurogenic inflammation via the antidromic release of neuropeptides from the axon terminal of nociceptive trigeminal fibers that innervate meningeal blood vessels. The TNC also receives impulses from trigeminal vascular afferents, which are activated by sterile perivascular

neurogenic inflammation. This two-way system could account for migraine that is triggered either from the vascular system by vasodilator substances or arteriography or from die central mechanism of cortical spreading depression or activation of brainstem pain modulatory centers.

Treatment and Management

When a diagnosis of migraine is made, the nature of the disorder should be explained to the patient and reassurance given that it is a painful but generally benign condition that can, in most instances, be controlled or alleviated. The lack ol a cure for migraine should be mentioned, li is important that patients be made to feel that the physician understands that their headaches are a legitimate medical problem and does not consider their headaches to arise from psychological factots. A normal CT or MRI scan offers considerable reassurance. Many patients are more interested in knowing that they do not have a brain tumor or other potentially lethal condition than they are in obtaining relief from the pain.

Avoidance of trigger factors is important in the management of migraine, but -.imply advising a patient to avoid stress and relax more is usually meaningless. Advice to reduce excessive caffeine intake, to stop smoking, and to reduce alcohol intake may be more useful. Current medication use should be reviewed and modified if necessary. The use of drugs known to cause headaches, such as rcserpine, indomethacin, nifedipine, theophylline derivatives, caffeine, vasodilatots (including the long-acting nitrates), and alcohol, should be discontinued or other agents should be substituted if possible. Use of estrogens and oral contraceptives should be discontinued if they are suspected of contributing to the headaches, although in some patients this may not be possible. Exercise programs to promote well-being, correction of dietary excesses, and avoidance of prolonged fasts and irregular sleeping habits can be helpful.

The topic of dietary factors in migraine is difficult. Radical alterations in the diet are rarely justified and seldom effective. Avoidance of foods containing nitrites, such as hot dogs and pteserved cold cuts, and of prepared foods containing monosodium glutamate can be helpful. Avoiding monosodium glutamate can be difficult because it is a constituent of many canned and ptepared foods and is widely used in restaurants, especially in the preparation of Chinese dishes. Ripened cheeses, fermented food items, red wine, chocolate, chicken liver, pork, and many other foods have been suspected of precipitating headaches. These foods mostly contain tyramine, phenylethylamine, and ocltip.iiiiiii;-. All <uY;iM<!ii.il 'VMiriK ulriil ilii's an offending foodstuff, but in our experience, dietary precipitation of migraine is uncommon. Other headache authorities disagree. In some migraineurs attacks are precipitated by strong odors, especially of the perfume or aromatic type. Avoiding the use of strong-smelling soaps, shampoos, perfumes, and other items (e.g., fabric softeners and aftershave lotions! can be helpful for some individuals.

Kveryone is under stress at some time as part of living. People with migraine are not under more stress than any other group of the population, although their responses to stress may differ on the basis of personality and the effectiveness of their defense mechanisms. Many people react to stress by mechanisms that increase the blood pressure, increase the production of gastric acid, or produce symptoms of increased gastrointestinal motility. Others develop various dermatological conditions. The migraincur seems to react with the cerebral and cranial circulations by mechanisms that arc far more complex than this statement would imply.

Helping the patient deal with or avoid stress is difficult. It may be helpful to use a minor tranquilizer or sedative if the response to stress is overwhelming and if the source of the stress is temporary. Long-term stress management requires the help of a psychologist or other appropriately trained professional. Many techniques are used, including biofeedback, relaxation training, and hypnosis. There is evidence that biofeedback, relaxation training, and cognitive behavioral training are useful (Campbell et al. 2000)

Pharmacotherapy. Medical therapy can be administered prophylactically to prevent attacks of migraine or symptomatically to relieve the pain, nausea, and vomiting of an attack. Prophylactic therapy is needed when the frequency or duration of attacks or the dread of attacks seriously interferes with the patient's lifestyle. Other indications for prophylaxis include the occurrence of severe or prolonged neurological symptoms or a lack or response to symptomatic treatment. In general, a prophylactic program should be considered if attacks occur as often as 1 day per week.

Symptomatic Treatment. Symptomatic treatment should usually be started as early in the development of an attack as possible. If an aura is recognized, patients should take most medications during it rather than waiting for the pain to begin. One exception is the subcutaneous form of sumatriptan, which is less effective if taken before the onset of the headache phase. It must be recalled, though, that once the attack is fully developed, otal preparations are almost always less effective because of decreased gastrointestinal motility and poor absorption. If vomiting develops, oral preparations are no longer appropriate.

For many patients, a simple oral analgesic, such as aspirin, acetaminophen, naproxen, or ibuprofen, or an analgesic combination with caffeine may be effective. Caffeine aids absorption, helps to induce vasoconstriction, and may reduce the firing of serotonergic brainstem neurons. However, the use of caffeine-containing combination analgesics more than 2 days per week may lead to increased incidence of headaches. The addition of 10 mg of metoclopramide by mouth may be helpful with any simple analgesic regimen. The patient should rest in a dark, quiet

room with an ice pack on the head, which provides the best situation for the analgesic to relieve the pain. If sleep occurs, the patient often awakens headache free. In some countries, walk-in headache clinics provide a patient with a simple analgesic, an antinausea agent, and a place to sleep for a few hours. In North America, both patients and physicians have come to expect a quick fix; thus, stronger and stronger analgesics and other drugs have been given to those with a headache. Drug addiction is a major problem in some patients who are treated this way. Induction of sleep, control of nausea, simple analgesics, and other non-narcotic agents should be more widely used.

Although increasingly less available, and supplanted in some cases by newer agents, ergot preparations remain important in the symptomatic treatment of migraine. The actions of ergotamine tartrate and other ergot preparations are complex. They are both vasoconstrictors and vasodilators, depending on the dose and the resting tone of the target vessels. Internal and external carotid vessels are believed to read differentl) to therapeutic doses ol these preparations. The external carotid vessels are constricted by ergot preparations. There is no convincing evidence that the internal carotid vessels are similarly affected. The ergot preparations probably exert their effects on migraine via agonist activity at 5-HT receptors. The use of ergotamine tartrate in migraine necessitates intelligent administration by both patient and physician if it is to be effective and if side effects are to be minimized. Oral preparations arc far less effective than those given rectally or parcnterally.

It is important to know the amount of ergotamine in the various preparations and to be familiar with the dose limits and the signs and symptoms of ergotism. Table 75.6 shows the composition and strength of some ergotamine preparations available in the United States. Evidence for the efficacy of these agents in the treatment of migraine is largely based on uncontrolled clinical observations.

When available to the patient, 2 mg of ergotamine tartrate should be administered by mouth as soon as the patient recognizes the symptoms of an acute migraine attack. This dose can be combined with a simple oral analgesic-caffeine combination, and the ergot preparation can be taken again in 1 hour. Possibly a better regimen, but one that is inconvenient and unpleasant to some patients, is to administer ergotamine tartrate by rectal suppository. At the onset of the aura or pain, a 1- or 2-mg rectal suppository of ergotamine tartrate should be inserted and a simple analgesic taken orally. The etgot preparation can be given again in 60 minutes. Expeticnce in the course of several artacks can be used to determine the amount of ergotamine needed to obtain relief. With subsequent attacks, the entire dose can be taken at the onset. If nausea is troublesome, metoclopramide in doses of 10 mg orally aids absorption of the ergotamine tartrate and may prevent vomiting. For patients who are close to vomiting or who are vomiting, an antiemetic suppository, such as chlorpromazine (25-100 mg) or prochlorperazine {25 mg), can be helpful. Analgesics in rectal suppository form include aspirin and acetaminophen, either of which may provide some relief.

With frequent attacks of migraine, care musr be taken to avoid the vicious cycle wherein ergotamine is used so often that the drug-induced vasoconstriction is almost continuous. If this occurs, a lew hours of abstinence from ergotamine leads to relative vasodilatation and results in a withdrawal headache. Such patients often awaken with a vascular headache, obtain relief with a further dose of ergot.inline, arid thus perpetuate the vicious cycle. A sntiil.it-phenomenon can occur with caffeine in people dependent on coffee or caffeine-containing soft drinks. If more than 6 mg of ergotamine is required per week, an alternative preparation should be used.

Ergotamine must be used cautiously in patients with hypertension and in those with peripheral vascular disease. It is contraindicated in patients with coronary artery disease and in women who are pregnant. Administration of ergotamine to patients in whom the aura is particularly prolonged or characterized by a major neurological deficit is also considered unwise. The fear of potentiating the vasospasm to the point of cerebral infarction may be unjustified, but the potential risk can be avoided by withholding potent vasoconstrictors. As an alternative to ergotamine in the symptomatic treatment of migraine, the sympathomimetic agent, isometheptene mucare, is useful. Ir is available in proprietary preparations combined with acetaminophen and dichloralphenazone. It has the advantage of not increasing nausea and of being well tolerated, but it may fail to give relief for severe attacks.

Dihydroergotamine (DHE) has been used for Treatment of migraine since the 1940s. Its poor oral bioavailability limits its administration to the parenteral and intranasal routes (Tables 75.7 and 75.8). Patients can be readily taught to self-administer this drug by each of these routes. This medication should be considered when nausea and vomiting limit the LSL- ol" oral medications or when other medications are ineffective. Although the effect of DHE is slower than that of sumatriptan (see Table 75.8), it does have similar efficacy after 2 hours, and it is associared

Table 75.6: Ergotamine preparations available in the United States

Brand.	*Route of administration*	*F.rgot.nninc <:n:)*	*Caffeine (mg)*	*Belladonna (mg)*	*Other (mg)*
Ercaf	Oral	Ergotamine tartrate (1)			
Bellersal-S	**Oral**	Ergotamine tartrate (0.6)		0.2	Pbenobarbital (30)
Cafergot	**Rectal**	Ergotamine tartrate (2)	100		

Table 75.7: Serotonin (5-HT) agonists used in acute migraine Treatment

Drug	*Route(s)*	*Dose*	*May repeat doses if headache recurs*	*Maximum dose per 24 hr*
Dihydroergotamine	IV	0.5, 1.0 mg	1 hr	3 mg
(DHE-45)	IM	0.5, 1.0 mg	1 hr	3 mg
	SC	0.5, 1.0 mg	1 hr	·' "ig
(Migranal)	Nasal spray	2 mg (0.5 mg/spray) one spray in each nostril, repeat in 15 min		3 mg
Almotriptan (Axcn)	Oral	12.5 mg	2 hr	25 mg
Eletriptan (Replax)	Oral	20, 40 mg	2 hr	80 mg
Frovatripran (Frova)	Oral	2.5 mg	2 hr	7.5 mg
Naratriptan (Amerge)	Oral	1 mg, 2.5 mg*	4hr	5 mg
Rizatriptan (Maxalt)	Oral	5 mg, 10 mg*	2hr	30 mg
Sumatriptan (Imitrex)	Oral	25 mg, 50 mg, 100 mg	**2 lir**	300 mg
	SC	6 mg	2 hr	12 mg
	Intranasal	5 mg, 20 mg*		40 mg
Zolmitriptan (Zonug)	Oral	2.5 mg*, 5 mg	2hr	10 mg
	Intranasal	5 mg	*I* hr	10 mg

""These are the recommended starting dosages based on efficacy and mlerability.
Recommended dosage in U.K.

with a lower recurrence of headache in 24 hours. It is associated with increased nausea in some patients, and it may need to he comhined with an antiemetic agent. When given intravenously in an acute medical care setting, the use of an antiemetic is mandatory.

IViptans. The developmcni "1 sumatriptan heralded a new class of antimigraine agents that are highly selective at certain 5-HT receptors. These agents, sometimes called *triptans,* together with the less selective ergot preparations, have strong agonist activity at the 5-HT] 15 receptor, which mediates crania! vessel constriction, and at the $5\text{-}HT_m$ receptor, which leads to inhibition of the release of sensory neuropeptides from perivascular trigeminal affcrents. The CNS is largely impermeable to sumatriptan, and hence its action is presumably in the periphery. However, it has hecn shown experimentally that activation of 5-HTm/5-HTn> receptors can also attenuate the excitability of cells in the TNC, which receives input from the trigeminal nerve. According'.v. newer 5 \ \'\\\-*J.*> H'l . .u;(.iri>ts act at central as well as peripheral components of the trigeminal vascular system, and at least part of their clinical action may be centrally mediated.

Sumatriptan can be administered orally, intranasally, and by subcutaneous injection (Table 75.9; see also Tables 75.7 and 75.8). Given as a 6-mg subcutaneous injection, either

Table 75.H: Siihciiraneons and intranasal serotonin (5-HT) agonists

*>"£	Dose *fax*	*Headache response (%)** 1 hr	2 hr	4 hr	*Recurrence of headache*
Dihydroergotamine					
Subcutaneous	1	57	73	85	18
Intranasal	2	46	47-61	56-70	14
Sumatriptan					
Subcutaneous	6	70	75	83	55-40
Intranasal	20	55	*M)*	X \	35^0
Zolmitriptan					
Intranasal	5	*55*	70	78	25

^Headache response is defined as a reduction of headache severity from moderate or severe pain to mild or no pain.
Recurrence of headache within 24 hours after initial headache response.
NA = not available,

Tabic 75.9: Oral serotonin (5-HT) agonists

Drug	*Dose (mg)*	*Headache response (%)** *I hr*	*2 hi*	*4 hr*	*Recurrence of headache**
Almotriptan	12.5	35	57	NA	23%
Eletriptan	20.0	20	49	NA	30
	40.0	**to**	60	NA	22
Frovatriptan	2.5	NA	42	61	10-25%
	1.0	19	42	51	17-28%
Naratriptan	2.S	21	48	67	
	5.0	30	60	\-\	30-35%
Rizatriptan	10.0	37	67-77	NA	
	25	NA	52	68	35^0%
Sumatriptan	50	NA	50	7d	
	100	NA	56	75	
Zolmitriptan	2.5	38	64	75	31";,
	Vii	44	*66*	77	

Note: Composite data from product information inserts and literature.
*Headache response is defined as a reduction in headache severity from moderate or severe pain to mild or no pain.
Recurrence of headache within 24 hours after initial headache response.
NA — not available.

self-administered using the manufacturer's auto-injector device or by conventional subcutaneous injection, sumatriptan resulted in significant pain relief at 1- and 2-hour time points after drug administration (see Table 75.8}. For subjects who had no significant pain relief after 1 hour, administration of a second dose of 6 mg provided little further benefit. Zoimattiptan is available as an oral and intranasal preparation.

There are now seven triptans available in the United States. All seem to have a beneficial effect on migraine-associated symptoms, including nausea, photophobia, and phonophobia, which also improves the patient's ability to return to notmal functioning. Table 75.9 provides a comparison of the currently available oral triptans. Side effects of sumatriptan by injection include local reaction at the injection sitc$_v$ usually of mild-to-moderate severity, and a transient tingling or flushed sensation that may be localized or generalized. A more unpleasant sense of heaviness or pressure in the neck or chest has also been described in a small percentage of recipients. It rarely lasts more than a few minutes and is generally not associated with electrocardiogram changes or other evidence of myocardial ischemia. However, because sumatriptan has been shown to produce a minor reduction in coronary artery diameter, it should be used with caution in patients who have significant risk factors for coronary artery disease and should not be given to patients with any history suggestive of coronary insufficiency. It is also contraindicated in patients with untreated hypertension or peripheral vascular disease and in those using ergot preparations. It should not be given to women during pregnancy or lactation or to patients with hemiplegic or basilar migraine.

The potential side effects of all the oral triptans are quite similar. They consist of tingling, flushing, and a feeling of fullness in the head neck or chest.

In general, both the indications and contraindications for these newer 5-HTj agonists are the same as those for sumatriptan. They have not been shown to he safe when administered within 24 hours of ergot preparations or other members of the triptan class.

At this time, there is no evidence to allow accurate prediction of which of these agents will be most effective in a given patient. A few practical guidelines can be given based on the clinical situation and knowledge about available agents. If severe nausea or vomiting occurs early in an attack, the parenteral or intranasal routes should be used. I-'or individuals whose headaches peak rapidly, almotriptan, rizatriptan, and zolmitriptan should be considered, given their early response rates. Some patients may prefer nasal or injectable routes (sumatriptan, DHE, and zolmittiptan). For patients with benign but intolerable side effects from this group of medications, naratriptan, almotriptan, or frovatriptan should be considered, given their favorable side effect profiles. Finally, i! [.here is recurrence of headache after initial relief, DHE, frovatriptan, or naratriptan should be considered. However, it must be remembered that after administration of a triptan, the use of another triptan or any ergotamine derivative within the next 24 hours is contraindicated. If one agent is used and fails, it seems reasonable, barring major side effects, to try another agent in the class.

There is evidence that some of these agents have a lower oral bioavailability when taken during acute migraine attacks than when taken intetictally. Accordingly, it is logical to consider combining these with metoclopramide to improve gastric emptying. Furthermore, experience suggests that coadministration with a nonsteroidal anti-inflammatory drug (NSAID) might be helpful, especially in individuals whose headache responded only partially or who tend to have a headache tceurrence after initial relief (Peroutka 1998).

Symptomatic treatment of migraine with typical aura is essentially the same as that desctibed previously, although subcutaneous sumatriptan is not effective if taken during the aura phase. Modification of the aura is rarely possible or needed.

For many patients, an attack of migraine becomes a harrowing experience. After a variable period, they go to an emergency room or physician's office expecting relief. These patients pose a difficult problem tor the physician. The simplest treatment and generally what the patient wishes or demands is injection of a combination of a opioid, most often meperidine (75-100 mg), and an agent for nausea, such as cblorpromazinc (25-50 mg), promethazine hydrochloride (12.5-25.0 mg), or prochlorperazine (5-10 mg). This is an effective treatment and one that can be used if the physician is sure the patient genuinely has a headache of major proportions. Unfortunately, the complaint of headache is all too easy to simulate as a drug-seeking behavior. The decision to treat with an opioid must be made in each case on the basis of the patient's behavior, the physician's knowledge of the previous history from emergency room records, and the local knowledge of the nursing and emergency room staff. Unfortunately, many patients with headache who report to emergency rooms are given less than adequate relief for fear of indulging drug-seeking behavior. To avoid using opioids, one can use neuroleptic agents acutely, with or without DHE. DHF, 0.5-1.0 mg, with metoclopramide, 10 mg by intravenous injection, is an effective treatment for acute headache and provides an alternative to the use of an opioid. Similarly, prochlorperazine, 10 mg intravenously over 3-4 minutes alone or combined with DHF, can be effective. Sumatriptan, 6 mg subeutaneously, may provide relief of both the headache and the associated symptoms. Some evidence points to the possibility of magnesium deficiency having a role in the pathogenesis of migraine, and intravenous infusion of 1 g of magnesium sulfate results in rapid relief of headache pain in patients with low serum ionized magnesium levels (Bigal et al. 2002). Alternatively, chlorpromazinc, 5 mg injected intravenously every 10 minutes to a maximum of 25 mg,

is also an effective agent when used acutely. The latter agent often produces hypotension, and patients should first receive a bolus of 250-500 mL of *5%* dextrose in one-half normal saline. (Dehydrated patients should always receive appropriate intravenous hydration.) Some patients develop acute extrapyramidal symptoms after treatment with neuroleptic agents. These can be treated with parenteral diphenhydramine, 25-50 mg. The neuroleptic agents do produce sedation, and patients should be advised not to operate a motor vehicle after treatment. Injectable ketorolac, 60 mg given intramuscularly, is another alternative to the narcotic or sedative agents. The use of this NSAID in elderly patients, those who are dehydrated, or those having any history of renal insufficiency should be avoided. A single dose of dexamethasonc combined with other parenteral antimigraine agents has been used for the emergency room treatment of attacks of intractable migraine.

When a migraine lias lasted for many days with little or no relief, the term *status migrainosus* has been used. Dehydration, tiredness due to lack of sleep, and continued pain may necessitate admission to a hospital to terminate the attack. Fluid replacement, correction of electrolyte imbalance, and suppression of vomiting with meto-L-lopi-.iniide. chlorpi'oina/ine, or prochlorperazine generally result in improvement. DHE combined with an antiemetic initially, given intravenous!) every S hours, may aborl migraine status. It is effective, but increased nausea and vomiting may be a reason to switch to an alternative regimen. Corticosteroids, such as dexamethasone or prednisolone, can be administered. A dose of prednisolone of 20 mg every 6 hours initially, followed by a rapidly tapering dose over 2-3 days, may help abort status migrainosus. It is best to avoid narcotic and benzodiazepine agents when treating status migrainosus.

Prophylactic Treatment. When the attacks of migraine occur weekly or several times a month or when they occur less often but arc very prolonged and debilitating, a preventive program is appropriate. Attacks of migraine that occur in a predictable pattern can also respond to prophylactic medication. For example, menstrual migraine can be treated in this way (see Prophylactic Menstrual Migraine Therapy, later in this chapter).

jS-*Adrenergic Blockers*

/J-Adrenergic antagonists are widely used for the prophylaxis of vascular headaches (Silberstein 2000). Propranolol is effective in *55-93%* of patients. These figures do not mean that the migraine attacks stopped but that the patients with responding headaches reported at least a 50% reduction in the frequency and severity of their attacks. In other studies, more than 50% of patients reported having a favorable response to a placebo.

Propranolol should be administered in doses of 80-240 mg per day and, if tolerated, should be given a trial of 2 to 3 months. Compliance is increased with the use of a long-acting form of propranolol that can be given once daily. Side effects are not usually severe. Lethargy or depression may occur and may be a reason for discontinuation of the medication. Hypotension, bradycardia, impotence, insomnia, and nightmares can all occur. As with all ^-adrenergic blocking agents, administration of propranolol should be discontinued slowly to avoid cardiac complications. It is contraindicated in people with a history of asthma and should be used with caution in patients using insulin or oral hypoglycemic agents because it may mask the adrenergic symptoms of hypoglycemia. The benefit of propranolol in migraine may be separate from its action as a /J-adrencrgic blocking agent, but its exact mechanism of action is unknown.

Almost all the available ^-adrenergic blocking agents have been tested for their potential use in migraine. Timolol, nadolol, atenolol, and metoprolol have each been shown to have approximately the same benefit in migraine as propranolol.

A n tidep ressa n ts

Amitriptyline and other tricyclic antidepressants can be helpful in migraine prophylaxis (Silberstein 2000), just as they are useful in the prevention of muscle contraction icnsitei! headaches. The benefit seems to lie independent of their antidepressant action. Blockade of noradrenaline uptake at catecholamine terminals and inhibition of serotonin reuptake may be related, but the action of antidepressants in migraine is unclear at present. Used in doses of 10-150 mg at night, amitriptyline, imipramine, desipramine, or nortriptyline may all provide some reduction in attacks of migraine, although evidence of efficacy in clinical trials is available only for amitriptyline. Side effects can be rather troublesome. Morning drowsiness, dryness of the mouth, weight gain, tachycardia, and constipation are common. The anticholinergic side effects may decrease with time. If tolerated, the tricyclic agents should be given a trial of at least 3 months after a therapeutic dose is reached. The optimal dose for migraine prophylaxis must be determined by titration to the effective or maximum tolerated dose within the therapeutic range (usually 40-150 mg).

The efficacy of newer antidepressants of the selective serotonin reuptake inhibitor type, such as fluoxetine and sertraline, has not been consistently demonstrated in clinical trials, and these drugs have a relatively limited role in the prophylaxis of migraine. Headache is a common side effect of several drugs in this class of antidepressants.

Use of the monoamine oxidase inhibitor (MAOI) phenelzine for migraine prophylaxis is based on the agent's inhibiting the breakdown of serotonin, which would thereby continue to act as a constrictor of cranial vessels. Unfortunately, the dietary restrictions that must be carefully followed if a hypertensive crisis is to be avoided limit

the widespread use of these inhibitors for prevention of migraine, h'or patients with particularly severe and intractable attacks, the MAOIs should be considered. The patient must be given a list of a mine-containing foodstuffs to he avoided, such as strong cheese, red wine, beer, yeast products, cream, broad beans, fermented foods, yogurt, and many others. Dangerous drug interactions can occur with preparations such as sympathomimetic agents, L-dopa, central anticholinergics, tricyclic antidepressants, and opioids, especially meperidine. Side effects of MAOIs include hypotension as well as hypertension, agitation, hallucinations, retention of urine, and inhibition of ejaculation,

Calcium-Channel Blockers

The calcium-channel antagonists prevent spasm of arteries by inhibiting contraction of smooth muscle. Although the relevant mechanism by which they affect migraine is not known, their use in migraine was originally based on their ability to prevent vasoconstriction and on their other actions, including prevention of platelet aggregation and alterations in release and re-uptake of serotonin. Several clinical trials have indicated some benefit for verapamil, nimodipine, and tlimari/.inc in preventing recurrent migraine. Nifedipine seems to cause a generalized headache as a side effect and has little to add to migraine prophylaxis. Verapamil in doses of 80-160 mg three times a day reduces the incidence of migraine with aura, but it is not as useful in migraine without aura. Experience with diltiazem is too limited to permit an assessment of its value at this time.

Anticonvulsants

Over the past several years, anticpileptic drugs have been the fastest expanding class of drugs in the prophylactic arsenal for migraine. Although the mechanism by which the drugs act in migraine prevention is not known, they are all modulators of the y-aminobutyric acid system.

In the early 1990s sodium valproate was shown in several blinded, placebo-controlled studies to have a beneficial effect in the prophylactic treatment of migraine (Silberstein 2000). Fifty percent of patients showed a response with a 50% or better reduction in migraine incidence. Valproic acid is usually given in the form of divalproex sodium and is generally effective at a range of 500-1750 mg per day taken in divided doses. Side effects include sedation, dizziness, increased appetite, increased bleeding time, increased fragility of hair, and an asymptomatic increase in liver function test values. Valproate should not be used in women who are at risk of becoming pregnant because it is associated with an increased risk of neural tube defects in the infants of women taking it during the first trimester. Gabapentin has been shown to be effective in the reduction of migraine incidence (Mathew ct al. 2001), It also has beneficial effects in somatic pain and may be a good choice if a patient has neck pain, back pain, or painful peripheral neuropathy as well as migraine. It appears to be relatively well tolerated although dizziness and sedation may limit its use in some patients. The therapeutic dose range for gabapentin is 600-2400 mg per day. Topiramatc is the most recent addition to the antimigraine armamentarium. Its efficacy for migraine has been demonstrated in several small blinded series (Storey et al. 2001). Topiramate has effects not only on y-aminobutyric acid but also on non-NMDA glutamate and carbonic anhydrase activity. It may have prominent sedating and cognitive side effects, making a slow gradual titration of the drug (15 mg per week initially) to the therapeutic range of 70-200 mg per day the most successful strategy. Other side effects include paresthesia and weight loss, the latter making topiramate a particularly attractive choice for many patients. It is also associated with a mildly increased risk nl kidney stones.

Serotonergic Agents

Methysergidc may be an effective prophylactic agent for all types of vascular headache. At this time, though, its manufacturer has ceased its production in the United States, and whether it will reappear is uncertain. Historically it has been a very useful agent despite its potential for producing serious complications, such as retroperitoneal, pulmonary, and heart valve fibrosis, which seriously limit its use as a long-term prophylactic agent. It should be reserved for the most intractable migraine and should be given for periods of only 6 months at a time. Between such courses, methysergide should be discontinued for 4 weeks. A clinical examination, urinalysis, and serum creatinine determination may be undertaken to detect any evidence of the fibrotic complications. Some authorities also advise obtaining a chest roentgenogram, scrum creatinine level, and an abdominal CT or MRI scan. If there are no signs of side effects, treatment with the drug can be restarted and continued for another 6 months. The incidence of fibrotic complications is low, perhaps 1 in 1000 patients. If fibrosis does develop, it may resolve if methyscrgide is immediately and permanently withdrawn, but this is not always the case.

Whenever methysergidc is prescribed, it must be started very slowly. A fraction of a 2-mg tablet is the initial dose, followed by a gradual increase ovet 7-10 days to the minimal effective dose, generally in the range of 6-8 mg in three or four divided doses per day. Rapid introduction of the drug leads to nausea, abdominal cramps, pain in the legs (possibly due to venospasm), hallucinations, and agitation. Methysergide is a derivative of lysergic acid *" diethylamide. It can act as a serotonin antagonist peripherally and as a serotonin agonist centrally, but its mode of action in vascular headaches is incompletely understood.

Cyproheptadine is also a peripheral serotonin antagonist. It also has weak antibradykiuin activity and prevents platelet aggregation. In adults, it has a minor role in the

prevention of migraine, but it is more effective in children. At all ages, it causes drowsiness and may cause significant weight gain.

Other Prophylactic Agents

Riboflavin administered orally in a dose of 400 mg per day has been shown to be effective in migraine prophylaxis in a prospective, randomized, controlled study that enrolled a relatively small number of subjects. The effect on the frequency of attacks was not statistically significant until the third month of the trial (Schocncn et al. 199S). There are minimal side effects associated with this treatment.

Oral magnesium supplementation has also been shown in double-blinded, placebo-controlled, randomized studies to be effective in migraine prophylaxis. Oral magnesium supplementation with 600 mg of a chelated or slow-release preparation is recommended. Magnesium-induced diarrhea and gastric irritation are the most common side effects (Mauskop and Altura 1998).

Aspirin, 325 mg taken every other day for the prevention of cardiovascular disease, reduces the incidence of migraine slightly. The NSAIDs have been tried for migraine prophyl.iM-„ wiili some bcnchl. 1 hoy arc, however, helpful for providing analgesia during the acute attack.

Botulinum toxin A injection in the treatment of migraine is supported by an increasing body of anecdotal evidence from small MTICS .iiul n conirulled •.iin.U ^i I bets: cm ci al. 2000b). The treatment may exert its effect by reducing the release of proinflammatory and vasodilating neuropeptides from nociceptive terminals. Botulinum toxin blocks the release of glutamate from nociceptive terminals and therefore may reduce or inhibit the development of peripheral and central trigeminal sensitization. Doses of up to 100 units ate injected in muscles of the forehead, as well as temporalis, splemus capitis, and trapezius. The effect, when it occurs, appears within 7-10 days and persists for up to 3 months. Side effects are minimal when lateral forehead injection is avoided. For patients who do not tolerate or do not comply with daily drug usage or who may prefer an injectable agent rather than chronic oral therapy, botulinum toxin may be a viable option.

Hormones and Migraine

Migraine occurs equally in both sexes before puberty, but it becomes three times more common in women after menarehe. Approximately 25% of women have migraine during their reproductive yeats. The changing hormonal environment throughout a woman's life cycle, including menarehe, menstruation, oral contraceptive LLSC, pregnancy, menopause, and hormonal replacement therapy (HRT), can have a profound effect on the course of migraine.

Menstrual Migraine. Migraine attacks are associated with menses in one of three ways. The attacks may occur exclusively during menstruation and at no other time during the cycle. This association is referred to as *true menstrual migraine* (TMM), and it has recently been proposed that TMM be defined as attacks that occur between days —2 and +3 of the menstrual cycle (MacGregor 1996). The incidence of TMM according to this definition is approximately 7%. Mote commonly, migraine attacks occur throughout the cycle but increase in frequency or intensity at the time of menstruation. This association occurs in up to 60% of female migraineurs. Finally, premenstrual migraine can occur between days —7 and —3 before menstruation as part of premenstrual syndrome or late-luteal phase dysphoric disorder. This disorder is characterized by a cluster of symptoms in the luteal phase, including depression, irritability, fatigue, appetite changes, bloating, backache, breast tenderness, and nausea. These different relationships between migraine and the menstrual cycle can reliably be determined by reviewing headache diaries, and their distinction is important because pathophysiology may differ as would the therapeutic approach.

Numerous mechanisms have been proposed to explain the pathogenesis of menstrual migraine. There is abundant clinical and experimental evidence to support the theory that estrogen withdrawal before menstruation is a trigger tor migraine in some women. Estrogen withdrawal may modulate hypothalamic /t-endorphin, dopamine, ^-adrenergic, and serotonin receptors. This complex relationship causes significant downstream effects, such as a reduction in central opioid tone, dopamine receptor hypersensitivity, increased trigeminal mechanorcceptor receptor fields, and increased cerebrovascular reactivity to serotonin, These changes, which occur during the luteal phase of the cycle, may be germane to the pathogenesis of menstrua] migraine,

Several lines of investigation have implicated both prostaglandins and melatonin in the pathogenesis of menstrual migraine. Prostaglandins and melatonin are important mediators of nociception and analgesia, respectively, in the CNS. The concenttation of prostaglandin F_2 and nocturnal melatonin secretion increase and decrease, respectively, during menstruation in female migraineurs. These observations are the basis for the clinical use of NSAIDs and melatonin for the prophylaxis of mensttual migraine.

Management of Menstrual Migraine, A direct link between menstruation and headache attacks must be established by asking the patient to keep a diary card of migraine attacks and menstrual periods for at least 3 consecutive months. The nature of this relationship determines subsequent therapy. For example, for patients who have both menstrual and nonmenstrual attacks (menstrua I-associated migraine), a standard prophylactic medication might be used throughout the cycle rather than the perimenstrual use of a prophylactic agent. The goals of therapy should be clearly outlined in addition to the

dosages, benefits, and side effect profile of each recommended medication. A headache dian should ideally be started by the patient in an effort to identify other nonhormonal triggers. Biofeedback and relaxation therapy can be helpful in selected patients and should be used whenever possible. Lifestyle factors, such as regular meals, sufficient sleep, and regular aerobic exercise, are important items to emphasize. These simple efforts can have a significant impact on the patient's headache burden and may limit the incidence of attacks that require pharmacological intervention.

Acute Menstrual Migraine Therapy. The goal of acute menstrual migraine therapy is to decrease the severity and duration of pain as well as the associated symptoms of an individual migraine attack, including nausea, vomiting, photophobia, and phonophobia. Some women may control attacks of menstrual migraine quite adequately with abortive therapy only (Figure 75.fi).

The acute management of menstrual migraine does not differ from the treatment of migraine unassociated with menstruation. Mild attacks (which are relatively rare) can hr managed with acetaminophen or NSAIDs. Moderatc-to-severe attacks can be treated by using an oral triptan. If there is significant nausea and vomiting, however, an alternate route of administration is necessary. In this setting, parenteral therapy with sumatriptan, DHE, ketorolac, or a neuroleptic, such as prochlorperazine, is appropriate. Alternatively, both sumatriptan and DHE are available in a nasal formulation and can he helpful in patients with significant gastrointestinal upset. The combination of an antiemetic with any of these medications may not only alleviate nausea and vomiting but may also potentiate the efficacy of these compounds.

Prophylactic Menstrual Migraine Therapy. Prophylaxis may either be perimenstrual (cyclic) or continuous (noncyclic) (Table 75.10). Many of the regimens suggested for perimenstrual migraine prophylaxis depend on regular menstruation. Perimenstrual prophylaxis commences a few days before the period is expected and is continued until the end of menstruation. In women whose cycles are difficult to predict, continuous prophylaxis with standard migraine prophylactic agents, such as tricyclic antidepressants and beta blockers, can be quite effective if taken continuously.

NSAIDs arc considered to be a first-line agent for both acute and prophylactic therapy in patients with either

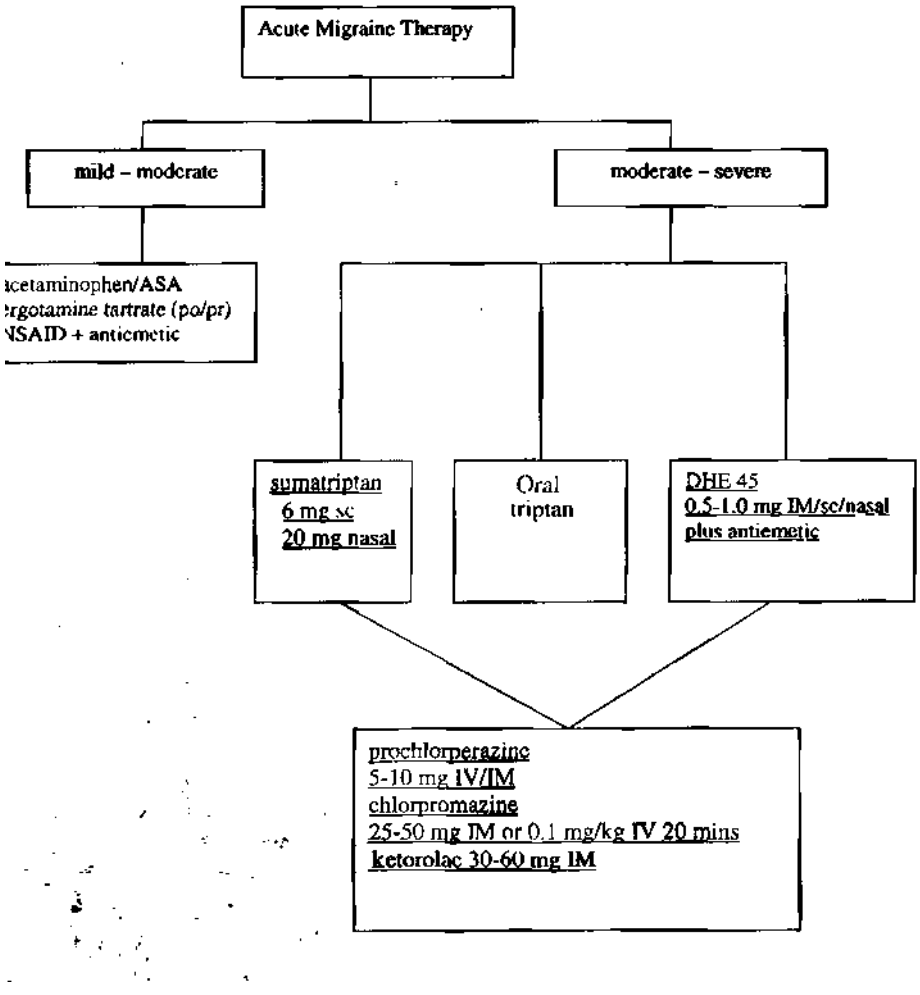

FIGURE 75.6 Algorithm for acute treatment of menstrual migraine. (ASA = acerylsalicylic acid: 1)1 II-. • dihydroergotamine; NSAID = nonsteroidal anti-inflammatory drug.)

Table 75.10; Nonhormonal prophylaxis for menstrual migraine

Cyclic (perimenstrual) days —3 through +3
- Nonsteroidal anti-inflammatory drugs
  - Naproxen sodium 5.50 nig hid
  - Mefenamic acid 250 mg tid
  - Ketoprofen *IS* mg tid
- Triptans and ergots
  - Sumatriptan 25 mg tid
  - Narairiptan 1.0 mg tid or 2.5 mg bid
  - Frovatriptan 2.5 mg once daily
  - Zolmitriptan 2.5 mg bid
  - Ergotamine tartrate + caffeine (Wigraine) 1 mg qhs or bid
  - Dihydroergotamuie 0.5-1.0 mg (SC, 1M, or intranasal) bid

Noncyclic (throughout cycle)
- Tricyclic antidepressants
  - Nortriptyline or amitriptyline 10-150 mg qhs
- Beta blocker
  - Propranolol or nadolol 40-240 mg daily
- Calcium-channel blocker
  - Verapamil 240-480 mg daily
- Anticonvulsant
  - Divalproex 250-500 mg bid
- Dopamine agonists
  - Bromocriprine 2.5-5.0 mg tid
- Oilier
  - Magnesium 360-600 mg daily

menstrua I-associated migraine or TMM when the timing of menstruation is predictable. Different classes of NSAlDs should be tried because response may vary in a given individual. Ergot derivatives in the form of ergotamine tartrate, etgonovine maleate, and DHE can also be effective when used as a symptomatic or prophylactic drug around the time of menstruation. Concerns about habituation or rebound headaches are minimal given the limited duration of treatment when used drugs are used perimenstrually.

For those with TMM, attacks can also be prevented by stabilizing estrogen levels during the late luteal phase of the cycle. Estrogen levels can be stabilized by maintaining high levels with estrogen supplements or by maintaining low levels that result from a natural or medically induced menopause (Table 75.11).

Estradiol implants, percutaneous estradiol gel, and estrogen patches produce reasonably stable levels of estrogen and rhcit use can be an effective preventive strategy. If periods are less predictable, suppression of the ovulatory cycle with high, static estrogen levels can be accomplished with either a low-dose combined estrogen-progestin oral contraceptive pill taken continuously for 3-4 months or with two 100-ug patches replaced every 3 days in combination with cyclic progestogens. Treatments that suppress the cycle by reducing estrogen levels (danazol), inducing a medical menopause (goserclin [Zoladexj), or modifying the effect of estrogen (tamoxifen) have also been anecdotally reported to be successful in the treatment of resistant menstrual migraine. They are not commonly used in clinical practice, howevct, because the menopausal side effects of these medications can be unpleasant. Theit use should be reserved for patients with recalcitrant migraine. Progesterone atone is ineffective in the treatment of menstrual migraine.

Table 75.11: Hormonal prophylaxis for menstrual migraine

Static high-maintenance levels
Transdermal estradiol (1 x 100 ug days —3/—1/+2)
Combined oral contraceptive or transdermal patch !.i 4 mosl
Percuraneous esrradiol (1.5 mg daily days —3 ro +6)
Static low-maintenance levels
Danazol 200-600 mg/day
Tamoxifen 5-15 mg/day (days 7-14 luteal cycle)
Goserclin (treatment limited to 6 mo)

Bromocriptine, a dopamine (D_2) receptor agonist, may decrease perimenstrual symptoms of breast engorgement, irritability, and headache when administered during the luteal phase of the cycle. Efficacy is enhanced, however, when the medication is used continuously throughout the cycle rather than perimenstrually (Herzog 1997).

The use of magnesium for the acute and prophylactic treatment of migraine and menstrual migraine has received considerable attention over the past few years. Low levels of systemic magnesium have been found in women with menstrual migraine, and MRS studies have demonstrated reduced lewis <1 mlI.KVIIUI.U magnesium in the cerebral cortex of migrameurs. Low levels of intracellular magnesium may lead to neuronal hypei excitability and spontaneous depolarization, which may be the central process by which a migraine attack is initiated. This has led some investigators to study the effect of magnesium on both the acute and prophylactic management of menstrual migraine (Mauskop and Altura 1998).

Some physicians still advocate the use of hysterectomy and oophorectomy in women with intractable PMS and menstrua] migraine whose headaches tespond to medical ovariectomy. There ;iu- no loiigicrni tulUm -up ur controlled studies to conclusively substantiate this position. Because no study has been placebo controlled, the positive results seen in some studies may reflect the daily postoperative use of estrogen. Although two thirds of women who have physiological menopause experience migraine relief, the opposite effect may occur with surgical menopause with bilateral oophorectomy. A retrospective study of 1300 women also demonstrated the unfavorable effects of surgical menopause on migraine (Granclla ct al. 1993). Therefore, until convincing evidence demonstrates otherwise, hysterectomy with or without oophorectomy is *not* currently recommended for women with menstrual migraine.

Oral Contraception in Female Migraineurs. Migraine prevalence is highest in women during their reproductive years, the very population who use oral contraceptive therapy. Oral contraceptives have a variable effect on migraine. Migtainc may begin *dc novo* after a woman starts taking oral contraceptives, pre-existing migraine may

worsen in severity or frequency, or the characteristics of the migraine attack may change. For example, aura symptoms may develop in a woman who for years may have had migraine without aura. On the other hand, migraine attacks may lessen after an oral contraceptive is started, particularly in women whose migraine attacks had a very close relationship to menstruation. In the majority of women, however, the pattern of migraine does not change appreciably alter ney a/irt raking .111 oral conrau'prive, particularly with the lower doses of estrogen and progestin now found in most oral contraceptives.

The concern ahout the use of synthetic estrogen in women with migraine pertains to the increased risk of ischemic stroke in this population, relative to age-matched women without migraine. There is now convincing evidence that female migraineurs have a greater risk of experiencing ischemic stroke. Tzourio and colleagues (19951 found migraine to be strongly associated with the risk of ischemic stroke in young women (odds ratio 3.5), and this association was independent of other vascular risk factors. The risk of ischemic stroke was particularly increased in women with migraine who were using oral contraceptives (odds ratio 13.9), were heavy smokers (odds ratio 10.2}, or who had migraine with aura (odds ratio 6.2). It has been estimated that the incidence of ischemic stroke in young women with migraine with aura who use oral contraceptives is 28 and 78 per 100,000 women aged 25-34 and 35-44, respectively. This is in contrast to the incidence of ischemic stroke of approximately 4 and 11 per 100,000 women in the general population in the same respective age groups. Although the relative risk of ischemic stroke is increased in this group, it is important to hear in mind that the absolute risks are still small.

The International Headache Society Task Force developed evidence-based recommendations for the use of oral contraceptives and hormone replacement therapy in migraineurs (Bousser et al. 2000). When prescribing combination oral contraceptives (COCs) in women with migraine, their recommendations were the following:

- Identify and evaluate risk factors.
- Diagnose migraine type, particularly the presence of aura.
- Recommend that women with migraine should stop smoking before starting COCs.
- Treat other conditions, such as hypertension and hyperlipidemia.
- Consider non-ethinylestradiol methods in women who are at increased risk of ischemic stroke, particularly in those who have multiple risk factors. Some of these contraceptives are as or more effective in preventing pregnancy than COCs and include progestogcn-only hormonal contraception. Observational studies suggest that progestogen-only hormonal contraceptive use is not associated with an increased risk of ischemic stroke, although quantifiable data are limited.
- High-dose COCs (>50 pg cthinylestradiol), particularly those containing first-generation progestogens, are no longer recommended for routine use.
- Low-dose formulations (<50 pg ethinylestradiol) containing either second- or third-generation progestogens should be used when possible. Second-generation progestogens include ethynodiol diacetate, levonorgestrel. and norethisteronc. Third-generation progestogens include desogestrel, gestodene, and norgestimate.

Migraine symptoms that may necessitate further evaluation or cessation of COC include the following:

- New pei sisting headache
- New onset of migraine aura
- Increased headache frequency or intensity
- Development of unusual aura symptoms, particularly prolonged aura

With respect to contraindications for the use of HRT, the Task Force concluded that there was no evidence proving that migtaine is a risk factor for ischemic stroke m women older than age 45. In addition, there are insufficient data to support an increased risk of ischemic stroke in women with any type of migraine who are using HRT. Consequently, the usual indications and contraindications for HRT should be applied.

Migraine and Pregnancy. Pregnancy has a variable effect on migraine. Although approximately 70% of women experience improvement or remission of migraine symptoms during pregnancy, the attacks can either remain unchanged or worsen. Moreover, migraine may even begin for the first time during pregnancy. Remission or improvement occurs more often in women with pre-existing menstrual migraine, whereas worsening is more common in those with a history of migraine with aura. The majority of women who develop migraine during pregnancy have migraine with aura. Although there is a trend for improvement in the second and third trimesters, there is no significant correlation between improvement or worsening of migraine and a specific trimester.

If remission occurs during pregnancy, migraine often recurs in the postpartum period, particularly 111 those with a history of menstrual migraine or migraine associated with estrogen withdrawal. Postpartum migraine occurs most often 3-6 days after delivery. As with pregnancy itself, migraine may first begin in the postpartum period, although this is a very rare occurrence.

The use of medication to treat migraine during pregnancy should be limited. For most tnild-to-moderate attacks, nonpharmacological treatment, including biofeedback, rest, and relaxation therapy, should be used. Acetaminophen may be combined with codeine, but the indiscriminate use of codeine may present a risk to the fetus during the first or second trimester.

For patients with severe attacks or status migrainosus, the risk to the developing fetus may be greater than the judicious of medications. The intravenous use of neuroleptics, supplemented with eithet intravenous opioids or corticosteroids, is an effective strategy for these patients. Either chlorpromazine or prochlorperazine (10 mg) delivered in 4 mL of crystalloid or 50 mL of normal saline as a bolus over 10-15 minutes can be effective for both the headache as well as the nausea and vomiting associated with a severe attack. Mcthylprednisolone (50-250 mg) delivered intravenously can also be an effective method to terminate a severe acute migraine attack or status migrainosus during pregnancy. Methylprednisolone is preferred over dexamcthasonc because the latter more readily crosses the placenta.

Migraine in Menopause. Just as with pregnancy, the effect of menopause on the course of migraine is somewhat unpredictable. Although in two thirds of women with a previous history, migraine decreases with a physiological menopause, migraine can either regress or worsen at menopause (Silberstein 2001), and in a minority of women, migraine or its functional equivalents may begin after menopause.

Women with menopausal symptoms resulting from erratic or diminished estrogen secretion may benefit from HRT. Few published studies have assessed the effects of HRT on migraine in perimenopausal women, but the evidence available appears to highlight the importance of both route and method of administration. With any preparation of estrogen, the lowest effective dose should be used. In general, parenteral or transdermal preparations provide a more physiological ratio of estradiol to estrone and a steady-state concentration of estrogen. They are also more suitable delivery systems for women with migraine or for those whose headaches are worsened by oral estrogen replacement therapy (Silberstein 2001). Also, continuous rather than interrupted HRT may be more effective in female migraineurs, particularly if their headaches had been associated with estrogen withdrawal.

Migraine may be worsened by the use of cyclic progestins. Tor women who require combined estrogen and progesterone therapy after hysterectomy, use of a transdermal progestin patch usually circumvents this problem.

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

Cluster Headache

Among the many painful conditions that affect the head and face, the one known by the most names is also unique in several other respects. Cluster headache, Horton's headache, histaminic cephalalgia, or migrainous neuralgia, as the condition is variously known, is without doubt the most painful recurrent headache and the one that produces the most stereotyped attacks. Despite its readily recognizable features, the syndrome continues to be misdiagnosed as trigeminal neuralgia or sinus or dental disease and therefore is ineffectually treated.

Classification and Terminology

In episodic cluster headache, attacks of pain occur daily for days, weeks, or months before an attack-free period of remission occurs. This respite may last from weeks to years before another cluster of attacks develops. In *chronic* cluster headache, attacks of pain occur for more than 1 year without a remission longer than 2 weeks (ICD 10 Guide for Headache 1997). This chronic form of the disease may develop *de novo* or may evolve from episodic cluster headache. Chronic cluster headache can therefore be divided into primary and secondary chronic types.

Clinical Features

Cluster headache is predominantly a disease of men. Onset typically begins in the third decade of life although its onset has been described as early as 1 year of age and as late as the seventh decade.

Periodicity is a cardinal feature of cluster headache. In most patients, the first cluster of attacks, the cluster period, persists, on average, 6-12 weeks, and is followed by a remission lasting for months or even years. The duration of the cluster period is often strikingly consistent for a given patient. A common pattern is one or two cluster periods per year. With time, however, the clusters may become seasonal and then occur more often and last longer. During a cluster, the patient may experience from one to three or more attacks in 24 hours, and the attacks commonly occur at similar times throughout the 24 hours for many days. Onset during the night or 1-2 hours after falling asleep is common. In some patients, this may correspond to the onset of REM sleep. At times, several attacks per night can result in sleep deprivation in patients with chronic cluster headache, particularly when they avoid sleep fot fear of inducing a further attack. With increasing age, the distinct clustering pattern may be less recognizable. In some patients, perhaps as many as 10%, periods of relief become less common, and the condition enters the chronic phase in which attacks may occur daily for months or years. In these patients, the condition may persist into old age, but in nearly 50% the attacks eventually cease.

Whether the patient is in the episodic or the chronic phase of headache, the attacks of pain are identical for all individuals. The pain is strictly unilateral and almost always temains on the same side of the head from cluster to cluster; rarely, it may switch to the opposite side in a subsequent cluster. The pain is generally felt in the retro-orbital and temporal regions but may be maximal in the cheek or jaw (lower syndrome). It is usually described as

steady or boring and of terrible intensity (so-called suicide headache). Graphic descriptions of feeling the eye being pushed out, or an auger or hot poker going through the eye are very common.

Onset is usually abrupt or preceded by a brief sensation of pressure in the soon-to-be-painful area. An occasional patient may describe tension and discomfort in the limbs and neck ipsilateral to the pain, either during the attack or just preceding it. Aura symptoms (as seen in migraine) have been reported to precede cluster attacks (Silberstein et al. 2000a). The pain intensifies very rapidly, peaking in 5-10 minutes and usually persisting for 45 minutes to 2 hours. Toward the end of this time, brief periods of relief may be followed by several transient peaks of pain before the attack subsides over a few minutes. Occasionally, attacks last twice as long, or, even less commonly, the attacks may seem to merge together, producing 12 or more hours of pain. After the attack, the patient is then completely free from pain, but exhausted; however, the respite may be transient because another attack may occur shortly.

During the pain, patients almost invariably avoid the recumbent position because doing so increases the intensity of the pain. Unlike patients with migraine, they are restless and prefer to pace or sit during an attack. Some remain outdoors, even in freezing weather, for the duration of the attack. Otherwise rational persons may strike their heads against a wall or hurt themselves in some other way as a distraction from the intense head pain. Most patients prefer to be alone during [he attack. Some appl\ ice to the painful region, others prefer hot applications; almost all press on the scalp or the eye to try to obtain temporary relief. During the pain, many patients consider suicide; a few attempt it.

During the pain of cluster headache, the nostril on the side of the pain is generally blocked; this blockage in turn leads to ipsilateral overflow of tears caused by blockage of the nasolacrimal duct. The conjunctiva may be injected ipsilaterally, and the superficial temporal artery may be visibly distended. Profuse sweating and facial flushing on the side of the headache have been described but are rare. Nasal drainage usually signals the end of the attack. Ptosis and miosis on the side of the pain are common. This partial Horner's syndrome may persist between the attacks and is believed to be due to compression of the sympathetic plexus secondary to vasodilatation or other changes in the region of the carotid siphon. Photophobia during the painful stage is less common than in migraine, but it may occur and may be accompanied by phonophobia. Gastrointestinal symptoms are not usual features of cluster headache attacks. Although nausea occurs in up to 50% of patients, vomiting is rare (Bahra et al. 2002). In some patients, nausea may be due to the medication ingested. Facial swelling, most often periorbital, may develop with repeated attacks. Rarely transient localized swellings of the palate ipsilateral to the pain can be observed. More commonly, the patient complains that the palate feels swollen, but no abnormality can be detected by the examiner, even during an attack.

Patients with cluster headaches have a high incidence of duodenal ulceration and elevated gastric acid levels that may approach those found in the Zollinger-Ellison syndrome. They also tend to have coarse facial skin of the *peau d'oratvge* type, deep nasolabial folds, and an increased incidence of hazel eye color. Many of the patients are heavy cigarette smokers and tend to use more alcohol than age- and sex-matched control subjects.

Investigations

In most patients, the diagnosis is so certain on clinical grounds that special neurological investigations are unnecessary. However, imaging studies are warranted in any patient presenting with an atypical episodic cluster headache or for patients with headache in the chronic phase. As part of the management, however, it may be advisable to obtain a contrast-enhanced MRI scan to help reassure the patient and the relatives that the extremely painful attacks are not due to some major intracranial abnormality. On occasion, examination of the eyes should include measurement of the ocular tension to detect glaucoma. Tests of a general nature are needed to determine any conttaindications to the use of various medications.

Pathop bysiolog)'

The pathogenesis of cluster headache is not entirely understood. Any explanation for the etiology of cluster headache must account for the cyclically occurring attack-susceptible periods, The periodicity of cluster headache is probably related to hypothalamic dysfunction. Changes have been shown in the levels of melatonin, Cortisol, prolactin, ^-endorphin, and testosterone between cluster periods and remissions.

The most direct evidence in support for a role of the hypothalamus in cluster headache comes from neuroimaging. PET imaging studies showing activation in the ipsilateral ventral hypothalamic gray matter during nitroglycerin-induced cluster attacks (May et al. 1998). In addition, a morphometry study of MR] scanning technology has shown an increase in volume in the diencephalon corresponding to the inferior hypothalamus (May et al. 1999).

Although vasodilatation has been generally believed to be responsible for the pain. PET studies of experimental pain and cluster headache have shown that carotid artery dilation is not specific for cluster headache but is seen with other types of ophthalmic division pain; it appears ro he an epiphenomenon of a primary neural process (May et al. 1999). *

Moskowitz in 1993 emphasized the role of the trigeminovascular connections and substance P in the pathogenesis of vascular head pain. Further evidence suggested activation of the trigcminovascular system as manifested by increased levels of calcitonin gene-related peptide in blood

sampled from the external jugular vein ipsilateral to an acute spontaneous attack of cluster headache. Vasoactive intestinal polypeptide levels were similarly elevated in the cranial venous blood during a cluster attack, demonstrating activation of the cranial parasympathetic nervous system (Goadsby and Edvinsson 1994).

Several observations suggest that histamine may play a role in causing this condition. During painful attacks, increased histamine levels have been detected in the blood and urine, but whether this increase is a primary or secondary phenomenon remains unknown. Morphological studies of the increased number and abnormal distribution of mast cells in the forehead skin of patients with cluster headache support the ihcon thai local release ol histamine is involved in some way in this condition, F.vidence to the contrary, however, comes from the observation that blockade of H_r and H2-histamine receptors by antihistamine drugs has no effect on the painful attacks.

Epidemiology

Compared will: tension headache and migraine, the syndrome of cluster headaches is uncommon. In many headache clinic populations, migraine is 10-50 times more common than cluster headache. In the general population, the comparative percentages vary somewhat because people with migraine do not always seek help, whereas the intensity of cluster headache can rarely be endured in silence. Data from the Republic of San Marino showed a prevalence rate of cluster headache of S6 per 100,000 (prevalence rate for men of 115.3 per 100,000) with an incidence rate of 2.5 per 100,000 per year (Tonon et al. 2002).

The diagnosis of cluster headache is essentially clinical and depends on obtaining an accurate history from the patient. It is helpful to have confirmation from the spouse or relatives of the periodicity, rapidity of onset and resolution, and presence of conjunctival injection, rhinorrhea, ptosis, and altered behavior during the attack. Despite the stereotyped nature of the attacks from episode to episode and from patient to patient, the diagnosis is often missed for several years. Conditions that cause episodic, unilateral head and facial pain should be considered, but they are easy to exclude. Trigeminal neuralgia, sinusitis, dental disease, and glaucoma may superficially mimic the pain of cluster headache; however, in each, the temporal profile, lack of associated autonomic features, and past history allow easy differentiation. Similarly, migraine, temporal arteritis, and the headache of intracranial space-occupying lesions should not be difficult to differentiate from cluster headache. Episodic headache due to phcochroinocyronia or hypoglycemia produced by endogenous or exogenous insulin is likely to be bilateral and unaccompanied by tearing, nasal stuffiness, or ptosis. Orbital, retro-orbital, and frontal pain associated with incomplete Horner's syndrome can result from ipsilateral dissection of the carotid artery; unlike the pain of cluster headache, however, it is not episodic and does not produce the restlessness so characteristic of this condition. The pain associated with Tolosa-Hunt syndrome and Raeder's paratrigeminal syndrome is accompanied by oculomotor or trigeminal nerve dysfunction, a feature that should easily prevent confusion with cluster headache. Similarly, pain from compression of the third cranial nerve by an aneurysm should be easy to distinguish from cluster headache pain, especially when partial or complete third cranial nerve palsy is detected.

A number of primary headache syndromes collectively referred to as the *trigeminal-autonomic cephalalgias* may resemble cluster headache (Goadsby and Lip ton 1997). The trigeminal-autonomic cephalalgias are characterized by discrete, short-lasting, episodic attacks of intense, unilateral, orbital-temporal region pain with prominent ipsilateral autonomic features. These disorders differ mainly in the shorter duration and higher incidence of individual attacks. Interestingly, as attack incidence increases, attack duration tends to decrease. The differentiation between cluster headache and other paroxysmal hemicranias has important therapeutic implications. The paroxysmal hemi- i inm,is rypically respond dramaticall; to iiuloitie:l:aeiri therapy.

Treatment and Management

Care should be taken to reassure the patient that the syndrome, even though unbearably painful, is benign and not life threatening. Pain reduction but not cure should be promised.

The frequency, severity, and brevity of individual attacks of cluster headache and their lack of response to many symptomatic measures necessitate the use of a prophylactic program to-- most paiienls. 1'iie :ivaliucr:! plaa is dcier mined by several factors, including whether the phase of the disorder is episodic or chronic and whether other disease states, such as hypertension and coronary or peripheral vascular insufficiency, arc present.

Pharmacological Management

Acute (Symptomatic) Therapy. Given the rapid onset and short time to peak intensity of the pain of cluster attacks, fast-acting symptomatic treatment is imperative. Oxygen, subcutaneous sumatriptan, and subcutaneous or intramuscular DHE provide the most rapid, effective, and consistent relief for cluster headache attacks,

Oxygen delivered at a flow rate of 8-10 liters per minute via a nontebreathing face mask can he dramatically effective for aborting a cluster attack. Oxygen is believed to help because of its vasoconstrictor properties. Although portable regulators arc available, the major drawbacks to the use of oxygen are the inconvenience, lack of accessibility, and the need to have the regulator and cannister available at all times.

Administration of sumatriptan by subcutaneous injection in a dose of 6 mg is an effective means of aborting an individual cluster attack. However, preemptive treatment before the anticipated onset of an attack does not prevent the attack and, thus, the drug is not used for cluster headache prophylaxis. Sumatriptan nasal spray is less effective than the subcutaneous formulation.

DHE is available in injectable and intranasal formulations. DHE-45 administered intravenously provides prompt and effective relief of a cluster attack. The intramuscular and subcutaneous routes of administration provide slower relief. The potential role of intranasal DHE (2 mg) has not been validated in a controlled fashion.

Other potential symptomatic options include zolmitriptan and intranasal lidocainc administered by dripping 4% viscous lidocainc into the nostril ipsilateral to the pain.

Preventative Pharmacotherapy. Use of an effective preventative regimen cannot be overemphasized. The goals of preventative therapy are to produce a rapid suppression of attacks and to maintain a remission over the expected duration of the cluster period. Preventative therapy in cluster headache can be divided into transitional and maintenance prophylaxis.

Transitional Prophylaxis. Transitional prophylaxis involves the short-term use of corticosteroids, ergotamine, or DHE. This typically induces a rapid suppression of attacks while one of the maintenance agents can rake effect.

During the initial cluster, or when the patient's past history suggests that a cluster will be of limited duration, relief can usually be obtained by administering a short course of corticosteroids. Several regimens are effective, such as 60 mg of prednisone as a single daily dose for 3-4 days followed by a 10-mg reduction after every third or fourth day to thereby taper the dose to zero ovet IS or 24 days. Alternatively, an intramuscular injection of triamcinolone (80 mg) or methylprednisolone (80-120 mg) can be used to give a tapering corticosteroid blood level. Whichever program is used, the patient usually obtains relief from the headaches until the lower doses or blood levels of corticosteroids arc approached. The course can be repeated several times, but thereafter the risk of side effects suggests that an alternative prophylactic regimen should be used if the cluster has not tun its course.

Ergotamine tartrate can be given orally or by rectal suppository on retiring to prevent nocturnal attacks of headache. This approach may only postpone the attack until morning, when it may be more troublesome if it occurs when the patient is at work. Prophylactic use of ergotamine tartrate can nevertheless be valuable, but great care must be taken to regulate the dose if chronic ergotism is to be avoided. Most patients with cluster headache can be given 2 mg of ergotamine tartrate daily for several weeks withonl adverse effects. X.iii-i .i and peripheral paresthesias are common side effects of ergot regardless of the route of administration. DHE is a well-tolerated ergot derivative that can be given in a dose of 0.5-1.0 mg every 6-8 hours in an attempt to prevent headaches, but this dose should be continued for only a few days to avoid ergotism.

In addition, an occipital nerve block ipsilateral to the cluster headache may be useful as a transitional measure in some patients. This can provide temporary relief when the use of other medications may be contraindicated or poorly tolerated.

Maintenance Prophylaxis. Maintenance prophylaxis refers to the use of preventative medications throughout the anticipated duration of the cluster period. The preventative medication is started at the onset of the cluster period in conjunction with either corticosteroids or ergotamine derivatives, but these are continued after these initial suppressive medications arc discontinued.

The calcium-channel blockers, particularly verapamil, are considered first-line preventative therapy for both episodic and chronic cluster headache. They are generally well tolerated and can be used safely in conjunction with ergotamine, sumatriptan, corticosteroids, and other preventative agents. Doses in the range of 80-160 mg three times a day often result in a dramatic decrease in the frequency and intensity of attacks. Subsequent reduction in benefit can be overcome by an increase in dose or by a drug holiday, followed by reinrroduction of the agent. The favorable side effect profiles of the calcium-channel blockers make them a logical choice over the more toxic and troublesome agents, such as methysergide and lithium.

Methysergide in a dose ranging from 4 to 10 mg per day is effective for reducing or preventing cluster headache in about 60% of patients. The side effects, which include leg cramps, nausea, and fluid retention, are usually minor, and the drug seems to be better tolerated in patients with cluster headache than in those with migraine. The risk of retroperitoneal and other types of fibrosis is important only when methysergide must be taken for months or longer, For the episodic phase ol cluster headache. this drug nay be needed for only a few weeks; therefore, the risk of serious side effects is low. If methysergide gives relief, the lowest effective dose should be determined and the use of the preparation continued for 2^4 weeks after the last attack. It can be restarted if the headaches return after discontinuation. If the cluster period is very long or if the patient has chronic cluster headaches, methysergide can be taken for *2-6* months. It should be discontinued for 4 weeks, during which time an abdominal CT or MR1 scan, chest roentgenogram, and determination of serum creatinine level are recommended by some authorities. If the patient has no signs of fibrosis, treatment with methysergide can be continued for an additional 3-6 months, after which the drug should again be temporarily stopped. Unfortunately, as mentioned earlier, its manufacturer has ceased its production in the United States.

For patients who have chronic clustet headache with attacks that occur daily for years, relief may be obtained with lithium. Lithium carbonate, 300 mg three times a day,

can be given initially and the dose adjusted at 2 weeks to obtain a serum lithium level of about 1.0 mliq/liter. Side effects at this level include a mild tremor of the limbs, gasttointestinal distress, and increased thirst. The therapeutic range is very narrow, and blood levels of more than 1.5 mEq/liter are to he avoided. Nephrotoxicity, goiter formation, and a permanent diabetes insipidus-like state have been reported after lithium treatment. In chronic cluster headache, lithium may have a beneficial effect within 1 week; however, the response is typically delayed for several weeks. Although attacks may recur after some months, a renewed response to lithium may occur if the drug is withdrawn and then reintroduced after a few weeks. In patients whose headaches respond to lithium, use of the drug should be discontinued every few months to determine whether the cluster headaches have subsided. While lithium is being given, it is necessary to monitor the blood level at regular intervals to avoid the development of serious side effects. Thiazide diuretics should not be used concurrently because they can cause a rapid elevation of blood levels of lithium.

Despite the available treatments, management of patients wit!) chronic differ headache car, be extreme^ difficult because many of their headaches do not respond or respond only briefly to the programs already described. In such patients, a combination of several meditations may give relief. On the basis of clinical experience, the combination of verapamil and topiramatc or verapamil and lithium can prove quite effective. For particularly resistant headaches, triple therapy may be necessary, consisting of verapamil with methysergide or either topiramate or valproate plus lithium. Corticosteroids can be useful in chronic cluster headache to provide brief remissions for fixed periods. Nonetheless, long-term use of corticosteroids in patients with chronic cluster must be resisted.

In patients for whom conventional, first-line therapy is ineffective, poorly tolerated, or contraindicated, one may consider adjunctive therapy with a number of potential agents including intranasal capsaicin, indomethaeui, c hi or promazine, and clonidine (Dodick and Campbell 2001).

Surgical Treatment. Thirty to 50 years ago, injection of alcohol into the gassenan ganglion and trigeminal root section was used in the treatment of chronic migrainous neuralgia (cluster headache). These procedures did nor gain widespread acceptance and were gradually abandoned because of the high incidence of complications, including neuroparalytic keratitis, postoperative herpes keratitis, and anesthesia dolorosa of the denervated area.

Recently, interest has been renewed in the surgical relief of this condition. Onofrio and Campbell reported their results in a series of 26 patients with intractable chronic cluster headaches treated surgically. Their patients had radio frequency thermocoagulation of the gassenan ganglion or sensory root section of the trigeminal nerve through a posterior fossa approach. Approximately two thirds of the patients obtained excellent-to-good relief of pain. In most of the remaining patients pain was not relieved because of the production of incomplete first-division anesthesia, and in several subjects, pain persisted despite dense trigeminal sensory loss in all three divisions of the nerve. Keratitis and anesthesia dolorosa are serious complications of any procedure causing destruction of the trigeminal nerve. Thermocoagulation of the gasserian ganglion and injection of glycerol into Meckel's cave have been effective fot providing pain relief in this condition. More recently, stereotactic radiosurgery with the gamma knife under local anesthesia has been used to treat patients with chronic cluster headache refractory to medical therapy (Ford et al. 1998); unfortunately, this technique does have a significant failure rate. More recently, Frazini et al. (2003) reported a complete response in five patients with medically refractory chronic cluster headache after stereotactic implantation of a stimulating electrode into the periventricular hypothalami]",. The r.ttioiia!c tor ".his procedure is based on the activation of the periventricular hypothalamus seen on PET scanning of patients during attacks of cluster headache. The morbidity and adverse events of this procedure thus far appear to be minimal, but the long-term safety and durability of this procedure await long-term prospective follow-up data on these and other patients,

Indomethacin-Responsive Headache Syndromes

lndomethacin-responsive headache syndromes (IRHSs) represent a unique group of primary headache disorders that are characterized by a prompt, absolute, and often permanent response to indomethaein. IRHSs can easily be confused with cluster headache because of the facial autonomic features associated with individual headaches. In addition, attacks may occur during sleep and can be triggered by alcohol, features that also characterize cluster headache. However, IRHSs can be distinguished from cluster headache by their short duration, with the exception of hemicrania continua, and by the high frequency of attacks. Several other primary short-lasting headache syndromes respond either partially or entirely to indomethaein. although with less consistency. These include idiopathic stabbing headache and benign cough, exertional, and sexual headache, which arc described elsewhere in this chapter.

Paroxysmal Hemicrawas

The paroxysmal hemicramas are primarily disorders of young adults, with typical onset in the second and third decades. The female-to-male ratio is approximately 2 to 1, which in addition to the differences in attack profile (frequency and duration), contrasts with cluster headache for which there is an overwhelming male predominance.

Chronic and episodic paroxysmal hemicranias differ predominantly in their temporal profile. Chronic paroxysmal hemicrania, as the name implies, occurs daily, with multiple discrete attacks occurring throughout a 24-hour period. Episodic paroxysmal hemicrania is characrerized by bouts of attacks sepatated by remission periods. The headache bouts can range from 2 weeks to 5 months, and remission periods can last 1-36 months. Both disorders are associated with daily attacks of severe, short-lived, unilateral pain, which is often maximally felt in the orbital-periorbital or temporal region, although extratrigeminal pain in the ear or occiput can occur. The characteristic attack frequency is more than or equal to 5 per day (range, 1-40/day) (Boes and Dodick 2002). Each attack lasts approximately 20 minutes (range, 2-120 minutes). Similar to cluster headache, each paroxysm is accompanied by at least one robust ipsilateral autonomic feature, which may include lacrimation, ptosis, eyelid edema, conjunctival injection, nasal congestion, or rhinotrhea (Goadsby and Lipton 1997).

Hemicrania Continua

As the name implies, hemicrania continua is characterized by a continuous unilateral headache of moderate intensity that may involve the entire hemicranium or simply be confined to a focal area. The female-to-malc ratio is approximately 2 to 1, and the average age of onset is 28 years (range 5-67 years) (Peres et al. 2001). Although invariably continuous, this disorder may sometimes resemble a prolonged unilateral migraine attack lasting several days to weeks, with headache-frcc remissions. The continuous headache is often punctuated by painful unilateral exacerbations lasting 20 minutes to several days. Attacks may alternate sides, and unilateral attacks may rarely become bilateral. These periods of increasing pain intensity are often but not invariably accompanied by one or more autonomic features, which arc usually more subtle than that seen in the paroxysmal hemictanias or cluster headache. Stabbing head pains ("ice-picks") are often a feature of this disorder, usually on the ipsilateral side, and usually during a period of exacerbation. Because of its daily persistence, hemicrania continua may be seen in the context of medication overuse, which may alter the clinical features and affect the response to treatment. Therefore, a higher index of suspicion may be required in these cases.

Treatment

The response of IRHSs to indomethacin is often quite striking, although the mechanism is not yet understood. Despite this dramatic response, all patients require neuroimaging to exclude a structural cause because organic condirions that mimic IRHS have been desctibed. Indomethacin is effective in doses ranging from 25 to 300 mg daily. The usual starting dose is 25 mg three times daily with meals. The dose is titrated according to the patient's response and the side effect profile. A slow-release preparation is available for patients with nocturnal breakthrough headaches. A treatment response is usually seen within 48 hours. Tachyphylaxis is not a feature, but medication withdrawal is often met with recurrence of the headaches. Nevertheless, once an effective dose is achieved and maintained for several weeks, a tapering schedule is recommended in an effort to find the lowest effective dose possible, which often varies from patient to patient. If indomethacin is contra indicated or in the rare circumstance in which it is ineffective in treating paroxysmal hemicrania or hemicrania connnua, other medications, with anecdotal reports of success, may be tried. In paroxysmal hemicrania, these include celecoxib, NSAIDs (ibuprofen, ketoprofen, aspirin, piroxicam, naproxen, diclofenac, and phenylbutazone), calcium-channel blockers (verapamil, nicardipine, and flunari/.inc), corticosteroids, acetazolamide, crgotamine, and lithium. In hemicrania continua, there is anecdotal evidence for the effectiveness of rofecoxib, celecoxib, NSAIDs (aspirin, naproxen, ibuprofen, diclofenac, and piroxicam), acetaminophen with caffeine, DHF, methysergide, corticosteroids, lamotrigine, gabapentin, and lithium. The natural history of these disorders is not known, but long-term treatment appears to be required in the majority of patients.

SUNCT

SUNCT is a moderately severe unilateral cephalalgia characterized by neuralgiform pain of very short duration (15-120 seconds). These painful paroxysms are usually felt in or around the eye and can sometimes be triggered by cutaneous stimuli or neck movements. Their incidence ranges from 1 or 2 per day to up to 30 per hour, but patients are typically free from pain between paroxysms. The ipsilateral conjunctival injection and lacrimation are very prominent. Unlike trigeminal neuralgia, the pain occurs exclusively in a cranial nerve V_L distribution, whereas the brevity and high frequency of attacks in SUNCT should make the distinction with cluster headache quite clear. Treatment with carbamazepine has been reported to be partially effective in several patients. I.amorngine has been effective in several patients when given in an open fashion (D'Andrca ct al. 2001). There is anecdotal evidence for the effectiveness of gabapentin, and one patient has had a response to topiramare. The role of neurosurgical intervention in the treatment of SUNCT is uncleat, and it should only be considered as a last resort,

Primary Stabbing Headache

Persons subject to migraine may describe brief, extremely sharp twinges of pain that occur without warning and that can be felt anywhere in the head, including the orbit. The pains are graphically described as being like a spike being

driven into the skull, hence the term *ice-pick headache* (idiopathic stabbing, jabbing headache), but similar pains have been described under different terms by other authors. Similar jabbing pains may occur spontaneously (50%) or in association with another underlying headache disorder, such as cluster headache, chronic paroxysmal hemicrania, and tension-type headache (Pareja et al. 1996). Ice-pick-like head pain has also been described in patients with giant cell arteritis. Some patients report precipitants for this type of pain, including sudden postural changes, physical exertion, and transition from darkness to light. Because of the brevity of the pain, the sporadic nature of attacks, and the common occurrence of spontaneous remissions, treatment is not usually required and reassurance generally suffices. However, in patients with "ice-pick status," in whom stabs of pain occur often, the treatment of choice is indomethacin, administered in a regimen similar to that described for the paroxysmal hemicranias.

Other Types of Headache and Facial Pain

Headache Associated with Metabolic Abnormalities

Carbon dioxide retention and exposure to carbon monoxide can both lead to a vascular headache. The presumed mechanism is vasodilatation. Chronic hypcrcapnia from chronic obstructive pulmonary disease can lead to chronic-headaches and eventually to raised intracranial pressure with papilledema. Carbon dioxide retention and oxygen desaturation due to sleep apnea of both the primary and the obstructive type can result in nocturnal and early morning headaches that diminish with activity. Tissue anoxia due to anemia or lack of oxygen, as occurs at high altitude, can each produce a throbbing vascular headache. Hypoglycemia can cause a headache that has vascular features.

Hypertension is rarely the cause of headaches unless there is a rapid and major increase in blood pressure. The headache of a pheochromocytoma characteristically occurs with dramatic suddenness and is associated with a significant elevation in blood pressure. Occasionally, early-morning headache is a sign of sustained hypertension. Preeclampsia with the accompanying high blood pressure can lead to headaches during pregnancy. The onset of severe headache around the time oi delivery ma) indicate the onset of eclampsia.

Tension-Type or Muscle Contraction Headache

Almost everyone has a headache at some rime when stressed, overworked, or angry. Such headaches, which can also result from muscular strain due to working in a physiologically unsound position, rapidly subside with relaxation, sleep, or ingestion of simple analgesics. The prevalence of this type of headache is unknown because medical help is sought only when the condition becomes sufficiently frequent or chronic to interfere with the patient's lifestyle.

Chronic headaches that are not associated with focal neurological symptoms and do not have the gastrointestinal features of migraine are often diagnosed as tension headaches and have historically been ascribed to persistent contraction of the scalp, neck, and jaw muscles. The term *tension* has been tacitly taken to mean both emotional tension and muscle tension, thus implying both pathogenesis and pain mechanism. The International Headache Society classification ot headache has instituted a small but important change in the terminology of tension or muscle contraction headache. The word *type* has been added after tension, thus the term *tension-type headache* is now used to bring attention to the fact that actual muscle tension or sustained contraction may not be a key factor in the pathophysiology of this common head pain (ICD 10 Guide for Headaches 1997).

The concept of muscle contraction causing headache has been questioned in recent times, and the distinction between vascular headaches and tension-type headaches has become much less certain. liMG studies of neck and scalp muscles during headache do not show a difference between people with migraine and those with the clinical diagnosis of muscle contraction headache. Pericranial muscle spasm and tenderness are as common in migraine as in muscle contraction headache. Provocation of headache by alcohol and nitroglycerin is almost as common in subjects with a history of tension-type headaches as in those with a history of migraine. Similarly, patients thought to have tension-type headaches may report throbbing pain. The platelet serotonin concentration is low in patients prone to frequent tension-type headaches. Similar findings have been noted in patients with migraine. Autogenic training and relaxation therapy are as helpful in migraine as in muscle contraction headaches. These observations and many others have led to the concept that muscle contraction headache and migraine may not be entirely different disorders but are the extreme ends of a continuum or spectrum of headache. However, evidence in favor of tension-type headache and migraine being separate conditions comes from Schocncn and Bendtsen (2000). They showed tliat exteroceptive suppression of voluntary contraction of the jaw muscles in response to electrical stimulation of the labial commissure is abnormal in subjects with tension-type headaches but not in those with migraine or other types of headache.

Many patients with chronic daily headaches have a history of episodic headaches of the common migraine type. The evolution or transformation of one type of headache to another may be associated with overuse of analgesics and ergot preparations. Depression may also be an important factor.

Clinical Symptoms. Tension-type headaches, which can begin at any age, are generally bilateral (commonly

occipitonuehal, bitemporal, or bifrontal). They are often described as being like a tight hand around the head, a sense of pressure, or a bursting sensation. The pain may wax and wane throughout the course of a day or may be described as being present and steady for days, weeks, or even years at a time. Despite the complaint of a constant headache, sleep may be undisturbed. In general, tension-type headaches are not associated with nausea and vomiting and are much less commonly associated with light and sound sensitivity than migraine.

Physical Findings and Laboratory Studies. Physical examination in acute tension-type headache is generally unrevealing. Chronic tension-type headache may be associated with tenderness in the cervical paraspinal muscles, restricted neck motion, and tenderness over the temporalis muscles and in scattered areas over the scalp. Laboratory studies are unhelpful, except to rule out other conditions. The FSR should be determined in elderly patients with headache to help exclude temporal arteritis. The recent onset of headaches in any patient older than age 40, even when the symptoms are clearly those of muscle contraction headache, warrants a CT or MRI scan of the head to look for intracranial disease. Many serious structural intracranial diseases can cause symptoms that mimic benign muscle contraction headache. Cervical spine films may be needed to detect bony and joint disease that can trigger sustained contraction of the cervical and scalp muscles, leading to secondary tension headache.

Psycho logical Factors. Anxiety, depression, repressed resentment, anger, and hostility have all been identified as factors contributing to the production of tension-type headaches, but the prevalence of these emotions in the population without headaches is unknown. Although psychosocial stress, anxiety, and depression are important in patients with chronic headaches, it is uncertain whether they are always causative factors or are due to the chronic pain.

The somatoform disorders, including hypochondriasis, somatization disorder (previously called *hysteria),* and the somatoform pain disorder, can have headache as part of the clinical picture. Together with headaches as a manifestation ot somatic delusions, these are now classified under tension-type headaches, with the recognition that scalp and neck muscle contraction is not a primary factor in the pathogenesis.

Pathogenesis. The long-held belief that emotional tension leads to muscle tension and hence to headache is too simplistic. A growing number of authorities suspect that a far more complex central mechanism is responsible for the pain. Disturbances originating in the hypothalamus and spreading by way of the mamillothalamic tract to the upper brainstem and influencing the antinociceptive mechanisms have been suggested. Alterations in central pain modulation and changes in serotonin and endorphin levels are also likely to be important in chronic ten si on-type headache. The role of the descending tract and nucleus of the trigeminal nerve and its relationship to noxious input from the cervical spine via the upper cervical roots is currently being studied.

Course and Prognosis. Chronic tension-type headache, especially when it becomes a daily event, can persist for years, ft is difficult to manage and rarely responds completely to any therapeutic regimen. Spontaneous remissions may occur, and in some patients the condition subsides with age. Secondary depression, drug addiction, and chronic pain behavior are often the result of chronic headaches.

Treatment and Management. An understanding, sympathetic physician who communicates an interest in the patient's headache will achieve far better results than one who dismisses the patient with the exhortation to relax more or the statement that the headache is all due to "nerves," Many patients arc more interested in knowing that the headache is not due to a serious intracranial pathological condition than in obtaining relief of pain. Reassurance that the headache is not serious can be given only after a thorough examination and after appropriate investigations, including neuroimaging. Such reassurance may considerably relieve the patient's anxieties and thereby relieve the headaches.

Techniques to promote relaxation of the scalp and neck muscles can be helpful; these methods include stretching exercises, the application of heat and massage to the neck, biofeedback conditioning, and relaxation training. Although short-term results confirm the efficacy of these techniques, long-term beneficial effects are nor so obvious. Many patients revert to their muscle-contracting habits unless the relaxation techniques are frequently reinforced.

For occasional mild tension-type headache, aspirin or acetaminophen may be sufficient treatment. More severe headaches usually require a prescription analgesic, but no specific preparation has been shown to be better than another. Aspirin or acetaminophen in combination with propoxyphene or butabarbital and caffeine is often effective for temporary relief but should be avoided for repeated, long-term use because of the risk of paradoxical worsening of the headache related to analgesic rebound. NSAIDs, such as naproxen or lbuprofen, are often helpful. Preparations containing codeine or dihydrocodeine are often avoided because of the risk of dependency; however, these preparations are occasionally useful to carry patients through brief, difficult periods when headaches occur more often than usual. Muscle relaxants and the major and minor tranquilizers arc generally ineffective for long-term management of tension-type headache but are useful for short-term relief.

The most effective prophylactic drug is amitriptyline. Controlled trials have shown an improvement of more than 50% in more than *65%* of patients. The usual dose is

50-150 mg per day, but higher doses may be needed. The drug is better tolerated if given as a single bedtime dose. Side effects include those listed for this agent under Migraine, earlier in this chapter. Elderly patients may also he troubled by confusion and orthostatic faintness, but the latter side effect is minimized by the bedtime dose regimen. A satisfactory response does not depend on the presence of underlying depression.

Chronic tension-type headache can be the most difficult headache to treat. Transient improvement often follows introduction of any treatment, hut most patients continue to complain until the headaches lessen or subside spontaneously. This improvement usually occurs with some change for the better in the subject's life or when a reaction to stress diminishes.

Headache Attributed to Head or Neck Trauma

Subdural Hematoma. Bleeding into the subdural space is generally due to tearing of one or more of the bridging veins that cross the space to reach the venous sinuses, particularly the sagittal sinus. Most subdural hematomas occur over the convexity of the cerebral hemispheres, but they can occur in the posterior fossa or adjacent to the tentorium. In 50-80% of patients there is a history of head trauma. Chronic subdural hematomas may cause headache via enlargement of the lesion without serious neurological signs for a considerable time. Changes in personality, alterations in cognitive abilities, a subacute dementia, and nonspecific symptoms, such as dizziness and excessive sleepiness, may be present for weeks or months. Focal seizures, focal weakness, or sensory changes, and, ultimately, decreasing levels of consciousness may occur. Symptoms of chronic subdural hematoma, including headache, may fluctuate and occur intermittently. Episodic cerebral manifestations may mimic transient ischemic attacks. Headache is the single most common symptom and often is a severe bitemporal pain. Headache due to subdural hematoma is more common in young people, who have less cerebral atrophy than elderly patients. In the presence of atrophy, a larger hematoma can accumulate before it stretches and deforms pain-sensitive structures. Subdural hematoma should be considered in an elderly person with recent onset of headaches. Once suspected, a subdural hematoma should be sought with a CT scan or MRI. Treatment of subdural hematomas is discussed in Chapter 56B. Once the lesion is drained or when it is spontaneously absorbed, headaches tend to resolve.

Headaches, dizziness, difficulty concentrating, irritability, decreased libido, and fatigue are common complaints after **lieail** injur) **Kenitl** ami li.ini.ui.in .!'i'H)'i. Vrinus **lead** trauma, resulting in major brain damage, causes post-traumatic headaches less often than seemingly minor head injuries. This difference may be more apparent than real because the seriously injured patient may have so many symptoms that headache is of less importance than other complaints. Headache is far more common after industrial and traffic accidents than after trauma sustained in sporting activities or in circumstances in which litigation is not a factor. Despite this, few still hold to the postulates claiming that post-traumatic syndrome is a neurosis that persists until there is a compensation settlement and that it is not seen in professional and managerial people or after serious head trauma.

The headache that occurs as part of the post-traumatic (or postconcussive) syndrome can be generalized and resemble a tension-type headache, localized to the site of the head injury, or hemicranial and resemble migraine. The physical examination is often unrevealing, although scalp tenderness and decreased motion of the cervical spine are often found. Examination by CT scan rarely reveals any abnormalities, although unexpected subdural hematomas are occasionally found. Examination of patients with head injuries with MRI has revealed a higher than expected incidence of previously undetected small extracerebral hematomas, cortical contusions, and indeterminate changes in the cerebral parenchyma. Other observations to support the organic basis for the post-traumatic syndrome arc that EEG findings are frequently abnormal and there are transient or long-lasting abnormalities in the visual evoked responses and brainstem evoked responses in some subjects.

Treatment of post-traumatic syndrome and post-traumatic headache is difficult. Encouragement, reassurance, and a sympathetic attitude on the part of the physician are essential. All the treatments useful for tension-type headaches, migraine, occipital neuralgia, and neck sprains may be needed. Physical therapy, biofeedback, and psychotherapy each have a place in treatment. Drug treatment may include analgesics (nonopioid), NSAIDs, and antidepressants. The tricyclic antidepressants and gabapentin can be particularly helpful.

Recovery from post-traumatic syndrome, including the headache, may be significantly delayed. Most patients who continue to have headaches for more than 2 months after the trauma continue to have them for 1-2 years (Ramadan and Keidcl 2000). Treatment can be difficult and the results disappointing.

Post-traumatic syndrome may develop more commonly when patients believe that the evaluation shortly after the injury has been incomplete. Their initial fear and that of their relatives is that a skull fracture or brain injury has been overlooked. Physicians know that a skull fracture is generally unimportant unless it is depressed or results in a CSF leak, but any head injur)- or skull fracture has serious implications to the patient. Emergency room physicians and others caring for patients with a bead injury should therefore conduct a thorough examination, obtain whatever radiological investigations seem indicated, and then, if appropriate, reassure the patient that no serious damage has been caused. If the history included a period of unconsciousness or if there is a simple skull fracture, a limited period of bed rest followed by a graduated return

to full activity should be advised. Cervical spine injuries should not be overlooked in the patient with a head injury.

Post-traumatic dysautonomic cephalalgia usually follows a neck injury, often from blunt trauma. The patient develops a throbbing unilateral headache, ipsilateral mydriasis, and facial sweating. Overactivity of the cervical sympathetic system seems to be induced by the neck injury. This rare syndrome responds to treatment with propranolol. Minor head trauma, such as that occurring when a soccer ball is hit with the head, may be rapidly followed by a headache indistinguishable from migraine. This syndrome may occur repetitively with minor head trauma. A head injury can also be followed by recurring attacks of migraine, even in the absence of a history of similar headaches.

Cold-Stimulus Headache. "Ice cream" headache is a common experience. It occurs when an extremely cold substance comes into contact with the roof of the mouth and the upper incisors. The pain, which is most often felt midfrontally, begins within seconds of the cold stimulus, peaks in 20-60 seconds, and subsides in about the same time. It is less commonly felt bitemporally or even in the occipital region. The complaint is more common in migraineurs than in the general population. Migraineurs may feel an ice cream headache on the side where their migraine is located. The pathogenesis is not completely understood, but reflex vasoconstriction may be involved. Accompanying the pain is a decrease in the skin temperature of the forehead of 1°C. There is evidence to suggest that active migraine facilitates perception of forehead pain induced by a cold palatal stimulus. The pain can be prevented by avoiding ice-cold food and drink.

Neck-Tongue Syndrome. The neck-tongue syndrome was initially described by Cyriax in 1962. Paroxysmal pain and paresthesias in one half of the tongue precipitated by neck movement are the cardinal features of the neck-tongue syndrome. The tongue discomfort has been accompanied by a varied constellation of other symptoms. Occipital pain, discomfort in the trapezius region, ipsilateral hand paresthesias, and neck pain have been described. All can be precipitated by neck movement. The exact mechanism remains speculative. Atlantoaxial subluxation, cervical spondylosis, and lesions of the upper cervical cord and the emerging cervical nerves have been suggested. Neural anastomosis between the glossopharyngeal nerve and the hypoglossal nerve via the pharyngeal plexus may explain the unusual syndrome. The condition is generally considered benign. In rhe absence of any structural abnormality management is conservative. Treatment includes the use of anti-inflammatory agents and temporary immobilization of the neck in a cervical collar (Chedrawi et al. 2000).

Atypical Facial Pain. *Atypical facial pain* is a term far too readily applied to any obscure pain in the face. A more preferable term is *facial pain of unknown cause.* It is not appropriate to attribute all causes of idiopathic facial pain to psychogenic mechanisms.

The diagnosis of atypical facial pain should be considered only when all facial pains due to disturbances of anatomy and pathophysiology have been excluded. Exhaustive radiographic and other imaging techniques may be necessary to exclude conditions such as nasopharyngeal and sinus neoplasms, bony abnormalities of the base of the skull, and dental conditions, such as cryptic mandibular and maxillary abscesses. The evaluation may also require a chest roentgenogram or chest CT scan if referred pain from lung cancer is suggested by the history (smoker) or examination (digital clubbing).

Patients in whom atypical facial pain is eventually diagnosed are usually middle-aged and predominantly female. They complain of deep, poorly localized pain. Generally unilateral, but occasionally bilateral, the pain may be described in graphic terms, such as tearing, ripping, or crushing, or often as aching and boring. The pain is usually present all day and every day and gradually worsens with time. It is not influenced by factors such as alcohol consumption, heat, or cold or by factors that trigger trigeminal neuralgia. Local anesthetic blocks of the trigeminal nerve do not relieve the pain. Many patients have already undergone extensive dental, nasal, or sinus operations, to no avail. Depression may be present; most patients are preoccupied with the pain, yet there is no convincing evidence that the pain is due to the depression, When no symptomatic etiology is identified, treatment centers around the use of tricyclic medications, often combined with other antimigraine or antineuralgic medications.

Cranial and Facial Neuralgias

Trigeminal Neuralgia. One of the most severe pains known, trigeminal neuralgia, was first desctibed by John Fothergill in 1775.

Clinical Symptoms, The pain of trigeminal neuralgia is paroxysmal. It is felt within the distribution of one or more divisions of the trigeminal nerve. The pain is often •r:s',i\dvd by a sensory stimulus to the skin, mucosa, 01 teeth innervated by the ipsilateral trigeminal nerve. The pain is described as electric shocklike, shooting, or lancinating. Each attack lasts only seconds, but the pain may he repetitive ,u short intervals MI that the individual attacks blur into one another. After many attacks within a few hours, the subject may describe a residual lingering facial pain. Attacks of trigeminal neuralgia are most common in the second and third divisions of the nerve. Pain confined to the ophthalmic division is extremely rare. Although the tongue is supplied by the mandibular division of the nerve, it is uncommon for the pain to spread into the tongue, even when the lower lip and mandible are involved.

Physical Findings. In primary trigeminal neuralgia, there is no sensor;. impairment and the motor division of the nerve is intact. Examination of the face may be difficult because the patient is reluctant to let the examiner stimulate the skin for fear of triggering an attack. Male patients occasionally present with one portion of the face, the trigger zone, unshaven. Initiation of the pain by chewing, brushing the teeth, and talking and even by cold drafts striking the face is commonly reported. Attacks of pain during sleep are tare. Weight loss, dehydration, and secondary depression can occur if the attacks occur often.

When trigeminal neuralgia occurs as a result of a lesion involving the gasserian ganglion, main sensory root, or root entry zone in the pons (secondary trigeminal neuralgia), there may be associated physical signs. These include sensory loss in the fifth cranial nerve distribution, weakness and atrophy of the muscles of mastication, and involvement of ad|acent cranial nerves. When trigeminal neuralgia occurs bilaterally, it is often due to multiple sclerosis,

Laboratory and Radiological Findings. In classic trigeminal neuralgia, there are no accompanying laboratory or radiogtaphie abnormalities, EMG and nerve stimulation techniques, such as blink reflex studies, reveal normal responses. Trigeminal neuralgia due to structural lesions, such as a meningioma or schwannoma of the posterior fossa or compressing the gasserian ganglion or malignant infiltration of the skull base, is associated with the expected abnormalities on studies such as CT scans and MRI.

Pathology, Histological changes are seen within the gasserian ganglion in patients with trigeminal neuralgia. Vacuolated neurons, segmental demyelinarion, vascular changes, and other abnormalities were more common in ganglia from patients with a history of trigeminal neuralgia than in control specimens. Demyelination of the axons in the main sensory root may be associated with compression by vascular loops.

Pathogenesis and Etiology. The cause of trigeminal neuralgia is probably multifactorial. Multiple sclerosis, cerebellopontine angle tumors, schwannomas, and other local lesions account for a very small proportion of cases and most cases have long been called idiopathic. The work of Jannetta has revitalized Dandy's vascular loop-nerve compression theory. Jannetta found arterial compression of the posterior root in *59%* of patients and venous compression in 25%. Vaseulat compression is believed to increase with age and to result in changes in the trigeminal sensory root and root entry zone that results in prolongation of electrical impulses within the nerve and re-excitement of the axons, leading to repetitive neuronal discharges. The vascular compression theory has, however, not found universal support.

Epidemiology. Trigeminal neuralgia begins after the age of 40 years in 90% of patients. It is slightly more common in women.

Course and Prognosis. Once trigeminal neuralgia has developed, it is likely to have an exacerbating and remitting course over many years. During exacerbations, the painful attacks may occur many times a day for weeks or months at a time. A spontaneous remission may occur at any time and last for months or years. The reasons for these fluctuations are unknown.

Treatment and Management. Treatment of trigeminal neuralgia due to a focal lesion compressing the sensory root of the trigeminal nerve is surgical exploration and decompression of the nerve. Management of primary trigeminal neuralgia can be either medical or surgical.

Carbamazepineis the most effective drug for the treatment of trigeminal neuralgia, and the condition responds in approximately 75% of patients. Administration of the drug must be initiated with small doses of 50-100 mg and increased slowly as tolerated. Vertigo, drowsiness, and ataxia are common side effects, especially in elderly patients, if the preparation is introduced too quickly. Therapeutic doses generally range from 600-1200 mg per day. Once the pain is controlled completely, the dose can be tapered every few weeks to determine whether a remission has developed. Regular blood counts should be obtained for the first few months and thereafter, generally once a year while carbamazepine is administered, in view of the earlier reports of agranulocytosis with this preparation.

Second-line options for the management of trigeminal neuralgia include phenytoin, baclofen, and valproate. Other drugs that have been used include gabapentin, clonazepam, lamotrigine, oxcarbazepine, and topiramate (Sindrup and Jensen 2002). The above drugs should be considered for trial, alone or in combination, when carbamazepine is either not helpful or not tolerated. Nonetheless, given the beneficial effects of gabapentin in other neuropathic conditions and its benign side-effect profile, an initial trial with this drug may be an alternative option to carbamazepine.

On occasion, one may encounter a patient in the midst of a severe attack. A useful technique in this situation is the administration of intravenous fosphenytoin at a dose of 250 mg. Anesthetizing the ipsilatcral conjunctival sac with the local ophthalmic anesthetic proparacaine has also proved most effective in providing relief from pain for several hours to days.

The simplest nonmedical therapy is an alcohol block of the peripheral branch of the division of the trigeminal nerve that is painful. The mental or mandibular nerve can be blocked with 0.50-0.75 mL of absolute alcohol to control mandibular division trigeminal neuralgia. The infraorbital and supraorbital nerves can also be injected for pain involving the second and first divisions. Relief of pain occurs in a high proportion of patients so treated, but relapse is likely in most after 6-18 months. The procedure can be repeated once or twice, but thereafter it is prudent to perform a more proximal and lasting procedure because the further injection of alcohol is likely to be ineffective.

The advantages of a peripheral alcohol injection include the lack of morbidity and the temporary nature of the sensory loss. Preservation of corneal sensation is also an advantage. Avulsion or section of the peripheral branches has been used for control of pain but is now rarely used.

For many patients, especially those who are elderly or who have complicating medical conditions, percutaneous radiofj-eqiu'ncy thermocoagulation ol the trigeminal nerve sensory root as it leaves the gasserian ganglion is the procedure of choice. Authors have reported pain relief in up to 93% of patients. Recurrence rates vary with the period of follow-up. The procedure can be repeated when relapse occurs. Complications include damage to the carotid artery, the adjacent cranial nerves, and the trigeminal nerve motor root. Corneal sensory loss can lead to serious eye complications. *Anesthesia dolorosa,* a distressingly painful sensation in the numb area, occurs occasionally. Troublesome dysesthesias of the face are more commonly encountered.

Section of the sensory root of the trigeminal nerve via a middle fossa or posterior fossa approach is used for the treatment of trigeminal neuralgia less often than previously. This decline has largely been due to the increasing use of the technique of microvascular decompression advocated by Jannetta. In his 1991 series of 1185 patients, 70% had excellent relief of pain continuing 10 years after the trigeminal nerve and the compressing vessel were separated (Barker et al. 1996). Relief of pain without the production of anesthesia is the major advantage of the procedure. The disadvantages include the need for a posterior fossa exploration, with a reported mortality of between 1 and *2%* and the risk of injury to other cranial nerves, most commonly IV, VII, and VIII. Despite the inherent risks of a retromastoid craniectomy, microvascular decompression is associated with the longest duration of pain relief, preserves facial sensation, and remains the only surgical treatment that directly addresses the presumed mechanism (Elias and Burchiel 2002). When no vascular loop is found at the time of operation, the options include performing a partial or complete sensory root section or subsequently performing a radiofrequency procedure.

For a young patient whose condition does not respond to medical treatment, posterior fossa microvascular decompression should be considered. For an elderly patient or a patient with other medical complications, however, radiofrequency thermocoagulation is the procedure of choice because of its case of performance, possibly preceded by an alcohol block so that the sensation of facial numbness can be experienced before the more permanent procedure.

More recently, several new procedures have shown promise in patients with trigeminal neuralgia refractory to medical management and have added to the surgical armamentarium. Percutaneous balloon compression of the trigeminal ganglion has been shown to be an effective and technically simple treatment. However, the early recurrence rate is higher than reported for radiofrequency thermocoagulation. Stereotactic radiosurgery with the gamma knife has also been shown to be an effective therapy for trigeminal neuralgia and is the least invasive surgical option (Kond/iolka et al. 2002). Dogmatic recommendations relating to the particular interventional or surgical procedure cannot he made. Patients offered such treatment need to be informed of the track record of the surgeon performing the procedure.

Glossopharyngeal Neuralgia

The pain associated with neuralgia of the ninth cranial nerve is similar in quality and periodicity to that of trigeminal neuralgia. The pain is lancinating and episodic and may be severe. It is felt in the distribution of the glossopharyngeal nerve and the sensory distribution of the upper fibers of the vagus nerve. Pain in the throat, the tonsillar region, the posterior third of the tongue, the larynx, the nasopharynx, and the pinna of the ear is often described by patients with this rare neuralgia. The pain is usually triggered by swallowing, chewing, speaking, laughing, or coughing. The pain is unilateral in most patients. Bilateral involvement does occur, but it is very rare. The age group involved is generally older than 40 years of age. Bradycardia and syncope can occur when the painful attack strikes.

Secondary glossopharyngeal neuralgia may be due to oropharyngeal malignancies, peritonsillar infections, and other lesions at the base of the skull. Most occurrences have been thought to be idiopathic, but vascular compression of the ninth cranial nerve has been described.

Carbamazepine and phenytom have been administered with mixed success in glossopharyngeal neuralgia. Intracranial section of the glossopharyngeal and upper rootlets of the vagus nerve almost always produces complete pain relief.

Geniculate Neuralgia (Nervus Inter me dius Neuralgia of Hunt)

The sensory root of the geniculate ganglion, the nervus intermedins of Wrisberg, innervates the inner ear, the middle car, the mastoid cells, the eustachian tube, and part of the pinna of the ear. A syndrome of pain in the ear, pinna, and auditory canal has been ascribed to neuralgia of the geniculate ganglion and nervus intermedins. There is no known pathological condition. Clinical features of this syndrome are not well defined. If one were to characterize geniculate neuralgia by paroxysmal pain of great intensity but short duration in the ear, pinna, or auditory canal, this syndrome must be exceedingly rare. Some would argue that geniculate neuralgia, unlike the neuralgias already described, need not be lancinating and episodic but tends to be more prolonged. It may be sharp or burning. It occurs in middle-aged adults and more often in women than in men.

Treatment with carbamazepine is appropriate, **but** the rarity of the condition has prevented accumulation of any meaningful results. Excision of the nervus intermedins and the geniculate ganglion via a middle fossa approach has provided relief (Pulec 2002).

Geniculate Herpes Zoster or Ramsay Hunt Syndrome

Presumed infection of the geniculate ganglion with herpes zoster virus results in ear pain with radiation to the tonsillar region ipsilaterally. Vesicles are found in the external auditory canal and on the pinna. Less often, they are also seen on the anterior pillar of the fauces. "The infection may affect the chorda tympam, leading to loss of taste on the anterior two-thirds of the tongue. In almost all patients, the main trunk of the facial nerve is involved, causing facial paralysis. Adjacent nerves may also become involved, most commonly the eighth, which leads to hearing loss and vertigo. The exact site of the herpes infection is debated and may be within the brainstem rather than confined to the geniculate ganglion. Treatment is symptomatic. Recovery of facial nerve function tends to be less complete than after idiopathic Bell's palsy.

Occipital Neuralgia

A headache in the occipital region may be due to entrapment of the greater or lesser occipital nerves on one or both sides. The patient may have a histoty of trauma to the back of the head, but more commonly the condition develops spontaneously. Chronic contraction of the neck and posterior scalp muscles may be responsible for entrapment of the occipital nerves.

The pain is described as shooting from the nuchal region up to the vertex. In addition to the lancinating pains, dull occipital discomfort may be present. Percussion over the occipital nerves should reproduce the symptoms, and discrete tenderness should be evident in the area of the nerve low in the occipital region. Local anesthetic and corticosteroid can he infiltrated around the nerve as a diagnostic procedure. While the area remains anesthetized, the spontaneous pain should be relieved, and pain should not be triggered by percussion over the nerve. In many instances, this treatment results in long-term relief. Avulsion or nerve section should be avoided because these procedures often do not give complete relief and may lead to formation of a neuroma.

Postherpetic Neuralgia

Herpes zoster infection of the trigeminal nerve almost always involves the ophthalmic division. The typical eruption is strictly unilateral and involves the forehead and upper part of the eyelid. It may be accompanied by a keratitis that can permanently scar the cornea. Pain during the acute phase is severe and may require opioid analgesics. Antiviral drugs and prednisone can decrease the pain during this stage. In elderly patients, the acute phase may be followed by a terribly distressing, long-lasting, painful dysesthctic stage. Postherpetic neuralgia can be defined as persistent pain occurring I month after the healing of the herpetic rash. Postherpetic neuralgia occurs in about 10% of patients with herpes zoster ophthalmicus.

The pain of the acute attack may merge into the postherpetic stage. The pain is constant, with superimposed lancinating pains. Terms such as *burning, stabbing,* and *tearing* are used to describe the pain. The site of the previous eruption may be either hypoesthctic or hypercsthetic.

Inflammatory changes and the results of such inflammation have been found throughout the peripheral and central trigeminal pathways and even as far caudal as the lower portion of the descending trigeminal tract in the cervical cord. Thus, the pain is a central phenomenon, which explains why peripheral surgical procedures to relieve postherpetic neuralgia are generally ineffective.

Once developed, postherpetic neuralgia may persist indefinitely, although with time it may become less severe. Many elderly patients with this distressing pain become depressed, lose weight, and become withdtawu. Treatment of established postherpetic neuralgia is difficult and in many instances ineffective. Randomized, controlled trials have supported the use of tricyclic antidepressants, gabapentin, and oxycodone.

The use of topical capsaicin is nor practical in trigeminal disttibution postherpetic neuralgia, and the use of lidocaine patches is not recommended in this circumstance. Intrathecal methyl prednisolone has been reported to be efficacious in intractable postherpetic neuralgia, but this study did not enroll patients with painful regions innervated by the trigeminal nerve (Kotani et al. 2000). Procedures to denervate the affected area of skin, trigeminal destructive procedures, and trigeminal tractotomy have been used for control of pain, but they arc rarely used at present.

Other Neuralgias

Vanna-, painful syndromes ol the head and neck have Ivrn described as neuralgias. Specific nerves have been incriminated with little to suppott the claim. Many of the syndromes have features resembling those of cluster headache. Similar temporal profiles, similar accompanying autonomic features, and similar responses to treatment indicate that the mechanisms underlying these syndromes may be identical to those responsible for cluster headache. Examples include Sludcr's sphenopalatine neuralgia, Vail's vidian neuralgia, Gharlin's ciliary neuralgia, and Gardner's petrosal neuralgia. With the possible exception of the condition described by Sluder, there is little to be gained by adhering to the belief that specific painful syndromes are due to disturbances of these nerves.

Headache in Children and Adolescents

Headaches are very common in children and their prevalence increases in adolescence. Data from multiple studies have shown the prevalence of headache of any type to be in the range of 37-51% in 7 year olds, growing steadily to 57-82% in 15 year olds. Prepubertal boys arc more often afflicted than girls whereas after puberty, headaches occur more often in girls {Lewis et al. 2002).

Obtaining the child's history of head pain can be challenging because most subjects younger than 10 years of age are unable to give clear details about the temporal profile of the headache, its frequency, and its characteristics. The examiner is very dependent on the observations of the parents. It is important to recognize the effect of the headache on the child's behavior. Does the youngster continue to play, want to go to bed, refuse food, refuse to go to school, and then appear to recover? It is also important to determine whether the headache is episodic and separated by periods of welt-being, as occuts with migraine; chronic and progressive, as might occur with a brain tumor; or chronic and nonprogressive, as might occur with a psychogenic headache or depressive equivalent,

The neurological examination in a child should evaluate the same factors as in an older patient, including careful assessment of the fundus. In addition, the head size should be measured, the fontanclles examined, and the developmental markers checked.

Investigations are undertaken after a thorough history and physical examination of the child. Neuroimaging is not done routinely. Features that are associated w'ith a the presence of a space-occupying lesion include (1) headache onset of less than 1 month, (2) absent family history of migraine, (3) abnormal neurological findings on examination (including gait abnormalities), and (4) the presence of seizures (Lewis et al. 2002). The child with a constant, nonprogressive headache may need a psychological evaluation, and the family dynamics may require full evaluation. Reports from teachers are of value in assessing the child's performance.

Migraine

Migraine is the most common cause of headaches in children referred to a neurologist. Although migraine can manifest all the features seen in older patients, migraine attacks in children arc often shorter and occur less often than those in adults, and unilateral location is not a specific feature of juvenile migraine. It can be triggered by similar factors at all ages, including stress, fever, head trauma, and sleep and eating pattern changes In girls, the onset of migraine may coincide with menarche.

Nonpharmacological approaches to treatment include elimination of known triggers and training in biofeedback and relaxation techniques. Biofeedback and relaxation training may be of benefit in patients older than 9 years of age,

Pharmacological treatment of migraine in children includes many of the agents used in adults, but the details depend on the age of the child. In children younger than 6 years of age, acetaminophen (10-15 mg/kg per dose) or ibuprofen (10 mg/kg per dose) combined with rest in a dark quiet room works well. In older children, medications such as a variety of the NSAIDs and butalbital-containing analgesic compounds may be used. The potential for analgesic-induced rebound headaches can be avoided if repeated long-term use is not undertaken. Opioid medication should be avoided.

The results of treatment with preparations of 5-HTT agonists have been mixed in older children and adolescents. In some studies, the efficacy has not been as great as has been demonstrated in adults probabh as a function of the shorter average duration of attacks. Nevertheless, sumatriptan in doses ol 2\~ nig orally and greater, tizatriptan at 5-10 mg orally, and zolmitriptan at 2.5-5 mg have been useful in some patients with moderate-to-severe attacks (Lewis 2002). Ergotamine is now rarely used given its higher rate of side effects and lower efficacy.

Both suppository and oral forms of antiemetics are helpful in patients when migraine attacks are accompanied by significant nausea and vomiting. Promethazine in a dose of 0.25-0.5 mg/kg per dose up to three times daily, ttimethobenzamide 100-200 mg up to three times daily, prochlorperazine 0.25-0.5 mg/kg every 4-6 hours, and metodopramide 1-2 mg/kg (<10 mg) every 6-8 hours can be useful. Antiemetics should be used with caution in children because of the potential for dystonic reactions (Lewis 2002).

For acute incapacitating headaches, parenteral DHE and sumatriptan have been effective. The intravenous form of DHL in a dose of 0.1-0.2 mg with 2 mg of metodopramide has been an effective acute treatment. Subcutaneous injection of sumatriptan with a dose adjustment of 0.06 mg/kg to a maximum of 6 mg can be efficacious (Lewis 2002).

For children and adolescents with repeated migraine attacks (one a week or several prolonged attacks per month), prophylactic treatment should be considered. Unfortunately, data from controlled trials for preventative agents are lacking in these age groups. Propranolol in an initial dose of 0.5-1.0 mg/kg in two daily divided doses (to a maximum of 10 mg twice daily) can be gradually increased until a therapeutic response occurs or side effects preclude further increases. As in adults, a clinical response may not occur for several weeks. If use of a jfj-adrenergic blocking agent is ineffective or contra indicated, one of the calcium-channel antagonists may be tried, such as verapamil. Cyproheptadine, long known to he an antihistamine and antiserotonin agent, is also a calcium-channel

antagonist and may be helpful in migraine prophylaxis. It is effective in less than 50% of patients, though, and drowsiness and weight gain arc common side effects. Tricyclic antidepressants, such as notttiptyline and amitriptylinc, are sometimes effective prophylactic agents. Their side effect profile (particularly cardiac) limits their use in children. Sodium valproate and gabapemin, useful prophylactic agents for migraine in adults, are sometimes helpful in children and adolescents.

Migraine Variants of Childhood

There are some periodic syndromes that occur in childhood that appear to be variants or precursors of migraine. *Cyclical vomiting* is characterized by episodic attacks of repeated vomiting (at least 4 emeses per hour) and severe nausea, pallor and lethargy; they typically last 1 to 72 hours. The episodes usually begin between 1 and 3 years of age. They are associated with pallot and lethargy. *Abdominal migraine* is typified by attacks of abdominal pain lasting I to 72 hours. The pain is typically of midline location, of dull quality, and of modetate or severe intensity. Anorexia, nausea, vomiting, and pallor are common accompanying features. Cyclical vomiting and abdominal migraine usually begin between 4 and 10 years of age. In *benign paroxysmal vertigo of childhood,* brief attacks of vertigo lasting minutes to hours occur suddenly and may be associated with nystagmus, vomiting, and pulsatile headache. *Benign paroxysmal torticollis* is manifested by tecurrent episodes of head tilt to one side, usually lasting 4 hours to 4 days (not always to the same side) and stops spontaneously. Pallot, irritability, malaise, and vomiting usually accompany the attacks, which begin in infancy. Ataxia may occur in older children. Many individuals with these symptoms develop more typical migraine at some time (Al-Twaijri and Shevell 2002). *Alternating hemiplegia of childhood* consists of episodes of alternating hemiplegia beginning before 18 months of age and may be associated with other paroxysmal phenomena including tonic spells, dystonic posturing, chorcoathetoid movements, and oculat motor abnormalities. In all of these syndromes, no evidence of othet etiologies is present on examination or investigations.

Tension-Type Headache

Chronic tension-type headaches in children are similar to the same condition in adults. Life stresses are often the underlying cause. Depression and anxiety may result from peer pressure, excessive parental expectations, conflict with teachers, and physical or sexual abuse. The headache is often diffuse, present to some degree almost continuously, and unaccompanied by any physical signs. Refusal to go to school and other secondary gain mechanisms may be obvious. Treatment is difficult and may require psychotherapy and family counseling.

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Chapter 76
Cranial Neuropathies

Patrick J. Sweeney and Maurice R. Hanson

This chapter covers the cranial nerve (CN) disorders, with the exception of the olfactory (CN I) (see Chapter 20), optic (CN II) (see Chapters 14, 15, and 40), and cochlcovestihular (CN VIII) (see Chapters 18, 19, and 41) nerves. Because of their complexity, we devote more attention to the neuroanatomy of the lower CNs (VII, IX, X, XI, and XII) than to the upper CNs.

OLFACTORY NERVE (CRANIAL NERVE I)

See Chapter 20.

OPTIC NERVE (CRANIAL NERVE II)

See Chapters 14, 15, and 40.

OCULOMOTOR NERVE (CRANIAL NERVE III)

Neuroanatomy

Arising from paired nuclei in the dorsal midbrain, beneath the superior colliculus, the oculomotor CN components derive from individual cell groups that include parasympathetic fibers from the Edinger-Westphal nucleus. The fibers pursue a curved course through the tegmentum and cerebral peduncles of the midbrain, some traversing the red nucleus itself. Emerging from the side of the interpeduncular fossa, they pass forward through the lateral wall of rhe cavernous sinus into the orbit through the superior orbital fissure. Markinovic and Gibo (1994) provide an extensive review of rhe vascular supply of the oculomotor nerve (CN III).

Brainstem Syndromes

Dysfunction of the third CN can occur anywhere from its nuclear origins in the midbrain to its final terminations in the orbit. As the fascicles pass through the midbrain and exit from anteromedial aspects of the cerebral peduncles, well-defined syndromes can result, allowing anatomical localization of the problem. Thus it is possible for a strategically located lesion to involve selectively both of the third CNs or even just a portion of their nuclear origins. Current neurology and ncuro-ophthalmology texts differ somewhat in their descriptions of these named midbrain syndromes (Table 76.1).

Posterior circulation disturbances with infarction or hemorrhage are common causes of these rare syndromes. Less commonly, demyelinating disease and neoplasia, primary or metastatic, may be etiological factors. Symmetrical pu>M- *uv.v,* hi- :i sign ol caudal midline nuclear involvement of the third CN. Silverman, Lui, and Galetta (1995) provide a comprehensive teview of brainstem syndromes and crossed paralysis. (See also Chapter 22 for a discussion of brainstem syndromes affecting the third CN.)

Aneurysmal Involvement of the Oculomotor Nerve

After the fascicles of the oculomotor nerve exit the brainstem, they fuse in the interpeduncular fossa. Any extra-axial mass in this subarachnoid area could involve one or both oculomotor nerves. Aneurysms of both the posterior communicating artery and the basilar bifurcation may produce internal ophthalmoplegia, with a dilated and relatively fixed pupil as its initial manifestation. Oculomotor dysfunction is also relatively common as a complication of surgery on a basilar bifurcation aneurysm. The palsy is likely due to retraction of the nerve during surgery. When it occurs in isolation, the prognosis for recovery is good, with resolution occurring over several months. On the other hand, when the third CN dysfunction is accompanied by a hemiparesis, recovery is often incomplete.

In the past the dictum that compressive third nerve etiologies invariably produce pupillary paralysis and microscopic vascular etiologies spare the pupil has been widely believed. However, because of the ftequency of overlapping factors such as aging and vascular risk factors, this clinical guideline is less reliable in plotting a course of action (Trobe 1998).

Raised inttactanial pressure, from whatever cause, may produce transtentorial uncal herniation with extrinsic compression of the third CN on the margin of the tentorium. Because of the peripheral location of the pupilloconstrjctot fibers, or theit vulnerability to compression, a unilateral pupillary enlargement on the side of the lesion may be the earliest sign of increased intracranial pressure (Hutchinson's pupil).

Table 76.1: Terminology for midbrain syndromes

Syndrome	*Milter and Newman (Walsh and Hoyt)*	*CLisrr*	*I i-ifii- • ':ii /••'*	*Original description*
Benedict's (1889)	Oculomotor palsy	Oculomotor palsy	Oculomotor palsy	Oculomotor palsy
	Contra la [era 1 chorea, tremor, ballismus, or aril cms is	Contralateral ataxia and intention tremor	>	Contralateral hemiparesis
	LS: rhird nF, RN	LS: third nF, RN	LS: third nF, RN, CP	Contralateral involuntary movements or tremor LS: third nF, CP, SN?, RN?
Claude's (1912)	Oculomotor palsy Contralateral asyncrgia, ataxia, dysmctria, dysdiadocliokinesia LS: third nF, RN, BC	Not mentioned	Oculomotor palsy l .13111 i. L :. t Hi : ll . U . I M . I , and slow rubral tremor LS: third nF, RN	Oculomotor palsy Contralateral ataxia asynergy, dysdiadocliokinesia
Nothnagel's (1879)	Oculomotor palsy Ipsilateral ataxia LS: third nF, BC	Not mentioned	Oculomotor palsy with vertical gaze palsy LS: third nF and ?	±Trochlear palsy, iscnsory loss LS: third nF, RN, SCP (ifourth nerve, ML, MLF) Bilateral oculomotor palsies of varying degree and usually as) mmetrical ±Nysragmus Gait ataxia LS: superior and inferior colliculi

BC = brachium conjunctivum; CP = cerebral peduncle; LS = lesion site; ML = medial lemniscus; MLF = medial longitudinal fasciculus; RN = red nucleus; SCP = superior cerebellar peduncle; SN — substantia nigra; third nF = third cranial nerve fascicle.
Source: Used with permission from Liu, L C. T., Crenner, C. W., Logigian, E. L., et al. 1992, "Midbrain syndromes of Benedikt, Claude and Nothnagel: Setting the record straight," *Neurology,* vol. 42, pp. 1820-1822.

Trauma

The third CN in the subarachnoid space can be injured in head trauma. Even minor head trauma may produce a third nerve palsy as the initial sign of parasellar or clival tumor, presumably because the oculomotor nerves are already stretched over the rumor or are partially encased and fixed by the tumor and hence vulnerable to sudden mechanical stress. A third nerve palsy triggered by mild head injury should prompt investigation for a basal tumor.

Cavernous Sinus Syndromes

As the third CN enters the cavernous sinus, it courses forward in the upper aspects of the lateral sinus wall, above the trochlear and trigeminal nerves. In this location, it is prone to compromise by a variety of pathological processes that may simultaneously compromise other cavernous sinus structures, t impression *A\\d* dysfunction of the third, fourth, or sixth CNs in the cavernous sinus may be i..iu^J by .1 i-:i!'!>;id arury enlarged by diswiinn, bin tinmore likely cause of ocular motor palsies in spontaneous carotid dissection is interruption of the nutrient arteries supplying the nerves.

Thrombophlebitis of the cavernous sinus is a potentially life-threatening condition secondary to contiguous infection in the surrounding sinuses, eye, or nose. Involvement of the third CN, along with any other CNs or vascular structures traversing this cavity, can result in a clinical picture of a sick and septic patient with headache, with varying degrees of ophthalmoplegia, chemosis, and proptosis. If the condition is untreated, the initial unilateral picture may become bilateral via spread through the circular sinus. In the immunosuppressed or poorly controlled diabetic in acidosis, mucormycosis must be considered in the diffetential diagnosis. This fungal infection, caused by either *Rhizopus* or *Mucor* species, often produces nasal turbinate necrosis and a serosanguineous nasal discharge. Surgical debridement of the area and intravenous amphotericin B may save the patient from otherwise certain death. Other fungal infections, such as *Aspergillus,* may produce similar manifestations.

Aneurysms of the carorid artery in the cavernous sinus, as well as primary and metastatic neoplasia, are important causes of third or sixth nerve dysfunction. A coexisting involvement of both parasympathetic and sympathetic pupillary function suggests localization to this area.

Infarction of the third CN in the cavernous sinus involves the central cote of the nerve, sparing peripheral pupilloconstrictor fibers, producing a characteristic painful pupil-sparing palsy of CN III. In the past, this was offered as a reliable sign of noncompressive disease that obviated the need for invasive studies, such as angiography. Vascular versus compressive etiologies can often be predicted from how the iridoplcgia and ophthalmoplegia evolve during the first 7 days of the illness.

Superior Orbital Fissure and Orbit

The third CN passes through the superior orbital fissure in its passage from the cavernous sinus into the orbit. It is often difficult to distinguish lesions of CN III in the orbit from those of the superior orbital fissure and those in the proximal orbit. Coexisting optic nerve dysfunction suggests orbital involvement. Involvement of maxillary division facial sensation suggests that the lesion extends at least as far back as the midcavcrnous sinus. Although the superior :irbiral :issi;re ma\ be bivolved ir almost an\ or the conditions mentioned previously, the Tolosa-Hunt syndrome merits special comment. Usually appearing in the fourth through sixth decades of life, this syndrome manifests over several weeks as a steady, boring, unilateral orbital pain. Palsies of the third, fourth, or sixth CNs, in any combination, are possible. Optic nerve involvement is unusual. Although first-division trigeminal sensory involvement may occur, involvement of the maxillary division is uncommon. Both sexes are affected equally, and spontaneous remissions are reported. The entity is diagnosed by exclusion of other space-occupying lesions in the area of the superior orbiral fissure and its contiguous parts. Corticosteroid responsiveness is the rule. Pathological examination reveals nonspecific inflammatory granulation tissue filling the cavernous sinus.

Distal Branch Syndromes

As the oculomotor nerve enters the orbit, it subdivides into superior and inferior branches. The former, passing lateral to the optic nerve, supplies the superior rectus and levator palpcbrae superioris muscle. The inferior branch, the larger of the two, supplies the inferior and medial rectus muscles and inferior oblique muscle. A twig of nerve passing to the inferior oblique also supplies, through the short ciliary nerves, the sphincter of the pupil and ciliary body. Selective paralysis of these terminal branches has multiple causes, including orbital trauma, but may be idiopathic.

Isolated superior branch oculomotor palsies produce a characteristic picture of unilateral ptosis, with weakness of the superior rectus and preserved pupillary, medial, and inferior rectus muscle function. The cause is often idiopathic and presumed in lv viral, bin internal carotid artery aneurysms, located either in the intracavernous portion or on the posterior communicating artery, may damage nerve fibers in the oculomotor nerve before division into its terminal superior and inferior branches. Myasthenia gravis may occasionally cause a similar picture.

Aberrant Regeneration Phenomena

Aberrant regeneration phenomena are oculomotor synkinesias that encompass a variety of signs, the most classic of

which is lid retraction on adduction or depression (pseudo-Graefe's sign) of the ipsilatcral eye.

TROCHLEAR NERVE

Neuroanatomy

The trochlear nerve, or fourth CN, is unique among the CNs m several ways. It originates from cells beneath the inferior colliculus just above the medial longitudinal fasciculus and caudal to the third CN complex. It is the only CN to exit on the dorsal aspect of the brainstem and is [lie only CN thai is completely crossed. Thus fibers from the right fourth CN nucleus cross in the anterior medullary velum to reach the left orbit, and vice versa. It is also the smallest of the CNs to the extraocular muscles and has only approximately 2100 axons as compared with the oculomotor nerve, which has 15,000, and the abducens nerve, which has 3500. The fourth CN travels forward in the lateral wall of the cavernous sinus beneath the third CN and above the trigeminal nerve to reach the orbit and ultimately the superior oblique muscle.

Congenital Versus Acquired Palsies

The diplopia in traumatic fourth nerve palsies usually subsides in less than 1 year. When trauma is excluded, a small number of patients are found with congenital fourth nerve palsies. Im.ie.e rilnne, vr>inbiiH\l with vertical diplopia occurs only in acquired cases of recent onset, not in congenital fourth nerve paralysis.

Etiology

Trauma is the most common cause of trochlear nerve palsy in adults. Twenty percent of traumatic cases are bilateral, Head impact at the time of trauma may produce disruption of the crossing fibers in the anterior medullary velum, perhaps by distention of the fourth ventricle. Transient ipsilatcral trochlear nerve paresis may occur after anterior temporal lobectomy for intractable seizures (Jacobsen, Warner, and Ruggles 1995).

The etiology of a large number of palsies of CN IV remain undetermined. Vascular ischemic disease from hypertension, diabetes, and atherosclerosis accounts for approximately one fifth of eases. On very rare occasions, aneurysm in such disparate locations as the cavernous sinus and the posterior fossa may produce a fourth nerve paralysis. Myasthenia gravis must always be considered in the differential diagnosis of any ocular muscle palsy of nontraumatic origin. On rare occasions, fourth nerve palsy may follow an attack of herpes zoster ophthalmicus, but its onset may be delayed up to 4 weeks after the rash.

In a child, fourth nerve palsy prompts consideration of congenital origin, with head trauma being the second most common cause.

TRIGEMINAL NERVE

Neuroanatomy

The trigeminal nerve, or fifth CN, is a mixed motor and sensory nerve. The larger lateral portion of the fifth CN transmits sensation from sharply defined cutaneous fields on the face, oral cavity, and nasal passages. The smaller motor branch provides motor function to the muscles of mastication and travels with the third division.

The ophthalmic, maxillary, and mandibular nerves enter the cranial cavity through the superior orbital fissure, foramen rotundum, and foramen ovale, respectively, to unite in the gasserian (semilunar) ganglion situated on the cerebral surface of the petrous bone.

Atrophy and fatty replacement of muscle mass can be visualized with magnetic resonance imaging (MRI) when the mandibular division of CN V has undergone motor denervation (Russo, Smoker, and Weissman 1997).

Trigeminal Sensory Neuropathy

Trigeminal sensory neuropathy presents with sensory disturbance in one or more divisions of the nerve. Patients with a benign form have no associated neurological defects and have preservation of the corneal reflex. The paresthesias may resolve completely in a matter of months, with only a small percentage of patients developing other conditions, such as trigeminal neuralgia. Sinister etiologies include infiltrating neoplasms or vasculitis. In this population, patients usually have other neurological signs associated with the facial numbness. If intraoral sensation is impaired sufficiently, there may be difficulty in chewing and swallowing. Perineural spread of facial skin cancer and nasopharyngeal carcinoma may occur months or years after excision of the malignancy (Catalano, Sen, and Btller 1995; Su and Lui 1996).

Trigeminal sensory neuropathy may be associated with scleroderma and other connective tissue disease. Distinguishing features of connective tissue disease are bilaterality, associated pain, and paresthesias that are not confined to individual nerve territories. Typically, the trigeminal motor pathway is spared. The site of involvement may be the cisternal portion of the nerve or gasserian ganglion, where motor and proprioceptive fibers bypass the sensory root (Forster et al. 1996).

Interferon-ty, used in the treatment of a variety of malignancies, may produce intermittent or continuous sensory disturbance in the trigeminal distribution (Read, Crawford, and Pender 1995).

In controlling the paresthesias ami neuropathic pain associated with these disorders, a literature review by McCleanc (2000) points to the effectiveness of lamotngine in these situations.

Numb Ciiin and Cheek Syndromes

Numbness of the lower lip may be the initial manifestation of metastatic disease to the lower jaw, affecting primarily the inferior alveolar nerve. Metastatic lung and breast cancers are the most common primary tumors.

There are also neoplastic causes of numbness in the malar region. History of basal or squamous cell carcinomas of the face should be sought. There may he a spread of this type of tumor along regional nerves to the skull base and into the intracranial space, with meningeal involvement. As a result of mandibular bone atrophy from aging, the elderly may develop stenosis at the mental nerve foramen with paresthesias in the ipsilateral chin. A similar phenomenon has been reported with scleroderma (Fischoff and Sirois 2000).

Trigeminal Nctjralgia

See Chapter 75 for a discussion of trigeminal neuralgia.

Traumatic Neuropathies

Both cranial and facial trauma may affect the peripheral infraorbital and supraorbital branches of the trigeminal nerve. Cavernous sinus tumors may also involve the trigeminal nerve, but often there is associated contiguous CN involvement that localizes the site of the disease. Trigeminal nerve branch injury can rarely result from dental anesthetic injections.

Lingual nerve (a branch of the mandibular division of CN V) injury may occur after surgery on the third molar and after laryngeal mask airway placement (Laxton and Kipling 1996). These patients present with complaints of paresthesias on the ipsilateral tongue surface.

Herpes Virus Infections

Viral infection with herpes simplex and herpes zoster may occur. The recurring herpes simplex mucous membrane lesions that occur throughout an individual's lifetime are associated with lifelong residence of that virus in the trigeminal ganglia. Herpes zoster, which is the result of lifelong varicella zoster virus residence in the ganglion, produces a much more fulminating infection, with disabling pain. Preherpetic neuralgia may precede the rash by several days and is followed by postherpetic neuralgia in about one third of the patients. The ophthalmic division of the trigeminal nerve is most commonly affected.

ABDUCENS NERVE

Neutoan atomy

Of all the motor nuclei of the extraocular nerves, those of the abducens nuclei lie farthest from rheir muscles of termination and originate at the lowest level in the brainstem. They lie just below the floor of the fourth ventricle, close to the midline, in the caudal pons. In contrast to the trochlear nerve, but in common with the oculomotor fibers, the abducens or sixth CN fibers have a considerable intramedullary extent. The axons course ventrally and in a somewhat caudal direction through the brainstem parenchyma to emerge at the pontomedullary junction.

The nerve then makes a right-angle turn to pass upward along the face of the clivus; it turns anteriorly at Dorello's canal and passes into the medial aspect of the cavernous sinus, where it lies just beneath the internal carotid artery, The abducens nerve supplies the lateral rectus muscle.

Brainstem Syndromes

As with the other CNs, lesions at different foci in the brainstem produce distinct syndromes. This anatomy explains the rare combinations of ipsilateral sixth nerve palsy, gaze palsy, and peripheral seventh CN weakness (Millard-Cubler syndrome) and of sixth nerve palsy and contralateral hemiplegia (Foville's syndrome). Infarction in the territory of anteroinferior cerebellar artery is probably the most common cause of these syndromes. Foville's syndrome is often combined with varying degrees of ipsilateral Horner's syndrome, facial hypesthesia, and hearing loss. A characteristic disorder, referred to as *one-and-a-half syndrome,* consists of preservation of abduction in only one eye, which also exhibits jerk nystagmus in the abducted position, while the other eye lies fixed in midline for all attempts at lateral movement.

See Chapter 22 for a discussion of brainstem syndromes affecting the abducens nerve.

Extra-Axial Posterior Fossa Syndromes

It is possible for any cerebellopontine angle tumor to cause varying combinations of trigeminal, facial, and auditory nerve dysfunction. Chordomas of the clivus may selectively involve the sixth nerve in its climb along the clivus. In the preantibiotic era, medial extension of middle ear infection or mastoiditis resulted in osteitis of the petrous pyramid and paralysis of CN VI as it approached Dorello's canal

and the petroclinoid ligament (Gradenigo's syndrome). Metastatic disease to the same area or primary neoplasia, such as cholesteatoma, may produce a similar painful sixth nerve palsy. In the middle-aged to elderly adult with abducens nerve palsy and a combination of cervical [ymphadenopathy, serous otitis media, and blood-tinged nasal discharge, evaluation must exclude a nasopharyngeal carcinoma. Both unilateral and bilateral abducens paresis may occur in the syndrome of spontaneous intracranial hypotension (Berlit, Berg-Dammer, and Kuchne 1994).

For a discussion of cavernous sinus syndromes, see Oculomotor Nerve, earlier in this chapter.

Pathophysiology

Of all the oculomotor palsies, abducens nerve paresis is the one most frequently reported and at the same time most often indeterminate in cause. In the middle-aged to elderly adult population, especially if there is a history of hypertension or diabetes, small-vessel ischemic infarction of the nerve is the most likely cause. The microscopic neuroanatomy of the abducens nerve, as well as of rhe oculomotor and trochlear nerves, reveals rhat they are penetrated by small nutrient vessels, occlusion of which produces infarction. If the sixth nerve palsy is bilateral, however, ischemia is seldom the cause, and neoplasia, demyelinating disease, subarachnoid hemorrhage, meningeal infection, and increased intracranial pressure must be considered.

Unilateral or bilateral abducens weakness is also encounteted as part of Wernicke's disease in the nutritionally deprived alcoholic population. Myasthenia gravis may produce isolated weakness of ahduction, mimicking abducens nerve palsy.

Abducens. Nerve Palsy in Childhood

In children, abducens nerve palsies are most frequently due to neoplasia (13%) and trauma (40%). Often the neoplasm is a primary brainstem glioma, and abducens weakness may be the first sign of disease. In the newborn period, abducens nerve paresis may be a transitory and benign finding. Amblyopia may be a complication of sixth nerve paresis in children, and close monitoring to prevent this complication is warranted (Aroichane and Rcpka 1995).

FACIAL NERVE (CRANIAL NERVE VII)

Neuroanatomy

The facial nerve is the most complex of the CNs because of its multiple motor, sensory, and autonomic components, and its long, tortuous intracranial and extracranial course. The nerve is the motor nerve to the mimetic muscles of the face. It also contains secretory fibers to the salivary and lacrimal glands, and the mucous membranes of the oral and nasal cavities. There are also somatic pain fibers from the external auditory canal and a small strip between the mastoid and the pinna, as well as taste fibers from the ipsilateral two thirds of the tongue.

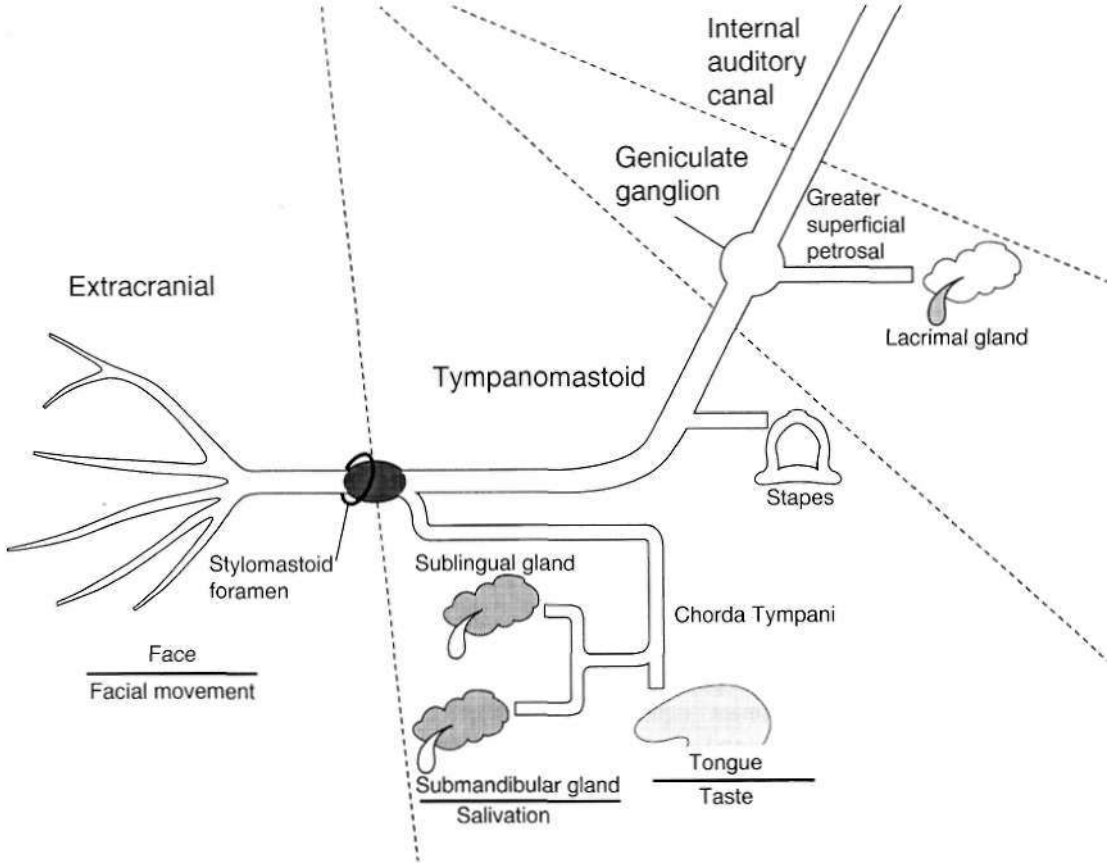
The facial nerve has two principal roots. Seventy percent of the nerve fibers arise from motor neurons of the facial nucleus; thirty percent are mixed sensory and autonomic fibers, forming the nervus intermedius of Wrisberg. The facial motor nucleus is located in the ventrolateral portion of the caudal pons. Its fibers coutse from the dorsal aspect of the nucleus to the medial side of the sixth CN nucleus, at which point they curve laterally around the dorsal surface of the sixth CN nucleus, forming the facial colliculus in tlu- t'liior ni tlu- fourth uiiii:.lf. The fibers then pursue a ventrolateral course through the pontine tegmentum to exit from the lower body of the pons between the olive and restiform body. Fibers for voluntary and reflexive facial movements are anatomically separate rostral to the lowei pons (Urban et al. 1998).

The sensory root of the facial nerve (the nervus intermedius) is a combination of sensory and parasympathetic nerve fibers that include special visceral afferent fibers arising from the bipolar neurons within the geniculate ganglion, which supply taste fibers to the anterior two thirds of the tongue by way of the chorda tympani. The centra) portions of these branches traverse the nervus intermedins and terminate in the nucleus solitarius. Visceral efferent fillers arisir.s', fruir. the superior salivatorv nuclei course in the nervus intermedius and travel with the greater superficial petrosal nerve to the synapse in the sphenopalatine ganglion, yielding postganglionic fibers to the lacrimal and palatine glands. Still other preganglionic efferents continue in the chorda tympani to the submandibular glands. After leaving the pons, the motor and sensory roots of the facial nerve course through the cerebellopontine angle cistern for approximately 24 mm before entering the internal auditory canal. Within the canal, CN VII occupies a position anterior and superior to CN VIII.

From the internal auditory canal to the stylomastoid foramen, CN VII traverses a torruous course of approximately 33 mm.

The facial nerve is the longest and most complex of the CNs (Figure 76.1), consisting of six segments: intracranial, internal auditory canal, labyrinthine or petrous, tympanic, mastoid, and intraparotid. The labyrinthine, tympanic, and mastoid segments are in the fallopian canal.

After the facial nerve (with the nervus intermedius) leaves the internal auditory canal, it begins its long course through the fallopian canal, beginning with the labyrinthine segment, which is approximately 3—4 mm long. The nerve enters the fallopian canal at the petrous bone and runs at a right angle to the petrous pyramid. The geniculate ganglion is included in this segment, giving rise to the greater superficial petrosal nerve. This is the narrowest portion of the fallopian canal, and the nerve occupies up to 80% of



HCiURI- 7h. I J In, schematic ol the facial nerve shows the- major subdivision- .nu! ILUMI.IU-. die |nioci]ial functions thai mighi he impaired at the level of a lesion and distal to it. For example, a lesion at the level of the geniculate might produce impaired taste and glandular secretions, as well as hyperaeusis (in addition to facial paralysis).

the available diameter. In addition, the labyrinthine portion is the only segment without anastomosing atterial arcades, making it vulnerable to ischemia and compression. The labyrinth and tympanic segments of the fallopian canal form an acute angle of approximately 75 degrees, predisposing the nerve to vascular lesions and traumatic injury. I'he tympanic portion 12-13 mm) courses behind the cochlea and semicircular canal, ending with the beginning of the mastoid segment (15-20 mm) that continues along the anterior wall of the mastoid process. It is the longest segment of the nerve and has two major branches. The first branch goes to the stapedius muscle. The second branch is the chorda tympani, the terminal branch ol the ncrvus intermedins. This branch courses anteriorly and superiorly over the incus and under the malleolus, crossing the tympanic cavity to exit the temporal bone through the petrotympanic fissure, joining the lingual nerve to innervate the submandibular and sublingual glands. The chorda tympani also contains the taste fibers from the anterior two thirds of the tongue.

CN VII ends its course in the fallopian canal by exiting through the stylomastoid foramen, giving off several branches, which include an inferior branch to the posterior belly of the digastric and stylohyoid muscles. The main trunk of the facial nerve entets the parotid gland, dividing into upper and lower parts. The upper division gives rise to frontal, zygomatic, and buccal branches; the lower trunk gives rise to the mandibular and cervical branches. Approximately 17 paired muscles of facial expression are innervated by these various branches. An upper group of muscles raises the eyebrows, moves the forehead, and is involved in frowning. An intermediate group is involved in closing the eyelids and wrinkling the nose, and an inferior group is involved in smiling, laughing, whistling, wrinkling the chin, and raising the upper lip. The only facial muscle that is not innervated by CN VII is the levator palpebra superioris, which is innervated by the oculomotor nerve.

Supranuclear lesions produce a different pattern of facial paralysis than do infranuclear and nuclear lesions (Table 76.2). The traditional explanation is that the lower face has primarily a contralateral innervation, whereas the upper face has both ipsilateral and contralateral innervation. However, a contributing factot is that the conical representation of the upper face is in the anterior cingulate gytus, and not the motot cortex (Morecraft et al. 2001).

There is a disparity between emotional facial mimetic expression and voluntary facial movement that is best

Table 76.2: Clinical differential features of upper motor neuron versus lower motor neuron facial weakness

Upper motor neuron lesions	*Lower motor neuron lesions*
Unilateral paresis of voluntary movements of lower face with sparing of the frontalis muscle	Unilateral paresis of all mimetic muscles, including the frontalis muscle
Facial muscle weakness less apparent with emotional than with voluntary action	Degree of facial weakness similar with emotional and voluntary movements
Preservation or accentuation of facial reflexes	Suppression of facial reflexes
Preserved taste, anterior two thirds of tongue	Possible impairment of taste
Normal lacrimarion	Possible abnormality of lacrimation

explained by different pathways subserving these functions {Holstege 2002).

Clinical Evaluation

The symptoms of facial nerve disease depend on several factors, including size of lesion, severity of the disorder, acuteness of onset, and whether the lesion or lesions are bilateral or unilateral. A sudden severe unilateral infranuclear paralysis, as seen in Bell's palsy, produces (in addition to an obvious cosmetic embarrassment) significant dysarthria, pooling of saliva, drooling, and decreased tearing; it also allows food to collect between the gum and the cheek as a tesult of buccinator weakness. Depending on the size of the lesion, there may also be perversion of taste and hyperacusis. On the other hand, a moderate degtcc of weakness of the lower face, as seen with a unilateral corticobulbar lesion, may produce few complaints relative to the face, particularly if attention is distracted by ipsilateral limb weakness or if language dysfunction is present because of a dominant hemisphere lesion. Bilateral corticobulbar disease, as with multiple lacunae, is much more devastating to speech and swallowing functions. Unilatetal facial weakness of slow evolution, as seen with a pontine glioma, may go unnoticed by a patient, although it is obvious to the examinet. This is consistent with the general clinical observation that objective neutological deficits more apparent to the examiner than to the patient are usually of gradual evolution.

Facial reflexes may aid in establishing or localizing lesions of the facial nerve. Some arc true myotatic reflexes, and others represent associated movements. A variety of stimuli, such as noise, sudden light, and pain, can elicit a blink reflex that uncovers unilatetal facial weakness.

The bilateral orbicularis oculi (blink or glabellar) reflex is elicited by tapping over the supraorbital ridge or root of the nose. It should be elicited by holding a hand over the top of the forehead, to avoid a visual blink response. With early, mild, or resolving unilateral facial paresis, the ipsilateral glabellar reflex is diminished. The afferent pathway is via the first division of CN V, with a rapid unilateral monosynaptic component and a delayed bilatetal polysynaptic component. A variation of this reflex is the orbicularis oculi stretch teflex, elicited by gtasping the lateral orbital skin between the thumb and index finger and tapping the thumb with a reflex hammer. A similar bilateral blink response is present. The afferent impulses, howevet, atisc from stretch receptors in the muscle.

Anothct stretch reflex is the orbicularis oris reflex, elicited by percussing the uppet lip and producing elevation of the lip and angle of the mouth. Like most othet myotatic responses, these reflexes are diminished or abolished by segmental dysfunction and preserved or heightened with bilateral corticobulbar lesions.

Bell's phenomenon is a true associated movement. With attempted closure of the eyes against resistance, the globes move up and out. This normal movement can be observed with the incomplete eyelid closure in Bell's palsy.

The stapedial reflex is particularly helpful in diagnosis. Stapedius muscle contraction, activated by strong acoustic stimuli, pulls the stapes out of the round window, attenuating intense sound waves. Reduction ot absence of this reflex results in hyperacusis or phono phobia. It can be quantified by measuring acoustic impedance (see Chaptet 41) but can be tested at the bedside using the stethoscope loudness imbalance test. A stethoscope is placed in the patient's ears, and a gently vibrating tuning fork is placed on the bell. With notmal hearing, the perception of sound is symmetrical. With greater activation, the sound laterali7.es to the side of the facial paresis (in some cases) because the attenuating effect of the stapedius muscle is reduced or absent.

The sensory functions of CN VII are not easily tested, arc rather cumbersome, and are not always reliable. Testing taste sensation is desctibed in Chapter 20.

With any facial paresis, it must first be determined whether the lesion is affecting the upper motor neuron or the lower motor neuron. In most instances, it is obvious, but when it is less clear, cettain critical observations can usually settle the issue.

Upper motor neuron disorders with unilateral facial paresis affect the voluntary movements of the lower face with relative sparing of the orbicularis oculi, frontalis, and corrugator supercilii muscles. There are certain circumstances in which this rule is violated:

- During recovery from Bell's palsy, if the upper facial groups recover before the lower groups, and if recovery is incomplete, as may occasionally occur in incomplete acute lesions

If nuclear lesions are restricted to the caudal portions of the nucleus, as in polio, and at some stages of motor neuron disease

If an extracranial lesion involves only the lower division of the facial nerve, as sometimes happens after radical neck dissection or with parotid tumors

In upper motor neuron lesions, there is preservation of the blink and stapedial reflexes; lacrimal and taste sensibilities also remain unimpaired. This may also be true for lower motor neuron lesions. If reflex functions are involved, however, this is strong evidence that the lesion is not upper motor neuron.

In lower motor neuron lesions, the degree of weakness is the same with voluntary and emotional movements. With upper motot neuron involvement, particularly of the prefrontal cortex, the face is relatively symmetrical, with a normal emotional smile, and the movement of the involved side may actually be exaggerated, despite the unilateral weakness on voluntary contraction. The latter observation is probably the only one that consistently separates upper motor neuron from lower motor neuron lesions.

A large number of congenital and acquired disease states may damage the facial nerve anywhere along its course, from its brainstem nuclear origin to its peripheral terminations in the face.

Congenital Disorders

Congenital disotders of the facial nerve must be distinguished from traumatic damage to the facial nerve as a result of birth injury. Difficult forceps delivery, periauricular ecchymosis, hemotympanum, and swelling often provide clues to a traumatic cause, but many patients seem to have an uncomplicated birth history,

In contrast to infants with traumatic facial paralysis, newborns with congenital disorders of facial palsy have a poor prognosis for improvement in facial nerve function. Clues pointing to a congenital cause may be other birth defect stigmata, especially microtia and external auditory canal atresia. Congenital malformations elsewhere in the body, such as limb deformity or hypoplasia of the pectoral muscle, also suggest a congenital cause for the facial palsy. There are a number of well-recognized syndromes of congenital facial palsy, including cardiofacial syndrome and Mobius' syndrome. Cardiofacial syndrome comprises facial asymmetry when crying but not at rest and may result from isolated weakness of the depressor anguli oris and depressor labii inferioris muscles of the lower lip. It does not interfere with smiling or sucking and does not result in drooling, but it may be associated with congenital heart defects and other anomalies.

Mobius' syndrome consists of a spectrum of abnormalities; most cases occur on a sporadic or familial basis. The mutation in one large family with dominantly inherited Mobius' syndrome was mapped to the long arm of chromosome 3. The most consistent features arc congenital paresis of CNs VII and V1I1 with variable orofacial and limb malformation. Necropsy has shown defects ranging from hypoplasia to agenesis of the respective CN nuclei.

Toxins

Peripheral facial paralysis may occur in thalidomide embryopathy. Medical and occupational exposure to the antiseptic solution chlorocreso), used in electrode paste and various dcrmatological skin ctcams, may produce transient facial paralysis. Ingestion of the antifreeze component ethylene glycol, eithet in a suicide attempt or for inebriation, may also cause bilateral peripheral facial weakness, either permanent ot temporary.

Traumatic Facial Palsy

A peripheral facial paralysis occurring in the context of head trauma should always raise the possibility of basilar skull fracture. Basilar temporal bone fractures are generally categorized as eithet longitudinal (extending medially along the bony external canal) or transverse (crossing the long axis of the pettous pyramid). Both types of fracture may be accompanied by facial nerve palsy.

Transient facial palsy may oivur 1:1 up in *?.(.)%* or patients undergoing sphenoidal electrode insertion for prolonged video electroencephalographic monitoring. The mechanism is likely related to the effect of local anesthesia on the peripheral branches of the facial nerve.

Pregnancy

Cohen et al. (2000) reviewed the occutrcncc of Bell's palsy in pregnancy. They concluded that (1) women of reproductive age are affected two to four times more often than men of the same age, (2) pregnant women are affected three times more often than nonpregnant patients, and (3) most cases occur in the third trimester or in the puerperium. The authors concluded neonatal outcome is unaffected, recovery is good, and treatment of the palsy with corticosteroids is conttoversial. In women developing Bell's palsy while pregnant, there is an increased risk of hypertensive disorders of pregnancy such as preeclampsia (Shmorgun, Chan, and Ray 2002)

Bilateral Facial Palsy

Bilateral simultaneous peripheral facial weakness can be part of the clinical spectrum in several syndromes.

Best known is the facial diplegia of varying intensity that accompanies the Guillain-Barre syndrome. Bilateral facial weakness in the presence of aseptic meningitis or with a slightly erythematous indurated face resembling painless cellulitis should raise the possibility of Lyme disease. The conjunction of Lyme aseptic meningitis and facial weakness is sometimes referred to as *Banmuarth's syndrome.* Recurrent bilateral facial palsy is also sometimes seen in sarcoidosis and at the time of seroconversion in human immunodeficiency virus infection.

Keane (1994) provided an authoritative review on the topic of bilateral facial palsy. In his extensive series, 22 of the 44 patients reported had self-limited causes, including Bell's palsy and Guillain-Barre syndrome.

Schattner et al. (2001) revisited the topic adding acute lymphoblastic leukemia to the differential diagnosis.

Tumor involvement of the facial nerve itself is not common, but it remains an important consideration in the differential diagnosis, particularly with slowly progressive (over many days to several weeks) peripheral facia! weakness. Metastatic invasion of the temporal bone is the most common type. Breast, lung, and prostate are the most common primary tumors. Direct extension of regional tumors and primary schwannomas of the facial nerve also occur. In all these cases, the onset and course are slow and progressive. Parotid gland cysts and tumors, both benign and malignant, may involve terminal branches of the facial nerve that produce varying degrees of peripheral weakness. Obtaining a history of facial skin cancer in a patient presenting with a partial facial palsy or facial paresthesia is important because perineural spread of tumor can present long after "complete" excision of a skin malignancy (Catalano, Sen, and Biller 1995).

Bell's Palsy

The appearance of a severe, unilateral, intranuclear facial palsy is one of the most distinctive in clinical medicine. The most common cause of an acute, acquired, nontraumatic lesion is Bell's palsy, in which there is a flaccid paresis of all mimetic muscles on the involved side. In a severe case, the affected side is smooth and the brow droops, but the palpebral fissure is widened. The angle of the mouth is depressed, and the cheek balloons on expitation. The lid remains open (lagophthalmos), and on attempted closure, the globe turns up and out (Bell's phenomenon). The lower lid is everted with excessive tearing (epiphora). Facial movements arc paralyzed to voluntary and involuntary contractions, and various facial reflexes are lost. Traditional teaching posits discrete anatomical localization along the various segments of CN VII in Bell's palsy based on the test results of taste, the stapedial reflex, lacrimation, and mandibular deviation. Although there may be some validity to these observations in early lesions, the localization is much less precise in practice. As a general rule, proximal lesions at or before the geniculate ganglion may affect taste and lacrimation, as well as the stapedial reflex, whereas those distal to the geniculate ganglion produce only muscle weakness. The incidence of Bell's palsy in the general population is approximately 20 cases per 100,000, with a peak incidence in the third decade. The typical patient complains of an acute onset of facial palsy, which may evolve over 24-48 hours, often accompanied by retroauncular pain. This disorder affects males and females of all ages and is believed to be of viral origin (most often herpes simplex). It often begins with pain in or behind the ipsilatcral car, suggesting an ear infection. Unilateral weakness invariably follows within several days and usually achieves maximal paralysis within 48-72 hours. Patients may report tingling paresthesias on the involved side of the face early in the course, but this symptom is seldom prominent. Impairment of taste and hyperacusis (due to weakness of the stapedius muscle) is present in many cases. The oral phase of swallowing was found to be disturbed in 79% of patients with Bell's palsy (Scc-il, Aydogdu, and Ertekin 2002) due primarily to weakness of the orbicularis oris and buccinator muscles, resulting in the accumulation of food in the mouth. MRI shows contrast enhancement of the involved nerve (Sartoretti-Schcfer ct al. 1998).

Eighty to eighty-five percent of patients recover completely within 3 months of onset. Incomplete paralysis at the onset is perhaps the most favorable prognostic sign. Electrophysiological demonstration of lack of excitability of the facial nerve to electrical stimulation and electromyographic evidence of denervation of the involved facial muscles after 2-3 weeks establish severe axon loss. This implies a more prolonged and probably incomplete recovery, with risk of aberrant regeneration of the facial nerve fibers. Har-El and McPhee (2000) have successfully employed transcranial magnetic stimulation in the laboratory to determine the integrity of the facia! nerve immediately after trauma, bypassing the time limitations imposed by wallerian degeneration.

The prognosis is less favorable in the syndrome of facial nerve palsy with geniculate herpes (Ramsay Hunt syndrome), which involves pain and vesicles in the external auditory canal or soft palate. Scvcdia-Cayabyab and Spaeey (2002) have documented recurring Bell's palsy secondary to herpes zoster infection; acyclovir treatment produced cessation of the episodes. This report adds herpes zoster to the differential diagnosis of recurrent Bell's palsy along with sarcoid and Lyme disease. Recurrent Bell's palsy may be associated with a deeply furrowed tongue (lingua plicata) and recurrent facial edema in Melkersson's syndrome; the prognosis is initially good, but permanent paralysis may eventually result after many recurrences.

Aberrant regeneration may have several variations, rhe most prominent being involuntary tearing of the eye on the involved side when eating ("crocodile tears") or synkinesis of the facial musculature when chewing. This often takes the form of a jaw-winking phenomenon, wherein the lid

closes on the involved side when the jaw opens (Marin-Amat syndrome). The onset of Bell's palsy in an elderly person should prompt the physician to consider the possibility of diabetes or hypertension before the administration of prednisone, which is an often prescribed but controversial treatment.

Infections

Infection of the central nervous system by *Borrelia burgdorferi* (Lyme meningitis) is an increasingly recognized cause of peripheral nerve weakness in endemic areas. Leprosy also affects the facial nerve (see Chapter 59A).

Hemifacial Spasm

In hemifacial spasm, there are recurring episodes of involuntary unilateral spasms of the facial musculature invariably beginning about the lateral canthus of the eye on the involved side and gradually spreading downward, over many months to several years to involve the remainder of the facial musculature. Although mass lesions such as meningioma are rarely encountered as the etiology, Janetta has documented the common cause to be neurovasculature compression from a redundant vascular loop. Hypertension appears to be a predisposing factor if the hemifacial spasm occurs on the left but not the right side of the face (DeFazio ct al. 2000).

COCHLEAR-VESTIBULAR NERVE (CRANIAL NERVE Vm)

See Chapters 18, 19, and 41.

GLOSSOPHARYNGEAL NERVE (CRANIAL NERVE DC)

Neuroanatomy

Fibers of the glossopharyngeal nerve, or CN IX, originate from several nuclear complexes (tractus solitarius [gustatory nucleus], nucleus ambiguus, and inferior salivatory nucleus) in the brainstem. They pass outward as several distinct subsets of fibers, to emerge from the medulla between the inferior olive and the inferior cerebellar peduncle, caudal to the seventh CN and rostral to the U'lidi (:N. UN IX exits the skull through the jugular foramen along with CN X and CN XI and comes to lie between the internal jugular vein and the internal carotid artery (Remley and Latchaw 1993). It ultimately reaches the lateral wall of the pharynx by tracking along the inferior border of the srylopharyngeus muscle.

Clinical Features

Isolated lesions of the glossopharyngeal nerve are extremely uncommon. Almost invariably, involvement of this nerve occurs in conjunction with that of the vagus, accessory, and hypoglossal nerves. Isolated paralysis of the glossopharyngeal nerve produces slight and usually transient difficulty in swallowing, due to involvement of the stylopharyngeus muscle, and temporary decrease in parotid gland secretions.

Peripheral dysfunction of the nerve may be due to blunt neck trauma, such as nonfatal suicidal hanging, diseases of the middle ear, and pharyngeal abscesses.

Glossopharyngeal Neuralgia

See Chapter 75.

VAGUS NERVE (CRANIAL NERVE X)

Neuroanatomy

The vagus nerve is the longest of all the CNs. In many respects, its origins and functions are similar to those of the glossopharyngeal nerve.

The motor fibers of the vagus arise from the nucleus ambiguus and the dorsal motor nucleus of the vagus. The sensory portions have cell bodies of origin in the jugular and nodose ganglia. Exiting the skull through the jugular foramen, the vagus travels within the carotid sheath between the internal jugular vein and the carotid artery, giving off pharyngeal branches and superior and inferior (recurrent) laryngeal nerves (Remley and Latchaw 1993), Spontaneous dissection of the internal carotid artery may present with an isolated vagal neuropathy (Moussouttas andTuhnm 1998).

Brainstem Lesions

Supranuclear involvement of the vagus nerve is significant only when it is bilateral, producing a pseudobulbar-type syndrome with dysphagia and dysarthria. Nuclear involvement of the vagus nerve may be encountered as part of motor neuron disease in patients with progressive bulbar palsy. Poliomyelitis and primary brainstem neoplasms may also produce dysfunction at a nuclear level. (See Chapter 22 for a fuller discussion of brainstem lesions affecting the vagus nerve.)

Vascular lesions within the medulla may involve the vagus nerve. Wallenberg's syndrome is the most common presentation, with the acute onset ni v.r.;'.ul:i -> (lineup), vertigo, and ataxia. On examination, an ipsilateral Horner's syndrome, crossed (ipsilateral face and contralateral body) loss of pain and temperature sensation,

ipsilateral cerebellar tremor, and weakness of the ipsilateral oral pharynx constitute the clinical picture.

Systemic Disorders

Vagal nerve dysfunction with vocal cord paresis is sometimes the initial manifestation of multiple system atrophy (see Chapters 77 and 83). The recurrent laryngeal branches of the vagus nerve may be damaged as a result of primary thoracic disease, the left more often than the right because it is longer. Of clinical value in localizing lesion sites in vagal disease is that the pharyngeal branches depart the vagus high in the neck; therefore the absence of sensory changes in the pharynx suggests that the lesion is below this level. Tumors of the mediastinum and lung are the most common causes of an isolated vocal cord palsy. Cytomegalovirus infection of the laryngeal nerves with hoarseness may occur in patients with acquired immunodeficiency syndrome.

Sl'INAL ACCESSORY NERVE (CRANIAL NERVE XI)

Neuroanatomy

The spinal accessory nerve is entirely motor in function and composed of two portions: a smaller cranial part ("accessory" to the vagus) and the larger spinal portion (arising from the upper five cervical cord segments). The cranial portion, with the vagus and glossopharyngeal nerves, supplies the musculature of the pharynx and larynx, whereas the spinal portion innervates the sternocleidomastoid and upper portions of the trapezius musculature.

The spinal portion emerges as a series of rootlets between the dentate ligament and the dorsal horns of rhe spinal cord. Merging, they ascend and pass through the foramen magnum. Here they join the accessory rootlet originating from the nucleus ambiguus in the caudal medulla oblongata. These fused components then pass through the jugular foramen with CN TX and CN X. After exiting the skull, a branch travels with the vagus, and the spinal accessory nerve proper continues, supplying the sternocleidomastoid and trapezius muscles (Figure 76.2).

The principal action of the sternocleidomastoid draws the occiput toward the side of the contraction, rotating the face to the opposite side. Contracting together, the sternocleidomastoid muscles flex the cervical spine. The upper trapezius retracts the head and elevates, retracts, and rotates the scapula; it also elevates the abducted arm above the horizontal. With bilateral contraction, the head draws back and the face up. The trapezius is also innervated by branches of the cervical plexus. The supranuclear innervation is complex. Corticobulhar fibers to the trapezius are principally crossed, but fibers destined for the sternocleidomastoid terminate predominantly in the ipsilateral nuclei (De Toledo and Dow 1998),

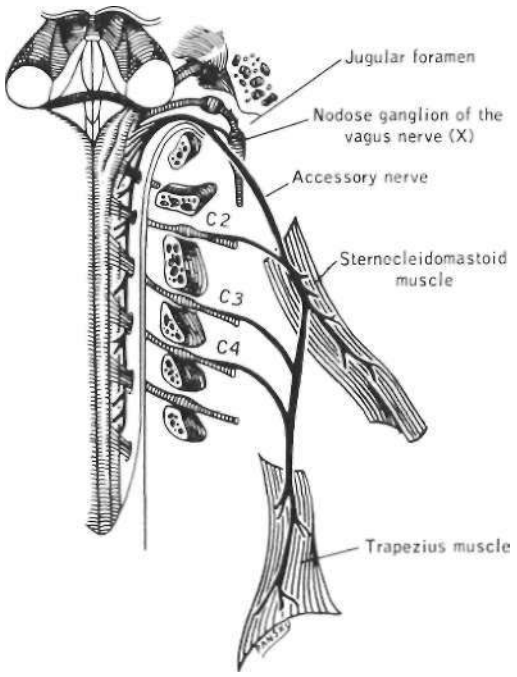


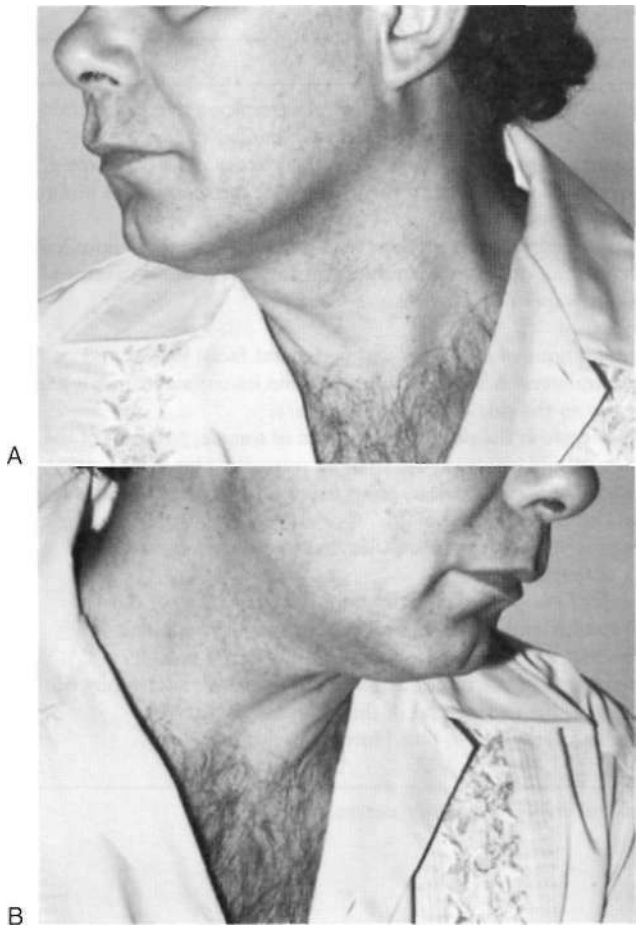
FIGURE 76.2 Course and distribution of the spinal accessory nerve. (Reprinted with permission from House, E. L. &: Pansky, R. 1967, *A Functional Approach to Neuroanatomy*, 2nd ed, McGraw-Hill, New York.)

Although the spinal accessory nerve is regarded as purely a motor nerve, the symptoms of its dysfunction are both motor and sensory, the latter being predominantly pam. In acute lesions, traumatic or inflammatory, the pain is steady, severe, and localized to the neck and top of the shoulder. Pain, however, may be delayed until the patient starts to use the arm. Paresthesias arc common and often diffuse, taking the form of pins and needles, coldness, and throbbing sensations. When the sternocleidomastoid muscle is involved unilaterally, there is loss of bulk, which is best demonstrated by turning the chin against resistance (Figure 76.3).

The findings with a unilateral lesion include an obvious drooping of the affected shoulder. With the arms hanging loosely at the sides, the fingertips touch the thigh at a lower level on the affected side. Winging of the scapula is due to paresis of the middle trapezius muscle, whereas loss of abduction more than 90 degrees is due to weakness of the upper trapezius. Winging due to trapezius palsy is more prominent with abduction of the arm; the superior angle of the scapula moves farther from the midline (Figure 76,4),

Wirh a long thoracic nerve lesion, the winging is increased with forward flexion of the arm.

Evaluating supranuclear lesions may be confusing because of the ipsilateral innervation of the sternocleidomastoid muscle. In hemispheric lesions, the weakness of the sternocleidomastoid is on the same side as the lesion (De Toledo and Dow 1998). If this is not recognized, the signs



1'IGURE 76.3 (A) Normal left sternocleidomastoid muscle with forceful thrust of chin to the right. Note the prominent left sternocleidomastoid muscle. (B) The same maneuver as that shown in A, but to the left, showing loss of bulk of the right sternocleidomastoid muscle.

may indicate that the patient with a left hemiparesis has a right accessory nerve lesion and therefore a lower brainstem problem rather than a more rostral lesion. Cortical, capsular, and high brainstem lesions affecting the corticobulbar fibers may result in decreased strength on turning the head away from the side of the lesion. Dissociated weakness may also cause confusion when the sternocleidomastoid muscle is involved and the trapezius is not.

Etiology and Management

The most common cause of eleventh nerve palsies are iatrogenic, secondary to nerve injury during surgery involving the posterior triangle, particularly lymph node biopsies. The symptoms are often delayed for 1-2 weeks, followed by pain and weakness. If hiss ol function is complete or the extent of the lesion is unknown, exploration with reanastomosis of the nerve is probably the best approach. Electrodiagnosis with nerve conduction studies

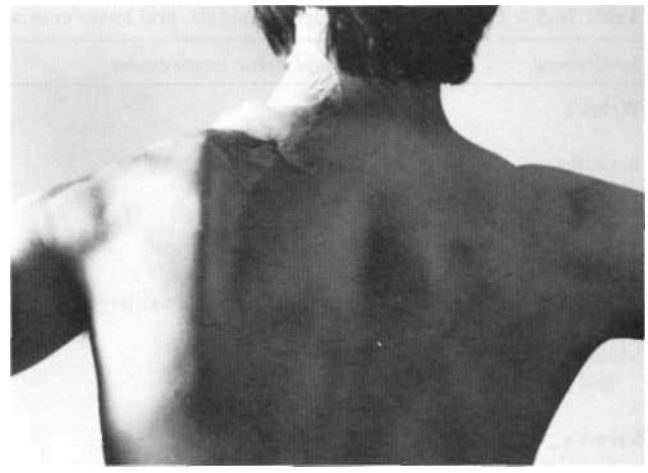


FIGURE 76.4 Spinal accessory lesion on attempted abduction of the left arm, demonstrating scapular winging.

and needle examination done after the third week postinjury may assist in determining whether the lesion is partial or complete. Traumatic lesions other than those with iatrogenic causes include shoulder injuries, bites, stretching of the nerve, and radiation.

Supranuclear involvement, as from stroke, usually causes only modest dysfunction of CN XI, manifested by contralateral drooping of the shoulder and weakness of the upper portions of the trapezius muscle, as well as weakness of head turning away from the side of the hemispheric lesion. Nuclear involvement of CN XI occurs in motor neuron disease, syringobulbia, and syringomyelia and is associated with muscle paresis, atrophy, and fasciculations,

A large group of named syndromes (Table 76.3) occurs with involvement of this nerve and other medullary structures. Isolated peripheral involvement is uncommon and, as with central involvement, is usually attended by evidence of involvement of other structures. Causes include internal jugulai \ cm C.UIIHII.IILOII. biting injures n> the neck, shoulder dislocation, unsuccessful attempts at suicidal hanging, and radical neck dissection. Selective trapezius involvement has occurred in patients undergoing carotid endartcrectomy; traction on the sternocleidomastoid muscle during surgery may produce stretch injury to the branch to die trapezius. In myotonic dystrophy, atrophy of the sternocleidomastoid muscle, simulating selective spinal accessory nerve involvement, is prominent.

A benign self-limited isolated paralysis of the eleventh CN may be analogous to other types of spontaneous and restricted neuropathies, such as Bell's palsy or long thoracic nerve palsy. An abrupt onset of sharp pain localized to the posterior sternocleidomastoid region is followed by resolution of the pain and the typical features of an accessory nerve lesion, with winging of the scapula and drooping of the affected shoulder.

Matz and Barbara (1996) and London, London, and Kay (1996) provide excellent reviews of the diagnosis and treatment of iatrogenic spinal accessory nerve injury.

Table 76.3: Syndromes of the upper, middle, and lower cranial nerves

Syndromes	*Cranial nerve involvement*	*Clinical abnormalities*
Weber's	III	Oculomotor palsy with contralateral hemiplegia due to pyramidal tract involvement at the base of the midbrain
Benedikt's	III	Oculomotor palsy with contralateral corticospinal signs, tremor, and cerebellar ataxia due to involvement of the red nucleus and the corticospinal tract
Tolosa-Hunt	Varying combinations of III, IV, V (ophthalmic or maxillary) and VI	Multiple designated cranial nerve palsies with cavernous sinus lesions; coexisting optic nerve dysfunction suggests a distal cavernous sinus, superior orbital fissure locus
Millard-Gubler and Fovilie's	VI and Vll	Combinations of ahducens and peripheral facial palsies and contralateral hemiplegia from pontine lesion; sometimes a gaze palsy to the side of a lesion (Foville's)
Verntt's (jugular foramen)	IX, X, and XI	Loss of taste at the posterior one third of tongue; paralysis of the VC, palate, and pharynx; paralysis of trapezius plus SCM
Schmidt's	X and XI	Paralysis oi the -. • H IL p.il.iK', pli.ir yu\. ,nnl MIVIU; i — i I. i L . i .il u i/akncss of the trapezius and SCM
Tapia's	X and XII	Paralysis of the pharynx and larynx; paralysis and atrophy of die tongue
Jackson's	X, XI, and XII	Patesis of the palate, pharynx, and larynx; paresis of the trapezius and SCM; paresis and atrophy of the tongue
Collet-Sicard	IX, X, XI, and XII	Anesthesia of the palate; paresis of the VC and palate; weakness of the trapezius and SCM; paresis and atrophy of the tongue; hemianesthesia of the pharynx and larynx
Villaret's	IX, X, XI, XII, and cervical sympathetic	Same as Collet-Sicard, plus Horner's syndrome

Note: Unless otherwise noted, the clinical abnormality is ipsilateral to the involved nerve or nerves.
SCM = sternocleidomastoid; VC = vocal cord.

HYPOGLOSSAL NERVE (CRANIAL NERVE XII)

Neuroanatomy

A purely motor nerve, the hypoglossal nerve (CN XII) supplies innervation to the extrinsic and intrinsic muscles of the tongue. Arising from the hypoglossal nucleus beneath the floor of the fourth ventricle in the caudal medulla, it courses ventrally through the brainstem to exit between the pyramidal tract and the olivary eminence. The rootlets coalesce and pass through the hypoglossal canal to exit the skull. The nerve travels briefly with the ninth, tenth, and eleventh CNs before it separates at approximately the mastoid level and passes on to the tongue musculature (Figure 76.5).

A lesion of the hypoglossal nerve causes ipsilateral weakness and wasting of the tongue, which deviates to the weak side when protruded.

Clinical Syndromes

Isolated involvement is rare but occasionally occurs in the context of inadvertent nerve trauma incurred at the time of carotid endarterectomy because of the proximity of CN XII to the carotid bifurcation; the dysfunction is usually temporary.

The review by Keane (1996) of 100 cases of twelfth nerve palsy provides an overview of common etiologies for dysfunction in CN XII. Tumors, predominantly malignant, produced nearly one half of the palsies (49 cases). Gunshot wounds made trauma the second most common cause (12 cases), and stroke (6 cases) the third. Aneurysms or dissection of the carotid artery may selectively compress the twelfth CN (Lemmerling et al. 1996). Primary bony disease and malformations affecting the base of the skull (as seen with platyhasia and Pager's disease) may produce mechanical damage to the nerve. Giuffrida et al. (2000) emphasized that after appropriate exclusionary studies, a transient twelfth nerve palsy can be encountered that is analogous to the more common and invariably benign seventh nerve Bell's palsy.

Keane (2000) also reviewed his extensive experience with combined twelfth and sixth nerve palsies. He confirmed the observation made in 1947 by Godtfrcdsen that combined dysfunction of these two CNs (Godtfredsen's syndrome) suggests the presence of an aggressive tumor. In Kcane's experience, a metastatic lesion to the clivus was the most common etiology, followed by nasopharyngeal carcinoma that was infiltrating posteriorly.

Vertebrobasilar vascular disease may produce an ipsilateral hypoglossal paralysis (medial medullary syndrome) (see Chapter 22). In medial medullary syndrome, as a result of occlusion of cither the vertebral arterv or the anterior

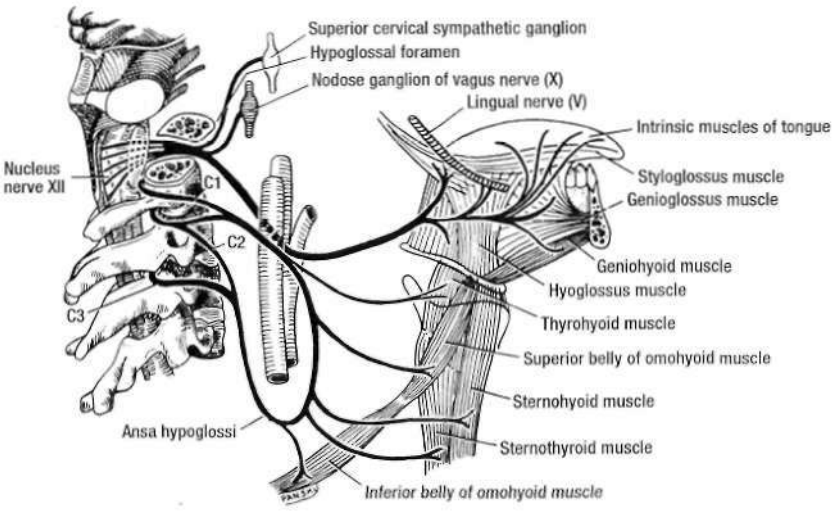


FIGURE 76.5 Origin, course, and distribution of the hypoglossal nerve. (Reprinted with permission from Mouse, E. L. & Pansky, B. 1967, *A Functional Approach to Neuroanatomy,* 2nd ed, McGraw-Hill, New York.)

spinal artery high in the neck, there is ipsilateral paralysis of the tongue (nucleus or root fibers), with a contralateral corticospinal tract lesion causing paresis of the arm and leg. The syndrome also involves diminished proprioceptive and tactile sense caused by medial lemniscus involvement.

Motor neuron disease and poliomyelitis may involve the hypoglossal nuclei, causing progressive tongue atrophy with fasciculations.

JUGULAR FORAMEN SYNDROME

This section covers the lower CN syndromes when they are affected as a group.

Neuroanatomy

The jugular foramen is located between the lateral portion of the occipital bone and the petrous portion of the temporal hone. It is a canal coursing anteriorly, inferiorly, and laterally in an intracranial-to-extracranial projection. Two compartments of the foramen are recognized. The anteromedial compartment (the *pan nervosa)* contains the inferior petrosal sinus and the glossopharyngeal nerve. The pars venosa contains the vagus and accessory nerves, as well as a portion of the jugular bulb. There are many variations on this theme, and there is no agreement on position of the nerves in the jugular foramen or on the constancy of the separation of these compartments.

After exiting the cranial base, CN IX is anterolateral and CN XI medial and next to the carotid sheath. CN X runs deeper between the internal jugular vein and internal carotid artery (Lustig and Jacklcr 1996). Upon leaving the jugular foramen, the three CNs enter the posterior retropharyngeal space, along with CN XII. This space is bordered posteriorly by the cervical spine, medially by the pharynx, anteriorly by the parotid gland and muscles attached to the styloid process, and superiorly by the base of the skull and the jugular foramen. The space contains the last four CNs, the internal jugular vein, the carotid artery, and the cervical sympathetic nerves. After exiting this space, the nerves separate and follow their individual courses.

Clinical Features and Etiology

The most common causes of the jugular foramen and allied syndromes are primary and metastatic tumors, vascular lesions, trauma, inflammatory, and iatrogenic lesions.

The most common primary tumors are schwannomas, glomus tumors, and meningiomas. Schwannomas constitute approximately 25% of all tumors in the head and neck, but schwannomas of nerves IX, X, and XI, in the absence of neurofibromatosis, arc decidedly rare, constituting approximately 3% of all intracranial schwannomas.

A neuroirnaging review of the appearance of schwannomas of the jugular foramen (Eldevjk, Gabrielson, and Jacobsen 2000) emphasized a characteristic picture with a sharply demarcated, contrast-enhancing lesion enlarging the jugular foramen with rounded bony borders and a sclerotic rim. Schwannomas are more common in women, with the average age at diagnosis in the fourth decade. The symptoms generally manifest when the tumor is large and are determined by both origin and size of the tumor. Most cases present with hearing loss and dizziness indistinguishable from acoustic neuroma. Other presentations are the jugular foramen syndrome or a neck mass. The clinical signs indicate dysfunction of CNs IX, X, and XI in 80%, hearing loss in 70%, and facial palsy in 25%. Contemporary diagnosis of these tumors involves both computed tomographic scan and MR],

Glomus jugulare tumor is a highly vascular tumor that may involve the glossopharyngeal nerve, as well as the other nerves (vagus and accessory) traversing the jugular foramen, and can enlarge sufficiently to damage the facial

and hypoglossal nerves. The patient usually presents with pulsatile tinnitus followed by conductive hearing loss, Because the tumor partially or completely occludes the intravascular portion of the jugular vein, the patient may also present with increased intracranial pressure. Other symptoms encompass a spectrum of nonspecific dizziness, he.ill lehe, .nil c.iMehe. Otolo:'jcal evimin.inor ~omerimes reveals the pulsating dark red lesion behind the eardrum. Biopsy of these tumors is contraindicated because of their hypervascularity. Treatment often consists of initial radiotherapy, followed if necessary by surgical removal of the tumor en bloc with the jugular bulb.

The most common neoplastic causes of jugular foramen syndrome are either primary nasopharyngeal tumors that spread locally to the cranial base or distant metastases from breast, Ling, prostate, and Kmph tissue.

Villarer's syndrome consists of unilateral lesions of the last four CNs (IX-XII) and I lorner's syndrome (see Tabic *763).* The syndrome results from lesions occupying the posterior retropharyngeal space, such as parotid tumors, enlarged lymph nodes, nasopharyngeal carcinomas, pharyngeal abscesses, carotid artery aneurysms, giant cell arteritis, and penetrating wound trauma (Tiliket et al. 1996).

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Chapter 77
Movement Disorders

Kathleen M. Shannon

MOVEMENT DISORDERS AND THE BASAL GANGLIA

Neurologists often equate movement disorders with disease or dysfunction of the basal ganglia, and no chapter on inn: emcnl disorders would be complete without .: dis cussion of basal ganglia anatomy, physiology, and patho-physiology. The implied connection is a natural one. In some movement disorders, such as parkinsonism, chorea, and ballism, the link to the basal ganglia is supported by climcopathological, biochemical, functional neuroimaging, and electrophysiological data, whereas in other movement disorders, such as tremor, dystonia, and tics, dysfunction of the basal ganglia is implied but not proven. Clinico-pathologica! studies relate' [he ^gns ol P.irkinson's disease (PD) to deficient dopaminergic neurotransmission in the striatum consequent to the death of dopaminergic neurons in the substantia nigra pars compacta (SNc). Choreic movements in Huntington's disease (HD) are linked to the death of medium spiny neurons in the caudate and putamen. I Icmiballism is typically associated with structural lesions in the contralateral subthalamic nucleus (STN) or its afferent

or efferent connections. Changes in basal ganglia neurotransmission are well described in many movement disorders, and deepening understanding of basal ganglia neurotransmission has yielded promising symptomatic therapies in many such conditions. Functional ncuroimaging studies with specific radiopharmaceutical agents demonstrate abnormal function of basal ganglia structures, and intraoperative electrophysiology studies demonstrate abnormalities in neuronal firing rates and patterns in the STN and globus pallidus (GP) in parkinsonism and chorea. Animal models, including the l-methyl-4-phenyl-1,2,3,6-tetrahydropyridinc (MPTP) model of PD, excitotoxic and transgenic models of HD, and the STN lesion model of hemiballismus (HIS) confirm the central role of disordered basal ganglia function in these conditions. In other movement disorders, such as dystonia, the link with basal ganglia function is more complex. For example, although secondary dystonias may result from structural lesions in the contralateral putamen, other sites of pathology include the thalamus, rostral brainstem, and cerebellum. Functional ncuroimaging studies in patients with dystonia show abnormal activation of the lenticular nucleus, but also the cortex, brainstem, and cerebellum. In other movement disorders, such as essential tremor (ET), stiff person syndrome (SPS), and hemifacial spasm, we now know the dysfunction lies outside of the basal ganglia, often in the brainstem, cerebellum, spinal cord, or even in the peripheral nervous system.

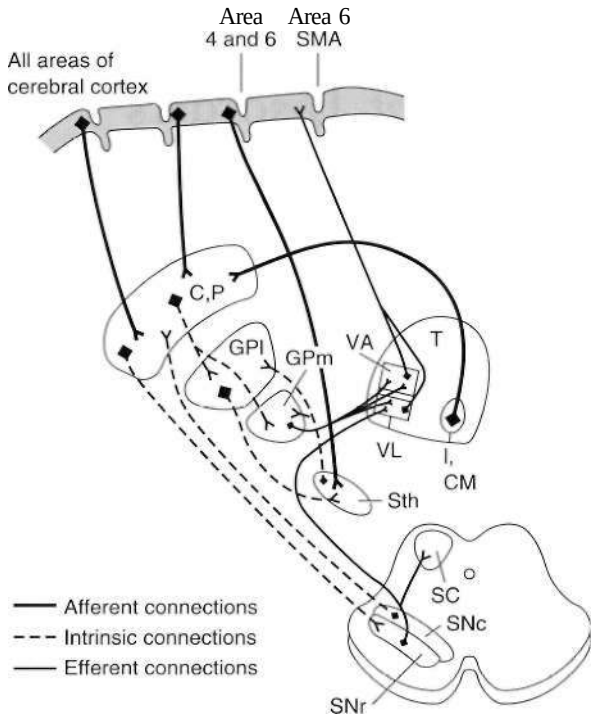


FIGURE 77.1 Schematic tint wing of the interconnections between the basal ganglia and its afferent and efferent connections. C, P — caudate putamen; GPI = lateral (external) globus pallidus; GPm = medial (internal) globus pallidus; Sth = subthalamic nucleus; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; SC = superior eolliculus; T = thalamus; VA = ventral anterior; VL = ventrolateral; CM = centromedian nucleus of the thalamus.

Basal Ganglia Anatomy

There is no clear consensus on which structures should be included in the basal ganglia. For the purposes of this discussion, we consider those structures in the striatopallidal circuits involved in modulation of the thalamocortical projection—the caudate nucleus, the putamen, the external segment of the GP (GPe), and the internal segment of the GP {GPi). In addition, we consider related structures, the two divisions of the SN (the pars compacta [SNc] and the pars reticulata [SNrP, and the STN.

The *caudate nucleus* is a curved structute that traverses the deep hemisphere at the lateral edge of each lateral ventricle. Its diameter is largest at its head, tapering to a small tail. It is continuous with the *putamen* at the head and tail. The caudate and putamen together arc called the *striatum,* and they form the major target for projections from the cerebral cortex and the SN. The putamen and the GP together form a wedge-shaped structure called the *lenticular nucleus.* The GP is divided into two parts, the GPe and the GPL The GPi is structurally and functionally homologous with the SNr. The SNr and SNc extend the length of the midbrain ventral to the red nucleus and dorsal to the cerebral peduncles. The STN is a small lens-shaped structure at the border of the brainstem and cerebrum. The basal ganglia and its relation to the thalamus and overlying cortex are illustrated in Figure 77.1.

Functional Organization of the Basal Ganglia and Other Pathways

Afferent projections to the striatum arise from all areas of the cerebral cortex, the intralaminar nuclei of the thalamus, mesencephalic SN, and ftom the locus ceruleus and raphe nuclei. There is also a projection from the cerebral cortex to the STN. The major efferent projections are from the GPi and SNr to the thalamus and brainstem nuclei such as the pedunculopontine nucleus. The GPi and SNr project to ventral anterior and ventrolateral thalamic nuclei. The GPi also projects to the centromedian thalamic nuclei and the SNr projects to the mcdiodorsai thalamic nuclei and superior eolliculus. The ventral anterior and ventrolateral thalamic nuclei then project to the motor and premotor cortex. Throughout, these projections are somatotopically organized (Yelnik 2002).

The basal ganglia has dense internuclear connections exemplified by the box and line circuit diagrams that have become entrenched in the literature. Five parallel and separate closed circuits through the basal ganglia have been proposed. These are the *motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal,* and *limbic* loops. It is now

Table 77.1: Divisions of the striatum

Division	*Origin of striatal afferents*	*Striatal nucleus*	*Termination of basal ganglia efferents*	*Function*
Sensorimotor	Motor cortex	[illegible]	[illegible] Primary motor cortex Supplementary motor area	Movcmnii
Associative	Fronral cortex Parietal cortex Temporal cortex Occipital cortex	Dorsal caudate	Prefrontal cortex	Cognition
I iinlii.	Hippocampus Amygdala Cingulate cortex Temporal cortex Orbitofrontal cortex	Ventral striatum	Anterior dngukue Medial orbitofrontal	Emotion Motivation

generally agreed that these loops form three major divisions, *sensorimotor, associative,* and *limbic,* that are related to *motor, cognitive,* and *emotional* functions, respectively (Table 77.1), The functions of the *sensorimotor* striatum are subserved mainly by the putamen, which derives its afferent cortical inputs from both motor cortices. Sensorimotor pathways arc somatotopically organized and the pathway ultimately terminates in the premotor and primary motor cortices and the supplementary motor area. Cognitive functions are managed by the *associative striatum.* In this pathway, the dorsal caudate nucleus receives afferent input from the homolateral frontal, parietal, temporal, and occipital cortices. Projections from this pathway ultimately terminate in the prefrontal cortex. The *limbic striatum* subserves emotional and motivational functions. Its input derives from the cingulate, temporal, and orbitofrontal cortices, the hippocampus, and the amygdala. It comprises mainly the ventral striatum with ultimate projections to the anterior cingulate and medial orbitofrontal cortices (Yclnik 2002). Whether these divisions are interconnected or organized in parallel remains a topic of debate.

Within each basal ganglia circuit lies an additional level of complexity. Each circuit contains two pathways by which striatal activity is translated into pallidal output. These two pathways, named the *direct* and *indirect* pathways, depending on whether striatal outflow connects directly with the GPi or first traverses the GPe and STN. The direct and indirect pathways have opposite effects on outflow neurons of the GPi and SNr. A closer look at the motor circuit illustrates this principle (Figure 77.2A).

In the motor *direct pathway,* excitatory neurons from the cerebral cortex synapse on putaminal neurons, which in turn scud inhibitory projections to the GPi and its homologue, the SNr. The GPi/SNr sends an inhibitory outflow to the thalamus (Figure 77.2B). Activity in the direct pathway disinhibits the thalamus, facilitating the excitatory thalamocortical pathway and enhancing activity in its target, the motor cortices. Thus the direct pathway constitutes part of an excitatory cortical-cortical circuit that likely functions to maintain ongoing motor activity. In the *indirect pathway,* excitatory axons from the cerebral cortex synapse on putaminal neurons. These neurons send inhibitory projections to the GPe. The GPc sends an inhibitory projection to the STN. The net effect of these projections is disinhibition of the STN. The STN in turn has an excitatory projection to the GPi (see Figure 77.2C). Activity in the indirect pathway thus excites the GPi/SNr, which in turn inhibits the thalamocortical pathway.

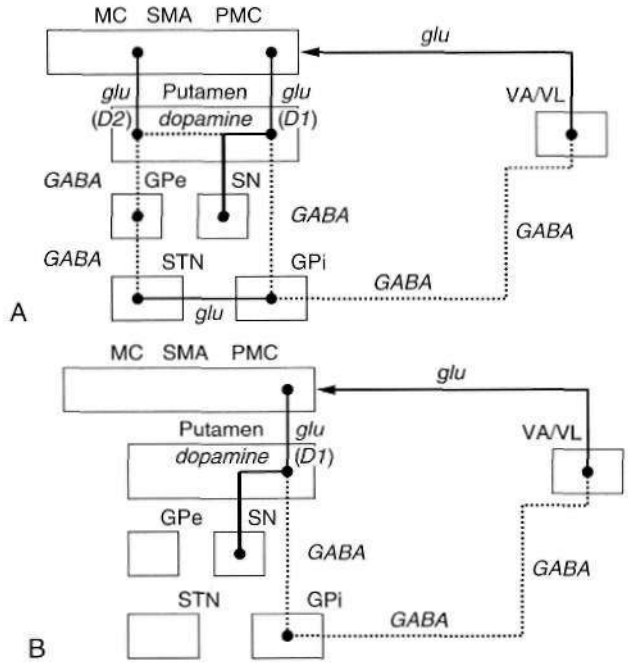
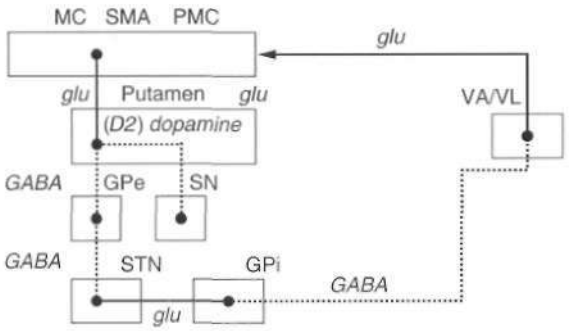


FIGURE 77.2 Schematic drawing of the internuclear connections of the basal ganglia, including (A) direcr and indirect pathways and depicting (B) the direcr pathway. (See Figure 77.3 for a depiction of the indirect pathway.) Excitatory pathways in solid lines, inhibitory pathways in dotted lines. MC = motor cortex; SMA = supplementary motor area; PMC = premotor cortex; GPe = external segment of the globus pallidus; SN = substantia nigra; STN = subthalamic nucleus; GPi = internal segment of the globus pallidus; VA/VL = ventral anterior/vcntrolateral thalamic nuclei; glu = glutamate; GARA = y-amiuobutyric acid; D^ = dopamine D2 receptor; D_t — dopamine D] receptor. *Continued*

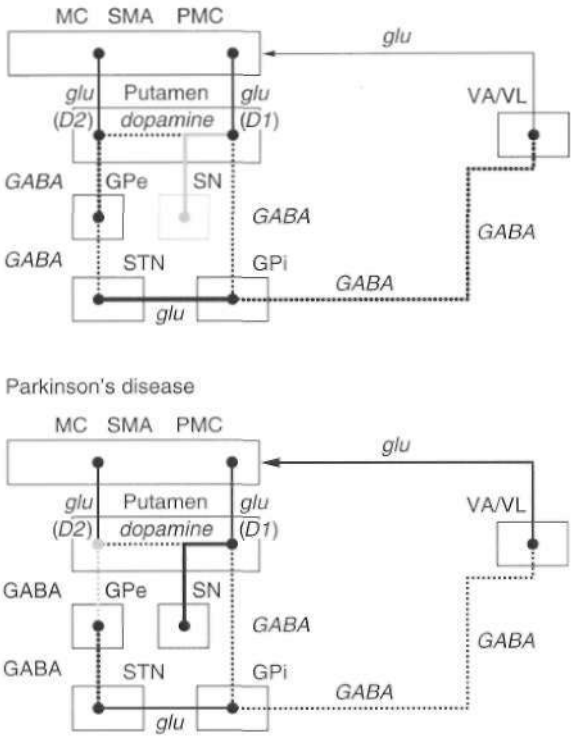


F1CURE 77.2, cont'd.

Thus the net effect of increased activity in the indirect pathway is cortical inhibition.

The striatum also receives robust afferent input from the SNc. This projection from the SNc, an important modifier of striatal activity, facilitates activity in the direct pathway and inhibits activity in the indirect pathway, thus promoting cortical excitation through both pathways (see Figure 77.2A).

Disorders ol the basal ganglia result in prominent motoi dysfunction, though not generally in frank weakness. The absence of direct primary or secondary sensory input and the lack of a major descending pathway below the level of the brainstem suggest that the basal ganglia moderates rather than controls movement. In the simplest sense, the direct and indirect pathways have opposite effects on the cerebral cortex. The direct pathway is important in initiation and maintenance of movement and the indirect pathway helps with suppression of extraneous movement. From this model of basal ganglia connectivity, hypotheses about the motor function of the basal ganglia have been proposed. One hypothesis is that the relative activities of the direct and indirect pathways serve to balance the facilitation and inhibition of the same population of thalamocortical neurons, thus controlling the scale ol movement. A second hypothesis proposes that direct pathway-mediated facilitation and indirect pathway-mediated inhibition of different populations of thalamocortical neurons serve to focus movement in an organization reminiscent of center-surround inhibition. These hypotheses relate activity in the direct and indirect pathways mainly to rates of firing in the STN and GPi. Thus death of neurons in the SNc decreases activity in the direct pathway and increases activity in the indirect pathway. These changes cause an increased rate of tiring of subthalamic and GPi neurons with excessive inhibition of thalamocortical pathways and produce the behavioral manifestations of bradykinesia in PD (Figure 77.3A). On the other hand, selective loss of indirect pathway neurons, as in HD, interferes with supptession of involuntary movements. Choreic involuntary movements arc the usual result (see Figure 77.3B). Direct electrophysiological recordings of the STN and GP during stereotactic functional neurosurgical procedures confirm that the GPi and STN arc overly active



B Huntington's disease

FIGURE 77.3 Schematic drawing of the functional activities in the direct and indirect pathways in Parkinson's disease and Huntington's disease. (A) Reduced dopaminergic facilitation of the direct pathway and inhibition of the indirect pathway due to death [jf dlip.linilu T;.'.il !\-IIN>II*- C.1UM-. ilKTV.'I-.I'll (iritis', .IIIii ilKtV.ISIII inhibition of thalamocortical pathways, producing bradykinesia. (B) Loss of striatal neurons leads to reduced activity in the indirect pathway, causing reduced inhibition thalamocortical pathways with the production of excessive or involuntary movements.

in patients with PD. The activity of these nuclei returns toward normal with effective pharmacotherapy, and chorea is associated with lower firing rates of neurons in these nuclei. Unfortunately, this model does not completely explain some important features of movement disorders. For example, bradykinesia and chorea coexist in HD and in treated PD. Thalamic lesions that might be expected to wotsen parkinsonism by reducing excitatory thalamocortical activity do not do so. Pallidal lesions that might be expected to worsen chorea by decreasing inhibition of thalamocortical pathways instead are dramatically effective at reducing chorea. The model is even more problematic when applied to dystonia. It has been suggested that in dystonia, there is overactivity of both the direct and indirect pathways. Yet, intraoperative recordings in dystonia have shown low rates and abnormal patterns of neuronal firing in the GPi. A simple change in firing rate of the STN or GPi is thus insufficient to explain the underlying physiology of dystonia. It is likely that disordered patterns and synchrony of pallidal firing as well as changes in sensorimotor

integration and the control of spinal and brainstem reflexes are important. These factors are under investigation, but current models remain useful for understanding the rationale of pharmacological and ablative surgical procedures for certain movement disorders.

Although much of the emphasis has been on GPi and SNr effercnts to the thalamocortical system, there is growing evidence that descending pathways, particularly to the zona incerta and pedimculopontine nucleus, are important in movement disorders. The pedunculopontine nucleus appears to play a role in the genesis of akinesia. A number of other pathways also seem particularly relevant to myoclonus, including a corticolemni seal thalamocortical circuit and a spinobulbar-spinal circuit that primarily involves the spinoreticular tracts, nucleus reticularis gigantocellularis of the medullary reticular formation, and the reticulospinal tracts. The Guillain-Mollart triangle is a network connecting the red nucleus, dentate nucleus, and inferior olive, which has been implicated in palatal tremor (formerly known .is *j-.djtdi mytn limns),* [he propnospinal pathways and segmental spinospinal loops are important in the genesis of propriospinal and spinal segmental myoclonus, respectively.

Table 77.2: Pharmacology of the basal ganglia

fathway	*Transmitter*
Striatal affcrents	
Cerebral cortex -> striatum	Glutamate
Cerebral cortex —* STN	Glutamate
Lotus ecruleus —• striatum	Norepinephrine
Locus ceruleus —* SN	Norepinephrine
Raphe nuclei -> striatum	Scroronin
Raphe nuclei -*• SN	Serotonin
Thalamus - striatum*	Acetylcholine?
SNc -» striatum	Clutamate?
	Dopamine, choleeystokinin
Intrinsic connections	
Striatal interneurons	GABA, acetylcholine,
Striatum -*• GPi	M ill l.l [OSI, 11,11,
Striatum -» SNr	neuropeptide Y, nitric acid,
Striatum —> GPe	calretinin
Globus pallidus externa -» STN	GABA, substance P
Subthalamic nucleus ->•	GABA, dynorphin, substance P
GPi, SNr, GPe	GABA, enkephalin
	CABA, glutamate
Striatal effercnts	
GPi — thalamus	GABA
SNpr —* thalamus	CABA

CABA = y-aminobutyric acid; GPe = external segment of the globus pallidus; CPi = internal segment of the globus pallidus; SN = substantia nigra; SNc = subsrantia nigra pars compacra; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus.

Biochemistry

Our understanding of basal ganglia pharmacology is growing rapidly. Along with this growth is an expanding spectrum of practical applications for pathology, neuroimaging, and therapeutics. For example, catecholamine and amino acid neurotransmitters coexist with peptides. This co-localization may allow histopathological differentiation among medium spiny striatal projection neurons that secrete K-aminobutyric acid (GABAergic), further elucidating the specific nature and progress of striatal neu rode generation. Neuroimaging technology has been aided by the development of radiopharmaceutical ligands with such discrete targets as the dopamine transporter on the presynaptic dopamine neuron and subpopulations of dopamine receptors on the postsynaptic neuron. The pharmaceutical industry is searching for ways to provide better targeted and more physiological stimulation of neurotransmitter receptors and is expanding its investigations from the primary targets themselves to approaches that may modify responsiveness of the primary targets.

The major neurotransmitters of the basal ganglia arc outlined in Table 77.2 (see also Figure 77.2). Most excitatory synapses of the basal ganglia and its connections, including those from the cerebral cortex to the striatum, the STN to the Gl'i, and the thalamocortical projections, use *glutamate.* Projections from the striatum to the GPe and Gl'i and from the GPe to the STN and from the GPi to the thalamus arc inhibitory and employ *GABA.* Medium spiny GABAergic neurons in the direct pathway colocalize substance P and dynorphin. GABAergic neurons in the indirect pathway colocalize enkephalin. *Dopamine* is the major neurotransmitter in the nigrostriatal dopamine system; it has excitatory or inhibitory actions depending on the properties of the stimulated receptor. *Acetylcholine* is found in large aspiny striatal interneurons. *Norepinephrine* is important in the autonomic nervous system, lateral tegmentum, and locus ceruleus. *Serotonin* is found in the dorsal raphe nucleus of the brainstem, the hippocampus, cerebellum, and spinal cord.

For each of rhese neurotransmitters, multiple types of receptors may exist. Glutamate is active at a number of types of ligand-gatcd ion channel receptors named for their selective agonists: N-methyl-D-aspartate (NMDA); a-amino-3-hydroxy-5-methy]-4-isoxazole propionic acid (AMPA); and k a mate. The NMDA receptor has been the focus of particular attention because of its potential role in excitotoxic neuronal injury. There arc also mctaborropic glutamate receptors. There are two classes of GABA receptors, named GABA,\ and GABA^. $GABA_A$ receptors are ligand-gated chloride channels. There are many subtypes of this receptor. The GABAu receptor is a mctaborropic receptor. Five types (D[through D_5) and two families (D] and D2) of dopamine receptors have been identified. The D_5 family of receptor is adenylate cyclase dependent and contains subtypes Di and D5. D] receptors reside primarily in the direct pathway, cerebral cortex, and limbic system, D^ receptors arc located primarily in the indirect pathway, cerebral cortex and limbic system,

as well as the pituitary gland. There are two families of *acetylcholine* receptors, nicotinic and muscarinic. There are two subtypes of nicotinic and five subtypes of muscarinic receptors. Most striatal cholinergic receptors are muscarinic. In the *norepinephrine* system, there are two primary receptor systems, *a* and *fi.* There are 14 distinct receptor subtypes of *serotonin* receptors including G protein-coupled receptors in the 5-HTj, 5-HT_2, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 families and the 5-HT_3 type ligand-gated ion channels. Drugs targeting specific subpopulations of receptors are in use or under development for movement disorders, but there remains a knowledge deficit about the relative clinical utility of specific rcccpror agonists and antagonists,

NEURODEGENERATION AND "TOXIC PROTEINS"

Many of the neutodegenerative movement disorders share the property of neuronal damage caused by the accumulation of aggregation-prone proteins that have toxic effects (Table 77.3). In order for a protein to function normally, it must be properly synthesized and folded into its normal three-dimensional structure. Nascent proteins are aided in folding by molecular chaperones. Proteins that are not properly folded arc otherwise damaged, or beyond their useful lives are degraded by the ubiquitin-dependent proteasome protein degradation system (Taylor ct al. 2002). In the ubiquitin-dependent proteasome system, proteins are first iabeled for degradation by attachment of a polyubiquitin chain (Figure 77,4). Ibis three-step process involves activation, conjugation, and ligation, steps catalyzed by three types of enzymes, $E_{1;}$ E_2, and E_3, respectively. Polyubiquinated protein enters the 26S proteasome, a cylindrical complex of peptidases. The end products of proteasome action are protein fragments and polyubiquitin. The polyubiquitin is then degraded and recycled to the cellular ubiquitin pool, a process requiring enzymatic action by ubiquitin carboxy terminal hydrolase 1 (McNaught and Olanow 2003).

Recent ultrastructural work has elucidated that many degenerative movement disorders can be linked to abnormal synthesis, folding or degradation of specific proteins or protein families. Thus, a number of akinetic-tigid disorders involve the alpba-synuelein or tau proteins. Certain other disorders are linked to abnormalities in pathways involving proteins with expanded polyglutaminc tracts (poh/Q). Among these disorders, clinical and pathological differences depend on the distribution of protein aggregates or in the abnormal configuration they assume when they aggregate. The *synudeinopathies* include PD, diffuse Lcwy body disease, and multiple system atrophy (MSA). The *tauopathies* include progressive supranuclear palsy (PSl'i, corticobasal degeneration (CBD), familial frontotemporal dementia with parkinsonism (FTDP), postencephalitic parkinsonism (PEP), post-traumatic parkinsonism, and amyotrophic lateral sclerosis (ALS) PD of Guam. The *poiyQ* disorders include HD, dentalin'iibr.d-pallidoluysian atrophy (DRPLA), and spinocerebellar ataxias.

The cascade of pathogenic events linking abnormal protein aggtegation to cell death is the subject of intense investigation. AliJituirJ'. .is>,s.\ivj.'.,iu-s arc the nn^: striking physical change in surviving cells, the actual role of the aggregate remains a mystery. Indeed, many now believe that the formation of aggregates may be a protective mechanism sequestering the wayward protein from vulnerable cell processes. Misfolded proteins may produce the most mischief as they form protofibrils. A number of mechanisms have been described. In some cases, these are specifically related to the type of protein, but in many other cases, they are nonspecific mechanisms shared by all the misfolded protein diseases. Some potential mechanisms of ncuro degeneration related to misfolded protein stress arc listed in Table 77.4. The mutant protein may be unable to perform a vital function or may interfere with the function of the wild type protein. Mutant protein, protofibrils, or aggregates might intetfere with other proteins. Interference with transcription factors may be particularly important in this regard. Mutant proteins may activate caspases or in other ways activate the apoptotic cascade. They may interfere with intracellular transport or other vital processes. They may suppress activity of the proteasome, enhancing protein aggregation. They may interfere with mitochondrial function, making cells more vulnerable to excitotoxicity. Oxidative stress may be enhanced and there may be microglial activation (Taylor et al. 2002).

Despite that most of these abnormal proteins are widely expressed in neuronal and non-neuronal tissues,

Tabic 77.3: Toxic proteins ;ind neurodegenerative movement disorders

Alpha-synuciein	*Tan*	*Volyglutamine tract*
Parkinson's disease	*Four-repeat tau*	Huntington's disease
Diffuse Lewi' body disease	Progressive supranuclear palsy	Spinocerebellar ataxia (SCA-3)
Multiple system atrophy	Corticobasal degeneration	Denfatorulir.il p^illnJoluysian atrophy
	Frontotcmporal dementia with parkinsonism (chromosome 17)	
	All six isoforms	
	Parkinsonism dementia complex of Guam	
	Postencephalitic parkinsonism	
	Pronto temp oral dementia with parkinsonism (chromosome 17)	

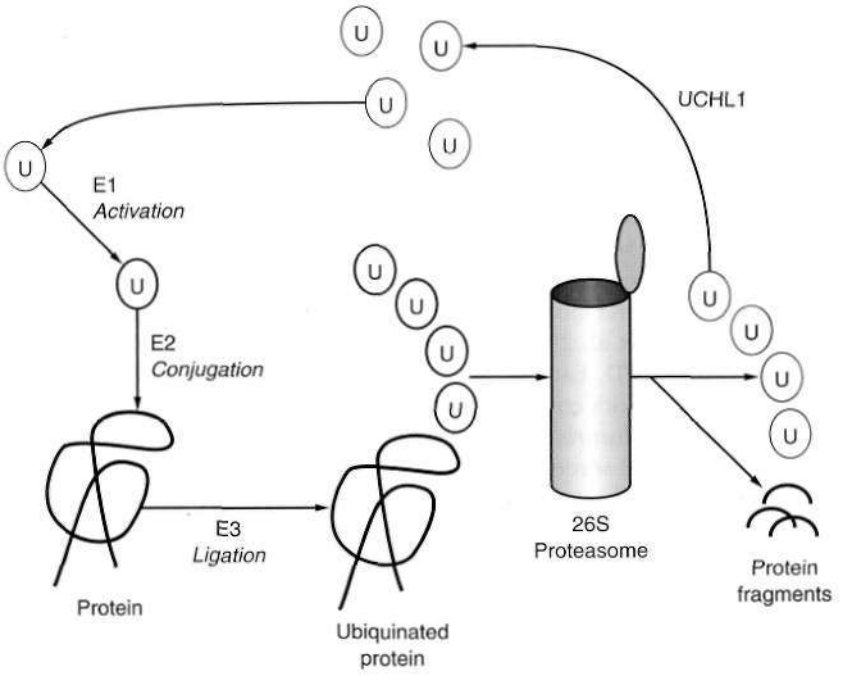


FIGURE 77.4 Ubiquitin-de pen dent proteasomc proteolysis. Once a protein is tagged for degradation, it is tagged with a poiyubiquitin chain, a three-step process involving first activation, then conjugation followed by ligation. The ubiquinated protein enters the 26$ protcasome, where it is degraded into protein fragments and the poiyubiquitin chain is degraded back to monomcric ubiquitin, U = ubiquitin; UCHL1 = ubiquitin catboxy-terminal hydtolase.

these diseases wreak their particular havoc within the nervous system, suggesting that nervous system cells are especially vulnerable to misfolded protein stress. Within nervous tissue itself, certain neuronal populations seem selectively vulnerable to the effects of certain aberrant proteins. This preferential degeneration of specific neuronal populations ultimately determines the phenotypc of the disorder. The key to successful neuroprotection will lie in careful reconstruction of the intracellular crime scene. Potential therapeutic interventions might include reducing translation of the aberrant protein, upregulating molecular chaperoncs, or facilitating protein ubiquination or proteasomal function. Other options include reducing oxidative stress, improving mitochondrial function, and blocking proapoptotic processes. Many of these interventions might be suitable for any of the candidate diseases, although others might be disease specific. A single intervention might produce a benefit of small magnitude and significant neuroprotection might be achieved only with a combination of treatment interventions. Animal studies hint that neuroprotective interventions early enough in the protein aggregation neurodegeneration might actually be able to partially reverse extant neurodegenerative changes. For example, in a conditional transgenic HD model that allows the transcription of the mutant gene to be turned off, reversal of behavioral and pathological changes may be seen {Yamamoto ct ah 2000).

Table 77.4: Mechanisms of neurodegeneration related to misfolded protein stress

Loss of protein function
Interaction of the mutant protein with the wild-type protein
Interaerion with other proteins including transcription factors
Caspase activation
Interference with mitochondrial function
Oxidative stress
Microglial activation

PARKINSONIAN SYNDROMES

Parkinson's Disease (Idiopathic Parkinson's Disease, Paralysis Agitans)

Although described by others before him, James Parkinson is attributed with rendering the first cogent description of PD. In his monograph, *The Shaking Palsy* (1817), he identified the hallmark features of the illness through descriptions of cases observed in the streets of London. Over time, the specific terms *PD* and *idiopathic PD* have come to be reserved for the clinical syndrome of asymmetrical parkinsonism, usually with rest tremor, in association with the specific pathological findings of loss of dopaminergic SN neurons with eosinophilic cytoplasmic inclusions (Lewy bodies). Dopamine deficiency in parkinsonian brain homogenates was described by Horny kiewicz in 1959, a discovery that ultimately led to highly effective pharmacotherapy with L-dopa and direct-acting dopamine agonists (DAs). Recently, a genetic form of parkinsonism that is clinically indistinguishable from PD has been linked to missense mutations in the alpha-synuclein gene. This discovery undermined the concept that PD represents a homogeneous disease but also revealed the importance of disordered protein handling in the genesis of PD. In its present context, PD is best considetcd a syndrome with genetic and environmental etiologies.

Epidemiology and Clinical Features

In community-based series, PD accounts for more than 80% of all parkinsonism, with a prevalence of about 360 per 100,000 and an incidence of 18 per 100,000 per year. I'D is a disease of aging, showing a gradual increase in prevalence beginning after the age of 50 years and a steep increase in prevalence after age 60 years. Disease before the age of 30 years is very rare and often suggests a hereditary form of parkinsonism. Prevalence rates in the United States are higher than those in Africa and China, but the role of race remains unclear. Within the United States, race-specific prevalence rates vary, with some studies suggesting a similar prevalence among whites and American blacks. Unfortunately, blacks make up only a small fraction of most specialty clinic populations, thus .ire under-represented in clinic-based studies and clinical trials.

Typically the onset and progression of PD are gradual. The most common presentation is with rest tremor in one hand, often associated with decreased arm swing and shoulder pain. Hradykinesia and rigidity are often detectable on the symptomatic side, and midline signs such as reduced facial expression or mild contralateral bradykinesia and rigidity may already be present. The presentation may be delayed if hradykinesia is the earliest symptom, particularly when the onset is on the nondominant side. The disorder usually remains asymmetrical throughout much of its course. With progression of the illness, generalized hradykinesia may cause difficulty with arising from a chair or turning in bed. The gait and balance arc progressively affected and falls may occur. Sudden arrests in movement, also called *freezing* or *motor blocks,* soon follow, first with gait initiation, turning and traversing narrow or crowded environments, and then during walking. Bulbar functions deteriorate, impairing communication and nutrition. The Hoehn and Yahr stage, first described before effective dopaminergic treatment became available, accurately outlines the milestones in progression of the illness from mild unilateral symptoms through the end-stage nonambulatory state (Table 77.5).

Nonmotor symptoms are universal in PD and contribute prominently to declining quality of life. *Autonomic symptoms* include reduced gastrointestinal transit time with postprandial bloating and constipation, urinary frequency and urgency sometimes with urge incontinence, impotence, disordered sweating, and orthostatic hypotension. *Cognitive and behavioral changes* are universal as well. Attention and concentration wane. Executive dysfunction with diminished working memory, planning, and organization is common. Global dementia occurs in about 30% of patients, increasing in frequency with the age of the patient. Those with prominent early executive dysfunction and more severe motor signs seem particularly at risk (Levy et al. 2002). *Anxiety* and *mood disorders* are common in PD. Each is seen in as many as 40% of patients with PD, with considerable overlap (Walsh and Bennett 2001). *Sleep disturbance* is nearly universal in PD and is multifactorial. Disordered sleep onset and maintenance lead to fragmentation of nocturnal sleep. A variety of motor movements including restless legs and periodic leg movements of sleep may be seen and many patients have rapid eye movement (REM) sleep behavior disorder (RBD) with active motor movements during REM sleep. Some patients have sleep apnea. Vivid dreams and nightmares are very common, particularly in treated patients. Sleep disorders in PD variably relate to pathological changes of the disease itself, arousals due ro immobility, comorbid primary sleep disorders, and side effects of antiparkinsonian medications. Many patients with PD are excessively sleepy during the day, sometimes with serious consequences such as unintended sleep episodes while driving. In most cases, this excessive daytime drowsiness is related to dopaminergic drugs (Ondo et al. 2001). *Fatigue* is a common and complex symptom of PD. The differentiation of fatigue from excessive daytime sleepiness, depression, apathy, and other conditions can be difficult, and there is not yet a useful body of literature on its assessment and treatment.

Table 77.5: Hoehn and Yahr stage

Stage	
I	Unilateral involvement only, minimal or no functional impairment
II	Bilateral or midline involvement, without impairment of balance
III	First sign of impaired righting reflex, mild to moderate disability
IV	Fully (ic\ eloped, severe]; disabling disease; [Utiem Mill able to walk and stand unassisted
V	Confinement to bed or wheelchair unless aided

PD is a clinical diagnosis, and it is not usually difficult to diagnose a patient with unilateral or asymmetrical rest tremor, hradykinesia, and rigidity. Clinicopathological studies have found that the syndrome that best reflects the typical pathological changes of PD is an asymmetrical illness with rest tremor along with rigidity or hradykinesia, and significant improvement with i.-dopa supplementation, in the absence of other diagnoses known to cause parkinsonism. The presence of this syndrome carries a positive predictive value of 92%, with a sensitivity of 90%. Misdiagnosed cases generally are found to have MSA, PSP, or subcortical vascular disease. When making the diagnosis of early PD, the clinician should be aware of a number of "red flags" (Table 77.6). Cognitive impairment within the first year should raise the possibility of Alzheimer's disease, dementia with Lewy bodies (DLB), CBD, PSP, or ETDP. Symmetrical or prominent midline or bulbar signs suggest MSA or PSP. Early gait disorder with falls points to the diagnosis of PSP or to subcortical vascular disease. Dependence on a wheelchair within 5 years of onset is suggestive of PSP, MSA, or vascular parkinsonism. Early orthostatic hypotension or incontinence points to the

Tabic 77.6: "Red flags" in the diagnosis of Parkinson's disease

Early or prominent dementia
Symmetrical signs
Bulbar dysfunction
Early gait disorder
Falls within the first year
Wheelchair dependence within 5 years
Early autonomic failure
Sleep apnea
Gasping respirations
Apraxia
Alien limb
Cortical sensory loss

autonomic dysfunction of MSA. Severe sleep apnea or sighing or gasping respirations also suggest MSA. Apraxia, alien limb, or cortical sensory loss may be seen in CRD.

Routine laboratory studies are not helpful in the diagnosis of PD, and their use should be directed by other clinical indications. Neuroimaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) are also not helpful in making a diagnosis of PD, because they are generally normal or show only incidental abnormalities. Sometimes, neutoimaging abnormalities can be useful in suggesting alternative diagnoses such as PSP or MSA, The radiopharmaceutical 6-[^{18}FJ-fluorodopa (F-dopa) is taken up by dopaminergic neurons in the SN and metabolized to 6-[^{11t}Fl-fluorodopaminc. Positron emission tomography (PET) scans using this radiopharmaceutical agent show reduced E-dopa uptake in dopaminergic nerve terminals in the putamen and caudate proportional to the severity of degeneration in the ipsilateral SN and symptoms in the conttalateral hemibody (Plate 77.1). Although these tests make useful contributions to PD research, they are not clinically available at this time. Single-photon emission CT* (SPECT) with radioligands that label the dopamine transportet on nerve terminals in the striatum is another research tool, and its clinical relevance is now being studied. There is no role for routine electrophysiological testing in the diagnosis of PD. Because identified genetic causes are rare, there is as yet no role for routine genetic testing in PD.

Pathology

The most striking pathological changes in PD occur in the SNr. The SN appears pale to the naked eye. Microscopic chanties include nciuncal loss, gliosis, and the presence of extracellular pigment. Surviving neurons may show characteristic cytoplasmic inclusions (Plate 77.11). The inclusions, called *Lewy bodies*, have a dense eosinophilic core and a pale halo. They contain hyperphosphorylatcd neurofilament proteins, lipids, iron, ubiquitin, and alpha-synuclein (Jellinger 2002). Pigmented nuclei elsewhere in the brainstem, including the locus ceruleus, dorsal motor nucleus of the vagus, and others, may also show Lewy bodies and characteristic degenetative changes. The substantia innominata and intermediolateral cell column in the spinal cord also are affected. Patients with PD and dementia show more diffuse Lewy body pathology of comorbid Alzheimer's disease (Apaydin et al. 2002).

Etiology

Studies of large numbers of patients with PD have suggested that PD is a multifactorial illness with likely genetic and environmental determinants. Although strongly hereditary PD is rare, there is a tendency for familial aggregation of I'D. Twin studies suggest that hctcdity plays a relatively small role in the population at large, but the hereditary component is greater if one twin has disease onset at younger than 50 years of age (Tanner et al. 1999). Moreover, PPT studies of twins suggest that most monozygotic co-twins of patients with PD show subclinical declines in dopamine innervation, strengthening the evidence for a significant hereditary contribution irrespective of age at onset.

Families whose pedigrees suggest dominant!y inherited PD are rare, making up no more than 5% of the PD population at latge. Most of these families show no identified genetic mutation. However, linkage studies have suggested genetic susceptibility factors on chromosomes 5, 6, 8, 9, 10, 16, and 17. Association studies point to genes for monoamine oxidase B (MAO-B), N-acetyltransferase-2 detoxification enzyme, tau, and glutathione transferase detoxification enzyme, but the relevance of these associations is not yet known {Tan et al. 2000).

Evidence for environmental causes of PD comes primarily from two sources—the fortuitous discovery of parkinsonism in parenteral drug users exposed to the contaminant MPTP and epidemiological associations of sporadic PD or other parkinsonisms with certain lifestyle ot occupational exposures. More than two decades ago, the discovery that a handful of drug addict-, had developed ; \CUTI i.-dup.i-responsive form of parkinsonism following parenteral administration of a meperidine analogue contaminated with the mitochondrial protoxin MPTP suggested that environmental toxins might cause PD, The discovery of MPTP-induccd parkinsonism in humans was a sentinel event in our understanding of the disease because it pointed to a class of environmental toxins that might be important in sporadic disease. Although MPTP spawned the development of reproducible models of disease in many kinds of animals, its role in human disease is limited to the cluster of cases in drug addicts and a few others. Intriguing studies have confirmed that certain pesticides such as paraquat and rotcnone can reproduce the pathology of PD in animals, but their role in human disease remains undefined (Grcenamyre et al. 1999).

Epidemiological studies suggest that exposure to environmental metals or organic toxins may be associated

with an increased risk of PD or an earlier age at onser of PD (Tsai et al. 2002). Case-control studies have suggested that the risk of PD is increased in persons who have worked in the agricultural industry, who have been exposed to pesticides, or who have sustained significant head injury, Exposure to welding seems to predispose to earlier onset L-dopa-rcsponsive PD, possibly as a result of manganese poisoning. On the other hand, the risk of PD seems less in those with a high dietary intake of antioxidant-rich foods, as well as caffeine drinkers and those who have smoked cigarettes (Ross and Petrovitch 2001), These epidemiological studies have failed to find a "smoking gun" in the etiopathogenesis of PD.

Irrespective of genetic or environmental influences, the central feature of ncurodegeneration in PD is aggregation of alpha-synuclein. In PD, the natural tendency of alpha-synuclein to aggregate is likely enhanced by genetic factors controlling the protein synthesis, secondary processing or degradation and environmental factors such as aging, oxidative stress, and toxic exposures. Misfoldcd alpha-synuclein triggers mechanisms in the cell (see previous discussion) that ultimately lead to its demise.

Trent meat

A preclinical period lasting years to decades and a slow progression rate make PD an ideal candidate for *neuroprotection.* The increased understanding of disease etiopathogenesis suggests many candidate neuroprotective agents (Table 77.7). Neuroprotective trials to this point have been somewhat disappointing. Pie lirsi and larr.iM iuuro protective trial, DATATOP, randomized patients with early PD to treatment with placebo, tocopherol, selegiline (deprenyl), or both, using the time until patients needed potent symptomatic dopaminergic therapy, L-dopa, as a proxy endpoint for disease progression. The selective MAO-B inhibitor selegiline successfully delayed this endpoint, but interpretation of the study was contaminated by its mild antiparkinsonian and antidepressant properties, as well as potential effects of its amphetamine metabolites. A similar magnitude effect was shown in a latge randomized placebo-controlled study of another MAO-B inhibitor, lazabemide, but this drug is no being actively developed. A third MAO-B inhibitor, rasagiline, has been shown to have modest symptomatic benefit. Its effect on disease progression is under study. A recent randomized placebo-controlled study of three doses of coenzyme Q_{J0} suggested a slowing of decline in function in the 1200-mg-per-day group. This finding warrants *w* litional study in a larger group of research subjects (Siiults et al. 2002). Two intriguing studies comparing the effects of carbidopa-L-dopa (CD-LD) and DAs (pramipexole and ropinirole) on decline in functional ncuroimaging markers of presynaptic dopaminergic function in early DD suggested a slower loss of dopamine neurons in patients tteated with DAs than with CD-LD (Marek ct al. 2002). Although these studies are thought provoking, they require independent confirmation using clinical measures.

Tabic 77.7: Candidate neuroprotective approaches in Parkinson's disease

Mechanism	*Potential neuroprotective approaches.*
Oxidative stress	Antioxidants, for example, monoamine oxidase inhihitors, coenzyme Qm
Mitochondrial dysfunction	Coenzyme QKJ, creatine
Excitotoxicity	Glutamate antagonists, for example, riluzole
(iaspase ;li iw.UKiii	Caspasc inhibitors, for example, minocycline
Apoptosis	Antiapoptotic agents, for example, mixed lineage kinase inhibitors
Inflammation	Anti-inflammatory drugs
Trophin deficiency	Neil rotropfi ins

Symptomatic Treatment of Parkinson's Disease. Six types of medications arc available for the symptomatic treatment of PD: anticholinergics, amantadine, L-dopa, monoamine oxidase inhibitors (MAOIs), catcchol-O-methyltransferase (COMT) inhibitors, and DAs (Tabic 77.8). *Anticholinergics* such as trihexyphenidyl and benztropine antagonize the effects of acetylcholine at muscarinic receptors postsynaptic to striatal intcrneurons. They reduce tremor and rigidity but have no effects on bradykinesia. Toxicity relates to antagonism of acetylcholine at central receptors, causing confusion, and peripheral receptors, causing blurred vision, dry mouth, constipation, and utinary retention. Although *amantadine* has been available for nearly four decades

Table 77.8: Commonly used antiparkinsonian drugs

Drug	*Usual starting dose*	*Usual daily dose*
Anticholinergics		
Trihexyphenidyl	1 mg	2-12 mg
Benztropine	0.5 mg	0.5-6.0 mg
Bipendin	1 mg	2-16 mg
Amantadine	100 mg	100-300 mg
L-DOPA (with carbidopa)		
Immediate release	100 mg	150-800 mg
Controlled release	100 mg	200-1000 mg
Dopamine agonists		
Bromocriptine	1.25 mg	15-40 mg
Pergolide	0.05 mg	2-4 mg
Pramipexole	0.375 mg	1.5^4.5 mg
Ropinirole	0.75 mg	8-24 mg
C-alx'rgoline	0.25 mg	0.25^1.0 mg
Catcchol-O-methyl transferase inhibitors		
Entacapone	200 mg with each dose	200 mg with each dose
Toleapone	300 mg	600 mg

(it was originally marketed as an antiviral agenr), irs antiparkinsonian mechanisms have been poorly understood. It has been thought to stimulate release of endogenous dopamine stones, to block reuptake of dopamine from the synaptic cleft, and to have anticholinctgic properties. However, recently, it has been found to have antiglutamatergic properties and as such is the only antiparkinsonian drug that improves L-do pa-induced dyskinesia. *CD-LD* combines L-dopa, the immediate precursor of dopamine *w h* carbidopa, an aromatic acid decarboxylase inhibitor thrit prevents its peripheral metabolism, Its global antiparkinsonian efficacy is so dramatic and predictable that a positive therapeutic response is used to define the disease its*If. Advetse effects of CD-ID include nausea and von ;i ting, orthostatic hypotension, sedation, confusion, sleep disturbance, altera nous of dream phenomena, hallucinations, and dyskinesias, A number of direct-acting DAs are available including bromocriptine, pergolide, pramipexole, and ropinirole. Cabergoline is available in the United States, but it does not have Food and Drug Administration (FDA) approval for the treatment of PD and is prohibitively priced. Lisuride, piribedil, and apomorphine are not available in the United States. DAs cause side effects similar to those of L-dopa, although orthostatic hypotension, sleepiness, and hallucinations are more common or severe. DA monotherapy is associated with a very low incidence of dyskinesia. Agents that interact with the metabolism of L-dopa or dopamine are also available for the treatment of PD (Figure 77.5). *Selegiline* blocks MAO-B-dcpcndent dopamine degradation and has modest effects in potentiating the action of L-dopa. COMT inhibitors block peripheral degradation of peripheral levodopa *(entacapone* and *tolcapone)* and central degradation of L-dopa and dopamine (tolcapone), increasing central L-dopa and dopamine levels. Hcpatotoxicity associated with tolcapone has limited its use. Triple-combination therapy containing L-dopa, carbidopa, and entacapone became recently available for pancms with modcralcb advanced I'D,

Symptomatic treatment should begin when the patient is noticing functional, occupational, or social disability related to PD symptoms. Prospective studies have suggested that about 70% of patients with PD will require symptomatic therapy within 2 years of disease onset. Less potent therapies such as selegiline and amantadine may be useful for initial therapy, but CD-LD or DAs arc the choices when more potent therapy is indicated. The choice between CD-LD and DA for initial therapy remains controversial. There is universal agreement that CD-LD is the most potent and best tolerated drug in the modern PD arsenal, but there are concerns that it might be toxic to dopaminergic neurons and that it promotes the development of motor fluctuations.

The argument that L-dopa might be toxic to dopaminergic neurons is based on the recognition that dopamine metabolism increases oxidative stress and the observation that i.-dopa is toxic to cultures of mesencephalic neurons in vivo. There is no in vivo evidence in laboratory animals that i.-dopa accelerates disease progression, and it is difficult to reconcile the potential of dopamine toxicity with the obvious fact that the drug prolongs life in patients with PD. A 9-month study, called *ELLDOPA*, compared different doses of L-dopa with placebo and found no evidence of L-dopa toxicity.

Clinical experience with CD-LD treatment of PD suggests that there is a progressive increase in the

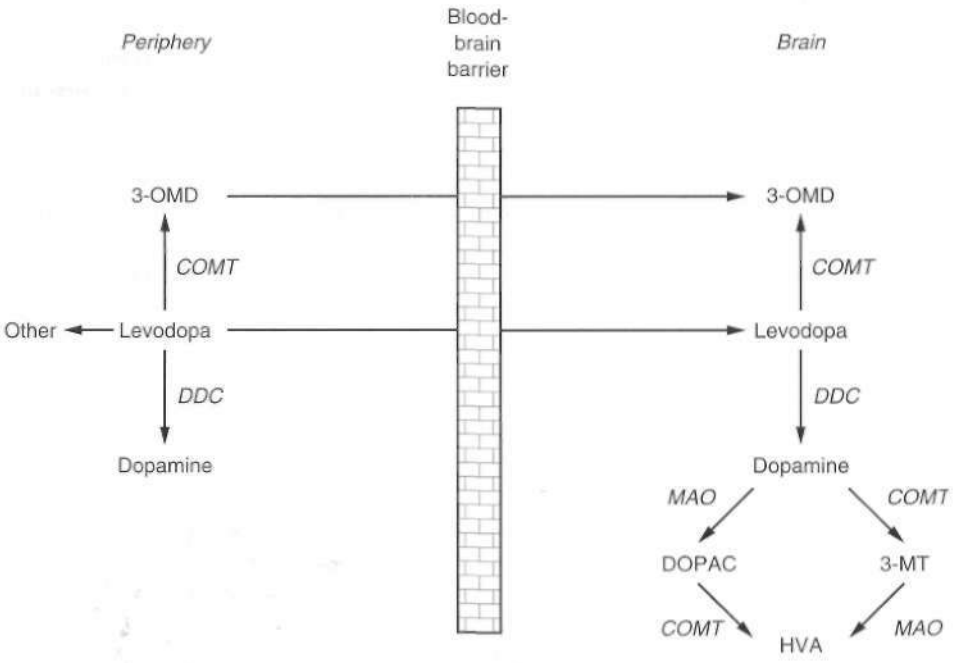


FIGURE 77.5 Peripheral and central L-dopa and dopamine Meta holism. COMT = catechol-O-methyl transferase; DDC = dopa decarboxylase; DOl'AC = dihydroxyphenylacetic acid; HVA = homovanillic acid; MAO = monoamine oxidase; 3-MT = 3-methyttyrosine; 3-OMD = 3-O-methyldopa.

prevalence of drug-related motor fluctuations (wearing off, dyskinesia) over time that relates mainly to the seventy of the underlying PD. Wearing off results from loss of continuous receptor stimulation. Experimentation in animal models relates the development of dyskinesia to changes in striatal glutamate receptor sensitivity consequent to pulsatile stimulation of striatal dopamine receptors. Continuous dopamine receptor stimulation with L-dopa or with long-acting dopamine receptor agonists prevents or reverses this phenomenon. Two pivotal clinical trials studied whether more sustained dopamine receptor stimulation afforded by DA (pramipexole and ropinirole) therapy was less likely to induce motor fluctuations and dyskinesia than therapy with the shorter half-life agent CD-LD. In both studies, the efficacy of CD-LD for the primary symptoms of PD was superior to that of DA, even though open-label supplementation with CD-LD was allowed during the study. CD-LD was better tolerated than DA, which caused more edema, sleepiness, and hallucinations than CD-LD (Table 77.9). In both studies, the risk of development of dyskinesia or motor fluctuations was substantially reduced in the DA monotherapy group and even in subjects who ended the study on CD-LD and DA (Parkinson Study Group 2000; Rascol et al. 2000). At this time, it remains unclear whether the delay in development of early dyskinesias and fluctuations is worth the poorer efficacy and tolerability and greater expense of agonists. Clearly, by the second decade of therapy, all patients arc on L-dopa, often in combination with DA, and it is not yet clear whether initial treatment will influence overall function or quality of life at this point in the disease. In many specialty centers, otherwise healthy and cognitively intact patients younger than 70 years are usually treated first with DAs and less healthy, cognitively impaired, and elderly patients are started on L-dopa.

Irrespective of initial treatment, virtually all patients with PD experience an evolution of their response to L-dopa that includes wearing off and other motor fluctuations. The middle years of PD treatment can best be characterized as the years of optimizing drug delivery. The first step in rational pharmacotherapy of PD at this stage is characterizing the pattern of response to the therapeutic agents, a step wholly reliant on the patient history. The patient should be asked to describe the severity of symptoms in the morning on arising and the magnitude and duration of benefit from incremental doses of antiparkinsonian drugs. The usefulness of historical information may be augmented by careful patient education on symptom recognition and the development of a shared vocabulary. Completing motor diaries (Figure 77.6) helps both the patient and the treating physician recognize the patterns ot motor response and adjust the medications accordingly.

Table 77.9: Frequency of common side effects in comparative trials of dopamine agonists and L-dopa

Side effect	*Ropinirole* (%)	*Pramipexole* (%)	*L-Dopa (%)*
Nausea	**48.6**	**36.4**	**43.1**
Somnolence	27.4	**32.4**	**18.2**
Insomnia	25.1	**25.8**	**22.8**
Dizziness	: 1.1	**25.8**	***11.6***
Hallucination	**17.3**	***9.3,***	**3.3**
Depression	**14.5**	**15.2**	**17.9**
Headache	kO	**20.5**	**16.7**
l\:km;l	**14.0**	17.9	**6.8**
Anxiety	**11.7**	**11.3**	**7.9**
Orthostatic |blood pressure	, 1.7	**6.0**	**11.2**
Constipation	**9.5**	**20.5**	**12.6**

Wearing off is the most common type of motor fluctuation. It is the predictable return of parkinsonism in advance of the next scheduled antiparkinsonian dose. *On off is* the unpredictable reappearance of parkinsonism at a lime when central levels <-l Linlip.irkinsnninn drugs **are** expected to be within the target therapeutic range. *Delayed on* is a prolongation of the time required for the central antiparkinsonian drug effect to appear. Dose *failure* is the completed failure to develop a favorable response to an incremental dopaminergic dose. *Protein-related offs* occur when the transport of L-dopa across the intestinal wall is impeded by competition for facilitated transport by large amounts of neutral amino acids. A variety of dyskinesias can further complicate the picture of midstage PD. *Peak-dose dyskinesias* are usually choreiform or stereotypical movements present at the peak of the therapeutic response; dystonic movements are seen less commonly. *Off-period dystonia* usually appears in the more severely affected foot in the morning before the first daily doses, sometimes reappearing during wearing off. *Diphasic dyskinesias* arc usually large-amplitude dyskinetic movements of the lower body during the time of increasing and decreasing L-dopa levels.

Armed with a few basic principles and a commonsense approach, the clinician can usually smooth out fluctuations for most patients (Table 77.10). Delay to onset of therapeutic benefit can be hastened by avoiding or reducing protein ingestion or by crushing the L-dopa tablet and mixing it with a carbonated beverage. The duration of benefit increases when the incremental dose is increased or dopamine metabolism is blocked with an MAO inhibitor or COMT inhibitor. The brittle patient with motor fluctuations and dyskinesia may do better on smaller, more frequent L-dopa doses. A homemade solution of liquid L-dopa allows very tight titration of the resulting 1-mg/mL of i.-dopa solution and is particularly useful in young fluctuators (Table 77.11).

In addition to the fluctuating response typical of moderate PD, patients with advanced disease may have acquired j,-dopa-resistant motor symptoms such as freezing, progressive gait dysfunction, dysarthria and dysphagia, and recurrent falling. Other features of the advanced illness, including cognitive impairment, autonomic dysfunction,

Time	Medication	Meal	Asleep	Off	On	Dyskinesia
Midnight— 1:00 A			X			
1:00 —2:00 A			X			
2:00 —3:00 A			X			
3:00 — 4:00 A			X			
4:00 —5:00 A			X			
5:00 — 6:00 A				X		
6:00 — 7:00 A	1 Sinemet Va Mirapex	X		X		
7:00 — 8:00 A					X	
8:00 — 9:00 A					X	X
9:00 —10:00 A				X		
10:00—11:00 A				X		
11:00 — noon	1 Sinemet 1/2 Mirapex	X		X		
1:00 — 2:00 P				X		
2:00 —3:00 P					X	X
3:00 — 4:00 P	1 Sinemet			X		
4:00 — 5:00 P					X	
5:00 — 6:00 P					X	X
6:00 — 7:00 P		X			X	
7:00 — 8:00 P	Va Sinemet			X		
8:00 —9:00 P					X	X
9:00 —10:00 P					X	X
10:00 — 11:00P				X		
11:00 —midnight		X				

FIGURE 77.6 Sample diary in Parkinson's or her disease. For each hour, the patient indicates whethet and which antipatkinsonian drugs he or she has taken then places a mark to indicate his or her motor state for most of the hour.

Table 77.10: Management of drug-related motor fluctuations in Parkinson's disease

Wearing off
Adjust L-dopa dose and interdose interval
Shorter interval
Smaller increment, especially if dyskinesia is a problem
liquid carbidopa/L-dopa
Add catechol-O-methyl transferase inhibitor
Entacapone
Tolcapone
Add dopamine agonist
Add amantadine
Add selegiline
Dyskinesia
Adjust L-dopa dose and interdose interval
Smaller increment
Shorter interval, if needed
Add dopamine agonist and reduce L.-dopa dose
Add amantadine
Add atypical antipsychotic
Morning dystonia
Chew or crush first dose, take with carbonated beverage
Add dopamine agonist
Add baclofen
Add anticholinergic
On-off fluctuations
Careful identification/management of predictable fluctuations
Add dopamine agonist

and psychiatric complications, may limit the types and dose of tolerated medications. *Freezing,* sudden immobility of the feet while walking, often with falls, may be seen in the off period or in the on period. Although off-period freezing docs improve with optimization of medications, on-period freezing may be resistant to treatment. Behavioral strategies such as sensory cues may be helpful. Dysarthria and dysphagia are often treated by speech therapists, although documentation of improvement from these techniques is scant. *Cognitive impairment* increases mainly with the age of the patient and with disease severity. Pteliminary reports suggest that cholinesterasc inhibitors might be useful in PD-associatcd dementia, but these studies require confirmation in carefully controlled trials. *Autonomic dysfunction* can be managed conservatively, with salt supplementation, fludrocortisone, midodrinc for orthostatic hypotension, urological medications for bladder dysfunction, and dietary changes for constipation. *Hallucinations* occur in about 30% of treated patients; a loss of insight that the visions are not real or the appearance of psychotic thinking signals a particularly disabling complication. Hallucinations often improve with atypical antipsychotics such as quetiapine and clozapine. Cholinesterase inhibitors may reduce hallucinations in some patients. Sleep disorders may respond to hypnosedatives, tricyclic antidepressants, or nighttime dopaminergic therapy. Excessive daytime sleepiness may respond to methylphenidate or modafinil.

Table 77,11: Liquid L-dopa

Recipe
10 tablets of car hi do pa/Ldo pa
1 liter of water
500 mg of ascorbic acid
Powdered drink mix for taste
Calculating the dose
Divide rhe total daily dose into 13 increments
Increase the first morning dose increment by 10-20%
Give 13 hourly doses from 7:00 AM through 7:00 PM
Give one dose of Sinemet CR at 8:00 PM
i itriite .is needed using motor fluctuation diaries as a guide

Surgical Treatment of Parkinson's Disease. Despite decades of experience with the medical treatment of PD, many patients with moderate to advanced disease have a poor quality of life because of fluctuating medication response, troublesome dyskinesia, or i.-dopa-unresponsive symptoms. For these reasons, there has been a resurgence of interest in surgical approaches to motor dysfunction in PD. Palliative surgical approaches include stereotactic destruction of physiologically defined overactive brain nuclei (thalamotomy, pallidotomy), deep brain stimulation (DBS) using implanted pulse generators, and the implantation of cellular sources of dopamine. Surgical approaches aimed more at the degenerative process itself include delivery of trophic factors using implanted pumps or by gene therapy and cellular transplantation.

Stereotactic *thalamotomy* reduces or eliminates contralateral rest tremor and reduces rigidity in 75-85% of patients, but there is no effect on bradykinesia, and bilateral procedures can harm speech and cognition. *Thalamic DBS* is similarly efficacious {Rehncrona et al. 2003) but is better tolerated and can be performed bilaterally without serious effects on speech and cognition. Stereotactic *posteroventral pallidotomy* effectively reduces contralateral L-dopa-induced dyskinesia and modestly improves akinesia in the off state. Overall, about 70% of patients improve. Contralateral dyskinesia improves most of the time, about 90%, Off-period motor disability improves by about 30%, although most studies show[T] no substantial improvement over that produced by L-dopa m the on state. There is a 1.2% risk of death and about a 3.8% risk of intracerebral hemorrhage or infarction from pallidotomy (de Bic et al. 2002). *Pallida! DBS* has had limited study, but its efficacy seems equivalent to structural pallidal lesions. In a large multiccnter study, 38 patients with bilateral pallidal DBS showed significant reductions in off time and in the severity of disability in the off period, dyskinesias were improved, but l.-dopa dose could not be reduced {Deep-Brain Stimulation for Parkinson's Disease Study Group 2001). *Subthalamic DBS* has become the preferred surgical procedure for patients with advanced PD, despite the lack of a well-designed randomized efficacy trial, STN stimulation is associated with 44-52% improvement in

motor severity in the off state and a smaller improvement in the on state. Unlike other surgical procedures, STN DBS allows reductions in antiparkinsonian drug dose (Deep-Brain Stimulation for Patkinson's Disease Study Group 2001). Pharmacological suppression of excessive STN firing may be possible with a gene therapy approach that uses adc no-associated viral vector delivery of glutamic acid decarboxylase, the enzyme that synthesizes GABA. This technique is now in preliminary human trials.

PD is a condition that seems ideally suited for neurotransplantation. Most symptoms relate to degeneration of a single cell type in a ncuro.inatrimically small defined region, and dramatic improvements can be obtained by replacing the product of the degenerating cells. Animal experimentation supports the concept that human fetal SN cells implanted into the striatum survive and establish functional connections with target neurons there. Early trials of *adrenal medullary autografts* showed disappointing results and unacceptable morbidity. *Xenografts* appear poorly efficacious and are haunted by concerns about cross-species mtivuon. Open trials ol bilateral human fetal SN transplants into the putamen suggested substantial improvements in the primary symptoms of PD, significant improvements in PET scan measures of dopaminergic function, and robust survival of engrafted cells. The first randomi/.ed, sham surgery-controlled study of human fetal transplantation involved 40 patients with advanced PD. These patients were randomly assigned to sham surgery (bilateral burr holes without dura! penetration) or implantation of tissue obtained from two fetal brains per side. Despite changes in PET scans that confirmed increases in dopaminergic innervation and autopsy evidence of cell survival, there was no improvement in the primary endpoint, a global measure of improvement. There were significant improvements (18-34%) in objective rating scales, particularly in the subgroup of transplant recipients who were 60 years old or younger. However, some patients developed dyskinesias or dystonia, even in the absence of exogenous dopaminergic stimulation. In some cases, subsequent surgeries were required to control these dyskinesias (Freed et al. 2001). for the present, it is clear that without major refinements, human feral transplantation is not likely to be a useful intervention for PD.

Delivery of trophins or other substances directly to the brain parenchyma has been a recent focus of investigation. *Glial-derived neurotrophic factor* (GDNF) is a neuropeptide with neurotrophic properties for dopaminergic neurons. In rat models of PD, intracerebral administration has both protective and restorative effects. A phase II trial of monthly intracerebroventricular bolus injections of GDNF in 85 patients with moderately advanced PD showed the treatment was poorly tolerated. No efficacy was demonstrated, likely because the compound did not penetrate into the target tissue area (Nutt et al. 2003). Early clinical trials of intrastriatal GDNF pumps are in progress. Delivery of GDNF to the striatum using lentiviral or other vectors has shown some promise in animal models of PD, but clinical trials have not begun.

Irrespective of the type of surgical approach, neurosurgery for PD should be performed only by experienced functional neurosurgeons in centers with multidisciplinary teams including movement disorders neurologists, physiologists, and other support personnel. Patient selection is very important. The best surgical results arc achieved in younger, cognitively unimpaired patients with a robust response to dopaminergic therapy and good function in the on state. Many surgeons will not operate on patients who arc older than 75 years, because of an increased risk of morbidity in the elderly. Other common reasons to exclude patients include cognitive or psychiatric impairment, insufficient clinical severity, neurounaging abnormalities, and poor motivation or comorbid systemic illness. It is important to recognize that long-term outcomes have not been established for most surgical procedures.

Genetic Parkinsonisms

A number of genetic parkinsonisms have been described (Table 77.12). These discoveries have helped elucidate the ways in which single-gene abnormalities might predispose to a degenerative disease and have helped shed light on the cellular processes that underlie sporadic PD as well. Two missense mutations in the ;tlpha->yiniclcin gene on the fourth chromosome *(PARK1)* have been described in two Mediterranean pedigrees with highly penetrant asymmetrical I.ewy body parkinsonism (Polymeropoulos 1998), The onset of parkinsonism is often before age 45 years and affective disturbance is more common and prominent than in sporadic PD. However, clinical overlap with sporadic PD is considerable and individual cases of PARK1 are indistinguishable from sporadic PD. Both described mutations accelerate the production of alpha-synuclein protofibrils. High levels of oxidative stress in dopaminergic neurons and catecholamine-induccd inhibition of the conversion of toxic to stable alpha-synuclein may explain the selective vulnerability of dopaminergic neurons to the alpha-synuclein mutation.

A much more common inherited parkinsonism is *PARK1. PARK2* is a recessively inherited early onset parkinsonism linked to mutations on the sixth chromosome. *PARK2* is an early onset parkinsonism with mean onset near 30 years of age. *PARK2* is often a symmetrical parkinsonism, with prominent dystonia at onset. There is a robust response to antiparkinsonian therapy, although these patients are plagued by early and ultimately severe motor fluctuations. Dozens of causative mutations have been discovered. Homozygous mutations result in the absence or truncation of the parkin protein, a ubiquitin ligasc involved in the ubiquitin proteasome protein degradation system. The substrates for parkin have not

Table 77.12: Genetic forms of parkinsonism

Variant (chromosome)	*Pattern*	*Onset (yr)*	*Dementia*	*Asymmetry*	*Tremor*	*Dopa response*	*Other signs*	*Pathology*	
								Nigral degeneration?	*Lewy bodies?*
PARK1 (4)	AD	30-50	++	+++-	+++	-H~H		Yes	Yes
PARK2 (6)	AR	20-50		±	±	+++	Dystonia	Yes	Rarely
PARK3 {4}	AD	50s	±	1.	+++	1-		Yes	Yes
PARK4 (4)	AD	Early	++	+++	+++	+++	Tremor	Yes	Yes
PARK5 (4)	AD?	50s		+++	+++	+++		Yes	Yes
PARKS (1)	AR	30s		+++	+++	+++		?	?
PARK7(1)	AR	30s		+++	++	+++	Dystonia	?	?
PARKS (12)	AD	40-60	-	+++	+++-	+++		Yes	No
PARK 10(1)	?	Eate	?	?	f	?		?	?

been conclusively demonstrated, but rau and alpha-synuclein may be among them. Because the proteins are not ubiquinated, Lewy bodies do not generally form. Parkin mutations are thought to cause up to 77% of parkinsonism with onset before age 20 years, but only 3% of parkinsonism between 30 and 45 years (Lucking et al, 1998).

A mutation in the ubiquitin carboxy-terminal hydrolase (UCH-L1) gene *(PARKS)* has been described in a German sibling pair with parkinsonism. This enzyme is important in dissociation of monomeric ubiquitin from the polyubiquirin chain after proteolysis, thus in tecycling ubiquitin. The pathology of this hereditary parkinsonism is not known.

Two consanguineous pedigrees from the Netherlands and Italy *(PARK?)* have been found to have homozygous mutations in the DJ-1 gene on chromosome 1, with resulting loss of function of the highly conserved **DJ-1** protein, believed to be involved in cellular protection against oxidative stress (Bonifati er al. 2002).

Point mutations in the noncoding region of NR4A2 (Nl'RKl) gene on chromosome 2 have been described m some patients with otherwise typical idiopathic PD (Le et al. 2003). NR4A2 is a member of the nuclear receptor superfamily of proteins. It is thought to be essential for differentiation and maintenance of nigral dopaminergic neurons.

In other forms of familial parkinsonism, linkage to various regions of the genome has been described, although the causative genes remain unknown. In some northern European families, parkinsonism is linked to the second chromosome *(PARK3).* Onset, presentation, and course are similar to idiopathic PD. A kindred from Iowa has an autosomal dominant parkinsonism with reduced penetrance that is linked to the fourth chromosome *(PARK4).* These patients show early onset, slowly progressive L-dopa-responsivc parkinsonism with behavioral and psychiatric distutbances and blepharospasm. A genetic locus on chromosome 1 is responsible for *PARK6* and a locus on chromosome 12 is responsible for *PARKS,* a Iow-penetrance autosomal dominant parkinsonism seen in a Japanese family. One family with maternal inheritance and a mitochondrial DNA mutation has been reported, but the relative importance of mitochondrial DNA abnormalities remains unknown in the PD population at latge.

Dementia with Lewy Bodies

1)1.B is the second most prevalent degcnenur, e dementia after Alzheimer's disease. It is a progressive dementia characterized especially by fluctuating cognitive impairment, prominent disruption of attention and visuospatial abilities, visual hallucinations, and parkinsonism. RBD and depression are also very common. Patients with DLB arc extremely sensitive to dopamine receptor antagonists and experience severe parkinsonism when treated with neuroleptics. Characteristic pathological changes include cortical and brainstem Lewy bodies. Spongiform changes, neurofibrillary tangles, and dystrophic Lewy neuritis may also be seen, and overlap with Alzheimer's disease is considerable. Treatment of DLB is difficult. Although antiparkinsonian agents are used to treat parkinsonian signs, the degree of sensitivity of parkinsonian signs to dopaminergic therapy has not been well defined. Psychiatric and behavioral changes may improve with atypical antipsychotics. An open-label study found improvements in delusions, apathy, agitation, and hallucinations with rivastigmine treatment, but these findings should be corroborated in controlled clinical trials.

Multiple System Atrophy

MSA is a relatively new diagnostic designation that includes disorders with various combinations of pyramidal, extrapyramidal, cerebellar, and autonomic features. Within this category are subtypes named for their predominant clinical manifestations. **The** more purely parkinsonian MSA *{MSA-P)* replaces the term *striatonigral degeneration.* Cerebellar MSA *{MSA-Q* replaces the term *olivopontocerebellar atrophy. Autonomic MSA [MSA-A)* replaces the term *Shy-Drager syndrome.*

MSA is considerably more rare than PD, with a prevalence of 4-5 per 100,000. It is a disease of adulthood

affecting men and women, with a mean age at onset of 54 years. The clinical distinction between I'D and MSA can be difficult and misdiagnosis is common. The most common signs in pathologically confirmed cases are parkinsonism (87%), autonomic dysfunction (74%), cerebellar ataxia (54%), and pyramidal signs (49%). MSA-P usually presents with symmetrical parkinsonism, often without tremor. Although there may be a positive response to L-dopa, this is generally relatively short lived. Many patients develop midline dystonia, especially antecolic head posture and stridor, and dystonia that is induced or worsened by L-dopa is common (Plate 77.111). Patients often have involuntary gasping or deep sighing when awake and apnea during sleep. Autonomic signs include orthostatic hypotension, incontinence, and impotence. Patients with MSA-C have parkinsonism with prominent cerebellar signs, especially wide-based ataxic gait. Autonomic signs are variably present. Patients with MSA-A generally present with autonomic failure. Early signs are incontinence in women and impotence in men. Orthostatic hypotension is the rule. There seems to be substantial residual sympathetic tone in MSA, so orthostatic hypotension is generally accompanied by supine hypertension, making treatment difficult.

Clinical tests of autonomic dysfunction may be helpful in diagnosis or treatment. Testing of cardiovascular reflexes such as heart rate variability- at rest and during forced respiration, as well as blood pressure changes during head-up tilt, may help establish a clinical diagnosis of MSA. A lack of responsiveness of growth hormone to clonidine challenges and denervation on rectal sphincter electromyography (EMG) are also characteristic findings. T2-weighted MRI brain scans may show a hyperintense rim at the lateral edge of the dorsolateral putamcn, with decreased signal within the putamcn. Cruciform hyperintensity within the pons, the "hot cross **bun**" sign, may also be a helpful sign. Although MRI brain scans differentiate MSA from PD, they do not adequately distinguish among the subtypes of MSA (Bhattacharya et al. 2002).

At autopsy, MSA brains show neuronal loss and gliosis in the striatum, SN, locus ceruleus, inferior olive, pontine nuclei, Purkinje's cells, intermediolateral cell column, and Onuf's nucleus in the sacral spinal cord. There are characteristic cytoplasmic inclusions in the glia, especially the oligodendroglia. These glial cytoplasmic inclusions contain alpha-synuclcin (Plate 77.1V). There is a severe depletion of cholinergic neurons in the pedunculopontine nucleus and laterodorsal tegmental nucleus. The etiology of MSA remains unknown. There are no known genetic forms of the illness and no known risk factors.

Treatment of MSA is very difficult. There arc no specific interventions, and symptomatic therapies provide only partial relief of disability. Parkinsonism may respond to i.-dopa, particularly early in the disease course, but the results are not dramatic or sustained. DAs are not helpful and may be poorly tolerated because of orthostatic hypotension. There is no effective treatment for the cerebellar signs. Orthostatic hypotension may improve with nonpharmacological measures such as liberal salt and water intake, compressive stockings, and sleeping with the head up, but most people require pharmacotherapy with fludrocortisone, midodrinc, or other agents. Treatment of orthostatic hypotension often worsens supine hypertension. Even in the best hands, MSA has a poor prognosis, with a mean survival of 7-9 years.

Progressive Supranuclear Palsy

In 1964, Steele, Richardson, and Olszewski described a progressive illness characterized by vertical supranuclear ophthalmoplegia, axial rigidity, pseudobulbar palsy, and mild dementia. P.uholn^ical findings inckided neuronal loss, gliosis, neurofibrillary tangles, and granulovacuolar degeneration in neurons of the brainstem. PSP is a rare disease; prevalence estimates range from 1.39-6,4 per 100,000, Men are affected more often than women. PSP typically begins in the sixth to seventh decades of life with gait disorder and falling. Patients develop an akinetic-rigid state with symmetrical signs and prominent axial rigidity. In contrast to the flexed posture of patients with PD, those with PSP may have an extended trunk or retrocolic neck posture. A characteristic facial appearance with a wide-eyed stare, furrowing of the forehead, and deepening of other facial creases allows experienced clinicians to make an instant diagnosis (Plate 77,V). Pseudobulbar palsy with dysarthria and dysphagia lend the patient a characteristic dysarthria with spasticity, hypokinesia, and ataxia, and often "silent" aspiration. Frontal lobe features are common. There is striking executive dysfunction early in the disease course and concrete thought, difficulty shifting set, decreased verbal fluency, and personality changes such as impulsiviry and poor judgment are nearly universal, Apraxia is often seen. A progressive apathetic dementia ensues. Supranuclear vertical gaze palsy may not appear until later in the disease course, and some patients may never develop gaze palsy. Atypical presentations are often seen, especially pure dementia, PSP is rapidly progressive. By the fourth year of illness, half of patients need assistance for walking and have dysarthria and visual symptoms, Dysphagia becomes prominent shortly thereafter. The median interval from onset to wheelchair dependence is 8.2 years. The diagnosis of PSP is usually made by clinical criteria. Electro-oculographic recordings in PSP show decreased amplitude and normal latency of horizontal saccadic eye movements. Typical MRI signs of PSP include midbrain atrophy, increased signal in the midbrain and GP, atrophy or increased signal in the red nucleus, third ventricle dilatation, and atrophy of the frontal or temporal lobes (Schrag et al. 2000a)

At autopsy, the midbrain in PSP is atrophied and the sylvian aqueduct is dilatated. The SN is depigmented and appears orange and shrunken. The locus ceruleus may also

show some depigmentation, but this is less prominent than in idiopathic PD. Other structures may also show atrophy, most notably the frontal lobe, STN, and superior cerebellar peduncle. Histopathologically, the degenerative process involves mainly the basal ganglia, dicncephalons, and brainstem. There are tufted astrocytes in the motor cortex and the striatum, and the typical neuronal lesion is the globose neurofibrillary tangle, made up of hypcrphosphorylated four-repeat tau protein filaments (Plate 77.VI).

PSP almost always occurs sporadically, yet an increasing number of familial cases suggest a genetic etiology in some cases. Pedigrees with apparent dominant and recessive inheritance have been described. Affected families may show phenotypical heterogeneity, with some affected persons showing dementia, dystonia, gait disorder, or tics. Mutations in the tau gene have been reported in patients with a familial PSP-like illness, but these have been quite rare and mutations are not believed responsible for most PSP cases. However, patients with PSP are homozygous for a common haplotype that contains a normally occutring polymorphism in the tau intron immediately preceding exon 10 (Morris et al. 2002). No toxic, viral, or other environmental risk factors have been described.

According to retrospective reviews of response to various treatments, dopaminergic agents, particularly i.-dopa, aid about 40% of patients. A few patients improve with amitriptylinc, imipramine, methysergidc, or 5-hydroxytryptophan, DAs have not shown efficacy in small clinical trials. A randomized placebo-controlled trial of donepezil showed modest cognitive improvements but poor tolerability (Litvan et al. 2001). Botulinum toxin injections may be useful to treat blepharospasm or retrocollic neck posture in PSP (Muller et al. 2002). The prognosis of PSP is poor with a median duration of survival of 10 years.

Corticobasat Degeneration

In 1967, Rebeiz et al. described three patients with akinetic rigidity, apraxia, dystonia, tremor, and aphasia, who at autopsy had pale achromatic ballooned neurons similar to those seen in Pick's disease. The condition was named *corticodentatomgral degeneration with neuronal acbromasia* in 1989 but has since become known as *CBD.* Although CBD generally brings to mind a particulat motor syndrome of asymmetrical rigidity, apraxia, and cortical sensory dysfunction, its underlying pathological features may be seen in other clinical syndromes including progressive aphasia and frontal lobe dementia (Dickson et al. 2002).

CBD is exttcmely rare. The mean age at onset is 60-64 years. In its most recognizable form, it is predominantly a motot disease, but it is a clinically heterogeneous disorder. Motor signs include parkinsonism with strikingly asymmetrical rigidity, asymmetrical dystonia, myoclonus, apraxia, alien limb, and cortical sensory loss. Cognitive signs range from subfluent aphasia in patients with predominantly right-sided motor signs to a generalized dementia.

Patients with CBD have cortical atrophy on MRI, with widening of the sylvian and interhemisphcric fissures and dilatation of frontal, parietal, and temporal sulci. In about half, atrophy is asymmetrical {Schrag et al. 2000a). Fluorodeoxyglucosc (FDG) PET scans show hypomcrabolism in the thalamus and motor cortex contralateral to the more involved arm {Luttc et al. 2000), SPKCT scans show significant asymmetry of cortical blood flow in CBD (Zhang et al. 2001). One study found elevated levels of tau protein in cerebrospinal fluid (CSF) in CBD patients, but this test is not clinically available.

At autopsy, patients with a clinical syndrome consistent with CBD have gross brain atrophy. Typical microscopic changes arc tau-positive neuronal and glial lesions, especially gray and white matter astrocytic plaques and threadlike lesions, and neuronal loss in the cortex and SN. The inclusions are formed of hypcrphosphorylated four-repeat tau (Forman et al. 2002). Overlap with other conditions including Alzheimer's disease, l'SP. I'D, progressive aphasia, frontotemporal dementia (FTD), and hippocampal sclerosis is common.

As with other tauopathies, the etiology of CBD is unknown. There are no familial forms of the illness and no mutations in the tau gene have been identified. There is clinical and pathological overlap with other tauopathies, and patients with CBD share a similar tau haplotype with patients with PSP.

There is no treatment for the degenerative process. Parkinsonian features are not dramatically responsive to dopaminergic drugs, but about 20% of patients have some improvement in parkinsonism with L-dopa. Benzodiazepines, particularly clonazepam, may help myoclonus. Botulinum toxin injections may improve function in dystonic limbs early in the disease and help relieve pain and facilitate care in advanced disease. The prognosis is poor, with a reported median survival after onset of about 7 years.

Lrontotempnr.il Degeneration **Willi 1'arkiiiMiiiism Linked** to Chromosome 17

FTD is a group of illnesses characterized by behavioral changes and neuropsychological evidence of frontal lobe dysfunction. They include Pick's disease, pallidopontonigral degeneration, disinhibition-dementia-parkinsonism-amyotropby, familial multiple system tauopathy with presenile dementia, familial subcortical gliosis, FTD, FTD with ALS, FTD with inclusion body myopathy, and FTDP-17. In up to 60% of patients with FTD, there is a positive family history. Genetic loci on chromosomes 17 (FTDP-17), 9 {FTD with ALS, and FTD with inclusion body myositis), and 3 (FTD) have been described.

There is considerable phenotypical and genotypical heterogeneity in FTDP-17. The disorder most often begins

in the fifties or sixties with personality and behavioral changes, including disinhibition and aggressiveness, and frontal executive dysfunction. Other common signs include social misconduct, stereotyped verbalizations, impaired recent memory, and parkinsonism. Some families present with early parkinsonism. Many mutations have been reported in the tau gene. They comprise mainly three groups: mutations in the coding region for a microtubule-binding domain, resulting in a dysfunctional protein; mutations outside the microtubule-binding domains; and mutations that alter the ratio of three- to four-repeat tau isoforms. Pathological findings include tau-positive neuronal and glial inclusions distributed variably throughout the brain (Lantos et al. 2002). In patients with prominent parkinsonism, there is severe neuronal loss in the SN. The response of parkinsonism to symptomatic treatment is not known. The prognosis is poor, with death occurring within 10 years.

Bilateral S tri at op a Hid o dentate Calcification (Fahr's disease)

Calcification of the basal ganglia has many causes. It is an incidental finding in up to 1% of all CT brain scans. Basal ganglia calcifications can also be seen in infectious, metabolic, and genetic disorders affecting this brain region. There are familial and sporadic forms. When symptoms occur, they usually begin in adulthood, between age 30 and 60 years. Cognitive dysfunction, cerebellar signs, dysarthria, pyramidal signs, psychiatric illness, gait disorder, and sensory impairment are common. About half of symptomatic patients have movement disorders. Among these, parkinsonism and chorea are most common. Fewer than 10% of patients have tremor, dystonia, athetosis, or orofacial dyskinesia. The presence of symptoms correlates with the amount of calcification (Manyam et al. 2001). Calcification is most often seen in the GP but may also occur in the caudate, putamen, dentate, thalamus, and cerebral white matter, as well as internal capsules. Calcium is deposited in the perivascular extracellular space. Dominant and recessive inheritance patterns have been described. No specific information is available about treatment.

Parkinsonism-Demenria Complex of Guam

A high incidence of an ALS-likc illness among the Chamorros, indigenous people of Guam, was noticed more than 50 years ago. In the same population, a smaller number of people had a syndrome of parkinsonism with dementia, the parkinsonism-dementia complex (PDC). Some people had both motor neuron disease and PDC. Early in its course, PDC appears variably, like PD, atypical parkinsonism, or PSP; however, in rhe end stages, it most resembles PSP. Familial aggregation of cases has been noted, but prior attempts to elucidate a hereditary basis to the illness proved fruitless. A similar constellation of ALS and PDC has been reported on the Kii peninsula of Japan.

Pathologically, the disorder is characterized by neuronal degeneration and abundant neurofibrillary tangles in the brain and spinal cord. A recent reanalysis of a patient registry suggests that both the spouses and the offspring of persons with PDC have a significantly higher risk of themselves developing ALS-PDC, suggesting both environmental and genetic risk factors (Plato et al. 2002). The critical age for exposure to the environmental factor was adolescence or early adulthood. Despite extensive analysis of the diet and other environmental factors, the etiology of PDC Guam remains unknown, although neurotoxic damage from the cycad nut has been implicated.

Guadeloupean Parkinsonism

Over the past .5 years, a focus of atypical parkinsonism has been described in the French West Indies. So-called *Guadeloupean parkinsonism* shows clinical features of L-dopa-unresponsive parkinsonism, postural instability with early falls, and pseudobulbar palsy. More than 25% of these patients have a phenotype like PSP (Caparros-Lefebvre et al. 2002). The etiology of this form of parkinsonism is unknown, but exposure to dietary or other environmental toxins is suspected.

Vascular Parkinsonism (Lower Half Parkinsonism)

As many as 3-6% of patients with parkinsonism have a vascular etiology, but the true frequency is unknown. Vascular changes are common, but the cause and effect arc not always clearly established. Among stroke patients, parkinsonism is more common in patients with lacunar stroke. Vascular parkinsonism usually presents as a gait disorder with prominent start and terminal hesitation, as well as freezing. Postural instability and a history of falls are common. Many patients have dementia and cortico-spinal findings of incontinence. The pathology includes subcortical vascular disease with preservation of dopaminergic cells in the SN,

The symptoms of vascular parkinsonism are unlikely to show a significant response to L-dopa, but a therapeutic trial is worth pursuing because as many as half of the patients improve somewhat. Amantadine may help some patients. Physical therapy may also be useful.

Postencephalitic Parkinsonism

Between 1916 and 1927, there was a worldwide epidemic of encephalitis lethargica, which killed about 250,000

persons and left an additional 250,000 with chronic disability. These survivors of the acute illness developed parkinsonism, usually within 10 years of the infection. PEP resembles PD, although more prominent behavioral and sleep abnormalities occur early in the disease course, extraocular movements are often abnormal, and oculogyric crises are common. Other common movement disorders include chorea, dystonia, tics, and myoclonus. Pyramidal tract signs are common. The pathological appearance of PEP includes degeneration of SN neurons with neurofibrillary tangles in surviving neurons. Although the etiology is presumed to be a virus, none has ever been identified. There have been no subsequent epidemics of encephalitis lethargica, although sporadic cases of PEP are occasionally reported. The symptoms of PEP tend to be L-dopa responsive, but behavioral complications such as hallucinations and delusions are common, limiting therapy.

Drug-Induced Parkinsonism

Dopamine receptor-blocking drugs reproduce the major clinical features of PD, although signs arc usually symmetrica! and the tremor is more often present during posture holding than at rest. The most common causes of drug-induce parkinsonism (DIP) are the typical neuroleptic antipsychotic drugs, antidopaminergic antiemetics, and drugs that deplete presynaptic nerve terminals of dopamine, such as reserpme and tetrabenazine. Among the newer or "atypical" antipsychotics, the relative propensity to cause DIP is as follows: risperidone > ziprasidone > olanzapine > quetiapine > clozapine. This ranking reflects their respective affinity for the D_2 receptor. A number of other drugs have been associated with DIP, including selective serotonin reuptake inhibitors, lithium, phenytoin, of-methyldopa, valproic acid, and the calcium-channel antagonists flunarizine and cinnarizinc, which are not marketed in the United States. DIP generally appears subacutely, after weeks to months of therapy. Although it is reversible, DIP may resolve very slowly, over a period of up to 6 months, and symptomatic treatment with anticholinergics, amantadine, or L-dopa may be required. Occasionally, parkinsonism docs not resolve, suggesting the offending drug likely has unmasked an underlying parkinsonism.

Toxin-Induced Parkinsonism

In 1982, a number of young California drug addicts developed acute and severe parkinsonism after intravenous injection of a synthetic heroin contaminated by MPTP. Subsequent study showed that the offending toxin was the metabolic product of MPTP produced by monoamine oxidase, 1-methyl-4-phenyl-propion-oxypiperidine (MPP^+). Postmortem examination in patients 10 years after the original exposure showed severe loss of SN neurons without Lewy body formation. Interestingly, despite the 10-year interval between exposure to the toxin and death, there was evidence of an active neurodegenerative process, including extracellular melanin and active neuronophagy. This suggests that intracellular mechanisms may promote neurodegeneration after a distant environmental insult (Langston et al. *1999).* MPTP-induced parkinsonism is L-dopa responsive, but the response is complicated by the early development of motor fluctuations and dyskinesias, which may become severe, and psychiatric complications such as hallucinations. Cognitive function usually remains intact.

Acute *carbon monoxide* poisoning is associated with parkinsonism, MRI scans show high-intensity white matter lesions and necrosis of the GP bilaterally. Cognitive signs including decreased short-term memory, attention, and concentration are common. Patients with neurological sequelae of carbon monoxide intoxication may experience gradual clinical and radiological improvement over months to years.

Manganese toxicity is associated with L-do pa-unresponsive symmetrical parkinsonism with dystonic features such as oculogyric crisis. The disorder may progress for years following cessation of exposure. Striatal MRI T2-weighted hyperintensity may be present during the acute phase of the poisoning. F-dopa **]'TT** -;c;uis in subjects with manganism show normal presynaptic dopamine function, suggesting postsynaptic pathology. The fungicide maneb (manganese cthylene-bis-dithiocarbamate) has also been shown to induce a toxic parkinsonism.

TREMOR

Physiological Tremor

A fine rremor of the outstretched limbs is a universal finding. Physiological tremor appears to originate in the heartbeat, mechanical properties of the limbs, firing of motoneurons, and synchronization of spindle feedback. Its frequency ranges from 7-12 Hz. It is usually not noticeable except with electrophysiological recording, but its amplitude is accentuated by fatigue, anxiety, fear, excitement, stimulant use, and medical conditions such as hyperthyroidism (Tabic 77.13).

Essential Tremor

Epidemiology and Clinical Features

ET is one of the most common movement disorders. In population-based studies, the prevalence increases steadily with age, occurring in up to 5% of patients older than 60 years. The prevalence is higher in men than in women and in whites than in nonwhites. In its purest form, FT is a

Table 77.13: Physiological classification of tremor

Mechanical oscillations
  Physiological tremor
I)sdll:lli<!l]K ll.lSL'll 1111 I <-l ILXI- ,
  Neuropil thi^ i rem or
Oscillations due to central neuronal pacemakers
  Palatal tremor
  Essential tremor
  OnluMtaiii tremor
  Parkinsonian rest tremor
  Holmes's tremor
Oscillations due to disturbances in fecd-forward-feedback loops
  Cerebellar tremor
  Holmes tremor

Table 77.14: Diagnostic criteria for essential tremor (Consensus Statement of the Movement Disorders Society on Tremor)

Inclusion criteria for the diagnosis of essential tremor
  Bilateral, largely symmetrical postural or kinetic tremor in hands/forearms that is visible and persistent
  Additional or isolated head tremor may occur, but without abnormal posturing
Exclusion criteria
  Other neurological signs, especially dystonia
  Known causes of enhanced physiological tremor
  Evidence for psychogenic origin
  Primary orthostatic tremor
  Isolated voice tremor
  Isolated posirion- or task-specific tremor
  Tsolarcd tongue or chin tremor
  Isolated leg tremor

monosymptom.!tic illness characterized by gradually increasing amplitude postural and kinetic tremor of the forearms and hands (with or without other body parts), in the absence of endogenous or exogenous triggers or other neurological signs. In clinic-based scries, as many as 50% of patients exhibiting ET do not conform to this clinical picture, suggesting substantial heterogeneity (Jankovic 2002). The clinical definition of ET is problematic, because there are no pathological, biochemical, genetic, or other established and validated diagnostic criteria.

The median age at onset is 15 years, but there is a bimodal distribution and virtually all patients are symptomatic by the age of 65 years. The typical patient becomes aware of a barely perceptible postural or action tremor, usually in the distal arms and hands. The head and lower limbs are less commonly affected. Head tremor (titubation) is milder than limb tremor and is predominantly of a sidc-to-side "no-no" type. Tremor of the face, trunk, and voice are rarely seen. The kinetic tremor is higher in amplitude than the postural tremor and is the major determinant of disability. Handwriting is particularly troublesome (Plate 77.VII). A striking improvement following ingestion of a small amount of ethanol is seen in 50% of patients and may be helpful in diagnosis. Over time, the tremor worsens, causing increasing functional disability. Only a fraction of affected persons seek medical attention and there is often a long latency from onset to presentation for care. At the time of diagnosis, nearly all patients with ET have^ significant social, functional, or occupational disability, an'd as many as 25% must make occupational adjustments as a result of tremor-related disability. ET is thought to be a monosymptomatic illness without changes in cognition, strength, coordination, or muscle tone, and the neurological examination is usually normal. However, detailed studies of patients with ET have demonstrated frontostriatal cognitive deficits, changes in tandem gait, and other, albeit subtle, evidence of cerebellar dysfunction (Stolze et al. 2001). The worsening of ET over time likely relates to two phenomena. First, the frequency of tremor in ET decreases over time, and its amplitude increases. This results from decreased attenuation of lower frequency tremor secondary to age-related changes in the mechanical properties of limbs and muscle. A second possible contributor is true progression of the underlying disorder. According to recent studies, the severity of ET relates to disease duration independent of aging and age-related changes in mechanical properties of the muscles and limbs.

The diagnosis of ET is made by history and physical examination. Diagnostic criteria for ET are listed in Table 77.14. The tremor of ET has a frequency between that of PD and physiological tremor. Although EMG recordings of tremor may demonstrate both simultaneous contraction of agonist and antagonist muscles and the typical frequency tremor, such findings are not pivotal to the diagnosis.

Etiology

As many as two thirds of patients give a positive family history of tremor, and first-degree relatives of patients with ET are 5-10 times more likely to have ET than first-degree relatives of control subjects. Direct questioning or examination of first-degree relatives increases the yield of family history to as high as *96%,* In some families, pedigree analysis suggests ET is an autosomal dominant trait, with virtually complete penetrance by the age of 50 years. Hereditary ET is genetically heterogeneous, with several described loci including FFTl (ETM1) on chromosome 3, and HTM2 on chromosome 2, and a candidate locus on chromosome 4 (Higgins et a I. 1998). Twin studies suggest both hereditary and environmental factors are important in JiM-n-r c\p: i^sion.

The mechanism of disease production in these genetic disorders remains unknown and no consistent pathological structural changes have been found in postmortem brain or nervous tissue. F7T is believed to relate to the action of a central generator (see Table 77.13). A number of lines of evidence point to cerebellar dysfunction in ET; abnormal tandem gait is one example. The tremor may resolve following ipsilateral cerebellar lesions. Motor control studies show evidence of abnormal production of ballistic

movements in a partem that suggests abnormalities in cerebellar timing. PET scans have shown evidence of bilaterally increased cerebellar activity at rest and during tremor. The demonstration of reduced N-acety I-[.-aspartate (NAA) relative to total creatine in the cerebellar cortex by-magnetic resonance spectroscopy (MRS) suggests that the cerebellar disorder may be degenerative. Patients with ET may have higher blood levels of £i-carbolinc alkaloids. These endogenous compounds, also found in plant-derived foods, increase the synchrony of neuronal firing in the inferior olive and cause tremor in experimental animals and humans.

Treatment

Patients with mild ET whose main source of disability is tremor during meals and whose tremors respond to ethanol often benefit from a cocktail before meals. The two most commonly used pharmacological treatments are ^-adrener-gic blockers and primidone. Placebo-controlled studies have shown that /S-adrcnergic blockers such as 120-320 mg of propranolol per day reduce tremor amplitude in 40-50% of patients. Common side effects of these beta-blocker drugs include bradycardia, fatigue, nausea, diarrhea, rash, impotence, and depression. Beta blockers are contra-indicated in patients with congestive heart failure, asthma, third-degree atrioventricular block, and diabetes. Primidone improves ET about 50% in short-term con-trolled trials and has been suggested to be more effective for head tremor than other agents. Because of the risk of acute side effects such as vertigo, nausea, and unsteadiness, primidone is usually started at a dose of 25 mg at bedtime and then titrated as tolerated to its effective dose range of 50-350 mg daily. It can be given as a single nighttime dose or in divided dose increments. Long-term primidone therapy is usually well tolerated. Propranolol and primi-done combination therapy may be more effective than cither agent alone. Double-blind crossover studies have suggested topiramarc, alprazolam, or gabapentin may reduce ET, but these results require confirmation (Connor 2002). Other drugs, such as clonazepam, acetazolamide, methazolamide, flunarizine (not available in the United States), nimodipinc, and theophylline have not conclusively been shown to be effective in ET. Botulinum toxin may be helpful, particularly in patients with prominent head tremor. Botulinum toxin treatment of hand tremor improves tremor amplitude, but function may not improve, presumably because of secondary hand weakness.

Stereotactic thalamotomy has been reported to suppress contralateral tremor as much as 75% in up to 90% of cases. The effect appears to be long lasting. Side effects of this procedure are relatively common, although most are transient, and bilateral thalamotomy may cause speech difficulty, so it should be avoided (Pahwa et al. 2000). Thalamic DBS has shown very good efficacy in controlling ET. Tremor improves as much as 80% contralateral to the implantation, and bilateral stimulation can be performed safely. Long-term follow-up shows that efficacy remains good for 6-7 years (Rehncrona et al. 2003). Adverse effects of the surgery and subsequent stimulation include a low incidence of intracranial hematoma, postoperative seizures, dysarthria, paresthesia, dyscquilibrium, headaches, dys-praxia, and word-finding difficulty. Problems with the stimulator use It are relatively uncommon but include lead fracture or migration, and failure of the impulse generator. Reoperation may be necessary ro correct device-related adverse effects {Pahwa et al. 2000). In a prospective randomized single-blind comparison of thalamotomy and thalamic stimulation in severe tremor, the procedures were equally efficacious, although thalamic stimulation was better tolerated (Schuutman et al. 2000). DBS should be considered for cognitively intact, otherwise healthy patients wall disabling medicatioii-resisraiii tremor.

Dystonic Tremor

Three types of tremor are associated with dystonia. Some family members of persons with hereditary dystonia may have isolated tremor *{dystonia-gene-associated tremor),* suggesting the conditions may be allelic or that tremor in these cases may be a forme fruste of dystonia. In other cases, a person with dystonia of one or more body parts may have pure tremor in other body parts, for example, cervical dystonia may be accompanied by postural hand tremor *[tremor associated with dystonia).* Lastly, tremor may he part of the dystonia, sharing body distribution and directional preponderance with the dystonic movement *{dystonic tremor).* Dystonia-gene-associated tremor and tremor associated with dystonia are treated the same way as ET, whereas dystonic tremor is treated as part of the underlying dystonia (sec latet discussion).

Primary Writing Tremor

Primary writing tremor is a rare condition characterized by a 4-7 Hz tremor in the hand during the assumption of a writing posture or during the writing task itself. Most patients are men. About one third have a positive family history of writing tremor and a similar number give a history of improvement after ethanol ingestion. Surface EMG shows isolated extensor tremor, alternating tremor in flexors and extensors, or co-contraction of flexors and extensors. Writing tremor may he difficult to distinguish clinically from ET and from task-specific or writing dystonia. Phcuomenologically, it does not show the phe-nomenon of overflow usually seen in dystonia, and electrophysiological studies suggest it is distinct from both conditions. Accelerometry suggests that the primary writing tremor reflects the normal rhythmic movement of writing, but the amplitude of the movements is enhanced.

The tremor may respond to /^-adrenergic blockade or primidone or anticholinergic medications, but botulinum toxin injections provide the most consistent relief. Thalamic DBS has also been reported effective in some cases.

Orthostatic Tremor

Orthostatic tremor is high-frequency (14-18 Hz) isometric tremor that presents with tremor in the legs during quiet standing. Patients may not be aware of the tremor, but complain of unsteadiness and sensory complaints in the legs that are relieved by leaning against a stationary object or by walking. Leaning on the arms may precipitate a similar frequency tremor in the arms, and a tremor of the closed jaw has also been reported. Orthostatic tremor may he visible or palpable and can be confirmed by the appearance on EMG of high-frequency tremor when standing. Unlike parkinsonian tremors and ETs, orthostatic tremor shows significant side-to-side coherence, suggesting a central generator, PET scans have shown increases in resting cerebellar activity similar to those seen in ET. A recent study has suggested that coherent high-frequency tremor in the legs may be a normal response to perceived unsteadiness when standing still, and that orthostatic tremor may be an exaggeration of this response (Sharott ct al. 2003), Clonazepam is thought to be the most effective pharmacological treatment, although there are reports of benefit from L-dopa and gabapentin.

Neuropathic Tremor

Tremors associated with neuropath} arc usually postural and kinetic tremors with a frequency between three and six cycles per second. Demyelinating neuropathies have a particular association with tremor. The diagnosis is made when a typical tremor affects a person with neuropathy in the absence of other tremorogenic neurological disorders. The pathophysiology of neuropathic tremor is believed to be disordered feedback control related to abnormal peripheral sensory input. Some patients develop tremor after a peripheral injury, sometimes associated with abnormal posture as well as reflex sympathetic dystrophy or complex regional pain syndrome (Jaukovie 2001). The mechanism of this peripherally induced movement disorder is not understood. Pharmacological treatment is usually disappointing, but some patients respond to beta blockers or clonazepam.

Cerebellar Tremor

The tremor typically associated with cerebellar disease is a slow tremor that is absent during rest but appears and progressively increases in amplitude with movement, particularly with fine adjustments in movement required for a precise movement. Sitting or standing unsupported may induce a tremor of the trunk and head (titubation). A variant of cerebellar tremor is known as *Holmes' tremor*, or *rubral tremor.* Rubral tremor is present during rest, posture holding, and action. At rest, it is slower and less rhythmic than parkinsonian rest tremor. Rubral tremor results from acquired structural lesions in the ipsilateral cerebellar dentate nucleus and superior cerebellar peduncle. The usual causes are multiple sclerosis, stroke, and head injury. Pharmacological treatment of Holmes* tremor is difficult, although some patients respond to i.-dopa. Thalamotomy or thalamic DBS may be useful in some cases.

Fragile X Premutation

Male carriers of the fragile X premutation have been found to have a neurodegenerative syndrome characterized by the onset after age 50 years of intention tremor, gait ataxia, and executive cognitive dysfunction (Leehcy ct al. 2003). Bilateral cerebellar hypenntensities have been reported on T2-weightcd MRI studies in some cases, No information is yet available about pathology, pathophysiology, or treatment.

Palatal Tremor

PT is the term now applied to the condition also known as *palatal myoclonus* characterized by rhythmic movements of the soft palate. Although it is rhythmic, like tremors, the movement consists of repetitive, rather than oscillatory, contractions of agonists only, so it shares similarities with segmental myoclonus (see later discussion). There are two types of PT depending on the presence or absence of a structural lesion of the brainstem or cerebellum. Patients without an underlying structural lesion are considered to have essential PT, and those with underlying structural lesions arc considered to have symptomatic PT. Essential and symptomatic PT can be distinguished by clinical features and neuroimaging (Table 77.15).

Essential PT is very rare. It affects men and women equally. Patients with essential PT complain of audible ear

Tabic 77.15: Features ot essential and symptomatic palatal tren

	Gender	*Muscle*	*Ear clicks*	*Regional tremor*	A i *K I Imttini*^
Essential palatal tremor	M = F	Tensor veli palatini	Yes	No	None
Symptomatic palatal tremor	M > F	Levator veli palatini	No	Yes	Olivary hypertrophy

clicks. The movements usually disappear during sleep. In essential FT, the palatal movements are produced by rhythmic movement of the tensor veli palatini muscle. *Symptomatic PT* is more common than essential PT and affects men more often than women. Symptomatic or secondary PT is not associated with ear clicks, because the levator veli palatini rather than the tensor veli palatini is involved. Simultaneous tremor of other regional structures with cranial nerve innervation may be seen. Some patients have oscillopsia from pendular nystagmus. Laryngeal involvement may interrupt speech or may cause rhythmic involuntary vocalizations. Rhythmic limb tremor may be seen. In patients with symptomatic PT, hypertrophy of the superior olive is demonstrable on MRI brain scans. Causative structural lesions are found in the brainstem or cerebellum within the Guillaiu-Mollaret triangle, which connects the dentate nucleus with contralateral red nucleus and inferior olive (Deuschl and Wilms 2002), Many underlying etiologies have been reported, including neurodegenerative, infectious, inflammatory, dcinye I mating, traumatic, ischemic, and other disorders. Characteristic pathological changes include enlargement of olivary neurons with vacuolation of the cytoplasm. Astrocytic proliferation with aggregates of argyrophilie fibers may also be seen.

The pathophysiology of PT is incompletely understood, but it is believed that in symptomatic PT, damage to the dentato-olivary tract induces synchronization of cells in the inferior olive. The firing rhythm appears to be determined by membrane properties of the olivary neurons. This rhythm is then propagated through the inferior cerebellar peduncle to the contralateral cerebellar hemisphere, where it interferes with oculomotor, cerebelloreticular, and cerebellospinal system*. [Vii^thl and Wiims 200.V:.

Treatment of PT is difficult. Because of the rarity of the condition, there ate no randomized controlled clinical trials of therapeutic agents. Phenytoin, carbamazcpinc, clonazepam, diazepam, trihexyphenidyl, and baclofen are considered first-line agents in the treatment of PT, Second-line drugs include 5-HTP, and presynaptic amidopaminergic drugs such as tetrabenazine. Sumatriptan has been reported to aid a single patient. Injections of hotulinum toxin into the tensor veli palatini muscle have been reported beneficial in essential PT.

CHOREA

Huntington's Disease

The first complete description of I 11) is attributed to George Huntington, in 1872. He accurately reported the salient clinical features of the disease, its pattern of transmission from parent to child, and its dismal prognosis, HD is a highly penetrant autosomal dominant disease characterized by a progressive movement disorder associated with psychiatric and cognitive decline, culminating in a terminal state of dementia and immobility.

Epidemiology and Clinical Features

Prevalence figures for HD vary depending on the geographical area, but the best estimate is 10 per 100,000. The disorder is reported in all races, although it is much more common in Scotland and Venezuela and less common in Hnland, China, Japan, and black South Africans. HD usually begins between the ages of 30 and 55 years, although it has been reported to begin as early as age 2 years and as late as age 92 years. About *5%* of cases begin in patients younger than 21 years; the juvenile phenotype differs from the adult phenotype, and patients are often misdiagnosed. HD is a progressive degenerative disease that affects movement, behavior, and cognitive function (Kirkwood et al. 2001). Common symptoms of the early, middle, and advanced stages of the illness are outlined in Table 77. Id.

When clinical illness begins, it does so gradually and it is best to define a "zone," rather than a time of onset. Patients with HD may present with motor signs (about 60%), with behavioral signs (about 15%), or with both motor and behavioral signs (about 25%). Patients themselves may be unaware or unconcerned about early cognitive and motor changes. Concerned family members often bring them to medical attention. A change in the ability to generate saccadic eye movements and their speed is often the earliest sign. A blink or head thrust may be required to initiate saccadic eye movements. The motor disorder usually begins with clumsiness and fidgetiness that evolves into chorea. The presence and severity of chorea vary markedly from subject to subject and over time. In addition to chorea, patients with HD have hradykmesia and motor impersistence, with difficulty sustaining ongoing movement. They may be unable to maintain forced eye closure, hold the mouth open, or protrude the tongue for long periods. With advancing disease, there is progression of bradykinesia and dystonic movements appear. The chorea may become

Table 77.16: Symptoms of Huntington's disease

Early	*Middle*	*Late*
Clumsiness	Unsteadiness	Weight loss
Chorea	Dropping things	Speech disorder
Irritability	Gait disorder	V.\ allow ing disorder
Sadness	Sleep disorder	Bladder incontinence
Depression	< ognim c dysfunction	Bowel incontinence
Decreased motivation	Decreased memory	
Sexual dysfunction		

Source: Adapted with permission from Kirkwood, S.C., Su, J. L., Couneally, P., &C Foroud, T. 2001, "Progression of symptoms in [he early and middle stages of Huntington disease," *Arch Neurol* vol, 58, no. 2, pp. 273-278.

somewhat less prominent or may continue to worsen. The gait disorder of HD is complex, with chorea, parkinsonism, lapses in tone of antigravity muscles, and ataxia. The walking patient with HD resembles a marionette, lurching, swaying, dipping, and bobbing. Tandem walking becomes difficult, then impossible. Ultimately, intractable falls lead to the wheelchair- or bed-bound state. Dysarthria and dysphagia progressively impair communication and nutrition, Most patients spend the last several years of their lives in nursing home settings and die of complications including pneumonia and head injury. Mean survival is 17 years, but the natural history varies and is influenced by genetic and environmental factors. Generally, patients with onset at a younger age have the largest number of CAG repeats and tend to progress more rapidly than patients with onset at an older age (see later discussion). The juvenile phenotype differs from the adult phenotype, with prominent parkinsonism and dystonia, even early in the course, and with myoclonus and seizures.

Behavioral changes contribute mightily to disability in HD. Ninety-eight percent of patients show one or more behavioral symptoms (Paulsen et al. 2001) (Table 77.17). The most common changes in early disease are irritability, anxiety, and mood disturbance, irritability may be accompanied by verbal or physical aggression. Patients with HD often have a low threshold for anger and react to minimal provocation with an explosive response. Depressed mood is very common and 30% of patients meet criteria for major depressive disorder. Mania and hypomania are seen less commonly than depression. The risk of suicide is increased as much as sixfold over the general population. Unmarried and childless persons living alone, those who are depressed, and those with a family history of suicide are particularly at risk. Fear of the disease leads to an increased risk of suicide, even in first-degree relatives of affected individuals who are at autopsy found not to have inherited the mutant gene. Psychosis is rare and it may be difficult to treat. Obsessive-compulsive disorder has been reported but can be difficult to differentiate from frontal lobe personality with perseveration. Apathy increases in concert with disease severity and is a nearly universal feature of advanced disease. Behavioral and psychiatric disorders may predate the onset of overt HD by as long as a decade, reflecting early pathological changes in the nonmotor areas of the striatum. Because some behavioral signs may be episodic and respond to pharmacotherapy, their severity does not progress in a linear fashion with cognitive and motor cl!;in;:cs. Ik'h.u ior.il signs seem to ntiprow :n ilu KTIIUM.II stages of the illness, but ascertainment may be hindered by the severe physical disability of such patients.

Table 77.17: Behavioral symptoms in Huntington's disease

Symptom	%
Dysphoria	*69*
Agitation	*61*
Irritability	*65*
Ap:llh\	*56*
Anxiety	**52**
Disinhibicion	**35**
Euphoria	31
Delusions	**12**
Hallucinations	2

Source: Adapted with permission trtmi Paulsen, J. S., Ready, R. E., Hamilton, J. M., et al. 2001. "Neuropsychiatry aspects of Huiiiin^mn's diseasu," / *Xrtirnl Nctirositrg Fsychialry* vol, 71, no. 3, pp. 310-314.

Cognitive changes are universal in HD. The dementia of HD tits the description of subcortical dementia with disordered attention, concentration, motivation, insight, judgment, and problem solving rather than traditional cortical signs such as aphasia and apraxia. Executive dysfunction renders affected persons unable to work, drive, and manage family finances relatively early in the disease course, but prominent global dementia occurs later.

The diagnosis of HD in a patient with a typical clinical picture and a confirmed family history is straightforward. Unfortunately, the family history may be vague or it may be negative because of competitive mortality, misdiagnosis, denial, inaccurate parental information, or obfuscation. In addition, there is a small but definite new mutation rate as expansion occurs with transmission of a premutation. Although there is a broad differential diagnosis of chorea, there are few alternative causes of the fully developed syndrome. When the clinical suspicion of HD is high, the most cost-effective diagnostic procedure is genetic testing. Neuroimaging studies can show generalized or preferential striatal atrophy, but these findings are not specific for the disorder. Although volumetric analysis of the striatum shows declining volume even in presymptomatic gene carriers, many obviously symptomatic patients do not have clinically apparent striatal atrophy. Somatosensory evoked potentials are abnormal in 94% of patients with HD and abnormalities correlate with clinical signs of the illness. However, the use of these and other electrophysiological studies for diagnosis or measuring illness progression remains unproven. The direct DNA test for the CAG repeat expansion in the huntingtin gene is highly sensitive and specific.

The availability of the HD genetic test makes possible the identification of mutant gene carriers long before they become symptomatic. However, because of concerns about the potential for occupational, insurance, and social discrimination and the lack of neuroprotective treatment interventions, only 3-5% of eligible at-risk subjects pursue testing. Those who pursue testing do so either to help with reproductive choices or because their uncertainty about the future is unbearable. Women are more likely to request presymptomatic resting than men at equal risk. Although prenatal testing is also available, relatively few prenatal

tests have been performed. Interested researchers, working in concert with lay organizations, have outlined principles that guide clinicians in the preparation of potential gene carriers for predictive genetic testing. These guidelines discourage genetic testing in asymptomatic minors and recommend genetic and psychological counseling before and after testing. One obvious concern is the risk that once given a positive genetic test result, the patient may have a major depression or other psycho pathology or may attempt suicide. When carefully managed, presymptomatic test programs are safe. In studies of life events after gene-carrier detection, less than 1% of patients have a potentially severe adverse outcome such as attempted or completed suicide or hospitalization for psychiatric illness (Almqvist et al. 1999). Adverse outcomes may be seen in patients whose predictive test suggests they are not gene carriers, the "survivor guilt" phenomenon. Depressive symptoms in such patients tends to become apparent several months after the testing process is completed, A premorbid history of depression increases the risk of an adverse outcome of testing, irrespective of test result, confirming the need for careful screening and counseling in genetic testing programs.

Pathology

The pathology of HL) includes prominent neuronal loss and gliosis in the caudate nucleus and putamen along with regional and more diffuse atrophy (Plate 77.VIII). At autopsy, only 20% of the loss of total brain weight is explained by the striatal atrophy, suggesting a very widespread degenerative process. Large cortical neurons in layer VI are also involved, as are neurons in the thalamus, SNr, superior olive, lateral tuberal nucleus of the hypothalamus, and deep cerebellar nuclei. Within the striatum, GABAergic medium spiny neurons bear the brunt of the degenerative process. Early, there is preferential loss of GABAergic neurons that co-localize enkephalin, dynorphin, and substance P. These neurons are thought to predominate in the indirect pathway, accounting for difficulties suppressing adventitious movement early in the disease course. With disease progression, all GABAergic medium spiny neurons are affected, including those in the direct pathway, explaining the emergence of parkinsonism in later disease. Juvenile-onset disease, more severe from the beginning, resembles late-stage HD with degeneration of GABAergic neurons in both pathways.

Etiology

HD is a dominantly inherited condition caused by an unstable expanded GAG trinucleotide repeat in exon 1 of the huntingtin gene on the tip of the short arm of chromosome 4. Normal alleles have fewer than 30 GAG repeats in this region. Alleles with 30-35 repeats do not cause clinical disease but may become unstable, particularly when transmitted by a man. Alleles with 36-39 repeats may cause disease, but the penetrance is reduced. Everyone with 40 or more CAG repeats in the huntingtin gene will develop the clinical illness unless there is early mortality due to another cause. Because of the inherent instability of the huntingtin gene, there may be expansion of the mutation with an increase *u:* repeat number during inrergenerational transmission. Because repeat instability of this mutation is much more common in spermatogenesis than in oogenesis, the offspring of men may have substantially greater CAG repeat lengths than their fathers. This feature accounts for the phenomenon of anticipation in HD. In large studies, there is an inverse correlation between the CAG repeat **length** and **the** age at disease onset. The extreme manifestation of this relationship is the association of juvenile-onset illness with repeat lengths of 60 or greater and onset within the ri:-,r decide with repeat k-iiiuhs o: 80 or greater. About 5% of patients present before the age of 21 years; in nearly all cases of juvenile-onset disease, the mutant allele is inherited from the father. Likewise, very late disease presentations often are associated with repeat lengths between 36 and 41. The correlation between repeat length and age at onset is driven by a very tight relationship of these two factors at the two ends of the mutation spectrum. Indeed, although one can construct tables of median age at onset versus CAG repeat length (Table 77.18), the repeat length accounts for only abour 70% of the variance in age at disease onset, suggesting that other genetic or environmental factors ate important. For this reason, the CAG repeat length is not a particularly useful tool for making predictions about disease onset and severity in individual patients.

HD is a true dominant condition. Homozygotes do not have an earlier onset or more severe form of the illness, suggesting the disorder results from a toxic effect of the mutant protein, a so-called "gain of function." The huntingtin gene controls the synthesis of huntingtin,

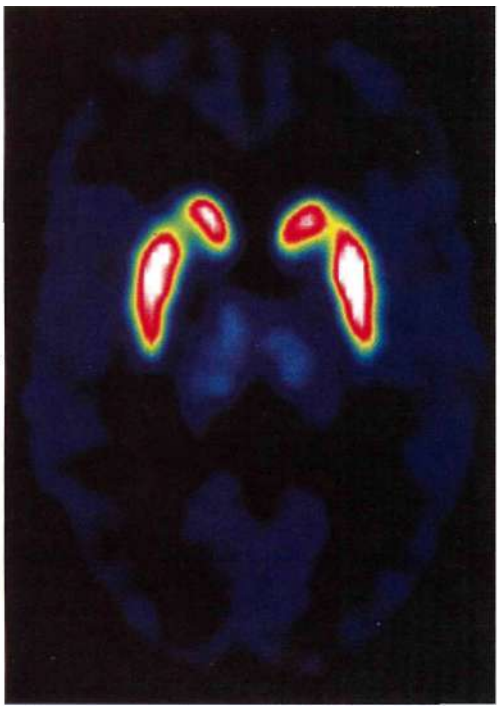
Table 77.18: CAG-repeat length and age at onset of Huntington's disease

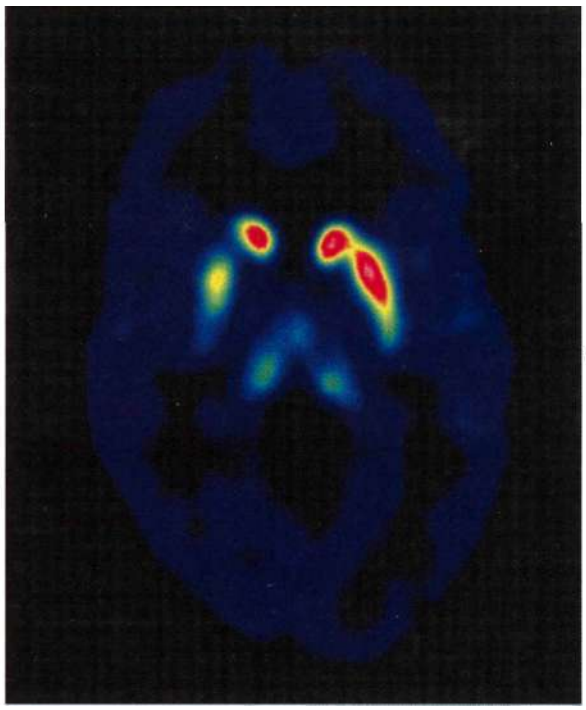
CAG *ffl*	*Median onset (95% confidence interval)*
V)	*66 (72-59)*
·in	*59* (61-56)
41	54 (56-52)
\2	49 (50-48)
43	44 (45^2)
44	42 (43-40)
45	37 (39-36)
46	36 (37-35)
I"	33 (35-31)
IS	32 (34-30)
49	28 (32-25)
50	27 (30-24)

Source: Data used with permission from Rubinsztein, R., et al. *Am J Hum Genet* vol. 59, pp. 16-22.

Early Parkinson's disease
Dopamine Transporter PET Studies
[C-ll]RTI-32

A

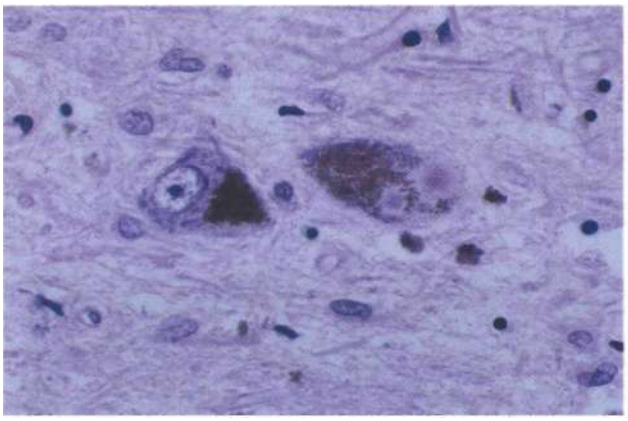


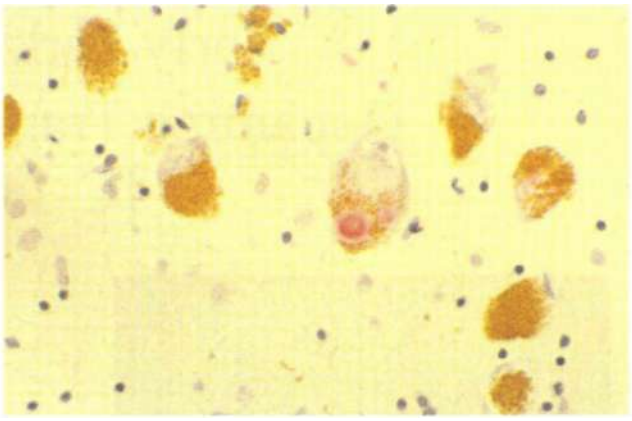


B

Control Parkinson's Disease

PLATE 77.1 Positron emission tomography scan with [' 'CJ-RTI-32, which labels the presynaptic dopamine transporter in a normal control (A) and a subject with early Parkinson's disease (B). There is asymmetrically reduced uptake in the Parkinson's disease, indicating asymmetrical loss of presynaptic dopaminergic neurons. (Courtesy Mark Guttman, M.D.)





B

PLATE 77.11 Brainstem Lewy bodies. (A) Hematoxylin and eosin-stained section of substantia nigra with a pigmented neuron containing two Lewy bodies. Each is an eosinophilic cytoplasmic inclusion with a halo, displacing neuromelanin. (B) Alpha-synuclein-immunostaincd Lewy body in a neuron of the substantia nigra. The alpha-synuclein protein is stained red in this preparation. (Courtesy Elizabeth Cochran, M.D.)

PLATE 77.111 Still images from videotapes taken 5 years apart in a woman with symmetrical parkinsonism and poor response to L-dopa. The images Illustrate the development of antecollis, suggestive of the diagnosis of parkinsonian multiple system atrophy.

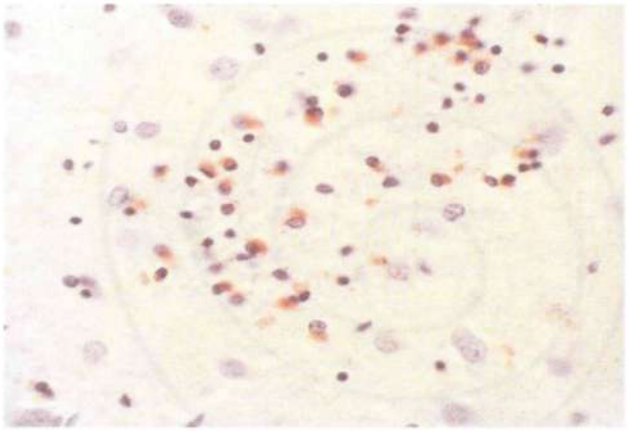


PLATE 77.IV Glial cytoplasmic inclusion, immunostained with alpha-synuelcin, in the basal ganglia, typical of multiple system atrophy. Pathological section obtained from the brain of the patient illustrated in Plate 77.111. (Courtesy Elizabeth Cochran, M.D.)

PLATE 77.V Typical facial expression of a patient with progressive supranuclear palsy, illustrating worried or surprised appearance, with furrowed brow and fixed expression of lower face.

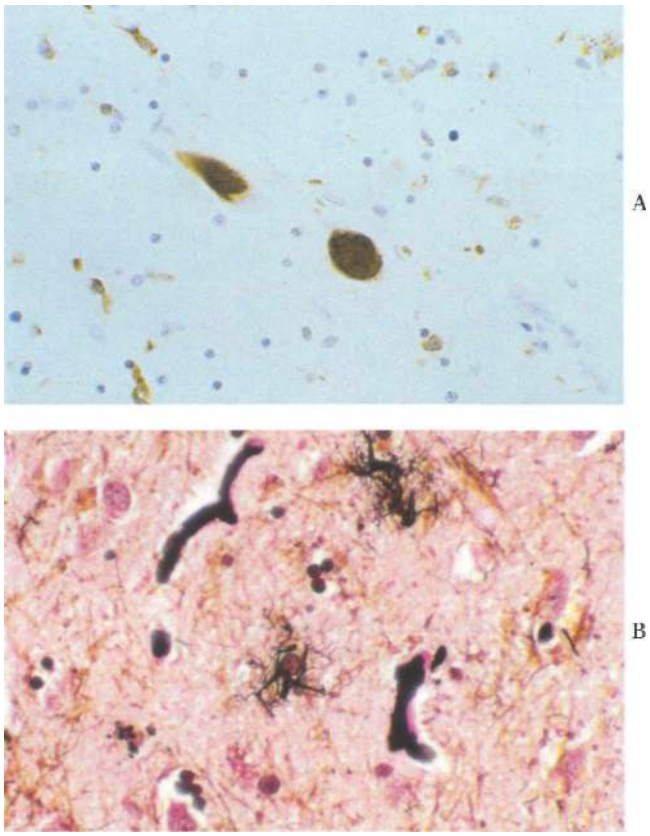


PLATE 77.VI Globose neurofibrillary tangle and tufted astrocytes in progressive supranuclear palsy. (A) Tau-immunostained globose neurofibrillary tangles in neurons of the globus pallidus. (B) Gallyas silver-stained tufted astrocytes in the globus pallidus of a patient with progressive supranuclear paisy.

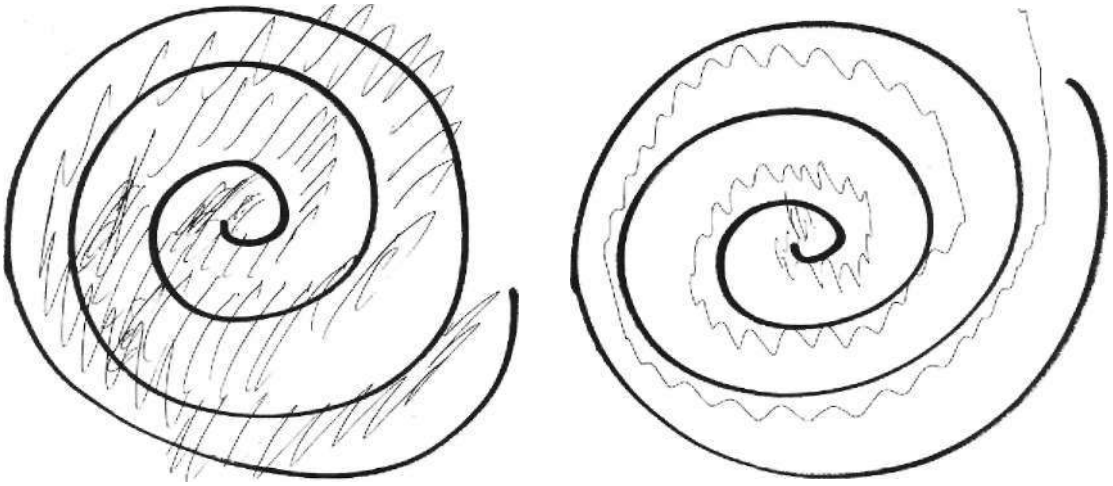


PLATE 77.VII Writing sample from a man with asymmetrical postural and action tremor of essential tremor.

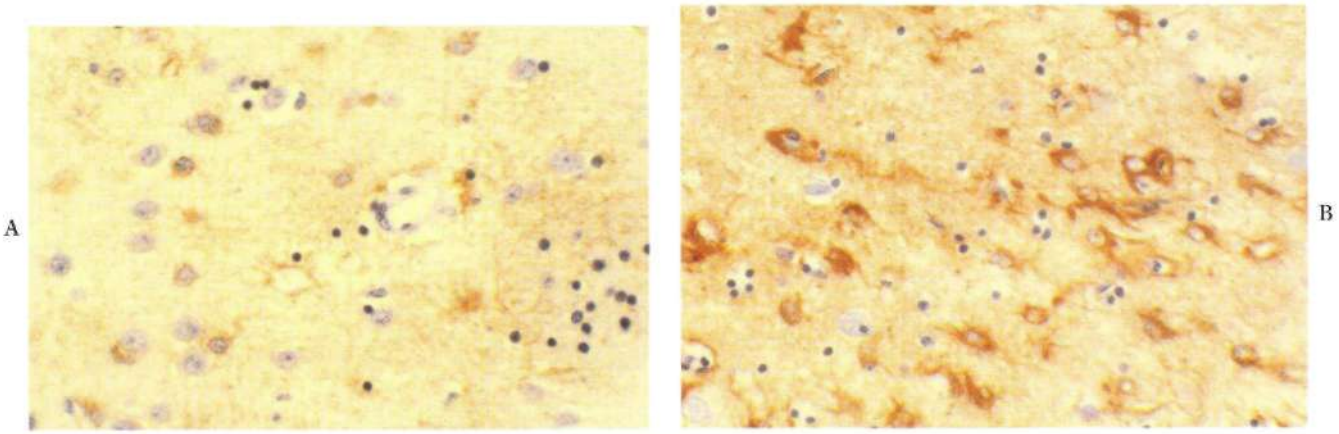
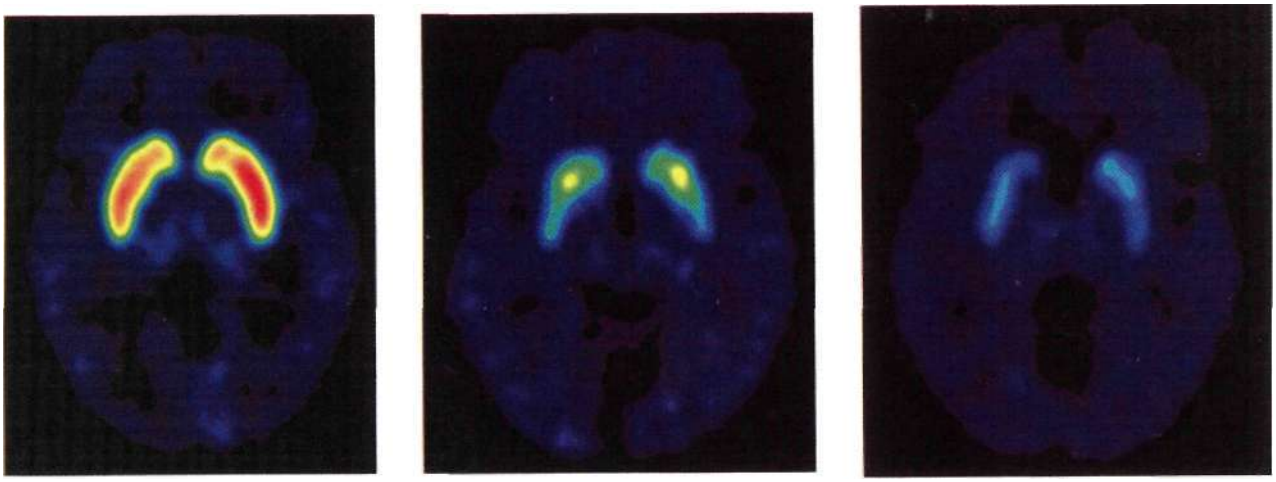


PLATE 77.VIII Pathology of Huntington's disease. (A) Glial fibrillary acidic protein immunostain of the caudate nucleus of a normal brain. (B) Glial fibrillary acidic protein immunostain of the caudate nucleus of a patient with Huntmgton's chorea. Note the decreased neuronal density and marked reactive astrocytosis, in comparison to the normal brain. (Courtesy Elizabeth Cochran, M.D.)

Huntington's Disease
Dopamine D-2 Receptor PET Studies
[C-ll]Raclopride



Control | Asymptomatic gene carrier | Symptomatic

PLATE 77.IX ["CJ-Raclopride positron emission tomography scans of a normal control subject, an asymptomatic carrier of the Huntington's disease gene, and a person with symptomatic Huntington's disease, showing progressive loss of D_2-receptor-bearing striatal neurons.

a widely expressed protein of uncertain function. Huntingtin is a cytoplasmic protein, hut ubiquinated, mutant, proteolytic N-terminal huntingtin fragments form protein aggregates in the cytoplasm and nucleus of neurons. Mutant huntingtin causes misfolded protein stress. Huntingtin interacts with huntingtin-associated protein, a protein selectively exptesscd in the striatum, and glyceraldehyde-3-phosphate, an enzyme essential for glycolysis, and other proteins (huntingtin-interacting proteins 1 and 2), A number of lines of evidence point to impaired mitochondrial function in HD, including abnormalities in complex I, II, III, and IV in caudate nuclei of affected brains. PET studies show reductions in striatal glucose metabolism and loss of dopamine Dj-receptor-bearing neurons in the striatum (Plate 77.IX) and MRS studies have suggested increased brain lactate levels. Systemic administration of the mitochondrial toxin 3-nitroproprionic acid models the disease in animals. Intrastnatal administration of the excitotoxins kainate and qurnolinic acid also reproduce the striatal lesions of HD. One theory that tics these animal models together is that of indirect excitotoxicity. Mitochondrial energy failure increases the vulnerability of the cell to excitotoxic injury because the resulting change in cell membrane potcnii.il result in '.oss ol thr magnesium ion ftom the KMDA-receptor-associated ion channel, allowing ligand-associated depolarization of the post-synaptic receptor and excitotoxic-mediated damage. Huntingtin may also interfere with the function of |n>-a-,vjiap:it density proum-95, a scaffolding protein associated with NMDA and kainate receptors, rendering these gluramate receptors hypersensitive. Mutant huntingtin also interferes with gene transcription, leading to an alteration in cell phenotypc and disrupting many cell functions. Mutant huntingtin may block the normal function of huntingtin to upregulate brain-derived neurotrophic factor. Mutant huntingtin likely also triggers apoptotic cell death (Evert et al. 2000).

Treatment

As in all other neurodegenerative disorders, no treatment is yet proven to favorably influence disease progression. [.ike other neurodegencrations, many potential types of interventions might prove useful, such as blocking transcription of the mutant gene, enhancing chaperonc function, interfering with association and aggregation of the protein, improving cell biocnergctics and mitochondrial integrity, and interfering with the triggers of and the ultimate steps in the process of apoptosis. Clinical trials of antioxidants designed to slow down the progression of the disease have been disappointing. One large-scale study assessed the potential neuroprotective effects of the mitochondrial complex I booster coenzyme Q_{10} (600 mg per day) or the antiexcitotoxic agent remacemide (600 mg per day) on the decline of the total functional capacity score over 30 months. The study demonstrated a trend toward slowing the decline in this measure of disability in the coenzyme Q]o treatment arm, but this did not achieve statistical significance. Remacemide showed no evidence of neuroprotection. A number of other potential strategies have shown promise in transgenic disease models, although they have not been studied in human safer)' and efficacy trials. These include the caspase inhibitor minocycline, creatine, lithium, ethyl eicosapentaenoic acid, cystaminc, bile acids, inhibitors of transglutaminase, and others. Like other neurodegenerative disease, there is no gold standard for determining disease severity or its rate of change over time. Studies relying on clinical rating scales must be quite large. For example, if one were to design a study of a neuroprotective agent that would slow HD progression 20%, it would require 940 subjects per treatment arm and a 30-month study duration to achieve 80% power to detect the protective effect (Marder et al. 2000). Because the number of potential subjects is relatively small (35,000), prioritizing agents for clinical testing are important,

One intriguing discovery in HD is that in ttansgenic models, turning off the huntingtin gene not only stops progression of the experimental illness but also teverses pathological findings, including aggregates, and is associated with clinical improvement (Yamamoto et al. 2000). Apparently, continued production of the mutant protein is required for maintenance of cell dysfunction and ultimately for cell death. This argues for a period of cellular dysfunction before death and raises the possibility that neuroprotection might have the potential to at least partially reverse extant clinical features of the disease.

Appropriate symptomatic treatment of HD begins with an assessment of the nature of the patient's complaint. Patients with chorea are often unaware of or untroubled by their involuntaty movements. Although typical neuroleptics represent the conventional approach to chorea, they have been shown not to improve function in HD and arc not used as much as in the past. Preliminary study suggests the glutamate antagonist amantadine may improve chorea in HD and is well tolerated in doses up to 400 mg (Verhagen Metman et al. 2002). Antidopaminergic drugs, particularly tetrabenazine, have been found effective in reducing chorea in patients with HD (Ondo et al. 2002). Tetrabenazine is available in many European countries and Canada and is currently studied in multiple centers in the United States. Atypical antipsychotics such as olanzapine may also be useful and may be preferable to typical neuroleptics because of lower risk of tardive dyskinesia (TD) with long-term use. Some patients * with prominent bradykinesia improve on dopaminergic therapy. Although psychiatric symptoms are ubiquitous in HD, there is little literature on the classification and appropriate treatment of these symptoms. Selective serotonin reuptake antagonis seem to improve irritability. aggression, depression, and obsessive-compulsive symptoms.

Irritability may respond to carbamazepine or valproic acid. Olanzapine has been reported to be useful in patients with irritability and aggression.

Dentatorubral-Pallidoluysian Atrophy (Haw River Syndrome)

DRPLA is an inherited neurodegenerative disease that appears to be rare outside Japan. Typical symptoms of DRPLA include chorea, ataxia, myoclonic epilepsy, dystonia, parkinsonism, psychosis, and dementia. Onset is usually in the twenties with death about 20 years later. Anticipation occurs with paternal transmission of the gene. The pathology of DRPLA includes degeneration of the dentate and red nuclei, the GP, and the STN. Ncurodegeneration may also be found in the cerebral white matter, putamen, medulla oblongata, and spinal cord (Oyanagi 2000). Neuronal nuclear inclusions stain for uliKjuitin and atrophin-1. There is also evidence for aberrant phosphorylation of the DRPLA protein complex and the nuclear membrane (Yazawa 2000). DRPLA is associated with an expansion of CAG trinucleotide repeat, in a gene on chromosome 12. In this region of the genome, the normal trinucleotide repeat length is 7-23. In DRPLA, the CAG repeat length is between 49 and 75. Because of the polyglutamine stretch in the mutant protein, neurodegeneration likely relates to interactions between the protein, other cellular components, and cellular proteins. The *Haw River syndrome,* described in a multigenerational African American family, is caused by the same repeat expansion as DRPLA. Clinical differences include lack of myoclonic epilepsy and the presence of subcortical white matter demy el i nation, basal ganglia calcifications, and neuroaxonal dystrophy. No information is available about the treatment of DRPLA, but as in HD, the clinician should be guided by the nature and severity of symptoms.

Neuroacanthocytosis and the McLcod Syndrome

The term *acantbocyte* is derived from the Greek word for "thorn." Acamhocytes arc contracted erythrocytes with unevenly distributed thorny projections, often with terminal bulbs. Acamhocytes are seen in peripheral blood smears in patients with three neurological syndromes: *abetalipoproteinemia neuroacanthocytosis* and the *McLeod syndrome* (Rampoldi ct al, 2002). A broad spectrum of movement disorders is seen in neuroacanthocytosis and the McLeod syndrome.

Epidemiology and Clinical Features

All forms ⋈ iicuroacanthocyrosis are rare disorders. Autosomal recessive *neuroacanthocytosis* is characterized by onset at around age .35 years of a progressive syndrome that includes a movement disorder and behavioral and cognitive changes. The movement disorder predominantly consists of chorea, dystonia, and tics; parkinsonism may occur in more advanced stages. There is also prominent orofacial dystonia with dystonic tongue protrusion interfering with eating. In addition, many patients exhibit lip and tongue biting and prominent dysarthria and dysphagia. Behavioral changes resemble those seen in HD with anxiety, depression, obsessive-compulsive disorder, and emotional lability. Subcortical dementia is a late feature. Seizures develop in about 50% of patients. There may he myopathy or axonal neuropathy, and the creatine kinase level is elevated. In patients with neuroacanthocytosis, acamhocytes usually make up 5-20% of peripheral blood erythrocytes. Autopsy changes include atrophy of the caudate, putamen, GP, and SN with marked neuronal loss and gliosis. The cerebral cortex is relatively spared. Mutations in the *CHAC* gene on chromosome 9 that lead to the production of a truncated protein, chorein, of unknown function have been found in this syndrome. Homologous proteins in animals seem important in intracellular trafficking.

McLeod's syndrome is an X-linked recessive disorder linked to a number of mutations in the *XK* gene, a gene for the Kell group of erythrocyte membrane glycoprotein antigens on the X chromosome. McLeod's syndrome usually begins around 50 years of age and has a slowly progressive course. The most common clinical feature is an axonal peripheral neuropathy. Some patients have evidence of myopathy as well, and all have elevations in serum creatine kinase level. The central nervous system illness is characterized by limb chorea. Oral movements and lip and tongue biting are less common than in neuroacanthocytosis. Facial tics are common, and some patients have dystonia. Seizures may be seen. Subcortical dementia and behavioral changes occur later in the disease course in about 50% of patients. Cardiomyopathy and hemolytic anemia are other common manifestations. Neuroimaging studies may show caudate atrophy with secondarily enlarged lateral ventricles. Increased T2-weighted signals in the lateral putamen may be seen on MRI scans. Pathological changes include intense caudate atrophy, loss of small cells, and gliosis in the dorsolateral putamen with less severe changes in the GP. Milder changes may be present in the thalamus, SN, and anterior horns of rhe spinal cord. Neurons in the cerebral cortex, STN, and cerebellum are spared. The reported mutations in the *XK* gene result in absence or truncation of the protein product. Kell is an endothelin processing enzyme. Endothelins arc important in proliferation and development of neural crest-derived cells and arc thought to be important in neurotransmitter release in dopaminergic neurons. No information is available about treatment of neuroacanthocytosis, but the physician should be guided by the clinical manifestations.

Benign Hereditary Chorea

Benign hereditary chorea (BHC) has been defined as a nonprogressive syndrome of inherited childhood-onset chorea wirh a good outcome in the absence of an underlying degenerative disease. Chorea is presenr from early childhood, usually from the first decade of life. It is nonprogressive and often associated with mild cognitive impairment (Brccdvcld et al. 2002). Some patients have dysarthria and dystonia. In many cases, the chorea improves during adolescence and young adulthood. The diagnostic rubric has been applied somewhat sloppily. Review of cases in the literature suggests that many cases so classified are more consistent with alternative diagnoses such as HD, myoclonic or other dystonias, ataxia-telangiectasia, or myoclonus. BHC is genetically heterogenous, but some families have a mutation in a region on chromosome 14 that harbors the 7777-'J gene, a transcription factor essential for lung, thyroid, and basal ganglia organogenesis (Breedveld et al. 2002). Symptomatic therapy of chorea with dopa mine-receptor blockers or dopainme-depleting drugs may be necessary.

Sydenham's Chorea

Sydenham's chorea (SC) is one of the major manifestations of rheumatic fever, but it typically appears months after the index infection. Because of the widespread availability of antistreptococcal therapy, SC is extremely rare in developed conn tries. It is a disorder of children, mainly girls, between the ages of 5 and 75 years, with a mean age at onset of 8.4 years. The chorea begins insidiously but progresses over a period of weeks, and it generally resolves within about 6 months. Choreic movements arc usually generalized, but hemichorea may also be seen. Behavioral accompaniments such as restlessness, irritability, and obsessive-compulsive traits are common. It is a self-limited disorder, usually lasting up to *6* months. About 20% of cases recur and multiple recurrences occur rarely. Knlargemeni oi the basal ganglia may hi- seen on MRI brain scan. Pathologically, SC is characterized by inflammation of the cortex and basal ganglia. Ann -basal ganglia antibodies can be detected by enzyme-linked immunosorbent assay and Western immu nob lotting and have a high sensitivity and specificity (Church et al. 2002). The mechanism of basal ganglia damage is likely molecular mimicry with cross-reaction between antibodies directed againsr streptococcal antigens and striatal antigens. Because it is often self-limited, the decision to treat SC depends on the magnitude of each patient's disability. A recent comparative trial suggested that valproic acid is the most effective treatment, followed by carbamazepinc and haloperidol. Because SC tends to be self-limited, periodic attempts should he made to wean therapy. Later in life, people who have survived SC may have a recrudescence of chorea in the presence of hormonal stress such as during pregnancy or estrogen treatment.

Ballismus (Hemiballismus, Hemichorea)

Ballismus is a dramatic proximal, ballistic, flinging movement. Ballism most commonly affects the limbs on one side of the body (HB), but involvement in both legs (paraballismus) and both sides of the body (biballismus) has been reported. Ballism is usually classified with the choreas for a number of reasons: Ballistic and choreic movements typically coexist, over time ballistic movements arc often replaced by choreic ones, and animal models employing subthalamic lesions result in a mixture of choreic and ballistic movements. HB is relatively rare, but its true prevalence in an at-risk population, such as patients with acute strokes, is unknown. The mean age at onset is 48-75 years. The tempo of development of the movements varies with its underlying etiology. HB related to stroke appears suddenly or emerges more slowly in a recovering plegic limb. HB related to inflammation or tumor arises gradually. HB usually results from a relatively small lesion in the contralateral STN or in its afferent or efferent connections. Rarely, lesions in other locations, including even ipsilateral cerebral cortex and striatum have been linked to HB. Although the underlying lesion is usually cerebrovascular disease in the elderly and infectious or inflammatory disease in younger patients, any type of structural lesion, appropriately placed, can produce the characteristic movement. Metabolic disorders such as nonketotic hyperglycemia and drug exposure may also cause HB (Table 77.19). Loss of subthalamic excitation of the GPi results in a loss of inhibitory drive to the thalamus, thus excessive motor activity. Low firing frequency of the STN has been confirmed in a few cases using intraoperative recording.

In the past, HB was thought to have a uniformly grave prognosis, with death resulting from exhaustion or cardiovascular collapse. In parr, this is related to a literature that was heavily based on clinicopatbological material. Better symptomatic and supportive care doubtless has improved survival and quality of life for patients with HB. More recent literature suggests that survival closely relates to the mortality of the underlying etiology, for example, survival rates following vascular HB mirror those of vascular disease, with only 32% survival and 27% stroke-free survival 150 months following the onset of the movciiK-111 disnrdi-v iRisfic ct al. 2i'^2;. The movements often regress or become more choreic over several months. However, they can be quite exhausting or disabling when present, and treatment is usually indicated acutely and in patients whose movements do not resolve spontaneously. Drugs with antidopaminergic properties arc expected to reduce this excessive thalamocortical drive, and thus benefit patients with HB. Although the rarity of the condition has

Tahle 77.19: Etiology of hemiballismus

- Structural lesions
  - Cerebrovascular disease
    - Infarction
    - Transient ischemic attack
    - Hemorrhage
    - Arteriovenous malformation
    - Subarachnoid hemorrhage
    - Subclavian steal syndrome
  - Infection
    - Syphilis
    - Tuberculoma
    - Toxoplasmosis
    - Acquired immunodeficiency syndrome
    - Influenza A
  - Tumor
    - Pituitary microadenoma
    - Metastasis
  - Immune mediated
    - Systemic lupus erythematosus
    - Sydenham's chorea
    - Behcet's disease
    - Scleroderma
  - Other
    - Static encephalopathy
    - Head injury
    - Demyelinating disease
    - Thalamotomy
    - Heredodegenerative disease
- Metabolic
  - Nonketotic hyperosmolar hyperglycemia
- Drug induced
  - Phenytoin and other anticonvulsants
  - Oral contraceptives
  - Neuroleptics (tardive)

precluded controlled clinical trials, there is ample evidence from case series and reports that dopamine antagonists and dopamine depletcrs effectively decrease choreic movements. Beneficial results have also been obtained using gabapentin and valproic acid. Periodic efforts should be made to taper or discontinue these therapies when possible. Stereotactic thalamotomy or pallidotomy may be considered in patients who prove refractory to medications (Suarez et al. 1997).

Senile Chorea

Senile chorea is an idiopathic disorder characterized by the development in old age of continuous mouthing, chewing, or tongue movements. Prevalence estimates vary, but as many as one third of some populations may be affected. The diagnosis of senile chorea should be made with caution, because extensive investigation often reveals an alternative diagnosis, For example, among 12 senile patients with chorea, 11 were found to have HD, antiphospholipid antibody syndrome, hypocalcemia, TD, or Fahr's disease. Pharmacological therapy should be considered for patients with disabling movements. Antidopaminergic drugs are the most effective, but their use should be accompanied by close surveillance for the development **of TD.**

TARDIVE DYSKINESIA

TD is a movement disorder that develops in the context of chronic dopamine-receptor blockade, usually in patients who arc chronically treated with neuroleptic drugs or antiemetics. The prevalence of TD is as high as 20% of patients treated with typical neuroleptics. TD usually requires a minimum of 6 weeks or more of dopamine-receptor blockade, but onset as soon as after the first dose has been reported. Reported risk factors include age, female gender, affective disorder, and edentulousness. Although the stereotypical form of TD is most common, other movement disorders, such as chorea, akathisia, dystonia, tics, and myoclonus, may be seen as part of TD. Tardive parkinsonism has also been reported, but some of the patients with parkinsonism persisting years following withdrawal of the offending neuroleptic have been found to have pathological evidence of PD. The classic appearance of TD is repetitive, stereotypical (e.g., chewing) movements of the mouth, tongue, and lower face {oral-buccolingtial dyskinesias). In contrast to HD, the upper face tends to be spared (sec Chapter 24). Choreic movements may also affect the trunk and pelvis, causing respiratory dyskinesia and pelvic thrusting. Limb chorea and restlessness (akathisia) may also be seen.

The pathophysiology of TD is incompletely understood. Denetvation supersensitivity of the dopamine receptor is the most likely cause. PET studies document upregulation of D_2 receptors in neuroleptic-treated patients (Silvestri et al. 2000). There are other theories including oxidative stress and insufficiency of GABA. Genetic susceptibility factors that might be involved in increased risk of TD include polymorphisms of the dopamine D_3 receptor gene and the 5-HTc serotonin receptor gene (Scgman et al. 2000).

The most important intervention in TD is to prevent its occurrence. For example, in prospective studies, high-risk subjects treated with atypical rather than typical antipsychotics appear to have a reduced risk of TD compared with historical controls. Because patients may not complain about early or mild movements, the clinician must carefully examine neurolep tic-treated patients for early signs of TD, Neuroleptics should be discontinued, if possible, or an atypical antipsychotic drug should be substituted. Some studies suggest tocopherol might improve TD symptoms. Mild TD may improve with benzodiazepines or baclofen, Catecholamine-depleting drugs, particularly tetrabenazine, are often very useful in the treatment of severe TD (Jankovic and Beach *1997).*

DYSTONIA

Childhood-Onset Generalized Primary Dystonia

Epidemiology and Clinical Features

Most cases of primary generalized dystonia are inherited and begin in childhood (Nemeth 2002). Generalized dystonia is quite rare, with an estimated prevalence of about 1.4 per 100,000. The most common form of childhood-onset primary generalized dystonia, also referred to as DYT7 or *Oppenbeirri's dystonia* and previously called *dystonia musculorum deformans* is an autosomal dominant disorder with relatively low penetrance. Particularly common in persons of Ashkcnn/i Jewish descent, the reported prevalence of DYT1 dystonia is as high as 20-30 per 100,000. Half of patients are affected by age 9 years and onset in patients older than 40 years is extremely rare. The earliest symptom is usually an action-induced dystonia in the leg or arm. Onset in the cervical, facial, laryngeal, or pharyngeal region is rare. In about 70% of patients, dystonic movements spread to the trunk and other limbs, and the condition generalizes over about 5 years. Patients with earlier onset and onset in the leg are more likely to develop generalized dystonia than those presenting later or with arm dystonia. Generalized dystonia produces severe disability, and most patients with this severe form of the illness are nonambulatory. Even in generalized disease, however, laryngeal and pharyngeal dystonia remains rare. The diagnosis of childhood-onset primary generalized dystonia is made clinically in a patient with onset after the age of 26 years of limb dystonia, with subsequent spread, the absence of other movement disorders with the exception of tremor, normal intellect and neurological examination, and absence of a pronounced response to L-dopa.

A number of other childhood-onset generalized dystonias have been described, but none accounts for large numbers of cases. *DYT2* has been assigned to recessively inherited limb-onset dystonia in gypsies. However, there have been no families in whom recessive inheritance can be eon tinned, so the existence of this syndrome is tentative. The designation *DYT4* applies to an Australian family with dominantly inherited laryngeal and cervical dystonia that often generalizes over time. The disorder begins between adolescence and 40 years. Its genetic locus is unknown. DYT6" is a dystonia seen in Mennonite families that localizes to the chromosome 8. This autosomal dominant dystonia begins during the late second decade of life with a DYTI-like phenotype or with cranioccrvical or focal dystonia. *DYT13* mapped to chromosome 1 presents as cranioeervical or arm dystonia with some tendency to generalize.

Routine laboratories and neuroimaging studies do not contribute to the diagnosis. Simultaneous recording of EMG activity from antagonist muscles often reveals simultaneous contraction of antagonistic muscles and spread or overflow of activity to muscles not involved in the intended action. Such studies are not required for the diagnosis. DNA testing is available for DYT1 dystonia, but the low penetrance of the disease limits the usefulness of this test for prenatal or presymptomatic diagnosis.

Pathology

Pathological studies in childhood-onset primary generalized dystonia arc limited. No consistent structural or pharmacological changes have been detected in postmortem brain.

Etiology and Pathogenesis

The low penetrance of DYT1 dystonia, combined with variable expression that may range from an asymptomatic state to severe life-threatening dystonia (dystonic storm), may obscure its hereditary nature in many families {Opal et al. 2002). The disorder is genetically homogeneous in Ashkenazi Jews, 90% of whom are found to have the *DYT1* mutation. Non-Jewish patients are genetically more heterogeneous. The DYT1 mutation is a GAG deletion in the torsin A gene on chromosome *9* with an estimated frequency of 1 per 2000 to 1 per 6000 in Ashkenazi Jews and about 1 per 20,000 to 1 per 30,000 in non-Jewish populations. The high prevalence of DYT1 in Ashkenazi jews is related to a founder mutation estimated to have originated about 350 years ago in Lithuania or Byelorussia and the subsequent large increase in the population from a limited number of ancestors.

The pathogenesis of generalized dystonia remains poorly understood. Torsin A is a protein of unknown function that is homologous to the adenosine triphosphatases and heat-shock proteins. Its structure suggests a role in endoplasmic reticulum function, intracellular trafficking, or vesicular release. Mutant torsin A may interfere with these functions or may contribute to misfolded protein stress. There is experimental, clinical, neuroimaging, and electrophysiological evidence of dysfunction at the cortical, subcortical, brainstem, cerebellar, and spinal levels. Dystonia produced in nonhuman primates by repetitive hand movements is associated with inappropriate spread of the cortical representation of the affected hand. There is disordered sensory function in human dystonics and certain sensory inputs influence motor output in these patients. Deep brain recordings support abnormally low firing rates in the GPi with an abnormal pattern of firing as well. During sustained dystonia, there is increased metabolic activity in the midbrain, cerebellum, and thalamus. Functional neuroimaging of the dopamine system suggests decreased dopamine neurotransmission in the striatum, but decreased striatal dopamine has not been confirmed in postmortem tissue {Hurukawa et al. 2000b), Because dystonia may respond to pallidal lesions or stimulation, a central role of the GPi has been proposed. It is likely, however, that

the pathophysiology of dystonia involves many factors including changes in the rate and pattern of neuronal firing, the degree of synchronization of firing, and aberrant focusing of sensory input (Vitek 2002).

Treatment

Rather limited information is available on the medical treatment of child hood-onset primary generalized dystonia. Absent an obvious neurotransmitter deficiency or excess, there is no compelling rationale for the use of any particular pharmacotherapy, and no drug has been found to be universally effective for symptom control (Table 77.20). In the absence of genetic confirmation of the DYT1 mutation, a trial of dopaminergic therapy should be considered, because patients with dopa-responsive dystonia {see later discussion) have such a gratifying response. In patients younger than 20 years, about 50% will respond well to high-dose anticholinergic therapy. The response rate is better in patients treated within 5 years of onset. Baclofen, clonazepam, benzodiazepines, and dopamine-depleting medications may be useful in some patients. The treatment of childhood-onset primary generalized dystonia is a trial-and-crror process. Treatment should be initiated with very small doses and the dose should be increased slowly and gradually. Botulinum toxin injections may be considered to treat one or a few particularly problematic body areas in patients with generalized dystonia. Chronic intrathecal baclofen has been reported to help some patients with dystonia, especially those with concomitant spasticity, Stereotactic thalamotomy is said to benefit about 66% of patients who have been operated on, but some patients worsened and side effects were common. Thalamotomy may he most useful for patients with dystonia of the distal limb. More recent reports suggest that axial symptoms might improve after bilateral pallidotomy or pallidal DBS. Patients with the DYT1 mutation seem most likely to improve (Coubes et al. 2000).

Table 77.20; Medical treatment of dystonia

Drug	*Starting dose (tug/day)*	*Usual dose (tng/day)*	*Response rate {%)*
Anticholinergics			51
Trihexyphenidyl	1	6-80	
Procyclidine	2.5	10-30	
Bcnztr opine	0.25	4-15	
Baclofen	10	30-120	20
Benzodiazepines			
Clonazepam	0.25	4	10-16
I. o raze pa m	0.5	1-16	
Diazepam	2.5	10-100	
Carbidopa/ i -dnpa	12.5/50	37.5/150-75/300	Good response in dopa-responsive dystonia
Dopamine deplctcrs	0.25	4-6	25
Reserpine	250	1000-3000	
Mc tyro sine	12.5	50-300	
Tetrabena/inc			

Adult-Onset Primary Focal and Segmental Dystonia

Epidemiology and Clinical Features

A community-based postal survey of primary dystonia suggested the prevalence of adult-onset primary focal or segmental dystonia was 12.9 per 100,000. Cervical dystonia and blepharospasm were most commonly represented. The focal and segmental primary dystonias generally begin in adulthood with dystonic movements in the band and arm, neck, or face. When spread occurs, the ultimate distribution tends to maintain a segmental pattern. For most such dystonias, the women are somewhat over-represented, *Cervical dystonia* is the most frequently diagnosed form of focal dystonia, accounting for about half of focal dystonia cases. Patients with cervical dystonia present with neck pain, difficulty maintaining a normal head position, and sometimes tremor. Although across patient populations, the movements may occur in any single plane, or commonly in several planes, there is a directional preponderance to the movements. Sensory tricks are common (see Chapter 24) and include resring the head against a wall or high-backed chair or touching the chin or back of the head lightly with one hand. Spontaneous remissions may be seen in as many as 20% of patients, although recurrence is very common. About 20% of patients with focal dystonia have dystonic movements of the eyelids, *blepharospasm.* Symptoms of blepharospasm are often preceded by a gritty or otherwise abnormal sensation in the eye. Increased blinking may follow, or frank spasms of eyelid closure m.n begin. Symptoms of blepharospasm are typically worse with driving, reading, or watching television. Improvement induced by placing a finger alongside the eye is a common finding. Blepharospasm may be accompanied by *oromandibular dystonia* (cranial dystonia), or the latter may occur in isolation. Otomandibular dystonia typically causes involuntary jaw opening or closure, tongue prorrusion, dysarthria, and dysphagia. Because the actions of eating and speaking activate the dystonia, these tasks are particularly affected. Sensory tricks in oromandibular dystonia include touching the face or inserting something, such as candy or the tip of a pencil, into the mouth. Vocal cord involvement with *adductor* or *abductor dysphonta* affects pdonation, resulting in a harsh and sttanglcd, or breathy voice, respectively. Whispering and singing are often relatively unaffected in such patients. The *occupational* or *task-specific dystonias* are those that arise in the context of

repetitive or skilled use of a body part. The most common task-specific dystonia is *writer's, cramp,* in which action dystonia of the arm and hand develop during writing. Hair stylists, musicians, court reporters, and others who work repetitively with the hands may find these specific skills similarly affected. Players of wind instruments may develop dystonia of embouchure, with difficulty maintaining the proper mouth and lip posture. Occasionally, an adult patient will present with a pure *truncal* dystonia, with flexion, extension, or lateral bending. Isolated *foot dystonia* in an adult is very rare and suggests an underlying structural lesion, a parkinsonian disorder, or 5PS. The diagnosis of adult-onset primary focal or segmental dystonia is made clinically. Ncuroimaging studies are useful if an underlying cause is suspected (see Secondary Dystonia, later in this chapter) but arc generally normal. Simultaneous recording of agonist and antagonist muscles may show inappropriate co-contraction, but this is not required for diagnosis.

Etiology and Pathogenesis

Many studies have suggested that focal and segmental dystonia might have a genetic basis. About 25% of adult-onset focal or segmental dystonia patients have a positive family history of dystonia, which would be consistent with an autosomal dominant condition with low penetrance. Some families with clear dominant inheritance have been reported and there is already one identified locus of focal dystonia, *DYT7,* in a large German family. This family-shows an autosomal dominant pattern of inheritance with reduced penetrance and adult onset of cervical dystonia, dysphoria, or hand tremor. The locus has been mapped to chromosome IS.

The pathogenesis of adult-onset primary focal or segmental dystonia is unclear, but similar mechanisms to childhood-onset primary generalized dystonia are proposed. Studies suggest that there is reduced inttacortical inhibition in dystonia, believed related to impaired cortical and striatal GABA levels (Levy and Hallett 2002). Several lines of evidence suggest that abnormal central somatosensory processing may lead to insufficient sensorimotor integration in dystonia. PET scans suggest an abnormal pattern of regional glucose metabolism with hypermetabolism of the basal ganglia, cerebellum, and supplementary motor area (Trost et al. 2002). Recent studies have suggested disordered copper metabolism with increased lenticular concentrations of copper and manganese. Changes in trace minerals may affect cellular function or lead to cellular death (Becker et al. 1999).

Treatment

Medical treatment of adult-onset primary focal and segmental dystonia is difficull and employs those agents typically used in generalized dystonia. Adults are less able to tolerate effective doses of these agents, so the response to therapy is somewhat more disappointing than that seen in children. Botulinum toxin injections, on the other hand, are very helpful in the treatment of focal and segmental dystonia. Botulinum toxin is injected subcutaneously over the facial muscles or directly into larger deeper muscles that underlie pain and inappropriate movement in other focal dystonias. Many, though not all, clinicians use EMG to help guide toxin injection. Botulinum toxin injections have been proven effective in the treatment of blepharospasm and other facial dystonias, as well as cervical dystonia. Clinical experience suggests they are very useful in the treatment of oromandibular, laryngeal, truncal, and limb dystonia. Overall, more than 75% of treated patients report moderate to marked improvement in dystonic pain or posture. The procedure is generally well tolerated, with excessive weakness of injected muscles or occasionally neighboring muscles (he most often reported side effect. The mechanism of action of botulinum toxin appears complex. Botulinum toxin not only blocks neuromuscular transmission, producing weakness in the injected muscles, but also normalizes intracortieal reciprocal inhibition, possible by an effect on muscle spindle input. Botulinum toxin injections have a brief duration of action, requiring repeated injections every 3-6 months. Secondary resistance occurs in some chronically treated patients, especially those injected frequently with higher doses of the toxin (Jankovic, Vuong, and Ahsan 2003).

Patients who fail to respond to botulinum toxin injections may be offered surgical interventions. Blepharospasm can be tteated by orbital myectomy. Good results are obtained in some patients with cervical dystonia following selective peripheral denervation of the muscles participating in the production of abnormal head movement. A prospective open study of selective peripheral denervation for patients with cervical dystonia with botulinum toxin resistance showed 68% of patients wetc functionally improved after surgery. Pain control was less sustained than control of movement, and posterior cervical dysesthesias were a common side effect. Pallidal DBS has been tried in some patients with refractory cervical dystonia with good results. More study is required to determine the utility of the technique in this diagnosis (Volkmann and Benecke 2002).

X-Linked Dystonia-Parkinsonism (DYT3; Lubag's Syndrome)

DYT3 or Lubag's syndrome is an X-linkcd condition with progressive dystonia and parkinsonism affecting Filipino adult men descended from maternal lines from the Panay Island. The disorder is heterogeneous, and affected men may show dystonia, parkinsonism, tremor, chorea, or myoclonus. This phenotypical heterogeneity is evident in colorful descriptions of the disorder in the local dialect.

"Lubag" means intermittent and "Wa-eg" sustained twisting or posturing, suggesting the predominantly dystonic form of the illness. "Sud-Sud" refers to shuffling gait, suggesting the parkinsonian form of the illness. Lubag affects men in the fourth or fifth decades, although much earlier onset cases have been described. Symptoms predominantly relate to dystonia, although parkinsonism is present in more than 30% of patients. A nearly pure parkinsonian phenotype is thought to predict a more benign prognosis.

PET studies have shown both postsynaptic and presynaptic dopaminergic changes. In some patients, parkinsonian symptoms are r-dopa-responsive, although there are reports rh.it t.-dopa worsens symptoms in some predominantly dystonic patients.

D op a-Responsive Dystonia (DYT5)

Dopa-responsive dystonia (DRD) is an uncommon condition, with a prevalence of 0.5-1.0 per 1,000,000. Girls are preferentially affected. DRD is a childhood-onset generalized dystonia with a dramatic, sustained and uncomplicated response to low doses of i.-dopa. The disorder begins in the first decade of life with an action dystonia in the foot. The condition then progresses to the fully formed illness that ranges in severity' from mild focal to disabling generalized dysronia. Early onset cases may be mistakenly diagnosed as cerebral palsy. The most characteristic historical feature is prominent diurnal fluctuation. Affected patients may be almost normal in the morning, becoming progressively more disabled over the course of the day with peak disability late in the evening. Parkinsonian symptoms become part of the clinical picture over time. DRD is usually dominantly inherited with incomplete penetrance (DYT5). DYT5 results from mutations in the guanosine triphosphate cyclohydrolase-l *(GTPCH1)* gene on chromosome 14. (Eurukawa et al. 2000a). More than 50 mutations of the gene have been discovered, and therefore DMA testing is currently not feasible. *GTPCH1* is an enzyme involved in the synthesis of tetrahydrobiopterin, a cofactor for tyrosine hydroxylase. Other mutations affecting enzymes involved in tetrahydrobiopterin synthesis have also been i in plica red in DRD. A recess ively inherited DRD relates to mutations in the gene for tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of i.-dopa. Patients with the DRD have low levels of tyrosine hydroxylase, and therefore low levels of dopamine. F-dopa PET and postmortem studies confirm normal numbers of dopaminergic neurons. DRD responds very well to low[r] doses of L-dopa (100-300 mg daily) in combination with carbidopa. Patients with DRD do not develop the motor fluctuations and dyskinesias associated with chronic L-dopa therapy in PD. Anticholinergic drugs may also be useful.

Another childhood-onset dystonia related to deficient dopaminergic neurotransmission is *aromatic acid decarboxylase deficiency.* This disorder is recessively inherited. Dystonia, parkinsonism, oculogyric crises, autonomic symptoms, and progressive neurological impairment begin in childhood. There are deficiencies in central biogenic amines including dopamine, norepinephrine, epinephrine, and serotonin. i'>ce.uise llie enzyme deficiency is distal to l. dopa in the dopamine synthetic pathway, the symptoms are not L-dopa responsive. However, direct-acting DAs and MAOIs may be useful (Swoboda et al. 1999).

Myoclonus Dystonia (DYT11)

In myoclonus dystonia (MD), dystonia is the predominant symptom, but tremor and myoclonus are present as well. Some patients have pure myoclonus. Symptoms usually begin before the teenage years and predominantly affect the head, arms, and upper body. Ehe involuntary movements may be exquisitely sensitivity to ethanol. Psychiatric features including affective disorder, obsessive-compulsive disorder, substance abuse, anxiety, phobic or panic disorders. and psychosis have been described. Cognitive decline has also been reported (Dohcny et al. 2002). No other neurological deficits are seen and the course is usually benign. Ehe pathology is unknown. A number of heterozygous mutations in the E-sarcoglycan gene on chromosome 7 have been reported in families with MD. Another suggested locus is on chromosome 18. Mutations in the torsin A *{DYT1)* gene and the D_2 dopamine receptor gene have also been described, but e-sarcoglycan mutations were subsequently described in these families as well. There is likely another locus on chromosome 18 (Furukawa and Rajput 2002). MD responds poorly to medical therapy, but beneficial responses to valproic acid and trihexyphenidyl have been reported. VIM stimulation has been reported to be beneficial in MD in a single case (Trottenberg et al. 2001).

Rapid-Onset Dystonia Parkinsonism (DYT12)

Rapid-onset dystonia parkinsonism (RDP) is a very rare disorder in which signs of parkinsonism and upper body dystonia develop subacutely. Onset ranges from childhood ro adulthood. Dystonia preferentially affects bulbar muscles and progresses over a period of days to weeks but then remains stable. Although sporadic cases have been reported, most cases belong to a small number of families showing dominant inheritance with incomplete penetrance. A genetic locus on chromosome 19 has been discovered. Eow levels ot homovanillic acid (IIVA) have been detected in the spinal fluid, but PET scans using presynaptic markers fail to demonstrate a loss of dopaminergic neurons (Brashear et al, 1999), There is no evidence of

neurodegeneration and RDP symptoms do not improve with administration of L-dopa, suggesting a functional deficit (Nemeth 2002).

Wilson's Disease (Hepatolenticular Degeneration)

Epidemiology and Clinical features

Wilson's disease (WD) is a rare heredodegenerative disorder thought to affect 1-2 per 100,000 persons. It is related to abnormal copper disposition. In childhood, the liver progressively accumulates copper. Many patients present in childhood wiE 1 I •.ympmniN and signs ol liver disease, ranging from cirrhosis to fulminant liver failure. Once cirrhosis has deyelopcd, extrahepatic copper deposits begin to form, especially in the brain, eyes, and kidneys. Some patients present with hemolytic anemia, hypersplenism, or renal failure. Nearly half of all patients with WD present with central nervous system symptoms and signs (l'andit et al. 2002). Neurological signs usually present during adolescence or early adulthood, but presentations up to the age of 51 years have been reported. Neurological presentations include parkinsonism, postural and kinetic tremor, ataxia, titubation chorea, seizures, dysarthria, or dystonia. A fixed stare with a smiling exptcssion and drooling are classic features of the illness but are not seen in all cases. Dystonia is a common sign, ptescnt in 37% at presentation in one series. Dystonia may he focal, segmental, or generalized (Svetel et al. 2001). Sensation is spatcd. Dementia, if present, is mild. Psychiatric signs are very common and may be quite disabling. Mood and personality disorders, behavioral changes, and psychosis are reported. In the ptesence of neurological signs, ophthalmological examination, including slit-lamp examination essentially always demonstrates copper deposition in Descemet's membrane (Kayser-Fleischer rings) (sec Chapter 24). Many patients with WD also have sunflower cataracts. Laboratory studies often show abnormalities in hepatic enzymes, aminoaciduria, low uric acid, and demineralization of bone. MRI scan usually shows decreased signal intensity (hypodensity) in the striatum and supetior colliculi and increased signal intensity in the midbrain tegmentum {except for red nucleus) and in the lateral SNr giving the appearance of "face of the giant panda" on T2-weighted images. Low serum ceruloplasmin, elevated 24-hour copper excretion, and the presence of Kayser-Fleischer rings are useful in making the diagnosis, which is confirmed by demonstrating elevated hepatic copper (Pandit et al. 2002).

Pathology

Gross inspection of the brain often reveals cerebral atrophy and shrunken, discolored putamen and GP. Microscopically, WD brains show both preferential striatal and generalized neuronal loss. There is diffuse gliosis with Alzheimer's types I and 11 astrocytes, as well as Opalski's cells, cells of microglial origin.

Etiology and Pathogenesis

WD is an autosomal recessive disorder of copper metabolism related to mutations in the *ATP7B* gene on chromosome 13 (Pandit et al. 2002). riecause there are so many different mutations, genetic testing is not clinically available. This gene regulates a copper-transporting adenosine triphosphatase. Although the neurological disorder clearly relates to harmful effects of intracellular copper, the precise mechanisms of cell dysfuncrion and death are not well understood.

Treatment

The goal of treatment of WD is to reduce the body burden of copper and to prevent its reaccumulation. Traditionally, acute chelation began with n-pcnicillamine, but more recent treatment strategics stress somewhat less toxic therapies such as tticntine and zinc or tetrathiomolybdate. The effectiveness of initial de-coppering is monitored by serially measuring urine copper excretion and plasma copper levels. Although there may be an acute deterioration associated with the mobilization of copper stores, most patients improve over time. Long-term therapy must be maintained, usually with tricntine and zinc. D-Penicillaminc is associated with a number of systemic toxicities including dermatopathy, neuromuscular junction disorders, thrombocytopenia, and Goodpasture's syndrome. Asymptomatic siblings should be tested for the disease, because timely treatment prevents the illness. Orthotopic liver ttansplantation is curative but has been used largely in patients with luhuinaiit hepatic failure who have not yet devel oped significant neurological signs (Emre et al. 2001), The response of neurological symptoms to liver transplantation is not completely understood.

Neurodegeneration with brain iron accumulation (pan tothenate kinase-associated neurodegeneration [PKAN], Hallervorden-Spatz disease; hypoprebetalipoptotcinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration [HARP]).

A number of disorders cause neurodegeneration with brain iron accumulation (Hayflick et al. 2003). The classic form of neurodegeneration with brain iron accumulation is *PKAN* formerly known as I lallcrvorden-Spatz disease. It is an autosomal recessive neurodegenerative disorder presenting in childhood with the insidious onset of dystonia and gait disorder. Rigidity, dysarthria, spasticity, dementia, retinitis pigmentosa, and optic atrophy develop and progress relentlessly until death in early childhood. "12-weighted MRI brain scans show areas of reduced attenuation in the GP surrounding an area of hyperintensity, the "eye of the tiger" sign. Autopsy studies show a brown discoloration of the GPi and SNr, reflecting pathological

accumulation of iron. Microscopic changes include neuronal loss, gliosis, loss of myelinated fibers, and axonal swellings (spheroids). Virtually all families with typical PKAN have mutations in the pantothenate kinase gene *(PANK2)* on chromosome 20. Pantothenate kinase is an important regulatory enzyme in coenzyme A synthesis. There are atypical forms of the illness that begin later and are more slowly progressive. These cases often present with early speech disorder and often have personality changes suggesting FTD. Although the Mill scan shows evidence of iron accumulation, the "eye of the tiger" sign is not seen, and these patients do not have mutations in the *PANK2* gene. *HARP syndrome,* a constellation including hypoprebetalipoproteincmia, acanthoeytosis, retinitis pigmentosa, and pallidal degeneration, has also been linked to mutations in this gene (Ching ct al. 2002). The precise mechanism of neurodegeneration is unknown (Zhou et al. 2001).

Post-Traumatic Dystonia

Dystonia resulting from brain trauma most often presents as hemidystonia, but cervical, segmental, axial, or spasmodic dysphonia can also be seen (Krauss and Jankovic 2002). Most reported post-traumatic dystonias occur in men, reflecting a male preponderance among patients with head injury. Most cases have occurred in children or adolescents who have survived severe head injury. Often, the dystonia emerges as a traumatic hemiparesis improves or resolves. There may be a latent period between the trauma and the development of the dystonia from 1 day to 6 years, followed by slow progression of dystonic symptoms. Younger patients tend to have longer latencies than those who are older at the time of the head injury. Focal lesions in the caudate, putamen, or thalamus contralatetal to the affected side arc usually found on neuroimaging studies. Lesions of the mesencephalon or dentatothalamic pathways have also been found. The prognosis of this form of post-traumatic dystonia is poor, with a low rate of spontaneous improvement. Most cases arc refractory to medical therapy, although some may respond to anticholinergic drugs. Botulinum toxin injections may be helpful. DBS or stereotactic thalamotomy, or pallidotomy may be helpful, although the magnitude of response is much less than that seen in patients with primary dystonia.

Dystonia may also occur after peripheral injury (Jankovic 2002). For example, oromandibular dystonia may follow dental surgery or facial and jaw trauma. Limb dystonia has also been reported to occur after peripheral trauma, often in the context of causalgia or reflex sympathetic dystniphy. TJii-ic .i:e no ..Kveptcd clniic.il criteria for this diagnosis, and differentiation from psychogenic disease may be difficult. The response of this condition to medical or other therapies is disappointing.

Tardive Dystonia

Tardive dystonia (TDy) should be differentiated from transient acute dystonic reaction and from the more typical TD. In a review of 11 studies of psychiatric patients chronically exposed to neuroleptics, 2.7% developed TDy. Men are more likely to develop TDy, and they develop it at a younger age than women. All of the typical antipsychotics, as well as antiemetics with dopamine-receptor-blocking properties, have been associated with the development of TDy (Kiriakakis et al. 1998). Symptoms of TDy begin insidiously after days to decades of neuroleptic therapy, Although rare cases have been re ported after a <hori deration ot therapy, the median duration of exposure to neuroleptics at the time of onset is 5.1 years. TDy usually presents as focal or segmental dystonia, such as blepharospasm, oromandibular, or cervical dystonia, but the most typical presentation is a truncal dystonia in a young man associated with pronating movements of arms and extension of the elbows. There is a relationship between age at onset and distribution of the dystonic movements with trunk and leg symptoms in younger persons and face, jaw, and neck involvement in older persons. The extent of spread is determined in part by age, with more generalized movements in younger patients, but it usually remains segmental, In comparison with primary focal or segmental dystonia, there is more rctrocollis and anrecollis. Dystonic symptoms may improve over a period of 5 years if the offending neuroleptic agent is withdrawn, although recovery is less common than in patients with choreic TD. Young patients with a shorter duration of neuroleptic exposure have the gteatest likelihood of remission (Kiriakakis et al. 1998).

Like TD, TDy has been thought to relate to changes in the postsynaptic dopamine receptors. However, evidence is accumulating that suggests that neuroleptics arc toxic to the striatum. Apoptotic cell death has been described in animals chronically exposed to neuroleptics (Galili et al. 2000). Oxidative stress and excitotoxicity have been implicated in this process. The brains of TDy patients show basal ganglia cell loss and gliosis.

As with TD, the primary treatment of TDy is prevention. Once TDy has developed, every attempt should be made to rid the patient of the offending neuroleptic. Neuroleptic-dependent patients should be managed with atypical antipsychotics, if possible. Tetrabenazine, anticholinergics, benzodiazepines, and baclofen have all been reported to help p.it lent>, will; I I)\ KiriaLikis ci al. I '"JSi. Botulinum toxin injections can be particularly helpful in patients having disability from blepharospasm or with cervical or truncal dystonic movements.

Paroxysmal Kinesigenic Dyskinesia (DYT10)

Paroxysmal kinesigenic dyskinesia (PKD) is a disorder of childhood onset characterized by attacks of involuntary

movements that include prominent dystonia, chorea, or other hyperkinesias. Because the attacks are often nor witnessed and therefore appropriate phenomenological categorization is not possible, the less specific term *paroxysmal dyskinesia* is preferred to the alternative term, *paroxysmal kinesigenic epilepsy* (Jaiikovic and Deinirkiran 2002). Boys make up 80% of cases. There is often a family history. Patients typically recount that episodes are triggered by rapid movement, often in response to an unexpected stimulus such as the telephone ringing. There may be a premonitory sensation in an affected limb. The movements may be unilateral or bilateral. The spells last less than 1 minute and occur up to 100 times daily (Houser et al. *J999).* There is a tendency for spells to decrease in adulthood. Diagnosis depends on careful history taking, because the examination usually shows no abnormalities, typical spells may not be elicited in the examination setting, and neuroimaging and electrophysiological studies are usually normal. Two loci for PKD (DYT10) have been localized to chromosome 16, suggesting a family of genes on that chromosome that might be important in producing the syndrome, although causative genes have not yet been discovered. PKD is usually very responsive to anticonvulsant medications. Carbamazepine and phenytoin are most frequently used, but there have been recent reports that levctiracctam is effective and well tolerated.

Paroxysmal Nonkinesigenic Dyskinesia (DYT8)

Paroxysmal nonkinesigenic dyskinesia (PNKD) usually licgiiis in ir.tiiik;-. .iii!: .itlciis boys more than girls. I he spells of PNKD occur less often but are more prolonged than those in PKD. Their frequency ranges from several episodes per month to several episodes per day and their duration is generally between 10 minutes and several hours. They are not precipitated by action but may be triggered by ethanol, caffeine, fatigue, or stress (Jankovic and Deinirkiran 2002). Genetic loci for PNKD (DYT8) have been discovered on chromosomes 1 and 2. CSF monoamine metabolites have been reported to decrease during an attack (Jarman et al. 2000). MRS and PET scans using the D2-selective radioligand raclopridc do not show any significant abnormalities in these patients. Unlike PKD, PNKD does not show a dramatic response to anticonvulsants. Some patients respond to clonazepam, other benzodiazepines, carbamazepine, gabapentin, anticholinergics, L-dopa, acetazolamide, and neuroleptics.

Secondary Paroxysmal Dyskinesia

Secondary paroxysmal dyskinesia has been thought to be rare. However, in one series, 26% of paroxysmal dyskinesia cases occurred in the context of another nervous svstem disease (Blakeley and Jankovic 2002). Underlying etiologies include cerebrovascular disease, trauma, infection, and metabolic encephalopathy. The clinical manifestations of secondary paroxysmal dyskinesia are heterogeneous. Some are kinesigenic and some are not. Some are associated with premonitory sensations and others have no warning signs. Treatment of the underlying cause may improve the dyskinesia.

TICS

Tourette's Syndrome

Epidemiology and Clinical Features

Prevalence estimates for Tourette's syndrome (TS) vary from 10-700 per 100,000, depending on the population studied and the study methods used. Although the prevalence is greater among children in special schools and those with disorders in the autism spectrum, the vast majority of patients with TS have normal intelligence. Boys are more commonly affected than girls. TS begins in childhood or during early adolescence, but most often begins between the ages of 2 and 10 years. Typical early signs of TS are cranial motor tics including eye blinks, stretching of the lower face, and shaking the head (see Chapter 24). Vocal tics include sniffing, throat clearing, grunting, whistling, chirping, and words, including profane words (coprolalia). Over time, the tics wax and wane and new tics enter and leave the repertoire. Tics may be simple or complex and can resemble any voluntary or involuntary movement. Patients with TS have both motor and vocal tics. Symptoms tend to increase throughout childhood, with peak expression in adolescence, and become somewhat less troublesome in adulthood. Behavioral changes arc very common in TS, especially attcntion-deficit/hyperactivity disorder (ADHD), conduct disorder, or obsessive-compulsive disorder. The latter association is particularly intriguing, because girls in families with a history of TS may have pure obsessive-compulsive disorder without tics. Obsessions in TS predominantly concern symmetry and counting. The diagnosis of TS rests entirely on the history and physical examination. The neurological examination is usually normal, as are neuroimaging and electrophysiological study results. No pathological changes have been described in patients with TS, but limited study of postmortem brains has suggested reduced levels of brainstem serotonin, pallidal glutamate, and cortical cyclic adenosine monophosphate.

Etiology and Pathogenesis

Clinical evidence strongly suggests that TS is a hereditary disease {Jankovic 1991:. The concordance of i'S among monozygotic twins is 86%, and segregation analyses are consistent with an autosomal dominant, sex-influenced

trait. However, despite this evidence, definite mendelian inheritance has not been established and no genetic locus has yet been identified. Because there is a robust response to dopa mine-receptor-bloc king medications, altered central neurotransmission has been proposed to underlie TS. PET studies suggest increased dopaminergic innervation of the ventral striatum, and abnormal regulation of dopamine release and reuptake,

Treatment

The first step in the treatment of TS is the definition of the sources of disability. Treatment should be reserved for patients who arc experiencing interference from tics in the educational, social, or family spheres. Disabling tics are most effectively suppressed by neuroleptic medications such as haloperidol and pimozide. In a double-blind controlled comparison, pimozide was more efficacious and better tolerated than haloperidol. Sulpiride and tiapride, which are not available in the United States, may also be helpful in the treatment of tics. Risperidone and olanzapine have been shown to be effective' in small uncontrolled trials, and ziprasidone has shown preliminary efficacy, although clozapine has not. Fluphenazine and tetrabenazine are also very effective in the treatment of tics with minimal side effects. Very-low-dose pergolidc (0.15-0.3 mg daily) has also shown some preliminary efficacy for tics (Gilbert et al. 2000). It is thought to work by selective action at presynaptic dopamine autoreccptors. Baclofen has been said to effectively decrease tic-related impairment, though not tics themselves in a small placebo-controlled trial (Singer et al. 2001). Other treatments suggested to be effective in small or uncontrolled studies include cannabinoids, nicotine, donepezil, antiandrogenic agents, kctanserin, ondansetron, and selective serotonin reuptake inhibitors. Obsessive-compulsive disorder responds to selective serotonin reuptake inhibitors. Comorbid ADHD can be safely treated with clonidine, methylphenidate alone, and in combination (Tourcttc Syndrome Study Group 2002). Guanfacine, tomoxetine, desipramine, deprenyl, and nortriptyline have also been proposed to treat ADHD inTS.

Adult-Onset Tics

Adult-onset tics are much rarer than childhood-onset tics and usually represent recurrences of child hood-onset tics. .Many affected patients have childhood histories of obsessive-compulsive tendencies and family histories of tic disorders. Adult-onset tic disorders often develop after a triggering event and are more severe and socially disabling than the more typical early onset disease. Tics in adulthood are relatively resistant to pharmacotherapy (Eapen et al. 2002). Other causes of adult-onset tics, such as the use of cocaine or other central nervous system stimulants, tardive tics, and neuroacanthocytosis, should be considered in the differential diagnosis.

POSTINFECTIOUS AUTOIMMUNE NEUROPSYCHIATRY DISORDERS ASSOCIATED WITH STREPTOCOCCAL EXPOSURE

Postinfectious autoimmune neu to psychiatric disorders associated with streptococci (PANDAS) is a controversial entity that has been recently linked to TS. Children with PANDAS have explosive onset of obsessive-compulsive disorder, tics, hyperactivity, and choreiform movements in the prepubertal years. There is an association with prior group A beta-hemolytic streptococcal infection, although the syndrome is distinct from rheumatic fever and Sydenham's chorea (Garvey et al. 1998). Affected children have enlargement of the caudate, putamen, and GP by volumetric MRI. Antineuronal antibodies against putaminal antigens have been detected in the plasma of patients with TS. An autoimmune molecular-mimicry mechanism has been proposed. A double-blind placebo-controlled crossover study of penicillin in patients with PANDAS failed to show that penicillin prevented symptom recurrences, but adequate prevention of streptococcal infection was not achieved. Intravenous immune globulin and plasmapheresis reduced obsessive-compulsive symptoms, but tic scores were improved only in the plasmapheresis group. These improvements were sustained for 1 year. PANDAS is not a universally accepted syndrome and additional research is required to better define its role in TS (Garvey et al. 1998).

MYOCLONUS

Essential Myoclonus

Essential myoclonus (EM) is diagnosed when myoclonus is present as an isolated neurological sign or is accompanied only by tremor or dystonia. EM can be sporadic or inherited. Dominantly inherited EM usually presents before the age of 20 years. EM is usually multifocal myoclonus with upper body predominance. Although spontaneous jerks are seen, they are exacerbated by action. Alcohol may dramatically suppress the myoclonus. Sporadic forms of this illness are also described. (MD is discussed earlier in this chapter.) MD and EM are allelic disorders linked to the e-sarcoglycan gene on chromosome 7.

Hereditary Gcniospasm (Chin Tremor)

Hereditary geniospasm is characterized by involuntary vertical movement of the tip of the chin with quivering and mouth movements. Geniospasm may be spontaneous

or stress induced. Trembling becomes apparent in infancy or early life. Trembling episodes last minutes. The attacks become somewhat less frequent with age. The disorder is genetically heterogeneous, with linkage to chromosome 9q 13-21 in some, but not all families (Grimes et al. 2002). Geniospasm has been suggested to be a form of hereditaty EM.

Posthypoxic Myoclonus (Lance-Adams Syndrome)

The first cases of posthypoxic myoclonus (PHM) were described in 1963 by Lance and Adams. PHM is a generalized myoclonus that occurs with recovery from the acute effects of severe brain hypoxia. The most common etiologies of the hypoxia are respiratory arrest (especially asthmatic), anesthetic and surgical accidents, cardiac disease, and drug overdose. The typical patient is in coma for several days to 2 weeks. Myoclonus and seizures may be present during the comatose phase. After recovery from coma, myoclonic jerks become apparent, especially with voluntary movements, which trigger volleys of high-amplitude jerks and intermittent pauses in the activated body part. The myoclonic movements typically flow to body parts not directly involved in the voluntary movements. The ampliunle ni the myoclonus is directly proportional to the delicacy of the attempted task, producing extreme disability in the performance of activities of daily living. Gait is disturbed not only by positive myoclonic jerks, but also by negative myoclonus, resulting in falls. Other neurological signs are always present and include seizures, dysarthria, dysmerria, ataxia, and cognitive impairment.

CSF studies have shown low levels of 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin. A role for GABA in this disorder is suggested by the production of myoclonus by injecting GABA antagonists into the rat thalamus. Autopsies in patients with PHM show changes lelated to hypoxic brain damage but do not reveal any specific structural changes in brainstem raphe nuclei. Myoclonus in posthypoxic rats responds to serotonin agonists that stimulate particular subtypes of serotonin receptors (5-HT_{1B}, .S-HT_{2A}/2is> arid possibly 5-HTto) (Pappert et al, 1999). Other studies in rat models have suggested that basal serotonin levels are normal, but there is an abnormality in release of serotonin by potassium chloride and NMDA.

There is some tendency for improvement in myoclonus over time, but most patients have significant disability related to the movements. GABAergic drugs such as valproic acid and clonazepam are usually used in the treatment of PHM. Each is associated with improvement in about 50% of treated patients. Levctiracetam has been recently reported to he effective in an open-label trial in chronic myoclonus (Genton and Gelisse 2001). Other GABAergic drugs such as vigabatrin and gabapentin have not shown promise. Piracetam improves PHAN by an imperfectly understood mechanism that does not involve serotonin or GABA. It is available in Europe and Canada, though not in the United States. L-5-HTP administered with carbidopa may be useful, but this investigational agent has limited access and gastrointestinal side effects limit its tolerability. The effects of L-5-HTP may be enhanced by concomitant use of a selective serotonin reuptake inhibitot.

Startle and Hyperekplcxia

Hypetekplexia is a startle syndrome, characterized by muscle jerks in response to unexpected stimuli. Two forms of startle have been described. Families with autosomal dominant and recessive inheritance have been described. The major form of the illness is characterized by continuous stiffness beginning in infancy, and exaggerated startle culminating in tails. Some patients have seizures and low intelligence. In the minor form, there is only excessive startle, with hypnic myoclonic jetks. Startle in patients with hyperekplcxia differs from normal startle because it has a lower threshold, is more generalized, and fails to normally habituate with tepeated stimuli. Electrophysiological studies in well-characterized cases suggest the origin of the pathological startle in the lower brainstem, possibly the medial bulbopontine reticular formation. The disorder is genetically heterogeneous, with most mutations occurring in patients with the major form of the illness. Most defined mutations involve the «i-subunit of the inhibitory glycine receptor. Symptomatic hyperekplexia has been reported to result from infarct, hemorrhage, or encephalitis. Clonazepam is the treatment of choice (Brown 2002).

Spinal Myoclonus and Propriospinal Myoclonus

Spinal myoclonus (SM) is a syndrome of involuntary-rhythmic or semirhythmic myoclonic jerks in a muscle or group of muscles. The myoclonic jerks may be unilateral or bilateral. In some cases, they are stimulus sensitive. The jerks relate to spontaneous motoneuron discharge in a limited area, often a single segment of the spinal cord. Propriospinal myoclonus is a more widespread disorder in which myoclonic jerks are propagated up and down the spinal cord from a central generator. Most patients with propriospinal myoclonus have had minor spinal cord trauma with normal MRI findings, but the disorder has been reported in severe spinal eord injury, multiple sclerosis, human immunodeficiency virus, or Lyme infection, syringomyelia, spinal cord tumors, and spinal cord infarction (Nogues et al. 2000). Propriospinal myoclonus has been reported to affect particularly the transition from wake to sleep.

Toxin- and Drug-Induced Myoclonus

A number of drugs and environmental agent with central nervous system toxicity have been shown to cause myoclonus (Table 77.21). Criteria for drug- or toxin-induced myoclonus include verified exposure, temporal association, and exclusion of genetic or other causes. The myoclonus produced by drugs and toxins is often multifocal or generalized, stimulus sensitive and action sensitive, and accompanied by other suggestive nervous system signs, particularly by encephalopathy signs. Metrizamide and diclofenac may cause segmental myoclonus. Treatment requires withdrawal of the causative drug and symptomatic treatment, if required with clonazepam, valproic acid, or levetiracetam.

MISCELLANEOUS MOVEMENT DISORDERS

Hemifacial Spasm

Data from Olmsted Comity, Minnesota, suggest that the prevalence of hemifacial spasm is 14.5 per 100,000 in women and 7.4 per 100,000 in men. Hemifacial spasm is characterized by twitching of the muscles supplied by the facial nerve. The disorder usually begins in adulthood, with an average age at onset of 45-52 yeats. Although there are some familial cases, most are sporadic. In typical cases, twitching first affects the periorbital muscles but spreads to other ipsilateral facial muscles over a period of months to years. The spasms arc synchronous in all affected muscles. In about 5% of patients, the opposite side of the face becomes affected, but when bilateral, the spasms are never synchronous on the two sides. The spasms of hemifacial spasm may be clonic or tonic, and often, a paroxysm of clonic movements culminates in a sustained tonic contraction. Although the spasms occur spontaneously, they may be precipitated or exacerbated by facial movements or by anxiety, stress, or fatigue. The affected muscles may be weaker than their contralateral counterparts. Some patients have evidence of regional cranial neuropathy such as altered hearing or trigeminal function. Detailed neuroradiological workups using routine and specialized MRI techniques may demonstrate compressing vascular structures in most, if not all, patients with hemifacial spasm. Mm,' advanced ^canning techniques Mich as high-resolution T1- and T2-weighred spin-echo or gradient-echo imaging with gadolinium provides maximum visualization of the root entry zone (Port 2002). Yet, serious underlying causes are rare, and many clinicians do not toutinely image patients with typical hemifacial spasm unless the clinical picture is atypical or the patient is being considered for surgery.

Tabic 77.21: Drugs associated with myoclonus

Anesthetics
LtonmLitc, chlonilose
Antibiotics, antihelminthics, antiviral drugs
Penicillin, Imlpencm, quinolones, piperazinc, acyclovir
Anticonvulsants
Phenytoin, phenobarbital, primidone, valproic acid, carbamazepine, gabapentin, lamotngine, vigabatrin
Antihistamines
Sodium bicarbonate (baking soda)
Benzodiazepine withdrawal
Psychotropic medications
Tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitor, lithium, buspirone, neuroleptics
Antineoplastic drugs
Chlorambucil, p red nimustine, ifosfamide
Narcotics
Morphine, meperidine, hydromorphone, fentanyl, sufentanil, diamorphine

In cases of hemifacial spasm, the facial nerve root entry zone generally shows axonal demyehnation or nerve degeneration. Hemifacial spasm is thought to result from compression of the facial nerve at the root exit zone, usually by vascular structures. Tumors or other space-occupying lesions are found in about 5% of patients. Vessels commonly implicated are the posterior inferior cerebellar artery, the anterior inferior cerebellar artery, or the vertebral artery. When tumors are present, they are most commonly epidermoid, neuroma, meningioma, astrocytoma, and parotid tumors.

There are two main theories of pathogenesis. The first proposes that in the area of compression-induced demyelination, an "ephapse," or false synapse, forms. Mechanical irritation or other regional changes induce ectopic activity in the region, which is then conducted antidromically within the nerve fiber. The main competing theory proposes that the aberrant signals arise from the facial nerve nucleus, which reorganized as a result of deranged afferent information.

Traditionally, patients with hemifacial spasm have been treated with anticonvulsants, typically carbamazepine, and more recently gabapentin. Other agents said to be useful include baclofen, anticholinergics, halopcridol, and clonazepam. The clinical availability of borulinum toxin injections revolutionized the treatment of hemifacial spasm. Botulinum toxin injected into the periorbital subcutaneous tissue produces clinically meaningful improvement in ilmost 100% of patients and side effects are mild and transient, Botulinum toxin injections must be administered every 3-6 months. Follow-up of chronically treated patients shows the injections retain their efficacy at least 10 yeats (Defazio et al. 2002).

A number of surgical techniques have been used in hemifacial spasm. These include removal of the orbicularis oris or other affected muscles, selective destruction of parts of the facial nerve, decompression of the facia) canal, or radiofrequency thermocoagulation of the netve. Intracranial microvascular decompression of the nerve is

successful in relieving spasms in up to 90% of patients, but complications such as facial nerve injury and hearing loss occur in up to 15% of patients (Samii et al. 2002).

Painful Legs-Moving Toes Syndrome

Painful legs-moving toes syndrome (PLMTS) is a very rare condition characterized by pain in the legs and spontaneous movements of the foot and toes. The pain usually precedes the onset of involuntary movements and varies in constancy and intensity. In some cases, the condition is painless. The toe and foot movements arc complex, combining flexion, extension, abduction, and adduction in various sequences, at frequencies of 1-2 Hz. The movements may be precipitated or aborted by moving or repositioning the foot or toes, but they cannot be simulated voluntarily. Similar movements have been described in the arms, with or without accompanying pain. In most cases, there is an underlying cause, although there is little consistency from case to case. PLMTS has been associated with injuries to the spinal cord and cauda equina, spinal nerve roots, peripheral neuropathy, and soft tissue or bony limb trauma. EMG studies show that the movements are produced by long bursts of normal motor unit firing with normal recruitment patterns. PLMTS doubtless has a central origin. Central reorganization consequent to altered afferent information from the periphery has been proposed, but a precise location and mechanism of these changes remain unknown.

Treatment of PLMTS is very difficult. Many medications have been tried, including baclofen, benzodiazepines, anticonvulsants, and antidepressants, but none has emerged as effective. Lumbar sympathetic block or epidural stimulation may give transient relief. Spontaneous resolution is very unusual.

Stiff Person Syndrome

SPS is rare and no information is available about its epidemiology. SPS is a syndrome of progressive rigidity of axial and proximal appendicular muscles with muscle hypettrophy and extreme lumbar lordosis. Intense spasms are superimposed on a background of continuous symptoms. Gait is slow and stiff legged. Some authors divide SPS into three syndromes: stiff trunk syndrome, stiff limb syndrome, and rapidly progressive encephalomyelitis with rigidity (Barker el al. I99K). l'.MC! examination shows continuous firing of normal motor units.

SPS is associated with autoimmune disorders, such as type I diabetes, thyroiditis, myasthenia gravis, pernicious anemia, and vitiligo. High titers of antibodies to the 65-kd fraction of GAD are present. It is thought that SPS results from dysfunction of descending suprascgmcntal pathways possibly secondary to immune-mediated inhibition of GABA synthesis. Paraneoplastic SPS has been reported with breast and other cancers.

Untreated, SPS progresses to extteme disability. Diazepam at doses of 20-400 nig per day is the most effective symptomatic treatment. Clonazepam, baclofen, valproic acid, clomdine, vigabatrin, and tiagabine have also been reported to be effective. Plasmapheresis and immunosuppression have been reported to have variable effects on the condition. In a recent placebo-controlled crossover study of nilr.lv Pilous inininne j-'Juhtiliii, active [rr;i! mm! v,as uwk/i ated with clinical improvement and decreases in anti-GAD antibody titers (Dalakas ct al. 2001). Intrathecal baclofen and local intramuscular injections of botulinum toxin have been lielpti:) :n Mime cases.

Psychogenic Movement Disorders

Psychogenic movement disorders (PMDs) make up a small part of any clinical movement disorders practice. The most common PMD is tremor, but dystonia, myoclonus, and parkinsonism are also seen. In many cases, the symptoms are abrupt in onset and associated with a specific trigger. Clinically, distractibiliry is common, as ate stimulus sensitivity and entrainment with voluntary activities. Other psychogenic symptoms are often present. About 25% of patients have a comorbid organic movement disorder. About half have an Axis 1 psychiatric disorder, most often depression. The long-term outcome of patients with PMDs is unknown. In a series of 88 subjects with documented PMD, interviews were conducted an average of 3 years after diagnosis; 52.5% of survivors were interviewed, and 95% had active or remote primary psychiatric illness (major depression and anxiery or both). Nearly half had personality disorders. In only 10% had the PMD remitted, but half of these patients had new psychogenic symptoms. Patients with PMD did not acknowledge the psychiatric origin of their PMD (Feinstein et al. 2001). No specific information is available about treatment.

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Chapter 78
Disorders of the Cerebellum, Including the Degenerative Ataxias

S. H. Subramony

Cerebellar ataxia can he the result of a variety of insults to the cerebellum and its connecting pathways. The cerebellum can be the seat of pathology in many well-recognized diseases of the central nervous system (CNS) and may be involved in such processes in isolation or in combination with other structures. Thus ataxia can he either the major feature of the disease or one of its various clinical signs. In addition, progressive degeneration of the cerebellum and its connections resulting in ataxia can result from a number of genetic abnormalities. Finally, the term *sporadic ataxia* or *idiopathic ataxia* is used for those diseases in which ataxia related to cerebellar degeneration occurs in the absence of a definite genetic or acquired etiology (Ahclc ct al. 2002). In this chapter, I briefly discuss some of the well-defined acquired causes of ataxia, summarize the current understanding of the inherited ataxias, and address the issue of sporadic ataxia.

ACQUIRED ATAXIAS

In many patients, progressive ataxia results from environmental insults and other well-recognized disorders involving the nervous system. In any patient presenting with cerebellar ataxia, such disorders as ischemic or hemorrhagic stroke involving the cerebellum, previous episodes of cerebral hypoxia, primary or metastatic tumors, and demyelinating diseases such as multiple sclerosis can be diagnosed by appropriate imaging studies and other investigations. Many of these diseases tend to have an acute or subacute evolution, rather than the chronic course associated with degenerative ataxias. However, other diseases can present with ataxia in which the major imaging abnormality may be an atrophic cerebellum akin to the finding in degenerative ataxias. Some of these are briefly discussed. Table 78.1 lists acquired causes of ataxia.

1 lypothyroidism

Occasional patients with hypothyroidism develop a mild gait ataxia in conjunction with their systemic symptoms. Thyroid functions need to be tested in patients with progressive ataxia. Thyroid replacement can improve the neurological symptoms.

Toxic

Alcohol

Alcohol remains the major exogenous agent causing ataxia. A significant proportion of alcoholics have midline cerebellar degeneration at autopsy. Clinically, this disease is characterized by a progressive gait disturbance of a cerebellar type with little in the way of upper limb ataxia, speech difficulties, or eye movement abnormalities. This may reflect the relative sparing of the cerebellar hemispheres. Imaging studies typically reveal vermian atrophy, Chronic alcoholism can also produce significant cerebellar atrophy in the absence of major clinical deficits (Hillborn etal. 1986).

Chemotherapy

Some cancer chemotherapcutic agents may produce ataxia as an adverse effect. 5-Fluorouracil (5-FU), a fluorinated pyrimidine that acts by incorporating into RNA and interfering with RNA function, has been used to treat

Tabic 78.1: Acquired causes of ataxia

Disorder	*Diagnostic process*
Vascular disease	History of strokes, imaging
Hypoxic encephalopathy sequel	History of hypoxic episode
Demyelinating disease	Remitting and relapsing episodes, imaging
Posterior fossa tumor	Imaging
Craniovertebra 1 junction anomaly	Imaging
Hypothyroidism	Thyroid studies
Toxic disorders	History
Alcohol, chemotherapy, metals Solvents, anticonvulsants	
Infections (see text)	Imaging, CSF, serology
Acute cerehellitis, postinfectious, BickcrstafPs encephalitis, HIV, CJD	
Autoimmune disease	
Paraneoplastic	Anti-Hu, anti-Yo, anti-Ri, others
Gluten ataxia	Anti-gliadin, anti-endomysial
Ann GAD ataxia	Anti-GAD

CJD — Creutzfeldt-Jakoh disease; CSF = cerebrospinal fluid; GAD = glutamate decarboxylase; HIV = human immunodeficiency virus.

breast and gastrointestinal cancer. Conventional doses of 5-FU may cause cerebellar ataxia if there is an abnormality of pyrimidine metabolism in the form of dihydropyrimidinc dehydrogenase deficiency. Higher doses of 5-FU can cause* a panccrcbcllar syndrome that has an acute to subacute evolution.

When cytosine arabinoside is given in high doses (3 g/m for 8-12 doses as opposed to the conventional 100-200 mg/m for 5—7 days), a significant number of patients develop a cerebellar syndrome. Pathologically, this is characterized by loss of Purkinje cells, gliosis, loss of dentate neurons, and spongiform changes.

Metals

Organic mercury poisoning has occurred in epidemic form as a result of contamination from mercury-containing fungicides. Mercury appears to be particularly toxic to cerebellar granule cells and visual cortex and causes a syndrome that includes paresthesias, ataxia, and restricted visual fields. Manganese may cause not only parkinsonism but also ataxia. Gait ataxia associated with other signs such as confusion and myoclonus has also been described with bismuth toxicity resulting from excessive intake of bismuth subsalicylate (Pepto-Bismol).

So bents

Chronic solvent abuse, especially of toluene, can cause persistent neurological deficits including ataxia. Spray paint and paint thinners are the usual sources. Cognitive deficits and pyramidal tract signs often accompany the ataxia and dysarthria.

Anticonvulsants

The issue of cerebellar atrophy and anticonvulsant use, especially phenytoin, is controversial. Ttansient cerebellar signs associated with supratherapeutic levels of drugs have been seen with many anticonvulsants. More persistent ataxia and documented Purkinje cell loss has been primarily seen in epileptics treated with phenytoin for prolonged periods of time. Cerebellar atrophy occurs in phenytoin-treated patients but may not always be associated with overt ataxia. The pathogenesis of this syndrome remains unclear. The various hypotheses include a direct toxic effect of phenytoin, a result of repeated hypoxia related to seizures, the effect of the seizure-related electrical discharge on cerebellar Purkinje cells, and the possibility that both the seizures and the cerebellar pathology are secondary to a unifying underlying pathology such as prenatal injuries. Another intriguing possibility is that both the sei/.ures and the progressive cerebellar syndrome could result from a single underlying gene mutation. It is probably best to avoid phenytoin in an epileptic patient if either ataxia or cerebellar atrophy is present.

Infectious

Ataxia can be one of the features of postinfectious encephalomyelitis but usually accompanies a more diffuse cerebral process (Coyle 2000). A more restricted cerebellar syndrome has been seen in children after viral infections. Connolly et al. (1994} have proposed that this diagnosis be considered when children develop an acute ataxic disorder that is not associated with a more diffuse process reflected by seizutes, meningismus, or obtundation. In most children, LIIIS condition is preceded b\ a nonspeeifk viral syndrome or varicella with a peak incidence at the age of 5-6 years. A similar syndrome following Epstein-Barr virus infection or vaccinations occurs in the teenage years. Cerebrospinal fluid (CSF) analysis may show some elevation of protein and a modest mononuclear pleocytosis and magnetic resonance imaging (MRI) scans often reveal signal density changes in the cerebellum (Figure 78.1). Such a disorder may occur in adults as well (Klockgether et al. 1993). Prognosis for recovery is excellent with residual dysfunction seen in a distinct minority.

Similarly a combination of ataxia, ophthalmoplegia, and other lower cranial nerve palsies can occur as a result of brainstem encephalitis (Bickerstaff's encephalitis). Clinically, this disorder resembles the Miller Fisher variant of Guillain-Barre syndrome from which it is distinguished by the presence of high-signal lesions in the brainstem on MRI scans (Fargas et al, 1998).

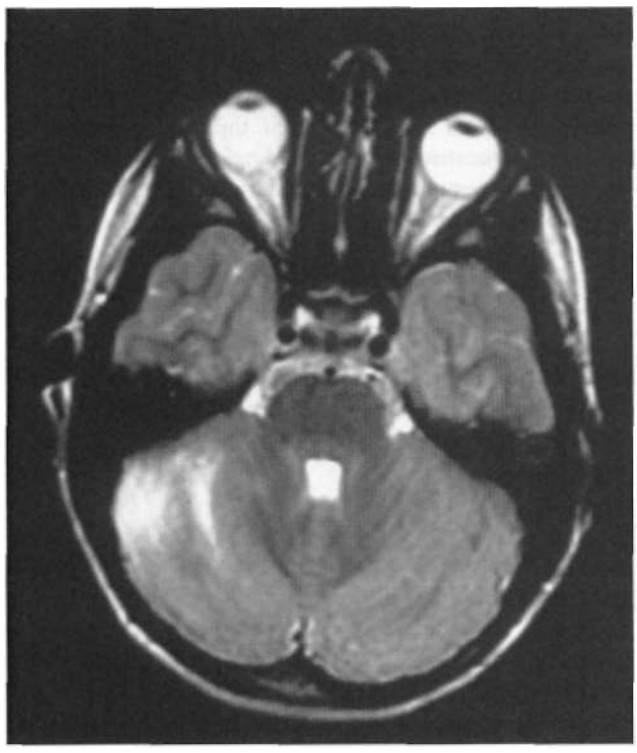


FIGURE 78.1 Signal density change in the cerebellum io a child with acute cerebellar ataxia of childhood. (Courtesy Dr. V. Vedanarayanan, Department of Pediatries, University of Mississippi Medical Center.)

Human immunodeficiency virus (HIV) infection can result in many neurological syndromes, including ataxia. Most patients with ataxia in the presence of HIV infection have discrete, well-recognized lesions such as lymphomas, chronic meningeal infection, progressive multifocal leukoencephalopathy, or toxoplasmosis. Also, approximately 30% of patients with HFV dementia have an ataxic syndrome at the onset of their illness before cognitive decline begins. Other authors have described isolated progressive cerebellar ataxia that does not evolve into HIV dementia in a small number of patients (Tagliatti et al, 1998). These patients had a rapid evolution of their ataxia leading to a chair-bound status in less than a year; MRI revealed cerebellar atrophy. Pathological examination in a small number of patients has revealed marked granule cell loss.

The relationship between possible human T-lymphotropic virus type II (HTLV-1I) infection and ataxia has been raised by some anecdotal experience but remains to be proven.

Creutzfeldt-Jakob disease (CJD) should also be considered in the differential diagnosis of patients presenting with progressive ataxia. CJD is typically a rapidly progressive dementing illness related to the accumulation of mutant prion protein, which results from post-translational modification of the normal prion protein. Among patients with classic CJD, close to 17% have early ataxia and more than 60% have cerebellar pathology at death. Jellinger, Heiss, and Dcisenhammer (1974) noted that the ataxic variant of CJD began with minor behavior symptoms followed by ataxia. Upper motor neuron signs were common; myoclonus occurred only in 25% and dementia evolved late. Survival among these patients was slightly longer than in typical CJD with a mean time to death of 16 months and a range of 7 weeks to 8 years. Pathologically, the cerebellum shows striking granule cell loss. Patients suspected of having CJD can be tested for the presence of the 14-3-3 protein in the CSF and for codon 129 homozygosity in the prion gene. CSF tau protein assay by enzyme-linked immunosorbent assay, already readily available in routine laboratories, has been found to have a 92% positive predictive value in diagnosing CJD; 74 of 77 patients with probable CJD had tau protein levels of more than 1300 pg/mL, whereas only 2 of 28 patients with Alzheimer's disease had such high levels, and even lower percentage in other dementias (Otto et al. 2002).

Interestingly, both Gerstmann-Straussler-Scheinker (CSS), an autosomal dominant form of CJD associated with codon 102 mutation, and growth hormone-related CJD have a cerebellar presentation. The new variant CJD also may have a cerebellar presentation (Will et al. 1996).

Autoimmune Causes of Ataxia

Paraneoplastic Cerebellar Degeneration

This is a rapidly progressive pancerebellar syndrome that reaches its nadir within a few months of onset. It produces a severe ataxic disease associated with dysarthria and oscillopsia. Diplopia and vertigo may also occur. Many patients also develop other neurological signs including dementia, extrapyramidal signs, hearing loss, and dysphagia. MRI typically shows atrophy of the cerebellum, although some high-signal density changes may occur in the deep white matter. CSF usually shows a mononuclear pleocytosis and oligoclonal bands may be present. It is believed that in many cases the syndrome results from an autoimmune process triggered by the cancer. The anti-Yo antibody is usually seen in ovarian cancer and primarily causes a cerebellar syndrome. The anti-Hu antibody is seen with small cell cancer of the lung and typically causes a multifocal disorder, the most common of which is a sensory ganglionopathy. Purkinjc cell degeneration has been noted in about 25% of patients with anti-Hu antibody. The anti-Ri antibody has been seen in patients with truncal ataxia and opsoclonus in the setting of breast cancer. Patients who exhibit a combination of ataxia and Lambert-Raton syndrome against a background of small cell cancer of the lung usually have no demonstrable antibodies. The nomenclature of these antibodies is under debate. Thus the

anti-Yo, anti-Hu, and anti-Ri antibodies may he equated with the Purkinje cell antibody type 1 (PCA-1), the antiiicuronal antibody type 1 (ANNA-1), and the anti-neuronal antibody type 2 {ANNA-2), respectively. Other antibodies that have been related to paraneoplastic cerebellar ataxia include the anti-Ta, anti-Ma, anti-CV2, and antiglutamate antibodies (Henzen-Logmans et al. 2000; Posner and Dalmau 2000).

Ataxia with Gluten Sensitivity

Following the observation that cerebellar ataxia can often be a neurological complication of celiac disease, Hadjivassiliou et al. (1998) looked for gluten sensitivity among a group of patients with sporadic ataxia. Sixty-eight percent of these patients had antigliadin antibodies, contrary to 5% of neurological controls. Malabsorption did not appear to be the cause of the ataxia. Other studies have noted a lower prevalence of gliadin antibodies in patients with idiopathic ataxia or none at all (Pellechia et al. 1999; Combaross et al. 2000; Burk el al. 200] . Busharactal. (20:11) have reported that patients with idiopathic ataxia and those with a definite genetic form of ataxia had a similar occurrence of gluten sensitivity, taising doubts about the significance of the gliadin antibodies. Recent immunocytochemical studies, however, have supported the idea that these antibodies do indeed bind to Purkinje cells of the cerebellum (Hadjivassiliou et al. 2002). Patients with gluten sensitivity usually have slowly progressive ataxia associated with brisk tendon reflexes, peripheral neuropathy, and often, mild cognitive changes. Myoclonus and eye movement abnormalities have been desctibed as well. Nervous system pathology has been characterized by cerebellar Purkinje cell loss, infiltration by T lymphocytes, and posterior column degeneration. A variable proportion of patients have typical celiac disease on duodenal biopsy, even when there are only minor gastrointestinal symptoms; some have either normal biopsies or simply lymphocytic infiltrates. Whether a gluten-free diet or other irnmuno-modutation will improve gliadin antibody-associated ataxia is unclear.

Ataxia and Antiglutamate Decarboxylase Antibodies

Recently, a number of reports have noted the presence of antibodies to glutamate decarboxylase (GAD) among a small number of patients with progressive ataxia (Honnorat et al, 1995; Said et al. 1997). The patients have been usually middle-aged women. Ataxia was occasionally associated with petipheral neuropathy, slow saccades, and in some cases stiff person syndrome. Many patients had multiple organ-specific antibodies including those directed against thyroid cells, parietal cells, and pancreatic islet cells, and insulin-dependent diabetes was an invariable accompaniment. The antibodies occut in higher titers than those found in adult-onset diabetes, and there is evidence that they bind to presynaptic nerve terminals around cerebellar Purkinje cells. GAD is the enzyme that synthesizes y-aminobutyric acid (GABA) from glutamate and it is believed that the antibodies may be pathogenic because of their binding to GABA terminals. Intravenous immune globulin may cause partial remission of symptoms.

Nutritional

Acquired vitamin E deficiency occurring in the setting of fat malabsorption can cause ataxia. Examples include cystic fibrosis and cholestatic liver disease.

INHERITED ATAXIAS

The initial recognition that progressive balance difficulties related to pathology in the cerebellum and its connecting pathways could have a genetic basis is attributed to Nicholas Friedreich, who published a series of papers describing siblings with such a disease, now known as *Friedreich's ataxia* (FA). As early as 1893, Pierre Marie noted the clinical and genetic heterogeneity among the inherited ataxias. During much of the twentieth century, inherited ataxias that did not quite fit the Friedreich mold were often labeled *Marie's ataxia.* Also, many patients have progressive ataxia of a degenerative nature, clinically and pathologically resembling the inherited ataxias and yet having no discernible genetic basis. Much of the last 100 years saw the detailed clinical and pathological descriptions of these patients and attempts to understand them on a clinicopathological basis. Nevertheless, the clinical, neuro-pathological, and genetic heterogeneity of the disorders did not allow a universally acceptable classification. Based on an extensive clinical study of many families, Harding wrote a clinical genetic classification that served as a prelude to an increasingly gene-based listing of the inherited ataxias. A classification that is based on the recent understanding of phenotype-genorype correlations is still needed. This section summarizes the current information regarding the inherited forms of ataxia.

Autosomal Recessive Ataxias

Table 78.2 lists various autosomal recessive ataxias based on specific gene loci. Most of these diseases begin in childhood or early adult life; however, onset late in life is possible. Singleton patients may occur in many families. Typically, parents do not manifest any symptoms because they are heterozygous for the mutation. If the sibship size is large or when extended pedigrees are obtained, other involved persons may be found; the disotders affect both males and females. Consanguinity among the parents may be found but is not essential.

Table 78.2: Autosomal recessive ataxias with known gene loci

Disease	*Gene locus*	*Gene*	*Mutation*
Friedreich's ataxia	9ql3-21.l	X2.5	GAA expansion
Ataxia-telangiectasia*	llq22-23	ATM	Point mutations/deletions
Ataxia with oculomotor apraxia"	9pl3	Aprataxin	Point mtirations/deletions/insertions
A [TU-	llq21	MRE11	I'oint mutations
SCAN-1*	I4q31	II >!' I	Point mutations/deletions/insertions
AVI D	***H***	aTTP	Point mutations
ARSACS	13qll	SACS	Point mutations
Ataxia, neuropathy, high ar-femprotein	9q33-34	Unknown	Unknown
IOSC A	10q24	Unknown	Unknown
Ataxia, deafness, optic atrophy	6p21-23	Unknown	Unknown
Unverricht-Lundborg disease	21q	Cystatin B	Repeat expansion

These all involve mutations in DNA repair genes. Xeroderma pigmentosum and Cockayne's syndrome are other multiple system DNA repair detects in which one may see ataxia.
ARSACS = autosomal recessive spastic ataxia of Charlevoix-Saguenay; ATLD = ataxia-tclangiectasia-like disorder; AVED = ataxia with isolated vitamin E deficiency; IOSC A = infantile onset spinocerebellar ataxia; SCAN-1 = spinocerebellar ataxia with axonal neuropathy 1; TDP = tyrosyl DNA phosphodiesterase; TTP — tocopherol transfet protein.

Friedreich '$ Ataxia

Clinical Features. The prevalence of FA has been estimated to be 2 x 10^{-5} (Pandolfo 1999). Classic descriptions of the disease include an age at onset of younger than 25 years, typically early in adolescence (Harding 1981). Onset is with increasing gait difficulties and neurological examination reveals gait ataxia, loss of proprioceptive sense in the lower limbs, and absence of deep tendon reflexes, cither generalized or in the lower limbs. These findings are related to the early pathology in the dorsal root ganglion cells and the occasional patient may have symptoms that can be mistaken for a hereditary neuropathy. However, most patients exhibit signs indicating involvement of the CNS, including dysarthria, upper motor neuron findings such as extensor plantar responses and eye movement abnormalities such as square wave jerks. Rarely, patients may present with cardiac disease or .: spinal deformity and later develop neurological disease. Patients tend to lose ambulation about 9-15 years after onset. At this stage, patients have increasing ataxia of both upper and lower limbs, profound proprioceptive loss, areflexia, weakness of lower limb muscles, dystonia, flexor spasms, and increasing dysarthria and dysphagia (Hou and Jankovic 2003). Optic atrophy and hearing loss may occur in many patients.

Systemic abnormalities that occut include abnormal electrocardiogram recordings, hypertrophic cardiomyopathy in about 50% of the patients, and diabetes in 10%. Skeletal abnormalities such as spinal deformities and foot deformities are common. The mean age at death among patients with FA has been reported to be late in the fourth decade; however, this information comes from studies performed before the availability of FA mutation analysis. Cause of death is usually cardiac, but the respiratory compromise related to spine deformiry may also contribute.

Nerve conduction studies show early absence or reduction of sensory nerve potentials in a diffuse fashion, reflecting the loss of large sensory axons in peripheral nerves. This is correlated with loss of myelinated fibers in sural nerve biopsies. Central motor conduction studies show evolving abnormalities and may reflect the progression of the disease. MRI scans of the brain reveal no abnormalities in the cerebellum; rather, the upper cervical cord shows atrophy. Pathologically. iluTc is loss ni dorsal root ganglion cells, resultant degeneration of the dorsal columns, degeneration of spinocerebellar and corticospinal tracts, and loss of cells in the cerebellar dentate nucleus,

The Friedreich's Ataxia Mutation. The mutation in FA is an unstable expansion of a repeated trinucleotide (GAA) sequence within the first intron of the gene X 25 on chromosome 9ql3-21.1 (Campuzano et al. 1996) (Figure 78,2). More than 80% of the normal alleles have fewer than 10 GAA repeats. Long normal alleles with 12-40 repeats are believed to serve as a reservoir for expansion into mutations that appear restricted to Indo-Caucasian populations (Pandolfo 1999). Expanded alleles have 66-1000 repeats. Because the disease is recessively inherited, both copies of the gene have to be mutated to produce disease. In nearly 95% of the affected persons, the GAA expansion occurs in both alleles (homozygous expansion), although the size of the expansion can be different in the two alleles. Patients with clinical findings compatible with FA but with only a heterozygous expansion of the GAA repeats constitute the remaining 5%; such patients are found to have point mutations in the unexpanded allele. Commercially available FA mutation analysis cannot distinguish between such compound heterozygotcs and unaffected carriers of the disease. Homozygous point

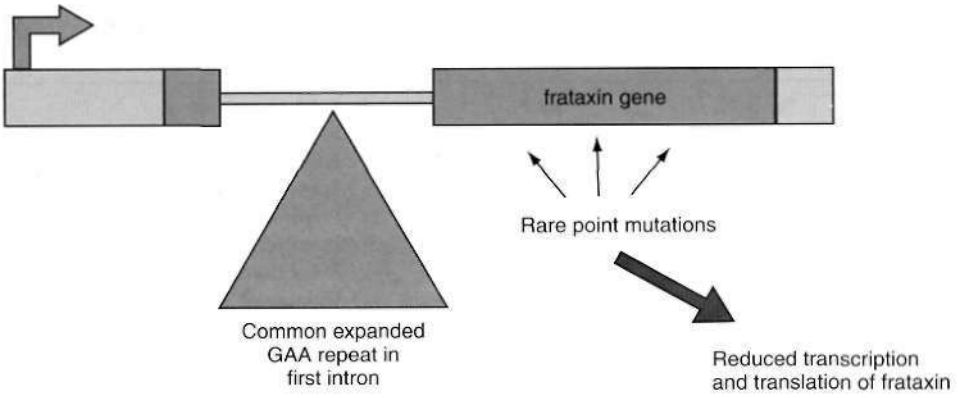


FIGURE 78.2 Schematic representation of the GAA expansion in the first intron of the gene X 25 on chromosome 9 in Friedreich's ataxia. (Courtesy Dr. H. Paulson, University of Iowa.)

mutations have not been found in patients with the diagnosis of FA.

Since the identification of the FA mutation, wc have realized that many patients with a phenotype very atypical for classic FA carry the FA mutation (Durr et al. 1996; Filla et al. 1996; Montcrmini et al. 1997). Approximately 15% of patients with homozygous GAA expansion have neurological signs that are identical to those of classic FA hut have an age at onset of later than 25 years (late-onset FA). Other patients with the GAA expansion have the typical age at onset hut retain their tendon reflexes or even have exaggerated reflexes (FA with retained reflexes). There are patients who combine a later onset with retained reflexes ;-, well; in addition, vcr\ Life unset ol mild gail ataxia, spastic paraparesis, and even chorea has been rarely associated with the FA GAA expansion (Hon and Jankovic 2003). As with other trinucleotide repeat diseases, there is an inverse correlation between the size of the GAA repeat and the age at onset; this correlation is better with the smaller of the two expanded alleles. Cardiomyopathy and diabetes also tend to occur in patients with larger (>700) GAA repeats. However, not all of the variation in age at onset and severity of disease can be cortelated with the GAA size alone. Other genetic and possibly environmental factors may contribute to this variation. We already know that the size of the GAA expansion exhibits somatic mosaicism, so the severity of pathology in a particular tissue may depend to some extent on the repeat size in that tissue.

Point Mutations. Approximately 5% of patients with FA have heterozygous GAA expansion in one copy of the gene and a point mutation m the second copy. Both missense and truncating mutations located in the carboxy terminal half of the frataxin gene appear to be associated with typical FA phenotype (Cossee et al. 1999). Missense mutations in the amino terminal half such as the G130V mutation appear to result in a milder phenotype with less ataxia, greater spasticity, and absence of d\ sartbria.

Pathogenesis. The presence of the expanded GAA sequence in the first intron of the gene results in reduced transcriptional and translations) efficiency, leading to a partial deficienc) ol the protein frataxin (I'uccio and Koenig 2000; Lodi, Taylor, and Schapira 2001; Pandolfo 2001). The lack of documented homozygous point mutations causing FA suggests that the complete absence of frataxin may be incompatible with life, and this has been further supported by the inability to create transgenic animal models of the disease by complete knockout of the gene. The reduced transcriptional efficiency of the mutated gene has been attributed to an unusual "sticky DNA" configuration of the expanded repeat (Sakamoto et al. 1999). The exact role of frataxin in normal biology is still not clear, but many studies suggest that it is a mitochondrial protein. Knockout of the frataxin homologue in yeast leads to accumulation of iron in the mitochondria, a finding of interest in view of the presence of iron in the cardiac muscle in human disease. Rotig et al. (1997) have shown that activity of enzymes that contain iron-sulfur clusters is impaired in cardiac muscle biopsies of patients with FA, It has been hypothesized that this impairment is related to oxidative stress induced by the presence of excess iron that can induce such stress via the Fenton reaction. However, it is also possible that the deficiency of iron-sulfur cluster enzymes may he directly related to the reduced amounts of frataxin. Recent conditional knockout mouse models of FA, in which frataxin deficiency confined to cardiac and neural tissue has been achieved, appear to support this concept. Frataxin appears to be important in making mitochondrial iron available to such processes as synthesis of Fe-S cluster enzymes and heme synthesis. MRI has suggested excess iron in the dentate nucleus of patients with FA and there is magnetic resonance spectroscopy evidence of impaired respiratory capacity of skeletal muscle in FA. Thus FA is an example of a nuclear-encoded mitochondrial disease related to impaired respiratory activity of mitochondria.

Treatment of Friedreich's Ataxia. Based on the ability of the coenzyme Q analogue idebenone to suppress iron induced oxidative damage, early studies have shown a reproducible response of the hypertrophic cardiomyopathy of FA to idebenone treatment (Rustin et al. 1999;

Hausse et al. 2002). Improved bioencrgetics of cardiac and skeletal muscle have been shown to occur in response to coenzyme Q and vitamin F. (Lodi ct al. 2001).

In addition, many attempts have been made at symptomatic therapy for patients with FA with possible neurotransmitter replacements such as cholinergic, scrotoninergic, and GABAergic drugs, which have shown variable and usually less than optimal results.

The supportive care of patients with FA includes adequate rehabilitation efforts aimed at mobility, using appropriate devices. Monitoring and caring for the systemic complications are also important. This includes skeletal deformities, cardiomyopathy, and diabetes.

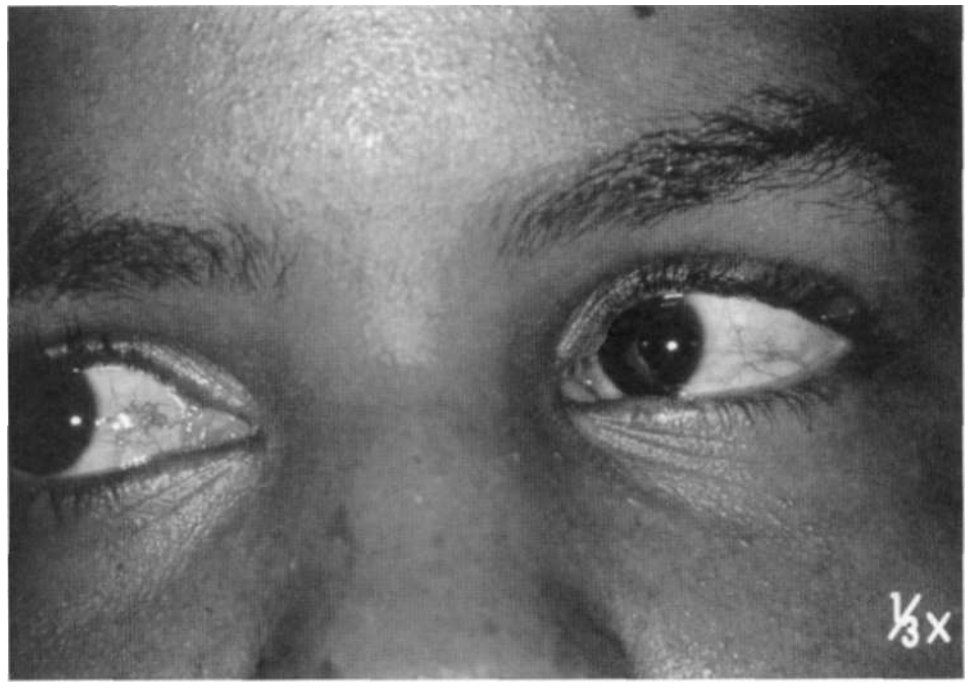
A tax ia-Telangiectasia

Ataxia-telangiectasia (AT) occurs with a frequency of three per million. Typically, the disease has its onset in the first decade. Children develop progressive ataxia associated with hypotonia, areflexia, peripheral neuropathy, and choreoarhetosis. Also, they exhibit a characteristic oculomotor apraxia, requiring head thrusts for saccadic eye movements. Telangiectasias develop over the conjunctivae (Figure 78.3), ear lobes, and other areas during the second half of the first decade. MRI scan of the brain shows atrophy of the cerebellum. AT is associated with increased risk of malignancies, especially hematological and infections related to immune deficiency. Increased susceptibility to radiation damage has been shown to cause chromosomal translocations and has been used in a fibroblast survival assay as a diagnostic test. Many patients have decreased immunoglobulin A (IgA) levels; decreased immunoglobulin E and immunoglobulin M levels, lymphocytopenia, and skin anergy may also occur. In addition, elevation of *a*-fetoprotein in the serum is a consistent finding in AT.

AT is caused by truncating mutations of the gene ATM on chromosome I 1 (Savitsky et al. 1995; Halazoncitis and Shiloh 1999). More than 300 mutations of this gene have been associated with AT, and mutation detection may not be the best way to make a definitive diagnosis. The protein product of ATM has sequence similarities to phosphatidyl-3-kinase and may be involved in checkpoint responses to DNA damage, explaining many of the systemic features of the illness. The neurological illness itself is still not directly treatable; however, children with AT requite supportive rehabilitation efforts, as well as monitoring and management of the various systemic features.

Ataxia with Isolated Vitamin E Deficiency

The occurrence of a childhood-onset recessive ataxia associated with isolated vitamin E deficiency {AVED} is related to mutations in the gene encoding the a-tocopherol transfer protein (a-TTP) on chromosome 8 (Ouahchi et al. 1995). a-TTP is a hepatic protein involved in the processing of vitamin H for transport in the chylomicrons. The severity of the phenotype associated with a-TTP mutations depends on residual protein activity; the childhood-onset disease has considerable resemblance to FA, causing ataxia, areflexia, proprioceptive loss, and dysarthria. A recent report of 43 patients with AVED noted age at onset from 2-52 years; patients with AVED had a lower incidence of



EIGURE 78.3 Conjunctival telangiectasia in a patient with ataxia-telangiectasia.

cardiomyopathy and more frequent head titubation, compared with patients with FA (C Cavalier et a I. 1998). vitamin F levels should be obtained in all persons with sporadic ataxia of childhood or young adult onset. Patients with AVED have typically less than 1.8 mg/L of vitamin E in serum. Treatment with large doses of vitamin E will elevate the levels and perhaps slow progression of the disease.

A beta tip op ro teinem ia

Mutations in the microsomal triglyceride transfer protein cause this rare disease (Sharp et al. 1993). The diagnosis can be established by the presence of retinopathy, malabsorption including that of vitamin E, low serum cholesterol levels, and the presence of acanthocytes. Serum lipoprotein electrophoresis can also establish the diagnosis.

Autosomal Recessive Ataxia of Charlevoix-Saguenay

Autosomal recessive spastic ataxia of Charlevoix-Saguenay is a childhood-onset disease that has been described from a population isolate in the Canadian province of Charlevoix-Saguenay and is characterized by spastic ataxia. Onset is in early childhood; neurological findings include spasticity, cerebellar eye movement abnormalities, and limb ataxia. Progression is vow and MHM:I a;;;' .11 dr.ilh is in the late fifties. The mutation causing this has been shown to involve a gene on chromosome 13, The protein product of this gene has similarities to chaperone proteins and has been named *sacsin* (Engert et al. 2000). Families from other parts of the wotld have been linked to the same locus. Thus the true prevalence of this disorder among childhood ataxias remains to be determined.

Autosomal Recessive Ataxia with Oculomotor Apraxia

Autosomal recessive ataxia with oculomotor apraxia is characterized by early onset of ataxia, autosomal recessive inheritance, and some features resembling AT such as oculomotor apraxia, loss of deep tendon reflexes, and cerebellar atrophy. Setum albumin level is decreased and total cholesterol level is elevated. Other systemic features of AT such as malignancies are not seen. Two groups have identified the gene mutation involving the aprataxin gene. Aprataxin is widely expressed and shares homologies with histidine-tnad (HIT) proteins and with DNA binding C2H2 zinc-finger proteins. It may be involved in DNA repair as well (Date et al. 2001; Moreira et al. 2001).

Other DNA Repair Defects Causing Ataxia

An AT-like disorder (ATLD) has been recently linked to mutations in another DNA repair gene known as MRE11 {Stewart et al. 1999). Similarly, mutations in tyrosyl-DNA phosphodiesterase 1 (TDP-1), another DNA repair enzyme, causes spinocerebellar ataxia (SCA) with axonal neuropathy (SCAN-1). These patients do not have any systemic features that characterize AT and ATLD (Takashima et al. 2002). Cockayne's syndrome and xeroderma pigmentosum are diseases caused by DNA repair defects in which systemic disease predominates the phenotype, but CNS features including ataxia are often present. Mutations in genes encoding components of the nucleotide excision repair pathway occur in these diseases (Chu and Maync 1996).

Infantile-Onset Olivopontocerebellar Atrophy

Infantile-on set olivopontocerebellar atrophy has been reported from a population isolate in Finland. The disorder begins with clumsiness soon after children begin walking. Neurological signs include ataxia, peripheral neuropathy, areflexia, athetosis, and extensor plantar reflexes. Speech is impaired and hearing loss occurs. Ophthalmoplegia, optic atrophy, seizures, learning deficits, and skeletal deformities are other features. The gene has been mapped to 10q24 (Nikahet al. 1997).

Other Genetically Defined Autosomal Recessive Ataxias

Other recessive ataxias have been genotyped in a limited number of families. These include an FA2 locus on 9p, ataxia, neuropathy, and high w-fetoprotein (9q), ataxia, deafness, and optic atrophy (6p), and ataxia with increased saccadic speed (lp) (Bemontet al. 2000; Christodoulu et al. 2001; Swartz et al. 2002).

Ataxias with Defined Biochemical Errors

Many childhood-onset and young adult-onset ataxias are related to metabolic errors that can be diagnosed by specific laboratory tests, rather than by gene-based tests. In many of these diseases, ataxia forms only a parr of the phenotype. Table 78.3 lists some of these diseases. Some of these are amenable to various forms of therapy including dietary manipulations.

Clinically Defined but (Likely) Genetically Heterogeneous Syndromes

Many children and young adults with progressive ataxia still have undefined genotypes. The term *early onset ataxia with retained reflexes* was originally used to describe a syndrome of ataxia with onset in childhood with some resemblance to FA except for the preservation of deep tendon reflexes. We now know that many of these patients carry the FA mutation; in others, however, the genotype remains unknown. Similarly, Cordon Holmes originally described the syndrome of recessive ataxia associated with hypogonadism in 1907. This may also be genetically hetetogeneous, although in some patients with such a disorder, mitochondrial mutations have been described.

Tabic 783: Ataxias in which specific biochemical abnormalities may confirm or point to the diagnosis (some also appear in Table 78.2}

Disorder	*Laboratory tests*
WHL>	Low vitamin H levels
Abetalipoproteinemia	Low vitamin K levels, high cholesterol, abnormal lipoprotein electrophoresis
AOA	Low albumin, high cholesterol
V!	High a-fetoprotein, low IgA
Cercbrotendinous xanthomatosis	High serum eholestanol
Ad ren o I e u k od y str o p h y	Serum long chain fatty acids
Ataxia with CoQ deficiency	Low CoQ in muscle biopsy
Vanishing white matter disease	MRI, MRS
Late onset GMj gangliosidoses	Hexosaminidase in fibroblasts
CDG syndromes	Transferrin isoelectric focusing
Mitochondrial diseases	Lactic acid levels, RRF in muscle
Sialidosis	Neuraminidase
Maple syrup urine disease	Urine amino adds
Organic acidurias	Urine organic acids, ketone bodies
Urea cycle defects	Plasma ammonia
Pyruvate dehydrogenase deficiency	Lactate levels

AOA = ataxia with oculomotor apraxia; AT = ataxia-telangiectasia; AVED = ataxia with isolated vitamin E deficiency; CDG = carbohydrate-deficient glycoprotein; CoQ = coenzyme Q; M!U = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; RRF = ragged red fibers.

The term *Ramsay Hunt syndrome* is used for the association of ataxia and myoclonus or myoclonic epilepsy. One form of this, Unverricht-Lundborg syndrome, is related to mutations in the cystatin P> gene (Pennachio et al. 1996). Others have mitochondrial DNA mutations or other disorders of intermediary metabolism such as ceroid lipofuscinosis or sialidosis (Table 78.4).

Mitochondrial Diseases and Ataxia

Progtessive ataxia is often an intrinsic feature of many mitochondrial cytopathies related to mutations in the mitochondrial DNA (mtDNA). The association of ataxia with myopathy, external ophthalmoplegia, or other features of mitochondriopathies such as short stature, endocrine deficiencies, elevated CSF protein, and retinal pigmentary degeneration may suggest a mitochondrial disease. Some mtDNA mutations have been specifically associated with ataxia, including the nt8344 mutation tclatcd to myoclonic epilepsy with ragged red fibers (MF.RRF) and the nt8993 mutation in the adenosine triphosphatase gene associated with neurogenic weakness, ataxia, and retinitis pigmentosa. Other classic mtDNA syndromes such as progressive external ophthalmoplegia, Kcarns-Sayre syndrome, and mitochondrial, encephalopathy, lactic acidosis, and strokclike episodes can also be associated with ataxia in a variable proportion of patients. Because mtDNA mutation may give rise to complex tissue distribution of symptomatology related to replicative segregation of the mutant mtDNA and to variable tissue susceptibility to oxidative deficiency, it is possible that isolated CNS symptomatology telated to such mutations may be difficult to define by studies of peripheral tissues.

Autosomal Douiiiiani Ataxias

Autosomal dominant ataxias have onset usually in the third to fifth decade of life, although there is wide variability in age at onset. The disease occurs in each generation of the pedigree; the offspring of affected parents have a 50% risk of inheriting the disease in general. Male-to-malc transmission of the disease is definite evidence for autosomal dominant inheritance. Since the 1990s, the genetic heterogeneity among the dominant ataxias has been more than amply documented (Subramony and Filla 2001) (Table 78.5). Progressive dominant ataxias are labeled *SCA,* followed by

Table 78.4: Young-onset ataxias with some distinctive clinical features but as yet poorly understood at a genetic level

Disorder	*Comments*
Early onset ataxia with retained reflexes	Some have FA or ARSACS mutation; others are genetically undefined
Ataxia with hypogonadism (Holmes's ataxia}	Associated hypogonadism
Ataxia with myoclonus (RamsayHunrsyndro me)	Heterogeneous;somemayhavemitochondr!aldisease;othcrsceroidlipofuscinosis, sialidosis, or other biochemical errors

ARSACS = autosomal recessive spastic ataxia of Charlcvoix-Saguenay; FA = Friedreich's ataxia.

Table 78.5: Autosomal dominant ataxias that have been genotypically defined

Disease	*Locus*	*Gene*	*Mutation*
SCA-1	6p22.3	Ataxin 1	CAG expansion
SCA-2	12q24.12	Ataxin 2	CAG expansion
MJD (SCA-3)	14q21	Ataxin 3	CAG expansion
SCA-4	16q22.1	Unknown	Unknown
SCA-5	11p11-q11	Unknown	Unknown
SCA-6	19p13.2	CACNA1	CAG expansion
SCA-7	3p14.1	\l.i \ir.	CAG expansion
SCA-8	13q21	SCA-8	CTG expansion
SCA-10	22q13	SCA-10	ATTCr expansion
SCA-11	Uq14-21.3	SCA-11	Unknown
SCA-12	5q32	PPP2R2B	CAG expansion
SCA-13	19q13.3-13,4	SCA-13	Unknown
SCA-14	19q13.4	SCA-14	Unknown
SCA-15	Reserved	SCA-15	
st; A- i ••	8q23-24-.l	SCA-16	Unknown
SCA-1 "	6q27	TBP	CAG expansion
SCA-18	7q31-32	Unknown	Unknown
SCA-19	Reserved	Unknown	Unknown
SCA-21	7p21.3-15.1	Unknown	Unknown
SCA-22	Reserved	Unknown	Unknown
SCA-23	20p13-12.2	Unknown	Unknown
DRPLA	12p	Atrophin	CAG expansion
EA-1	12p	KCNA1	Point mutations
EA-2	19p	CACNA1	Point mutations

DRPI A = dentatoruhml-pallidoluysian atrophy; EA = episodic ataxia; MJD = Machado-Joseph disease; TBP = TATA-binding protein.

a number to denote the chromosomal locus. Dominant ataxias that are named differently include Machado-Joseph disease (MJD) (earlier known as SCA-3) and dentatorubral-pallidoluysian atrophy (DRPI A), In addition, at least two gene loci are known for episodic ataxia (EA-1 and EA-2) syndromes. The absence of symptomatic disease in cither of the affected parent with autosomal dominant ataxia is rare but can occur for a number of reasons. Examples include reduced penetrance of the disease, onset of disease in a child before onset of symptoms in the affected parent because of anticipation, death of the involved parent before onset of symptoms, and wrong paternity. De novo mutations and expansion from an intermediate si/.e allele to a pathogenic allele in disorders related to repetitive nucleotide sequences may be oilier explanations.

Clinical Features of Dominant Ataxias

Overall, progressive dominant ataxias related to different gene mutations have ovetlapping clinical features (Subramony 1999). Gradually progressive ataxia associated with an array of cerebellar signs forms the core feature of most of these diseases. Patients exhibit progressive ataxia of gait associated with clinical signs of limb ataxia such as dysmettia and adiadokokinesia. Speech is dysarthric, often with spastic components. Eye movement abnormalities related to cerebellar dysfunction are common and include abnormal pursuit and inaccurate saccades in addition to nystagmus. Many, but not all, of the disotdcrs are also associated with clinical signs referable to pathology in CNS structures other than cerebellum and its connections (Diaz et .-.'.. $I^{1})$"!); Seijuims and tioulinho P'^{1}' >; Goldfarb et al. 1996; Schols et al. 1996; Gomez et al. 1997), Oculomotor abnormalities unrelated to cerebellar dysfunction include gaze palsy, ptosis, blepharospasm, and an "ocular stare," Many patients have additional bulbar deficits such as facial atrophy, facial fasciculations, tongue atrophy and fasciculations, and poor ability to cough. Upper motor neuron signs such as brisk reflexes with or without spasticity, and Babinski's signs occur early in many dominant ataxias. Extrapyramidal signs including akinetic-rii',id syndromes, hypomimic fades, chorea, athetosis, and dystonia (Figure 78.4) tend to occur variably in dominant ataxia in different stages of the illness. Evidence of peripheral nerve disease occurs often and includes distal sensory loss and loss of deep tendon reflexes, as well as amyotrophy, (n selected dominant ataxias, there can be associated cerebral signs such as cognitive decline or seizures; in others, there is evidence of retinal disease with visual loss (Figure 78.5).

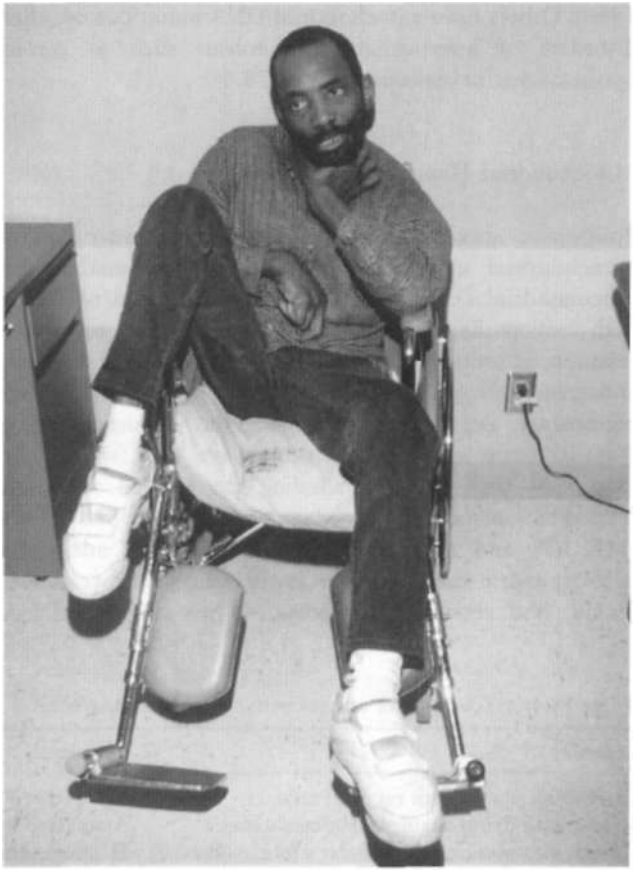


FIGURE 78.4 Dystonia in a patient with Machado-Joseph diseasi.

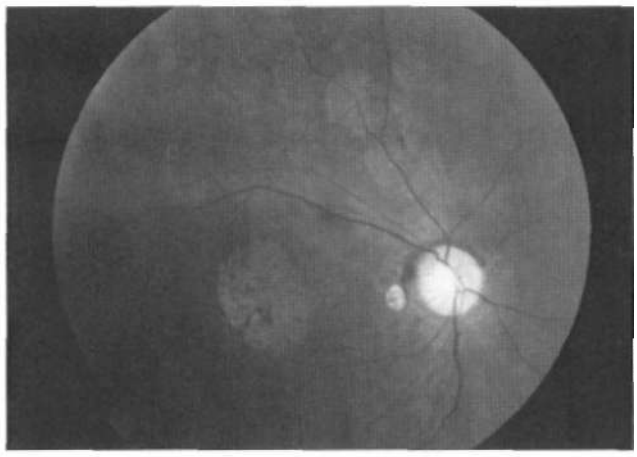


FIGURE 78.S Maculoparhy in a patient with spinocerebellar ataxia type 7.

The motor syndrome is inexorably progressive with loss of ambulation over 10-15 years. A faster rate of progression is correlated with earlier onset of disease.

Individual gene mutations often exhibit considerable phenotypical heterogeneity. Some of the clinical heterogeneity within members of the same family is related to duration of the disease; for example, previously present nystagmus may disappear as the saccadic system gets involved or brisk deep tendon reflexes may disappear because of increasing peripheral nerve pathology. Other differences in clinical signs are related to the severity of the gene mutation itself and other intrinsic and extrinsic factors.

The underlying gene mutation docs affect the clinical picture to some degree, but clinical differences between the various genotypes are not sufficient to permit confident clinical diagnosis of the genotype without the appropriate mutation analysis. Table 78.6 summarizes some clinical features that may help in the clinical differentiation of various progressive dominant ataxias.

The EA syndromes cause intermittent episodes of imbalance, dysarthria, vertigo, and abnormal eye movements that last from minutes to hours. At least two different gene mutations give rise to EA. EA-1 is associated with brief episodes of ataxia and no interictal cerebellar abnormalities; however, many patients have skeletal muscle myokymia interictally. In EA-2, the ataxic episodes arc longer and may be associated with some interictal abnormalities such as nystagmus. Some patients with EA-2 also develop progressive ataxia.

Imaging and Other Laboratory Studies in Dominant Ataxias

MRI and computed tomographic scans of the brain are useful to exclude many disorders causing ataxia other than the inherited causes such as strokes, tumors, and multiple sclerosis. The dominant ataxias arc associated with progressive atrophy of the cerebellum; in addition, there may also be atrophy of the pons, medulla, middle cerebellar peduncles, and upper cervical cord (Klockgether et al. 1998) (Figure 78.6). There can be some hyperintensity of the middle cerebellar peduncles on T2-weighted images. Imaging studies alone are insufficient to differentiate the various genotypes. SCA-1, SCA-2, and SCA-3 are usually associated with pontocerebellar atrophy, and SCA-6 with isolated cerebellar atrophy. Experience with other disorders is limited. Many of the dominant ataxias arc also associated with evidence of an axonal polyneuropathy on nerve conduction studies *:\nii* abnormal hrainstem-evoked responses.

Table 78.6: Distinctive phenotypical features of some dominant ataxias; in general, the various genotypes resemble each other closely

Phenotypical feature	*Disorders*
Age at onset	Young adult: SCA-1, SCA-2, MJD; older adult: SCA-6; childhood onset frequent in SCA-7/DRPLA
Degree of anticipation	More in SCA-7, DRPLA
Benign course	SCA-6
Upper motor neuron signs	SCA-1, -7, -8, MJD; rare in SCA-2
Akinetic-rigid/ Parkinson's signs	MJD, SCA-2, SCA-17
Chorea	Prominent in DRPI.A; late in SCA-2, -1, MJD
Action tremor	SCA-12, 16
Very slow saccades	Early in SCA-2, -7; late in SCA-1, MJD; never in SCA-6
Downbeat nystagmus	SCA-6, EA-2
Generalized a reflex ia	SCA-2, SCA-4, older adult-onset MJD
Visual loss	SCA-7
Vi/.UIYS	SCA-10, early onset DRPLA, SCA-7

DRPI.A = dcntatorubral-pallidoluysian atrophy; EA = episodic ataxia; MJD = Machado-Joseph disease; SCA = spinocerebellar ataxia.

Neuropathology

SCA-1, SCA-2, and SCA-7 are usually associated with fairly widespread pathology in the nervous system including loss of Purkinjc cells in the cerebellum, pontine neurons, and olivary neurons (Figure 78.7). In addition, other structures such as dorsal root ganglion cells, Clarke's column cells, and cranial and lower motor neurons may be affected, together with their tracts. In MJD, cerebellar Purkinje cells are relatively spared, but there is severe involvement of pontine neurons, Clarke's column cells, and nigral cells. Spinal motoneurons and vestibular nuclei arc also involved. SCA-6 is characterized by isolated involvement of the Purkinje cells and olivary neurons (Robitailic- et al. *1997)* (Figure 78.8).

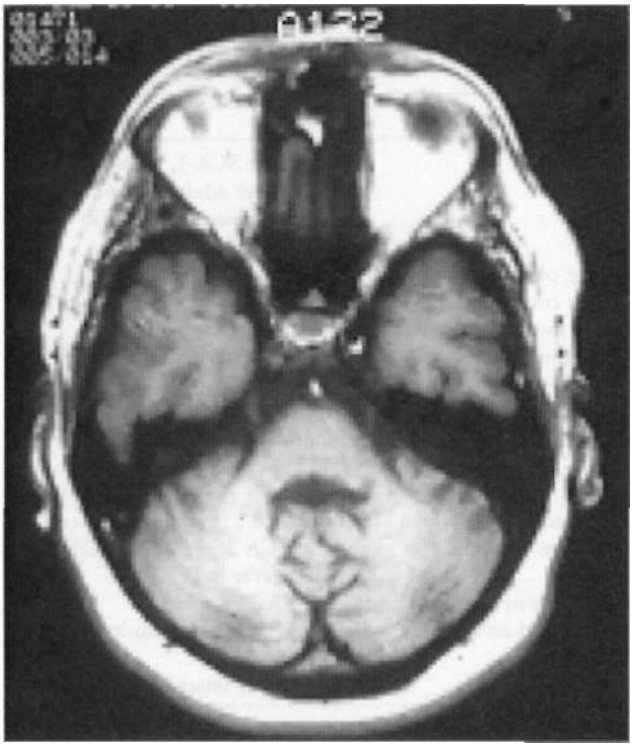


FIGURE 78.6 Magnetic resonance imaging scan of the brain in a patient with spinocerebellar ataxia type 1, showing ponto-cerebellar atrophy.

FIGURE 78.8 Isolated cerebellar atrophy in a patient dying with spinocerebellar ataxia type 6.

Gene Mutations and Phenotype—Genotype Correlations in Dominant Ataxias

Both unstable expansions of repeated nucleotide sequences {Figure 78.9) and point mutations have been related to dominant ataxias. At least eight dominant ataxias arc related to unstable expansions of CAG repeats inherited in a heterozygous fashion (Orr ct al. 1993; Kawaguchi et al. 1994; Nagafuchi ct al. 1994; Pulst et al. 1996; Zuchenko et al. 1997; David et al. 1998; Holmes et al. 1999; Zuhlke et al. 2001); all are progressive diseases. Because CAG codes for glutamine and the protein product of the mutated gene contains excess number of gluta mines, many such diseases are examples of polyglutamine disorders. All the CAG expansion diseases are characterized bv an inverse correlation between the number of repeats in the expanded alleh and thi' age ;i(u:iscl. 1 argcr repeal sizes are also associated with more rapid progression of the disease and with more rapid atrophy of posterior fossa structures. Thus the phenotypical heterogeneity within single genotypes is related to a complex interaction between the size of the repeats in a particular individual, the duration of the disease, and additional environmental and genetic factors of unknown nature. The unstable nature of these expansions causes a change in the size of the repeats from one generation to the next, accounting for the variability in age at onset and some of the phenotypical heterogeneity. The observed anticipation in age at onset of many dominant ataxias can be at least partly explained by the expansion of these unstable repeats. Typically, paternal transmission of the disease is associated with a greater tendency for expansion. The SCA-6 CAG expansion, which involves

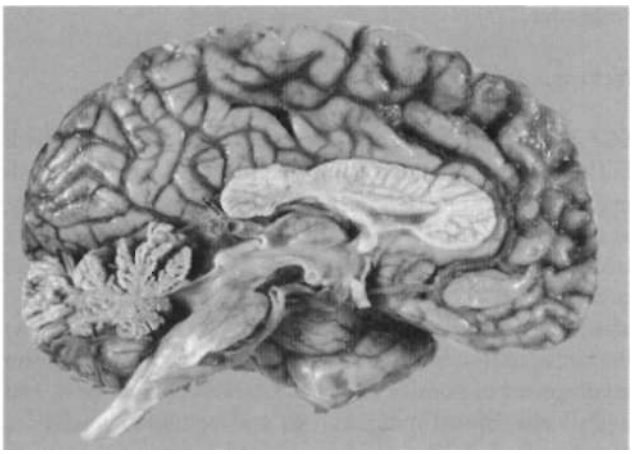


FIGURE 78.7 Gross features showing cerebellar and brainstem atrophy in a patient dying with spinocerebellar ataxia type 1.

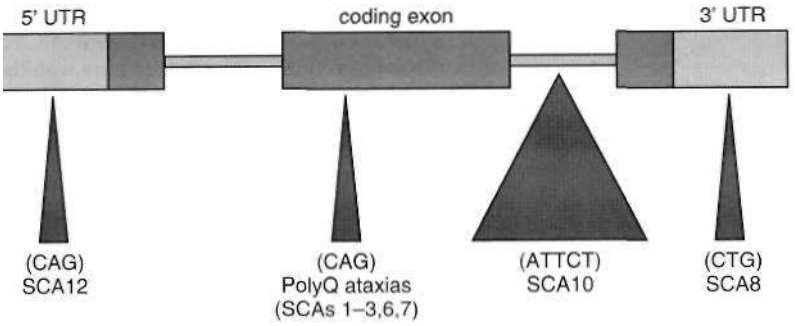


FIGURE 78.9 Schematic representation of various repetitive nucleotide expansions in dominant ataxias. (Courtesy Dr. H. Paulson, University of Iowa.)

the wi-SLibiinit of the neuronal calcium channel gene, is exceptional in that it is transmitted in a stable fashion for the most part.

The recently described SCA-8 has been related to an unstable expansion of a CTG tract in the V untranslated region of the gene on chromosome 13 (Koob et al. 1999). The primary roie of this expansion in causing ataxia has been controversial because the same CTG expansion has also been found in patients with other disorders such as stroke and Parkinson's disease and even in general population samples (Stevanin et al. 2000; Worth et al, 2000). The vertical transmission of the expansion has been extensively studied in only one family by Koob et al. (1999), in which a significant lod score was calculated; even in this family, there were several nonpenetrant individuals who had expansions of the repeat into a larger than normal but presumably nonpathogenic range. Thus the interpretation of an expanded SCA-8 CTG repeat in an individual with ataxia remains controversial, and the possibility exists that either the expansion is not fully penetrant or the real mutation is somewhere else but in linkage dysequilibrium with the expansion. The CTG tract in the SCA-8 gene is transcribed to a messenger RNA (mRNA) but not translated into a protein.

Still another form of repeat expansion occurs in SCA-10, a disorder typified by progressive ataxia and epilepsy. The mutation is a large unstable expansion of a pentanucleotide repeat (A'lTCT) on chromosome 22 (Matsuura et al. 2000).

The CAG expansion in the recently reported SCA-17 involves the TATA binding protein (TBP) gene (Zuhlke et al, 2001). This is of interest because TBP is a critical player in transcription, and transcriptional dysregulation may occur in many of the other polyglutamine diseases as well.

The EA syndromes are related to point mutations. In EA-1, the mutation involves a potassium channel gene (KCNA1) on chromosome 12 (Browne et al, 1994). EA-2 has been related to both nonsense and missense mutations in the ai-subunit of the calcium-channel gene (CACNA1) (Ophoff et a I. 1996). Poor penetrance and phenotypical variability have been well documented in EA-2 (Danier et al, 1999).

A number of dominant ataxias have been localized to specific chromosomes, but the mutations are as yet undefined. These include SCA-4 (chromosome I6q), SCA-5 (chromosome lip), SCA-11 (chromosome 15q), SCA-13 (chromosome I9q), SCA-14 (chromosome 19q), and SCA-16 (chromosome 8q), SCATS (chromosome 7q), SCA-21 (chromosome 7), and SCA-23 (chromosome 20p) (Ranum et al, 1994; Flanigan et al. 1996; Worth et al, 1999; Herman-Bert et al. 2000; Miyoshi et al. 2001; Yamashita et al. 2000; Takashima et al. 2002; Brkanac et al. 2002; Verbcck et al, 2002; Vuillaumc et al. 2002). Still others are known to be in as yet unknown loci and these include SCA-9, SCA-15, and SCA-22 (Storey et al. 2001; HUGO Web site).

Pathogenesis

The pathogenesis of the dominant ataxias has been the subject of intense research since the mid-1990s (Paulson 1999; Zoghbi and Orr 2000; Or 2001). The CAG expansion disorders have been particularly scrutinized by many workers. The SCA-1, SCA-2, SCA-3, and SCA-7 proteins, as well as the DRPLA protein, have all been novel proteins of unknown function and have been named ataxins 1, 2, 3, and 7, and atrophin, respectively. In all these diseases, evidence has accumulated for the gain-of-function hypothesis (Figure 78.10). This states that the disease is caused by the acquisition of a novel toxic function by the protein product of the mutated gene, rather than by the deficiency of the protein, which is typical of many recessive diseases. This idea is consistent with the fact that disease occurs from a single copy of the mutated allele. In all these diseases, the mutated allele is transcribed and translated into its respective protein product in a widespread fashion. Because CAG codes for glutamine, the mutant protein has a longer stretch of glutamines than wild type protein; thus the CAG expansion diseases have also been called *polyglutamine disorders.* The distribution of the protein has also been shown to be different in diseased brain. Normally, most of the proteins have a diffuse cytoplasmic localization with some additional nuclear presence. However, in diseased brain tissue, the protein has been shown to accumulate as aggregates within the nucleus in SCA-1, SCA-3, and SCA-7, as well as in DRPI.A (Orr 2001). In SCA-2,

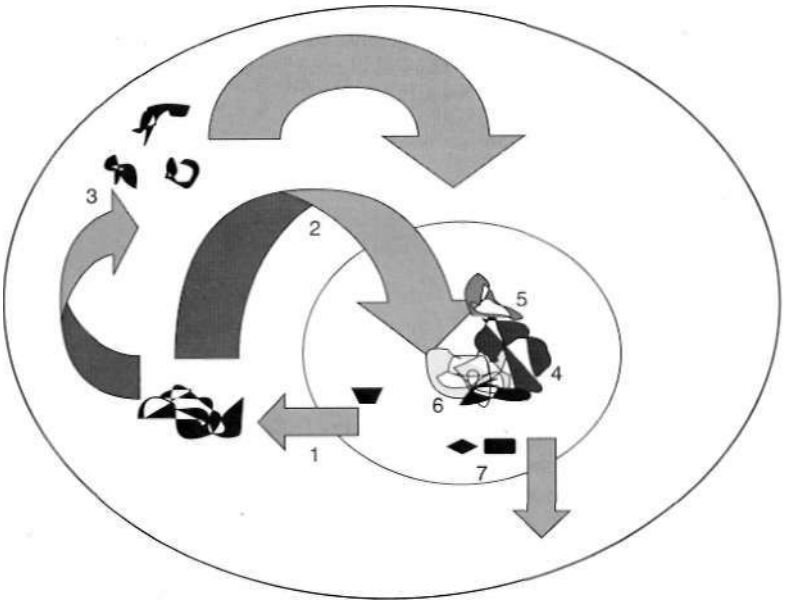


FIGURE 78.10 Diagrammatic representation of some current ideas about the pathogenesis of CAG expansion disorders. 1. The mutant gene with the CAG expansion is transcribed and translated to *a* mutant protein with an excess number of glutamines. 2. The mutant protein enters the nucleus where it forms aggregates (4). 3. In some situations, truncation of the mutant protein by caspases or similar enzymes might possibly create fragments of the protein containing the polyglutamine tract and such fragments may then enter the nucleus. 4. Formation of nuclear inclusions (Nls). In selected situations, aggregates may occur in the cytoplasm ;is well. 5,fi. Nls recruit a variety of other nuclear proreins including the ubiquitin-proteasome system, the heat shock protein system, and transcription factors. The list of proteins associated with NI is slowly growing. 7. Secondary events may include r ra user i prion a 1 dysregulation of other critical genes or as yet unknown pathways such as depletion of critical nuclear proteins.

aggregation of the protein appears to he predominantly in the cytoplasm. Nuclear inclusions (Nls) have heen shown to contain the mutated protein in each instance, and the expanded ghitamine tract is important in the formation of the NI. The Nls also have heen shown to recruit a variety of other proteins such as members of the heat shock protein (hsp) chaperone system and the ubiquitin-proteasome pathway. These findings support the idea that the mutated protein assumes a misfolded configuration (Paulson 1999). The presence of Nl has been reproduced in many transgenic and transfection models of the CAG expansion disorders. Genetic engineering of the hsp and ubiquitin-proteasome pathway has been shown to modify the intensity of NI formation in these model systems and to alter the toxicity of the mutant protein. Also, in some model systems, such as those for MJD and DRPLA, truncated construct[1]; of the gene containing the CAG expansion have been more efficient in causing pathology. Whether truncation of the mutant protein occurs in human tissue in the case of the ataxias is not yet established, although many of the proteins do have caspase sites. In addition, the essential role of NI in the pathogenesis of neuronal death has been questioned. In fact, in SCA-1 transgenic mouse, genetic manipulation has been able to disassociate the NI from neuronal loss; the deletion of a self-association domain from the ataxia-1 gene prevented the formation of NI, but the pathology was not diminished. On the other hand, deletion of a nuclear localization signal preventing nuclear entry of the mutated protein was enough to prevent neurological disease, establishing the importance of nuclear entry. This has given rise to the idea that interference in essential nuclear functions by the mutated protein may be an important mechanism of disease. Such secondary events may include binding to essential nuclear proteins including transcription factors and downregulation of other essential genes.

The SCA-6 CAG expansion may cause disease by a mechanism different from the aforementioned scenario, although aggregation of the calcium-channel protein in the cytoplasm has been reported (Ishikawa et al. 1999). Expression studies of the mutated channel protein also have suggested that altered calcium-channel function may play a role (Restituito et al. 2000). This may also he true for the point mutations in the calcium-channel gene associated with EA-2.

SI'OH UMC ATAXIAS

The occurrence of progressive cerebellar ataxia clinically resembling inherited ataxias but with no definite genetic etiology has been recognized for more than 100 years. The term *sporadic ataxia* has been used for such a process when other well-established causes of cerebellar ataxia have been excluded. Some of the common causes of ataxia such as multiple sclerosis, strokes, and tumors can be easily excluded by imaging studies. Other causes of ataxia such as alcohol and hypothyroidism have nonspecific imaging findings and can be diagnosed only by appropriate history and laboratory studies. There is little understanding of the etiopathogenesis of truly sporadic cases of ataxia. Sporadic ataxia with childhood or young adult onset may still have undefined single-gene mutations as the underlying cause. When sporadic ataxia has onset in older adults (idiopathic late-onset ataxia), it may be the result of a complex interplay of genetic and environmental factors. It should be noted that among patients with a diagnosis of sporadic

ataxia, a very small percentage test positive for one of the known gene mutations. It is difficult to make specific recommendations regarding the gene tests that need to he obtained in a patient with sporadic ataxia (Tan and Ashizawa 2001). The FA GAA expansion and the SCA-6 CAC, expansion may be the most likely to yield a positive result (Abele et al. 2002). One should consider some of the mutation analyses in patients with sporadic ataxia if the family history is not very clear or the clinical picture is more typical for one of the genetically determined ataxias. Among patients with idiopathic late-onset ataxia, some have added noneerebellar signs and some do not (Klockgcther et al. 1990).

Sporadic Cortical Cerebellar Atrophy

Sporadic cortical cerebellar atrophy usually has onset in patients older than 50 years and results in a progressive ataxia not associated with other neurological deficits even many years after onset. MRI scans and pathological examination usually show isolated cerebellar atrophy, but this correlation is not absolute. The disease has a slow progression with a median life span of more than 20 years after onset.

Sporadic Ataxia with Added Noncerebellar Deficits

Patients with sporadic ataxia with added noncerebellar deficits initially have slowly progressive ataxia bur soon develop additional signs such as upper motor neuron signs, ophthalmoplegia, parkinsonian features, and autonomic failure. In keeping with this, both MRI and pathological examination show cerebellar and brainstem degeneration; the autonomic structures may be affected as well. Thus the L1UIIL.I1 picture of this disorder merges with that of the olivopontocerebellar atrophy form of multiple system atrophy (MSA). Among patients with idiopathic progressive ataxia, 25-35% will transition to probable MSA over 5-10 years (Gilman et al. 2000). The clinical evidence for this in most will be added parkinsonian and autonomic deficits, but in a few, only autonomic failure develops. Such signs include orthostatic hypotension, incontinence, erectile dysfunction, rigidity, and facial hypomimia. Older age at onset and a more rapid progression to a disabled state suggest a higher risk of such transmission. Median survival after such transition was only *3.5* years. Sphincter electromyography and cardiovascular autonomic testing may be useful to confirm the diagnosis of MSA. Signs of autonomic failure are uncommon in the inherited ataxias, although bladder dysfunction is not uncommon in late stages.

CIJNTCAL APPROACH TO PATIENTS WITH DEGENERATIVE ATAXIAS

A careful clinical approach to patients presenting with progressive ataxia allows accurate diagnosis and appropriate management (Figure 78.11). The age at onset, the tempo of progression, associated neurological and systemic signs, and the availability of family history all can be considered in making a diagnosis. Imaging studies, especially MRI ol the brain, allow diagnosis of those disorders in which characteristic morphological abnormalities underlie ataxia, such as infarcts, mass lesions, or dcmyclinating plaques. Other laboratory studies of value include thyroid function, vitamin E and P;_ levels, serology for syphilis, gliadin and antt-GAD antibodies, antibodies associated with paraneoplastic syndtomes, and possibly CSF examination for pleocytosis, oligoclonal bands, and malignant cells. In young adults and children, specialized biochemical tests, as indicated in Table 78.3, may be indicated.

Tabic 7S.7: Normal and pathogenic range of repeat expansions associated with inherited ataxias

Disease	*Repeat*	*Norma!*	*Intermediate*	*Expanded*
FA	. .\ : ı	*h* 40		66 to >1000
SCA-1	CAG	6-44		39-82
SCA-2	CAG	14-31	32-33	33-64
V1Jl.)	CAG	12-40		54-86
SCA-6	CAG	4-18		19-30
SCA-7	CAG	4-27	28-36	37-200
SCA-8	CTG	16-91		107-127[2]
SCA-10	ATTCT	10-22		1000-4500
SCA-12	CAG	*<29*		66-78
SCA-17	CAG	25-44		50-63
(TBP)DRPLA	CAG	7-35		44 SS

Note: In SCA-1, the normal and pathogenic ranges overlap. However, the pathogenic-ally expanded repeat can be distinguished from the normal repeat by the absence of CAT interruptions.
DRPLA = dentatorubral-pallidoluysian atrophy; FA = Friedreich's ataxia; M)D = Machado-Joseph disease; TBP = TATA-hinding protein.

Table 78.8: Geographical variation in the prevalence of various genotypes among autosomal dominant ataxias

Area	*SCA-1*	*SCA-2*	*MJD*	5C4-6	*SCA-7*	DRPLA	*Unknown*
United States	6	15	20	12	5		42
Germany	*9*	10	42	22			17
United Kingdom	*35*	40	9				9
Prance	15	15	33	2			35
Japan	3	5	43	11		20	18
India	8	25	5	0	0	0	62
Australia	16	*6*	12	17	2		47
China (Soong)	5	11	47	11	3	1	22

Source: Data summarized with permission from Storey, E., du San, D., Shaw, J, H,, et al. 2000, "Frequency of spinocerebellar ataxia types 1, 2, 3, 6 and *7* in Australian patients with spinocerebellar ataxia," *Am] Med Genet,* vol. 95, pp. 351-357,

DNA testing is now available for EA, SCA-1, SCA-2, MJD, SCA-6, SCA-7, SCA-8, **SCA-10,** SCA-12, SCA-17, and DRPI.A (Table 78.7). Gene testing is possible for AT, autosomal recessive ataxia of Charlevoix-Saguenay, AVED, ataxia with oculomotor apraxia type 1, and EA syndromes but is not readily available. Patients with features compatible with specific inherited ataxias, as discussed earlier in this chapter, are candidates for such DNA testing. Such testing is very accurate and relatively inexpensive. However, the genetic heterogeneity of the

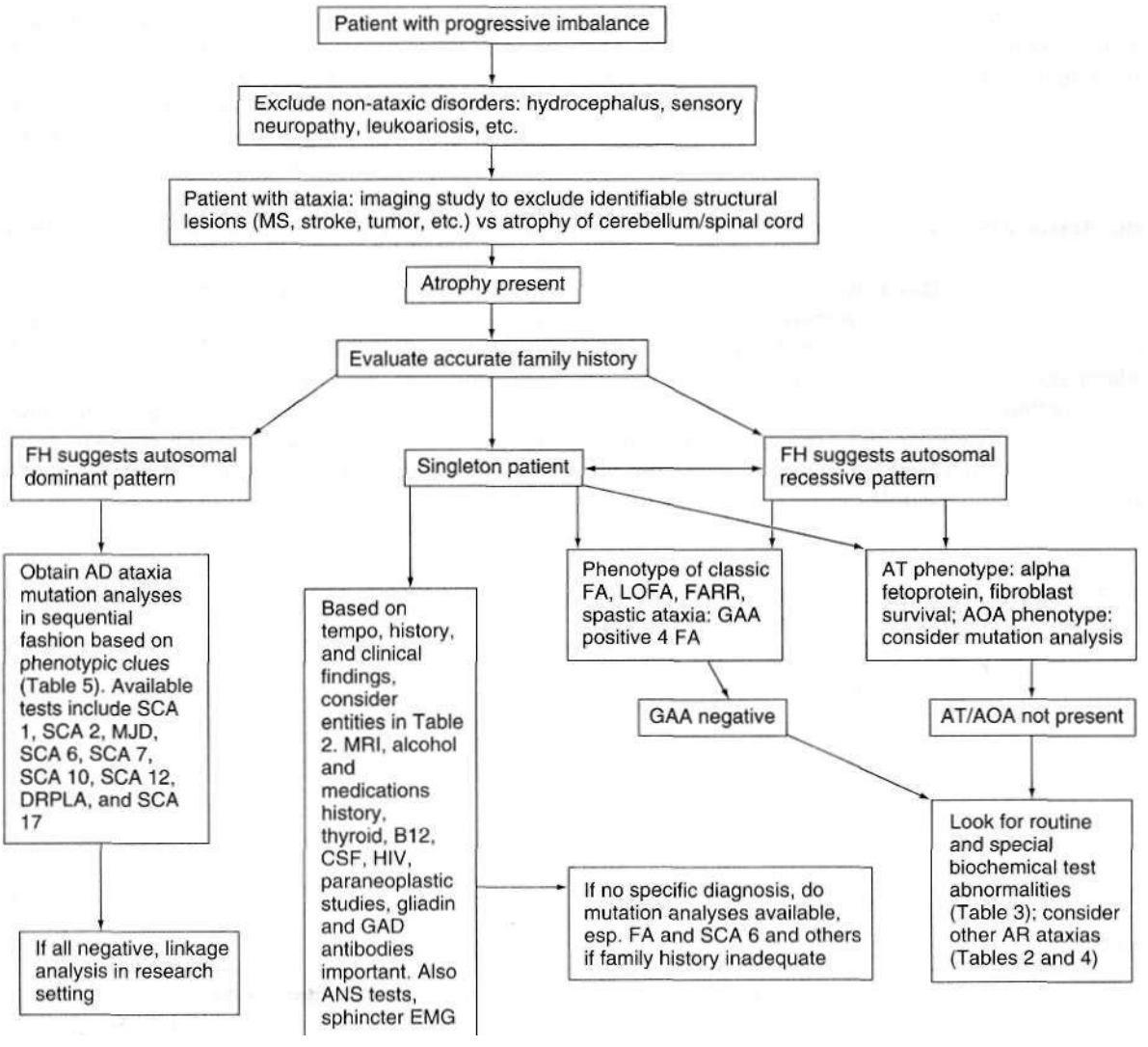


FIGURE 78.11 An algorithm for a diagnostic approach to patients with progressive ataxia.

ataxias, the overlapping phenotypes, and the fact tliat there arc unknown genotypes all make such tests less than optimal. Some of the phenotypical features discussed earlier can serve as guidelines to select appropriate mutation analyses. In addition, information regarding ethnic predilections among the ataxias may also guide the selection of tests (Tahle 78.8). Thus FA is restricted to European, Indian, and Middle I'.astem populations. Ataxia with oculomotor apraxia is the most common recessive ataxia in Japan and second only to FA in Portugal. Among dominant ataxias, MJD is the most common in Germany, |ap,tn, China, and most South American countries. SCA-2 appears co he more prevalent in the United Kingdom, Italy, and India. SCA-6 is common in Japan, DRPI.A constitutes close to 20"o oi dominant ataxias in some parts ol Japan but is uncommon elsewhere. Lastly, certain population isolates have a high incidence of certain ataxias, such as SCA-1 among the Iakut in Siberia, SCA-2 in eastern Cuba, and MJD in the Azorean islands.

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Chapter 79
Disorders of Bones, Joints, Ligaments, and Meninges

Richard B. Rosenbaum and David P. Ciaverella

Because of their proximity to the nervous system, disorders of the bones, joints, ligaments, and meninges can cause several myelopathic and radiculopathy syndromes and can affect the cranial nerves and intracranial contents. This chapter considers many of these disotders, both congenital and acquired. Chapters of overlapping interest include Chapters 27, 56C, 57b, and 66.

CONGENITAL AND INHERITED SPINAL DISORDERS

Disorders of the craniocervical junction include bony abnormalities of the occiput and foramen magnum, dysfunction of connecting ligaments, hindbrain malformations, upper cervical skeletal deformities, and syringomyelia or syringobulbia (Mcnzes 1997). Many of these are congenital; their embryogenesis is discussed in Chapter 66, Magnetic resonance imaging (MRI) and computed tomogtaphic (CT) scanning have improved the detection, understanding, and treatment of these anomalies.

Craniocervical Deformities

Occipitalization of the Atlas

Occipitalization ot assimilation of the atlas refers to congenital partial or complete fusion of the atlas (first cervical vertebra) to the occiput (Figute 79.1). The anterior arch of the atlas may fuse to the lower end of the clivus or the posterior arch of the atlas may fuse to the occiput. The anomaly is often asymptomatic until early adult life and may become symptomatic after trauma. Unilateral occipitalization of the atlas is one cause of torticollis in young children. The loss of movement between the occiput and atlas increases the stresses at the atlantoaxial joint, predisposing it to gradual degeneration or traumatic dislocation. Patients with occipitalization of the atlas may have associated anomalies, such as the Klippel-Feil anomaly, basilar impression, or Chiari malformation.

Basilar Impression

Basilar impression or *invagination* refers to abnormal cephalad position of the fotamen magnum (Goel et al. 1998).

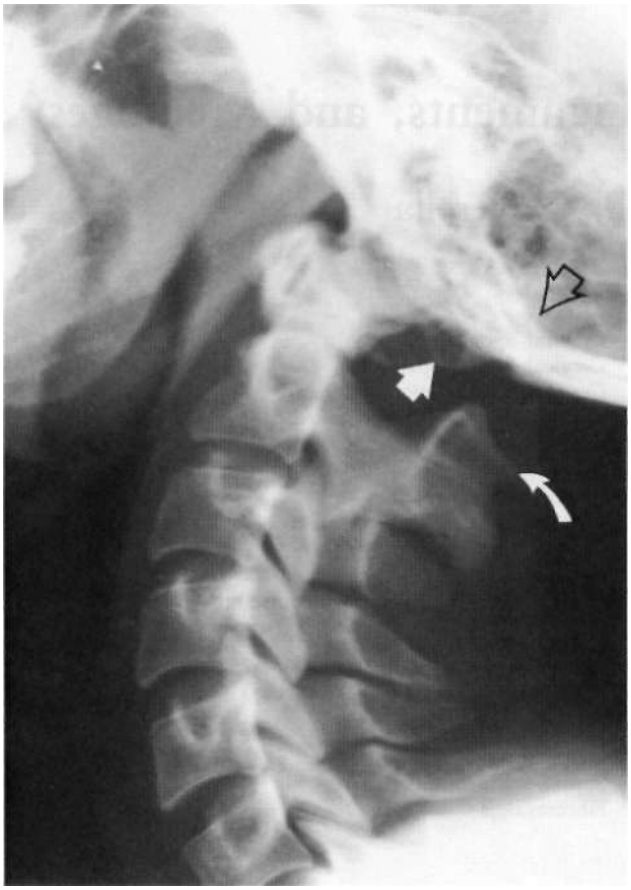


FIGURE 79.1 Occipitalization of the atlas. Radiograph shows fusion of the lamina of the atlas to the occiput *(open arrow).* The lamina contains the circular arcuate foramina *[arrow),* through which the vertebral arteries pass. The spinous process of the atlas *{curved arroiv)* has fused with C2, making this a partial incorporation of CI into the skull base. There is a broad spectrum of variations in this congenital anomaly. (Courtesy Erik Gaensler.)

Several radiological lines (Chamberlain's, McGregor's, McRae's, digastric) (Figure 79.2) and measurements can be used to make the diagnosis. Congenital basilar impression may occur in isolarion or may be associated with conditions such as achondroplasia, occipital dysplasia, Down syndrome, Hurler's syndrome, Klippel-Feil anomaly, and cleidocranial dysplasia. Some instances of basilar impression are familial. The skeletal anomaly is often accompanied by anomalies of the neuraxis, including Chiari 1 or II malformation and syringomyelia. Basilar impression can cause compression of the brainstem (Figure 79.3) or cerebellum, or rarely vertebral artery compression, leading to vertebrobasilar ischemia. It is often asymptomatic, particularly when mild and unaccompanied by other anomalies.

Platybasia or *flattening of the skull* refers to straightening of the angle between the clivus and the floor of the anterior fossa. It infrequently accompanies basilar impression; it can occur also as an isolated radiographic finding without any adverse neurological consequences.

Klippel-Feil Anomaly

Patients with the Klippel-Feil anomaly (congenital synostosis of the cervical vertebrae) (Figure 79.4) have short necks, low haitlines, and limitation of cervical motion. The diagnosis is confirmed by radiographic demonstration of fused cervical vertebrae. The condition is congenital, caused by failure of normal segmentation of the cetvical vettebrae between the third and eighth weeks of fetal development. Although familial instances oecut, most cases ate isolated and idiopathic. The anomaly can cause direct nerve root, cetvical spinal cord, or vcrrebtal or spinal artety compression, Neck pain is common. Hearing loss is the most common symptom of cranial neuropathy. Mitror

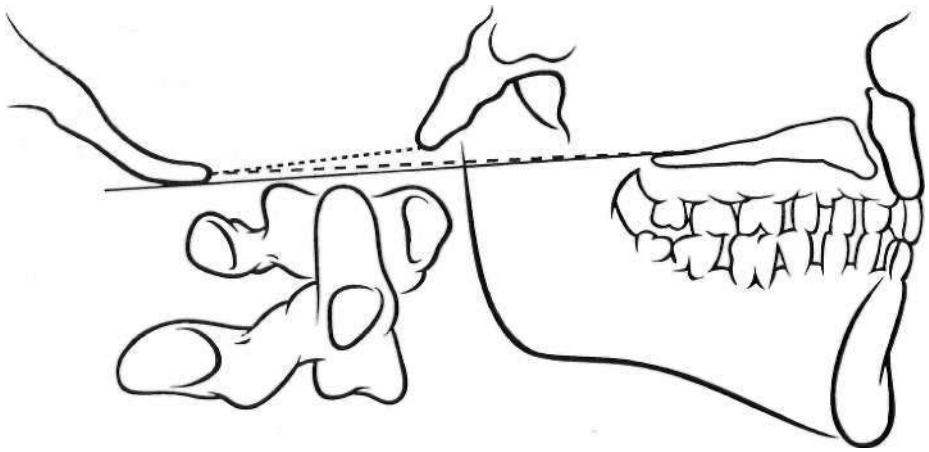


FIGURE 79.2 Chamberlain's line *(dashes)* extends from the roof of the hard palate to the posterior lip of the foramen magnum; McGregor's line *(solid)* extends from the roof of the hard palate to the most caudal portion of the occipital bone; McRae's line *[dots]* extends from the anterior lip of the foramen magnum ro the posterior lip of the foramen magnum. The tip of the odoiitoid is normally not more than 5 mm above McGregor's line and not above Chamberlain's or McRae's line. (Modified with permission from Roscnhaum, R. B, Campbell, S. M., *&c* Roscnhaum, J. T. 1996, *Clinical Neurology of Rheumatic Diseases,* Burtcrworth-Heinemann, Boston.)

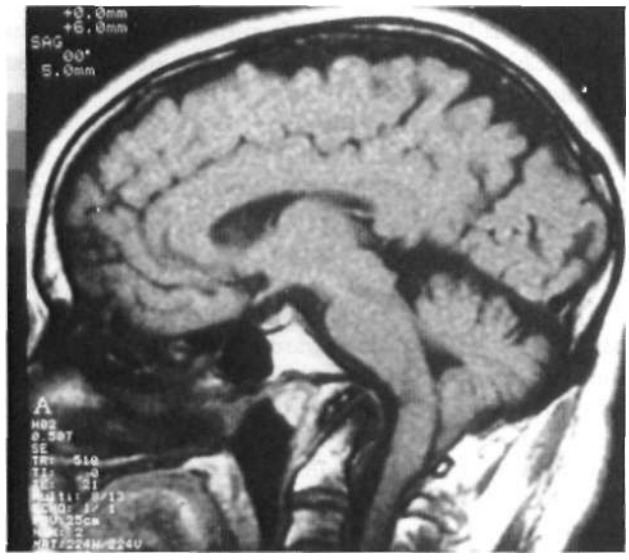


FIGURE 79.3 Magnetic resonance image of a patient with basilar impression showing angulation of the brainstem.

movements of the hands may occur in children with Klippel-Feil anomaly and are attributed to incomplete decussation of the pyramidal tracts. Patients with Klippel-Feil anomaly can have a wide variety of associated abnormalities of brain, spinal cord, or skeletal development, especially congenital scoliosis ot Sprengel's deformity with unilateral shoulder elevation. Patients may develop hydrocephalus, syringomyelia, or syringobulbia. However, most patients with Klippel-Feil anomaly have no neurological symptoms or signs.

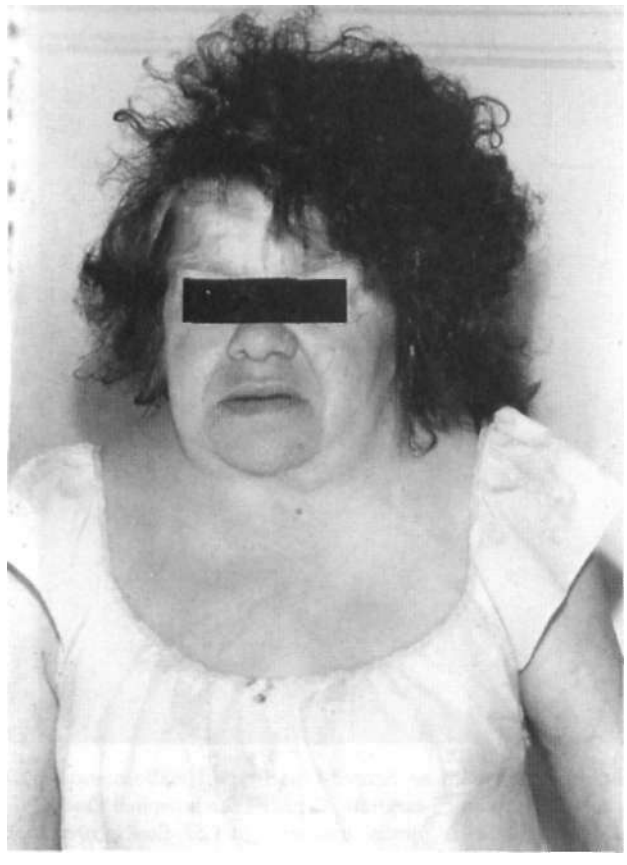


FIGURE 79.4 Patient with Klippel-Feil syndrome showing short neck,

Atlantoaxial Dislocation

Various congenital or acquired conditions can disrupt the integrity of the atlantoaxial joint, leading to its dislocation (Table 79.1). In horizontal subluxation, CI usually moves anteriorly to C2. The movement can be assessed by measuring the separation between the dens and the anterior arch of CI on flexion radiographs; in adults, the separation should not exceed *3.5* mm. Patients with horizontal atlantoaxial joint subluxation are likely to compress their spinal cords if the diameter of the spinal canal at the level of the dens is less than 14 mm, and they are unlikely to if the diameter is more than 17 mm. The actual relationship between the cord and the subluxing bones is best imaged wiili MRI or CI myelography, which should include I iix i< >n and extension views. In some patients, particularly those with acquired inflammatory disease, such as rheumatoid arthritis (RA), inflamed adjacent soft tissue contributing to cord compression is best characterized by MRI.

Patients with congenital atlantoaxial dislocation may have associated abnormalities such as Chiari I malformation or diastcmatomyelia. They can develop secondary syringomyelia. Atlantoaxial subluxation in patients with long-standing RA is a prime example of acquired

Table 79.1: Mechanisms of atlantoaxial dislocation

[. Congenital
- A. Os odontoideum (failure of the odontoid to fuse with the body of the axis)
  - 1. Isolated
  - 2, With connective tissue dysplasias (e.g., Down syndrome, pscudoacbondroplasia, multiple epiphyseal dysplasia, spondyloepiphyseal dysplasia, Morquio's disease, Klippel-Feil anomaly, Conradi's syndrome)
- B. Hypoplastic dens
  - 1. With connective tissue dysplasia
  - 2. With incomplete segmentation (e.g., occipital assimilation of atlas, basilar invagination, incomplete segmentation of C2, C3, and so forth)
- C. Other anomalies of C2 (e.g., bifid dens, tripartite dens with os apieale, agenesis of all or part of dens)
- D. Laxity of the transverse arlantal ligament (e.g., Down syndrome)

II. Acquired
- E. Traumatic, acute or chronic un-united dens fracture
- F. Infectious
- G. Neoplastic (e.g., neurofibroma)
- H. Arthritic (e.g., in rheumatoid arthritis, ankylosing spondylitis, renal amyloidosis)
- I. Bone disease (e.g., vitamin D-resistant rickets and others associated with basilar invagination)

abnormality of the atlantoaxial joint and is discussed in more detail later in this chapter. Patients with atlantoaxial subluxation may be asymptomatic, particularly if their spinal canal diameter is generous. However, they are vulnerable to spinal cord trauma during intubation or other neck motion under anesthesia, or in relation to a whiplash injury. Patients at risk of atlantoaxial dislocation, such as those with Down syndrome or chronic RA, should have lateral flexion and extension cervical spine radiography performed before general anesthesia so the anesthesiologist can plan appropriate care during intubation.

Arnold-Chiari Malformation and Syringomyelia

Arnold-Cbiari Mai format ion

Chiari (1891, 1896) described four types of malformations with cerebellar tonsillar displacement. Cleland (1883) had previously written about them. Arnold (1894) reported a case of Chiari II malformation. In current usage, the terms *Arnold-Cbiari* and *Chiari malformation* are often used interchangeably for all four types.

Chiari 1 malformation (Figure 79.5) is characterized by abnormal extension of the cerebellar tonsils below the foramen magnum and is sometimes accompanied by rostral displacement or extension of the medulla. Slight extension of the tonsils below the foramen is normal in childhood, and normal values decrease with increasing age (Table 79.2). Cerebellar tonsillar displacement below the foramen magnum results from downward herniation of the brain caused by mass lesions or sagging of the brain in patients with low intracranial pressure. Patients with Chiari malformations of all types often have hydrocephalus, syringomyelia, or syringobulbia. Patients may have associated bony abnormalities such as basilar impression, occipitalization of the atlas, or CI-level spina bifida.

Chiari I malformations can be asymptomatic (Meadows et al. 2000). Clinical manifestations, which typically begin in young adulthood, can include headaches, visual

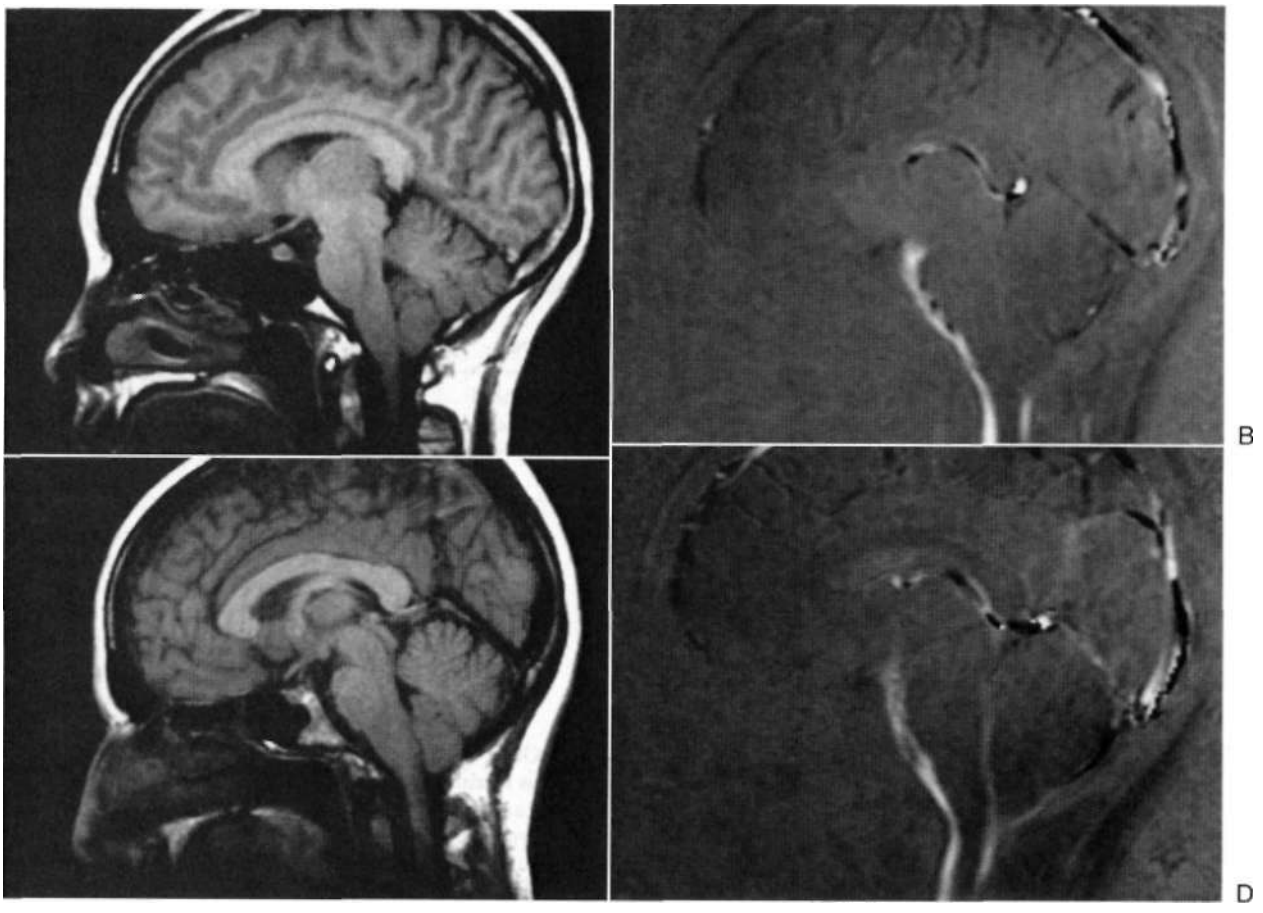


FIGURE 79.5 (A) Sagittal magnetic resonance imaging (MRI) scan of a patient with an Arnold-Chiari type I malformation. This midline Tl-wcighted image demonstrates low cerebellar tonsils, 8 mm below the foramen magnum. (Id VI RI ferebrospirial fluid (CSF) flow study of the same patient demonstrates diminished flow signal at the cerebellar tonsils, indicative of CSF flow propagation abnormality. Notice the normal CSF flow signal below the tonsils and anterior to the brainstem. (C) Sagittal MRI of a patient with low-lying cerebellar tonsils at 6 mm below the foramen magnum, and (D) CSF flow study demonstrating normal flow signal ar the level of the cerebellar tonsils. This is indicative of normal propagation of CSF flow through the foramen magnum.

Tabic 79.2: Suggested upper limits of normal for position of the cerebellar tonsils below the foramen magnum

Decade of life	*Distance below the foramen magnum {nun)*
First	6
Second or third	5
Fourth to eighth	4
Ninth	3

Source: Data used with permission from Mikulis, D. J., Diaz, O., Egglin, T. K., et al. 1992, "Variance of the position of the cerebellar tonsils with age: Preliminary report," *Radiology,* vol. 183, pp, 725-728.

disturbances, neurootologica! complaints, cranial nerve dysfunction, and sleep apnea (Milhorat et al. *1999).* Motor, sensory, sphincter, and reflex disturbances suggestive of myelopathy can occur whether or not a syrinx is present. Despite speculation and public interest, there is no scientific confirmation of an association between Chiari I malformation and fibromyalgia or chronic fatigue syndrome (Garland and Robertson 2001).

The malformation is best seen on sagittal MRI scans of the brain and cervical spine, which allows assessment of the shape of the posterior fossa, search for any accompanying syrinx, and extent, if any, of brainstem compression. Magnetic resonance cerebrospinal fluid (CSF) flow imaging of CS! pulsation at tin.' for .inu-n magnum in both systole and diastole may provide further information about the significance of tonsillar ectopia, the potential for development of syringohydromyelia, and value of decompressive surgery.

Surgical treatment of Chiari I malformation is aimed at brainstem decompression; any associated syrinx will often improve after improvement in CSF flow.

Chiari II malformation combines the features of Chiari I with caudal displacement of the medulla and fourth ventricle. The brainstem is elongated and distorted at the foramen magnum. Usually, patients have a lumbar myelomeningocele.

In Chiari III malformation, the displaced cerebellar and brainstem tissue extends into an infra tentorial meningocneephalocele.

Chiari IV malformation is characterized by cerebellar and brainstem 1npi>pl;w:i i.i;kr ih.in dn-p aivneni and is probably a variant of the Dandy-Walker malformation.

Hydromyelia, Syringomyelia, and Syringobulbia

Hydromyelia is an abnormal dilatation of the central spinal canal, which almost always communicates with the fourth ventricle. A syrinx is a cavity in the spinal cord (syringomyelia) or brainstem (syringobulbia) (Figures 79.6 through 79.8). The cavity may be connected with a dilatated central spinal canal or may be separate from the central canal. There are several causes of syringomyelia.

Clinical Presentation. The prototypical presentation of a syrinx is the combination of lower motor neuron signs at the level of the lesion (usually in the arms or lower cranial nerves), a dissociated suspended sensory loss (impaired pain and temperature sensation but preserved light touch, vibration, and position sense in a cape or hem i-cape distribution on the arms and upper trunk), and spinal long tract dysfunction below the level of the lesion. However, few patients show this total picture, and the clinical features vary with the size, location, and shape of the cavity and with associated neurological conditions.

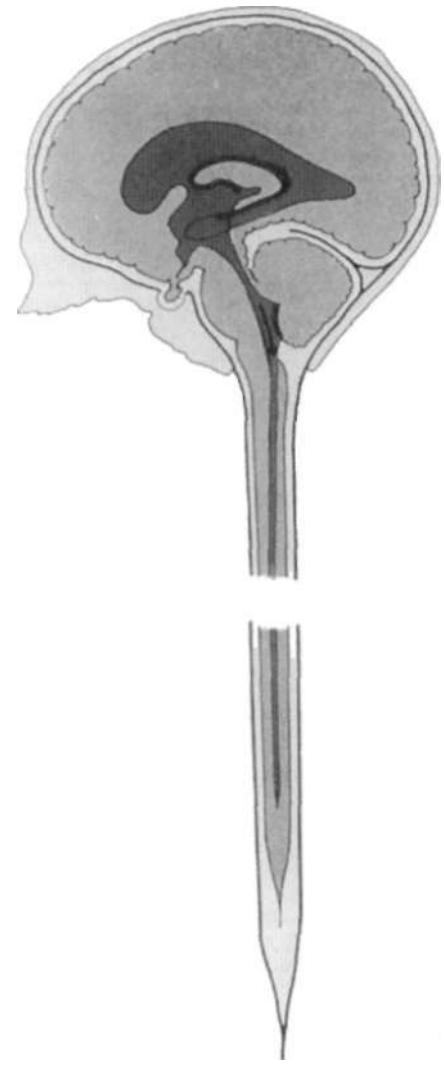


FIGURE 79.6 Diagrammatic representation of persistent central i anal extending throughout the length of the spinal cord.

Fain is a prominent symptom in most patients with syringomyelia. Common complaints include neck ache, headache, back pain, radicular pain, and areas of segmental dysesthesia. Some patients have trophic changes corresponding to the segmental dysesthesia. Sytingomyelia can cause neuropathic monoarthritis (Charcot's joints), most commonly in a shoulder or elbow.

Most syringes are in the cervical spinal cord. Those developing from hydromyelia of the central canal are usually associated with Chiari I or II malformations,

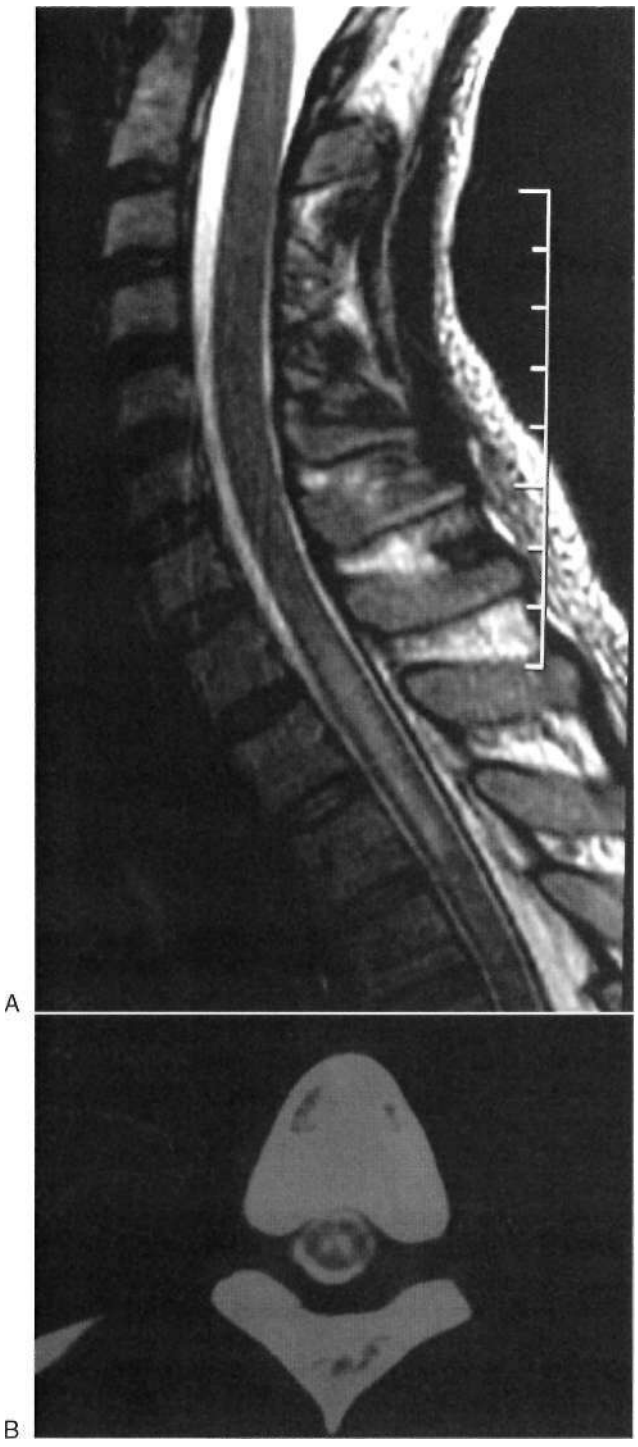


FIGURE 79.7 (A) Sagittal T2-weighted magnetic resonance imaging demonstrates intramedullary signal abnormality posterior to the T1-T3 level of rhe spinal cord. Possible causes include edema, myelomalacia, or syringohydromyelia. (B) Axial computed tomographic myelogram performed at a 3-hour delay demonstrates filling of the area of signal abnormality with myelography contrast that had been injected into the lumbar subarachnoid space. The filling of the cavity with contrast is consistent with syringohydromydia but would not be expected in cases of cord edema or myelomalacia.

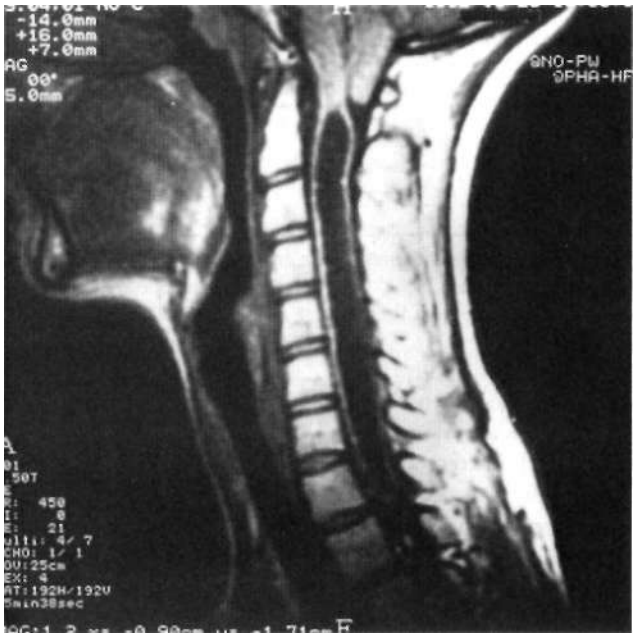


FIGURE 79.8 Magnetic resonance image demonstrates a large syringomyelic cavity in the cervical cord.

communicating hydrocephalus, or abnormalities at the craniocerebral junction. Hydromyelia and these associated syringes may be noted as asymptomatic abnormalities on MRI scans obtained to study the cranial problems. When the syrinx enlarges as an asymmetrical localized paracentral outpouching from the hydromyelia, particularly at its cranial or caudal ends or at its level of greatest axial cross section, the paracentral extensions often lead to local segmental signs such as cranial nerve dysfunction in patients with syringobulbia, as well as segmental lower motor neuron signs and dissociated sensory changes at the level of spinal involvement. Patients with eccentric cavities have some combination of long tract and segmental signs depending on the location of the cavity and of any associated cord pathology such as tumor, ischemia, or contusion. A syrinx associated with a spinal cord tumor can occur at any level of the spinal cord.

Although either CT or MRI can demonstrate a syrinx, MRI is more sensitive for complete evaluation of the cord and surrounding soft tissues. CT myelography can be useful in discerning syringohydromyelia, which will commonly fill with contrast on delayed images, because of communication with the CSF through the central canal of the spinal cord (see Figure *79.7A* and B}.

Causes

Communicating and Noncommunicating Syringes. The terms *communicating* and *noncommunicating syringes* indicate whether the syrinx is in communication with the CSF pathways. However, it is often difficult to determine this, even at autopsy, and hence these terms are mainly of use in discussions of etiology. It is better to classify syringomyelia according to its associations.

Abnormalities of the Cervicomedullary Junction

The exact mechanism of production of the syrinx m patients with abnormalities of the cervicomedullary junction and posterior fossa is controversial (Oldfield 2001). The central canal of the spinal cord is normally widely open during embryonic life and becomes atretic after birth. It can be found occasionally to be patent in the adult (see Figure 79,6). It is more commonly dilatated (hydromyelia) when associated with abnormalities of the cervicomedullary junction, including Chiari anomalies types I and 11 and the Dandy-Walker malformation. Syringes often arise in association with hydromyelia and are formed as out-pouchings of the dilatated central canal (see Figures 79.7 and 79.8). One hypothesis is that the posterior fossa abnormalities interfere with the passage of CSF from the fourth ventricle through the foramina of Luschka and Magendic into the subarachnoid space. The consequence is transmission of bulk flow and the various pressure waves of the CSF (arterial, venous, respiratory, and so forth) down the central canal of the spinal cord, leading to dissection of a syrinx into the substance of the spinal cord. Noncongenital abnormalities at the cervicomedullary junction that sometimes cause syringomyelia include arachnoiditis and meningiomas.

Syrinx Associated with Spinal Cord Tumors

Syringomyelia accompanies 25-60% of intramedullary spinal tumors; conversely, 8-16% of syringes are caused by tumors (Figure 79.9). Intramedullary tumors in von Hippel-Lindau syndrome or neurofibromatosis are particularly likely to be accompanied by syringes. The syrinx extends from **the** tumor, more often rostrally than caudally.

Syrinx Associated with Spinal Cord Trauma

Syringes develop as late sequelae in perhaps 3% of cases of serious spinal cord trauma. Symptoms of usually ascending long tract or segmental spinal cord dysfunction develop months or years after the acute traumatic myelopathy has stabilized, improved, or even become asymptomatic. Pain is often a prominent symptom. Findings usually evolve gradually but occasionally worsen suddenly after events such as *a* cough or Valsalva maneuver. The cavity is usually eccentric, arising from an area of post-traumatic myelomalacia, then spreading rostrally or caudally.

Syrinx Associated with Other Focal Spinal Cord Pathologies

Any illness causing arachnoid inflammation can lead to formation of a noncommiinicating syrinx. Reported causes include meningitis, subarachnoid hemorrhage, spinal trauma, epidural infections, epidural anesthesia, myelography with oil-based dyes, and spinal surgery, but many cases of focal arachnoiditis are idiopathic. Syringes can develop as a complication of various intramedullary pathologies including trauma and tumors (see previous discussion), spinal ischemic or hemorrhagic strokes, radiation necrosis, or transverse myelitis.

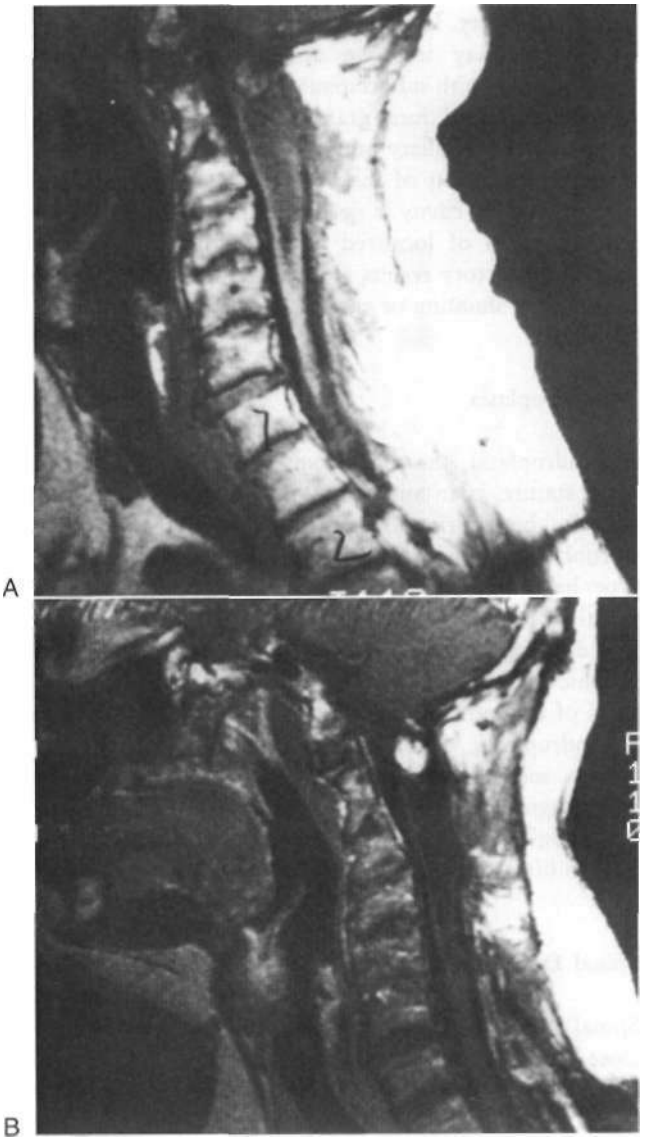


FIGURE 79.9 Magnetic resonance image demonstrates syrinx associated wirh spinal cord tumor (hcmangioblastoma). (A) Tl-weighted image shows enlargement has a nodule on the upper cervical cord caused by a low-signal central mass suggestive of a cyst. The upper border of the cyst has a nodular component. (B) Postgadolimum image shows that the nodule intensely enhances, which is classic for hcmangioblastoma. (Courtesy Erik Ciaensler.)

Treatment. Indications for and approaches to surgical therapy for syringes are far from standardized (Goel and Desai 2000). The cavity may be drained by simple myelotomy or by shunting to the subarachnoid, peritoneal,

or pleural cavity. In patients with Chiari I malformations, the syrinx may improve after decompression of the malformation with suboccipital craniectomy, tipper cervical laminectomy, and dural grafting. When the syrinx extends from an intramedullary tumor, resection of the tumor often leads to regression of the syrinx, so no specific surgical drainage of the cavity is needed. When the syrinx extends from an area of localized arachnoiditis, some surgeons report satisfactory results after resection of the arachnoiditis without shunting or entering the cavity.

Achondroplasia

Achondroplasia, the most common cause of abnormally sin in stature, is ,*m* autosomal dominant disorder of endochondral bone formation caused by a specific mutation of a fibroblast growth factor receptor gene. The mutant genotype has complete penetrance, and approximately three fourths of cases occur because of spontaneous mutation. The diagnosis can be confirmed by pathognomonic radiographic changes or by DNA testing. Neurological complications of achondroplasia are common (Table 79.3). Young achondroplasia children should be observed for complications such as hydrocephalus, compression at the foramen magnum, thoracolumbar kyphosis, and sleep apnea. Neurological complications of spinal stenosis tend to occur later in life.

Spinal Dysraphism

Spinal dysraphism is congenital failure of the neural tube to close during fetal development (Botto et al. 1999). In spina bifida occulta the vertebral elements fail to fuse, but the thecal and neural elements remain within the spinal canal. In spina bifida cystica {also called *spina bifida aperta),* the meninges protrude out of the spinal canal through the bony defect; neural elements may be contained within the protruding sac.

Tabic 79,3: Neurological complications of achondroplasia

Macrocrania, with or without hydrocephalus
Foramen magnum abnormalities with cervicomedullary compression
Respiratory disturbances, including sleep apnea and sudden infant death syndrome
Syringomyelia, diastematomyelia
Spinal stenosis with spinal cord or nerve root compression
Infantile hypotonia
Cortical atrophy
Atlantoaxial subluxation
Psychomotor delay (most have normal intelligence)

Source; Adapted with permission from Ruiz-Garcia, M., Tovar-Baudin, A,, Del Castillo-Ruiz, V., et al. 1997, "F.arly detection of neurologic:)! manifestations in achondroplasia," *Child Nerve Syst,* vol. 13, p. 208.

Spina Bifida Occulta

Spinal bifida occulta is usually asymptomatic. It is most common at posterior elements of L5-S1 and is usually noted as an incidental finding on spinal plain radiography (Figure 79.10). Cutaneous abnormalities may be associated (Table 79.4). Orthopedic foot deformities, urinary or rectal sphincter dysfunction, or focal neurological abnormalities can indicate that the spina bifida occulta is associated with compression or malformation of neural tissues or with spinal cord tethering.

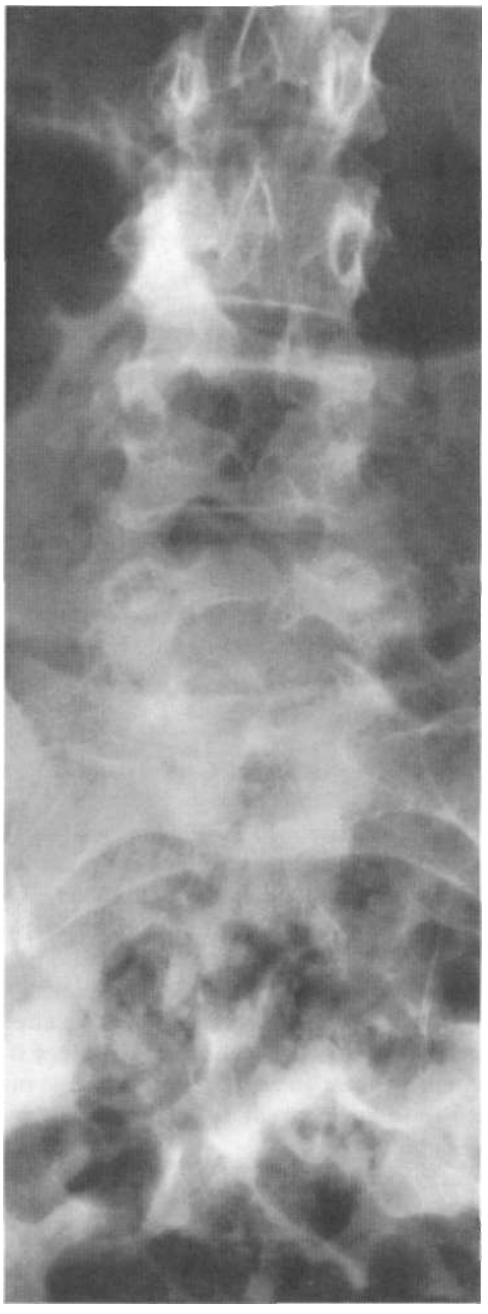


FIGURE 79.10 Lumbar spine radiograph shows spina bifida occulta.

table "9.4: l)urs.il midlife skir findings associated with spina bifida occulta

WmnKIIk.'II I'JIIU.II I'dlii
Dermal sinus or dimple
Hairy tuft
Hemangioma
Lipoma
Nevus
Pilonidal sinus
kiuiiMi/iu.m lail
Spinal aplasia cutis

Myelomeningocele

Myelomeningocele and meningocele (spina bifida cystica) are congenital defects of spinal closure that when present are often visible on examination of the back of the newborn (Figures 79.12 and 79.13). When the skin and vertebral canal are unclosed, a sac of meninges is directly visible. The defect is most common in the lumbar region. If it contains nerve roots or spinal cord, it is a myelomeningocele; if neural elements are absent from the sac, it is a meningocele. It is often accompanied by hydrocephalus and may be accompanied by cerebellar tonsillar herniation (Chiari II malformation), syringomyelia, or cerebral malformations such as poly microgyria. Initial surgical treatment in utero or in the neonatal period can provide cosmetic repair and decrease the risk of infection; hydrocephalus can be shunted. Any existing myelopathic or radiculopathic neurological deficit is likely to persist after surgery. The infants are at risk for later development of tethered cord syndrome (sec Tethered Cord Syndromes, later in this chapter) or of spinal dermoid or epidermoid inclusion cysts.

Myelomeningocele is the most common major birth defect. An impottant cause is maternal folate deficiency, and most cases would be prevented if women with childbearing potential routinely took 0.4 tng of folic acid daily. Other risk factors include family history of neural closure defects, and maternal treatment with antiepilcptic drugs such as valproic acid. Pregnant women can be screened for serum cr-fetoprotein levels, which are elevated when the fetus has neural closure defects. The defects also can iv delected by fetal ultrasound.

Tethered Cord Syndromes

Congenital abnormalities of the spinal cord or cauda equina can prevent normal cephaiad movement of the conus mcdullaris during early life (McLone and La Marca 1997) (Table 79.5). A child or even an adult with these abnormalities can develop progressive neurological dysfunction due to traction on the cord or nerve roots. The most common neurological finding is unilateral lower motor neuron dysfunction in one leg, but patients can also have sensory, upper motor neuron, or sphincter dysfunction. Children also may present with orthopedic foot deformities or scoliosis.

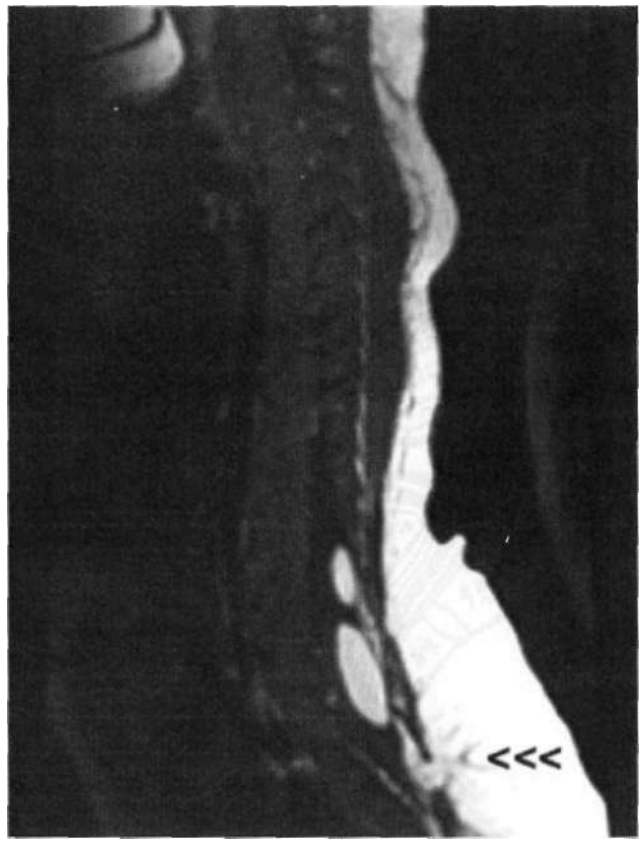


FIGURE 79.11 Sagittal T]-weighted magnetic resonance image demonstrates several findings. The conus medullaris is low lying; there are lipomas of the filum terminale (bright signals within the central canal); and there is spina bifida with protruding lipomyelomeningocele through the defect *(arrowheads).*

Diastematomyelia (Figure 79,14) is a congenital malformation of the spinal cord characterized by sagittal division of a portion of the cord into two hemicords. In most instances, the division is located in the lower thoracic or lumbar regions. Diastematomyelia is often accompanied by skin abnormalities, such as a tuft of hair at the level of the lesion. If each hemicord is enclosed in its own arachnoid sheath, the sheaths are usually separated by a bony, cartilaginous, or fibrous spur and by dura in the cleft between the two portions of the cord. The spinal cord is usually tethered by the spur, leading to progressive neurological dysfunction as the spinal cord attempts to move upwards upon the spur during growth. The diagnosis can often be suspected on plain radiography, which shows widening of the interpeduncular distance and a posterior bony bridge at the level of the lesion. MRI scans or CT myelography can confirm the diagnosis (see Figure 79.14), Surgical therapy consists of attempts to free all structures tethering the cotd by removing the spurs and dura in the cleft and cutting the filum terminale if abnormal.

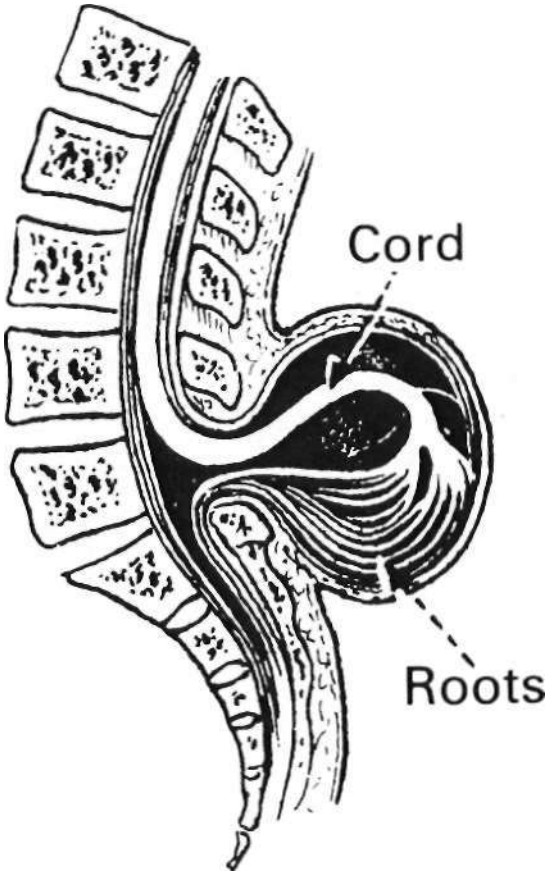


FIGURE 79.12 Diagrammatical representation of myelomeningocele.

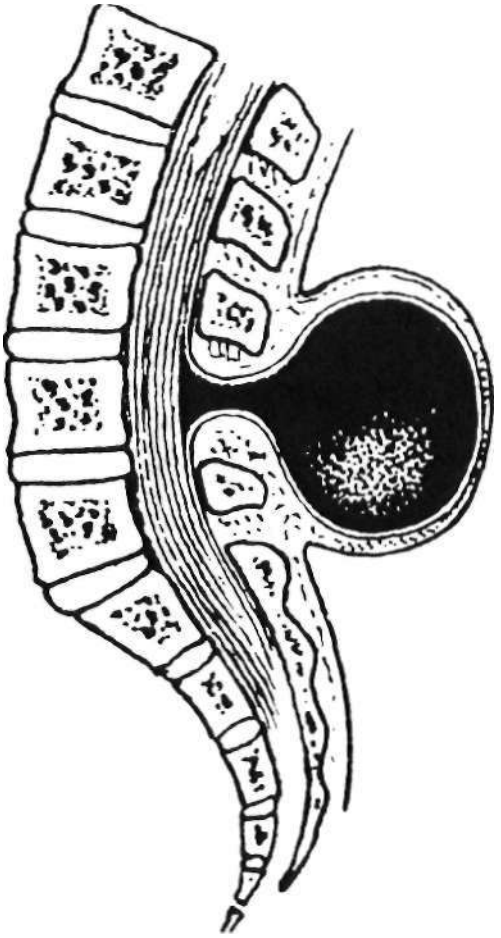


FIGURE 79.13 Diagrammatical representation of meningocele.

Clinical Correlations. A single patient often has more than one of the conditions discussed {Figure 79.15). Thus a patient with one of the Chiari hindbrain malformations also may have some combination of bony abnormalities of the foramen magnum or cervical spine, syringomyelia, and meningomyelocele.

The clinical manifestations of craniocervical deformities are protean depending on which neural structures and associated anomalies are involved. When a patient has these problems, diagnosis and treatment starts by analyzing each component. MRI and CT scans have greatly eased the analytical ptocess. Many patients arc asymptomatic or first present with neurological complaints in adult life. Patients may have short necks or abnormal neck posture or movement, particularly if there is an element of skeletal deformity (e.g., Klippel-Fcil anomaly and occipitalization of the atlas). Findings attributable to the brainstem or cerebellum may occur with Chiari malformations, compression of the brainstem (e.g., basilar impression or vertical displacement of the dens), or syringobulbia. Uncommonly, atlantoaxial disease or basilar invagination can cause compromise of vertebrobasilar circulation, causing posterior circulation strokes or transient ischemic attacks. Specific findings suggestive of disease at the foramen magnum include downbeat nystagmus or the combination of long tract signs with lowet motor neuron dysfunction in the lower cervical spinal cord; the lower

Table 79.5: Causes of tethered spinal cord

Primary causes
Dermal sinus tract
Dias tenia romyclia
Dural hands
Intraspinal lipoma or tumor
Meningocele, myelomeningocele, anterior sacral meningocele
Neuroenteric cyst
Sacral agnesis
Tight filum terminale
Secondary causes
Arachnoiditis
Dermoid
Re-tethered spinal cord
Suture granuloma
1 r:iiiin I

Source; Adapted with permission from McLonc, D. G. *He* La Marca, F. 1997, "The tethered spinal cord: Diagnosis, significance, and management," *Sem'm Pediatr Neurol,* vol. 4, pp. 192-208.

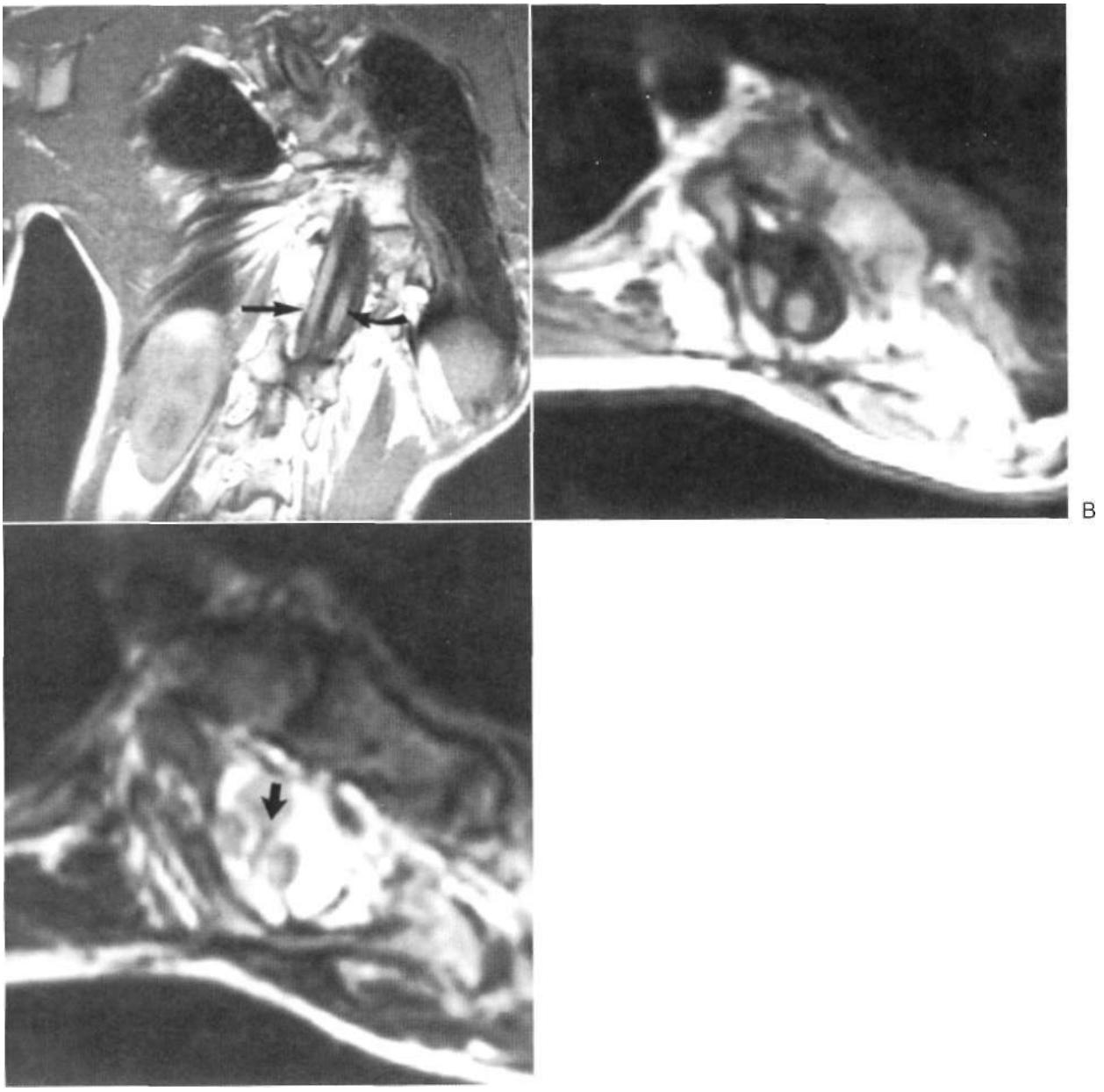


FIGURE 79.14 Magnetic resonance image of a patient with diastematomyelia. (A) Sagittal Tl-weighted image shows severe scoliosis and division of the spinal cord into right *[arrow)* and left *(curved arrow)* hemicords. (B) Axial Tl-weighted image confirms the presence of two hemicords. (C) Axial gradient-echo image demonstrates two separate subarachnoid spaces divided by a central fibrous spur *(arrow).* (Courtesy Erik Gaensler.)

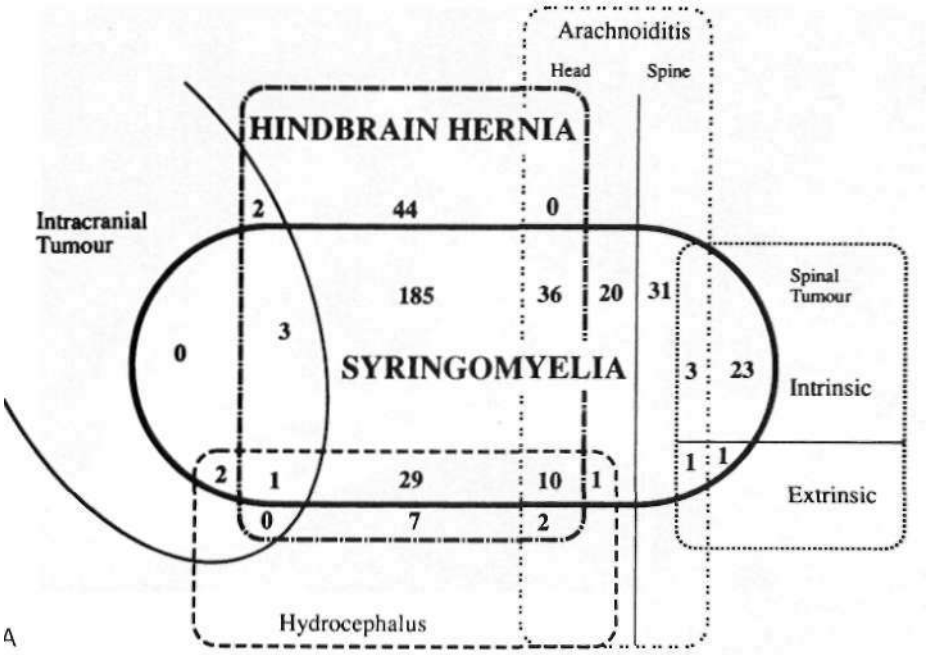
motor neuron dysfunction has been attributed to impaired spinal venous drainage at the foramen magnum.

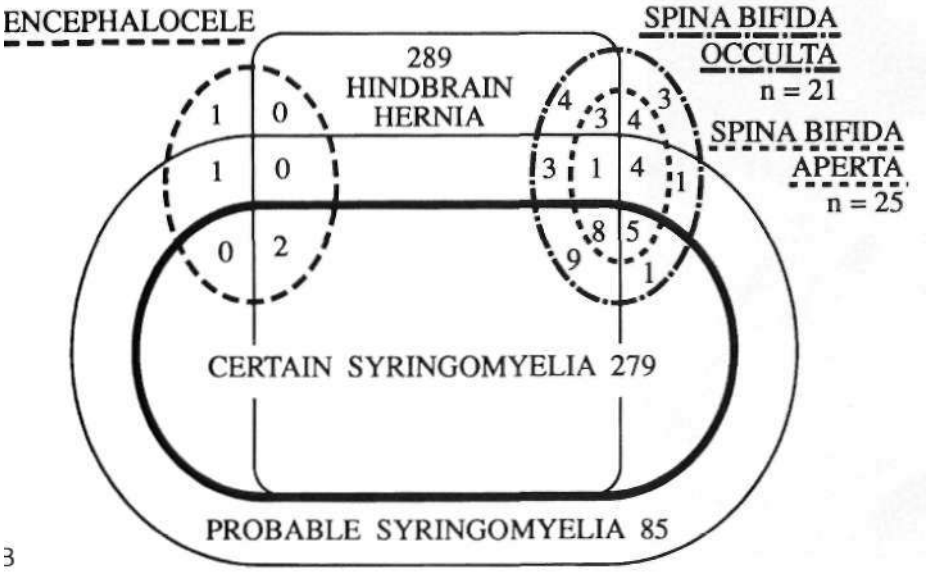
Spinal cord syndromes can be caused by syringomyelia or by extramedullar}' cord compression (e.g., by the dens with atlantoaxial dislocation or by spinal stenosis in Klippel-Eeil anomaly). Additional neurological dysfunction can occur when the anomalies form part of more widespread developmental failure (e.g., lumbar effects of myelomeningocele in Chiari II malformation or accompanying cerebral malformations in Klippel-Feil anomaly).

SPINAL DEFORMITIES AND METABOLIC BONE DISEASE

Osteoporosis

Osteoporotic vertebral compression fractutes occur most commonly in the thoracic and thoracolumbar spine (Figure 79.16). Most occur in postmenopausal women. By age 75 years, nearly one fourth of women have vertebral compression fractures; although these may lead to kyphosis and loss of body height, most are painless. In younget men and





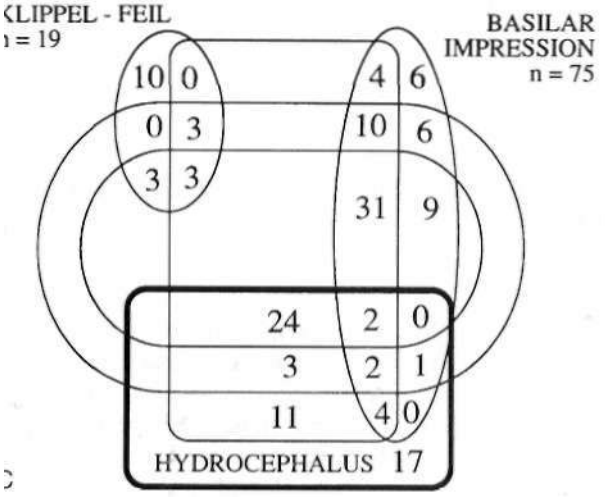


FIGURE 79.15 Venn diagrams show the overlap of various craniospinal abnormalities from patients seen at a center specializing in syringomyelia. (A) Findings in 346 patients with syringomyelia and 304 patients with Chian malformations (hindbrain hernia). (B) Findings in patients with dysraphism syndromes compared with patients with syringomyelia or Chiari malformations. (C) Findings in Klippel-Feil anomaly or basilar impression compared with patients with syringomyelia *{ovals)* or Chiari malformations *{round rectangle).* (Reprinted with permission from Williams, B. 199], "Pathogenesis of syringomyelia," in *Syringomyelia; Current Concepts in Diagnosis and Treatment,* ed U. Batzdorf, Willi a ins & Wilkins, Baltimore.)

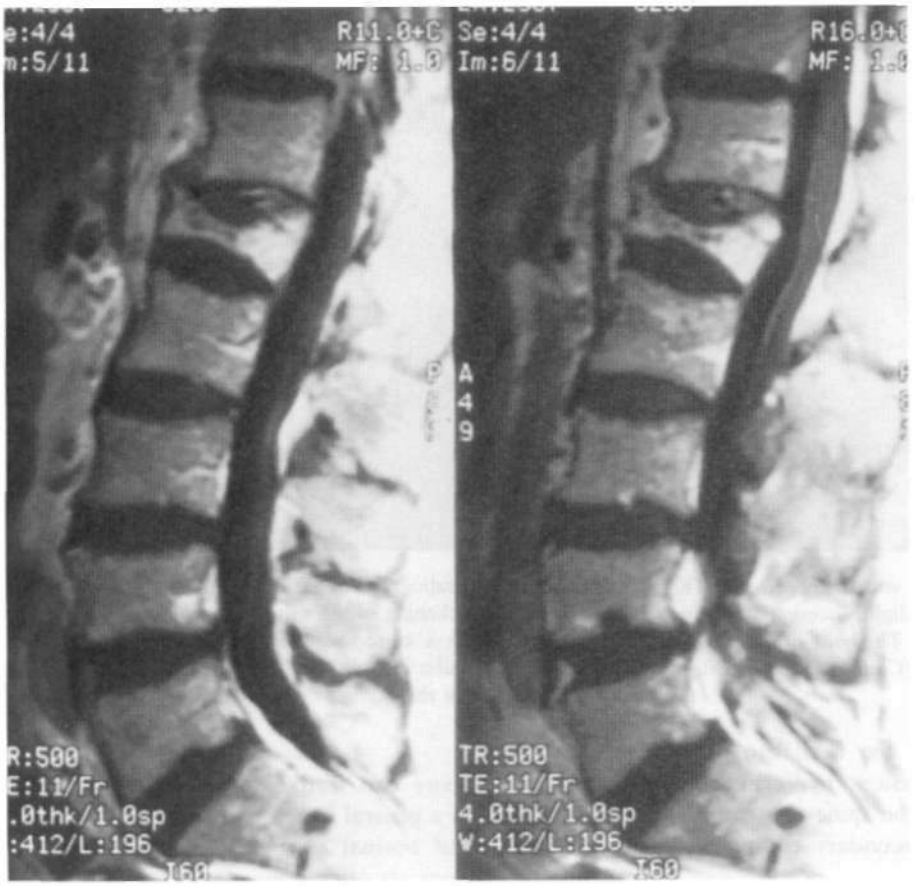


FIGURE 79.16 Spinal magnetic resonance image of patient with vertebral compression fracture secondary to osteoporosis. T1-weighted images of the lumbar spine show 70-80% loss of height of the midportion of the II vertebral body with relative preservation of the height of the posterior portion of the vertebral body. The bright appearance of the vertebra indicates preservation of the fat within the marrow compartment, which would be dark if replaced by tumor. (t .on: ley I r.k (..ICII-.IIT. •

women, acute post-traumatic compression fractures arc more likely to be painful. The pain usually is centered at **the level** of the compression and is accompanied by loss of spinal range of motion. Pain increases with activity, decreases with bed rest, and resolves slowly, sometimes incompletely. Percutaneous vertebroplasty with poly-iru-t/iyliiiciii.kTyl.iir c.i:i decrease the duration "I pain (Mathis et al. 2001). Transient radiculopathic pain or spinal cord compression are uncommon complications of this procedure.

Compression fractures not due to metastases infrequently lead to spinal cord or nerve root compression, so if a compression fracture is accompanied by a focal neurological compression syndrome, the possibility of a metastatic vertebral lesion should be considered. MRI features that favor a malignant cause of the compression fracture include decreased Tl-weighted and increased T2-weighted signal in the vertebral body, pedicle involvement, and associated epidural or paravertebral mass (Do 2000}.

Osteogenesis Imperfecta

The various types of osteogenesis imperfecta are inherited connective tissue disorders manifested by brittle osteopenic bones and recurrent fractures. Four types are known, with variations in severity and in associated findings such as short stature, blue sclera, bearing loss, scoliosis, and skeletal abnormalities. Potential neurological complications of osteogenesis imperfecta include communicating hydrocephalus, basilar invagination, macrocephaly, skull fractures, and seizure disorder. The basilar invagination can lead to brainstem compression (Hayes et al. *1999).* Spinal cord compression, syringomyelia, Chiari I malformation, Dandy-Walker cysts, leptomeningeal cysts, microcephalus, or central nervous system tumors are rarer associations.

Osteomalacia and Rickets

Osteomalacia and rickets are conditions of deficient bone mineralization. Usually long bones arc more involved than the spine. Spinal pain, kyphosis, and compression fractures can occur in osteomalacia, bui compression ot -.pina. cord or nerve roots is rare. Basilar impression can occur in patients with osteomalacia. The neuromuscular complications of osteomalacia are discussed in Chapter H5.

Osteopetrosis

Osteopetrosis is a rare disease characterized by increased bone density caused by impaired bone resorption (Figure 79.17). It may be inherited as an autosomal dominant or

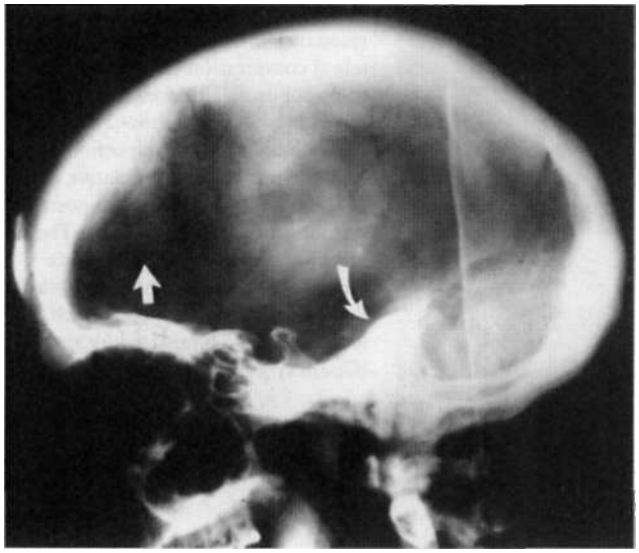


FIGURE 79.17 Radiograph of patient with osteopetrosis. The skull is extremely dense. The radiograph is slightly overexposed; note the darkness of the central areas *{arrow).* The bone of the petrous apex *{curvedarrow)* is particularly dense. (Courtesy Erik Gaensler.)

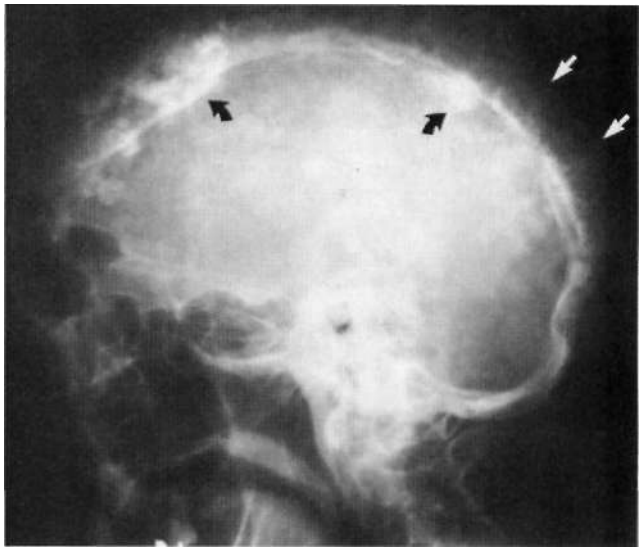


FIGURE 79.18 Radiograph of patient with Paget's disease of the skull. Note the thickening of the calvaria *{white arrows)* and the bony sclerosis with a cotton-wool appearance *{curved arrows).* The patient has basilar invagination; note the high position of the dens with respect to the clivus. (Courtesy Erik Gaensler.)

recessive disorder. Osteopetrosis of the skull can cause cranial neuropathies, basilar impression, hydrocephalus, or syringomyelia. Osteopetrosis of the spine can contribute to spinal canal stenosis with secondary compressive myelopathy.

Pager's Disease

Paget's disease is a focal metabolic bone disease of excessive osteoclastic bony destruction coupled with reactive osteoblastic activity (Poncelet 1999) (Figure 79.18). The incidence increases with age and varies among ethnic groups, with a high incidence (nearly 5%) in elderly whites of Northern European descent. Men are slightly more commonly affected. The current leading pathogenic hypothesis is that a chronic viral infection of osteoclasts causes the illness and genetic factors affect susceptibility. The condition is usually asymptomatic and discovered only because of laboratory or radiographic abnormalities. However, it may cause symptoms by bone or joint distortion, fractures, compression of neurological tissue by calcification, hemorrhage, or focal ischemia caused by a vascular steal by the metabolically hyperactive bony tissue. It may also cause hypercalcemia, especially if the patient becomes bed bound. Uncommonly, neoplasms, especially osteogenic sarcoma, can develop in pagetic bone.

Diagnosis

Pager's disease usually can be diagnosed by characteristic findings on radiography. Osteolytic activity can cause well-demarcated round patches of low bone density. Osteoblastic activity can lead to thickening of cortical bone and then to a general increase in bone density, often with distortion of normal organization. Osteolytic and nsicnNastic findings arc often present together,

Although most patients with Paget's disease have elevation of serum bone alkaline phosphatase and of markers of bone resorption, focal skeletal disease with neurological complications may occur in patients without laboratory abnormalities. Alkaline phosphatase levels, when elevated, are helpful not only in making the diagnosis but also in following response to treatment.

Cranial Neurological Complications

Paget's disease of the skull can lead to head enlargement, Patients often complain of headache. The most common focal neurological manifestation is hearing loss. Paget's disease of the cribriform plate can disrupt olfaction. Other cranial mononeuropathies, including optic neuropathy, trigeminal neuralgia, and hemifacial spasm, can occur. Distortion of the posterior fossa or basilar invagination can lead to brainstem or cerebellar compression, hydrocephalus, or syringomyelia. Patients with Paget's disease of the skull occasionally develop seizures. The pagetic skull is more • Li 11 IL- : ,i 1>I L t;> b k n L i u ; l i o i n :i 1:01 I: • i mi, ; , which can lead to epidural hematoma.

Spinal Neurological Complications

Symptomatic Paget's disease of the spine occurs most often in the lumbar region, where it can cause monoradiculopathies or a cauda equina syndrome. The disease may

involve adjacent vertebra) bodies and the intervening disc-space or may cause root compression by extension from a single vertebral body. The differential diagnosis in patients with Paget's disease and neurological dysfunction in a single limb includes peripheral nerve entrapment by pagetic bone.

Paget's disease of the spine leading to myelopathy is more often thoracic than cervical. A variety of mechanisms arc reported, including extradural extension of pagetic bone, distortion of the spinal canal by vertebral compression fractures, spinal epidural hematoma, or sarcomatous degeneration leading to epidural tumor. In a few cases of myelopathy, imaging shows no evident cord compression, and vascular steal from the cord by hypermetabolie bone in the vertebral body is suggested. In support of this hypothesis, drug treatment of Paget's disease in these patients can lead- to improved spinal cord *t*unction.

Treatment. The potent bisphosphonates are the drugs of first choice for treatment of Paget's disease. Other treatment options include calcitonin, plicamycin, ipriflavone, or gallium nitrate. Within 1-2 weeks of treatment, bone pain may improve, and serum alkaline phosphatase levels may decrease. Some patients experience significant neurological improvement after treatment, but improvement is often delayed 1-3 months. In cases with severe cord compression, surgical decompression is indicated, but drug treatment before surgery decreases the risk of operative bone hemorrhage. Patients with cranial neuropathy have less impressive responses to drug therapy. Patients with hydrocephalus may benefit from ventricular shunting.

Juvenile Kyphosis

Juvenile kyphosis (Scheuermann's disease) manifests as thoracic or thoracolumbar 1-. •-•hnM-. m .idolcM-i-nK. Spinal pain is more likely to accompany lumbar than thoracic disease. Spinal radiography shows anterior vertebral wedging. Neurological abnormalities are uncommon, but spinal cord compression can occur from thoracic disc herniation or direct effects of severe kyphosis.

Scoliosis

Scoliosis, with or without kyphosis, which develops as an idiopathic painless condition in childhood and adolescence, is usually not accompanied by neurological abnormalities. Most cases are idiopathic, but a minority have an accompanying tumor, spondylolisthesis, syrinx, or Chiari I malformation. Indications for spinal MRI include pain, progression suddenly or after spinal maturity, thoracic curvature to the right, or abnormal neurological examination (Oestreich, Young, Young Poussaint 1998). Spinal cord compression is a rare complication of idiopathic scoliosis and is particularly rare if no kyphosis is present. In each patient presenting with scoliosis and myelopathy, an important consideration is whether the myelopathy caused, rather than resulted from, the scoliosis.

Patients with congenital scoliosis, unlike those with idiopathic scoliosis, usually have anomalous vertebrae and may have other associated developmental problems such as Klippel-Feil anomaly or diastematomyelia. Scoliosis caused by skeletal disease, such as achondroplasia, is more likely than idiopathic scoliosis to lead to spinal cord compromise. Myelopathy can result also from spinal cord distraction during treatment of scoliosis with traction or surgery.

Scoliosis can be caused by various neurological diseases including cerebral palsy, spinocerebellar degenerations (e.g., Friedreich's ataxia), inherited neuropathies (e.g., Charcot-Marie-Tooth disease), myelopathies (e.g., syringomyelia), paralytic poliomyelitis, spinal muscular atrophy, dysautonomia (e.g., Riley-Day syndrome), and myopathies (e.g., Duchcnne's muscular dystrophy). Scoliosis is the most common skeletal complication of neurofibromatosis type 1. Scoliosis that develops in adulthood can often be traced to an underlying cause such as trauma, osteoporotic fracture, degenerative spondylosis, or ankylosing spondylitis; it can result in local back pain, nerve root compression, or spinal canal stenosis.

Diffuse Idiopathic Skeletal Hyperostosis

Diffuse idiopathic skeletal hyperostosis (DISH) (Forestier disease, ankylosing hyperostosis) is a syndrome of excessive calcification that develops with aging, more often in men than in women. The diagnosis is made by spinal radiographs that show "flowing" calcifications along the anterior and lateral portion of at least four contiguous vertebral bodies without loss of disc height and without typical radiographic findings of ankylosing spondylitis (Figure 79.19). Patients are often asymptomatic but may have spinal pain or limited spinal motion. Large anterior cervical calcifications can contribute to dysphagia, hoarseness, sleep apnea, or difficulty with intubation. A rare complication is myelopathy caused by spinal stenosis if the calcifications are present also within the spinal canal. Like patients with ankylosing spondylitis, patients with diffuse idiopathic skeletal hyperostosis can develop spinal fractures after relatively minor trauma.

Ossification of the Posterior Longitudinal Ligaments or Ligamcntum I'lavum

Ossification of the posterior longitudinal ligament anterior to the spinal canal (Figure 79.20) and ossification of the ligamcntum flavum posterior to the spinal canal are uncommon syndromes of acquired calcification. The posterior longitudinal ligament extends the length of the spine, scpatating the posterior aspects of the discs and

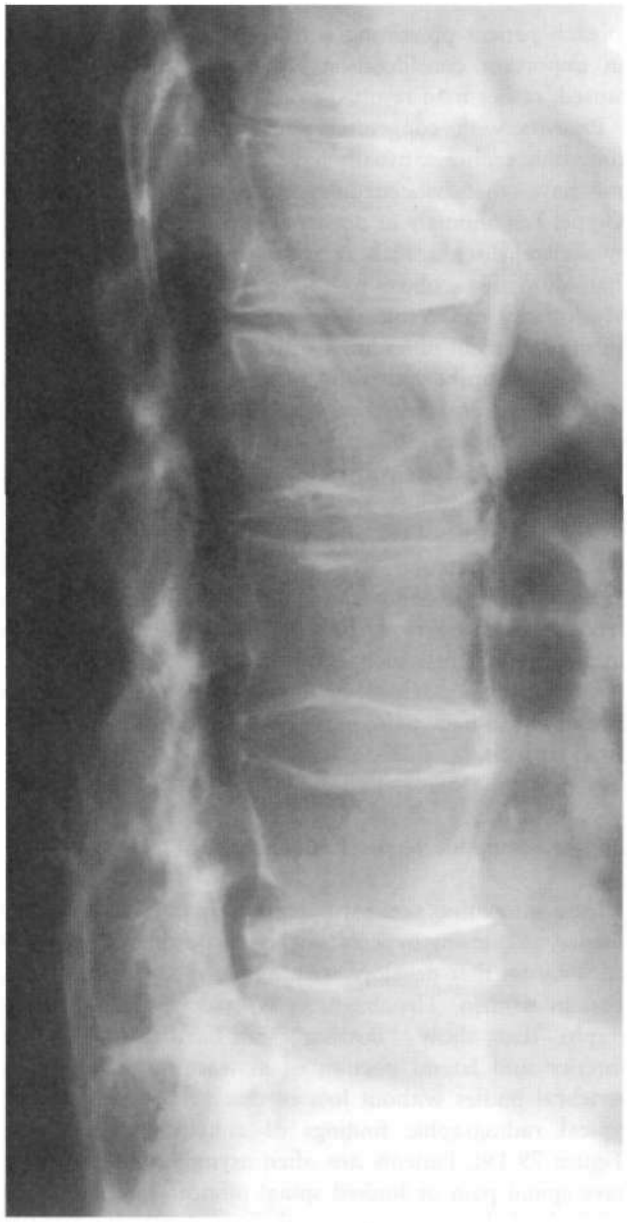


FIGURE 79.19 Lateral thoracic spinal radiograph shows diffuse idiopathic skeletal hyperostosis. Note the flowing calcification of the anterior osteophytes with preservation of disc heights. (Reprinted with permission from Roscnbaum, R. B., Campbell, S. M., & Rosenbaum, J. T. 1996, *Clinical Neurology of Rheumatic Disease,* Butterworth-1 ieineinann, Boston.)

vertebral bodies from the thecal sac. The ligamentum flavum is in the dorsal portion of the spinal canal, attaching the laminae and extending to the capsules of the facet joints and the posterior aspects of the neural foramina. Either ligament can ossify in later life, apparently independently of the usual processes of spondylosis and degenerative arthritis. Ossification of the posterior longitudinal ligament occurs more commonly in Orientals than in non-Orientals. It may be visible on lateral spinal radiography but is usually asymptomatic. It is better seen by CT scan, in which it is distinguished from osteophytes by favoring the middle of the vertebral bodies rather than concentrating at the endplates. Thickness of the calcification can range from 3-15 mm. Ossification of the posterior longitudinal ligament is most likely to be symptomatic in the cervical spine where it can contribute to cord compression if it is rhiek or it the canal is lunbr- narrowed K congenital md degenerative changes.

The ligamentum flavum can contribute by hypertrophy or ossification to spinal stenosis, most often in the lower thoracic or lumbar spine, affecting the cord or cauda equina. Risk factors for development ot ossification of the ligamentum flavum include trauma, hemochromatosis, calcium pyrophosphate deposition disease, diffuse idiopathic skeletal hyperostosis, ankylosing spondylitis, or ossification of the posterior longitudinal ligament.

DEGENERATIVE DISEASE OF THE SPINE

Spinal Osteoarthritis and Spondylosis

Osteoarthritis of the spinal facet joints manifests radiographically as joint narrowing, sclerosis, and osteophyte formation. Spondylosis refers to degenerative disease of the intervertebral discs, visible on radiography as disc space narrowing, vertebral endplate sclerosis, and osteophyte development. Spinal osteoarthritis and spondylosis are inevitable consequences of aging that are visible on routine spinal radiography in more than 90% of people by age 60 years. They are usually asymptomatic but cause compression of the spinal cord or nerve roots in a minority of people. Nonetheless, they are the most common cause of compressive myelopathy or radiculopathy, accounting for far more neurological disease than all the other conditions discussed in this chapter combined,

In youth, the intervertebral discs consist of a gelatinous central nucleus pulposus and a firm collagenous annulus fibrosus. The disc herniation syndromes occur when the nucleus pulposus bursts through a tear in the annulus fibrosus. This herniation can compress the nerve roots or spinal cord, depending on the spinal level involved. Rarely, disc material breaks into the thecal sac or a fragment ruptures into an epidural vein. Disc herniation is most likely to occur in young adults.

By age 40 years, most adults have some disc degeneration with dehydration and shrinkage of the nucleus pulposus, necrosis and fibrosis of the annulus fibrosus, and sclerosis and microfractures of the subchondral bone at the vertebral endplate. Compression of neurological tissue can develop from a combination of disc herniation, osteophyte formation, ligament hypertrophy, congenital stenosis of the spinal canal, low-grade synovitis, and deformity and misalignment of the spine.

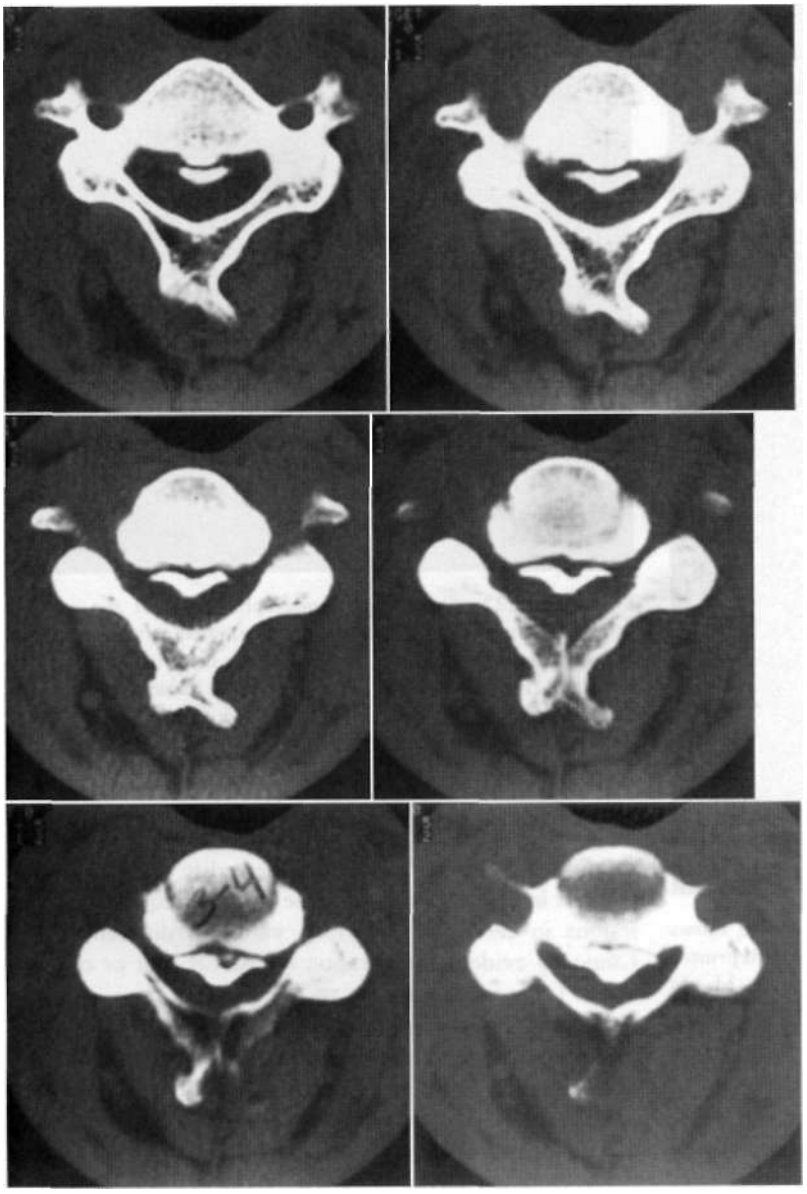


FIGURE 79.20 Computed tomographic scan of a patient with ossification of the posterior longitudinal ligament. Note the continuous bony ridge that is present at every level, nor just at the disc space. In contrast to calcified degenerative spurs, these ligamentous calcifications are not connected to the vertebral bodies. (Courtesy Erik Gaensler.)

Cervical Spondylosis

The cervical spinal column includes 37 joints that are continually in motion throughout life. Cervical osteoarthritis and spondylosis are ubiquitous with increasing age (Figure 79,21), These disorders can be attributed only rarely to specific activities or injuries. Patients with dystonia and other cervical movement disorders may be predisposed to premature cervical spinal degeneration. Because cervical osteoarthritis and spondylosis are so commonplace, it is usually difficult to ascertain their role in contributing to the pathogenesis of chronic neck pain or headache. Cervical spine surgery is rarely, if ever, indicated for treatment of headache or neck ache in the absence of cervical radiculopathy or myelopathy.

Cervical Radiculopathy

Clinical Presentation

The symptoms of cervical radiculopathy often appear suddenly. Although disc herniation or nerve root contusion can be caused by acute trauma, many cases become symptomatic without an identifiable preceding traumatic event. Disc herniation is more likely to be the cause in patients younger than 45 years; neural foraminal stenosis by degenerative changes becomes more likely with increasing age. Pain is usually in the neck with radiation to an arm; patients may also have headache. Radiculopathic arm pain may increase with coughing or with the Valsalva maneuver. Arm pain may increase with neck rotation and flexion or extension to the side of the pain (Spurliug's sign).

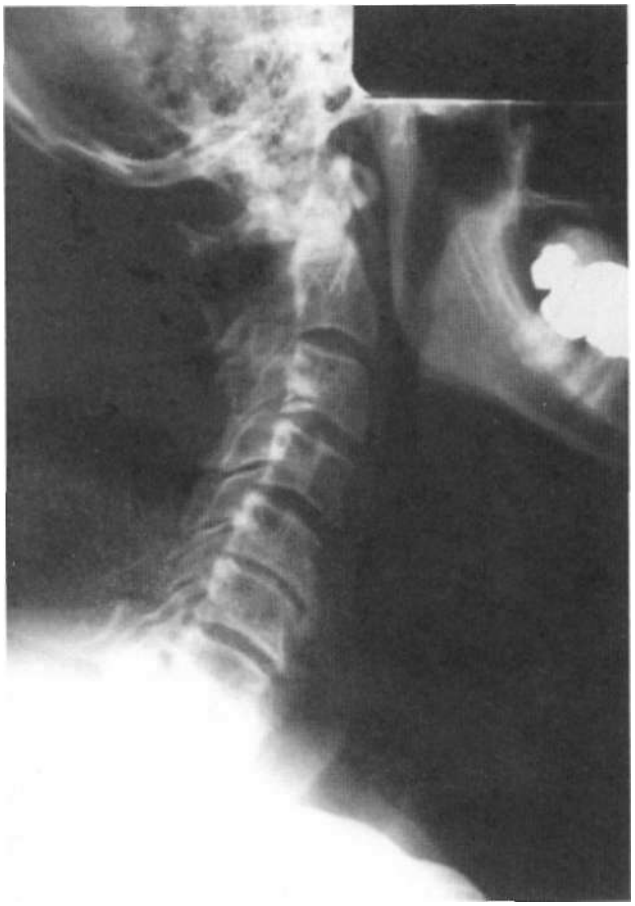


FIGURE 79.21 Lateral radiograph of the cervical spine shows typical changes of spondylosis and osteoarthritis. (Reprinted with permission from Rosenbaum, R. B., Campbell, S. M., Sc Rosenbaum, J. T. 1996, *Clinical Neurology of Rheumatic Disease,* Buttcrworth-Heinemarin, Boston.)

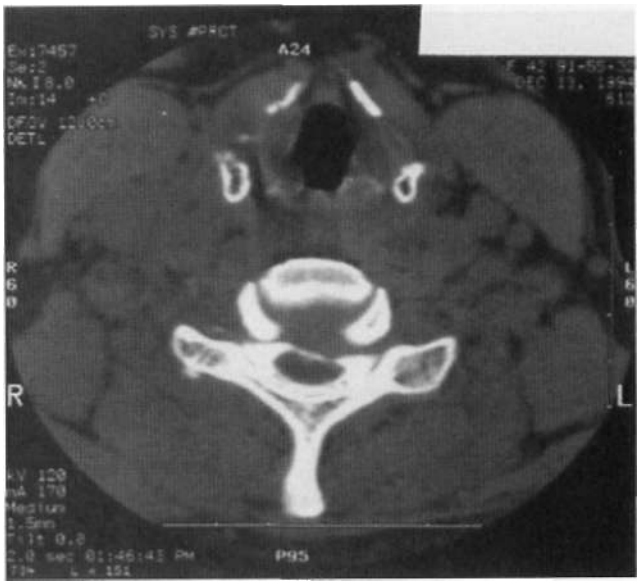


FIGURE 79.22 Computed tomographic scan of the cervical spine with intrathecal contrast shows herniated cervical disc. The spinal cord *{gray)* and thecal sac *(white)* arc distorted on the left by the disc. (Reprinted with permission from Rosenbaum, R. B,, Campbell, S. M., & Rosenbaum, J. T. 1996, *Clinical Neurology of Rheumatic Disease,* Buttcrworth-Heinemann, Boston.)

Spondylosis, osteophytes, and disc herniations at the C4-C5 level can affect the C5 root, causing pain, paresthesias, and sometimes loss of sensation over the shoulder, with weakness of the deltoid, biceps, and brachioradialis muscles. The biceps and supinator reflexes may be lost. Spread of the biceps reflex to the finger flexors, an increased triceps reflex, or an inverted biceps reflex (absent or reduced biceps reflex with reflex contraction of the finger flexors, or rarely the triceps) suggest the presence of a myelopathy at the C6 level. Spondylotic lesions at the *C5-C6* level can affect the C6 cervical root and cause paresthesias in the thumb or lateral distal forearm and weakness in the brachioradialis, biceps, or triceps. The biceps and brachioradialis reflexes may be diminished or inverted. Lesions at the C6-C7 level, compressing the C7 root, cause paresthesias, usually in the index, middle, or ring fingers, and weakness in C7-inncrvated muscles, such as the triceps and pronators. The triceps tendon reflex may be diminished.

The C5, C6j and C7 roots are the ones most commonly involved in cervical spondylosis, because they are at the level of greatest mobility, where disc degeneration is greatest in the cervical spine. The relative frequency of root lesions in cervical spondylosis varies in different series. Clinically evident compression of the C8 root or of roots above *CS* is more rare.

Cervical radiography is of little value in diagnosing or excluding cervical radiculopathy. MRI scanning of the cervical spine is usually helpful in identifying nerve root compression in patients with cervical radiculopathy. Cervical myelography followed by CT scanning is sometimes more sensitive than MRI (Figure 79.22). However, MRI may show nerve root compression, particularly in the neural foramina, which is invisible by CT. CT myelography is also better than MRI for distinguishing disc herniation from osteophytes. However, cervical MRI or CT myelography must be interpreted with caution because degenerative abnormalities are so commonly seen in the asymptomatic spine. Electromyography and nerve conduction studies can be useful in difficult diagnostic cases, both by identifying an affected motor nerve root and myotome and by helping to exclude other diagnoses, such as brachial plexopathy or peripheral neuropathy (Nardin et al. 1999).

Treatment

Most instances of cervical radiculopathy improve significantly over 4-8 weeks, regardless of treatment. Various treatments such as nonsteroidal anti-inflammatory drugs, use of a soft cervical collar, physical therapy, or cervical

traction give similar results. Patients with a typical clinical presentation and little or no neurological deficit usually can he managed with these noninvasive approaches without radiography or electrodiagnostic studies. When patients have intractahlc weakness or pain or have not improved with nonoperative therapy, surgical nerve root decompression is usually successful; however, there is little randomized, controlled comparison of nonoperative therapy and surgery (Fouyas, Statham, and Sandercock 2002). Anterior cervical discectomy is used more widely than posterior cervical laminectomy.

Cervical Spondylotic Myelopathy

Myelopathy caused by compression of the cervical spinal cord by the changes of spondylosis and osteoarthritis usually develops insidiously, but it may be precipitated by trauma or progress in stepwise fashion. Typical findings are a combination of leg spasticity, upper extremity weakness or clumsiness, and sensory changes in the arms, legs, or trunk. Either spinothalamic tract-mediated or posterior column-mediated sensory modalities may be impaired. Sphincter dysfunction, if it occurs, usually is preceded by motor or sensory findings. Neck pain is often not a prominent symptom, and neck range of motion may or may not be impaired. Some patients experience leg or trunk paresthesia induced by neck flexion (Lhermitte's sign).

The anterior-posterior diameter of the cervical spinal cord is usually 10 mm or less. Patients rarely develop cervical spondylotic myelopathy if the congenital diameter of their spinal canal exceeds 16 mm. In congenitally narrow canals, disc protrusion, osteophytes, hypertrophy of the ligamentum flavum, ossification of the posterior longitudinal ligament, and vertebral body subluxations can combine to compress the spinal cord. The relation between the spinal canal and the spinal cord can be imaged by MRI or CT myelography (Figure 79.23). MR1 provides more intramedullary detail such as secondary cord edema or gliosis. CT provides better images of calcified tissues. Even with excellent cross-sectional imaging of the spinal canal, the clinical correlation between neurological deficit and cord compression is imperfect; dynamic changes in cord compression and vascular perfusion undoubtedly contribute to the pathogenesis of cervical spondylotic myelopathy.

The natural history ot cervical spondylotic myelopathy is variable. Some patients may have stable neurological deficit for many years without specific therapy, whereas other patients may have gradual or stepwise deterioration. Some patients improve with treatments such as bed rest, soft collars, or immobilizing collars, but these treatments have not been assessed in controlled trials. Many patients with cervical spondylotic myelopathy are treated by surgical decompression with variable surgical results (Figure 79,24). Surgical and nonsurgical treatment results are best when the neurological deficit is mild and present less than *6* months and when the patient is younger than 70 years. Anterior cervical discectomies are generally performed for spondylotic lesions at a limited number of levels, whereas posterior laminectomy, sometimes with an expanding laminoplasty, is generally performed for congenital spinal canal stenosis.

Vertebral Artery Stroke Caused by Cervical Osteoarthritis

Compression of a vertebral artery by an osteophyte is a rare cause of stroke in the vertebrobasilar circulation. The vertebral arteries pass through the foramina in the transverse processes from C6-C2. Osteophytes from the uncinate joints can compress the arteries. The compression may occur only with head turning. However, the turning usually leaves the contralateral vertebral artery uncompressed, so ischemic symptoms are usually limited to those patients who have both osteophyte arterial compression on one side and a contralateral hypoplastic, absent, or occluded artery,

Thoracic Spondylosis

Degenerative changes are less common in the thoracic than in the lumbar or cervical spines (Vanichkachorn and Vaccaro 2000). Thoracic osteophytes are more likely to develop on the anterior or lateral aspects of the vertebral bodies and infrequently cause clinical radiculopathy. Thoracic disc herniations arc visible on MRI in many-asymptomatic individuals. Thoracic disc herniations occur most often in the lower thoracic spine. These rarely cause cord or root compression and may regress spontaneously.

Thoracic myelopathy caused by disc herniation probably has an annual incidence of approximately I case per i million. Most cases occur between ages 30 and 60 years. Symptoms often develop insidiously, without identifiable preceding trauma. Back pain may or may not be present. Patients have some combination of motor and sensory findings of myelopathy; sphincter dysfunction is present in more severe cases. Thoracic MRI, CT, or myelography can confirm the diagnosis (Figure 79.25). The treatment is surgical decompression.

Lumbar Spondylosis

Low Back Pain

Approximately 80% of people experience episodes of acute low back pain, which usually resolve within a few days. These episodes often recur, and approximately 4% of people report chronic low back pain. Pain-sensitive structures in the lumbar region include the nerve roots,

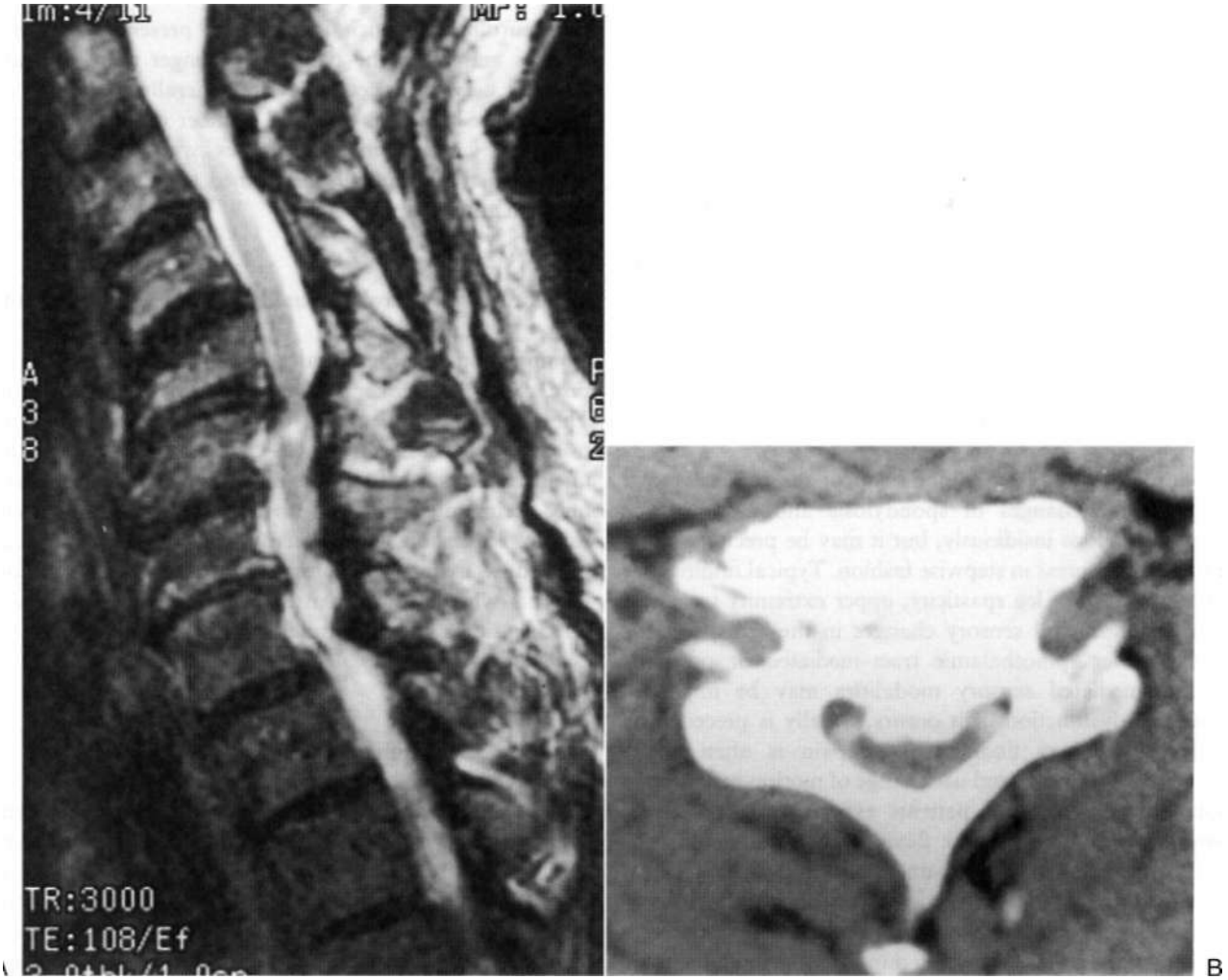


FIGURE 79.23 Cervical spondylotic myelopathy. (A) The sagittal T2-weighted magnetic resonance imaging scan shows maximal compression of the thecal sac and spinal cord at C5-C6. (B) The axial computed tomographic scan with intrathecal contrast at this level shows a large osteophyte arising from the posterior aspect of the vertebral hody; the spinal cord at this level is compressed, and the thecal sac is so compressed that little of the white intrathecal contrast is visible. (Reprinted with permission from Rosenbaum, R. B., Campbell, S. M., & Rosenbaum, J. T. 1996, *Clinical Neurology of Rheumatic Disease*, Burterworth-Heinemann, Boston.)

zygapophyseal joints, sacroiliac joints, intervertebral ligaments, muscles, fascia, annulus fibrosis and circumferential portions of the discs, and vertebral periosteum. Controlled local anesthetic injection studies suggest that in some patients, the cause of low back pain can be localized to specific zygapophyseal joints or sacroiliac joints. In other patients, injection of contrast media into lumbar discs reproduces pain, suggesting that the lumbar disc is the source of pain in these patients. However, this localization cannot be achieved reliably by history or physical examination, and with current therapeutic techniques, invasive testing for localization is not valuable in planning therapy. Furthermore, localization of the source of pain is unsuccessful in many patients. Thus in clinical practice, "nonspecific lm\ h,;c \ pain" i- .1 i< minimi ly made diagnosis.

The findings of osteoarthritis and lumbar spondylosis on radiography (osteophytes, endplate sclerosis, disc space narrowing) appear gradually with increasing age and are rarely absent by age 60 years (Figure 79.26). The presence or absence of these findings does not correlate with symptoms and demonstrating them is of no diagnostic or therapeutic value. Therefore radiography of the lumbar spine is indicated only when alternative diagnoses such as compression fractures, neoplasia, or infections are being seriously considered. The Agency for Health Care Policy and Research has recommended that spinal radiography be reserved for patients with "red flags" for trauma, tumor, or infection (Table 79.6). Kven limiting radiography to patients meeting these guidelines results in many needless radiographs. For example, hack pain in a patient older than 50 years need not be an indication for imaging studies, unless other findings suggest a condition more serious than nonspecific low back pain.

Lumbar disc disease has multifactorial etiologies, including body habitus, type and amount of physical activity,

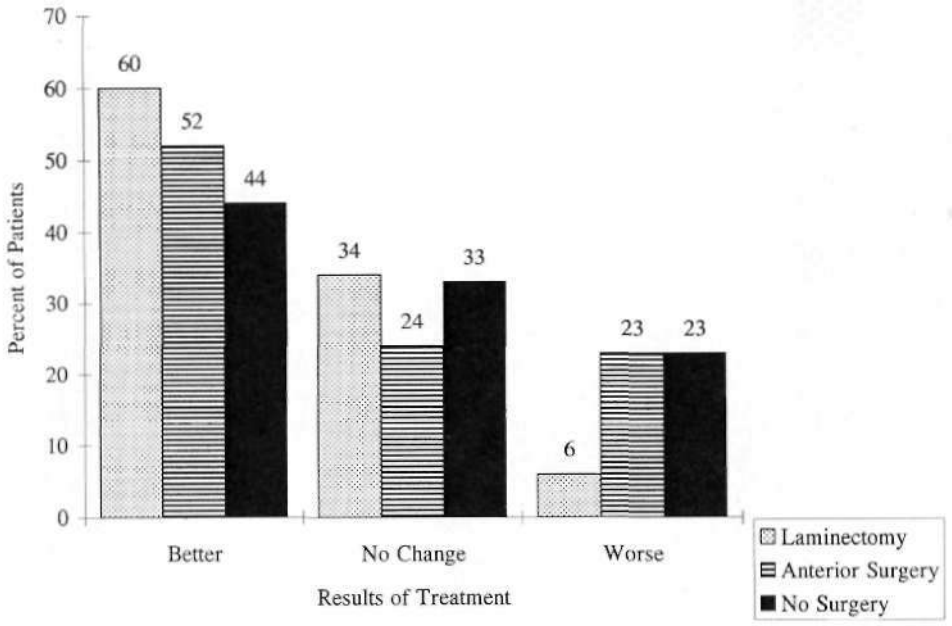


FIGURE 79.24 Results of treatment of cervical spondylotic myelopathy. (Reprinted with permission from Rosenbaum, R. B., Campbell, S. M., £c Rosenbaum, J. T. 1996, *Clinical Neurol*V>*gy of Rheumatic Disease,* B u tter wort h -H c ine ma nn, Boston.)

acute injury, and genetic predisposition. The genetic factor is illustrated by the tendency for lumbar disc herniations to occur in families (Marini 2001). Allelic differences in collagen IX, a component of the annulus fibrosus, nucleus pulposus, and endplates, appear to affect the risk of developing symptomatic disc herniations (Paassilta et al. 2001).

Spondylolysis and Spondylolisthesis. Spondylolisthesis is displacement of one lumbar vertebral body relative to an adjacent vertebral body. Some cases are caused by spondylolysis, a discontinuity in the vertebral pars interarticularis, which disrupts the normal stabilizing effect of the facet joints. Other causes of spondylolisthesis include congenital vertebral anomalies, degenerative spondylosis,

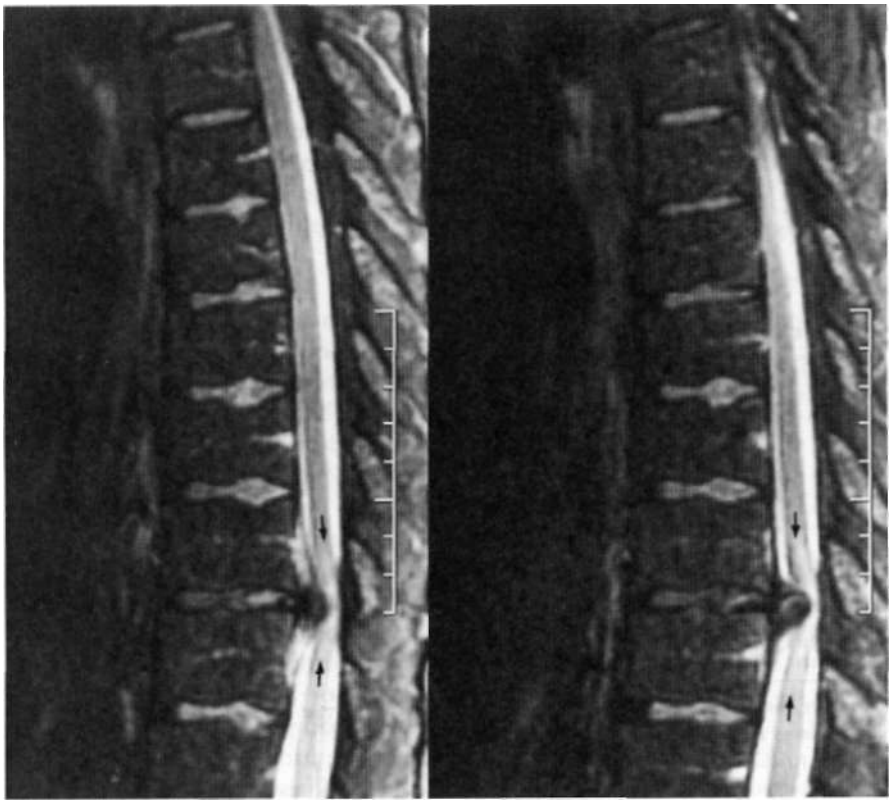


FIGURE 79.25 Thoracic magnetic resonance image of a patient with thoracic disc herniation. This large acute disc herniation at T10-T11 consists of extrusion of most of the nucleus pulposus into the spinal canal. There is secondary narrowing of the disc space. There is spinal cord edema *(arrows)* above and below the level of spinal cord compression. (Courtesy Erik Gaensler.)

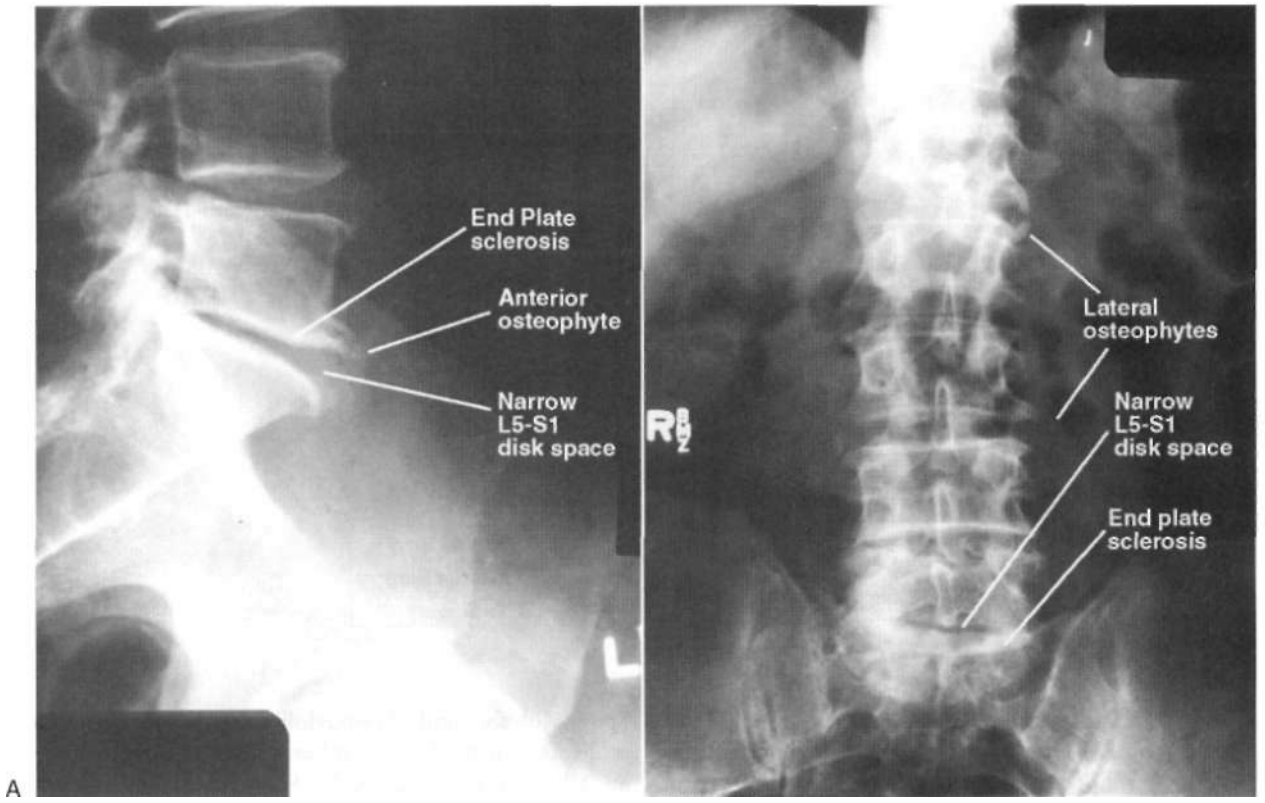


FIGURE 79.26 (A) Anteroposterior and (B) lateral radiographs of the lumbar spine showing osteophytes, disc space narrowing, and sclerosis of the vertebral body articular plates, (Reprinted with permission from Rosenbaum, R. B., Campbell, S. M., &c Rosenbaum, J. T. 1996, *Clinical Neurology of Rheumatic Disease,* ftuttcrworth-Heinemann, Boston.)

and vertebral trauma. Spondylolysis occurs in 5-7% of the population and is usually asymptomatic. Spondylolisthesis is often painless or may cause low back pain that sometimes radiates to the buttocks. Spondylolytic spondylolisthesis is a common cause of back pain in adolescents. Occasionally, spondylolisthesis can advance to the point of compressing nerve roots in the neural foramina or causing lumbar canal stenosis.

Table 79.6: Indications for lumbar spine radiography in patients with acute low hack pain

Red flags for trauma
Major trauma (e.g., motor vehicle accident, fall from height)
Minor trauma or even strenuous lifting in older or potentially osteoporotic patient
Prolonged corticosteroid use
Osteoporosis
Age older than 70 years
Red flags for tumor or infection
Age older than 50 years or younger than 20 years
History of cancer
Constitiition.il symptoms (e.g., fever, chills, weight loss)
Risk factors for spinal infection (e.g., recent bacterial infection, intravenous drug use, immunosuppression!
Pain that is worse when supine or is severe at night

Source: Adapted with permission from Agency for Health Care Policy and Research. 1994, *Acute Low Back Problems in Adults. Assessrne?it and Treatment: Quick Reference Guide for Clinicians,* U.S. Department of I lealth and Human Services, Roekville, Md.

Lumbar Radiculopathies. The back and leg neurological examination is key to decision making in patients with low back pain. Perhaps 1-2% of patients with acute low back pain have significant lumbar nerve root compression. Three syndromes merit specific diagnostic consideration.

Monoradiculopathy

Clinical Fresentatio?!. Patients with an acute lower lumbar or lumbosacral monoradiculopathy caused by nerve root compression present with unilateral leg pain (sciatica) radiating into the buttock, lateropostetior thigh, and distally, sometimes with paresthesia. Patients usually also have low back pain. Pain may increase with movement, coughing, sneezing, or Valsalva maneuver and decrease with rest. Pain often increases when the straightened ipsilateral leg is raised while the patient is supine (straight-leg-raising test, Laseguc's sign) or when the leg is straightened at the knee while the patient is seated. The most commonly compressed nerve roots are 1.5, usually by L4-L5 disc herniation, or SI, usually by L5-S1 disc herniation. For L5 radiculopathy, the findings are typically medial foot and hallux pain; paresthesia, especially on the medial dorsal foot; and weakness in the extensor hallucis

Iongus muscle, ankle dorsiflexors, and peroneal muscles. SI nerve root compression can lead to Literal foot pain and paresthesia, depressed ankle jerk, and weakness of peroneal muscles and less frequently of ankle plantar flexors. When the radiculopathy is mild, the patient may have no objective neurological deficit.

Diagnostic Studies. Disc herniations, osteophytes, spondylolysis and spondylolisthesis, facet joint hypertrophy, and hypertrophy or calcification of intraspinal ligaments can compress nerve roots of the cauda equina within the spinal canal ot in the lateral recesses and neural foramina through which the roots exit the spinal canal. The anatomical relations between the nerve roots and the surrounding tissues are well visualized by lumbar MRI or CT myelography figure 79.27). Each technique has high sensitivity for demonstrating causes of nerve root compression. On occasion when a patient has strong clinical evidence of lumbar radiculopathy but initial imaging studies do not show the cause of the compression, a second complementary imaging study is indicated. For example, imaging with a lumbar MRI usually is sufficient for most clinical purposes, but occasionally a patient

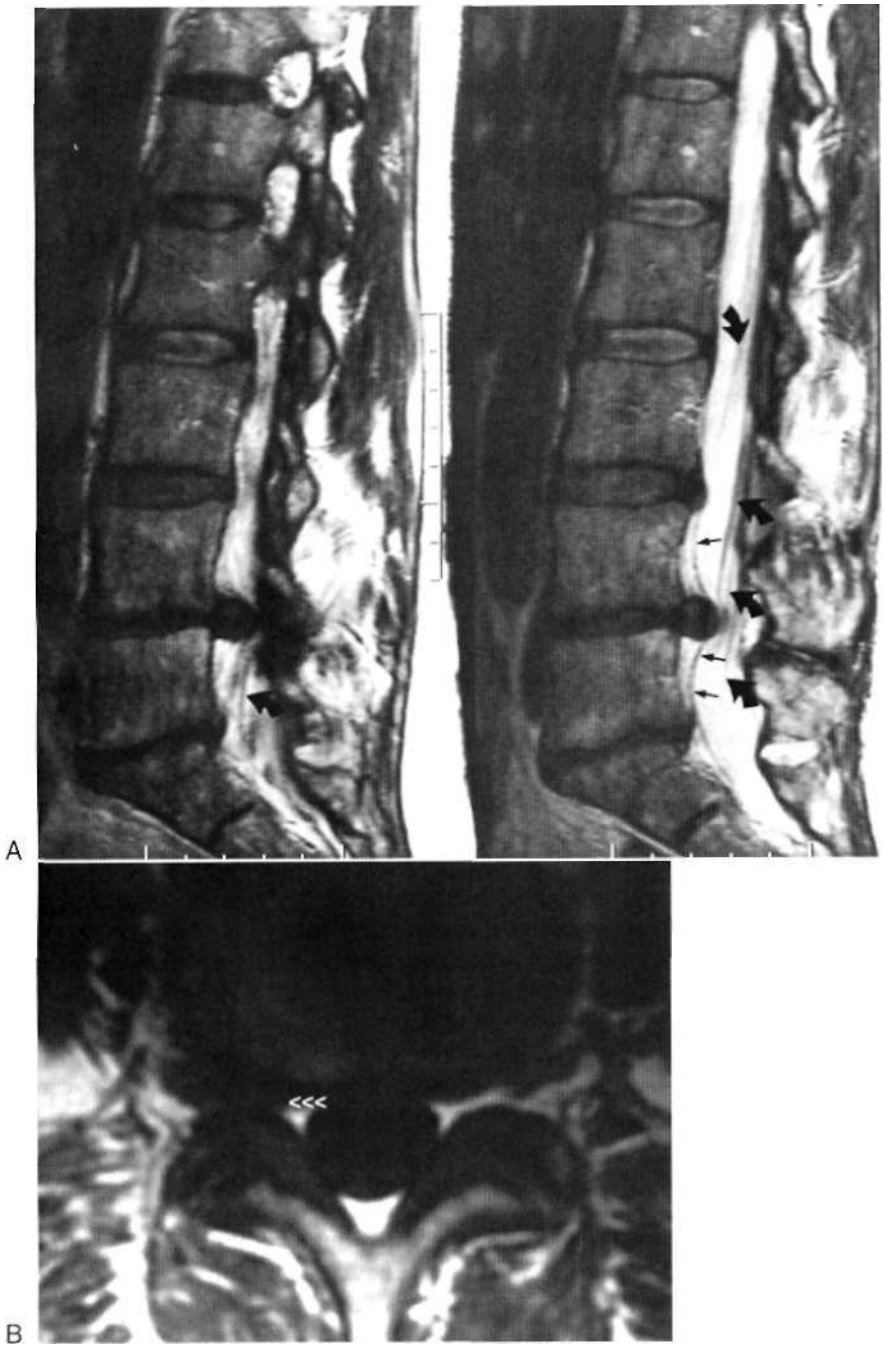


FIGURE 79.27 (A) Lumbar magnetic resonance image (MRI) of a patient with lumbar disc herniation at L4-L5. The ventral dura is displaced *{straight arrows)* posteriorly. The roots of the cauda equina are compressed *(curved arrows). (B)* Axial Tl-weighted MRI demonstrates an intraforaminal focal disc protrusion (herniation) within the right neural foramen *(arrowheads).* This is well delineated because of the thin images angled to the disc space and the contrast of bright fat within the neural foramen. Notice the nerve roots as the oval structures exiting each neural foramen. (A, Courtesy Fj-ik Gacnslcr.)

also needs CT myelography to clarify the anatomy. I nli i!iui:.;klv a I spinal imaging modalities frequently show anatomical abnormalities that are not the cause of symptomatic nerve root dysfunction; all imaging results must be interpreted carefully in clinical context.

Electromyography can aid in neurological localization by demonstrating neuropathic abnormalities in specific myotomes, It is relatively insensitive because it detects only compression affecting motor roots severely enough to cause axonal interruption. However, in complex cases, it is particularly helpful in separating monoradiculopathy from other conditions such as dvsfunction ot multiple roots, plexopathies, or peripheral neuropathy.

Treatment. Most sufferers of low back pain and sciatica recover within 6 weeks using simple, nonoperative therapies such as brief periods of bed rest, activity limitations as required by pain, simple analgesics, and physical or manipulative therapies. Evidence indicates that prolonged immobilization is detrimental and that early mobilization results in more rapid recovery. Many patients with acute low back pain and sciatica can be managed at this stage based on clinical examination without spinal imaging studies. Patients who have progressive weakness or sensory loss or who have severe pain that fails to improve after 6 weeks of nonoperative therapy can be considered tor surgical nerve root decompression. The patients least likely to benefit from lumbar nerve root surgery are those who lack objective neurological signs of nerve root dysfunction or who lack corresponding imaging evidence of nerve root compression.

A few patients develop a chronic low back pain syndrome or have repeated exacerbations of acute low back pain. Back-strengthening exercises and the avoidance of maneuvers that put strain on the lower back, together with the judicious use of nonsteroidal anti-inflammatory drugs, generally improve such patients' pain. Workers who are off work with low back pain for longer than 6 months have a guarded prognosis for return to work. Physicians caring for patients with low back pain lasting longer than 4 weeks need, whenever possible, to emphasize exercise to avoid deconditioning and early return to graded work.

When surgery is performed for lumbar nerve root compression, the surgical technique depends on the clinical details such as the cause of compression and the number of nerve roots compressed. In patients with sciatica caused by disc herniation, the most common surgical approach is microsurgical discectomy with minimal removal of the lamina. Perhaps 90% of patients reporr excellent relief of neuropathic pain after surgery. Many are able to return to physically strenuous work. However, a small proportion of patients postoperatively develop more severe chronic pain problems *(failed back syndrome),* which particularly occurs when patients selected for surgery have neither clinical evidence of radiculopathy nor corresponding neuroimaging evidence of nerve root compression. Patients with chronic pnMopiTa'.ive p./ I iiv.ii'v careful neurological evaluation to consider such problems as surgery done at the wrong level, incomplete removal of extruded disc fragment or other matter compressing the nerve root, progression of spinal degeneration, postoperative arachnoiditis, and psychosocial issues interfering with recovery.

Acute Cauda Equina Syndrome

Acute cauda equina syndrome presents as low back and leg pain caused by compression of multiple lumbosacral nerve roots. Patients may have bilateral leg pain and neurological deficits in the distribution of multiple nerve roots. Particularly worrisome findings are sacral sensory loss or impaired function of the rectal and urinary sphincters. Acute Cauda equina compression occurs in fewer than 1% of all patients who have lumbar or lumbosacral disc prolapses. The cause is usually a large midline disc herniation, most often at L4-L.5 or I.5-S1. When an acute cauda equina compression occurs, the patient needs urgent spinal imaging and decompressive surgery, because the window of opportunity for restoration of neurological function is limited to perhaps 48 hours.

Lumbar Canal Stenosis

Lumbar canal stenosis results from various anatomical changes that decrease the normal cross-sectional area of the spinal canal including congenitally small canal size, degenerative osteophytes, spondylolisthesis, facet joint hypertrophy, thickening of the ligamentum flavum, and disc herniation. It usually develops insidiously with aging and rarely becomes symptomatic before age 40 years. Men are more often affected than women. Stenosis is often asymptomatic. Patients often have some low back pain. The classic symptom of lumbar canal stenosis is neurogenic intermittent claudication: leg discomfort elicited by walking or by certain postures such as standing straight, which is relieved within minutes by stopping walking or changing posture. This is to be contrasted with the relief within seconds of stopping walking m vascular claudication. The pain may be anywhere in the legs or buttocks and may include numbness or paresthesia.

Patients sometimes can decrease their discomfort by bending forward while they walk and may be able to bicycle without difficulty. They may develop leg symptoms with sustained erect posture or after lying with their back straight. In contrast, vasogenic intermittent claudication may be elicited by almost any leg exercise and is not elicited or relieved by any specific postures.

Most patients with neurogenic intermittent claudication do not have objective signs of nerve root dysfunction. However, occasionally a patient manifests progressive neurological deficits from chronic cauda equina compression. Some patients develop leg weakness or other abnormal neurological signs following exercise, and neurological

examination before and after precipitation of the pain is a helpful part of the evaluation of neurogenic claudication. Patients with congenital lumbar canal stenosis are more likely to have congenital stenosis of the cervical canal and may have signs of a cervical myeloradiculopathy.

Diagnostic Studies

Spinal canal stenosis can be studied by MRI, CT, and myelography (Figure 79.28). MRI is best at demonstrating sagittal relationships, such as the role of spondylolisthesis in narrowing the canal. CT is best at studying calcified tissues and distinguishing disc from osteophyte, especially within the neural foramina. No imaging modality quantifies the extent of nerve root comptession, and clinical correlations between symptoms and apparent reduction in size of the spinal canal are imperfect. In choosing which patients would benefit from decompressive surgery, one should rely more heavily on clinical findings than on the appearance of the canal in imaging studies.

Treatment

Patients who have neurogenic intermittent claudication may have stable symptoms for many years without developing progressive neurological deficit. Some even note regression of symptoms aftct months of recurrent claudication. These patients may be managed with mild analgesics. Some describe decreased discomfort if they walk with a slight stoop or using a cane. Those patients with intractable leg pain or progressive neurological deficit can be treated with wide laminectomy of the stenosed spinal canal, which usually improves claudication. Back pain is much less likely TO improve after surgery. Those with severe or multilevel stenosis ate least likely to benefit from surgery.

INFECTIOUS DISEASES OF THE SPINE

Pyogenic Vertebral Osteomyelitis and Epidural Abscess

Vertebral osteomyelitis and spinal epidural abscess (see Chapter 59) are uncommon conditions that present with focal spinal pain and tenderness. Epidural abscesses in the anterior spinal canal are more likely than those in the posterior canal to be associated with osteomyelitis; in cither location, they can cause radiculopathic pain, compromise of nerve root function, or spinal cord compression. Some patients with spinal epidural abscess or with vertebral osteomyelitis are afebrile at presentation, but nearly all have an elevated sedimentation rate. Early in the infection, routine spinal radiography may be norma). If the diagnosis is being considered, an MRI scan (Figure 79.29) of the involved area is sensitive for detecting vertebral body abnormalities and is particularly helpful to assess for epidural or paravertebral infection. Spinal CT is useful if MRI is unavailable or contraindicated. Osteomyelitis may involve any vertebral body but is least common in the cervical vertebrae. Often in pyogenic, but infrequently in granulomatous, osteomyelitis, the MRI shows involvement of the adjacent disc space. The most common causative

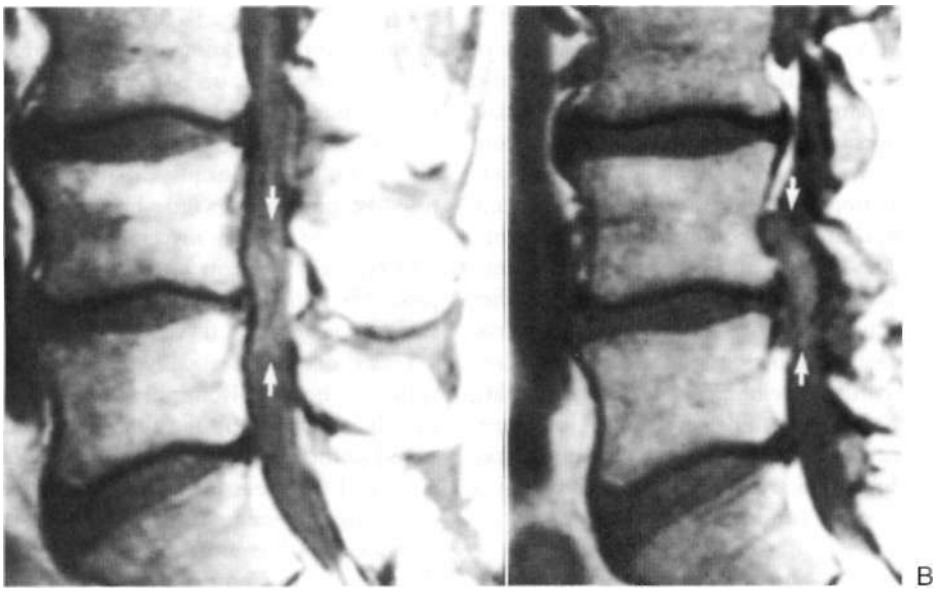


FIGURE 79.28 Magnetic resonance image of patient with lumbar spinal stenosis. (A) Midline and (B) parasagittal images of the lumbar spine show narrow anteroposterior dimensions of the spinal canal consistent with spinal canal stenosis (see normal dimensions in Figure 79.27). The 1.4-1,5 disc herniation *(arrows)* that fills the entire spinal canal is actually much smaller than the herniation shown in Figure 79.27. (Courtesy Erik Gaensler.)

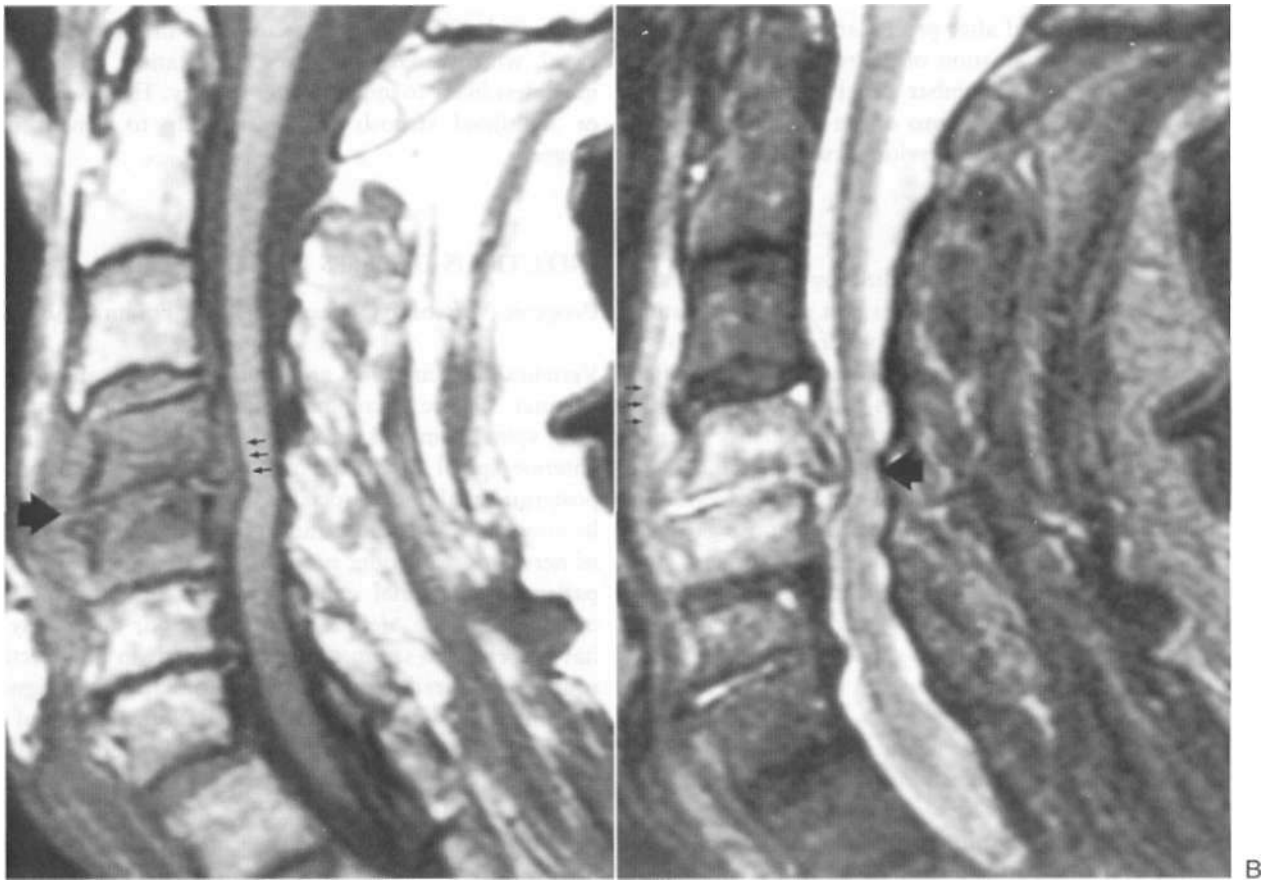


FIGURE 79.29 Magnetic resonance image of a patient with pyogenic vertebral osteomyelitis. (A) Tl-weighted sagittal image shows replacement of the normal marrow fat of the C4 and C5 vertebrae with low-signal intensity edema, with narrowing of the disc space *{arrow)* and thickening of the epidural soft tissue *(small arrows).* (B) T2-weighted image shows mild spinal cord compression *[arrow]* and hype nn ten sin- of the anterior longitudinal ligament, consistent with superior extension of the infectious process *(small arrows).* (Courtesy Erik Gaensler.)

organism is *Staphylococcus aureus,* but a wide variety of other bacteria can be responsible. Polymicrobial infection is uncommon after hematogenous infection but can occur when the source is open trauma or contiguous spread from other tissues. Osteomyelitis and spinal epidural abscess usually occur by hematogenous spread and arc more likely following septicemia. Diabetes, alcoholism, acquired immunodeficiency syndrome (AIDS), and other forms of immunosuppression increase the risk of its development. Other risk factors are intravenous drug use or spinal trauma. Cases may be iatrogenic following spinal surgery. When cases are diagnosed before development of spinal instability or compression of the spinal cord or nerve roots, long-term antibiotic therapy can be curative. Spinal instability may require surgical stabilization. Neurological compression is an indication for emergent surgical decompression.

Granulomatous Vertebral Osteomyelitis

Tuberculosis (TB) of the spine (Pott's disease) is one of the more common forms of nonpulmonary TB and by far the most common gtanulomatous spinal infection. The risk is highest in regions or populations where TB is endemic. In the United States high-risk factors are immigration from an endemic area, AIDS, homelessness, and drug or alcohol abuse. Other organisms capable of causing granulomatous osteomyelitis include brucellosis, a variety of fungi, *Nocardia,* and Actinomyces. Granulomatous spinal infection typically presents with insidious progression of back pain. The patient often has symptoms of systemic infection such as weight loss, fever, night sweats, or malaise.

Pott's disease classically presents with destruction of vertebral bodies. Routine spine radiography results are usually abnormal by the time the diagnosis is made, and spinal deformity is a common complication. MRI or CT is needed to assess for contiguous abscess in the epidural or paraspinal spaces and to evaluate possible nerve root or spinal cord compression when the spine is deformed (higure 79.30). Compression of spinal cord or nerve roots can occur in vertebral TB by vertebral deformity or collapse, epidural abscess, granulation tissue, or bony sequestrum. Patients may develop delayed neurological complications after apparently successful treatment of the infection.

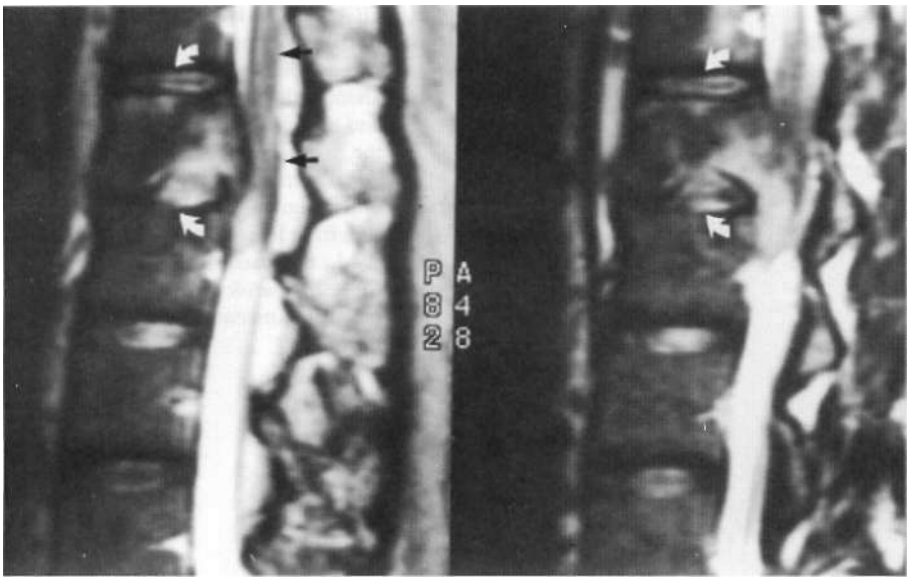


FIGURE 79.30 Magnetic resonance image of a patient with tuberculous vertebral osteomyelitis. T2-weighted images show destruction of rhe posterior inferior portion of the TI2 vertebra, with a soft tissue mass projecting posteriorly into the spinal canal, compressing the conus medullars *{arrows).* Note that the T12 and LI discs *(curved arrows)* are relatively well preserved, which is a distinguishing feature of spinal tuberculosis. (Courtesy Erik Gaensler.)

This may be caused by infarction from endarteritis obliterans, delayed degenerative bony changes, or reactivation of infection. Neurological compression is most common with thoracic vertebral disease, hence the eponym *Pott's paraplegia-* cauda equina compression is uncommon in TB. Treatment of vertebral TE requires long-term multiple-drug antituberculous therapy. Spinal surgery may be needed depending on the degree of spinal destruction or deformity and is often required in cases of neurological compression.

Inflammatory Joint Disease

Rheumatoid Arthritis

Systemic Presentation. RA is a chtonic, inflammatory, symmetrical destructive immune-mediated polyarthritis. In population studies, 0.2-2.0% of the population is affected, women twice as often as men. The cause of RA is unknown, but genetic factors are evident in familial cases and susceptibility is linked to some human leukocyte antigen-DR (HLA-DR) types. The most commonly affected joints are the small joints of the hands and feet. The diagnosis is based primarily on characteristic clinical findings. Serological testing for rheumatoid factor can support the diagnosis. However, many patients have seronegative RA, and, conversely, there are numerous other causes for elevation of rheumatoid factor. Radiography shows juxta-articular demitieralization or characteristic joint erosions in advanced cases.

Pathogenesis. The immimopathogenesis of RA includes T- and B-cell activation, angiogencsis and cellular proliferation in the synovium, inflammation in soft tissue, and eventual destruction of cartilage and bone. Cytokine release, immune complex deposition, and vasculitis can all contribute to the inflammatory process. The inflamed proliferative rheumatoid synovium is called *pannus.* In the spine, pannus can disrupt stabilizing ligaments, particularly of the atlantoaxial joint, and thick pannus can add to compression of nervous tissue. Rheumatoid inflammatory tissue can form nodules in soft tissue; on the rare occasions that these nodules form in the dura, they can conttibutc to rheumatoid pachymeningitis.

Neurological Manifestations. Common neurological complications of RA are carpal tunnel syndrome and other nerve en trap men ts, peripheral neuropathy, and myopathy; these are discussed in Chapters 55, 82, 84, and 85. RA can evolve to a rheumatoid vasculitis that like other medium-sized vessel vasculitides has the potential to cause ischemic mononeuritis, mononeuritis multiplex, or, rarely, stroke.

Headache and neck ache are common in patients with RA. These are often caused by rheumatoid disease of rhe cervical spine. Focal neurological dysfunction is a rarer and later manifestation of spinal RA. Patients with RA, of course, develop the ubiquitous changes of spinal osteoarthritis and spondylosis. In addition, early in RA, cervical radiography may show rheumatoid changes such as erosions and sclerosis at vertebral endplates and apophyseal joints. Patients may have cervical subluxations. Disc space narrowing may occur at upper cervical discs, without associated osteophytosis.

Patients with progressive RA can develop subluxation at the atlantoaxial joint. Lateral atlantoaxial joint subluxation rarely causes focal neurological dysfunction but can contribute to neck ache and headache. Horizontal atlantoaxial joint subluxation, often combined with adjoining soft tissue pannus, can cause myelopathy, especially in patients with a smaller congenital canal diameter (Figure 79.31). The earliest neurological sign is usually hyperreflexia; assessment of gait and strength in patients with advanced RA is often difficult because of their peripheral

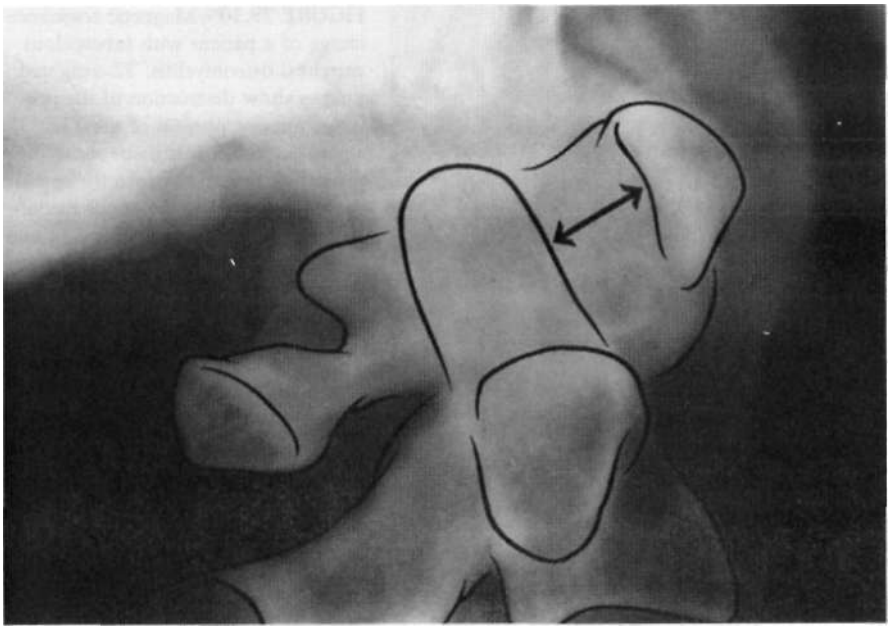


FIGURE 79.31 Lateral radiographs of the flexed neck of a patient with rheumatoid arthritis and anterior atlantoaxial subluxation. The odontoid and pedicle of C2 and the elements of the ring of CI are outlined. The atlantoaxial separation *{double arrow)* is also shown. (Reprinted with permission from Rosenbaum, R. B., Campbell, S. M., & Rosenbaum, J. T. 1996, *Clinical Neurology of Rheumatic Disease,* Bultcrworth-Heinemann, Boston.)

joint pain and deformity. Vertical subluxation can lead to spinal cord or brainstem compression or rarely to vertebral artery compression or injury.

Choosing which patients will benefit from surgical stabilization of the subluxed joint is a clinical challenge. Findings of progressive myelopathy or brainstem dysfunction are usually indications for surgery if the general health of the patient permits. Neurological dysfunction caused by atlantoaxial subluxation usually occurs in patients who are already severely debilitated by their disease. Many patients do not regain neurological function after surgical stabilization of the subluxation; goals arc limited to preventing deterioration. The 5-year survival of patients at this late stage of RA is perhaps 50%.

Patients with RA may also develop spinal subluxations, usually in the cervical spine, at levels caudal to the atlantoaxial joint. These subluxations can lead to spinal cord compression. Subaxial subluxations may progress after surgical stabilization of the atlantoaxial joint. A rare late manifestation of RA is rheumatoid pachymeningitis. The dura may develop either focal rheumatoid nodules or diffuse infiltration by inflammatory cells. In rare instances, toed ilin.il disease can lead to spinal cord, cauda equina, or cranial nerve compression or to focal cerebral complications such as seizures.

I}iflammatory Spondyloarthropathies

Clinical Presentation. The inflammatory spondyloarthropathies include ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and the arthritis of inflammatory bowel disease. Ankylosing spondylitis is characterized by inflammatory low back pain, loss of spinal range of motion, sacroiliitis, and, as it advances, radiographic evidence of sacroiliitis and spondylitis (Figure 79.32). The clinical symptoms of inflammatory lumbosacral spine disease are insidious onset of low back (and sometimes buttock) pain, lasting more than 3 months, prominent morning stiffness, and improvement with activity. Most patients become symptomatic before age 40 years, and men are affected more commonly than women. Other organ systems are affected commonly in patients with inflammatory spondyloarthropathies; manifestations include uveitis, mucocutaneous lesions, peripheral arthritis, gastrointestinal disease, cardiac disease, and enthesopathy (entheses are sites of

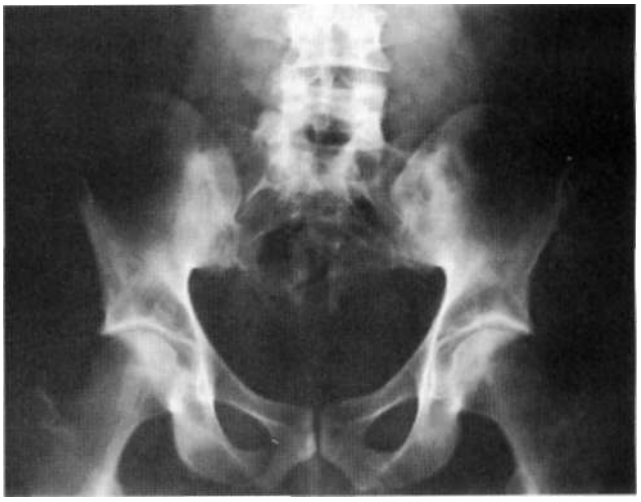


FIGURE 79,32 The anteroposterior radiograph of the sacroiliac joint shows sacroiliitis with some preservation of the left sacroiliac joint. (Reprinted with permission from Rosenbaum, R. B., Campbell, S. M., & Rosenbaum, J. T. 1996, *Clinical Neurology of Rheumatic Disease,* Butte r worth-He in emaun, Boston.

insertion of ligament or tendon to bone). The syndesmophytes that form where spinal ligaments join vertebral bodies arc one form of enthesopathy. Examples of other sites of enthesopathy are the foor (Achilles tendinitis, plantar fasciitis, heel pain}, fingers or toes (dactylitis or sausage digits), and symphysis pubis, clavicle, and ribs.

Reactive arthritis (formerly called *Reiter's syndrome)* is classically preceded by venereal or gastrointestinal tract infection. The triad of reactive arthritis is arthritis, conjunctivitis, and urethritis, but many patients do not have all thtee manifestations. Inflammatory low back pain is common in patients with reactive arthritis, and up to one fourth of patients develop radiological evidence of sacroiliitis ot spondylitis.

Pathogenesis. The inflammatory spondyloarthropathies are generated by" a combination of genetic and environmental factors. In ankylosing spondylitis, the genetic factor is clearest, with perhaps 90% of patients expressing the gene fot HLA-B27. However, only approximately 5% of people expressing this gene develop ankylosing spondylitis. In the other spondyloarthropathies, the prevalence of HI.A-1127 positiviiy is lower. In reactive arthritis, the environmental factors arc clearest, with many patients experiencing a preceding gastrointestinal or genitourinary tract infection with organisms such as *Shigella, Salmonella, Yersinia, Campylobacter,* or *Chlamydia.* The inflammatory process is presumably mediated by autoimmune T cells with tissue specificity leading to inflammation at such sites as joints, entheses, and the eye.

Spinal Neurological Complications. The neurological complications of the inflammatory spondyloarthropathies generally do not occur until spinal disease is clinically advanced with loss of spinal range of motion and kyphosis and radiologieally evident with vertebral body squaring and syndesmophytes. Spinal complications include atlantoaxial joint subluxation, spinal fractures and pseudoarthroses, disco vertebral destruction, spinal canal stenosis, and cauda equina syndrome caused by lumbar arachnoid diverticula (Table 79.7).

Table 79.7: Spinal complications of ankylosing spondylitis based on 105 hospitalized patients

	Anatomically abnormal	*Neuro logically abnormal*
Spinal fracture	13	*7*
Disco vertebral destruction	4	0
Atlantoaxial subluxation	1	(1
Spinal canal stenosis	2	2

Source: Data used with permission from We in stein, P., Karpman, R. R., Gall, E. P., et a). 1982, "Spinal injury, spinal fracture, and spinal stenosis in ankylosing spondylitis," *J Ncurosurg,* vol. 37, pp. 609-616. (Reprinted from Roscnbaum, R. B., Campbell, S. M., &r Rosenbaum, J. T. 1996, *Clinical Neurology of Rheumatic Disease,* Butterworth-Heinemann, Boston.)

Subluxation of the atlantoaxial joint is a late and uncommon complication of inflammatory spondyloarthropathy. Diagnosis and management issues are the same as those for patients who develop atlantoaxial disease as part of RA. The fused spondylitic spine is particularly susceptible to fracture, especially in the midecrvical region. The most common fracture site is C6, followed by C5 and C7. After even minor trauma, the patient with advanced spondylitis needs radiographic assessment of the cervical spine to detect fractures if possible before myelopathic complications. Much more rarely, patients with spondylitic rigid spines develop post-traumatic myelopathy caused by epidural hematomas or cord contusions.

Destruction of a disc, particularly in the low lumbar or high thoracic region, is a late complication of spondylitis (Figure 79.33). The adjacent vertebral bodies also may be involved. An initiating trauma is not always identified. The destruction may be asymptomatic or painful. The pain increases with movement and decreases at rest, in contrast to typical inflammatory low back pain. An epidural inflammatory response leading to cord compression can occur.

Cauda equina syndrome with insidious evolution of leg pain, sensory loss, leg weakness, and sphincter dysfunction is a late complication of inflammatory spondyloarthropathy. Imaging studies (MRI, CT, myelogtaphy) show posterior lumbosacral arachnoid diverticula (Figure 79.34). Although arachnoiditis may play a role in development of this syndrome, the presence of the diverticula distinguishes it from most cases of chtonic adhesive arachnoiditis.

Other unusual complications of spondyloarthropathy include lumbar monoradiculopathy secondary to disc herniation or osteophytes, spinal canal stenosis, and from the era when spinal radiation was used to treat spondylitis, radiation-induced cauda equina sarcoma.

Nonspinal Neurological Complications. Rare nonspinal complications of inflammatory spondyloarthropathies include brachial plexopathy or tarsal tunnel syndrome. Proximal weakness and atrophy, sometimes with mild elevations of serum creatine kinase level, often occur in advanced cases of spondylitis, suggesting an inflammatory myopathy. In patients with psoriatic arthritis, the myopathy is occasionally painful. A number of case reports detail unusual neurological sequelae in patients with reactive arthritis (Table 79.8).

Laboratory Abnormalities. Patients with inflammatory spondyloarthropathies sometimes have mild elevations of CSF protein levels with normal glucose and cell counts. They can have unexplained abnormalities of visual, auditory, and somatosensory evoked responses.

Possible Associations with Multiple Sclerosis. Case reports and small series link the occurrence of multiple sclerosis and ankylosing spondylitis in the same patient,

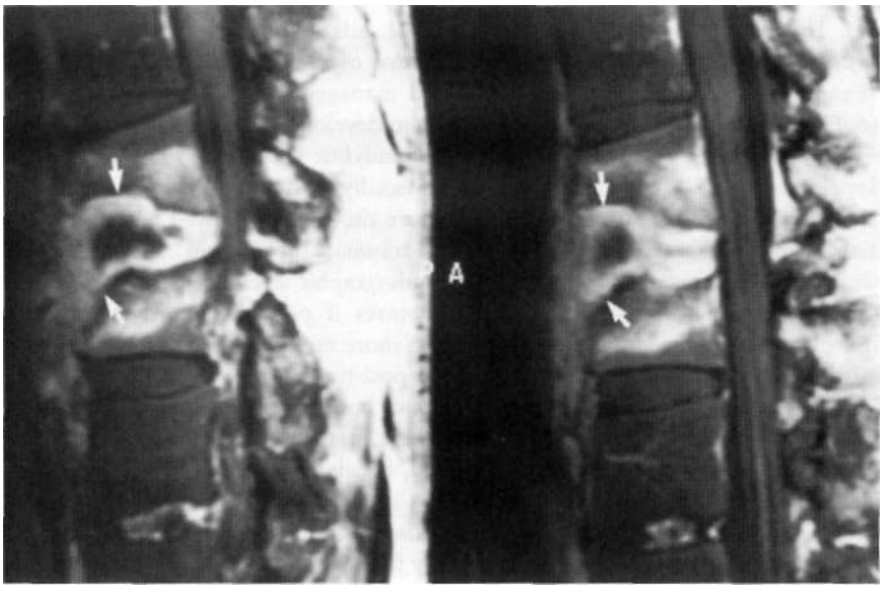


FIGURE 79.33 Magnetic resonance image shows disco vertebra I destruction *{arrows)* in a patient with ankylosing spondylitis. There is a chronic fracture in the lower thoracic spine, which is otherwise rigid because of bony fusion. Chronic hypcrmobility at this single nonfused segment has occurred, leading to exuberant fibrous tissue development. The fibrous tissue enhances on this post-gadolinium-enhanced Tl -weighted image. This appearance can be mistaken for infectious spondylitis (see Figure 79.29) if the presence of a bamboo spine on plain films is overlooked. (Courtesy Erik Gaensler.)

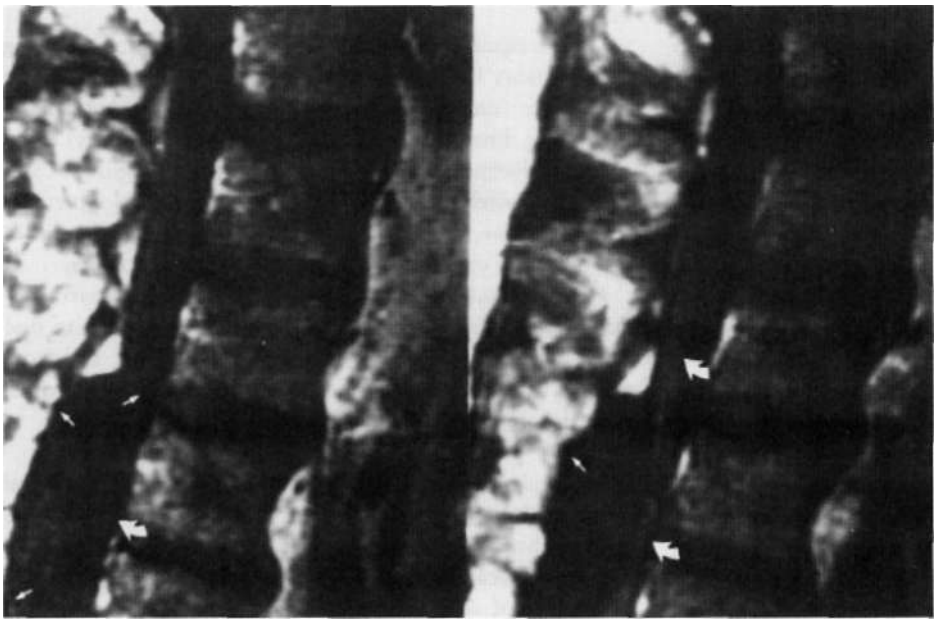


FIGURE 79.34 Magnetic resonance image of the lumbar spine shows a posterior lumbar arachnoid diverticulum in a patient with ankylosing spondylitis. The spinal canal is expanded at T12T.1 by a mass that shows signal intensity equivalent to cerebrospinal fluid on these Tl-weighted images. Isointensity to cerebrospinal fluid suggests an arachnoid cyst, and the small arrows outline the internal margins of the cyst. The curved arrows show the nerves of the cauda equina, which have been displaced anteriorly. (Courtesy Erik Gaensler.)

Table 79.8: f:\iiiiiplcs **(>1 neurological complications of reactive** arthritis

Acute transverse myelitis
Brainstem dysfunction
Encephalitis
Neuralgic amyotrophy
Personality change
Seizures
Unilateral ascending motor neuropathy

Source: Reprinted with permission from Rosenbaum, R. B., Campbell, S. M.; & Rosenbaum, J. T. 1996, *Clinical Neurology of Rheumatic Diseases,* Butterworth-Hememann, Boston.

but insufficient data exist to determine whether a true association exists between the two illnesses. Evaluation is complicated because either condition might cause a myelopathy, transient vision loss (iritis versus optic neuritis), or evoked response abnormalities.

Epidural Lipomatosis

Epidural lipomatosis is a non-neoplastic accumulation of fatty tissue in the thoracic or lumbar epidural space that can occur idiopathically but is more commonly a

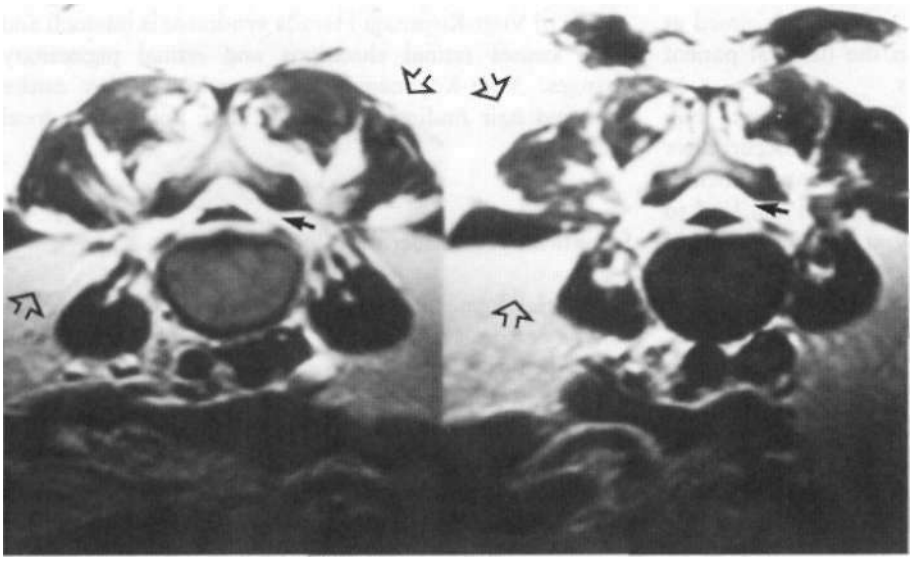


FIGURE 79.35 Magnetic resonance image shows epidural lipomatosis. T1-weighted axial images show markedly increased fat *{arrows)* within the spinal canal compressing the thecal sac, which is quite small. Note that the patient is quite obese, with large amounts of fat in the retroperitoneutn and posterior paraspinous tissues *[open arrows).* (Courtesy Erik Gaensler.)

complication of chronic corticosteroid excess, obesity, or hypothyroidism (Koch et al. 2000). A typical patient has been on corticosteroids for more than 6 months and is obese and cushingoid; spinal radiography typically shows diffuse osteoporosis. Criteria for the diagnosis include (1) history consistent with segmental spinal cord compression or nerve root compression, (2) epidural fat thickness of more than 7 mm in the region of compression, and (3) a body mass index of more than 27.5 kg/m^2 (Figure 79.35), The compressive tissue can regress when corticosteroid doses are decreased, but the compression of neurological tissue may be severe enough to require laminectomy.

Chronic Meningitis

Most cases of chronic meningitis arc caused by infection (see Chaptet 59), neoplasia (see Chapter 58), or sarcoidosis (see Chapter 55). Behcet's syndrome, isolated central nervous system angiitis (sec Chapter 57), systemic lupus erythematosus, Sjogren's syndrome, or Wegener's granulomatosis are included in a comprehensive differential diagnosis. Some other chronic or recurring meningitic syndromes merit discussion.

Chronic Adhesive Arachnoiditis

Chronic focal or diffuse inflammation of the spinal theca can cause neurological symptoms caused by inflammation, adhesion, and distortion of nerve roots or spinal cord. This condition is termed *chronic spinal arachnoiditis* or *chronic adhesive arachnoiditis.* However, the process usually involves all layers of the meninges and in its chronic stages may be fibrotic rather than inflammatory. Calcification of the meninges (arachnoiditis ossificans) is an occasional late finding. The clinical manifestations are of a gradually ascending painful cauda equina syndrome, followed by an ascending myelopathy as the arachnoiditis spreads up the **spinal** cord. Death may result in 3-10 years from decubiti, urosepsis, and other complications of severe paraplegia.

Adhesive arachnoiditis occasionally complicates a variety of surgical or medical violations of the thecal sac {Table 79.9). Focal arachnoiditis is most common in the cauda equina following lumbar disc surgery or myelography, particularly if oil-based contrast has been used for the latter. The symptoms can include local or radicular pain, radicular paresthesia, and less commonly more severe findings of oligoradiculopathy such as motor loss or sphincter dysfunction. The diagnosis can usually be made by spinal MRI, which may show clumping of nerve roots, nodules in the subarachnoid space, loculation of spinal fluid, and local areas of enhancement. The nerve roots may clump at the periphery of the thecal sac, usually adjacent to an area of previous surgery, or in the center of the sac, usually in areas of spinal stenosis. The extent of the MRI findings correlates poorly with the severity of the clinical nerve root dysfunction. Spinal fluid may show increased CSF protein levels and mild to moderate mononuclear pleocytosis. Surgical debridement of the arachnoiditis is sometimes attempted but is usually unsuccessful and may lead to increased neurological deficit. Epidural or intrathecal corticosteroids arc sometimes tried, but there is no proof of their efficacy, and there are reports of arachnoiditis

Table 79.9: Causes of adhesive arachnoiditis

Myelography, especially with oil-based dyes
Spinal surgery
Ankylosing spondylitis
Intrathecal or epidural chemical exposure, e.g., spinal anesthesia, corticosteroids
Granulomatous infection, e.g., tuberculosis
Ruptured dermoid or epidermoid cyst

caused by their use. Therefore most treatment is aimed at symptomatic pain control, except in the unusual patient with progressive neurological deficits.

Arachnoiditis of the spinal cord is less common than arachnoiditis of the cauda equina. It can occur after apparently successful treatment of granulomatous meningitis or of epidural or vertebral infection and can lead to myelopathy. Arachnoiditis, especially at the craniocervical junction, can cause syringomyelia.

Recurrent Meningitis

Patients with recurrent attacks of acute bacterial meningitis need to be screened for dural CSF leaks or fistulas, parameningcal infections, and immunodeficiency (see Chaptet *59).* Recurrent meningitis also can be caused by chemical irritation from leaking dermoid tumors or craniopharyngiomas. Drug-induced meningitis, most common as an idiosv ncralii reaction to noiiMcniidn .inii inflammatory drugs, can recur with repeated drug exposures. Rarely, recurrent meningitis can complicate systemic inflammatory diseases such as systemic lupus erythematosus, Sjogren's syndrome, Behcet's disease, Lyme disease, familial Mediterranean fever, or sarcoidosis.

Mollaret's meningitis is another form of recurrent aseptic meningitis. Attacks are self-limited, lasting a few days. The spinal fluid shows a mixed pleocytosis; sometimes large macrophagc-like cells (Mollaret's cells) arc present as well. Some cases are caused by herpes virus infections, but a causative organism is not always identified.

Uveomeningitis Syndromes

The combination of chronic or recurrent meningitis and uveitis has a specific differential diagnosis (Table 79.10). Often ophthahnological chatacterization of the uveitis can further limit the differential diagnosis. For example, the uveitis of Vogt-Koyanagi-Harada syndrome is bilateral and often causes retinal elevations and retinal pigmentary changes. Vogt-Koyanagi-Harada syndrome also causes skin and hair findings such as vitiligo, poliosis, or focal alopecia.

Tabic 79.10: Causes of combined uveitis and meningitis

Acute multifocal placoid pigmentary epithelioparhy
Acute retinal necrosis
Behcet's syndrome
Human T-lymphotropic virus type 1 infection
Infection in immunocompromised host
Isolated central nervous system angiitis
Lyme disease
Primary central nervous system lymphoma
Sarcoid
Syphilis
Systemic lupus erythematosus
Vopt-Koyanagi-Harada syndrome

Source: Reprinted with permission from Rosenbaum, R. B., Campbell, S. M., & Rosenbaum, J. T. 1996, *Clinical Neurology of Rheumatic Diseases,* Butterworth-Heinemann, Boston.

Superficial Hemosiderosis

Superficial hemosiderosis is a rare disorder that causes slowly progressive cerebellar ataxia, mainly of gait, and sensorineural deafness, often combined with manifestations of myelopathy, such as spasticity, brisk reflexes, and extensor plantar responses, bladder disturbance, or sensory signs. Less common features include dementia, anosmia, or anisocoria, and more rarely extraocular motor palsies, neck or backache, bilateral sciatica, or lower motor neuron signs (5-10% each). Men are more often affected than women (3:1). The diagnosis may not be suspected clinically, but the neuroraetiological abnormalities arc striking. MR1 shows a black rim around the posterior fossa structures and spinal cord and less often the cerebral hemispheres on T2-weighted images (Figure 79.36). These paramagnetic signal changes represent encrustation of the brain surfaces with hemosiderin. The adjacent neural tissue atrophies, with accumulation of ferritin in microglia and Rergmami's cells in the cerebellum. Superficial siderosis is presumably secondary to chronic or recurrent blood leakage into the subarachnoid space. It has been described after hemispherectomy, head or spine trauma, and in association with chronically or recurrently bleeding intracranial aneurysms, arteriovenous malformations, and spinal tumors. However, the CSF analysis may be normal, and not all patients have an identifiable source of bleeding. Treatment relies on identifying and arresting the source of bleeding; chelation therapy does not appear to be effective.

Fibromyalgia

Fibromyalgia, a syndrome defined by widespread musculoskeletal or soft tissue pain and multiple tender points, is part of the differential diagnosis of many patients with spinal pain. The American College of Rheumatology classification criteria for the diagnosis define pain as *widespread* when it is bilateral, above and below the waist, and axial. To meet the classification criteria, a patient must have tenderness to palpation at 11 or more of 18 specific points (Figure 79.37), but the validity of these tender points as diagnostic criteria has been cogently questioned. Typically, patients have multiple symptoms including fatigue, stiffness, nonrcstorative sleep, headaches, and mood disorders. Patients may have many symptoms of neurological import such as weakness, paresthesia, and dizziness. Nonetheless, theit neurological examinations ate normal, unless they have a separate neurological Illness.

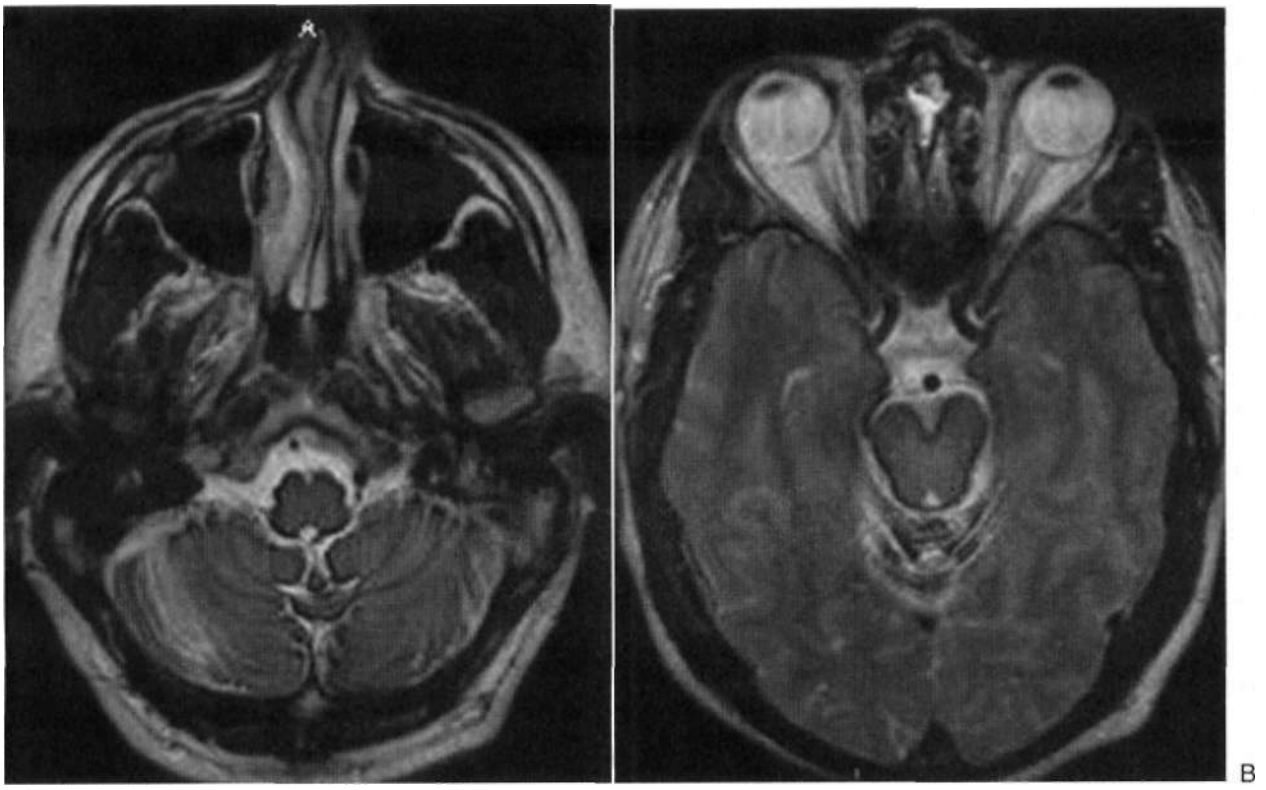


FIGURE 79.36 (A, B) Axial T2-weighted magnetic resonance images demonstrate a thin ring of hypointensity surrounding the medulla and midbrain, indicating hemosiderin deposition along the leptomeninges. (Courtesy Jim Anderson, Oregon Health Sciences University, Portland, Oregon.)

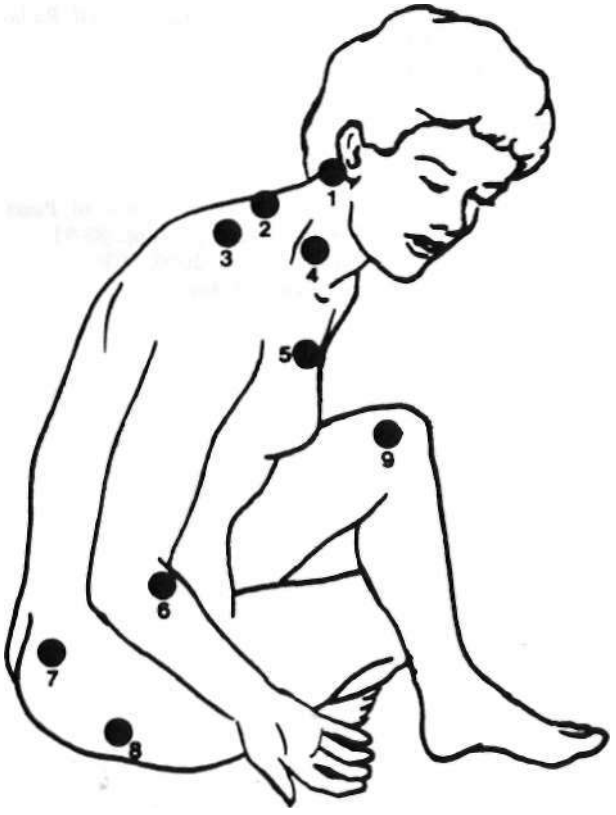


FIGURE 79.37 The tender point location of fibromyalgia. The nine paired tender points recommended by the 1990 American College of Rheumatology Criteria Committee for establishing a diagnosis of fibromyalgia are (1} insertion of the nuchal muscles into occiput; (2) upper border of the trapezius, midportion; (3) muscle attachments to upper medial border of scapula; (4) anterior aspects of the C5, C7 intenransverse spaces; (5) second rib space approximately 3 cm lateral to the sternal border; (6) muscle attachments to lateral epicondyle, approximately 2 cm below the bony prominence; (7) upper outer quadrant of gluteal muscles; (8) muscle attachments just posterior to the greater trochanter; and (9) medial fat pad of knee proximal to joint line. A total of 11 or more tender points in conjunction with a history of widespread pain is characteristic of the fibromyalgia syndrome. (Reprinted with permission from Bennett, K, M, 1997, "The fibromyalgia syndrome: Myofascial pain and the chronic fatigue syndrome," in *Textbook of Rheumatology,* 5th ed, eds W. N. Kelley, E. D. Harris, Jr., S. Ruddy, et al., WB Saunders, Philadelphia.)

Diagnostic neurological investigations, such as brain imaging, muscle biopsy, or electrodiagnostic studies, are norma! or show minor nonspecific abnormalities.

The cause of most cases of fibromyalgia is unknown. Behavioral and biological factors both contribute to the clinical presentation of the syndrome (Oof ford and Clauw 2002). Neuroscientific research on the pathogenesis of fibromyalgia has examined muscle, sleep, neuroendocrine function, and central pain processing, including studies using functional brain imaging (Bradley et al. 2002). Symptoms and signs of fibromyalgia can occur in association with an autoimmune disease, such as systemic lupus erythematosus, or other systemic illness, such as hypothyroidism. Focal trauma can cause localized, self-limited soft tissue myofascial pain. The pathogenic role of trauma, on-the-job injury, or workplace stress is controversial. Treatment includes a supportive doctor-patient relationship, tricyclic antidepressants, aerobic exercise, and avoiding inactivity.

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Chapter 80
Disorders of Upper and Lower Motor Neurons

Brian Murray and Hiroshi Mitsumoto

The marriage of clinical nenroscience and molecular biology has greatly advanced our understanding of motor neuron disorders over the last decade. Through cellular, animal, and Inn nan research, there has been a veritable explosion in new information relating to the pathogenesis of both hereditary and acquired disorders of the motor system as it extends from the brain to the anterior horn cell. In addition, a host of prospective, controlled trials are yielding new treatment options for several disorders that were hitherto unbeatable. In this chapter, we review the causes, diagnosis, and treatment of the motor neuron diseases according to whether the disorder affects upper motor neurons (UMNs), the lower motor neurons (LMNs}, or both UMNs and LMNs.

DISORDERS Ol UPPER MOTOR NEURONS

Neuroanatomy of Upper Motor Neurons

The UMN is the motor neuron, the cell of which lies within the motor cortex of the cerebrum, and the axon of which forms the corticobulhar and corticospinal tracts. It is distinguished from the LMNs lying in the brainstem motor nuclei and the anterior horns of the spinal cord that directly innervate skeletal museles. The UMNs are rostral to the LMNs and exert direct or indirect supra-nuclear control over the LMNs (Mitsumoto, Chad, and Pioro 1997) (Table 80.1).

Motor Cortex

In the cerebral cortex, UMNs are located in the *prtmary motor cortex* (Brodmann's area 4) and the *premotor areas* (brodmann's area 6), which are subdivided into the *supplementary motor area* (sometimes called the *secondary motor cortex)* and the *premotor cortex,* respectively. The somarotopic organization and topographic specificity of the corticospinal projection appear to be far more complex and broader than was previously thought, *Betz's cells* (giant pyramidal neurons) are a distinct group of large motor neurons in layer 5 of the primary motor cortex and represent only a small portion of all primary motor neurons

Table 80.1: Upper motor neurons and their descending tracts

The motor areas
The primary motor neurons (Betz's giant pyramidal cells and surrounding motor neurons)
The premotor areas (the supplementary motor area and ptemotor cortex)
Corticospinal and corticobulbar tracts
Lateral pyramidal tracts
Ventral (uncrossed) pyramidal tracts
Brainstem control
Vestibulospinal tracts
Reticulospinal tracts
Tectospinal tracts
Limbic motor control

with axons in the corticospinal tracts. Individual motor neurons in the primary motot cortex initiate and control the contraction of small groups of skeletal muscles subserving individual movements. The entire motot area of the cerebral cortex controls the highest levels of voluntary muscle movement, including motor planning and programming of muscle movement.

Corticospinal and Corticobulbar Tracts. Axons from the motor areas form the corticospinal and corticobulbar tracts. Axons arising from neurons in the primary motor cortex constitute only one third of all the corticospinal and corticobulbar tracts. Among these, Betz's cell axons make up 3-5% of the tract, and the remaining fibers from the primary motor cortex arise from other neurons in layer 5 of :1K- pnman mom:- concx. Another one iln:\: ol the axons in these tracts arc detived from Brodmann's area 6, which includes the supplementary motor and the lateral premoror cortex. The remaining third is derived from the somatic sensory cortex (areas 1, 2, and 3) and the adjacent temporal lobe region. The corticobulbar tract projects bilaterally to the motot neurons of cranial nerves V, VII, IX, X, and XII. Most corticospinal fibers (75-90%) decussate in the lower medulla (pyramidal decussation) and form the lateral corticospinal tract in the spinal cord (the pyramidal tracts). The remaining fibers descend in the ipsilateral ventral corticospinal tract. The lateral corticospinal tract projects to ipsilateral motor neurons and their interneurons that control extremity muscle contraction, whereas the anterior corticospinal tract ends bilaterally on ventromedial motor neurons and interneurons, which control the axial and postural muscles. These corticospinal axons provide direct glutamatergic excitatory input to alpha motoneurons.

Brainstem Control. In a broad sense, several brainstem nuclei can be considered part of the UMN system because they exert supranuclear influence on the LMN population in the spinal cord. The projections from the brainstem to spinal cord LMNs are highly complex. The fibers originating in the medial and inferior vestibular nuclei in the medulla descend in the medial vestibulospinal tract and terminate both on medial cervical and thoracic motor neurons and on interneurons. They excite ipsilateral motor neurons but inhibit contralateral neurons. The lateral vestibulospinal tracts originating in the lateral vestibular nucleus (Dciter's nucleus) activate the extensor motor neurons and inhibit the flexor motor neurons in both the upper and the lower extremity.

The brainstem reticular formation also sttongly influences the spinal motor neurons, exerting widespread polysynaptic inhibitory input on extensor motor neurons and excitatory input on flexor motor neurons. The reticulospinal tracts modulate various reflex actions during ongoing movements. The brainstem reticular formation receives supranuclear control from the motor cortex via the cortical reticulospinal pathway, to act as a major inhibitot of spinal reflexes and activity. Therefore a lesion of the corticoreticular pathway can disinhibit reticulospinal control of the LMNs. The tectospinal tract originates in the superior colliculus and controls eye and head movement. Muscle tone is altered by variations in the balance between inhibitory input (mediated by the dorsal reticulospinal tract) and faeilitatory input (mediated by the medial reticulospinal tract and to some extent by the vestibulospinal tract) upon muscle stretch receptors.

Limbic Motor Control. The limbic system is involved in emotional experience and expression and is associated with a wide variety of autonomic, viscetal, and endocrine functions. It strongly influences the somatic motor neurons: The emotional status and experience of an individual determines overall spinal cord activity and the limbic motor system also influences respiration, vomiting, swallowing, chewing, and licking (at least in animal studies). Furthermore, the generation of pseudobulbar signs in amyotrophic latctal scletosis (ALS) is closely related to an abnormal limbic motor control, particularly in the periaqueductal gray and nucleus retroambiguus. The latter nuclei project to the somatic motor neurons that innervate pharyngeal, soft paiatal, intercostal, diaphragmatic, abdominal, and probably laryngeal muscles. Pseudobulbar symptoms may appear when UMN control over these motor nuclei is impaired, and thus limbic motot control is disinhibited. There appears to be some degree of emotional regulation by the cerebellum: The recently described "cerebellar cognitive affective syndrome" can arise when stroke, tumor, or infection interrupts connections between the cerebellum and cerebral association and paralimbic regions (Schmahmann and Sherman 1998).

Signs and Symptoms of Upper Motor Neuron Involvement

Loss of Dexterity

Loss of dexterity is one of the most characteristic signs of UMN impairment. Voluntary skillful movements require

Table 80.2: Signs and symptoms of upper motor neuron

Loss -.i tk-xii -MI-
LOSS of muscle strength (weakness!
Spasticity
Pathological hyper-reflexia
Pathological reflexes
Increased redeyes in an atrophic limb
Pseudobulbar (spastic bulbar) palsy

the integrated activation of many interneuron circuits in the spinal cord; such integration is ultimately controlled by the corticospinal tract and thus by UMNs. Loss of dexterity may be expressed as stiffness, slowness, and clumsiness in performing any skillful motor actions; in particular, rapid repetitive motions, such as foot or finger tapping, are impaired (Table 80.2).

Loss of Muscle Strength (Weakness)

Although muscle strength is reduced, the degree *n*\ muscle-weakness resulting from UMN dysfunction is generally mild. Extensor muscles of the upper extremities and flexor muscles of lower extremities may become weaker than their antagonist muscles because the UMN lesion disinhibits brainstem control of the vestibulospinal and reticulospinal tracts.

Spasticity

Spasticity is the hallmatk of UMN disease. The pathophysiology of spasticity is complex and controversial: It seems to reflect altered firing of alpha motoneurons and interneurons within the spinal cord, together with increased activity of group II nerve fibers derived from muscle spindles. There is an excess level of excitatory input to gamma motoneutons via excess synaptic levels of excitatory neurotransmitters such as serotonin, noradrenaline, and glutamate. In addition, there is reduced inhibitory glycinergic and y-aminobutyric acid (GABAergic) neurotransmission. The result is a state of sustained increase in muscle tension when the muscle is lengthened. Clinically, muscles exhibit a sudden resistive "catch," midway during passive movement of the limb. However, when a sustained passive stretch is continued, spastic muscles quickly release the tension and relax, an event often described as the "clasp-knife phenomenon." In muscles that are severely spastic, passive movement becomes more difficult and even impossible. Sustained increases in muscle tone lead to a slowing in motor activities, which may be clinically demonstrated by asking a patient with spasticity to carry out rapid repetitive motor activities such as finger or foot tapping. In some patients with UMN degenerations, the increase in tone may be minimal.

Pathological Hyper-reflexia and Pathological Reflexes

Pathological hyper-reflexia is another crucial manifestation of UMN disease. The Babinski sign (extensor plantar response) is the most important sign in the clinical neurological examination and is characterized by extension of the great toe (often accompanied by fanning of the other toes) in response to stroking the outer edge of the ipsilatcral sole upward from the heel with a blunt object.

Pseudobulbar (Spastic Bulbar) Palsy

Pseudobulbar palsy (or spastic bulbar palsy) develops when there is disease involvement of the corticobulbar tracts that exert supranuclear control over those motor nuclei that control speech, mastication, and deglutition. The prefix "pseudo-" is used to distinguish this condition from "true" bulbar palsy that results from pure I.MN involvement in brainstem motor nuclei. Articulation, mastication, and deglutition are affected in both pseudobulbar and bulbar palsies, but the degree of impairment in pseudobulbar palsy is generally milder. Spontaneous or unmotivated ctyiug and laughter uniquely characterize pseudobulbar palsy. This is also termed *emotional lability,* labile affect, or *emotional incontinence* and is often a source of great embarrassment to the patient.

Laboratory Evidence of Upper Motor Neuron Involvement

Nettroimagmg

Brain magnetic resonance imaging (MRI) sometimes shows abnormal signal intensity in the corticospinal and corticobulbar tracts as they descend from the motor strip via the internal capsules to the cerebral peduncles. In AI.S, a disorder of UMNs (and LMNs), these signal changes are best appreciated on T2-weighted (increased signal in the internal capsules) and proton density (low signal in the preccntral cortex) images and probably represent wallerian degeneration. However, theses changes do not appear to be sufficiently sensitive or specific, and efforts continue to evaluate other potential MRI techniques, such as diffusion tensor and volumetric MRI, which may serve as markers of UMN disease (Ellis et al. 2001; Smith 2002).

Magnetic Resonance Spectroscopy Imaging

Proton density magnetic resonance spectroscopy ('H-MRS) is a noninvasive nuclear magnetic resonance technique that combines the advantages of MRI with in vivo biochemical information. N-acery(aspartate, a neuronal marker, is significantly reduced relative to creatine:phosphocreatine level (used as an internal standard because all cells, including glial cells, contain creatine and phosphocreatine),

Table 80.3: Disorders of upper motor neurons and their key characteristics

Disorders	*Key characteristics*
Primary lateral sclerosis	A diagnosis ɨ4 exclusion
Hereditary spastic paraplegia	Heredity, usually autosomal dominant, spastin gene mutation, other mutations (see text)
HTLV-1-associated myelopathy	Slowly progressive myelopathy, endemic, and positive HTLV-1
HTLV-2-associated myelopathy	Amerindian, IV drug abuser
Adrenomyeloneuropathy	X-linked recessive inheritance may have adrenal dysfunction myelopathy, very long chain fatty acid
Lathyrism	History of consumption of chickling peas
Konzo	Eastern African, cassava root consumption

HTLV = human T-lymphotropic virus; IV = intravenous.

in the sensorimotor cortices of patients with ALS who have UMN signs. Alterations in the measured levels of these metabolites using 'H-MRS can be used in the detection of UMN dysfunction early in the evolution of ALS and be used to monitor progression over time (Kaufmann and Mitsumoto 2002; Suhy ei al. 2(102;.

Transcranial Magnetic Stimulation

Another technique is transcranial magnetic stimulation (TMS), which electro physiologically evaluates UMN function. TMS over the scalp at the region of the motor cortex induces motor evoked potentials thai are recorded at the skeletal muscle and variations in the response pattern of the motor evoked potential have been correlated with UMN involvement (Auer-Grumbach et al. 2000).

Primary Lateral Sclerosis

Primary lateral sclerosis (PLS), first described by Frb in 1875, is a rare motor neuron disease variant that accounts for 2-4% of all cases of ALS and has traditionally been distinguished by a lack of LMN involvement. This has led some to argue that PLS is not a variant of ALS but is an entirely distinct entity. However, a recent prospective study tevealed several features that indicate not only some degree of LMN involvement but also disease extension beyond the motor system (Le Forestier, Maisonobe, Piquard 2001}. It typically presents in patients in their early fifties as a slowly evolving, spastic paraparesis that spreads to the upper extremities and eventually causes pseudobulbar palsy. Othet features include cramps, fasciculations, and sometimes urinary urgency, but such complaints arc neither prominent nor universal. Although muscle weakness is present, the main deficits are in dexterity and gait due to spasticity. The rate of progression can be exceedingly slow, often progressing over many years to the point where the patient manifests a robotic gait, debilitating generalized spasticity, and prominent pseudobulbar palsy. Muscle atrophy is a very late feature, if it occurs at all. There are no clinically detectable sensory changes, but derailed somatosensory evoked potential studies may be abnormal. Neuropsychology test batteries may define subtle cognitive deficits due to frontal cortical involvement, but dementia is not a prominent feature. A few patients may exhibit abnormal voluntary eye movements.

The underlying pathogenesis of PLS remains undefined. Pathological changes appear to be restricted to a striking loss of layer 5 Betz's cells in the frontal and prefrontal motor cortex (and other smaller pyramidal cells) and laminar gliosis of layers 5 and 5 with degeneration of the corticospinal tracts. Spinal anterior horn cells are spared. A recent study of a patient using serial MRI identified extensive involvement not just of the motor and premotor cortex but also extension of atrophy into sensory cortex suggesting possible selective loss of motor ptojection neurons {Smith 2002) (Table 80.3).

Diagnosis

The diagnosis of PLS is essentially one of exclusion. There have been rare reports of UMN-onset ALS where the interval between onset of UMN signs and subsequent LMN signs was 8, 9, and 27 years, respectively. As such, it is vital to periodically reassess patients who are diagnosed with PLS in case they develop late signs of LMN involvement that would reclassify their disorder as UMN-onset ALS,

All definable causes for generalized UMN involvement should be excluded by appropriate testing. These include structural abnormalities (Chiari malformation and intrinsic *AIII]* extrinsic spinal cord lesions) and myelopathies such as multiple sclerosis, human immunodeficiency virus (HIV) myelopathy, human T-lymphotropic virus type 1 (HTLV-1) myelopathy, Lyme disease, syphilis, or adrcnomyeloiieuroparhy. Spondylotic cervical myelopathy and multiple sclerosis are probably the most common causes among these disorders. The family history must be negative, to rule out hereditan spastic paraplegia :IIM' /ramilial spastic paraparesis, spinocerebellar ataxia (SCA), hexosaminidase-A (Hex-A) deficiency, familial ALS (FALS), or adrenomyeloneuropathy. Paraneoplastic syndromes (especially in association u ith breast cancer) and Sjogren's syndrome may also clinically resemble PLS.

Treatment

No specific pharmacotherapies are available for this condition. However, antispasticity drugs such as the $GABA_B$ agonist baclofen and the central a_2 agonist

tizanidine may be tried for symptomatic treatment. Severe spasticity sometimes requires the insertion of an intrathecal baclofen pump. Pseudobulbar affect lability may be controlled with tricyclic antidepressants or selective serotonin reuptake inhibitors. Recent evidence suggests that a combination of dextromethorphan and quinidine may also be useful in managing emotional lability. Good supportive care is essential.

Hereditary Spastic Paraplegia

HSP (or familial spastic paraparesis) is a genetically and clinically heterogeneous group of disorders rather than a single entity. The clinical feature common to all cases is progressively worsening spasticity of the lower extremities, often with variable degrees of weakness. Its estimated prevalence is 0.5-11.9 in 100,000, but its worldwide prevalence may actually be underestimated because of the benign nature of the disease in many families. Although the most common mode of inheritance is autosomal dominant, it may also be inherited in a recessive or X-linked fashion. The clinical syndrome may be broadly classified as the *pure* form and the *complicated* form. In the pure form, patients develop only lower extremity spasticity. However, the complicated form may also include optic neuropathy, deafness, ataxia, ichthyosis, amyotrophy, peripheral neuropathy, dementia, autoimmune hemolytic anemia, and thrombocytopenia (Evans's syndrome), extrapyramidal dysfunction, mental retardation, and bladder dysfunction. Age at onset is extremely variable, from early childhood to [lie ninth decade oi life.

Genetic linkage studies of families around the world have mapped loci to several autosomes including chromosomes 2, 3, 8, 11, 12, 14, 15, and 19, as well as on the X chromosome. An estimated 40% of all families arc linked to an autosomal dominantly inherited locus on chromosome 2p22-21, which encodes a 616-amino acid protein called *spastin.* More than 50 mutations of various types (missense, nonsense, frameshift, and splice site) have been identified that affect the *spastin* gene. Spastin is a highly conserved member of the AAA family of proteins ((adenosine triphosphatase [ATPase] associated with various cellular activities). Its exact role in the pathogenesis of HSP has yet to be defined, although there is evidence that HSP may involve a disturbance in the interaction of spastin with cellular tubulin, thus disrupting axonal transport. Pathologically, degeneration of the longest corticospinal tracts and to a lesser degree the posterior columns of the spinal cord is seen. Genes have been discovered for five other types of HSP. Mutations in the *SPG3A* gene on 14qll-q21 encoding the novel protein, atlastin, give rise to an autosomal dominant form of pure HSP. This protein shares structural homology to guanylate-binding protein 1, which is a member of the dynamin family. Dy nam ins arc known to be important in intracellular trafficking of various kinds of vesicles. Autosomal dominant pure HSP linked to 2q24-34 is caused by a mutation in the *SPG 13* gene, which encodes a mitochondrial heat shock protein, whereas recessively inherited complicated HSP linked to chi-orinsi'Mi;- Ifn; is c.niscd by .1 imitation in a gene encoding a mitochondrial protein known as *paraplegin.* The genes for two different X-linked complicated HSP have been identified; in the first, mutant LI (neural) cell adhesion molecule (LICAM) may disrupt neuronal migration or differentiation; in the second, mutant proreolipid protein is found in association with changes in white matter (Fink 2002).

Diagnosis

The diagnosis of HSP is based on evidence of a family history. When there is no family history, excluding definable causes other than spastic paraplegia is essential; the differential diagnosis is the same as discussed earlier for PLS. Because there may be no clear family history in the recessive form, the diagnosis of autosomal recessive spastic paraparesis is difficult. Patients may exhibit the striking feature for corticospinal tract lesions of hyper-reflexia and spasticity with brisk abdominal reflexes and flexor plantar responses; this constellation is a strong clue to the diagnosis of HSP.

Treatment

At present, treatment of spastic paraplegia is limited to symptomatic interventions, supportive care to reduce spasticity, and orthotics, such as canes, walkers, and wheelchairs. Antispasticity drugs, such as baclofen, tizanidine, diazepam, or dantrolene, are often suboptimal, and patients with very disabling spasticity may require intrathecal baclofen administered through an implanted pump.

Human T-Lyniphotropic Virus Type 1-Associated Myelopathy or Tropical Spastic Paraparesis

HTLV-1 causes a chronic progressive myelopathy that is referred to as tropical spastic paraparesis (TSP) in the Caribbean or HTLV-1-associated myelopathy (HAM) in Japan. This retrovirus is endemic in the Caribbean area, southwestern Japan, equatorial Africa, South Africa, and parts of Central and South America. Recent evidence implicates high levels of activated HTLV-1-specific helper T cells and cytotoxic T cells in the pathogenesis of this syndrome; these immune cells appear to become activated in response to interactions with retroviral env and tax proteins.

11AM/TSP is a chronic, insidiously progressive myelopathy that typically begins after age 30 years. In addition to slowly progressive spastic paraparesis, patients complain of lower extremity paresthesias, a painful sensory neuropathy,

and bladder dysfunction, and some patients may also develop optic neuropathy and SCA. Overall, evidence of LMN involvement may be scant and objective sensory findings may be difficult to detect. The definitive diagnosis of TSP/HAM requires HTI.V-1 -positive serology in blood and cerebrospinal fluid (CSF). The most sensitive and specific CSF detection involves a combination of polymerase chain reaction amplification of viral DNA, together with evidence of an increased HTLV-1-spccific antibody index and oligoclonal bands (Puccioni et al. 2001). At present, no antiviral agents effectively treat TSP/HAM, but a recent case report showed partial benefit when using plasmapheresis {Narakawa et al. 2001). As more is learned about the molecular etiology of HAM/TSP, future therapies will likely target the pathogenic effects of HTf.V-1-reactive T cells.

Human T-Lympbotropic Virus Type 2-Associated Myelopathy

Though phylogenerically similar in many respects, HTLV-1 and HTLV-2 are still antigenically distinct. Nonetheless, using enzyme-linked immunosorbent assays and Western blot techniques, many laboratories worldwide often report the presence of seroindeterminate HTLV-1/2. It has long been thought that myelopathy in such seroindeterminate cases is due to HTLV-1 rather than HTLV-2, but cases are now being described of a syndrome characterized by spastic paraparesis, diffuse hyper-reflexia, spastic bladder, and periventricular white matter changes on MR] in patients infected with HTLV-2, but not HTLV-1. This retrovirus is endemic in some Amerindian tribes and is now often encountered worldwide among intravenous drug abusers. As such, it is worthwhile to test CSF and serum for the presence of this virus in known intravenous drug abusers who present with a spastic paraparesis (Silva et al. 2002).

Adrenomyeloneuropathy

Adrenomyeloneuropathy is a variant of adrenoleukodystrophy, an X-linked recessive disorder caused by mutations in the *ABCDl* gene on chromosome Xq28 that encodes a ubiquitously expressed integral membrane peroxisomal adenosine triphosphate-binding cassette transporter protein. Mutations in this gene lead to abnormal peroxisomal beta-oxidation, which results in the harmful accumulation of very-long-chain fatty acids (VLCFAs) in affected cells. It has recently been proposed that excessive levels of VLCFAs may interfere with the membrane components of both neurons and axons (Powers et al. 2000). The most common phenotype, adrenoleukodysr.rophy, affects young boys 4-8 years of age who develop severe adrenal insufficiency, progressive cognitive deteri-<>ia:i(in, Mi/uri-.. blindness, dealness, and spastic qiauln paresis. In contrast, the milder adrenomyeloneuropathy is clinically characterized by slowly progressive spastic paraparesis and mild polyneuropathy in adult men with or without sensory symptoms and sphincter disturbances. Mild adrenal insufficiency may also be present. Adult female carriers may present with slowly progressive spastic paraparesis. Obtaining a detailed family history and appropriate testing is crucial. In adrenomyeloneuropathy, sural nerve biopsies arc characterized by the loss of both myelinated and unmyelinated axons with some degree of onion bulb formation. In addition, electron micrographs of the sural nerve biopsy specimen may show cha ractcfistic empty lipid clefts in Schwann cells. Nerve conduction studies and needle electrode examination may reveal a predominantly axon-loss type of sensorimotor polyneuropathy with a lesser component of demyelination. The diagnostic test of choice, however, is to demonstrate increased VLCFA levels in plasma, red blood cells, or cultured skin fibroblasts.

Plant Fxeitotoxins

Lathy7ism

Lathyrism is a chronic toxic nutritional neurological disease caused by long-term (or subacute) ingestion of large quantities of flour made from the drought-resistant chickling pea *(l.athyrus sativus)* and is an important example of a disease in which a natural excitotoxin causes selective UMN impairment. The responsible neurotoxin is *fi-N*-oxalylamino-L-alanine (BOAA), an a-amino-3-hydroxyl-5-mcthyl-4-isoxa/olepropionare (AMPA) glutamate receptor agonist. Ingestion of this neurotoxin results in increased intracellular levels of reactive oxygen species and subsequent impairment of the mitochondrial oxidative phosphorylation chain. Degeneration is most prominent in those Betz's cells of the motor cortex (and corresponding pyramidal tracts) that subserve lower extremity function. Lathyrism has been found in the indigenous populations of Bangladesh, China, Ethiopia, India, Romania, and Spain. It was also described in the concentration camps during World War II. The condition may occur in epidemic form when malnourished populations increase consumption of flour made from L. *sativus* chickling peas in drought-prone areas during times of food shortage. A recent analysis of an epidemic of neurolathyrism in Ethiopia showed that boys aged 10-14 years were most often affected and that increased risk was associated with cooking grass pea foods in traditional clay pots (Getahun et al. 2002). The onset of clinical toxicity is either acute or chronic, manifesting as muscle spasms, cramps, and leg weakness. In addition to spastic paraparesis, there may be sensory (including leg formications) and bladder dysfunction. Occasionally, there is a coarse tremor of the upper extremities. Although irreversible, the disorder is self-limiting and there is no apparent shortening of life span.

Konzo ("tied legs") is another toxic nutritional disorder of cortical motor neurons caused by chronic dietary ingestion of a neurotoxin derived from flour made from short-soaked cassava roots. The disorder is endemic in protein-deficient communities in Tanzania, Zaire, and Eastern Africa and in times of famine can occur in epidemic form. The neurotoxic effect of chronic cassava root ingestion likely is derived from the liberation of cyanohydrins from the flour, which may be further metabolized to thiocyanate. The latter in turn may excessively stimulate the AMPA glutamate receptor subtype precipitating excitotoxic neuronal injury. As with lathyrism, there appears to be a selective effect on the lower extremity-directed Ber/'s cells of the cerebral cortex and their corresponding corticospinal tracts. As such, the clinical syndrome is also very similar to lathyrism; patients typically present with spastic paraparesis (although some may exhibit only lower extremity hyper-reflexia). Occasionally, one may detect weakness of the upper extremities but not to the same degree as that of the lower extremities.

DISORDERS OF LOWER MOTOR NEURONS

Neuroanatomy of Lower Motor Neurons

Interneurons

The interne urons constitute most of the anterior horn cells of the spinal cord and determine the final output of the LMNs. The interneuron system receives supranuclear excitatory and inhibitory motor control from the brainstem descending tracts, corticospinal tracts, and limbic system; this system also receives afferent information, directly and indirectly, from the afferent peripheral nerves. The interneuron system forms intricate neuronal circuits involving automatic and stereotyped spinal reflexes, to coordinate and integrate the activation of synergist muscles while inhibiting antagonist muscles, contralateral muscles, and sometimes even a distant motor pool. The same interneuron network that mediates such automatic and stereotyped reflex behavior is also known to act as the basic functional unit involved in highly skillful voluntary movements. Ultimately, all of the interneuronal paths converge on the LMNs that innervate skeletal muscles, which Sherrington has called the *final common path.*

Lower Motor Neurons

LMNs are located in the brainstem and spinal cord and send out motor axons that directly innervate skeletal muscle fibers. Spinal cord LMNs are also known as *anterior horn celts* and are clustered in nuclei forming longitudinal columns; those innervating the distal muscles of the extremities arc located in the dorsal anterior horn, whereas those innervating proximal muscles of the extremities are in the ventral anterior horn. Those LMNs that innervate the axial and truncal muscles are the most medially located. The normal cervical and lumbar enlargements of the spinal cord are the result of markedly enlarged lateral anterior horns containing the LMNs for the upper and lower limb muscles.

Large spinal cord LMNs are called *alpha motoneurons* and are the principal motor neurons innervating muscle fibers. Medium-sized motor neurons *(beta motoneurons)* innervate both extrafusal and intrafusal (muscle spindle) fibers and intermediate and small motor neurons *(gamma motoneurons* or *fusimotor neurons)* innervate only spindle muscle fibers. The rest of the small anterior horn cells are *interneurons.*

Alpha motoneurons are among the largest neurons of the nervous system. Each has a single axon that branches to its target muscles and a number of large dendrites that provide an extensive receptive field. The motor unit is the smallest unit of the motor system and consists of one alpha motoneuron, its axon, and all of its target muscle fibers,

Motor axons originating from LMN cell bodies (perikarya) leave the central nervous system (CNS) through the anterior (or ventral) spinal roots to become a part of the peripheral nervous system. Motor axons subsequently intermingle with sensory and autonomic nerve fibers in individual peripheral nerves. All peripheral nerve fibers are ensheathed by Schwann cells, and all motor axons are myelinated. The environment of the peripheral nervous system is controlled by the blood-nerve barrier and perineuria! sheath. Neurotrophic factors are thought to be absorbed at the axon terminal, but other macro molecules, neurotoxins and viral particles included, can also enter the motor axons at this site.

Signs and Symptoms of Lower Motor Neuron Involvement

Loss *of Muscle Strength (Weakness)*

The loss of an LMN will result in the denervation of its motor unit, whereas an impaired LMN may lead to abnormal or impaired activation of its motor unit. In either case, the number of fully functional motor units is decreased, which reduces overall muscle twitch tension.

In a disease that causes chronic motor unit depletion, neighboring axons belonging to healthy motor neurons may reinnervatc denervated muscle fibers belonging to a diseased motor unit. In this way, existing motor units are continually modified in the face of persistent losses of motor axons to maximize muscle strength. For example, in patients who have recovered from acute poliomyelitis, more than 50% of LMNs are usually found to be depleted before muscle weakness is clinically detected. Healthy individuals have more than enough motor units available to offset an unexpected loss of motor neurons (Table 80.4}.

Table SO.4: Signs and symptoms of lower motor neuron involvement

Loss of muscle strength (weakness)
Muscle a trophy-
Hypo re flcxia
Muscle hypotonicity or flaccidity
Fasciculations
Muscle cramps

Muscle Atrophy and Hyporeflexia. Muscle fiber denervation causes muscle fiber atrophy, and thus progressive LMN involvement results in reduced overall muscle volume and size. Hyporeflexia occurs with LMN involvement because the loss of active motor units reduces the overall muscle twitch tension; thus muscle stretch reflexes elicit less tension (diminished tcflexcs) or no visible twitch (absent reflexes).

Muscle Hypotonicity or Flaccidity

Hypotonicity, or *flaccidity,* refers to the decrease or complete loss of normal muscle resistance to passive manipulation. In contrast to spasticity, the muscle lies inert and flaccid.

Fasciculations

Fasciculations are spontaneous contractions of muscle fibers belonging to a single (or part of a) motor unit. Clinically, fasciculations appear on the muscle surface as fine, rapid, flickering, and sometimes vermicular contractions that occur irregularly in time and location. The impulse for the fasciculation appears to arise from hyperexcitable motor axons anywhere in their course. Fasciculations can occur both in healthy individuals and in patients with LMN involvement, so fasciculations themselves do not indicate LMN disease.

In general, the larger the muscle the greater the size of the fasciculations, but the sine of the motor unit is also a factor. In tongue muscles, for example, fasciculations produce small vermicular movements on the tongue surface. Fasciculations usually do not cause -ny joint displacement but when fasciculations occur in muscles going to the fingers, joint movements can occur (mini-polymyoclonus). Large fasciculations may be found in large muscles undergoing a highly chronic reinnervating process such as chronic spinal muscular atrophy (SMA) and the postpoliomyelitis syndrome.

Muscle Cramps

Muscle cramps are common in the general population and are another common symptom of LMN involvement. The pathogenesis of cramps in LMN disease is poorly understood, as it is in normal individuals. Cramps and fasciculations are likely to share a common pathogenic mechanism, such as hyperexcitability of the motor neurons. Muscle cramps are clinically defined as an abrupt, involuntary, and painful shortening of the muscle, which is accompanied by visible or palpable knotting, often with abnormal posture of the affected joint; they can be relieved by stretching or massaging.

Laboratory Evidence of Lower Motor Neuron Involvement

Electrodiagnostic Examination

The electrodiagnosric examination (LDX) consists of nerve conduction studies and needle electrode examination (see Chapter 36B). The loss of motor units is reflected in the loss of compound muscle action potential (CMAP) amplitudes. In a primarily demyelinatiug process, there may be a slowing of conduction velocity and in severe cases conduction block. In a primarily axon loss process, there is usually only a modest degree of conduction velocity slowing commensurate with dropout of large myelinated axons. Sensory nerve conduction studies ate normal in pure LMN disorders.

The needle electrode examination is crucial in obtaining electrophysiological evidence of abnormal motor units in LMN disorders. Muscle fibers that are actively denervated discharge spontaneous electrical activity, such as fibrillation potentials and positive sharp waves. Fasciculation potentials may also be detected, but as an isolated EDX finding, they are insufficient evidence of an axon loss disorder. The recruitment pattern during voluntary muscle activation is also altered in neurogenic disease, with a reduced number of motor units that have an increased firing rate; this reflects a compensatory effort on the part of surviving motor units to maintain a particular force.

Because denervation of muscle fibers triggers a reiimervation process, motor units are continuously remodeled. Early in the reinnervating process, newly formed neuromuscular junctions are electrically unstable, and thus the action potentials of the muscle fibers vary in amplitude. Furthermore, newly regenerated axons that reinnervate denervated muscle fibers tend to have slow conduction velocities, causing a prolonged conduction time within one motor unit. All these changes alter the configuration of the motor unit potential so that it becomes irregular and polyphasic. In a chronic reinnervating process, surviving motor units may reinnervate a greater number of muscle fibers, resulting in a potential that is broader in duration and higher in amplitude. Therefore the shape of a typical chronic neurogenic motor unit potential is polyphasic, broad, and high in amplitude, providing clear evidence of IAIN involvement.

Motor unit number estimation (MUNE) is a specialized neurophysiologies! tool that can estimate the number of functioning motor units that remain in a progressive

neurogenic process. Various techniques are in use including a statistical method and a multipoint stimulation technique, but issues of reproducibility remain, so MUNE remains largely a research tool.

Muscle Biopsy

Although EDX usually provides sufficient evidence of L.V1N involvement, muscle biopsy may also reveal early evidence of muscle fiber denervation. Denervated muscle fibers are small, angular, and stain darkly by oxidative enzyme and nonspecific esterase stains. As the denervation process progresses, small groups of atrophied muscle fibers (group atrophy) may appear. In normal human muscle, the different muscle fiber types that are distinguished using ATPasc stain appear in a random distribution, sometimes mistetmed a "checkerboard pattern." In chronic denervating disease, repeated denervation and reinncrvation eventually result in loss of this random pattern and in very chronic neurogenic disease large areas of the biopsy consisting of just one muscle fiber type, a process called *fiber type grouping.*

Magnetic Resonance Imaging

MR] neurography is a relatively novel technique in sequence acquisition that can detect early signal change both in injured axons and in denervated muscle on T2-weighted and short tau inversion recovery images. These signal changes can distinguish focal sites of nerve entrapment, regenerating nerve fibers, nerve tumor, and nerve transection. Those segments of peripheral nerve that are difficult to study using standard EDX, such as very proximal portions of the sciatic nerve and the above-elbow segment of the ulnar nerve, may be visualized with this technique. The MRI muscle signal change can occur as early as 4 days after a traumatic nerve injury and is reversible as long as reinnervation takes place. As such, this emerging field is being applied to the noninvasive evaluation of entrapment neuropathies, nerve trauma, peripheral nerve tumor surgery, brachial plexopathy, radiculopathies, and peripheral neuropathies (Grant et al. 2002).

Acute Poliomyelitis

Poliomyelitis (acute anterior poliomyelitis) is one of the most dramatic disorders causing acute LMN dysfunction. The disease is caused by poliovirus, a single-stranded RNA enterovirus belonging to the picornavirus family. The mode of spread is via the fecal-oral route, the virus first entering lymphoid tissue before being borne in the bloodstream to the CNS. Before the introduction of oral poliovirus vaccine, epidemics of acute paralytic poliomyelitis were relatively common in temperate zones and primarily affected children and young adults (infantile paralysis). In 1988 the World Health Organization resolved to eradicate poliomyelitis worldwide. However, this has yet to be achieved. The oral poliovirus vaccine itself is responsible for very rare cases of acute paralytic poliomyelitis in the developed world with an estimated risk of 1 case in 2.5 million vaccines ingested. Non-polioviruses can cause a paralytic polio-like syndrome, and it is still important that physicians be acquainted with this syndrome.

Clinical Features

After a brief 3-6 day incubation period, a viremia occurs, during which approximately 90% of individuals remain asymptomatic. However, most of the remaining 10% develop an acute, flu-like illness with cough, malaise, diarrhea, myalgia, headache, and fever. This self-limited, "abortive" polio usually lasts 2-3 days and patients do not progress to develop acute muscle weakness, although recent evidence indicates that some such patients may develop features of the postpolio syndrome many years later (Bruno 2000). Between 2-3% of patients develop aseptic meningitis characterized by severe headache due to meningeal irritation. This is typically self-limited and resolves within 7-14 days. Fewer than 1% of patients who ingest poliovirus develop the acute paralytic syndrome, characterized by localized fasciculations, severe myalgia, hyperesthesias, and usually fulminant focal and asymmetrical paralysis. Any muscle can be affected, including the diaphragm and intercostal muscles; the leg muscles are the most commonly affected, and the bulbar muscles the least common.

Physical examination reveals severe LMN-typc muscle weakness with hypoactive or absent deep tendon reflexes, decreased muscle tone, and fasciculations. With progression of the disease, muscle atrophy occurs. Objective signs of sensory loss are not characteristic. The risk of paralytic disease seems to increase with patient age and with the level of virulence of the virus. Most patients with paralytic disease recover significant strength. Improvement may begin as early as the first week after the onset of paralysis, and it has been estimated that 80% of recovery will occur by 6 months. Eutther improvement may be modest, but it may continue over the ensuing 18-24 months. Up to two thirds of patients are left with some degree of significant functional impairment.

Laboratory Features

Motor nerve conduction studies performed 21 or more days after the onset (see Chapter 36B) may reveal low-amplitude CMAPs. There is no evidence of significant demyelination-rclatcd motor slowing or conduction block. Sensory nerve action potentials (SNAPs) arc normal. When needle electrode examination is performed in the acute phase, profuse axon loss may be detected in the form of positive sharp waves and fibrillation potentials. In addition, fasciculations may be prominent. As motor axon loss

progresses, evidence of neurogenic motor unit potential changes may be detected. The CSF typically shows a pleocytosis, with polymorphonuclear cells predominating during the acute stages and lymphocytes predominating later in the disease. CSF protein levels are mildly to moderately increased. Identification of CSF poliovirus-specific immunoglobulin M (IgM) antibody allows a specific-diagnosis, Stool cultures are positive* for poliovirus in nearly 90% of patients by the tenth day of illness. Traditionally, the diagnosis is established by documenting a fourfold or greater increase in antibody titer against poliovirus in sera from the acute as compared to the convalescent phase.

Differential Diagnosis

Acute paralytic disease caused by enteroviruses other than poliovirus and West Nile virus can manifest identically to acute poliomyelitis. The documentation of an increase in neutralizing antibody titers of these other viruses from acute compared to convalescent sera or isolation of the virus in culture is the only way to make a cotrect diagnosis. Although acute paralytic poliomyelitis has a distinct clinical presentation, Guillain-Barre syndrome may mimic it because acute paralysis of the skeletal muscles occurs in both. Guillain-Barre syndrome has some sensory signs and symptoms, although it can present with predominantly motor symptoms. A dramatic or abrupt paralysis following severe pains and fasciculations is unusual in Guillain-Barre syndrome. A careful analysis of the CSF and electromyographic (FMG) findings should differentiate these diseases. Acute immune-mediated motor neuropathy (acute motor axonal neuropathy) should also be considered in the differential diagnosis. This motor neuropathy, which resembles Guillain-Barre syndrome, usually presents with rapidly progressive weakness in distal extremity muscles without sensory symptoms. One must also consider myasthenia gravis, neuralgic amyotrophy, acute intermittent porphyria, periodic paralysis, tic paralysis, and acute rhabdomyolysis.

Treatment

The treatment of acute paralytic poliomyelitis consists of aggressive general supportive care. Most patients will require hospitalization in an intensive care unit to optimize close monitoring of ventilatory and cardiovascular function. After the acute illness, aggressive rehabilitation is the mainstay of continued treatment.

Vaccination

Ultimately, the best cure for polio is prevention. Two vaccines are available, the Sabin and the Salk. The Sabin trivalent oral poliovirus vaccine contains all three live attenuated serotypes of poliovirus and is almost 100% effective in preventing acute paralytic poliomyelitis. Adults who plan to travel to areas where poliomyelitis is prevalent should receive an extra dose of this vaccine. Immunocompromised individuals, their household contacts, and adults who have never received poliovirus vaccine previously should receive the Salk formalin-inactivated poliomyelitis vaccine rather than the Sabin vaccine because there is an increased risk of these individuals developing acute paralytic poliomyelitis if the oral poliovirus vaccine is used.

Progressive Postpoliomyclitis Muscular Atrophy

In the United States alone, it is estimated that 250,000-640,000 people survived acute poliomyelitis, the last epidemic of which occurred in 1952. Many years after recovery from acute poliomyelitis, some patients experience progressive weakness, called progressive postpoliomyclitis muscular atrophy (PPMA). The reported incidence of PPMA among polio survivors ranges from 28,5-64.0%; an accurate estimate of the incidence is not known. By definition, patients with PPMA have recovered from acute poliomyelitis and the disease course has been stable fot at least 10 years after the recovery. Although PPMA appears to be well defined, an unusually wide disparity in the reported occurrence raises the concern that the identity of PPMA may be more ambiguous than previously thought. Although here we use the term *I'VMA* to describe a progressive LMN syndrome, terms such as *postpolio syndrome* or *late effects of remote polio* may be more appropriate because patients who have had remote poliomyelitis may develop a multitude of symptoms in addition to progressive muscle weakness and wasting (Table 80.5).

Etiology

The etiology of PPMA has yet to be established. Chronic persistent poliovirus infection is a possibility, but numerous studies have failed to convincingly identify poliovirus

Table 80.5: Characteristic features of progressive postpolio myelitis muscular atrophy

Medical history
Recovery from acute poliomyelitis
•\ l"ii;; si.shlf 11 iiirsf, at IMM I 0 yr
Signs and symptoms
Progressive weakness usually in previously affected muscles
Accompanying overstress muscle pains and arthralgia
Laboratory studies
EMG is helpful to identify evidence of previous polio infection
None of tests is specific for PPMA
Diagnosis
Exclusion of other treatable diseases
Treatment
Symptomatic and supportive care

EMG = electromyography; PPMA = post poliomyelitis muscular atrophy.

in PPMA. Similarly, there is a lack of solid evidence to implicate a persistent immune-mediated mechanism, which might explain the presence of oligoclonal bands in the CSF and occasional lymphocytic infiltrates in the muscle and spinal cords of patients with PPMA. The "peripheral disintegration model" is the most widely held theory. In the immediate aftermath of the acute paralytic poliomyelitis, there is ovcrsprouting of new axon terminals from surviving LMNs. This compensatory distal reinnervation expands the size of motor units and provides effective motor function; this stabilizes muscle strength for many years. However, this extensive nerve sprouting also increases the metabolic burden of surviving LMNs, so alter many years, an unidentified process first causes nerve terminal dysfunction presenting as fatigue and then nerve terminal disintegration presenting as muscle weakness and atrophy. It is possible that the normal age-related neuronal loss may be the process causing this late degeneration.

Clinical Features

Patients with PPMA note a stable course for many years after the acute poliomyelitis infection. These patients then experience progressive new muscle weakness and atrophy in previously affected muscles or sometimes in muscles that were apparently not affected by the original poliomyelitis. Needle electrode examination reveals that the muscles that were not clinically affected by acute poliomyelitis often have clear evidence of previous disease, indicating that PPMA is unlikely to affect muscles not affected during the acute poliomyelitis. Muscle cramps and fasciculations may accompany the new weakness, hut they are often present in stable muscles in these patients as well. Other common symptoms include pain, generalized fatigue, cramps, fascit :• ulations, sleep disturbances, cold intolerance, dysphagia, and dysarthria. The most common clinical presentation is that of insidious onset of muscle and joint pain with progressive weakness in muscles that were previously affected by acute paralytic poliomyelitis. Generalized fatigue is a characteristic accompaniment and is uften called the *polio wall.* As patients realize that their motor function is becoming progressively impaired after a lifelong compensation, they may become severely depressed. The neurological examination reveals focal and asymmetrical muscle weakness and atrophy, but it may be difficult to determine which weakness and atrophy is new and progressive and which is remote and static. Pasciculations can be unusually coarse and large in keeping with the giant motor units that may be seen during needle electrode examination.

Laboratory Features

Because **EMG** provides definitive evidence of remote poliomyelitis and excludes diseases mimicking PPMA, it is an indispensable lest when PPMA is suspected. It is extremely important to remember that the EMG studies do not provide the diagnosis of PPMA, however. In patients with PPMA, the motor nerve conduction studies may be abnormal {low CMAP amplitudes) when recorded from affected muscles. The needle electrode examination of affected weak muscles typically shows a reduced number of motor units and chronic neurogenic motor unit potentials. Giant motor units may be present, indicative of chronic denervation and reinnervation. Modest numbers of fibrillation potentials and occasional fasciculations may be observed in affected muscles. Sensory nerve conduction studies are normal. The muscle biopsy specimen usually shows acute and chronic neurogenic atrophy and often marked fiber type grouping; however, these biopsy findings are not diagnostic of I'PMA.

Diagnosis

A history of clinical stability for at least 10 years after recovery from acute poliomyelitis is an absolute prerequisite for considering the diagnosis of I'PMA. When this requirement is satisfied, PPMA is then a diagnosis of exclusion. All potential diseases causing progressive, focal, and asymmetrical weakness must be excluded. Cervical or lumbosacral radiculopathy, electrolyte abnormalities, endocrine diseases, diabetic amyotrophy, connective tissue disorders, entrapment neutopathies, inflammatory myositis, inflammatory neuropathy, and vasculitis are among the diseases to be ruled out by appropriate laboratory studies, including blood tests, neuroimaging, EMG, and lumbar puncture.

True AI.S is slightly more common in patients with remote poliomyelitis than in the general population. The diagnosis of ALS must be considered in patients with PPMA. Although ALS involves both UMN and LMN involvement, the progressive focal muscle weakens and atrophy seen in PPMA may raise the possibility of the progressive muscular atrophy (PMA) variant of ALS.

Treatment

No specific pharmacotherapy is available to treat PPMA. Thus management must focus on general supportive measures that preserve function. The care plan should focus on avoiding fatiguing activities that aggravate symptoms; mndifyins-, ^.cliv^ics tr. conserve energj and weight reduction for those who are overweight; and treating underlying medical disorders that reduce overall well-being. Careful screening and treatment for possible sleep apnea and depression are important.

Physical therapy should focus on nun fatiguing aerobic exercise and modest isometric or isokinetic exercise and stretching maneuvers are especially important. Studies have demonstrated that resistive exercise training can increase muscle strength over a period of more than 1 year. In patients with more serious functional decline, appropriate assistive devices must be prescribed so patients can maintain activities of daily living. Those whc> develop respiratory

insufficiency must be fully evaluated by pulmonologists to rule out primary pulmonary disease. Noninvasive positive pressure ventilatory assistance should be considered. Those patients whose employment or lifestyle involves significant physical exertion may need to substantially modify their work duties and other activities.

Multifocal Motor Neuropathy

Originally described in 1988, multifocal motor neuropathy (MMN) is a treatable motor neuropathy that superficially resembles motor neuron disease. MMN is characterized by a pure motor syndrome that develops in association with motor nerve fiber demyelination. The classic form of this is associated with elect".diagnostic evidence of multifocal demyelination conduction blocks and elevated titers of antibodies against d.Vl, gangliosidcs. Clinically, patients develop slowly progressive multifocal muscle weakness and atrophy (Table 80.6).

Etiology

The etiology of MMN is not established. However, the presence of high titers of anti-GMi ganglioside antibodies in approximately half (range 20-84%) of these patients suggests an autoimmune disorder with a predilection for myelinated motor nerves. Many experimental studies support this hypothesis; rabbits immunized with GM_L ganglioside develop ;i neuropath) resembling MMN; the adnxonnl GM) ganglioside content is greater in motor nerve fibers than sensory nerve fibers; anti-GMi antibodies can bind to the nodes of Ranvier and anterior horn cells; the antibody can alter K^+ and Na^{H}" currents in myelinated axons; many cases of MMN respond to immunomodulatory treatment. On the other hand, patients who are anti-GM, antibody negative are clinically and clcctrodiagnostically identical to those who are antibody positive. In addition, anti-GM i antibodies are not disease specific; low titers are detectable in approximately 5% of patients with ALS, a disorder not characterized by the presence of demyelinating conduction block, whereas extremely high titers may indicate a monoclonal gammopathy. These findings suggest that other antibodies may have a role to play in the pathogenesis ol MMN.

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Signs and symptoms
Slowly progressive, asymmetrical muscle weakness and atrophy in the distal arm
Laboratory features
Multifocal conduction dlocks in motor nerve conduction studies
Elevated titers of serum anti-GM j antibodies
Differential diagnoses
Benign focal amyotrophy
Progressive muscular atrophy
Spinal muscular atropdy
Chronic inflammatory demyelinating neuropathy
Treatment
Intravenous human immunoglobulin infusions
Cyclophosphamide

Clinical l-eatures

The age at onset is generally 20-75 years, and men are more often affected than women. Patients typically present for initial evaluation about 1 or more years after onset of -.yiuproins and the course rhri extends o\er many ve;irs. Many patients have been misdiagnosed as having ALS. Although MMN is associated with disability, most patients remain in the workplace and uncomplicated MMN is generally not a fatal disorder. Clinically, MMN is characterized by asymmetrical, slowly progressive weakness that most commonly begins in the distal upper extremities in the distribution of two or more individual peripheral nerves. Muscle weakness is usually greater than would be expected from the degree of muscle atrophy. MMN may also affect the lower extremities, often with slowly progressive foot-drop or focal leg weakness and atrophy. Rare presentations include respiratory failure from phrenic nerve involvement, bulbar dysfunction from hypoglossal nerve involvement, and ophthalmoplegia. In the early stages, the degree of muscle weakness is far in excess of the degree of muscle atrophy, indicative of a primarily demyelinating disorder rather than one of axon loss. In affected muscles, the muscle stretch reflexes are usually preserved albeit diminished. Regions with normal strength have normal reflexes. Fasciculations are not uncommon, which may raise concerns that one is dealing with LMN-onset ALS. However, subsequent examinations never reveal clear U.VfN signs to suggest a diagnosis other than MMN. Some patients may report paresthesias or reduced sensation, but objective sensory signs are either absent or clinically insignificant.

Laboratory Studies

A thorough EDX study is imperative to establish the diagnosis of MMN, The original American Ac.nlenn of Electrodiagnostic Medicine (AAEM) criteria required the presence of focal conduction block along two or more-motor nerve fibers, particularly at sites that are anatomically distinct from common entrapment sites. However, it is now recognized that some cases may have focal conduction slowing along segments of motor nerve rather than actual conduction block. Prolonged distal latencies, prolonged F-wave latencies, and temporal dispersion of CMAPs may also be seen. There may even be some degree of axonal degeneration (positive sharp waves and fibrillation potentials) detected on EDX (Taylor et al. 2000). Sensory nerve conduction studies are normal whether they arc recorded from pure sensory or mixed sensorimotor nerves.

High titers of serum IgM anti-GM, antibodies support a diagnosis of MMN. However, it is important to remember that low titers may be detected in ALS and extremely elevated anti-GM, antibodies (>1:40,000) should prompt an investigation for an IgM monoclonal gammopathy. CSF protein concentration is usually normal but may he modestly etc va led to less tii.m Kill ni(',.AU..

Differential Diagnosis

Although focal asymmetrical muscle weakness and atrophy occur both in ALS and in MMN, the former is characterized by the additional presence or later development of prominent UMN and pseudobulbar findings. It is thus crucial to perform follow-up examinations to distinguish between these disorders. PMA is a rare pure LMN syndrome that often presents with focal and asymmetrical weaknesses in distal extremity muscles, thus closely mimicking MMN. However, the weakness in PMA is regional rather than in the distribution of major motor nerves (as seen in the earlier stages of MMN). PMA is associated with neither conduction blocks nor high titers of anti-GM! antibodies and does not respond to immunomodulatory treatment.

One of the useful clinical clues is that weakness exceeds atrophy.

The combined electro diagnostic and serological criteria that support MMN serve to differentiate it from other predominantly motor disorders such as adult-onset SMA, benign focal amyotrophy/monomelic amyotrophy, and acute neuralgic amyotrophy (Parsonage-Turner syndrome). The classic anti-Hu antibody-associated paraneoplastic syndrome is a subacute sensory neuronopathy, but a recent retrospective analysis of 20 patients revealed that 5% of presentations were pure motor in nature and 10% were multifocal in distribution (Camdessanche et al. 2002). Furthermore, a subacute paraneoplastic pure motor neuropathy has been described in the setting of an underlying lymphoproliferative disorder.

There are many similarities between MMN and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Both are characterized by the presence of dcmyclination-range motor conduction slowing and/or conduction block. However, there are significant differences. MMN characteristically involves distal upper extremity muscles in an asymmetrical fashion, whereas CIDP typically involves proximal muscles in a symmetrical fashion. A remitting and relapsing course is uncommon in MMN but common in CIDP. Although CIDP can manifest as a predominantly LMN syndrome, clinical and electrodiagnostic sensory abnormalities arc the rule, which is in stark contrast to MMN. Reflexes are characteristically absent in CIDP, whereas they are usually present but diminished in MMN. CSF protein levels do not exceed 100 mg/dL in MMN and are usually normal, but very high CSF protein levels are not uncommon in CIDP. CIDP responds well to corticosteroids and plasma exchange, whereas these treatments are generally not effective in MMN.

MMN must also be clearly differentiated from multifocal acquired demyelinating sensory and motor neuropathy (MADSAM or Lewis-Sumner syndrome). This disorder may very closely mimic MMN. It presents in the same age-group and in the same tippet limb-predominant asymmetrical fashion in the distribution of multiple different distal peripheral nerves. Reflexes are usually diminished rather than absent. However, clinical examination and EDX typically reveal sensory abnormalities, which distinguish this unusual disorder from MMN. MADSAM may respond to intravenous immune globulin (IVIG) therapy or prednisone. Other immune-mediated demyelinating neuropathies, such as a nti-myel in -associated glycoprotein (anti-MAG) antibodies or polyneuropathy with monoclonal gammopathy, cause not only severe muscle weakness but also prominent sensory loss and often other systemic signs.

There has been a report of a small series of patients *(n* = 9) with a slowly progressive or nonprogressive pure axonal MMN in the absence of anti-GM, antibodies. No electrodiagnostic features of demyelination were detected, but there was evidence of a "relatively indolent axonal process." This condition, referred to as *multifocal acquired motor axonopatby,* may respond to corticosteroids or IVIG infusions (Katz et al. 2002).

Treatment

Although MMN is considered an immune-mediated disease, neither plasma exchange nor corticosteroids are effective and may even worsen the condition. The treatment of choice is IVIG prepared from pooled human immunoglobulin G (IgG) (Van den Berg-Vos et al. 2000). To date, four separate randomized placebo-controlled trials have shown the benefit of this therapy in MMN. Clinical improvement may be noticed within a matter of hours, but generally one may expect a benefit within 15 days. It appears that those patients who ate younger, who are anti-GMi antibody positive, have conduction blocks, and who are clinically milder at onset have the best response. In general, conduction blocks are not altered by this therapy despite improvements in clinical motor function. Similarly, treatment does not appear to reduce anti-GM i antibody titers. A total dose of 2 g/kg given as a slow intravenous infusion in divided doses over 2-5 days can improve strength in more than 50% of patients. The duration of benefit varies between patients, ranging from 2 weeks to *6* months or more. It is usually necessary to tailor the particular schedule on a case-by-case basis depending on how the individual responds and how long the effect lasts. A typical maintenance schedule is 400-600 mg/kg once every 3-8 weeks. Serum immunoglobulin A (IgA) should be checked before treatment: Those who have congenital IgA deficiency-may suffer an anaphylactic reaction to second and later infusions because of the presence of a small amount of IgA

contamination in the pooled IgG infusion. Side effects of iVIG include headaches, aseptic meningitis, allergic reactions {including acute renal failure), strokes, myocardial infarctions, and fluid overload. IVIG treatment is expensive; therefore objective documentation of improvement, including quantitative muscle strength testing and quantitative motor function testing, is important to prove efficacy.

Apart from IVIG, there have been no prospective, double-blind, randomized, placebo-controlled treatment trials completed to assess the value of alternative immunomodulatory treatments for MMN (Umapathi et al. 2002). However, several small scries and case reports show that cyclophosphamide treatment is also effective, ft is the only immunosuppressive treatment that may induce *a* long-term benefit and it does so in more than 50% of patients with MMN. I f i >', I • cunuiLime lilt-lime ik >,:-, (>7\i g) increase the risk of neoplasia, especially of the bladdet. Thus cyclophosphamide is reserved for more severe cases that cannot tolerate or do not respond to IVIG. Six monthly treatments with intravenous cyclophosphamide (1 g/M^2), each preceded by two plasma exchanges, are the recommended regimens. This regimen not only produces a sustained motor improvement but also a sustained 60-80% reduction in serum anri-GM, antibody liter in two thirds of patients. One or two more additional treatments may be given if the patient is not improving and anti-GM, antibody titers do not decline. There is often a 3-6-month delay in improvement after starting cyclophosphamide therapy, and remission usually lasts for 1-3 years, after which time antibody titers often rise and weakness recurs. Retreatment may then be necessary.

Several small case series have recently reported beneficial effects of interferon-/Ma in refractory cases of MMN. In addition, rituximab, a chimeric monoclonal antibody directed against the B-cell CD20 epitope, was effective in improving motor outcome in four patients with MMN. Clearly, further prospective controlled trials are necessary to define nie potential use ot interferon ,mtl IIKI:K>C1OI:;I1 antibody therapy in MMN.

Benign Focal Amyotrophy

Most diseases affecting LMNs begin as muscle weakness in a focal area and in one extremity. In most cases, the disease steadily and relatively rapidly spreads from one extremity to another. However, there is a condition involving a limited number of myotomes in one extremity that does not spread. The terms *benign focal amyotrophy, monomelic amyotrophy,* or *juvenile segmental muscular atrophy* are used to describe this intriguing entity (Donofrio 1994).

Etiology and Pathogenesis

The etiology is unknown. Autopsy studies have shown thai the affected cervical spinal cord is flattened; the anterior horn is markedly atrophied and giiotic and the numbers of both large and small motor neurons are reduced. Some researchers believe that this is a mechanically induced disease being the result of local compression of the dura and spinal cord against vertebrae during neck flexion. However, surgical decompression has not altered the course of the diseases, and this theory is no longer widely held. Another school of thought is that this is a segmental, perhaps genetically determined, SMA. Indeed, rare familial occurrence has been reported and a case of Werdnig-Hoffmann disease was found in a close relative of a patient who had benign focal amyotrophy. This may, of course, have been purely coincidental.

Clinical Features

The disease usually begins in the later teens, but many cases can present in the fourth decade. More than 60% of patients are men. Although originally described in men from India and japan, the disorder is now recognized around the world. The most common presentation is one of an idiopathic, slowly progressive, painless weakness and atrophy in one hand or forearm. The distribution of muscle weakness varies markedly from case to case, but a characteristic feature is that the condition remains limited to only a few myotomes in the affected limb. Muscle stretch reflexes arc invariably hypoactive or absent in muscles innervated by the involved cord segment but are normal elsewhere. UMN signs are not present. Approximately 20% have hypesthesia to pinprick and touch, usually located on the dorsum of the hand. The cranial nerves, pyramidal tracts, and the autonomic nervous system arc spared. Weakness and atrophy may progress steadily for the initial 2-3 years, but approximately 75% of patients have .stabilized within 5 years. I lit arm is affected in approximately 75% ol the patients, whereas the leg is affected in the remaining 25%,

Laboratory Studies

There are no pathognomonic laboratory or electrodiagnostic tests for this condition. Their main purpose is to exclude alternative diagnoses. Motor nerve conduction studies are either normal or reveal only slight reduction in the CMAPs and SNAPs are modestly reduced in up to one third of patients. The needle electrode examination may show some fibrillation and fasciculation potentials and chronic neurogenic motor unit changes are prominent. The C5-to-Tl myotomes are most commonly involved when the arms arc affected. Although benign focal amyotrophy clinically presents as a unilateral disorder, it may rarely involve the opposite side to a minor extent, and careful needle electrode examination may unearth neurogenic changes *on* the contralateral sitle. Tin scrum creatine kinase (CK) level may be modestly elevated, but other routine laboratory test results are normal. Cervical MKI may reveal segmental spinal cord atrophy or occasionally

an area of increased signal on T2-weighted scans of the cervical spinal cord enlargement. "Incidental" spondylosis and canal stenosis detected by MRI should be carefully evaluated before the diagnosis of benign focal amyotrophy is established.

Differential Diagnosis

Two diseases must be distinguished from benign focal amyotrophy: ALS, which is almost always a relentlessly progressive terminal disease, and MMN, which is treatable. A small proportion of ALS presents as an LMN monomelic disease albeit in an older patient population. It is only with follow-up examination that the more widespread anterior horn cell disorder becomes apparent and UMN signs appear. In classic ALS, the deep tendon reflexes will usually become abnormally brisk even in the presence of severely weak and atrophied muscles. The generalized widespread nature of motor neuron involvement, as detected on EMG, can distinguish ALS from the segmental motor neuron involvement of benign focal amyotrophy. The slowly progressive focal weakness that is distinctive of benign focal amyotrophy may also be the presenting picture of MMN, but detailed motor nerve conduction studies and serum tests for elevated titers of anti-GM! antibodies can differentiate these two conditions.

Cervical or lumbosacral radiculopathy may also appear in a manner somewhat akin to benign focal amyotrophy. However, radicular pains and sensory impairment are typical of radiculopathies. Neuralgic amyotrophy/ Parsonage Turner syndrome is typically heralded by severe pain before the onset of weakness and wasting in the distribution of predominantly motor nerves derived from the brachial plexus. It may also involve selected sensory nerves. Most cases arc monophasic and do not progress over years as does benign focal amyotrophy, although hereditary neuralgic amyotrophy can present as recurrent bouts of brachial plexopathy. Cervical syringo-myelia or a benign tumor involving nerve roots or the spinal cord may also cause progressive weakness in a monomelic fashion. Careful EMG studies and neuroimaging should differentiate these diseases.

Treatment

The term *"benign"* in *benign focal amyotrophy* is used to distinguish it from the "malignant" motor neuron disease as seen in ALS. Although this condition is certainly not life threatening, it still seriously impairs motor function in the involved extremity. Supportive care consisting of physical and occupational therapy and effective use of assistive devices (splinting and braces) is the main treatment component. Tendon transfers can be considered in selected patients with focal weakness in a muscle group whose function is crucial for certain activities of daily living.

Infantile and Juvenile Spinal Muscular Atrophy

The incidence of infantile and juvenile SMA is estimated to be I in 6000-10,000 births; SMA is one of the most common genetic causes of death and disability[7] in childhood. It is inherited by autosomal recessive transmission, with a gene frequency in the general population of about 1 in 80. Autosomal dominant childhood SMA is rare and probably accounts for less than 2% of all childhood cases. X-linked SMA associated with arthrogryposis and bone fractures has also been described. Traditionally, SMA is classified as one of the three types based on the age at onset: SMA type 1 (infantile SMA or Werdnig-Hoffmann disease); SMA type 2 (intermediate SMA); and SMA type 3 (juvenile SMA or Kugel berg- Welander disease) (Nicole et al. 2002) (Table 80.7).

Genetics and Etiology

Al! three types of autosomal recessive childhood SMA have been mapped to chromosome .SqlL2 -5ql3.3, which suggests that they are allelic disorders. The normal 5q region on each chromosome contains two inversely homologous copies of the survival motor neuron *(SMN)* gene, termed *SMN1* (t.elomeric) and *$MN2* (centromcric). The 5q region also contains the neuronal apoptosis inhibitory protein *(NAIP)* gene, the *p44* gene (encoding a subunit of the basal transcription factor, TKI1H), and the *H4F5* gene. It has recently been shown that *SMN1* is *the* SMA gene and that the severity of SMA relates to the dosage of *SMN1* inherited by the patient. The SMN1 protein is functionally absent in the vast majority (95-98%) of cases of SMA, and small amounts are present m the remaining few percent. The *SMN2* gene, which is unique to humans, is characteristically present in all patients (although up to 5% of the normal population may have loss of this gene). Although mutations in the .SMN/ gene

"['able SO.7: Childhood and adult spinal muscular atropines

SMA *type*	*Age at onset*	*Survival/prognosis*	*Inheritance*	*Defective gene*
Infantile SMA (Werdnig-Hoffmann)	Birth to 6 mo	Death by 2 yr old	AR	SMN gene
Intermediate SMA	Before IN mo	No walking, adulthood	AR	SMN gene
Juvenile (Kugel berg-We lander)	After 18 mo	Adulthood	AR	SMN gene
Adult-onset SMA	After 20 yt	Slow progression	AR	Unknown

AR ~ autosomal recessive; SMA = spinal muscular atrophy; SMN = survival motor neuron.

produce the disease, the clinical phenorype is related to the expression of *SMN2.* More copies of *SMN2* are present in patients with milder disease than in those with severe disease.

SMN is a ubiquitously expressed 38-kd polypeptide that is important in the processing of the primary transcripts of other genes. It is associated with both nuclear and cytoplasmic complexes involved in messenger RNA splicing and interacts with other proteins, such as fibrillarin, which arc important in the regulation of ribosomal RNA processing and modification, and p53, which is important in regulation of the cell cycle. Within the nucleus, SMN1 forms macTomolccular complexes with other nuclear proteins such as gemin 2, 3, and 4, which are important in the assembly of spliceosomal small nuclear ribonucleoproteins. Recent research using transgenic animal models indicates that impaired production of macromolecular complexes may lead to motor neuron degeneration.

It has yet to be discovered why human spinal motor neurons are selectively vulnerable to SMN1 protein deficiency. Certainly SMN is heavily expressed in the nucleus and cytoplasm of spinal motor neurons but is also expressed in all tissues. Perhaps selective motor neuron vulnerability reflects the absence of a vital interaction with other proteins important in RNA processing that are also heavily expressed in motor neurons and axons. SMN protein is obviously vital for normal cellular function. In mice, which only have one *SMN* gene, complete absence of SMN protein is lethal at the embryonic stage. Humans, however, are never completely without at least one *SMN* copy on one chromosome. In human SMA, it is possible that SMN2 protein is able to compensate for the loss of SMN1 in all tissue types except spinal motor neurons, where only partial protection is afforded. Incomplete compensation may be due to the slight difference in coding sequence between *SMN'i* and 5MN2; there is a cytosine-thymine change in the coding sequence for exon 7. Because of this change, 90% of the SMN2 transcript lacks exon 7 and the resulting protein is unstable and rapidly degraded. In the complete absence of SMN1 therefore, only 10% of normal SMN2 protein may be available to bear the entire cellular burden. Thus increasing the copy number of *SMN2* in the cell should reduce the severity of disease.

Clinical features

Spinal Muscular Atrophy Type 1, Infantile Form (Wcrdnig-Hoffmann Disease). The disease begins at or before birth or within the first few months of life. By definition, children with SMA type 1 are never able to sit without support and death from respiratory failure and pneumonia usually occurs before age 2 years. About one third of mothers notice decreased fetal movements toward the end of the pregnancy. The symptoms include severe hypotonia, a weak cry, respiratory distress, and absent head control, as evidenced by an inability to lift the head when placed prone and severe head lag when the infant is pulled from a supine to a seated position (a "floppy" baby) (Figure 80.1). The baby's posture at rest also takes a characteristic "frogleg" position, with the thighs externally rotated and abducted and the knees flexed. Limb weakness is severe, generalized, and worse proximally. The infant is unable to sit and raise its arms or legs from the examining table, but there may be antigravity movements of the hands and flickering movements of the feet. Muscle stretch reflexes are usually absent and the sensory examination is normal. Contractures usually do not develop in the early phases but may develop after several months of immobilization. Bulbar muscle weakness makes feeding laborious, causes a continuous gurgling, and eventually leads to aspiration pneumonia. Fasciculations of the tongue are reported in about 50% of affected infants. In contrast to bulbar and extremity muscles, the facial muscles are only mildly affected, if at all, giving these children an alert expression. Fxtraocular movements are always normal. Intercostal muscles are severely weakened but diaphragmatic strength is preserved. This dysequilibrium of ventilatory muscle function causes outward flaring of the lower ribeage and gives rise to a bell-shaped chest deformity.

Spinal Muscular Atrophy Type 2 (Intermediate Form; Chronic .Spinal Muscular Atrophy). The signs and svmptoms of SMA type 2 usually begin before the age of 18 months. Although the symptoms may be present at birth, an insidious progressive weakness occurs during the first year of life and delayed motor milestones are often the first clue to neurological impairment. Both parents and physicians commonly observe a fine hand tremor, which also suggests the diagnosis. The distribution, pattern, and progression of weakness are similar to that found in SMA type 1, but the type 2 disease is quantitatively much milder and progression is slower than in type i.

Most children eventually are able to roll over and sit unsupported, but they rarely achieve independent walking, In the sitting position, weakness of trunk muscles produces a characteristic rounded kyphosis, and as the shoulders weaken, the child becomes immobilized and wheelchair bound. Contractures of the hips and knees, clubfoot deformities, severe scoliosis, and dislocation of the hips may eventually develop. Observation of the fingers may reveal fine, small-amplitude involuntary movements called *minipolymyoclonus.* The long-term prognosis varies markedly; some die in childhood because of respiratory failure, but many others survive into the third or fourth decade of adulthood.

Spinal Muscular Atrophy Type 3, Juvenile Form (Kugelberg-Welander Disease). The onset of the juvenile form of SMA is typically after 18 months of age (usually between 5-15 years) and usually presents with difficulty in walking. As weakness in hip-girdle muscles increases, the child develops a waddling (Trendelenburg's) gait, with an

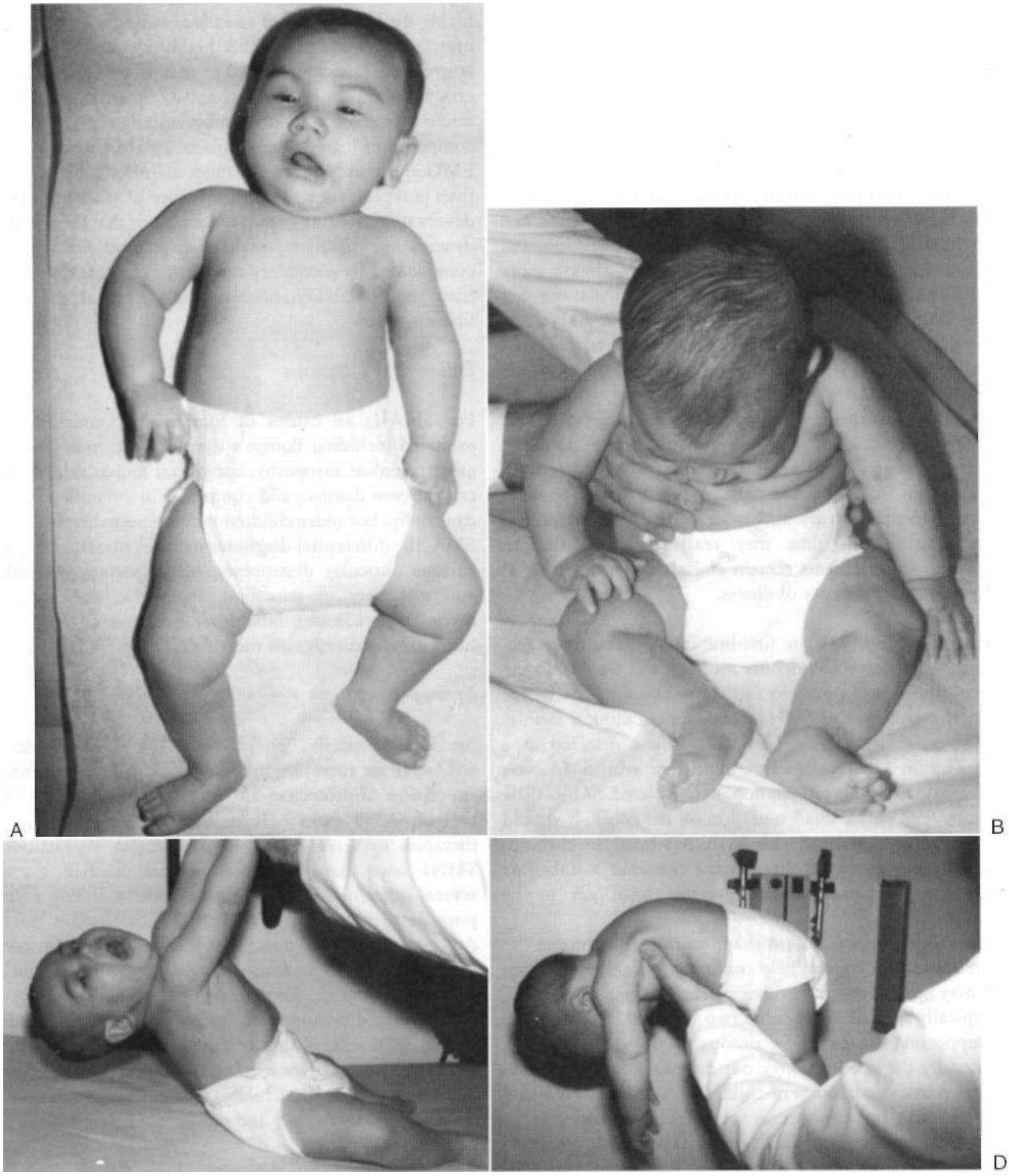

FIGURE 80,1 A 6-monrh-old baby with Werdnig-Hoffmann disease. (A) The baby has a typical "frogleg" posture. The mouth is triangular, and the facial expression suggests facial weakness. (B) On sitting, the baby cannot sustain his head upright. (C) When the baby is pulled by the arms, the head falls back. (D) When the body is held supine, the head and extremities drop by force of gravity, and there is no active body motion. (Courtesy Neil Friedman, Cleveland Clinic Foundation.)

exaggerated lumbar lordosis and trouble climbing stairs. As the weakness progresses, the patient starts using a Gowers' maneuver to arise from lying supine on the floor. Pseudohypertrophy of the calf muscles is sometimes reported, but this may be an illusion resulting from relative preservation of calf muscles as compared to thigh muscles. The disorder has an appearance not unlike a limb-girdle muscular dystrophy, but the pattern of muscle involvement is often somewhat different. **Eventually, wasting** and weakness of the neck, shoulders, and arms develop, but weakness in the lower extremities is nearly always more severe than in the upper extremities. Fasciculations are more prominent than in SMA-1 and SMA-2 and a fine action tremor is common. Reflexes are uniformly reduced or absent and the sensory examination is normal.

The clinical course of SMA-3 is one of slowly progressive limb-girdle weakness, but there may be long periods of stability that last for years. The eventual degree of disability is difficult to predict. In general, if onset is before the age of 2 years, it is likely that the patient will be unable to walk by the age of 15 years and most patients will require a wheelchair by the time they reach their mid-thirties. However, some patients remain ambulatory for as long as 30 years after the onset of illness.

Laboratory Studies. The first-line investigation is molecular genetic analysis to identify mutations in the SMN gene on chromosome 5q and no further workup is necessary if there is a mutation of *SMN1* in the correct clinical setting. However, if a mutation of *SMN1* is not detected in a patient with a clinical picture consistent with SMA, one can assay for the combination of a deleted *SMN* allele on one gene and a small mutation on the other. It should be remembered that not all SMA is related to chromosome 5cj region abnormalities; some cases are X-linked or autosomal dominant and the genes have yet to be identified.

If SMA is the suspicion, it is appropriate to carry out the more traditional tests to help confirm the diagnosis. Serum CK may be elevated to 10 times normal levels in SMA-3 but is typicall; normal in the otk-r two types. i[·].l)X is valuable in supporting the diagnosis, although it may be technically limited by the need to carry out the test under conscious sedation in a small infant or child. CMAPs may be reduced in amplitude, but conduction velocities and sensory nerve conduction study results are normal. The needle electrode examination may reveal evidence of acute denervation in the form of fibrillation potentials and positive sharp waves, along with fasciculation potentials and evidence of motor unit remodeling due to a chronic process of denervation and reinnervation. Reduced recruitment of large, polyphasic motor units is therefore characteristic, although full voluntary activation may be hampered by sedation. Complex repetitive discharges are an electrodiagnostic feature of SMA-3. Muscle biopsy can confirm the diagnosis of infantile SMA because the histological changes are highly distinct: Sheets of rounded, atrophied type 1 and 2 muscle fibers are present. A highly characteristic pattern is grouped fascicular atrophy, that is, entire fascicles or groups of fascicles are atrophied, whereas neighboring fascicles (often containing almost entirely type 1 fibers) are composed of hypertrophied fibers. In SMA types 2 and 3, EMG and muscle biopsy changes are more fully developed than in type 1, showing clear evidence of acute and chronic denervation. It is important to remember that long-standing dencrvating disorders, such as childhood SMA, can he complicated by secondary myopathic changes that include fiber size variability, fiber splitting, internal nuclei, and fibrosis.

Differential Diagnosis

For SMA-1, all causes of infantile hypotonia must be excluded including Pompc's disease, centronuclear myopathy, ncmaline myopathy, congenital muscular dystrophy, central core disease, and congenital or infantile myotonic dystrophy. For older children with suspected types 2 and 3 SMA, the differential diagnoses includes myasthenia gravis, various muscular dystrophies, inflammatory myopathies, and a variety of structural, metabolic, and endocrine myopathies. Clinical, laboratory, and muscle biopsy features usually distinguish these disorders with relative ease.

Treatment

No disease-specific pharmacotherapy is available for SMA. Future therapies may be focused on increasing the expression of protective *SMN2* gene product or stabilization of *SMN1* exon 7. It may also be possible to design therapies that are based on the protein interactions of SMN1 once these have been further clarified. As with several other neurodegenerative disorders, it may even be possible to use pluripotent stem cells to replace dead or dying neurons and muscles. However, the mainstay of current treatment is focused on supportive care, including physiotherapy, respiratory care, nutritional support, orthotics, and orthopedic interventions. Typical Werdnig-Hoffmann disease is almost uniformly fatal by age 2 years. However, because some affected infants survive beyond infancy and live into childhood, aggtessive management including physiotherapy and respiratory therapy is essential in all cases.

The management objectives in young children with the intermediate form arc twofold: (1) maintaining active mobility and independence as long as possible and (2) preventing the development of contractures and kyphoscoliosis. Any devices, even a scooter board, should be considered to maintain mobility. Because all patients invariably become wheelchair bound, they should be fitted for an electric-powered wheelchair. However, the timing of wheelchair use is critical because its use hastens the development of contractures and scoliosis. Stretching

exercises in major joints should be part of the patient's daily routine.

Patients with SMA have normal or increased intelligence. They attend school, and when they reach adulthood often work outside the home and live independently. A well-coordinated multidisciplinary approach is essential when attempting to optimize residual function, especially during periods of disease progression. Physical therapy for stretch exercise and chest clapping, occupational therapy for maintaining activities of daily living, an evaluation at a seating clinic to obtain the best wheelchair, and orthopedic evaluation to delay or if necessary correct scoliosis are among the most important aspects of management. It is also vital to pay attention to the emotional well-being of the patient, particularly during adolescence.

Maintaining an upright position delays the development of scoliosis. Therefore a specialized evaluation for wheelchair at a comprehensive seating clinic is critical. A back brace may also potentially delay the development of scoliosis, but bracing in these patients is still controversial. Bracing probably does little to retard the onset or progression of scoliosis and may actually impair function in some patients because bracing reduces spinal flexibility and tespitatory vital capacity. Potential benefits from bracing include reduced back discomfort and the ability to sit for longer periods.

Progressive scoliosis eventually requires surgical correction in most patients with juvenile SMA. In general, surgery should be delayed until growth ceases. However, in some patients who have never ambulated or who lost ambulation very early, surgical intervention for severe scoliosis may be considered even before growth has ceased. Improved aesthetics, ⊱ il.uu ❧. aiui M;IIN:;: cu:nk>n are among the benefits; however, lack of body flexibility, reduced pulmonary function, and general decline in overall motor function may occur after surgery. Pros and cons for scoliosis surgery must he openly discussed with the patient, although for most the benefits outweigh the disadvantages. Preoperative and postoperative physiotherapy and occupational therapy assessments are critical steps for the patient who contemplates spinal fusion for progressive scoliosis in SMA (Mitsumoto et al. 1997).

Genetic Counseling and Prenatal Diagnosis

SMA is one of the most devastating diseases of childhood and the parents of affected children and their relatives should receive genetic counseling, including determination of carrier status of .SMN genes. The available carrier detection test determines the SMN I gene dosage in an individual and is best catricd out in a family where an .SMN deletion has been found previously in an affected individual or for an individual who is about to marry a known carrier with a known .S'MN deletion. Noncarriers will have a single copy of the normal *SMN1* on each chromosome, whereas carriers will have only one normal and one mutated *SMN* gene. However, this standard test is not absolutely accurate in the setting of genetic variations. For example, up to 3% of the population may have a duplication of the *SMN1* gene on one chromosome and none on the other and it may require a hybrid technique to identify this variant. In those rare individuals, whose SMA is due to spontaneous *de novo* mutations in the *SMN1* gene, the parents will have normal *SMN1* genes.

Childhood Autosomal Dominant Spinal Muscular Atrophy. Autosomal dominant SMA is exceedingly rare, accounting for less than 2% of all childhood cases. Because of the rarity of this disorder, the natural history of autosomal dominant SMA k nm WL'.I Jc--;icd. i'ypii.illv, juvenile autosomal dominant SMA is a relatively benign disease.

Arypical Spinal Muscular Atrophies

Fazio-Londe Disease (Progressive Bulbar Paresis of Childhood). Fazio-Londe disease is a rare form of sporadic, autosomal dominant, or autosomal recessive progressive facial and bulbar palsy. Affected children are normal at birth but develop progressive bulbar palsy (PBP) and eventual respiratory failure with little or no evidence of involvement of other motor neurons and with usually normal extraocular motility. The differential diagnosis includes a structural brainstem lesion, myasthenia gravis, and the Miller Fisher variant of Guillain-Barre syndrome. Accurate diagnosis is important because of the implications for prognosis and treatment.

Adult-Onset Spinal Muscular Atrophy (Spina) Muscular Atrophy Type 4)

True adult-onset disease accounts for probably less than 10% of all cases of SMA with an estimated prevalence of 0.32 in 100,000. By definition, the symptoms of adult-onset SMA must begin in patients older than 20 years. The mean age at onset is the mid-thirties. The course is relatively benign; only a small proportion of patients become wheelchair bound over 20 years. The clinical presentation is very similar to that of SMA-3.

Inheritance and Genetic Abnormalities

Although autosomal recessive inheritance accounts for almost all (98%) of childhood SMA cases {type 1, 2, and 3), it constitutes only 70% of adult-onset SMA cases. Homozygous deletions in the 5MNJ gene responsible for childhood SMA are only rarely found in adult-onset SMA; homozygous deletions of the *SMN2* gene may be more commonly identified (Moulard et al. 1998). The remaining adult-onset SMA cases are autosomal dominant and are not linked to chromosome 5. This latter group is rather heterogeneous, and in time, it may well transpire that

it represents a series of quite separate disorders sharing certain SMA-like phcnotypical similarities.

Clinical Features

The characteristic clinical presentation is that of a slowly progressive limb-girdle weakness leading to difficulty in walking, climbing stairs, and rising from a chair or the floor. Fasciculations are an important finding and occur in 75% of patients. Quadriceps muscle weakness is often a prominent feature. Muscle cramps may occur but are not a prominent feature. Bulbar signs and bony deformities such as scoliosis arc rare and respiratory muscles are not affected. Although the distribution of muscle weakness is usually confined to limb-girdle muscles, it can be generalized or even distal predominant (Figure 80.2). Many cases have a distribution of weakness reminiscent of the limb-girdle imacular dysl noli it's, lead hi:-, ID i'.n- oldfi **term nl** pscudomyopathic SMA.

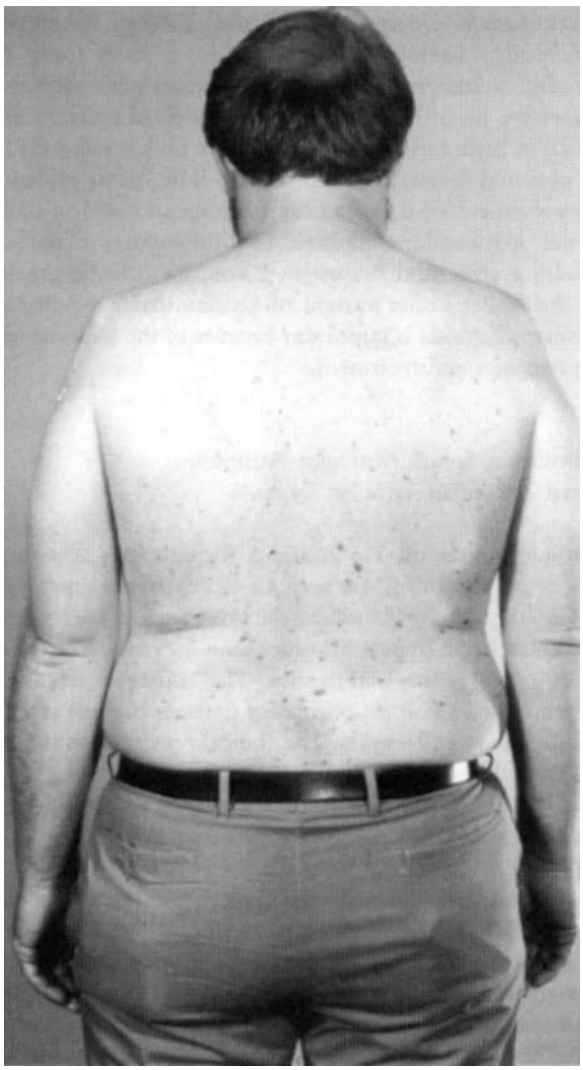

FIGURE 80.2 A patient with mild adult-onset proximal spinal muscular atrophy and marked shoulder-girdle muscle atrophy. Note subluxation at both shoulder joints and marked deltoid **muscle atrophy.**

Laboratory Features

Both serum CK and aldolase arc typically elevated to levels less than 10-fold the normal values. Motor nerve conduction studies may reveal normal velocities and reduced CMAPs in the presence of normal SNAPs. Needle electrode studies show marked chronic neurogenic motor unit changes and modest, if any, evidence of acute denervation. Myopathic changes are also common. Fasciculation potentials may be found in involved muscles.

Muscle biopsy typically shows evidence of a markedly chronic dencrvating disease process similar to that described in SMA-3, but with frequent changes of myopathy, with marked variation in fiber size, split fibers, necrotic fibers undergoing phagocytosis, and regeneration,

Differential Diagnosis

Limb-girdle muscular dystrophy may be difficult to distinguish from adult-onset SMA; it can be autosomal recessive, is often adult onset, and affects predominantly proximal muscles. The pattern of muscle weakness is often a pointer to the diagnosis; for instance, in adult-onset SMA, the triceps muscles may be weaker than the biceps, the opposite of the situation in iimb-girdle muscular dystrophy. Although muscle biopsy reveals a primary myopathy rather than a neurogenic process, one should be aware that some degree of secondary myopathic changes could occur in long-standing SMA. Immunohistochemistry and Western blotting can now be performed on muscle biopsy to distinguish SMA from Duchenue's and Becker's muscular dystrophy and the various limb-girdle muscular dystrophies with known protein deficiency, including sarcoglycanopathies, calpainopathies, and dysferlinopathies (Piccolo ct al. 2002). Other myopathics may also need to be considered including polymyositis and adult-onset acid maltase deficiency.

CIDP may mimic SMA because of chronic proximal muscle weakness, but the tendon reflexes are usually diffusely absent in CIDP and some are preserved in SMA. Electrodiagnostic studies reveal a demyelinating polyradiculoneuropathy and CSF protein levels arc increased in CIDP. It may be very difficult to distinguish between distal-predominant adult-onset SMA and hereditary motor and sensory neuropathy type 2 (neuronal form of Charcot-Maric-Tooth disease). Motor-predominant variants, such as hereditary motor neuronopathy type 5 (HMN-5), may present with a slowly progressive LMN-prcdominaut disorder affecting distal greater than proximal limb muscles. In HMN-5, transcranial magnetic stimulation studies may reveal prolonged central conduction times along motor pathways, a finding that is mirrored by brisk deep tendon reflexes in many cases. EDX characteristically shows

changes most consistent with a disorder of anterior horn cells, and sensory nerve studies are often normal (Auer-Grumbach M et al. 2000). Hex-A deficiency in infants is well known as the cause of Tay-Sachs disease, a rapidly terminal gangliosidosis. The same enzyme deficiency in adults (although the type of missensc mutation differs from the infantile form) causes a very different disease, which can have a similar phenotype to adult-onset SMA, although later other neuronal systems often become involved. Although most reported cases have been in Ashkenazi Jews, adult forms clearly occur in other populations. In the absence of a family history of SMA, it can be most difficult to distinguish adult-onset SMA from the PMA variant of ALS. However, several features distinguish between these conditions. Adult-onset SMA progresses very slowly, whereas PMA progresses relatively rapidly (though usually slower than classic ALS). Adult-onset SMA is mainly associated with muscle biopsy and EDX evidence of a markedly chronic disease, whereas PMA findings are consistent with more acute denervation and thus more modest evidence of neurogenic motor unit remodeling.

Treatment

No specific pharmacotherapy is available. Treatment is supportive and symptomatic. Generally, adult-onset SMA progresses very slowly, and patients often learn how to cope with the disease quite well. For patients who engage in physical work, appropriate vocational rehabilitation may help patients accommodate themselves to their eventual physical disabilities.

Kennedy's Disease (X-I.inked Recessive Bulbospinal Neuronopathy)

In 1968, Kennedy and colleagues reported a new X-linked recessive SMA with bulbar involvement and gynecomastia. The primary pathology was thought to be in the l.MNs, but sensory system involvement was later recognized, which led to a new term, *bulbospinal neuronopathy.* Recent progress in molecular genetics has shown Kennedy's disease to be a trinucleotide repeat disease. Though rare, it is more common than adult-onset SMA. Clinically, Kennedy's disease can be easily mistaken for ALS, and thus diagnosis of the disease is important because it has a much better prognosis than ALS (Table 80.8).

Tabic 80.8: Characteristic features of Kennedy's disease

Pathogenesis
X-linked recessive inheritance
Abnormal CAG expansion in the gene encoding androgen receptor protein
Neurological manifestations
Slowly progressive limb-girdle muscle weakness
Slowly progressive moderate bulbar dysfunction
Muscle cramps and prominent faseiculan'ons
Facial faseiculations
S y stem i e ma n i festa ti on s
Gynecomastia (60-90%)
Endocrine abnormalities (testicular atrophy, feminization, infertility)
Diabetes mellitus
Laboratory studies
Markedly abnormal sensory nerve conduction studies
Hlevated serum creatine kinase
Abnormal sex hormone levels
Ahnormal CAG repeats in the androgen receptor gene

Pathogenesis

In 1991, La Spada and colleagues found the gene abnormality responsible for Kennedy's disease: a cytosinc-adenine-guanine (CAG) trinucleotide repeat expansion on the andtogen receptor gene located on the X chromosome. In normal individuals, the repeats range from 17-26 in this coding region, whereas in patients with Kennedy's disease, the repeats range from 40-65. There are two independent components to the symptoms of Kennedy's disease, one androgen dependent and the other androgen independent. "Fhe gynecomastia and testicular atrophy seen in Kennedy's disease may be associated with the classic function of the androgen receptor, and thus the severity of symptoms might be related directly to the receptor's affinity for androgen. Studies of cultured scrotal skin fibroblasts found that direct high-affinity- d ihyd rotes to ste rone binding is decreased in some patients. The abnormal expansion of CAG repeats involves the first exon, an amino-terminal transactivating domain of the androgen receptor protein, The expansion of the CAG repeat in an androgen receptor causes a linear decrease in the transactivation function but does not completely eliminate androgen receptor activity. The residual androgen receptor activity is sufficient to ensure normal development of male primary and secondary sexual characteristics, as evidenced by the fact that affected men arc phenotypically male and usually fertile.

The subtle decline of androgen receptor transactivation may eventually lead to the loss of integrity of certain tissues that require continuously high androgen levels. Continuous androgen activity is probably required in spinal and bulbar motor neurons; for example, androgens are crucial for normal male development of motor neurons in the rat spinal nucleus of the bulbocavetnosus and for regenerating facial motor neurons in rats and hamsters. Therefore continuous androgen receptor function may be crucial to maintain normal motor neuron function throughout life.

As with most other trinucleotide repeat expansion disorders, such as Huntington's disease and several SCAs, the trinucleotide repeat expansion mutation appears to confer a toxic gain of function on the gene product rather than a loss of function. In fact, complete absence of the androgen receptor leads to an entirely different disorder

called *andmgen-insensitwity syndrome.* The mutant androgen receptor Ic.uU to an altered reeeptor-DNA interaction or receptor-protein interaction that interferes with neuronal function. The CAG repeat encodes an unusually long polyglutamine tract in the androgen receptor protein, which appears to alter the normal protein moiety resulting in mutant protein aggregation. Indeed, ubiquitinated neuronal inclusions have been identified in this disorder, and it has been suggested that these mutant protein aggregates interfere with proteasomal breakdown of cellular proteins and/or interfere with tubulin mediated cellular transport.

Clinical Features

Being an X-linked syndrome, this is a disorder of men who remain largely asymptomatic until after age 30 years. Prominent muscle cramps, muscle twitching, difficulty walking, and limb-girdle muscle weakness are the characteristic symptoms. Dysarthria and dysphagia occur in fewer than half the patients. Muscle weakness is typically LMN in type, involving the proximal hip and shoulder-girdle muscles, and is associated with decreased or absent reflexes, muscle atrophy, and occasionally, calf pseudohypertrophy. Kennedy's disease usually causes no respiratory muscle weakness. Coarse muscle fasciculations can be prominent in the extremities and trunk and hand/finger tremor is not unusual. Facial and particularly perioral fasciculations are highly characteristic, if not pathognomonic, of this disease, being present in more than 90% of patients. The tongue shows chronic atrophy, often as a longitudinal midline furrow. Although weakness in the facial and tongue muscles is nearly always present, bulbar symptoms are less often reported. Neurological examination of the sensory system may reveal only modest impairment.

Gynecomastia is one of the unique features of Kennedy's disease and is found in 60-90% of patients (Figure 80.3). Fndocrine abnormalities include testicular atrophy, feminization, and infertility in approximately 40% of patients. Diabeies mcllinis is also reported in II) 20% ot patients. It has recently been recognized that female carriers may manifest subtle neurological deficits such as late-onset btilbat dysfunction.

An inverse relationship exists between the number of CAG repeats and the age at disease onset. The greater the number of the repeats, the younger the age at onset. This is an example of genetic anticipation. However, the number of repeats has no correlation with other features, such as the severity of weakness, serum CK level, and presence or absence of gynecomastia, impotence, or sensory neuronopathy. The phenotypical expression varies markedly within and among the families. The course is one of slowly progressive **LMN** disease. If bulbar dysfunction is severe, the prognosis becomes less favorable (Mitsumoto et al. 1997).

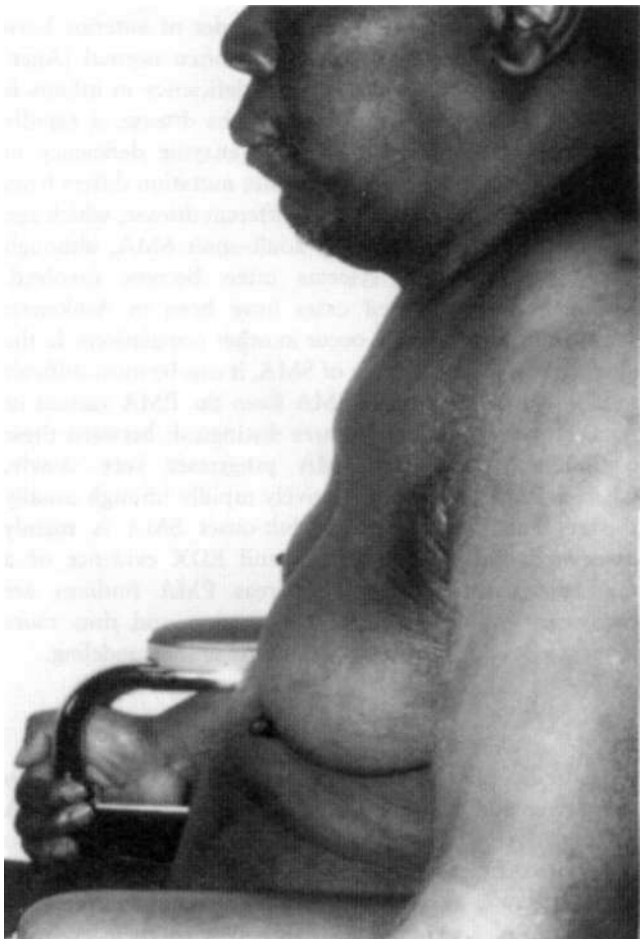

FIGURE 80.3 A man with X-linked recessive bulbospinal muscular atrophy (Kennedy's disease) showing gynecomastia.

Laboratory Studies

Molecular genetic testing is available to identify the abnormal expansion of the CAG repeat in the exon 1 ol the androgen receptor gene on the X chromosome. CK levels may be elevated as high as 10 times normal. **Serum** androgen levels are either normal or decreased, whereas estrogen levels are elevated in some patients. The estrogen-to-androgen ratio is also increased in some patients; however, there is no consistent finding regarding sex hormone levels.

EMG is highly useful. Motor nerve conduction study results are generally normal, although one third of the patients have reduced-amplitude CMAPs. Needle electrode examination of these patients shows prominent chronic denervation changes in motor units, but evidence of acute denervation is usually only modest. One of the most unique abnormalities in Kennedy's disease is EDX evidence consistent with a sensory neuronopathy. Another unique change is the presence of prominent fasciciilation potentials in the face (especially in the perioral region) and limbs.

Muscle biopsy shows modest denervation, prominent reinnervation, and fiber type grouping, that is, histological

findings consistent with those of a chronic SMA type of denervation. Sural nerve biopsy usually reveals a marked loss of myelinated fibers and the replacement of lost nerve fibers with connective tissue.

Differential Diagnosis

The clinical features, such as progressive limb-girdle weakness, bulbar signs, muscle cramps, and prominent fasciculations, resemble those of ALS, but a careful physical examination should provide sufficient clues to distinguish one from the other. Generally, ALS progresses rapidly, whereas Kennedy's disease is a largely indolent disorder. The EDX in Kennedy's disease shows abnormal sensory nerve conduction studies, which is highly unusual for any motor neuron disease, particularly ALS. Kennedy's disease may also be easily mistaken for adult-onset SMA because of the slowly progressive limb-girdle weakness in both, but bulbar involvement is very unusual in SMA. Hereditary sensorimotor neuropathy, limb-girdle dystrophy, or facioscapulohumeral muscular dystrophy also may mimic Kennedy's disease. Careful EDX studies and muscle or nerve biopsy analyses should distinguish these disorders. Ultimately, a molecular gene study to identify the abnormal CAG repeats in the androgen receptor gene will yield the answer.

Manifested Carrier

The female children of an affected male patient are all obligate carriers, as is the mother, except in the rare case of a new mutation. Male children of affected individuals cannot inherit the mutant gene on the X chromosome. Female siblings of an affected patient have a 50% chance of carrying the affected gene on the X chromosome. Through a process know ii .is *skeined X chromosome inactwalion* (lyoniziition), female carriers can present with neuromuscular symptoms, such as exertional muscle pain, cramps, and late-onset bulbar dysfunction, and the EDX may detect mild chronic denervation in both upper and lower limb muscles.

Treatment

Supportive and symptomatic therapy is the key to treatment, as outlined in the section on adult-onset SMA. Muscle cramps may be problematic but may he relieved by quinine sulfate, baclofen, or vitamin E. Patients with symptomatic diabetes require appropriate medical management.

In Kennedy's disease, dysarthria and dysphagia may cause marked disability. Although severe loss of bulbar function is rare in Kennedy's disease, speech therapy and appropriate communicative devices should be offered when appropriate. Careful nutritional management is also important. Enteral feeding provided via gastrostomy is the most effective and practical means to meet nutritional and fluid requirements. Genetic counseling is important for patients, potential carriers, and male siblings.

Progressive Muscular Atrophy

PMA, first described by Aran in 1850, is a disease that exclusively involves LMNs during its entire clinical course and comprises approximately 8% of all adult-onset motor neuron diseases, h has been questioned whether ['MA is an independent disease or represents one end of the spectrum of ALS. However, the recent description of a rapidly progressive PMA presentation in some cases of FALS and the finding of pyramidal tract pathology in some autopsied sporadic PMA cases lends support to the conclusion that PMA is indeed an ALS variant (Cervenakova ct al. 2000). For clinical therapeutic research trials, PMA must clearly be distinguished from ALS and is nor even included in the revised El Escorial criteria. However, PMA can he considered identical to ALS in all aspects of day-to-day patient care.

Etiology

All hypotheses about the cause of ALS are also applicable to PMA (see Etiology, under Amyotrophic Lateral Sclerosis, later in this chapter).

Clinical Features

By definition, the signs and symptoms of PMA are LMN in type throughout the entire clinical course. During the early stages of the illness, however, whether the disease will evolve into the ALS phenotype is uncertain, because most such cases do eventually develop UMN signs. Thus it is generally agreed that not until 3 years after rhe onset of the disease can one conclude that the disease will not spread to involve UMNs. Although PMA occurs in both sexes, nen arc slightly more often affected than women. The age at onset of PMA is younger than that of ALS, and the disease progresses more slowly so the average survival is longer; in one study, the mean duration of disease was 159 months (Norris et al. 1993).

A common presentation is that of focal asymmetrical muscle weakness in the distal extremities with gradual spread to other contiguous muscles. The weakness and muscle atrophy is purely LMN in type and eventually involves both the upper and the lower extremities. A less common presentation is that of proximal rather than distal muscle weakness. Bulbar and respiratory involvement eventually develops but is not as common in the early stages as in classic "spinal" ALS.

Laboratory Studies

The CK level can reach 10 times normal, particularly when patients are physically active. Patients with PMA do not have high titers of anti-GM[antibodies. The EMG examination reveals findings consistent with a widespread disorder of anterior horn cells and is useful to exclude other

diagnostic possibilities such as CIDP, MMN, or myopathy. Muscle biopsy will show denervation atrophy but is usually unnecessary unless the clinical features are unusual enough to suggest an alternative diagnosis.

Differential Diagnosis

PMA is usually a fatal disease and has no cure. Therefore the diagnosis of PMA should be made carefully after all other potentially treatable or definable diseases are excluded. In a recent review, 17 of 89 patients originally diagnosed with PMA were subsequently shown to have alternative diagnoses, including MMN, CIDP, inflammatory myopathy, and myasthenia gravis (Visscr ct al. 2002),

MMN may present with focal and asymmetrical weakness in the absence of UMN signs but may be distinguished by the relative disparity between weakness and atrophy, by typical electrodiagnostic features, and by the presence of anti-ganglioside antibodies. CIDP is readily differentiated on the basis of clinical and electrodiagnostic findings of sensory involvement, high CSF protein levels, and response to immunotherapy. Important clues that should lead one to suspect inclusion body myositis (IBM) are elevated serum CK to levels more than expected in typical PMA and a selective weakness in wrist flexors, finger flexors, and quadriceps muscles. EMG in IBM should show evidence of a primary necrotizing myopathy with or without additional neurogenic changes, but quantitative EMG may be required to clearly identify the myopathic nature of this disorder (Dahby et al. 2001). Muscle biopsy characteristically reveals rimmed vacuoles. Adult-onset SMA is a far more indolent disorder than I'M A and the very chronic process of denervation and re in nervation in SMA leads to fiber type grouping in muscle biopsy, which is not a characteristic feature of the I ess-protracted PMA. It is important to carry out regular follow-up examinations on patients with PMA, to search for signs of UMN involvement that indicate the diagnosis of ALS that has a rather worse average prognosis (Mirsumoto et al. 1997),

Treatment

The treatment of PMA is identical to that of ALS, as summarized later in this chapter.

Subacute Motor Neuronopathy in Lymp ho proliferative Disorders

A subacute, progressive, and painless motor neuron syndrome may rarely develop in patients who have Hodgkin's and non-Hodgkin's lymphoma with or without a paraproteinemia (Rudnicki and Dalmau 2000). Although UMN signs may develop in a small number of patients, an LMN syndrome is typical, with patchy, asymmetrical lower extremity predominant muscle weakness and wasting being the most common presentation. Neuropathology shows a loss of anterior horn cells and ventral root nerve fibers; some have evidence of inflammation in the anterior horns of the spinal cord. In some patients, the disease may be relatively benign; the rate of progression of muscle weakness and atrophy tends to slow down with time, and in rare instances, the motor syndrome may respond to treatment of the underlying lymphoproliferative disorder. However, the prognosis appears to be less favorable in those who develop a combined UMN and LMN disorder. Twenty percent of all cases so far reported with motor neuron presentations in the setting of lymphoproliferative disease had myeloma or macroglobulinemia (Rowland and Shneider 2001). The pathogenesis of this ALS-likc disorder is undetermined, but an immune mechanism may be at play; small patient series and case reports reveal that some patients who develop this LMN syndrome may have various autoantibodies (such as antisulfatide antibody), paraproteinemia, increased CSF protein, and/or oligoclonal bands.

Postirradiation Lower Motor Neuron Syndrome

Radiation directed to the lumbar paravertebral area for the treatment of testicular cancer can cause a pure LMN syndrome in the lower extremities that first appears many years after the irradiation. Sensory abnormalities and sphincter dysfunction are rare, and the EDX findings are consistent with a disorder of the cauda equina (the SNAPs are spared). The disease usually progresses over the first few years after symptom onset but subsequently becomes arrested (Bowen et al. 1996).

DISORDERS OF BOTH UPPER AND LOWER MOTOR NEURONS

Amyotrophic Lateral Sclerosis

ALS is a neurodegenerative disorder of undetermined etiology that primarily affects the motor neuron cell population. It is progressive and most patients eventually succumb to respiratory failure. The first detailed description in the literature was by Jean Martin Charcot in 1869, in which he discussed the clinical and pathological characteristics of "la sclerose laterale amyotrophique," a disorder that affected both UMNs and LMNs (Goetz 2000). ALS is known by several other names including Charcot's disease, motor neuron disease, and in the United States, "Lou Gehrig disease" in remembrance of the famous "Iron Horse" of baseball who was diagnosed with ALS in the late 1930s.

The World Federation of Neurology Research Group on Neuromuscular Disorders has classified ALS as a disorder of motor neurons of undetermined cause, and several variants are recognized. Included in this group are

PLS and PBP. As previously mentioned, PMA is also thought to be a variant of ALS despite its exclusion from cutrcnt clinical research trial criteria. It is important to recognize that ALS is a progressive dynamic disorder. Some cases present with the classic combination of UMK and LMN signs, but others may be UMN onset, LMN onset, or bulbar onset and only later develop signs of involvement of the other parts of the motor system (Table 80.9).

Between 5-10 ' . of A IS is familial rathe:" than sporadic. the most common inheritance pattern being autosomal dominant. Thus one comes across the terms, *sporadic ALS* (SALS) and *FALS.* A few other conditions have a phenotypical expression similar to that of ALS including Western Pacific ALS-parkinsonism-dementia complex (PDC) (or Guamanian ALS) and juvenile ALS.

The incidence and prevalence rates for non-Western Pacific ALS are surprisingly uniform throughout the world. The incidence is estimated at 1-3 per 100,000 and the prevalence varies from 6-8 per 100,000. Several epidemiological studies have suggested that the incidence of ALS may have increased in the past two decades and that this is a disease-specific finding rather than due to factors telated to better national health care, economic prosperity, or case ascertainment. In sporadic spinal ALS, men are more often affected than women by a ratio of 1.2-1.6:1. Howe vet, several clinical papers have shown that there is a slight female predominance in the bulbar-onset variety and that there appcats to be no consistent pattern of gender predominance in familial forms of the disease.

ALS is reported to occur as early as in the second decade of life, but the most common onset is in the patient's early sixties. It is notably rare in the vety oldest segment of the general population, that is, those older than 8.5 years. This has yet to be explained (Mitsumoto, Chad, and Pioro 1997). The mean disease duration from symptom onset to death is approximately 3 years, although some patients live for more than a decade, whereas others may succumb within a matter of a few months. Although no specific environmental factors have been linked with certainty to an increased tisk of ALS, epidemiological research suggested increased morralirv rates for ALS .untnis'. eledrical utility workers who were chronically exposed to electromagnetic fields (Johansen and Olson 1998), Population-based casc-control studies have also ascertained increased risk in those with a high dietary intake of glutamatc and in smokets (Nelson et al. 2000a, 2000b). A host of environmental trace elements have been evaluated as potential causative agents for ALS including selenium, aluminum, iron, manganese, copper, zinc, cadmium, and lead, but there is no convincing evidence that any one of these plays a major part in ALS pathogenesis,

Etiology

Significant inroads have been made into understanding the pathogenesis of SALS and FALS. Several hypotheses have been put forward, including that of viral infection, activation of the immune system, exogenous toxins, and hormonal disturbances. However, there has been insufficient evidence to implicate any of these as the major cause of motor neuron degeneration in ALS. Perhaps the most significant breakthrough in understanding the cause of ALS (be it sporadic or familial) came in 1993, when Rosen et al. identified mutations in the gene encoding an enzyme called copper/zinc superoxide dismutase (SODl) in patients with FALS. SODl mutations, which can cause elevated intracellular levels of reactive oxygen species, are now identified in up to 20% of all patients with FALS. Most recently, mutations in a gene encoding a novel protein called alsin have been identified in a form of recessively inherited juvenile-onset ALS of North African origin. This ptotein shares structural homology to a guanine nucleotide exchange factor, which suggests a role in altered cell signaling (Shaw 2001).

A significant body of basic and clinical research lends strong support to a new theory of ALS pathogenesis, which proposes selective motor neuron damage from a complex chain of injurious events involving excitotoxins, oxidative stress, neurofilament dysfunction, altered calcium homeostasis, mitochondrial dysfunction, enhanced motot neuron apoptosis, and proinflammatory cytokines (Cleveland and Rothstcin 2001). A number of ALS susceptibility genes have also been proposed, mutations of which are known to occur in small ALS populations or individual cases but which do not appear to account for the majority of SALS cases. The focus of the following discussion is on the role of excitotoxins, free radicals, neurofilaments, immune activation, inflammation, and candidate genes as they apply to the pathogenesis of SALS. The role of SOD) mutations and mutant alsin in disease pathogenesis is discussed in more detail in the sections covering FALS and juvenile ALS.

Pathogenesis of Sporadic Amyotrophic Lateral Sclerosis

Glutamatc Exci to toxicity and Free Radical Injury, Glutamatc, which is the most abundant ftce amino acid in the CNS, is one of the major excitatory amino acid (LAA) neurotransmitters. Glutamatc produces neuronal excitation and participates in many neuronal functions, including neuronal plasticity. In excess, however, it causes neurotoxicity. There are two types of glutamatc receptors: (I) ionotropic and (2) metabotropic. The former is an integral, cation-specific (particularly Ca^{+}) ion channel type, which is further grouped into two major subtypes depending on receptor characteristics: the N-methyl-D-aspartate (NMDA) teceptors and the non-NMDA receptors (AMPA-kainate receptor). Metabotropic receptors are coupled to G proteins and cyclic guanosine monophosphate (cGMP), modulating the production of intracellular messengers and influencing ionotropic glutamate teceptors. In ALS, motor neurons appear to receive the glutamate excitotoxic signal through non-NMDA receptors rather than NMDA teceptors.

The significance of glutamate excitotoxicity in neuro-degencration is strengthened by the observation that exogenous glutamate receptor agonists result in clinically observable neurotoxicity. Lathyrism (see previous section on UMN disease) is associated with chronic neurotoxicity exerted by /3-N-oxalylamino-L-alanine (BOAA), an AMPA receptor agonist. A similar disorder, Konzo, may also be due to glutamatc-mediated damage to cortical motor neurons. An outbreak of food poisoning associated with contaminated mussels that clinically presented with chronic dementia and motor neuron disease was caused by domoic acid, another potent non-NMDA receptor agonist. In patients with ALS, a series of endogenous glutamate abnormalities have been demonstrated; for example, EAA is significantly increased in serum, plasma, and CSF. On the other hand, glutamate in CNS tissue and the glutamare-to-glutamine ratio are significantly decreased in ALS. When glutamate metabolism is studied by loading with oral monosodium glutamate, plasma glutamate levels increase to a significantly greater degree in patients with ALS than in healthy patients. These studies clearly support the idea that glutamate excitotoxicity is involved in the pathogenesis of ALS, if not actually the cause.

Glutamate is normally released from presynaptic axon terminals into the synaptic cleft where it binds to its receptors causing signal transduction to occur. After signal transduction, interstitial glutamate must be reabsorbed into its main reservoir, the surrounding astrocytic glial cells. This absorption process involves specific transporter proteins known as GI.T (glutamate transporter) or EAAT (excitatory amino acid transporter) proteins, which have been subclassified according to their distribution within cells of the CNS. Among these, the astrocytic glutamate transporter, termed GLT1 or EAAT2, is markedly reduced in the motor cortex and anterior horn cells of patients with ALS, which supports earlier evidence that interstitial or extracellular (including CSF and plasma) glutamate is increased in ALS. Rothstein et al. found intriguing abnormalities in the DNA encoding GLT1 in more than 60% of patients with ALS (predominantly the sporadic form). However, subsequent research suggests that GLT1 does not appear to be a candidate gene for FALS or SALS.

Impaired glutamate transport reduces clearance of glutamate from the synaptic cleft, which may leave excessive amounts of free excitatory neurotransmitter to repeatedly stimulate the glutamate receptor and thus allow calcium ions enter the neuron. Excess calcium ions are usually buffered by intracellular calcium-buffering proteins, such as parvalbumin or calbindin, and by mitochondria that may also function as an extra calcium reservoir. Low levels of parvalbumin, calbindin, and altered mitochondrial function have been detected in ALS models. When calcium ion levels exceed this reduced buffering capacity, they may catalyze activity in specific destructive enzymes that are not activated under normal conditions including xanthine oxidase, phospholipase, and nitric oxide synthase. These enzymes produce ftee radicals, including reactive oxygen and nitrogen species, which cause harmful nitration of tyrosine residues on key neuronal proteins and ultimately may also cause apoptosis. It has recently been proposed that regional differences in the levels of activity of buffering systems and in glutamate receptor subtype expression may explain the selective vulnerability of certain motor neuron pools within the CNS.

Immunological and Inflammatory Abnormalities. Several pieces of evidence implicate an immune process in the pathogenesis of ALS. Immune complexes have been identified in gut and renal tissue from patients with ALS. Furthermore, up to .10% of patients with ALS may have a monoclonal gammopathy and fewer than 5% have low-level titers of anti-GMi antibody. Moreover, serum antibodies to [.-type voltage-gated calcium channels have been found in some patients with ALS but not in others. Activated spinal cord microglial cells, elevated inflammatory cytokine levels, and most recently, marked increased expression of cyclooxygcnase-2 have also been found in ALS tissue samples (Yasojima et al. 2001; Aimer et al. 2002) (Figure 80.4). However, all available immunotherapies, including cyclophosphamide, IVIG, plasmapheresis, corticosteroids, and total lymphoid irradiation, have failed to alter the course of ALS (Murray and Mitsumoto 2002}. Although this might indicate that immune mechanisms are not of primary importance in the pathogenesis of ALS, there is hope that cell-targeted immune therapy and anti-inftamnuinry therapy may :v usclal.

Neurofilament Dysfunction. Abundant neurofilaments are present in the cytoskeleton of motor axons w[r]here they are vital for bi-directional axonal transport. Abnormal axonal spheroids, consisting of neurofi lament-derived material, have been identified in tissue from patients with ALS. Subsequent research shows that abnormally slow axonal transport (referred to as "axonal strangulation") may be important in ALS, perhaps as a result of oxidative stress-induced neurofilament injury (Lamonte et al. 2002). However, it is possible that increased levels of neuro-filament may actually represent a protective reaction of the cell body to harmful calcium levels or to other substances.

Mutations in the genes for neurofilament subunits appear to confer increased risk for the later development of SALS (Cleveland and Rothstein 2001). The neurofila-ment heavy chain is thought to be important in the correct spacing of neurofilaments from each other and thus in the regulation n! axonal diameter. In rare cases of SALS (and very rarely FALS), mutations have been found in the heavy-chain gene segment that encodes an amino acid repeat motif. Over express ion of another intermediate motor neuron-specific protein called *peripheric* may lead to accumulation of toxic intraneuronal aggregates,

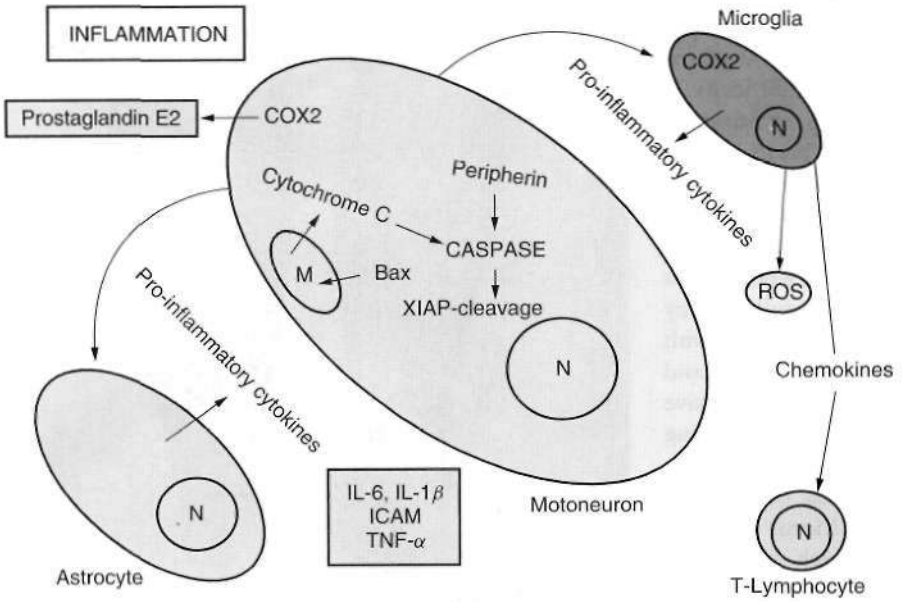

FIGURE 80.4 The role of inflammation in amyotrophic lateral sclerosis pathogenesis.

as has been demonstrated in patients with SALS and in mice with SOD1 mutations. In fact, selective motor neuron toxicity in the setting of pcriphcrin overexpression appears to occur in mice that lack light subunits, which implies that the light subunit may somehow prevent a harmful interaction between peripheral and other neurofilament subunits. Furthermore, proinflammatory cytokines appear to increase the duration of peripheral overexpression at sites of neuronal injury (Beaulicu, Kriz, and jalien 2002).

Susceptibility Genes for Sporadic Amyotrophic Lateral Sclerosis. The survival motor neuron (SMN) proteins are encoded by inversely homologous genes located on chromosome 5q (see Spinal Muscular Atrophy, earlier in this chapter). In one study, no deletions in the SMNl gene were found in SALS *(n* = 177) or FALS *(n* = 66), but a pure adult-onset LMN disorder associated with homozygous deletion of the SMN2 gene was described in five cases (Moulard et al. 1998). A French study of 167 patients with ALS revealed that the SMNl gene copy number was abnormal in 16% of cases compared with only 4% of controls, which suggests that the SMNl gene may be a susceptibility factor for ALS (Corcia et al. 2002).

Other rare mutations have been identified in patients with ALS, including in the APEX nuclease gene, cytochrome oxidase *c* subunit gene, the copper chaperone of SOD! gene, and the leukemia inhibitory factor gene. As with the genes for GLT1/EAAT2, neurofilament heavy chains, SMN protein, and the apolipoprotein H_4 genotype, there is insufficient evidence to implicate these mutations in the direct pathogenesis of all ALS, but they may act as genetically determined susceptibility factors.

Clinical Features

It is widely agreed that when the clinical symptoms of ALS first appear, the biological disease must have been developing for some time and is well into its course. Electrophysiological investigations in patients in the early stages of the disease suggest that an extensive remodeling of motor units takes place by continuous denervation and reinnervation process before affected individuals can recognize muscle weakness. A study in patients with acute poliomyelitis estimated that as many as 50% of the motor neurons are lost before muscle weakness is detected. Therefore an important preclinical asymptomatic stage likely precedes progressive muscle weakness in ALS.

Muscle weakness in ALS usually begins in a focal area, first spreading to contiguous muscles in the same region before involvement of another region. The first presentation may appear very similar to a focal mononeuropathy; this is sometimes called the *pseudo-neuritic presentation,* More commonly, however, limb weakness appears to occur in muscles derived from more than one peripheral nerve and/or nerve root distribution; this is called a *monomelic presentation.* Onset of muscle weakness is more common in the upper than the lower extremities (classic, spinal ALS), but in approximately 25% of patients, weakness begins in bulbar-innervated muscles (bulbar-onset ALS). On rare occasions (1% or 2% of patients), the weakness starts in the respiratory muscles (dyspnea onset). Some patients present with weakness that is restricted to one side of the body (Mills' hemiplegic variant) and up to 10% of patients appear with bilateral upper extremity wasting, which is known as the "flail arm" or flail person in the barrel variant.

Symptoms of muscle weakness vary, depending on which motor function is impaired. For example, when weakens begins in the hand and fingers, patients report difficulty in turning a key, buttoning, opening a bottle cap, or turning a door knob (Figure 80.5). When weakness begins in the lower leg, footdrop may be the first symptom or the patient may complain of instability of gait, falling, or fatigue when walking (Figure 80.6). When bulbar muscles are affected, the first symptoms may be slurted speech, hoarseness, or an inability to sing or shout, which may be soon followed by progressive dysphagia (Figure SO.7). Indeed, patients with bul bar-on set ALS often initially consult car, nose, and throat specialists and not only experience progressive impairment in bulbar function but also excessive drooling (sialorrhea) and weight loss. Pseudobulbar palsy may present with inappropriate or forced crying or laughter (see Signs and Symptoms of Upper Motor Neuron Involvement, earlier in this chapter), which is often a source of great emotional distress for patients. Excessive forced yawning may also be a manifestation of pseudo-bulbar palsy. In the rare patient who presents with progressive respiratory muscle weakness, the first port of call may be to a pulmonologist or even to the intensive care unit; the diagnosis of ALS is then made when the patient cannot be weaned from the ventilator. Head-drop (or droop) may be a feature in ALS and is caused by weakness of cervical and thoracic paraspinal muscles (Figure 80.8). However, weakness in these muscles is more commonly seen in myasthenia gravis and polymyositis.

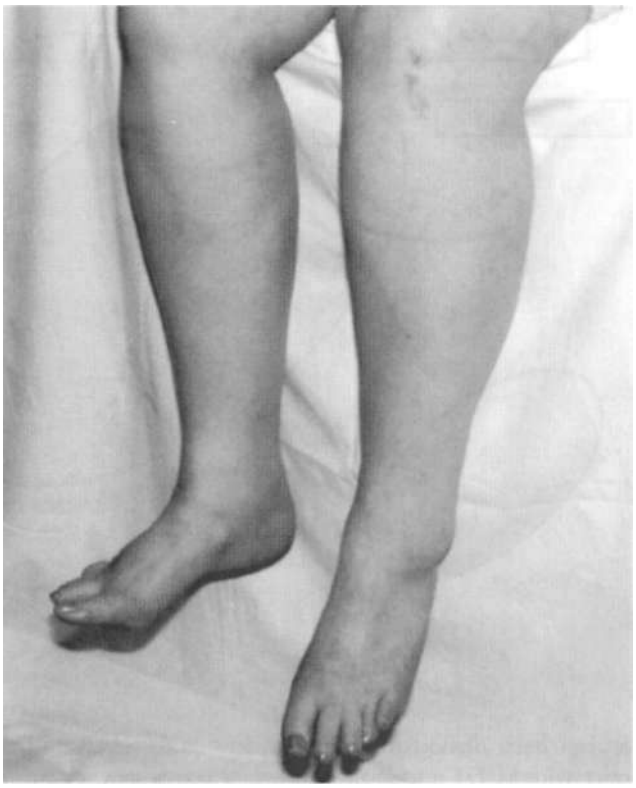

FIGURE NO.6 A typical left footdrop in a 45-year-old patient whose amyotrophic lateral sclerosis began 2.5 years earlier with bulbar symptoms. When she was asked to dorsiflex both feet, she was able to move her right foot only. The footdrop developed 6 months before the photo was taken, and the patient wears a left ankle-foot orthosis.

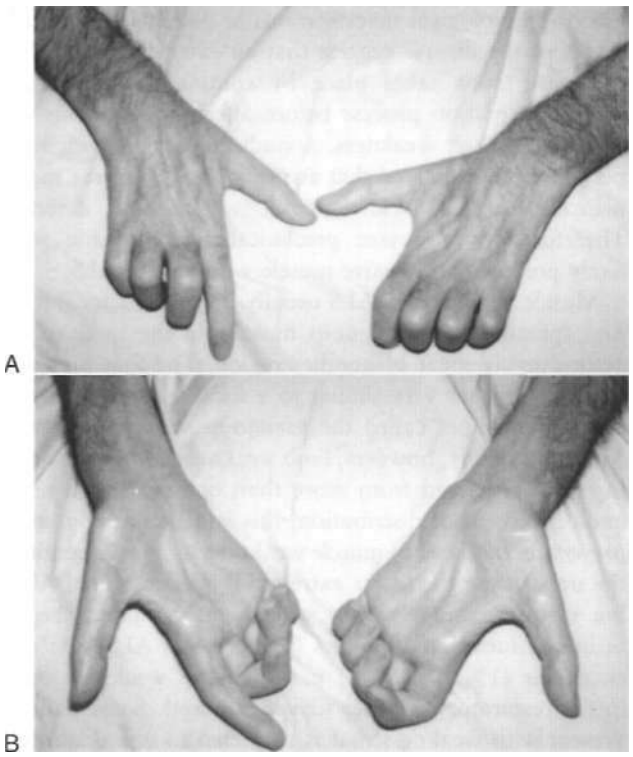

FIGURE 80,5 (A, B) Severe intrinsic hand muscle atrophy in a patient with amyotrophic lateral sclerosis. Note the "claw hand" and atrophy of muscles innervated by both ulnar and medial ncn i's.

Fascicular ions are not commonly the presenting feature of ALS, but they develop in almost all patients soon

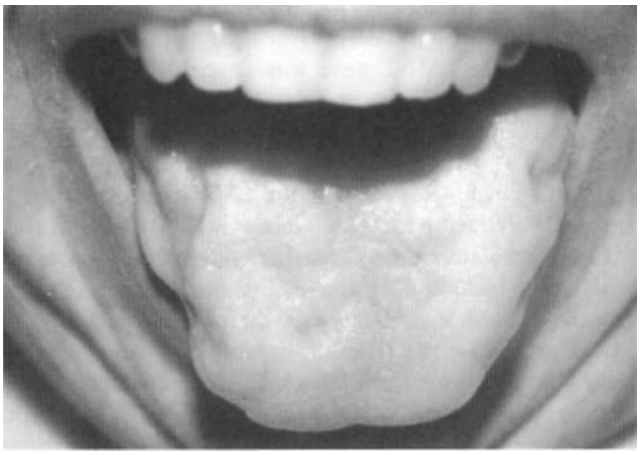

FIGURE HO.7 Atrophy of the tongue in amyotrophic lateral sclerosis,

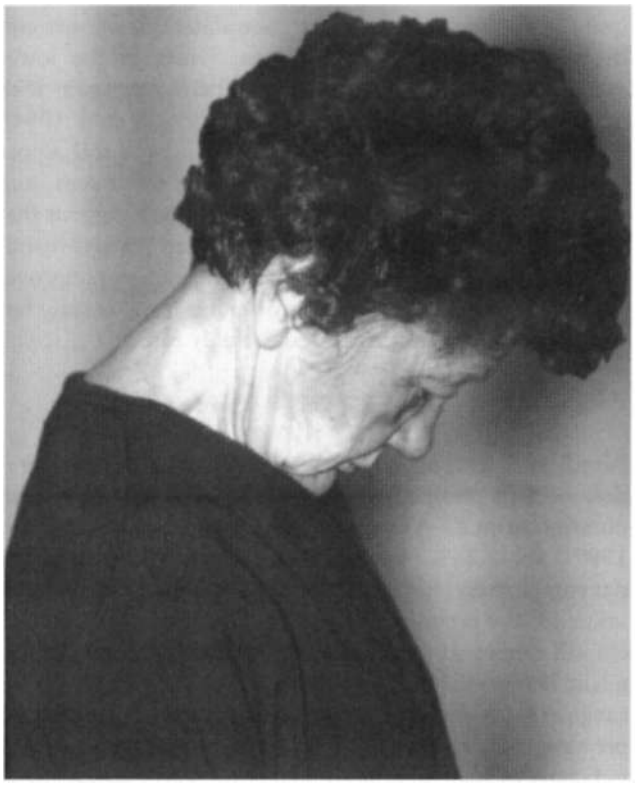

FIGURE 80.8 Patient with amyotrophic lateral sclerosis showing head droop caused by weakness of the thoracic and cervical pa rasp in til muscles,

after onset. In fact, absence of fasciculations should prompt one to seriously reconsider the diagnosis. In some patients, waves of fasciculations, called Lambert's waves, are seen spreading across the chest or back. Muscle cramps are one of most common symptoms in patients with ALS and often precede other symptoms by many 11 ninth-,. Although cramps arc common in health',- individuals and most commonly occur in calf muscles, in ALS they can occur in unusual muscles such as in the thigh, abdomen, hack, upper extremity, hand, neck, jaw, and even the tongue.

Other signs and symptoms include exertional tatn;ue that mimics myasthenia. As dysphagia worsens, reduced caloric intake worsens fatigue and accelerates muscle weakness. Aspiration of liquids, secretions, and food becomes a risk. Patients may complain that they produce copious amounts of abnormally thick oral secretions, which may drool excessively from the mouth. This sialorrhea is made worse as perioral muscles weaken and/or head-drop develops. Weight loss is often rapidly progressive; indeed it has been suggested that this does not simply reflect poor caloric intake but represents a form of ALS cachexia. Marked loss of muscle bulk exposes joints and associated connective tissues to abnormal mechanical stresses that can lead to joint contractures, joint deformities, painful pcricapsulitis, and bursitis. Sleep disturbances, in the form of increased awakenings from increased hypopneas and hypoxia, have been shown to be common in ALS and contribute to daytime sleepiness, morning headaches, and fatigue, As respiratory difficulty worsens, patients may be unable to lie supine because of worsening diaphragmatic weakness and thus compensate by using multiple pillows. In more advanced stages, patients are unable to he in bed at all. Other manifestations of ventilatory failure include dyspnea on exertion and eventually dyspnea at rest. As the disease advances, motor function is progressively impaired and activities of daily living (e.g., self-hygiene, bathing, dressing, toileting, walking, feeding, and verbal communication) become difficult. Accordingly, a patient's quality of life starts to progressively deteriorate. It may be difficult to distinguish daytime fatigue, broken sleep, affect lability, and sighing from depression, but it is vitally important to be aware of the latter. Depression is a common and underdiagnosed problem in ALS, which not only negatively affects quality of life but also shortens survival.

Atypical Features

There arc certain clinical features that are unusual if not absent in AI.S including sensory loss, dementia, extrapyramidal dysfunction, eye movement abnormalities, autonomic disturbances, and abnormal sphincter control. When patients have these signs, the diagnosis of ALS should not be made until all possible alternative diseases are excluded. Although the sensory system is characteristically spared, some patients do report vague sensory symptoms such as numbness or aching and there is electrophysiological evidence that ascending afferent pathways may be involved despite the absence of objective sensory loss on physical examination. Overt dementia is estimated to occur in approximately 5% of non-Western Pacific ALS where it may even be the presenting feature. It is usually of the frontotemporal dementia (FTD) variety, and most commonly presents with word-finding difficulties, deficits in visual perception, and abnormal confrontation naming. Patients may exhibit poor judgment and other deficits in executive processing. There is some evidence that this form of dementia or cognitive impairment is much more common not only in bulbar-onset ALS but also in all subtypes of ALS, One needs to be cautious that language disturbances (especially anomia) may be masked by dysarthria. A prospective neuropsychological study of cognition in ALS identified deficits in up to a third of patients and a subsequent study reported an incidence of FTD in almost 50% in patients with bulbar-onset ALS. Of 36 cases meeting criteria for FTD, 5 (14%) also met criteria for definite ALS (Lomen-Hoerth, Anderson, and Miller 2002). Dementia in ALS is pathologically distinct from other dementing illnesses; the most reliable pathological marker of cognitive impairment in SALS is

Table 80,9; Practical classification of amyotrophic lateral sclerosis

- Sporadic ALS
  - Classic (spina l-onscr) ALS
    - Mills' hemiplegic variant
    - Psendoncuritic presentation
    - Flail arm presentation
    - Monomelic presentation
    - LIMN onset
    - LMN onset
    - Bulbar onset
    - Dyspnea onset
  - Progressive muscular atrophy
  - Primary lateral sclerosis
  - Progressive bulbar palsy
- Familial ALS
  - Autosomal dominant
    - SOD1 missense mutations
    - Autosomal dominant linked to chromosome 9q34 (childhood)
  - Autosomal recessive
    - *SODl* (Asp90-Ala) mutation
    - ALS linked to chromosome 2q33 *[ALS1N* gene)
    - ALS linked to chromosome 15ql5
  - \ linked iliiiinri.uil Al S
- Disinbihition, dementia, parkinsonism, amyotrophy complex linked to chromosome 17q21
- ALS with iron to temporal dementia linked to chromosome 9q21-22

ALS = amyotrophic lateral sclerosis; LMN = lower motor neuron; UMN = upper motor neuron.

superficial linear spongiosis in neocorticai, entorhinal, and cingulate tissue (Wilson et al. 2001).

The motor neurons of Onufrowicz in the sacral cord are essentially spared in ALS, and thus patients generally do not complain of significant problems with sphincter control (although some may report mild urgency of micturition). Similarly, eye movements are typically normal in ALS; it takes detailed quantitative testing to be able to identify abnormal vertical ocular saccades. Approximately 5% of patients with ALS exhibit signs of extrapyramidal tract dysfunction, usually in the form of retropulsions during attempted ambulation. Autonomic symptoms do not come to the attention of patients with ALS, although there is electrophysiological evidence of abnormal sweat production and cardiac denervation in the early stages of disease in sonic panciiis : Keck et il. 200 >).

Natural History of the Disease

It has been estimated that up to 40% of anterior horn cell motor neurons are lost before the clinical detection of motor abnormalities; this suggests that a prolonged preclinical phase may be part of ALS. However, once the clinical phase-is evident, there appears to be a generally linear decline in motor function over time. There is a characteristic pattern of spread of disease. When onset is in one upper extremity, spread is often first to the contralateral side, then the ipsilateral lower extremity, the contralateral lower extremity, and finally the bulbar region. Onset in the lower extremity often follows a similar pattern, yet again with final involvement of the bulbar region (Brooks et al. 1994). Bulbar-onset ALS tends to spread to the distal upper extremities first, with spread to thoracic myotomes, and then the lower extremities. Overall, the pattern suggests that rostral-caudal involvement is faster than caudal-rostral spread. During the course of the disease, transient improvement, plateaus, or sudden worsening can occur, but spontaneous improvement is exceedingly rare.

Prognosis

Based on several epidemiological studies the median duration of ALS ranges from 23-52 months and the mean duration from 27-43 months (Mitsumoto, Chad, and Pioro 1997). About 25% of patients survive 5 years and 8-16% of patients survive beyond 10 years. A number of factors influence the prognosis of ALS including the age at onset, clinical type, and duration from onset to the time of diagnosis. However, it must be emphasized that there is a wide range of rates of progression in each category of patient; the previous rate of progression in a particular patient is a better indicator of prognosis than any other feature. In general, the younger the patient, or the longet the duration between onset and diagnosis, the better the prognosis. A worse prognosis is found in those whose rate of progression is rapid within the first 6 months of diagnosis (Chio et al. 2002). Several clinical subtypes harbor a better prognosis; these include PLS, I'M A, pseudobulbar (rather than bulbar) palsy, the pseudo-neuritic presentation, and the flail-arm variant. Those who survive beyond 46 months and those who are psychologically well adjusted or not depressed have a better prognosis. Those who have low-amplitude CMAPs in the setting of notmal sensory potentials (the *generalized low motor-normal sensory* pattern) as revealed by nerve conduction studies appear to have a poor prognosis. Dyspnea-onset ALS has a shorter survival. Low serum chloride levels are associated with a short-term survival without ventilatory support because they reflect accumulation of bicarbonate due to respiratory failure (Stambler et al. 1998). Data on bulbar-onset AI.S vary, bur mean survival ranges between 12 and 26 months. Malnutrition is an independent risk factor for poor outcome.

Laboratory Studies

In some instances a diagnosis of definite ALS can be reached based on the history and clinical examination alone. However, often the diagnosis is not so obvious and further investigations are necessary. Because there is no single test that can make a diagnosis of ALS, all of these investigations are performed to exclude other disorders that may clinically mimic ALS and its variants. All such testing is an extension of a thorough history and physical

examination and includes blood tests, the EDX, and neuroimaging.

There is no single blood test that may objectively diagnose SALS. However, there are several blood tests that are usually performed for the evaluation of patients with suspected ALS. The list includes serum CK concentration, blood count, chemistry panel (including calcium, phosphate, and magnesium), *Venereal Disease Research Laboratories* test results, GM| autoantibody titers, sedimentation rate, serum pro rem unmunofixation or Immunoelectrophoresis, thyroid function studies including thyroid-stimulating hormone, and vitamin B12 levels. The CK concentration may be modestly elevated, particularly early in the disease. Patients oldet than 50 years and smokers of any age should have a chest radiograph taken. If any lesion is identified, an anti-Hu antibody level should he determined. Certain patients may have clinical features that suggest a disorder of the neuromuscular junction and may therefore benefit from testing for antibodies against the acetylcholine receptor or voltage-gated calcium channel. If there is biochemical evidence of adrenal insufficiency, it is pnnlcnl in oh lin ;i \ cry long-chain fatly acid **[VI** CI'A) assay to investigate for possible adrenomyeloneuropathy. Young-onset ALS with atypical clinical features should prompt the physician to obtain a Hex-A assay. If there is a positive family history, it is important to counsel the patient in preparation for SOD1 mutation analysis. There arc no specific features on muscle biopsy to distinguish ALS from other neurogenic disorders and this test should be reserved for cases that are more suggestive of a myopathy.

The EDX examination is an invaluable tool in the investigation of ALS and its variants (see Chapter 36B). It serves as an adjunct to the clinical examination and is particularly useful in determining the presence or extent of LMN disease. Again, none of the EDX findings is ALS specific, but they can strongly suppott the diagnosis. Furthermore, this investigation may be repeated at intervals to more objectively monitor disease progression. Sensory nerve conduction study results are characteristically normal, unless the patient happens to have a coincidental mononcuropathy or polyneuropathy. Motor nerve conduction study results may be normal, although the conduction velocity and CMAP amplitude may be diminished in keeping with the extent of motor axon loss. There should be no evidence of conduction slowing or block, which would suggest a primarily dcmyclinating disorder. Severe motor axon loss may give rise to the "generalized low motor-normal sensory" EDX pattern, which may portend a poorer prognosis.

The needle electrode examination characteristically reveals a combination of acute (positive sharp waves and fibrillation potentials) and chronic (neurogenic firing pattern with evidence of increased amplitude and duration, polyphasic motor unit potentials) changes in a widespread distribution that is not in keeping with any single root or peripheral nerve distribution. Fasciculation potentials are usually identified; their absence should prompt an investigation for another disorder. Other common findings include moment-to-moment amplitude variation that indicates impaired motor unit stability and repetitive discharges known as *doublets.* Mention should be made of a special EDX finding, the split-hand phenomenon; in some patients, EDX reveals severe changes in muscles of the lateral hand (thenar eminence) but relative sparing of the medial hand (hypothenar eminence). EDX changes should be observed in a certain topographical distribution and ideally should be carried out in at least three of the four regions of the neuraxis (bulbar, cervical, thoracic, and lumbosacral).

Neuroimaging studies of the brain and spinal cord are important to exclude structural, inflammatory, or infiltrative disorders that may cause UMN signs (Mitsumoto, Chad, and Pioro 1997) (see Chapter 37). Furthermore, T2-wcightcd and proton density MRI scans of btain may also reveal abnormal signal within the motor tracts as they extend from the motor cortex to the brainstem. These changes are thought to represent wallerian degeneration. Nonspecific atrophy of the frontal and patietal cortex may also be appreciated. Novel MRI techniques such as magnetization transfer ration (MTR) and diffusion tensor **MRI** may also reveal specific changes in the motor tracts in ALS. Research using positron emission tomography (PET) has shown increased activity in several ipsilateral and contralareral cerebral cortical regions beyond the motor cortex, which supports the current theory that ALS is not a disorder solely of motor neurons, but that this cell population is especially vulnerable to the injurious process involved. Proton density MRI data may not only support the diagnosis but also provide useful motor neuron-specific information with which to track disease progression and response to therapy. Significantly abnormal values of the ratio of N-acetylaspartate (NAA) to creatine or choline have been detected in the motor tract of patients with probable or definite ALS when compared to controls and abnormalities in these levels change over time {Chan et al. *1999;* Suhy et al. 2002).

Diagnosis

In May 1990, at El Escorial, Spain, the World Federation nl Neurology established J agnostic criteria for Al S, which were later modified at Airlie House, Virginia (1998) (wAvw.wfnals.org). These criteria include clinical, electrodiagnostic, and pathological components. The clinical criteria divide candidates into those with definite, probable, lab-supported probable, possible, and FALS based on a careful history and examination of four regions of the neuraxis: bulbar, cervical, thoracic, and lumbosacral. The purpose of establishing these criteria was to facilitate entry of appropriate candidates into clinical research trials, but they have been proven invaluable in rhe assessment of all patients with ALS.

A patient is referred to as having "definite ALS" if there is clinical evidence of both UMN and LMN signs in three or

more regions. "Probable ALS" is diagnosed in those with UMN and LMN signs in two regions. "Possible ALS" implies that a patient cither has UMN and LMN signs in one region only or has UMN signs alone in two regions. In addition, "possible ALS" may be applied to those with LMN signs in two regions as long as these are detected rosrmlly to the L'MN siting- "lab supported probable ALS" refers to those patients who have clinical evidence of possible ALS but also have laboratory evidence of more widespread LMN involvement. The EDX is most valuable in providing such additional information. Follow-up examinations may be helpful in assessing patients with ALS, as disease progression may move a patient up a category, which not only may clarify the diagnosis but also may allow entry of that patient into research trials.

Differential Diagnosis

The differential diagnosis of ALS is rather extensive; motor symptoms and signs may be present in many other neurological and systemic disorders. Because there are no specific diagnostic markers for ALS, differentiating all other motor neuron diseases that may produce signs and symptoms of UMN, LMN, or both UMN and LMN involvement is essential for establishing the correct diagnosis. One may approach this task in an anatomical fashion and consider how ALS may appear similar to other disorders of the brain, brainstem, spinal cord, anterior horn cell, nerve root, peripheral nerve, neuromuscular junction, and muscle. Alternatively, one may approach this task in terms of the presentation; is it UMN only, LMN only, combined UMN-LMN, bulbar only, and so on? Are there any atypical features, such as prominent bladder or sensory involvement that suggest another diagnosis? For example, when UMN involvement is prominent, PLS, spastic paraparesis, or HAM should he considered, whereas pure LMN involvement suggests that one should also consider PMA, MMN, adult-onset SMA, or Kennedy's disease.

Severe cervical spondylosis may impinge upon the cervical cord and the nerve roots and thus present with both UMN and LMN signs. Because pain, spastic bladdet, and posterior column signs are not always present, F.MG and neuroimaging may he required to distinguish it from ALS. Neuroimaging is also invaluable in assessing other disorders ol the brainstem and spinal cord that nay superficially mimic certain features of ALS such as intrinsic or extrinsic tumors, foramen magnum meningiomas, syringobulbia, and syringomyelia. Multiple sclerosis usually presents with UMN signs, but on rare occasions, LMN signs develop when ventral root exit zones are affected by demyelinating plaques. Neuroimaging and lumbar puncture studies should distinguish the two conditions. GDI[1] may manifest as a predominantly LMN disorder, hut some patients also have demyelinating lesions in the CNS that cause additional UMN signs.

It may be difficult to differentiate PBP from bulbar myasthenia gravis, as even repetitive stimulation studies and testing for serum antibodies against acetylcholine receptor may be negative in the latter. Follow-up examinations, however, usually reveal the insidiously progressive nature of the motor neuron disorder. Bulbar symptoms in ALS may be mistaken for brainstem stroke, but the progressive nature of bulbar symptoms and negative brainstem **MRI** will usually clarify the picture. On rare occasions, the increased tone, dysarthria, and sialorrhea of Parkinson's disease may be confused with ALS. However, the former is characteristically responsive to i.-dopa and tremor is often prominent. Multiple system atrophy may present with a combination of UMN and LMN signs, together with dysarthria and dysphagia. However, cerebellar ataxia, eye movement abnormalities, sphincter disturbance, and dysautonomia are usually prominent features. SCA types 2 and 3 (Machado-Joseph disease) are also part of the differential diagnosis. Other diseases that mimic ALS include adult Hex-A deficiency, adrenomyeloneuropathy, and certain motor paraneoplastic syndromes. Hyperthyroidism may present with prominent UMN signs, weight loss, and fasciculations but also features tremor, heat intolerance, and tachycardia. Hyperparathyroidism may present with an LMN or even myopathic disorder that mimics PMA. Both the benign fasciculation syndrome and cramp fasciculation syndrome nun- lead to rclcnaL lor [he evaluation ol ALS, hut these patients do not have any other symptoms or signs that suggest a widespread progressive disorder of motor neurons.

/ *reatment*

See Table 80.10.

Presentation of the Diagnosis of Amyotrophic Lateral Sclerosis. The first step in the management of ALS is to present the diagnosis in a compassionate, yet informative manner. Because many patients and their families find it difficult to absorb the information at first, a second appointment a short time later is often required. The decision-making process must include the patient and the

Table 80.10: Comprehensive care and management for patients with amyotrophic lateral sclerosis

Presentation of the diagnosis oF ALS
Specific pharmacotherapy
Symptomatic treatment
Team approach at ALS clinic
Ethical and legal issues
Physical rehabilitation
Speech and communication management
Nutritional care
Respiratory care
Home care and hospice care

ALS = amyotrophic lateral sclerosis.

family. At the appropriate time, it is important to bring up issues such as advance directives and issues regarding terminal care. Providing information on progress in research, newly available pharmacotherapies, and the possibility of active participation in clinical trials may increase hope for patients (Miller ct al. 1999).

Specific Pharmacotherapy. In 1996, riluzole (Rilutek) was approved by the United States Food and Drug Administration (FDA) as the first specific drug for the treatment of ALS. It is believed to principally function as an antiglutamate agent, although its mechanism of action is not yet fully understood. The two studies that led to riluzole approval showed that survival was significantly longer in patients with ALS who took 50 mg of riluzole twice a day compared with those who took placebo, although this survival benefit was only modest and was disproportionately beneficial in bulbar-onset disease, A subsequent systematic meta-analysis of three randomized trials carried out in French and Belgian populations has shown a significant survival advantage at *6,* 9, 12, and 15 months but not at 3 or 18 months. The median prolongation of survival was calculated at only 2 months. However, data from uncontrolled studies in other populations that were followed over longer periods have reported survival benefits of up to 20 months (Miller et al. 2002). In addition, riluzole appears to maintain patients in a milder state of disease for a longer period. Side effects are relatively uncommon and minor and include fatigue, gastrointestinal upset, and dizziness. Furthermore, there may an increase in liver function test results. To minimize side effects, we recommend 50 mg per day in the evening, and after a week or two, the patient can increase the dose to the regular dose of 50 mg twice a day. The cost of the drug (approximately S8000-S9000 per year) appears to be one of the main factors in whether patients elect to take riluzole.

Several agents with antiglutamate activity have been assessed in clinical trials including lamotngine, branched-chain amino acids, topiramate, dextromethorphan, and gabapentin. None of these has been proven to be of clinical benefit, although dextromethorphan has been shown to be of benefit in the treatment of pseudobulbar affect.

A series of agents with antioxidant and/or neuroproreetant properties have been studied in ALS including, L-deprenyl, N-aeety[cysteine, and calcium-channel blockers, but so far none has been shown to be of benefit. A trial of vitamin E taken orally at a dose of 1000 ug per day also did not show a clinical benefit. Nonetheless, many patients take high doses of natural antioxidants including combinations of vitamin E, vitamin C, flavonoids, coenzvme Qm, or all of them in various combinations. Many patients are taking creatine, a naturally occurring muscle component important in mitochondrial function that is widely available as an over-the-counter supplement in health food stores. As with coenzyme QJQ, there is experimental evidence that creatine improves motor function in transgenic SOD1 animal models of ALS, and trials are currently under way in humans (Klivenyi et al. 1999).

Neurotrophic factors are a heterogeneous group of basic peptides belonging to the cytokine family that are produced in regulated amounts from various tissues and are important in cellular proliferation, differentiation, maintenance, maturation, and repair. A number of recombinant neurotrophic factors have been studied in well-designed trials including ciliary neurotrophic factor, brain-derived neurotrophic factor, insulin-like growrh factor (IGF-1, Myotrophin), and glial cell-derived neurotrophic factor. Results from these trials have generally been disappointing, although some benefits have been noticed in certain. ALS subpopulations. It has been proposed that these negative findings may reflect poor drug delivery to target tissue and that future efforts should focus on trying to more closely mirror the natural biology of these and other neurotrophic factors: Systemic and intrathecal routes of administration do not appear to achieve adequate tissue levels and necessitate high doses that cause unpleasant side effects. The potential clinical benefits of IGF-1 are once again under investigation (Mitsumoto and Tsuzaka 1999). Another agent under clinical investigation is buspirone, an anxiolytic agent that also has neurotrophic factor-like effects.

Xaliproden (Sanofi SR57746A) is a novel small nonpeptide molecule with both neurotrophic and ncuroprotcctant properties and good CNS penetration. Preliminary trials suggested that this agent might be ot benefit in ALS. Based on evidence of benefit in cell culture systems and transgenic animal models, several other new agents are being investigated for potential use in the treatment of ALS. These include novel AMPA receptor antagonists, cyclooxygenase-2 antagonists, modified catalases, copper chelators, caspase inhibitors (such as minocycline), antiapoptotic antiviral agents (indinavir), anabolic steroids (oxandrolone), and modulators of cell signaling pathways. It may also be of benefit to administer several agents in combination, such as an antiglutamate agent with one or more neuioprotecrants and neurotrophic factors. Finally, there is early evidence from animals that gene therapy and/or stem cell therapy may be effective in the trearment, maintenance, and possibly even the regeneration of the motor neuron system, although many practical and ethical issues must be addressed before such treatment becomes a reality (Murray and Mitsumoto, 2002).

Aggressive Symptomatic Treatment. Although specific pharmacotherapy is still markedly limited for the treatment of ALS, symptomatic treatment can substantially improve a patient's symptoms and discomfott. Table 80.11 summarizes specific pharmacological and nonpharmacological symptomatic treatments (Miller et al. 1999).

Muhidisciplinary Team Approach at Amyotrophic Lateral Sclerosis Clinic. The care of patients with ALS has become increasingly complex. As a consequence, many patients are taken care of by ;; uuihidiseiplmary •.e.un rather

Table 80.11: Symptomatic treatment in amyotrophic lateral sclerosis

Symptoms	*Pha rtna cotherapy*	*Other therapy*
Fatigue	Pyridostigmine bromide	Energy conservation
	Antidepressants	Work modification
	Amantadine hydrochloride	Assistive devices
Spasticity	Baclofen	Physical therapy
	Tizanidine	Rangc-of-motion exercises
	Dantrolene sodium	
	Diazepam	
Cramps	Quinine sulfate	Massage
	Baclofen	Physical therapy
	Vitamin E	
Fa stimulations	Carbamazepine	Assurance
Sialorrhea	Anticholinergic drugs	Mechanical cleaning
Thick mucinous saliva	Beta blocker	None
Pseudobulbar laughing or crying	TCA	
	SSR1	
	L-d opa/ca r bi d o pa	
	Lithium	
Secretion and expectoration	Dextromethorphan	Hydration
	Organ id in	Moist air; aspiration devices; insufflator/exsufflator
Aspiration	Cisapride	Modified food consistency
		Tracheostomy
		Modified laryngectomy and tracheal diversion
Joint pains	Anti-inflammatory drugs	Range-of-motion exercises
	Analgesics	Heat
Depression	TCAs	Counseling
	SSRI	Support group meetings; psychiatry
Insomnia	Zolpidem tartrate	
	Lorazepam	
	Opioids	
Respiratory failure	Bronchodilators	Hospital bed
	Morphine sulfate	Nocturnal noninvasive ventilator
		1PPB
Constipation	Increase oral liquid	Noninvasive ventilation; permanent ventilation
	Metamucil	FJxercise
	Dulucored suppositories	
	Lactulose and other laxative	

1PPB = intermittent positive pressure breathing; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

than by a single treating physician. The team often consists of neurologists, a nurse coordinator, physical therapists, occupational therapists, dietitians, speech pathologists, and social workers. Pulmonary specialists and other health professionals should also be available. Using this holistic approach, the aim is to maintain physical independence for as long as possible and to provide psychosocial support to patients and families {Mitsumoto, Chad, and Pioro 1997),

Ethical and Legal Issues. ALS is almost invariably a relentlessly progressive and terminal disorder. Thus physicians must raise the issues of the living will and durable power of attorney for health care relatively early after the diagnosis is made to allow the patient and family to prepare-ahead. However, it should be emphasized that such decisions are not final and may even be reversed at any time. Furthermore, some patients either do nor wish ro or cannot make such decisions.

Physical Rehabilitation, The main goal of rehabilitation for patients with ALS is to improve their ability to carry out activities of daily living for as long as possible without causing undue physical or emotional strain. Physical therapy also prevents complications secondary to disuse of muscles and immobilization, such as a frozen shoulder. Various types of exercise are employed that maintain or enhance strength, endurance, and range of motion. There have been concerns that exercising ALS-affected muscles to the point of fatigue may actually be harmful, but this has not been borne out in the literature.

The occupational therapist is another valuable member of the ALS care team. A range of assistive and adaptive devices is employed to improve mobility and comfort and to cany out activities ot daily living. For example, walkers, wheelchairs, splints, and collars are useful to manage wrist-drop, footdtop, head-drop, and gait instability. Successful rehabilitation also includes an evaluation of the

home environment and customized home equipment can easily help preserve a patient's independence and safety [Mitsumoto, Chad, and Pioro 1997),

Speech and Communication Management. Speech and communication dysfunction is probably one of the most serious factors reducing quality of life in the patient with ALS. Ideally, speech pathologists should assess speech and communication soon after the diagnosis is made so that the patient can maintain independent communication for as long as possible. To maximize communicative ability, we use a six-step approach as the disease progress:

- Step 1. Maximize intelligibility strategies (e.g., teaching the patient to speak slowly and face to face)
- Step 2. Introduce energy-conserving techniques
- Step 3. Train the patient's main listener or communication partner
- Step 4, Introduce nonverbal techniques (gestures and other body language)
- Step 5. Incorporate assistive (such as a palatal prosthesis) and augmentative communication devices and techniques
- Step 6. Refer for a complete augmentative and alternative communication evaluation by a speech pathologist

Numerous communication devices are available that vary in sophistication and complexity, ranging from simple and relatively inexpensive mechanical devices, such as alphabet or picture hoards, to specialized electronic devices such as a voice synthesizer.

Nutritional Care. Dysphagia and aspiration are distressing and dangerous complications of Al.S and are particularly prominent in the bulbar-onsct variety. As oral intake progressively declines, there is acceleration in weight loss and malnutrition, which not only aggtavates muscle weakness but also shortens survival. Therefore in every patient with Al.S, the nutritional status must be carefully evaluated at each visit. One of the best indicators of a change in nutritional status is a change in body weight. However, a detailed history of oral intake is also important, as is whether or not the patient has been coughing or choking during swallowing and whether there has been an increase in the duration of meals or an inability to finish meals. Although physicians can take such a history, evaluation by an experienced dietitian is often most helpful. Initially, patients should change the form and texture of their food and use a high-calorie food supplement, but eventually, such measures become insufficient to maintain the patient's weight, and proactive enteral tube feeding becomes imperative.

Percutaneous endoscopic gastroscopy (PEG) is a standard minor surgical procedure that not only improves quality of life but also prolongs survival by several months. Although it is a relatively simple surgery for otherwise healthy patients who have dysphagia, patients with ALS pose particular difficulties and often have impending respiratory failure that may complicate the procedure. The ALS Practice Parameters advocate placement of PEG tube in consenting patients with dysphagia, whose seated predicted forced vital capacity is more than 50% (Miller ct al. 1999). However, it has recently been shown in a small series of patients that a PEG may be performed for patients with a forced vital capacity of less than 50% predicted if noninvasive positive pressure ventilation is also used during the procedure (Gregory et al. 2002). It is important to emphasize that those who receive a PEG tube can continue to eat by mouth and that the purpose of enteral feeding is to provide calories and fluid and not merely to prevent aspiration. Indeed aspirarion is a continued risk to the patient even after PEG tube insertion, and if recurrent aspiration of PEG contents becomes a persistent problem, one can recommend percutaneous enteral jejunostomy (PEJ), which further reduces (but still does not eliminate) the risk.

Respiratory Care. Respiratory failure is the most common cause of death in ALS. Indeed, dyspnea-onset ALS presents with obvious ventilatory difficulties and it is for this reason that it harbors a particularly poor prognosis. However, it is important to make patients and family members aware that almost all forms of ALS will eventually be complicated by ventilatory failure, although symptoms may go largely unnoticed until relatively late in the disease course. It should he made clear to the patient that although positive pressure ventilation via a tracheostomy may indefinitely prolong life, there is no effect on the disease itself. In fact, by prolonging the natural history of the disorder, there is a strong possibility that atypical symptoms may arise, such as dementia, visual changes, sensory loss, and incontinence. Most patients and their physicians opt for the noninvasive approach. One technique, bilevel positive airway pressure ventilation (BiPAP), slows the rate of pulmonary decline, improves symptoms, and prolongs survival (Kleopa et a I. 1999; Ahoussouan et al. 2001). The current recommendation is that patients be offered noninvasive ventilatory assistance at the onset of dyspnea, when the forced vital capacity falls to less than 507o predicted, or a when a rapid rate of decline in pulmonary function occurs. However, it should be remembered that progressive weakness and wasting of perioral muscles would eventually prevent adequate use of the BiPAP mask; nasal pillows can be helpful in this circumstance and are often better tolerated than the mask at all stages. Furthermore, BiPAP does not prolong life indefinitely and these patients still face the difficult decision of whether to use an invasive ventilator. When the decision has been made to withdraw from ventilatory support, or when noninvasive means of ventilatory assistance are no longer sufficient, it is imperative that all attempts should be focused on effective and compassionate palliation. Judicious amounts of opioids, oxygen, and anxiolytics should be prescribed to allow the patients to live their final days with dignity and in as much comfort as possible.

Home Care and Hospice Care. When the patient's condition deteriorates, home care or admission to an alternative care site is required. Close collaboration among patients, their caregivers, home care nurses, and ideally the ALS clinic team will ensure effective and satisfying home care. When a patient has no caregiver, a site other than the home should he chosen for extended care. Hospice care provides highly effective palliative care to patients and their families. Just as important, hospice philosophy strongly affirms life so that patients who are in the terminal stages of their disease can maintain their independence and dignity to the gteatest degree possible.

Familial Amyotrophic Lateral Sclerosis

Between 5-10% of all ALS is familial, with the majority of cases being inherited in an autosomal dominant pattern. It is quite possible that the true frequency of FALS is an underestimate; anything less than a detailed family history may fail to identify an affected family member. ALS-1 is a form of late-onset motor neuron disorder that accounts for 15-20% of all cases of FALS (and thus 1-2% of all ALS) and is associated with mutations in the gene that encode SOD1 located on chromosome 21q21 (Siddique and Lalani 2002). Most cases are inherited in an autosomal dominant pattern, but a recessive variant has also been identified. ALS-2 is a rare, recessively inherited disorder mapped to a gene on chromosome 2q33 that encodes a novel protein that one group has dubbed a I sin. Al.S-4 and ALS-5 are also recessively inherited and have been mapped to chromosomes 9q2 l-q22 and 15ql5-q22, respectively. Fheir causative genes have yet to be identified. Most recently, a large European family has been identified with adult-onset autosomal dominant ALS linked to chromosome 18q21 (Hand et al. 2002). Fhis is currently classified in the ALS-3 category, but somewhat confusingly, ALS-3 has also been assigned to denote all familial cases that have yet to be linked to a chromosomal locus or associated with an inherited genetic mutation.

Autosomal Dominant Familial Amyotrophic Lateral Sclerosis

Genetics and Protein Chemistry

There are three SOD isoenzymes, termed SOD1, SOD2, and SOD5. The first of these, SOD1, is *A* cytosolic enzyme that scavenges the free radical by-products of oxidative respiration and is known to be important in the pathogenesis of some forms of FALS. Neither mitochondrial SOD2 nor extracellular SOD3 appears to be directly pathogenic in human ALS.

SOD1 is a 32-kd homodimeric protein encoded by a gene containing five exons located on chromosome 21, Faeb monomer contains one atom of copper and one of zinc. The zinc moiety maintains the dimer formation, which doubles the dismutasc activity. However, it is the copper within the active site that is important in catalyzing the conversion of 0_2~ to $Hi0_2$ and 0_2. SODl is ubiquitously expressed in every cell of every eukaryotic organism and its sequence and structure arc highly conserved. The biological importance of this protein is also evident in its great abundance within some cells; it accounts for as much ns 1% of nil protein of the CNS.

To date, more than 100 distinct point mutations have been found in all five exons of the SODl gene, the majority of which are missense mutations that usually result in the incorporation of a wrong amino acid into the gene product. Splice junction mutations, deletions, and insertions have also been detected in FALS (Siddique and Lalani 2002).

Pathogenesis

A simple pattern of loss of enzyme function has not been demonstrated in SODl-associatcd FALS. Mutant SODl proteins are often unstable, with activities ranging from completely normal or unaffected (aspartic acid replaced with alanine in codon 90) to entirely absent (glycine replaced with arginine in codon 85), and roral SODl enzyme activity correlates poorly with the severity of FALS. Moreover, SODl-knockout mice (animals genetically engineered to be born with no SODl proteins) are found to have no apparent motor neuron disease.

The weak association between enzyme activity and disease occurrence has led to an alternative hypothesis that there is a toxic gain of function in mutated SODl. Considerable support for this theory has come from cell culture and transgenic animal studies. Toxic gamed properties in human disease may arise from one or several processes (Cleveland and Rothstein 2001):

- Altered conformation of the copper-bound active site in mutant SODl protein may generate oxidative stress through an interaction with aberrant substrates such as hydrogen peroxide and peroxynitrite. Zinc-deficient mutant SODl may interact with nitric oxide to produce peroxynitrite, which in turn may cause harmful nitration of tyrosine residues on key intracellular proteins.
- Mutant SODl proteins have been shown to clump together as intracellular aggregates. These aggregates may interfere with proteasomal breakdown of ubiquirinatcd proteins or imp;vr axonal transport of various substances.
- SODl mutations may catalyze the inactivation of GIT I and thus cause excitotoxic cell injury via excessive influx of calcium into motor neurons. In addition, mutant SODl may also disturb calcium homeostasis through disruption of mitochondrial function.

- Both in vitro and in vivo research shows that mutant SOD1 protein is associated with enhanced programmed cell death (apoptosis). Increased expression or proapoptotic and reduced expression of antiapoptotic members of the bcl-2 family have been demonstrated in transgenic mutant SOD] mice. Furthermore, activated caspases, the effectors of apoptosis, have been demonstrated both in the anterior horn cells of transgenic SOD1 mice and in human ALS tissue. An experimental nonselective caspase inhibitor called *zVAD-fluorometbyl ketone* has been shown to prolong survival and improve motor performance in mutant SOD1 mice (Murray and Mitsumoto 2002).

Clinical features

There is a large degree of phenotypical variability in the expression of SODl-associated FADS, not only between different families but also between individual members of the same family. Furthermore, penetrance is rather variable and age dependent. Generally, the diagnosis of FALS can be established only by the fact that other family members in successive generations are or were affected by ALS, Unfortunately, a reliable history is not always available. The clinical features of individual FALS patients overlap considerably with those of patients with SALS, but there may be subtle differences between the two. For example, lower-limb onset is more common in FALS, whereas bulbar onset is rare. The age at onset for FALS averages at about 46 years, which is at least 10 years earlier than that of SALS; the male-to-female ratio is 1:1 in FALS but about 1.2-1.6:1 in SALS. Neuropathological analysis in FALS shows frequent posterior column involvement, although clinical signs for this pathological change are not usually apparent.

Certain clinical featutes arc often stereotypical within some families. For example, the two most common mutations, alanine replaced with valine at codon 4 in exon 1 (A4V) and histidine replaced with arginine at codon 43 in exon 2 (H43R), are associated with rapid progression, and most patients die within I year. In contrast, other mutations, such as histidine replaced with arginine at codon 46 in exon 2 (H46R) and glycine replaced with arginine at codon 37 in exon 2 (G37R), are associated with a disease duration averaging more than 15 years. SOD!-linked FALS presenting with predominantly LMN signs is associated with a mutation in which valine replaces leucine at codon 84 in exon 4 (L84V).

Auiosomal-Reeessivc and X-Linked Mutations

Substitution of aspartic acid with alanine at codon 90 in exon 4 (D90A) of the SOD1 gene can result in both autosomal dominant and recessive FALS. Although encountered worldwide, D90A FALS is particularly prevalent in Scandinavian countries where a common founder effect has been identified (Andersen et al. 1996). In Scandinavian counttics, the pattern of inheritance is autosomal recessive and only homo/.ygotes are clinically affected. Patients may present with atypical features such as sensory symptoms, urinary urgency, decubitus ulcers, posterior column dysfunction, and, rarely, ataxia,

Non-Scandinavian D90A families have been studied in Europe and the United States, in whom the pattern of inheritance is autosomal dominant. In these families, disease occurs in the heterozygous state, which suggests that Scandinavians may have a genetic protective factor on one or both gene copies that ensures normal cellular function until both alleles are affected.

X-linked dominant ALS, featuring a combination of both UMN and LMN signs, has been reported, the gene locus being on chromosome Xpll-Xq12 (Hong et al. 1998).

Juvenile familial Amyotrophic Lateral Sclerosis

An autosomal dominant form of juvenile-onset ALS has been mapped in one family to an interval of 5cM that harbors the ALS4 gene on chromosome 9q34, This autosomal dominant disorder, classified as ALS-4, typically manifests in the second decade of life (mean age is 17 years) with difficulty in walking, followed by weakness and wasting of intrinsic hand muscles and distal lower limbs. Progression is slow, so p; incuts become wheelchair bound by the sixth decade and sparing of bulbar musculature is a characteristic finding. An almost identical disorder has subsequently been described in three families diagnosed with distal HMN (spinal Charcot-Marie-Tooth disease). This disorder is also linked to the ALS4 locus. The authors have thus raised the possibility that ALS-4 and this HMN may be the same disorder (De jonghc et al. 2002).

Recessive juvenile ALS has been described in families of North African origin but is also present in Europe (ALS-5). The clinical syndrome is similar to SALS except for a younger age at onset. It has been linked to chromosome 15qlS-q22, but the pathogenic gene has not been identified.

Another juvenile recessive ALS syndrome, as yet unlinked to a chromosome site, has been described with a combination of both UMN and LMN signs. Symptoms and signs are more prominent in the lower extremities and bulbar function is spared,

Recessive juvenile ALS has also been mapped to chromosome 2q33 (ALS-2). Although it was originally described in consanguineous families from Tunisia, it has also been discovered in families from Saudi Arabia and Kuwait. The phenotype of this disorder varies according to the family of origin; in the Tunisian family, it presents as an ALS-iikc disorder with onset in the first or second decade of life; in the Kuwaiti family, the phenotype is similar to early onset PLS. Further work identified a new ALS gene called *ALS2* that encodes a protein that has been called alsin.

Sequence homology analysis of this protein suggests that it may function as a guanine-nucleotide exchange factor and thus be important in intracellular cell signaling and cytoskeleton organization. It appears that loss of function of this protein causes selective injury to motor neurons despite the fact that it is widely expressed in many tissue types. Furthermore, an ALS phenotype occurs when there is a onc-basc-pair deletion on exon 3, whereas a milder PLS presentation occurs in those with a rwo-base-pair deletion on exons 5 and 9. It has been proposed that the milder PLS phenotype occurs because of some residual function in a mutated longer protein product or an intact short protein product. Much has yet to he discovered about the structure and function of this protein, but the discovery of an ALS phenotype from a loss of function mutation, rather than a toxic gain of function, will likely lead to exciting new research into new models of ALS pathogenesis (Shaw 2001).

Amyotrophic Lateral Sclerosis-Parkinsonism-Dementia Complex (Western Pacific Amyotrophic Lateral Sclerosis)

In 1954, Mulder and colleagues described a disorder characterized by a combination of ALS and parkinsonism that was the most common cause of death in the adult-native Chamorro population on the Western Pacific island of Guam. A similar disorder was subsequently described in western New Guinea and the Kii peninsula of Japan, with an ALS incidence between 50 and 150 times than elsewhere. Clinically, about 5% of patients develop a predominantly ALS type of disorder, whereas 38% manifest principally with a combination of parkinsonism and dementia. The pathology of tins unusual disorder bears similarities to that of Alzheimer's disease (AD), with prominent loss of CNS neurons and the presence of abundant tau-immunoreactive neurofibrillary tangles. Alpha-synuclein pathology has recently been detected in the amygdala of affected brain tissue (Forman et al. 2002).

Multiple members of a single family may be affected, and it has recently been shown that fitst-degree relatives of patients with ALS-PDC have a significantly higher risk of developing the disease than controls. Despite these observations and a recent genetic association study implicating the tau gene as a susceptibility gene for ALS-PDC, accumulated epidemiological evidence MI ongb suggests that an environmental factor, rather than a genetic factor, is more important in disease pathogenesis, fhe incidence of the Guamanian ALS variant has rapidly declined over the past 50 years, a process thought to reflect the westernization of the region. Various environmental toxins have been implicated in the pathogenesis of ALS-PDC, chief among them being neurotoxins derived from the native cycad seed. This seed contains ^-methylamino [.-alanine (BMAA), an amino acid that is reversibly toxic to cortical and spina) motor neurons. They also contain a carcinogenic substance called *cycasin* that may act either alone or in concert with BMAA to damage motor neurons. Toxic sterol glucosides have recently been isolated from washed cycad flour, and it has been shown that they can cause the release of glutamate (Khabazian et al. 2002). Cox and Sacks (2002) have proposed a process of biomagnification of cycad toxins through the once popular Chamorro practice of eating flying foxes, which themselves feed on cycad seeds. The decline in the incidence of ALS-PDC may reflect the dwindling flying fox population on Guam through a massive increase in commercial hunting using firearms that were introduced to the island in the decades following World War II (Cox and Sacks 2002).

Spinocerebellar Ataxia Type 3 (Machado-Joseph Disease) (OMIM 109150)

Machado-Joseph disease is an autosomal dominant syndrome with onset varying from the third to seventh decade of life. Although cerebellar ataxia is the predominant clinical feature, patients with an early onset (age 20-30 years) often present with generalized spasticity and fasciculations of the face and tongue. Other characteristic findings include extrapyramidal signs, such as dystonia and rigidity, protuberant eyes, and progressive external ophthalmoparesis. Affected patients have a twofold to threefold expansion of a CAG trinucleotide on the ataxin-3 gene on chromosome 14q32.1. The expanded triplet repeat results in a mutant gene product containing an expanded polyglutamine tract, which appears to aggregate into intranuclear neuronal inclusion bodies and may interfere with (he function of the cellular proteasome in degradation of proteins (Schmidt et al. 2002). The Machado-Joseph disease phenotype may also occur in SCA-2, with slowly progressive ataxia, eyelid retraction, and facial fasciculations (Geschwind et al. 1997). Patients often have slow saccades or ophthalmoparesis and may have reduced or absent deep tendon reflexes. SCA-2 is caused by an expanded polygluta mine-encoding CAG triple repeat sequence on chromosome 12q.

Adult Hexosaminidase-A Deficiency (OMIM 606869)

Adult Hex-A deficiency is an autosomal recessively inherited late-onset GM_2 gangliosidosis (the other subtypes being infantile and juvenile). All three subtypes are caused by an abnormal accumulation of GM_2 ganglioside in neurons due to a deficiency in the activity of the lysosomal enzyme. Hcx-A is encoded by a gene on chromosome 15q23-q24 and normally degrades GM> ganglioside. Only about 10% of Hex-A activity is required for normal health, but in the severe infantile form of this disorder, also known as *Tay-Sacbs disease*, mutations in the w-subunit of Hex-A

result in complete deficiency of enzyme activity. Juveniles and adults with Hex-A deficiency, however, are compound heterozygotes with varying degrees of residual enzymnric activity and thus A deficiency is a later onset disorder with considerable variability in the phenotype.

The adult form may present as slowly progressive weakness of predominantly proximal muscles of the upper and lower extremities. In some patients, severe cramps may present in association with muscle weakness, mimicking SMA, In others, however, a combination of dysarthria, spasticity, and LMN signs may resemble ALS. Additional sensory, cerebellar, cognitive, psychiatric, and extrapyramidal features may later develop. The EDX may reveal prominent complex repetitive discharges and abnormal SNAPs. Generally, this constellation of symptoms and signs is not easily mistaken for ALS, but in the relatively early stages, patients with Hex-A deficiency may not manifest many features other than motor system dysfunction. Genetic counseling is important before assaying a patient's serum or leukocytes for deficiency of Hex-A activity.

Triple-A Syndrome (OMIM 231550)

Triple-A syndrome (Allgrove's syndrome) is a rare autosomal recessive disorder that derives its name from the combination of achalasia, dlacrima, and ddrenocorticotrophic insufficiency. The A A AS gene is located on chromosome 12ql3 and encodes a ubiquitous protein called *aladin*, which is heavily expressed in the neuroendocrine system and may be important in regulation of the cell cycle, cell signaling intracellular transport, and the cell cytoskeleton. The syndrome manifests a range of neurological problems, including mental retardation, optic atrophy, and seizures. A recent case report suggested that a further two A's be added to the name; they described a woman with additional features of autonomic disturbance (dry mouth, postural hypotension, and syncope) and bulbospinal amyotrophy (amyottophy of limbs and tongue with tongue fasciculations) (Goizet et al. 2002).

Disinhibhion-Dementia-Parkinsonism-Amyotrophy Complex (Wilhelmsen-Lynch disease) (OMIM 600274)

Disinhibition-dementi a-par kin son ism-amyotrophy complex (DDPAC) is an autosomal dominant progressive neurodegenerative disease described in a large Irish American family (family Mo) in the United States and is characterized clinically by disinbibited behavior (including excessive eating and inappropriate sexual behavior), personality changes, dementia, patkinsonian manifestations, and in two cases, amyotrophy with fasciculations. Autopsy studies showed widespread neuronal loss in the substantia nigra, cerebral cortex, and anterior horn of the spinal cord, together with extensive spongy degeneration in the temporal and frontal lobes. Subsequent research identified the presence of tau-immunorcactive inclusion bodies in affected regions of the CNS. Splice-site donor mutations in the gene encoding microtubule-associated protein tau are associated with DDPAC (Lynch et al. 1994).

Autosomal Dominant Frontotemporal Dementia with Motor Neuron Disease

Up to 5% of patients with SALS may also manifest overt signs of dementia, which is usually of the frontotemporal type. However, for more than half a century, various observers have pointed out that symptoms and signs of ALS and LTD appear to occur together in some families with increased frequency. A recent analysis of multiple pedigrees identified a locus for autosomal dominant ALS and FTD on chromosome 9q21-22. The mean age at disease onset in these families was about 54 years (range 40-62 years). Some patients developed symptoms and signs of ALS alone, but others also developed inappropriate behavior, impulsiveness, and eventually impaired memory. Both neuroimaging and pathological studies revealed frontotemporal atrophy and histology identified gliosis, vacuoles, rare Pick's bodies, and some neurofibrillary tangles and senile plaques (Hosier et al. 2000).

Adult Polyglucosan Body Disease

Polyglucosan body disease is a very rare, late-onset, slowly progressive disorder characterized by a combination of UMNand LMN signs, cognitive decline, distal sensory loss, and disturbances of bladder and bowel function. MRI of the brain may reveal diffuse white matter signal increase on T2-wcighted images. The diagnosis is clinched by the finding of characteristic pathological changes in tissue from peripheral nerve, cerebral cortex, spinal cord, or skin. Axons and neural sheath cells contain non-membrane-bound cytoplasmic periodic acid-Schiff-positive polyglucosan bodies. Ultrastructural examination shows that the inclusions consist of 6-8 nm branched filaments and arc most abundant in myelinated nerve fibers. In Ashkenazi Jewish patients (and one reported non-Ashkenazi Jewish patient), the disorder is caused by a deficiency of the glycogen-branching enzyme, but in other patient populations, this enzyme activity is normal. The recent (albeit inadvertent) generation of muscle polyglucosan bodies in a transgenic mouse engineered to overexpress glycogen synthase in the presence of normal levels of glycogen-branching enzyme suggests that an imbalance in the activities of these two enzymes is the possible molecular mechanism underlying this unusual disorder (Raben et al. 2001). It is interesting to note that two types of polyglucosan body may be seen in ALS, Lafora's bodies

and corpora amylacea, although neither is considered a characteristic pathological feature.

Paraneoplastic Motor Neuron Disease

There is evidence rhat motor neuron disease may rarely be a paraneoplastic phenomenon. Patients may present with features that are rather typical of pure "spinal" ALS or manifest in a manner akin either to PMA or PLS. Other motor neuron manifestations may represent only one part of a larger paraneoplastic syndrome, such as anti-Hu antibody associated encephalomyelitis, with atypical features such as dysautonomia or ataxia. Unfortunately, most paraneoplastic motor disorders are unresponsive to treatment of the underlying tumor. Rare motor disorders have been described in association with other paraneoplastic antibodies, including anti-Yo antibody in a patient with ovarian carcinoma, and a novel antincuronal antibody in a patient with breast cancer. A subacute, painless, and progressive LMN disorder has been well characterized in lymphoma (both Hodgkin's and non-Hodgkin's types). Patients may eventually develop UMN signs and some may improve either with treatment of the cancer or spontaneously. Elevated CSL protein levels or the presence of a paraprotein in the blood should prompt a detailed investigation for lymphoma. Although there is insufficient evidence to conclude that there is increased risk of cancer in ALS, a combination of UMN and LMN signs has been well described in patients with breast, uterine, ovarian, and non-small cell cancer. This ALS-like disorder is quite rapidly progressive and does not appear ro respond either to treatment of the underlying cancer or to immune therapies. UMN signs and symptoms that mimic PLS may rarely occur in patients with breast tumors and may in fact precede the cancer diagnosis by a few months. In general, one should invesiigate for a paraneoplastic disorder if there arc atypical features such as ataxia, sensory loss, and dysautonomia, and it would seem to be prudent to carry out bteast screening on women with a PLS presentation.

Viral Hypothesis and Human Immunodeficiency Virus Type 1-Associated Motor Neuron Disorder

Many viruses are neurotropic, that is, they have a unique capacity to gain access to and teplicate within cells of the CNS. As such, viral infection may be important in the pathogenesis of ALS. Of the many candidate viruses, greatest attention has been paid to enteroviruses (including pohovirus) and retroviruses. However, an as yet unidentified virus may be the culprit.

Although rare cases of patients who previously had poliomyelitis later present with a combination of both UMN and LMN degeneration, there is insufficient evidence to implicate poliovirus in the pathogenesis of ALS. However, other as yet unidentified enteroviruses may be important. One study identified enteroviral sequences in 88.3% of AI.S spinal cord tissue, but only 3.4% of control tissue (Berger et al. 2000).

Tt appears that retroviruses may be closely linked to motor neuron pathology. Using a highly sensitive reverse transcriptase assay, investigators showed that *59%* of patients in their study group with motor neuron disease were positive but only 3% of controls. However, their findings suggested that a novel retrovirus might be present because none of the usual human retroviruses such as HTV-1 or HTLV-1 was identified (Andrews et al. 2000). It is already known that HTI V-l can very rarely cause an ALS-mimic syndrome that may be clinically distinguished by the presence of sphincter disturbance. Indeed, certain protein sequences of both HTLV-1 and HTLV-2 have been detected with increased frequency in the peripheral blood lymphocytes ol pa lieu is with \\I.S.

A retrospective review of 1700 cases of HIV-1-infected patients with neurological symptoms identified 6 cases presenting as a reversible ALS-like syndrome (Moulignicr et al. 2001), representing a 27-fold increased risk of developing an ALS-like disorder in that particular HIV-1 patient population. Overall, patients were somewhat younger than the normal ALS population, all but one being younger than 40 yeats at the time of diagnosis. Onset was characteristically in a monomelic pattern followed by a very rapid spread to other regions over a period of weeks. There were clinical features of both UMN and LMN involvement, with fasciculations, cramps, and bulbar symptoms. Two patients also had rapidly progressive dementia, with other features suggesting an additional diagnosis of AIDS-dementia complex. Sensory and sphincter disturbances were not apparent. CSK protein levels were sometimes mildly increased and a lymphocytic pleocytosis was evident in three patients, but all remaining laboratory results il ll\ -1 sempositivit} apart were negative. l.D.X revealed a widespread disorder of anterior horn cells in the absence of dcmyelinating conduction block, and MRI in one patient showed diffuse white matter signal increase suggestive of AIDS-dementia complex. In each case, antiretroviral therapy was beneficial either in stabilizing or in two instances curing the disease. No similar cases have been identified in this patticular study population since the introduction of highly active antiretroviral combination chemotherapy in the management of HIV infection, Another case report found similar clinical features in a 32-year-old HIV-positive patient who also enjoyed a complete response to antiretroviral therapy. MRI of brain showed increased T2-weighted signal in the brachium pontis with some minimal contrast enhancement. The resolution of motor symptoms coincided with a lack of detectable HIV in plasma and CSF. In addition, the abnormal MRI signal almost completely resolved (MacGowan, Scelsa, and Waldron 2001). Other forms of HIV may also be related ro the pathogenesis of motor neuron

disease; a pure LMN syndrome was described in a woman who was seropositive for HIV-2,

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Chapter 81
Disorders of Nerve Roots and Plexuses

David A. Chad

DISORDERS OF NERVE ROOTS

The anterior and posterior nerve roots run from the spinal cord to the dorsal root ganglia, where they unite to form the spinal nerve. They are susceptible to diseases specific to their location and to many of the disorders that affect the peripheral nerves in general. Although surrounded by a rigid bony canal, they are delicate structures subject to compression and stretching. Bathed by cerebrospinal fluid (CSF), they may be injured by infectious, inflammatory, and neoplastic processes that involve the leptomeningcs. Separated from the blood by an incomplete blood-nerve barrier, the dorsal root ganglion (DRG) neurons may be injured by circulating neurotoxins.

In the clinical sphete, it is usually not difficult to recognize that a group of symptoms and signs is caused by a lesion of a nerve root. Radicular pain and paresthesias are accompanied by sensory loss in the dermatome (the area of skin innervated by one nerve root), weakness in the myotome (defined as muscles innervated by the same spinal cord segment and nerve root), and diminished deep tendon reflex activity at a segmental level subserved by the nerve root in question. When many roots are involved by a disease process (polyradiculopathy), however, the clinical picture may resemble a disorder of the peripheral nerves, as in a polyneuropathy, or of the anterior horn cells, as in the progressive muscular atrophy form of amyotrophic lateral sclerosis (ALS). Diagnosis therefore may become more difficult. Clinicians then turn to laboratory studies for help in arriving at a diagnosis.

A disorder of the nerve roots is favored by abnormalities of the CSF (raised protein concentration and pleocytosis), of the paraspinal muscle needle electromyographic (EMG) examination (presence of positive shatp waves and fibrillation potentials), and of spinal cord magnetic resonance imaging (MRI) (compromise or contrast enhancement of the nerve roots *per se).*

The sections that follow cover some anatomical features relevant to an understanding of the pathological conditions that affect the nerve roots, as well as specific nerve root disorders.

Anatomical Features

Each nerve root is attached to the spinal cord by four to eight rootlets, which arc splayed out in a longitudinal direction (Stewart 1993). The dorsal roots are attached to the spinal cord at a well-defined posterolateral sulcus. The ventral rootlets are more widely separated and emerge over a greater area. At each spinal cord segment, a pair of dorsal and ventral roots unite just beyond the DRG to form a short mixed spinal nerve, which divides into a thin dorsal ramus and a thicker ventral ramus (Figure 8 1.1). The dorsal ramus innervates the deep posterior muscles of the neck and trunk (the paraspinal muscles) and the skin overlying these areas. The ventral ramus (the large anterior branch) contributes to the cervical, brachial, or lumbosacral plexus and thereby supplies the limb muscles.

The nerve roots lie freely in the subarachnoid space covered by a thin root sheath, which is a layer of flattened

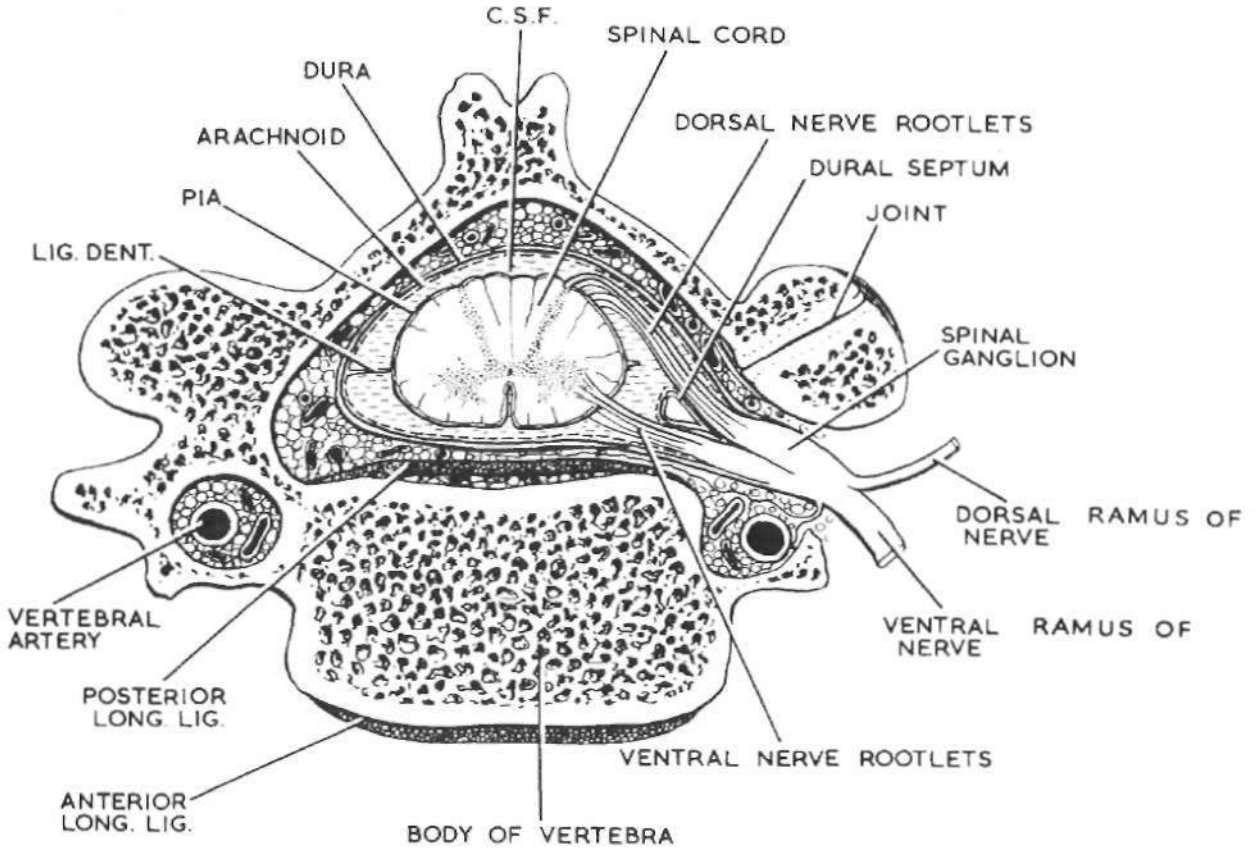


FIGURE 81.1 Relations of dura to bone and roots of nerve shown in an oblique transverse section. On the right, the telations between the emergent nerve and the synovial joint are seen, hut the joint between the vertebral bodies is not in the plane of the section. The dorsal and ventral roots meet at the dorsal root ganglion in the intervertebral foramen to form the mixed spinal nerve. The small dorsal ramus is the most proximal branch of the mixed spinal nerve and serves the cervical paraspinal muscles (not shown). The dura becomes continuous with the epineurium of the mixed spinal nerve at the intervertebral foramen. The posterior longitudinal *{Lung.)* ligament *{Lig.)* helps contain the intervertebral disc {not shown), preventing protrusion into the spinal canal. (C.S.F. = cerebrospinal fluid; Lig. dent. = ligament dentate.) (Reprinted with permission from Wilkinson, M. 1971, *Cervical Spondylosis: Its Early Diagnosis and Treatment,* WB Saunders, Philadelphia.)

cells continuous with the pial and arachnoidal coverings of the spinal cord. They lack the epineurial and perineuria] coverings found in peripheral nerves. Compared with spinal nerves, the roots have many fewer connective tissue cells in the endonenrium and considerably less collagen. A capillary network derived from the radicular arteries provides the blood supply to the spinal nerve roots (Levin 2002 .

Where the nerve roots form the mixed spinal nerve, the pial covering of the root becomes continuous with spinal nerve perineurium, and nerve takes the dutal nerve root sheath through the intervertebral foramen to become continuous with the epineurium of the mixed netve. At the intervertebral foramen, the root-DRG-spinal nerve complex is securely attached by a fibrous sheath to the transverse process of the vertebral body. In general, the DRG is located in a protected position within the mien. encbijl hii.uimu. hut ;it !:unhnr and S.KT;I1 levels, the DRG resides proximal to the neural foramina, in an intraspinal location (Levin 2002). There, they may be vulnerable to disc herniation and the complications of osteoarthritis (vide infra).

Nerve fibers, together with their meningeal coverings, occupy 35-50% of the cross-sectional area of an intervertebral foramen. The remaining space is occupied by loose areolar connective tissue, fat, and blood vessels. On computed tomographic (CT) and MRI scans, the fat acts as an excellent natural contrast agent that defines the thecal sac and nerve roots, allowing detection of nerve root compression.

The dorsal roots contain sensory fibers that are central processes of the unipolar neurons of the DRG, On reaching the spinal cord, these fibers either synapse with other neurons of the posterior horn or pass directly into the posterior columns. In the ventral root, most fibers ate essentially direct extensions of anterior horn motor neurons (alpha, beta, and gamma) or of neurons in the in ter mediolateral horn (preganglionic sympathetic neurons found in

lower cervical and thoracic segments). In addition, ventral roots contain a population of unmyelinated and thinly myelinated axons, which come from sensory and sympathetic ganglia (Hildebrand, Karlsson, and Risling 1997].

There are 31 pairs of spinal nerves that run through the intervertebral foramina of the vertebral column: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal (Figure 81.2). A feature of clinical relevance is the pattern formed by the lumbar and sacral roots as they leave the spinal cotd and make their way to their respective DRG to form spinal nerves (see Figure 81.2). In the adult, the spinal cord is much shorter than the spinal column, ending usually between LI and 1.2. Therefore the lumbar and sacral roots descend caudally from the spinal cord to reach the individual intervertebral foramina, forming the cauda equina; the concentration of so many nerve roots in a confined area makes this structure vulnerable to a range of pathological processes (vide infra).

Traumatic Radiculopathies

Nerve Root Avulsion

The spinal roots have approximately one tenth the tensile strength of the peripheral nerves because of lesser amounts of collagen and the absence of epineurial and penneurial sheaths in the roots. Therefore the nerve roots are the weak link in the nerve root-spinal nerve-plexus complex, and nerve root avulsion from the spinal cord typically results from a severe traction injury. Ventral roots are more vulnerable to avulsion than dorsal roots, a consequence of the dorsal roots having the interposed DRG and a thicker dural sheath. In most cases, root avulsion occurs in the cervical region. Lumbosacral nerve root avulsions are rare with only 35 cases reported between 1955 and 1996 and when they occur are generally associated with fractures of the sacroiliac joint with diastasis of the symphysis pubis or fractures of the pubic rami (Chin and Chew 1997).

In most cases, avulsion at the level of the cervical roots results in two distinct clinical syndromes. One is Erb-Duchenne palsy, in which the arm hangs at the side internally rotated and extended at the elbow because of paralysis of C5- and C6-innervated muscles (the supraspinatus and infraspinatus, deltoid, biceps). The second is Dejcrine-Klumpke palsy, in which there is weakness and wasting of the intrinsic hand muscles with a characteristic claw-hand deformity because of paralysis of C8- and Tl-innervated muscles. Injuries responsible for Erb-Duchenne palsy are those that cause a sudden and severe increase in the angle between the neck and shoulder, generating stresses that are readily transmitted in the direct line along the upper portion of the brachial plexus to the C5 and *C6* roots. Today, motorcycle accidents are the most common causes of this injury, but the incidence of C5 and C6 root avulsions in the newborn during obstetrical

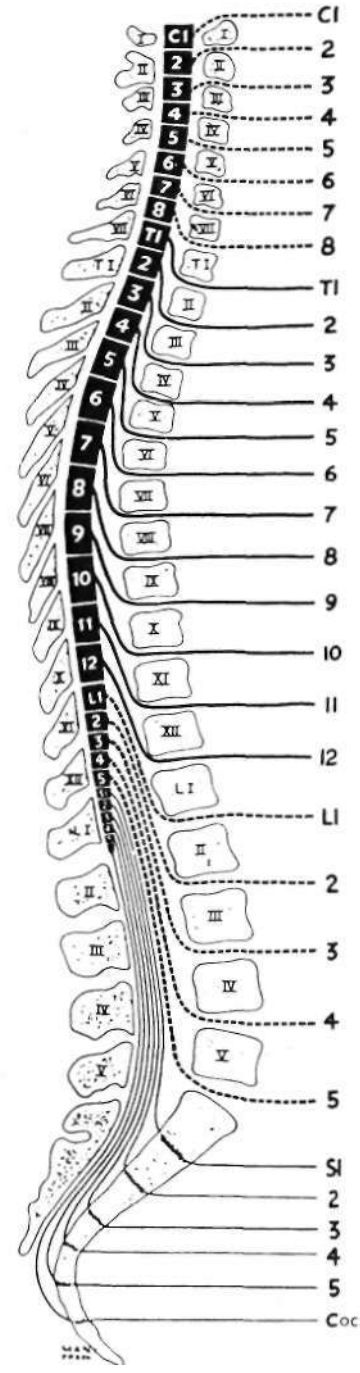


FIGURE 81.2 The relationship of spinal segments and nerve roots to the vertebral bodies and spinous processes in the adult. The cervical roots CI in *i',7* (i.e., all except C8) exit through foramina above the vertebral body of the same number. The C8 root passes through the C7-T1 neural foramen and all thoracic, lumbar, and sacral roots leave the spinal canal below the body of the vertebrae of the same number. The spinal cord is shorter than the spinal column, ending between vertebral bodies 1.1 and L2, The lumbar and sacral roots form the cauda equina and descend caudally, beside and below the spinal curd, ro exit at the intervertebral foramina. (Reprinted with permission from Haymaker, W. Si Woodhall, B. 1953, *Peripheral Nerve Injuries,* 2nd ed, WB Saunders, Philadelphia.)

procedures is increasing with the decline in the use of cesarean section. Brachial plexus injuries in the newborn are discussed in Chapter 86. The Dejerine-Klumpke palsy occurs when the limb is elevated beyond 90 degrees and tension falls directly on the lower trunk of the plexus, C8, and Tl roots. Such an injury may occur in a fall from a height in which the outstretched arm grasps an object to arrest the fall, leading to severe stretching of the C7, C8, and Tl roots.

Clinical Features and Diagnosis. At the onset of root avulsion, flaccid paralysis and complete anesthesia develop in the myotomes and dermatomes served by ventral and dorsal roots, respectively. Clinical features supplemented by electrophysiological and radiological studies help determine whether the cause of severe weakness and sensory loss is root avulsion or an extraspinal plexus lesion. For example, C5 root avulsion results in virtually complete paralysis of the rhomboids and spinatus muscles (innervated primarily by C5) and a varying degree of weakness of the deltoid, biceps, brachioradialis, and serratus anterior {which receive additional innervation from C6). A clinical sign of Tl root avulsion is an ipsilateral Horner's syndromi- caused by damage to preganglionic sympathetic fibers as they traverse the ventral root to their destination in the superior cervical ganglion.

The electrophysiological tests include the measurement of a sensory nerve action potential (SNAP) and needle EMG examination of the cervical paraspinal muscles. In the setting of an isolated C5 root avulsion, the SNAP should be preserved, despite complete anesthesia in the dermatome because the peripheral axons and the DRG cell bodies remain intact. Needle EMG of the cervical paraspinal muscles permits separation of damage of the plexus and of ventral root fibers because the posterior primary ramus, which an-:--. |HM lic\nid LV l)R(, ami proximal re tinplexus as the first branch of the spinal nerve, innervates these muscles (see Figure 81.1). Thus cervical paraspinal fibrillation potentials support the diagnosis of root avulsion. Paraspinal muscles have also been evaluated radiologically in the setting of root avulsion. Contrast-enhanced MRI studies of the cervical paraspinal muscles showing severe atrophy were accurate in indicating root avulsion injuries, and abnormal enhancement in the multifidus muscle was the most accutatc among paraspinal muscle findings (Hayashi et al. 2002), Intraspinal neuroimaging using postmyelographic CT or MRl usually demonstrates an outpouching of the dura filled with contrast or CSF at the level of the avulsed root. This post-traumatic meningocele results from tears in the dura and arachnoid sustained during root avulsion. Postmyelographic CT with 1- to 3-mm axial slices provides accurate diagnosis on the status of nerve roots in 85% of patients, compared to 52% for MRI (Carvalho et al. 1997). Gadolinium-enhanced MRI appears to offer a promising noninvasive means to evaluate traumatized nerve roots by visualizing the spinal cord surface at the root entry /one ("root-stump" enhancement) and by noting enhancement of intradural nerve roots (Hayashi et al. 1998}.

In most cases, these tests are helpful in ascertaining whether root avulsion has occurred. Sometimes, however, clinical assessment is difficult and results of testing are ambiguous. The physical examination may be limited because of severe pain. An absent SNAP indicates sensory axon loss distal to the ORG but docs not exclude coexisting root avulsion. Even when rhis test of sensory function points to avulsion of the dorsal component of the root, the status of the ventral root may remain uncertain if paraspinal fibrillation potentials are not found. There arc two reasons for their absence: First, they do not appear for 7-10 days after the onset of axonotmesis, and second, even if the timing of the needle EMG is right, they may not be seen because of innervation of the paraspinal muscles from multiple segmental levels. Finally, imaging studies are nor always diagnostically accurate, at times disclosing classic post-traumatic meningoceles in patients without root avulsion (but only dura] tear) or revealing normal findings in true root avulsion (dc Verdier, Collctti, and Terk 1993). The difficulty in establishing a definitive diagnosis of root avulsion based on FMG and ncuroiinaging in some cases has led to a potentially important role for intraoperative evoked potentials to establish whether the root in question is in continuity (Oberle et al. 1998).

Treatment. Root avulsion produces a severe neurological deficit that has long been considered an unbeatable injury. Carlstedt et al. (1995), however, repotted on a patient who had an avulsion injury involving C6-T1 in whom they were able to implant successfully two ventral roots (C6, directly; and C7, via sural nerve grafts) into the spinal cord through slits in the pia mater. The surgical treatment of patients with avulsion injuries is an area of active ongoing investigation with the promise that if continuity between spinal cord and nerve roots can be restored, subsequent recovery of function may be possible (Fournier et al. 2001). Until repair of spinal nerve roots has become a more effective and reliable procedure, other approaches to management will be needed. When paralysis of the limb is complete, amputation may be indicated. With a less profound degree of injury, muscle and tendon transplants are sometimes used. In the case of a more restricted injury affecting only the low cervical roots and T1, eatly below-elbow amputation plus a below-elbow prosthesis has been recommended. The sometimes intractable pain of cervical root avulsion injuries may be successfully treated with dorsal root entry zone coagulation procedures (Samii et al. 2001).

Disc Herniation

beginning in I he third or fourth decade of life, cervical and lumbar intervertebral discs are liable to herniate into the

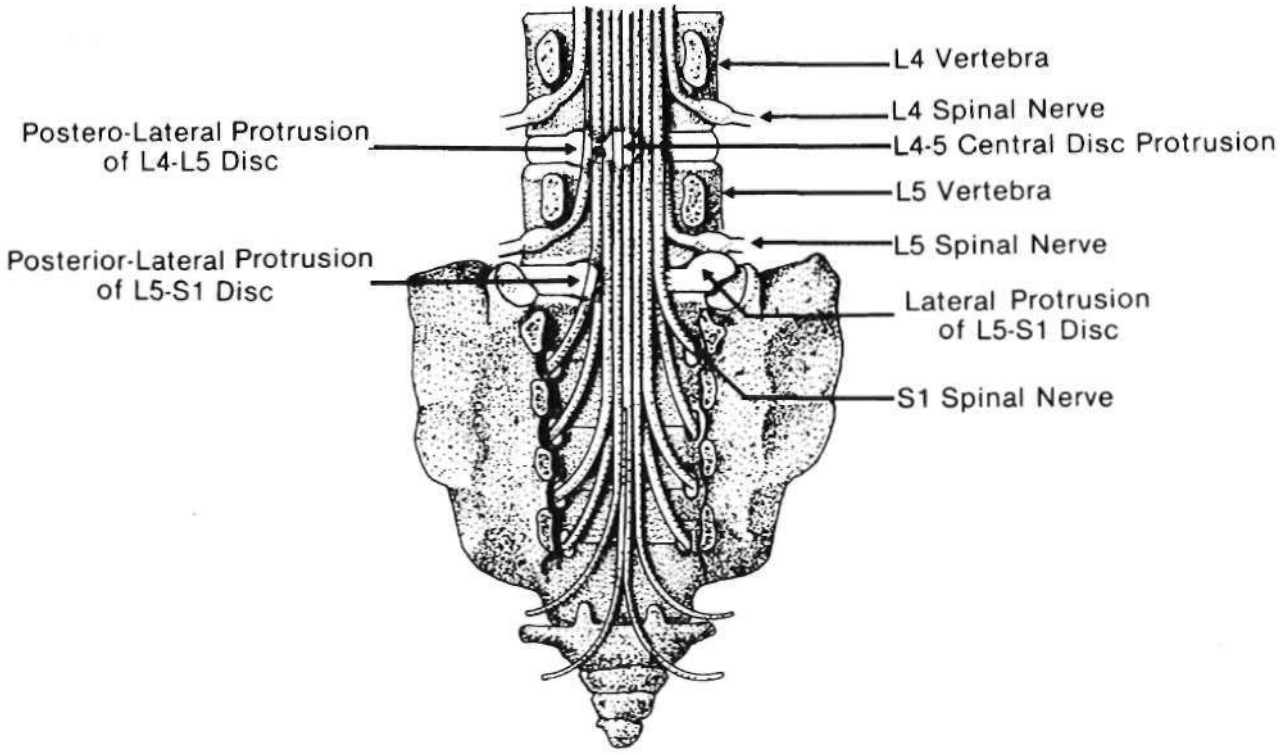


FIGURE SI.3 Dorsal view of the lower lumbar spine and sacrum, showing the different types of herniations and how different routs and the cauda equina an be compressed. (Reprinted with permission from Stewart, J. D. 1993, *focal Peripheral Neuropathies,* 2nd cd, Raven Press, New York.)

spinal canal or intervertebral foramina and impinge on the spinal cord (in the case of cervical disc herniations), nerve roots (in both cervical and lumbosacral regions), or both (at the cervical level, where on occasion large central and paracentral disc herniations may produce a myeloradiculopathy) (see Chapter 79). Two factors contribute to this alteration in the intervertebral discs: degenerative change and trauma. The fibers of the annulus fibrosus that surround the nucleus pulposus lengthen, weaken, and fray with age and use, thereby allowing the disc to bulge posteriorly. In the setting of such changes, relatively minor ttauma leads to further tearing of annular fibers and ultimately to herniation of disc material. This "soft-disc" herniation occurs mainly during the third and fourth decades of life when the nucleus is still gelatinous. In fact, although disc herniations may be preceded by unaccustomed strain or direct injury, in many instances, there is no history of clinically significant trauma preceding the onset of radiculopathy.

Reinforcing the annulus fibrosus posteriorly is the posterior longitudinal ligament, which in the lumbar region is dense and sttong ccnttally and less well developed in its lateral portion. Because of this anatomical feature, the direction of lumbar disc herniations tends to be posterolateral, compressing the nerve roots in the lateral recess of the spinal canal, I.ess commonly, more lateral (foraminal) herniations compress the nerve root against the vertebral pedicle in the intervertebral foramen (Figure 81.3). On occasion, the degenerative process may be particularly severe. This leads to large rents in the annulus and posterior longitudinal ligament, thereby permitting disc material to herniate into the spinal canal as a free fragment with the potentially damaging capacity to migrate superiorly or inferiorly and compress two or more nerve roots of the cauda equina. Most cervical disc herniations are posterolateral or foraminal.

In the cervical and lumbar regions, alteration in the integrity of the disc space is a component of a degenerative condition, tetmed *spondylosis,* characterized by osteoarthritic changes in the joints of the spine, the disc *per se* (desiccation and shrinkage of the normally semisolid, gelatinous nucleus pulposus) and the facet joints. [mmunohistochemica! examination of herniated cervical discs points to an inflammatory process associated with neovascularization and increased expression of matrix mctalloproteinase and inducible nitric oxide (NO) synthetase (Furusawa ct al. 2001), The release of NO by disc cells may contribute to the process of disc degeneration by inducing apoptosis of disc cells (Kohyama et al. 2000). Because it spawns osteophyte formation, spondylosis leads to compromise of the spinal cord in the spinal canal and the nerve roots in the i met vertebral foramina. The restriction in the dimensions of these bony canals may be exacerbated by thickening and hypertrophy of the ligamentum flavum,

which is especially detrimental in patients with congenital cervical or lumbar canal stenosis.

In the cervical region, nerve root compression in patients older than 50 years is often caused by disc herniation superimposed on chronic spondylotic changes. Isolated "soft" cervical disc herniation tends to occur in younger people in the setting of neck trauma. In the lumbosacral region, isolated acute disc herniation is a common cause of radiculopathy in the younger patient (<40 years), whereas bony root entrapment with or without superimposed disc herniation is the more typical cause of lumbosacral radiculopathy in the patient older than 50 years.

Clinical Features. Root compression from disc herniation gives rise to a distinctive clinical syndrome, which in its fully developed form comprises radicular pain, dermatomal sensory loss, weakness in the myotome, and reduction or loss of the deep tendon reflex subserved by the affected root. Nerve root pain is variably described as knifclike or aching and is widely distributed, projecting to the sclerotome (defined as deep structures, such as muscles and bones innervated by the root). Typically, root pain is aggravated by coughing, sneezing, and straining at stool movement (actions that produce Valsalva maneuver and raise intraspinal pressure). Accompanying the pain are paresthesias referred to the specific dermatome, especially to the distal regions of the dermatomes; indeed, these sensations sttongly suggest that the pain has its origins in compressed nerve roots, rather than spondylotic facet joints. Sensory loss caused by the compromise of a single root may be difficult to ascertain because of the overlapping tetritories of adjacent roots, although loss of pain is usually more easily demonstrated than loss of light touch (Figure 81.4).

Most radiculopathies occur in the lumbosacral region; compressive root lesions in this area account for 62-90% of all radiculopathies. Cervical radiculopathies are less common, comprising 5-36% of all radiculopathies encountered.

In the lumbosacral region, 95% of disc herniations occur at the L4-L5 or L5-S1 levels; L3-L4 and higher lumbar disc herniations are very uncommon (Stewart 1993; Deyo and Weinstein 2001). Knowing that the L4 root exits beneath the pedicle of L4 through the 1,4-1.5 foramen and that 1,5

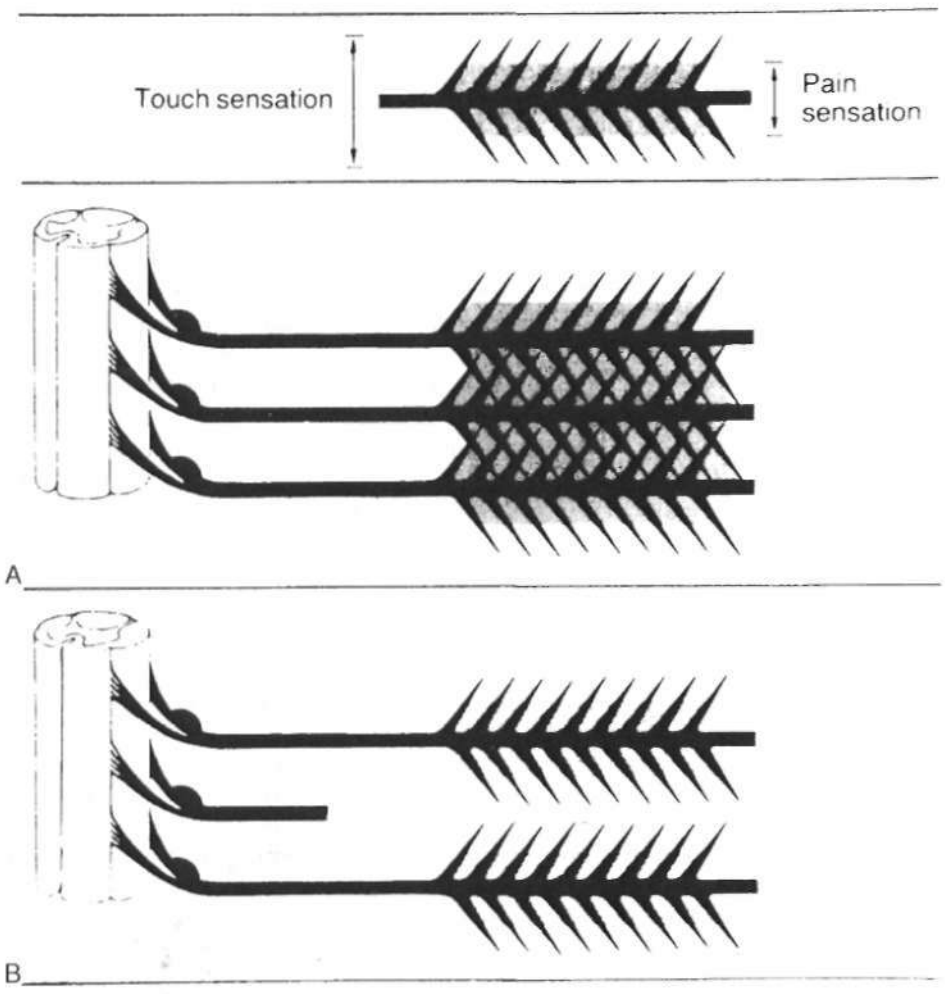


FIGURE 81.4 The zones of radicular touch and pain sensation. The area for rouch sensation *{hatched)* supplied by one single roor is wider than the area of pain sensation *(gray).* The areas of pain sensation do not overlap or at most overlap incompletely, whereas the areas of touch sensation of a single root are completely overlapped by those of the ulj.H'cir roiiK i A). A.V(>IV,111:-1\ . monoradicular lesions (B) produce a hypalgesic or analgesic zone while touch sensation remains intact or only minimally impaired. Only after tw» roots are involved is an anesthetic zone present. (Reprinted with permission from Mumenthaler, M. & Schliack, H. *1991, Peripheral Nerve Lesions. Diagnosis and Therapy,* Thieme, New York.)

exits through the L5-S1 foramen, one might predict that disc herniation at these levels would generally compress the L4 and L5 roots, respectively (see Figure 81.3). In perhaps only 10% of cases of the disc herniating far laterally into the foramen is there compression of the exiting nerve root. More commonly, the posterolateral disc herniation compresses the nerve root passing through the foramen below that disc. Thus 1.4-1.5 and 1.5-SI herniations usually produce 1.5 and SI radiculopathies, respectively.

In an SI radiculopathy, pain radiates to the buttock and down the back of the leg (classic sciatica), often extending below the knee; paresthesias are generally felt in the lateral ankle and foot. The ankle jerk is generally diminished or lost, and weakness may he detected in the plantar flexors and gluteus maxinms.

In an 1.5 radiculopathy, the distribution of pain is similar, but paresthesias are felt on the dorsum of the foot and the outer portion of the calf. The ankle reflex is typically normal, but there may be reduction of the medial hamstring reflex. Weakness may be found in L5-inncrvated muscles served by the peroneal nerve, including the extensor hallucis longus, tibialis anterior and peronei, as well as the tibialis posterior (served by the tibial nerve) and the gluteus medius (innervated by the superior gluteal nerve). Weakness may be restricted to the extensor hallucis longus. A positive straight-leg-raising test result is a sensitive indicator of 1.5 or SI nerve root irritation. The test is deemed positive when the patient complains of pain radiating from the back into the buttock and thigh with leg elevation to less than 60 degrees. The test result is positive in *95%* of patients with a proven disc herniation at surgery. A less sensitive but highly specific test is the crossed straight-leg-raising test, when the patient complains of radiating pain on the affected side with elevation of the contralateral leg.

The less common L4 radiculopathy is characterized by pain and paresthesias along the medial aspect of the knee and lower leg. The patellar reflex is diminished, and weakness may be noted in the quadriceps and hip adductors (innervated by the femoral and obturator nerves, respectively). When large herniations occur in the midline at either the L4-L5 or the 1.5-SI level, many of the nerve roots running past that level to exit through intervertebral foramina below that level may be compressed, producing the cauda equina syndrome of bilateral radicular pain, paresthesias, weakness, and attenuated reflexes below the disc level, as well as urinary retention. This is a surgical emergency requiring urgent decompression.

In the cervical region, it is likely that the high degree of the greater mobility at levels C5-C6 and C6-C7 promotes the development of cervical disc degeneration with annulus fraying and subsequent disc protrusion. Cervical nerve roots emerge above the vettebra that shares the same numerical designation. Therefore C7 exits between C6 and C7, and spondylotic changes with or without additional acute disc herniation would be expected to compress the C7 nerve root. Similarly, disc protrusion at C5-C6 and C7-T1 would compress the C6 and C8 roots, respectively. In the classic study of Yoss et al. (1957), clinical and radiological evidence of radiculopathy was found to occur most often at C7 (70%), less frequently at C6 (19-25%), uncommonly at C8 (4-10%) and C5 (2%). Radiculopathy involving the Tl root is a clinical rarity (Levin 1949).

Involvement of C6 is associated with pain at the tip of the shoulder radiating into the upper part of the arm, lateral side of the forearm, and thumb. Paresthesias arc felt in the thumb and index finger. The brachioradialis and biceps reflexes are attenuated or lost. Weakness may occur in the muscles of the *C6* myotome supplied by several different nerves, including the biceps (musculocutaneous nerve), deltoid (axillary nerve), and pronator teres (anterior interosseus branch of the median nerve). The clinical features of C5 radiculopathies are similar, except that the rhomboids and spinatus muscles are more likely to be weak.

When the C7 root is compressed, pain radiates in a wide distribution to include the shoulder, chest, forearm, and band. Paresthesias involve the dorsal surface of the middle finger. The triceps reflex is usually reduced or absent, A varying degree of weakness usually involves one or more muscles of the C7 myotome, especially the triceps and the flexor carpi radialis. Less common C8 root involvement presents a similar clinical picture with regard to pain. Paresthesias, however, are experienced in the fourth and fifth digits, and weakness, when it occurs, affects muscles innervated by several nerves, including finger extensor muscles (posterior intcrosseus branch of radial nerve), finger abductors and adductor muscles (ulnar nerve), and thumb abductor and opposer muscles (median nerve).

Diagnosis. Diagnosis is aided by a variety of imaging techniques, including plain radiography, myelography, CT myelography, and MRI (sec Chapter .37). Although plain radiography is not helpful in the identification of herniated disc *per se,* in both the cervical and the lumbar area, it reveals spondylotic changes when present. It also may be useful in the identification of less common disorders that produce radicular symptoms and signs, such as bony metastases, infection, fracture, and spondylolisthesis.

In the cervical region, the best methods for assessing the relationship between neural structures (spinal cord and nerve root) and their fibro-osscous surroundings (disc, spinal canal, and foramen) arc postmyelography CT (unenhanced CT reveals little more than the presence of bony changes) and MRI. MRI is equivalent in diagnostic capacity to postmyelography CT and therefore is preferred. In the lumbosacral region, CT is an effective method ot evaluation of disc disease, but when available, **MRI** is considered the superior imaging study because of excellent

resolution; multiplanar imaging; the ability to see the entire lumbar spine, including the conns; and the absence of ionizing radiation.

A variety of ncurophysiologicnl tests are used to assess patients with disc herniation, including motor and sensory nerve conduction studies, late responses, somatosensory evoked potentials, nerve root stimulation, and needle electrode examination. Sensory conduction studies are useful in the evaluation of a patient suspected of radiculopathy because SNAPs are typically normal (because of the lesion being rostral to the DRG in the intervertebral foramina) even in the face of clinical sensory loss, in contrast to the situation in plcxopathy and peripheral nerve trunk lesions, where SNAPs are attenuated or absent. In the specific instance of L5 radiculopathy, however, because the I "i l')K(! may rcsua- proximal to the neural foramen (vide supra), if intraspinal pathology is severe enough, compression of the 1.5 DRG may lead to loss of the superficial peroneal nerve SNAP (Levin 199S).

Needle EMG is the most useful procedure in the diagnosis of suspected radiculopathy. A study is considered positive if abnormalities {especially acute changes of denervation, including fibrillation potentials and positive sharp waves) are present in two or more muscles that receive innervation from the same root, preferably via different peripheral nerves; no abnormalities should be detected in muscles innervated by the affected root's rostral and caudal neighbors. Reduced motor unit potential (MUP) recruitment (manifested by decreased numbers of MUPs firing at an increased rate) and MUP abnormalities of reinnervation (high-amplitude, increased duration, poly phasic potentials) are also sought by the needle electrode but are not as reliable as fibrillation potentials in establishing a definitive diagnosis of radiculopathy. Absence of fibrillation potentials docs not, however, exclude the diagnosis of radiculopathy. Two main reasons for this exist. First, examination in the first 1-3 weeks after onset of nerve root compromise may be negative because it takes approximately 2 weeks for these potentials to appear, (At the early stages in the process of nerve root compression, the only needle electrode examination manifestation of radiculopathy might be reduced MUP recruitment resulting from either axon loss, conduction block, or both.) Second, fibrillation potentials disappear as denervated fibers arc rcinnervated by axons of the same or an adjacent myotome beginning 2-3 months after nerve root compression (Figure 81.5). (Thus in the later phases of nerve root compression, the only needle EMG changes indicative of radiculopathy might be

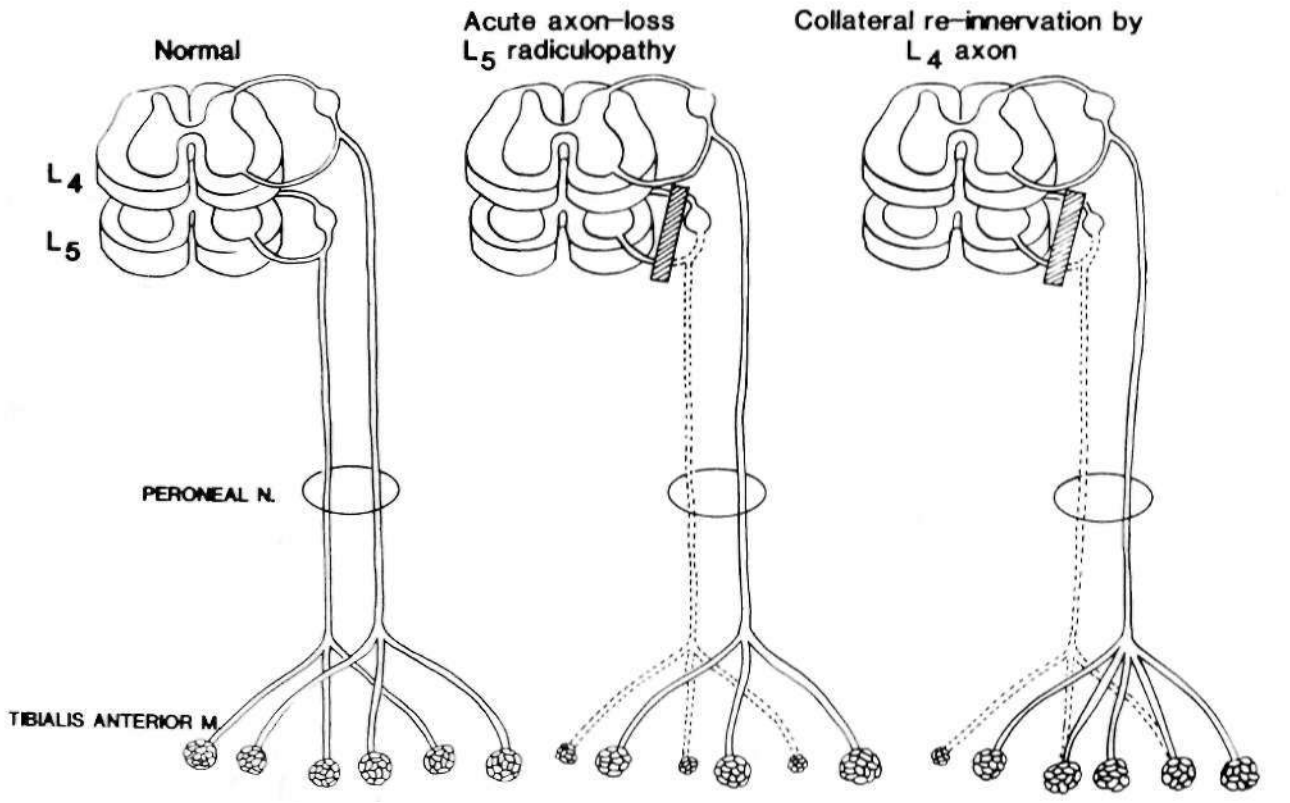


FIGURE 81.5 Diagram illustrating how muscle (M.) fibers denervated by a radiculopathy are reinnervated by collateral sprouting despite persisting root compression, (N, = nerve,) (Reprinted with permission from Wilbourn, A. J. 6i Aminoff, M. J. 1988, "The electrophysiologic examination in patients with radiculopathies," *Muscle Nerve,* vol. 11, pp. 1099-1114.)

chronic neurogenic changes of reduced recruitment and MUP remodeling.) The distribution of fibrillation potentials is relatively stereotyped for C5, C7, and C8 radiculopathies, whereas C6 radiculopathy has the most variable presentation; in one half of patients, the findings are similar to C5 radiculopathy, whereas in the other half, findings are identical to C7 radiculopathy (Levin, Maggiano, and Wilbourn 1996). A patient with the uncommon disc compression of Tl was found to have-isolated fibrillation potential activity of the abductor pollicis brevis (Levin 1999).

Treatment. For cervical disc protrusion and spondylotic radiculopathy, the mainstay of treatment is conservative management—a combination of a period of reduced physical activity with use of a soft cervical collar, physiotherapy, and ahti-inflammatory and analgesic agents. Most patients improve, even those with mild to moderate motor deficits. Indeed, in some cases herniated cervical discs have been observed to regress on MRI images; a circumstance that appears more likely to occur if disc material has extruded and becomes exposed to the epidutal space (Mochida et al. 1998). Although there appears to be a short-term benefit to surgical decompression of an affected nerve root with regard to pain, weakness, or sensory loss, at 1 year, there is no significant difference between the outcome of surgical or conservative management (Fonyas et al. 2001). A surgical approach may be warranted, however, in selected cases: (1) if thete are clinical and radiological signs of an accompanying new onset of myelopathy, (2) if there is untenanting pain despite an adequate trial of conservative management, or (3) if there is progressive weakness in the territory of the compromised nerve root.

In the lumbosacral region, disc herniation and spondylotic changes respond to conservative management in more than 90% of patients. Bed rest had been recommended as the centerpiece of patient care, but controlled trials have demonstrated that back-strengthening exercises under the direction of a physical therapist, performed within the limits of the patient's pain, result in more rapid resolution of pain and return to normal function (Vroomcn et al. 1999). Follow-up MRI studies in conservatively managed patients indicate reduction in size or disappearance of herniated nucleus pulposus corresponding to improvcmenl in clinical findings (Komori ct a I. 1996). Epidural corticosteroid injection may help relieve pain but does not improve neutological function or reduce the need for surgery (Carette et al. 1997). Three situations occur, however, in which surgical referral is indicated: (1) in patients presenting with cauda equina syndtome (for which surgery may be required urgently), (2) if the neurological deficit is severe or progressing, or (3) if severe radicular pain continues after 4-6 weeks of conservative management.

Diabetic Polyradiculoneuropathy

Diabetic neuropathies can be classified anatomically into two major groups: symmetrical polyneuropathies and asymmetrical focal or multifocal disorders. Examples of the latter include the cranial mononeuropathies and the conditions covered in this section: thoracoabdominal and lumbosacral polyradiculoneuropathies. Though treated separately in the following paragraphs, they often coexist in an individual patient. Occasionally, a similar syndrome can occur in the cervical roots.

When there is predominant involvement of the thoracic roots, the presenting symptoms are generally pain and paresthesias of rapid onset in the abdominal and chest wall. The trunk pain may be severe, described variably as burning, sharp, aching, and throbbing. It may mimic the pain of acute cardiac or intra-abdominal medical emergencies and may simulate disc disease, but the rarity of thoracic disc protrusions and the usual development of a myelopathy help exclude this diagnosis. Findings of diabetic thoracoabdominal polyradiculoneuropathy include heightened sensitivity to light touch over affected regions; patches of sensory loss on the anterior, lateral, or posterior aspects of the trunk; and unilateral abdominal swelling due to localized weakness of the abdominal wall muscles (Longstreth 1997).

Diabetic lumbosacral polyradiculoneuropathy involves the legs, especially the anterior thighs, with pain, dysesthesia, and weakness, reflecting rhe major involvement of upper lumbar roots. A variety of names have been used to describe it, including *diabetic amyotrophy, proximal diabetic neuropathy, diabetic lumbosacral plexopathy, diabetic femora! neuropathy,* and *Bruits-Garland syndrome.* Because it is likely that the brunt of nerve pathology falls on the nerve roots, it can be designated as diabetic polyradiculoneuropathy. Motor, sensory, and autonomic fibers are all affected by the disease process (Dyck, Norcll, and Dyck 1999).

In most patients, onset is fairly abrupt, witli symptoms developing over days to a couple of weeks. Early in the course of the condition, the clinical findings are usually unilateral and include weakness of muscles supplied by [.211 roots iiMo]>M>;is. quadriceps, and hip adductors), reduced or absent patellar reflex, and mild impairment of sensation over the anterior thigh. As rime passes, there may be *territorial spread,* a term used by Bastron and Thomas in 19S1 to describe proximal, distal, or contralateral involvement as the polyradiculoneuropathy evolves. Worsening may occur in a steady or a stepwise fashion, and it may take several weeks to progress from onset to peak of the disease, At its peak, weakness varies in seventy and extent from a mildly affected patient, with slight, unilateral thigh weakness, to a profound degree of bilateral leg weakness in the territory of the L2-S2 nerve roots. Upper extremity involvement appears to occur in approximately 15% of patients with diabetic lumbosacral radicular plexopathy as

a unilateral or asymmetrical sensorimotor neuropathy that primarily affects hands and forearms. Like the lumbosacral syndrome, EMG findings suggest a multifocal axon-loss process localized to roots, plexus, or peripheral nerve (Karz et al. 2001). Rarely, the process of territorial spread is so extensive that ir involves a multiplicity of nerve roots along the entire spinal cord and leads to profound generalized weakness, a condition designated *diabetic cachexia.*

Diabetic polyradiculoneuropathy tends to affect patients in the sixth or seventh decade of life, who are known to have non-insulin-dependent diabetes of several years' duration. The syndrome of painful polyradiculoneuropathy, whether referable to thoracic or lumbosacral roots, may, however, be the presenting manifestation of diabetes. In 30-50% of patients, the disorder is preceded by substantial weight loss of 30-40 pounds.

1 abnnitory studies disclose devated fasting blood glucose in the vast majority of patients; when values arc normal, they ate found in treated diabetics. The erythrocyte sedimentation rate is usually normal, but in a subgroup of patients with diabetic lumbosacral polyradiculoneuropathy, it is elevated, a clue perhaps to an immune-mediated pathogenesis (vide infra). The typical electrodiagnostic findings comprise features of a sensorimotor axon-loss polyneuropathy with additional needle electrode examination findings of lumbosacral root and plexus involvement (active and chronic denervation changes in paraspinal, pelvic-girdle, and thigh muscles). Although clinical findings may point to unilateral involvement, the electrodiagnostic examination generally discloses bilateral signs. Imaging studies of the thoracic and lumbosacral spinal canal with CT, myelography, and MRI are typically normal and almost always necessary to exclude a structural abnormality of the nerve roots that may simulate diabetic polyradiculopathy. The CSF protein level is usually increased to an average of 120 mg/dL, but in some patients, values exceed 350 mg/dL; pleocytosis is not a feature of this condition. Biopsy of proximal nerve sensory branches reveals axon loss and dcmyclination; in more severely affected patients, inflammatory cell infiltration and vasculitis is found {Said et al. 1994). Further studies of nerve biopsy specimens indicate that a microscopic vasculitis {involvement of small arterioles, venules, and capillaries) leads to ischemic injury, which in turn causes axonal degeneration and secondary segmental demyelination (Dyck, Norell, and Dyck 1999). The presence of a small-vessel vasculitis with distinctive pathological features including transmural polymorphonuclear leukocyte infiltration of postcapillary venules and endothelial deposits of immunoglobulin M (IgM) and activated complement supports an immune-mediated inflammatory pathogenesis for this disorder (Kelkar, Masood, and Parry 2000).

Electrophysiological studies have suggested that a demyelinating polyneuropathy indistinguishable from chronic inflammatory demyelinating polyneuropathy occurs frequently in diabetes and may be the cause of a severe motor sensory polyneuropathy, sometimes with features of a plexopathy (Sharma et al. 2002a, 2002b).

The natural history of diabetic polyradiculoneuropathy is for improvement to occur in most patients, although the recovety phase is lengthy, ranging between 1 and 18 months with a mean of 6 months. Pain and dysesthesias improve or disappear entirely in 85% of patients; numbness improves or recovers in 50%; and strength is partially or completely restored in 70%. In some patients, episodes recur.

Therapy is usually directed toward ameliorating the severe pain of this condition. The tricyclics, especially nortriptyline (with a better side-effect profile than amitriptyline), selective serotonin reuptake inhibitors (such as sertraline and nefazodone hydrochloride), anticonvulsants (gabapentin and carbamazepine), clonazepam, baclofen, clonidine, mexiletine, intravenous lidocaine, and topical capsaicin may have a role separately or in combination. Histopathological findings {vide supra) indicative of an immune-media ted pathogenesis have led to treatment of selected patients with intravenous immunoglobulin or immunosuppressive treatment or both (Krendcl, Costigan, and Hopkins 1995; Younger, Rosoklija, and Hays 1998). Although immunotherapy may be beneficial, spontaneous improvement in some patients with painful proximal diabetic neutopathy with different patterns of inflammatory nerve lesions has been described (Said et al. 1997). Prospective studies have suggested a role for immunotherapy in the treatment plan of diabetic polyradiculoneuropathy where electrophysiological findings arc those of chronic infla minatory dc:mduutmg poK in'iinipailn (Sharma et al. 2002a, 2002b).

The major differential diagnostic considerations are polyradiculoneuropathies related to degenerative disc disease and infectious, inflammatory, and neoplastic processes. These can usually be excluded by history, examination, and routine laboratory investigations, including CSF analysis. In our experience, however, the clinical presentation provoking the most anxiety is the frail elderly patient not known to be diabetic who has weight loss and the abrupt onset of lower extremity pain and weakness that progresses over months. In such a patient, the specter of neoplasia looms large, and thorough imaging studies of the nerve roots and plexuses are mandatory.

Neoplastic Polyradiculoneuropathy (Neoplastic Meningitis)

A wide variety of neoplasms are known to spread to the leptomeninges. These include solid tumors (carcinoma of the breast and lung and melanoma), non-Hodgkin^{n}s lymphomas, leukemias, and intravascular lymphomatosis (Viali et al. 2000), Although neoplastic polyradiculoneuropathy usually occurs in patients known to have an underlying neoplasm, meningeal symptoms may be the first

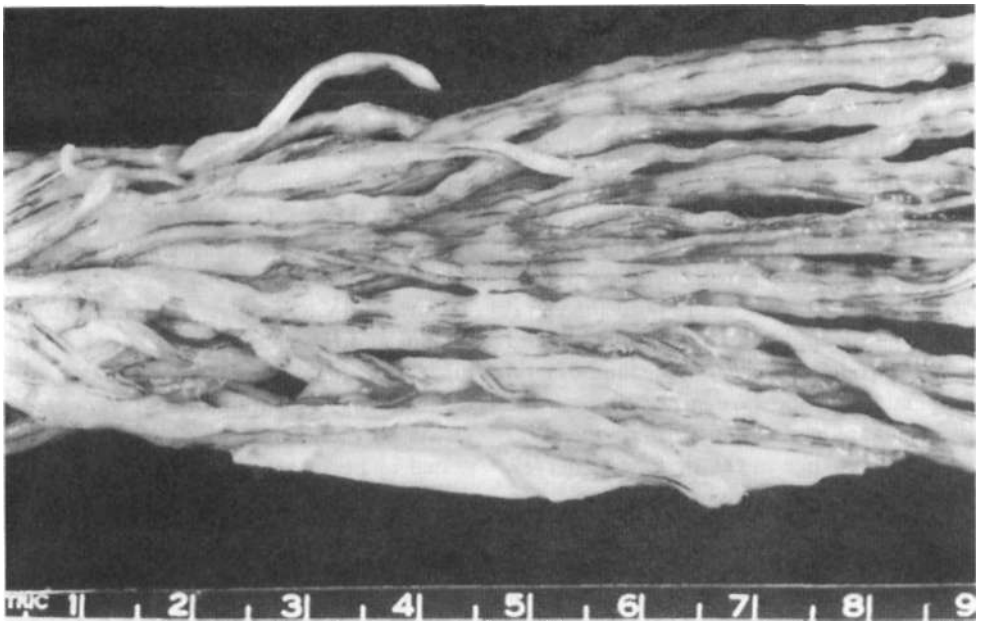


FIGURE 81.6 Cauda equina in leptomeningeal carcinomatosis. Seeding of multiple nerve roots by adenocarcinoma produces a nodular appearance. (Courtesy Dr. T. W. Smith, Department of Pathology [Neuropathology!, University of Massachusetts Medical Center, Worcester.)

manifestation of malignancy. The clinical features of neoplastic polyradiculoneuropathy include radicular pain, dermatoma) sensory loss, areflexia, and weakness of the lower motor neuron type (Balm and Hammack 1996). Often, the distribution of the sensory and motor deficits is widespread and simulates a severe sensorimotor polyneuropathy. Often, associated clinical manifestations result from infiltration of the meninges, such as nuchal rigidity, confusion, and cranial polyneuropathies.

At postmortem examination, the cauda equina shows discrete nodules or focal granularity (Figure 81.6). Microscopy discloses spinal roots encased by tumor cells, which appear to infiltrate the root. It is presumed that disturbed nerve root function results from several mechanisms, including nerve fiber compression and ischemia.

The most revealing diagnostic procedure is the lumbar puncture, which is almost always abnormal, disclosing one or more or the following: mononuclear pleocytosis, reduced CSF glucose, elevated protein, and neoplastic cells. Spinal fluid cytology is, however, persistently negative in about 10% of patients with leptomeningeal carcinomatosis (Grossman and Krabak 1999}. A sensitive electrophysiological indicator of nerve root involvement is a change in the F wave. In the symptomatic patient with cancer, prolonged F-wave latencies or absent F responses should raise suspicion of leptomeningeal metastases. Postmyelqgraphy CTadds srrong evidence in support of the diagnosis if it demonstrates multiple nodular defects on the nerve roots. Spinal MRI, especially with gadolinium enhancement, however, is the test of choice in the patient with cancer in whom leptomeningeal involvement of the spine is suspected {Watanabe, Tanaka, and Takeda 1993). Approximately 50% of patients with neoplastic meningitis and spinal symptoms have abnormalities on these studies. Gadolinium-enhanced MRI of the brain discloses abnormalities, including contrast enhancement of the basilar cisterns or cortical convexities and hydrocephalus.

Standard therapy for neoplastic meningitis that increases median survival to 3-6 months includes radiotherapy to sires of symptomatic disease, intrathecal chemotherapy [methotrexate, thiotcpa, and Ara-C), and optimal treatment of the underlying malignancy. A complication of aggressive treatment is a necrotizing leukoenecphalopathy that becomes symptomatic months after treatment with radiation and intrathecal methotrexate (Grossman and Krabak 1999).

Infectious Radiculopathy

Tabes Dor sal is

Tabes dorsalis, the most common form of neurosyphilis, begins as a spirochetal *{Treponema pallidum)* meningitis (see Chapter 59). After 10-20 years of persistent infection, damage to the dorsal roors is severe and extensive, producing a set of characteristic symptoms and signs. Symptoms are lightning pains, ataxia, and bladder disturbance; signs are Argyll Robertson pupils, areflexia, loss of proprioceptive sense, Charcot joints, and trophic ulcers. Lancinating or lightning pains are brief, sharp, and stabbing; they are more apt to occur in the legs than elsewhere. Sensory disturbances, such as coldness, numbness, and tingling, also occur and are associated with

impairment of light-touch, pain, and thermal sensation. Sudden visceral crises, characterized by the abrupt onset of epigastric pain that spreads around the body or up over the chest, occur in some 20% of patients.

Most of the features of tabes dorsaiis can be explained In lesions D] rlu' posterior roots. Ataxia is caused by flu-destruction of proprioceptive fibers; insensitivity to pain is the result of partial loss of small myelinated and unmyelinated fibers; and bladder hypotonia with overflow incontinence, constipation, and impotence is the result of sacral root damage. Pathological study discloses thinning and grayness of the posterior roots, especially in the lumbosacral region, and the spinal cord shows degeneration of the posterior columns. A mild reduction of neurons in the ORG occurs, and there is little change in the peripheral nerves. Inflammation may occur all along the posterior root.

The CSF is abnormal in active cases. The opening pressure is elevated in 10% of patients. Fifty percent of patients have a mononuclear pleocytosis (5-165 cells/mL). More than 50% have mild protein elevation (45-100 mg/dL, with rare instances of values between 100-250 mg/dL), and 72% have positive CSF serology. In all cases of neurosyphilis, antibodies specific for T. *pallidum* are found, and the preferred treatment is aqueous penicillin C, 2-4 million units intravenously every 4 hours for 10-14 days, with careful CSF follow-up. CSF examination 6 months after treatment should demonstrate a normal cell count and decreasing protein content. If not, a second course of therapy is indicated. The CSF examination should be repeated every 6 months for 2 years or until the fluid is normal.

Polyradiculoneuropathy in Human Immunodeficiency Virus-Infected Patients

Cytomegalovirus (CMV) polyradiculoneuropathy is a rapidly progressive, opportunistic infection that usually occurs late in the course of human immunodeficiency virus (HIV) infection, when the CD4 count is very low (<200 cells/pL) and acquired immunodeficiency syndrome (AIDS)-defining infections are present. Uncommonly, it is the initial manifestation of AIDS (Anders and Goebel 1998}. Patients often have evidence of systemic CMV infection (retinitis, gastroenteritis!. The presentation is marked by the rapid onset of pain and paresthesias in the legs and perineal region, associated with urinary retention and progressive ascending weakness of the lower extremities. Examination discloses a flaccid paraparesis, absent deep tendon reflexes in the legs, reduced or absent sphincter tone, and variable loss of light-touch, vibration, and joint position sense.

The CSF has an elevated protein level, depressed glucose level, polymorphonuclear pleocytosis, and a positive CMV polymerase chain reaction (PCR) (Anders and Goebel 1998). CMV may be isolated from CSF cultures. The nee.lie 1'.\Ki discloses widespread tibrill.uion p<>leii(iaU in lower extremity muscles, and sensory conduction studies may reveal an associated distal sensory neuropathy that is common in the late stages of HIV infection. Imaging of the lumbosacral region is usually normal, but adhesive arachnoiditis has been described. The pathological features are marked inflammation and extensive necrosis of dorsal and ventral roots. Cytomegalic inclusions may be found in the nucleus and cytoplasm of endothelial and Schwann cells (Figure 81.7).

Untreated CMV polyradiculoneuropathy is rapidly fatal within approximately 6 weeks of onset. The antiviral nucleoside analogue ganciclovir may benefit some patients if treatment is instituted early; improvement occurs over weeks to months. Viral resistance to ganciclovir is suggested by persistent pleocytosis and depressed CSF glucose and should prompt consideration of an alternate antiviral agent, such as foscarnet; unlike ganciclovir, it does not require intracellular phosphorylation for its effect.

Other causes of rapidly progressive lumbosacral polyradiculoneuropathy in the HIV-infected patient are meningeal lymphomatosis, *Mycobacterium tuberculosis,* and axonal polyradiculoneuritis associated with HIV infection *per se* (Corral et al. 1997). Additionally, one must consider acute inflammatory demyelinating polyradiculoneuropathy. Syphilis has an accelerated course in the patient with AIDS, and syphilitic polyradiculoneuropathy may present with rapidly progressive pain, paraparesis, muscle wasting, and hyporeflexia. In addition to markedly elevated CSF protein level, hypoglycorthachia, and brisk pleocytosis, the CSF and serum Venereal Disease Research Laboratories serology results are positive. Intravenous penicillin leads to prompt improvement. Other considerations include herpes simplex virus type 2 and varicella zoster virus infections that involve the lumbosacral nerve roots and the spinal cord, producing a radiculomyelitis. *Toxoplasma gondii* may also cause myelitis, presenting as a subacute conus medullaris syndrome that simulates the clinical features produced by CMV polyradiculoneuropathy. In the case of T. *gondii,* MR1 may reveal abscess formation.

Lyme Radiculoneuropathy

Lyme disease is caused by the spirochete *Borrelia burgdorferi* transmitted by the deer tick *Ixodes dammini* and is most prevalent in the American northeast and upper Midwest. It is a multisystem disease affecting skin, peripheral nervous system, central nervous system (CNS) (referred to as *neuroborreliosis),* musculoskeletal system, and heart. To help bring order to the understanding of this illness, it may 1IL- LI:\ ILIL-J inlo three clinical stages. Stage I follows within 1 month of the tick bite and is marked by a characteristic skin rash in 60-80% of patients, designated *erythema chronica migrans* (oval or annular shape with a clear center in the area of the bite}, and influenza-like symptoms of fatigue, fever, headache, stiff neck, myalgias, and arthralgias. In stage 2, also known as the stage of

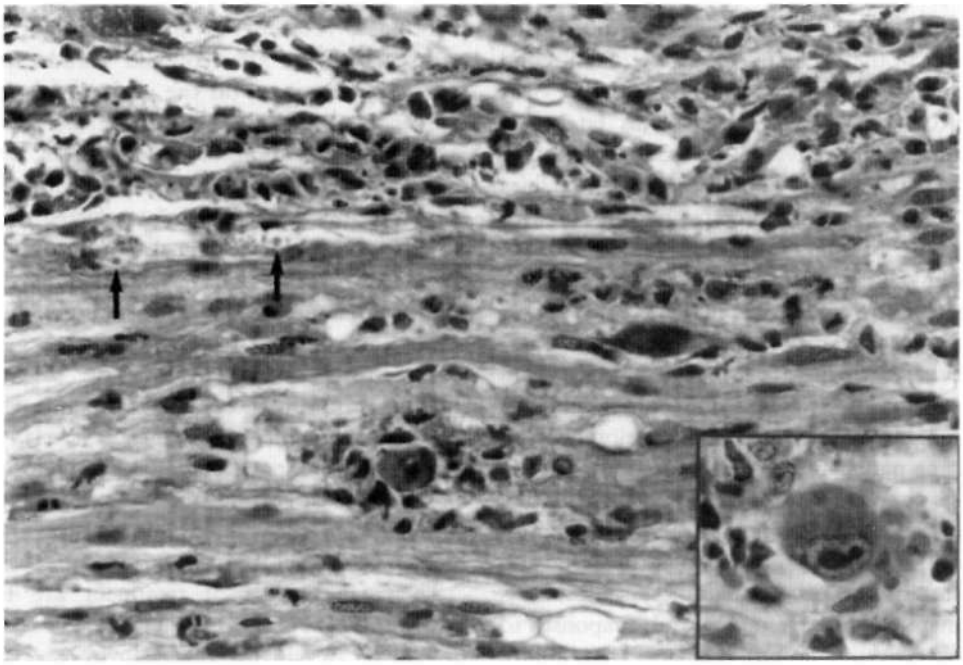


FIGURE 81.7 Cytomegalovirus polyradiculoneuropathy. Numerous mononuclear inflammatory cells are apparent, and the presence of myelin ovoids *(arrows)* reflects axon loss (hcmatoxylin-eostn stain, xlOO). Inset: A cytomegalic cell with intranuclear inclusion (hematoxylin-eosin stain, xl50). (Courtesy Dr. T. W. Smith, Department of Pathology [Neuropathology], University of Massachusetts Medical Center, Worcester.)

dissemination of the spirochete from the initial lesion, and occurring within weeks of the rash, peripheral nerve, joint, and cardiac abnormalities may appear. Stage 3, caused by late or persistent infection, may occur up to 2 years after the tick bite and is characterized by chronic neurological syndromes among them neuropathy, encephalopathy, myelopathy, and psychiatric disturbances and migratory oligoarthritis.

Nerve root and peripheral nerve abnormalities that characterize stage 2 develop in about 15% of untreated patients in the United States (Steere 2001}. Possible manifestations occurring within weeks after the onset of erythema chronica migrans include headache with lymphocytic (aseptic) meningitis, cranial neuropathy (especially facial mononeuroparhies, bilateral in 25% of cases), multifocal radiculoneuropathy, radiculoplexopathy, mononeuritis multiplex, myelitis, subtle encephalopathy, and cerebellar ataxia (Steere 2001). The clinical features of nerve root involvement include burning radicular pain, with sensory loss, and hyporeflexia in the territory of the involved roots. Nerve conduction studies provide evidence for an associated primarily axon-loss polyneuropathy, Chronic ncuroborrcliosis, seen in stage 3, occurs in some 5% of untreated patients and is characterized by an axon-loss polyneuropathy that is manifested as radicular pain or distal paresthesias (Steere 2001). In a nonhuman primate model of neuroborreliosis, spread of *B. burgdorferi* within the nervous system—lep to meninges, motor and sensory roots, ORG. but not the brain parenchyma—has been demonstrated. In peripheral nerve from such animals, spirochetes were seen in the perineurium (Steere 2001). Treatment of Lyme radiculoneuropathy with intravenous ceftriaxone (cefotaxime or penicillin G are acceptable alternates) for 2-4 weeks is associated with resolution of symptoms and signs in most patients.

Her pus Zoster

I lerpes zoster, also known as *shingles,* is a common, painful, vesicular eruption occurring in a segmental or radicular (dennatomal) distribution caused by the reactivation of latent varicella-zoster virus in DRG (see Chapter *59).* Primary infection presents as varicella (chickenpox) earlier in life, usually in epidemics among susceptible children (Gnann and Whitley 2002). Involvement may occur at any level of the neuraxis but is most commonly seen in the thoracic dermatomes, followed by the face. Zoster may present in a division of the trigeminal nerve (e.g., herpes zosrer ophthalmicus) where it is often accompanied by keratitis (a potential cause of blindness requiring immediate treatment), in the maxillary and mandibular nerves, and in the seventh nerve where it is associated with a facial palsy and ipsilateral external car or hard palate vesicles (known as the *Ramsey Hunt syndrome)* (Gildcn et al. 2000).

Zoster occurs during the lifetime of 10-20% of all people, with an incidence in the general population of approximately 3—5 per 1000 per year. The incidence is low in young people and increases with age (among persons older than 75 years exceeds 10 cases per 1000 person-years) and when immunocompetence is compromised,

For example, the incidence among HIV-positive individuals is 15-fold greater than that of a control group (Gnann and Whitley 2002). During primary infection, the virus colonizes the DRG. There, the virus remains latent for many decades, until it is reactivated, either spontaneously or when virus-specific cell-mediated immunity declines (secondary to specific conditions fly nip ho proliferative disorders, treatment with immunosuppressive drugs, organ transplant recipients, seropositivity for HIV] or normal aging), and travels down sensory nerves. Pathological changes, which are characterized by lymphocytic infiltration and variable hemorrhage, are found in the DRG and spinal roots; involvement of the ventral roots and, on occasion, the spinal cord explains the development of motor signs in some patients (see later discussion).

Herpes zoster is characterized by sharp and lancinating radicular pain (associated with itching and dysesthesias [alu-ivd Mrisiiiion]), sometimes accompanied hi fever and malaise and rash. In affected dermatomes, sensation is decreased yet there is allodynia (painful response to normally non-noxious stimulation) (Gilden et al. 2000). The cutaneous eruption (unilateral and respecting the midline) begins as an erythematous maculopapular rash and progresses to grouped clear vesicles that continue to form for 3-5 days (Gnann and Whitley 2002). These become pustules by 3^4 days and form crusts by 10 days. In the normal immunocompetent host, lesions resolve in 2—4 weeks, often leaving a region of reduced sensation, scarring, and pigmentation. Pain usually disappears as vesicles fade, but 8-70% of patients experience persisting, severe pain, termed *postherpetic neuralgia* (PHN), defined as "pain that persists more than 30 days after the onset of rash or after cutaneous healing" (Gnann and Whitley 2002). This complication is more likely to develop in the elderly, occurring in 50% of patients older than 60 years. In one half of patients affected with PHN, the pain resolves within 2 months, and 70-80% of patients are pain free by 1 year. Rarely, pain persists for years.

In the immunologically normal host, dissemination of the virus is rare, occurring in fewer than 2% of patients. In the immunocompromised patient, however, dissemination occurs in 13-50% of patients. Most often, spread is to distant cutaneous sites, but involvement of the viscera (lung, gastrointestinal tract, and heart) and CNS may occur. A serious complication of herpes zoster ophthalmicus is delayed contralateral hemiparesis caused by cerebral angiitis. The syndrome usually develops 1 week to 6 months after the onset of zoster and occurs in patients of all ages, 50% of whom are immunologically impaired. The mortality from cerebrovascular complications is 25%, and only approximately 30% of survivors recover fully.

An uncommon complication of cutaneous herpes zoster is segmental motor weakness, which occurs in 3-5% of patients (Merchut and Gruener 1996). Segmental zoster paresis is approximately equally divided between the arms and legs, reflecting weakness in cervical and lumbar myotomes, respectively; the diaphragm and abdominal muscles may be affected; and bladder and bowel dysfunction may occur (in the setting of lumbosacral zoster [Gilden et al. 2000]). The interval between skin eruption and paralysis is approximately 2 weeks, with a range of 1 day to 5 weeks. Weakness peaks within hours or days; spread to muscles served by unaffected segments does not usually occur. The prognosis for recovery is good, with 55% showing full recovery and another 30% showing significant improvement. One in five patients is left with severe and permanent residua.

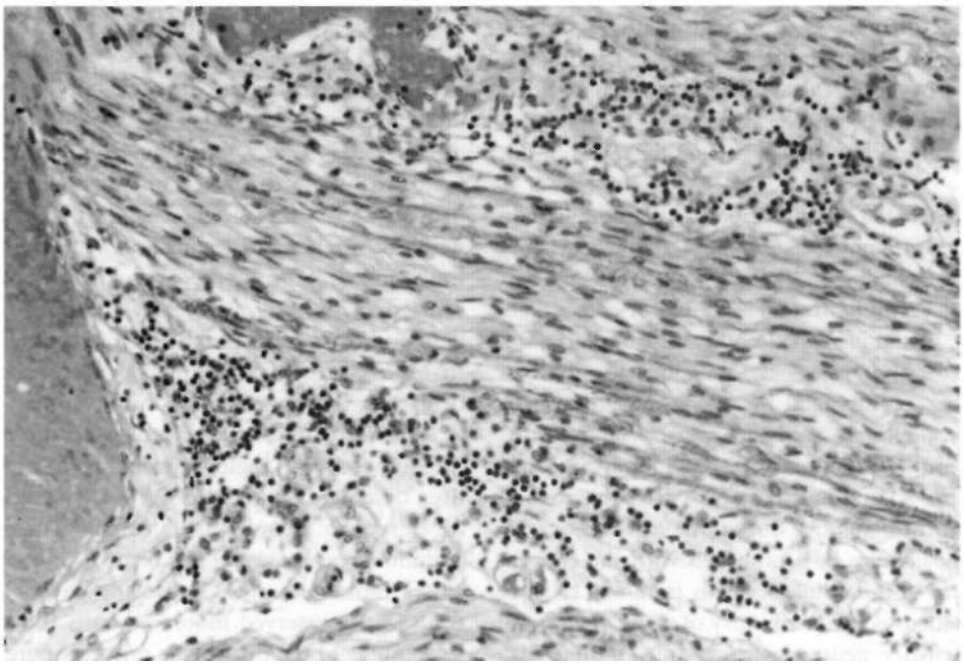
The histopathological correlate of herpes zoster is inflammation and neuronal loss in the DRG that correspond to the affected segmental levels. In the case of segmental zoster paresis, there is lymphocytic inflammation and vasculitis involving adjacent motor roots and the spinal cord gray matter with resulting motor fiber degeneration (Gilden et al. 2000).

The major goals of treatment are to relieve local discomfort, prevent dissemination, and reduce the severity of PHN. Acyclovir, valacyclovir, and famciclovir arc indicated for the immunocompetent patient older than 50 years with herpes zoster. They reduce the duration of viral shedding, limit the duration of new lesion formation, and accelerate healing and pain resolution. They are all safe and well-tolerated dtugs, but because of superior pharmacokinetic profiles and simpler dosing regimen, the latter two are preferred to acyclovir (Gnann and Whitley 2002).

The pain of PHN, described variably as continuous deep aching, burning, sharp, stabbing, and shooting, and triggered by light touch over the affected dermatomes, is often debilitating and difficult to treat (Watson 2000). Singly or in combination, tricyclics (amitriptyline or desipraminc), selective serotonin reuptake inhibitors (sertraline or ncfazodone hydrochloride), anticonvulsants (carhamazepine and gabapentin), oral opioids (oxycodone), and topical capsaicin cream or lidocainc parches are helpful in about 50% of patients. For intractable cases, intrathecally administered methylprcdnisolone and lidocainc has been shown to provide relief without adverse effects of arachnoiditis or neurotoxicity in more than 90% of patients treated (Kotani et al. 2000).

Acquired Dcinyelinating Polyradiculoneuropathy

Acquired dcmyclinating polyradiculoneuropathy has two major clinical forms. One develops acutely and is known as *Guilhin-Barre syndrome* (GBS); the other is chronic, progressive, or relapsing and remitting and is designated *chronic inflammatory demyelinating polyradiculoneuropathy* (CIDP). These disorders are described in detail in Ghapter 82 but ate mentioned here briefly because pathological changes may be pronounced in the spinal nerve roots, especially the ventral roots. There may be a dense mononuclear inflammatory infiltrate characterized by



F1GURK 81.8 Cauda equina in Guillain-Barre syndrome, A dense inu mom vicar infNnraU' in the eonnective tissue surrounding the nerve roots is shown (hematoxylin-eosin stain). (Courtesy Dr. 1. W. Smith, Department of Pathology (Neuropathology!, University of Massachusetts Medical Center, Worcester.)

lymphocytes, monocytes, and plasma cells (Figure SI .8), as well as nerve fibers display segmental demyelination with relative sparing of axons. Ncuroimaging with MRI discloses contrast enhancement of lumbosacral roots in both GBS and GDP (Berrorini et al. 1995). The predilection for root involvement in these conditions helps explain certain features, including the CSF formula, some neurophysiologies! findings, and disturbances in autonomic function that may be especially problematic in patients with GBS.

A CSF profile of albuminoeytological dissociation is characteristic of this syndrome. A high lumbar CSF protein concentration in the lace of a normal cisternal protein level supports the hypothesis that increased CSF protein derives largely from capillaries of the spinal roots. Nerve conduction studies usually disclose slowed motor conduction velocities, dispersed motot responses, and partial conduction block, but additional abnormalities include delayed or unobtainable F-wavc responses or H-rcflexcs, reflecting demyelination in nerve roots. Indeed, abnormalities of these late responses may be the sole finding in 10-20% of patients with GBS in the first few weeks of the illness. Last, a host of autonomic disturbances occur in GBS, some of which could be caused by involvement of preganglionic sympathetic fibers, which travel in the ventral roots en route to the paravertebral sympathetic ganglia.

Acquired Disorders of the Dorsal Root Ganglia

DRG may be selectively vulnerable to a variety of malignant and nonmalignant conditions. The resulting neurological disorder is a sensory neuronopathy syndrome whose clinical features are explained by the loss of Jarge- and small-diameter DRG neurons (Bryer and Chad 1999). Large cell dropout leads to kinesthetic sensory impairment, poor coordination, loss of manual dexterity, ataxia, and ateflexia; whereas small cell depletion contributes to a hyperalgesic state marked by burning pains and painful paresthesias.

Perhaps the best known of these uncommon conditions is paraneoplastic subacute sensory neuropathy (or neuronopathy), a disorder developing over weeks to months, characterized b\ ataxia and hyperalgesia while IHILM le strength is well preserved (Posner and Dalmau 1997). Some patients have clinical signs of brainstem and cerebral dysfunction, reflecting a more widespread encephalomyelitis. The neuropathy may antedate the diagnosis of cancer, usually small cell lung carcinoma, by months to years. The CSF profile discloses elevated protein concentration and a mild mononuclear cell pleocytosis. Nerve conduction studies reveal widespread loss of sensory potentials. Neuropathological features include inflammation and phagocytosis of the sensory neurons in the DRG. This condition is associated with the presence of specific antineuronal antibodies (anti-Hu), which are complement-fixing, polyclonal immunoglobulin G (IgG) antibodies that react with the nuclei of the CNS and sensory ganglia but not with non-neuronal nuclei. The antigens recognized by the anti-Hu antibodies have been characterized as protein antigens with molecular weights of 35-40 kd. The presence of identical protein antigens in small cell lung cancer cells and neuronal nuclei supports the view that the pathogenesis

of paraneoplastic subacute sensory neuropathy is immunologically mediated, with tumor antigens triggering the production of cross-reactive antibodies. Morphological studies provide evidence for both cytotoxic T-cell-media ted attack and humoral mechanisms in the pathogenesis of this **condition.**

Other causes of DRG neuronopathy include hereditary, toxic, and autoimmune disorders. Hereditary sensory neuropathies are usually marked by their chronicity, acrodystrophic ulcerations, fractures, bouts of osteomyelitis, and lack of paresthesias. Pyridoxine abuse and cisplatin neurotoxicity arc generally easily recognized. Sjogren's syndrome may be accompanied by ataxia and kinesthetic sensory loss very similar to subacute sensory neuropathy. The presence of antibodies to extractable nuclear antigens, such as anti-Ro (SS-A) and anti-La (SS-B) arc suggestive of the diagnosis, but their absence does not exclude Sjogren's syndrome. Diagnosis may be established with the demonstration of clusters of inflammatory cells in minor salivary glands (focal sialadenitis) from a biopsy of clinically normal lip mucosa. A sensory neuronopathy syndrome has also been associated with elevated titers of an autoantibody that reacts with the GDn, ganglioside, an acidic glycolipid—composed of a lipid component (ceramide), a carbohydrate nnnciy, and two sialic acid groups- pivscm on the surface of neurons in the DRG (O'Leary and Willison 1997).

Radiculopathies Simulating Motor Neuron Disease

Disorders of the motor toots may lead to clinical features that resemble those encountered in motor neuron disease. Detailed study of such motor neuron syndromes is important because it might provide clues to the pathogenesis of the most common form of motor neuron disease, ALS. Clinicians should consider **the** possibility of an ALS-mimic syndrome when a patient with clinical features of lower motor neuron involvement is found to have a monoclonal gammopathy (Chad and Harris 1999). In that instance, investigations must vigorously pursue the possibility that physical findings stem from ventral root involvement, rather than anterior horn cell degeneration. An elevated CSF protein level, along with a demyelinating process identified by nerve conduction studies, suggests a potentially treatable motor polyradiculoneuropathy.

In some patients with a lower motor neuron syndrome, the presence of a monoclonal gammopathy and raised CSF protein concentration with oligoclonal bands in the CSF increases the likelihood of detecting an underlying **lym**phoproliferative disease. In some instances of IgM monoclonal gammopathy, there is antibody specificity for the gangliosides GM|, asialo-GM,, and GDn, among others. In rare instances, immunotherapy that reduces the serum concentrations of IgM gangliosides is associated with improvement in the lower motor neuron syndrome, thereby suggesting a possible pathogenic role of antiganglioside antibodies.

The association between lower motor neuron findings and lymphoma has been known since the 1960s and is designated *subacute motor neuronopathy,* but the site of major pathology is not certain and could be at a root and a neuronal level. It is characterized by subacute, progressive, painless, often patchy, and asymmetrical weakness of the lower motor neuron type, with greater involvement of the arms than the legs. The illness often progresses independently of the activity of the underlying lymphoma and tends to follow a relatively benign course, with some patients demonstrating spontaneous improvement.

A postradiation lower motor neuron syndrome affecting the lumbosacral region, probably a radiculopathy, has been described occurring 3-25 years after radiation therapy for testicular neoplasms. In some patients, MR1 shows gadolinium enhancement. Neuropathological study discloses radiation-induced vasculopathy of proximal spinal roots with preserved motor neurons (Bowen et al. 1996). The course of the disorder is one of progression for several years and eventual stabilization.

DISORDERS OF THE BRACHIAL PLEXUS

Anatomical features

The brachial plexus is formed by five ventral rami (C5-TI), each of which carries motor, sensory, and postganglionic sympathetic fibers to the upper limb. It is a large and complex peripheral nervous system structure that contains 100,000-160,000 individual nerve fibers (Fcrrante and Wilbourn 2002). These five rami unite above the level of the clavicle to form the three trunks of the brachial plexus (Figure 81.9): C5 and C6 join to form the upper trunk; Tl and C8 unite to form the lower trunk; and C7, the largest of the five rami, continues as the middle trunk. (To review, a ventral ramus—anterior primary ramus—derives from a mixed spinal nerve that is formed in turn by the fusion of the posterior dorsal and ventral roots in the intervertebral foramen.) Beneath the clavicle, each trunk divides into an anterior and posterior branch, leading to six divisions, which become the three cords of the brachial plexus, the lateral, medial, and posterior. The cords, which lie behind the pectoralis minor, take their names from their relationship to the subclavian artery. The lateral and medial cords carry motor fibers to the ventral muscles of the limb. The lateral cord is formed from anterior divisions of the upper and middle trunks; the medial cord from anterior division of the lower trunk. The posterior cord carries motor fibers to the dorsal muscles of the limb; it is formed from posterior divisions of the upper, middle, and lower trunks.

The major named nerves of the upper limb derive from the cords. After contributing a branch to the formation

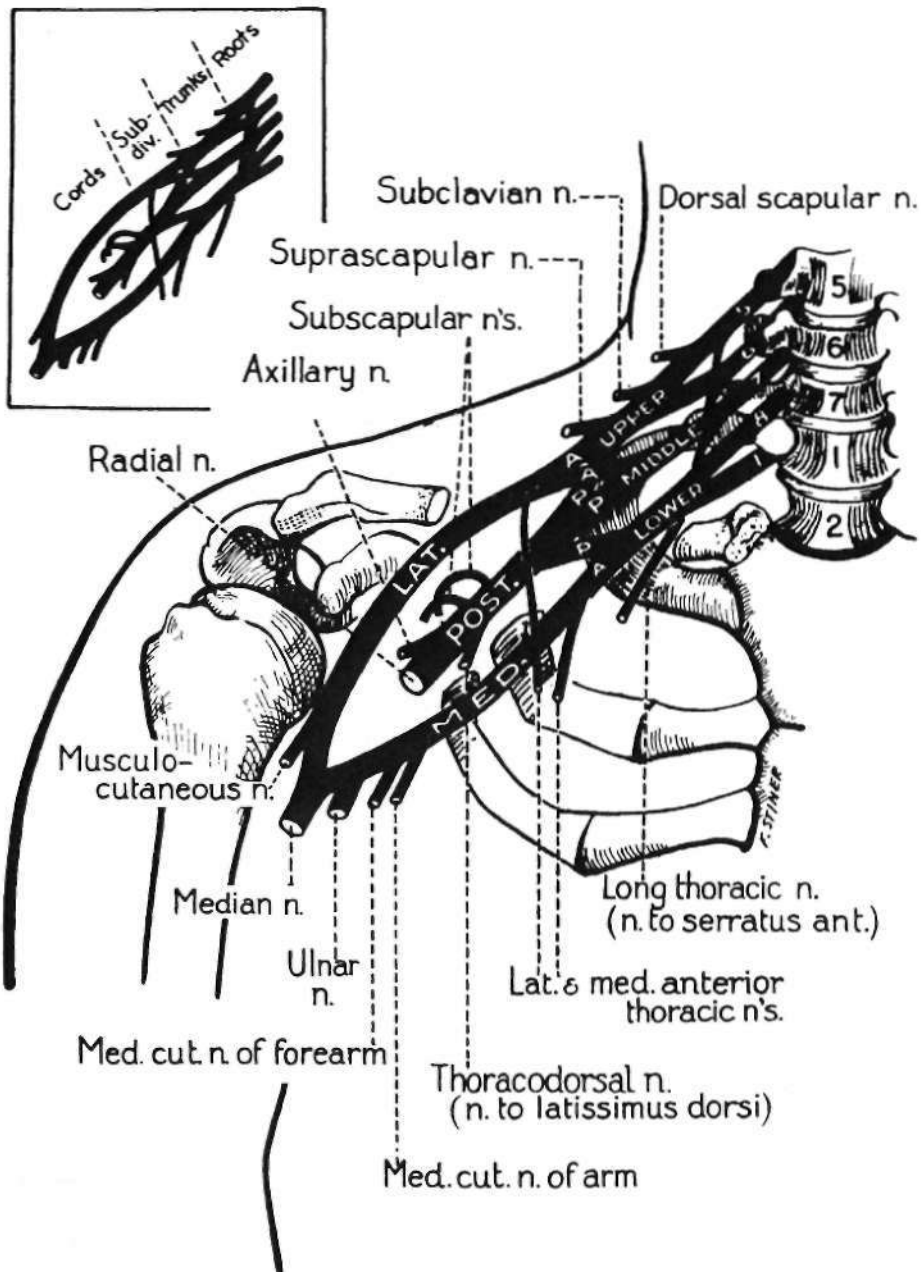


FIGURE 81.9 Brachial plexus. The components of the plexus have been separated and drawn out of scale. The five ventral rami {C5-T1) unite to form the upper, middle, and lower trunks of the plexus above the clavicle. Beneath the clavicle, each trunk divides into anterior *[ant.)* and posterior divisions. Three cords (lateral *[Lat.]*, posterior *[Post.]*, and medial *[Med.])* lie below the pectoralis minor muscle (not shown). Mnjor upper limh nerves (n's) originate from the cords. (cut. = cutaneous.) (Reprinted with permission linin I laymaker, W. & Woodhall, B. 1953, *Peripheral Nerve Injuries*, 2nd ed, WB Saunders, Philadelphia.)

of the median nerve, the lateral cord continues as the musculocutaneous nerve. Similarly, after making its contribution to the median nerve, the medial cord continues as the ulnar nerve. The posterior cord divides into a smaller axillary nerve, which leaves the axilla via the quadrangular space to supply the deltoid and teres minor and the larger radial nerve. Also, from the level of the cords, branches are distributed to the pectoralis major and minor muscles (from the lateral and medial cords, respectively) and to the subscapulars, latissimus dorsi, and teres major muscles (from the posterior cord). In addition to these motor branches, sensory branches also arise at a cord level: The posterior cutaneous nerve of the arm arises from the posterior cord, and the medial cutaneous nerve of the arm and the medial cutaneous nerve of the forearm come from the medial cord.

Nerve branches to the serratus anterior, levator scapulae, rhomboids, and supraspinatus and infraspinatus muscles derive from more proximal levels of the plexus. The first three muscles are supplied by branches of the anterior primary rami: the serratus anterior from C5, C6, and C7 (the long thoracic nerve) and the levator scapulae and rhomboids from branches of C5 (the dorsal scapular nerve). The supraspinatus and infraspinatus muscles are supplied by the suprascapular nerve, a branch of the upper trunk of the plexus.

Clinical Features and Diagnosis

Not surprisingly, disorders of the brachial plexus are determined in large part by its anatomical relationships (Ferrante and Wilbourn 2002): Because of its location between two highly mobile structures, the neck and the shoulder, it is vulnerable to trauma. And, because neighboring tissues such as lymph nodes, blood vessels, and lung parenchyma may themselves be targets of a variety of disease processes, the brachial plexus itself may be secondarily affected as an innocent bystander.

Neurological Examination

Patients with a brachial plcsaipathy present with a variety of patterns of weakness, reflex change, and sensory loss, depending on whether the whole or a portion of the plexus is disturbed. Most commonly encountered arc three patterns resulting from involvement of the entire plexus, the upper trunk, and the lower trunk; less commonly seen are partial plexopathies caused by selective cord lesions.

In a pan-plexopathy, paralysis of muscles supplied by segments C.5 through Tl occurs. The arm hangs lifelessly by the side, except that an intact trapezius allows shrugging of the shoulder. The limb is flaccid and areflexie, with complete sensory loss below a line extending from the shoulder diagonally downward and medially to the middle of the upper arm.

Lesions of the upper trunk produce weakness and sensory loss in a C5 and C6 distribution. Affected muscles include the supraspinati and infraspinati, biceps, hrachialis, deltoid, and brachioradialis, so the patient is unable to abduct the arm at the shoulder or flex at the elbow. If a lesion is so proximal that it involves the C5 ramus, the rhomboids and levator are also affected. The arm hangs at the side internally rotated at the shoulder, with the elbow extended and the forearm pronated in a "waiter's tip" posture. The biceps and brachioradialis re flexes are diminished or absent, and sensory loss is found over the lateral aspect of the arm, forearm, and thumb.

Lesions of the lower trunk produce weakness, sensory loss, and reflex changes in a C8 and Tl distribution. Weakness is present in both median- and ulnar-supplied intrinsic hand muscles and in the medial finger and wrist flexors. The finger flexion reflex is diminished or absent, and there is sensory loss over the medial two fingers, the medial aspect of the hand, and the forearm.

Cord lesions are usually found in the setting of trauma. A posterior cord lesion produces weakness in the territory of muscles innervated by both radial and axillary nerves. Sensory loss occurs in the distributions of the posterior cutaneous nerve of the forearm and the radial and axillary nerves. This results in sensory loss over the posterior aspect of the arm, the dorsal surface of the lateral aspect of the hand, and a patch of skin over the lateral aspect of the arm.

Lateral cord injuries produce weakness in muscles supplied by the musculocutaneous nerve as well as weakness in the muscles of the median nerve supplied by the C6 and C7 roots (the pronator teres and flexor carpi radialis muscles). The median and ulnar nerve fibers originating from C8 and Tl segments are spared, and thus there is no intrinsic hand muscle weakness. In medial cord lesions, there is weakness in all ulnar nerve-supplied muscles and in the C8 and Tl median nerve-supplied muscles.

Electro diagnostic Studies

Nerve conduction studies and needle EMG provide information that is helpful in confirming the clinical diagnosis of brachial plexopathy, in determining the character of the lesion—predominantly axon loss, demyelinating, or both—and in arriving at a judgment with respect to prognosis for recovery of function. In axon-loss brachial plexopathies, sensory nerve action potentials (SNAPs) and compound motor action potentials (CMAPs) are attenuated or lost depending on the severity of the disease process, because the amplitude of these responses correlates directly with number of conducting fibers. (In preganglionic lesions [at a root level], sensory responses are expected to lie spared, and only miiiiir responses will lie affected.) As long as at least some fast conducting fibers are spared, the conduction velocities and distal latencies are unaffected. In the case oi demyelinating lesions, however. nerve conduction velocities are typically slowed, motor evoked responses dispersed and distal latencies prolonged. (Most brachial plexus lesions are axon loss in nature [Ferrante and Wilbourn 20021.) The needle examination is very sensitive for detecting even mild motor fiber loss, because fibrillation potentials develop in affected muscles by 3 weeks after the onset of a disease process.

Ferrante and Wilbourn (2002) note that axon-loss brachial plexus neuropathies fall along a spectrum of .seventy that may be determined by the results of the electro diagnostic study. In the context of a minimal lesion affecting both sensory and motor fibers, SNAPs and CMAPs will typically be unaffected, but needle examination will disclose fibrillation potentials (because the loss of one motor fiber will result in the denervation of hundreds of muscle fibers). With an increase in lesion severity, SNAPs become attenuated while CMAPs are still spared. The most severe lesions compromise seusor\ responses and arlivl motor responses. Ferrante and Wilbourn (2002) observe that it is the CMAPs that are m fact the most useful for quantifying the amount of loss suffered by a nerve; in contrast, SNAPs may be attenuated, even absent with only partial lesions; and needle electrode examination, as we have seen, may reveal prominent fibrillation potentials with only mild motor axon loss. The needle examination is helpful in evaluating whether or not tecovery from axon-loss lesions is ongoing, because features of motor unit

potential remodeling (increased duration and complexity of motor unit potentials) indicate the ongoing process of collateral reinnervation, distal-to-proximal reinnervation, or both.

In a postganglionic plexopathy, numbness and sensory loss are associated with reduced or absent SNAPs because the lesion is located distal to the DRG. As we have seen, by contrast, in a pure radiculopathy, sensory loss is found in the face of a normal SNAP because the lesion is proximal to the DRG. In certain conditions, preganglionic and post-ganglionic lesions coexist, so the electrodi a gnostic studies disclose paraspiual muscle fibrillation and absent SNAPs. This situation is encountered most commonly in patients with traumatic plexopathics that damage the plexus and injure or avulse nerve roots *per se.* It is also found in peripheral neuropathies, such as diabetes, and in malignant plexopathics, in which tumor not only injures the plexus but also infiltrates the nerve roots by tracking through the intervertebral foramina. Specific EMG changes are covered under individual disorders of the plexus, later in the chapter.

Radiological Studies

Plain films of the neck and chest are often very helpful in evaluating arm weakness that is thought to be caused by a disorder of the brachial plexus. The presence of a cervical rib or long transverse process of C7 may provide an explanation for hand weakness and numbness, as seen in thoracic outlet syndrome. A lesion in the pulmonary apex, erosion of the head of the first and second rib, or the transverse processes of C7 and TI may reveal the cause of a lower brachial plexopathy, as found in cases of Pancoast's tumor. CT scanning and MRI of the brachial plexus are also useful in detecting mass lesions of the plexus and may allow early diagnosis and specific therapy (Bilbey, Lamond, and Mattrey 1994). CT-guided biopsy can be used to obtain cytological or histological material for precise diagnosis.

Traumatic Plexopathy

Three general categories of brachial plexus injury exist: (1) direct trauma; (2) secondary injury from damage to structures around the shoulder and neck, such as fractures of the clavicle and first rib; and (3) iatrogenic injury, most commonly seen as a complication of the administration of nerve blocks. Direct injury may be either open {gunshot wounds and lacerations) or closed (sttetch or traction). The main causes of brachial plexus palsies are traction and heavy impact. Injuries are usually secondary to motor-cycle and snowmobile accidents, but sporting accidents in football, bicycling, skiing, and equestrian events are also important. Supraclavicular injuries are more common and more severe and have a worse prognosis than infraclavicular injuries (Midha 1997}. Another form of brachial plexus traction is seen in rucksack paralysis. The straps of a rucksack or backpack pressed to the shoulders may exert heavy pressure in the region of the upper trunk of the brachial plexus and thus lead to weakness in the muscles supplied by the suprascapular and axillary nerves and sensory loss in the C5 and C6 distributions.

Early Management

The consequences of brachial plexus injury are weakness and sensory loss referable to a part or the whole of the plexus. The ultimate objective in management is to restore as much neurological function as possible with the hope of returning the limb to its preinjury status, but one must first ensure that the cardiovascular and respiratory systems are stable. In open injuries, there may be damage to great vessels in the neck and injury to the lung, in which case immediate operative intervention is necessary to save the patient's life. At the time of this early acute intervention, it is important to assess to what degree the various elements of the plexus have been injured. As far as possible, disrupted elements should be tagged for later repair. It may be difficult to suture damaged fascicles, and the formation of scar may prevent successful nerve regeneration. Most authors agree that nerve resection, grafting, and anastomosis are all very difficult in the acute situation because nerve continuity may be difficult to assess. If portions of a plexus have been sharply transected, however, primary repair should be carried out.

Long-Term Management

Once the patient's general condition has stabilized, a careful assessment of motor and sensory function should be made. At iln- stage, an important i-su- is wlii-thcr thi-rc has been root avulsion. This is a critical determination, with implications for management, because the outlook for return of motor and sensory function in territories supplied by avulsed roots is currently not good, although promising results of surgical repair have recently been noted. Root avulsion and its management are discussed m the section Disorders of Nerve Roots, earlier in this chapter. If Ilir I'-lrMi-- Heliums ;i it :n i.(>:Hinini\ and the nerve 11 bits have received a neuropraxic injury with minimal axonotmesis, then return of normal strength and sensation is expected. In the face of axonotmesis, the main factor limiting return of function is the distance the regenerating axon sprouts must traverse before making contact with end organs. Unless the muscles and sensory receptors are rcinnervated within approximately 1 year, a good functional result is unlikely. Thus recovery of proximal muscle strength from upper portions of the plexus is more likely than recovery of hand function when lower elements have been damaged.

Often, surgery must be performed to provide an exact intraoperative definition of the lesion's extent (see Chapter 56D) (Berger and Becker 1994). Intraoperative motor evoked potentials are helpful in assessing the functional state of anterior motor roots and motor fibers. Depending on the findings, neurolysis, nerve grafting, or re-neurotization is performed. Primary nerve reconstruction combined with joint fusion and tendon transfers provides a worthwhile return of function to many patients. The joint and tendon surgeries are best performed as secondary operations after a period of physiotherapy. Intensive physiotherapy and use of orthoses are often necessary to help restore maximum function. In general, the outcome after nerve grafting is relatively good for recovery of elbow flexors and extensors and for those of the shoulder girdle, but it is very pooi for forearm and hand ir.lniisic muscles. Ou.iliu "I life surveys after brachial plexus surgery indicate that 78% of patients report at least moderate satisfaction (Choietal. 1997).

Neurogenic Thoracic Outlet Syndrome

Although it is frequently diagnosed, neurogenic thoracic outlet syndrome is a rare entity, seen only once or twice a year in busy EMG laboratories. Most patients are women. The mean age at onset is 32 years, but patients as young as 13 and as old as 73 years have been reported. Pain is usually the first symptom, with either aching noted on the inner side of the arm or soreness felt diffusely throughout the limb. Tingling sensations accompany pain and are felt along the inner side of the forearm and in the hand. Most patients note slowly progressive wasting and weakness of the hand muscles. The physical examination discloses hand muscle weakness and atrophy, most marked in the lateral part of the thenar eminence. In a smaller number of patients, there is mild atrophy and weakness in the forearm muscles. Sensory loss is present along the inner side of the forearm. Except for the occasional Ravnaud's-type episode, vascular symptoms and signs are uncommon.

In many cases, cervical spine roentgenograms disclose small bilateral cervical ribs or enlarged down-curving C7 transverse processes. When not visualized in anteroposterior radiographs of the cervical spine, they can he seen on oblique views. MRI of the brachial plexus is a useful diagnostic method, revealing deviation or distortion of nerves or blood vessels and suggesting the presence of radiographically invisible bands (Panegyres et al. 1993). Electrodiagnostic studies on the affected side disclose a reduced median motor response with normal median sensory amplitudes along with a mildly reduced ulnar motor response and reduced ulnar sensory amplitude. The needle electrode examination typically discloses features of chronic axon loss with mild fibrillation potential activity in C8- and Tl-innervated muscles. The cluneal and electrophysiological findings point to a lesion of the lower trunk of the brachial plexus. Levin, Wilbourn, and Maggiano {1998) have refined our understanding of the precise lesion localization of the neurogenic thoracic syndrome. They compared electrophysiological results between a group of patients with true neurogenic thoracic outlet syndrome and a group with "brachial plexopathy" stemming from median sternotomy. In the former group, the findings pointed to severe axon loss in the medial antebrachial cutaneous nerve and the abductor pollicis brevis, both sharing Tl root innervation. In the latter, an iatrogenic disorder resulting from rib retraction, the findings indicated axon loss in the ulnar sensory and motor nerves, conforming most to involvement predominantly of C8. These findings suggest that thoracic outlet syndrome and median sternotomy brachial plexopathy are more accurately described as "extraspinal radiculopathies" with damage i<> the root fillers .n die level of die anterior primary rami (Levin 2002)—distal to the C8 or Tl nerve roots *per se,* but proximal to the lower trunk of the brachial plexus.

In most patients, a fibrous band extending from the rip of a rudimentary cervical rib to the scalene tubercle of the first rib causes angulation of either the C8 and Tl roots or the lower trunk of the brachial plexus (Figure 81.10). Surgical division of the fibrous band can be expected to relieve pain and paresthesias and arrest muscle wasting and weakness in the majority of patients; return of muscle bulk and strength, however, is unlikely.

Metastatic and Radiation-Induced Brachial Plexopathy in Patients with Cancer

Metastatic Plexopathy

Damage to the brachial plexus in patients with cancer is usually secondary to either metastatic plexopathy or radiation-induced injury. Lung and breast carcinoma are the tumors that most commonly metastasize to the brachial plexus; lymphoma, sarcoma, melanoma, and a variety of other types are less common. Tumor metastases spread via lymphatics, and the area most commonly involved is adjacent to the lateral group of axillary lymph nodes.

The hallmark of metastatic plexopathy is pain, which is often severe. It is generally located in the shoulder girdle and radiates to the elbow, medial portion of the forearm, and fourth and fifth digits of rhe hand. In many patients, the neurological examination discloses signs referable to the lower plexus and its divisions; more than one half the patients have Horner's syndrome, whereas few have lymphedema of the affected limb. The predilection for involvement of the C8 and Tl spinal nerves and the lower trunk can be explained by the fact that the lateral group of axillary lymph nodes that drain the commonly located sites (breast and lung J are in close contact with the divisions of

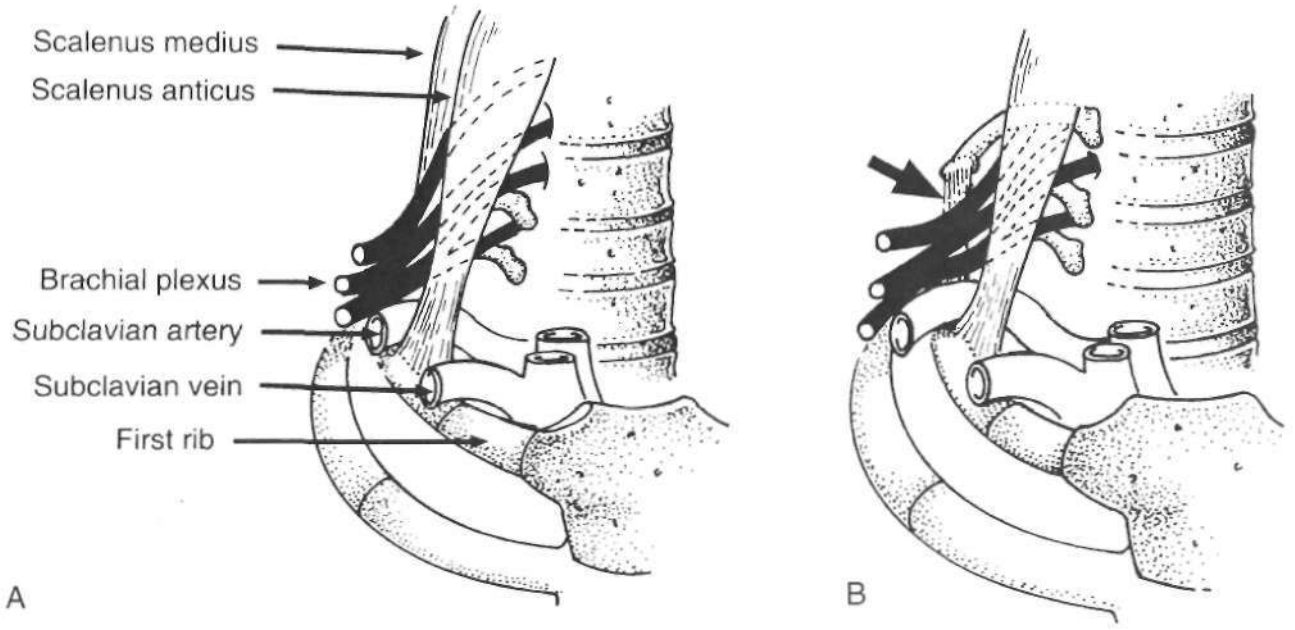


FIGURE 81.10 (A) The normal relationships of the subclavian artery and the brachial plexus as they course over the first rib between the scalenus medius and anterior muscles. {15} From the end of a short cervical rib arises a fibrous band *{arrow),* which attaches to the upper surface of the normal first rib. This stretches and angulates chiefly the lower trunk of the brachial plexus, causing neurogenic thoracic outlet syndrome. (Reprinted with permission from Stewart, J. 1), 1993, *Focal Peripheral Neuropathies,* 2nd ol, R.uvn I'IVSS. New York.)

the lower trunk; the upper trunk and its divisions arc remarkably free of lymph nodes. Some patients have signs indicating involvement of the entire plexus. In most of these patients, however, cervical CT myelography or MRI discloses epidural deposits that explain the upper plexus (C5 and C6 root) signs.

An important syndrome first described by Pancoast in 1932 is a superior pulmonary sulcus rumor, the vast majority of which are non-small cell bronchogenic carcinomas (Arcasoy and Jett 1997). The tumor arises near the pleural surface of the apex of the lung and grows into the paravertebral space and posterior chest wall, invading the C8 and Tl extraspinal roots, the sympathetic chain and stellate ganglion, the necks of the first three ribs, and the transverse processes and borders of the vertebral bodies of C7 through T3. The tumor may eventually invade the spinal canal and compress the spinal cord. Clinical features include a number of symptoms and signs: severe shoulder pain tadiating to the head and neck, axilla, chest, and arm; pain and paresthesias of the medial aspect of the arm and the fourth and fifth digits; and weakness with atrophy of intrinsic hand muscles.

On occasion, metastatic brachial plexopathy may be difficult to distinguish from radiation plexopathy (see Radiation-Induced Plexopathy, later in this section). Imaging studies are usually informative. In patients with metastases, MRI can identify a mass adjacent to the brachial plexus and reveal whether the tumor has encroached on the epidural space. CT remains a valued alternative investigation technique for this region because it provides good definition of the vertebral bodies. Nevertheless, sometimes exploration and biopsy by direct visualization may he the only definitive way to distinguish metastatic from radiation-induced plexopathy.

Results of the treatment of metastatic plexopathy are disappointing. Radiotherapy to the involved field and chemothetapy of the underlying tumor are the mainstays of treatment. Radiotherapy may relieve pain in 50% of patients but has little effect on return of muscle strength. A variety of procedures have been implemented to ameliorate the severe pain of this condition, including transcutaneous stimulation, paravertebtal sympathetic blockade, and dorsal rhizotomies.

In the patient with Pancoast's tumor, preoperative radiotherapy followed by extended surgical resection is the most common treatment, with an overall 5-year survival rate of 20-35% (Arcasoy and Jett 1997).

Radiation-Induced Plexopathy

Radiation-induced plexopathy is unlikely to occur if the dose is less than 6000 eGy. If more than 6000 cGy is given, the interval betw-een the end of radiation therapy and the onset of symptoms and signs of radiation plexopathy ranges from 3 months to 26 years, with a mean interval of approximately 6 years. The brachial plexus is more vulnerable to large fraction size, and thus fractions of

200 cGy or less are recommended. Cytotoxic therapy adds to the damaging effect of radiotherapy (Olsen et al. 1993). Limb paresthesias and swelling arc common complaints. Although the pain of radiation plexopathy is usually less intense than that of metastatic plexopathy, it may nonetheless be problematic (severe and persistent) requiring opioids; and in refractory cases responding to chemical sympathectomy (Fathers et al. 2002). Weakness is usually most prominent in muscles innervated by branches of the upper trunk, but involvement of the entire limb, from damage to the upper and lower portions of the plexus, has also been described. Indeed, in a group of women with radiation plexopathy following treatment for carcinoma of the breast, progressive weakness resulted in loss of hand function in 90% of patients (Fathers et al. 2002).

The relative resistance of the lower trunk of the brachial plexus to radiation injury is perhaps explained by the protective effect of the clavicle and the relatively shorter course of the lower trunk and its divisions through the radiation port. The pathogenesis of radiation damage is thought to involve two factors: radiation-induced endoneurial and perineuria! fibrosis with obliteration of blood vessels (triggered by small-vessel endothelial injury), and direct radiation-induced damage to myelin sheaths and axons. Arteritis (radiation-induced) of large vessels was found in a patient with delayed onset of brachial plexopathy following radiation therapy for breast carcinoma (21 years), who underwent arteriography for acrocyanosis in the affected limb (Rubin et al. 2001). The natural history of radiation-induced plexopathy is that of steadily increasing deterioration, although at times a plateau may be reached after 4-9 years of progression.

A diagnostic dilemma arises when symptoms and signs of brachial plexopathy develop in a patient who is known to have had cancer and radiation in the region of the brachial plexus, A painful lower trunk lesion with Horner's syndrome strongly suggests metastatic plexopathy, whereas a relatively painless upper trunk lesion with lymphedema favors radiation-induced plexopathy. **MRI** is inn always discriminating between metastatic and radiation because it may reveal an appearance of high signal intensity on T2-weighted images and contrast enhancement in cases of both radiation fibrosis and tumor infiltration (Wouter van Es et al. 1997). In the early and middle stages of radiation plexopathy, nerve conduction studies disclose features of de myelin a ting conduction block, but as time passes, studies reveal evidence of conversion to axon loss (Ferrante and Wilbourn 2002). Needle EMG is helpful in separating radiation-induced plexopathy from neoplastic plexopathy by the presence of myokymic discharges in the former. These are spontaneously occurring grouped action potentials {triplets or muitiplets) followed by a period of silence, with subsequent repetition of a grouped discharge of identical potentials in a semi rhythmic manner. They appear to result from spontaneous activity in single axons induced by local membrane abnormalities. They have not been reported in cases of tumor plexopathy.

Idiopathic Brachial Plexopathy

Arm pain and weakness are the cardinal manifestations of idiopathic brachial plexopathy. It occurs in all age-groups, but most patients are distributed fairly evenly between the third and seventh decades. Men arc affected two to thtee times more often than women; there appears to be a higher incidence among men engaged in vigorous athletic activities, such as weight lifting, wrestling, and gymnastics. Although half of the cases seem unrelated to any precipitating event, in others the neuropathy follows an upper respiratory tract infection, a flulikc illness, an immunization, or prior surgery, or :: occurs postpartum. Rare hereditary forms have also been described: a painless brachial plexopathy in patients with hereditary neuropathy with liability to pressure palsies and a painful or painless hereditary neuralgic amyotrophy with predilection for the brachial plexus (Pellegrino et al. 1996).

Clinic ill Features

The illness begins with the abrupt onset of intense pain, described as sharp, stabbing, throbbing, or aching, located in a variety of sites, including the shoulder, scapular area, trapezius ridge, upper arm, forearm, and hand. The pain may last from hours to many weeks, and then it gradually abates. Lessening of pain is associated with the appearance of weakness. This may have been present during the painful period but was not appreciated because the pain prevented the patient from moving the limb. Weakness may progress for 2-3 weeks after the onset of pain. Although pain subsides in most patients, it may continue for several weeks after weakness has reached its peak, and, rarely, it recurs episodically for a year or more. Paresthesias occur in approximately one third of patients but do not correlate with the severity or extent of weakness.

On examination, approximately one half of patients have weakness in muscles of the shoulder girdle, one third have weakness referable to both upper and lower parts of the plexus, and approximately l.i% haw evidence ol lower plexus involvement alone. Most appear to be incomplete because there is sparing of one or more muscles in the same root distribution. The patient may hold the arm in a characteristic posture, with flexion at the elbow and adduction at the shoulder, perhaps to reduce mechanical tension on the plexus.

Recognition is growing that the typical syndrome of brachial plexopathy need not always be associated with lesions of trunks or cords but can be caused by discrete

lesions of individual peripheral nerves, including the suprascapular, axillary, long thoracic, median, and anterior interosseous. Individual fascicular involvement—of the musculocutaneous nerve causing isolated brachialis wasting—has also been reported (Watson et al. 2001). Thus the term *brachial pi ex its neuropathy* may be appropriate. Sensory loss, found in two thirds of patients, most commonly over the outer surface of the upper arm and the radial surface of the forearm, is usually less marked than is the motor deficit. One third of cases are bilateral, but many fewer are symmetrical. In a small number of patients, unilateral or bilateral diaphragmatic paralysis occurs (Lahrmann et al. 1999), and the combination of acute shoulder pain with respiratory symptoms should suggest the diagnosis of brachial plexus neuropathy.

Diagnosis

The major differential diagnostic consideration in a patient with acute arm pain and weakness is cervical radiculopathy related to ccrvicogenic disease. In this condition, however, pain is usually persistent, neck stiffness is invariable, and it is unusual for radicular pain to subside as weakness increases. Nonetheless, an upper trunk brachial plcxopathy can simulate a *CS* or C6 radiculopathy. The cervical paraspinal needle EMG done several weeks after the onset of pain should be normal in brachial plexus neuropathy but show increased insertional activity and fibrillation potentials in cervical radiculopathy. Another differential diagnostic consideration is neoplastic plcxopathy, discussed earlier in this chapter, This entity is usually unremittingly painful, and neurological findings are most often referable to lower plexus elements. A third consideration might be a focal presentation of motor neuron disease, but pain is not a feature of this disease and sensation is .;K\a>s spared.

Electtodiagnostic testing is helpful in confirming the diagnosis and ruling out other conditions. Sensory studies are abnormal in *ouc* llniil ol patient-;; flit most ciiiiiiiion abnormality is reduced amplitude of sensory action potentials of the median, ulnar, and radial nerves. Also helpful are musculocutaneous nerve conduction studies, which disclose significant reduction in the amplitude of the biceps compound muscle action potential. Needle EMG is helpful because ir shows absence of fibrillation potentials in the cervical paraspinal muscles, thereby pointing to a pathological process distal to the DRG. Needle EMG is ilso lu-lpt'ul III Mining oui the problems ot localization, identifying lesions localized to the brachial plexus, individual peripheral nerves, or peripheral nerve branches. Finally, in a small number of patients, needle EMG is abnormal on the asyuipiomatn. side and on the symptom atic side, indicating that brachial plexus neuropathy can sometimes be subclinical. Other laboratory studies are not helpful. In general, there are no specific immunological abnormalities, but syndromes resembling brachial plexus neuropathy have been found in association with systemic lupus erythematosus.

Pathophysiology and Etiology

The pathophysiology and pathogenesis of the disotdet are not clear. An abrupt onset might suggest an ischemic mechanism; ptior history of a viral syndrome or an immunizarion raises the possibility of an immune-mediated disorder. Complement-dependent, antibody-mediated demyelination may have participated in the peripheral nerve damage and nerve biopsy findings in four cases of brachial plexus neuropathy, which tevealed florid multifocal mononuclear infiltrates, suggesting a cell-mediated component as well (Suarez et al. 1996). In some cases, rapid recovery bespeaks demyelination and remyeI ination; in others, a long recovery period is more in keeping with axonal degeneration followed by axonal regeneration. Indeed, a biopsy of a cutaneous radial branch in a severe case of plcxopathy showed profound axonal degeneration. In most patients, electrophysiological abnormalities are restricted to the affected limb, whereas in a small number of cases, there is evidence of a more generalized polyneuropathy. Nerve biopsy studies of patients with autosomal dominant attacks of brachial plexus neuropathy during symptomatic phases disclosed prominent perivascular inflammatory infiltrates with vessel wall disruption, suggesting that the hereditary disorder has an immune pathogenesis, possibly caused by genetic abnormalities of immune regulation (Klein et al. 2002).

Treatment and Prognosis

In the acute stage of the disotder, opioid analgesics are often required to control pain. A 10-day course of corticosteroids may be beneficial in a small number of patients. Arm and neck movements often aggravate pain; therefore, immobilization of the arm in a sling is helpful. With the onset of paralysis, range-of-motion exercises help to prevent contractures. In the small number of patients with significant permanent functional disability, orthotic devices may be helpful.

The natural history of brachial plexus neuropathy is benign; improvement occurs in the vast majority of patients, even in those with considerable muscle atrophy. Thirty-six percent have recovered by the end of 1 year, seventy-five percent by the end of 2 yeats, and eighty-nine percent by the end of 3 years. Although some patients think they have made a full functional recovery, careful examination may disclose mild neurological abnormalities, such as isolated winging of the scapula, slight proximal or distal weakness, mild sensory loss, or reduced retlex activity. In two thirds of patients, onset of improvement is noted in the first month after symptoms begin. Those who

continue to be bothered by pain and lack any signs of improvement within the first 3 months of the illness take a longer time to recover.

DISORDERS OF THE LUMBOSACRAL PLEXUS

Anatomical Features

The lumbar plexus is formed within the psoas major muscle by the anterior primary rami of lumbar spinal nerves LI, L2, L3, and L4. It is connected to the sacral plexus in the :nn- pelvis '^y tin .interior div'sion of 1.4 Figure 8 1.1 I A), Branches of the lumbar plexus include the iliohypogastric and ilioinguinal nerves arising from LI (with a contribution from T12), the lateral femoral cutaneous nerve of the thigh originating from the posterior divisions of L2 and L3, and the genitofemoral nerve arising from the anterior division of LI and L2. Other branches are the femoral nerve, formed from the posterior divisions of L2, L3, and L4 within the substance of the psoas muscle, and the obturator nerve, formed by the anterior divisions of L2, L3, and L4.

The lumbar plexus communicates with the sacral plexus via the anterior division of L4, which joins with L5 to form the lumbosacral trunk at the medial border of the psoas at the ala of the sacrum, The trunk enters the pelvis and joins the sacral plexus in the piriformis fossa. The sacral plexus, derived from the anterior rami of spinal nerves L4, L5, SI, 52, and S3, forms in ftont of the sacroiliac joint (Figure 81.1 IB). Like the lumbar plexus, the sacral plexus has anterior and posterior divisions. The anterior division contributes to the tibial portion, and die posterior division contributes to the peroneal portion of the sciatic nerve, which leaves the pelvis through the greater sciatic notch. A number of important branches come from the sacral plexus in the pelvis; the superior and inferior gluteal nerves arise from posterior divisions of the sacral plexus and supply the gluteus medius and minimus muscles and the gluteus maximus, respectively. The posterior cutaneous nerve of the thigh is formed by the anterior divisions of SI, S2, and 53. It passes through the greater sciatic fotamen into the buttock. The pudendal nerve originates from the undivided anterior primary rami of S2, S3, and S4 and extends into the gluteal region via the greater sciatic foramen.

Clinical Features

Neurological Examination

Lumbar plexopathy produces weakness, sensory loss, and reflex changes in segments 1.2 through L4, whereas sacral

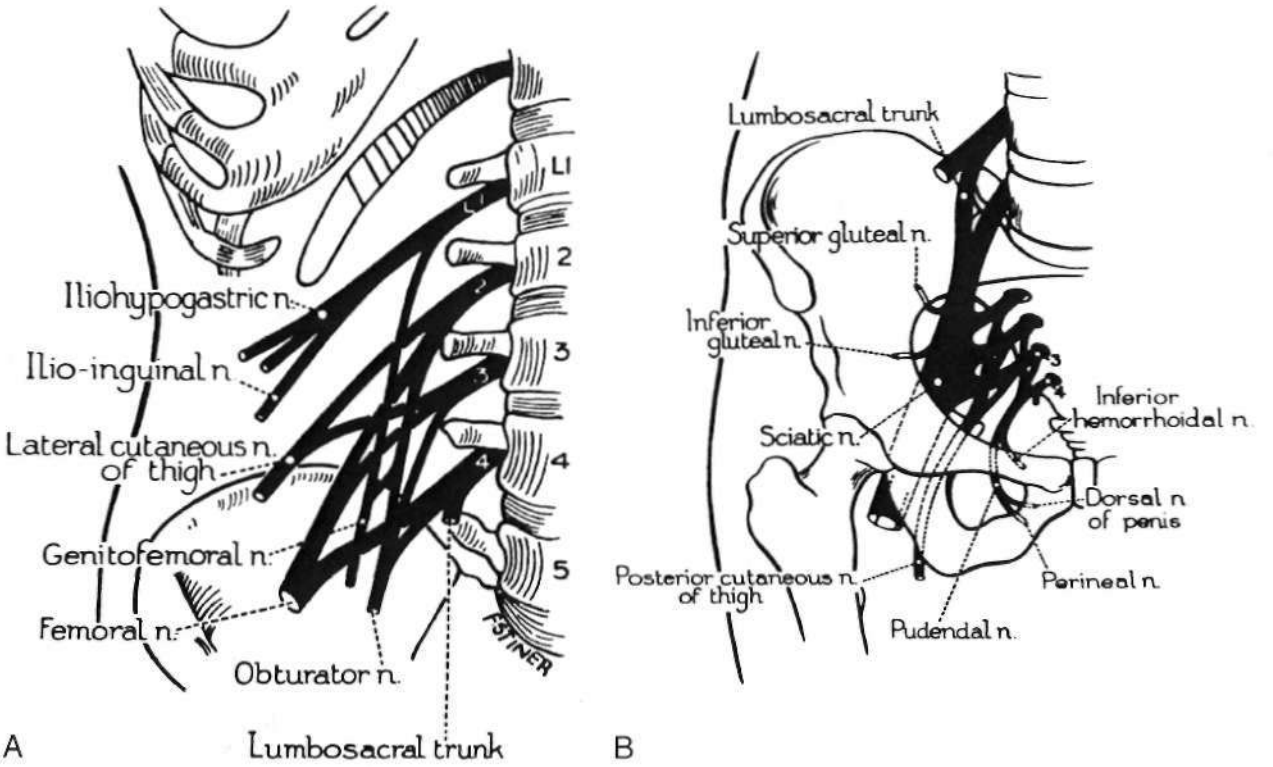


FIGURE 81.11 (A) The lumbar plexus is formed by anterior primary rami of lumbar spinal nerves (M'S) LI, L2, L3, and L4 (note the branches that arise from the plexus). (B) The sacral plexus is connected to the lumbar plexus by the lumbosacral trunk (note the branches that arise from the plexus in the pelvis). (Reprinted with permission from Haymaker, W. & Woodhall, K. 195.3, *Peripheral Nerve injuries,* 2nd ed, WB Saunders, Philadelphia.)

plexopathy leads to similar abnormalities in segments LJ through S3. Characteristic findings in lumbar plexopathy include weakness and sensory loss in both obturator- and femoral-innervated territories. Weakness of hip flexion, knee extension, and hip adduction, with sensory loss over the anteromedial aspect of the thigh, occurs; the knee jerk is absent or depressed. This combination of hip flexor and adductor weakness marks the disorder as either a plexopathy or radiculopathy. More precise localization depends on laboratory studies, including needle EMG, CT, and MRL

Findings in sacral plexopathy include weakness and sensory loss in the territories of the gluteal {motor only), peroneal, and tibial nerves. Extensive leg weakness involving the hip extensors and abductors, knee flexors, and ankle plantar flexors and dorsiflcxors exists. Sensory loss is found over the posterior aspect of the thigh, the anterolateral and posterior aspects of the leg below the knee, and the dorsolateral and plantar surfaces of the foot. Vasomotor and trophic changes may also be found in these areas. The ankle jerk is reduced or absent. Weakness of rhe gluteal muscles points to involvement of sacral plexus fibers proximal to the piriformis muscle in the ttue pelvis or to a more proximal sacral root level. As in lumbar plexopathy, accurate diagnosis often depends on electrodiagnostic studies and neuroimaging procedures.

Electrodiagnostic Studies

Electrodiagnostic studies are performed for several reasons. First, the EMG is helpful in identifying a motor sensory syndrome as a plexopathy and not a radiculopathy. The diagnosis of plexopathy is confirmed if the EMG discloses denervation (fibrillation potentials and positive sharp waves) and reduced recruitment (reduced numbers of motor units, firing rapidly) in muscles innervated by at least two lumbosacral segmental levels and involving at least two different peripheral nerves. An isolated plexopathy should not be associated with EMG abnormalities in paraspinal muscles. As will be seen, however, a number of pathological processes, including diabetes, radiation-induced changes, inflammation, vasculitis, and neoplasia may all involve the roots in addition to the plexus and produce a radicuioplexopathy. Second, EMG findings help to determine if a lumbosacral plexopathy is associated with a polyneuropathy. In the presence of the latter, signs of denervation and rcinnervation are found bilaterally, especially in the distal muscles. Third, EMG findings may strongly suggest a particular type of plexopathy; for example, myokymic discharges point to the diagnosis of radiation plexopathy.

Routine nerve conduction studies may help establish the diagnosis of plexopathy. Reduction in the amplitude of the sensory (sural and superficial peroneal) nerve action potentials indicates lo^s of axons distal to die l)K(r of SI and L5, respectively, F responses are also sometimes useful in the diagnosis of a plexopathy. Prolongation in F-wave latency with normal motor nerve conduction studies distally suggests a proximal lesion, either at a root or plexus level. Finally, conduction across the lumbar and sacral plexuses with root stimulation in a plexopathy may show an increased latency across a particular portion of the plexus.

Neuroimaging Studies

Bone destruction found in plain radiographs of lumbar and sacral vertebrae and the pelvis provides evidence for a structural plexopathy. Intravenous pyelography may demonstrate distortion of a ureter or the bladder. Barium enema may disclose displacement of the bowel. CT scanning of the abdomen and pelvis from a rostral point at the level of L1-E2 to a caudal point below the level of the symphysis pubis allows the regional anatomy of the entire lumbosacral plexus to be scrutinized (see Chapter 37).

The resolution of modern CT and MRI scanners allows identification of individual plexal components. The administration of oral or intravenous contrast is usually required to demonstrate the extent of structural abnormalities of the lumbosacral plexus, but it may not differentiate benign and malignant neoplasms, inflammatory masses, and hematoma. A normal MRI makes a structural plexopathy very unlikely. The CT may provide guidance for percutaneous needle biopsy of a lesion. Clues to the nature of a plexopathy are given in Table 81.1. An approach to evaluation of a plexopathy is summarized in Figure 81.12.

Differential Diagnosis

The differential diagnosis of lumbosacral plexopathy includes spinal root disorders, such as lumbosacral radiculopathy, polyradiculoneuropathy, cauda equina syndrome,

Tabic 81.1: Clues to the nature of a plexopathy

Structural disorders
I listory or pri-suiie of malignancy
Hemophilia or treatment with an anticoagulant
Pelvk trauma
Known atherosclerotic vascular disease and hypertension (aneurysm)
Pregnancy, labor, delivery
Abdominal (pelvic) surgery
Nonstructural disorders
Diabetes mellitus*
Vasculitis

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"Diabetics may develop a polyradiculoneuropathy that simulates a lumbosacral plexopathy.

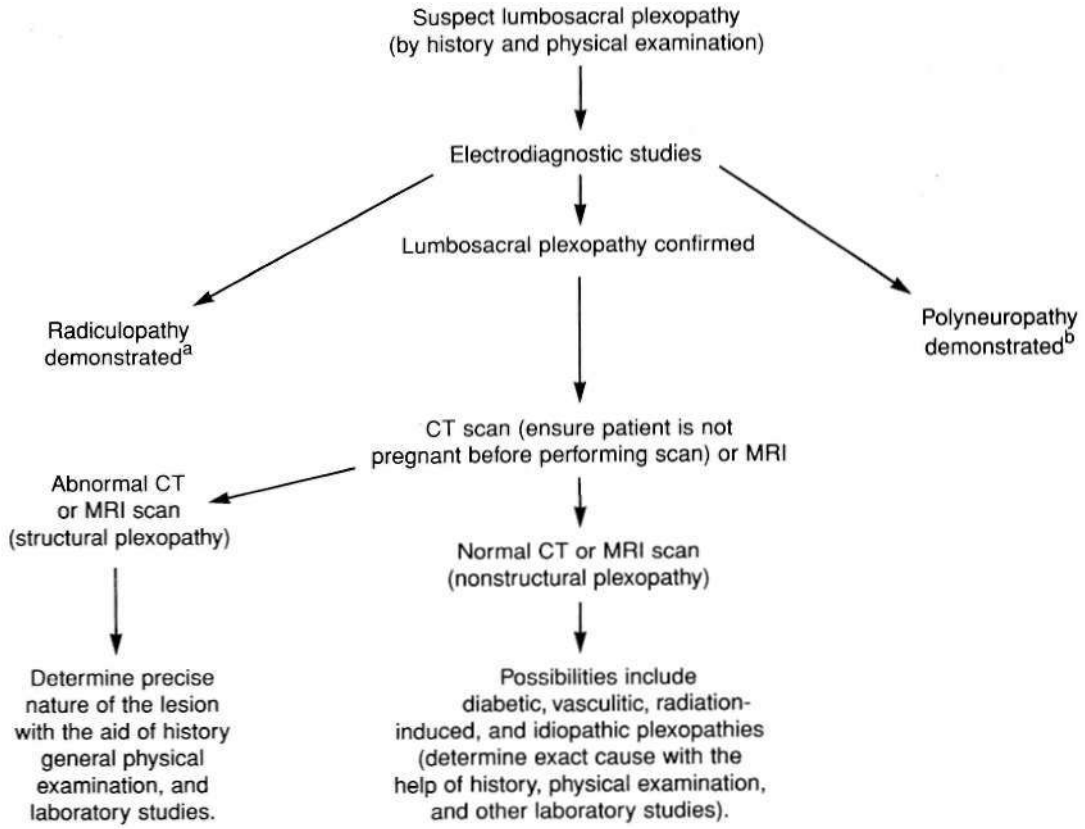

FIGURE 81.12 Approach to evaluation of lumbosacral plexopathy. Electrophysiological identification of radiculopathy may require spinal CT myelogram or MRI for confirmation and precise diagnosis. (CT computed tomography; MRI = magnetic resonance imaging.) "Radiculopathy is associated with plexopathy in diabetes, vasculitis, radiation, and malignancy. "Polyneuropathy may accompany plexopathies due to diabetes, vasculitis, and certain malignancies (paraneoplastic neuropathies).

anterior horn cell disorders, and myopathic conditions. Radiculopathies are usually painful, and the pain follows a predictable radicular distribution. Weakness is usually found in several muscles supplied by the same root, and the EMG usually demonstrates paraspinal muscle involvement. It is sometimes difficult to separate plexopathy from radiculopathy on clinical grounds alone, especially if several roots are involved.

Anterior horn cell disorders give rise to painless, progressive weakness with atrophy and fasciculation in the absence of sensory loss. When fully developed, such disorders should no! he contused will'; Ismsbiisacr.d plexopathy. In rare cases, however, a restricted anterior horn cell disorder, focal spinal muscular atrophy involving one leg, is seen. Absence of pain and sensory loss, normal imaging studies, and absence of diabetes and vasculitis all help point away from a disturbance of the lumbosacral plexus.

Myopathics are rarely confused with lumbosacral plexopathy, Myopathies with a focal, lower extremity onset can be distinguished from lumbosacral plexopathy by elevation of muscle enzymes, myopathic features on EMG (early recruitment of short duration, low-amplitude motor unit potentials), and muscle biopsy (variation in muscle fiber size, internalized nuclei, degeneration, regeneration, and inflammation),

Structural **Lumbosacral** Plexopathy

Hematoma

Patients with hemophilia and those receiving anticoagulants can develop hemorrhage in the iliopsoas muscle complex. It is important to recall that major components of the lumbar plexus, the femoral and obturator nerves, course from their origins in the lumbar paravertebral regions to their destinations in the thigh under cover of a tight layer of fascia. Over the iliac muscle, it is referred to as the *fascia iliaca,* and it becomes progressively thicker as it passes down, behind the inguinal ligament; at this site, it forms a dense and in distensible funnel enclosing the lower portions of iliacus and psoas.

Two major anatomical syndromes are associated **with** iliopsoas hematoma. In the first, the femoral nerve is the sole affected portion of the lumbar plexus. The hematoma arises in the iliacus and causes distention of the dense,

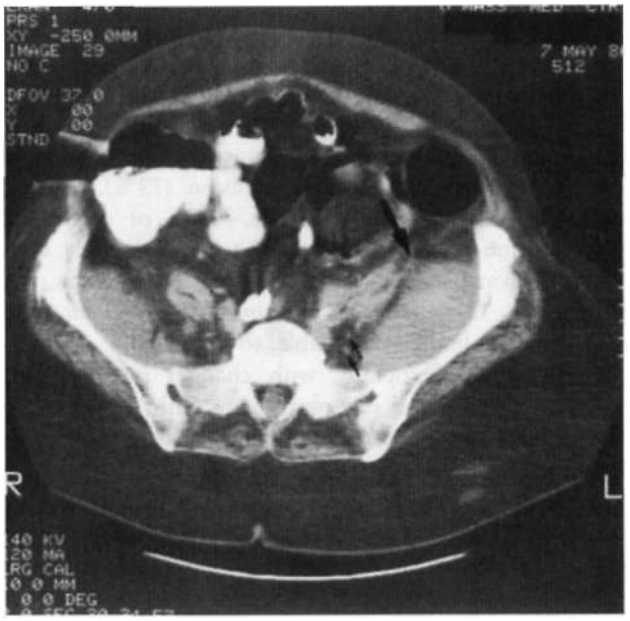

FIGURE **81.13** Hemorrhagic lumbosacral plexopathy. Computed tomographic scan at the L5-S1 level shows enlargement of die iliacus muscles, especially on the left side, owing to iliacus hematoma *(large arrow).* Small arrows indicate plexal elements. This large hematoma compresses the femoral and obturator nerves and the lumbosacral trunk.

overlying fascia above the inguinal ligament. In the second syndrome, hemorrhage arises in the psoas muscle or begins in the iliacus muscle and extends into the psoas. In this case, other components of the plexus, the obturator and lateral femoral cutaneous nerves, are involved.

Pain, often severe, is usually the first manifestation of a retroperitoneal hematoma. The pain is present in the groin and radiates to the thigh and leg. It is associated with gradually increasing paresthesias and weakness. When the femoral nerve is involved, weakness and sensory loss occur in its territory; when other components of the plexus are involved, changes are more extensive and conform to the territories supplied by the involved branches of the plexus. If the hemorrhage is large, a mass may develop in the lower abdominal quadrant. It typically arises from the lateral wall of the pelvis and can be seen in a CT scan to obscure the normal concavity of the innet aspect of the wing of the ilium (Figure 81.13). The patient usually lies in a characteristic posture with the hip flexed and laterally rotated because hip extension aggtavates the pain. Several days after the onset of the hematoma, a bruise may appear in the inguinal area or femoral canal. In most patients, recovery is satisfactory, although 10-15% of patients show no improvement. Pain usually disappeats within a week, and paresthesias and weakness resolve slowly.

Abscess

Psoas abscess was more common when tuberculosis was prevalent, but neurological complications, such as lumbar plexopathy and femoral neuropathy, were rare. This phenomenon was explained by the slow distention of the psoas sheath and by the fact that the abscess ruptured through the psoas fascia before the femoral nerve could be damaged by raised intra-psoas compartment pressure, Similarly, acute no *a* tuberculous psoas infection rarely produces nerve compression in cases of psoas abscess, presumably because the psoas fascia is distensible. Femoral neuropathy, however, does occur with iliacus muscle abscess because the fascia iliaca is relatively indistensiblc. Rarely, lumbar plexopathy is a complication of pelvic hydatidosis, caused by the tapeworm *Eckinococcus granulosus* (Serradilla et al. 2002).

Aneurysm

Back and abdominal pain ate often early manifestations of abdominal aortic aneurysms. Knowledge of abdominal and pelvic regional anatomy helps to explain the radiating characteristics of these pains. An expanding abdominal aortic aneurysm may compress the iliohypogastric or ilioinguinal nerve, leading to pain radiating into the lower abdomen and inguinal areas. Pressure on the genitofemoral nerve produces pain in the inguinal area, testicle, and anterior thigh. Compression of nerve trunks L5 through 52, which lie directly posterior to the hypogastric artery, may give rise to sciatica (Shields et al. 1997}. Thirteen percent of patients with aneurysms of the iliac artery will present with features of sciatica (Delgado-Garcia et al. 1999).

Hemorrhage from an abdominal aortic aneurysm may produce prominent neurological problems because of the retroperitoneal location of the hemorrhage or false aneurysm formation. In the case of an abdominal aortic aneurysm, a large retroperitoneal hematoma may injure the femoral and obturator nerves and even branches of the sacral plexus. Rupture of a hypogastric or common iliac artery aneurysm extends into the pelvis, compressing the L5 through S2 nerve trunk.

Ideally, the aneurysm should be diagnosed before rupture. Early recognition of an aneurysm is important because the mortality rate for operation on unruptured aneurysms is 5-7%, whereas that for symptomatic ruptured aneurysms is 35-40%. Unexplained back pain, leg pain, or pain radiating in the distribution of cutaneous nerves coming from the lumbar plexus should raise the suspicion of an aneutysm of the aorta or its major branches. A pulsatile mass felt while palpating **the** abdomen or, rarely, on rectal examination strongly suggests the presence of an aneurysm. Lumbosacral radiographs show a curvilinear calcific density, and abdominal sonography or CT scanning can confirm an aneurysm,

Trauma

Because of the relatively protected position of the lumbosacral plexus, traumatic lesions ate not common.

However, fracture of the pelvis, acetabulum, or femur or surgery on the proximal femur and hip joint may injure the lumbosacral plexus. Sacral fractures or sacroiliac joint separation accounts for most cases (68%) of traumatic lumbosacral piexopathy, while acetabular and femoral fractures are much less frequently implicated {14% and 9%, respectively) (Kutsy, Robinson, and Routt 2000). The latter, however, are more likely to cause injury to proximal nerves originating from the plexus. The mechanism of post-traumatic paresis in lumbosacral plexopathies may involve a number of factors, including nerve crush caused by fractured bone fragments; retroperitoneal hemorrhage; and traction as a result of hyperextension, hyperflexion, or rotation around the hip joint. Conservative measures appear to be the most appropriate way to manage post-traumatic injuries. More than two thirds of patients show good or moderate recovery of paresis after 18 months of follow-up after injury.

Pregnancy

The lumbosacral trunk may be compressed by the fetal head during the second stage of labor. This tends to occur in prolonged labor with midforceps rotation in a short, primigravida mother carrying a relatively large baby. A day or so after delivery, when the patient gets out of bed, she notes difficulty walking because of foot dorsiflexor weakness. Examination discloses weakness in dorsiflexion and inversion, with reduced sensation over the lateral aspect of the leg and dorsal surface of the foot. Nerve conduction studies disclose attenuation or absence of the superficial peroneal SNAP on the affected side, and needle EMG reveals denervation in muscles innervated by L5 below the knee (Katirji et al. 2002). The primary pathology is predominantly demyelination and the prognosis for complete recovery within 5 months is very good. In subsequent pregnancies, a trial of labor can be allowed as long as there is no evidence of disproportion or malpresentation. If labor proceeds, forceps should be used with great caution. Midforceps use in a woman with a previous obstetrical lumbosacral trunk palsy invites danger, it is prudent to perform cesarean section if the trial of labor is unsuccessful or if the infant is very large.

Femoral neuropathy may occur in a thin patient during cesarean section in cases managed with self-retaining retractors (Alsever 1996). In the thin abdominal wall, a deep, lateral insertion of retractor blades exerts pressure on the psoas and may injure the femoral nerve. After surgery, the patient notes weakness and numbness in the territory of the femoral nerve. Recovery is usually rapid and full. The obturator nerve may be compressed by the fetal head or forceps near the pelvic brim. Patients note pain in the groin and anterior thigh as well as weakness and sensory loss in the territory of this nerve.

Neoplasia

The lumbosacral plexus may be damaged by tumors that invade the plexus either by direct extension from intra-abdominal neoplasm or by metastases. Most tumors involve the plexus by direct extension (73%), whereas metastases account for only one fourth of cases. The primary tumors most frequently encountered are colorectal, cervical, and breast, as well as sarcoma and lymphoma. Three clinical syndromes occur: upper piexopathy with findings referable to the L1-L4 segments (31 %}; lower piexopathy with changes in the L4-S1 segments (51%); and pan-plexopathy with abnormalities in the LI-S3 distribution (18%). Neoplastic piexopathy typically has an insidious onset over weeks to months. Pain is a prominent early manifestation and is aching or cramping in quality. Weeks to months after pain begins, numbness, paresthesias, weakness, and leg edema develop. Incontinence or impotence occurs in fewer **than** 10% of patients. The most commonly encountered tumors arc colorectal in upper piexopathy, sarcomas in lower piexopathy, and genitourinary tumors in pan-plexopathies. The majority of neoplastic plexopathies **are** unilateral, although bilateral plexopathies, caused usually by breast cancer, occur in approximately 25% of patients. The prognosis in lumbosacral piexopathy caused by neoplasm is poor, with a median survival of 5.5 months.

Three special syndromes do not fit easily into upper, lower, or pan-plexopathy categories. In the first, there are paresthesias or pain in the lower abdominal quadrant or groin, with little or no motor abnormality. These patients are found to have a tumor next to LI leading to involvement of the ilioinguinal, iliohypogastric, or genitofemoral nerves. A second group has numbness over the dorsomedial portion of the foot and sole, with weakness of knee flexion, ankle dorsiflexion, and inversion. These patients have a lesion at the level of the sacral al.i, with involvement of the lumbosacral trunk. A third group presents with perineal sensory loss and sphincter weakness and have neoplastic involvement of the coccygeal plexus, caused usually by rectal tumors.

Neuroimaging with CT or MRI usually establishes the diagnosis of neoplastic piexopathy, but MRI is probably more sensitive (Taylor et al. 1997). Because pelvic neoplasms may extend into the epidural space, most often below the conus medullaris, MRI of the lumbosacral spine is indicated in most patients. On occasion, a plexus neoplasm is difficult to discern by the best neuroimaging procedures. Two main explanations for this phenomenon exist. First, patients who have received previous radiotherapy may have developed tissue fibrosis that cannot be distinguished from recurrent tumor. Second, some tumors track along the plexus roots and do not produce an identifiable mass. In these instances, ancillary imaging tests (high-resolution MRI, bone scan, plain films, intravenous

pyelogram), a biopsy of the plexus, or both may be required to determine the etiology,

Nonstructural Lumbosacral Piexopathy

Radiation Piexopathy

Radiation piexopathy usually produces slowly progressive, painless weakness. Pain develops in approximately one half of patients with radiation piexopathy, but it is not usually a major problem. Most patients with radiation piexopathy eventually develop bilateral weakness, which is often asymmetrical and affects predominantly the distal muscles in the L5-S1 distribution. In most patients, leg reflexes are absent, and superficial sensation is impaired. Symptoms referable to bowel or urinary tract are usually the result of proctitis or bladder fibrosis. The latent interval between radiation and the onset of neurological manifestations is between 1 and 31 yeats (median, 5 years), although very short latencies of less than *6* months have also been reported. An acute presentation of lumbosacral piexopathy 10 weeks following completion of radiation therapy for cervical cancer has also been observed (Abu-Rustum et al. 1999). No consistent relationship is evident between the duration of the symptom-free interval and the amount of radiation.

In most patients, radiation piexopathy is gradually progressive and results in significant or severe disability. CT and MRI of the abdomen and pelvis are normal. EMG discloses paraspinal fibrillation potentials in 50% of patients, suggesting that radiation damages the nerve roots in addition to the plexus; hence, a more appropriate designation is *radiation radiculoplexopathy.* In almost 60% of patients, the tMG discloses myokymic discharges, a feature that is only rarely seen in neoplastic piexopathy.

Vasculitis

Vasculitic neuropathy has generally been associated with the pattern of multiple mononeuropathy, but other neuropathic syndromes have also been described, including painful lumbosacral piexopathy. The portions of the peripheral nervous system most susceptible to vasculitis-induced ischemia are the segments of peripheral nerve-located at the midhumetus and midfemur levels, regions of nerve that appear to be watershed zones between vascular territories of the vasa nervorum. Proximal nerve trunks and nerve roots may also be vulnerable to the vasculitic process.

When a lumbosacral piexopathy syndrome occurs in a patient known to have a vasculitis, such as polyarteritis nodosa or rheumatoid arthritis, vasculitic piexopathy is an obvious diagnosis. The clinical diagnosis is more difficult in the setting of a seemingly idiopathic polyneuropathy or piexopathy because the process may be monosystemic and restricted to the peripheral nervous system. In such a case, a nerve biopsy may be required to establish the correct diagnosis,

Idiopathic f.umbosacral Piexopathy

Lumbosacral piexopathy may occur in the absence of a recognizable underlying disorder. Thus it can be considered a counterpart of idiopathic brachial plexus neuropathy (van Alfcn and van Engelen 1997). It may begin suddenly with pain, followed by weakness, which progtesses for days or sometimes many weeks. In many patients, the condition stabilizes, but in some, the course is chronic progressive or relapsing and remitting. Weakness is found in the distribution of upper and lower portions of the lumbosacral plexus in 50% of cases; major involvement occurs in the territory of the upper portion in 40% and in the lower portion in only 10% of patients. Most patients recover over a period of months to 2 years, although recovery is often incomplete. The EMG discloses a patchy pattern of denervation in the distribution of part or all of the lumbosacral plexus, but the paraspinal muscles are spared, indicating that the process docs not affect the lumbosacral roots. Dyek, Norell, and Dyck (2001) designated idiopathic lumbosacral piexopathy as *non-diabetic lumbosacral radicidoplexns neuropathy* and found that it resembles diabetic polyradiculoplcxopathy (see earlier section) in terms of its clinical presentation (subacute, asymmetrical, and painful with delayed and incomplete recovery) and pathological findings (ischemic injury and microvasculitis), and suggested that it probably has an immune pathogenesis. Indeed, preliminary data from controlled trials suggest that immune-modulating therapy may be beneficial (Verma and Bradley 1994; Dyck and Windebank 2002).

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Chapter 82
Disorders of Peripheral Nerves

E. Peter Bosch and Benn K. Smith

CLINICAL APPROACH TO DISORDERS OF PERIPHERAL NERVES

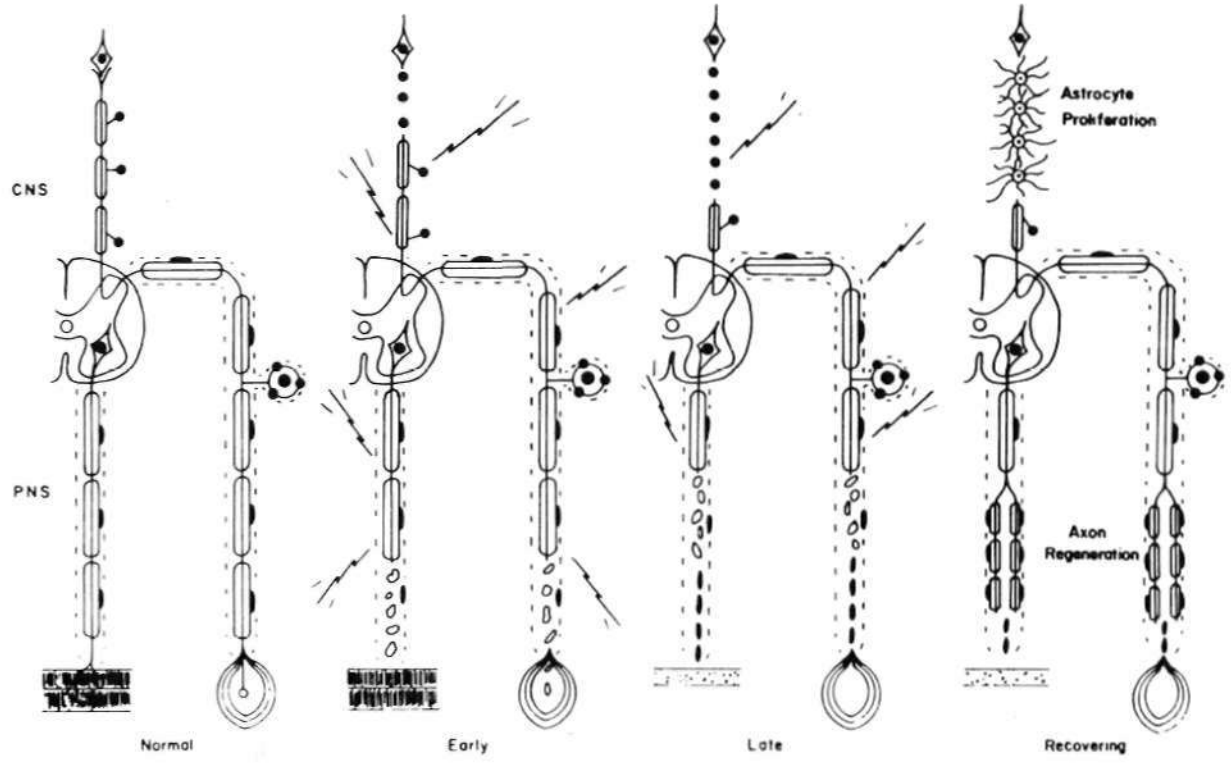
Peripheral neuropathies are caused by deranged function and structure of peripheral motor, sensory, and autonomic neurons. The main causes of neuropathy arc entrapment, Hansen's disease, diabetes, and other systemic diseases; inherited disorders; inflammatory demyelinating, ischemic, and paraneoplastic conditions; deficiency states; and toxins. A logical systematic diagnostic approach consists of (1) a careful history, (2) a detailed physical examination, and (3) electrophysiological studies, which not only confirm the presence of a peripheral nerve disorder but also may shorten the list of diagnostic possibilities. Further laboratory studies are often performed based on the outcome of the initial evaluation to arrive at a specific diagnosis. It is possible to establish a specific diagnosis in up to 75% of patients evaluated in tertiary referral centers by experts in neutomuscular disorders.

Pathological Processes Involving Peripheral Nerves

Despite the large number of causes of neuropathy, the peripheral nerve has a limited repertoire of pathological reactions to physical or metabolic insults. In general, these pathological reactions can be divided into four main categories: (1) wallerian degeneration, which is the response to axonal interruption; (2) axonal degeneration or axonopathy; (3) primary neuronal (perikaryal) degeneration or neuronopathy; and (4) segmental demyelination. The patient's symptoms, the type and pattern of distribution of signs, and the characteristics of nerve conduction study abnormalities provide information about the underlying pathological changes.

Any type of mechanical injury that causes interruption of axons leads to wallerian degeneration (degenctation of axons and their myelin sheaths) distal to the site of transection. Whereas motor weakness and sensory loss arc immediate in the distribution of the damaged nerve, distal conduction failure does not DI\ ur until 3 [vl] J;ivv Liter as the distal nerve trunk becomes progressively inexcitable. Motor response amplitudes begin to decline by the third to fifth day after injury and excitability is lost by the seventh to ninth day. For sensory nerves the loss of evoked potentials is delayed a further 2-3 days. The temporal sequence of wallerian degeneration is length dependent, occurring earlier in shorter than in longer distal nerve stumps. Denervation potentials ate typically seen in affected muscles 10-14 days after injury. Axonal interruption initiates morphological changes of the nerve cell body, termed *chromatolysis,* and produces a reduction in proximal axonal caliber. Regeneration from the proximal stump begins as early as 24 hours following transection but proceeds slowly and is often incomplete. The quality of recovery depends on the degree of preservation of the Schwann cell-basal lamina tube and the nerve sheath and surrounding tissue, as well as the distance of the site of injury from the cell body, and the age of the individual.

Axonal degeneration, the most common pathological reaction of peripheral nerve, signifies distal axonal breakdown resembling wallerian degeneration, presumably caused by metabolic derangement within neurons (Figure 82.1). Systemic metabolic disorders, toxin exposure, and some inherited neuropathies are the usual causes of axonal degeneration. The myelin sheath bteaks down concomitantly with the axon in .i process that starts at the most distal part of the nerve fiber and progresses toward the nerve cell body, hence the term *dyi/t^-hack neuropathy.*



FIGURK 82.1 A diagram of the main pathological events of distal axonal degeneration or axonopathy. The jagged lines indicate that either a toxin or a metabolic insult acts at multiple sites along motor and sensory axons in the peripheral nervous system (PNS) and central nervous system (CNS). Axonal degeneration begins at the most distal part of the nerve fiber and progresses proximally by the late stage. Recovery occurs by axonal regeneration but is impeded by astroglial proliferation in the CNS. (Reprinted with permission from Schaumburg. H. H., Spencer, P. S., *&c* Thomas, P. K. 1983, *Disorders of peripheral nerves,* Davis, Philadelphia.)

A similar sequence of events may occur simultaneously in centrally directed sensory axons, resulting in distal degeneration of rostral dorsal column fibers. The selective length-dependent vulnerability of distal axons could result from the failure of the perikaryon to synthesize enzymes or structural proteins, from alterations in axonal transport, or from regional disturbances of energy metabolism. In some axonopathies, alterations in axon caliber, either axonal atrophy or axonal swelling, may precede distal axonal degeneration. Clinically, dying-back neuropathy presents with symmetrical, distal loss of sensory and motor function in the lower extremities and extends proximally in a graded manner. The result is sensory loss in a stocking-like pattern, distal muscle weakness and atrophy, and loss of ankle reflexes. Axonopathies result in low amplitude sensory nerve action potentials iSKAPs) and compound muscle action potentials (CMAPs), but they affect conduction velocities only slightly. Electromyography (EMC) of distal muscles shows acute, chronic, or both kinds of denervation changes (see Chapter 36B). Because axonal regeneration proceeds at a maximal rate of 2-3 mm per day, recovery may be delayed and is often incomplete.

Neuronopathy designates primary loss or destruction of nerve cell bodies with resultant degeneration of their entire peripheral and central axons (Figure 82.2). Either lower motor neurons or dorsal root ganglion cells may be affected. When anterior horn cells arc affected as in anterior poliomyelitis or motor neuron disease, focal weakness without sensory loss is the result. *Sensory neuronopathy* or *polygangtionopathy* means damage to dorsal root ganglion neurons that results in the inability to localize the limb in space, diffuse areflexia, and sensory ataxia. A number of toxins such as organic mercury compounds, doxorubicin, and high dose pyridoxinc produce primary sensory neuronal degeneration. Immune-mediated inflammatory damage of dorsal root ganglion neurons occurs in paraneoplastic sensory neuronopathy and other conditions. It is often difficult to distinguish between neuronopathies and axonopathies on clinical grounds alone. Once the pathological processes are no longer active, sensory deficits become fixed, and little or no recovery takes place.

The term *segmental demyelination* implies injury of either myelin sheath or Schwann cells, resulting in breakdown of myelin sheaths with sparing of axons (Figure *823).* This occurs in immune-mediated demyelinating neuropathies and in hereditary disorders of Schwann ccll-myelin metabolism. Primary myelin damage may be produced c\pcni:iciit:ilb by mvclmoioxic agents, such :is diphtheria toxin, or mechanically by acute nerve compression.

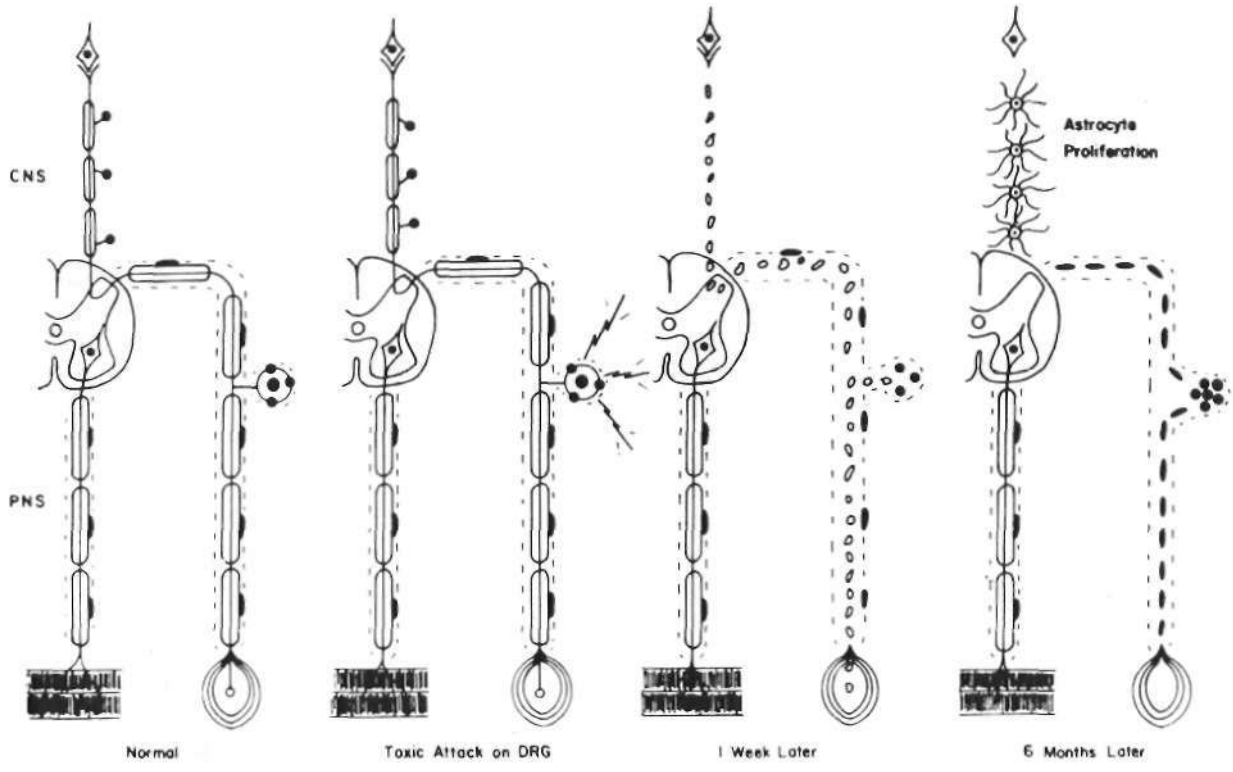


FIGURE 82.2 A diagram of the main pathological events of a sensory neuropathy or ganghopathy. A toxin, identified by the jagged lines, produces destruction of dorsal root ganglion (DRG) neurons, which results in degeneration of the peripheral-central axonal processes. Recovery is poor, as no axonal regeneration can take place. (CNS = central nervous system; PNS = peripheral nervous system.) {Reprinted with permission from Scha um burg, H. H., Spencer, P. S., Sc Thomas, P. K. 1383, *Disorders of peripheral nerves,* Davis, Philadelphia.)

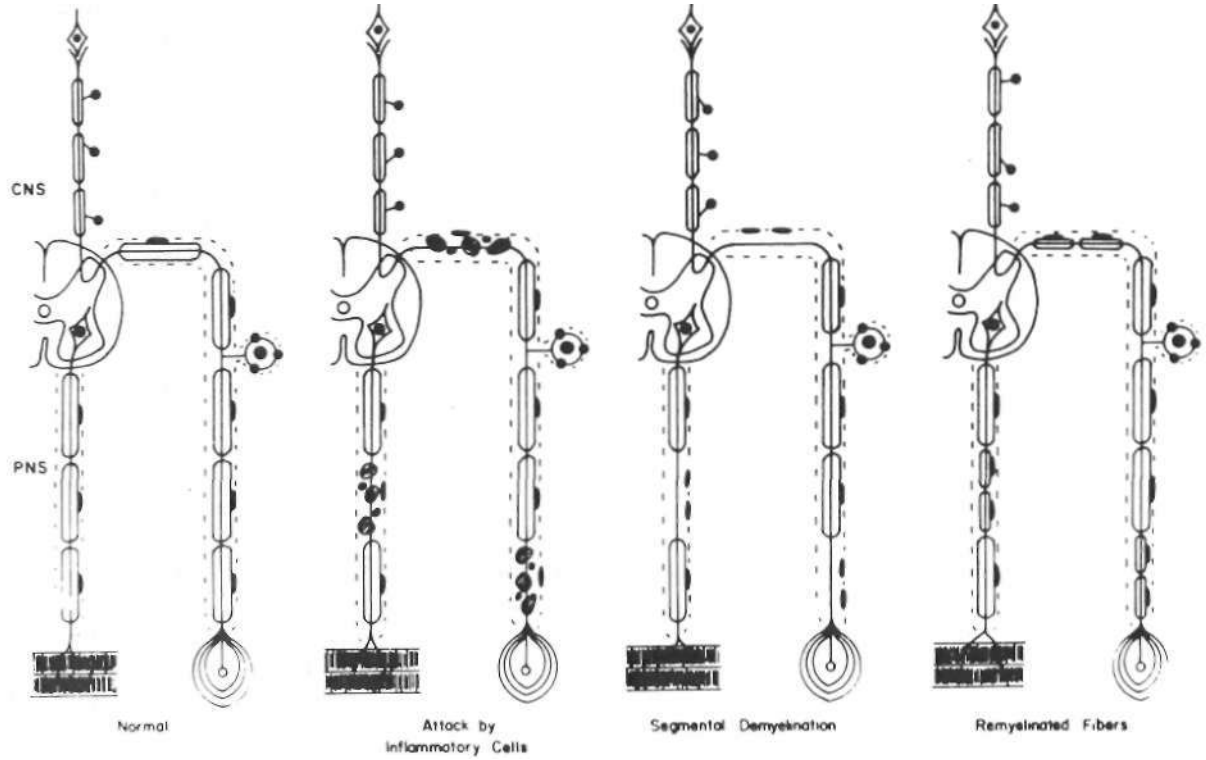


FIGURE 82.3 A diagram of the main pathological events of primary segmental demyelination in immune-mediated inflammatory polyradiculoneuropathies. The attack by inflammatory cells causes patchy multifocal demyelination along the nerve fibers but spares their axons. Recovery occurs by remyelination. The demyelinated segments become invested by several Schwann cells, resulting in a decrease in the internodal length of those areas. (CNS = central nervous system; PNS = peripheral nervous system.) {Reprinted with permission from Schaumburg, H. H., Spencer, P. S., & Thomas, P, K. 1983, *Disorders of peripheral nerves,* Davis, Philadelphia.)

Demyelination also may occur secondary to alterations in axonal caliber, cither atrophy or swelling, which may cause myelin remodeling over many consecutive internodes. Axonal atrophy and secondary demyelination are seen typically in uremic neuropathy. Remyelination of demyelinated segments usually occurs within weeks. The newly formed rernyelinated segments have thinncr-than-normal myelin sheaths and internodes of shortened length. Repeated episodes of demyelination and remyelination produce proliferation of multiple layers of Schwann cells around the axon, termed an o«io« *bulb.* The physiological consequence of acquired demyelination (i.e., inflammatory demyelination, but not hereditary myelinopathies) is conduction block, resulting in loss of the ability of the nerve action potential to reach the nerve, thereby producing weakness, though the axon remains intact, and hence there is little muscle atrophy. Relative sparing of temperature and pinprick sensation in many demyelinating neuropathies reflects preserved function of unmyelinated and small-diameter myelinated fibers. Early generalized loss of reflexes, disproportionately mild muscle atrophy in the piTsena ol proximal .ind distal weakness, neuropathic tremor, and palpably enlarged nerves are all clinical clues that suggest demyelinating neuropathy. Nerve conduction studies or analysis of single osmicated teased nerve fibers can provide confirmation of demyelination. Demyelination is considered if motor and sensory nerve conduction velocities (NCVs) arc reduced to less than 70% of the lower limits of normal with relative preservation of response amplitudes. The presence of partial motor conduction block, temporal dispersion of CMAPs, and marked prolongation of distal motor and F-wave latencies are all features consistent with acquired demyelination (see Chapter 36B). Recovery depends on remyelination, and therefore clinical improvement may occur within days to weeks. In many neuropathies, axonal degeneration and segmental demyelination coexist.

Diagnostic Clues from the History

The symptoms of neuropathic disorders fall under the general headings of motor, sensory, or autonomic disturbances. The inquiry should seek both negative and positive symptoms. Muscle cramps, fascieulations, myokymia, or tremor are positive manifestations of motor nerve dysfunction. In polyneuropathies motor symptoms produce early distal toe and ankle extensor weakness, resulting in tripping on rugs or uneven ground. Complaints of difficulty walking do not distinguish muscle weakness from sensory,

pyramidal, extrapyramidal, or cerebellar disturbance. If the fingers are weak, paiiems may complain of difficulty in opening jars or turning a key in a lock.

Positive sensory symptoms include prickling, scaring, burning, and tight bandlike sensations. Unpleasant sensations arising spontaneously without apparent stimulus are called *paresthesia.* The presence of spontaneously reported paresthesia is helpful in distinguishing acquired (paresthesias occurring in more than 60% of patients) from inherited (parasthesias reported in only 17% of patients) neuropathies. *Allodynia* refers to the perception of nonpainful stimuli as painful. Painful hypersensitivity to noxious stimuli is called *hyperalgesia.* Neuropathic pain, the extreme example of a positive symptom, is a cardinal feature of many neuropathies. Neuropathic pain often has a deep, burning, or drawing character that may be associated with jabbing ot shooting pains and typically increases during periods of rest.

Autonomic dysfunction can be helpful in directing attention toward specific neuropathies that have prominent autonomic symptoms. It is important to ask about orthostatic lightheadedness, fainting spells, reduced or excessive sweating, and heat intolerance, as well as bladder, bowel, and sexual dysfunction. Anorexia, early satiety, nausea, and vomiting are symptoms suggestive of gastroparcsis. The degree of autonomic involvement can be documented by noninvasive autonomic function studies (Low 1993) (see Chapter 83).

Histotical information regarding onset, duration, and evolution of symptoms provides important clues to diagnosis. Knowledge about the tempo of disease (acute, subacute, or chronic) and the coutse (monophasic, progressive, or relapsing) narrows diagnostic possibilities. Guillain-Barre syndrome (GBS), acute potphyria, vasculitis, and some cases of toxic neuropathy have acute presentations. A relapsing course is found in chronic inflammatory demyelinating polytadiculoneutopathy (C1DP), acute porphyria, Refsum disease, hereditary neuropathy with liability to pressure palsies (HNPP), familial brachial plexus neuropathy, and repeated episodes of toxin exposure.

In patier.is will: a chionii.- iiulnkni course over many years, inquiries about similar symptoms and foot deformities such as pes cavus in immediate relatives often point to a familial neutopathy. Inherited neuropathies are a major cause of undiagnosed neuropathy, accounting for 30—40% of patients teferted to tertiary centers for diagnosis. .Molecular genetic testing or the clinical and electrophysiological evaluation of relatives of patients with undiagnosed neuropathy may corroborate that the disorder is familial. Many neuropathies are caused by systemic disease. The presence of constitutional symptoms such as weight loss, malaise, and anorexia suggests an underlying systemic disorder. Inquiry should be made about preceding or concurrent associated medical conditions (diabetes mellitus, hypothyroidism, chronic renal failure, liver disease, intestinal malabsorption, malignancy, connective tissue diseases, human immunodeficiency virus [HIV] seropositivity); drug use, including over-the-counter vitamin preparations (vitamin Bg); alcohol and dietary habits; and exposure to solvents, pesticides, or heavy metals.

Diagnostic Clues from the Examination

The first step is to determine the anatomical pattern and localization of the disease process and the involvement of motor, sensory, or autonomic neurons inferred from the examination. Single root (monoradiculopathy) and brachial or lumbar plexopathies produce typical unilateral motor and sensory signs and symptoms (see Chapter SI).

Mononeuropathy means focal involvement of a single netve and implies a local process. Direct trauma, compression or entrapment, vascular lesions, and neoplastic infiltration are the most common causes. Electrophysiological studies provide a more precise localizarion of the lesion than may he possible by clinical examination and can scpatate axonal loss from focal segmental demyelination. Nerve conduction studies may reveal widespread changes, indicating an underlying neuropathy that predisposes ro nerve entrapment, such as in diabetes mellitus, hypothyroidism, acromegaly, alcoholism, and HNPP.

Multiple mononeuropathy or mononeuropathy multiplex signifies simultaneous or sequential damage to multiple noncontiguous nerves. Confluent multiple mononeuropathies may give tise to motor weakness with sensory loss that can simulate a peripheral polyneuropathy. Electrodiagnostic studies ascertain whether the primary pathological process is axonal degeneration or segmental demyelination (Table 82.1). Approximately two thirds of patients with multiple mononeutopathies display a picture of axonal damage. Ischemia caused by systemic, nonsystemic, or monosystemic (peripheral nerve) vasculitis or microangiopathy in diabetes mellitus should be considered. Other less common causes are disorders affecting interstitial structures of nerve, namely infectious, granulomatous, leukemic, or neoplastic infiltration, including Hansen's disease, and sarcoidosis. In the event thai focal demyelination or motor conduction block leads to multiple

Table 82.1: Causes of multiple mononeuropatiiii's

Axonal injury
Vasculitis (systemic, nonsystemic)
Diabetes mellitus
Sarcoidosis
Hansen's disease (leprosy)
Human immunodeficiency virus 1 infection
Demye 1 ination/conduction block
Multifocal acquired demyelinating sensory and motor neuropathy
Multifocal motor neuropathy
Multiple compression neuropathies (hypothyroidism, diabetes)
Hereditary neuropathy with liability to pressure palsies

mononcuropathies, multifocal acquired demyclinating sensory and motor neuropathy, multifocal motor neuropathy, or hereditary liability to pressure palsies should be considered.

Polyneuropathy is characterized by symmetrical, distal motor, and sensory deficits that have a graded increase in severity distally and by distal attenuation of reflexes. The sensory deficits produce a stocking-glove pattern. By the time sensory disturbances have reached the level of the knees, paresthesias are noted in the tips of the fingers. When the sensory impairment reaches the midthigh, involvement of anterior intercostal and lumbar segmental nerves gives rise to a tent-shaped area of hypesthesia on the anterior chest and abdomen. Motor weakness is greater in extensor muscles than in corresponding flexors. For example, walking on heels is affected earlier than toe walking in most polyneuropathies. It is helpful to deter- 11111;• the relative extent of sensory, motor, and autonomic neuron involvement, although most polyneuropathies produce mixed sensorimotor deficits and some degree of autonomic dysfunction.

Mntar deficits tend to dominate the clinical picture in acute and chronic inflammatory demyelinating neuropathies, hereditary motor and sensory neuropathies, and in neuropathies associated with osteosclerotic myeloma, porphyria, lead and organophosphate intoxications, and hypoglycemia. Asymmetrical weakness without sensory loss suggests motor neuron disease or multifocal motor neuropathy with conduction block (Table 82.2}. The distribution of weakness provides important information. The facial nerve can be affected in several peripheral nerve disorders (Table 82.3). In most polyneuropathies the legs are moiv si/vm-k al'liiicd ih.iii the arm;,. Notable excep tions to this rule are lead neuropathy, which frequently presents with wrist drop, multifocal motor neuropathy with conduction block, familial amyloid neuropathy type 2, occasionally porphyria, and adult-onset Tangier disease. Polyradiculoneuropathies cause both proximal and distal muscle weakness. The nerve root involvement is confirmed by denervation in paraspinal muscles on needle EMG.

Table H2.2: Ncuronopathics and neuropathies with predominantly moror manifestations

Motor neuron disease*
Multifocal motor neuropathy[3]"
Guillain-Barre syndrome
Acute motor axonal neuropathy*
Porphyric neuropathy
Chronic inflammatory polyradiculoneuropathy
Neuropathy with osteosclerotic myeloma
Disherit lumbar rsdiculoplexopathy
Hereditary motor sensory neuropathies (Charcot-Marie-Tooth disease)
Lead intoxication

"Pure motor syndromes with normal sensory nerve action potentials.

Table 82.3: Neuropathies with facial netve involvement

Guillain-Barre syndrome
Chronic inflammatory polyradiculoneuropathy (rare)
Lyme disease
Sarcoidosis
Human immunodeficiency virus 1 infection
Gelsolin familial amyloid neuropathy (Finnish)
Tangier disease

For example, proximal and distal weakness is encountered in acute and chronic inflammatory demyelinating radiculoneuropathies, osteosclerotic myeloma, porphyria, and diabetic lumbar radiculoplexopathy.

Predominant sensory involvement may be a feature of neuropathies caused by diabetes; carcinoma; Sjogren's syndrome; dysprotcincmia; acquired immunodeficiency syndrome (AIDS); vitamin B_{12} deficiency; celiac disease; intoxications with cisplatin, thalidomide, or pyridoxine; and inherited and idiopathic sensory neuropathies.

Autonomic dysfunction of clinical importance is seen in association with specific acute (e.g., GBS) or chronic {e.g., amyloid and diabetic) sensorimotor polyneuropathies, Rarely, an idiopathic panautonomic neuropathy can be the exclusive manifestation of a peripheral nerve disorder without somatic nerve involvement (Table 82,4).

Loss of sensation in peripheral neuropathies usually involves all sensory modalities, but occasionally the impairment may be restricted to selective sensory modalities. The latter situation makes it possible to correlate the type of sensory loss with the pattern of afferent fiber loss according to fiber diameter size (Figure 82.4). Pain and temperature sensation are mediated by unmyelinated and small myelinated A'; libers, -A hereas vibratory vnsi, proprioception, and the afferent limb of the tendon reflex are subserved by large myelinated *Act* and A^i fibers. Light touch is mediated by both large and small myelinated fibers. Quantitative sensory testing assessing both vibratory and thermal detection thresholds has become a useful addition to the bedside sensory examination in controlled clinical trials. Its use in routine clinical practice remains

Table 82.4: Neuropathies with autonomic nervous system involvement

Acute
Acute panautonomic neuropathy (idiopathic, paraneoplastic)
Guillain-Barre syndrome
Porphyria
I'oxit: viiiii Milk-. •„IL11r
Chronic
Diabetes mellitus
Amyloid neuropathy (familial and primary)
Paraneoplastic sensory neuronopathy {malignant inflammatory sensory polyganglionopathy)
Human i mm u no deficiency virus-related autonomic neuropathy
Hereditary sensory and autonomic neuropathy

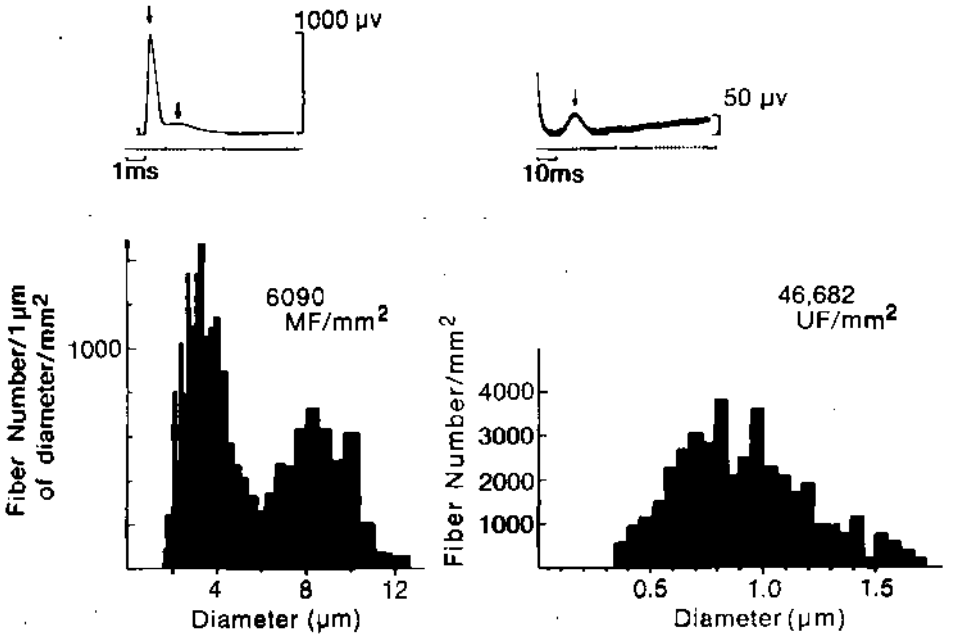


FIGURE 82.4 Myelinated fiber (ME) and unmyelinated fiber (UE) size-frequency histograms of a normal sural nerve. Fiber size distribution is bimodal for ME but ummodal for UR The ME tli n~~it y iv. iKirrn.il MII.II HIT-,:- ranges from 6000 to 10,000 fibers/mm^1 of fascicular area. The number of UEs is normally approximately four times that of Mi's. The corresponding compound nerve action potential recorded from the sural nerve in vitro is shown at top. Three distinct peaks indicated by arrows are, from left to right, Act, A<S, and C-potentials, which correspond to large MF, small ME, and UF peaks, respectively.

limited because the test is still subjective in that it requires patient cooperation and is time-consuming. In polyneuropathies preferentially affecting small fibers, diminished pain and temperature sensation predominate, along with burning pain, painful dysesthesias, and autonomic dysfunction. There is relative preservation of tendon reflexes, balance, and motor strength, and hence few abnormal objective neurological signs are found on examination, A pattern of sensory loss that is very characteristic (though still dependent upon the patient's subjective response) is distal loss of pinprick sensation, above which is a band of hyperalgesia (exaggerated pain from noxious stimuli), with normal sensation above this level.

Because routine sensory conduction studies assess only large myelinated fibers, such studies may be entirely normal in selective small fiber neuropathies. Quantitative sensory testing assessing cooling and heat-pain thresholds, tests of sudomotor function, and skin biopsy with analysis of intraepidermal nerve fiber density may be necessary for confirmation. Sweating mediated by unmyelinated sympathetic cholinergic fibers is often involved. The quantitative sudomotor axon reflex that evaluates sweating is a highly specific and sensitive method (sensitivity of 80%) to confirm small nerve fiber damage. Skin biopsies that demonstrate loss of intraepidcrmal nerve fibers is an alternative sensitive method for documenting small fiber neuropathy (MendelI and Sahenk 2003), About 10% of patients with normal sudomotor testing will have abnormal skin biopsies. This useful technique is currently limited to few academic centers. Relatively few disorders cause selective small fiber neuropathies (Table 82.5).

Selective large fiber sensory loss is characterized by areflexia, sensory ataxia, pseudoathctosis (involuntary movements of fingers and hands when the arms are outstretched and the eyes are closed), and loss of joinr position and vibration sense. A feature of sensory ataxia is ∴ positive Romberg sign, meaning disproportionate Kiss of balance with eyes closed compared with eyes open. Striking sensory ataxia together with inability to localize the limb in space or asymmetrical truncal or facial sensory loss directs attention to a primary disorder of sensory neurons or polyganglionopathies. The differential diagnosis of ataxic sensory neuropathies is limited (Table 82.6),

Palpation of peripheral nerves is an important though unreliable part ot I lie examination, i lypertrophy of a single nerve trunk suggests either a neoplastic process (neurofibroma, Schwannoma, or malignant nerve sheath tumor) or localized perineurial hypertrophic neuropathy. Generalized or multifocal nerve hypertrophy is found in a limited number of peripheral nerve disorders including leprosy, neurofibromatosis, Charcot-Marie-Tooth (GMT) disease types 1 and 3, acromegaly, Refsum's disease, and rarely CIDP.

Certain tell-tale signs of the skin and its appendages may direct the experienced examiner to a specific diagnosis

Table 82.5: Small fiber neuropathies

Idiopathic small fiber neuropathy
Diabetes mellitus and impaired glucose tolerance
Amyloid neuropathy (early familial and primary)
HIV-associared distal sensory neuropathy
Hereditary sensory and autonomic neuropathies
Fabry's disease
Tangier disease
Sjogren's (sicca) syndrome

Table 82,6: Sensory ataxic neuropathies

Sensory neuronopathics (polyganglionopathies)
Paraneoplastic sensory neuronopathy
  Sjogren's syndrome
  Idiopathic
Toxic polyneuropathies
  Cisplatin and analogues
  Vitamin B_s excess
Demyel in ati ng po lyradicu loneurop ath ies
  Guillain-Barre syndrome (Miller Fisher's variant)
  Immunoglobulin M monoclonal gammoparhy of undetermined significance

Tabes dorsalis produces severe ataxia with damage to the sensory nerve fibers at the root entry zone of the dorsal roots.

(Table 82.7): Alopecia is seen in thallium poisoning; tightly curled hair in giant axonal neuropathy; white transverse nail bands termed MceV *lines* in arsenic or thallium intoxications; telangiectasias over the abdomen and buttocks in Fabry's disease; purpuric skin eruptions of the legs in cryoglobulinemia and some vasculitides; skin hyperpigmentation or hypertrichosis in POEMS syndrome (characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes); enlarged yellow-orange tonsils in Tangier disease; pes cavus and hammer toes in CMT disease; and overriding toes and ichthyosis in Refsum's disease.

Electrodiagnostic Studies

It is helpful to follow a decision-making pathway initially based on the overall pattern of distribution of deficits, followed by the electrophysiological findings, and finally the clinical course (Figure 82.5). Electro diagnostic studies, carefully performed and adapted to the particular clinical situation, play a key role in the evaluation by (1) confirming the presence of neuropathy, (2) providing precise localization of focal nerve lesions, and (3) giving information as to the nature of the underlying nerve pathology (see Chapter 36B).

Tahle 82.7: Neuropathies with skin, nail, or hair manifestations

Disease	*Skin, nail, or hair manifestations*
Vasculitis	Purpura, livedo reticularis
CryOglohiikiiriiH.i	PlIipiMM
Fabry's disease	Angiokeratomas
Leprosy	Skin hypopigmentation
Osteosclerotic myeloma (POEMS syndrome)	Skin hyperpig mentation
Variegate porphyria	Bullous lesions
Refsum's disease	Ichthyosis
Arsenic or thallium intoxication	Mees" lines
Thallium poisoning	Alopecia
Giant axonal neuropathy	Curled hair

POF.MS = polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

Nerve Biopsy

N'erve biopsy should be performed only in centers with established experience with the technique; otherwise little useful information is likely to be obtained. The sural nerve is selected most commonly for biopsy because the resultant sensory deficit is restricted to a small area over the heel and dorsolateral aspect of the foot, and because its morphology has been well characterized in health and disease. The superficial peroneal nerve represents an alternative lower extremity cutaneous nerve suitable for biopsy and has the advantage of allowing simultaneous access to the peroneus brevis muscle through the same incision. This combined nerve and muscle biopsy procedure increases the yield of identifying suspected vasculitis (Collins et al. 2000). In patients with proximal involvement of the lower limbs, the intermediate cutaneous nerve of the thigh combined with a muscle biopsy can be selected. Nerve biopsy has proved to be particularly informative when techniques such as single teased fiber preparations, scmithin sections, ultrastructural studies, and morphometry are applied to quantitate the nerve fiber pathology. Relatively few disorders exist in which a nerve biopsy is essential for diagnosis (Table 82.8; Said 2002). In general, nerve biopsy is most useful in suspected vasculitis and amyloid neuropathy. It is helpful in the recognition of CIDP, inherited disorders of myelin, and some rare axonopathies in which there are distinctive axonal changes such as giant axonal neuropathy and polyglucosan body disease. The availability of molecular genetic tests for CMT type I A, hereditary liability to pressure palsies, and familial transthyretin amyloidosis has decreased the necessity for nerve biopsy in these conditions. Nerve biopsy is an invasive procedure and is associated with a 15% complication rate. Minor wound infections, wound dehiscence, and stump neuromas may occur. Approximately one third of patients (particularly those without much sensory loss initially) report unpleasanl sensory symptoms at the biopsy site after 1 year (Gabriel et al. 2000). The area of the original sensory deficit declines by 90% after 18 months because of collateral reinnervation (Theriault etal. 1998).

Punch skin biopsy is a promising, minimally invasive technique to evaluate cutaneous innervation in sensory neuropathies. Intraepidermal networks of unmyelinated nerve fibers can be demonstrated by immunostaining with the panaxonal marker protein gene product 9.5 and the use of confociI microscopy. The density of intraepidermal nerve fibers has been found to be reduced in skin biopsies obtained from patients with idiopathic, HIV-associated, and diabetic sensory neuropathies (Kennedy et al. 1999). This technique does not permit the study of melinated fibers or the detection of interstitial pathological processes.

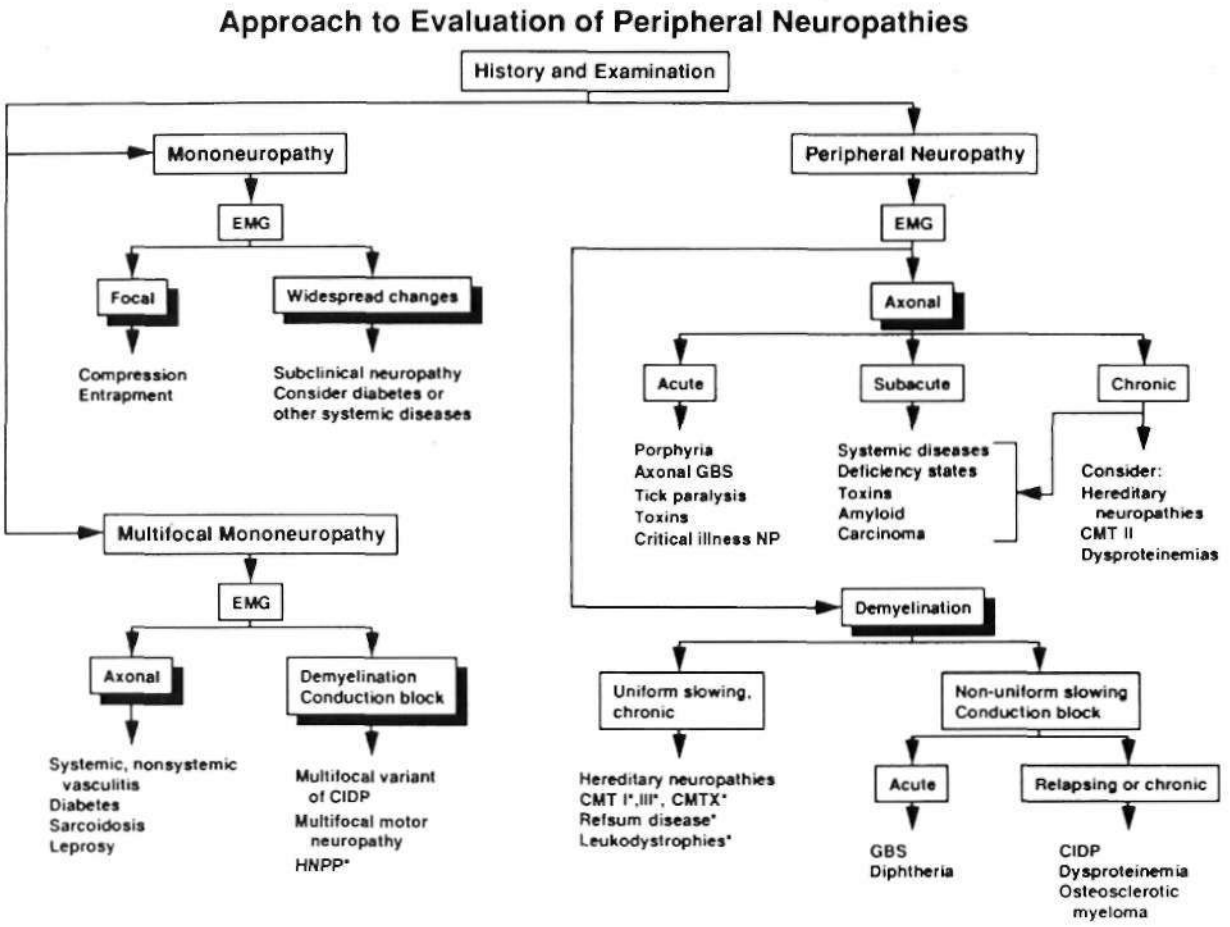


FIGURE 82.5 Diagnostic approach to the evaluation of a patient with peripheral neuropathy. Electromyography (EMG] denotes clectrodiagnostic studies. DNA diagnostic resting or specific biochemical tests are available for those conditions marked with asterisks. C1DP —chronic inflammatory dcmyclinating polyradiculoneuropathy; CMT = Charcot-Marie-Toorh disease; CMTX — Chareot-fvtarie-Tooth disease X-linked; GBS = Guillain-Barrc syndrome; HNPP = hereditary liability to pressure palsies; NP = neuropathy.

Other Laboratory Tests

The clinical neuropathic patterns and the results of clectrodiagnostic studies guide the experienced clinician to select the most appropriate laboratory tests. A few laboratory tests slit mid he *a* brained routinely in all patients with peripheral neuropathy. These include complete blood count, sedimentation rate, chemistry profile, fasting blood sugar, thyroid studies, vitamin Bj2 level, and serum protein electrophoresis with immunofixation electrophoresis. It is important to screen for monoclonal proteins in all patients with chronic undiagnosed neuropathy, particularly those older than *b0* years, because 10% ot suck patients have a monoclonal gammopathy. Several serum autoantibodies with reactivity to various components of peripheral nerve have been associated with peripheral neuropathy syndromes, and reference laboratories offer panels of nerve antibodies for sensory, sensorimotor, and motor neuropathies. It must be emphasized that the clinical relevance of most autoantibodies has not been established for the management of patients, and that their use is not cost-effective. Those of greatest clinical utility are listed in Table 82.9 (Kissel 1998).

An ever increasing number of molecular genetic tests for inherited neuropathies is available at reference

Table 82.8: Indications for nerve biopsy

Nerve biopsy results show diagnostic abnormalities
Vasculitis*
Amyloidosis"
Sarcoidosis*
Hansen's disease (leprosy)
(,1.1 in .iMiiul neuropathy
Polyglucosan body disease
Tumor infiltration
Nerve biopsy results show suggestive abnotmalides
Charcot-Maric-Tooth disease types 1 and 3
Chronic inflammatory demyelinating polyradiculoneuropathy
Paraproteinemic neuropathy (immunoglobulin M monoclonal gammoparhy with anti-myelin-a^sociiited glycoprotein antibody)

'Consider combined nerve and muscle biopsies.

Table 82.9: Neuropathies associated with serum autoantibodies

Autoantibody	*Disease (% positive)*
Antibodies .-gainst gangliosidcs	
CM! (polyclonal lgM)	Multifocal motor neuropathy (70%)
GM|, GDIa (polyclonal IgG)	Guillain-Barre syndrome (30%)
GQlb (polyclonal IgG)	Miller Fisher variant (>95%)
Antibodies against glycoproteins	
Myelin-associated glycoprotein (monoclonal IgM)	Ig\l monoclonal gammopathy of undetermined significance neuropathy (50%)
Antibodies against RNA-binding proteins	
Anti-I lu, antineuronal nuclear antibody 1	Malignant inflammatory polyganglionopathy (>95%)

Ig = immunoglobulin.

laboratories (see Inherited Neuropathies). Cerebrospinal fluid {CSF) examination is helpful in the evaluation of suspected demy el mating neuropathies and poly radiculopathies related to meningeal carcinomatosis or lymphomatosis. In two large unselected series of patients with initially undiagnosed peripheral neuropathy referred to specialized centers, a definite diagnosis could be made in 76-87%. Inherited neuropathies, CIDP, and neuropathies a SMH.1 ate J wit a OIIUT diseases accounted foi most diag noses. The improved diagnostic rate was in large measure because of detailed clinical and laboratory evaluations and study of relatives of patients with undiagnosed neuropathy.

Chronic Idiopathic Axonal Polyneuropathy

Despite all efforts, a group of acquired neuropathies remains idiopathic. Acquired chronic sensorimotor and sensory neuropathies are common in individuals older than 50 years, with an estimated prevalence of more than 3%. Chronic idiopathic axonal neuropathy afflicts patients in the fifth or sixth decade and has either mixed sensorimotor or pure sensory features. Patients complain of tingling, prickling, numbness or burning of the feet, and stiffness of the toes. There is loss of pin-prick together with loss of vibratory sensation in the feet, absent ankle reflexes, and mild toc-cxtensor weakness. These abnormal signs must be distinguished from normal manifestations of the aging peripheral nervous system (PNS). Loss of vibratory sense that is restricted to the the toes can be a normal finding in healthy elderly controls (e.g., present in 28% of individuals aged 65 years and older). Absent ankle reflexes are found in 38% of healthy controls older than *65* years. Nerve conduction and nerve biopsy studies are compatible with a length-dependent a\u:ul ccmop.r.liy. Absent sural SNAPs combined with spontaneous muscle fiber activity in the anterior tibialis muscle supports the diagnosis of neuropathy as such abnormalities are tarely found in healthy, older individuals (Vrancken et al. 2002). Idiopathic small fiber neuropathy presents with painful, burning feet, with or without numbness. The condition also occurs in older patients without associated systemic diseases or exposure to identifiable toxins. Most patients have elevated thermal thresholds on quantitative sensory examination and impaired distal sweating, measured by the quantitative sudomotor axon reflex test. Sural SNAPs are preserved if there is exclusive small-fiber involvement but are frequently reduced or absent in painful sensory-neuropathies affecting both large and small fibers. Reduced intraepidermal nerve fiber density on punch skin biopsy-provides objective evidence of distal small fiber neuropathy in these patients (Lacomis 2002). There is recent evidence that impaired glucose tolerance may be associated with chronic axonal sensory neuropathies of unknown cause. Among 73 patients referred for distal idiopathic sensory neuropathy and screened with glucose tolerance testing, *56%* had abnormal results, either impaired glucose tolerance (36%) or frank diabetes (Sumner et al. 2003).

Both idiopathic sensorimotor and sensory polyneuropathies pursue a very slow progressive course or reach a stable plateau. Even after a course of more than 10 years severe disability docs not occur. Independent ambulation is almost always maintained,

The management of these common neuropathies centers on the treatment of neuropathic pain and patient education about the favorable long term outcome (Wolfe and Barohn *1998).*

PAIN IN PERIPHERAL NEUROPATHY

Pain is one of the cardinal symptoms of peripheral nerve disorders. Neuropathic pain can occur spontaneously without provocation (stimulus-independent) or be provoked by noxious or non-noxious stimuli. *Hyperalgesia* is an. increased pain response to noxious stimuli. *Allodynia* is the sensation of pain elicited by non-noxious stimuli (e.g., from contact with clothing, bedsheets, or air-flow).

The sensation of pain in peripheral neuropathies is generated by nerve impulses triggered when free nerve endings (nociceptors) in sensitive tissues, particularly the skin, respond to noxious stimuli. A number of neurophysiologies! studies have determined that both small myelinated *AS* fibers, and unmyelinated nociceptive C fibers, mediate the afferent impulse of pain stimuli.

Intraneural microstimularion of human sensory nerves showed that stimulating *AS* nociceptors evokes an acute sensation of sharp, well-localized pain. In contrast, the stimulation of polymodal C nociceptors evokes a sensation of delayed, more diffuse burning pain. Peripheral nerve injury results in the upregulation of sodium channels in nociceptive terminals and unmyelinated axons that leads to ectopic activity in sensitized C fibers and spontaneous firing in nociceptive primary sensory neurons. The increase in peripheral activity generates a cascade of secondary changes in the dorsal horn with the end-result of central sensitization in second and third-order neurons. The peripheral and central sensitization involves a number of recently recognized neurobiological events which involve altered expression of sodium channels, increased glutamate activity at N-methyl-D-aspartate (NMDA) receptors, down regulation of y-aminobutyric acid (GABA) receptors and opiod receptors. Reorganizational changes can occur at the level of the dorsal horn and dorsal root ganglion, These include the sprouting of sympathetic axons into the dorsal root ganglion forming baskets around nociceptive neurons, and the sprouting of non-nociceptive *Afi* central axon terminals into the superficial dorsal horn (Woolf and Mannion 1999). For a more detailed discussion of neuropathic pain mechanism, sec Chapter 50,

Neuropathic pain can be a prominent presenting symptom in a great number of peripheral neuropathies (Table 82.10; Mendell and Sahenk 2003). Pain is characteristic of neuropathies with predominant small fiber involvement, but even in large fiber neuropathies a sufficient number of small fibers may be damaged to cause pain. The poor clinical correlation between morphological changes seen in nerve biopsy specimens and pain is not surprising if one considers that ectopic impulses may arise from regenerating axonal sprouts or dysfunctional fibers at more proximal or distal sites than the nerve segment examined at biopsy. Neuropathic pain usually affects distal skin and subcutaneous structures, may be constant or intermittent (stabbing, electrical jolts), may often have a temporal pattern of worsening ;it periods ol rest in bedtime, ;iinl is described with words such as *searing, burning,* or *icy-cold.* Sensory examination should use techniques to elicit abnormal positive sensory phenomena, Allodynia can be elicited by light touch or nonpainful cold stimuli using tuning forks kept in a refrigerator. When testing for hyperpathia, single and repeated pinpricks are used. Patients with hyperpathia may often complain of summation (pain perception increases with repeated stimulation) and aftersensations (pain continues after stimulation has ceased). Nerve trunk pain, a second type of neuropathic pain, is a deep-seated, sharp, knifelike proximal pain along nerve roots or trunks that improves with rest or optimal position but is aggravated by movement. Nerve trunk pain seems to be mediated by spontaneous impulses arising from nervi nervorum innervating nerve sheaths of affected nerve roots or trunks. Muscle pain and tenderness may develop with acutely evolving denervation of muscle as it occurs in GBS or acute poliomyelitis.

Table 82.10: Peripheral neuropathies frequently associated with pain

Diabetic neuropathies
- Painful symmetrical polyneuropathy
- A s y mme trica 1 po ly ra d icu lo p lex op a th y
- Truncal mo no neuropathy
- Brachial and lumbosacral plexopathy

Idiopathic distal small-fiber neuropathy
Guillain-Barre syndrome
Vasculitic neuropathy (sometimes)
Toxic neuropathies (sometimes)
- Arsenic, thallium
- Alcohol
- Vincristine, cisplatin
- Di de o x yn ucleo s i des

Amyloid neuropathies: primary and familial
Paraneoplastic sensory neuronopathy
Sjogren's syndrome
Human immunodeficiency virus-related distal symmetrical polyneuropathy
Uremic neuropathy
Fabry's disease
Hereditary sensory autonomic neuropathy

Management of Neuropathic Pain

Regardless of the underlying cause, the management of neuropathic pain is identical for all painful neuropathies (see Chapter SO). Symptomatic treatment of neuropathic pain seldom provides complete relief. At best, current therapies refill !ii .1 ;"" id", reduction -n p.iin. Simple analgesics (aspirin, acetaminophen, and certain nonsteroidal anti-inflammatory drugs) are rarely beneficial. Most patients require additional pharmacotherapy. Drugs from several different pharmacological classes have been shown to be safe and effective in alleviating neuropathic pain. These include tricyclic antidepressants (TCAs), anticonvulsants, sodium-channel blockers, opioids and non-narcotic analgesics, and topical agents (Galer 1995). In general, once an agent is selected for treatment, the medication is started at the lowest possible dosage and slowly titrated by increasing the dose every 3-7 days until significant pain relief or intolerable side effects occur. Many treatment failures can be attributed to insufficient dosing or intolerance caused by rapid dose escalations. The use of the following drugs can be supported by the results of randomized controlled studies. To compare efficacy among the different agents the number needed to treat (NNT) is given whenever possible. The NNT is an estimate of the total number of patients who need to be treated to achieve 50% pain reduction (Sindrup and Jensen 2000).

TCAs have been established to reduce pain independent of their effect on mood. These drugs block the reuptake of norepinephrine and serotonin, two neutotransmitters

that are implicated in nociceptive modulation, and inhibit sodium channels. Tricyclic antidepressants are effective for both constant and lancinating, paroxysmal pain. Based on the evidence of several controlled studies in patients with painful diabetic neuropathy, they are very efficient, with an NNT between 2 and 3. Treatment should be initiated with low-dose (10-25 mg) amitriptyline, desipramine, or nortriptyline given at bedtime and increased by similar increments no more than twice weekly. Most studies have shown that doses of tricyclics of 75-150 mg (less for elderly patients) arc required for pain suppression. At such high-dose levels, sedation, confusion, anticholinergic effects (constipation, dry mouth, urinary retention), and orthostatic hypotension are common side effects, particularly in elderly patients. Desipramine and nortriptyline cause less sedation and less orthostatic hypotension and have fewer anticholinergic effects than amitriptylinc. TCAs should be started with caution in elderly patients and in patients with ischemic heart dieasc, narrow angle glaucoma, or prostatism. Selective serotonin reuptake inhibitors are less effective than TCAs in relieving neuropathic pain.

Venlafaxinc is a potent inhibitor of norepinephrine and serotonin reuptake but has fewer side effects than TCAs. YiT'.if;i\ir;' *ill* i mg iLuly'i showed benefit with an NNT ol 5 in a cohort of 40 patients with painful neuropathies but was less efficacious than imipramine (Sindrup ct al. 2003). Bupropion (300 mg daily), a specific inhibitor of norepinephrine reuptake, reduced neuropathic pain by 30% in a small group of patients.

Anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine, and gabapentin) are considered second-line agents compared with antidepressants but are frequently given to suppress shooting or stabbing pains. Carbamazepine reduces neuronal membrane excitability by blocking sodium channels. In painful diabetic neuropathy carbamazepine (1000-1600 mg daily) was compared to placebo, and the NNT was 3, equivalent to that of TCAs. In practice, intolerance to side effects limits its use. It is important to initiate treatment with carbamazepine at a low dose {50 mg twice daily) and increase slowly to avoid initial symptoms of nausea, disequilibrium, and memory impairment. Oxcarbazepine, a keto-acid analogue, is better toletated.

Gabapentin is an anticonvulsant with unknown mechanism of action. Its effect may be mediated by binding to voltage dependent calcium channels expressed in the substantia gelatinosa of the dorsal horn. Two controlled studies demonstrated benefit in patients with painful diabetic neuropathy. The NNT was 4. When compared head to head with amitnptylme, gabapentin had equal efficacy but fewer side effects. Treatment is initiated at 300 mg at bedtime. The dose is escalated by 300 mg increments every 3-5 days until adequate pain relief is achieved. The median effective dose ranges from 900-1600 mg, although some patients require doses of 3600 mg per day.

Lamotrigine acts by by blocking sodium channels and by inhibiting the presynaptic release of glutamine. Lamotrigine (200—400 mg daily) resulted in moderate pain relief in controlled studies of painful diabetic and HIV-associated neuropathies (Eisenberg et al. 2001).

Mexilctinc, the oral analogue of hdocame, is the prototype of a sodium channel blocker. There have been inconsistent results with the use of mexilctinc. Two of the studies showed a beneficial effect in patients with diabetic neuropathy whereas four other studies failed to demonstrate benefit, resulting in an NNT of 38.

Tramadol, a non-narcotic centrally acting analgesic, has been proved effective in painful neuropathies related to diabetes and other causes in two clinical trials in doses ranging from 200-400 mg per day (Harati et al. 1998). The combined NNT for both studies was 3.4. Low-affinity binding to ^-opioid receptors and inhibition of norepinephrine and serotonin uptake contribute to its analgesic action. The drug is generally well tolerated but nausea and constipation occur in about 20% of patients,

High-dose dextromethorphan, a low-affinity NMDA glutamate antagonist, provided partial relief in painful diabetic neuropathy but was associated with significant sedation and ataxia.

Narcotic analgesics should be limited to patients who have failed adequate treatment trials of other agents. Randomized, controlled studies of oxycodone and levorphanot have demonstrated efficacy of opiods in postherpetic neuralgia and painful diabetic neuropathies (Rowbotham et al. 2003). Specific guidelines for chronic opioid therapy in neuropathic pain have been published and should be followed.

Topical agents that act through local skin absorption have the advantage of minimal or no systemic side effects and may be useful in patients with painful, burning feet. Capsaicin, an extract of chili peppers, presumably produces relief of pain through the depletion of substance P in unmyelinated nociceptive fibers. Capsaicin cream {0.025% or 0.075%) is applied to the affected area of skin three to four times a day. An initial intense burning frequently occurs after its application before any improvement is seen. h\ i:-.e \li:,iU v o>r:iin.H\l tor .u leasi 4 weeks before rejecting its effectiveness. Patches containing 5% lidocainc have been shown to reduce pain in postherpetic neuralgia. Some patients may receive relief from burning feet and allodynia by topical application of such patches on areas of excessive pain.

It may be necessary to use drugs in combination to achieve optimal pain relief. For example, if pain is still poorly controlled on a maximum tolerated dose of gabapentin, tramadol or a TCA may be added. There are no data from clinical trials to provide guidance regarding which combination to choose. Nonpharmacological treatments including low-intensity transcutaneous electrical nerve stimulation, acupuncture, medical hypnosis, and meditation may reduce the perception of pain and suffering. A comprehensive pain management program should be considered for patients with chronic refractory neuropathic pain.

ENTRAPMENT NEUROPATHIES

Entrapment neuropathy is defined as a focal neuropathy caused by restriction or mechanical distortion of a nerve within a fibrous or fibro-osseous tunnel or less commonly by other structures such as bone, ligament, other connective tissues, blood vessels, or mass lesions. Compression, constriction, angulation, or stretching arc important mechanisms that produce nerve injury at certain vulnerable anatomical sites (Tables 82.11 and 82.12). The term entrapment is a useful one in that it implies that compression occurs at particular sites where surgical intervention is often required to release the entrapped nerve, such as in the case of the median nerve at the wrist in moderate to severe carpal tunnel syndrome. Overuse has been implicated as the cause of entrapment neuropathies in certain occupations, including the playing of musical instruments by professional musicians.

In chronic entrapment, mechanical distortion of the nerve fibers leads to focal demyelination or, in severe cases, to wallerian degeneration. Morphological studies show a combination of active demyelination, remyelination, wallerian degeneration, and axonal regeneration at the site of entrapment. Endoncurial swelling, collagen proliferation, and thickening of perineuria! sheaths accompany the nerve fiber changes. Ischemia is not a significant contributing factor to nerve fiber damage in chronic compression. In contrast, ischemia plays a more significant role in nerve injury associated with acute compression secondary ro space-occupying lesions such as hematoma or the compartment syndromes.

The characteristic feature of entrapment neuropathy is either short segment conduction delay or conduction block across the site of entrapment (see Chapter 36B). In severe cases, wallerian degeneration gives rise to extensive denervation in affected muscles. Nerve conduction study measurements together with EMG are essential for diagnosis and reliable documentation of the site and severity of nerve entrapment. Although plain radiography, computed tomography (CT), or magnetic resonance imaging (MR!) may be of occasional value in identifying rare structural abnormalities, these imaging procedures arc not required for routine diagnosis.

Double Crush Syndrome

When a sizable cohort of patients with clcctrodiagnostic evidence of distal upper limb entrapment neuropathies was found to have either electrophysiological or radiological and clinical evidence of cervical radiculopathy, Upton and McComas proposed that focal compression of single nerve fibers proximally might so alter axoplasmic transport as to render the distal nerve more susceptible to symptomatic entrapment neuropathy, resulting in a double crush syndrome. Although the concept of double crush syndrome has since been invoked in a wide variety of entrapment neuropathies, often as an explanation for failed decompressive surgeries of the neck or limb or as a rationale to decompress a nerve in multiple proximal to distal sites along its course, this phenomenon is of uncertain validity (Wilbourn and Gilliatt 1997).

Upper Extremities

Median Nerve Entrapment at the Wrist (Carpal Tunnel Syndrome)

Carpal tunnel syndrome is by far the most common entrapment neuropathy. This entrapment occurs in the tunnel through which the median nerve and flexor

Tabic 82.11: Entrapment neuropathies of upper limbs

Nerve	*Sits of compression*	*Predisposing factors*	*Major clinical features*
Median	Wrist (carpal tunnel syndrome)	Tenosynovitis, arthritis, etc.	Paresthesia, pain, thenar atrophy
	Anterior interosseous	Strenuous exercise, trauma	Abnormal pinch sign, normal sensation
	Elbow (pronator teres syndrome)	Repetitive elbow motions	Tenderness of pronator teres, sensory loss
Ulnar	Elbow (cubital tunnel syndrome)	Elbow leaning, trauma	Clawing and sensory loss of fourth and fifth fingers
	Guyon's canal	Mechanics, cyclists	Hypothcnar atrophy, variable sensory loss
Kadij	Axilla	Crutches	Wrist drop, triceps involved, sensory loss
	Spiral groove	Abnormal sleep postures	Wrist drop, sensory loss
	Posterior interosseous	Elbow synovitis	Paresis of finger extensors, radial wrist deviation
	Superficial sensory branch (cheiralgia paresthetica)	Wrist bands, hand cuffs	Paresthesias in di irsi. . . . .' hand
Suprascapular	Suprascapular notch	Blunt trauma	Atrophy of supraspiiiatus and infraspinatus muscles
Dorsal scapular	Scalene muscle	Trauma	Winging of scapula on arm abduction
Lower trunk of the brachial plexus or C'S/TI roots	Thoracic outlet	Cervical rib, enlarged C7 transverse process	Atrophy of intrinsic hand muscles, paresthesias of hand and forearm

Table 82.12: Entrapment neuropathies of lower limbs

Nerve	*Site of compression*	*Predisposing factors*	*Major clinical features*
Sciatic	Sciatic notch	Endometriosis, intramuscular injections	Pain down thigh, footdrop, absent ankle jerk
	Hip Piriformis muscle	Fracture dislocations	
	Popliteal fossa	Popliteal Baker's cyst	
Fibular	Fibular neck	Leg crossing, squatting	Footdrop, weak evertors, sensory loss in dorsum of foot
	Anterior compartment	Muscle edema	Footdrop
Posterior tibial	Medial malleolus (tarsal tunnel syndrome)	Ankle fracture, tenosynovitis	Sensory loss over sole of foot
Femoral	Inguinal ligament	Lithotomy position	\\ ,ik Liu:. I'siniMiiii. .lbseni knee jerk
Lateral femoral cutaneous	Inguinal ligament (mcralgia paresthetica)	Tight clothing, weight gain, utility belts	Sensory toss in lateral thigh
Ilioinguinal	Abdominal wall	Trauma, surgical incision	Direct hernia, sensory loss in the iliac crest, crural area
Obturator	Obturator canal	Tumor, surgery, pelvic fracture	Sensory loss in medial thigh, weak hip adduction

digitorum tendons pass. Because the transverse carpal ligament is an unyielding fibrous structure forming the roof of the tunnel, tenosynovitis or arthritis in this area often produces pressure on the median nerve.

Symptoms consist of nocturnal paresthesias, most often confined to the thumb, index, and middle fingers. Patients complain of tingling numbness and burning sensations, often awakening them from sleep. Referred pain may radiate to the forearm and even as high as the shoulder (Stevens el al. 1999), Symptoms are often worse after excessive use of the hand or wrist. Objective sensory changes may be found in the distribution of the median netve, most often impaired two-point discrimination, pinprick and light touch sensation, or occasionally hyperesthesia, with sparing of the thenar eminence. Thenar (abductor pollicis brevis muscle) weakness and atrophy-may be present with prolonged entrapment (Figure 82.6). The syndrome is frequently bilateral and usually of greater intensity in the dominant hand. A positive Tinel's sign, in which percussion of the nerve at the carpal tunnel causes paresthesias in the distribution of the distal distribution of the median nerve, is present in approximately 60% of affected patients, but is not specific for carpal tunnel syndrome. Flexing the patient's hand at the wrist for 1 minute (Phalen's maneuver) or hyperextension of the wrist (a reversed Phalen's maneuver) can reproduce the symptoms. Carpal tunnel syndrome may alter sensory hand somatotopy in the parietal cortex.

Work-related wrist and hand symptoms (repetitive motion injury) from cumulative trauma in the workplace

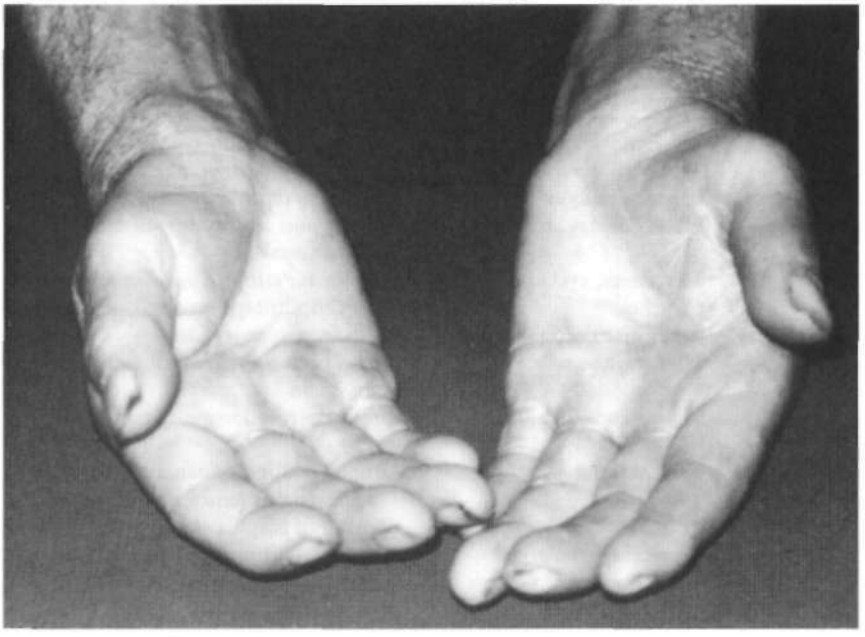


FIGURE 82.6 Thenar atrophy in chronic bilateral carpal tunnel syndrome.

have received increasing attention by the general public in recent years (Thomsen et al. 2002). Although a proportion of these cases have bona fide carpal tunnel syndrome, longitudinal natural history data suggest that the majority of industrial workers do not develop symptoms of carpal tunnel syndrome (Nathan ct al. 1998), Symptoms consistent with hand and wrist arthritis in a variety of occupational settings are now recognized as being much more common than complaints suggesting carpal tunnel syndrome (Dillon, Petersen, and Tanaka 2002). Carpal tunnel syndrome appears to occur in work settings that include repetitive forceful grasping or pinching, awkward positions of the hand and wrist, direct pressute ovet the carpal tunnel, and the use of handheld vibrating tools. Increased risk for the syndrome has been found in meat packers, garment workers, butchers, grocery checkers, electtonic assembly workers, musicians, dental hygienists, and housekeepers. The highest reported incidence of work-related carpal tunnel syndrome based on the number of carpal tunnel surgeries performed was 15% among a group of meat packers (Dawson 1993). Although computer keyboard use has long been thought to be related to developing carpal tunnel symptoms, recent data suggest that there is no convincing correlation between intensive keyboard use and the subsequent development of median neuropathy at the wrist (Stevens et al. 2001), This study found an overall prevalence of carpal tunnel syndrome of 3.5% in the study population, which is similar to that found for the general population by others {Papanicolaou, McCabe, and Firrell 2001).

The most sensitive electrodiagnostic test for carpal tunnel syndrome is the median nerve sensory conduction study, which exhibits a delayed sensory latency across the wrist in 70-90% of patients. Recording the latency at short distances over the course of the median nerve from palm to wrist and comparing this latency with the latency for the ulnar nerve at the same distance (palmar nerve conduction studies) can increase the sensitivity of sensory conduction studies (Stevens 1997). Most cases with moderate to severe involvement have prolonged median nerve distal motor latency. Some patients with carpal tunnel syndrome have significantly narrower-than-averagc carpal canals.

Diseases and conditions that have been found to predispose to the development of carpal tunnel syndrome include pregnancy, diabetes, obesity, age, rheumatoid arthritis, hypothyroidism, amyloidosis, gout, acromegaly, certain mucopolysaccharidoses, arteriovenous shunts for hemodialysis, old fractures at the wrist, and inflammatory diseases involving tendons or connecrive tissues at the wrist level (Becker ct al. 2002). On rare occasions, carpal tunnel syndrome may be familial.

Mild carpal tunnel syndrome must be distinguished from early median nerve involvement in polyneuropathy; occasionally the two conditions coexist.

In cases with only mild sensory symptoms, treatment with splints in neutral position, nonsteroidal anti-inflammatory agents, and local corticosteroid injection often suffice. Although nonoperative treatments have been advocated (Osterman, Whitman, and Porta 2002), a comparison of splinting versus surgery suggested that the latter may have a better longterm outcome than the former (Gerritsen et al. 2002). Evidence for the use of oral pyridoxine for carpal tunnel syndrome is conflicting at best and comes with the risk of toxic sensory polygauglionopathy (see Toxic Neuropathies, larer in this chapter). Use of a range of devices and appliances to protect the band against carpal tunnel syndrome, including gel-padded gloves, has shown little if any improvement in objective measures of nerve function. Severe sensory loss and thenar atrophy suggest the need for surgical carpal tunnel release. Although open surgical sectioning of the volar carpal ligament is still performed by some surgeons, the procedure is increasingly being approached using fiberoptic techniques, often resulting in more than 90% of patients having prompt resolution of pain and paresthesias {Mirza and King 1996), Improvement in distal latencies may lag behind the relief of symptoms. Comparing with preoperative values, nerve conduction studies demonstrate improveineur in those with moderate abnormalities preoperatively, whereas patients with severe or no abnormalities on baseline nerve conduction studies had poorer results (Bland 2001). A correlation between patients seeking workers' compensation who hire attorneys and poorer operative outcomes has also been reported (Katz J. N. et al. 2001). Older individuals may not improve as much as younger patients (Porter et a I. 2002), and factors such as poor mental health, significant alcohol consumption, longer disease duration, and male gender also portend a poorer outcome. Rarely, symptoms persist after operation. Poor surgical results usually are associated with incomplete sectioning of the transverse ligament, surgical damage of the palmar cutaneous branch of the median nerve by an improperly placed skin incision, scarring within the carpal tunnel, or an incorrect preoperative diagnosis. Surgical re-exploration may be required in diagnostically certain cases with poor response to the initial operation (Steyers 2002).

Other Entrapment Syndromes of the Median Nerve

Anterior Interosseous Nerve Syndrome. The anterior interosseous nerve is a pure motor branch of the median nerve that supplies the flexor pollicis longus, pronator quadrants, and flexor digitorum profundus muscles of the index and middle fingers. In the relatively rare anterior interosseous nerve syndrome, rhe nerve may be compressed by fibrous bands attached to the flexor digitorum superficialis muscle. Isolated involvement of this nerve more often occurs spontaneously in the context of a partial idiopathic brachial plexus neuropathy (Parsonage-Turner syndrome) or less commonly as a restricted form of multifocal motor neuropathy with conduction block. Patients often complain of pain in the forearm or elbow. The clinical manifestations

of an anterior interosseous nerve lesion include the inability to fk-x ilk- Ji.sUl dialings ol the thumb .11111 index finger. This makes it impossible to form a circle with those fingers. Nerve conduction study results of the median nerve are normal. In;: the -rotor latency from dhow to *r\-.s* pronator quadratus muscle is often prolonged, EMG is necessary to document denervation in muscles innervated by the anterior interosseous nerve.

Spontaneous recovery usually occurs, and therefore surgery may not be necessary unless penetrating injury, fracture, or progressive deterioration and weakness is detected.

Pronator Teres Syndrome. In the pronator teres syndrome, the median nerve is compressed in the proximal forearm between the two heads of the pronator teres muscle, a fibrous arcade of the flexor digitorum superficialis muscle, or the lacertus fibrosus. This entrapment may develop in individuals engaged in repetitive pronating movements of the forearm. Patients complain of paresthesias and numbness of the radial fingers, as well as pain and tenderness in the proximal forearm that is increased by resistance to pronation. Weakness of the flexor pollicis longus and abductor pollicis brevis is demonstrated, whereas pronation of the forearm is normal. Nerve conduction study results of the median nerve may sometimes show slowing in the elbow-wrist segment. In contrast to the carpal tunnel syndrome, the distal median motor and sensory latencies at the wrist are normal. Injection of corticosteroids into the pronator teres muscle and immobilization often provide relief of symptoms, but on occasion surgery may be necessary,

Median Nerve Entrapment at the Ligament of Struthers. A supracondylar spur of the humerus is present in a small proportion of normal individuals. A fibrous band, the ligament of Struthers, extends from this spur to the medial epicondyle and may compromise the median nerve along with the brachial artery. Clinical symptoms resemble the pronator teres syndrome, but the radial pulse diminishes when the forearm is fully extended in supination because of the concomitant entrapment of the brachial artery, Electrodiagnostic studies may allow differentiation from the pronator teres syndrome, because the ligament of Struthers syndrome involves the pronator teres muscle.

Ulnar Nerve Entrapment

Ulnar Nerve Entrapment at the Elbow. Ulnar mononeuropathy is the second most common entrapment or compression mononcuropathy, although it is considerably less common than carpal tunnel syndrome. Ulnar neuropathies at the elbow are caused by direct compression in the retrocondylar groove or entrapment as the nerve passes through the cubital tunnel, a fibro-osseous canal, the floor of which is formed by the medial ligament of the elbow joint, and the roof by the aponeurosis of the flexor carpi ulnaris muscle (Khoo, Carmichael, and Spinner 1996), The term *tardy ulnar palsy* is applied to an ulnar nerve lesion developing years after elbow trauma (usually fracture of the humerus). Other possible sources of injury of the ulnar nerve at the elbow include direct compression following general anesthesia while the patient recovers in bed (Stewart and Shantz 2003) or periods of unconsciousness, repetitive chronic trauma, and arthritis of the elbow joint. Symptoms and signs sometimes attributed to ulnar neuropathy after coronary bypass surgery are most often the result of stretch injury to the lower trunk of the brachial plexus. Ulnar nerve lesions at the elbow cause weakness of the flexor carpi ulnaris, flexor digitorum profundus of the ring and little fingers, and the intrinsic hand muscles. Pinch strength is reduced by weakness of adductor pollicis, flexor pollicis brevis, and first dorsal interosseous muscles. As a compensatory maneuver during attempted pinch of the thumb and index fingers, the flexor pollicis longus, a median nerve-innervated muscle, is used involuntarily and flexes the distal phalanx of the thumb (Fromcnt's sign). Weakness of the interossei muscles results in inability to produce a forceful extension of the interphalangeal joints as used in finger-flicking movements. Prominent atrophy of the first dorsal interosseous muscle ensues, together with clawing of the fourth and fifth fingers, the result of lumbrical weakness with secondary hyperextension of the metacarpophalangeal joints. The small muscles of the hand are always more severely involved than the forearm muscles (length-dependency or "dying-back" pattern). Sensory loss or hypesthesia involves the fifth finger, part of the fourth finger, and the hypothenar eminence and extends to the dorsum of the hand. Electrodiagnostic tests are useful in localizing the entrapment at the elbow. Focal slowing or localized reduction in the CMAP amplitude may be found in the elbow segment in more than 75% of cases (Azrieli et al. 2003). In the remaining patients localization is less precise because of predominant axonal loss.

Conservative treatment should be attempted in patients with mild symptoms or in those with symptoms brought on by occupational causes. Avoidance of repetitive elbow flexion and extension or direct pressure on the elbow may alleviate the symptoms. Elbow protectors are helpful in patients with a history of excessive elbow leaning. Conservative treatment should be continued for at least 3 months before surgery is considered. Surgical approaches to the ulnar nerve lesion at the elbow include simple release of the flexor carpi ulnaris aponeurosis, anterior transposition of the netve trunk, and resection of the medial epicondyle. The choice of procedure should be tailored to the specific lesion found at surgery. Only approximately 60% of patients benefit from surgery, and some experience worsening of symptoms.

Ulnar Nerve Entrapment at the Wrist in (he I Inar Tunnel (Guyon's Canal). Distal to the wrist, the ulnar nerve

enters Guyon's canal, which is formed between the pisiform bone and the hook of the hamate, covered by the volar carpal ligament and the palmaris brevis muscle. Within Guyon's canal the ulnar nerve divides into its terminal deep and superficial branches. Depending on the exact location of entrapment, motor or sensory impairment may occur alone or in combination. Because the palmar cutaneous branch leaves the ulnar nerve proximal to the wrist and does not enter Guyon's canal, sensory loss is confined to the palmar surface of the ulnar-innervatcd fingers. Ulnar nerve entrapment in Guyon's canal occurs much less frequently than at the elbow. The usual cause is chronic or repeated external pressure by tools, bicycle handlebars, the handles of canes, or excessive push-ups. Compression also may be caused by degenerative wrist joint ganglia, rheumatoid arthritis, or distal vascular anomalies. The diagnosis is confirmed with prolonged distal motor latencies to the first dorsal interosseous or abductor digiti minimi muscles and when denervation is documented in ulnar-innei vated hand muscles. MR] through Guyon's canal may demonstrate a structural lesion if compressive trauma is not the cause; in such cases surgical exploration may be tequired.

Radial Nerve Entrapment

Radial nerve compression in the axilla may result from crutches or from the weight of a sleeping partner's head (honeymoon palsy) or may occur at the spiral groove of the humerus during drunken sleep wherein the arm is draped over a chair (Saturday night palsy) (Spinner, Poliakoff, and Tiel 2002). Lesions at the axilla are characterized by weakness of the triceps brachii, brachioradialis, supinator, and extensor muscles of the wrist and fingers. If compression occurs in the spiral groove of the mid-upper arm, the triceps brachii is spared, resulting in weakness confined to the brachioradialis, wrist, and finger extensors. Minimal sensory abnormalities may occur over the dorsum of the hand, thumb, index finger, and middle finger. Radial nerve lesions caused by pressure usually improve in 6-8 weeks. This compression neuropathy must be differentiated from radial nerve injury caused by fractures of the humerus. The radial nerve is often involved in isolation or in combination with other single nerves in multifocal motor neuropathy with conduction block.

Posterior Interosseous Nerve Syndrome. The posterior interosseous nerve, or deep radial nerve, is a pure motor branch of the radial nerve in the forearm. Before entering the supinator muscle, the radial nerve supplies the brachioradialis, extensor carpi radialis longus and brevis, and supinator muscles. The rest of the extensor muscles, including the extensor carpi ulnaris, are innervated by the posterior interosseous nerve. The nerve appears most vulnerable to entrapment at the level of the supinator muscle. This uncommon syndrome occurs in association with rheumatoid arthritis, trauma, fracture, soft tissue masses, or strenuous use of the arm. The clinical manifestations of a posterior interosseous nerve lesion are an inability to extend the fingers at the metacarpophalangeal joints and radial deviation of the wrist on wrist extension caused by the weakness of the extensor carpi ulnaris muscle. EMG confirms the diagnosis by demonstrating denervation in the muscles supplied by the posterior interosseous nerve with sparing of more proximal radial-inncrvatcd muscles.

In rheumatoid arthritis, local injection of corticosteroids may be helpful. If the syndrome is progressive, surgical exploration, including synovectomy or decompression of the posterior interosseous nerve, may become necessary (Shergill et al. 2001).

Cheiralgia Paresthetica. A mononeuropathy of the superficial dorsal sensory branch of the radial nerve occurs as a result of trauma from tight wristbands or handcuffs and is called cheiralgia paresthetica. Paresthesias and pain in the distribution of the superficial sensory branch of the radial nerve characterize this benign, self-limiting condition. The symptoms can be aggravated by ulnar flexion of the hypcrpronated forearm. A small area of hypoesthesia in the dorsoradial aspect of the hand is frequently identified. Nerve conduction study results can show a low amplitude or absent dotsal radial SNAP.

Musculocutaneous Nerve Entrapment

The musculocutaneous nerve arises from the upper and middle trunks of the brachial plexus, penetrates the coracobrachialis muscle, and courses down the anterior aspect of the upper arm berween the two muscles it innervates, the biceps brachii and brachialis. Although most often involved in idiopathic brachial plexus neuropathy, this nerve also may be damaged with shoulder dislocations, following genetal anesthesia, or with vigorous exercise such as weight lifting. In carpet carrier's palsy, the nerve is compressed by repetitive carrying of heavy objects on the shoulder that arc held in place by the arm (Sander et al. *1997).* The differential diagnosis includes *C6* radiculopathy, restricted brachial plcxopathy, and rupture of the biceps tendon.

Clinically, patients with musculocutaneous mononeuropathy present with weakness and atrophy of the biceps brachii and brachialis muscles, diminished biceps brachii reflex, and sensory loss over the lateral aspect of the forearm anteriorly. EMG demonstrates denervation limited to the biceps brachii and brachialis muscles. Nerve conduction studies show a reduced musculocutaneous biceps CMAP and a low-amplitude lateral antebrachial cutaneous sensory response.

Spontaneous recovery is the rule. Local corticosteroid injection may provide some relief of pain. Surgical decompression is contemplated if no improvement occurs.

Suprascapular Nerve Entrapment

The suprascapular nerve is a pure motor branch of the upper trunk of the brachial plexus, which passes through the suprascapular notch to innervate the supraspinatus and infraspinatus muscles. Entrapment occurs after repetitive forward traction of the shoulders. This nerve also may be involved in a restricted form of idiopathic brachial plexus neuropathy. Diffuse aching pain in the posterior aspect of the shoulder is a cardinal symptom. Atrophy and weakness are confined to the infraspinatus and supraspinatus muscles. Slow and steady abduction of the arm starting from a vertical position alongside the chest is not possible with a severe lesion of the suprascapular nerve. 1 endoil ruptures of the rotator cuff need to be considered in the differential diagnosis. FMG shows denervation restricted to the supraspinatus and infraspinatus muscles. Local corticosteroid injection may give temporary relief of pain, although surgery is sometimes required (Antoniou et al. 2001).

Intercostobracbial Nerve Syndrome

The intercostobrachial nerve is a cutaneous sensory nerve derived from the second and third thoracic nerve roots and supplies the skin on the medial surface of the upper arm and axilla as well as the adjacent chest wall. It may be injured in modified radical mastectomy and other surgical procedures involving the axilla and lateral pectoral tegion (Wallace et al, 1996).

Neurogenic Thoracic Outlet Syndrome

Neurogenic thoracic outlet syndrome with objective neurological deficits is very rare, and the diagnosis is usually incorrect.

Lower Extremities

Entrapment neuropathies of lowet limbs arc shown in Table 82.12.

Sciatic Nerve Lesions

The sciatic nerve consists of two distinct nerves, the posterior tibial and the common fibular (peroneal) nerves, which share a common sheath from the pelvis to the popliteal fossa. The ^L:,uic nerve is occasionally vulnerable to entrapment as it crosses over the sciatic notch leaving the pelvis. Most sciatic nerve lesions result from trauma, such as fracture dislocations, hematomas in the posterior thigh compartment, intramuscular injections, and complications of hip replacement surgery (Plewnia, Wallace, and Zochodne 1999). Recurrent sciatic mo no neuropathy may be caused by endometriosis involving the nerve at the sciatic notch. Direct compression of the sciatic nerve is rare but occasionally occurs during coma, anesthesia, or prolonged sitting on a hard surface (toilet scat palsy). Either or both divisions of tile nerve may be compressed by a Baker cyst in the popliteal fossa,

A complete sciatic nerve lesion results in weakness of knee flexors and all muscles below the knee, as well as sensory loss of the entire foot except for the small region supplied by the saphenous nerve over the medial malleolus. The fibular division is more commonly involved than the posterior tibial in proximal lesions of the sciatic nerve and may mimic a common fibular neuropathy. In such patients, evidence of denervation in the short head of the biceps femoris and posterior tibialis muscles and abnormal sural or medial plantar SNAPs help localize partial proximal sciatic nerve lesions (Yuen and So 1999). On rare occasions, the pyriformis muscle may entrap the sciatic nerve trunk as it passes through or over the pyriformis muscle (the pyriformis syndrome). However, this clinical picture is almost always the result of lumbosacral root, sacral plexus, or sciatic nerve damage at other locations.

Common Fibular (Peroneal) Nerve Entrapment

Entrapment of the common fibular (peroneal) nerve is the most frequent entrapment neuropathy in the leg. Because of confusion between the terms *peroneal* and *perineal,* the Federative Committee on Anatomic Terminology has renamed the peroneal nerve the *fibular nerve.*

This nerve is particularly vulnerable in the region of the fibular neck as it passes through the origin of the fibularis (pcroneus) longus muscle. Near this opening, the nerve divides into three main terminal divisions: the superficial, deep, and accessory fibular nerves. A common fibular nerve lesion leads to weakness of foot **and** toe extension **and** foot eversion, wirh a footdrop and steppage gait. Sensory impairment is found over the lateral aspect of the lower leg and the dorsum of the foot. Direct pressure to the fibular head area, habitual leg crossing, weight loss, or a recurrent stretch injury as a result of an unstable ankle causing excessive foot inversion may result in fibular neuropathy. Improperly applied plaster casts or unrecognized pressure on the nerve in debilitated or unconscious patients may also be responsible for this nerve injury.

Fibular mononeuropathy needs to be differentiated from anterior tibial compartment syndrome, in which the deep fibular nerve is compressed by muscle swelling within the anterior compartment, caused by injury, heavy exercise, trauma, or ischemia. This results in an acute syndrome of severe lower leg pain, swelling, and weakness of foot and toe extensors. The anterior tibial compartment must be decompressed rapidly by fasciotomy to prevent irreversible nerve and muscle damage.

Electrodiagnostic studies are useful for localizing lesions and may provide clues to the underlying cause and a guide to prognosis. Although it is often possible by nerve

conduction studies to demonstrate focal conduction block or localized slowing in the region of the fibular head, contrary to common belief, the mosr frequent patho-physiological process is axonal loss regardless of the cause. EMG is important to exclude other sites of injury such .is the sciatic nerve, lumbosacral plexus, and L5 nerve root.

The prognosis is uniformly good in cases of acute compression, whereas recovery is delayed in those with stretch injuries. Bracing with a custom-made plastic ankle-foot orthosis is necessary to improve the gait in the presence of severe footdrop. The few patients who do not improve spontaneously after 3 months, or those who have pain or a slowly progressive fibular nerve lesion, may require MRI studies and surgical exploration (Kim and Kline 1996).

Posterior Tibial Nerve Entrapment (Tarsal Tunnel Syndrome)

Entrapment of the posterior tibial nerve occurs behind and immediately below the medial malleolus. In this region, the laciniate ligament covers the tarsal tunnel through which the nerve passes together with the tendons of the tibialis posterior, flexor digitorum longus, and flexor hallucis longus muscles, as well as the posterior tibial artery and veins. Burning pain occurs in the toes and the sole of the foot. If the calcaneal sensory branches are involved, pain occurs at the heel. Examination usually reveals plantar sensory impairment and wasting of the intrinsic foot muscles. Percussion at the site of nerve compression or eversinn of the foot may elicit pain and paresthesia. Electrodiagnostic study results should confirm the entrapment of the posterior tibial nerve at the tarsal tunnel by demonstrating mvolvcmenl til motor fibers to the abductor digiti minimi and abductor hallucis muscles as well as involvement of the medial and lateral plantar sensory fibers with sparing of the sural nerve. EMG is important to exclude involvement of muscles proximal to the foot such as the gastrocnemius muscle. The majority of suspected cases of tarsal tunnel syndrome turn out to have generalized peripheral neuropathy, SI radiculopathy, or non-neurological foot pain. Electrodiagnostie findings arc sometimes complicated by previous failed surgical procedures in the foot that may have injured the nerves of interest.

Local injection with corticosteroids underneath the laciniate ligament may temporarily relieve the symptoms. Surgical decompression is needed for permanent results in those rare cases m which objective evidence of this syndrome exists.

Sural Nerve Lesions

Although the vast majority of sural nerve lesions are iatrogenic as the result of diagnostic sural nerve biopsy, mononeuropathy of the sural nerve has been reported with a number of other conditions including lower limb vein stripping surgery, Baker's cyst surgery, local trauma, tightly laced high-topped footwear such as ski boots or ice skates, and rarely as the initial presentation of vasculitic mononeuriris multiplex.

Femoral Nerve Lesions

Femoral mononeuropathy is rare but may occur as the result of direct trauma or acute compression rather than from chronic entrapment.

Lateral Femoral Cutaneous Nerve Entrapment (Meralgia Paresthetica)

The lateral femoral cutaneous nerve, which is a pure sensory nerve, passes medial to the anterior superior iliac spine under the inguinal ligament to enter the thigh under the fascia lata and supplies the skin of the anterolateral part of the thigh. The site of entrapment is usually at the level of the inguinal ligament. Rarely, the nerve can be affected in its proximal segment by retroperitoneal tumors or be injured during appendectomy. The disorder is most often seen in association with obesity but may occur with enlargement of the quadriceps muscles from increased exercise and from pregnancy, ascites, or other conditions that increase intra-abdominal pressure. Direct compression by a belt or corset, fracture of the anterior portion of the ilium, or pelvic tilt causing undue stresses on the abdominal musculature are other causes. Patients develop numbness, painful burning, and itching over the anterolateral thigh. Pressure at the inguinal ligament medial to the anterior superior iliac spine elicits referred pain and dysesthesias.

Electrophysiological study results of the femoral nerve and quadriceps femoris muscle are normal, which helps to exclude lumbar radiculopathy.

A local anesthetic nerve block may have diagnostic value. Trcarmcnt consists of symptomatic measures such as rest, analgesics, and weight loss. Postural abnormalities should he corrected. Neurolysis is rarely beneficial.

Ilioinguinal Nerve

The ilioinguinal nerve is analogous to an intercostal nerve. Muscle branches innervate the lower portion of the transverse abdominal and internal oblique muscles. The cutaneous sensory nerve supplies the skin over the inguinal ligament and the base of the scrotum or labia. As the nerve takes a zigzag course, passing through the transverse abdominal and internal oblique muscles, it is subject to mechanical irritation. Pain is referred to the groin, and weakness of the lower abdominal wall may result in the formation of a direct inguinal hernia. Trauma, surgical procedures, and scar tissue are frequently responsible. Increased abdominal muscle tone, caused by abnormal

posture as seen in chronic back pain or Parkinson's disease, also can result in this neuropathy.

Conservative treatment includes rest and nonsteroidal anti-inflammatory agents. Neurolysis may be required in refractory cases when a mechanical lesion is suspected.

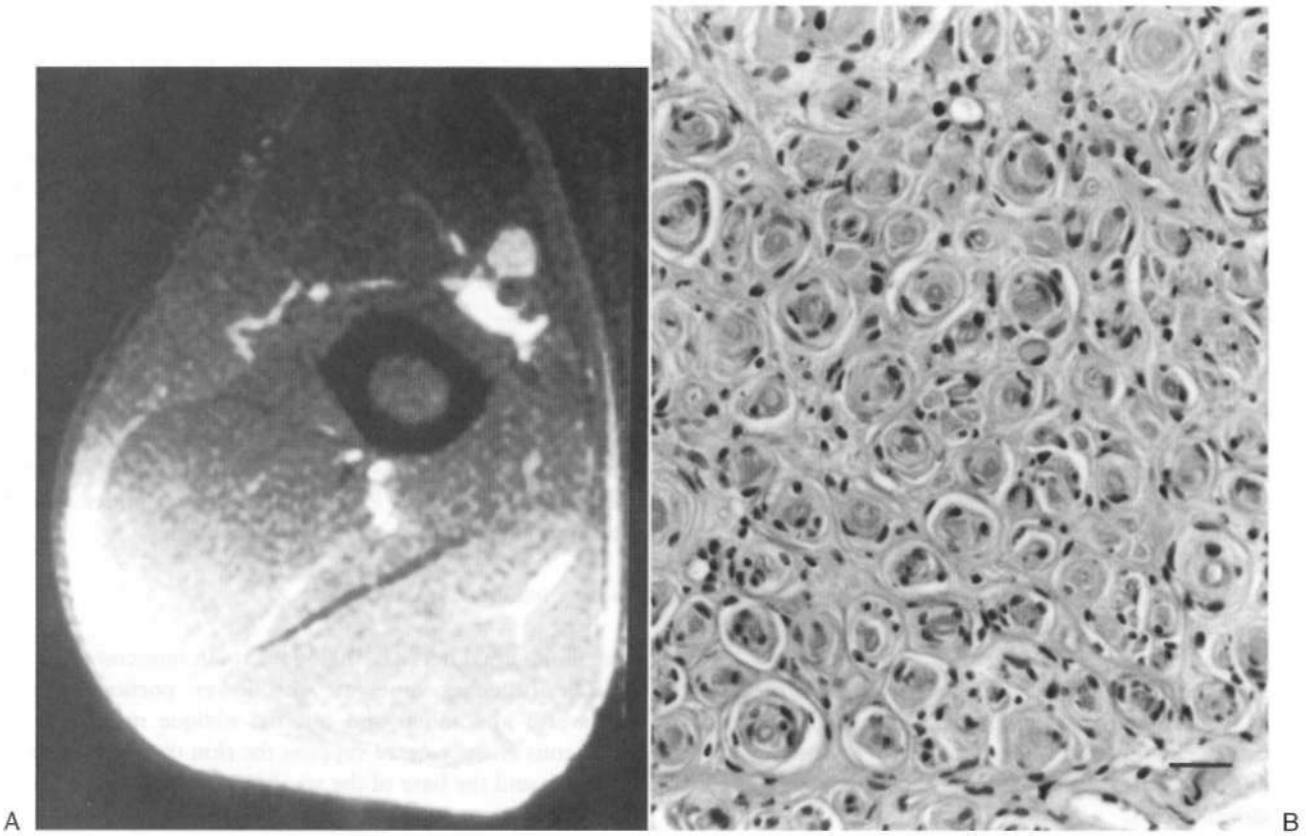
Obturator Nerve

The obturator nerve is vulnerable to entrapment as it passes through the obturator canal, for instance, by an obturator hernia or osteitis pubis. It is most often associated with pelvic malignancies (prostate, cervical, or uterine cancers), but can also be seen as a surgical complication, with trauma, and m the sctiing of diabetes mellitus. The entrapment produces radiating pain from the groin down the inner aspect of the thigh. There is weakness of hip adduction and sensory impairment in the upper medial thigh. Many patients appear to have hip-flexor weakness as a false localizing sign. Although this phenomenon may be explained by pain, it is more likely due to mechanical disadvantage of the hipflexors in the presence of weak thigh adductors, CT or MRI scanning of the pelvis is helpful in finding primary or metastatic pelvic tumors (Rogers et al. 1993).

This entrapment neuropathy is treated conservatively. If such treatment fails, or if symptoms progress to involve other nerves in the region, careful search for occult pelvic or retroperitoneal malignancy must be pursued.

Localized Perineurial Hypertrophic Mono neuropathy

A slowly progressive painless mononeuropathy that cannot be localized to entrapment sites and is caused by a focal fusiform enlargement of the affected nerve, termed *localized hypertrophic neuropathy,* is an uncommon condition affecting young adults (Simmons et al. 1999). The fusiform enlargement is mainly composed of "onion bulb-like whorls" formed by layers of perineurial cells (Figure 82.7B). The lamellae of the whorls stain for epithelial membrane antigen. The cause of the perineurial cell proliferation is not known. The condition may involve any major nerve trunk but is seen more frequently in the upper limbs, particularly the posterior interosseous nerve.



I•I(il."Ki' S2.7 (A) Axial magnetic resonance imaging of the right upper arm 10 cm proximal to the epicondyles demonstrates a focal enhancing enlargement of the median nerve after gadolinium administration. The fusiform enlargement of the nerve extended approximately 4 cm in length and measured 7 mm in diameter at its greatest thickness on serial axial cuts. (B) Fascicular biopsy specimens of the enlarged median nerve segment shows numerous onion bulb-like structures. By immunochemistry, the onion bulbs consist of epithelial membrane antigen-positive cells, confirming their perineurial cell origin. (Hematoxylin and eosin; original magnification *xSO;* bar = 20 |im.) (Courtesy Dr. P. J. Uyck, Mayo Clinic, Rochester, MN.)

It typically results in painless, slowly progressive weakness and atrophy in the distribution of the affected nerve, Sensory symptoms arc minor, although sensory nerve fibers are obviously involved. Electro diagnostic study results show an axonal mononeuropathy and help in the precise localization of the focal nerve lesion. MRI shows a focal enlargement of the affected nerve, increased signal on 12 weighted images, and enhancement with gadolinium (Figure 82.7A).

Surgical exploration and a fascicular biopsy by a surgeon experienced in peripheral nerve microsurgery confirm the diagnosis and excludes malignant peripheral nerve sheath tumors, which can be difficult to exclude on clinical grounds alone. Surgical resection of the involved nerve segment with graft repair offers the possibility of some recovery in selected cases (Gruen, Mitchell, and Kline 1998).

HEREDITARY NEUROPATHIES

The hereditary neuropathies constitute a complex, heterogeneous group of diseases, which frequently shate insidious onset and indolent course over years to decades. The number of such disorders in which the metabolic deiec. is known, such as in familial amyloid neuropathies, Refsum's disease, Fabry's disease, porphyria, hypolipoproteinemias, and many forms of CMT disease, is increasing rapidly. i or other inherited neuropathies classification still depends on clinical phenotype, mode of inheritance, and class of neurons predominantly affected. These conditions include hereditary motor neuropathy or spinal muscular atrophy (see Chapter 80), hereditary motor and sensory neuropathy, and hereditary sensory and autonomic neuropathy (HSAN). Major advances in understanding the molecular basis of inherited neuropathies have come from identifying chromosomal loci or causative genes for a given disease phenotype. These investigations have led to the discovery of 15 genetic loci and an ever increasing number of genes, each of which codes for a specific gene product (including PMP-22, myelin protein zero [P_0], connexin-32, the early growth response gene-2, and the periaxin gene), all of which are essential to myelin function (Lupski 1998; Kamholz et al. 2000; Berger, Young, and Suter 2002),

Hereditary neuropathies are common disorders, the inherited nature of which may remain unrecognized in a surprisingly large percentage of patients. Eliciting historical evidence of long-standing neuromuscular complaints, obtaining detailed family histories, looking for skeletal abnormalities such as hammer toes or high arches, and performing neurological evaluations in relatives arc means of identifying previously unsuspected inherited neuropathy. Spontaneously reported paresthesia is three times more common in acquired than in inherited neuropathies. The possibility of an inherited neuropathy cannot be dismissed even in the face of a truly negative family history. Such a situation may arise in cases of early death of one or both parents, few blood relatives, or autosomal recessive disease. Available diagnostic DNA testing shows that one third of isolated cases may result from *de novo* gene mutations (Boerkoel et al. 2002).

Charcot-Marie-Tooth Disease (Hereditary Motor and Sensory Neuropathy)

The syndrome of peroneal muscular atrophy or CMT disease was first described in the second half of the nineteenth century by Charcot and Marie in Paris, and Tooth m London. CMT disease is the most common inherited neuropathy, with an estimated prevalence of 1 in 2500 in the United States. Clinical studies combined with electrophysiological and sural nerve biopsy investigations of a large number of families with peroneal muscular atrophy allowed a separation into two main groups: (1) the hypertrophic or dcmyelinating form of CMT disease or CMT1, also referred to as hereditary motor and sensory neuropathy (HMSN) type I, in which there is marked reduction in motor NCVs and nerve biopsy findings of demyelination and onion bulb formation; and {2) the axonal form of CMT disease (CMT2), or HMSN type II, in which motor NCVs arc normal or near normal, with nerve biopsy findings of axonal loss without dcmyclination (Harding 1995). The peroneal muscular atrophy phenotype without sensory involvement on either clinical or electrophysiological examination has been classified as hereditary distal spinal muscular atrophy. In addition to CMT types 1 and 2, there are rare cases of severe demyelinating neuropathy with onset in early childhood that are referred to as *Dejerirte-Sottas disease.*

Both CMT1 and CMT2 display autosomal dominant inheritance. A minoriry of cases occur sporadically or in siblings only and have therefore been attributed to autosomal recessive inheritance or to *de novo* gene mutations. Because a great variability in clinical expression exists among affected kin in the dominant disotders, a recessive inheritance can only be accepted after clinical and electrophysiological examinations of both parents have proved to be normal; even then nonparental conception and new mutations have to be considered. CMT with X-linked inheritance (CMTX) phenotypically resembles CMT1.

Charcot-Marie-Tooth Disease I

In CMT I, symptoms often begin during the first or second decade of life. Presenting symptoms include foot deformity *And* difficulties in running or walking. Symmetrical weakness and wasting is found in intrinsic foot, peroneal, and anterior tibial muscles. Similar distal involvement of the upper limbs develops later in two thirds of patients. Inspection reveals pes cavus and hammer toes in nearly 75% of adult patients; mild kyphosis in approximately

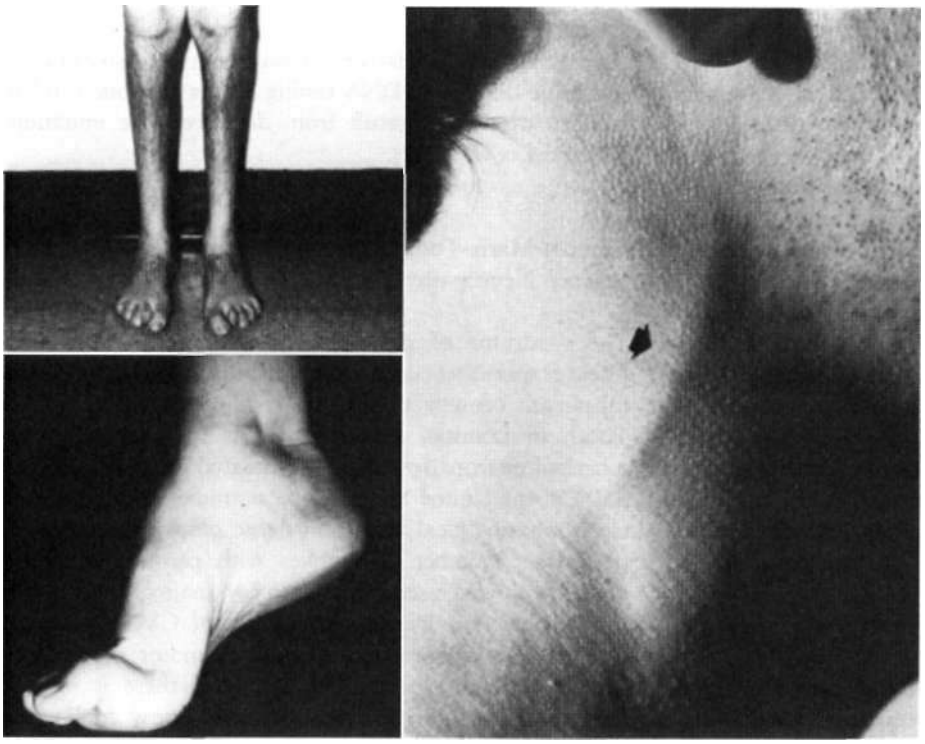


FIGURE 82.8 I eg atrophy, pes cavus, and enlarged great auricular nerve *(arrow)* are evident in a patient with Chare or-Marie-Tooth type 1 disease.

10%; and enlarged, hypertrophic peripheral nerves in as many as *25%* (Figure 82.8). Absent ankle reflexes are universal and frequently are associated with absent or reduced knee and upper limb reflexes. Some degree of distal sensory impairment (diminished vibration sense and light touch in feet and hands) is usually found by examination, lint *rwrcW* ;'jvvs rise m symptoms. Occasionally, paiienis have an essential or postural upper limb tremor. Such cases have been referred to as *Roussy~Lei/y syndrome,* although convincing evidence suggests that this is not a separate clinical or genetic syndrome. Severity in affected kin varies considerably. Approximately 10% of patients arc asymptomatic but have slowing of NCVs. At the other end of the clinical spectrum, there are patients with severe neurological deficits who may become wheelchair dependent.

Motor nerve conduction studies show uniform slowing by more than 25% of the lower limits of normal in all nerves. Motor conduction of upper limb nerves proves more useful than studies of lower limb extremity nerves because distal fiber degeneration in the legs is often complete. A conduction velocity below 38 m per second in the forearm segment of the median nerve is proposed as a cutoff value to distinguish between CMT disease types 1 and 2. In a prospective study of CMT1A, the median motor NCV was slowed to less than 43 m per second in all subjects with documented chromosome 17pl 1.2-12 duplications (Kaku et al. 1993). Sensory conductions are similarly abnormal. SNAPs are usually absent with surface recordings. Motor nerve conduction studies provide an early, age-independent, easily accessible marker for clinical involvement. Routine hematological, biochemical, and CSF studies provide normal results. Sural nerve biopsy typically shows the changes of a hypertrophic neuropathy characterized by onion bulb formation, increased frequency of fibers with demyelinated and remyehnated segments, an increase in endoneurial area, and loss of large myelinated fibers (Figure 82.9).

Charcot-Marie-Tooth Disease 2

CMT2 constitutes one third of all autosomal dominant CMT disease. Clinical symptoms begin later than in CMT1, most commonly in the second decade, but may be delayed until middle age or beyond. Foot and spinal deformities tend to be less prominent in CMT2. The clinical features closely resemble those of CMT1 but differ in that peripheral nerves are not enlarged and upper limb involvement, tremor, and general areflexia occur less frequently. However, in individual cases it is often impossible to determine the type of CMT disease on the basis of clinical findings alone. Approximately 20% of patients arc asymptomatic. CMT2B linked to chromosome 3q13 has prominent sensory loss with ulcerations (De Jotlghe et al. 1997). A distinct subgroup of severely affected patients, designated CMT2C, develop vocal cord, intercostal, and diaphragmatic muscle weakness. Because of respiratory failure, life expectancy is shortened in these patients (Dyck, Litchy, and Kratz 1994).

Motor NCV may be normal or mildly reduced. SNAPs are either absent or reduced in amplitude. Sural nerve biopsy specimens show preferential loss of large myelinated

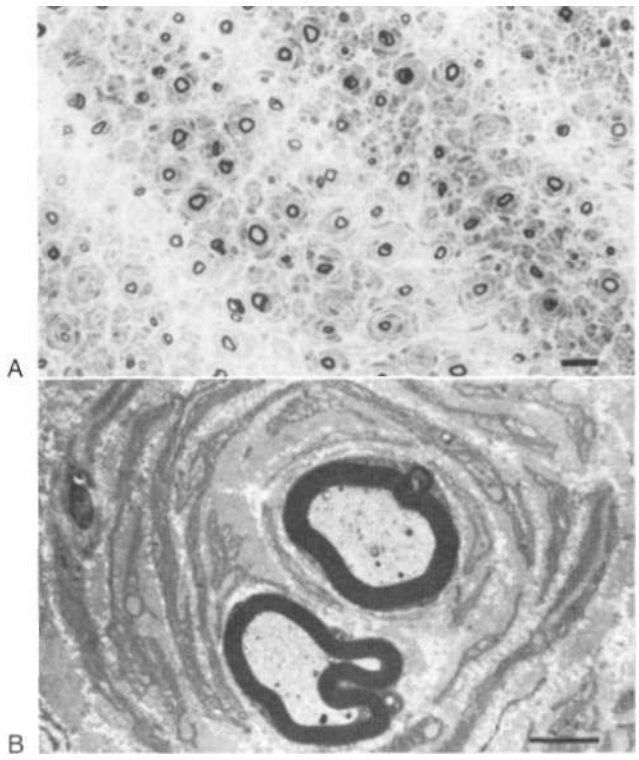


FIGURE *82.9* Chareot-Maric-Tooth disease type 1. (A) Semithin transverse section of sural nerve showing numerous onion bulbs. (Toluidine blue; bar = 20 urn.) (B) Elecrron micrograph of **.in** (n **in in** bulb **foim.ilinn.** Twn small **mvil-.-.-.icil libers art'** surrounded by multiple layers of Schwann cell processes. (Bar = 0.5 urn.}

fibers without significant demyelination; there may be clusters of regenerating myelinated fibers.

Linkage studies to identify the genes for CMT2 indicate that the disorder is genetically heterogeneous. CMT2 has been mapped to chromosomes 1 (lp35-36, designated CMT2A), 3 (3ql3-22, CMT2B), 7 (7pl4, CMT2D), and 12 (12q24, CMT2C) (Saito et al. 1997). Within the last few years the first gene defects (e.g., mutations of the neurofilament light chain, the kinesin superfamily, and specific myelin protein 0 gene mutations) have been identified in CMT2.

X-linked Charcot-Marie-Tootb Disease

CMTX is phenotypically similar to CMT1. Affected male subjects tend to be more severely affected, whereas affected females may have a mild neuropathy or be asymptomatic. No male-to-male transmission occurs. Transient ataxia, dysarthria, unci weakness associated with central nervous system (CNS) white matter abormalities on MRI studies have been described in patients when they returned from high altitude travel (Paulson et al. 2002). NCVs in men show significant slowing, whereas in women the slowing parallels the loss of CMAP amplitude. Brainstem auditory evoked responses are often abnormal,

Charcot-Marie-Tootb Disease 3 or Dejerme-Sottas Disease

CMT3, or Dejerine-Sottas disease (DSS), is an uncommon progressive hypertrophic neuropathy with onset in childhood. Motor development is delayed; proximal weakness, global areflexia, enlarged peripheral nerves, and severe disability are the rule. Although originally the disorder was thought to be autosomal recessive, the majority of cases are sporadic and in some instances have been shown to result from a new dominant mutation.

Motor conduction velocities arc severely slowed, often to less than 10 m per second. The CSF protein is frequently increased. Pathologically, pronounced onion bulb changes are associated with hypomyclination and myelinated fiber loss. Defective myelination is confirmed by an increased axon-to-fibcr diameter ratio. Cases of congenital hypomyeliuation neuropathy probably represent a variant of CMT3 at the far end of a spectrum of defective myelination. I >SS i-. miu^KLilK :II'UTU;.:,ITICUI:S .L11.i is caused bj differenl structural myelin protein and transcription factor gene mutations.

Charcot-Marie-Tootb Disease 4

CMT4 is an autosomal recessive neuropathy characterized by onset in early childhood and progressive weakness, leading to inability to walk in adolescence. NCV studies are slowed (20-30 m per second); CSF protein is normal. Nerve biopsy shows loss of myelinated fibers, hypomyclination, and onion bulbs. To date, 10 chromosomal loci and 5 genes are identified. Affected families of ethnic Tunisian background are linked to chromosome 8 (8q21.1) and designated CMT4A (Othmane et al. 1993).

Complex Forms of Cbarcot-Maric-Tooth Disease

A number of families with peroneal muscular atrophy exhibit additional features such as optic atrophy, pigmentary retinal degeneration, deafness, and spastic paraparesis. Cardiac involvement is encountered in occasional patients, but prospective family studies find no association between cardiomyopathy and CMT disease. A syndrome of CIDP responding to prednisone and immunosuppression has been reported in patients with inherited CMT disease, providing evidence that nongenetic factors may play a role in clinical expression of the mutant gene. Any patient with a hereditary neuropathy who suffers a recent rapid deterioration should be considered for a secondary CIDP.

KhilcciiUir Utt'a/Wi's of (barcnt Marie Tooth Disease and Related Disorders

Major advances have been made in recent years in the molecular genetics ol CMT or hereditary motor and sensory neuropathies (Figure 82.10; Kamhol/. et al. 2000;

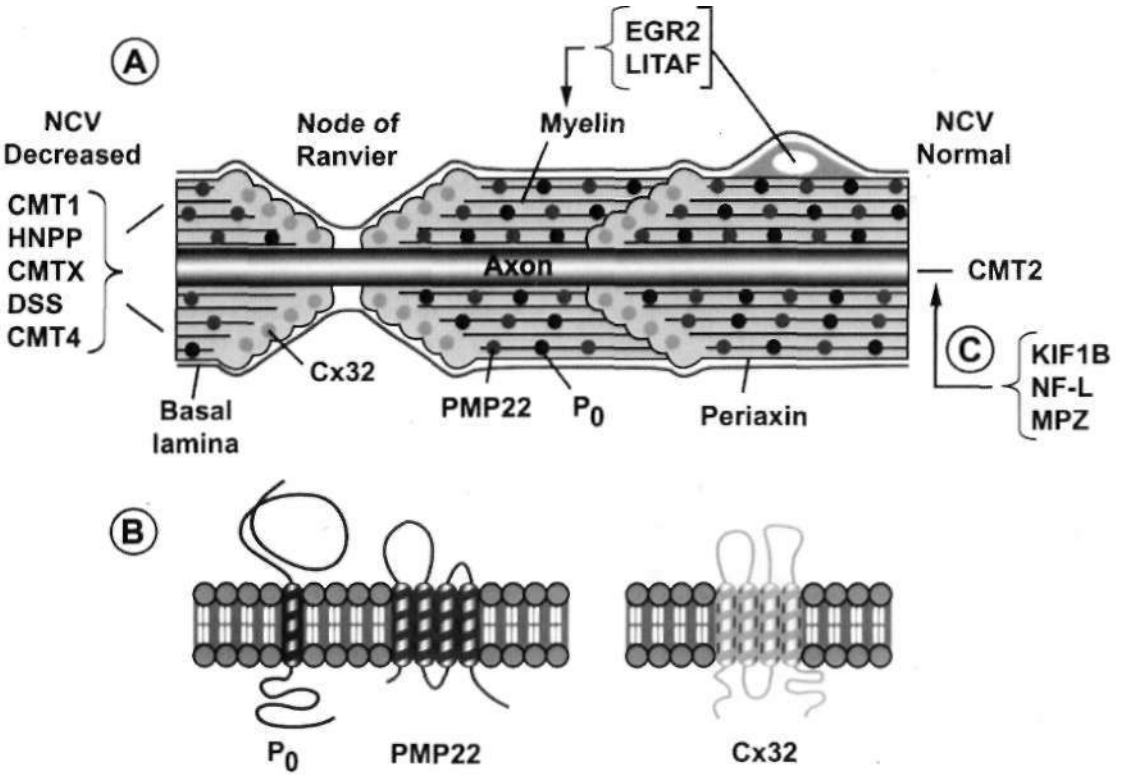


FIGURE 82.10 (A) Charcot-Marie-Tooth disease (CMT) and related disorders: CMT1, CMT with X-linked inheritance (CMTX), hereditary neuropathy with liability to pressure palsies (I INPP), Dejerine-Sottas syndrome (DSS), and CMT4 are inherited disorders of myelin. CMT2 is a primary axonal disorder. Alterations in dosage of peripheral myelin protein-22 (PMP-22) gene account for the majority of patients with CMT1A and HNPP. (B) Point mutations of these genes (connexin-32 [Cx32], myelin protein zero |MPZ, P_0], PMP-22, EGR2, periaxin) result in CMTX, CMT1B, CMT1A, DSS, and CMT4. Mutations of the LITAF gene result in CMT1C. (C) Point mutations of the KTF1B and NF-L genes and specific MPZ missense mutations result in CMT2. (NCV = nerve conduction velocity.) (Adapted with permission from I.upski, J. R. 1998, "Molecular genetics of peripheral neuropathies," in *Molecular neurology*, ed J. D. Martin, Scientific American, New York. All rights reserved.)

Bennett and Chance 2001; Berger, Young, and Suter 2002). Most CMT1 patients have DNA rearrangements on chromosome 17pll.2 as the molecular mechanism of their disease. A 1.5-mcgabase tandem duplication accounts for 70% of CMT1A cases. The peripheral myelin protein-22 (PMP-22) gene lies within the CMT1A duplication, resulting in three copies of the dosage-sensitive PMP-22 gene. PMP-22 is a membrane glycoprotein found in the compact portion of the peripheral myelin sheath. A minority of CMT1A patients have mis-sense mutations in the PMP-22 gene, similar to the natural mouse mutants trembler and trembler-J that have a severe hypomyelinating neuropathy. The normal function of PMP-22 remains unknown. A deletion of the same 1.5-megabase region on chromosome I7pll.2 is found u: *SS"-,. n* p.a-.iTiis with HNPP resulting in a single copy of the normal PMP-22 gene (Lupski, Chance, and Garcia 1993). The CMTIA duplication or HNPP deletion is caused by reciprocal recombination events that occur in male germ cell meiosis. The PMP-22 duplication or deletion can be detected in blood samples using pulse-field electrophoresis followed by hybridization with specific CMTIA duplication junction fragments or cytogenetic testing with a PMP-22 probe by fluorescence in situ hybridization.

Myelin Gene Mutations

Myelin protein zero (P_0; gene symbol MPZ) is the major peripheral myelin glycoprotein and is thought to function as an adhesion molecule in the formation and compaction of peripheral myelin. Mutations in the gene encoding for MPZ, located on chromosome lq22-23, have been associated with CMT1B, DSS, and congenital hypomyclination neuropathy. Different MPZ mutations have resulted in divergent morphologic effects on myelin sheaths consisting of uncompacted myelin or focal myelin foldings (Gabrefils-Fcsten et al. 1996). Specific MPZ mis-sense mutations have been reported with a CMT2 phenotypc showing only mild slowing of nerve conduction velocities (Marrosu et al. 1998). The Thr 124 Met mutation in the MPZ gene has been detected in several families with a distinct CMT2 phenotypc characterized by late onset, marked sensory loss, and sometimes deafness and pupillary abnormalities (De Jonghe et al. 1999).

The *early growth response 2 gene (ECR2)* encodes a zinc-finger transcription factor expressed in myelinating Schwann cells lli;u regulates the expression ol myelin proteins including PMP-22, Po, Cx32, and periaxin (Kamholz et al. 2000). EGR2 gene mis-sense mutations have been reported in patients with CMT1D, DSS, or congenital hypomyelination neuropathy (Warner et al. 1998; Timmerman et al. 1999).

Connexin-32 (Cx32) is a gap junction protein found in noncompacted paranodal loops and Schmidt-Lantcrmann incisures of Schwann cell cytoplasm, which is encoded by a four-exon gene located on chromosome Xq. As a gap junction protein, Cx32 forms small channels that facilitate transfer of ions and small molecules between Schwann cells and axons. Cx32 is also expressed in oligodendroglial cells in the central nervous system. This may explain the common abnormal brainstem auditory evoked potentials found in affected males. More than 200 different mutations in Cx32 have been identified in CMTX families. Genotypc-phenotype correlations among patients with Cx32 mutations suggest that most mis-sense mutations result in a mild clinical phenotype, whereas nonsense and framcshift mutations produce more severe phenotypes (Ionascscu et al. 1996a). CMTX is the second most frequent cause of CMT1, accounting for 10-20% of patients.

The designation CMT1C is reserved for autosomal dominant CMT1 families not linked to either CMT1A or CMT1B. Three such families showed linkage to chromosome 16pl3. Mis-sense mutations were found in the *LITAF* (lipopolysaccharide-mduccd tumor necrosis factor-a factor) gene, which encodes a lysosomal protein that may play a role in protein degradation pathways (Street et al. 2003).

Periaxin is a cy to skeleton-associated protein that links the cytoskcleton of the Schwann cell with the basal lamina, which is necessary to stabilize the mature myelin sheath. Periaxin frameshift and nonsense mutations have been found in families with DSS and autosomal recessive CMT type 4F (Takashima et al. 2002).

Point mutations of signal transduction proteins such as myotubularin-related protein-2 (MTMR2), N-myc downstream regulated gene-1 (NDRG1), andganglioside-induced differentiation-associated protein-1 (GDAP1) are found in severe childhood-onset, autosomal-recessive demyclinating neuropathies or CMT4, Mutations of MTMR2 give rise to a severe demyclinating neuropathy characterized by redundant loops of focally folded myelin (Houlden et al. 2001). GDAP1 mutations may be the most common cause of autosomal recessive CMT and can result in demyelinating as well as axonal phenotypes (Nelis et al. 2002).

In general, DNA rearrangements such as PMP-22 duplication or deletion result in milder clinical phenotypes than point mutations for structural myelin proteins or the transcription factor gene I'.RG2, Most known imitations cause disease manifestations in the heterozygous state, behaving as cither gain-of-function or loss-of-funetion-dominant mutations. Rare recessive mutations in PMP-22, EGR2, MTMR2, NDRG1, and periaxin have been reported (Lupski 2000). DNA sequencing tests are available for PMP-22, Cx32, MPZ, F.GR2, and periaxin in commercial laboratories.

Charcot-Marie-Tooth Disease Type 2

CMT2 is a genetically heterogeneous group of axonal neuropathies with normal or slightly slow nerve conduction velocities inherited in an autosomal dominant pattern, CMT2 accounts for approximately 30% of CMT patients (De Jonghe 1998; Vance 2000). Although molecular genetic research has been less productive in CMT2, three responsible gene defects have been identified. Genetic linkage studies have mapped five different disease loci on chromosomes lp35, 3ql3-q22, 7pl4, 8p2l, and 12q24 (Table 82.13). CMT2A, linked to chromosome lp35, is caused by a mutation in a microtubule motor KIFIB^ gene encoding for a kinesin superfamily of proteins involved in axonal transport of synaptic vesicle precursors (Zhao et al. 2001). CMT2B, linked to chromosome 3ql3-q22, has prominent distal sensory loss with ulcerations (De Jonghe et al. 1997; Auer-Grumbach et al. 2000). CMT2C, linked to chromosome 12q24, is characterized by vocal cord and diaphragmatic paralysis (Klein et al. 2002). CMT2D, linked to chromosome 7p15, involves prominent weakness and wasting of hand muscles (Ionasescu et al. 1996b). Mutations in the neurofilament light chain gene (NF-I.) have been found in several families with linkage to chromosome 8p21; this neuropathy is designated CMT2F, (Mersiyanova et al. 2000). These patients often have early onset and a severe clinical phenotype (Jordanova et al, 2003). A DNA sequencing test for NF-L is commercially available. The CMT2 phenotype with only mild slowing of nerve conduction velocities is sometimes caused by specific mutations in -In- MPZ gene and Cx32. Such families with CMTX do not show male-to-male transmission {Birouk et al. 1998).

CMT can be classified by mode of inheritance (autosomal dominant, X-linkcd, and rarely autosomal recessive), chromosomal locus, or causative genes (see Table 82.13). The classification remains fluid and may change as experts alter and revise these designations based on new molecular findings. An up to date listing of loci and genes can be found at the CMT mutation database (http://molgen-www.uia.ac.be/CMTMutations/). DSS, previously designated as CMT3, may no longer be a useful designation because it is genetically heterogeneous, caused b\ different structural myelin protein and transcription factor gene mutations. One proposal is to reserve CM 13 tor rare axonal types of autosomal recessive neuropathy (Vance 2000).

Reappraisal of Electrophysiological Studies of Inherited Demyelinatmg Neuropathies

Uniform conduction slowing has been used to differentiate CMT1 from acquired demyelinating neuropathies

Tabic 82.13: Molecular genetic classification of Charcot-Marie-Tooth disease and related disorders (2002)

Disorder	*Locus*	*Gene*	*Mechanism*	*Testing available*
CMT1				
CMTIA	17pll.2	PMP-22	**Duplication>pin**	Yes
CMT1B	Lq22-q23	I'M!/	pm	**Yes**
CMT1C	16pl3.1	LITAF	pm	—
CMT1D	H)q21	EGR2	**pm**	Yes
CMTX				
CMTX1	Xql3.1	Cx32	pm	Yes
CMTX2	Xq24	**j**	J	—
CMT2				
CMT2A	Lp35	KIFIB^	pm	—
CMT2B	3ql3-q22	?	**)**	—
CMT2C	I2q24	)	**;**	—
CMT2D	7pI5	>	>	—
CMT2E	8p21	NF-L	pm	Yes
CMT2P_0	*[qZ2*	PMZ	pm	Yes
HNPP	L7pll.2	PMP22	Deletion >pm	Yes
DSS				
	Iq22-q23	PMZ	pm	**Yes**
	17_P11.2	PMP22	ıtttı	Yes
	L0q21-q22	EGR2	pm	Yes
AR CMT				
CMT4A	8q21	GDAP1	pm	—
CMT4B	l1q22	MTMR2	pm	—
CMT4C	.<k|23-q33	}	**;**	—
CMT4D	8q24	NDRG1	pm	Yes
CMT4E	10q21-q22	EGR2	**pm**	Yes
CMT4E	I9ql3	Periaxin	pm	—

AR = autosomal recessive; CMT = Charcot-Marie-Tooth disease; CMTX = X-l inked CMT; Cx32 = connexin-32; DSS = Dejerine-Sottas syndrome; EGR2 = early growth response 2 gene; GDAP1 = ganglioside-induced differentiation-associated protein 1; HNPP = hereditary neuropathy with liability to pressure palsies; KJF1B0 = microtubule motor KIF1R/J; I.ITAF gene = lipopolysac-c ha ride- induced tumor necrosis tactor-a factor; MTMR2 = myotubu latin-related protein 2; NDRGI =N-myc downstream regulated gene 1; NF-L = neurofilament light chain gene; pm = point mutations; PMP-22 = peripheral myelin prorein-22; PMZ = myelin protein zero gene.

(Lewis and Sumner 1982). The nerve conduction studies of patients with uniform slowing result in conduction slowing in all nerves and along the entire length of nerves, suggesting that inherited myelinopathies affect conduction in all nerves and nerve segments to the same degree. The conduction slowing evolves over the first 5 years of age and does not change appreciably after the age of 5 years. Neurological deficits correlate with reductions in CMAP and sensory nerve action potential amplitudes, indicating that clinical weakness results from reduced numbers of axons. In contrast, acquired dcmyelinating neuropathies result in multifocal or nonuniform conduction slowing together with excessive temporal dispersion and conduction block. Lewis and colleagues (2000) revisited the topic of electrophysiological studies in inherited demy el in a ting neuropathies and correlated conduction changes with molecular diagnoses.

Uniform conduction slowing is found in CMTIA with PMP-22 duplication or point mutations; CMT1B with MPZ point mutations; DSS, including PMP-22, MPZ, and EGR2 gene mutations; metachromatic leukodystrophy; Cockayne's disease; and globoid cell leukodystrophy. In DSS, severe nerve conduction slowing below 10 m per second is consistently found. Temporal dispersion and amplitude reduction on proximal stimulation may be found in such cases due to high electrical stimulation thresholds in hypertfophic nerves. Motor conduction block can also be found in rare CMT1B patients with specific MPZ mutations (Street et al. 2002)

Multifocal conduction slowing is typically seen in HNPP, CMTX, adreuomyeloncuropathy, Pelizaeus-Mer/.bacher disease with proteolipid protein-null mutation, and Refsum's disease.

Nerve conduction velocities in CMTX with Cx.32 mutations range from near normal to intermediate slowing in the 30- to 40-m per second range. There is debate as to whether CMTX should be classified as a primary axonal or demyelinating disorder (Birouk et al. 1998). Careful studies of individual patients suggest nonuniform conduction slowing consistent with demyelination (Gutierrez et al. 2000; Lewis 2000). Conduction changes in affected women can be subtle and frequently are in the range found in patients with CMT2. Before considering a diagnosis of CMT2 in such cases, it is important to review the family history, In kindreds with no male-to-male transmission, the presence of intermediate conduction velocities (>42 m/s) in female carriers and delayed brainstem auditory evoked response latencies in affected men is highly supportive of Cx32 mutations (Nicholson, Yeung, and Cotbett 1998). Certain mutations in MPZ, NF-L and GDAP1 genes can be associated with either demyelinating or axonal phenotypes.

Practical Molecular Diagnostic Testing for Patients with Charcot-Marie-Tooth Disease and Related Disorders

Molecular diagnostic testing should be considered in CMT and related peripheral neuropathies. Commercial reference laboratories can detect PMP-22 duplication/deletion or point mutations by DNA sequencing of PMP-22, Cx32, MPZ, EGR2, periaxin, and NF-L in samples of peripheral blood (Table 82.14). In families with at least two-generation involvement, known male-to-male transmission, and uniform conduction slowing, the PMP-22 duplication test should be obtained and, if normal, followed by PMP-22 and MPZ DNA sequencing. Patients who have neither the CMTIA duplication nor malc-to-male transmission should be screened for Cx32 mutations. Given the high spontaneous mutation rate, the diagnoses of CMTIA and HNPP should even be considered in the absence of a positive family history. Because of the severe consequences of vincristine therapy in CMT patients, the CMTIA duplication should be ruled out in any patient with either unexplained chronic neuropathy or a family history of

Table 82.14: Selected CMT phcnotypes and molecular diagnostic resting

Test	*CMTl*	*HNPP*	*CMTX*	*CMT2*	*DSS/CHN*
PMP-22 dupj del FISH	X, duplication	X, deletion			X, duplication
DNA sequencing					
Cx32	X			X	
PMP-22	\	X			X
MPZ	X			X	X
EGR2	X				X
Periaxin					X
Nl 1					

CMTl = Charcot-Marie-Tooth disease type 1; CMTX = X-linked CMT; Cx32 = connexin-32; DSS/CHN = Dejerine-Sottas syndrome/ congenital hypomyelination neuropathy; EGR2 nearly growth response 2 gene; FISH = fluorescence in situ hybridization; HNPP = hereditary neuropathy with liability to pressure palsies; MPZ = myelin protein zero; NF-L = neurofilament light chain gene; PMP-22 dup/del = peripheral myelin prorein-22 duplication or deletion is detected by pulse field gei electrophoresis or cytogenetic testing with FISH.

neuropathy before the initiation of cancer chemotherapy (Graf et al. 1996). DNA sequencing tests for Cx32, MPZ, and NF-L mutations are available for selected patients with the axonal CMTl phenotypc. The PMP-22 duplication test followed by DNA sequencing of PMP-22, MPZ, EGR2, and periaxin should be considered in childhood cases with severe demyelinating neuropathy suggestive of DSS or congenital hypomyelination neuropathy,

Treatment and Wdiiagcnivnt

The rates of progression of CMTl and CMT2 arc slow, disability occurs relatively late, and life span may be normal. Management is mainly symptomatic. Patients should be instructed in proper foot care and advised to wear broad, well-fitting shoes. Insoles may be used to distribute body weight more evenly in patients with foot deformity. Ankle-foot braces or orthopedic procedures are indicated for severe footdrop. Patients should be warned to avoid neurotoxic drugs because of greater susceptibility to agents such .is vincristine. Tlu- isU'.:-.lun;- .uU.uiccs "• ihi- molecular understanding of CMT neuropathies will likely bear fruit in the clinical management of patients in the future.

Hereditary Neuropathy with Liability to Pressure Palsies

HNPP is an autosomal dominant disorder of peripheral nerves leading to increased susceptibility to mechanical traction or compression. Patients present with recurrent episodes of isolated mononeuropathies, typically affecting, in order of decreasing frequency, the common peroneal, ulnar, brachial plexus, radial, and median nerves. Painless brachial plexus neuropathy is seen in up to one third of patients. Most patients experience the initial episode in the second or third decade of life. Attacks usually are provoked by compression, slight traction, or other minor trauma. Most attacks are of sudden onset, painless, and usually followed by complete recovery within days or weeks. Less common presentations include transient, positional sensory symptoms, progressive mononeuropathy, chronic sensory polyneuropathy, CMT phenotype with pes cavus, and a diffuse, chronic sensorimotor neuropath) resembling chronic inflammatory demyelinating polyneuropathy (Mouton ct al. 1999). About 15% of mutation carriers remain asymptomatic.

Nerve conduction studies in patients with HNPP associated with PMP-22 deletion typically consist of prolonged distal motor latencies with only mild slowing of forearm segments of median and ulnar nerves, focal slowing of ulnar and fibular nerves at compression sites, and diffuse reduction of sensory nerve action potential amplitudes (Mouton et al. *1999;* Dubourg et al. 2000). Prolonged median distal motor latencies and abnormal sensory conduction studies are frequently found in asymptomatic carriers (Infante et al. 2001).

Sural nerve biopsy specimens demonstrate focal sausage-like thickenings of myelin termed *tomacula* (Figure 82.11), segmental demyeliiiacion, and axonal loss.

Linkage studies show a 1.5-megabase deletion of chromosome 17pl 1.2-12 that includes the PMP-22 gene and corresponds to the duplicated region in CMT1A in 85% of affected patients with HNPP. The remaining patients have a variety of mutations in PMP-22 that lead to frameshift or nonsense mutations causing functional changes in the protein (Lenssen et al. 1998; van de Wetering et al. 2002). Molecular diagnosis of the 17pl 1.2 deletion is available in reference laboratories and has replaced nerve biopsy as means of diagnosis. Testing should be considered regardless of family history in any patient presenting with painless multiple mononeuropathies, brachial plcxopathy, or recurrent demyelinating neuropathy (Tyson et al. 1996). The primary treatment strategy is to prevent nerve injury by avoiding pressure damage.

Giant Axonal Neuropathy

Giant axonal neuropathy (GAN) is a rare autosomal recessive multisystem disorder of intermediate filaments

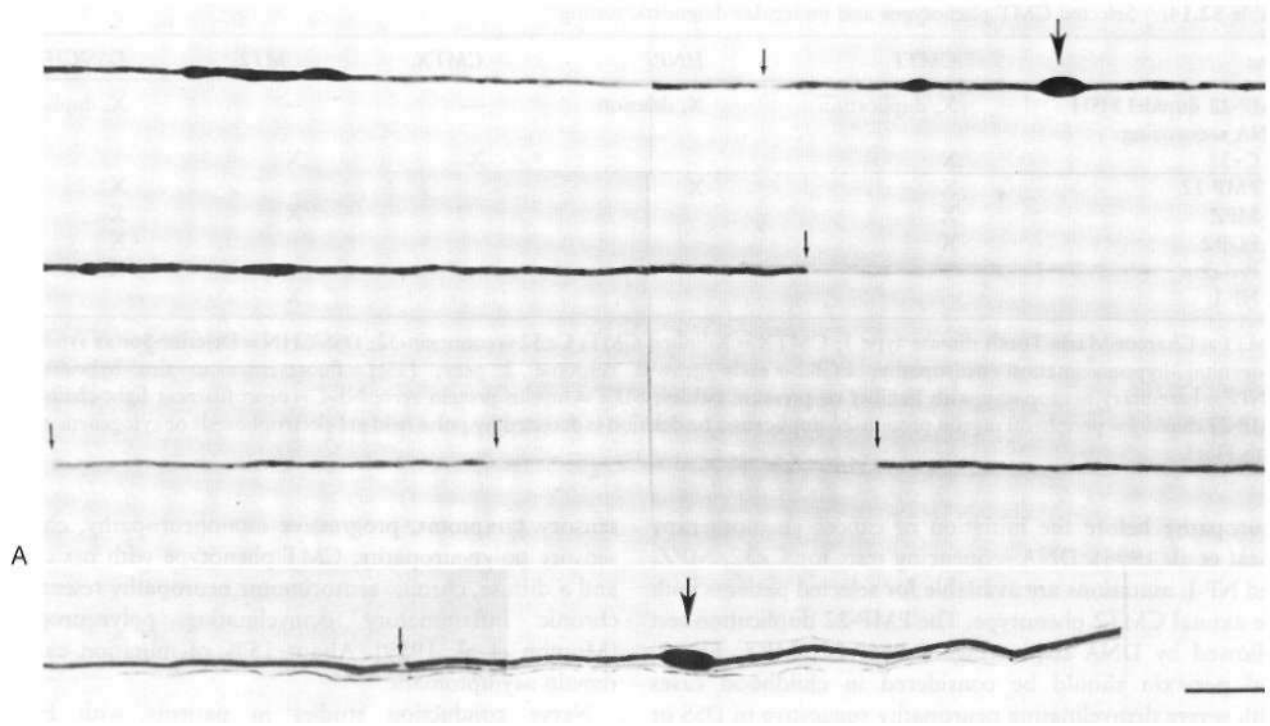


FIGURE 82.11 Single teased nerve fibers from a patient with hereditary liability to pressure palsies, showing examples of focal sausage-shaped enlargements of the myelin sheath *{large arrows)* in two fibers (A, U). Fiber A shows thinly remye! mated inter nodes. Successive nodes of Ranvier *(thin arrows)* can be followed from left to right. (Bar= 100 urn.) (Reprinted with permission from Bosch, E. P., Chili, H. C., Martin, M. A., er al. 1980, "Brachial plexus involvement in familial pressure-sensitive neuropathy: Electrophysiologic and nt(irphulo;u. finding," *Ana* \V;;.:.i/, vol. S. pp. nil) ➪Il I.j

affecting the peripheral and central nervous system. GAN presents as a slowly progressive axonal sensorimotor neuropathy in early childhood and leads to death by late adolescence. Most affected children have tightly curled hair and distal leg weakness. Some develop a peculiar gait disturbance with a tendency to walk on the inner edges of the feet (Figure 82.12). With disease progression, evidence of CNS involvement occurs, including optic atrophy; nystagmus; cerebellar ataxia; upper motor neuron signs and intellectual decline; and abnormal visual, auditory, and somatosensory evoked potentials. MRl of the brain demonstrates cerebellar and cerebral white matter abnormalities. Nerve conduction studies show reduced CMAP and SNAP amplitudes with normal to only slightly reduced conduction velocities. Sural nerve biopsy demonstrates the pathognomonic changes of large focal axonal swellings

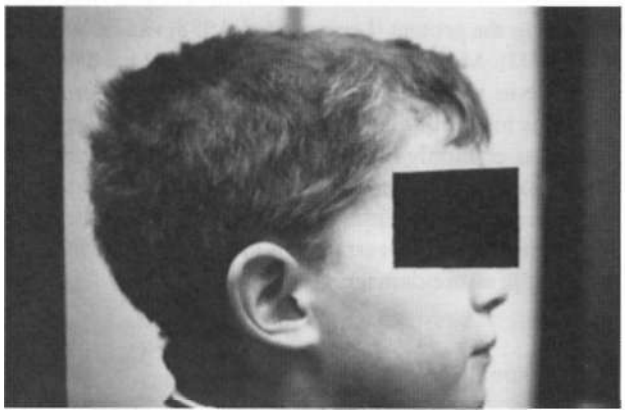


FIGURE *H2A2* i 'fitly curled hair in a young child with giant axonal neuropathy.

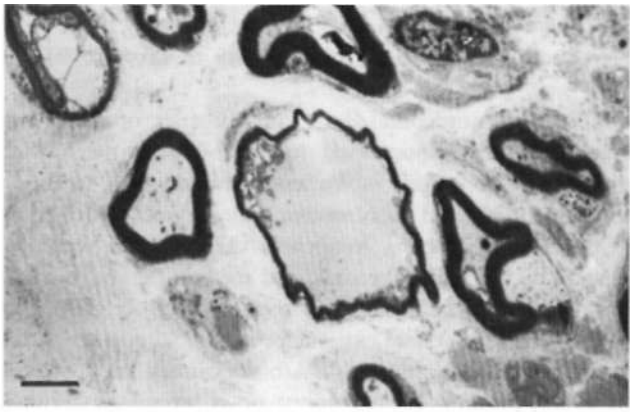


FIGURE 82.13 Giant axonal neuropathy. Electron micrograph of a giant axon filled with neurofilaments and with an attenuated myelin sheath. (Bar = 1 *irn.)*

that contain densely packed disorganized neurofilaments (Figure 82.13). The disease locus was mapped to chromosome 16q24. Giant axona! neuropathy is caused by mutations of the GAN gene which encodes a novel protein called gigaxonin (Bomont et al. 2000; Kuhlenbaumcr ct al. 2002). Gigaxonin is a ubiquitously expressed cytoskelctal protein and a member of the kelsch superfamily which is involved in diverse cellular functions and may be important in the cross-linking of intermediate filaments (Hermann and Griffin 2002).

Hereditary Sensory and Autonomic Neuropathy

HSAN is a group of neuropathies characterized by prominent sensory loss with autonomic features but without significant motor involvement. Currently, these neuropathies are divided into five main groups based on inheritance, clinical features, and populations of sensory neurons affected (Table 82.15). HSAN is distinctly rare compared with GMT. Genetic studies have led to successful chromosomal localization and gene mutations in HSAN I, III and IV. Sensory loss in HSAN predisposes to unnoticed, recurrent trauma that may lead to neuropathic (Charcot) joints, nonhealing ulcers, infections, and osteomyelitis resulting in acral mutilations aerodystrophic neuropathy). These complications are preventable by avoiding trauma to the insensitive distal limb segments.

Hereditary Sensory and Autonomic Neuropathy Type I

HSAN' type I is an autosomal dominant disorder that is the most common familial sensory neuropathy. Symptoms begin in the second to fourth decade with sensory loss and subsequent tissue injury mainly affecting the feet and legs. Sensory loss initially affects pain and temperature perception more than touch-pressure sensation, but includes all modalities as the disease progresses. Patients present with calluses on the soles, painless stress fractures, neuropathic foot and ankle joints, and recurrent plantar ulcers. If ulcers arc neglected and become infected, severe acromutilations may result (acrody strop hie neuropathy) (Figure 82.14).

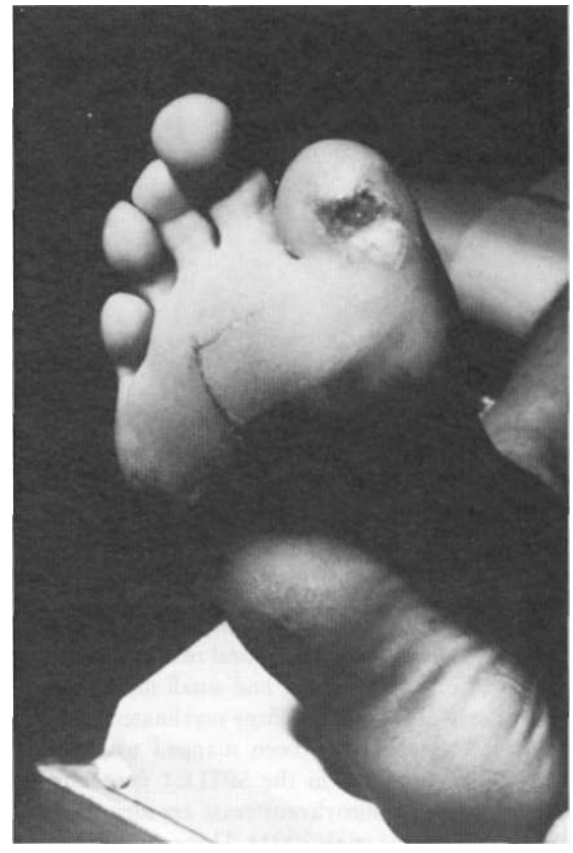


FIGURE 82.14 Nonhealing foot uker in a 33-year-old man with hereditary sensory and autonomic neuropathy type I. In his kinship, 10 individuals are affected in three generations.

Lancinating or shooting pains ate often prominent. Distal muscle weakness and wasting are present in all advanced cases. Such motor involvment creates confusion with CMT 2B with dense sensory loss (linked to chromosome 3ql 3) or with certain axonal MPZ gene mutations. Variable neural hearing loss, or, rarely, spastic paraparesis may be seen in HSAN type I. Some families present with burning feet or neurogenic arthropathy suggesting clinical as well as genetic heterogeneity among patients with HSAN type 1 (Dyck et al. 2000a).

Table 82.15: Hereditary sensory and auronomie neuropathies

Disease	*inheritance*	*t · ICIIS*	*(..·:::·*	*Clinical features*
HSAN l(HSNI)	AD	9q22	**SPTLC1***	Small > large MF sensory loss, distal weakness, onset in second to fourth decade
HSAN II	AR		)	Pansensory loss in infancy
HSAN **III** (FD)	AR	9q31	1KBKAP"	Sensory loss, autonomic dysregulation, absent tears, fungiform tongue papillae
HSAN IV	AR	lq21	TRKA/NGF receptor	Inseusitvity to pain, anhidrosis at birth, nl SNAPs
HSAN V	AR			Insensitiviry to pain at birth, nl SNAPs, absent small MF

AD = autosomal dominant; AR = autosomal recessive; FD = familial dysautonomy; IKBKAP = IKAP, the protein encoded by 1KBKAP gene is a member of the human elongator complex; HSAN = hereditary sensory and autonomic neuropathies; MF = myelinated fibers; nl SNA['=-norrnal sensory nerve action potential; SPTLCl =SPTLC1 encodes serine palmitoyltransferase long chain 1; TRKA/NGF = TRKA encodes for the high affinity NGF (nerve growth factor) receptor; * =molecular gene testing is clinically available.

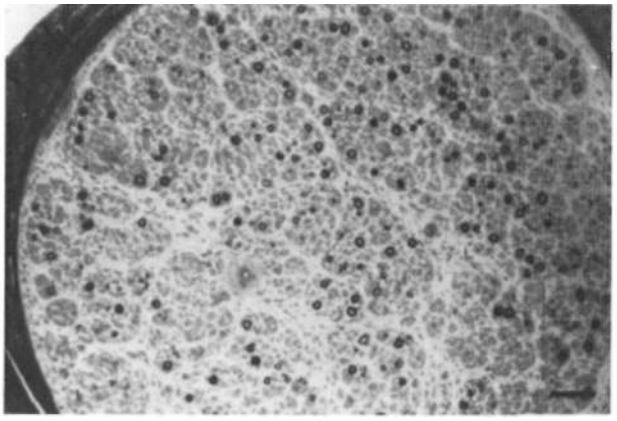


FIGURE 82.15 Semithin transverse section of sural nerve from a patient with hereditary sensory and auitmomic neuropathy rs pi- I. Note loss of large and small myelinated fibers. (Toluidine blue; bar = 50 urn.)

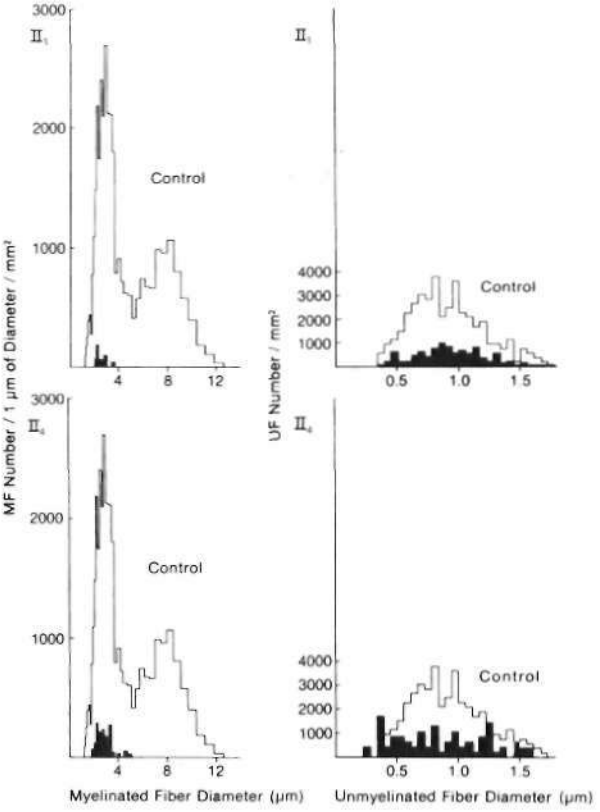


FIGURE 82.16 Sural nerve fiber size-Frequency histograms of myelinated fibers (ME) *[left]* and unmyelinated fibers (UF) *(right)* of two affected siblings with hereditary sensory and autonomic neuropathy type I] *[black bars)* and control nerve *{white ban).* In the patients, the number of myelinated fibers was less than 500/mm^2 and that of the unmyelinated fibers less than 10,000/mm^2.

SNAP amplitudes are reduced late in the disease. Motor conduction velocities remain normal but CMAP amplitudes arc reduced in advanced cases. Sural nerve biopsy confirms a severe loss of unmyelinated and small myelinated axons and to a lesser degree loss of large myelinated fiber (Figure H2.15). HSAN type 1 has been mapped to chromosome 9t|22.1-22,3, Mutations in the SPTI.C1 gene encoding a subunit of serine palmitoyltransferase are identified in 90% of patients (Dawkins et al. 2001). These mutations result in increased *de novo* ceramide synthesis. Since ceramide plays a role in the regulation of programmed cell death, the neuronal degeneration in 1 [SAN type I may be caused by ceramide-induced apoptosis. Molecular genetic testing is clinically available. HSAN type I is genetically heterogeneous as families without linkage to chromosome 9q22 have been described (Aucr-Grumbach et al. 2000).

Hereditary Sensory and Autonomic Neuropathy Type II

HSAN type II is recessively inherited and rarely begins later than infancy. All sensory modalities are affected and involve distal upper and lower limbs more than trunk and face. The hands, feet, lips, and tongue are at risk for mutilation because ol generalized paninndal::y seiw>n loss. Autonomic symptoms include bladder dysfunction and impotence. Associations with spastic paraplegia, retinitis pigmentosa, motor weakness, or neurotrophic keratitis have been described. The clinical course is slowly progressive, with progressive axonal loss. SNAPs ate absent. Sural nerve biopsy specimens show almost complete absence of myelinated fibers and reduced unmyelinated fiber populations (Figure 82.1 6). No chromosomal linkage has been identified in this group of patients.

Hereditary Sensory and Autonomic Neuropathy Type III

HSAN type 111 or familial dysautonomia (FD) is an autosomal recessively inherited sensory neuropathy affecting children of Asbkenazi Jewish ethnicity with prominent autonomic manifestations. Symptoms begin at birth and include poor feeding, esophageal dysmotiliry, episodes of vomiting, recurrent pulmonary infections, attacks of fever, and cardiovascular instability. Emotional stimuli provoke i|iiM'.lk- hypcru-iisioi], pn>l;iM^i sweating, and marked skin blotching caused by defective autonomic control. Hypotonia in infancy contributes to delayed motor milestones. Later in childhood, hyporeflexia, insensitivity to pain, gait ataxia, stunted growth, and scoliosis become apparent. Defective lacrimation (absence of overflow tears with crying), absence of fungiform papillae of the tongue giving it a smooth appearance, and pupillary hypersensitivity to parasympathomimetic agents arc tell-tale signs. Patients ate at risk to develop profound hypoxemia following anesthesia or with high-altitude ttavel as a result of diminished respiratory response to hypercapnia and hypoxia.

Motor NCVs are generally normal, whereas SNAP amplitudes are frequently reduced. A marked reduction in the density of unmyelinated axons and small myelinated fibers is seen in sural nerve biopsy specimens.

The number of neurons in the sympathetic, parasympathetic, and spinal ganglia is reduced. Linkage studies have mapped the gene locus to chromosome 9q31-q33, The diagnosis is established by molecular genetic testing of the IKBKAP gene, which encodes an essential protein named *IKAP* of the human elongation complex. The major FD mutation is a splice mutation that results in aberrent tissue-specific mRNA splicing (Slaugenhaupt and Gusella 2002).

I'D is a potentially life threatening disorder with a high mortality due to aspiration pneumonia or autonomic crises. Improved supportive treatment has extended the survival of patients into adulthood (Axelrod et al. 2002),

Hereditary Sensory and Autonomic Neuropathy Type IV

HSAN type IV is a rare autosomal recessive disorder characterized by congenital insensitivity to pain with anhidrosis, repeated episodes of fever, self-mutilating behavior, and mild mental retardation. Tendon reflexes and SNAPs are preserved. Cutaneous sensory nerves show selective loss of unmyelinated axons and small myelinated fibers. Confirmation of a neuropathic abnormality in cases of congenital indifference to pain without apparent neurological signs therefore depends on the morphometric study of unmyelinated and myelinated fiber populations in nerve biopsy specimens and is supported by quantitative sensory testing, and lack of sweating by the quantitative sudomotor axon-reflex test. Intradermal histamine injection produces a wheal but no flare response. Skin biopsy has demonstrated a lack of intradermal nerve fibers and sweat glands devoid of nerve fibers (Verze et al. 2000), The gene locus for HSAN type IV maps to chromosome lq21-22. Mutations in the *trkA* gene encoding the tyrosine kinase receptor for nerve growth factor (NGF) have been described in patients with HSAN type IV (Indo 2002), These findings indicate that the NGF-trkA system plays a crucial role in the development of unmyelinated nociceptive and sudomotor fibers.

Clinically similar cases with selective loss of only small myelinated fibers have been designated HSAN type V. Mutations in the trkA gene have been found in some cases suggesting that the two disorders may be allelic (Houlden et al. 2001).

Treatment and Management

The prevention of stress fractures and plantar ulcers is of utmost importance. This can be achieved by meticulous foot care, avoiding barefoot walking, daily inspection of feet and shoes, and proper skin care with moisturizing lotions. Whenever plantar ulcers develop, weight bearing should be discontinued until the ulcers heal. Infusion of pamidronate, a bisphosphonate has been helpful in the management of Charcot's neurogenic arthropathy,

Neuropathy Associated with Spinocerebellar Ataxias

Friedreich's ataxia is an autosomal recessive neurodegenerative disease characterized by degeneration of large sensory neurons and spinocerebellar tracts, cardiomyopathy, and increased incidence of diabetes (see Chapter 78). Even in the early stages of the disease, examination reveals lower limb areflexia and impaired joint position and vibration sense, with preserved pain and temperature sensation. Pes cavus and hammer toes occur in approximately 90% of cases.

Motor NCVs arc normal or slightly reduced, and SNAPs are invariably reduced or absent. A selective loss of large myelinated fibers occurs in the sural nerve. Friedreich's ataxia is the result of a large GAA triplet repeat expansion on chromosome 9ql3-q21.1 leading to loss of frataxin expression (see Chapter 78). Peripheral nerve involvement has been found in association with other spinocerebellar ataxias, most notably spinocerebellar ataxia type 3 (SCA3) in older patients and SCA type 4.

Familial Amyloid Polyneuropathy

Familial amyloid polyneuropathy (FAP) is a group of autosomal dominant disorders characterized by the extracellular deposition of amyloid in peripheral nerves and other organs. Amyloid is a fibrillar protein characterized by (1) green birefringence of Congo red-stained sections viewed in polarized light; (2) the presence of uonbranched 10-nm amyloid fibrils on electron microscopy; and (3) a *fi*-pleated sheet structure on x-ray diffraction. More than 10 different proteins can be deposited as amyloid in tissues. In FAP one of three aberrant proteins (transthyretin, apolipoprotein A1, or gelsolin [Falk, Comenzo, and Skinner 1997J) can be found in the peripheral nerves. In acquired, primary systemic amyloidosis, polypeptides of immunoglobulin light chain origin arc deposited in tissues as amyloid, which is referred to as *AL amyloid* (sec Primary Systemic Amyloidosis, later in this chapter).

The classification of FAP was traditionally based on clinical presentation. Progress in understanding the protein composition and molecular genetics of these disorders justifies a different approach (Table 82.16).

Transthyretin Amyloidosis (Familial Amyloid Polyneuropathy Types I and 11)

The majoriry of patients with FAP have mutations of the plasma protein transthyretin (TTR). This is a transport protein for thyroxin and retinol-binding protein, is predominantly synthesized in the liver, and consists of a single polypeptide chain of 127 amino acid residues. The gene for TTR is located on chromosome 18ql 1.2-ql2.1. Mutations ot the TTR gene result in transcriptions of aberrant proteins with predisposition toward amyloid

Table 82.16: Familial amyloid neuropathies

Aberrant protein	*Type*	*Decade of onset*	*Neuropathy*	*Associated lesions*
TTR	FAP I	Third through fifth	Sensorimotor neuropathy, autonomic neuropathy	Heart, kidney
TTR	FAP II	Fourth through fifth	Carpal tunnel syndrome	Heart
Apolipoprotein Al	FAP III	Third through fourth	Sensorimotor neuropathy	Kidney, peptic ulcers
Gelsolin	FAP IV	Third	Cranial	Corneal lattice dystrophy

FAP = familial amyloid polyneuropathy; TTR = transthyretin.

formation and deposition in peripheral nerve, heart, kidney, eye, and rarely leptomeninges.

TTR-related amyloid polyneuropathies demonstrate two disparate clinical phenorypes. The original cases described by Andrade in Portugal are referred to as FAP type I. Two other large foci of patients are found in Sweden and Japan. This is the most common form of FAP and has been observed in many ethnic groups. The neuropathy begins insidiously in the third and fourth decades with dissociated sensory impairment (loss of pain and thermal sense) in the lower extremities, often associated with lancinating pain and paresthesia. Autonomic dysfunction common]j includes impotence, postural hypotension, bladder dysfunction, distal anhidrosis, and abnormal pupils with scalloped margins. Gastrointestinal symptoms characterised by constipation alternating with diarrhea, delayed gastric emptying, and weight loss may be prominent. Eventually panmodality sensory loss, distal wasting, weakness, and areflexia develop. Systemically, amyloid is deposited in the ocular vitreous, heart, and kidneys. The disorder is relentlessly progressive. Patients usually die of cardiac or renal failure or malnutrition 10-15 years after onset.

Electrophysiological studies reveal a distal axonal neuropathy that affects sensory fibers earlier and more prominently than motot fibers. Early changes include low-amplitude or absent SNAPs, mild reduction in CMAP amplitudes, and preserved motor conduction velocities. Evidence of denervation is found in distal leg muscles. Until specific biochemical and genetic studies became available, the diagnosis was confirmed by the presence of amyloid in tissue biopsy specimens. In early cases, sural nerve biopsy specimens show a predominant loss of unmyelinated and small myelinated fibers. Amyloid deposits are usually seen within the endoneurium or around vasa nervorum. Immunostaining with antibodies to TTR can frequently identify the specific type of amyloid. The pattern of myocardial involvement varies according to specific TTR mutations. Many but not all mutations have evidence of myocardial infiltration on echocardiography. The mechanisms ui nerve fiber injury and their relationship u> am; loid deposits are incompletely understood. It has been proposed that the preferential deposition of amyloid in sensory and autonomic ganglia interferes with neuronal function, leading to length-dependent axonal degeneration. An alternative theory suggests that endoneurial edema associated with amyloid deposition in blood vessels and the endoneurium results in ischemic nerve fiber injury.

Rukavina and colleagues described a more restricted form of the disease, referred to as FAP type II, which presents with carpal tunnel syndtome in the fourth or fifth decade and slowly progresses to peripheral polyneuropathy. Autonomic manifestations are absent. Vitreous opacities are common and cardiac involvement may develop. Surgical decompression of the carpal tunnel provides symptomatic relief. Demonstration of amyloid infiltration of the flexor retinaculum obtained at surgery establishes the diagnosis.

More than 80 different amino acid substitutions of the TTR protein have been identified as causing the clinical phenorypes, referred to as *FAP I* and //, Among these, substitution of valine by methionine at position 30 (VaBOMet) is by far the most frequent and found in clusters in distinct atcas of Portugal, Sweden, and Japan. Other TTR variants, including isoleucine 33, alanine 60, and tyrosine 77 substitutions, have similar features of generalized polyneuropathy with varying degrees of autonomic involvement, A serine substitution at position 84 and histidine at position 58 are the two TTR mutations seen most commonly in FAP type II, beginning in the upper limbs with carpal tunnel syndrome. The age of onset varies greatly with specific TTR mutations. Even in families with the VaBOMet mutation variation in age of onset is observed in different geographic regions (Ikeda ct a I, 2002), Specific TTR mutations may produce unique phenotypes with predominantly cardiac ot lepto meningeal amyloidosis (Hund et al. 2001).

Apolipoprotein AI Amyloidosis (Familial Amyloid Polyneuropathy Type III, Van Allen)

The clinical manifestations of the type III variant have much in common with those of type I except for early renal involvement and a high incidence of duodenal ulcers among affected individuals. Uremia is the most common cause of death, typically occurring 12-15 years after the onset of neuropathy. An abertant fragment of apolipoprotein Al with a substitution of arginine for glycine accumulates in the tissues in FAP type III.

Gelsolin Amyloidosis (Familial Amyloid Polyneuropathy Type IV, Meretoja)

Gelsolin amyloidosis was first described in Finland, but subsequently isolated cases have been reported elsewhere. Symptoms begin in the third decade with corneal clouding

caused by a fine network of amyloid filaments, referred to as *lattice corneal dystrophy.* This is followed in the fifth decade by progressive cranial neuropathies with prominent facial palsy and skin changes producing a typical baggy skin over the atrophic face. Other bulbar signs may develop together with mild peripheral neuropathy without autonomic dysfunction.

Gelsolin, the amyloid protein isolated from tissues of FAP type IV, is an actin-binding protein found in plasma, leukocytes, and other cell types. The gelsolin gene maps to chromosome 9. Amino acid substitutions (asparagine or tyrosine at position 187) result in amyloid-forming mutant gelsolin.

DNA *Diagnosis of Familial Amyloid Polyneuropathy*

The diagnosis of FAP requires several steps. Initially, the diagnosis is established by confirming the presence of amyloid in nerve and muscle, rectal biopsies, or a sample of subcutaneous abdominal fat. Immunostaining using specific antibodies against one of the three aberrant proteins may identify the tesponsible protein. In sporadic cases, the more common AL amyloidosis should be excluded by a search for clonal plasma cell dyscrasia (see Primary Systemic Amyloidosis, later in this chapter). If no evidence of plasma cell dyscrasia exists, TRR can be identified by isoelectric focusing of the serum, which separates vatiant and wild-type TTR. The finding of a variant TTR should prompt genetic testing. DNA isolated from peripheral leukocytes or tissue can be amplified with the polymerase chain reaction and specific oligonucleotide primers used to amplify regions of the gene of interest, thereby demonstrating specific point mutations. DNA testing for the most common TTR mutations (Mcr-30, Ile-33, Ala-60, Tyr-77, Ser-84) is readily available in reference laboratories. Mutation analysis of the entire TTR gene detects more than 99% of amyloidogcnic mutations.

Treatment

The prognosis of TTR amyloidosis varies with the specific mutation, age of onset, and otgan involvement. Supportive measures are essential for both the neuropathy and specific organ system involved, including cardiac pacing, dialysis, parenteral nutrition, and physical therapy. Because over 90% of TTR is synthesized in the liver, orthotopic liver transplantation has been proposed as definite therapy for this disorder. Transplantation results in rapid clearance of the variant TTR from serum; it may halt progression of neurological deficits in patients with mild neuropathy and stop the rate of axonal degeneration; autonomic dysfunction remains largely unchanged (Adams et al. 2000). The reported 5-year survival rate is approximately 80%. Liver transplantation is recommended for patients who are younger than 50 years, have mild neuropathy (walking unaided), and have no significant cardiac or renal involvement. Transplanation is not effective in cardiac or leptomeningeal amyloidosis. Alternative treatment modalities with agents which stabilize the variant TTR and inhibit fibril formation are under investigation,

Porphyric Neuropathy

Hepatic porphyrias are caused by inactivation of one of a pair of allelic genes that encodes for an enzyme of the heme biosynthctic pathway. The consequent 50% reduction of enzyme activity provokes a compensatory overproduction of porphyrins and their precursors through the negative feedback regulation by heme of the first and rate-limiting enzyme of the heme hiosynthetic pathway, ^-aminolevulinic acid synthase (ALA-S). These dominantly inherited disorders include acute intermittent porphyria (A1P), variegate porphyria (VP), and hereditary ctipropor phyria (HCP). A fourth disorder referred to as *plumboporphyria* is inherited as an autosomal recessive trait and is caused by a deficiency of 3-aminolevulinic acid (ALA) dehydratase (Table 82.17). Mote than 90 mutations in the PBG deaminase gene have been identified that decrease enzyme activity and cause AIP (F.lder, Hift, and Meissner 1997). These partial enzyme defects remain latent until precipitating factots trigger acute attacks. Precipitating factors include certain inducing drugs, the menstrual cycle, alcohol, hormones, and fasting (cither intentional or during an intercurrent illness). Precipitating factors share the ability to induce hepatic 5-ALA synthase, the rate-limiting enzyme in heme biosynthesis, which leads to the overproduction and overexcretion of porphobilinogen (PBG) and 5-ALA.

Clinical Features of the Acute Porphyric Attack

The manifestations of the acute attack are identical regardless of the specific type of hepatic porphyria. All clinical symptoms can be explained by dysfunction of the autonomic nervous system, PNS, and CNS. Characteristically, porphyric attacks fits! occur during the third and fourth decades of life and are five times more common and severe in women than men. The most frequent presenting symptoms arc abdominal pain, nausea, vomiting, and severe constipation. Other autonomic manifestations are tachycardia, labile hypertension, orthostatic hypotension, .Hid difficulty with micturition. Only a few patients progress to develop the more ominous motor neutopathy or CNS involvement. Onset of the predominantly motor neuropathy is subacute, with generalized, proximal, or asymmetrical muscle weakness developing over days or weeks. The arms rather than the legs may be affected first, and proximal muscles may be preferentially involved. Muscular activity before onset of symptoms may influence the pattern of weakness. Cranial nerve involvement is common. In severe cases, flaccid quadriplegia with

Tabic 82.17: Porphyric neuropathies

	Acute intermittent porphyria	*Variegate porphyria*	*Hereditary coproporphyria*	*Plumboporphyria*
Enzyme defect	PBG deaminase	Protoporph yrinogen oxidase	Coproporphyrinugen oxidase	AI A dehydratase
Inheritance	AD	AD	AD	AR
Chromosome	1lq24	lq22	3ql2	9q34
Photosensitive eruption	None	I'resml	ı'lvv'llt	None
Porphyrin excretion				
Urine				
PBG	+++	+++	+++	0
ALA	+++	+-H-	+++	+++
1 *u,*	+	+	+	Negative
Co pro	Negative	+4-	4-4-4-	+
Feces				
Copro	Negative	+	4-4-4-	Negative
Proto	Negative	+++	+	+

AD = autosomal dominant; ALA = aminolevulinic acid; AR = autosomal recessive; copro = coproporphyria PBG = porphobilinogen; proto = protoporphyrin; uro = uroporphyrin; 4-4-4-, ++, + = a relative indication of quantity excreted.

respiratory failure ensues. Rapidly progressive muscle wasting is a striking feature. Tendon reflexes are diminished or absent, but paradoxically ankle jerks may be retained. Sensory impairment may occur in a distal stocking-glove distribution or may affect the trunk and proximal limbs in an unusual bathing suit pattern. In exceptional cases a bilateral radial motor neuropathy without abdominal pain may be the only manifestation of AIP (King et al. 2002). The rate of improvement is variable. Some patients rapidly recover function, suggesting a reversible acute toxic-metabolic neuronal injury. Those with fixed weakness caused by axonal degeneration improve slowly (mean time to recovery, 10.6 months for proximal muscles and nearly twice as long for distal muscles). The protean CNS manifestations during severe attacks include anxiety, confusion, delirium, seizures, and coma.

Patients with VP and HCP develop cutaneous photosensitivity during adult life. The skin manifestations consist of blisters, hyperpigmentation, hypertrichosis, and increased skin fragility. AIP occurs in all ethnic groups, but is most common in individuals of Scandinavian or English descent. VP is also common among South Africans of Afrikaans descent.

Laboratory Studies

The biochemical hallmark of the porphyric attack is the marked elevation of PBG and ALA in blood and urine. Rapid screening tests for urinary PBG such as the Watson-Schwartz and Hocsch tests give positive test results during virtually all acute attacks and are useful in an emergency. A positive screening test result must be confirmed with quantitative urinary determinations of PBG and ALA. Levels of urinary ALA and PBG may decrease rapidly after an attack of VP or HCP, but remain elevated in AIP. Subsequently, Stool assays for protoporphyrins aiul cupru porphyrins are necessary to distinguish VP and HCP from AIP, The diagnosis of <S-ALA dehydratase deficient is supported by increased urinary excretion of ALA without accompanying PBG elevation. Certain medical ions and disorders other than porphyrias are associated with increased urinary porphyrins, including lead poisoning, liver disease, alcoholism, chronic renal failure during hemodialysis, and hereditary tyrosinemia (Tefferi, Solberg, and Lllcfson 1994). CSF is normal. Hyponatremia related to inappropriate antidiuretic hormone release is common.

Electrophysiological studies in patients with porphyric neuropathy reveal low-amplitude CMAPs but normal or borderline slow motor conduction velocities. SNAPs are reduced in amplitude or absent. EMG obtained early in the course reveals poor recruitment of normal motor unit potentials. Denervation changes appear later, first in the paraspina) and proximal muscles and subsequently in distal muscles. Morphological study results support length-dependent axonal degeneration and preferential loss of large myelinated axons (Suarez et al. 1994).

Pathogenesis

The hepatic porphyrias have a lifelong genetic defect in hepatic heme synthesis. In AIP, a partial defect of PBG deaminase activity can be demonstrated in erythrocytes, fibroblasts, and hepatocytes. Individuals bearing the mutation responsible for AIP can be identified readily by measuring red cell PBG deaminase. In HCP, the block is more distal, involving coproporphyrinogen oxidase, whereas in VP it involves protoporph yrinogen oxidase, with resultant excessive fecal excretion of coproporphyrin and protoporphyrin, respectively. Assays for the latter two enzymes in skin fibroblasts are limited to research laboratories. F.n/.yme assays may mislead and should not be used in place of porphyrin analysis.

The mechanism of the neuronal axonal injury remains uncertain. The two leading hypotheses implicate neuronal

heme deficiency with impaired energy metabolism or direct neurotoxicity of ALA.

Treatment and Management

The treatment of patients with acute hepatic porphyria involves three important steps: (1) prevention of attacks; (2) attempts to repress hepatic <5-ALA synthase activity, thereby reducing porphyrin production; and (3) supportive care, Ideally, attacks should be prevented by avoiding drugs and situations that induce them. Among the inducing drugs, barbiturates are the most common precipitants, followed by sulfonamides, analgesics, nonbarbiturate hypnotics, anticonvulsants, and female sex hormones. Intentional fasting and alcohol consumption should be avoided. Gonadotropui-relL'asiug hormone agonists may benefit women with recurrent attacks related to the menstrual cycle. The attack must be treated promptly, as outlined in Figure 82.17. First, all offending drugs are removed and any intercurrent infection is treated. A high-carbohydrate diet orally or by nasogastric feeding (at least 400 g daily, or the equivalence of glucose or levulose infusions) results in reduced porphyrin precursor production. Persistent symptoms or neurological deficits that progress for 24 hours after carbohydrate loading are indications for treatment with hematin (a hydroxide of heme), which represses the activity of hepatic o-ALA synthase and may restore cytochrome functions by replenishing an endogenous heme deficit. Hematin therapy, at the recommended dose of six infusions of 4 m^/kg body weight at 12-hour intervals, has resulted in consistent reduction of porphyrin precursors in serum and urine, and clinical improvement in more than 80% of attacks. The only placebo-controlled study suggested a more modest clinical benefit of intravenous hematin. Early administration of hematin is advocated to correct the metabolic insult before neuronal damage becomes irreparable.

Supportive treatment consists of the correction of fluid imbalance, close attention to respiratory function, and physical therapy. Abdominal pain can often be controlled with simple analgesics, but may require narcotics. Sedation with chlorpromazine is often helpful. The treatment of seizures poses a difficult therapeutic problem because most anticonvulsants may exacerbate the disease. Intravenous diazepam or parental magnesium sulfate are both effective and safe for immediate seizure control.

Fabry's Disease

Fabry's disease is an X-linked lysosomal storage disorder caused by a deficiency of the lysosomal enzyme a-galactosidase A, which results in the accumulation of the glycolipid globotnacylccramide (ceramidetrihexoside) within vasculat endothelial cells of the kidneys, heart, brain, and skin. Over time, progressive vascular disease leads to renal failure, cardiac disease, and strokes. Skin involvement gives rise in the typical angioki raromas, \\ Hi.li are dark red, punctate telangiectases found mainly over the lowet part of the trunk, buttocks, and scrotum (Figure 82.18). A painful small fiber neuropathy develops in childhood or adolescence. Distal paresthesias and lancinating pain are intensified by exertion, fever, or hot environments. Autonomic dysfunction includes diminished sweating, impaired tear and saliva formation, and decreased intestinal motility. Except for impairment of temperature sensation, overt neurological signs are absent. Female carriers often show clinical involvement but rarely develop the renal failure, which is characteristic of affected men.

NCVs are mildly reduced in two thirds of patients. Deposition of glycolipid in small neurons of sensory and peripheral autonomic ganglia results in neuronal degeneration and selective loss of small myelinated and unmyelinated fibers in sural nerve biopsy specimens. Ultrastructurally, perineuria!, endothelial, and perithelia! cells contain typical lamellated glycolipid inclusions. Leukocyte preparations or skin fibroblasts are used for the diagnostic tf-galactosidase assay.

Analgesics, phenytoin, or carbama/.epine, along with avoidance of aggravating factors, are effective for pain

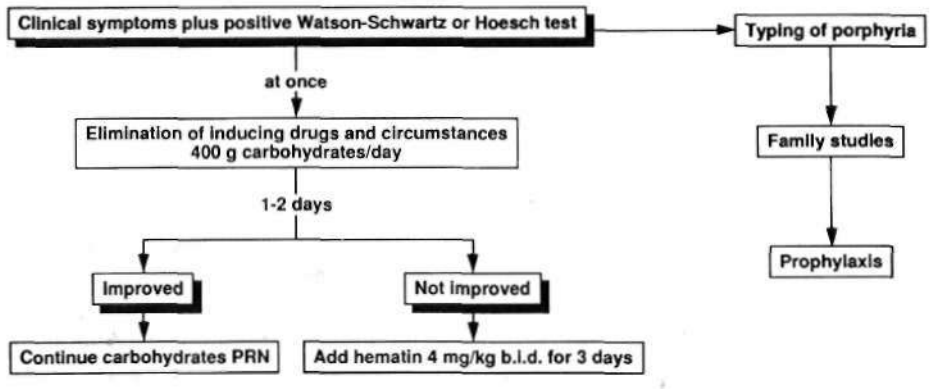


FIGURE 82.17 Management of acute porphyric attack. (PRN = as needed.) (Reprinted with permission from Bosch, K. P. & Pierach, C. A. 1987, "Acute bepatic porphyria," in *Current therapy in neurologic disease,* cd R. T. Johnson, Decker, Toronto.)

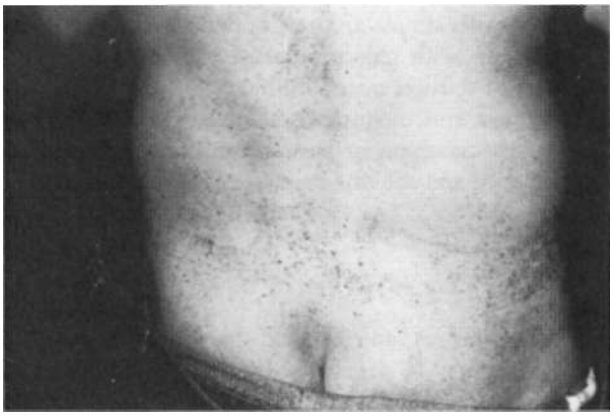


FIGURE 82.18 Fabry disease. Typical angiokeratomas arc clustered over the lower part of the trunk.

relief. Recombinant a-galactosidase A replacement therapy has been shown to be safe and effective in the removal of microvascular endothelial deposits from target organs (Enget al. 2001).

Leukodystrophies with Neuropathy

The leukodystrophies result from inherited abnormalities of myelin metabolism thar may affect both the CNS and PNS. Peripheral nerve involvement is seen in metachromatic leukodystrophy (MLD), Krabbe's disease, adrenomyeloneuropathy, and Cockayne's syndrome. Recognition of an associated neuropathy may he helpful in the differential diagnosis of the underlying leukodystrophy. Mis-sense mutations in proteolipid protein, a major component of central myelin, cause a spectrum of X-linked CNS disorders without peripheral neuropathy, including Pelizaeus-Merzbacher disease and hereditary spastic paraparesis. Proteolipid protein is expressed also in Schwann cells and compact peripheral myelin. Absence of proteolipid protein expression caused by a frameshift mutation has been reported to produce a demyelinating neuropathy with less severe CNS manifestations (Gabern et al. 1997).

Metachromatic Leukodystrophy

MI.D is an autosomal recessive disorder of sulfatide metabolism caused by deficiency of the lysosomal enzyme arylsulfatase-A (ASA) and subsequent accumulation of sulfatides in brain, peripheral nerve, and other tissues. The storage of sulfatides affects central and peripheral myelin, leading to progressive dcmyclination. The ASA gene is localized to chromosome 22q13, and thus far over 60 mutations have been identified. Some gene mutations have been correlated with different clinical phenotypes.

Three main clinical forms have been divided by age of onset: (1) late infantile (6 months to 2 years), (2) juvenile (3-16 years), and (3) adult. Peripheral nerve involvement characterized by a progressive gait disorder, hypotonia, and lower limb arcflcxia is an early manifestation that frequently precedes CNS involvement in late infantile and early juvenile MI.D, In contrast, behavioral abnormalities and progressive dementia predominate over subtle neuropathic signs in adult-onset MI.D. A homozygous mis-sense mutation has been described in an adult patient presenting with an isolated polyneuropathy without CNS involvement {Felice et al. 2000), Marked uniform slowing of nerve conduction is seen in late infantile and juvenile cases. Reduced NCVs and delayed visual and somatosensory evoked potential latencies arc present in most adult cases. Extensive segmental dcmyelination and abnormally thin myelin sheaths are seen in nerve biopsy specimens of ail MLD variants, along with metachromatic inclusions within Schwann cells and macrophages. Peripheral nerve biopsy therefore otters a means ot continuing the diagnosis, although this is rarely needed now. The diagnosis of MI.D is supported by MR] of the brain and confirmed by an increased urinary sulfatide excretion and abnormal ASA en/.vine assays in leukocytes or fibroblasts.

Bone marrow Transplantation may increase brain levels of ASA sufficiently to stop disease progression.

Globoid Cell Leukodystrophy

Globoid cell leukodystrophy, or Krabbe's disease, is an autosomal recessive disease caused by an inherited deficiency of the lysosomal enzyme galactocerehroside *fi*-galactosidase. The gene for Krabbe's disease has been localized to chromosome 14q31. The disorder is characterized by extensive CNS and peripheral nerve demyelination and the presence of multinucleated macrophages (globoid cells) in the cerebral white matter. The classic presentation in early infancy consists of rapidly progressive deterioration in intellectual and motor development, accompanied by hypcrtonicity, opisthotonic posture, optic atrophy, and seizures. In the late-onset form, peripheral neuropathy and spasticity may be the only manifestations. Peripheral nerve involvement is demonstrated by marked uniform slowing of motor conduction velocities. Segmental demyelination, together with ultrastructurally characteristic tubular or crystalloid inclusions within Schwann cells and macrophages, is seen in sural nerve. Hematopoietic stem cell transplantation provides a source of the missing enzyme and can thereby prevent and reverse the CNS manifestations (Krivit et al. 1998).

Adrenomyeloneuropathy

Adrenoi-nyeloneuroparbv (AMN), rhe adult piieiiiilype ol adrenolcukodystrophy, is an X-linkcd recessive disorder of fatty acid metabolism characterized by adrenal insufficiency, progressive myelopathy, and peripheral neuropathy. A defect in beta-oxidation of saturated very-long-chain

fatty acids (VLCFA) in peroxisomes leads to the accumulation of tetracosanoic (C24:0) and hexacosanoic (C26:0) acid in tissues and body fluids in affected patients. A significant increase of VLCEA levels in plasma, fibroblasts, or both allows reliable detection in patients and heterozygote female carriers. The defective gene (ABCDl) is located in the region Xq28 and codes for a peroxisomal membrane protein referred to as *ALD protein* that belongs to the ABC transporter protein family (Moser 1997). Adrcnomyeloneuropathy presents in the second to third decades with progressive spastic paraparesis, distal muscle weakness, sensory loss, and sphincter disturbances. Neurological features frequently are preceded by clinical or laboratory evidence of hypoad renal ism. Approximately 10% of patients have primary adrenal insufficiency without evidence of nervous system involvement. At least 20% of female carriers develop spasric paraparesis similar to that in men, but less severe and later in onset.

Electrophysiological studies are helpful in identifying peripheral nerve involvement that may escape clinical detection because of prominent upper motor neuron signs, Nerve conduction studies demonstrate a distal axonoparhy with low CMAP amplitudes and mildly reduced NCVs. Less than 10% of patients have significant nerve conduction slowing suggestive of dcmyelination (van Geel et al. 1996). Sural nerve biopsy shows loss of myelinated fibers, occasional small onion bulbs, and curvilinear lamellar lipid inclusions ir Schwann a'lls. [iram MRI M-HI I.-•.-':-. are abnormal, demonstrating white ma net changes in one half of patients with AMN at some time in the course of their disease.

Dietaty restriction of VLCFA combined with the administration of oleic and erucic acids (Lorenzo's oil) lower plasma levels of VLCFA, but have no effect in arresting the rate of neurological progression (van Geel et al. 1999). Adrenal insufficiency responds readily to corticosteroid replacement, In contrast to the cerebral form, patients with AMN arc not considetcd suitable candidates for bone marrow transplantation.

Phytanic Acid Stotagc Disease (Refsum's Disease)

Refsum's disease, heredopathia atactica polyneuritiformis, is a rare autosomal recessive disorder of phytanic acid metabolism. The gene defect has been localized to chromosome 10 and encodes the peroxisomal enzyme phytanoyl-CoA-hydroxylase. The defect in the enzyme that initiates the alpha-oxidarion pathway of ^-methyl substituted fatty acids leads to phytanic acid accumulation in serum and tissues. Phytanic acid is derived exclusively from dietary sources, mainly chlorophyll, dairy products, meats, and fish oils. Clinical onset spans from childhood to the third decade of life. The cardinal manifestations include pigmentary retinal degeneration, with night blindness or visual field constriction, chronic hypertrophic neuropathy, ataxia, and other cerebellar signs such as nystagmus and intention tremor. Initially, the neuropathy affects the lower limbs with distal leg atrophy, weakness, areflexia, large fiber sensory impairment, and sometimes palpably enlarged nerves. Weakness becomes generalized later in the illness. In addition to pes cavus, overriding toes caused by symmetrically short fourth metatarsals are a helpful sign for Refsum's disease. Progressive sensorineural hearing loss, anosmia, cardiomyopathy, and ichthyosis are common. The course may be either progressive or fluctuating with exacerbations and remissions. Exacerbations are often precipitated by fasting, which mobilizes phytanic acid from endogenous fat stores.

Motor conduction velocities arc markedly slowed, and SNAPs are reduced or absent. CSF protein is increased in the range of 100-700 mg/dL. Sural nerve biopsy reveals a hypertrophic neuropathy with prominent onion bulb formation. The diagnosis is confirmed by elevated serum levels of phytanic acid.

Chronii dietary rrrarnioni by ivitniini;; ilu- t-\ou,enoiis sources of phytanic acid (<10 nig/day) and its precursor phytol results in reduction of serum phytanic acid levels and clinical improvemenr. The diet should provide sufficient calories to avoid weight loss. Plasma exchange has been used ro lower toxic scrum phytanic acid levels more rapidly in critically ill patients.

Tangier Disease

Tangier disease is an autosomal recessive disorder named after Tangier Island, VA, the origin of the first described cases. It is characterized by severe deficiency of plasma alpha or high-density lipoproteins, resulting in the deposition of cholesterol esters in many tissues, including the reticuloendothelial system and peripheral nerves. The accumulation of lipids leads to enlarged yellow-orange tonsils, which may provide a clue to the diagnosis. In adolescence or adult life, approximately one half of the affected patients develop one of two distinct neuropathic syndromes. The first is a progressive symmetrical neuropathy, with dissociated loss of pain and temperature sensation in the face, arms, and upper trunk combined with faciobrachial muscle wasting and weakness. These findings bear a superficial resemblance to sytingoinyelia. The second syndrome consists of relapsing multifocal mononeuropathies involving the cranial, trunk, or limb nerves.

High-density lipoprotein and serum cholesterol are markedly reduced, whereas triglyceride concentrations are elevated. A neuropathic disorder is confirmed by absent or low-amplitude SNAPs and reduced conduction velocities. Nerve biopsy specimens from patients with the multiple mononeuropathy variant have shown segmental demyelination and remyelinarion. By contrast, a preferential loss of small myelinated and unmyelinated axons is found

in the syringomyelialike variant. Typically abundant lipid vacuoles in vliv./.mi CL-!1S are nrcseiu in both. No specific treatment is known.

Abetalip o protein em ia (Bassen-Kornzweig Syndrome)

Abetalipoproteinemia is a rare autosomal recessive disorder of lipoprotein metabolism. The condition is associated with gene defects coding for the microsomal triglyceride transfer protein, resulting in abnormal very-low-density lipoprotein secretion. Fat malabsorption is present from birth and results in a severe deficiency of the fat-soluble vitamins A, E, and K. Steatorrhea, hypocholesterolemia, and abnormally spiky red cells (acanthocytes) are present from birth. Most untreated patients develop retinitis pigmentosa, peripheral neuropathy, and spinocerebellar degeneration during the first two decades of life, A progressive, mainly large fiber sensory neuropathy occurs, with gait ataxia, areflexia, impaired proprioceptive sensation, and modest distal weakness. Patients have absence of serum *fi*-lipoproteins and very low levels of vitamin E.

Clinical manifestations of vitamin E deficiency can also be found in familial vitamin E deficiency caused by mutations of the a-tocopherol transfer protein gene. These gene mutations result in the failure to incorporate ^-tocopherol in very low density lipoprotein in the liver and lead to low vitamin E levels in the absence of malabsorption (Martinello et al. 1998).

Dietary fat restriction and large oral doses of vitamin E (100 mg/kg/day) can prevent the onset of symptoms or arrest progression of neurologic complications in abetalipoproteinemia and familial vitamin E deficiency.

Mitochondrial Cytopathies and Polyneuropathy

The molecular basis has been established for several mitochondrial cytopathies, including Kcarns-Sayre syndrome, MELAS (mitochondrial myopathy, encephalopathy, /actic acidosis, and stroke), and MERRF (myoclonus epilepsy with /-agged-red /ibers; see Chapter 85). In these syndromes, myopathy is the predominant neuromuscular manifestation, although a mild, often asymptomatic, sensory polyneuropathy is detected commonly by system a tic electrophysiological and pathological studies. Peripheral neuropathy is a presenting clinical feature in three mitochondrial syndromes: neurogenic weakness, ataxia, and retinitis pigmentosa syndrome; mitochondrial ncurogastrointestinal encephalomyelopathy; and sensory ataxic neuropathy associated with dysarthria and chronic progressive external ophthalmoplegia. The last subgroup of patients presents with a familial, disabling ataxic sensory neuropathy and progressive ophthalmoparcsis that is associated with multiple mitochondrial DNA deletions (Fadicet al. 1997).

INFLAMMATORY DEMYELINATTNG POLYRADICULONEUROPATHIES

Inflammatory dcmyclinating polyradiculoneuropathies are acquired and immunologically mediated. These neuropathies can be classified by their clinical course into two major groups: an acute inflammatory demy el inn ting polyradiculoneuropathy (All)l'), or CHS, *:\\\<.]* C1DP. In GBS, the maximal deficits develop over days (maximum 28 days), followed by a plateau phase and gradual recovery. Chronic forms pursue either a slowly progressive or a relapsing course.

Acute Inflammatory Dcmyclinating Polyradiculoneuropathy (Guillain-Barre Syndrome)

In 1916, Guillain, Barre, and Strohl emphasized the main clinical features of GBS: motor weakness, areflexia, paresthesias with slight sensory loss, and increased protein in CSF without pleoeytosis (albuminocytological dissociation). Our current understanding of the pathology was greatly enhanced when Asbury and co-workers described multifocal inflammatory demyelination of spinal roots and peripheral nerves. The frequent finding of motor conduction block and reduced NCVs provided electrophysiological confirmation of widespread demyelination, Improvement in modern critical care has dramatically changed outcomes in CBS. The mortality has fallen from 33% before introduction of positive pressure ventilation to the current rate of approximately 5-10%. The diagnosis of GBS depends on clinical criteria supported by electrophysiological studies and CSF findings (Table 82.18). These diagnostic criteria define AIDP, which is the most common form of GBS in Europe and North America. Observations

Tabic S2.18: Diagnostic criteria for the Guillain-Uarre syndrome

Features required for diagnosis
Progressive weakness of both legs and arms
A reflex i;l
Clinical features supportive of diagnosis
Progression ,:•.,!• Jiiys [o -1 wks
Relative symmetry of signs
Mild sensory symptoms or signs
Cranial nerve involvement (bifacial palsies)
Recovery beginning *2—4* wks after progression ceases
Autonomic dysfunction
Absence of fever at onset
Laboratory features supportive of diagnosis
Flevated cerebrospinal fluid protein with <1() cells/pl
Elcctrodiagnostic features of nerve conduction slowing or block*

^Features supporting an axona) process are seen in acute motor :i\onal neuropathy and acute motor sensory axortal neuropathy.
Source: Adapted from Asbury, A. K. & Coniblath, D. R. 1990, "Assessment of current diagnostic criteria for Gui I linn-Barre syndrome," *Ann Neurol,* vol. 27 (Suppl.), pp. .S21-S24.

Table 82.19: Classification of the Guillain-Barre syndrome subtypes

Acute inflammatory demyelinaring polyradiculoneuropathy
Acute motor axonal neuropathy
Acute motor sensory axonal neuropathy
Millar-Fisher syndrome
Acute pandysautonomia
Sensory GBS

have confirmed that axonal immune-mediated injury may produce similar clinical presentations, ifeasby and colleagues first called attention to axonal GBS, noteworthy for its severity and poor recovery. This axonal variant is called *acute motor sensory axonal neuropathy* (AMSAN) because of involvement of both motor and sensory fibers. A second, pure motor axonal form called *acute motor axonal neuropathy* (AMAN) has been described in northern China where it occurs in summer epidemics in children and young adults. A tentative classification of GBS subtypes has been proposed based on variant clinical expressions and different electrophysiological and pathological findings (Table 82.19; Griffin et ai. 1996).

Clinical Features

GBS is a nonseasonal illness that affects persons of all ages. With the decline of acute anterior poliomyelitis, GBS is the most common acute paralytic disease in Western countries. The mean annual incidence is 1.8 per 100,000 population. Incidence rates increase with age from 0.8 in those younger than 18 years to 3.2 for those 60 years and older.

Approximately two thirds of patients report a preceding event, most frequently an upper respiratory or gastrointestinal infection, surgery, or immunization 1–4 weeks before the onset of neurological symptoms (Govoni and Granicri 2001; Table 82.20). The agent responsible for the prodromal illness often remains unidentified. Specific infections linked to GBS include cytomegalovirus (CMV), Epstein-Barr virus, varicella zoster virus, hepatitis A and B, 111V, *Mycoplasma pneumoniae,* and *Hemophilus influenzae.* The most common identifiable bacterial organism linked to GBS and particularly its axonal forms is *Campylobacter jejuni,* a curved gram-negative rod that is a common cause of bacterial enteritis worldwide. Evidence of C. *jejuni* infection from stool cultures or serological tests was found in *26%* of patients with GBS admitted to hospitals in the United Kingdom, compared with 2% of case controls (Rccs, Gregson, and Hughes 1995). Retrospective studies from the United Stares, Holland, Germany, and Australia report serological evidence of recent C. *jejuni* infection ranging from 17-39% of patients with GRS. C, *jejuni* infection may play an even greater role in northern China where infection rates of 76% in patients with AMAN and 42% in patients with AIDP were found (Ho et a). 1995). Epidemiological data suggested a slight increase in cases of GBS following the 1976 A/New Jersey influenza vaccine, although no excess risk of developing GBS was seen with subsequent influenza vaccines. A current risk estimate of GBS after influenza vaccination is one in a million persons vaccinated. Ptior CBS should not preclude the administration of influenza vaccines in high risk individuals. Other vaccines (notably tetanus and diphtheria toxoids, rabies, and oral polio vaccines); drugs, including streptokinase, suramin, gangliosides, and heroin; and Hymenoptera stings have been associated in a few cases. Several cases have occurred in immunocompromised hosts with 1 lodgkin's lymphoma or in pharmacologically immunosuppressed patients after solid organ or bone marrow transplantation.

Table 82.20: Antecedent events of Guillain-Barre. syndrome (70% in large series]

Antecedent event	*Percentage*
Respiratory illness	58
Gastrointestinal illness	22
Respiratory and gastrointestinal illness	10
Surgery	5
Vaccination	3
Other	2
Serological evidence of specific infectious agents	
Campylobacter jejuni	26*
Cytomegalovirus	15*
Human immunodeficiency virus 1	?
Epstein-Barr virus	8
Mycoplasma pneumoniae	10

? = variable depending on patient population. Eight percent in retrospective study from large urban medical center.
"Percentages according to case-con trolled prospective studies.

Patients may initially present with patesthesia, sensory symptoms with weakness, or weakness alone. The fairly symmetrical weakness of the lower limbs ascends proximal I y over hours to several days to involve arm, facial, and oropharyngeal muscles, and in severe cases respiratory muscles. Less often, weakness may begin in proximal or cranial nerve innervated muscles. Its severity varies from mild involvement, in which patients are still capable of walking unassisted, to quadriplegia. Hyporeflexia or arcflexia arc invariable features but may be missing early in the course of the disease. By definition progression ends by 1–4 weeks into the illness; if it continues longer, the condition is termed either *subacute inflammatory demyelinating polyradiculoneuropathy* if progression continues for 4-10 weeks or CiDP if there is chronic progression or multiple relapses. Cranial nerve involvement ranges from 45-75% in different series. Facial paresis, usually bilateral, is found in at least one half of patients. Involvement of extraocular muscles and lower cranial nerves is seen less often. Occasional patients develop facial myokymia. Pseudotumor cerebri with papilledema occurs as a rare complication and is almost always caused by chronically elevated intracranial pressure. The proportion of patients developing respiratory failure and requiring assisted ventilation seems to increase with age and ranges from

12% in epidemiological series to 30% in hospital-based series. Sensory loss is not a prominent feature and is limited frequently to distal impairment of vibration sense. Moderate to seven.' pain occurs in S.v'.. of patients on admission to the hospital. Interscapular or tow back pain with radiation into the legs is most common, sometimes causing concern about the possibility of an epidural hematoma or abscess. Dyscsthctie extremity pain described as burning or tingling is present in approximately one half of patients, whereas myalgic limb pain associated with joint stiffness is less common (Moulin et al. 1997). Unusual clinical variants with restricted patterns of weakness may cause diagnostic difficulties. Isolated weakness of the face, oropharynx, neck, and arms without involving the legs is a distinctive feature of the pharyngeal-cervical-brachial variant. Rarely, weakness remains confined to the lower limbs, resembling a cauda equina lesion. Autonomic dysfunction of various degrees has been reported in 65% of patients admitted to the hospital (Zochodne 1994). Its manifestations may be related to either increased or decreased sympathetic activity. Signs of decreased sympathetic {orthostatic hypotension, anhidrosis) or decreased parasympathetic {urinary retention, gastrointestinal atony, or iridoplegia) function may be seen. Signs of excessive sympathetic activity include episodic or sustained hypertension, sinus tachycardia, tachyarrhythmias, episodic diaphoresis, and acral vasoconstriction. Excessive vagal activity accounts for sudden episodes of bradycardia, heart block, and asystole. These vagal spells may occur spontaneously or may be triggered by tracheal suctioning. Serious cardiac arrhythmias with hemodynamic instability tend to be more frequent in patients with severe quadriparesis and respiratory failure. Autonomic dysfunction can result in eiectrocardiographical changes including T-wave abnormalities, ST-segment depression, QRS widening, QT prolongation, and various forms of heart block.

Guillam-Barre Syndrome Variants

Several variations from this typical presentation have been described. Their link to GBS is supported by preceding infectious episodes, diminished reflexes, elevated CSF protein levels, and immune-mediated etiologies.

The Miller-Fisher syndrome (MFS), which accounts for 5% of cases, is characterized by ophthalmoplegia, ataxia, and areflexia. Patients present with diplopia followed by gait and limb ataxia. Ocular signs range from complete ophthalmoplegia, including unreaenve pupils, to external ophthalmoparesis with or without ptosis. Cranial nerves other than ocular motor nerves may be affected. Motor strength is characteristically preserved, although overlap with typical GBS seems to occur when some patients develop quadriparesis. The ataxia is attributed to a peripheral mismatch berween proprioceptive input from muscle spindles and kinesthetic information from |omt receptors. Patients present with rapid onset of symmetrical, multiple cranial nerve palsies, mosr notably bilateral facial palsy (polyneuritis cranialis), that may be a *forme fruste* of this syndrome. Elcctrodiagnostic studies demonstrate an axonal process affecting predominantly sensory fibers with only mild motor conduction abnormalities. SNAP amplitudes arc reduced or absent. Motor conducrion srudies, including F-wave latencies, are usually normal. Most patients have increased CSF protein without plcocytosis one week after onset. Brain MRI scans do not demonstrate brainstem or cerebellar lesions, though there are reports of cases appearing to be identical to MFS where there have been MRI brainstem lesions. Gadolinium enhancement of ocular motor nerves has been reported. Serum IgG antibodies to the ganglioside GQ1b are found in acute phase sera of mosr parienrs with MFS and GBS with ophthalmoplegia, which suggests that the antibodies are disease-specific and related to the pathogenesis (Chiba et al. 1993). MFS has a benign prognosis, with recovery after a mean of 10 weeks.

Acute pandysatttonomia is characterized by the rapid onset of combined sympathetic and parasympathetic failure without somatic sensory and motor involvement, although reflexes are usually lost during the course of the illness. These patients develop severe orthostatic hypotension, anhidrosis, dry eyes and mouth, fixed pupils, invariant heart rate, and disturbances of bowel and bladder function. About half of the patients have autoantibodies to ganglionic acetylcholine receptors which may play a pathogenetic role by blocking cholinergic transmission in autonomic ganglia (Venimo LI al. 2000). (iangliome receptor blocking antibodies serve as serological markers of autoimmune autonomic neuropathies and are elevated in both acute pandysautonomia and paraneoplastic autonomic neuropathy.

Feasby and coworkers drew attention to cases of fulminant GBS with poor prognosis for recovery (AMSAN), All patients had a hyperacute course progressing to a peak deficit in less than 7 days, developed profound quadriparesis with severe muscle wasting, and required prolonged respiratory support. Electrodiagnostic studies showed markedly reduced or absent C'MAPs with distal supramaximal stimulation without conduction delay and absent SNAPs. The subsequent appearance of abundant fibrillation potentials on needle EMG, together with persistently mexcitable motor nerves, and poor recovery suggested a primary axonopathy as the underlying disease process. Ex tensive wa lie nan axonal degeneration without significant inflammation or demyelination has been described in ventral and dorsal roots and in peripheral nerves at autopsy (Griffin et al. 1996).

Sporadic cases of a pure motor variant presenting with acute flaccid paralysis without clinical or electrophysiological involvement of sensory nerves have been observed in large series of patients with GBS. These case descriptions are similar to AMAN occurring in epidemic proportions among children and young adults in northern China during

summer months (McKhann et al. 1993). AMAN differs from GBS by electrophysiological study results that demonstrate reduced compound muscle potential amplitudes but normal motor disral latencies and conduction velocities. Autopsy studies of some cases have shown noninflammatory wallcrian-likc degeneration of ventral roots and motor axons in mixed nerves. However, nerve biopsy studies in others have shown intrusion of macrophages between the axon and the surrounding myelin sheath, with relatively little axonal degeneration. Extensive axonal degeneration of motor nerve terminals was confirmed by motor point biopsy in a patient with AMAN. Most patients with AMAN recover as rapidly as patients with AIDP (Ho et al. 1997), The rapid clinical recovery rates and the paucity of pathological findings in some fatal cases could be explained by either conduction block of motor axons at nodes of Ranvier because of macrophage intrusion or by axonal degeneration of motor nerve rerminals. Extensive axonal degeneration of motor nerve terminals was confirmed by motor point biopsy in a patient with AMAN. Antecedent C. *jejuni* infection was found by using serological tests in 76% of AMAN patients from northern China, which suggests that this organism plays a major role in the pathogenesis.

The exisrance of a sensory variant of GBS affecting mainly sensory nerve fibers has long been suspected but rarely confirmed. Such patients present with acute sensory loss, areflexia, high spinal fluid protein, and nerve conduction features of demyelination (Oh, LaGanke, and Claussen2001).

Laboratory Studies

CSF examination and serial electrophysiological studies arc critical for confirming the diagnosis of GBS. Other laboratory studies are of limited value. Mild transient liver enzyme elevations without obvious cause are found in approximately one third of patients. Hyponatremia is seen most frequently in ventilated patients because of inappropriate secretion of antidiuretic hormone. Deposition of immune complexes may rarely lead to glomerulonephritis and result in microscopic hematuria and proteinuria. In the first week of neurological symptoms the CSF protein may be normal but then becomes elevated on subsequent examinations. In approximately 10% of cases, the CSF protein remains normal throughout the illness. Transient oligoclonal IgG bands and elevated myelin basic protein levels may be detected in some patients. Moderate CSF pleocyrosis is a distinctive feature of GBS associated with HIV infection. Abnormalities of electrophysiological studies are found in approximately 90% of established cases and reflect an evolving picture of multifocal demyelination associated with secondary axonal degeneration. The most common electrophysiological abnormalities include prolonged distal motor and F-wave latencies, absent or impersistent F waves, conduction block, reduction in distal CMAF amplitudes with or without temporal dispersion, and slowing of motor conduction velocities (Cros and Triggs 1996). Conduction block of motor axons is the electrophysiological correlate of clinical weakness and is recognized by a decrease of greater than 30% in CMAP amplitude from disral to proximal stimulation in the absence of temporal dispersion. Electrodiagnostic studies may not be diagnostic early in the course of the disease. Absent H-reflexes, delayed or absent F waves, and low amplitude or absent SNAPs in the upper extremity combined with normal sural SNAPs are changes supportive of the diagnosis in the first week of illness (Gordon and Wilbourn, 2001). Needle EMG initially shows decreased motor unit recruitment. Subsequently, if any amount of axonal degeneration occurs, fibrillation potentials appear 2—4 weeks after onset. Electrodiagnostic studies performed in the patients enrolled in the North American GBS Study found abnormalities of distal motor latencies and F-wave latencies in approximately one half of patients studied within 30 days of onset. Partial motor conduction block (30%), slowing of motor conduction velocity (24%), and reduced distal CMAP amplitudes (20%) were less frequent. In cases with axonal degeneration, reduced CMAP and SNAP amplitudes are found. Such patients tend to have a slower and less complete recovery than those whose weakness is related primarily to conduction block. Electrodiagnostic parameters arc the most reliable indicators of prognosis. A distal CMAP amplitude of less than 20% of the lower limit of normal was associated with poor outcome in the North American GBS Study.

Lumbosacral spinal MRI may demonstrate gadolinium enhancement of lumbar roots. The value of specific serological tests in the diagnosis of GBS is limited. Elevated serum antibodies to *Mycoplasma,* CMV, or C. *jejuni* can pinpoint the preceding infection. Serological tests for C. *jejuni* infection arc difficult both to perform and interpret. The proportion of GBS cases associated with *Campylobacter* infection remains uncertain but seems to range from 17-76% in various parts of the world. Preceding *Campylobacter* infection li.i-. brer, linked u> .]\<>n;il variants, worse ourcome, and high titers of anti-GMj, anri-GDu,, anti-$GD_{[:1}$, and anti-GalNAc-$GD_{1:}$, gangliosidc antibodies of the IgG class {Jacobs, van Doom, and Schmitz 1996). Other studies confirmed the presence of IgG antiglycolipid antibodies in 10-40% of patients with GBS but failed to show a correlation with *Campylobacter* infection ii lo et al. 1995). FJevated anti-GQib gangliosidc antibodies are consistently found in MFS. Anti-galactocerebroside antibodies have been detected in patients with precedent *Mycoplasma* infection. Complement fixing antibodies to peripheral nerve myelin are present in most patients during the acute phase of GBS.

Differential Diagnosis

Care should be taken to distinguish GBS from other conditions leading to subacute motor weakness (Table 82.21).

Table 82.21: Differential diagnostic considerations in Guillain-Barre syndrome

1. Acute neuropathies
   Hepatic porphyrias
   Critical illness neuropathy
   Diphtheria
   Toxins
   Arsenic, thallium, organophosphates, lead
   Neurotoxic fish and shellfish poisoning (ciguatoxin, retrodotoxin, saxitoxin)
   Buckthorn
   Tick paralysis
   Vasculitis
   Inflammatory meningoradiculopathies
   Lyme disease, cytomegalovirus lumbosacral ra d i c u 1 omy e Io pa thy
II. Disorders of neuromuscular junction
   Botulism, myasthenia gravis
HI. Myopathies
   Hypokalemia, hypophosphatemia
   R ha bdomyo lysis
   Polymyositis
   Intensive care myopathy
IV. Central nervous system disorders
   Poliomyelitis
   West Nile virus poliomyelitis
   Rabies
   Transverse myelitis
   Basilar artery thrombosis

Among the neuropathies with acute onset, acute porphyria, diphtheria, and occasional toxic neuropathies (arsenic, thallium, buckthorn, acrylamide, organophosphorous compounds, and w-hexane) must he considered. Flaccid general weakness and failure to wean from the ventilator are common features of critical illness neuropathy that develops in patients confined to the intensive care unit with sepsis and multiorgan failure. Elcctrodiagnostic features of an axonal neuropathy and normal CSF findings distinguish critical illness neuropathy from GBS. A related syndrome, the acute myopathy of intensive care, follows the use of nondepolarizing neuromuscular blocking agents in combination with intravenous corticosteroids. Metabolic disturbances (severe hypophosphatemia, hypokalemia, hypermagnesemia), myopathies, disorders of neuromuscular transmission, and tick paralysis should be considered also. Botulism develops after the consumption of contaminated foods, with symptoms of oph thai mo paresis and facial and bulbar weakness. Nerve conduction studies reveal low-amplitude compound muscle potentials. High-frequency repetitive nerve stimulation ot maximal voluntary contraction leads to an incremental response that is typical for presynaptic neuromuscular transmission defects. Acute brainstem infarcts, spinal cord compression, epidural abscess and postinfectious transverse myelitis may present diagnostic difficulties before upper motor neuron signs develop and before results of elcctrodiagnostic and CSF studies become available. Among other signs, early urinary retention and a sharply demarcated sensory level on the trunk suggest spinal cord disease and call for spinal MRI. CSF pleocytosis (>50 cells per ul) casts doubt on the diagnosis of uncomplicated GBS and suggests inflammatory meningoradiculopathies caused by Lyme disease, **HIV** infection, or CMV in acquired immunodeficiency syndrome. Anterior poliomyelitis causes rapidly evolving asymmetrical weakness accompanied by fever and CSF pleocytosis. A poliomyelitis-like condition producing flaccid paralysis is seen in up to 27% of patients with neurological complications of West Nile virus infection. A common pitfall to avoid is misdiagnosis of early GBS as hysterical weakness.

Pathology

Classic pathological studies of AIDP have demonstrated endoneurial perivascular mononuclear cell infiltration together with multifocal demyelination. The peripheral nerves may be affected at all levels from the roots to distal intramuscular motor nerve endings, although the brunt of the lesions frequently falls on the ventral roots, proximal spinal nerves, and lower cranial nerves. Intense inflammation may lead to axonal degeneration as a consequence of a toxic bystander effect. Ultrastructural studies have shown that macrophages play a major role in demyelination by stripping off myelin lamellae from its axon. The inflammatory infiltrates consist mainly of class 11-positive monocytes and macrophages and T lymphocytes. The expression of class II antigen is increased in Schwann cells, raising the possibility that Schwann cells may present the antigen to autoreactive T cells and activate the desttuction of myelin. Extensive primary wallerian-like degeneration of motor and sensory roots and nerves without significant inflammation or demyelination is found in cases of AMSAN.

Pathogenesis

A considerable body of evidence points to an organ-specific autoimmune disorder mediated by autoreactive T cells and humoral antibodies to still incompletely characterized periphera nerve antigens (1 laming. Willison, and Kieseier 2002). A preceding infection may trigger an autoimmune response through molecular mimicry in which the host generates an immune response against an infectious organism that shares epitopes with the host's peripheral nerves. At the onset of disease, activated T cells play a major role in opening the blood-nerve barrier to allow circulating antibodies to gain access to peripheral nerve antigens. T-cell activation markers (interleukin-6, interleukin-2, soluble intcrleukin-2 receptor, and interferon-^) and tumor necrosis factor-a, a proinflammatory cytokine released by T cells and macrophages, are increased in serum of patients. In addition, adhesion molecules and matrix metalloprotcinases arc critically involved in facilitating recruitment and transmigration of activated T cells and

monocytes through the blood-nerve barrier. Soluble E-selectin, an adhesion molecule produced by endothelial cells, and metailoproteinases are increased in patients with GBS during the early stages of disease. A cell-mediated immune reaction against myelin components is supported by experimental allergic neuritis, the accepted animal model for AIDP. Experimental allergic neuritis can be produced by the injection of peripheral nerve myelin or PNS-specific myelin basic protein P2.

Several observations indicate that humoral factors participate in the autoimmune attack on peripheral nerve myelin, axons, and nerve terminals: (1) immunoglobulins and complement can be demonstrated on myelinated fibers of affected patients by immunostaining; (2) MPS and AMAN are strongly associated with specific anti-ganglioside antibodies; (3) serum from MFS and AMAN patients contains IgG antibodies that block neuromuscular transmission in a mouse nerve-muscle preparation; (4) complement Cl-fixing antiperipheral nerve myelin anti-body can be detected in the serum of patients during the acute phase of GBS; *(5)* plasmapheresis or immunoglobulin infusions result in clinical improvement; and (6) intraneural injection of GBS serum into rat sciatic nerve results in secondary infiltration of the injection site at the time of the appearance of the hind limb weakness.

Understanding of the immune mechanisms of GBS and its axonal variants was enhanced by the detailed immu.no.-histochemical and ultrastructural studies of clinically well-defined, autopsied cases from northern China. The earliest changes seen in AIDP within days of onset consisted of deposition of complement activation products and mem-brane attack complex on the outermost Schwann cell surface followed by vesicular myelin changes at the outermost myelin lamellae with subsequent recruitment of macrophages and progressive demyelination (Hafcr-Macko et al. 1996). Previously, the role of complement has been suspected by finding increased levels of complement activation products in CSF and soluble terminal comple-ment complexes in serum of patients with AIDP. The immune attack in AIDP appears to begin with binding of autoantibodies to specific epitopes on the outermost Schwann cell membrane with consequent activation of complement (Figure 82.19). The nature of the epitope in AIDP, although still uncertain, is likely a glycolipid. Pathological studies of early cases of AMAN found deposition of activated complement components and immunoglobulins at nodal axolemma. This was followed by disruption of the paranodal space, allowing the entry of complement and immunoglobulins along the axolemma, with subsequent recruitment of macrophages to affected nodes. Finally, macrophages were shown to invade the periaxonal space leading to wallerian-like degeneration of motor fibers (Hafcr-Macko et al. 1996; Figure 82.20). These findings suggest that AMAN is caused by an antibody- and complement-mediated attack on axolemmal epitopes of motor fibers. The most attractive candidate targets arc GM_r and asialo-GM_rlike gangliosides, which are present in nodal and internodal membranes of motor fibers. Certain C. *jejuni* strains associated with axonal GBS and MFS variants contain GM_rlike epitopes in their polysaccharide coats. Anti-GM| and GQlb antibodies that cross-react to these lipopolysaccharide epitopes arc found in a high proportion of patients with AMAN and MFS and some patients with GBS. These observations have led to the concept of molecular mimicry in which epitopes of the infectious agent elicit antibodies that cross-reacr with shared epitopes on axons. The nerve fibers thereby become the inadvertent targets of an immune response directed against an infectious organism. The anti-ganglioside anti-bodies obtained from AMAN and MFS patients block neuromuscular transmission in an in vitro nerve-muscle preparation. The blocking activity of these IgG antibodies can be neutralized by intravenous immunoglobulin (Bucbwald et al. 2002). Furthermore, rabbits immunized wiili GM I develop AMAN. thereby fulfilling the postulates for an autoimmune pathogenesis (Sheikh and Griffin 2001). AMSAN may be caused by a more severe immune injury triggered by axonal epitopes because similar pathological changes affecting motor and sensory fibers have been observed in cases of AMSAN.

Treatment

Patients with rapidly worsening acute GBS should be observed in the hospital until the maximum extent of progression has been established. The reduction in mor-tality to less than 5% reflects improvements in modern critical care. Supportive care in intensive care units and the prevention of complications, of which respiratory failure and autonomic dysfunction arc the most important, provide the best chance for a favorable outcome (Bosch 1998). Respiratory and bulbar function, the ability to handle secretions, heart rate, and blood pressure should be closely monitored during the progressive phase. Respiratory failure requiring mechanical ventilation develops in up to 30% of patients with CBS. Signs of impending respiratory failure include deterioration in forced vital capacity (FVC), declining maximal respiratory pressures, and hypoxemia caused by atelecrasis. Initially, it may be necessary to monitor FVC and negative inspiratory pressure every 4-6 hours while the patient is awake. Patients should be monitored by pulse oxymetry, especially at nighr, for rhe early detection of oxygen desaturation. Clinical parameters that allow the prediction of future need of mechanical ventilation have been identified; rapid disease progression (onset to admission in less than 7 days), bulbar dysfunction, bilateral facial palsies, and autonomic instability. Serial measures of decline in respiratory function that could predict future respiratory failure included vital capacity of less than 20 mL/kg or a decline by 30% from baseline, maximal inspiratory pressure less than 30 cm, and maximal expiratory respiratory pressure of less than 40 cm of H_20

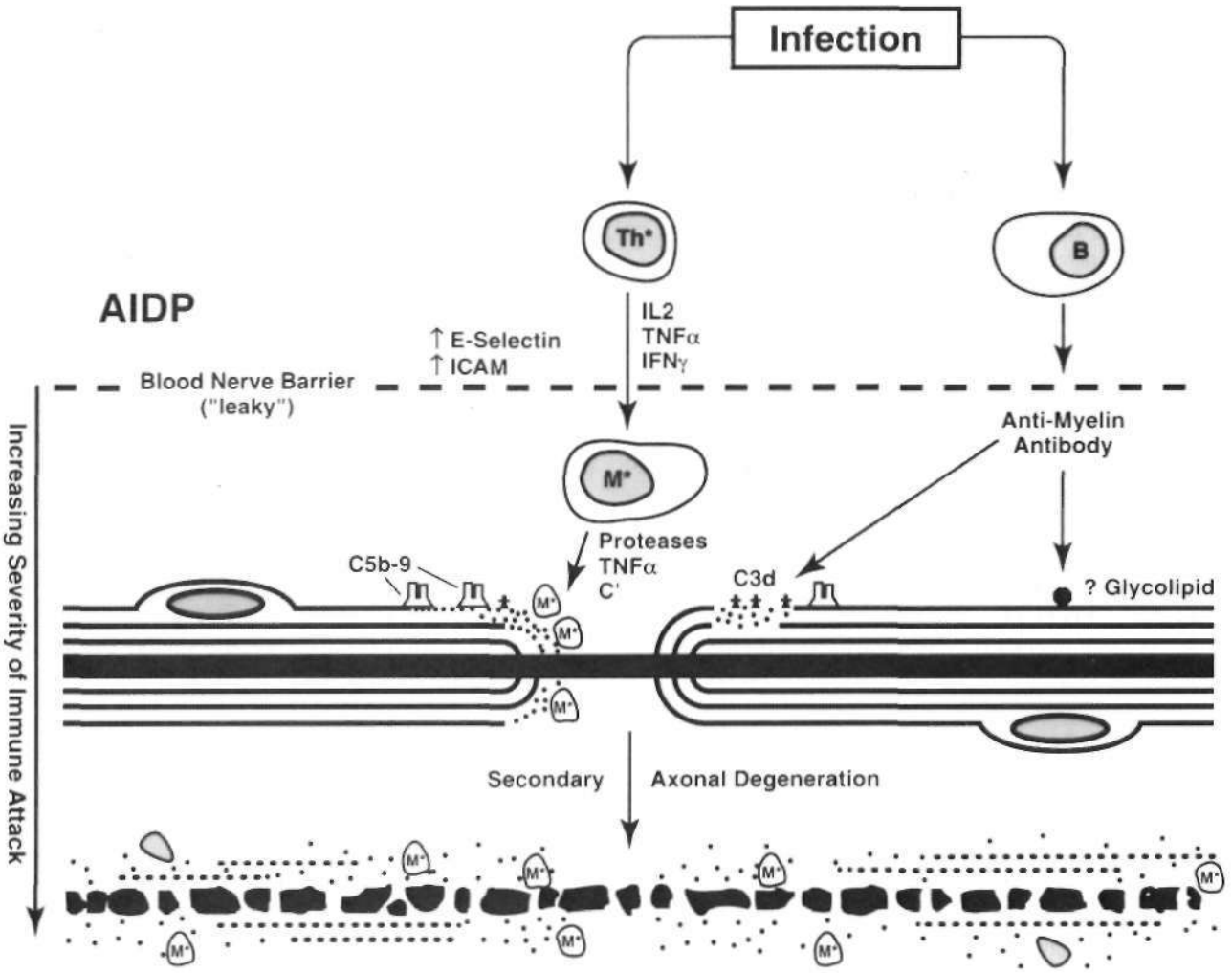


FIGURE 82.19 Immune injury to nerve fibers in acute inflammatory demyelinating polyradiculoneuropathy (AIDP). A preceding infection may trigger the formation of anrimyclin autoantibodies and activated T-hdper cells (Th*). Proinflammatory cytokines (tumor necrosis factors [TNFor], interferon-/ [INF/]) and upregulation of adhesion molecules (E-selectin, intercellular adhesion molecule jICAM|) facilitate the breakdown of the blood-nerve barrier to activated T cells, macrophages, and anrimyclin antibodies, Autimyclin anribodies react with epitopes on the abaxonal Schwann cell membrane with consequent activation of complement. Deposition of complement activation products (C3d) and membrane attack complex (C.5b-9) on the outermost Schwann cell membrane leads to vesicular myelin changes, followed by recruitment of macrophages (M*) and progressive demyelination. Intense inflammation may lead to secondary axonal degeneration. (B = Bcell; IL2 = interleukin 2.} (Reprinted with permission from Bosch, F.. P. 1998, "Gnillain-Barre syndrome: An update of acute immune-mediated polyradiculoneuropathies," *Neurologist,* vol. 4, pp. 21 1-226.)

(Lawn et al. 2001). This so called "20-30-40" rule allows patients at risk to be identified and transferred to an intensive care unit for even closer monitoring. In a series of 200 patients, short disease duration, inability to lift the head, and a vital capacity of less than 60% predicted the need for mechanical ventilation in 85% of patients with all three risk factors (Sharshar er at. 2003). Elective intubation for ventilatory assistance should be performed when FVC falls below 12-15 mL/kg or below 18 raL/kg in patients with severe oropharyngeal weakness, or when arterial Po_2 values fall below 70 mm Hg with inspired room air. When respiratory assistance is needed for longer than 2 weeks, a tracheostomy should be performed.

In the event of cardiac arrhythmias or marked fluctuations of blood pressure, continuous elccrrocardiographic.il and blood pressure monitoring allow early detection of life-threatening situations that require prompt treatment. Antihypertensive and vasoactive drugs must be used with extreme caution in the presence of autonomic instability. Tracheal suctioning may trigger sudden episodes of hypotension or bradyarrhythmia. Back and radicular pain often respond to nonsteroidal anti-inflammatory drugs. At times oral or parenteral opioids are required for adequate pain control. Increased metabolic requirements together with negative caloric intake caused by impaired swallowing may-lead to a state of relative starvation in severely affected

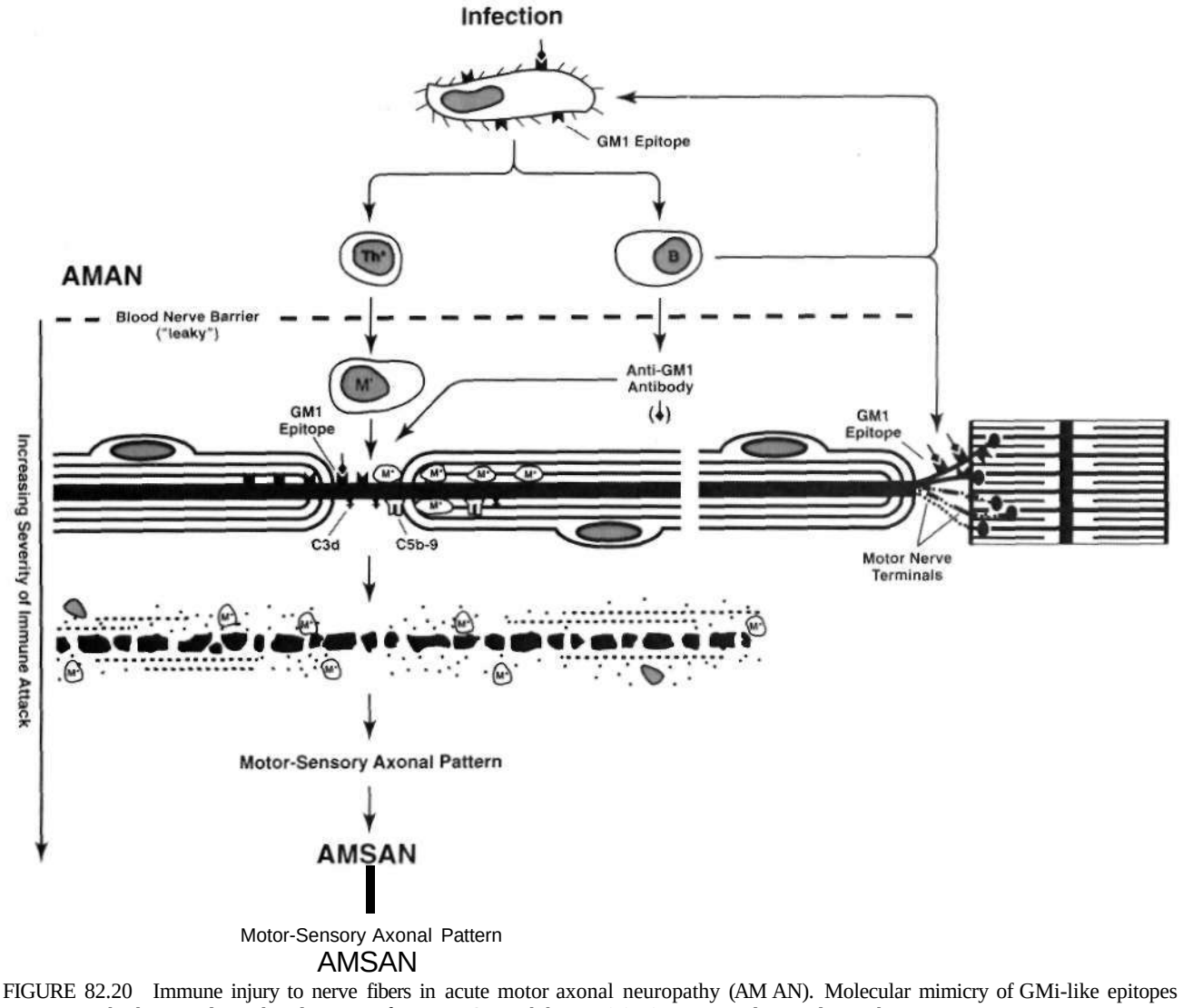


FIGURE 82.20 Immune injury to nerve fibers in acute motor axonal neuropathy (AM AN). Molecular mimicry of GMi-like epitopes common to both Iipopolysaccharide coats of certain *Campylobacter jejuni* strains and axonal membranes may cause an autoimmune response. Activated complement components (C3d, C5b-9) and immunoglobulins arc found at nodes of Ranvier and along axolemma of motor fibers. Macrophages (M*) are recruited to the targeted nodes and invade the periaxonal space, leading to wallenan degeneration. The lack of blood-nerve barrier at motor nerve terminals may make these distal axons vulnerable to circulating GM] antibodies. (AMSAN = acute motor sensory axonal neuropathy; R = B cell.) (Reprinted with pi-nuissiori irom linsdi 1' I. IOTX "Guillain-Barri: Syndrome: An update of acute immune-mediated polyradiculoneuropathies," *Neurologist*, vol. 4, pp. 211-226.)

patients. Nutritional requirements should be met by providing a high-caloric protein diet or by beginning enteral feedings as early as possible.

Subcutaneous heparin or low-molecular-weight heparin together with calf compression devices should be ordered routinely in immobilized patients to lower the risks of venous thrombosis and pulmonary embolism. Infections of the lung and urinary tract develop in almost half of patients with GBS in the intensive care unit. Prevention and prompt treatment of nosocomial infections are important aspects of care. Chest physiotherapy and frequent oral suctioning aid in preventing atelectasis in patients with impaired cough and sigh. Skillful nursing care with regular turning and attention to skin, eyes, mouth, bowel, and bladder are essential. Exposure keratitis is avoided in cases of facial diplegia by using artificial tears and by taping the eyelids closed at night. Pressure-induced ulnar or fibular nerve palsies are prevented by proper positioning and padding. Physical therapy is started early because it helps prevent contractures, joint immobilization, and venous stasis. Psychological support and constant reassurance about the potential for recovery are important for the morale of patients and family members. In the recovery phase, skillful physical therapy and rehabilitation hasten recovery.

Among specific therapeutic interventions aimed at mitigating the harmful effects of autoantibodies, plasma exchange and high-dose intravenous immune globulin (IVIG) infusions have been shown to be equally effective. Six large randomized, controlled trials involving more than 600 patients have established the benefit of plasma exchange in acute GBS by shortening the recovery time. Therapeutic plasma exchange is recommended for patients with moderate to severe weakness (defined as the ability to walk only with support or worse). Benefits are clearest

when plasma exchange is begun within 2 weeks of onset. The recommended plasmapheresis schedule entails a series of five exchanges (40-50 mL/kg) with a continuous flow machine on alternate days using saline and albumin as replacement fluid. The effect of plasma exchange in mildly affected patients and the optimal number of exchanges were investigated by the French Cooperative Group on Plasma Exchange (1997). Even mildly affected patients benefited from two exchanges. Four exchanges were optimal for moderate and severe cases. The Cochrane review confirmed the value of plasma exchange over supportive therapy in hastening the recovery from GBS when started within 30 days after disease onset (Raphael cr al. 2002). Treatment-related relapses tend to occur in approximately 10% of patients within 3 weeks after treatment. Plasmapheresis should be performed only in centers with experience in exchange techniques in critically ill patients. Most serious complications are linked to venous access problems including hematoma formation at puncture sites, pneumothorax after insertion of central lines, and catheter-related septicemia. Septicemia, active bleeding, and severe cardiovascular instability are contraindications for plasmapheresis. Cerebrospinal fluid filtration, a new treatment approach, has been compared to plasma exchange. Although no difference in outcomes was shown, the trial was too small to draw conclusions on the value of CSF filtration.

Three randomized trials comparing IV1G with plasma exchange demonstrated the benefit of five daily infusions of immunoglobulin (0.4 g/kg/day) given in the first 2 weeks of the disease (Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group 1997), Both treatment modalities were equally effective. There was no advantage of using both together. These findings were confirmed by another Cochran systematic review (Hughes et al. 2001b). Anti-idiotypic antibodies supplied by rVIG that have the potential to bind and neutralize pathogenetic antibodies are the proposed mode of action. Minor side effects such as headaches, myalgias and arthralgias, flulike symptoms, fever, and vasomotor reactions arc observed when infusion flow rates arc excessive. More serious complications, such as anaphylaxis in IgA-dcficicnt individuals who develop anti-IgA antibodies after the first course of lgA-containing IVIg infusions, aseptic meningitis, congestive heart failure, thrombotic complications (strokes *And* myocardial infarction), and transient renal failure, have rarely been reported (Brannagan 2002). There is a higher rate of vascular complications, particularly stroke and coronary thrombosis, in patients treated with the schedule of IVIG 1.0 g/kg/day for 2 days than in those receiving the more standard schedule of 0.4 g/kg/day for .5 days. The slower schedule is recommended. To prevent headache from a mild sterile meningitis, patients should be treated with acetaminophen 500-1000 g and ibuprofen 600 mg one hour before each infusion, and the dose can be repeated six hours later if headache develops. IVIg has become the preferred treatment for acute GBS because of ease of administration (Figure 82.21). The optimal effective dose of IVIG has not been established. Six daily infusions of 0.4 g/kg were reported to be superior to 3 daily infusions in patients who could not receive plasma exchange (Raphael ct al. 2001). In patients with hyperviscosity, congestive heart failure, chronic renal failure, or congenital IgA deficiency plasma exchange is preferred.

Corticosteroids have been advocated in the treatment of GBS but cannot be justified, because two randomized,

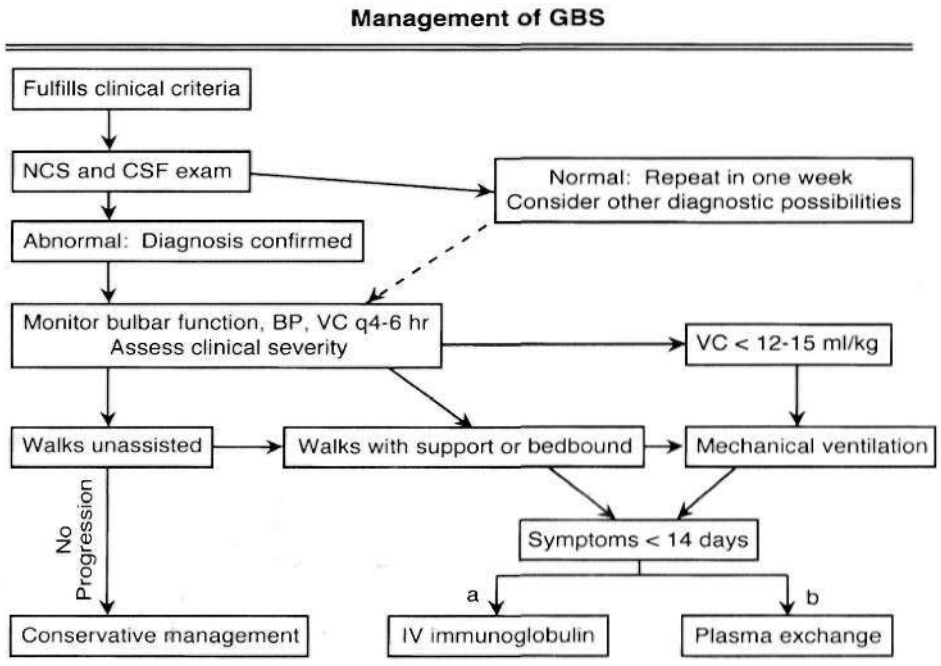


FIGURE 82.21 Decision-making pathway in the management of Guillain-Barre syndrome. Both treatment options, intravenous (IV) immune globulin *(a)* and plasma exchange *(b),* are •.-.IU.IIU i. Mil ;uii ms. I\ itiiiniini-globulin is preferred because of its ease of administration. {BP = blood pressure; CSF = cerebrospinal fluid; NCS = nerve conduction studies; VC = forced vital capacity.) (Reprinted with permission from Bosch, F,. P. 1998, "Guillain-Barre syndrome: An update of acute immune-mediated polyradiculoneuropathies," *Neurologist,* vol. 4, pp. 21 1-226.}

controlled trials, one using conventional doses of prednisolone and the other using high-dose intravenous methyl prednisolone, have found no benefit (Guillain-Barre Syndrome Steroid Trial Group 19931. The combination of IVIG with methyl prednisolone failed to find significant advantage over IVIG alone in one trial.

('.nurse and Prognosis

liy ilrhmlior., pa'kails should reach their **iraxirnam** deticil within 4 weeks of onset; if the disease progresses for longer, it is classified as subacute or CI DP. Up to 30% of patients develop respiratory insufficiency requiring assisted ventilation, and between 2% and 5% die of complications. After progression stops, patients enter a plateau phase lasting 2-4 weeks or longer before recovery begins. Although most patients recover functionally, 20% still have residual motor weakness 1 year later. Approximately 70% of patients complete their recovery in 12 months and 82% in 24 months. Approximately *V'4,* of patients may have a recurrence following recovery. The North American Guillain-Barre Syndrome Study Group found that older age (>60 years), ventilatory support, rapid progression reaching maximum deficit in less than 7 days, and low amplitudes of distal CMAPs (20% of lower limit of normal or less) were poor prognostic factors that were associated with a less than 20% probability of walking independently at 6 months. Acute hypoxic-ischemic and infectious episodes also probably worsen the prognosis.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Many similarities exist between CIDP **and the acute** form, GBS. Both disorders have similar clinical features and share the CSF albuminocytological dissociation and the pathological abnormalities of multifocal inflammatory demyclination, with nerve conduction features reflecting demyelination. *Av.* autoimmune basis is suspected lor bmh disorders although the supporting evidence remains incomplete. The major differences between the two conditions arc in the time course and their response to corticosteroids. **CIDP** has a more protracted clinical course, is rarely associated with preceding infections, has an association with human lymphocyte antigens, and responds to corticosteroid therapy. Two patterns of temporal evolution of **CIDP** can be seen. More than 60% of patients show a continuous or stepwise progressive course over months to years, whereas one third have a relapsing course with partial or complete recovery between recurrences. The age of onset may influence the course of the disease. In one large series, the age of onset was younger (mean 29 years) in those who had a relapsing course than in those pursuing a chronic progressive course (mean 51 years). A history of preceding infection is found in less than 10%. In contrast, pregnancy is associated with a significant number of relapses, occurring mainly in the third trimester and the immediate postpartum period. Human lymphocyte antigen-linked genetic factors may influence susceptibility to CIDP.

The prevalence of CIDP ranges from one to two per 100,000 of the populations in South East England and Australia (I.unn ct al. 1999), Although precise prevalence figures are not available for the United States, CIDP represents 13-20% of all initially undiagnosed neuropathies referred to specialized neuromuscular centers.

Clinical Features

The disease is seen at all ages, with peak incidence in the fifth and sixth decades. The majority of patients have symmetrical motor and sensory involvement, although occasional cases with predominantly motor involvement may be seen (Rotta et al. 2000). To fulfill diagnostic criteria for CIDP, weakness must be present for at least 2 months. Proximal limb weakness is almost as severe as distal limb weakness. In fact, the presence of proximal muscle weakness sets this neuropathy apart from most othets. Both upper and lower limbs are affected, although the legs are often more severely involved. Muscle wasting is rarely pronounced. These signs provide helpful clinical clues to separate **CIDP** patients from those with axonal neuropathies. Generalized hyporeflexia or areflexia is the rule. Sensory symptoms in a stocking-glove distribution (numbness or tingling) implicating large fiber involvement occur frequently, whereas pain is uncommon. Children differ from adults by a more precipitous onset and more prominent gait abnormalities. Additional findings, listed in decreasing order of frequency, are postural tremor of the arms, enlargement of peripheral nerves, papilledema, and facial or bulbar weakness. Massive nerve root enlargement causing myelopathy or symptomatic lumbar stenosis, or vision loss caused by progressive pseudotumor cerebri, are umisii.il el mi! al l-.-alinv-, VI id mm and 1 "> ^ •. .-, *l'>'"'i'i.*

Atypical clinical variants with different distribution of weakness and sensory deficits have received recent attention (Saperstein et al. 2001). A multifocal distribution of weakness and sensory deficits is seen in some patients. This multifocal form of CIDP initially identified by Lewis and Sumner (hence the term *Lewis-Sumner variant)* is also described by the acronym *MADSAM* (multifocal acquired demyelinating sensory and motor neuropathy). Electrophysiological studies demonstrating focal conduction block or severe slowing of nerve conduction distinguish this multifocal demyelinating neuropathy from the more common vaseulitic multiple mononeuropathies. Unlike multifocal motor neuropathy, patients with this multifocal variant of CIDP have clinical and electrophysiological involvement of both motor and sensory nerves, increased CSF protein, and a good response to corticosteroids. Some patients fulfilling the diagnostic criteria for CIDP

have only distal limb involvement (distal acquired symmetrical demyelinating neuropathy). Nearly two thirds of these patients have IgM monoclonal gammopathies, and though they have been reported to respond poorly to immune-modulating therapy (Katz et al. 2000), IVIG treatment is often beneficial. CIDP may be associated occasionally with a relapsing multifocal demyelinating CNS disorder resembling multiple sclerosis, with CNS demyelination confirmed by abnormal visual and somatosensory evoked potentials and brain MRI. A CIDP-likc syndrome may develop in cases of inherited neuropathy. These patients typically have a positive family history of affected kin and bony abnormalities such as pes cavus and hammer toes from an early age, but subsequently develop subacute deterioration with proximal muscle weakness and increased CSF protein. The newly acquired symptoms may respond to corticosteroid therapy; hence the term *prednisone-responsive hereditary motor and sensory neuropathy.*

Acquired demyelinating polyradiculoneuropathies meeting the diagnostic criteria for CIDP may be associated with HIV-I infection, systemic lupus erythematosus, monoclonal gammopathy of undetermined significance (MGUS) and plasma cell dyscrasias (macroglobulinemia, osteosclerotic myeloma, POEMS syndrome, Castleman disease), chronic active hepatitis, inflammatory bowel disease, and Hodgkin lymphoma. Compared with idiopathic CIDP, the patients with a monoclonal gammopathy tend to be older, have a more protracted course but less severe functional impairment at presentation, and seem to respond less well to immunomodulatory therapy (Simmons et al. f 993). There are patients with either insulin-dependent or non-insulin-dependent diabetes mellittis with associated polyradiculoneuropathy who meet the electrophysiological criteria for CIDP. Some of these patients respond to intravenous immunoglobulin therapy (Sharma et al. 2002a). Occasional patients with malignant melanoma or after therapy by vaccination with melanoma lysates develop CIDP. The association between melanoma and CIDP might be explained by molecular mimicry because both melanoma and Schwann cells are derived from neural crest tissue and share common glycolipid antigens (Weiss et al. 1998). Appropriate laboratory studies are necessary to separate these polyradiculoneuropathies from idiopathic CIDP without concurrent disease.

Laboratory Studies

The diagnosis of CIDP is supported by a laboratory profile including electrophysiological, CSF, and nerve biopsy findings (Table 82.22). There is a pattern of nerve conduction changes that strongly supports acquired multifocal demyelination. This includes (1) nonuniform reduction in motor conduction velocities below 70% of normal in at least two motor nerves; (2) partial conduction block (proximal CMAP amplitude or area <50-70% of distal; different authors recommend different thresholds for diagnosis of conduction block) or abnormal temporal dispersion in at least one motor nerve; (3) prolonged distal latencies in at least two motor nerves; and (4) absent F waves or prolonged F-wavc latencies in at least two motor nerves. Only 60% of patients with CIDP fulfill these criteria. Less restrictive electrophysiological criteria have been proposed (Nicolas et al. 2002). CSF protein values in excess of 45 mg/dL are found in 95% of oases ami levels above 100 mg/dL are common. CSF pleocytosis is rare except in HIV-associatcd CIDP. Anti-myclin antibodies directed against MPZ (P0) have been found in a small proportion of patients (Yan et al. 200 I). MRI scanning may demonstrate gadolinium enhancement of lumbar roots, providing radiological evidence of an abnormal blood-nerve barrier {Bertorini et al. 1995; Figure 82.22).

Table 82.22; Diagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy

I. Mandatory clinical criteria
  Progressive or relapsing muscle weakness for 2 months or longer
  Symmetrical proximal and distal weakness in upper or lower extremities
  Hyporeflexia or areflexia
11. Mandatory laboratory criteria
  Nerve conduction studies with features of demyelination (motor nerve conduction <70% of lower limit of normal)
  Cerebrospinal fluid protein level >45 mg/dL, cell count <10/|d
  Sural nerve biopsy with features of demyelination and remyelination including myelinated fiber loss and perivascular inflammation
III. Mandatory exclusion criteria
  Evidence of relevant systemic disease or toxic exposure
  Family history of neuropathy
  Nerve biopsy findings incompatible with diagnosis
]V, Diagnostic categories
  A. Definite: Mandatory inclusion and exclusion criteria and all laboratory criteria
  R, Probable: Mandatory inclusion and exclusion criteria and 2 of 3 laboratory criteria
  C. Possible: Mandatory inclusion and exclusion criteria and lof 3 laboratory criteria

Source: Adapted from Cornblath, D. R., Asbury, A. K., Albers, J. W., et al, "1991, "Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP)," *Neurolagy*, vol. 41, pp. 617-618.

Blood cell counts, sedimentation rate, and biochemical screening tests are important to exclude systemic disorders. Scrum and urine immunoetcctrophorcsis with immunofixation, a skeletal bone survey, or both are required to look for an associated monoclonal gammopathy or underlying osteosclerotic myeloma.

The changes in sural nerve biopsy specimens do not fully represent the pathological process taking place in motor roots or more proximal nerve segments. In one large series of biopsies, demyelinating features were seen in only 48%; 21% had predominantly axon a I changes, 13% had mixed demyelinating and axonal changes, and 18% were normal.

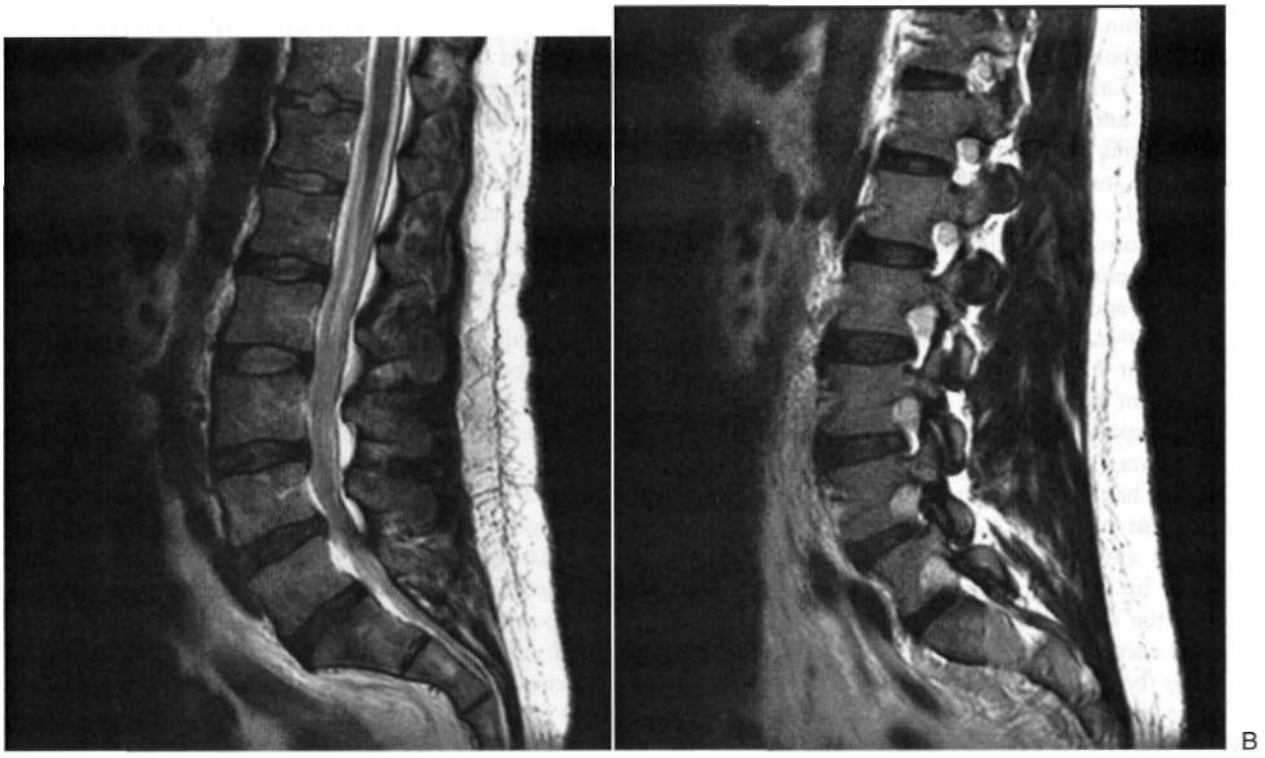


FIGURE 82.22 T2 weighted post-gadolinium sagittal lumbar MR: Diffuse enlargement of the cauda equina with abnormal enhancement in patient with C1DP (A). The hypertrophic nerve mots arc best appreciated in parasagittal images (B).

The value of nerve biopsy as a routine diagnostic tool for CIDP has been questioned. A study conducted in 64 patients with CIDP used multivariate logistic regression analysis of sural nerve biopsy finding and othet clinical and laboratory criteria to assess the value of nerve biopsy. Only high CSF ptotein (>100 mg/dL) and nerve conduction studies consistent with demyelination were strong predictors of CIDP. An independent predictive value of the sural nerve biopsy could not be demonstrated (Molenaar et al. 1998). Nevertheless, sutal netve biopsy may be helpful in support of the diagnosis and in excluding other causes of neuropathy. Typically, moderate reduction in myelinated **fibers,** endoneural and subperineurial edema, and segmental demyelination and remyelination occur. Onion bulb formations, a sign of repeated episodes of segmental demyelination and remyelination, may be absent or abundant, depending on chronicity. Endoneural and epineurial mononuclear inflammatory cells are a helpful diagnostic sign when ptesent. The presence of inflammatory infiltrates can be highlighted using immunocytochemical markers. One study demonstrated epineurial T cells in perivascular clusters and endoneural infiltration of macrophages and T cells.

Treatment

Prednisone, plasmapheresis, and IVIg are .ill effective in CIDP and arc the mainstays of treatment.

A single randomized controlled trial provided weak evidence to support the extensive use of corticosteroids. Daily single-dose oral prednisone is started at 60-80 mg {1.0-1.5 mg/kg for children). Improvement can be anticipated within 2 months; by 3 months 88% improve. Following improvement, the dose is converted to an alternate-day single-dose schedule. The initial daily dose is tapeted to alternate-day prednisone by reducing the even-d.u dnsr by 10 mg per week; high dose, alternate day prednisone is maintained until a remission or plateau phase is achieved. More than 50% of patients teach this point by 6 months. After attaining maximum benefit, a slow taper of prednisone (e.g., 10 mg/month followed by 5-mg decrements at doses below 50 mg on alternate days) can then begin. The individual patient's clinical improvement and side-effect profile setve as guides to the tapidity of the taper. Some patients are exquisitely sensitive to reduction in corticosteroid dosage, in which case this must be reduced slowly to avoid producing a severe relapse. Patients may need alternate-day prednisone (10-30 mg) for years to suppress disease activity. Side effects from prolonged prednisone use are significant. Osteoporosis causing vertebral compression ftaetutes, diabetes, and hypertension cataracts are the most common long-tetm complications. Patients should be followed for the development of cataracts, increased intraocular pressure, hypertension, truncal obesity, hyperglycemia, aseptic necrosis of bone, peptic ulcer disease, and susceptibility to infection. Ptccautions

taken to diminish complications include a low-sodium (2 g) and low-carbohydrate diet and proton pump inhibitors for all patients. Calcium and vitamin D supplements should be considered, and bone density should be monitored in an effort to limit osteoporosis. In patients with coexisting osteoporosis, oral bisphosphonates or nasal calcitonin may be beneficial.

Three controlled studies have confirmed the benefit of therapeutic plasma exchange for CIDP of both chronic progressive and relapsing course. Ten plasma exchanges performed over 4 weeks resulted in substantial but transient improvement in 80% of patients (1 lahn et al, 1996a). Improvement began within days of starting therapy, yet 70% of responders relapsed within 14 days after plasma exchange was stopped. The optimal schedule for plasma exchanges has no! been established, and prohabl) varies from patient to patient. A common approach employs three exchanges (50 mlikg) weekly for the first 2 weeks, followed by two exchanges per week from the third through the sixth week. Then the treatment frequency is repeated according to clinical response. Plasma exchange can only be performed in medical centers with special expertise in aphcresis and requires secure vascular access. Venous access problems may be overcome by placement of central venous catheters, although this approach carries the risk of pneumothorax, hematoma, brachial plexus injury, and serious infection. Plasmapheresis may be maintained for months and even years. The majority of patients needing prolonged plasmapheresis require the addition of prednisone for lasting benefit and stabilization.

The svstemanc Cochrane review of six controlled studies confirmed the benefit of high-dose !VIC in CIDP compared with placebo (Van Shaik ct al. 200.3). A double blind, sham-controlled trial of IVIG using 0.4 g/kg per day on 5 consecutive days resulted in significant improvement of 63% of patients with both chronic progressive and relapsing disease. Improvement was seen as e.irK as the tusi week oi treatment, whereas maximal benefit was reached at 6 weeks (Hahn et al. 1996b). Those patients who respond to the initial series of infusions may need maintenance infusions in single daily doses of 0.4-1.0 g/kg at intervals dependent on the disease response. The beneficial effect of IVIG was confirmed in a prospective study comparing IVIG (0.4 g/kg once a week for 3 weeks, followed by 0.2 g/kg weekly for the next 3 weeks) with plasmapheresis (Dyck, Litchy, and Kratz 1994). Both treatments were equally efficacious but short lived, and most patients required continued intermittent treatment for sustained improvement. One trial compared IVIG (2 g/kg given over 1 or 2 days) with oral prednisolone (60 mg for 2 weeks followed by a taper over 4 weeks) in a cross-over design. Both treatments resulted in improvement after 2 and *6* weeks, although IVIG tended to be slightly superior to oral prednisolone (Hughes et al. 2001a). The benefit of IVIG as the initial treatment of CIDP has also been established (Mendel! et al. 2001). In this randomized controlled study using IVIG (1 g/kg given on days 1, 2, and 21) in patients with untreated CIDP, a favorable response occurred in 79% of patients after 6 weeks with improvement starting within 2 weeks. The high level of effectiveness combined with low incidence of adverse events makes IVIG a good, although costly, first treatment choice. The therapeutic dose of IVIG has been empirically set at 2 g/kg. Much needs to be learned about optimal dosage schedule as each trial used different dosage and infusion regimens. The standard schedule of 0.4 g/kg daily for 5 days should be used for elderly patients and patients who have impaired renal or cardiovascular function or who have high serum viscosity. In general adverse reactions to PVIG therapy are usually minor and occur in no more than 10% of patients (Brannagan 2002). Infusion-related reactions include headaches, chills, nausea, and myalgias. These can be controlled by reducing the rate of infusion (<200 mL/hr) or by pretreatment with acetominophen and ibuprofen (sec previous discussion) or diphenhydramine. Thrombotic events including stroke, myocardial infarction, retinal vein occlusion, and deep vein thrombosis may occasionally occur in patients with cardiovascular risk factors and increased serum viscosity, particularly with infusion rates of greater than 0.4 g/kg per day. Patients with pre-existing renal disease, especially the elderly, and those with diabetes mcllitus and hypovolemia are at risk of developing acute renal tubular necrosis. This rare complication has been associated with IVIG products containing high concentrations of sucrose. Close monitoring of renal function, correction of hypovolemia, discontinuation of concomitant nephrotoxic drugs, and the use of products without sucrose are measures to prevent renal tubular necrosis in patients with kidney disease. The serum immunoglobulin A (IgA) level should be determined in each patient before the first infusion, because those with very low IgA levels may have allergic or anaphylactic reactions during later infusions. IVIG infusions may trigger migraine attacks and aseptic meningitis. Skin allergic reactions arc seen in about 6% of patients treated with IVIG.

In clinical practice, treatment with IVIG, plasma exchange, ot prednisone should be limited to those patients with neuropathic deficits of sufficient magnitude to justify the risks and expense of treatment (Figure 82.23). There is an increasing trend to use IVIG as the first line treatment. The best IVIG dosage schedule in patients with CIDP has not been established. Most patients receive an initial course of IVIG of 2 g/kg over 2-5 days. An essential aspect of the management of CIDP is the assessment of patients at baseline and at follow-up visits after treatment using objective and validated means of determining the severity of the neuropathic deficits, hollowing the initial post-treatment period of 3-6 weeks, responders are monitored at monthly intervals. When secondary deterioration occurs, patients ate retreated with single IVIG infusions (0.4—1.0 g/kg), depending on the severity of the relapse. The interval of repeat infusions is determined by the expected duration of the clinical benefit. For patients with residual

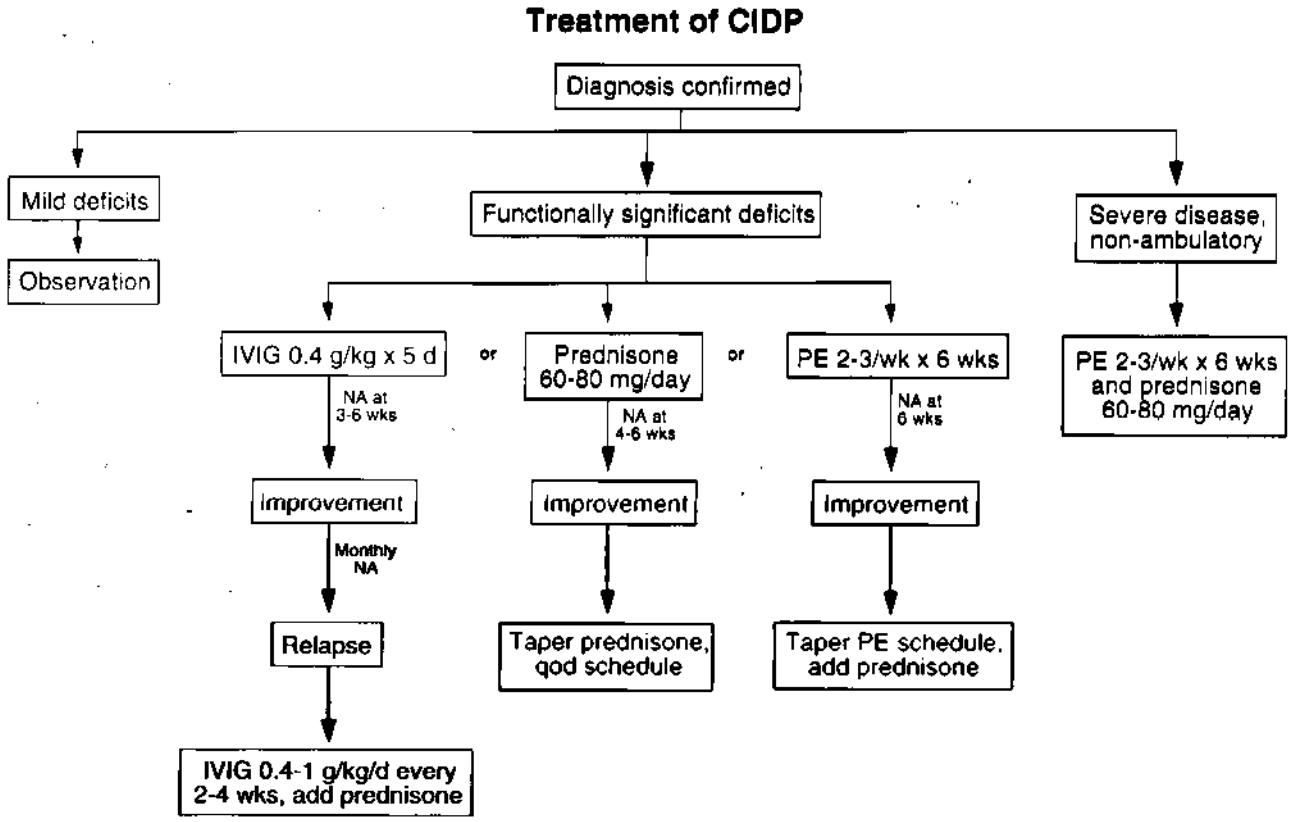


FIGURE 82.23 Dec is ion-ma king pathway in the management of chronic inflammatory demyclinating polyradiculoneuropathy. (IVIG = intf a venous immune globulin; NA = neurological assessment; PE= plasma exchange.)

deficits, small to moderate doses of prednisone may provide additional benefit. Patients who fail to respond to IVIG are treated either with plasma exchange or high-dose prednisonc. Plasma exchange is combined with prednisone for severely affected, nonambulatory patients because of the slightly higher response rates of these treatments. The absence of any therapeutic response from these immune-modulating therapies should lead to a reappraisal of the diagnosis.

Alternative forms of immunosuppressive treatment should be considered for patients with CIDP who arc refractory to prednisone, plasma exchange, and IVIG. None of the alternative agents, however, have proven efficacy in controlled trials. Azathioprine {2-3 mg/kg per day) or mycophcnolate mofetil (1000 mg twice daily) are used frequently as corticosteroid-sparing, adjunctive agents in long-term management. Use should be limited to patients with inadequate response to corticosteroids or those who require high corticosteroid maintenance doses with unacceptable side effects. Other immune interventions include cyclosporine A {5 mg/kg in two divided doses per day), monthly infusions of cyclophosphamide (lg/m^2 monthly for 3 to 6 months), and interferon-or (3 million IU subcutaneously three times a week for 6 weeks; Gorson et al. 1998). A small proportion of patients remain unresponsive or have significant residual deficits despite all efforts.

Prognosis

In contrast to the good prognosis in GBS, CIDP tends to be associated with prolonged neurological disability and is less likely to have spontaneous remissions. Although *95%* of patients with CIDP show initial improvement following immunosuppressive therapy, the relapse rate is high and the degree of improvement modest. Despite the initial responsiveness, only 40% of patients in one series remained in partial or complete remission while receiving no medication, The presence and degree of axonal loss have been considered responsible for incomplete recovery. Confirmation of this view was provided by a systematic study comparing clinical outcome and biopsy findings. In a series of 83 patients evaluated on average 6 years after onset, 56% had good outcome, 24% deteriorated and failed to respond to all treatments, and 11 % died of complications of the disease. Axonal loss on the nerve biopsy correlated with poorer outcome (Bouchard et al. 1999).

Multifocal Motor Neuropathy with Conduction Block

Multifocal motor neuropathy has received much attention because it is a treatable immune-mediated motor neuropathy that bears a superficial clinical resemblance to motor

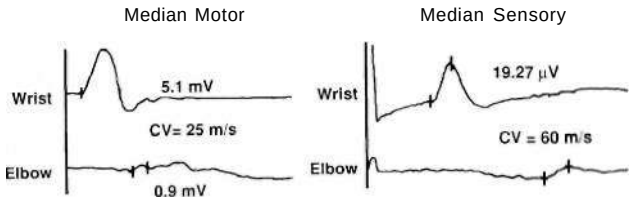
neuron disease. Whether multifocal motor neuropathy is a distinct nosological entity or simply a multifocal motor variant of CIDP is not established.

Clinical Features

Multifocal motor neuropathy is more common in men and mainly affects young adults; two thirds of affected individuals arc *45* years or younger. Progressive, asymmetrical, predominantly distal limb weakness and, to a lesser extent, atrophy develop over months to years. The upper extremities are more frequently affected than the lower. Wrist drop, grip weakness, or footdrop are the most common presenting features. Muscle cramps and fasciculations are common. Profound weakness in muscles with normal bulk or focal weakness in tile distribution of individual nerves rather than in a spinal segmental pattern are clues that should alert the clinician to suspect this disorder. Cranial nerve involvement is unusual. Tendon reflexes arc depressed or absent. Upper motor neuron signs are absent. Minor transient paresthesias are commonly reported by patients, but objective sensory deficits are usually absent. The course is slowly or less often stepwise progressive over months to years (Nobiie-Orazio 2001).

Laboratory Studies

The diagnosis depends on electrophysiological studies demonstrating persistent focal motor conduction block in one or more motor nerves at sites not prone to compression (see Chapter 36B). Additional features of multifocal motor demyelination are frequently present in nerve segments without conduction block, including motor conduction slowing, temporal dispersion, and prolonged F-wave and distal motor latencies (Katz et al. 1997). What makes multifocal neuropathy unique is that the block is confined to motor axons. SNAPs and sensory conduction are preserved (Figure 82.24). Abnormal amplitude reduction with proximal stimulation may be seen occasionally in other disorders; ttansient conduction block may occur in vasculitic neuropathy during the early stage of wallerian degeneration. There is no satisfactory explanation for the selective vulnerability of motor fibers. Kaji et al. (1993) reported a patient with pure motor weakness of the arm and proximal conduction block who underwent biopsy of a motor nerve branch adjacent to the site of focal conduction block that revealed scattered demyelinated axons and small onion bulbs without inflammatory changes. Needle EMG shows signs of denervation almost invariably confined to muscles that are clinically weak. Fasciculations are common, and myokymia may be seen. The spinal fluid protein is frequently normal although moderately increased protein levels (<100 mg/dL) can be found in one third of patients. The sural nerve frequently shows subtle pathological changes of demyelination and rcmyelination quite similar to those in CIDP but of lesser degree. These morphological abnormalities indicate that sensory nerves are involved in this disorder despite the lack of clinical or electrophysiological findings. MRI of the brachial or lumbosacral plexus may be helpful by demonstrating focal enlargement and increased signai intensities of affected nerve trunks (Van Es et al. 1997).



EIGURK 82.24 Partial motor conduction block of the median nerve. The compound muscle action potential (CMAP) was recorded from the abductor pollicis brevis muscle. Supramaximal stimulation at tlit; elbow produced an 80% drop in the amplitude of the median CMAP compared with stimulation at the wrist. Sensory conduction along the same nerve segment was preserved. (CV = conduction velocity.) (Courtesy Dr. J. C. Stevens.)

Attention has focused on a possible relationship between antiganglioside antibodies and acquired lower motor neuron syndromes. Among the gangliosides, GMj is abundantly found on the outer surface of neuronal membranes where potential binding sites could serve as antigenic targets. High titers of IgM anti-GM, antibodies can be found in up to 80% of patients with multifocal motor neuropathy and conduction block. High titers are occasionally (<15%) seen in amyotrophic lateral sclerosis and GBS variants including AMAN and the axonal form of GBS associated with *C. jejuni* infection, but rarely (<5%) in other peripheral neuropathies and non-neurological autoimmune disorders. Thus anti-GM| antibodies are neither specific nor required for the diagnosis of multifocal motor neuropathy but can be considered a marker for the disease.

The differential diagnosis of progressive limb weakness and atrophy without sensory symptoms is mainly restricted to motor neuron disease, including amyotrophic lateral sclerosis and its lower motor neuron form, progressive muscular atrophy, CIDP, and multifocal motor neuropathy (Table 82.23). Other conditions to be considered include post polio svudrome, lead- or dapsone-induced motor neuropathies, the hereditary motor ncuronopathies or spinal muscular atrophies, and hexosaminidase-A deficiency.

Treatment

Identifying patients with multifocal motot neuropathy is important because many such patients can be treated. In contrast to CIDP, prednisone or plasma exchange have little or no benefit. Treatment with IVIG is currently the preferred treatment because high dose cyclophosphamide previously reported to be effective is not an attractive drug for a chronic, non-life-threatening disorder. [VIG (0.4 g/kg body

Table 82.23: Differential diagnosis of multifocal motor neuropathy

Features	*Multifocal motor neuropathy*	*at>r*	*Amyotrophic lateral sclerosis*
Lower motor neuron weakness	Distal ot proximal, asymmetrical	Proximal and distal, usually symmetrical	Progressive
I IppiT motor neuron signs	Abseni	Absent	I'rcsi :n
Sensory loss	Absent	Present	Absent
Motor conduction block	100%	Frequent	Rare and transient
Sensory conduction	Normal SNAP	Low to absent SNAP	Normal SNAP
Cerebrospinal fluid protein	Normal (70%)	Elevated	Normal
Anti-GM i antibodies	80%	Absent	*<15* %

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; SNAP = sensory nerve action potential

weight per day for 5 consecutive days) has been reported to benefit 70% of patients in open uncontrolled and small double-blind, placebo-controlled trials il'irdenco el al. 2000). Improvement begins within three weeks of treatment but lasts only for weeks to months. Criteria have been proposed to predict a favorable response to IVIG (Van den Berg-Vos et al. 2000). Younger age at onset, a smaller number of affected limb regions, elevated GM1 antibody titers, definite conduction blocks, and higher distal CMAP amplitudes were found significantly more often in respondcrs. Most patients require maintenance infusions for years. Based on such observations, it is appropriate to initiate treatment with IVIG and continue maintenance infusions (0.4 g/kg once every 1-8 weeks) in patients who have a functionally meaningful response. Dose and frequency of repeated IVIG administration must be individualized for each patient, giving another dose just before the anticipated time of relapse. Despite IVIG maintenance therapy neurological improvement decreases over time, and electrophysiological studies demonstrate either new conduction blocks or axona! loss in long-term studies (Van den Berg-Vos et al. 2002). Oral cyclophosphamide or interferon-^! may reduce the frequency and dosage of infusions. For nonrcsponders, intravenous cyclophosphamide is indicated depending on the degree of disability and the patient's understanding of the seriousness of potential side effects such as bone marrow depression, gonadal damage, hemorrhagic cystitis, and a long-term increased risk of cancer. Pestronk et al, (1994) suggested that monthly intravenous cyclophosphamide (1 g/m) for 6-8 months, preceded on each occasion by two plasma exchanges, may be an effective treatment. As an alternative to cyclophosphamide, rituximab, a monoclonal antibody directed against the B cell surface marker CD20, has shown promising results in an open, uncontrolled study of patients with multifocal motor neuropathy (Pestronk et al. 2003).

PERIPHERAL NEUROPATHIES ASSOCIATED WITH MONOCLONAL PROTEINS

Patients undergoing evaluation for chronic peripheral neuropathy of unknown cause should be screened for the presence of a monoclonal protein (M protein). A monoclonal protein is produced by a single clone of plasma cells and usually composed of four polypeptides: two identical heavy chains and two light chains. The M protein is named according to the class of heavy chain (IgG, IgM, IgA, IgD, IgE) and type of light chain, *K* or *k.* Approximately 10% of patients with idiopathic peripheral neuropathy have an associated monoclonal gammopathy, which represents a sixfold increase over the general population. The pailm physiological relationship between the M protein and the neuropathy is often obscure but some M proteins have antibody properties directed against components of myelin or axolemma. Finding an M protein among patients with neuropathy may lead to the discovery of underlying disorders such as primary amyloidosis, multiple or osteosclerotic myeloma, macroglobulinemia, cryoglobulinemia, Castelman's disease, lymphoma, or malignant lymphoproliferative disease. In two thirds of patients with a monoclonal protein, no detectable underlying disease is found, and they are described as having MGUS. MGUS has replaced the term *benign monoclonal gammopathy* because up to one fourth of patients go on to develop malignant plasma cell dyscrasias after long-term follow-up, The risk of progression of MGUS to a malignant plasma cell proliferative disorder is about 1% per year (Kyle et al. 2002). The characteristic features distinguishing MGUS from other plasma cell dyscrasias are listed in Table 82.24.

Routine serum protein electrophoresis frequently lacks the sensitivity required to detect small M proteins. Immunoelectrophoresis or immunofixation is required to detect small amounts of M proteins, confirm the monoclonal nature, and characterize the heavy- and light-chain types. Urine studies detect excretion of light chains (Bencejones protein) that often accompany multiple myeloma or primary amyloidosis. All patients with neuropathy and associated M protein, as well as patients suspected of amyloidosis or myeloma, should have a 24-hour urine collection for detection of Bencc-Jones protein. Following discovery of an M protein, a complete blood cell count with differential is necessary, immunoglobulins should be quantitated, and a radiological skeletal bone survey is indicated to detect lytic or sclerotic bone lesions of

Tabic 82.24: Characteristic findings in monoclonal gammopathy of uiuk'UTimiu'd significance

Common monoclonal type	IgM, IgG, EgA
Common light chain	κ
Quantity	<3 g/dL
Urine light chains	Rare
Marrow plasma cells	<S%
Skeletal lesions	Absent
Complete blood cell count	Normal
Organomegaly, lymphadenopathy	Absent

Ig = immunoglobulin.

myeloma. If the monoclonal spike exceeds 1.5 g/dL, a bone marrow aspirate and biopsy should be obtained to differentiate a malignant plasma cell dyscrasia from MGUS. Rectal, fat, or cutaneous nerve biopsies may be required to confirm a suspected diagnosis of amyloidosis (Kissel and Mendell 1995).

Monoclonal Gammopathy of Undetermined Significance

Approximately 5% of patients with MGUS have an associated polyneuropathy. The frequency of monoclonal IgM is over represented in patients with neuropathy (60% IgM, 30% IgG, and 10% IgA) compared with patients with only MGUS. The light-chain class is usually *K* in contrast to patients with osteosclerotic myeloma or amyloidosis (Ropper and Gorson 1998).

Clinical Ventures

The clinical presentation of the neuropathies associated with different heavy-chain classes are generally indistinguishable from each other. Symptoms begin in later life with the median age of onset in the sixth decade, appear insidiously, and progress slowly over months to years. There is a male predominance. The most common presentation is a distal symmetrical sensorimotor polyneuropathy. Cranial nerves and autonomic functions arc preserved. Sensory impairment can be prominent with variable involvement of light touch, pinprick, vibration, and position sense. Muscle stretch reflexes are universally diminished or absent. The lower limbs are involved earlier and to a greater extent than the upper. In approximately one half of patients, a polyradiculoneuropathy occurs that shares clinical and laboratory features with CIDP. Patients with CIDP and MGUS tend to be older and have a more indolent course with fewer motor than sensory findings but poorer long-term functional outcome than the idiopathic CIDP group without M protein (Simmons et al. 1995). A predominantly sensory neuropathy may be seen in up to 20% of patients. Gait ataxia and upper limb postural tremor can be prominent, particularly in patients with IgM MGUS.

Laboratory Features

Electrophysiological studies show evidence of demyelination or more often both demyelination and axonal degeneration. Slow motor conduction velocities in the demyelinating range are more common in patients with IgM MGUS in which there is a predilection for distal demyelination. SNAPs are reduced in amplitude or unobtainable. EMG shows denervation. A small number of patients, usually with IgG MGUS, have electrophysiological featutes of a pure axonal neuropathy. When the frequency of MGUS in older patients is considered, the relationship between MGUS and neuropathy may be coincidental in these patients (Notcrmans et al. 1996a). Elevation of CSF protein is common, sometimes in excess of 100 mg/dL.

In at least 50% of patients with IgM MGUS neuropathy, the IgM monoclonal protein has reactivity against myelin-associated glycoprotein (MAG). MAG is a glycoprotein that makes up only 1% of peripheral nerve myelin. It is concentrated in periaxonal Schwann cell membranes, paranodal loops of myelin, and areas of noncompactcd myelin, where it plays a role as an adhesion molecule for interactions between Schwann cells and axons. Anti-MAG antibodies cross-react with other components of peripheral nerve including several complex glycosphingolipids, PMP-22, *and* the P„ protein of myelin. Which of these reactivities relates to the neuropathy is unclear. Antibody activity to MAG can be detected by "Western blot and enzyme-linked immunosorbent assay and can be demonstrated by immunocytochemical staining of nerves. Immunofluorescence studies show that IgM with anti-MAG activity binds to the periphery and periaxonal regions of myelinated fibers that correspond to the distribution of MAG. Ultrastructurally, the myelin lamellae show a widened periodicity {myelin splitting), which is considered the pathological hallmark of anti-MAG antibodies (Figure 82.25). No consistent binding of monoclonal proteins to myelinated fibers is seen in nerve biopsy specimens from patients with IgG and IgA MGUS. Sural nerve biopsy findings of patients with M proteins of all three immunoglobulin classes show nerve fiber loss, segmental demyelination, and axonal degeneration.

Approximately 15% of patients with IgM-MGUS neuropathy have autoantibodies directed against gangliosides, and those with IgM antibodies to GD1b and GQ1b have been associated with sensory ataxic neuropathies (Eurclings et al. 2001). Patients who have disialosyl-ganglioside IgM antibodies and cold agglutinins present with a chronic sensory ataxic neuropathy, areflexia, and fixed or relapsing-remitting ophthalmoplegia. This rare clinical syndrome has been described under the acronym *CANOMAD:* chronic ataxic weuropathy, ophthalmoplegia, **Ig-M** monoclonal protein, cold agglutinins and <fisialosyl antibodies (Willison et al. 2001).

The underlying mechanism of nerve fiber damage in MGUS neuropathy remains unknown, although an

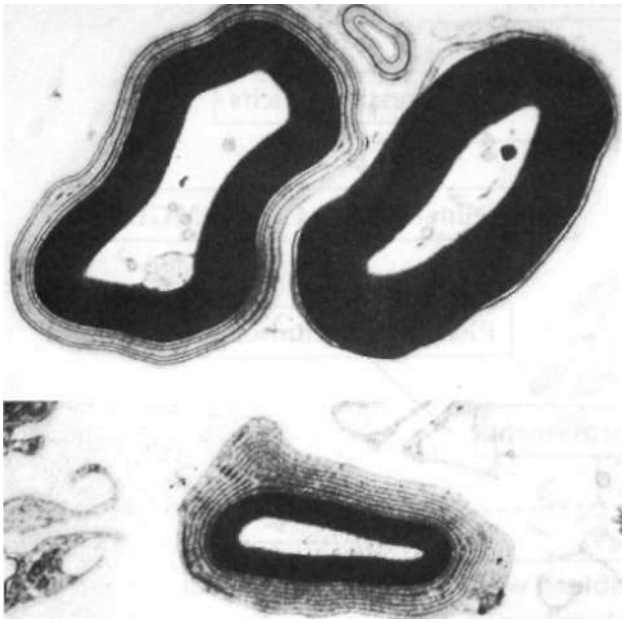


FIGURE 82.25 Electron micrographs showing fibers with myelin splitting. In the upper p;inel, the myelinating filler on the left shows splitting of the myelin lamellae tit the intra period line, whereas the nerve fiber on the right has normal compact myelin (x 15,000), The lower panel illustrates similar myelin splitting (x 20,000). The findings are characteristic of antimyclin-associated glycoprotein antibody deposits in the myelin sheath. (Reprinted with permission from Mendell, j. R., Barohn, R. J., Bosch, E. P., et al. 1994, "Continuum-peripheral neuropathy," *Am Acad Neurol.*, vol, 1, p. 42.)

immune-mediated etiology is suspected (latum 1993). The case for pathogenic activity of IgM antibodies directed against MAG and other glycosphingolipids is better established than that for other antigens or for IgG and IgA antibodies. On the other hand, the lack of correlation between the deposition of anti-MAG antibody and the degree of pathological nerve damage and the poor correlation between the amount of M protein in serum and the severity of neuropathy raise questions about causal linkage.

Treatment

The optimal treatment of MGUS neuropathy has not been established, and there are few controlled trials on which to base treatment decisions. The decision to treat depends on the severity of the neuropathy. Patients with minor deficits and indolent course are best followed without treatment. This view is supported by the long-term outcome of patients with IgM MGUS neuropathy. Neurological impairment did run differ between treated and untreated patients after an average follow-up of 8 years but current immune-modulatory treatments resulted in serious adverse events in half of the patients (Nobile-Orazio et al. 2000). The more closely the neuropathy fulfills the criteria for CIDP, the more likely the patient will respond to immune-modulatory therapies. Patients have been treated with plasmapheresis, IVIG, and prednisone, often in combination with immunosuppressants, with temporary benefit in about half of the treated patients. In 1991, Dyck and colleagues confirmed the short-term benefit of plasmapheresis in the IgG and IgA but not IgM subgroups in a randomized, controlled trial. Intravenous immunoglobulin (2 g/kg given over 1-5 days) may produce short term benefit in 50% of patients with IgM-MGUS (Comi et al. 2002).

Patients with progressive, disabling neuropathy caused by IgM MGUS with or without anti-MAG reactivity may respond to aggressive immune interventions aimed at lowering the IgM level. This may be achieved by intermittent courses of oral cyclophosphamide (300 mg/m body surface daily for 4 days) combined with prednisone (40 mg/m^2 body surface daily for 5 days) given at 4-week intervals for 6 months (Notermans et al. 1996b), combination treatment with two plasma exchanges followed by intravenous cyclophosphamide given monthly for 5-7 months, or fludarabinc. The initially reported benefit of interferon-a could not be confirmed in a randomi/.ed, cmitrolled 1ii.il. kni:\im.ik .1 rumod:>n:il i. D:'.O .mlibmlv directed against B cells, holds promise but is yet to be subject to controlled trials (Pcstronk et al. 2003). An algorithm for the treatment of MGUS neuropathy is proposed in Figure 82.26. Patients with rapid clinical deterioration of their neuropaihy despite treatment should be re-evaluated for the development of underlying malignant lymphoproliferative disorders or amyloidosis.

Waldenstrom Macroglobulinemia

Waldenstrom macroglobulinemia (WM) is characterized by proliferation of malignant lymphocytoid cells in bone marrow and lymph nodes that secrete an IgM monoclonal spike of more than 3 g/dL. WM typically affects elderly men; systemic symptoms of fatigue, anemia, bleeding, and hyperviscosity dominate. Peripheral neuropathy occurs in approximately one third of patients with WM and is a chronic symmetrical, predominantly sensory polyneuropathy similar to that associated with nonmalignant IgM M proteins. Other presentations include pure sensory or pure motor neuropathies, multiple mononeuropathies associated with cryoglobulins, and typical amyloid neuropathy, Anti-MAG reactivity is found in approximately 50% of WM patients with neuropathy. Patients with positive anti-MAG antibodies have slowed motor NGVs and prolonged distal latencies consistent with demyelination. Nerve biopsy findings are indistinguishable from those seen in IgM MGUS neuropathy. Patients with demyelinating polyneuropathy may respond to chemotherapy, plasmapheresis, or both, but the response appears to be less consistent than in IgM MGUS-related neuropathy.

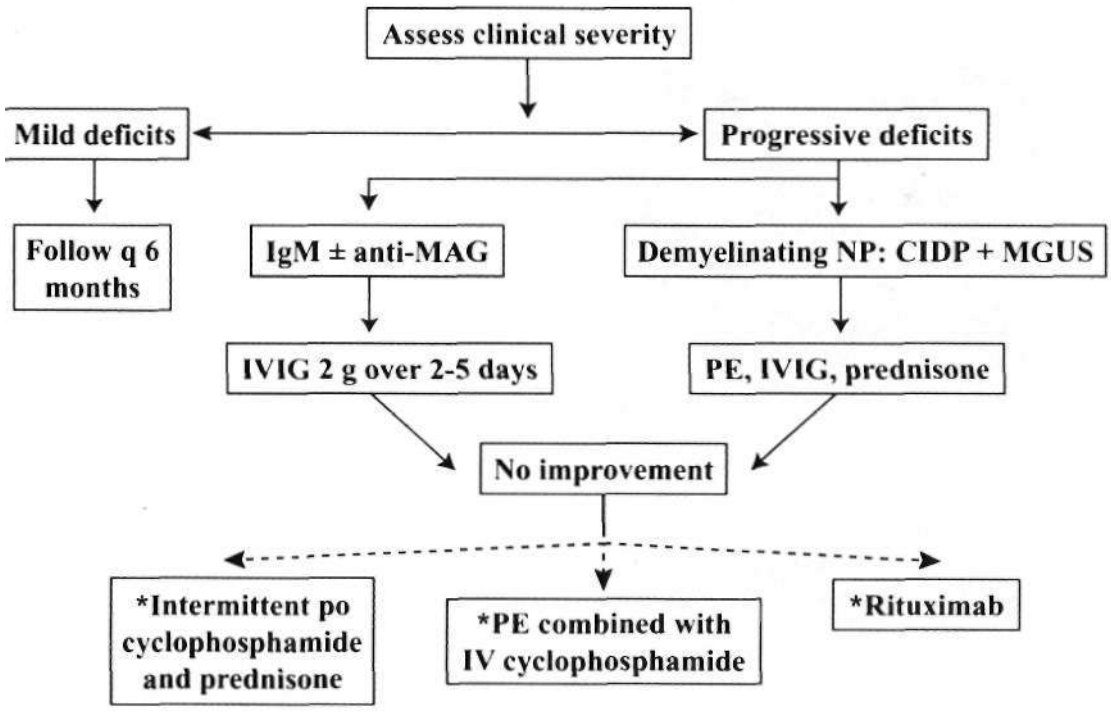


FIGURE 82.26 Decision-making pathway in the management of peripheral neuropathy with monoclonal gammopathy of undetermined significance (MGUS). (CIDP = chronic demyelinating polyradiculoneuropathy; IVIG = intravenous immune globulin; MAG = myelin-associated glycoprotein; NP = neuropathy; PE = plasma exchange. *There are anecdotes of improvement with these drugs hut controlled studies are not available to support their use.)

Multiple Myeloma

Polyneuropathy occurs in approximately 5% of patients with multiple myeloma. One third of patients arc found to have abnormalities on careful electrophysiological studies. The most common neurological complications of multiple myeloma are related to cord and root compression from lytic vettehral lesions. Diffuse bone or radicular pain resulting from vertebral body involvement, concurrent anemia, renal insufficiency, and hypercalcemia may provide clues as to the underlying disorder. The clinical manifestations of myeloma neuropathy are heterogeneous. Must patients present with mild distal sensorimotor polyneuropathy. Less frequently, a pure sensory neuropathy is seen. Furthermore, AL amyloidosis complicates multiple myeloma in 30-40% of cases, and these patients have a high likelihood of death within the next 2 years. Painful dysesthesias, preferential involvement of small fiber sensory modalities, autonomic dysfunction, and carpal tunnel syndrome are suggestive of amyloid neuropathy. Rectal, abdominal fat, or sural nerve biopsy specimens can be obtained in patients with progressive myeloma neuropathy to identify the patients with amyloidosis.

Nerve conduction and sural nerve biopsy studies arc consistent with an axonal process with loss of myelinated fibers. Treatment of the underlying myeloma may sometimes improve the neuropathy.

Osteosclerotic Myeloma and POEMS Syndrome

Osteosclerotic myeloir.,; occurs 1:1 less ill an .:"u i>: all patients with myeloma but 85% of these patients present with an associated peripheral neuropathy. In tins disorder, the plasma cell proliferation occurs as single or multiple plasmacytomas that manifest as sclerotic bone lesions. The neuropathy of osteosclerotic myeloma is different from that associated with multiple myeloma in several aspects; It occurs at an earlier age and mostly in men; it is a demyelinating, predominantly motor neuropathy with slow motor NCVs and elevated CSF protein levels, usually in excess of 100 mg/dL; an M protein is found in 90% of cases and virtually always composed of A light chains associated with IgG and IgA heavy chains; it responds to irradiation or excision of the isolated plasmacytoma; and it is associated with systemic manifestations referred to as Crow-Fukase or POEMS syndrome. To reiterate, POEMS is the acronym for polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes, facilitating recognition of the most constant features of this multisystem syndrome.

The neuropathy of osteosclerotic myeloma bears a striking resemblance to C1DP with symmetrical proximal and distal weakness with variable sensory loss. Cranial nerves are spared except for occasional cases of papilledema. The clinical and electrophysiological similarities between litis condition and *i'.UW* emphasize the need to screen for an occult M protein and sclerotic bone lesions in

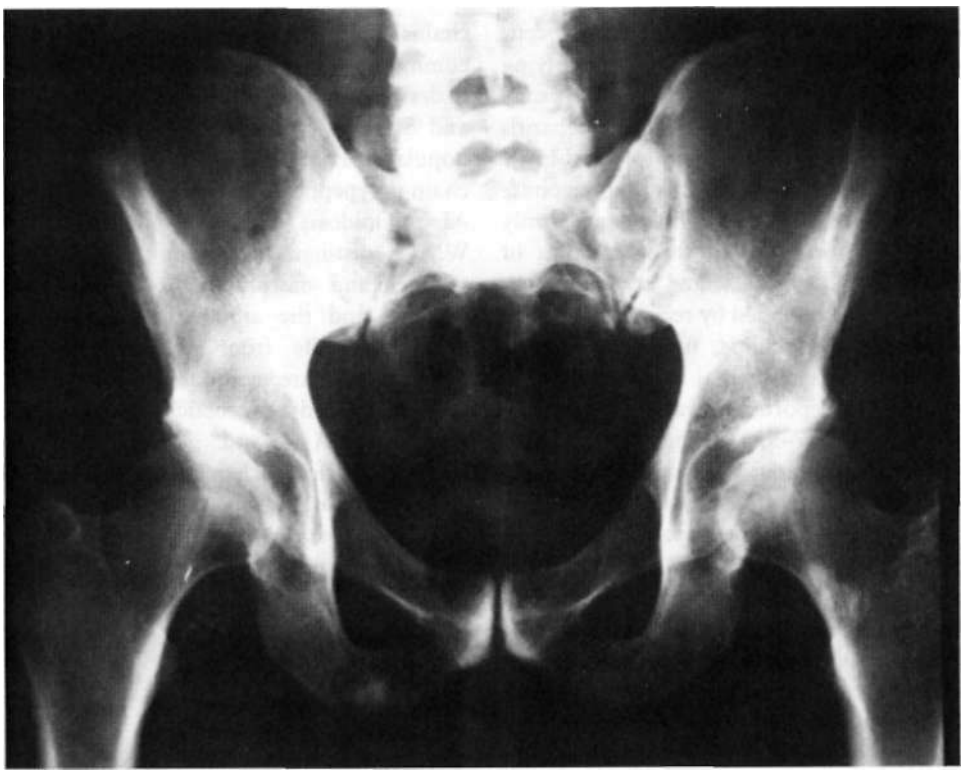


FIGURE 82.27 Radiography of the pelvis showing a dense sclerotic area in the upper sacrum and two smaller focal sclerotic lesions in the right pubic hone and the left femoral neck. Biopsy of one accessihle lesion confirmed osteosclerotic myeloma.

all adult patients presenting with an acquired demyclinating neuropathy.

The skeletal lesions can be single or multiple and tend to involve the axial skeleton, the majority being in the spine, pelvis, and ribs. Their radiographical appearance varies from dense ivory to mixed sclerotic and lytic lesions with a sclerotic rim (Figure 82.27). Radioisotope scans are less sensitive than radiographical skeletal surveys in detecting the lesions. Open biopsy is usually necessary to confirm the presence of an isolated plasmacytoma.

Most patients develop one or more of the multisystem manifestations of the POEMS syndrome. Hepatosplenomegaly is often encountered. Gynecomastia and impotence in men, secondary amenorrhea in women, diabetes mellitus, and hypothyroidism are the most common endocrinopathies, Hyperpigmentation, hypertrichosis, diffuse skin thickening, hemangiomas, and white nail beds are dermatological features. Pitting edema of the lower limbs, ascites, pleural effusions, and eh:':v • i 11: r. :·: die Miners are other signs. Approximately one fourth of patients with POEMS syndrome have no associated bone lesions. Some of these patients have Castleman's syndrome (a nonmalignant form of angiofollicular lymphadenopathy), and others have a plasma cell dyscrasia restricted to the lymphorericLilar system.

The pathogenesis of this multiorgan disorder is poorly understood. The associated plasma cell dyscrasia seems to play a crucial role, as clinical improvement follows the disappearance of the monoclonal ptoteins. Elevated levels of proinflammatory cytokines, such as tumor necrosis factot-a, interleukins, and vascular endothelial growth factor have been implicated in the multisystem manifestations (Gherardi et al. 1994).

The importance of recognizing this rate syndrome lies in its potential for treatment. Patients with solitary lesions are treated with tumoricidal irradiation, complete surgical extirpation, or both. Patients with multiple bone lesions receive radiation combined with prednisone and melphalan. High-dose chemotherapy with autologous blood steincell support is another option for patients with multifocal bone lesions or diffuse bone marrow plasmacytic infiltration (Jaccard et al. 2002), Substantial improvement of both neurological and systemic features is seen in some patients, but the response may take many months.

Cryoglobulinemia

Cryoglobulins are immunoglobulins that precipitate on cooling and redissolve on warming to body temperature. Cryoglobulins are classified into three groups; type I are monoclonal immunoglobulins that are associated with myeloma, mactoglobulinemia, and other lymphoproliferative disorders; type II consists of a mixture of a monoclonal protein, usually IgM-*- with antitheumaroid factor activity, and polyclonal IgG; and type III are polyclonal IgM and

IgG immunoglobulins. Mixed cryoglobulinemia may occur as a primary condition without any apparent underlying process, termed *essential mixed cryoglobulinemia,* or may he secondary to autoimmune diseases and chronic hepatitis C virus (HCV) infections. The detection of anti-HCV antibodies and HCV RNA in serum and ctyopreeipitate of most patients with essential cryoglobulinemia firmly establishes a causal role for HCV in the formation of cryoglobulins (Apartis et al. 1996). Mixed cryoglobulinemia is a systemic disease characterized by recurrent purpura of the legs and cutaneous vasculitis, often precipitated by cold temperatures, arthralgias, renal impairment, and peripheral neuropathy. The reported prevalence of peripheral neuropathy varies from 37-57% using electrophysiological criteria for confirmation. The most common presentation is a painful sensory or sensorimotor polyneuropathy or less often mono neuropathy multiplex (Tembl et al. 1999).

Electrodiagnostic studies show axonal changes with denervation, particularly in distal leg muscles. In most cases the sural nerve biopsy confirms necrotizing vasculitis or perivascular inflammation affecting small-sized epineurial vessels together with multifocal or global myelinated fiber loss and acute axonal degeneration. Low serum complement levels and the deposition of immunoglobulin in the walls of affected vessels suggest cryoprccipitablc immune complexes are responsible for the disease manifestations.

Treatment of cryoglobuiinemic neuropathy rests on expert opinion and uncontrolled trials. Patients with biopsy-proven vasculitis and progressive neurological deficits initially require immunosuppression with either oral or intravenous cyclophosphamide and corticosteroids. Plasmapheresis has been recommended for the rapid removal of cryoglobulins during acute exacerbations of neurological deficits or glomerulonephritis. Once clinical remission is achieved, immunosuppresive therapy is tapered off, and then specicfic treatment directed against the underlying HCV infection is offered. The recommended treatment regimen consists of peginterferon-a 2a in combination with ribavirin for 6 to 12 months.

Primary Systemic Amyloidosis

Systemic amyloidosis are multisystem disorders caused by extracellular deposition of insoluble fibrillar proteins arranged in a /i-plcated sheet conformation in various organs and tissues throughout the body. The /3-plcated sheet configuration seems to be responsible for the typical staining properties with Congo red stain, appearing red under normal light microscopy, but apple-green in polar ized light. Several unrelated proteins can form amyloid fibrils and cause specific acquired as well as inherited forms of amyloidosis. In both primary systemic amyloidosis and amyloidosis complicating multiple myeloma or WM, amyloid is composed of fragments of immunoglobulin light chains from the amino-terminal variable regions, or less commonly the complete immunoglobulin light chain, and is designated *AL* for amyloid light chain (Falk, Comenzo, and Skinner 1997). In primary (AL) amyloidosis clonal populations of nonproliferative plasma cells synthesize light chain polypeptides that are deposited in tissues as amyloid. Al, amyloidosis in association with multiple myeloma and WM is distinguished from primary amyloidosis by the number and morphology of plasma cells in the bone marrow and the amount of M protein in the serum, Amyloid fibrils from patients with familial amyloid neuropathies are composed of one of three aberrant proteins caused by genetic mutations: transthyretin, apolipoprotein A-1, and gelsolin (see Familial Amyloid Polyneuropathy, earlier in this chapter). Mutations in the genes encoding fibrinogen A, apolipoprotein A-II, lysozyme, and cystatin C are associated with non-neuropatbic familial amyloidosis. Immunohistocbemical techniques using specific antibodies can distinguish the different types of amyloidogenic proteins on biopsy material.

Clinical Features

Primary amyloidosis usually occurs after age 40, with a median age of onset of 65 years. Men are twice as likely to be affected. The initial symptoms are frequently fatigue and weight loss followed by symptoms and signs related to specific organ involvement. The organs most commonly affected, either individually or together, are the kidney, heart, liver, and the autonomic and peripheral nervous system. I'eripheral neuropathy occurs in 15-35% of patients and is the presenting manifestation in 10%. The majority have renal or cardiac presentations with peripheral neuropathy as a later manifestation. The neuropathy begins with painful dysesthesias in the legs and follows a chronic progressive course. Pain and temperature sensation are lost before light touch or vibratory sensation. Distal symmetrical weakness and a pansenson Ins^ evob.es I.IUT in the course of disease. Most patients develop features of autonomic dysfunction, including postural hypotension, impotence, gastrointestinal disturbances, impaired sweating, and loss of bladder control. Nearly 25% of patients develop a superimposed carpal tunnel syndrome caused by amyloid infiltration of the flexor retinaculum at the wrist. The constellation of painful dysesthesias, autonomic dysfunction, and a history of carpal tunnel syndrome should alert the clinician to the possibility of amyloidosis. Pitting edema related to hypoalbuminemia; spontaneous periorbital purpura caused by vascular infiltration; macroglossia, a sign occurring in 20% of patients (Figure 82.28); and hepatomegaly are typical findings on examination. Amyloid deposition between muscle fibers may cause pseudohypertrophy of muscles. Renal amyloidosis usually manifests as proteinuria and renal failure. Rapidly progressive congestive heart failure caused by cardiac infiltration is seen in one third of patients.

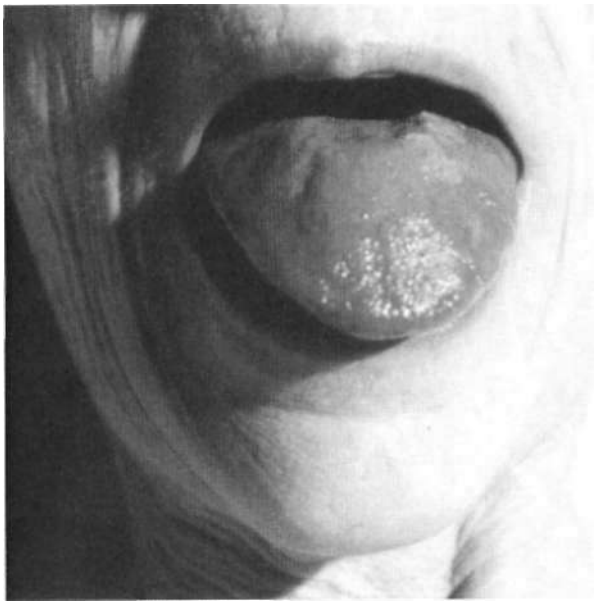


FIGURE 82.28 Macroglossia in AL amyloidosis. Tongue enlargement may be found in 20% of patients with AL amyloidosis. (AL = amyloid light chain.)

Laboratory Features

Electrodiagnostic studies show changes of axonal neuropathy, with low-amplitude or absent SNAPs and low-amplitude CMAPs but preserved motor conduction velocities. Distal median motor latencies are prolonged in patients with carpal tunnel syndrome. EMG frequently provides evidence of active denervation, A monoclonal protein or light chains are detected in 90% of patients by means of immu no fixation of serum or urine. Monoclonal *k* light chains are more common than *K* light chains (ratio of *X* to *K,* 3 to 1). A quantitative light-chain assay is the most sensitive method for detecting low level monoclonal proteins. Bone marrow examination reveals slightly increased plasma cells and clonal dominance of a light chain isotype by immunohistochemical staining.

The diagnosis is established by the histological demonstration of amyloid deposition in tissues. Abdominal fat aspiration, bone marrow aspirate, or rectal biopsy are convenient procedures that provide approximately an 80% yield of positive results. In patients with suspected amyloid neuropathy, combined muscle and sural nerve biopsy is the most sensitive technique that provides confirmation in more than 90% of cases. One tenth of patients wilh AI. amyloidosis lack monoclonal proteins in serum or urine by immunofixation and therefore are difficult to distinguish from familial or secondary amyloidosis. In most of these patients, a clonal dominance of plasma cells can be identified by immunocytochemical staining of a bone marrow specimen, or positive identification of AL amyloid can be achieved in tissue samples by immunohistochemical staining using labeled antibodies specific for human light chains. If confirmation of a plasma cell clone cannot be obtained, familial amyloidosis should be considered even in the absence of a positive family history. In such patients molecular genetic testing to identify TTR mutations is indicated (see Familial Amyloid Neuropathy, earlier in this chapter). Amyloidogenic mutations, most often in the genes encoding tor fibrinogen A and TTR, were found in 10% of 350 patients who had initially been misdiagnosed with presumed Al amyloidosis II .ulimann il ,il. 201)2). Results of sural nerve biopsy show amyloid deposition around blood vessels and within the endoneurial space (Figure 82.29), severe loss of myelinated and unmyelinated fibers, and active axonal degeneration. The pathogenetic mechanism of nerve fiber damage remains uncertain.

The prognosis in primary amyloidosis is poor, with a median survival of less than 18 months. Death is commonly caused by progressive congestive heart failure or renal insufficiency. Patients with amyloid neuropathy without cardiac or renal involvement have a more favorable prognosis, with a median survival of 40 months. The treatment of AL amyloidosis remains unsatisfactory but some aspects of disease may respond to chemotherapy that suppresses the underlying clonal plasma cell disorder. Intermittent oral melphalan and prednisone are reported to slow progression of renal and cardiac amyloidosis, but the treatment has no effect on the neuropathy. High-dose melphalan with autologous blood stem cell transplantation has shown promising results with improvement of neurological deficits in selected patients. Due to the high treatment-related mortality, stem cell transplantation is currently applicable to a minority of patients such as those with limited organ disease and no significant cardiac involvement (Comenzo and Gertz 2002).

NEUROPATHIES ASSOCIATED WITH SYSTEMIC DISORDERS

Diabetic Neuropathies

Diabetes mellitus is estimated to affect over 5 million people in the United States, and this number is growing by approximately *5%* per year. The complications specific to diabetes include retinopathy, nephropathy, and neuropathy. Patients with all forms of diabetes of sufficient duration, including insulin-dependent (IDDM) and non-insulin-dependent diabetes (NIDDM), are vulnerable to these complications (Nathan 1993). Diabetes is probably the leading cause of peripheral polyneuropathy in developed countries. Reliable estimates of the prevalence of diabetic neuropathy have only recently become available. The reported frequency of neuropathy among diabetics varies from 7-80%. This is due in part to bias of patient selection and different criteria used for the definition of diabetic neuropathy. The diagnosis of diabetic neuropathy should be based on clinical symptoms, objective neurological signs, and electrodiagnostic confirmation (Dyck 1988).

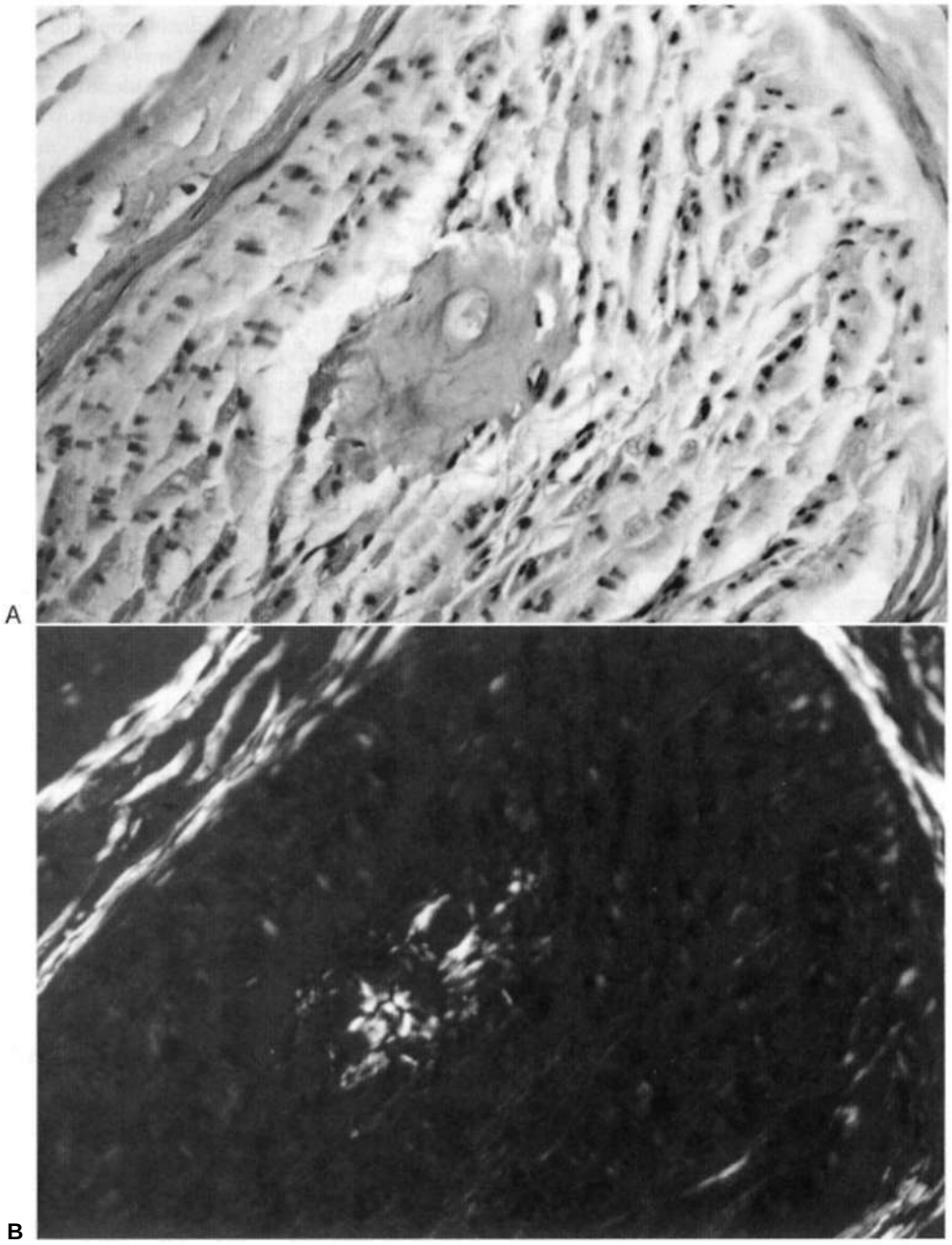


FIGURE 82.29 Amyloid neuropathy. (A) Sural nerve biopsy shows deposition of amyloid in the wall of an endoneural vessel and loss of myelinated fibers. (B) Under polarized light the Congo red-positive area shows apple-green birefringent deposits typical of amyloid. (Congo red, original magnification x250.)

Quality of life measurements provide an additional vantage point from which to judge the impact of neuropathy on everyday life (Padua et al. 2001). The risk of developing symptomatic neuropathy in patients without neuropathic symptoms or signs at the time of initial diagnosis of diabetes is estimated to be 4-10% by 5 years and up to 15% by 25 years. In a population cohort of diabetic patients, two thirds of diabetics had objective evidence of some type ol neuropathy, bill only 15% ol ID]XVI and 13% of NIDDM patients had symptomatic degrees of polyneuropathy (Dyck et al. 1993b). Among 894 women older than *65* years in Maryland, both age and diabetes were found to correlate with increased vibratory detection threshold values (Resnick et al. 2001). Longer duration of diabetes and male gender may predispose to the development of neuropathy in younger patients with IDDM. Those with NIDDM have an increased risk for neuropathy over time, as evidenced from a Finnish study which showed that 8.3% of such individuals have neuropathy at baseline, increasing to 41.9% after 10 years,

Tabic 82.25: Classification of diabetic neuropathies

Symmetrical polyneuropathies
- Distal sensory or sensorimotor polyneuropathy
- Small fiber neuropathy
- Autonomic neuropathy
- Large fiber neuropil thy

Asymmetrical neuropathies
- Cranial neuropathy (single or multiple)
- Truncal neuropathy (thoracic radiculopathy)
- Limb mononeuropathy (single or multiple)
- Lumbosacral radiculoplcxopathy (asymmetrical proximal motor neuropathy)
- Entrapment neuropathy

Combinations
- I'nl'i-.uliu.il'iiu-iiiiip.irlii
- Diabetic neuropathic cachexia
- Symmetrical polyneuropathies

with a yet higher percentage in those with low serum insulin concentrations (Partanen et al. 1995). In a cohort of 775 U.S. veterans with diabetes, 50% were found to have decreased foot sensation at baseline using monofilament sensory testing, arid an additional 20% developed hypoesthesia over the average *2.6* years follow-up period. Factors associated with an increased risk of decreased foot sensation included poor glycemic control, height, age, and alcohol consumption. Electrophysiological studies demonstrate subclinical conduction abnormalities in most patients with IDDM after 5-10 years of diabetes.

The many peripheral nerve manifestations associated with diabetes can be grouped into distinct clinical syndromes, each having a characteristic presentation and course. A useful classification divides the diabetic neuropathies into symmetrical polyneuropathies versus focal or multifocal neuropathies (Table 82.25). However, there is significant overlap between these syndromes.

Clinical features

Distal Symmetrical Polyneuropathy. Distal symmetrical polyneuropathy is the most common type of diabetic neuropathy. Many physicians incorrectly assume that the term *diabetic neuropathy* is synonymous with distal symmetrical polyneuropathy, because the latter constitutes perhaps three fourths of all diabetic neuropathies. Sensory loss predominates and autonomic symptoms correlate with severity. Most patients have minor motor involvement affecting the distal muscles of the lower extremities. Sensory disturbances have a stocking-glove distribution. Early sensory manifestations begin in the toes, gradually spreading proximally; when these reach above knee level the fingers and hands become affected. In more advanced cases, sensation becomes impaired over the anterior chest and abdomen producing a truncal wedge-shaped area of sensory loss (see Figure 31.7). The pattern of sensory impairment in diabetic distal symmetrical polyneuropathy follows a length-dependent dying-back process.

The distal symmetrica! polyneuropathy may be subclassified further into two major subgroups, depending on the nerve fiber type most involved: large-fiber and small-fiber variants. Although diabetic sensory neuropathy frequently forms a continuous spectrum ranging between these two polar types, selective nerve fiber involvement does occur, giving rise to relatively pure large- or small-fiber-type presentations.

The large-fiber variant presents with painless paresthesias beginning at the toes and feet, impairment of vibration and joint position sense, and diminished muscle stretch reflexes. In advanced cases, significant ataxia may develop due to sensory deafferentation. Earge-fiher involvement is often asymptomatic, but sensory loss may be found by careful examination,

A relatively common variant of diffuse diabetic polyneuropathy is *diabetic polyradiculoneuropathy.* Often beginning as a distal symmetrical polyneuropathy, this disorder comes to involve proximal segments of the peripheral nervous system including multiple lumbosacral roots, thoracic posterior primary rami, and less commonly cervical myotomes. Patients with ordinary distal symmetrical diabetic polyneuropathy are sometimes found by electromyography to have low grade, active denervation changes in multiple thoracic paraspinal muscle levels, which may herald the development of a more widespread neuropathy. The trigeminal "blink reflex" is often spared in advanced diabetic neuropathy and polyradiculoneuropathy, providing an important method to distinguish between this and immune related polyradiculoneuropathies such as chronic inflammatory polyradiculoneuropathies (Kirk et al. 1991). Much less commonly encountered is *diabetic polyradiculopatby,* in which peripheral sensory nerve conduction studies are normal and the focus of disease appears both clinically and eleetrodiagiiu-aicalK to be at the root level. There are patients with either IDDM- or NIDDM-associatcd neuropathy who meet electrodiagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy (Sharma et al. 2002a). Some of these patients respond to high dose intravenous immunoglobulin therapy, although a controlled clinical trial has not yet been completed (Sharma et al. 2002b),

In contra-,: to the large lihci ncu: op.it h\. I lie small fiber variant frequently presents w-irh pain of a deep, burning, stinging, aching character, often associated with spontaneous shooting pains and allodynia to light touch. Pain and temperature modalities are impaired with relative preservation of vibration and joint position sensation and muscle stretch reflexes. The small-fiber variant is often accompanied by autonomic neuropathy (Santiago et al. 1999). At times, a painful small-fiber neuropathy may develop soon after the onset of IDDM (Said et al. 1992).

It is now clear that peripheral neuropathy can occur before the onset of clinically diagnosablc diabetes mellitus, so-called *impaired glucose tolerance neuropathy.* Individuals with impaired glucose rolcrance, as determined by oral

glucose tolerance testing (OGTT), have been demonstrated to have symptoms, electrophysiological abnormalities, and intracpidcrmal nerve fiber density reduction consistent with a predominantly small fiber neuropathy, although with changes less pronounced than in their diabetic counterparts (Sumner et al. 2003). The implication for clinical practice is that patients with undiagnosed painful peripheral neuropathy should undergo OG1T (Singleton, Smith, and Bromberg 2001).

An acute painful neuropathy may be precipitated following initiation of treatment with insulin *(treatment-induced neuropathy).* Burning pain and paresthesias develop in the distal lower extremities shortly after establishing glucose control. Pain persists for weeks or up to several months. Pathological studies demonstrate active axonal regeneration, which may act as generators of spontaneous nerve impulse^ Resoiadon usualb occurs, perhaps when the axonal sprouts reach the sensory nerve terminals in the extremities. This phenomenon may he more common in the rare form of diabetes mellitus associated with a mitochondrial transfer RNA mutation at position 3243 (Suzuki etal. 1997).

In patients with newly diagnosed diabetes, there may be transient pain and paresthesias in the distal lower extremities (hyperglycemic neuropathy). The symptoms will usually resolve when the hyperglycemia is brought under control.

Diabetic neuropathic cachexia is a term referring to an acute painful diabetic neuropathy associated with precipitous, severe weight loss, depression, insomnia, and impotence in men. The syndrome is more common in men with poor glucose control. Improved glucose control and weight gain often result in recovery (Yuen et al. 2001).

Sensory loss makes patients with diabetes susceptible to repetitive, often unnoticed injuries that set the stage for foot ulcers and distal joint destruction *[acrodystrophic neuropathy).* Chronic foot ulceration is one of the more severe complications of diabetes mellitus, due to a combination of unnoticed, traumatic tissue damage, vascular insufficiency, and secondary infection (Laing 1998). Prevention is better than treatment. Daily inspection and proper foot care can prevent or lessen the severity of this complication (Birke et al. 2002).

Neuropathic arthropathy or a *Charcot joint* formation is a complication seen in patients with diahetes, who often have foot ulcers and autonomic impairment. Unlike the Charcot joint seen in syphilis, diabetic arthropathy tends to involve the small joints in the feet. The term *diabetic pseudotabes* is applied to patients having severe lancinating pains, loss of joint sensation, and diabetic pupillary abnormalities (pseudo-Argyll Robertson pupils).

Electrodiagnostic studies are helpful in confirming the diagnosis of distal symmetrical polyneuropathy. Generalized slowing of conduction velocities has been emphasized (Herrmann, Ferguson, and Logigian 2002), but this is not the most common feature in this type of diabetic neuropathy (Wilbourn 2002). Absent or decreased amplitudes of the sural nerve potentials or absent tibial H-reflexes are found in almost all patients. Active denervation in intrinsic foot muscles or decreased amplitudes of CMAPs together with mild slowing of conduction velocities in the motor nerves are found in more than two thirds of patients. Abnormal sensory nerve conduction studies are found in more than one half. Even in the small-fiber variant, EMG examination is often abnormal.

Diabetic Autonomic Neuropathy. Autonomic neuropathy usually correlates with the severity of somatic neuropathy. The spectrum of autonomic involvement ranges from subclinical functional impairment of cardiovascular reflexes and sudomotor function to severe cardiovasculat, gastrointestinal, or genitourinary autonomic dysfunction (Low 2002).

Orthostatic hypotension, resting tachycardia, or a heart rate unresponsive to respiration are the hallmarks of diabetic autonomic neuropathy. Significant orthostatic hypotension occurs mainly because of failure of the sympathetic nervous system to increase systemic vascular resistance in the erect posture, and compensatory cardiac acceleration is impaired. It is crucial to exclude confounding effects of medications or coexisting hypovolemia when diagnosing neurogenic postural hypotension. Vagal denervation of the heart results in a high resting pulse rate and loss of sinus arrhythmia. An increased incidence of painless or silent myocardial infarction is reported in diabetic patients with autonomic neuropathy.

Gastrointestinal motility abnormalities and fecal incontinence may occur. Delayed gastric emptying leads to nausea, early satiety, and postprandial bloating. Diabetic diarrhea, due to small intestine involvement, typically occurs at night, and is explosive and paroxysmal. Associated weight loss or malabsorption is rare. Bacterial overgrowth may occur and can often be successfully treated with small doses of tetracycline (250-500 mg/day in a single dose given at the onset of a diarrheal attack) in adult patients. Colonic atony produces constipation. Bladder atony leads to prolonged intervals between voiding, gradually increasing urinary retention, and finally overflow incontinence. The symptoms develop insidiously and progress slowly. Patients with diabetes who have neurogenic bladder should be encouraged to void routinely every few hours to prevent urinary retention. Impotence is often the first manifestation of autonomic neuropathy in men with diabetes, occurring in more than 60% and causing serious emotional distress. Autonomic dysfunction involves both erectile failure and retrograde ejaculation. The majority of men with diabetes with impotence have some evidence of associated distal symmetrical polyneuropathy.

Sudomotor abnormalities produce distal anhidrosis, causing compensatory facial and truncal sweating and heat intolerance. A peculiar hyperhidrosis called *gustatory sweating* is characterized by profuse sweating in the face

and forehead immediately following food intake. Pupillary abnormalities include constricted pupils with sluggish light reaction. A blunted autonomic response to hypoglycemia produces an inadequate sympathetic and adrenal response and hence an unawareness of hypoglycemia that may seriously complicate intensive insulin treatment.

Asymmetrical Proximal Diabetic Neuropathy or Lumbosacral Radiculoplexopathy. Since Garland coined the term "diabetic amyotrophy" to describe this special type of diabetic neuropathy, the clinical definition and limits have been confusing because the term itself is ambiguous. Some experts have suggested that this term be abandoned and replaced with diabetic proximal neuropathy, emphasizing the proximal motor weakness as a distinguishing clinical feature (Asbury 1977). Diabetic amyotrophy, thoracic radiculopathy, and proximal or diffuse lower extremity weakness should probably be grouped under the single term diabetic poly radiculopathy, since these disorders seem to be different presentations of the same basic involvement of multiple nerve roots or proximal nerve segments. The eponymic designation Bruns-Garland syndrome avoids anatomical inconsistencies. Clinically, asymmetrical weakness and wasting of pclvi-fcmoral muscles may occur either abruptly or in a stepwise progression in individuals with diabetes who arc older than 50 years. Most patients have NIDDM, but the onset is unrelated to the duration of glucose intolerance. Typically, unilateral severe pam m the lower back, hip, and anterior thigh heralds the onset of neuropathy. Within days to weeks weakness ensues, affecting proximal and distal lower extremity muscles (iliopsoas, gluteus, thigh adductor, quadriceps, hamstring, and anterior tibial muscles). In some cases, the opposite leg becomes affected after a latency of days to months. Reduction or absence of knee and ankle jerks are the rule. Numbness or paresthesias are minor complaints. Weight loss occurs in more than half of patients and is more pronounced than in individuals with nondiabetic lumbosacral radiculoplexopathy {Dyck, Norell, and Dyck 2001). The progression may be steady or stepwise, and may continue for many months. The result is often a debilitating, painful, asymmetrical motor neuropathy with profound atrophy of proximal leg muscles. Pain usually recedes spontaneously long before motor strength begins to improve. Recovery takes up to 24 months, because of the slow rate of axonal regeneration. In many cases mild to moderate weakness persists indefinitely (Barohn et al. 1991). Overlap with distal symmetrical polyneuropathy is noted in up to 60% of patients. Those with polyneuropathy more commonly have gradual onset of symptoms, bilateral findings, significant weight loss, and diffuse paraspinal muscle denervation. The typical HMG findings include low amplitude femoral nerve motor responses, prominent fibrillation potentials in thoracic and lumbar paraspinal muscles, and active denervation in affected muscles. Neuroimaging studies ot the lumbar spine, lumbosacral plexus, or both should be considered when lumbar root, Cauda equina lesions or structural lumbosacral plexopathy are suspected (sec Chapter 81). Sural nerve biopsy specimens in these individuals show multifocal nerve fiber loss suggesting ischemic injury and perivascular infiltrates, inferring an immune mechanism (Figure 82.30; Dyck et al, 2000b). A vascular pathogenesis of this proximal neuropathy was documented by autopsy showing infarcts of the proximal nerve trunks and lumbosacral plexus.

Truncal Neuropathy. Diabetic truncal neuropathy or thoracic radiculopathy involving the T4-T12 roots causes pain or dysesthesias in areas of the chest or abdomen. Bulging of the abdominal wall as a result of weakness of abdominal muscles may occur (Figure 82.31}.

This unique truncal pain is seen in older patients with NIDDM and may occur either in isolation or together with the typical lumbosacral radiculoplexopathy. The regions ot sensory loss or dysesthesia involve the trunk in a highly variable pattern affecting either the entire dermaromal distribution of adjacent spinal nerves or, more often, restricted areas limited to the distribution ot the dorsal or ventral rami of spinal nerves. Patients describe burning, stabbing, boring, beltlike pain. Contact with clothing can be very unpleasant. The onset may be either abrupt or gradual. The clinical picture can mimic intra-abdominal, intrathoracic, or intraspinal disease, or even herpes zoster, requiring careful differential diagnostic consideration. Neurological findings are limited to hypesthesia or hyperpathia over the thorax or abdomen. The symptoms maypersist for several months before gradually subsiding,

Electrodiagnostic studies are helpful by demonstrating active denervation in paraspinal and abdominal muscles, although these features are not specific for truncal mononeuropathy. Focal anhidrosis on the trunk correlating with the area of pain can be readily noted with the help of the thermoregulatory sweat test.

Limb Mononeuropathy. Single mononeuropathics, which are often seen in diabetic patients, arc thought to be caused by two basic mechanisms: nerve infarction or entrapment (Asbury 1977). Mononeuropathy secondary to nerve infarction has a stereotyped presentation, with the abrupt onset of pain followed by variable weakness and atrophy. Because the primary pathological lesion results in acute axonal degeneration, recovery tends to be slow. The median, ulnar, and fibular (peroneal) nerves are most commonly affected.

Mononeuropathics caused by nerve entrapment are more common than nerve infarctions. These rwo conditions can usually be distinguished by clinical and electrophysiological features. Entrapment neuropathy has an insidious onset and is found at characteristic sites. F.lectrodiagnostic studies demonstrate axonal loss in nerve infarction in contrast to focal conduction block and/or focal slowing in entrapment.

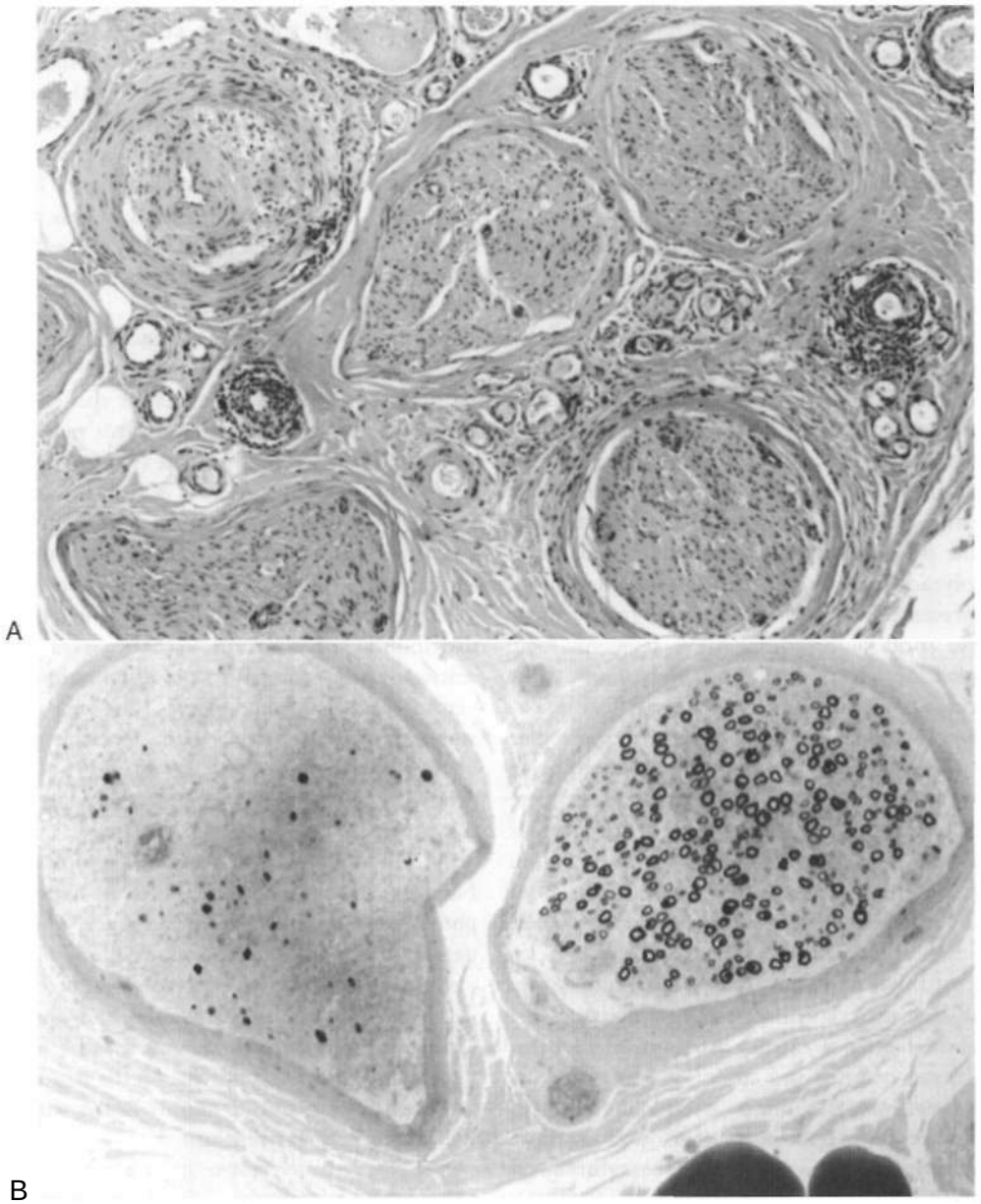


FIGURE 82.30 (A) Sural nerve biopsy from patient with diabetic lumbar radiculoplexopathy. Perivascular lymphocytic inflammation involves two epineurial arterioles. (Hematoxylin and eosin, original magnification *x25.)* (13) In the same patient, semithin transverse section illustrates selective involvement of one fascicle with marked loss of myelinated fibers, a pattern highly suggestive of nerve ischemia. (Paraphenyleuediamine-stained semithin cpoxy section, original magnification x80.) (Courtesy Dr. P. J. Dyck, Mayo Clinic, Rochester, MN.I

Multiple Mononeuropathies. Multiple mononeuropathies refers to the affection of two or more nerves. As in mononeuropathy, the onset is abrupt in one nerve, then other nerves ate involved sequentially at irregular intervals. Multiple mononeuropathies involving proximal nerves are considered the cause of "diabetic amyotrophy." Nerve infarction results from occlusion of the vasa nervorum. Because mononeuritis multiplex occurs most frequently in systemic vasculitis, this possibility should always be considered in the differential diagnosis of diabetic multiple mononeuropathies.

Cranial Mononeuropathies. A detailed description is given elsewhere (see Chapter 76). A third nerve palsy is the most commonly encountered diabetic cranial mononeuropathy. Pupillary sparing is the hallmark of diabetic third nerve palsy reflecting injury to centtifascicular axons but sparing the peripherally located pupillary motor fibers of the third nerve. With decreasing frequency, the fourth, sixth, and seventh nerves are affected. Acute ischemic nerve damage is the presumed cause of these cranial neuropathies. Patients with Bell's palsy have a significantly higher frequency of diabetes than an

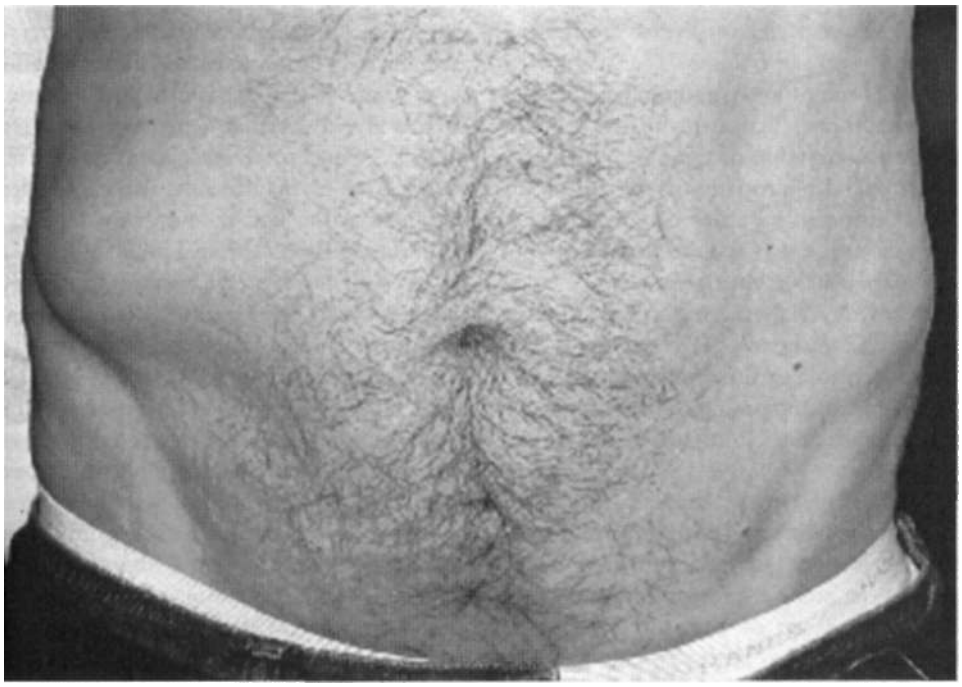


FIGURE 82.31 Bulging of the right lower thoracic abdominal wall at the level of the umbilicus associated with diabetic truncal monoradiculopathy.

age-matched population. Most make a full recovery in *3-5* months.

Thete are two serious, though somewhat rare, infectious syndromes closely linked to diabetes mellitus, which characteristically affect one or more cranial nerves by local inflammation. Rhinoccrcbral mucormycosis and "malignant" external otitis were often fatal before the advent of early diagnosis and effective treatment strategies (Smith 1998).

Increased Incidence of Entrapment Neuropathy. Diabetes mellitus is a risk factor for single or multiple entrapment neuropathies. Diabetes is found in 8-12% of patients presenting with carpal tunnel syndrome. Electrophysiological abnormalities consistent with carpal tunnel syndrome but without symptoms are found in one fourth of diabetic patients, while symptomatic carpal tunnel syndrome is found in 8% (Dyck et al. 1993b). Similar population studies indicate that the risk for carpal tunnel syndrome is about 2.2 times greater in female and 2.5 times greater m male patients with diabetes than in the general population. The reason diabetes predisposes to nerve entrapment is unknown, but aggravation of ischemia in nerves already sm^scd by chronic endoneurial hypoxia may be one factor. The possibility of occult diabetes should always be kept in mind in every case of entrapment neuropathy.

Laboratory Findings

The diabetes mellitus can be confirmed by finding one of the following: (1) a random plasma glucose of >200 mg/dL (11.1 mmol/L), associated with symptoms of hyperglycemia (polyuria, polydipsia, unexplained weight loss); (2) a fasting plasma glucose of >126 mg/dL (7.0 mmol/L); or (3) a 2-hout glucose of >2()0 mg/dL (11.1 mmol/L) after a 75-g glucose load in the OGTT. Any of these criteria is sufficient fot diagnosis, but each should be confirmed on a separate day. Impaired glucose tolerance (IGT) on the other hand is defined as plasma glucose levels between 140 and 200 mg/dL (7.8 and 11.1 mmol/L) 2 hours after a 75-g oral glucose load; the new category impaired fasting glucose (IFG) is defined as a fasting plasma glucose of between 110 and 125 mg/dL and is analogous to IGT (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997). Glycosylated hemoglobin (hemoglobin Ale) is a useful indicator of the long-term control of hyperglycemia, but is not generally used to diagnose diabetes, IGT, or IFG.

Evoked nerve action potential amplitudes are often reduced in patients with diabetes, while NCVs are typically slower in this group than in healthy subjects, all hough strict criteria for demyelinating neuropathy are not often met (Shanua et al. 2002a). Abnormalities occur more commonly in sensory than in motor fibers, in the legs more than in the arms, and in distal more than proximal nerve segments.

Pathology

The underlying pathological processes differ in the various types of diabetic neuropathy. Cranial and limb mononeuropathy and multiple mononeuropathies are thought

to be caused by small vessel occlusive disease (Smith and Dyck 1992).

The precise location of the primary pathological process in diabetic asymmetrical proximal neuropathy remains unsettled. Postmortem examination of the obturator nerve in a single case of proximal neuropathy showed multiple infarcts due to the occlusion of vasa nervorum. However, lumbar nerve roots were not examined. Studies of peripheral sensory nerves in patients with diabetic lumbosacral radiculoplexopathy provide evidence suggesting immune-mediated neuropathy and ischemia (Dyck, Norell, and Dyck 2001). Whether ischemic or inflammatory lesions in multiple lumbar roots, plexus, or proximal nerve segments are responsible for this particular neuropathy still remains to be proven.

The pathological lesions of symmetrical distal polyneuropathy have been extensivelj investigated Engelstad et al. 1997). The sural nerve shows loss of myelinated fibers, acute axonal degeneration, some degree of demyelination, and almost invariably evidence of a small endoneurial blood vessel vasculopathy. The latter is characterized by narrowing or closure of the endoneurial capillary lumen by hyperplastic endothelial cells, thickening of the capillary wall, and marked redundancy of basement membranes. Axonal degeneration has been shown to result from a dying-back centripetal degeneration of peripheral axons. Painless distal polyneuropathy affects predominantly the large nerve fiber populations, while painful distal diabetic polyneuropathy often shows marked depletion of small myelinated and unmyelinated fibers. In the latter condition, there is active axonal regeneration giving rise to abnormal netve impulses and neuropathic pain (Said etal. 1992).

The dcmyelinating process in diabetes has been interprclcd either as [he result ⊳! priman progressive axonal atrophy or from direct damage to Schwann cells, either by ischemia or metabolic disturbances. Extensive histometric studies of sural nerves demonstrate that the nerve fiber loss in diabetic neuropathy is distributed multifocaliy between and within different fascicles. The pattern of such multifocal nerve fiber loss is similar to that reproduced in experimental microsphere occlusion studies. Three-dimensional studies from nerves along proximal to distal segments indicate increasing nerve fiber depletion in distal nerve segments. This finding correlates with electrophysiological studies demonstrating a diffuse abnormality of NCVs with proximodistal gradients. The current investigations point to microvascular abnormalities contributing significantly to the development of both multifocal neuropathies and symmetrical polyneuropathies.

Pathogenesis of Diabetic Neuropathy

Although the causes of diabetic neuropathies remain unknown, currently accepted hypotheses focus on the possibilities of metabolic and ischemic nerve injury. Hyperglycemia has been implicated in many different pathogenic mechanisms in diabetic neuropathy (Simmons and Fcldman 2002). Hyperglycemia generates rheological changes that increase endoneurial vascular resistance and reduce nerve blood flow. Hyperglycemia also causes depletion of nerve myoinositol through a competitive uptake mechanism. In addition, persistent elevated blood glucose levels activate the polyol pathway in nerve tissue through the enzyme aldose reductase, which leads to the accumulation of sorbitol and fructose in nerve and induces nonenzymic glycosylation of structural nerve proteins (Thornalley 2002). Another adverse effect of hyperglycemia is auto-oxidation of glucose, which results iii the generation of toxic reactive oxygen intermediates (Sheetz and King 2002). Over-exuberant activation of protein kinase C has been linked to vascular damage in diabetic neuropathy (Eichberg 2002). These metabolic changes arc likcK to cause abnormal neuronal, Schwann cell, and axonal metabolism and subsequently impaired axonal transport. Direct measurements of sugar alcohols in sural nerves from patients with diabetes confirm increased levels of glucose, sorbitol, and fructose that correlate with the severity of the neuropathy. Endoneurial hypoxia is produced by decreased blood flow to the nerve and increased endoneurial vascular resistance. Once hypoxia is established, a vicious cycle of further capillary damage is set in motion that escalates hypoxia. F.ndoneurial hypoxia is thought to impair axonal ttansport and reduces nerve sodium-potassium-ATPase activity. The impairment of these functions causes axonal atrophy, leading to tednecd NCVs. Although the precise mechanisms leading to capillary abnormalities that initiate hypoxia ate unknown, the hypoxic hypothesis provides a framework for further research into the pathogenesis of diabetic neuropathy.

Unfortunately, basic research in diabetic neuropathy has focused almost exclusively on carbohydrate metabolism and, to a lesser extent, immune mechanisms, to the exclusion of the amino acid, electrolyte, and lipid biochemical abnormalities long known to be present in diabetes mellitus.

Treatment

The cotnetstone in the treatment of diabetes and its complications remains optimal glucose control. There is considerable evidence that good diabetic control is associated with less frequent and less severe peripheral nerve complications. Although the data arc less compelling for NIDDM, there is an association between poor glycemic control and neuropathic deficits (Adler et al. 1997). The Diabetes Control and Complication Trial (1995) showed that intensive glucose management by insulin pump or by multiple daily insulin injections in patients with IDDM reduces the development of neuropathy by 64% at 5 years compared to conventional therapy. Successful pancreatic transplantation is beneficial in preventing the progression

of diabetic neuropathy and the effect may be sustained in long-term follow-up (Navarro, Sutherland, and Kennedy 1997). Attempts to treat diabetic neuropathy by manipulating nerve metabolism have been disappointing. Clinical trials of myoinositol supplementation have shown conflicting results, and those of aldose reductase inhibitors have so far failed to produce convincing clinical improvement, though there were modest changes in nerve conduction and nerve pathology.

Despite promising preliminary evidence, neuropeptide treatments for diabetic neuropathy, such as NGF, have been disappointing (Apfel 2002). Based on experimental data suggesting that oxidative stress mediated by free radical species may be involved in diabetic neuropathy, two large multi-center randomized controlled clinical trials of *a*-lipoic acid have bqcn undertaken (A1.ADIN and NATHAN 1) (Ziegler 2002). The NATHAN 1 study is the first longitudinal multi-year human study to evaluate a pathogenicallv based treatment for diabetic polyneuropathy. A randomized controlled double blind human study ol intravenously administered a-lipoic acid in patient with symptomatic diabetic polyneuropathy showed improvement of sensory symptoms (Ametov et al. 2003). Despite two multi-center controlled clinical trials of or-linoleic acid in diabetic neuropathy, which showed lessening of neuropathic deficits and improvement in measures of nerve conduction (Keen et al. 1993; Horrobin 1997), because of licensing problems no further trials with this substance arc planned. Vascular endothelial growth factor (VEGF) gene transfer into small mammals has been shown to improve NCVs, increase blood vessel density, and enhance nerve blood flow (Schratzberger et al, 2001), giving impetus to pursuing this approach to human diabetic neuropathy. Because human C-peptide prevents neuropathy in diabetic rats in a dose-dependent fashion (Zhang et al. 2001), clinical interest has developed for this compound as well. For unclear reasons, a number of pathogenic ally sound therapeutic approaches using neuropeptides or other small molecules to halt progression or reverse diabetic neuropathy have shown great promise based on in vitro and in vivo animal studies, only to be proven ineffectual or unimpressive when carried out in human diabetic subjects.

Symptomatic treatment for pain, autonomic manifestations, and the complications of sensory loss can be offered to lessen the impact of neuropathic symptoms.

The use of intravenous methylprednisolone therapy is currently under investigation for patients with diabetic lumbosacral radiculoplexopathy. Use of high dose intravenous immunoglobulin or methylprednisolone has been reported to benefit patients with progressive deficits and biopsy evidence of inflammation in uncontrolled studies (Dyck and Windcbank 2002).

Several therapeutic interventions may reduce the symptoms of autonomic dysfunction. Patients with symptomatic orthostatic hypotension arc advised to sleep with the head of the bed elevated 6-10 inches. The head up tilt prevents salt and water losses during the night, and will combat supine hypertension. Practical suggestions include drinking two cups of strong coffee or tea with meals, eating more frequent small meals rather than a few large meals, and increasing the daily fluid intake (>20 oz per day) and salt ingestion (10-20 g per day). Elastic body stockings may be beneficial by reducing the venous capacitance bed, but are poorly tolerated by many patients. Plasma volume expansion can be achieved by fludrocortisone (0.1-0,6 mg daily). Nonsteroidal anti-inflammatoty drugs, which inhibit prostaglandin synthesis, represent the next class of drugs to be considered; ibuprofen, 400 mg four times a day, is better tolerated than indomethacin. Phenylpropanolamine (25-50 mg three times a day), a direct-acting alpha-agonist, was once used for orthostatic hypotension; although a sustained-release form of phenylpropanolamine can be obtained over-the-counter (e.g., Dcxatrim), the association of hemorrhagic stroke makes this medication an undesirable option (Morgenstcrn et al. 1997). Delayed gastric emptying is often relieved with metoclopramide; because it is a dopamine antagonist, extrapyramidal symptoms may occur at higher doses. Diabetic diarrhea may be treated with short courses of tetracycline or erythromycin, if appropriate. In some cases, clonidine has been reported to reduce the troublesome diarrhea.

Genitourinary complications of diabetic autonomic neuropathy require close collaboration with a urologist. Patients with a neurogenic bladder should be encouraged to adhere to a frequent voiding schedule during the day, which helps diminish the amount of residual urine. For more severe involvement, manual abdominal compression or intermittent sclf-carherenzation may be needed. Treatment of erectile impotence should be directed by a urologist, who can counsel the patient regarding the options of either oral treatment with sildenafil, pharmacological erections with direct injections into the corpora cavernosa, or penile implants.

Proper skin care in diabetics with cutaneous sensory loss, impaired sweating, and vascular disease is extremely important to prevent foot ulcers.

Peripheral Neuropathy in Malignancies

Advances in the diagnosis and management of malignancy have accelerated in recent years, leading to novel chemotherapeutie strategies and prolonged survival rates for many cancers. With these welcome improvements come an increasing awareness ot peripheral nerve complications in patients with various forms of neoplasm. The frequency with which neuropathy occurs in cancer depends on the type of neoplasm and the method of detection. If clinical criteria alone are used, 2-16% of cancer patients are estimated to have peripheral neuropathy. When quantitative sensory testing or electrophysiological studies are carried out, approximately 30-40% of patients have

abnormalities suggestive of peripheral nerve involvement (Amatoand Collins 1398).

Peripheral nerve complications may result from one or more mechanisms related to cancer or its treatment. These include (1) compression or invasion of nerve trunks or nerve plexus by direct extension of primary or metastatic tumor; (2) meningeal metastases with involvement of multiple nerve roots; (3) remote effects of cancer affecting neuronal cell bodies, nerve axons, Schwann cells or myelin, terminal axons, neuromuscular junction, and muscle; {4) entrapment neuropathies in individuals with profound cachexia; and (5) treatment with chemotherapy or radiation.

Compression/Invasion of Nerves

Apart from head and neck tumors invading cranial and cervical peripheral nerves, focal neuropathies from primary neoplasms are uncommon. Salivary gland cancers are known to affect the facial and other cranial nerves, often growing insidiously by perineuria! spread, thereby eluding early detection even by sophisticated imaging procedures. Nasopharyngeal carcinomas, meningiomas, and skull base tumors may interrupt cranial nerve fibers directly. Primary or recurrent neoplasms of the breast or lung apex in particular may invade the brachial Ht'\u-. Siir.ikirly. primary or recurrent pelvic or retroperitoneal cancers may involve the lumbosacral plexus (these conditions are discussed in Chapter 81),

Metastases

Discrete single metastatic lesions may rarely cause crania! or somatic mononcuropathy. The "numb chin" syndrome results from invasion of the inferior alveolar nerve by metastases to the mandible. Patients complain of numbness of the chin and lower lip. Leukemias, lymphomas, and breast cancer are the most common neoplasms responsible for the "numb chin" syndrome. More commonly widespread metastases arise in the leptomcninges from carcinoma or lymphoma leading to leptomeningeal carcinomatosis or lymphomatosis, respectively.

Entrapment

Individuals who lose substantial weight or are bedridden are subject to fibular (peroneal) and ulnar compression neuropathies (Rubin, Kimmel, and Cascino f 998).

Iatrogenic Neuropathies

ChemoiluTapcutic agents ilui cause pniiianh (HI i^lu-r.il neurotoxicity include vinca alkaloids, platinum compounds and taxancs, are discussed in the section on toxic neuropathy. The neurological complications of radiation plcxopathy are discussed in Chapters 64 and K3. Surgical resection of bulky cancers may result in trauma to peripheral nerves, which may be unavoidable because of inextricable adherence or transit of nerve fibers through the tumor mass.

Paraneoplastic Neuropathies

Paraneoplastic disorders are defined as remote effects of cancer, unrelated to treatment or deficiency states, that often involve both the central and petipheral nervous systems alone or in combination. In paraneoplastic neuromuscular disorders, sensory or autonomic ganglia, petipheral nerves, nerve terminals, neuromuscular junction and muscle may be affected, and thereby result in diverse clinical syndromes. Small cell carcinoma of the lung (SCLC) is the most common malignancy associated with paraneoplastic neurological syndromes bur carcinoma of breast, ovaries, kidney, prostate, thymoma, and Hodgkin's and non-Hodgk in's lymphoma have also been reported to be associated. The neurological symptoms may precede the detection of the underlying cancer by 4 to 12 months. The clinical course is often rapidly progressive, leaving the patients severely disabled in only a few weeks or months. Any neuropathy, especially a sensory or autonomic neuropathy of subacute onset occurring in a smoker, should raise suspicion ol a paraneoplastic disorder.

Paraneoplastic neurological syndromes are considered autoimmune disorders because of the presence of autoantihodics dcki.:cd in si-rum and CS1 nt some affected patients that are reactive with protein antigens in the neoplastic tissue and CNS neurons. Paraneoplastic neuropathies have been associated with an ever-increasing number of autoantibodies (Chan, Vernino, and Lennon 2001; Table 82.26).

The type 1 antincuronal nuclear antibody (ANNA-I or anti-Hu, named after the first two letters of the name of the patient in whom this antibody was first discovered) is associated with malignant inflammatory sensory polyganglioneuropathy, gastrointestinal dysmotility, autonomic neuropathy, and limbic encephalomyelitis. Small cell lung cancer is found in more than 80% of ANNA-I seropositive patients (Lucchinetti, Kimmel, and Lennon 1998). These polyclonal IgG autoantibodies are directed against *35* to 40 kDa proteins that belong to the Hu-family of RNA binding proteins expressed in nuclei of neurons and malignant cells. The type 2 antincuronal nuclear antibody (ANNA-II, or anti-Ri) was originally described in women with opsoclonusniyoelonns associated with breasi cancer. Inn may also he seen in men with peripheral neuropathy in association with lung cancer. ANNA-IH is highly associated with SCLC or adenocarcinoma of the lung in patients with sensorimotor neuropathies, cerebellar ataxia, and encephalomyelitis. Three IgC autoantibodies related to lung cancer are directed against neuronal cytoplasmic antigens. These are amphiphysin antibody (also related to breast carcinoma), type 2 Purkinje cell cytoplasmic antibody (PAC-2), and the collapsin response-mediator protein-5 antibody (CRMP-5).

Table 82,26: Autoantibodies in neuromuscular paraneoplastic syndromes

AntibvJy	*Neurological n xanifes tations*	*Types of tumors*
ANNA-1 (niiti-Hu)	MISP, GI dysmotility; autonomic N, PF.M	SCLC
ANNA-2 (anti-Ri)	Opsoclonus/myoclonus, jaw dystonia, ataxia, SMN	SCLC, breast carcinoma
ANNA-3	Sensory N, SMN, ataxia, PEM	SCLC, adenocarcinoma of lung, esophagus
CRMP-5 (anti-CV-2)	Dementia, SMN, vision loss, chorea	SCLC, thymoma
PCA-1 (anti-Yo)	Cerebellar ataxia, SMN	Ovarian, breast carcinoma
PCA-2	PEM, ataxia, autonomic and motor N	SCLC
Amphiphysin	Stiff man syndrome, sensory N	SCLC, breast carcinoma
P/Q type calcium channel	1 EMS	SCLC
N type calcium channel	LEMS, SMN	SCLC, breast, ovarian carcinoma
Ganglionic AChR	Autonomic N, GI dysmotility, PN hyperexcitabiliry	SCLC, thymoma
Voltage-gated potassium channel	PN h\ pcrcxcirabilin	Thymoma, lung carcinoma

AChR = acetylcholine receptor; ANNA = antineuronal nuclear antibody; CRMP-5 = eo]lapsm response-media tor prorcin-5; LEMS = Lambert-Eaton myasthenic syndrome; MISP = malignant inflammatory sensory polyganglionopathy; N = neuropathy; PCA-l=type 1 Purkinje cell cytoplasmic antibody; PCA-2 = rype 2 Purkinje cell cytoplasmic antibody; PEM = paraneoplastic encephalomyelitis; PN hyperexcitability = peripheral nerve hyperexcitability; SCLC = small-cell lung carcinoma; SMN = sensorimotor neuropathy.

CRMP-5 IgG (or anti-CV-2) antibodies are associated with SCLC and rarely thymoma and occur in patients with multifocal neurological signs, including sensory or sensorimotor neuropathies, chorea, optic neuropathy, and disturbance of smell and taste (Yu et al. 2001). Autoantibodies directed aginst neuronal ion channel antibodies include P/Q and N-type calcium channel antibodies, ganglionic acetylcholine receptor and voltage-gated potassium channel antibodies. P/Q type calcium channel antibodies are present in more than 90% of patients with Lambert-Eaton syndrome (LES). N-type calcium channel antibodies are markers for lung, breast, or ovarian cancers and are found in patients with various neurological manifestations including LES and peripheral neuropathy. Ganglionic acetylcholine receptor antibodies are found in patients with both idiopathic and paraneoplastic types of autonomic neuropathy (Vernino et aI. 2000). Voltage-gated potassium channel antibodies are detected in patients with autoimmune disorders of peripheral nerve hyperexcitability. These include neuromyotonia, myokymia, and cramp-fasciculation syndrome. These van- disorders can be seen in association with thymoma, lung cancer, and Hodgkin's lymphoma (Hart et al. 2002).

Peripheral neuropathies associated with carcinoma may be classified according to the distribution of involvement into the following clinical types: (1) malignant inflammatoty sensory polyganglionopathy; (2) autonomic neuropathy; (3) sensorimotor polyneuropathy (either axonal or demyclinating types); and (4) multiple mononouropathy.

Ma !i tit unit Inflammatory Sensory Polyganglionopathy

In 1948, Denny-Brown recognized the association between sensory neuropathy and cancer when he described two cases with rapidly progressive severe sensory loss and ataxia without weakness as a remote effect of bronchogenic carcinoma. The terms *subacute sensory neuropathy, carcinomatous sensory neuropathy, paraneoplastic sensory neuronopathy,* and *malignant inflammatory sensory polyganglioneuropathy* are synonyms to describe the distinct sensory neuropathy associated with cancer. The term *malignant inflammatory sensory polyganglionenropathy* is preferred because it emphasizes the sensory ganglion cell as the primary site of injury, while recognizing that other neurons including autonomic ganglia and CNS nerve cells arc often involved as well. The presence of an autoantibody directed against a nuclear protein that is shared by neuronal nuclei and tumor antigens, and the intense inflammatory response found in affected dorsal root ganglia, support an immune-mediated mechanism for this condition. Paraneoplastic syndromes affect only a small minority of cancer patients, occurring less commonly than direct tumor invasion or neurotoxic complications of chemotherapy.

Clinical Features. Patients are middle-aged or older, and many are heavy smokers. "Women are affected twice as often as men in the United States, in contrast to a European study and to the overall male predominance of SCLC; (Graus et al. 2001). The most common underlying neoplasm is SCLC (approximately 90%), followed in decreasing order of frequency by breast carcinoma, ovarian cancer, and lymphoma. In 9 of 10 cases neurological symptoms are the presenting features and precede the discovery of the tumor by several months. The median interval from onset of neuropathic symptoms to diagnosis of the underlying neoplasm is .5 months. Symptoms may develop fulminantly within days or more gradually over months. Numbness, painful paresthesia, and lancinating pain often begin in one limb and progress to involve all four limbs. Occasionally, the ttunk, face, or scalp are affected in somatotopic regions highly suggestive of

neuronopathies. There is global loss of all sensory modalities with a striking loss of proprioception and the ability to localize the limb in space, leading to sensory ataxia and pseudoathctosis of the upper extremities. Tendon reflexes are globally reduced or absent. Although muscle strength is preserved or only mildly decreased, patients are often severely disabled and unable to walk because of their sensory deficits.

Approximately one half of patients have symptoms and signs reflecting more widespread involvement of myenteric plexus neurons, autonomic ganglia, spinal cord, brainstem, cerebellum, and limbic cortex. These patients display varying degrees of gastrointestinal dysmotility, autonomic dysfunction, myelopathy, cerebellar signs, brainstem findings, and subacute dementia.

Laboratory Features. The CSF is frequently abnormal with either mild pleocytosis or elevated protein. Nerve conduction studies show low-amplitude or absent SNAPs with relatively preserved amplitudes of CMAPs. F.MGs may demonstrate minor abnormalities. The sural nerve frequently shows a combined loss of myelinated and unmyelinated fibers, axonal degeneration, and minimal axonal regeneration, sometimes with mononuclear inflammatory cells around epineurial vessels. The principal neuropathological features include degeneration of dorsal root ganglion cells with intense mononuclear cell inflammation, subsequent loss of sensory axons, and degenctation of the posterior roots, peripheral sensory nerves, and the posterior columns of the spinal cord. Many patients have pathological evidence of a more generalized encephalomyelitis characterized by inflammatory infiltrates and neuronal loss in hippocampus, brainstem, and spinal cord.

Patients presenting with sensory neuronopathy, encephalomyelitis, or gastrointestinal dysmotility associated with SCLC harbor characteristic autoantibodies in their serum and spinal fluid called type I antineuronal nuclear antibodies (ANNAT) or anti-Hu. About 90% of patients with sensory neuronopathy associated with SCLC' have significantly elevated titers of ANNA-1 antibodies by immunohistochemistry or Western blot analysis; low titers have been found in 16% of patients with SCLC without neurological disease. The reported sensitivity of positive ANNA-I antibodies is 88%, and the specificity is 99%. In contrast, all patients with idiopathic sensory neuronopathy without cancer are seronegative for ANNA-I antibodies. These results highlight the value of serological testing fot ANNA-I antibodies as an aid in the differential diagnosis of ataxic sensory neuronopathies. When a paraneoplastic neuropathy is suspected in relation to lung cancer, screening for an entite panel of autoantibodies that includes ANNA-I, CRMP-5, amphiphysin, PCA-2, ANNA-type 2, and ANNA-type 3, and calcium channel antibodies provides an even greater diagnostic yield. Seropositive patients should have chest CT or MRI because the tumor may go undetected by chest roentgenography. When cancer is not found by conventional radiological procedures, positron emission tomography (PET) should be considered.

Differential Diagnosis. The diagnostic possibilities of acquired sensory neuronopathies include malignant inflammatory sensory polyganglioneuropathy, the ataxic sensory neuronopathy associated with Sjogren syndrome or HIV infection, and idiopathic sensory neuronopathies. These conditions share similar pathological lesions characterized by an inflammatory ganglionopathy. The toxic sensory neuronopathies caused by high dose pyridoxine or following chemotherapy with cisplatinum arc readily excluded by history. Although it can be difficult to distinguish patients with malignant inflammatory sensory polyganglioneuropathy from those with other causes of sensory neuronopathy, (!) discovery of prominent dvsuurouomi.i, (2) neurological signs suggesting disease outside the dorsal root ganglion (and particularly CNS deficits), or (3) ANNA-I antibodies should prompt a careful search for malignancy, and especially SCLC.

Prognosis. The outlook for patients with paraneoplastic sensory neuronopathy is poor. Early diagnosis and prompt treatment of the underlying neoplasm provide the best chance to stabilize the condition. More often the neuronopathy pursues a relentless, independent course, despite treatment of the underlying tumor. Treatment with plasmapheresis, intravenous immune globulin, and immunosuppressive agents has had disappointing results. Nevertheless, minor modifications of the clinical course have been observed in a few patients receiving immunoinniluhinirv therapy [drau.ss el al. 200 f 1.

Paraneoplastic Autonomic Neuropathy

Subacute panautonomic failure may be associated with malignancies, most commonly SCLC. The majority of patients have focal or generalized gastrointestinal dysmotility presenting wirli abdominal pain, nausea, vomiting, and severe constipation with subtle or no sensory deficits. Ganglionic acetylcholine receptor and ANNA-I antibodies are found in most patients.

Sensorimotor Polyneuropathy

It is far more common for cancer patients to have distal symmetrical sensorimotor polyneuropathy than malignant inflammatory sensory polyganglioneuropathy. Clinically, these more frequently encountered length-dependent neuropathies are often of slow onset, progress gradually, and are indistinguishable from distal axonal neuropathies in individuals without malignancy. Sites of neoplasm reported in association with this nondescript polyneuropathy, in decreasing order of frequency, include lung, stomach, breast, colon, pancreas, and testis. Whether these neuropathies are paraneoplastic remains to be proven.

Acute and chronic polyradiculoneuropathies have occasional!) been linked In undciK MSL ni.ihs'.tuiicies. t. 1*S lias been reported in a few patients with Hodgkin's lymphoma. C1DP may occur in patients with leukemia, myeloma, melanoma, and lymphoma. Molecular mimicry of common antigens shared by both melanoma and Schwann cells may explain the increased association of CIDP with melanoma. It is important to recognize these acquired acute or chronic immune-mediated polyradiculoneuropathies in the clinical setting of malignancies because both respond to immunomodulatory therapies.

Multiple Mononeuropathies

Paraneoplastic vasculitis is recognized to occur in association with malignancies as a remote effect of cancer and frequenrly presents as cutaneous vasculitis in hairy cell leukemia and lymphoma. Peripheral nerve vasculitis is a rare complication of Hodgkin's and non-Hodgkin's lymphoma, SCLC, adenocarcinoma of the lung, prostate, endometrium, and renal cell cancer. Patients present with multiple mononeuropathy or painful, asymmetrical sensorimotor neuropathy that precedes the discovery of tumor in most. The association of vasculitis with SCLC and seropositive ANNA-I autoantibodies supports a paraneoplastic etiology. Two thirds of patients have responded to either chemotherapy of the underlying malignancy or cyclophosphamide with or without steroids (Oh 1997).

Lymphoma, Neurolymphomatosis, Leukemia, and Polycythemia Vet J

Neurological complications of lymphoma result from (1) direct involvement of the leptomeninges or brain; (2) compression ol [hi spinal cord or nerve roots b\ epidural masses; (3) bacterial, fungal, and viral infections; (4) complications of treatment (e.g., chemotherapy, radiation, bone-marrow transplantation); and (5) remote effects. Spinal cord compression is the most frequent complication, followed by varicella zoster virus infection and toxic neuropathies related to chemotherapy. Peripheral neuropathy unrelated to chemotherapy is found in approximately 5% of patients with lymphoma (Hughes, Britton, and Richards 1994).

Neurolymphomatosis is a rare condition with diffuse infiltration of peripheral and cranial nerves, plexus, or nerve roots by lymphoma cells. Patients present in several ways depending on the site of PNS involvement as ascending paralysis mimicking GBS, progressive polyradiculoneuropathy, Cauda equina syndrome, distal sensorimotor polyneuropathy, or multiple mononeuropathy. The diagnosis is confirmed by positive CSF cytology or lymphoma - tous infiltration of nerves as seen by cutaneous nerve biopsy or autopsy. Neurolymphomatosis responds poorly to systemic chemotherapy because the nerve-blood barrier limits the access of cytotoxic drugs (Odabasia et al. 2001).

Intravascular lymphomatosis or angiotropic large cell lymphoma is characterized by the proliferation of maligant lymphocytic cells within small blood vessels of the brain, spinal cord, peripheral nerves, and skin. Neurological manifestations include multifocal strokes, myelopathy with or without cauda equina lesions, and polyradiculoneuropathies. Intravascular lymphoma may be confirmed by biopsy of involved tissues such as skin, muscle, or peripheral nerve. Untreated the disease is rapidly fatal. Survival has been reported after chemotherapy (Oei, Kraft, and Sarnat 2002).

Acute and chronic demyelinating polyradiculopathies have been described in association with Hodgkin's and non-Hodgkin's lymphoma. About 8% of patients with monoclonal gammopathy have a low grade lymphoma or lymphocytic leukemia and may develop a distal demyelinating neuropathy in association with IgM paraproteinemia.

I.ymphoproliferative disorders may be overrepresented in patients with motor neuron disease. This association was initially restricted to lower motor neuron syndromes, named *subacute motor neuronopatby,* occurring as a remote effect ol lymphoma. Only a few patients with pure lower motor neuron syndromes have improved following treatment of the concurrent lymphoproliferativc disorder.

Neurological complications of chronic lymphocytic leukemia develop in the advanced stages of the disease. These include herpes zoster infection, followed by opportunistic infections and treatment related complications. Peripheral nerve involvement is rare (less than 1%) and consists of leukemic nerve infiltrations and immune-mediated neuropathies.

Neurological complications of acute leukemias stem from hemorrhage into the brain or nerve trunks; leukemic infiltration of the brain, lepromeninges, cranial nerves, spinal roots, and peripheral nerves; CNS infections; or chemotherapy-related neurotoxicity.

Mild distal sensory neuropathy is a rare complication of polycythemia vera. Positive sensory complaints such as pruritus, paresthesias, and burning feet are common. Polycythemia vera-associated pruritus, which is typically precipitated by contact with water, may be an agonizing aspect of the disease. Selective serotonin reuptake inhibitors such .is paroxetine or fluoxetine have been beneficial in alleviating pruritus.

Neuropathies Related to Bone Marrow Transplantation

Peripheral neuropathy is an uncommon complication of bone marrow transplantation. In a prospective study of 115 patients with leukemia undergoing allogeneic bone marrow transplantation, 4% developed neuropathy in the first three months after transplantation. There arc a number of potential neuromuscular complications that may occur in the post-transplant period: neurotoxicity of drugs used in the conditioning regimen, critical illness neuropathy,

corticosteroid myopathy, and immune-mediated polyradiculoneuropathies associated with graft-versus-host-disease (Openshaw 1997), Polymyositis, myasthenia gravis, neuromyotonia, and chronic polyradiculoneuropathies have all been described in association with chronic graft-versus-host-disease. The observed predominately motot polyradiculoneuropathy meets clinical and laboratory features for CIDP (Amato et ai. 1993). Patients improve after immunomodulatory therapy consisting of intravenous immunoglobulin, plasma exchange, or immunosuppressant therapy.

Acute inflammatory demyelinating polyradiculoneuropathy or GBS has been reported in patients after allogeneic and autologous bone marrow transplantation (Wen et al. 1997). Intravenous immunoglobulin or plasmapheresis arc considered effective treatments.

Neuropathy in Connective Tissue Diseases

Peripheral nerves, including cranial nerves, arc affected Irequvnlb in connective tissue disorders (Olney 1998). Peripheral nerve manifestations may develop in patients with well-established disease or may be the initial manifestation of an undiagnosed connective tissue disease. Neuropathy may occur as part of the multisystem disease process itself; it may be secondary to complications of other organ involvement (e.g., uremic neuropathy, nerve entrapment as a result of joint deformities), or iatrogenic drug toxicity. Finally, neuropathy may be coincidental and unrelated to the underlying disease. The pathogenesis of peripheral neuropathy in connective tissue disorders is complex and may vary with the specific disorder. Circulating itnmuiiu complexes detected in .i variety ol connective tissue disorders may play a significant role. Vascular lesions arc found in all types of connective tissue disorders. In some there is occlusion of the small vasa nervorum, whereas in others cpincurial arterioles and small arteries arc involved by necrotizing vasculitis, producing ischemic nerve damage.

Peripheral Nerve Vasculitis

The vasculitides represent a elinieopathological spectrum of disorders characterized by inflammation and destruction of blood vessel walls, leading to luminal occlusion and ischemia ot hemorrhage in the affected organ systems. Vasculitis can be observed in two clinical settings: primary vasculitis without known underlying cause, or secondary vasculitides whereby vasculitis occurs in the setting of infectious, malignant, or metabolic diseases or drug exposure. PNS involvement is a common complication of systemic vasculitis (50-80%), especially in polyarteritis nodosa and small vessel vasculitides because the small and medium-si zed vessels affected in these types of vasculitis correspond to the size of the vasa nervorum (Langford 2003). The types of vasculitis that may affect the PNS and the estimated frequency with which they present to neurologists are provided in Tabic 82.27. Systemic necrotizing vasculitis refers to a diverse group of diseases affecting multiple organ systems including the PNS and CNS. On the other hand, peripheral neuropathy may be the only manifestation of a more indolent condition, nonsystemic {or monosystemic) vasculitic neuropathy.

Table 82.27: Classification of vasculitides affecting the peripheral nervous system*

Systemic necrotizing vasculitis
- Classic polyarteritis nodosa (22%)
- Wegener's granulomatosis (1%)
- Clmrg-Strauss syndrome
- Microscopic polyangiitis (11%)

Vasculitis associated with connective tissue disease (14%)
- Rheumatoid vasculitis (18%)

Hypersensitivity vasculitis
(.i.i11; cell [teiiipiir.ili anerr.is
Localized vasculitis (organ-specific)
- Nonsystemic vasculitic neuropathy (34%)

'Relative frequency is based on more than 200 patients, with biopsy-proven vasculitis pooled from six neuromuscular centers.
Source: Adapted from Olney, R. K. 1998, "Neuropathies associated with connective tissue disease," *Semin Neurol,* vol. 18, pp. 63-72.

Polyarteritis nodosa, by far the most common vasculitis in this group, is characterized by necrotizing inflammation of medium-sized or small arteries affecting the kidneys, skeletal muscle, gastrointestinal tract, skin, PNS, and CNS. Peripheral nerve involvement occurs in 50-75% of patients. Hepatitis B surface antigen is found in one third of the cases. Churg-Strauss syndrome typically presents with asthma, cosinophilia, and systemic vasculitis of small and medium-sized vessels. The frequency of peripheral nerve involvement is similar to that seen in polyarteritis nodosa (Hattori et al. 1999). Wegener's granulomatosis affects the upper and lower respiratory tract accompanied by glomerulonephritis and necrotizing vasculitis. The PNS is involved in 10-20% of cases. Cranial nerve involvement and external ophthalmoplegia occurs in 11% of patients as a result of granulomatous infiltration of the orbit or cavernous sinus (Nishino et al. 1993).

When vasculitis develops in association with connective tissue disorders, the clinical and pathological features resemble polyarteritis nodoi.i. Anions: the connective tissue disorders, rheumatoid vasculitis is by far the most common cause of vasculitic neuropathy. Approximately 15-30% of patients cannot be catcgotized and are classified as *microscopic polyangiitis.* In the hypersensitivity vasculitides, cutaneous manifestations dominate the clinical picture, although peripheral nerves may be involved. Peripheral nerve lesions may complicate giant cell arteritis in 14% of cases. More than 10% of patients with vasculitic neuropathy present in the setting of malignancies, most commonly myeloproliferative or lymphoproliferattve disorders and infections including HIV and hepatitis B and C

virus. One third of patients with biopsy-proven vasculitic neuropathy lack evidence of systemic disease or a definable connective tissue disease (see following section, Non-systemic Vasculitic Neuropathy).

Non systemic Vasculitic Neuropathy

A restricted necrotizing vasculitis affecting only peripheral nerves and skeletal muscle is the most common cause of vasculitic neuropathy in patients presenting to a neurologist. Multiple mononeuropathies are the most common clinical presentation, followed by asymmetrical neuropathy or symmetrical distal polyneuropathy (Davies ct al. *J996).* I'hi'-r are generally no constitutional symptoms or scro logical .lhrmniulities, because joints, visceral organs, and skin are unaffected. The severity of symptoms and deficits varies considerably. The disease course is indolent and protracted over years without ever becoming life threatening. The diagnosis depends exclusively on results of nerve and muscle biopsy. The pathological features are identical to those seen in classic polyarteritis nodosa affecting small and medium-si^ed arteries in muscle and nerve.

Pathogenesis

The precise immunological events leading to vessel injury in vasculitis is not well understood. Immune complex deposition within vessel walls and T cell-dependent, cell-mediated cytotoxic reactions arc the two basic immunopathogenetic mechanisms causing destruction of vessel walls. Vascular endothelial cells may serve as antigen-presenting cells and have important functions initiating the cell-mediated immune process. Although drugs and certain infectious agents, including HIV-1 and hepatitis B and hepatitis C viruses, have been implicated as triggers of the immune responses, in most instances an etiological agent cannot be identified. Small vessel vasculitis and pathological features of ischemic nerve injury have been described in peripheral sensory nerves of patients with diabetic and nondiabetic lumbosacral radieuloplexopathies (Dyck, Norell, and Dyck 2001). The final common pathway of vasculitic neuropathy is the extensive occlusion of vasa nervorum at the level of epineurial arterioles of 50-300 urn diameter leading to nerve ischemia. Nerve ischemia results in axonal degeneration. Because of the random, focal nature of vasculitis, axonal degeneration typically shows a pattern of asymmetrical, patchy involvement both between and within nerve fascicles. The ischemia is most pronounced in proximal nerves, such as the fibulat division of the sciatic nerve at the mid-thigh or the ulnar nerve at the mid-upper arm, in watershed areas between the distributions of major nutrient arteries. The extensive branching and intermixing of nerve fibers may result in a more homogeneous nerve fiber loss in distal sensory nerves, which arc suitable for biopsy. Large myelinated fibers appear to be more susceptible to ischemia than unmyelinated fibers.

Clinical Features

In systemic vasculitis, there are multisystem signs together with fever, malaise, weight loss, and hypertension. The majority of patients with PNS involvement present with peripheral neuropathy as the initial manifestation of disease. Irrespective of the underlying vasculitic syndrome, the clinical features of vasculitic peripheral neuropathy are similar and depend on the extent, distribution, and temporal progression of ischemia. Three types of peripheral nerve involvement can be distinguished, although considerable overlap occurs between types (Figure 82.32): (I) multiple mononeuropathies with motor and sensory deficits restricted to the distribution of individual nerves (10-15%); (2) overlapping or confluent multiple mononeuropathies obscuring individual nerve involvement (60-70%) with severe flaccid weakness and pansensory loss in one or more extremities; and (3) subacute symmetrical, distal sensorimotor neuropathy caused by extensive widespread vasculitis (approximately 30%). This presentation of vasculitic neuropathy can be difficult to distinguish from other types of distal axonopathies and requires a high index of clinical suspicion. A detailed history may indicate that the neuropathy began focally and then followed a course of step-wise progression of deficits before becoming generalized. Initially, acute onset of deep-seated proximal pain in the affected limb is common. Burning pain, sensory loss, and weakness in the distribution of affected nerves develop over several days. However, a more chronic and indolent course with progressive deficits is not uncommon.

Laboratory Features

The laboratory evaluation of patients with suspected vasculitis should be directed toward identifying an underlying disorder or documenting serological abnormalities that may point to a specific vasculitic syndrome. These studies should include sedimentation rate, complete blood count with total eosinophil count, renal function, urinalysis, hepatic enzymes, rheumatoid factor, antinuclear antibody, extractable nuclear antigens, serum complements, antineutrophilic cytoplasmic antibodies, cryoglobulins, hepatitis B antigen and antibody, and hepatitis C antibody. Antineutrophilic cytoplasmic antibody (ANCA) is helpful in the diagnosis of Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis. Two types of ANCA can be detected with indirect immunofluorescence by using alcohol fixed neutrophils as substrate, producing two major staining patterns: cytoplasmic (c)-ANCA and perinuclear (p)-ANCA. c-ANCA directed against the neutrophil proteinase 3 (PR3 ANCA), is strongly (75-90%) associated with Wegener's granulomatosis. p-ANCA directed against the neutrophil en/.yme myeloperoxidase (MPO-ANCA) is found with variable frequency (5-50%) in microscopic polyangiitis, Churg-Strauss, and Wegener's granulomatosis.

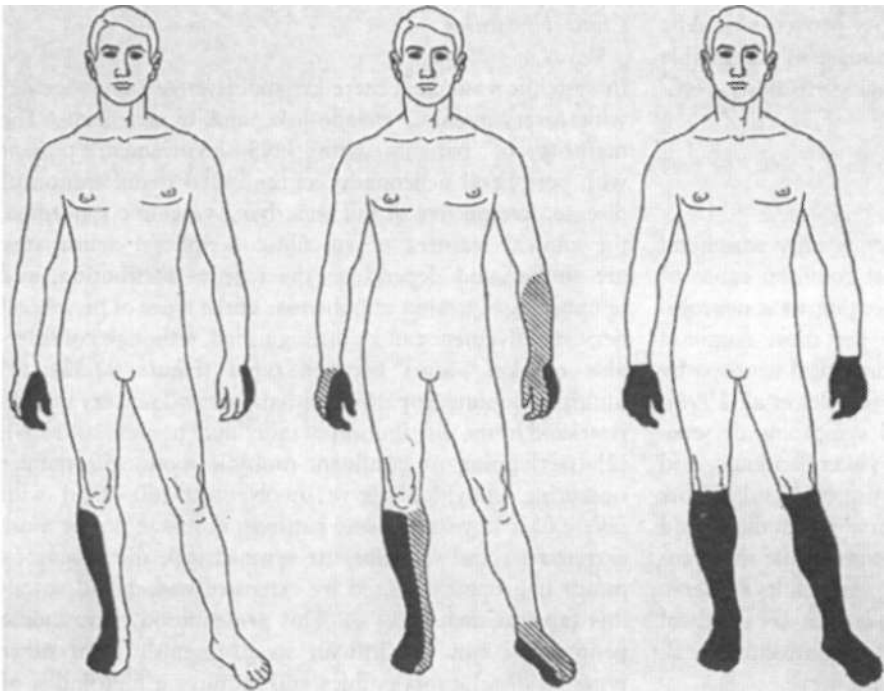


FIGURE 8232 Clinical patterns of neuropathic involvement in vasculitic neuropathy. The left figure illustrates multiple mononeuropathies or mononeuritis multiplex; the middle figure illustrates overlapping mulriple mononeuropathies obscuring individual nerve involvement; the right figure illustrates symmetric;!I sensorimotor polyneuropathy resulting from extensive proximal ischemic nerve lesions. (Reprinted with permission from Mendel!,]. R., Barohn, R. J., Bosch, E. P.,et al. 1994, "Continuum-peripheral neuropathy," *Am Acad Neurol,* vol. 1, p. 31.)

Electrodiagnostic studies are helpful in establishing the pattern of involvement and in documenting axonal nerve damage. Careful study may reveal that what clinically appeared to be a symmetrical polyneuropathy may in fact be an asymmetrical neuropathy, resulting from overlapping mononeuropathies. Nerve conduction studies rcve.il low-amplitude SNAPs and CMAPs in a multifocal distribution with normal or minimally reduced conduction velocities. Partial motor conduction block may be seen transiently with acute nerve infarcts. F.Y1G demonstrates more wide-Spread denervation than anticipated clinically. A definite diagnosis of vasculitis depends on confirmation of vascular lesions in nerve or muscle biopsies. Combined muscle and cutaneous nerve biopsies have been advocated as a way to increase the diagnostic yield. Of the cutaneous nerves suitable for biopsy, the superficial peroneal nerve is preferred because a simultaneous peroneus brevis muscle biopsy can be obtained through the same incision. In a cohort of patients with clinically suspected vasculitis the estimated sensitivity of a positive superficial peroneal nerve/ peroneus brevis muscle biopsy was 60% and increased to 86% if pathological features suggestive of vasculitis were included (Collins et al. 2000). A pathological diagnosis of vasculitis requires the presence of transmural mononuclear inflammatory cells and vessel wall necrosis (Figure 82.33). Cellular infiltrates are composed predominant];, of 1" cells and macrophages. Vascular deposits of immunoglobulins and complement including membrane attack complex can be demonstrated by immunostaining in more than 80% of cases. The nerve itself characteristically shows selective fascicular involvement with extensive liber loss or renin focal subfascicular or central fascicular loss of fibers with acute axonal degeneration. Osmicatcd teased fiber preparations demonstrate fibers at various stages of axonal degeneration,

Treatment

In systemic necrotizing vasculitis, disease activity must be suppressed rapidly to limit ongoing organ and nerve damage. Such patients are treated with a combination of prednisone and a cytostatic agent (usually cyclophosphamide). Treatment is started with daily prednisone (1 mg/kg per day) together with either oral cyclophosphamide at 2 mg/kg of body weight per day, or intravenous cyclophosphamide at 0.5 g/m body surface area per month, adjusted upward to 1 g/m on the basis of the patient's leukocyte count. For all but the most fulminant cases, cyclophosphamide should be started at a lower dose and worked up to the full dose over 3-6 weeks; the goal is to lower the total lymphocyte count to 750/mm^3. In fulminant cases, corticosteroids may be initiated by giving intravenous methylprednisolone (500-1000 mg) daily for 3 days followed by oral prednisone. The role of plasmapheresis in the management of severe vasculitis remains controversial but may provide additional benefit in patients with life-threatening disease (Allen and Bressler 1997), Cyclophosphamide is associated with substantial toxicity including bone marrow suppression, life-threatening infections, hemorrhagic cystitis, infertility, myeloproliferative disease, and bladder cancer. From the onset of treatment, complete blood cell counts should be monitored frequently. The dose of cyclophosphamide should be adjusted to maintain the total leukocyte count above 3000 per pi, and the total neutrophil count greater than 1500 per pi. Liberal fluid intake and frequent voiding may lessen the risk of

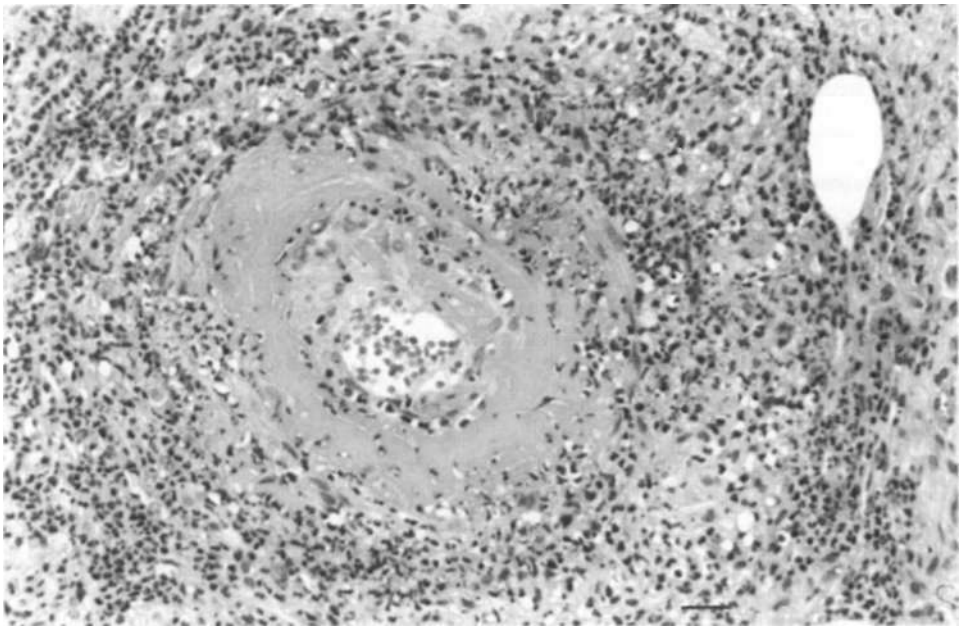


FIGURE 82.33 Sural nerve biopsy from patient with systemic vasculitis. A medium-si zed epineurial blood vessel with fibrinoid necrosis of its wall and perivascular and transmural mononuclear cell infiltration is shown. (Hematoxylin and cosin, x75; bar = 25 urn.)

hemorrhagic cystitis. Urine should be monitored for the presence of microscopic hematuria. Once clinical remission is achieved, prednisone can be tapered over a period of 4-6 weeks to a dosage of 1 mg/kg every other day. Patients are kept on both drugs until significant improvement occurs, at which time prednisone is gradually tapered further. Cyclophosphamide is maintained for 1 year after the disappearance of all traces of disease activity. In patients with non-life-thrcatening vasculitis prednisone given together with methotrexate (20-25 mg per week) has been found effective. Methotrexate may also be useful in maintaining remission. Combination immunosuppressive therapy results in an 80-90% remission rare in Wegener's granulomatosis and systemic necrotizing vasculitis. Physical and occupational therapy is indicated to optimize activities of daily living. Meaningful recovery has been reported in 60% at 6 months and 86% of patients at 1 year. Long term treatment results may be complicated by chronic sequelae from organ damage, disease relapses, and medication side effects. High dose prednisone is often adequate in patients with nonsystemic vasculitic neuropathy.

Rheumatoid Arthritis

Peripheral neuropathy occurs in 1-10% of patients with rheumatoid arthritis. At least four distinct types of peripheral neuropathies are seen in association with rheumatoid arthritis: (1) compression neuropathies, often found with early disease and caused by periarticular inflammation and fibrosis; (2) a distal, symmetrical, sensory polyneuropathy, possibly related to occlusive vasculopathy; (.3) mononeuropathy or multiple mononeuropathies; and (4) a severe fulminating sensorimotor polyneuropathy, both caused by rheumatoid vasculitis.

Compression neuropathies in rheumatoid arthritis occur as a result of joint deformity or, on rare occasions, rheumatoid nodules. Treatment includes splint applications, local corticosteroid injection, or surgical decompression.

A symmetrical, predominantly sensory polyneuropathy causes dysesthesias, paresthesias, and loss of sensation in a patchy, stocking-glove distribution. It is not associated with severe active rheumatoid arthritis; most patients recover partially or completely. The pathogenesis is pootly understood. Ischemia caused by occlusive vasculopathy or low-grade vasculitis has been suggested as a possible :n;tl).i:iMii. IVcauso [In- (lrusLiiusis :•. j'.ciir: a 11 > good, no specific treatment is recommended.

Systemic vasculitis develops in the setting of severe chronic rheumatoid arthritis, characterized by severe joint deformities, rheumatoid nodules, and cutaneous vasculitic lesions such as digital ulcerations, purpura, and livedo reticularis. Rheumatoid vasculitis is the second most frequently identified cause of vasculitic neuropathy, because rheumatoid arthritis is a common disorder affecting 2-5% of the general population. Acute mononeuropathy, mononeuropathy multiplex, and a distal symmetrical sensorimotor polyneuropathy develop as a result of widespread vasculitis. In contrast to other connective tissue disorders, cranial nerve involvement is rare.

The sedimentation rate and rheumatoid factor titer are always elevated. The C4 complement level is frequently low. Cutaneous nerve or muscle biopsy demonstrates a necrotizing vasculitis. The development of systemic vasculitis confers ;i poor prognosis in rheumatoid arthritis, with a reported 5-year survival rate of 60% (Puechal et al. 1995).

Treatment should be started with high-dose prednisone and oral cyclophosphamide. Early aggressive intervention may arrest the progression of neuropathy.

Systemic Lupus Erythematosus

CNS manifestations arc more prevalent than those of the PNS in systemic lupus erythematosus. Peripheral neuropathy develops in 6-21% of patients; the higher frequency is tuji'.J by usmg i| nan nun i\c sensory testing confined with extensive nerve conduction studies. A symmetrical, subacute, or chronic axonal polyneuropathy with predominant sensory symptoms is most common. Mononcuropathies of limb or cranial nerves, brachial plexopathy, and GBS or CIDP have occasionally been described in association with systemic lupus erythematosus. The basis for such associations is unknown but specific autoantibodies against peripheral nerve antigens or an immune-media ted vasculitis arc proposed pathogenetic mechanisms.

In sural nerve biopsy specimens, perivascular inflammatory cell infiltration is seen around cpincurial vessels, but only occasionally is there definite vasculitis. Immune complex deposition leading to vasculitis is the presumed cause of nerve damage.

If the polyneuropathy associated with systemic lupus erythematosus results in significant disability, immunosuppressive treatment should be considered. In patients with proven vasculitis, treatment with plasmapheresis, prednisone, and cyclophosphamide has led to improvement.

Systemic Sclerosis

Systemic sclerosis (scleroderma} is a connective tissue-disease characterized by excessive deposition of collagen. It affects the skin, gastrointestinal tract, lungs, heart, and kidneys. Neurological complications are uncommon, consisting mainly of myopathies. Peripheral nerve involvement unexplained by gastrointestinal or renal complications is rare. Peripheral sensorimotor neuropathy, isolated trigeminal neuropathy, and mononeuropathy related to carpal and cuhir.il tunnel syndromes have been reported. Multiple mononeuropathies are seen with greater frequency in CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclcrodactyly, and telangiectasia) syndrome than in control subjects. Frank vasculitis, perivascular inflammation, and multifocal fiber loss is found in sural nerve biopsy specimens of CREST patients with multiple mononeuropathies (Dyck, Hunder, and Dyck 1997).

Sjogren's Syndrome

Sjogren's syndrome is an autoimmune disorder of exocrine glands characterized by diminished lacrimal and salivary gland secretion resulting in dry eyes and dry mouth (sicca complex). The sicca complex is related to lymphocytic and plasma cell infiltration and destruction of lacrimal and salivary glands. Sjogren's syndrome occurs as a primary or secondary disorder in association with other connective tissue disorders. Peripheral nerve involvement occurs in 10-32% of patients with primary Sjogren's syndrome and has a strong predilection for women (9 to 1), Neuropathic symptoms often precede and overshadow the sicca symptoms and may be the major presenting complaint (Grant et al. 1997). A distal symmetrical sensory neuropathy with mixed large and small fiber deficits is the most common presentation. Less common patterns of nerve involvement include sensorimotor neuropathy, polyradiculoneuropathy, multiple mononeuropathies, painful dorsal root ganglionopathy, and trigeminal sensory neuropathy. A distinct subgroup of patients with sensory ataxic neuronopathy presents with loss of kinesthesia and proprioception caused by an inflammatory sensory polyganglionopathy (Figure 8234).

Laboratory abnormalities include elevated sedimentation rate, positive rheumatoid factor, and hypergammaglobulinemia. Antibodies to extractable nuclear antigens (especially SS-A) considered to be the most specific serological test for Sjogren's syndrome are less common in patients with neuropathy. The diagnosis depends on specific inquiry about sicca symptoms and ophthalmological tests for keratoconjunctivitis sicca (e.g., Rose Bengal staining of the cornea or Schirmer test: <5 mm wetting of a paper strip at 5 minutes). When an abnormal test result is found, a minor salivary gland biopsy of the lower lip showing chronic lymphocytic infiltrates is helpful for confirmation. Diagnostic criteria for Sjogren's syndrome have been proposed (Fox, Tornwall, and Michclson 1999). Reduced or absent SNAPs and normal or only mildly abnormal motor conduction studies are typical findings. High intensity lesions of the posterior columns may be detected on l'2-weighted MRI of the cervical cord in patients with sensory g.uiglionopathy (Mori et al, 2001). Sural nerve-biopsy frequently shows nonspecific perivascular lymphocytic (T cell) infiltrates together with diffuse decrease in myelinated fibers. Vasculitis is rarely found in patients with multiple mononeuropathies.

The role of immunosuppressive therapy is uncertain. Treatment recommendations arc based on small retrospective, uncontrolled series or individual case reports. Most reporl some inipiovrnvm w ith the use or ennicoste roids, either alone or in combination with immunosuppvs.s:ir.:s. nruir;ili/ing antibodies to tumor necrosis factor-ur, or intravenous immunoglobulin.

Trigeminal Sensory Neuropathy

Slowly progressive trigeminal sensory neuropathy is characterized by advancing unilateral or bilateral facial

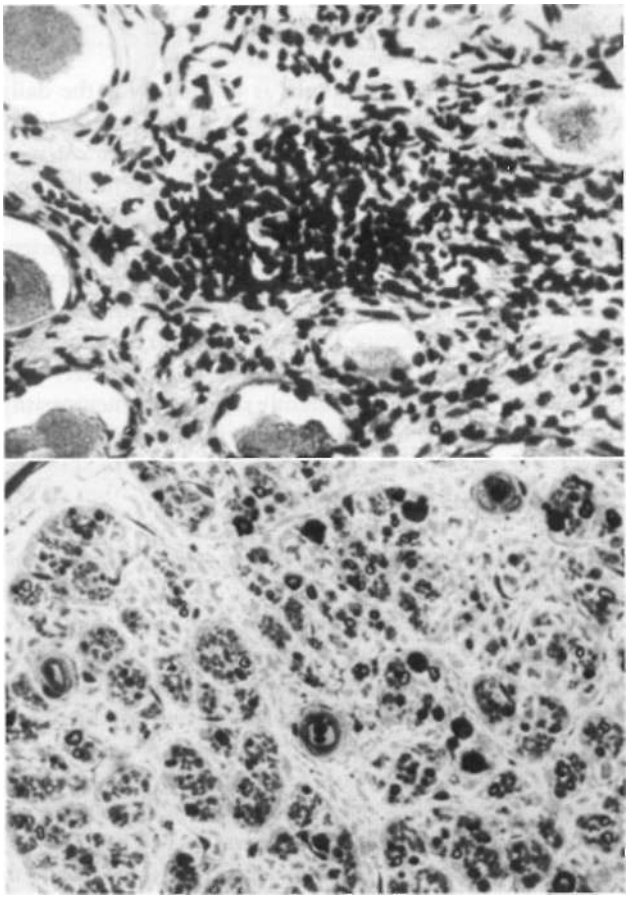


FIGURE 82.34 Thoracic dorsal root ganglion and sural nerve biopsies from patient witli Sjogren's syndrome and nonmalignant inflammatory sensory polyganglionopathy. In the upper panel, a prominent mononuclear cell infiltrate is seen adjacent to neuronal cell bodies, (Hematoxylin and eosin, x25.) The lower panel illustrates the sural nerve in the same patient showing marked decrease in fiber density and abnormality in size distribution of myelinated fibers. (Paraphenylenediamine-srained semithin epoxy section, x2.5.) (Reprinted with permission from Smith, B. E. 1992, "Inflammatory sensory polyganglionopathies," *Neurol Clin,* vol. 10, pp. 735-759.)

numbness. An association has been reported with several Lonnecme tissue diseases, including systemic sclerosis, mixed or undifferentiated connective tissue disease, Sjogren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, and dermatomyositis. Sensory loss begins in perioral and cheek areas and is often associated with painful paresthesia. The frequent bilateral involvement (70%), sparing of muscles of mastication, and negative neuroimaging study results help to distinguish this condition from other causes of facial numbness. Disfiguring neuropathic ulceration of the nares may occur. The trigeminal blink reflex study confirms an afferent lesion that is detected by delayed or absent ipsilateral R1 and bilateral R2 responses in 50% of patients. The precise etiology of this presumed immune-mediated cranial sensory ganglionopathy remains unclear. Immunosuppressive therapy is not recommended in isolated trigeminal sensory neuropathy.

Other causes of trigeminal neuropathy are acute toxic reactions to trichloroethylene and the "numb chin" syndrome associated with a carcinoma or leukemia (sec Chapter 76),

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder involving lung, lymph nodes, skin, and eyes. Neurological involvement (ncurosarcoidosis) occurs in approximately 5% of patients, and 6-18% of neurological manifestations arc caused by various forms of peripheral neuropathy (Scott 1993). Cranial neuropathies, particularly facial nerve palsy, are the most common neurological manifestations (73%). PNS involvement includes multiple mononeuropatlnes, bilateral phrenic nerve palsies, truncal sensory mononeuropathies, acute polyradiculoneuropathy resembling GBS, cauda equina syndrome, and chronic symmetrical sensorimotor neuropathy. The latter can produce severe wrist extensor and foot dorsiflexor weakness, and distal sensory loss in the legs. Neurological manifestations may be the presenting feature in more than 50% of cases or may develop at a time when there is little evidence of systemic sarcoidosis.

Electro diagnostic studies show evidence of axonal degeneration. Sarcoid granulomas may be seen in muscle and sural nerve biopsy specimens. The nerve damage has been attributed to granulomas and angiitis of vasa nervorum producing axonal degeneration (Said et al. 2002). Inflammatory changes in the CSF (such as pleocytosis, increased protein level, elevated IgG index, and occasionally hypoglycorrhachia) imply granulomatous lep-[omciiim;eal involvement. Gallium scanning is ohm UMILLI in the search for systemic involvement. An elevated scrum angiotensin-converting enzyme level may suggest active systemic sarcoidosis. Biopsies of lymph nodes, muscle, or conjunctiva or bronchoalvcolar lavage may be needed to obtain tissue for histological confirmation, because all the other tests are nonspecific.

The response to corticosteroid therapy in sarcoid neuropathy is generally favorable. In patients refractory to corticosteroids, cyclosporine, cyclophosphamide, or azarhioprine may be used as adjunctive therapy (Agbogu et al. 1995).

Alcoholic Neuropathy and Nutritional Deficiencies

Alcoholic Neuropathy (See also Chapter 63)

Alcoholic neuropathy is one of the most common peripheral neuropathies seen in general practice. Covert

alcoholism may only be uncovered by a focused history provided by family members. A close association between alcoholic neuropathy and nutritional deficiency is well established.

Clinical Features. The symptoms of alcoholic neuropathy-begin insidiously and progress slowly. Muscle weakness begins distally and spreads to more proximal muscles. Gait difficulty, weakness, and muscle cramps are common. Sensory loss and burning paresthesias are frequent. Hyperpathia and dysesthesias are troublesome in many patients. The legs are always more affected than the arms. Distal muscle wasting, loss of tendon reflexes, and sensory-loss of all modalities in a stocking-glove distribution are common. In advanced cases, sensory ataxia caused by loss of joint position sense may coexist with alcoholic cerebellar ataxia.

F.lectrodiagnostic studies show a predominantly axonal sensorimotor polyneuropathy. NCVs are only slightly diminished. Low-amplitude or absent SNAPs are common. EMG shows active denervation with chronic reinnervation in distal muscles. Sural nerve biopsy specimens demonstrate loss of nerve fibers of all sizes. Acute axonal degeneration is particularly common in patients after binge drinking, whereas axonal regeneration is frequently seen in chronic alcoholism.

Etiology. Deficiency of thiamine and other B vitamins, caused by inadequate dietary intake, impaired absorption, and greater demand for thiamine to catalyze the metabolism of the alcohol, is the major cause of polyneuropathy in alcoholic patients.

Treatment. Abstinence from alcohol, expert counseling, and a nutritionally balanced diet constitute the principal therapy. Supplementation with thiamine and other B vitamins is important. In patients with significant gastrointestinal symptoms, parenteral vitamin treatment is initially required. Improvement in the polyneuropathy may be very slow, because it requires axonal regeneration. For the management of painful alcoholic neuropathy, see the earlier section on neuropathic pain.

Niacin Deficiency (Pellagra Neuropathy)

Dietary deficiency of nicotinic acid (niacin) produces the syndrome of pellagra. Pellagra affects the gastrointestinal tract, skin, and nervous system resulting in the triad of dermatitis, diarrhea, and dementia. A distal sensorimotor polyneuropathy develops in 40-56% of patients with pellagra, and if diarrhea and skin changes are absent is clinically indistinguishable from rhiamine-deficiency neuropathy, Nonendemic pellagra rarely occurs in patients with alcoholism or malabsorption. Oral nicotinic acid is sufficient to treat symptomatic patients.

Pyridoxine (Vitamin BJ Deficiency

The regular diet of most adults is adequate for the daily-requirement of J.5-2.0 mg of vitamin B_6. Isolated pyridoxine deficiency, however, may occur during treatment with Lsoniazid (INH), hydralazine, or, rarely, penicillamine. These drugs structurally resemble vitamin B_{fi} and interfere with pyridoxine coenzyme activity, vitamin B^-deficient peripheral neuropathy is characterized by distal sensory and motor deficits of insidious onset. When using INH, supplementary pyridoxine (100 mg daily) is recommended. Paradoxically, high dose (500 mg/day and greater) pyridoxine may cause a predominantly sensory polyneuropathy (sec Toxic Neuropathies, later in this chapter).

Folate Deficiency Polyneuropathy

Folate deficiency may cause an axonal sensory polyneuropathy, characterized clinically by loss of joint position and vibratory sense and absent tendon reflexes. In addition, there may be evidence of spinal cord involvement, with spasticity of the legs and extensor plantar responses. In severe cases, encephalopathic symptoms may predominate. Macrocytic anemia is an important clue to either folate or vitamin B^ deficiency. Coexisting vitamin B12 deficiency must be excluded because in such cases folate therapy without cobalamin replacement may exacerbate neurological manifestations. Patients have been reported with neurological disease indistinguishable from subacute combined degeneration who rapidly responded to folate replacement.

Vitamin B_{lz} Deficiency Polyneuropathy: Subacute Combined Degeneration

Cobalamin (vitamin B_{12}) and folate are essential vitamins necessary for effective DNA synthesis. Animal products (meat, poultry, fish, and dairy products) are the primary dietary source of cobalamin. The average Western diet provides an excess of the vitamin (daily requirement, *3-9* ug), which is stored in the liver. Within the acid environment of the stomach cobalamin is released from dietary proteins. Free cobalamin initially binds to gastric glycoproteins known as R-binders. In the duodenum the cobalamin-R-binder complexes are degraded by pancreatic enzymes, The released cobalamin then binds avidly to intrinsic factor, a 60-kD glycoprotein produced by gastric parietal cells. The vitamin B^-intrinsic f_{ac}ror complex is absorbed by means of binding to intrinsic factor receptors in the terminal ileum. Malabsorption of cobalamin in patients with pernicious anemia is the result of intrinsic factor deficiency caused by-progressive autoimmune destruction of parietal cells from the gastric mucosa. Acquired malabsorption of vitamin B12 may occur also following gastric and terminal ileal resection and in the setting of a wide range of gastrointestinal disorders. Unusual causes include dietary insufficiency in

strict vegetarians (vegans) and intestinal infection with fish tapeworms. Intraoperative use or recreational abuse of nitrous oxide, which inactivates cobalamin-dependent enzymes, may cause neurological manifestations, particularly in patients with marginal cobalamin stores. Intracellular^, cobalamin is converted into two coenzymes required for the formation of methionine and succinyl-CoA synthesis. Reduced methionine synthesis may be responsible for the neurological manifestations of cobalamin deficiency.

Population surveys estimate that 2% of persons 60 years and older have undiagnosed pernicious anemia. The disease is especial!; common in Northern buropcans and blacks. The full-blown clinical picture of vitamin B12 deficiency consists of macrocytic anemia, atrophic glossitis, and peripheral and central neurological complications (Toh, Van Oriel, and Glecson 1997}. The latter include peripheral neuropathy and optic atrophy, as well as lesions in the posterior and lateral columns of the spinal cord (subacute combined degeneration) and in the brain. The peripheral neuropathy results in paresthesias and large fiber modality sensory loss (vibration and proprioception). The spinal cord manifestations consist of posterior column damage, which may include a sensory level, and upper motor neuron defects causing limb weakness, spasticity, and extensor plantar responses. Cerebral involvement ranges from subtle behavioral changes and forgetfulness to dementia or stupor. An unsteady gait, positive Romberg sign reflecting a sensory ataxia, diffuse hyper-reflexia, and absent ankle jerks should raise [lie suspicion of cobalaiiiini deficiency.

Nerve conduction studies show low-amplitude or absent SNAl's. Conduction velocities are normal. CNS involvement is suggested by abnormal visual and somatosensory evoked potential study results and is occasionally documented by symmetrical dorsal column lesions on cervical MRI. Evidence of axonal degeneration is found in sural nerve biopsy specimens. The diagnosis is confirmed by low serum vitamin B12 levels (<170 pg/mL) and normal serum folate concentration. Approximately 30-40% of patients with neurological symptoms caused by vitamin B_{12} deficiency have borderline low levels of 150-200 pg/mL. hi as many as 30% of patients, megaloblastic anemia with elevated red cell mean corpuscular volume (>94 fl) may be absent. Elevated serum methylmalonic acid and homocysteine levels, which are the substrates for cobalamin-dependent enzymes, are helpful when there is diagnostic uncertainty (Chanarin and Metz 1997). The two-part Schilling tests confirm that vitamin B_{12} deficiency is the result of intestinal malabsorption and is caused by intrinsic factor deficiency. Antibodies to intrinsic factor are found in 70% of patients with pernicious anemia; antiparietal cell antibodies arc more sensitive (90%) but lack specificity.

Initial treatment consists of daily intramuscular injections of 1 mg of cyanocobalamin or hydroxocobalamin in the first week, followed by weekly injections, until a series of 12 doses is completed. Then maintenance schedules of monthly injections of 100 ug or 1000 wg every 3 months has been found satisfactory in preventing relapses (Savage and Lindenbaum 1995). This treatment corrects the anemia and may reverse the neurological complications completely if given soon after their onset. Major neurological improvement can be expected to occur during the first 3-6 months of therapy. For maintenance therapy, oral administration of vitamin BQ is feasible in compliant patients, because 1% of vitamin $B|_2$ is absorbed without intrinsic factor mediation. The initial severity of neurological deficits, duration of symptoms, and hemoglobin level before treatment correlate with neurological outcome. The inverse correlation between degree of anemia and neurological damage is not understood.

Vitamin E Deficiency

Significant vitamin E deficiency is seen in children and young adults with chronic severe intestinal fat malabsorption, as occurs in cholestatic liver disease, cystic fibrosis, celiac disease, following extensive intestinal resections, and in the inherited disorder of abeta lipoprotein em i a (see Hereditary Neuropathies, earlier in this chapter). Rarely, vitamin E deficiency develops in the absence of fat malabsorption (Jackson, Amato, and Barohn 1996). Isolated familial vitamin *E* deficiency is an autosomal recessive disorder in which mutations in the ^-tocopherol transfer protein gene cause failure to incorporate *a*-tocopherol into very-low-density lipoprotein in the liver. Prolonged vitamin E deficiency of any cause may lead after years to a spinocerebellar syndrome with a large fiber sensory neuropathy, ataxia, proprioceptive loss, areflexia, ophthalmoplegia, and pigmentary retinopathy that may be indistinguishable from Friedreich's ataxia. Myopathy and peripheral nerve disease may predominate in some cases. In adults with chronic cholestasis it may take 2 years to deplete vitamin E stores and an additional 5-10 years to develop neurological complications.

Vitamin E deficiency results 111 a central and peripheral distal axonopathy of large-caliber axons affecting peripheral nerves and the posterior columns of the spinal cord. Lipofuscin-like accumulations are found in the Schmidt-La ntennaim clefts of large diameter myelin sheaths in sural nerve biopsy specimens. Impaired antioxidant protection may account for neurological and retinal lesions in long-standing deficiency. Electtopbysiological study results show normal NCVs and low-amplitude or absent SNAPs. vitamin E deficiency is established by low fasting plasma levels of vitamin E (<5 ug/mL). Laboratory studies used to confirm fat malabsorption include 72-hour fecal fat determination, vitamin A and D levels, amylase, liver function tests, peripheral blood smear to search for acanthocytes (present in Bassen-Kornzweig syndrome), and apolipoprotein B level.

Vitamin E supplementation is indicated regardless of etiology in all patients with low serum vitamin E levels.

Oral supplementation with vitamin E in large doses (initially 400 mg twice daily and up to 100 mg/kg per day) may result in neurological improvement ot cessation of further deterioration. If no absorption can be documented after large oral doses of standard vitamin E, a water-soluble form of tocopherol is recommended.

Neuropathy Associated with Malabsorption Syndromes

Intestinal malabsorption may lead to myopathy or periph-;T.I! neuropath). A can till search tor n u n iii.il.il^oi-prion or celiac disease should be part of the routine investigation ;il ;li]v;i: Mr, Willi neuromuscular disease oi obscure cause, particularly in patients with ataxia and peripheral neuropathy. Celiac disease (CD) or gluten-sen si five enteropathy is characterized by malabsorption due to inflammatory injury to the mucosa of the small intestine after ingestion of wheat gluten in genetically predisposed individuals. More than 90% of patients with CD express the human lymphocyte antigen HLA-DQ2 or DQ8, Patients with or without gastrointestinal symptoms may rarely (5-8%) develop varied neurological complications including a predominantly sensory axonal neuropathy, multiple mononcuropathies, cerebellar ataxia, myopathy, and encephalopathy (Hadjivassiliou, Griinewald, and Davie-Jones 2002). The cause of PNS involvement is poorly understood. Earlier studies have implicated vitamin deficiencies {B_{12}, E, D, folic acid, or pyridoxine). However, vitamin replacement rarely improves neurological deficits. Immunological factors have been proposed in patients without vitamin deficiencies and are supported by the common association of CD with other autoimmune disorders. The diagnosis is facilitated by highly sensitive and specific serological markers (antiendomysial and tissue transglutaminase antibodies) and established by small bowel biopsy. A strict gluten-free diet may stabilize the neurological disease process.

Severe sensorimotor or predominantly sensory neuropathies with ataxia or burning feet may occur in starvation. After gastric partitioning proccdutes for morbid obesity, the patients at risk for developing neurological complications are those with accelerated weight loss and frequent vomiting in the postoperative period.

Uremic Neuropathy

Peripheral neuropathy develops in 60% of patients with end-stage renal failure who require chronic dialysis. Severe uremic neuropathy has become less common as a result of earlier treatment with dialysis and renal transplantation.

Utcmic neuropathy is inexplicably more common in men than in women. The clinical features are those of a slowly progtessive, predominantly sensory polyneuropathy. Severe pains arc unusual, but cramps, unpleasant dysesthesias, and restless legs are common symptoms. Neurological signs include distal sensory loss, especially of vibratory sensation, absent reflexes, and symmetrical toe-extensor weakness. On occasions, .i rapidl; progressive, predominantly motor polyneuropathy mimicking GBS may develop during the initial weeks of dialysis. Such a fulminant severe neuropathy is also seen in the setting of concurrent critical illness or diabetes mellitus. An unusual feature of these cases is the relative absence of denervation potentials in clinically weak muscles on needle EMC. Some patients have improved by switching from conventional to high-flux hemodialysis, possibly related to enhanced removal of advanced glycosylation products (Bolton et al. 1997).

Chronic renal failure and the commonly associated malnutrition render peripheral nerves susceptible to compression neuropathies, such as the ulnar nerve at the elbow and the fibular nerve at the knee. Carpal tunnel syndrome may develop in more than 20% of patients on hemodialysis. Nerve compression from local edema secondary to the forearm arteriovenous shunts or ischemia from a fistula-induced vascular steal syndrome are likely mechanisms in the early course of dialysis. Patients on long-term hemodialysis may develop carpal tunnel syndrome because of the deposition of fo-microglobulin-derived amyloid in the carpal ligament. Ischemic monomelic neuropathy is an acute complication of the placement of a more proximal shunt between the cephalic vein and brachial artery; the monomelic neuropathy occurs mainly in diabetic patients with concomitant peripheral vascular disease. Ir is characterized by abrupt, painful sensory loss of the affected hand, and weakness of median, ulnar, and radial innervated distal muscles. Prompt sutgica! closure of the fistula is required to avoid permanent neurological deficits.

The diagnosis of uremic polyneuropathy should only be made in the context of chronic end-stage renal failure (creatinine clearance <10 mlVminute) of at least several months' duration. Drug toxicity or other systemic diseases, such as diabetes mellitus, vasculitis, or amyloidosis that may affect both kidneys and peripheral nerves, must first be excluded. CSF protein is often elevated, but rarely beyond 100 mg/dl.. Generalized slowing of motor and sensory NCVs is common, and distal latencies are prolonged. Late responses (H-reflex and F-wave latencies) become abnormally prolonged early in the course of chronic renal failure at a time when motor conduction velocities are still normal. EMG examination shows evidence of active denervation in distal foot muscles. Regular hemodialysis rarely improves impaired conduction velocities in patients despite clinical improvement. Sural nerve biopsy shows axonal loss of large myelinated fibers and segmental demyelination. Morphometry; investigations led to the conclusion that the segmental demyelination is secondary to primary axonal arrophy.

Occasionally exacerbation of the neuropathy occurs in patients with chronic renal failure at the onset of hemodialysis. Acute fluxes of water and solutes may be

the cause, and reduction in the intensity of dialysis is usually recommended.

The precise cause of uremic neuropathy remains unknown although a number of potential neurotoxins accummulate in end-stage renal disease (Gallassi et al. 1998). Ethylene oxide has been proposed as a contributing neurotoxin in patients on hemodialysis.

Treatment

Severe polyneuropathy in patients on chronic dialysis has become rare as a result of earlier initiation of treatment and improved techniques of hemodialysis using more biocompatible dialy/er membranes and high-flux dialyzers. Attention should be given to avoid drugs such as colchicine or nitrofurantoin, which arc potentially neurotoxic and may accumulate in renal insufficiency. Numerous investigations have been conducted to assess the long-term effects of hemodialysis on peripheral nerve function. A consensus has emerged that chronic hemodialysis will stabilize an existing uremic neuropathy in most patients. Manipulating the frequency or duration of dialysis may not alter its course. Chronic peritoneal dialysis provides no advantage over hemodialysis. Successful renal transplantation results in significant clinical, electrophysiological, and morphological recovery over a period of 3-12 months. However, renal transplantation may have little effect on the course of the neuropathy in diabetic patients with end-stage renal disease.

Peripheral Neuropathy in Liver Disease

Various peripheral neuropathies may develop as a direct consequence of acute and chronic liver disease. These disorders include cryoglobulinemia neuropathy linked to hepatatis C virus infection, vitamin E deficiency in chronic cholestatic liver disease, and neuropathies associated with end-stage liver disease and primary hilary cirrhosis. Viral hepatitis types A, B, and C have been reported as antecedent infections in Guillain-Barrc syndrome. Isolated cases of CI DP have been described in chronic hepatitis B and as a complication after orthotopic liver transplantation. Hepatitis B antigenemia is found in one third of patients with polyarteritis nodosa.

Although a clinically overt neuropathy is uncommon, electrodiagnostic studies arc frequently abnormal in patients with chronic liver disc-use. The highest frequency of neuropathy by clinical criteria (75%) and confirmed by electrophysiological studies in an even greater percentage (87%) was reported in a cohort of patients who were candidates for liver trans pi a nation for end-stage liver disease (lani et al. 1999). The neuropathy is not disabling and often remains clinically inapparent. Paresthesias in feet, distal loss of vibratory sensation, and loss of ankle reflexes are the most common findings. Electrophysiological abnormalities consist of reduced SNAPs and mild slowing of motor conduction velocities. Histological studies of the sural nerve show evidence of demyeIination and remyelination. A high incidence of autonomic dysfunction has been reported in patients with end-stage liver disease by means of formal autonomic testing. The presence of autonomic neuropathy in such patients has been associated with a five-fold increase in mortality over invi duals with normal autonomic function. Early liver transplantation should be considered for patients with autonomic neuropathy.

Patients with primary biliary cirrhosis may develop a sensory polyneuropathy or sensory ganglionoparhy. In a few patients with strikingly elevated serum lipid levels and cutaneous xanthomas, xanthomatous infiltration of cutaneous nerves has been found on nerve biopsy. In others an autoimmune process affecting sensory ganglia is suspected. The prevalence of associated autoimmune diseases is high in primary biliary cirrhosis, most notably Sjogren's syndrome, which in turn is linked to predominantly sensory neuropathies. Large fiber sensory neuropathies develop in children and young adults with chronic cholestatic liver disease and secondary vitamin E deficiency.

Endocrine Disorders Associated with Peripheral Neuropathy

Hypothyroid Neuropathy

Carpal tunnel syndrome is the most common peripheral nerve complication of hypothyroidism. One third of patients with hypothyroidism may have clinical evidence of a general polyneuropathy, which is predominantly sensory with paresthesias and muscle pain, distal sensory loss, and incoordination. Nerve conduction studies show absent or decreased SNAPs and slow motor conduction velocities. Sural nerve biopsy demonstrates deiiiyelin.itiou, remyelination, and increased glycogen and lysosomes in axonal and Schwann cell cytoplasm. Thyroid hormone replacement usually improves the neuropathy. Thyroid function studies should be checked in all patients presenting with carpal tunnel syndrome or a sensory polyneuropathy,

Acromegaly

Carpal tunnel syndrome is a well-recognized complication of acromegaly, but a generalized neuropathy also may develop independent of concomitant diabetes mellitus. Approximately one half of patients have distal paresthesias, sensory loss in a stocking-glove distribution, diminished muscle stretch reflexes, and distal muscle weakness. SNAPs are diminished and motor NCVs are slightly to moderately reduced. Nerve biopsy shows a reduced number of myelinated and unmyelinated fibers, and enlargement of nerve fascicles because of an increase in endoneurial and subperincurial tissue.

Hypoglycemic Amyotrophy

Primary hypoglycemia caused by an insulinoma may cause slowly progressive distal muscle atrophy and weakness. Painful paresthesias are common, but there are usually no objective signs of sensory loss. The amyotrophy may precede the onset of typical recurrent hypoglycemic episodes by a few years. Electrodiagnostic studies show evidence of acute denervation and reinncrvation.

Ischemic Monomelic Neuropathy

Ischemia caused by acute thromboembolic occlusion of major limb arteries or proximal arteriovenous shunt placement infrequently causes multiple axonal mononeuropathies that develop disrally in the ischemic limb (ischemic monomelic neuropathy). Abrupt lightning or burning pains affect the involved extremity. Sensory examination shows a graded impairment of all modalities, particularly those mediated by largc-dia merer fibers. Muscle strength is usually maintained, although distal weakness may often develop in severe cases. Tendon reflexes may be preserved.

Electro diagnostic studies provide evidence of multiple axonal mononeuropathies in the involved ischemic limb. SNAPs are either absent or markedly reduced in amplitude, and motor conduction velocities are slowed. Acute denervation is limited to very distal extremity muscles. Both large and small fibers appear to be affected equally.

Surgical endarrerectomy or bypass surgery may result in recovery ot neurological deficits in ,1 period of several months, even in long-standing ischemic neuropathy. Ischemic monomelic mononeuropathy following shunt placement demands immediate surgical closure of the arteriovenous fistula.

Severe aortoiliac occlusive disease or prolonged use of an intra-aortic balloon pump may occasionally lead to proximal sciatic and femoral nerve or lumbosacral plexus lesions.

Peripheral Neuropathy in Chronic Obstructive Lung Disease

Approximately 20% of patients with chronic obstructive lung disease may develop a mild, distal sensorimotor polyneuropathy that appears to be correlated with severe hypoxemia.

Critical Illness Polyneuropathy

Critical illness polyneuropathy is a common problem in intensive care units (ICU). The neuromuscular syndrome of acute limb and respiratory weakness after admission to the ICU tends to be underappreciated. It is a major cause of difficulty in weaning patients from the respiraror after cardiac and pulmonary causes have been excluded. Clinical evaluation of muscular weakness acquired in the intensive care unit is difficult because patients arc often cnccphalopathic or sedated, and the examination may be hindered by multiple lines required for intensive support. Most patients have generalized flaccid weakness with depressed tendon reflexes. Pain or paresthesias are not features of critical illness neuropathy. When prospectively investigated, at least 50% of critically ill patients admitted to intensive care units with sepsis and multiple organ failure for at least two wci-k- 11a •. i. i-li-Liruiliagiiostii features o] an axonal neuropathy.

Electrodiagnostic studies are necessary to establish the diagnosis. Nerve conduction studies reveal a distal axonal neuropathy with reduced CMAP and SNAP amplitudes, in conjunction with fibrillation potentials and decreased motor unit potentials on F.MG. CSF is almost always normal. Primary axonal degeneration, more severe distally than proximally, is seen at autopsy. The neuropathy is thought to be a complication of the systemic inflammatory response syndrome that is triggered by sepsis, severe trauma, ot burns. The pathophysiology of this syndrome is currently under intense investigation. Severe infections or trauma of any type appear to initiate a series of events that ultimately lead to impaired microcirculation and multiple organ dysfunction (Bolton 1995).

Critical illness myopathy is another cause of acquired weakness after admission to the intensive care unit and is difficult to distinguish clinically from its neuropathic counterpart. This complication usually occurs in patients with acute respiratory distress syndrome or severe asthma receiving intravenous corticosteroids, nondepolarizing neuromuscular blocking agents, or most commonly both. Plasma creatine kinase levels are transiently elevated. Muscle biopsy shows many fibers with loss of thick filaments (Lacomis et al. 1996). The presence of normal sensory conduction studies in the setting of small, short-duration, poly phasic motor unit potentials on EMG helps to support a diagnosis of critical illness myopathy. However, both conditions may occur concurrently. Severe weakness was found in 25% of consecutively admitted ICU patients who required mechanical ventilation. All patients had an axonal neuropathy on electrophysiological testing, and all patients who had a muscle biopsy had myopathic changes unrelated to denervation (De Jonghe et al. 2002). Repetitive nerve stimulation studies should be performed to exclude a defect of neuromuscular transmission caused by defective clearance of neuromuscular blocking agents.

Survivors recover spontaneously in 3-6 months following discharge from the intensive tare unit.

TOXIC NEUROPATHIES

Peripheral neuropathy is one of the most common reactions of the nervous system to toxic chemicals. Industrial. environmental, and biological agents; heavy metals; and

pharmaceutical agents are known to cause toxic neuropathies (see also Chapter 64). Medications, most notably anticancer drugs, are the leading offenders in clinical practice rod ay. Neurotoxic agents may produce distal axonal degeneration (axonopathy), nerve cell body degeneration (neuronopathy), or primary dcmyelination (myelinopathy) (see Pathological Processes Involving Peripheral Nerves, earlier in this chapter). For most toxic neuropathies the biochemical mechanisms underlying the pathogenesis of nerve damage remain poorly understood.

Most toxins produce symmetrical axona! degeneration in a dying-back pattern, beginning in the distal segments of long, large-caliber nerve fibers, eventually spreading proximally with continued exposure. A number of toxic axonopathies also affect the central nervous system with concurrent degeneration of dorsal column projections of sensory neurons and optic nerve axons. Central axon involvement has been linked to incomplete clinical recovery. Agents such as n-hexanc and organophosphates cause simultaneous degeneration of peripheral nerve, dorsal column, and corticospinal pathways, often resulting in spasticity, which may become apparent following recovery from the peripheral axonopathy. Electrophysiological investigations typically disclose an axonal pattern on nerve conduction studies.

The second type of toxin-induced injury targets nerve cell bodies such as the dorsal root ganglion cell. Cisplatm, methyl-mercury compounds, high-dose pyridoxine, and doxorubicin are examples of toxins that produce neuronal degeneration. When the neuronal insult leads to apoptosis and cell death, the resulting sensory neuropathy is often severe and irreversible with limited functional recovery.

Primary demyelination is a less common mechanism in toxic neuropathy hut occurs with diphtheria; buckthorn toxin; and exposure to perhexiline, amiodarone, or suramin. Slowed nerve conduction velocities can also be seen in certain forms of hcxacarbon neuropathy, as in habitual glue sniffers.

To establish a causal link between a putative neurotoxin and neuropathy, the following two clinical criteria should be met:

1. Exposure can be verified and temporally related to the onset of clinical symptoms. Neuropathic symptoms usually occur concurrently with the exposure or following a variable latency of up to several months.
   There must be neurological signs and abnormal e lee trod i agnostic study results. Because many toxic neuropathies arc subclinical, there may or may not be subjective symptoms.
2. Removal from the exposure results in cessation of the progression of symptoms and deficits. This is variably followed by improvement, although in certain axonopathies cessation of exposure may be attended by a worsening of symptoms for up to 4 months (so-called "coasting") before recovery begins.

In addition, the clinician must recognize that certain factors may increase susceptibility to toxic neuropathy, These include pre-existing neuropathy (for instance, CMT), simultaneous use of multiple neurotoxic drugs or compounds, and systemic disorders which cause impaired drug metabolism (Chaudrey et al. 2003). Any of these may increase the risk and severity of toxic neuropathy.

A focused history probing for a background of occupational, environmental, or drug exposure is important. Most toxic neuropathies present clinically with length-dependent sensorimotor or purely sensory deficits. Autonomic dysfunction is rarely a prominent feature, though exceptions include acrylamide, cisplatin, and *Vinca* alkaloids. Predominantly motor toxic neuropathy is rare, being limited to dapsonc, lead, and organophosphate-induced delayed polyneuropathy. Rarely do typical pathological features such as neurofilamentous axonal swellings in hexacarbon neuropathy, axonal vacuolation in thallium, or lamellar Schwann cell inclusions in amiodatone and perhexiline intoxication allow specific identification of the cause by nerve biopsy.

The most important steps in treatment involve recognition of the offending agent and elimination of exposure.

Industrial and Environmental Toxins

Industrial and environmental agents that cause toxic neuropathies are discussed in Chapter 64 (see also Shaumburg and Kaplan *1995).*

Drug-Induced Neuropathies

Many medications can cause peripheral neuropathy, which is generally reversible when the offending drug is discontinued. If the causal relationship between a potentially neurotoxic drug and neuropathy is established, additional investigations to search for alternative etiologies may be unnecessary. Premedication with such compounds as ncurotrophins may in the future allow clinicians to blunt or prevent the dose-limiting neurotoxic effects of anticancer drugs. Ncurotrophins are naturally occurring polypeptides (e.g., NCF, neurotrophin-3, brain-derived NGF, and insulin-like growth factor-1) that play a role in nerve regeneration and demonstrate neuroprotective properties in experimental studies.

Awareness of the possibility of drug-induced peripheral nerve damage is important. A careful drug history including over-the-counter nutritional supplements and vitamin preparations should be obtained in every patient with polyneuropathy. Some of the drugs reported to produce pcriphetal neuropathy are listed in Table 82.28. Many anecdotal reports of neuropathy possibly induced by other drugs may represent coincidental occurrences and remain to be substantiated.

Tabic 82.28: Neuropathies caused by pharmaceutical drugs

Drugs	*Clinical and pathological features*	*Comment*
Antineoplastic		
Cisplarin	S, DA, N	Binds to DNA; disrupts axonal transporr?
Suramin	SM, DA, SD	DA: inhibits binding of growth factors; SD: immunomodulating effects?
Taxanes (paclitaxel docetaxel)	S, DA	Promote microtubule assembly; disrupr axonal Transport
Vincristine	S>M, M, DA	Interferes with microtubule assembly; disrupts axonal transport
Antimicrobial		
Chloroquinine	SM. DA	Myopathy
Daps one	M, DA	Oprk atrophy
[soniazid	SM, DA	Pyridoxine antagonist
Metronidazole	S, DA	
Nirrofurantoin	SM, DA	
Anriviral (NRTIs)		
Didanosine (ddl)	SM, DA	Reversible neuropathy
Fialuridine (FIAU)	S, DA	Irreversible neuropathy; also myopathy
Lamuvidine (3TC)	S, DA	Least common NRTI neuroparhy
Sravudine (d4T)	SM, DA	More associated with lipodystrophy syndrome
/...Aii;ibii!.- •:Lkk	SM, DA	Single tnosi neurotoxic NRTI
Zidovudine (AZT)	-	Myoparhy only
Cardiovascular		
Amiodarone	SM, SD	Lysosomal lamellar inclusions, myopathy
Hydralazine	SM, DA	Pyridoxine antagonist
Perhexiline	SM, SD	Lipid inclusions
Other		
Colchicine	SM, DA	Neuromyopathy, raised creatine kinase levels
Disulfiram	SM, DA	
Gold	SM, DA	Myokymia
Lipid-lowering agents (statins)	s\i. DA	May also cause rhabdomyolysis
Nitrous oxide	S, DA	Inhibits vitamin B^-dependent methionine synthase; myeloparhy
Phenytoin	SM, DA	Asymptomatic in most
Pyridoxine	S, N, DA	Doses >250 mg/day
Thalidomide	S, N	
[.-Tryptophan (tainted)	SM, DA	Eosinophilia-myalgia syndrome

CNS = ecntral nervous system-active drugs; DA = disral axonopathy; M = motor; N = ncuronopathy; NRTI = nucleoside analogue reverse transcriprasc inhihiror; S = sensory; SD = segmental demyelination; SM = sensorimotor neuropathy.

Amiodarone

Amiodarone is a class III antiarrhythmic drug used in the management of refractory ventricular arrhythmias. Adverse effects include thyroid abnormalities, photosensitivity dermatitis, corneal microdeposits, hepatic dysfunction, pulmonary fibrosis, and a dose-dependent polyneuropathy. Sensorimotor polyneuropathy may develop in patients receiving long-term amiodarone (400 mg per day) therapy. There is moderate sensory impairment and distal and sometimes proximal muscle weakness. Electrophysiological studies show mild slowing of nerve conduction velocities as well as distal denervation. Nerve biopsy demonstrates loss of myelinated and unmyelinated fibers, axonal degeneration, and segmental demyelination. A distinctive feature is the presence of lysosomal lamellar inclusions in Schwann cells, fibroblasts, and endothelial cells resulting from inactivation of the lysosomal enzyme sphingomyelinase.

Amphetamines and Cocaine

Abusers of amphetamines and cocaine may develop multiple mono neuropathies associated with a necrotizing hypersensitivity angiitis.

Ch I or a mp benicol

Chloramphenicol can produce a peripheral and optic neuropathy following prolonged, high-dose therapy.

Chloroquine

Chloroquine is an antimalarial drug that is used also in the treatment of connective tissue disorders. Typically, a painful vacuolar myopathy with increased serum muscle enzymes develops after prolonged therapy. Chloroquine produces only mild neuropathy. Muscle and sural nerve biopsies show lamellar inclusions in muscle fibers and

Schwann cells. Other antimalarial agents in the same chemical class may cause a similar neuropathy,

Cisplatin

Cisplatin is used widely in the treatment of ovarian, hladder, and testicular malignancies as well as squamous cell carcinomas. Cisplatin exerts its chemothcrapeutic effects by cross-linking DNA, thereby disrupting cell division. Sensory polyganglionopathy is the dose-limiting side effect. Cisplatin causes a dose-dependent, predominantly large fiber sensory polyneuropathy. Ototoxicity is common, manifested by tinnitus and high-frequency hearing loss. Paresthesia, Lhermittc's sign, loss of tendon reflexes, prominent proprioceptive loss, and sensory ataxia usually occur when cumulative doses exceed 400 mg/m . Autonomic symptoms, especially gastroparesis and vomiting, are common and may reflect enteric ganglion cell loss, The neuropathy may develop as late as 4 months after the drug has been stopped ("coasting"). Nerve conduction studies show reduced or absent SNAPs. Nerve biopsy reveals loss of large myelinated fibers and acute axonal degeneration. Most patients receiving cumulative doses below 500 mg/m improve following cessation of therapy. Neurotrophins are currently under investigation to prevent or ameliorate the neurotoxicity of cisplatin. Carbiplatin is less neurotoxic.

Colchicine

Colchicine is used primarily for the treatment of gout. Subacute proximal weakness and an associated mild distal axonal neuropathy may occur in patients with mild renal insufficiency receiving conventional doses of colchicine, or in patients receiving long-term colchicine for suppression of gout. Markedly elevated serum creatine kinase levels and electro diagnostic findings of a neuromyopathic process occur. Both weakness and creatine kinase elevations typically remit after the drug is discontinued.

Dapsone

Dapsone is used in the management of leprosy and other skin disorders. High doses may cause a predominantly motor neuropathy characterized by weakness and atrophy of distal muscles, particularly intrinsic hand muscles. Severe optic neuropathy may occur also. Reduction of minor NCV is slight, even in the presence of severe denervation, suggesting an axonal neuropathy. Recovery is slow after the drug is discontinued.

Dideoxynu deosides

The nucleosides zakitabine (dideoxvcytidine or ddC), didanosine (dideoxyinosinc), and stavudinc arc inhibitors of reverse transcriptase used to treat HIV-1 infection. These agents cause a dose-limiting dysesthetic sensory neuropathy (Dalakas 2001). High doses of ddC produce an acute painful sensory neuropathy that may progress for 3 weeks after treatment is stopped. Lower doses cause a less painful, sensory neuropathy in 10-30% of patients. Pre-existing neuropathy, diabetes mellitus, heavy alcohol consumption, and low serum cohalamin levels are risk factors that predispose to nucleoside neuropathy. Partial reversal of symptoms following withdrawal of drug allows the ddC neuropathy to be distinguished from the clinically similar HEV-1-assoeiated distal sensory polyneuropathy.

Disopyramide

A few cases of reversible sensorimotor peripheral neuropathy have been associated with the cardiac antidysrhytlimic agent disopyramide (Briani, Zara, and Ncgrin 2002).

Disulfiram.

Disulfiram is used in the treatment of alcoholism. The incidence of neuropathy is dose-related, as most patients receiving daily doses of 500 mg or more develop nerve damage after 6 months. The clinical manifestations are initial distal sensory impairment and later progressive weakness. Nerve conduction studies and EMG indicate an axonal neuropathy. Acute axonal degenetation and loss of myelinated fibcts are seen in sural nerve biopsy specimens. After the drug is stopped improvement takes place over a period of months.

F.thambutol

Ethambutol is an antitubetculous drug that causes peripheral sensory and optic neuropathy after prolonged administration at doses above 20 mg/kg per day.

Et op aside

Etoposide is a semisynthetic derivative of podophyllotoxin with established antineoplastic activity in SCLC and lymphoma. Distal sensory axonal neuropathy develops in approximately 10% of patients after high-dose therapy with this agent.

Gold

Organic gold salts ate sometimes used in the treatment of rheumatoid arthritis. Toxic allergic reactions involving skin, kidneys, and blood are well known, whereas neurotoxic complications are uncommon. A dosc-relatcd, distal axonal polyneuropathy may develop in patients receiving gold therapy. Many have the distinctive features of profound myokymia, muscle aches, insomnia, and autonomic dysfunction such as sweating and labile hypertension. After the drug is discontinued improvement

is the rule. Isolated case reports suggest that gold therapy may precipitate a Guillain-Barre-like syndrome with rapidly ascending limb weakness, sensory paresthesia, and elevated CSF protein. In these cases, nerve conduction studies show evidence of demyelinating neuropathy.

Heroin

Both nontraumatic brachial and lumbosacral plexopathies have been reported in heroin addicts. On resumption of heroin use after a period of abstinence the symptoms recur in one third of patients. Intense pain is a common clinical presentation, whereas weakness and sensory impairment are less prominent. Spontaneous recovery occurs slowly over weeks or months. The mechanism of these plexopathies is unclear.

/ lydralazine

Hydralazine is an antihypertensive drug that can produce a lupus-like syndrome and rarely produces a predominantly sensory polyneuropathy. Distal "tingling asleep numbness" in the extremities without overt clinical signs may develop in 15% of patients on hydralazine. The neuropathy may be caused by pyndoxine deficiency by a mechanism similar to that associated with isoniazid. Symptoms improve after withdrawal ol the drug or with low dose vitamin B_6 supplementation (50-100 mg daily).

Isoniazid

INH is an effective antituberculous drug that interferes with vitamin B^-dependent coenzymes and thus leads to pyridoxine deficiency. INH is acetylated in the liver by the enzyme acety(transferase. Individuals unable to acetylate at a norma! rate (slow acetylators) maintain high blood levels of free INH for a longer time than do vapid acetylators and arc iheretore more susceptible to toxic neuropathy. The slow acetylation is inherited as an autosomal recessive trait. INH polyneuropathy occurs in approximately *2%* of patients receiving conventional doses (3-5 mg/kg per day), its incidence increasing with higher doses. Typically 6 months pass before neuropathic symptoms of paresthesia, impaired distal lower extremity sensation, and weakness begin. The primary pathological process is axonal degeneration affecting both myelinated and unmyelinated fibers, often with prominent axonal regeneration. Unless recognition of this complication is delayed, recovery is rapid. Co-administration of vitamin B_6 (50-100 mg daily) prevents the neuropathy.

Ltpid-Lowering Agents

The 3-hydroxymeihylglutaryl-(HMG)-CoA-reductase inhibitors or statins have grown in popularity for their lipid- and particularly cholesterol-loweting properties. A number of patients on these medications have been found to have a reversible, predominantly axonal distal sensorimotor peripheral neuropathy. An epidemiological study from Denmark concluded that long term exposure to statins increased the risk of developing polyneuropathy 4- to 14-fold compared with the background population (Gaist et al. 2002). Although less severe than the better known myopathy with rhabdomyolysis that can occur with the statin lipid-lowering agents, this toxic neuropathy appears to be much more common, often going unrecognized.

Metronidazole and Misonidazole

Metronidazole is used for the treatment of protozoal and anaerobic bacterial infections as well as inflammatory bowel disease. It may produce a predominantly sensory polyneuropathy following cumulative doses exceeding 30 g. Axonal degeneration of both myelinated and unmyelinated fibers can occur, with slow improvement after the agent is stopped. Misonidazole, a related compound used as an experimental radiation-sensitizing agent, causes a similar sensory neuropathy.

Nitrofurantoin

Nitrofurantoin is a broad-spectrum antibiotic used to treat urinary tract infections. A sensorimotor polyneuropathy of the distal axonal type may develop weeks to months after beginning therapy. Distal numbness, paresthesia, and weakness are common. Renal insufficiency predisposes patients to the development of neuropathy because of excessive tissue concentrations of nitrofurantoin, which is normally excreted by the kidneys. Elcctrophysiological studies show the typical changes of distal axonopathy. Improvement occurs after the medication is discontinued.

Nitrous Oxide

A predominantly sensory neuropathy and associated myelopathy develop in individuals repeatedly abusing or exposed to nitrous oxide (N_20), an inhalation anesthetic agent that is also used in the food industry as whipping cream propcllant. Neurological symptoms occur following intentional abuse or rarely through contamination in operating rooms or pediatric dental offices with faulty N_20 scrubbers. Sharp radicular pains are common symptoms, along with numbness and distal sensory loss. A Lhcrmittc's or reverse I .he mime's sign (neck flexion induces an electrical shock sensation traveling from the feet upward), increased reflexes, and extensor plantar signs may be present. Nerve conduction studies show decreased SNAP amplitudes. Nitrous oxide inhibits the vitamin $B|_2$-dependent enzyme methionine synthase, producing a clinical syndrome indistinguishable from vitamin !i|2 deficiency. Nitrous oxide anesthesia may even precipitate

subacute combined defeneration in patients with unrecognized cobalamin deficiency. Serum methylmalonic acid and homocysteine can be significantly elevated. Prognosis following cessation of exposure is good, unless the myelopathy is severe.

Perhexiline

Perhexiline maleate, previously used to treat angina pectoris, may cause hyperglycemia, abnormalities of liver function, and polyneuropathy. Mild to severe sensorimotor polyneuropathy commonly develops in patients treated with perhexiline (30CMO0 mg/day) for several months. Painful paresthesias, weakness, frequently involving proximal as well as distal muscles, and loss of reflexes occur, occasionally accompanied by orthostatic hypotension and papilledema, CSF protein is commonly elevated. Marked slowing of conduction velocities is characteristic. Sural nerve biopsy specimens show segmental demyelination and lamellar Schwann cell inclusions. Recovery occurs if the medication is stopped.

Phenytoin

Phenytoin, a widely used antiepileptic drug, may cause mild or asymptomatic polyneuropathy after many years of exposure. Typical manifestations are confined to lower extremity areflexia, distal sensory loss, and mildly reduced motor conduction velocities. The degree of abnormality is generally proportional to the duration of phenytoin treatment. Folate deficiency, which may develop during phenytoin therapy, is not related to the onset of neuropathy.

Pyridoxin?

High dose pyridoxine (vitamin B_6, 250-3000 mg/day) may cause a severe sensory polyganglionopathy. Painful paresthesias, sensory ataxia, and l.hermittc's sign are common features. Nerve conduction studies show low-amplitude or absent SNAPs. Severe depletion of myelinated fibers and acute axonal degeneration are found in sural nerve biopsy specimens. Pyridoxine use should be queried in all patients with sensory neuropathy. In experimental studies, high **dose pvi HI::\IIU-** IOO **i** iH'Aj!.' produced **widespread do: s.i I** root ganglion degeneration. The fact that most clinical cases gradually recover suggests that dysfunctional dorsal root ganglion neurons may regain their functional capacity despite severe sensory deficits early in the course of disease.

Sodium Cyanate

Sodium cyanate was previously used to treat sickle cell anemia. An insidious sensorimotof polyneuropathy may develop following prolonged therapy.

Suramin

Originally introduced as an antiparasitic agent, suramin is used currently as an antineoplastic drug for refractory malignancies. It acts by inhibiting DNA polymerase activity and displacm;; several growth laciors from tlicii respective receptors. Suramin neurotoxicity is the dose-limiting side el tea leading to two distinct patterns of neuropathy, one a length-de pen dent axonal polyneuropathy and the other a subacute demyelinating polyradiculoneuropathy (Chaudhry et al. 1 996). The distal sensorimotor neuropathy that occurs in 30-55% of patients presents with paresthesias and mild distal leg weakness. In vitro experiments suggest that NGF inhibition by suramin may be an important neurotoxic mechanism. Approximately 15% of patients develop a subacutely evolving, demyelinating polyradiculoneuropathy. Severe generalized flaccid weakness with bulbar and respiratory involvement, nerve conduction studies consistent with demyelination, increased **CS1**: protein levels, and perivascular inflammation on sural nerve hiopsy are rypical features making this neuropathy virtually indistinguishable from GRS. The severe neuropathy occurs predominantly at peak plasma suramin concentrations above 350 ug/mL. Suramin may induce inflammatory demyelination by its many immunomodulatory effects. Patients improve after drug discontinuation and with plasmapheresis.

Tacrolimus

Tacrolimus, an immunosuppressive agent used in organ transplantation, may trigger an immune-mediated neuropathy by its complex actions on T cells. The few patients who developed a subacute, multifocal demyelinating polyneuropathy resembling CIDP after initiation of tacrolimus improved following plasmapheresis or intravenous immunoglobulin (Wilson et al. 1994).

Taxanes

Paclitaxel (Taxol), a plant alkaloid isolated from the bark of the western yew, is used toi die irc.unu-nl ol ovarian cancer and other solid neoplasms. Taxol and its semisynthetic analogue docetaxel bind to tubulin and promote irreversible microtubule assembly, thereby forming bundles of disordered microtubules and disrupting axonal transport. A dose-related sensory ganglionopathy results with doses above 250 mg/m^2 body surface **area.** Cumulative dosages of greater than 1000 mg/m" invariably result in a sensory motor neuropathy. Burning paresthesias, sensory loss affecting all sensory modalities, and areflexia are followed by sensory ataxia and mild distal weakness. Disabling weakness is rare except in the presence of additional risk factors such as pre-existing diabetic neuropathy or combination therapy with other neurotoxic chemothcrapeutic agents such as cisplatin. Neurotrophic have prevented paclitaxel neutotoxicity in animal models.

Docctaxel (Taxotere) is used in metastatic breast and ovarian cancer causing a dose-dependent sensory neuropathy similar to its parent compound. Motor symptoms are present only in the most severely affected patients (Newetal, *1996).*

Thalidomide

Thalidomide was introduced as a sedative-hypnotic agent in the 1950s, but was taken off the market when its disastrous teratogenic properties became evident. The drug has, however, been found to be useful to treat erythema nodosum leprosum and other rare skin conditions, graft-versus-host disease, a number of complications of HIV infection, and multiple myeloma as well as other malignancies. This compound owes its therapeutic effects to its inhibition of tumor necrosis factor-c (TNF-a) production and anti-angiogenic properties. Thalidomide causes dorsal root ganglion degeneration with selective involvement of large-diameter sensory neurons. Painful distal paresthesia and numbness occur with palmar erythema and brittle nails as prominent signs. In most patients the neuropathy is dose related, occurring after high doses or chronic administration for more than 6 months. After discontinuation of the drug, symptoms and signs improve very little. A prospective study of 135 patients with dermatological problems found objective clinical and electrophysiological evidence of predominantly sensory neuropathy in 25% of those treated (Bastuj-Gann et al. 2002}. In this cohort the neuropathy-was found to be dose-related, with a relative risk for daily doses greater than 75 mg of 20.2, a relative risk of 8.2 for daily doses between 50 and 75 mg, and no neuropathy in patients on less than 25 mg each day. Cumulative dosages gteater than 100 g result in significant neuropathy. As thalidomide produces neurotoxicity in a dose-dependant manner, monitoring for peripheral neuropathy with sensory conduction studies in patients receiving thalidomide allows for early detection of neuropathy preventing severe disability.

Glutethimide, a structurally related hypnotic compound, may produce a similar sensory polyganglionopathy in patients taking high doses for many months.

L-Tryptophan

An unusual syndrome called eosinophiha-myalgia syndrome was recognized in 1989 in individuals taking preparation* coma in i lit: I .-tryptophan. In \'-->-)*l,* n-.ore than 1500 patients had been diagnosed in the United States. A contaminated L-tryptophan source originating from a single manufacturer was responsible for the epidemic. One of the chemical impurities associated with eosmoph ilia-myalgia syndrome, designated *peak* E, is an unusual dimeric form of L-tryptophan. This abnormal tryptophan metabolite may activate eosinophils and trigger immune-mediated mononuclear cell infiltrates in connective tissues of many organs. Eosinophilia-myalgia syndrome is a systemic illness characterized by myalgia, fatigue, arthralgia, skin rash, swelling, and induration of the limbs and an elevation of the blood eosinophil count (>1000 cells/ul). Many patients develop florid inflammatory myopathy. The onset of eosinophilia-myalgia syndrome may be delayed for months after i-tryptophan use, and clinical deterioration may peak months after stopping the medication. A severe axonal sensorimotor polyneuropathy may be a prominent feature in some patients (Smith and Dyck 1990). Electrodiagnostic studies are in keeping with an axonal process. EMG may show neurogenic and myopathic motor unit potential alterations. Pathological studies demonstrate acuteaxonal degeneration, epineurial and perineuria] inflammatory infiltrates, and associated inflammatory vasculopathy in sural nerves. Inflammation is observed also m biopsy specimens of muscle, skin, and subcutaneous tissues. The clinical and pathological findings resemble those of the Spanish toxic oil syndrome, which was caused by denatured rapeseed oil. In general, clinical severity of the neuropathy seems to be positively related to the total dose ingested. Prednisone is not of benefit.

Vinca Alkaloids

Vincristine, the Vinca alkaloid most used in chemother apeutic regimens, has length-dependent sensorimotor polyneuropathy as its dose-limiting side effect. Vinblastine and two semisynthetic derivatives, vindesine and vinorelbinc, are less neurotoxic. Vinca alkaloids function as mitotic spindle inhibitors. Their neurotoxicity is related to tubulin binding, which interferes with axonal microtubule assembly, thereby impairing axonal transport.

Vincristine produces a dose-dependent neuropathy with sensory symptoms beginning at 5 mg and motor symptoms at cumulative doses of 30-50 mg. There are several reports of vincristine-induced severe paralysis at conventional doses in patients with pre-existing hereditary neuropathies. Paresthesias, often starting in the fingers before the feet, and loss of ankle jerks are common initial findings. Distal muscle weakness and sensory impairment follow. Autonomic dysfunction, particularly gastroparesis, constipation, occasionally paralytic ileus, and urinary retention, is an early manifestation. Weakness, often accompanied by muscle pains, may evolve rapidly to severe motor impairment. Occasionally, isolated mononeuropathies have been reported. Cranial nerve involvement occurs infrequently and includes trigeminal sensory loss, ocular motility disorders, facial weakness, and recurrent laryngeal nerve palsies.

Electrophysiological studies reflect the degeneration of distal axons. SNAPs are reduced in amplitude, whereas nerve conduction velocities arc preserved. EMG shows denervation in distal muscles. The predominant pathological features are axonal degeneration and myopathic changes with spheromembranous inclusions in the muscle fibers on electronmicroscopy. Reduction in dose or

withdrawal from therapy at an early stage usually leads to complete recovery. Coadministration of glutamic acid or ORG 2766, an adrenocorticotropic hormone-derived synthetic peptide, has shown promising results reducing the severity of vincristine neuropathy in preclinical trials but there was no benefit in a clinical trial. Neurotrophins have neuroprotective effects in experimental studies as well, although there is reticence to use these compounds in patients with established neoplasms, due to the fear that growth factors may stimulate tumor growth.

NEUROPATHIES ASSOCIATED WITH INFECTIONS

Peripheral neuropathy occurs in a number of infectious diseases including viral, prion, bacterial, and parasitic infections.

Viral Infections and Neuropathy

Human Immunodeficiency Virus Type 1

HIV-1 infection is associated with a wide variety of peripheral neuropathy syndromes, with onset from the time of seroconversion to the late stages of AIDS (Table 82.29; see Chapter *59).* These arc divided into neuropathies occurring early and late in the course of disease. The CD4 count inversely parallels the frequency of neuropathy, with normal counts in inflammatory demyelinating neuropathies and low counts in distal symmetrical polyneuropathies and lumbosacral polyradiculopathy. The estimated prevalence of peripheral neuropathy in patients with HIV-1 infection ranges from 15-30% based on clinical findings and increases substantially if electrophysiological variables are used for inclusion. More than 75% of patients with AIDS have pathological evidence of peripheral nerve involvement at autopsy.

Acute and Chronic Inflammatory Demyelinating Polyradiculoneuropathies. Of the neuropathies that occur in HIV-1 infection, AIDP and CIDP predominate during seroconversion and the early stages of disease.

An acute inflammatory demyelinating neuropathy clinically and electrophysiological!)' indistinguishable from GBS is seen in individuals who ha\< pnsicve tcs! results *:oi-* HIV-1. Its clinical course, spontaneous recovery, or response to plasmapheresis or intravenous immunoglobulin therapy arc similar to IKin I 11V I related (.lis. I S! pruiein is elevated (>100 mg/dL), and pathologically dcmyclination with prominent inflammation in nerves and roots occurs. This acute polyradiculoneuropathy differs from run 1:1V i related GBS by a CSF pleocytosis ranging from 10-50 cells/ul and by HIV-1 seropositivity.

Similar to HIV-1 seronegative patients, CIDP may be seen in association with HIV-1 infection, CSF pleocytosis and prominent inflammatory infiltrates consisting primarily of cytotoxic-suppressor T lymphocytes and macrophages in sural nerve biopsy specimens separate these patients from those with seronegative CIDP. It is advisable to test for the presence of HIV-1 antibodies in those patients with acquired demyelinating neuropathies who have conceivable HIV-1 risk factors or suspicious laboratory results, such as CSF pleocytosis, positive hepatitis B serology, or polyclonal hypergammaglobulinemia. In one series from a large urban center, 8% of patients with inflammatory demyelinating neuropathies tested HIV-1 seropositive. Plasmapheresis or IVIG is the preferred treatment for both acute and chronic inflammatory demyelinating polyneuropathies if the illness is sufficiently severe to warrant intervention.

Tabic 82,29: Neuropathies associated with human immunodeficiency virus infection

Neuropathies	*Cluneal features*	*Human immunodeficiency virus 1 stage*
Distal symmetrical polyneuropathy	Pain, sensory loss	Late: CDC IV, AIDS, ARC
Autonomic neuropathy		
Treatment-induced	ddC, ddl, 3TC, d4T, F1AU	
Lumbosacral polyradiculoneuropathy	Cauda equina syndrome	Late: CDC IV, AIDS
CVIV radiculopathy	CSF pleocytosis (polymorphonuclear cells)	
Lymphoma	CSF cytology (malignant cells)	
Diffuse infiltrative lymphocytosis syndrome	CDS lymphocytosis	
Multiple mo no neuropathies	Limited to extensive mononeuropathies	CDC III-IV; ARC, AIDS
Vasculitis		
CMV		
Lymphoma		
Inflammatory demyelinating polyneuropathies	Guillain-Barre syndrome or CIDP; CSF pleocytosis	Harly: CDC Mil
Cranial mono neuropathy	Facial palsy	Early: CDC I-III
Sensory neuronoparhy	Sensory ataxia	Early: CDC I-III
Herpes zoster radiculitis	Dermatomal vesicular eruption	Early and late

AIDS = acquired immunodeficiency syndrome; ARC = AIDS-related complex; CDC I-IV= Centers for Disease Control and Prevention classification system for human immunodeficiency virus infection stages I-IV; CMV = cytomegalovirus; ddC, ddl, 3TC, d4T, FIAU = dideoxycytidinc, dideoxyinosine, lamuvidine, stavudine, fialuridine, respectively.

Mononeuropathy and Multiple Mononeuropathies. Although isolated involvement of single cranial nerves, and particularly the facial nerve, may occur in the asymptomatic or early stages of symptomatic HIV-1 infection, multiple mononeuropathies associated with HIV-1 disease more frequently occur late in the course of illness. These may be associated with superimposed infection (including herpes zoster, CMV, hepatitis C, and syphilis), lymphomatous infiltration, or necrotizing vasculitis.

Unilateral or bilateral facial neuropathy may accompany HIV-1 seroconversion. Patients with involvement of one or two cranial or spinal nerves in association with CD4 counts greater than 200/ul often have a good prognosis, and many recover spontaneously. Multiple mononeuropathies with severe deficits, on the other hand, are more likely to occur in immunocompromised AIDS patients with CD4 counts below 200/ul; these patients should be investigated for CMV infection. If CMV cannot be demonstrated, peripheral nerve vasculitis is the most likely etiology. Peripheral nerve biopsy in multiple mononeuropathies demonstrates multifocal decreased density of myelinated fibers, degenerating fibers, and interstitial abnormalities dominated by epineurial mononuclear cell infiltrates and vessel wall necrosis. Schwann cells may he infected directly by HIV-1 particles (Mahadevan et at. 2001).

When CMV is confirmed or even suspected clinically, treatment should begin immediately with ganciclovir. Other therapies that have been noted in case reports as being effective include corticosteroids, plasmapheresis, IVIG, and foscarnet. Use of corticosteroids might seem theoretically risky but is surprisingly well tolerated.

Distal Symmetrical Polyneuropathy. The most common neuropathy related to HIV-1 infection is painful distal symmetrical polyneuropathy. The onset occurs often with burning feet, painful paresthesia, and distal sensory loss, combined with mild distal weakness and autonomic dysfunction. In patients with symptomatic distal symmetrical polyneuropathy, nerve conduction studies show borderline- to low-amplitude sensory and motor responses, often accompanied by denervation changes in distal muscles. Electrophysiological evaluations of patients with HIV-1 infection demonstrate that as many as two thirds may have peripheral nerve involvement. Sural nerve biopsy shows loss of myelinated fibers and unmyelinated fibers with no distinctive interstitial abnormalities. Skin biopsy demonstrates reduction in nerve fiber density, increased frequency of fiber varicosities, and fiber fragmentation (Keswani et a I. 2002). The severity of neuropathic pain and elevation of distal cooling detection threshold values in distal symmetrical polyneuropathy appear to correlate with plasma HIV-1 RNA levels (Simpson et al, 2002).

Although the cause of distal symmetrical polyneuropathy in HTV-1 infection is unknown, direct infection of peripheral nerve is thought to be unlikely. Although low levels of HIV-1 in dorsal root ganglia macrophages may play a role, macrophage infiltration and the release of proinflammatory cytokines appear to be the primary mediators of the "dying hack" axonal degeneration. Specific treatment for distal symmetrical polyneuropathy in HIV-1 infection has been disappointing. Although symptomatic approaches may be helpful, clinical trials of NGF, peptide T, plasmapheresis, and accupuncture have not shown efficacy. Current interest in such agents as I.-acetylcarnitine and prosaptide may lead to further therapeutic trials (Simpson 2002).

A significant proportion of patients with 1 lIV-1-related distal symmetrical polyneuropathy have antibodies to human T-cell lymphotropic virus 2, suggesting eoinfection (Zehcnder et al. *1995).* Nutritional deficiencies (chiefly vitamin B]> and folate deficiencies) have also been implicated as have neurotoxic drugs including vincristine, dapsone, iNH, and nucleoside analogue reverse transcriptase inhibitors. Mounting evidence supports the observation that several nucleoside analogue reverse transcriptase inhibitors used in highly active antiretroviral therapy (IIAART) have contributed to both improved survival and an increase in toxic neuromuscular disorders in individuals infected with HIV-1 (Brinley, Pardo, and Verma 2001). Among these agents, zidovudine (AZT) may lead to myopathy, zalcitabinc (ddC), didanosine (ddl), and lamvudine (3TC) have been linked with neuropathy, whereas stavudine (d4T) and fialuridine (FIAU) cause neuropathy or myopathy and lactic acidosis (Dalakas 2001). A subset of HIV-1-positive patients with distal symmetrical polyneuropathy have been found to have necrotizing vasculitis (Bradley and Verma 1996).

Lumbosacral Polyradiculoneuropathy. Even though uncommon, acute lumbosacral polyradiculoneuropathy often associated with CMV infection is among the most devastating neurological complications in AIDS. Hie usual presentation is rapidly progressive flaccid paraparesis, sphincter dysfunction, perineal sensory loss, and lower limb areflexia (So and Olney 1994).

Electrophysiological studies show low-amplitude CMAPs and prolonged or absent F-wave latencies. Reduced or absent SNAPs are attributed to concomitant polyneuropathy. Within a few weeks of onset, EMG signs of active denervation become apparent. LSI- examination in CMV-related lumbosacral polyradiculoneuropathy shows plcocytosis (>50 per ul; typically with more than 40% polymorphonuclear cells), elevated protein levels, and low glucose concentrations. With this CSE profile, a presumptive diagnosis of CMV polytadiculoncuropathy can be made, leading to empiric therapy, even before the demonstration of positive CSF culture results. MR! with gadolinium may demonstrate enhancement of cauda equina nerve roots. Other rare causes of lumbosacral polyradiculoneuropathy in AIDS include syphilis, mycobacterial infections, toxoplasmosis, and leptomeningeal lymphomatosis.

Another condition associated with HIV-1 infection, diffuse infiltrative lymphocytosis syndrome, is a nonmalignant CDtJ lymphocytosis that may affect multiple viscera as well as peripheral nerve and may respond to either corticosteroid or antirctroviral treatment (Gherardi et al. 1998).

Empirical treatment with intravenous ganciclovir should be started promptly in AIDS patients with polymorphonuclear CSF pieocytosis and progressive flaccid paraparesis. Foscarnet alone or in combination with ganciclovir may be an alternative for patients who develop this syndrome daring ganciclovir treatment for systemic CMV infection. Although early antiviral therapy may preserve neurological function, long-term prognosis is poor.

Herpes zoster radiculitis occurs in perhaps 10% of HIV-l infected patients. Early in the course of HIV-1 infection, often at seroconversion or during the asymptomatic phase, ataxic sensory polyganglionopathy may develop; it remains unclear whether this syndrome or the associated degeneranon of ilu- ťiLKLi- ir.ici arc lvkucd directly in HIV [infection.

Cy Iomega lovirus

CMV commonly causes an asymptomatic infection. In immunocompromised individuals, however, a life-threatening disseminated illness may result, often with fatal men ingoeneep ha litis. Antecedent CMV infection has been associated with A1DP. In patients infected with the HIV-1 virus, severe painful lumbosacral polyradiculoneuropathy is known to occur (sec Lumbosacral Polyradiculoneuropathy, earlier in this chapter).

Epstein-Barr Virus

Although most well known as the chief cause of infectious mononucleosis, the Epstein-Barr virus is associated with a variety of neurological complications. Those with peripheral nerve manifestations include rhombencephalons with cranial nerve involvement, myelitis with spread to adjacent nerve roots, multiple mononeuropathies, and brachial as well as lumbosacral plexopathy.

Herpes Simplex Virus

Herpes simplex virus is a group of neurotropic DNA viruses that colonize primary sensory neurons. In the case of herpes simplex virus 1, the gasserian ganglion is most often affected, and repeated eruption of oral and labial ulceration ensues. With herpes simplex virus 2, a sexually transmitted disease, sacral dorsal root ganglion cells are the site of infection, leading to the periodic appearance of genital ulcers. Although segmental recurrence is most common, more widespread disease may result in disseminated eruptions in immunocompromised hosts. Antiviral treatment with acyclovir (200 mg five times daily for 10 days) or famciclovir (125 mg twice a day for 5 days) can reduce the duration of eruption and prolong the time to subsequent outbteak.

Herpes Zoster Virus

The most common symptomatic peripheral nerve viral infection is with the neurotropic varicella zoster (herpes) virus. It has been estimated that over the age of 70 years, the lifetime percent probability of segmental varicella zoster virus infection approximates years of life. The spectrum of peripheral neurological involvement in varicella zoster virus includes cranial zoster (chiefly affecting the trigeminal or less often the geniculate ganglion), radicular zoster (also called segmental zoster, zoster radiculopathy, or shingles), and polyradiculoneuropathy. Although sensory pathways are most affected, in cases with radicular zoster affecting one or two spinal root levels, there is *An* approximate 5% probability of significant motor involvement, leading to the designation segmental zoster paresis. Careful EMG study results show as many as 50% of segmental zoster patients may have subtle motor involvement (Haanpaa, Hakkinen, and Nurmikko 1997). In severe segmental zoster inflammation will often spread into the spinal cord, and can be responsible for long tract signs. Occasional patients present with painful unilateral dermatomal pain and CSF evidence of varicella zoster virus DNA, but no cutaneous vesicular eruption (zoster sine hcrpete). Treatment with famciclovir (500 mg three times a day for 7 days) or acyclovir (800 mg five times daily for 10 days) is indicated at the onset of symptoms.

/ lepatttis Viruses

Hepatitis B vitus infection has been reported in association with demyelinating GBS and with multiple mononeuropathies and necrotizing vasculitis.

Infection with hepatitis C virus is often transmitted by sexual contact, through blood transfusion, or via other means and may be particularly common in urban populations. I lepatitis C virus has been associated with essential cryoglobulinemia and may be its most common cause. The syndrome of hepatitis C virus infection, cryoglobulinemia, and vasculitic neuropathy has been recognized as a previously overlooked cause of multiple mononeuropathies. Although no controlled clinical trials have been carried out, individual patients have been observed to respond to immunosuppressive therapy followed by antiviral treatment of the underlying HCV infection (refer to preceding section on cryoglubulinemic neuropathy).

Human T-Celt Lympbotropic Virus Type i

Although the majority of patients infected by human T-cell lymphotropic virus type 1 present with a progressive spinal

cord syndrome and spastic paraparesis, sphincter disturbances, and impotence, many affected patients have dysesthesia and mild distal sensory loss, implicating additional involvement of peripheral nerve and dorsal column pathways. Because the syndrome is much more common in tropical regions, the terms *tropical spastic paraparesis* (TSP) or HTLV-1 associated myelopathy (HAM) have been used. CSF examination is essentially normal, but may show a mild lymphocytic pleocytosis. Somatosensory evoked potential studies are said to be abnormal in more than one half of patients. NCVs are minimally slowed in approximately one third of those studied. Progression is slow, although most patients eventually become severely disabled 10 years or more after onset of symptoms.

Tropical Ataxic Neuropathy

Tropical ataxic neuropathy is a predominantly sensory syndrome occurring in middle age that presents with burning feet, distal sensory loss, gait ataxia, and lower limb areflcxia. Mild distal lower motor neuron signs, optic atrophy, and sensorineural hearing loss may be present also. Although nuttitional, toxic, and infectious etiologies have been considered, some evidence suggests that infection with human '['-cell lymphotropic virus 2 may play a significant role.

West Nile Virus Motor Neuronopatby

West Nile virus infection may present with symmetrical or asymmetrical flaccid limb and facial weakness without sensory deficts and with few or no signs of encephalitis; the picture is like acute poliomyelitis (Li ct al. 2003).

Peripheral Neuropathy in Creutzfeldt-Jakoh Disease

Creutzfeldt-Jakob disease is a transmissible neurodegenerative disorder caused by prions, proteinaceous infectious particles (see Chapter 59). Prions interact with a normal host protein to produce clinical Creutxfeldt-Jakob disease, Although the CNS is the main target of Creutzfeldt-Jakob disease, a number of patients have been described with a demyelinating peripheral neuropathy that may precede cognitive and intellectual deterioration (Antoine et al. 1996).

Bacterial Infections and Neuropathy

Neuropathy Associated with Mycobacterium leprae

Hansen's disease (leprosy) is a major cause of neuropathy worldwide, especially in tropical and subtropical regions. As improvements in public health and use of mtiltidftig therapy have advanced, the prevalence of Hansen's disease, as measured by registered cases, has dropped from 5.4 million in 1991 to 0.9 million in 1996. The Centers for Disease Control and Prevention reports that in the United States there were 144 new cases in 1995, whereas the total number of reported U.S. cases was 7500. Of new cases, approximately 20% originate in this country (mainly Hawaii, Florida, Louisiana, and southern Texas), with the balance immigrating mainly from Asia or the South Pacific, and to a lesser extent from Mexico, India, and othct parts of the world.

Mycobacterium leprae is thought to be ttansmitted through the upper respiratory tract. Once the nasal mucosa is colonized, the organism spreads slowly to other regions, with an estimated incubation time of 3-10 years. Particularly vulnerable tissue are those with mean daily temperatures in the 27° to 30° C range, as this promotes more rapid bacterial growth. The skin and superficial nerve trunks arc particularly vulnerable, leading to cutaneous lesions, anesthesia, and paralysis of face and limb muscles. The disease is classified by host reaction to infection into two polar forms, tuberculoid and lepromatous, with three intermediate forms termed *borderline tuberculoid, intermediate borderline,* and *borderline lepromatous.* Recent data suggest that the Hansen bacillus has a proclivity for Schwann cell invasion. These cells may then serve as a sequestered reservoir of infection with relative protection from host defenses. One model for the early interaction of *Mycobacterium leprae* with peripheral nerve suggests that the bacillus activates a-dystroglycan receptors on Schwann cells via the G domain of laminin-2 (LN»2G), a major component of Schwann cell basal lamina (Rambukkana 2000).

The vigor of host cell-mediated immunity appears to dictate the course of events. Tuberculoid Hansen's disease is characterized by active cell-mediated immunity, intense delayed hypersensitivity response to lepra antigens such as lepromin, localized destruction of infected nerves by intense inflammators lesions, and rare organisms dctct ted in skin and nerve. Lepromatous Hansen's disease, on the other hand, is typified by unopposed proliferation of organisms, complete anergy to lepra antigens, and disseminated skin and nerve lesions with minimal inflammatory response. Intermediate forms share features of the two extremes. A comprehensive review of Hansen's disease neuropathy by Walters and Jacobs (1996) is recommended.

Clinical Features. The unique propensity of M. *leprae* to invade cutaneous nerves causes the cardinal symptom of sensory loss. In tuberculoid Hansen's disease sensory loss, initially affecting pinprick and temperature sensation, is detected within sharply demarcated bypopigmented skin lesions. Adjacent cutaneous nerves or mixed nerve trunks are apt to become involved. The associated intense inflammatory response can affect underlying nerve trunks and cause a mononeuropathy in the distribution of those nerves, which may become indurated and palpable because

of fusiform swelling. Attention should he paid to the palpation of peripheral nerves that course close to the skin surface, including the great auricular, ulnar, radial, common fibular, and sural nerves, in order to detect nerve enlargement. The predominant sensory loss, particularly for pain, can lead to painless trauma with acrodystrophic deformities and autoamputations.

Lepromatous Hansen's disease is characterized by symmetrica! hacillary infiltration of the skin with a predilection for cooler areas of the body, avoiding the scalp, palms, soles, and midline of the back. The skin may have multiple nodules, papules, macules, and ulcerations, or there may be diffuse cutaneous involvement with a waxy, myxedema-like appearance. Similarly, the distribution of sensory loss is telated to the local skin temperature, the coolest parts such as the pinna of the car; the tip of the nose; malar areas of the face; dorsal surfaces of the hands, forearms, and feet; and dorsolateral surfaces of the lower legs being affected first. Because of the minimal inflammatory response, nerve trunk involvement occurs late in this form. Commonly affected nerves include the ulnar, common peroneal, and superficial branches ot the facial and median nerves, in that order. The selective involvement of small branches of the facial nerve leads to the typical patchy nature of facial paralysis with early weakness of medial iotvheae elev.'Ltors. Preserved tendon relieves are an important differential diagnostic sign, in contrast to the loss of reflexes seen in most polyneuropathies.

Either spontaneously or during the course of treatment, acute leprosy reactions may complicate the insidious course because of a sudden alteration in the host-immune response. In the reversal reaction, which is usually seen in the borderline-lepromatous stage, patients develop an increase in cell-mediated immunity. This reaction is identified clinically by swelling and exacerbations of existing skin and nerve lesions. Marked reversal teactions can be associated with intensely painful nerve trunks, and total loss of sensory and motor functions may develop within hours because of the pronounced inflammatory reaction of the affected nerves. These acute reactions appear most commonly during the first year of therapy and require immediate treatment with systemic corticosteroids or other anti-inflammatory agents to prevent further nerve damage.

Nerve conduction studies show reduced amplitudes of CMAPs and SNAPs, together with focal conduction slowing at sites of nerve enlargement. For diagnosis and accurate classification, a skin punch biopsy is necessary and should be taken from the active borders of the lesions. The architecture of cutaneous nerves is destroyed by an intense granulomatous inflammation in tuberculoid Hansen's disease (Figure 82.35). In lepromatous disease, multiple acid-fast organisms are found in Schwann cells, foamy macrophages, and axons of involved nerves, together with recurrent demyelination and progressive nerve fiber loss.

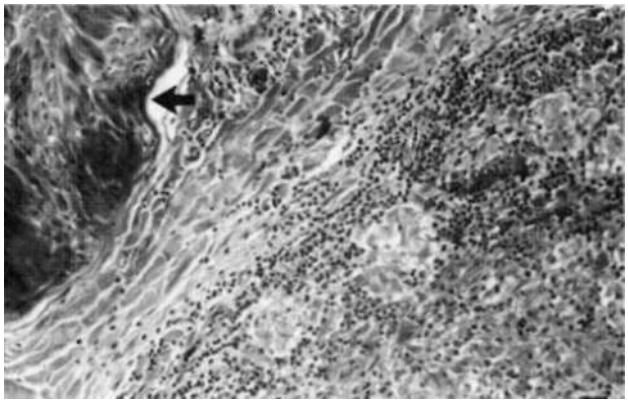


FIGURE 82.35 Tuberculoid leprosy. Biopsy of enlarged sural nerve demonstrates extensive epineurial inflammatory granuloma consisting of epithelioid and mononuclear inflammatory cells. The adjacent nerve fascicle *[arrow)* is devoid of myelinated fibers. (Hematoxylin and eosin; bar = 300 ^im.)

Treatment. Management consists of specific chemotherapy and prevention and treatment of deformities. The current recommendation for paucibacillary infections (those classified as indeterminate. : nlu rvnloid. or hordcr line tuberculoid Hansen's disease) is the combination of dapsone, 100 mg per day, and rifampin, 600 mg per day for at least 6 months, followed by dapsone monotherapy for *3-5* years. Patients with multibacillary infections (borderline or lepromatous leprosy) receive the same combination therapy, with the addition of clofazimine (50 mg daily). Treatment is continued for a minimum of 2 years or until skin smear results arc negative. For dapsone-resistant strains or patients with glucose-6-phosphate dehydrogenase deficiency, clofazimine and rifampin are used together, with consideration of a third agent, either ofloxacin (400 mg daily), clarithromycin (250 mg twice a day), or minocycline (100 mg daily).

Diphtheritic Neuropathy

Diphtheria is a localized infection of the upper respiratory tract or skin produced by *Cnrynebacterium diphtberiae.* The organism elaborates a protein exoloMii responsible tor the delayed systemic manifestations, including cardiomyopathy and segmental demyelination of nerve roots and peripheral nerves. Diphtheria toxin is used as an experimental model of PNS demyelination. Local injection of the toxin produces focal demyelination of nerve fibers without inflammation.

The disease is now rate except in poor socioeconomic conditions where immunization is inadequate. It begins with a pharyngeal infection associated with a characteristic grayish-white exudate. Neurological complications occur in approximately 15% of patients admitted with diphtheria. Neurological symptoms begin with paralysis of the soft palate, impaired pharyngeal sensation, and paralysis of

pupillary accommodation. Occasionally, the diaphragm becomes weak at this stage (Logina and Donaghy *1999).* A local limb neuropathy may appear adjacent to cutaneous diphtheria. The focal palatal-pharyngeal neuropathy may progress 3—15 weeks after the infection to a generalized mixed sensorimotor polyneuropathy, or less frequently to a sensory polyneuropathy presenting with ataxia in approximately 10% of patients (McDonald and Koeen 1993).

Culture of C. *diphtberiae* from the pharynx or the cutaneous ulcer establishes the diagnosis. CSF protein may be normal or elevated to more than 100 mg/dL. Mildly increased distal motor latencies and decreased NCVs arc seen in most patients 2 weeks after the onset of neurological symptoms. However, maximal slowing, with conduction velocities ranging from 15-35 m/sec tends to occur later when clinical recovery has already begun. The brunt of the pathological changes, segmental demyelination with sparing of axons, is seen in the dorsal root ganglia and nerve roots, which have an ineffective blood-nerve barrier to the toxin because of fenestrated capillaries.

Prompt administration of antitoxin within 48 hours of the ouset of the primary infection reduces the incidence and severity of neuropathy, but is likely to be ineffective if administered later in the course of disease. Respiratory support may be needed for severe cases. Recovery takes place over a period of weeks and is usually complete if antitoxin is given within 48 hours of symptom onset. In one series of 50 adults with diphtheritic polyneuropathy, identical rates of death (18%) and peak severity of neuropathic deficits (25% in the severe category) were recorded in those who received antitoxin on days 3-6 and those who did not receive it at all (Logina and Donaghy 1999).

Peripheral Manifestations of Lyme Borreliasis

Lyme disease is a multisystem illness caused by the tick-borne spirochete *Borrelia burgdorferi sensu la to* with characteristic early and late neurological manifestations. Most cases i.V?".. in ike L hi :i.-J Nuies h.ne been reported from nine states in the Northeast, uppet Midwest, and Pacific coastal regions. Endemic foci occur in northern and central Europe. It is now recognized that Lyme disease is distributed widely in temperate zones worldwide (sec Chapter 59).

From the initial appearance of the pathognomonic dartboard-like skin lesion, known as *erythema migrans,* a distinctive early neurological syndrome results in approximately 15% of patients. This consists of cranial neuropathy (usually facia! palsy), radiculoneuropathy, or lymphocytic meningitis, often in combination. These conditions usually abate without intervention over weeks to months, but they improve more rapidly with appropriate antibiotic treatment. Months to years after the initial infection, a late neurological syndrome may emerge. This consists of a predominantly sensory polyradiculoneuropathy that may present with distal sensory symptoms or proximal radicular pain and does not often resolve on its own, but rather regresses only after use of efficacious antibiotics {Logigian 1997).

Laboratory investigations helpful in the diagnosis of early Lyme disease include CSF analysis, which shows a lymphocytic pleocytosis and mild elevation of the total protein. Intrathecal production of anti-B, *burgdorferi sensu tato* antibodies can usually be documented in these cases. Electrodiagnostic study results in patients with chronic Lyme polyradiculoneuropathy confirm a multifocal or widespread axonal process, with borderline to low-amplitude distal responses, greater involvement of sensory rhan motor fibers, and little or no slowing of NCVs, F.MG often shows signs of chronic partial denervation in distal and proximal muscles, including fibrillation potentials and neurogenic motor unit potential changes. Sural nerve biopsy confirms axonal degeneration as well as interstitial alterations with perivascular and perineurial mononuclear inflammation. Serological confirmation of Lyme disease documents prior exposure, although scropositivity alone is not sufficient to establish a causal relationship, because in endemic .Hi .is II le.isl ID", nl ;iv. mpluiii.ilK :mlfvukul\ are seropositive. The diagnosis must depend on appropriate exposure in endemic regions and a plausible clinical context. High titers of anti-B. *burgdorferi sensu tato* antibody in CSF are helpful to link the peripheral neurological manifestations to Lyme disease. Polymerase chain reaction assays to identify spirochetal DNA in CSF are promising techniques (Schmidt 1997).

The majority of patients treated with intravenous ceftriaxone, 2 g daily for 2—4 weeks, improve slowly over 3-6 months. Oral antibiotic therapy with doxycycline or amoxicillin may be effective in mild cases without CSF abnormalities.

Parasitic Infections Associated with Peripheral Neuropathy

American Trypanosomiasis (Cbagas' disease)

American trypanosomiasis (Chagas' disease) occurs from the southern United States to southern Argentina and is known to have affected 17 million individuals, of whom approximately 5 million develop clinical symptoms attributed to the disorder. Chagas' disease is a parasitic infection caused by the flagellate protozoan *Trypanosoma cruzi-* The parasite is transmitted to humans by reduvid bugs of the order *Hemiptera* when the proboscides (sucking mouth parts) pierce the skin of their host to feed. The micro-organism is not introduced with the insect bite, but rather it is passively deposited in reduvid feces and subsequently penetrates the bite wound into the bloodstream.

Once the protozoan gains access to the host circulation three stages of disease ensue. The acute phase is marked variably by either no symptoms or alternatively by malaise,

local inflammation, gastrointestinal symptoms, and lymphadenopathy. The second phase, typically occurring approximately 3 months after initial inoculation, may last for years and is an asymptomatic period. During this time serological test results for trypanosomiasis become positive. The third or chronic stage affects approximately one third of patients and usually begins 10-20 years following the original reduvid bite. This phase is characterized by gastrointestinal, cardiac, and neurological manifestations. Approximately 10% of patients with chronic Chagas' disease develop a predominately sensory neuropathy.

Most patients with neuropathy complain of paresthesia in the distal lower limbs. On examination, distal hypesthesia and hyporeflexia are found, usually limited to the lower limbs, occasionally involving all four extremities, and rarely only in the distal upper limbs. Electrophysiological findings include low-amplitude sensory and motor responses, reduced NCVs, and distal neurogenic motor unit potential changes by EMG. Sural nerve biopsy demonstrates decreased density of large and small myelinated fibers, axonal clusters indicating regeneration, and on teased fiber preparations, paranodal and segmental demyclination (Sica et al. 1995). Although both itraconazole and allopurinol have shown to improve electrocardiographic abnormalities in Chagas' disease, there is little information regarding the efficacy of such therapy for the neuropathy (Apt et al. 2003).

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Chapter 83
Disorders of the Autonomic Nervous System

Christopher J. Mathias

The autonomic nervous system supplies and influences virtually every organ in the body (Figure 83.1). Its effector (efferent) component consists of two major divisions, the sympathetic and parasympathetic nervous systems, whose activity is influenced by several factors: afferent signals from different parts of the body, neurons in the spinal cord, and cerebral centers, mainly in the hypothalamus and brainstem. Autonomic dysfunction may result from lesions in one or more areas of the central or peripheral nervous system. This may result in a generalized disorder, either restricted to the autonomic nervous system (as in primary autonomic failure [PAF]) or involving other neurological systems (as in multiple system atrophy [MSA] or Shy-Drager syndrome) (sec also Chapter 77), Autonomic impairment may complicate disease processes affecting multiple organs (as in diabetes mcllitus or systemic amyloidosis) or may be localized. The latter may cause varying effects: minimal symptoms (in Horner's syndrome); considerable discomfort, which may be socially unacceptable (in gustatory sweating); and even life-threatening episodes (in carotid sinus hypersensitivity). The clinical problems in autonomic disorders, although often caused by failure, may result from the reverse; examples are increased activity causing hyperhid rosis or hypertension, which may occur in tetanus, Guillam-Barre syndrome, or high spinal cord lesions.

BASIC NEUROANATOMICAI., NEUROPHYSIOLOGY AL, AND NEUROCHEMICAL PRINCIPLES

The afferent pathways influencing the autonomic nervous system consist of virtually every sensory pathway (Figutc 83.2), as observed in the autonomic control of blood pressure. The major baroreccptor afferent: in the carotid sinus and aortic arch relay information to the brain through cranial nerves IX (glossopharyngeal) and X (vagal), Receptors in the heart and lungs (cardiopulmonary baroreceprors), skin, muscle, and viscera also influence blood pressure. Their role may be unmasked in tetraplegic patients with cervical cord transection above the spinal sympathetic outflow, in whom the peripheral sympathetic and cranial parasympathetic nervous systems function independently of the brain.

The major cerebral centers concerned with autonomic regulation include the insula, amygdala, hypothalamus, midbrain (Fdinger-Westphal nucleus and locus ceruleus), and brainstem (nucleus tractus solitaries and vagal nuclei). There is evidence in humans, using a combination of ncuroimaging and physiological studies, that other cerebral areas influence the central autonomic network (Critchley etal. 2000, 2001a).

The parasympathetic outflow consists of cranial and sacral efferents. Cranial efferents accompany cranial nerves III, VI, IX, and X and supply the eye, lacrimal and salivary glands, heart and lungs, and gastrointestinal tract with associated structures, down to the level of the colon. The sacral outflow supplies the urinary tract and bladder, the large bowel, and the reproductive system. Cerebral and spinal parasympathetic nuclei have specific control, for example, the Edinger-Westphal nucleus in pupillary control and OnuPs nucleus in the second and third sacral segments in urinary sphincter function. Most parasympathetic ganglia are close to target organs, and acetylcholine is the major transmitter at the ganglia and at postganglionic sites (Figure 83.3).

The sympathetic outflow is connected with major nuclei in the hypothalamus, midbrain, and brainstem and descends through rhe cervical spinal cord, where axons synapse in the intermediolateral cell mass. From the thoracic and upper lumbar spinal segments, myelinated axons emerge in the white rami and synapse in the paravertebral ganglia, which are some distance from the target organs. The major ganglionic transmitter is acetylcholine. Postganglionic fibers, which are unmyelinated, rejoin the mixed nerve through the gtay rami and innervate

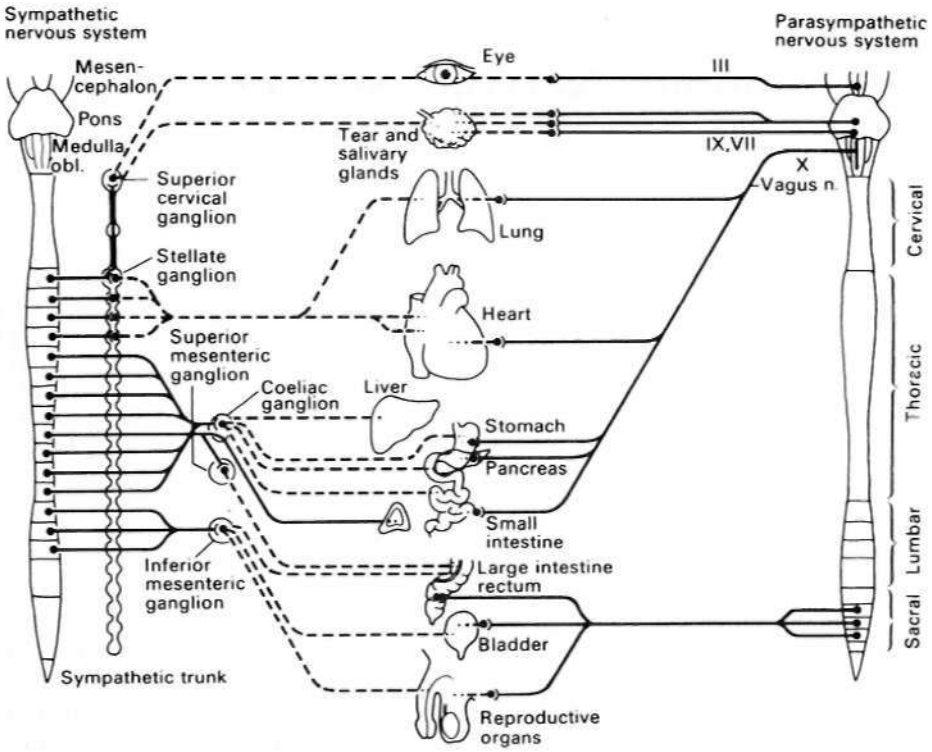


FIGURE 83.1 Parasympathetic and sympathetic innervation of major organs. (n. = nerve; obl. = oblongata.) (Reprinted with permission from Janig, W. 1987, "Autonomic nervous system," in *Human Physiology*, 2nd ed, eds R. F. Schmidt & G. Thews, Springer, Berlin, p. 333.)

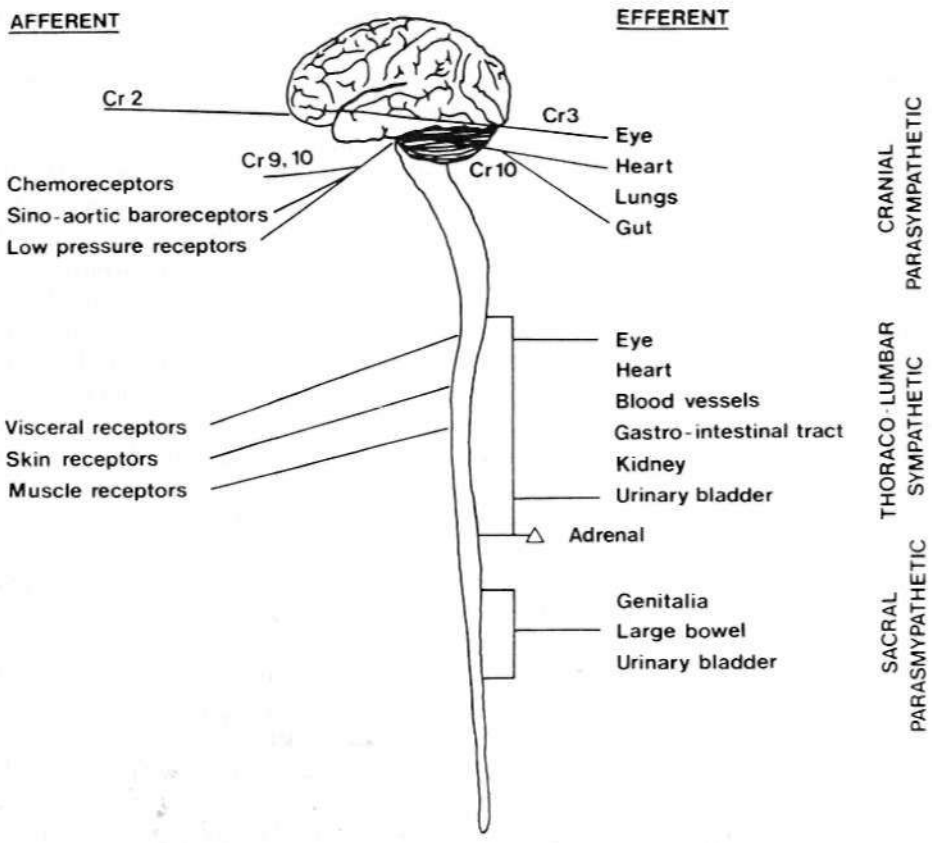


FIGURE 83.2 Schema to indicate the major afferent components that influence parasympathetic and sympathetic afferent activity. (Cr = cranial nerve.)

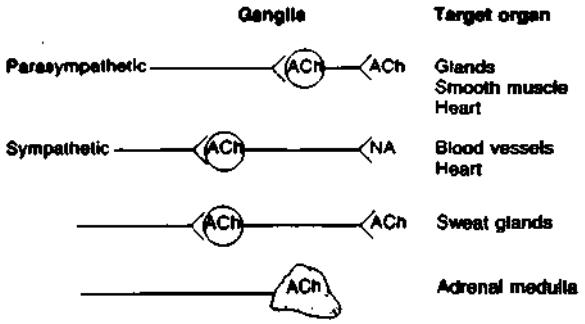


FIGURE 83.3 Outline of the major transmitters at autonomic ganglia and postganglionic sites on target organs. Ganglionic blockade at nicotinic receptors with hexamethonium prevents both parasympathetic and sympathetic activation. Atropine, however, only acts on muscarinic receptors at postganglionic parasympathetic and sympathetic cholinergic sites. (ACh = acetylcholine; NA = noradrenaline.)

target organs except for the adrenal medulla, which has only a preganglionic supply. The neurotransmitter at postganglionic sites is predominantly noradrenaline, although sympathetic cholinergic fibers (with acetylcholine as the transmitter) supply sweat glands.

There arc complex pathways in neurotransmitter formation, release, and function, as illustrated with the catecholamines (Figure 83.4). Many neurons have multiple neurotransmitters, which may be nonadrencrgic and noncholinergic. For example, vasoactive intestinal polypeptide is co-secreted with acetylcholine, which explains the inability of atropine to block all the effects of parasympathetic stimulation, whereas neuropeptide Y may be released with noradrenaline, thus accounting for the fact that or-adrenoceptor blockers may not completely prevent the effects of sympathetic neural stimulation. The availability of specific agonists and antagonists should help dissect the interactions of numerous peptides, amino acids, and amines at multiple sites in response to different stimuli. Despite the multiplicity of neurotransmitters and neuromodulators, however, the autonomic nervous system selectively controls responses in specific regional vascular territories and organs, making it a highly complex but precisely regulated and integrated system.

CLASSIFICATION

Autonomic disorders can be broadly divided into primary, in which no cause has been determined, and secondary (Table 83.1), which are due to specific diseases (such as

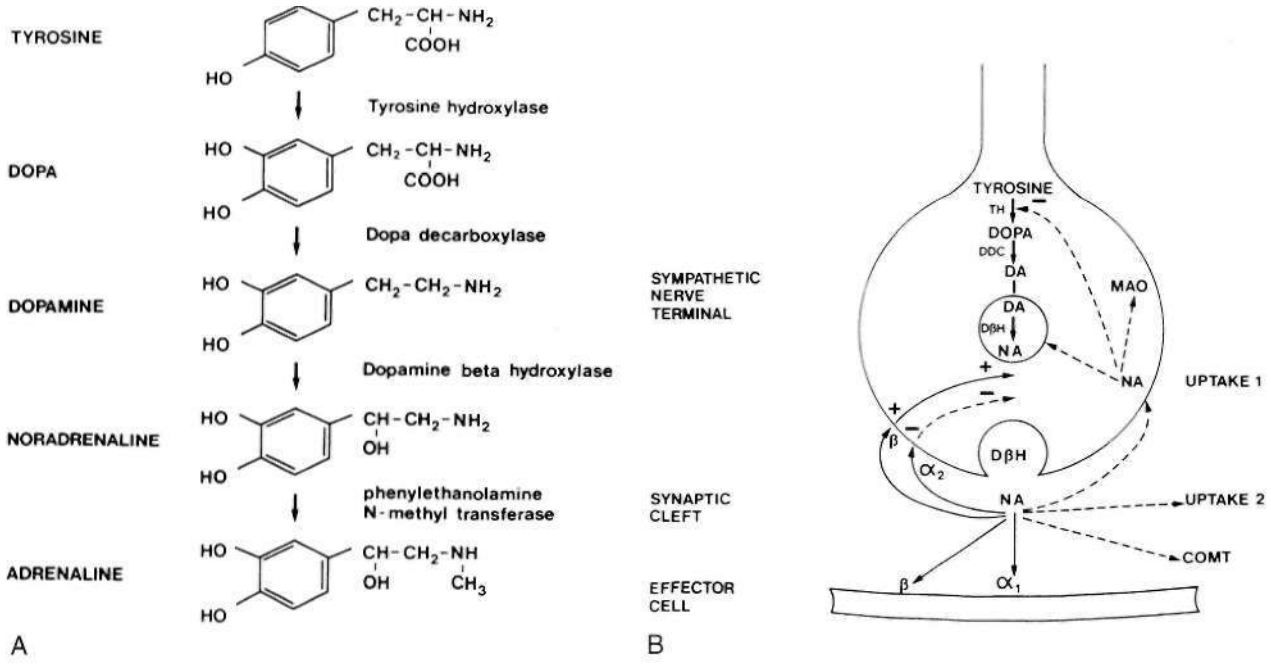


FIGURE 83.4 (A) Outline of biosynthetic stages and enzymes involved in the formation of noradrenaline and adrenaline from tyrosine. IB) Schema of some pathways in the formation, release, and metabolism of noradrenaline from sympathetic nerve terminals. Tyrosine is converted into dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase (TH). DOPA is converted into dopamine (DA) by dopa decarboxylase (DDC). In the vesicles, DA is converted into noradrenaline (NA) by dopamine /J-hydroxylase *(DfiH).* Nerve impulses release both *D0U* and NA into the synaptic cleft by exocytosis. NA acts ptedominantly on a_t-adrenoceptors but has actions on /S-adrenoceptors on the effector cell of target organs. It also has presynaptic adrenoceptor effects. Those acting ono^-adrcnoceptors inhibit NA release; those on ^-adrenoceptors stimulate NA release. NA may be taken up by a neuronal process (uptake 1) into the cytosol, where it may inhibit further formation of DOPA through the rate-limiting enzyme TH. NA may be taken into vesicles or mct.ibolr/.cd by-monoamine oxidase (MAO) in the mitochondria, NA may be taken up by a higher-capacity but lower-affinity extra neuronal process (uptake 2) into peripheral tissues, such as vascular and cardiac muscle and certain glands. NA is also metabolized by catechol-O-methyl transferase (COMT). Thus NA measured in plasma is the overspill not affected by these numerous processes.

Table 83.1: Classification of disorders resulting in autonomic dysfunction

- Primary (etiology unknown)
  - Ai utL' **.in..!** subacute d;. ••.nmnii 'ini.r.
    - Pure cholinergic dysautonomia
    - Pure pandysautonomia
    - Pan dysautonomia with neurological features
  - Chronic autonomic failure syndromes
    - Pure autonomic failure
    - Multiple system atrophy [Shy-Drager syndrome'
    - Autonomic failure with Parkinson's disease
- Secondary
  - Congenital
    - Nerve growth factor deficiency
  - Hereditary
    - Autosomal dominant trait
      - Familial amyloid neuropathy
      - Porphyria
    - Autosomal recessive trait
      - Familial dysautonomia (Riley-Day syndrome)
      - Dopamine ^-hydroxylase deficiency
      - Aromatic l-amino acid decarboxylase deficiency
    - X-linked recessive
      - Fabry's disease
  - Metabolic diseases
    - Diabetes mellitus
    - **Chronic renal failure**
    - Chrome liver disease
    - Vitamin B_u deficiency
    - Alcohol-induced
  - Inflammatory
    - Guillain-Barre syndrome
    - Transverse myelitis
  - Infections
    - Bacterial: tetanus
    - Viral: human immunodeficiency virus
    - Parasitic: *Trypanosoma cntzi;* Chagas' disease
    - Prion: fatal familial insomnia
  - Neoplasia
    - Brain tumors, especially of third ventricle or posterior fossa
    - Paraneoplastic, to include adenocarcinomas: lung, pancreas, and Lambert-Eaton syndrome
  - Connective tissue disotdets
    - Rheumatoid arthritis
    - Systemic lupus erythematosus
    - Mixed connective tissue disease
  - Surgery
    - Regional sympathectomy: upper limb and splanchnic denervation
    - Vagotomy and drainage procedures: "dumping" syndrome
    - **Organ transplantation: hcatt, kidney**
  - **Trauma**
    - Spinal cord transection
  - Miscellaneous
    - Subatachnoid hemorrhage
    - Syringobulbia and syringomyelia
- Neutally mediated syncope
  - Vasovagal syncope
  - Carotid sinus hypersensitivity
  - Micturition syncope
  - Cough syncope
  - Swallow syncope
  - Associated with glossopharyngeal neuralgia

Table 83.2: Drugs, chemicals, poisons, and toxins causing auroni imif d\ -.Inn.. . . .I

- Decreasing sympathetic activity
  - Centrally acting
    - Clonidine
    - Mcthyldopa
    - Moxonidine
    - Reserpine
    - Barbiturates
    - Anesthetics
  - Peripherally acting
    - Sympathetic nerve ending (guanethidinc, bethanidine)
    - **or-Adrcnoccptor blockade {phcnoxybcni'.aminc}**
    - ^-Adrenoceptor blockade (propranolol)
- Increasing sympathetic activity
- Amphetamines
  - Releasing noradrenaline (tyramine)
  - Uptake blockers (imipramine)
  - Monoamine oxidase inhibitors (tranylcypromine)
  - *fi*-Adrenoceptor stimulants (isoprenaline)
- Decreasing parasympathetic activity
  - Antidepressants (imiptamine)
  - Tranquilizers (phenothiazines)
  - Antidysrhythmics (disopyramide)
  - Anticholinergics (atropine, propantheline bromide, be nztt opine)
  - Toxins (hotuhnum)
- Increasing parasympathetic activity
  - Cholinomimetics (carbachol, bethanechol, pilocarpine, mushroom poisoning)
  - Anticholinesterases
    - Reversible carbamate inhibitots (pyridostigmine, neostigmine)
    - Organophosphorous inhibitors (pa rath ion, sarin)
- Miscellaneous
  - Alcohol, thiamine (vitamin B|) deficiency
  - Vincristine, perhexiline malcate
  - Thallium, arsenic, mercury
  - Mercury poisoning (pink disease)
  - Ciguatera toxicity
  - Jellyfish and marine animal venoms
  - First dose of certain drugs (prazosin, captopril)
  - Withdrawal of chronically used drugs (clonidine, opiates, alcohol)

diabetes mellitus) or for which there are strong associations, as with Holmes-Adit: syndrome or aging. Drugs arc a major cause of autonomic dysfunction, acting at single or multiple sites (Tabic 83,2), In neutally mediated syncope, there is an intermittent autonomic abnormality-, as occurs in vasovagal syncope and carotid sinus hypersensitivity. Tabic 83.3 provides examples of autonomic disorders in which localized deficits affect specific organs.

Primary Autonomic Failure

Disorders of primary autonomic failure are those in which autonomic failure is of unknown etiology. Most arc chronic autonomic failure syndromes.

Tabic 83.3: Examples of localised autonomic disorders

Homer's syndrome
Holmes-Adie pupil
Crocodile tears (Bogorad's syndrome)
Gustatory sweating (Frey's syndrome)
Reflex sympathetic dystrophy
Idiopathic palmar or axillary hyperhidrosis
Chagas' disease *(Trypanosomiasis cruzi)**
Surgical procedures
Sympathectomy (regional)
Vagotomy and gastric drainage procedures in "dumping" syndrome
Organ transplantation (heart, lungs)

'Listed here because it specifically targets intrinsic cholinergic plexuses in the heart and gut.

Surgery also may cause other localized disorders, such as Frey's syndrome (after parotid surgery).

Table 83.4: Some of the clinical manifestations in primary chronic autonomic failure

Cardiovascular: postural (orthostatic) hypotension
Sudomotor: anhidrosis, heat intolerance
Gastrointestinal: constipation, occasionally diarrhea, oropharyngeal dysphagia
Renal and urinary bladder: nocturia, frequency, urgency, retention, incontinence
Sexual: erectile and ejaeulatory failure in the male
Ocular anisocoria, Horner's syndrome
Respiratory: stridor, involuntary inspiratory gasps, apneic episodes
Other neurological deficits: parkinsonian and cerebellar or pyramidal features

Chronic Autonomic failure

These patients often have both sympathetic and parasympathetic failure {Table 83.4). Clinically they fall into three major categories (Figure 83.5). Patients with autonomic failure alone and no other neurological features have PAH. This group encompasses *idiopathic orthostatic hypotension* (without other neurological defects), a term that does not indicate the possible autonomic involvement of sweat glands, pupils, and urinary bladder, bowel, and sexual function. When primary chronic autonomic failure is associated with other neurological abnormalities and without a defined cause or association, the term *Shy-Drager syndrome* was used after the first neuropathologic.il description and linkage between orthostatic hypotension and neurological abnormalities. *MSA* is now used synonymously with *Shy-Drager syndrome.* At a consensus meeting of international experts, MSA was defined as a "sporadic, progressive disorder characterized by autonomic dysfunction, parkinsonism, and ataxia in any combination'[1] (SchatZ et al. 1996, Gtlman et al. 1998). There are three major clinical forms of MSA, based on the additional neurological features. The presence of parkinsonian features is associated with stria tonigral degeneration and loss of pigmented cells in the substantia nigra and locus eeruleus; this is the *parkinsonian* ot *striatonigrat degeneration form.* There may be cerebellar manifestations, with or without pyramidal signs, and association with atrophy of the cerebellum, olives, and pons (the *cerebellar* or *olivopontocerebellar atrophy form).* Many patients, especially as the disease progresses, have a combination of extrapyramidal, cerebellar, and pyramidal manifestations *(mixed* or *multiple form).*

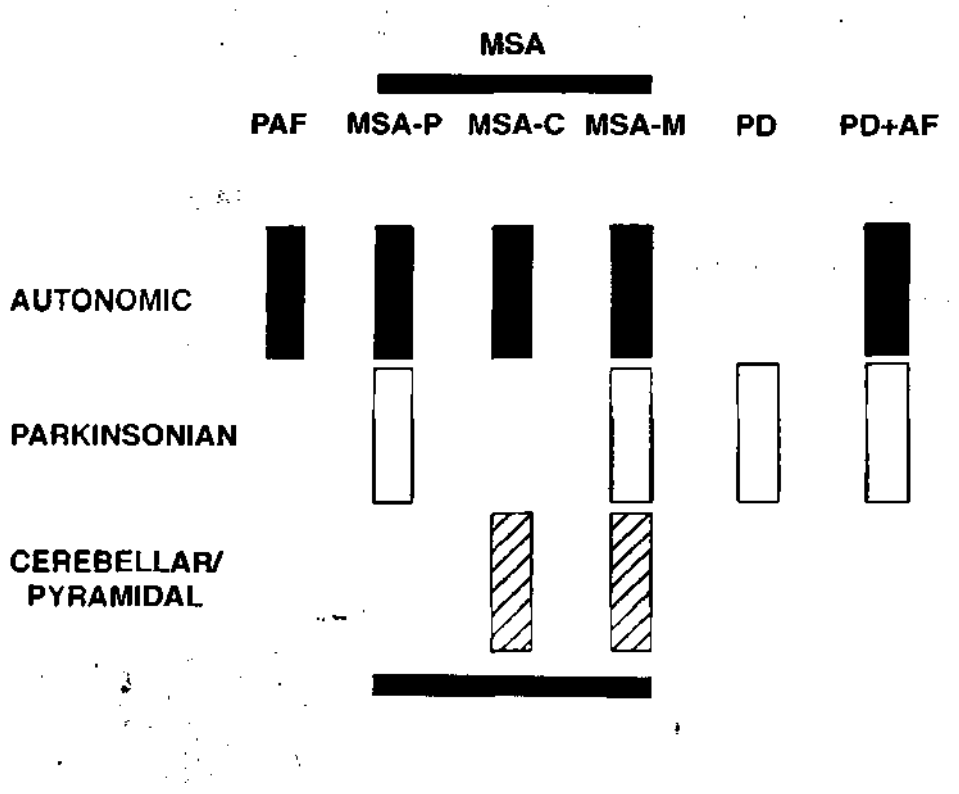


FIGURE 83.5 Schematic representation of the major clinical features of primary chronic autonomic failure syndromes. These include pure auronomic failure (PAF) and the three major neurological forms of multiple system atrophy (MSA): the parkinsonian form (MSA-P, synonymous with striatonigral degeneration), the cerebellar form (MSA-C, synonymous with olivopontocerebellar atrophy), and the mixed lorm (MSA-M, with both features). Also included are Parkinson's disease (PD) and the tarer subgroup with Parkinson's disease and autonomic failure (PD+AF). (Modified with permission from Mathias, C.J. 1997, "Autonomic disorders and their recognition," N *Engl] Med,* vol. 10, p. 721.)

In our autonomic units, which serves as a national referral centers, approximately 20% of patients have the parkinsonian form, 20% have the cerebellar form, and 60% have the multiple form. This distribution probably varies, depending on referral patterns, the special interests of the hospital, early consideration of the diagnosis, and the presence of an autonomic unit.

Extrapyramidal features may predate autonomic failure in the parkinsonian form of MSA, which may be difficult to differentiate from idiopathic Parkinson's disease, especially in the early stages. This problem has been highlighted in postmortem studies, in which 7-22% of patients who were thought to have idiopathic Parkinson's disease actually had MSA. Separating the two disorders is important because the prognosis is considerably poorer for patients with MSA, and the occurrence and nature of complications and the management of the conditions differ (Mathias and Williams 1994; Wcnning et al. 1994, 1997). There are some differences in the extrapyramidal features between MSA and Parkinson's disease (Quinn and Marsdcn 1993), but these may not be clinically valuable, especially in individual subjects in the early stages of the diseases. Although many patients with MSA do not respond favorably to L-dopa or experience substantial side effects, such as postural hypotension, a proportion with the parkinsonian form have a benefit, especially- in the early stages (Colosimo et al. 1995), as do the majority with idiopathic Parkinson's disease. Differentiation of the two groups is important for drug trials and interventional studies (e.g., as with substantia nigra implantation) because those with MSA arc unlikely to show a favorable response.

There is accumulating evidence of autonomic nervous system involvement in idiopathic Parkinson's disease. However, the extent and degree of autonomic dysfunction vary and appear to depend on factors that include age and duration of disease (Mathias 1998). There is a smaller group with apparent idiopathic Parkinson's disease in whom substantial cardiovascular autonomic failure may occur, often as a late complication (Goldstein et al. 2002). These patients usually are elderly and have been successfully treated with L-dopa and other antiparkinsonian drugs for many years. They thus differ clinically from those who have the parkinsonian forms of MSA. It is not clear if they ate a Special group with idiopathic Parkinson's disease who arc vulnerable to autonomic degeneration ot their autonomic failure is associated with old age, chronic drug therapy, or a combination of such factors.

In the different parkinsonian syndromes (other than MSA) the extent and degree of autonomic dysfunction relates to the underlying diagnosis. Cardiovascular autonomic failure is an exclusionary feature in progressive supranuclear palsy (Kimher et al. 2001). In dementia with Lewy bodies, orthostatic hypotension and autonomic failure may be severe and an early manifestation, even before the onset of parkinsonian features (Lamer et al. 2000; Hishikawa et al. 2000). Autonomic deficits have been described in patients with the Guam parkinsonian dementia complex, the Machado-Joseph syndrome (Kazura et a I. 2000), and Wilson's disease {Bhattacharyaetal, 2002; Meenakshi-Sundarametal. 2002).

In chronic primary autonomic failure syndromes, a common feature accounting for sympathetic dysfunction is loss of small sympathetic cells in the intetmediolateral cell column of the thoracic and lumbar spinal cord (Figure 83.6). In PAF, for which limited neuropathological data are available, there also is substantial neuronal cell loss in the paravertebral sympathetic ganglia (Matthews 2002). Some of the surviving ganglionic neurons in the paravertebral ganglia show Lewy bodies that are not found in MSA; these

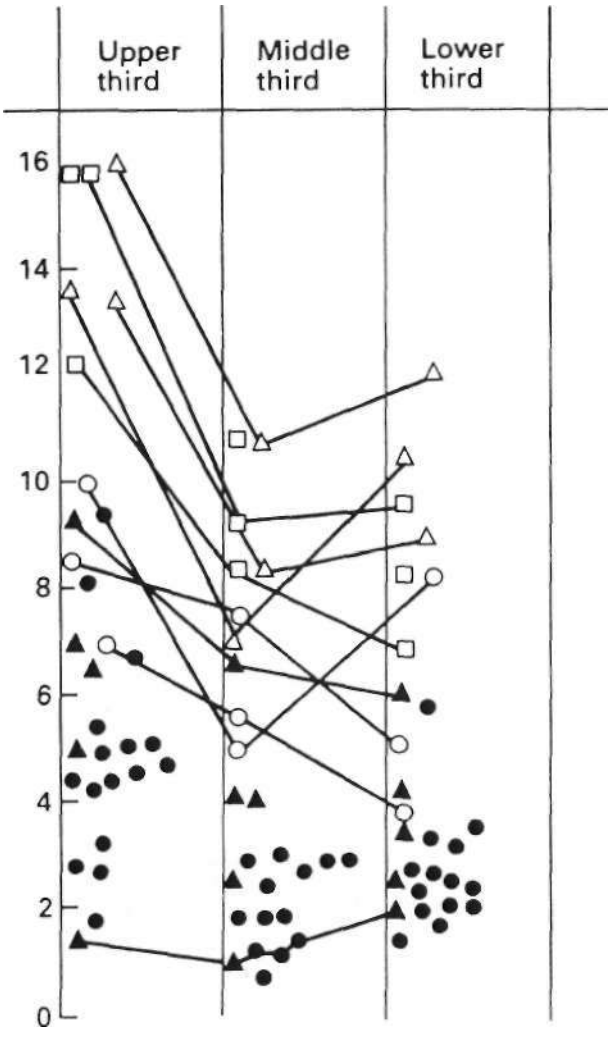


FIGURE 83.6 Cell counts in intermediolateral horns of upper, middle, and lower thoracic spinal cord. Figures indicate mean number of cells in ;i single lateral horn and 20-mm sections in control specimens. These include three patients with Parkinson's disease without autonomic failure (A), three patients with multiple system atrophy without autonomic failure (O), 16 patients with autonomic failure (•), and five patients with autonomic failure showing Lewy bodies in the brainstem (A). (Reprinted with permission from Oppenheimer, D. R., et al. 1980, "Lateral horn cells in progressive autonomic failure," / *Neurol Set,* vol. 46, pp. 393-404.)

include "eosinophilic bodies" of bi/.arre serpiginous form, now regarded as intraneuritic Lewy bodies. The absence of additional neurological features and the available biochemical and hormonal evidence, which excludes central cerebral involvement (Kimber et al. 1997b; Mathias and Polinsky 1999), are consistent with a peripheral sympathetic lesion in PAF. In MSA, the evidence points to predominantly cerebral autonomic lesions. In addition, there is cell loss in the intermediolateral cell column of the thoracic and lumbar spinal cord. A further feature is the involvement of neurons in the margins of the ventral horn ol the second ami ihiol ^ural segments (Omif's nucleus), which innervate the voluntary sphincters of the urinary bladder and anus. These nuclei arc spared in motor neuron diseases, which suggests that they are more likely to be parasympathetic than somatic neurons. It is not known if these cell groups are affected in PAF. In MSA, neurons of sympathetic ganglia usually are not severely reduced in number and do not exhibit major abnormalities, apart from a relative lack of Nissl material, which suggests partial denervation atrophy of long-standing duration.

In MSA, neuropathologies! studies indicate widespread abnormalities in the brain (Daniel 2002). In the parkinsonian form, the proportion of brainstem and cerebellum to whole brain is normal, unlike in the cerebellar form. In the parkinsonian form, the putamen is shrunken with gray-green discoloration, and in severe forms, there is a cribriform appearance. Atrophy and discoloration of the caudate nucleus and pallidum are less common. The substantia nigra shows decreased pigmentation. There is pallor of the locus ceruleus. In the cerebellar form, the pons and the middle cerebellar peduncles are reduced, with atrophy of the folia. On microscopy, there is cell loss and gliosis in the parkinsonian forms, particularly in the putamen, and especially in the posterior two thirds and dorsolateral regions, although this may be more widespread. Similar changes also occur in the caudate nucleus and globus pallidus but to a lesser extent than in the putamen. In the zona compacta of the substantia nigra, there is degeneration of pigmented nerve cells, as in the locus ceruleus. In the cerebellar form, the neuropathological changes may be indistinguishable from those with familial forms of olivopontocerebellar atrophy. There is cell loss in the cerebellum, olives, and pons. Purkinje's cell nerve loss is often focal, rarely complete, and not accompanied by basket cell loss and thus different from cerebellar anoxic damage, in which both cell groups arc vulnerable.

The parkinsonian forms of MSA show features indicative of striatonigral degeneration, while those with the less common cerebellar form show olivopontocerebellar degeneration. Despite characteristic pathological changes in one or the other system in the two forms, there is often widespread involvement ncuropathologically, consistent with in vivo findings using positron-emission tomography (PET) (Rinne et al. 1995). As the disease progresses, there is likely to be an increasing degree of cell loss and gliosis,

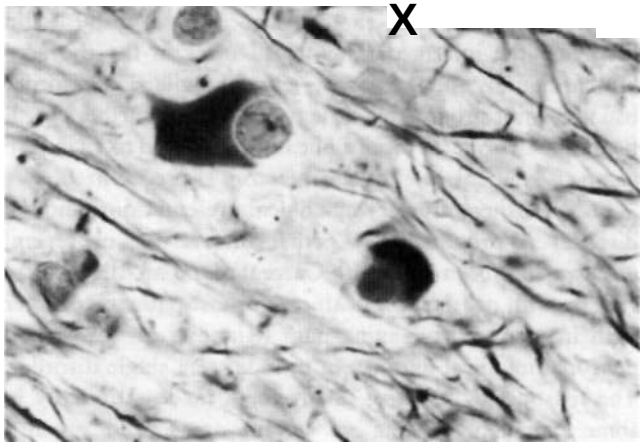


FIGURE 83.7 Photomicrograph showing appearance of oligodendrocyte glial cytoplasmic inclusions with modified Bielschowsky's silver impregnation and immunocytochemistry for cr-tubulin (frontal cortex, x 1250). (Reprinted with permission from Daniel, S. E. 2002, "The neuropathology and neuroehetnistry of multiple system atrophy," in *Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System*, 4th ed, eds C. J. Mathias Sc R. Bannister, Oxford University Press, Oxford, pp. 321-328.)

which probably accounts for the varying pathological descriptions provided over the years.

A key feature in MSA has been the presence of glial intraneuronal cytoplasmic nuclei inclusions (Papp and Lantos 1994) (Figure 83.7). These stain with antibodies against ubiquitin, a- and ^-tubulin, and r, thereby indicating a site of origin from cytoskeletal proteins. In MSA, they are present in large numbers and provide a pathological hallmark for the definition of the condition (Daniel 2002). They are also present in previously considered unaffected areas of the brain. Inclusions similar to those in MSA have been described in progressive supranuclear palsy, corticobasal degeneration, and familial olivopontocerebellar atrophy. However, in these conditions they arc rare, require careful search, and have distinct differences in T profile. In MSA, cr-synuclein is present in inclusions and appears different from that of dementia with Lewy bodies and Parkinson's disease (Campbell et al. 2001). These differences may contribute further ro our understanding of MSA and other parkinsonian syndromes.

In MSA, a number of additional sites may be involved. These include degeneration of the thalamus and vestibular complex. There is a reduction of Edinger-Westphal neurons. Cell loss in the hypothalamus is minimal but with an apparent depletion of various catecholamines and neurotransmitters, which may account for the neuroendocrine abnormalities and impairment of hypothalamic function reported. There often is atrophy of the dorsal motor nucleus of the vagus. Despite laryngeal dysfunction being common, cell loss has not been documented in the nucleus atnbiguus, which suggests a central biochemical deficit or more peripheral involvement or both.

In summary, in PAF, the evidence favors a distal lesion involving the intermcdiolateral cell mass in the thoracolumbar regions and the paravertebral ganglia. The disorder usually is not progressive. It is probable that further classification will occur in those clinically considered to have PAF as precise deficits or etiological factors are recognized.

In MSA, there are varying clinical presentations, and the disorder is progressive. Whether this is one or several diseases has been debated. Current data on the clinical course, with overlapping features in most patients together with in vivo neuroimaging data (Rinne et al. 1995) and neuropathological data, seem to indicate a single disorder. The reasons for selective involvement (at least initially in some patients), sparing of certain areas, and possible interaction with genetic and environmental factors remain to be determined.

Acute and Subacute Dysautonamias

In the Guillain-Barre syndrome, a variety of autonomic disorders have been described, from hyperactivity to primary autonomic failure. These disorders can result in marked cardiovascular changes, from hypertension and tachycardia to hypotension and bradycardia. There arc differences between the axonal and myelinated forms of the Guillain-Barre syndrome (Asahina ct al. 2001). Autonomic disturbances contribute to both morbidity and mortality.

Acute and subacute dysautonomias are rarer causes of primary autonomic failure. The precise reasons are unclear and may include viral infections, with immunological damage as a contributory factor. Two case reports have indicated a beneficial response to the intravenous administration of immunoglobulin, which favors an immunological etiology (Hcafiek! ct al. 1996; Smit et al. 1997). There are three clinical forms. In pure cholinergic dysautonomia, parasympathetic and sympathetic cholinergic pathways are impaired, resulting in alacrima, xerostomia, dysphagia, large bowel atony, detrusor muscle dysfunction, and, in men, erectile failure; anhidrosis also occurs. Thus only the cholinergic system is affected. There is a response to cholinomimetic agents, such as bethanechol, indicating preservation of postsynaptic cholinergic receptor function and suggesting a presynaptic lesion. In the other forms with pandysautonomia, the parasympathetic and sympathetic nervous systems are impaired. In some patients, there are no other neurological features, whereas in others, there may be additional neurological lesions, often involving peripheral nerves. These lesions have been demonstrated on sural nerve biopsy, which shows a reduction in the numbers of both myelinated and unmyelinated fibers.

Secondary Autonomic Dysfunction

The pathological changes of secondary autonomic dysfunction depend on the causative or associated disease or disorder. A brief description of some of the changes is provided in the following sections, based on the probable site of lesion within the nervous system,

Cerebral

Autonomic failure may result from specific lesions, especially in the brainstem. Posterior fossa tumors and syringobulbia may cause postural hypotension by ischemia or destruction of brainstem cardiovascular centers. Dcmyelination or plaque formation in multiple sclerosis may cause a variety of autonomic defects of cerebral origin, although it is difficult to exclude a spinal contribution (Thomaides et al. 1993; Kcselbrener et al. 2000). Autonomic failure in elderly patients may be largely central, due to widespread neuronal degeneration, although peripheral neural and target organ deficits may contribute.

Certain cerebral disorders cause a pathological increase in autonomic activity. In bulbar poliomyelitis, hypertension has been associated with damage in the lateral medulla. In cerebral tumors, distortion or ischemia of specific pressor areas, which have been defined experimentally and termed *Cusbing-sensitive areas,* may raise blood pressure by increasing sympathetic activity. This may account for the symptoms in a patient of Penfield, who had a tumor of the third ventricle and was thought to have diencephalic autonomic epilepsy. Similar mechanisms may also account for increased sympathetic activity, hypertension, and cardiac dysrhythmias associated with subarachnoid hemorrhage, although the local effects of various chemicals from extravasated blood also may influence cerebral centers. In tetanus, hypertension may result from increased sensitivity of brainstem centers through retrograde spread of tetanus toxin along the nerve fibers. In fatal familial insomnia, a prion disease predominantly involving the thalamus, there are abnormalities of autonomic function. These include increases in blood pressure, heart rate, lacrimation, salivation, sweating, and body temperature, along with altered hormonal arcadian rhythms in the presence of intact target organ function (Cortelli et al. 1997).

Spinal Cord

Damage to the spinal cord by trauma, transverse myelitis, syringomyelia, or spinal cord tumors may disturb or sever connections between the brain and the thoracolumbar sympathetic and sacral parasympathetic outflow. Spinal reflexes through unaffected areas in the cord below the lesion may be activated, resulting in abnormal peripheral autonomic activity.

Peripheral

Peripheral autonomic dysfunction is associated with a wide range of diseases and syndromes. It may involve a specific afferent pathway, as in carotid sinus hypersensitivity. The

lesion may involve efferent pathways only, as in dopamine ri hydroxylase (Dblli Jilkiuk}, which selectively causes deficiency of noradrenaline and adrenaline, with elevation of the precursor dopamine and preservation of other transmitters in sympathetic nerve terminals (Mathias and Bannister 2002a). In a brother and sister with this disorder, genetic studies indicated an autosomal recessive transmission. DBH genes have been identified on chromosome 9, linked to 9q34, and do not have any obvious deletions in this disorder, thus raising the likelihood of point mutations, recently have been described (Kim et al. 2002). In the Eaton-Lambert syndrome, the cholinergic system is primarily affected. In diabetes mellitus, different autonomic pathways may be affected as the disease progresses; the cardiac parasympathetic nerve is often involved first, with sympathetic dysfunction occurring later. There may be associated involvement of specific components of peripheral nerves in certain disorders. One of these is nerve growth factor deficiency, which results in the deficiency of DBH, the sensory neuropeptides, substance P, and calcitonin gene-related peptide. Another such disorder is the Riley-Day syndrome (familial dysautonomia), with mutation of the *IKAP* gene (Anderson ct al. 2001); pathological changes occur in both dorsal root and sympathetic ganglia.

In amyloidosis, deposits in the heart, blood vessels, and adrenal glands (causing adrenocortical deficiency) may compound autonomic dysfunction and thus increase the severity of orthostatic hypotension. There is increasing evidence of differences in autonomic dysfunction in the various mutations, resulting in familial amyloid polyneuropathy. Deposition of abnormal protein in autonomic nerves can affect cardiovascular, sudomotor, gut, bladder, and sexual function. The heart also may be affected directly, by amyloid deposition.

Autonomic dysfunction may complicate malignancies, including as a paraneoplastic syndrome (Waterman 2001), in which it is often not possible to determine the site of the lesion. Acquired immunodeficiency syndrome is associated with several autonomic abnormalities. Pheoehromoeytoma occasionally may be part of multiple endocrine neoplasia (such as Sipplc's syndrome) or may be associated with neurofibromatosis and other neuroectodermal syndromes (tuberous sclerosis, von Hippel-I.indau disease, and Sturgc-Weber syndrome). Carotid body tumors, ganglioneuromas, and neuroblastomas also arise from neuroectodermal tissue but arc less likely to result in abnormal catecholamine secretion.

Neurally Mediated Syncope

Neurally mediated syncope is a disorder in which there is intermittent dysfunction affecting the autonomic nervous system. This dysfunction results in bradycardia due to increased parasympathetic cardiac activity and hypotension due to withdrawal of sympathetic vasoconstrictor tone. It probably accounts for a substantial proportion of recurrent syncope and prcsyncope, in which a cardiac, nonautonomic neurological or metabolic cause has been excluded (Mathias ct al. 2001a). In the young, a common cause is vasovagal syncope. In elderly patients, carotid sinus hypersensitivity is increasingly recognized. Rarer causes include those associated with neoplasia affecting the glossopharyngeal nerve.

Situational syncope occurs in weigh differs; other examples are during micturition, defecation, or even laughing. There is an association between syncope and the first dose of certain drugs (prazosin and acetylcholinesterase inhibitors).

Drugs, Chemicals, and Toxins

Drugs, chemicals, and toxins may act by interfering with, or stimulating, sympathetic or parasympathetic activity (Tonkin and Hrewin 2002) (see Table S3.2). A minor side effect of a drug may unmask or worsen autonomic deficiency; an example is postural hypotension, which is usually enhanced by L-dopa in the parkinsonian and mixed forms of MSA. Drugs administered locally, such as the beta blocker timolol (ocular drops), the u^-agonist xytometazoline, and the «-agonist phenylephrine (intranasally), may enter the systemic circulation and have deleterious effects.

Alcohol may impair autonomic function cither directly, by causing a neuropathy, or through associated deficiencies, such as that of vitamin Bi (thiamine). The withdrawal of drugs, such as alcohol, opiates, and clonidine, especially when used in high doses chronically, may result in the reverse (sympathetic overactivity), with increased sweating, hypertension, and piloerection.

Vincristine is directly neurotoxic and may cause an .i-,-,tK lated autonomic neuropathy, as with pethexiline m.il eatc, an antianginal agent. The latter is mainly associated with a metabolic deficit, which slows its degradation. Thallium, arsenic, and mercury increase autonomic activity by mechanisms that are unclear. Botulism mainly results in cholinergic deficits, but there may be associated sympathetic involvement in severe cases. Consumption of reef fish containing ciguatera toxin may cause bradycardia through increased vagal tone, which can be reversed by atropine.

Localized Autonomic Disorders

In Horner's syndrome (see Table 83.3), the sympathetic fibers to the pupil, upper eyelid (the nonstriated portion of the levator palpebrae superioris, or Mtiller's muscle), facial sweat glands, and facial blood vessels are affected by lesions that could be in the brain (hemorrhage), spinal cord (trauma), or periphery (neoplasms affecting the cervical ganglia, as in Pancoast's syndrome). When only the eye is

involved, the lesion lies within the distribution of the internal carotid artery because the sympathetic nerves accompanying the external carotid artery arc intact, thus sparing the facial sweat glands and vessels (Raeder's syndrome).

Holmes-Adie pupil is a benign condition, usually seen in women, and is characterized by a dilated pupil that is sluggishly responsive to tight. The iris musculature is supersensitive to locally applied cholinomimetics, such as dilute mcthacholine or pilocarpine Hie pathologic change is thought to involve the parasympathetic ciliary ganglia. When the condition is associated with absent tendon reflexes, the term *Holmes-Adie syndrome* is used. The lesion is thought to involve the dorsal root ganglia, which accounts for the absent H wave on electrophysiological testing. Some patients have sudomotor abnormalities (Ross's syndrome), cardiovascular autonomic deficits, diarrhea, or a dry, chronic cough (Kimbcr ct al. 1998).

In the chronic form of Chagas' disease (after infection with *Trypanosoma cruzi),* there is fibrosis in the heart and damage to the sinus node and conducting system. The esophagus and colon often are involved after ganglionitis and destruction of Meissner's and Auerbach's plexuses, thus causing dilatation of the esophagus, stomach, or large bowel. In congenital megacolon (Hirschsprung's disease), parasympathetic ganglion cells from the intramural (Auerbach's) plexus are absent in localized segments of the rectum and sigmoid colon, often with sympathetic aplasia, and cause colonic narrowing with proximal distention.

Increased lamination due to an abnormal gustolacrimal reflex (crocodile tears or Bogorad's syndrome) results from cross-inncrvation of the lacrimal and salivary glands. It may be acquired after Bell's palsy (with the lesion at, or proximal, to the geniculate ganglion) or after surgery to the greater superficial petrosal nerve (which contains fibers to the lacrimal gland and the submandibular and sublingual salivary glands). It also may occur after damage to the lesser superficial petrosal nerve, which supplies the parotid glands. If bilateral, the disorder is usually congenital. A similar situation may occur in gustatory sweating, in which parasympathetic fibers to the salivary glands reinnervate the sweat glands that normally have a sympathetic cholinergic supply (auriculotemporal or Frey's syndrome).

Sympathetic nerve damage may occur win limb or brachial plexus injuries and be either pre- or postganglionic. Severe pain (causalgia) may result from abnormal connections between the efferent sympathetic nerves and somatosensory afferent nerves. Similar changes may occur in post-traumatic reflex sympathetic dystrophy (Sudeck's atrophy). The precise role of the sympathetic nervous system in such disorders is unclear (Kimber et al. 1997a) and is relevant to their management (Schott 1998).

Transplantation of organs such as the heart and kidneys leaves them bereft of their autonomic nervous supply. After cardiac transplantation, upregulation of ^-adrenoceptors may increase sensitivity to endogenous or exogenous catecholamines and could increase the risk from cardiac dysrhythmia. Renal function after transplantation does not appear to be impaired, although nocturnal polyuria may be attributed to lack of sympathetic control of tubular function. Re innervation may occur.

Clinical Features

Patients with primary chronic autonomic failure are usually middle-aged or elderly. There is a male predominance. Increased awareness of such disorders and earlier referral for autonomic investigation have resulted in recognition of a number of younger subjects, some in their mid-30s. A family history is unusual. Only two families with autonomic failure and additional neurological abnormalities have been reported, although from the descriptions available they were unlikeh to have VISA. In MSA, there is no evidence that genetic, environmental, or occupational risk factors contribute.

In secondary autonomic failure, the age of onset depends on the associated or causative disorder. Some may present at birth, as in Riley-Day syndrome (familial dysautonomia), which is transmitted as an autosomal recessive trait and usually affects siblings rather than successive generations. Riley-Day syndrome occurs mainly in Ashkenazi Jews, in whom there is a high prevalence of consanguinity. Patients with 1)B11 deficiency syndrome have autonomic problems from childhood. In familial amyloid polyneuropathy, the presenting features usually occur in adulthood. Patients with insulin-dependent diabetes of long duration may develop an autonomic neuropathy.

In vasovagal syncope there often is a strong family history, especially in those in whom the disease presents when they are teenagers (Mathias et al. 1998); whether environmental factors contribute remains unclear (Mathias etal. 2000).

Cardiovascular System

Hypotension. The symptoms from postural (orthostatic) hypotension often provide the first clue and are usually the reason for patients' requesting medical advice (Mathias et al. 1999). They mainly result from cerebral hypoperfusion (Table 83.5). Dizziness and visual disturbances (such as blurred VISUM'.. gra\ ing our, blacking out, or tunnel vision) may precede loss of consciousness. These occur on the patient's assuming the upright posture, especially when getting out of bed in the morning (Table *S3.6).* Food, alcohol, exercise, and a raised environmental temperature usually enhance symptoms. Straining during micturition and bowel movements, which often are affected in autonomic disorders, may induce attacks. Many recognize the association between postural change and the early symptoms of cerebral hypoperfusion and either sit down,

Table 83.5: Symptoms that result from postural (orthostatic) hypotension and impaired perfusion of organs

Cerebral hypoperfusion
Dizziness
Vision disturbances
blurred vision, color defects, scotoma, tunnel, graying out, blacking out
Loss of consciousness
Impaired cognition
Muscle hypoperfusion
Paraecrvical and suboccipital ("coat-hanger"] ache
Lower back or buttock ache
Calf claudication
Cardiac hypoperfusion: angina pectoris
Spinal cord hypoperfusion
Renal hypoperfusion: oliguria
Nonspecific: weakness, lethargy, fatigue, falls

lie flat, or assume curious postures, such as squatting or stooping. Occasionally, the blood pressure may fall precipitously, and syncope may occur rapidly, as in a drop attack. Loss of consciousness may result in injury. Seizures due to cerebral anoxia may occur in some patients. Postural hypotension can be considerably aggravated by drugs (such as i.-dopa) that normally cause minimal or no change in blood pressure. In diabetic patients with an autonomic neuropathy, administration of insulin, eithet by reducing blood volume through increasing transcapillary albumin escape or by vasodilatory effects, occasionally may exacerbate postural hypotension.

The fall in blood pressure and symptoms during postural change may vary considerably (Figures 83.8 and 83.9). Many patients tolerate an extremely low cerebral perfusion pressure without symptoms, presumably because of improved cerebrovascular autoregulation. This may explain why some patients' symptoms arc worse in the early stages of their disorder, as in those with high spinal cotd injuries, who later tolerate head-up postural change despite a similar fall in blood pressure. Some may hyperventilate, which should be discouraged because it further reduces cerebral perfusion thtough cerebral vasoconstriction. Symptomatic tolerance appears to develop with repeated head-up tilt and exposute to hypotension. Patients with spinal injuries soon learn that activation of skeletal muscle spasms or urinary bladdet contraction ttiggets spinal reflexes, and they use this to help reduce the postural fall in blood pressure. In eldetly patients, a relatively small fall in blood pressure may induce cerebral ischemia, especially in the presence of cerebrovascular insufficiency due to atheroma and stenosis.

Table 83.6: Factors influencing postural (orthostatic) hypotension

Speed of positional change
Time of day (worse in die morning)
Prolonged recumbency
Warm environment (hot weather, central heating, hot bath)
Raising intrathoracic pressure by micturition, defecation, or coughing
Food and alcohol ingestion
Water ingestion*
Physical exertion
Maneuvers and positions (bending forward, abdominal compression, leg crossing, squatting, activating calf muscle pump)
Drugs with vasoactive properties (including dopaminergic agents)

*This raises blood pressure in primary autonomic failure.
These maneuvers usually reduce the postural fall in blood pressure, unlike the others.

Postural hypotension, especially when severe, may be accompanied by symptoms of hypoperfusion in other organs. In some patients a troublesome featute is pain in the suboccipital, paraccrvical, and shoulder muscles, in a "coat-hanger" distribution. This differs from other types of neck pain, including cervical spondylitis, because it is associated with the upright position and is relieved on the patient's assuming the horizontal position. It is probably due to postural hypotension causing ischemia in neck muscles that need to be kept tonically active to maintain the head uptight. It has been described in primary autonomic failure (Bleasdale-Barr and Mathias 1998) and high spinal cord injuries (Cariga et al. 2002a). Neck and shouldct ache in a coat-hanger distribution specifically related to a postural fall in blood pressure is common; the mechanisms are unclear. Angina pectoris may occasionally occur, even in young patients with apparently normal coronary arteries. There may be symptoms suggestive of spinal cord ischemia during standing.

Hypotension and syncope may occut during events unrelated to postural change, as in neurally mediated syncope. A common cause, especially in young and otherwise healthy individuals with apparently normal autonomic reflexes, is vasovagal syncope, when both heart rate and blood pressure fall rapidly (Figure 83.10) because of increased vagal activity and sympathetic withdrawal. I car, sometimes induced by venipuncture, and assumption of the upright position, especially on a tilt table, may provoke such a response. A variant, more common in wartime, is DaCosta's syndrome (soldier's heart or neurocirculatory asthenia), in which dizziness and syncope on effort are accompanied by exhaustion, dyspnea, headache, palpitations, and pain over the heart. The symptoms resemble orthostatic intolerance and syncope that may occur in chronic fatigue syndrome (De Lorenzo et al. 1997).

These disorders differ from carotid sinus hypersensitivity, in which pressure over the carotid sinus due to turning the head or tightening of the collat may induce an attack. This disorder is being increasingly recognized in elderly patients, especially those who present with falls of otherwise unknown etiology (Mcintosh et al. 1993). Maintenance of heart rate alone, by a catdiac demand pacemaker ot atropine, may not prevent hypotension in such patients. Paroxysms of coughing may induce syncope, especially

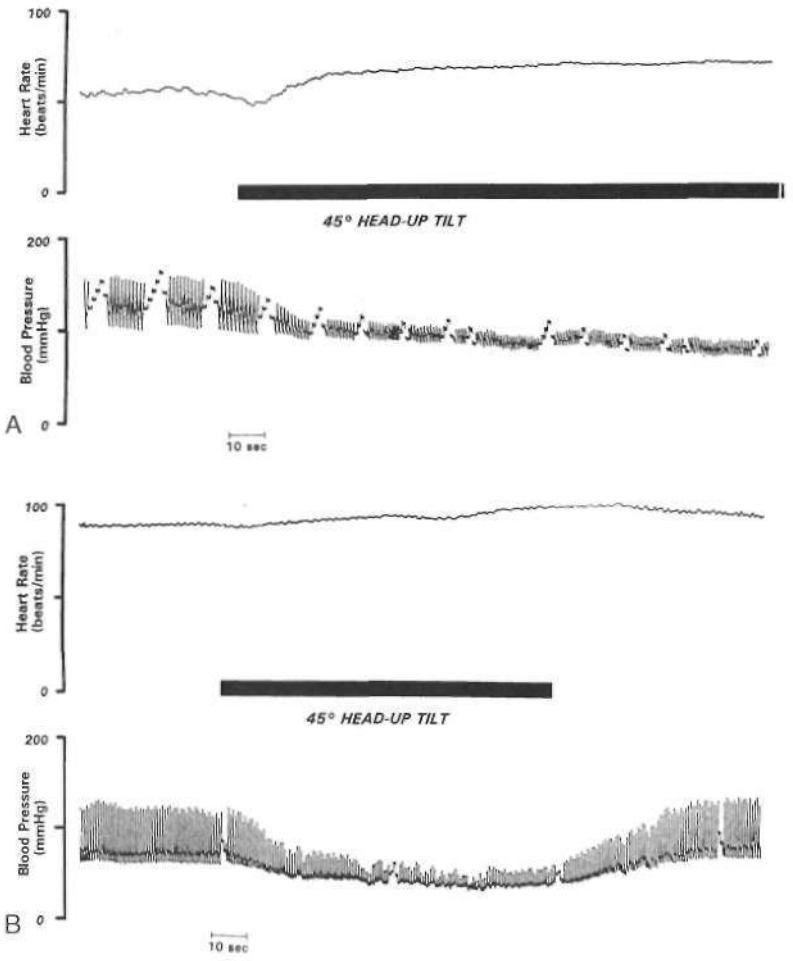


FIGURE 83.8 Blood pressure and heart rate measured by a noninvasive technique (with a Finapres [Ohmeda, BOC Health Care, UK]) in two patients with autonomic failure before, during, and after head-up tilt. (A) Blood pressure falls to low levels, but the patient could maintain head-up tilt with a low blood pressure for 20 minutes with few symptoms. This patient had autonomic failure for many years and could tolerate such levels, unlike the patient in (B), who had to be put back to the horizontal fairly quickly. She developed severe postural hypotension soon after surgery. (Reprinted with permission from Marhias, C. J. 1996, "Disorders affecting autonomic function in parkinsonian patients," Adv Neurol, vol. 69, p. .183.)

in patients with chronic obstructive airway disease. Micturition syncope usually is not accompanied by a detectable autonomic lesion. Hypotension appears to result from the combination of vasodilatation due to warmth or alcohol and straining during micturition. These actions raise intrathoracic pressure and induce a Valsalva maneuver while standing, which is compounded by release of the pressor stimulus arising from a distended bladder.

An increasingly recognised disorder is orthostatic intolerance with tachycardia (a rise of more than 30 heats per min)

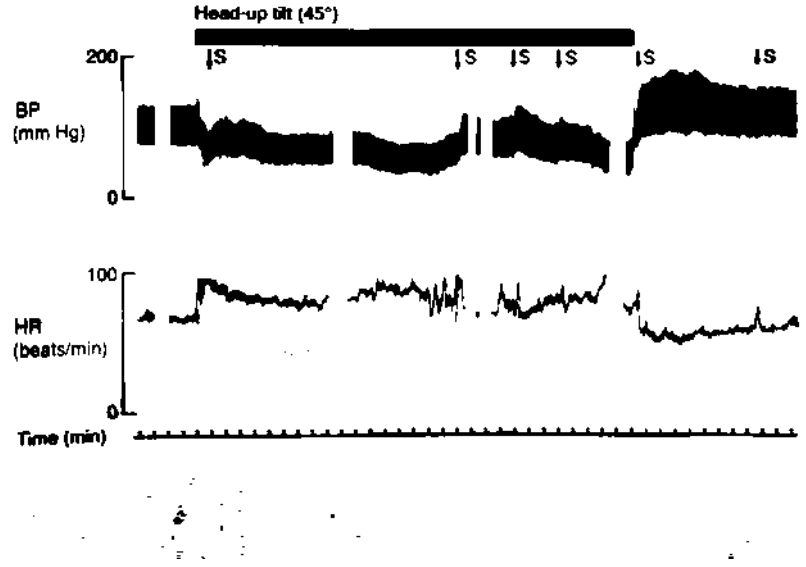


FIGURE S3.9 Inira-arterial recording of blood pressure (BP) and heart rate (HR) in a tetraplegic patient with a complete cervical spinal cord transection above the sympathetic outflow. There is an immediate fall in BP after head-up tilt, followed by a rise in BP during spontaneous skeletal muscle spasms (S). The slow recovery in BP may have been related to the release of renin and the subsequent formation of angiotensin II (measured at hreak-. in the record) because there is minimal or no change in plasma noradrenaline and adrenaline levels excluding significant sympathetic activations in response to postural challenge. On return to the horizontal, there is a BP overshoot. During tilt, heart rate rises due to an intact vagal efferent outflow. (Reprinted with permission from Mathias, C. J. &: Frankel, H. L. 1988, "Cardiovascular control in spinal man," *Annu Rev Physiol,* vol. 50, p. 577.)

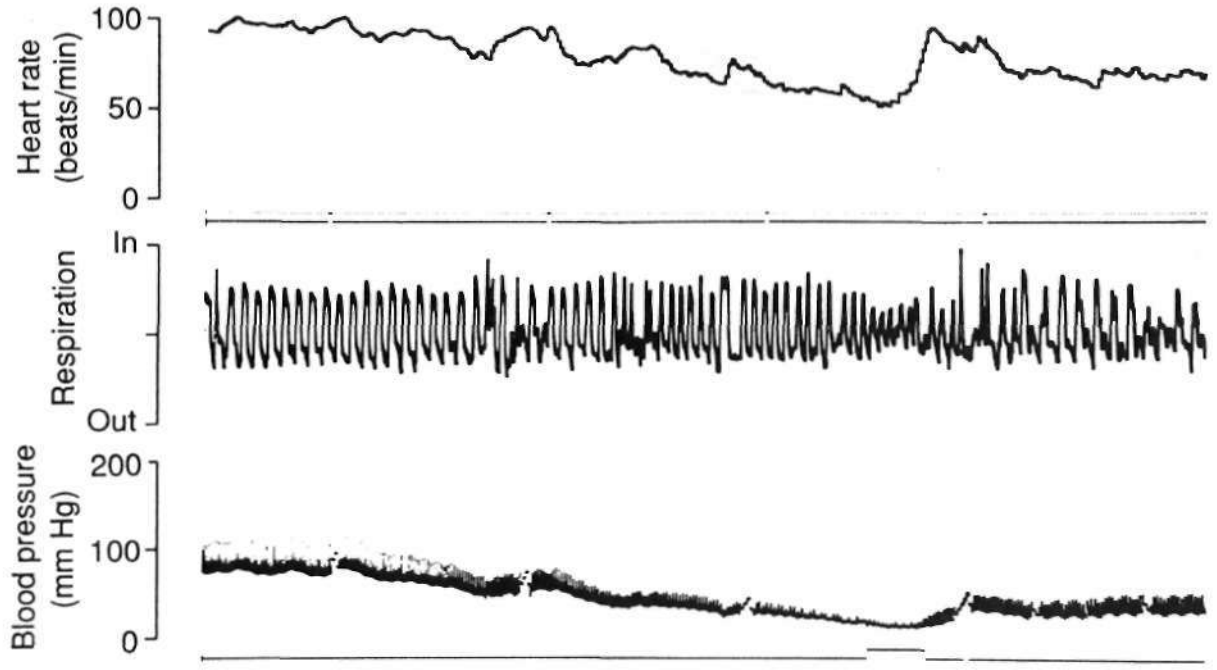


FIGURE 83.10 Blood pressure changes toward the end of a period of head-up tilt in a patient with recurrent episodes of vasovagal syncope. Blond pressure that was previously maintained begins to fall. There is also a fall in heart rate. There are relatively minor changes in respiratory rate, which can be derived from the time signal above it. Each minor dot indicates a second and the bolder mark indicates a minute. The patient was about to faint and was put back to the horizontal (indicated by the elevated time signal below), and then needed 5 degrees of head-down tilt. Blood pressure and heart rate recovered but still remained lower than previously. This patient had no other autonomic abnormalities on detailed testing. Blood pressure was measured noninvasively by the Finapres. (Reprinted with permission from Mathias, G J., & Bannister, *R.* 2002, "Investigation of autonomic disorders," in *Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System,* 4th ed, eds G. J. Mathias & R. Bannister, Oxford University Press, Oxford, pp. 169-195.)

on postural challenge, often without a fall in blood pressure (Lower al. 1995; Jacob et al. 2000). Ir commonly occurs in young women, and often disability disproportionate to the observed autonomic abnormality is seen. There may be a relationship to hyperventilation and panic attacks. It is probably a heterogeneous disorder (Khurana 1995). It may result from a partial autonomic neuropathy (Schondorf and Low 1993), has been associated with antibodies to nicotinic acetylcholine receptors (Vernino ct al. 2000), and has been attributed to a norepinephrine transporter defect in a family (Shannon et al. 2000). When the patient is upright, there is pooling in the lower limbs, in contrast to findings in vasovagal syncope (Stewart and Wcldon 2003). Improvement is often seen with beta blockers. Recovery may be spontaneous, but in some patients a variety of treatments are needed.

Hypertension. Hypertension may be sustained in cerebral tumors, subarachnoid hemorrhage, or bulbar poliomyelitis, whereas lability of blood pressure occurs in certain autonomic disorders. Supine hypertension often occurs in primary chronic autonomic failure. The mechanisms are unclear but include impaired baroreflex activity, adrenoceptor supersensitivity, an increase in central blood volume because of a shift from the periphery, and the effects of drugs used to prewm postanal avpotension. 1 leadache may occur. Papilledema, cerebral hemorrhage, aortic dissection, myocardial ischemia, and heart failure are possible but rarely reported complications.

Paroxysmal hypertension may occur in Guillain-Barre syndrome, porphyria, posterior fossa tumors, and pheochromocytoma, often without a precipitating cause. Hypertension in pheochromocytoma is usually associated with autonomous release of catecholamines, with or without other pressor substances from the tumor. In tetanus, hypertension may be precipitated by specific events, such as muscle spasms or tracheal suction. In high spinal cord lesions, contraction of the urinary bladder, irritation of the large bowel, noxious cutaneous stimulation, or skeletal muscle spasms can cause severe hypertension as part of autonomic dysreflexia, with an uninhibited increase in spinal sympathetic nervous activity (Mathias and Fraukel 2002) (Figure 83,11). This is often accompanied by a throbbing or pounding headache,

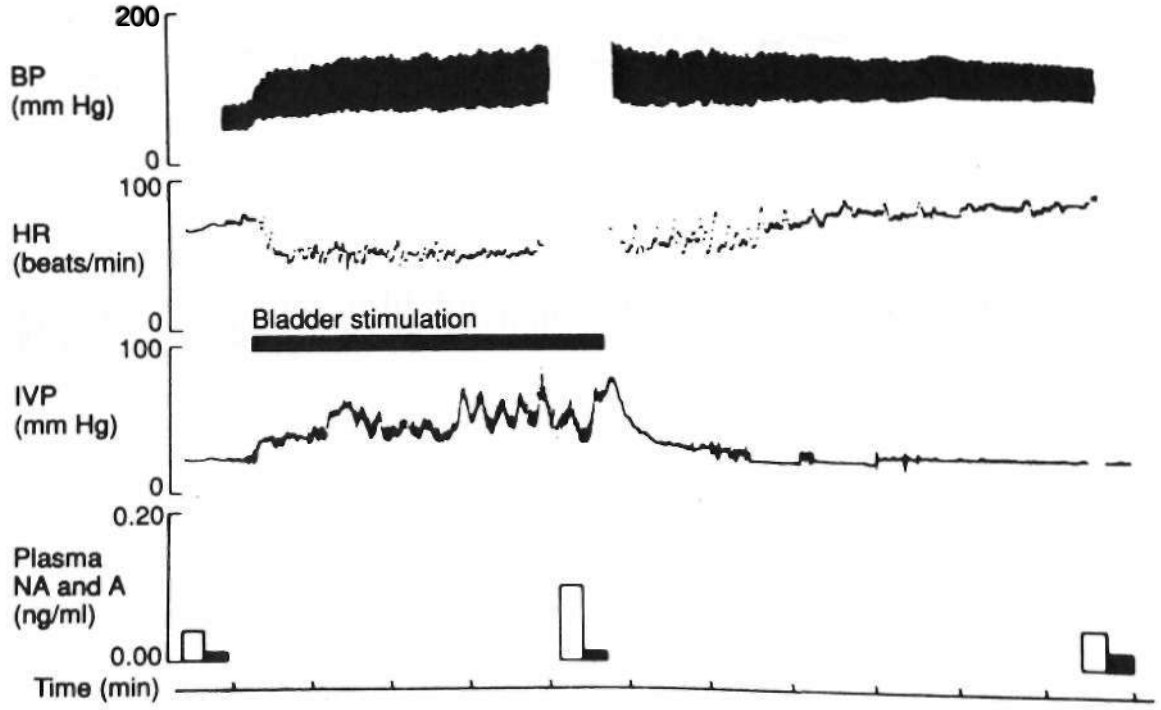


FIGURE 83.11 Blood pressure (BP), heart raw (HR), intravesical pressure (IVP), and plasma noradrenaline (NA, empty histogram), and adrenaline (A, filled histogram) in a tetraplegic patient before, during, and after bladder stimulation (BS) induced by suprapubic percussion of the anterior abdominal wall. A rapid rise in BP is accompanied by a fall in HR, which indicates increased cardiac vagal activity in response to the tise in BP. There is a rise in levels of plasma NA but not of adrenaline, which suggests sympathetic neural but not ad re no medullary activation. (Reprinted with permission from Mathias, C, J. & Frankel, H. L. 1986, "The neurological and hormonal control of blood vessels and heart in spinal man," *J Auton Nerv Syst*, suppl., pp. 457-464.)

bradycardia, sweating and flushing over **the** face and neck, and cold peripheral limbs due to vasoconstriction.

Increased sympathetic nervous activity may initiate or maintain hypertension in renovascular disease (such as renal artery stenosis), in transplant recipients who receive cyclosporine as immunosuppressive therapy, and in pre-eclamptic toxemia (Schobel ct al. 1996).

Cardiac Dysrhythmias. Tachycardia due to increased sympathetic discharge may occur with hypertension in the Guillain-Barre syndrome and in tetanus. In pheochromocytoma, it results from catecholamine release and /i-adrenoceptor stimulation.

Bradycardia (with hypertension) may occur in cerebral tumors and during autonomic dysreflexia in high spinal cord injuries. In the latter, the afferent and vagal efferent components of the baroreflex arc are intact, and the heart slows in an attempt to control the tise in blood pressure. In pheochromocytoma, bradycardia with escape rhythms and atrioventricular dissociation may occur in response to a rapid rise in pressure.

Severe bradycardia can occasionally be a problem if the vagi are intact when there is an inability to increase severe sympathetic activity, as in patients with high cervical cord transection who have diaphragmatic paralysis and need artificial respiration (Table 83.7). The intact vagi arc sensitive to hypoxia, and stimuli such as tracheal suction can induce bradycardia and cardiac arrest (Figure 83,12). Cardiac arrest may also occur in chronically injured tetraplegic patients during general anesthesia, especially when muscle paralysis followed by intubation is performed without parasympathetic blockade (Mathias and Frankel 2002).

In carotid sinus hypersensitivity, bradycardia and syncope may be difficult to distinguish from Stokes-Adams attacks. A cardiac demand pacemaker alone in some patients may not be of benefit because vasodilatation, hypotension, and syncope may occur despite preservation of heart rate.

In diabetes mellitus, the tendency to cardiac vagal neuropathy appears to increase the incidence of cardio-respiratory arrest during anesthesia, for reasons that are unclear. Disorders of cardiac conduction are common in Chagas' disease and may occur in amyloidosis.

Facial Vascular Changes

In autonomic failure, facial pallor usually occurs as blood pressure falls, with prompt restoration of color on the patient's assuming the supine position, when blood

Tabic 83.7: Some of the mechanisms accounting for bradycardia and cardiac arrest in tetraplegic patients with high cervical lesions on artificial respiration and the therapeutic interventions utilized

	Hylioxiti	*Tracheal suet inn*
Normal subjects	Primary response is bradycardia opposed by pulmonary (inflation) vagal reflex, which causes tachycardia.	Increases sympathetic nervous activity, causing tachycardia and raising blood pressure.
Tetraplegic patients	Only causes the primary response, bradycardia, as disconnection from respirator eliminates pulmonary (inflation) reflex.	Sympathetic nervous activity is severely impaired, even at a spinal level in the early stages. Vagal afferent stimulation may lead to unopposed vagal efferent activity.
	Increased vagal cardiac activity	
	Bradycardia and cardiac arrest	Demand pacemaker
Oxygenation	Reconnection to respirator	Atropine

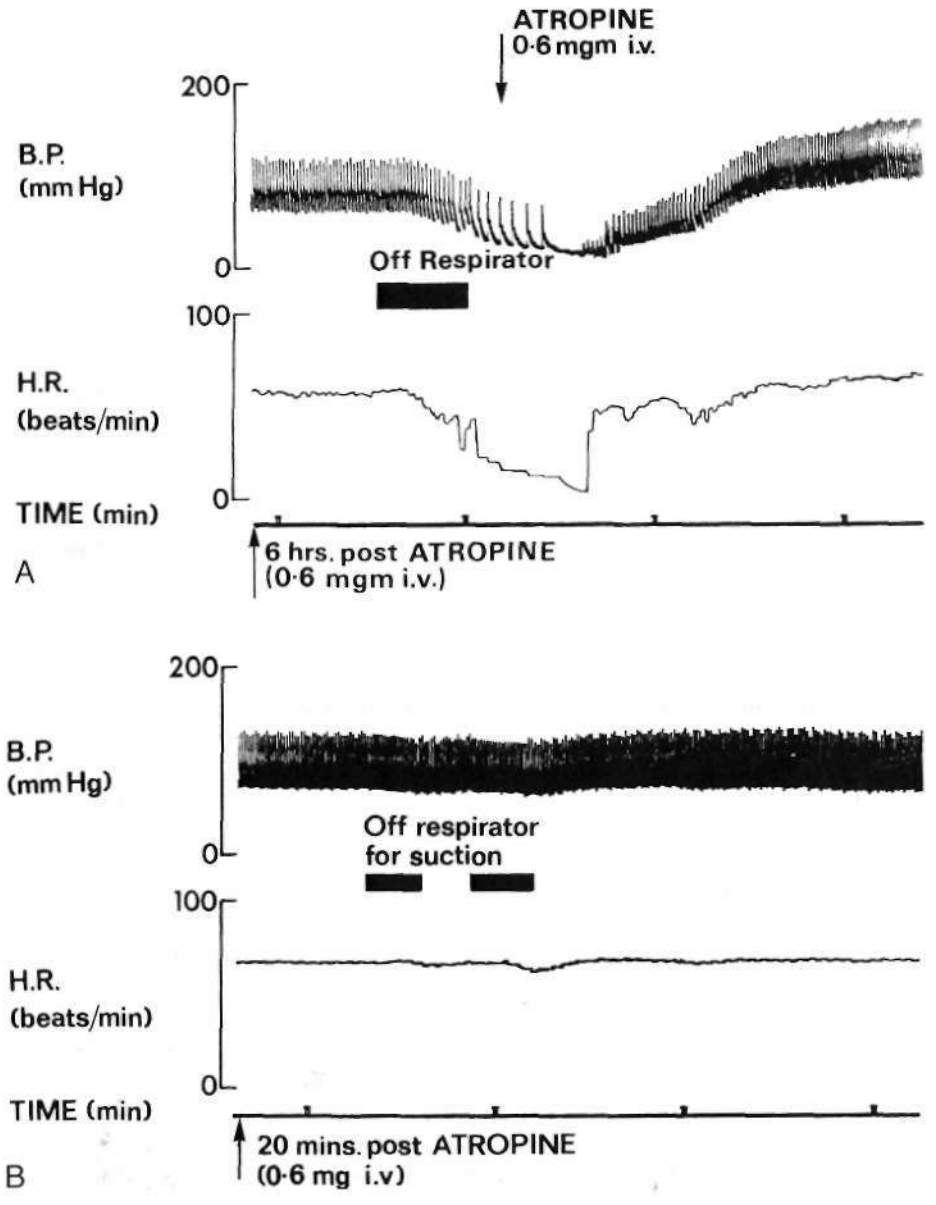


FIGURE 83.12 (A) The effect of disconnecting the respirator (as required for aspirating the airways) on blood pressure (BP) and heart rate (HR) of a recently injured tetraplegic patient (C4-C5 lesion) in spinal shock, *6* hours after the last dose of intravenous atropine. Sinus bradycardia and cardiac arrest (also observed on the electrocardiograph) were reversed by reconnection, intravenous atropine, and external cardiac massage. (Reprinted with permission from Frankel, H. L., Mathias, C. J., & Spalding, J. M. K. 1975, "Mechanisms of reflex cardiac arrest in tetraplegic patients," *Lancet,* vol. ii, p. 1183.) (B) The effect of tracheal suction 20 minutes after atropine. Disconnection from the respirator and tracheal suction did not lower either HR or BP. (Reprinted with permission from Mathias, C. j. [976, "Bradycardia and cardiac arrest during tracheal suction-mechanisms in tetraplegic patients," *Eur) Intensive Care Med,* vol. 2, p, 147.)

pressure rises. Facial pallor may occur during an attack in phcochromocytoma and is usually accompanied by sweating, headache, and hypertension. In the acute phase of high spinal cord lesions, facial vasodilatation may be accompanied by nasal congestion (Gutttnann's sign). The latter also may occur in patients taking (^-adrenoceptor blockers or sympatholytics, such as phenoxy ben/a mine, guanethidine, and reserpinc. In chronic tetraplegia, hypertension during autonomic dysreflexia is often accompanied by flushing and sweating over the face and neck. The mechanisms are unknown. In Harlequin syndrome, there is vasodilatation and anhidrosis on one side of the face due to sympathetic impairment, with apparent sparing of the pupils, although abnormalities may be unmasked with pharmacological testing (Drummond 2002). The signs favor a lesion that spares the first thoracic segment (from which oculomotor fibers often leave) and involves preganglionic fibers of the second **and** third thoracic roots, although the lesion usually is not identified.

Sweating

Anhidrosis or hypohidrosis is common in primary autonomic failure and is usually noticed during exposure to warm temperatutes. The eccrine glands, which are mainly **conc< rned *w* Ith :rill[X':.iHii'f** ivgul::r.' **'ti,** arc **prccniiiinantly** involved, whereas the apocrine glands, which are on the palms and soles and are influenced by circulating substances, including catecholamines, may remain functional. Occasionally, localized hypevhidrns-.s nun occur, which is probably a compensatory response to diminished activity elsewhere rather than a response to denervation hypersensitivity in an incomplete lesion.

Anhidrosis may be coiii;cnii;il wuhoi:: other feature (Cevoli et al. 2002) or may be an integral component of some of the hereditary sensory and autonomic neuropathies (Houlden et al. 2001; Indo 2002), such as congenital insensitivity to pain with anhidrosis (type IV).

Localized or generalized anhidrosis, sometimes with hypethidrosis, may be associated with Holmes-Adie syndrome (Ross's syndrome).

A band of hyperhidrosis above the lesion often occurs in patients with spinal cord injuries, with anhidrosis below the lesion. During autonomic dysreflexia in such patients, however, sweating usually occurs, but mainly over the face and neck. Facial and truncal hyperhidrosis may occur in Parkinson's disease. Hyperhidrosis may occur intermittently in pheochromocytoma. Generalized hyperhidrosis may accompany hypertension in tetanus and may be the major manifestation in infants with mercury poisoning (acrodynia or pink disease).

Localized hyperhidrosis caused by food (gustatory sweating) can be socially distressing and may occur in diabetes mellitus or after trauma or surgery, as a result of aberrant connections between nerve fibers supplying the salivary and sweat glands (Figure 83.13).

Minimally invasive thoracic endoscopic techniques for sympathectomy are being increasingly used because of their success in reducing axillary and palmar hyperhidrosis, but their use may be complicated by abnormalities of sweating in other sites. Approximately one half of patients may develop compensatory hyperhidrosis, usually of the trunk and lower limbs, that may be troublesome; the mechanisms are unclear.

Temperature Regulation

Hypothermia may occur in hypothalamic disorders and in elderly patients, in whom such lesions have been postulated. It usually is not a problem in primary autonomic failure. In patients with high spinal injuries, especially in the early phases, the combination of absent shivering thermogenesis and the inability to prevent heat loss by vasoconstriction can readily result in hypothermia. I lypothermia may be missed if only oral temperature is recorded without a low-reading thermometer (Figure 83.14).

Hyperpyrexia may be a problem in patients with anhidrosis who are exposed to high temperatures. Heat also increases vasodilatation and often enhances postural hypotension.

Gastrointestinal System

Xerostomia usually occurs in acute dysautonomias and especially in pure cholinergic dysautonomia. Dysphagia may be present due to impairment of esophageal function because the lower two thirds of the esophagus contains smooth muscle with autonomic innervation. Large bowel atony may occur, A barium meal should be avoided because it may solidify in the colon and require surgical removal. Dysphagia is unusual in PAF. It often occurs in the later stages of MSA. In primary autonomic failure, constipation is common. In secondary autonomic disorders, a wide variety of gastrointestinal manifestations may occur. The esophagus is often involved in Chagas' disease, with achalasia and megaesophagus causing vomiting. Gastroparesis in diabetes mellitus and amyloidosis may cause food stasis and vomiting. The tevcrse, increased gastric motility, is common in primary autonomic failure, but the relationship between postprandial hypotension and "dumping" is unclear. Paralytic ileus usually occurs in the early phases after spinal cord lesions and can cause abdominal distention and meteorism, which reduces mobility of the diaphragm, the major respiratory muscle in those with high lesions. In such patients, the vagus is intact and probably hyperactive, which may account for the tendency to increased gastric acid production, peptic ulceration, and gastrointestinal bleeding.

Constipation usually occurs in patients with sacral parasympathetic impairment. Diarrhea may occur, as in

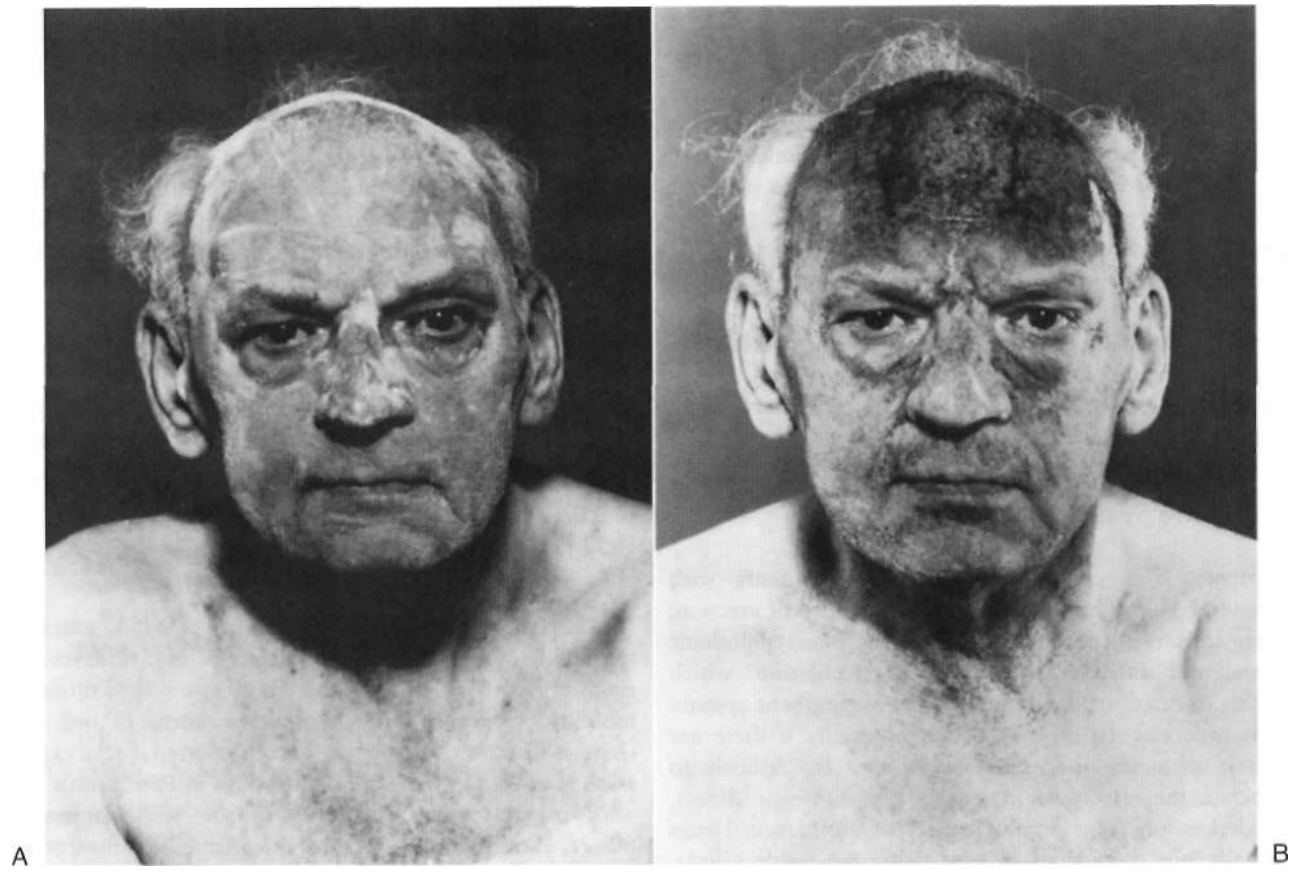


FIGURE 83.13 Sequential photographs showing the effects of quinazarin red (pale powder) before (A) and after (B) gustatory sweating induced by a cheese sandwich. There was profound sweating over the head and face.

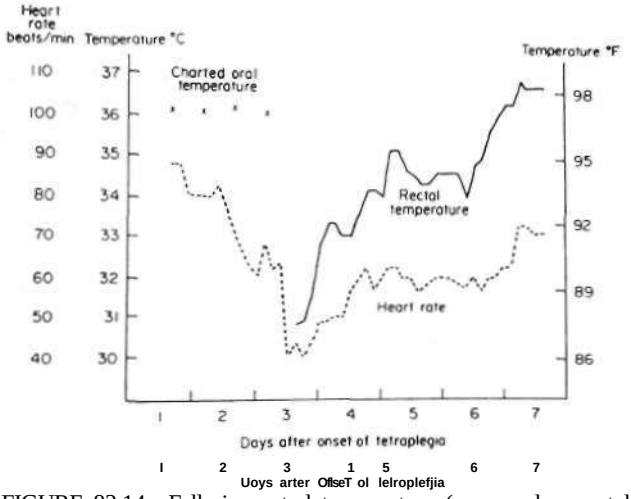


FIGURE 83.14 Falls in central temperature (measured as rectal temperature, *continuous line)* and heart rate *{interrupted line)* in a recently injured tetraplegic patient in a temperate climate, Measurements of oral temperature missed the hypothermia, which should be measured by a low-reading rectal thermometer. The impairment of shivering thermogenesis and the inability to vasoconstrict adequately predispose these patients to hypothermia, (Reprinted with permission ftom Pledger, G. *1962,* "Disorders of temperature regulation in acute traumatic paraplegia," / *Hone Joint Surg jBrj,* vol. 44, p. 110.)

diabetes mellitus, for reasons that are often unclear and include incomplete digestion, altered bowel flora, or abnormal motility.

Kidneys and Urinary Tract

Nocturia is common in primary autonomic failure and probably is the result of recumbency itself rather than abnormal circadian rhythms. Factors such as redistribution of blood from the peripheral into the central compartment, alteration in release of hormones that influence salt and water handling (e.g., renin, aldosterone, and atrial natriuretic peptide), and postural changes in renal hemodynamics may contribute. Nocturia may cause an overnight weight loss greater than 1 kg, resulting in a reduction in extracellular fluid volume, a lower morning blood pressure, and an increased tendency to postural symptoms that may incapacitate some patients until late morning (Mathias 2001).

Involvement of the urinary bladder may result in frequency, urgency, incontinence, or retention. Loss of sacral parasympathetic function, as in the early phase of spinal cord injury, causes an atonic bladder with urinary retention, whereas recovery of isolated spinal cord function results in a neurogenic bladder. With training, there is often controlled bladder emptying. Dyssynergia, however,

with detrusor contraction but not sphincter relaxation, may cause episodes of autonomic dysreflexia resulting in hypertension and, at times, urinary reflux that predisposes patients to renal damage, especially in the presence of a urinary tract infection. In older patients with primary autonomic failure, urinary symptoms initially may be attributed to prostatic hypertrophy in men or to pelvic muscle weakness, especially in muciparous women. Surgery usually is of no benefit. The use of drugs with anticholinergic effects may unmask urinary bladder dysfunction in autonomic failure,

Urinary infection is common when the bladder is involved. Some patients, including those with spinal injuries, are prone to urinary calculi, especially when immobility increases calcium excretion.

Reproductive System

Impotence is a common complaint in patients with autonomic failure and may result from failure of erection, which appears to depend mainly on the parasympathetic system, and difficulty in or lack of ejaculation, which appears to be controlled largely by the sympathetic system, Retrograde ejaculation may occur, especially if there are urinary sphincter abnormalities. It may be difficult to dissociate the effects of increasing age, systemic illness, and depression from organic causes of impotence. Drugs normally not considered to have autonomic side effects, such as thiazides used in the treatment of hypertension, may cause impotence. Priapism due to abnormal spinal reflexes may occur in patients with spinal cord lesions.

In women, autonomic impairment itself does not directly affect reproductive function. Menstrual disorders, if present, are usually due to an underlying disorder. Conception and successful vaginal delivery have been recorded in patients with high spinal cord transection and with primary autonomic failure.

Eye and Lacrimal Glands

The nonstriated component of the levator palpebra superions (Miiller's muscle) is innervated by sympathetic fibers, and mild ptosis is part of Horner's syndrome. If the lesion is bilateral, as in high spinal cord transection, this is difficult to detect,

A variety[7] of pupillary abnormalities may occur: miosis in Horner's syndrome, dilated myotonic pupils in Holmes-Adie syndrome, and small, irregular pupils in Argyll-Robertson syndrome due to syphilitic *{Treponema pallidum)* infection. Symptoms directly relating to the eye are usually minimal in such disorders. Drugs with anticholinergic effects may cause blurred vision due to cycloplegia; they also may raise intraocular pressure and cause glaucoma.

Impaired lacrimal production occasionally occurs in primary autonomic failure, sometimes as part of sicca or Sjogren's syndrome, along with diminished salivary secretion. Excessive and inappropriate lacrimation occurs in crocodile tears syndrome (gustolacrimal reflex).

Respiratory System

In MSA, episodes of apnea may occur in the later stages of the disorder. These are probably due to involvement of brainstem respiratory centers. Inspiratory stridor and snoring may result from weakness of the cricoarytenoid muscles, the main latyngeal abductors. In certain disorders, reflexes from the respiratory tract may cause profound cardiovascular disturbances. Tracheal suction in curarized patients with tetanus receiving artificial ventilation may result in severe hypertension and tachycardia, whereas in patients with high cervical cord transaction, bradycardia and cardiac arrest may occur.

Additional Neurological Involvement

In the parkinsonian and mixed forms of MSA, extrapyramidal manifestations consist mainly of bradykinesia and rigidity with minimal tremor; this causes difficulties in mobility, especially while the patient turns in bed and changes direction. Speech may become slurred, facial expression is affected to a lesser degree than in Parkinson's disease. In idiopathic Parkinson's disease with autonomic failure, extrapyramidal features often have been present for a long period and remain responsive to L-dopa therapy even after the additional features of autonomic dysfunction occur.

In the cerebellar form of MSA, cerebellar features predominate, with an ataxic gait, an intention tremor, cerebellar speech, and nystagmus. Ataxia may he difficult to separate from, or may be compounded by, the unsteadiness caused by postural hypotension. There also may be pyramidal involvement, with increased tone and exaggerated tendon reflexes with extensor plantar responses. A varying combination of extrapyramidal, cerebellar, and pyramidal features occurs in the mixed form of MSA, Sensory deficits are uncommon in MSA, although nerve conduction studies indicate a mixed sensorimotor axonal neuropathy (Pramstaller et al. 1995).

Patients with secondary autonomic failure have the neurological features that are part of, or a complication of, the primary disease. In diabetes mellitus, a somatic neuropathy often coexists with, or precedes, the autonomic neuropathy.

Psychological and Psychiatric Disturbances

In primary autonomic failure, dementia is unusual. In patients with MSA, detailed testing of cognitive function shows deficits in visuospatial organization and visiiomotor ability that arc similar to observations in Parkinson's disease (Monza et al, 1998; Pillon et al, 1995). Most patients with MSA arc not depressed, despite their disabilities and the probable deficit in central cnrecholamine levels; overall

they have a normal affective state, especially when comparisons are made with patients with Parkinson's disease (Pillonct al. 1995).

In PAF there is no psychological disorder, but the absent autonomic responses may result in subtle deficits. These patients appear less emotional than normal subjects and are less anxious when compared with similarly disabled patients with idiopathic Parkinson's disease without autonomic failure (Cntchlc^ et al. 2001b). In normal subjects, fear conditioning and perceptual awareness of a threat stimulus are associated with increased amygdala and insula activity; in PAF there is diminished conditioning related activity in both these areas (Critchley et al. 2002). Anxiety and tremulousness may occur in secondary disorders, as in pheochromocytoma. Psychological factors may contribute to vasovagal syncope (also called emotional syncope) and essential hypcrhidrosis. Frank psychiatric disturbances may complicate other conditions, such as porphyria.

Investigation

Investigation depends on the presenting problem and the primary or secondary disorder. The major aims of investigation are as follows:

- To determine whether autonomic function is normal or abnormal. Screening investigations often are restricted to a particular system, such as the cardiovascular system.
- To assess (if an abnormality has been observed) the degree of autonomic dysfunction, with an emphasis on the site of the lesion and the functional deficit.
- To ascertain whethet the abnormalities are of the primary or secondary variety because further investigations, prognosis, and management depend on the diagnostic category. In some disorders, as in generalized autonomic dysfunction, extensive investigation of various systems may be required (Table 83.8) (Mathias and Bannister 2002b).

The cardiovascular system provides an example of how investigations have been specifically designed to determine and elucidate the deficit, the site of the lesion, and the extent to which associated hormonal abnormalities contribute. As in the investigation of other systems, there has been an emphasis on developing noninvasive techniques that are safe and reliable and can be used for screening and repeated testing as well as for determining disease progrcs sion and the effects of therapy. Different laboratories that test autonomic function arc unlikely to have similar equipment and an identical set of procedures, despite attempts to standardize such approaches. High specificity and sensitiviry of the tests, although desirable, may not be practical in a global setting, especially because the findings often must be considered in the context of a wide variety of factors, including the patient's ability to cooperate in testing. The effect of drugs is another confounding factor, Significantly, the results must be linked with the relevant clinical symptoms and signs. These difficulties mainly arise- in patients with mild or moderate disease with questionable autonomic involvement, however, and are not usually relevant in patients with definite abnormalities.

Table 83.8: Outline of investigations in autonomic failure

- Cardiovascular
  - Physiological
    - Head-up tilt (60 degrees); standing; Valsalva maneuver
    - Pressor stimuli (isometric exercise, cold pressor, mental arithmetic)
    - Heart rate responses to deep breathing, hyperventilation, standing, head-up tilt, 30:15 R-R interval ratio
    - Liquid meal challenge
    - Exercise testing
    - Carotid sinus massage
  - Biochemical: plasma noradrenaline: supine and head-up tilt or standing; urinary catecholamines; plasma renin activity and aldosterone
  - Pharmacological
    - Noradrenaline: a-adrenoceptors, vascular
    - Isoprenaline: /(-adrenoceptors, vascular and cardiac
    - Tyramine: pressor and noradrenaline response
    - Edrophonium: noradrenaline response
    - Atropine: parasympathetic cardiac blockade
- Endocrine
  - Pharmacological
    - clonidme: plasma noradrenaline suppression serum and hormone growth stimulation
- Sudomotor
  - Central regulation thermoregulatory sweat test
  - Swi u gin rid response (<> intradermal acetylcholine, quantitative sudomotor axon reflex test (Q-SART), localized sweat test
  - Sympathetic skm response
- Gastrointestinal: barium studies, video-cine-fluoroscopy, endoscopy, gastric emptying Studies
- Renal function and urinary tract
  - Day and night urine volumes and sodium/potassium excretion
  - Urodynamic studies, intravenous urography, ulrrasound examination, sphincter electromyography
- Sexual function
  - Penile plethysmography
  - Intraeavernosal papaverine
- Respiratory
  - Laryngoscopy
  - Sleep studies to assess apnea and oxygen desaturation
- Eye
  - Sehirmer's test
  - Pupil function, pharmacological and physiological

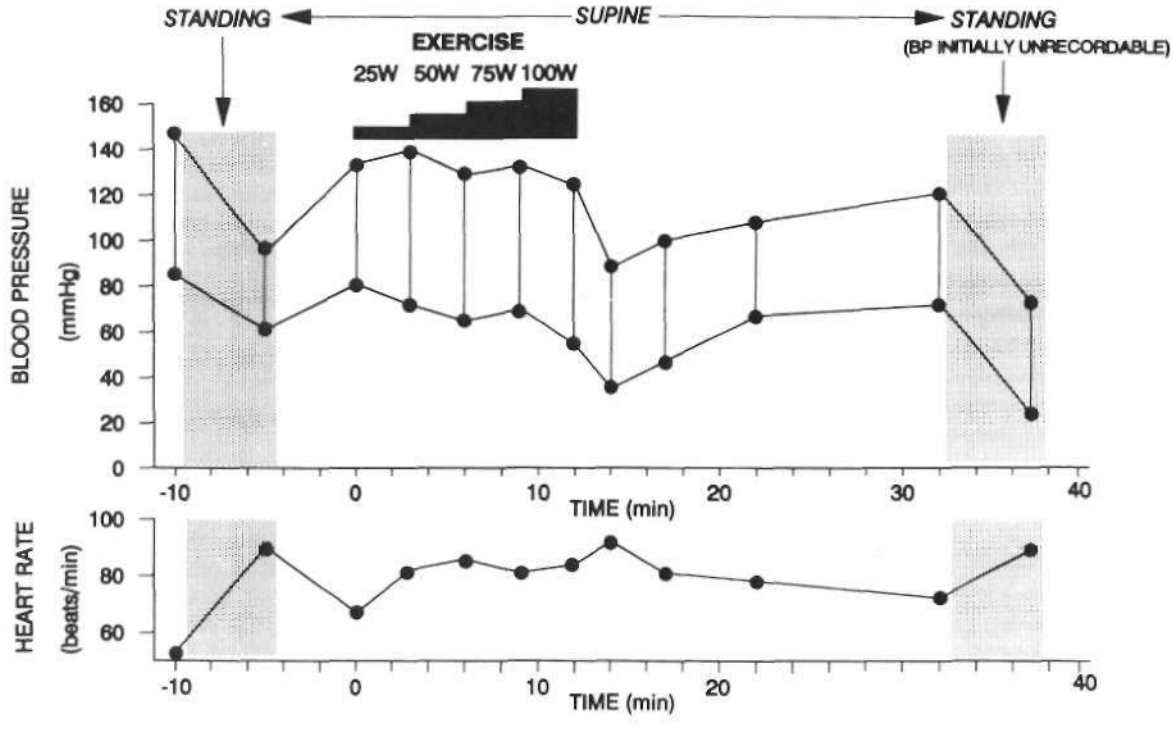
Source: Adapted with permission from Mathias, C. J., 8c Bannister, R. 2002, "Investigation of autonomic disorders," in *Autonomic l-Liiture. A Textbook of Clinical Disorders of the Autonomic Nervous System,* 4th ed, eds C. J. Mathias & R. Bannister, Oxford University Press, Oxford.

Cardiovascular System

A postural fall in blood pressure, especially if consistently more than 20 mm Ilg systolic or less in the presence of symptoms warrants further investigation. Head-up tilt is often used as the postural stimulus, especially when the neurological deficit or severe hypotension makes it difficult for the patient to stand. In some patients, postural hypotension may be unmasked by exercise (Smith and Mathias 1995) because vasodilatation in skeletal muscle is not appropriately counteracted by autonomic reflexes (Figure 8.3.15). Food ingestion also may be a provoking factor, presumably as a result of splanchnic vasodilatation not compensated for in other regions (Figure 83.16). There may be considerable variability in the basal supine levels and the postural fall in blood pressure; the greatest changes often occur in the morning and after a meal and physical exertion. Other, non-ncurogenic causes of postural hypotension must be considered (Table 8.3.9). The same may occur with drugs that cause vasodilatation, even if this is only a side effect of the agent.

Both blood pressure and heart rate can be accurately measured using noninvasive techniques, many of which are automated and provide a printout at preset intervals. Intermittenl ambulator) blood piTwio ami I'.IMII r.ilc recordings over a 24-hour period using small computerized devices are of particular value, especially in the home, for determining the effects of various stimuli in daily life (Figure 8.3.17), They may be of value in determining the beneficial effects of therapy in different situations. Beat-by-beat measurement of blood pressure and heart rate is essential in neurally mediated syncope (see Figure 83.14). This is especially so during carotid sinus massage, when the changes in blood pressure often are rapid, would be missed because of the slow response time of most noninvasive sphygmomanometers, and may be independent of changes in heart rate (Figure 83.18). The Finapres or Portapres machines enable noninvasive and beat-by-beat blood pressure and heart rate recordings with a finger cuff and provide a reliable measure of changes in blood pressure.

Screening investigations help determine the site and extent of the cardiovascular autonomic abnormality. Responses to the Valsalva maneuver, during which intrathoracic pressute is taiscd, depend on the integrity of the entire baroreflex pathway (Figure 83.19). Changes in heart rate alone, even in the absence of intra-arterial recording, provide a useful guide. In some patients, however, mouth pressure may increase without a corresponding



FIGURF. S3.15 Wood pressure (BP) and heart rate responses in a patient with pure autonomic failure while lying and standing, before and after exercise. The stippled area indicates the periods of standing. There was a fall in blood pressure on standing. Exercise was performed on a bicycle ergometer in the supine position, and unlike normal subjects, in whom there is a rise in blood pressure, there was little or no change. When exercise was stopped, blood pressure fell even while the patient was supine; after standing 20 minutes later, the blood pressure was initially unrecordable and the patient was near syncope. The observations were consistent with the patient's symptoms because he felt faint, not during exercise but on stopping exercise, i Reprinted with permission from Smith, G. D, P., Bannister, R., & Mathias, C.J. 1993, "Posr-exercise dizziness as the sole presenting symptom of autonomic failure,'[7] *Br Heart I,* vol. *69,* p. 359.)

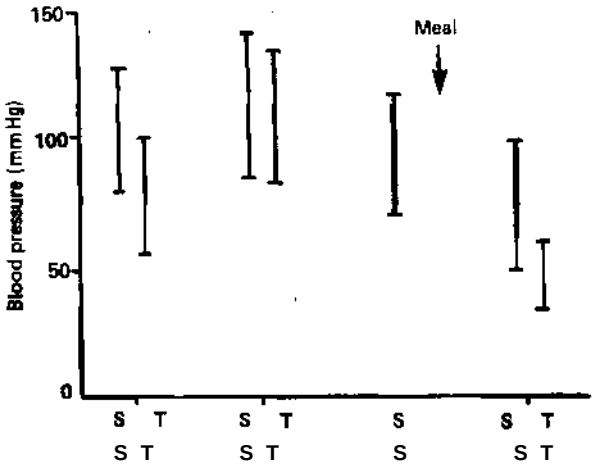


FIGURE 83.16 Systolic and diastolic blood pressure in a patient with multiple -.ysn-in atrophy while supine (S) and after 45-dcgree head-up tilt (T) on three occasions. On the first two, food intake was not controlled. The patient had nor eaten on the second occasion, however, when the postural blood pressure fall was negligible. On the third, supine blood pressure was measured while the patient was fasting and 45 minutes after the meal, Postprandial tilt caused a considerable fall in blood pressure, and the patient had to he returned to the horizontal within 3 minutes. (From Mathias, C. J., Holly, E., Armstrong, E., ct al. 1991, "The influence of food on postural hypotension in three groups with chronic autonomic failure: Clinical and therapeutic implications," / *Neurol Neurosurg Psychiatry*, vol. 54, p. 726.)

increase in intrathoracic pressure, resulting in a falsely abnormal response. Stimuli that raise blood pressure, such as isometric exercise (by sustained hand grip for 3 minutes), **;heC(ilil pi\-,,i>r K-,i** iinirHTsnu; Hie h.md m ice slush for 90 seconds), and mental atithmetic (using serial —7 or -17 subtraction), activate different afferent or central pathways, which then stimulate the sympathetic outflow. The heart rate responses to postural change, deep breathing (sinus arrhythmia), and hyperventilation provide further evidence of the integrity of cardiac vagal efferent pathways. Additional investigations may be needed to determine factors causing or contributing to postural hypotension and syncope. These include determining the responses to carotid sinus massage, food ingestion, and exercise. For patients with suspected carotid sinus hypersensitivity, resuscitation facilities should be available because carotid massage may cause profound bradycardia or cardiac arrest with hypotension. Hypotension only may occur with the subject upright, presumably because of the greater dependence on sympathetic tone, which is withdrawn after carotid sinus stimulation. To assess postprandial hypotension, the cardiovascular responses to a balanced liquid meal containing carbohydrate, protein, and fat arc determined while the patient is supine, with comparisons of the blood pressure response to head-up tilt before the meal and 45 minutes later. To evaluate exercise-induced hypotension, responses are obtained duting graded incremental supine exercise using a bicycle ergometer with measurement of postural responses before and after exercise (see Figure S3.15).

Table 83.9: Examples of non-neurogenic causes of postural hypotension

Low intravascular volume	
Blood/plasma loss	Hemorrhage
	Burns
	Hemodialysis
Fluid/electrolyte loss	Inadequate intake (anorexia nervosa)
	Vomiting
	Diarrhea (including losses from ileostomy)
	Renal/endocrine
	Salt-losing nephropathy
	Adrenal insufficiency (Addison's disease)
	Diabetes insipidus
	Diuretics
Vasodilatation	Drugs (glyceryl trinitrate)
	Alcohol
	Heat
	Pyrexia
	Hyperbradykinism
	Systemic mastocytosis
	Extensive varicose veins
	Systemic mastocytosis
Cardiac impairment	
Myocardial	Cardiomyopathy
Impaired ventricular filling	Atrial myxoma
	Constrictive pericarditis
Impaired output	Aortic stenosis

Note: In patients with autonomic failure or in those taking drugs that impair autonomic function, these disorders enhance postural hypotension considerably.

In patients with PAF, the supine basal level of plasma noradrenaline is low (suggesting a distal lesion) compared with those with MSA, in whom supine levels are often within the normal range (Figure 83.20), The reasons for the normal supine levels in MSA are unclear and may include the central nature of the disorder and impairment of noradrenaline clearance mechanisms in the periphery, In both groups, however, there is an attenuation or lack of rise in plasma noradrenaline levels during head-up tilt, which indicates impairment of sympathetic neural activity. In patients with high spinal cord lesions, basal plasma noradrenaline and adrenaline levels are low and do not rise with postural change. There is, however, a rise (but only moderately above the basal levels of normal subjects) during severe hypertension accompanying autonomic dysreflexia, which differentiates these patients from those with paroxysmal hyper tension due to a pheochromocytoma, in which plasma noradrenaline or adrenaline levels arc usually greatly elevated.

Extremely low or undetectable levels of plasma noradri'ualinc and adrenaline with delated plaMiia dopamine levels occur in sympathetic failure caused by deficiency of the enzyme DBH, which converts dopamine into noradrenaline. Plasma levels of this enzvme ate undetectable,

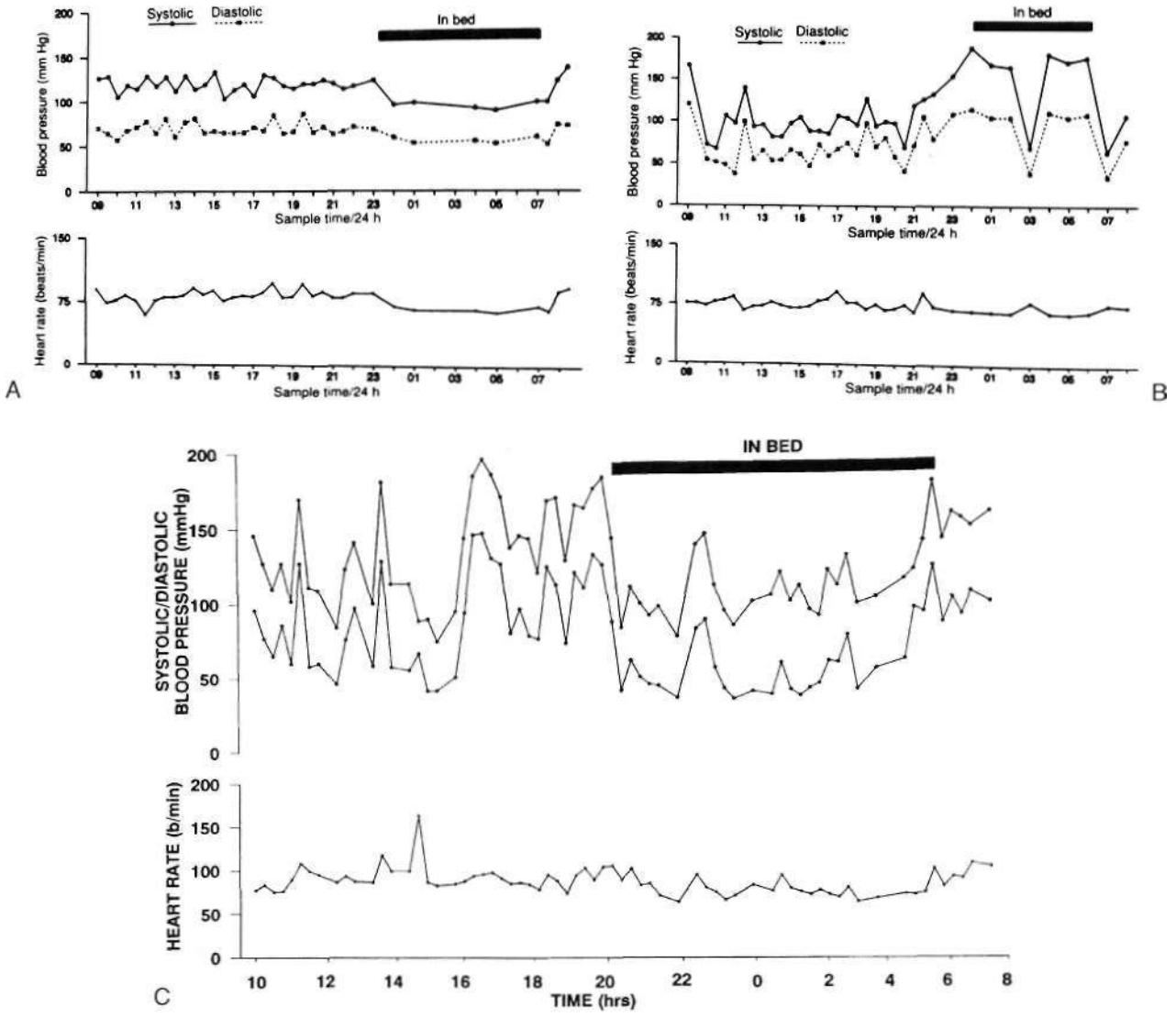


FIGURE S3.17 1 wenry-tour-hour noninvasive ambulatory blood pressure profile showing systolic and diastolic blood pressure and heart rate at intervals throughout the day and night. (A) Changes in a normal subject who did not have postural hypotension; there was a fall in blood pressure on sleeping. |B) Marked fluctuations in blood pressure in a patient with pure autonomic failure. The marked falls were usually the result of postural changes, either sitting or standing. Supine blood pressure, particularly at night, was elevated. Rising to micturate caused a marked fall in blood pressure (at 0300 hours). There was a reversal of the normal diurnal change in blood pressure. There were relatively small changes in heart rate considering the marked fluctuations in blood pressure. (Reprinted with permission from Mathias, C.J. & Bannister, R. 2002, "Investigation of autonomic disorders," in *Autonomic Failure. A Textbook of Clinical Disorders of* Vcri/oiM *.System*, 4th ed, eds C.J. Mathias & R. Bannister, Oxford University Press, Oxford, pp. 169-135.) (C) Changes in a patient with the Riley-Day syndrome (familial dysautonomia). The profile emphasizes the marked variability in blood pressure, with both hypotension and, at times, extreme hypertension. (Reprinted with permission from Mathias, C. J, 1996, "Disorders of the autonomic nervous system in childhood," in *Principles of Child Neurology*, ed B. Berg, McGraw-Hill, New York, p. 413.)

but this may occur in 10% of normal individuals and is not diagnostic of the disorder. Immunohistochemical studies confirm the absence of the enzyme in tissues such as skin.

Measurement of plasma renin activity and plasma aldosterone levels is useful in certain patients. In Addison's disease and adrenocortical failure, basal plasma renin levels are markedly elevated, whereas plasma aldosterone levels are low or absent. In diabetic autonomic neuropathy, there may be low levels of both plasma renin and aldosterone, which contribute to hyperkalemia.

Muscle and skin sympathetic nervous activity can be recorded directly by percutaneous insertion of tungsten microelcctrodes into the peroneal or median nerves. Muscle sympathetic activity is closely linked to the baroreccptor reflex, with a clear relationship to changes in blood pressure and discharge frequency. In patients with high spinal cord transection, there is reduced neural activity in

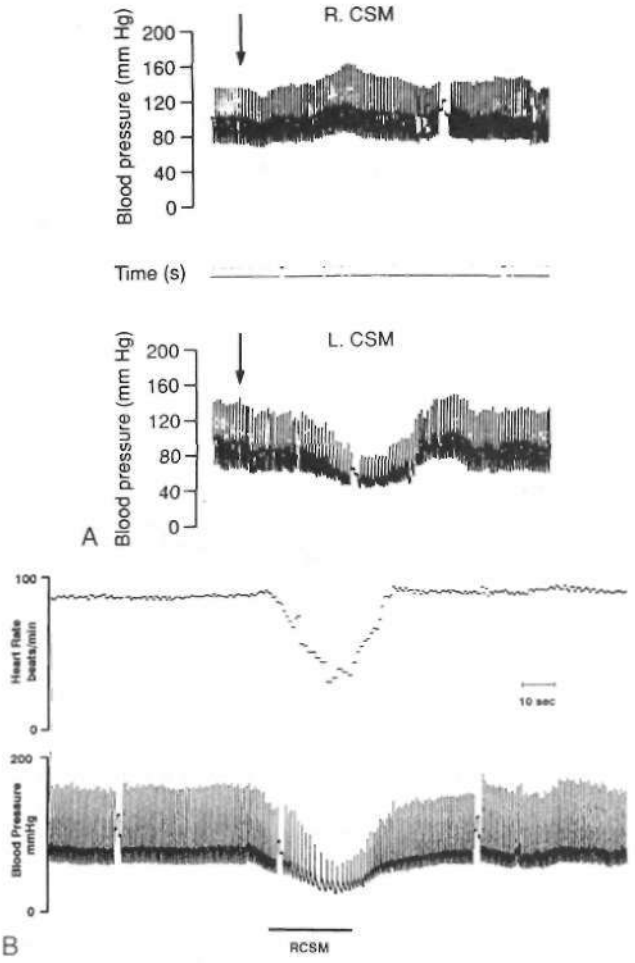


FIGURE 83.18 (A) Continuous noninvasive recording of finger arterial blood pressure (Finapres) before, during, and after carotid sinus massage on the right (R. CSM) and left (L. CSM). The fine dots indicate the time marker in seconds. The arrow indicates when stimulation began. Stimulation on the right for 10 seconds did not lower blood pressure .uid heart rate. On the left, carotid sinus massage caused a substantial fall in both systolic and diastolic blood pressure, during which the patient telt lightheaded and had graying out of visum. There was only a modest fall in heart rate. The syncopal attacks were abolished by left carotid sinus denervation, (Reprinted with permission from Mathias, C. J., Armstrong, E., Browse, N,, et a!., 1991, "Value of non-invasive continuous blood pressure monitoring in the detection of carotid sinus hypersensitivity," *Clin Auton Res,* vol. 2, p. 157,) (B) Continuous blood pressure and hean rate measured noninvasively (by Finapres) in a patient with falls of unknown etiology. Left carotid sinus massage caused a fall in both heart rate and blood pressure. The findings indicate the mixed (cardio-inhihitory and vasodepressor) form of carotid sinus hypersensitivity. (Reprinted with permission from Marhias, C. J. 2000, "Autonomic dysfunction," in *Oxford Textbook of Geriatric Medicine,* 2nd cd, ed J. Grimley-Evans, Oxford University Press, Oxford, pp. 833-852.)

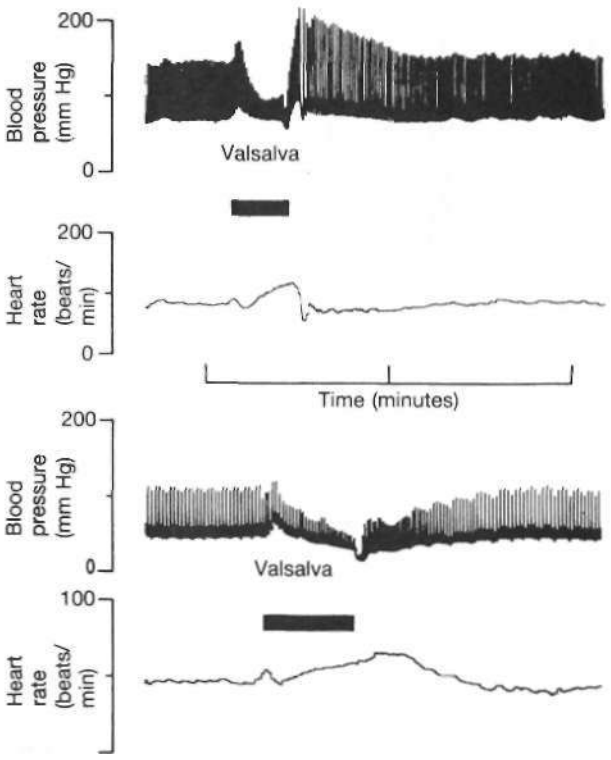


FIGURE 83.19 Blood pressure (BP) and heart rate (HR) before and during the Valsalva maneuver. In the upper trace, tin-expiratory pressure is maintained at 40 mm Hg in a subject with intact sympathetic reflexes. The fall in BP is accompanied by a rise in HR. The fall in BP is due to the reduction in venous return, which then stimulates sympathetic activity. RP then partially recovers. After release of intrathoracic pressure, there is a HP overshoot and the HR falls below the pre-Valsalva level. In rhe lower mice, in a patient with impaired autonomic function, raising intrathoracic pressure lowered BP substantially, with no BP recovery. Note that the HR scale differs from that of a normal subject. After release of intrathoracic pressure, there was no BP overshoot or immediate fall in HR below basal levels. BP slowly returned to pre-Valsalva levels. (Reprinted with permission from Mathias, C. J. & Bannister, R. 2002, "Investigation of autonomic disorders," in *Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System,* 4th ed, eds G. [. Mathias &: R, Bannister, Oxford University Press, Oxford.)

the basal state compared with that in normal subjects, This is consistent with their low plasma noradrenaline and blood pressure levels, presumably because of the lack of transmission of tonic brainstem sympathetic activity. Increased firing occurs in patients with Guillain-Barre syndrome, in association with hypertension and tachycardia. These microneurographic approaches have aided our understanding of the pathophysiological processes but are of limited clinical application, especially in the investigation of autonomic failure.

Pharmacological approaches help in determining the degree of sensitivity of different receptors and the functional integrity of sympathetic nerves and the cardiac vagi. 'i he pressor response to infusion oi noradrenaline provides a measure of a-adrenoceptor sensitivity; it is usually greater in patients with postganglionic sympathetic lesions. The hypotensive response to isoprenaline is related to /J.-adreno-receptor-mediated vasodilatation and is greater in the absence of corrective sympathetic reflexes. The heart rate

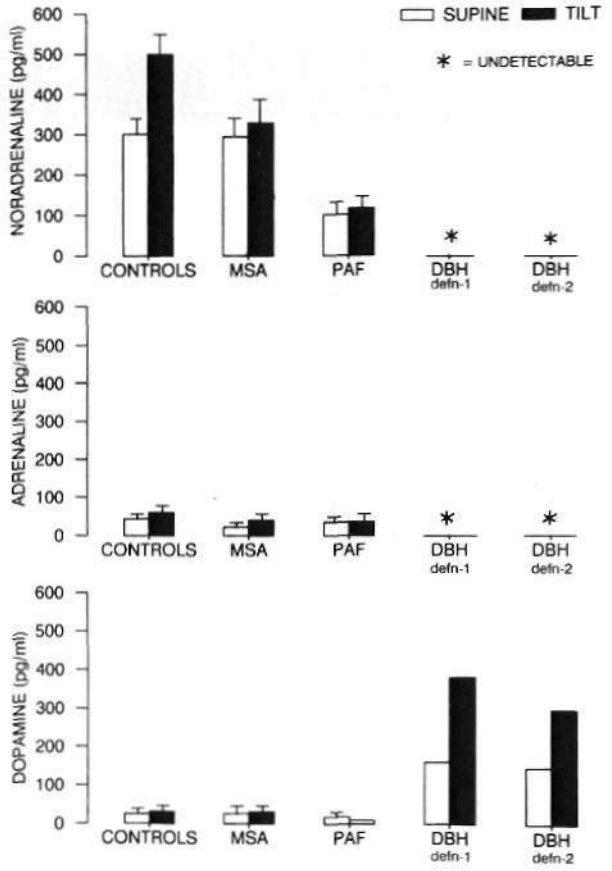


FIGURE 83.20 Plasma noradrenaline, adrenaline, and dopamine levels (measured by high-pressure liquid chromatography) in normal subjects (controls) and patients with multiple system atrophy (MSA, Shy-Drager syndrome) and pure autonomic failure (PAF), along with two patients with dopamine β-hydroxylase deficiency (DBH). Measurements were taken while patients were supine and after head-up tilt to 45 degrees for 10 minutes. The asterisk indicates levels below the detection limit, which are less than 5 pg/mL for noradrenaline and adrenaline and less than 20 pg/mL for dopamine. Bars indicate ± standard error of means. (Reprinted with permission from Mathias, C. J., & Bannister, R. 2002, "Investigation of autonomic disorders," in *Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System*, 4th ed, eds C. J. Mathias & R. Bannister, Oxford University Press, Oxford, pp. 169-195.)

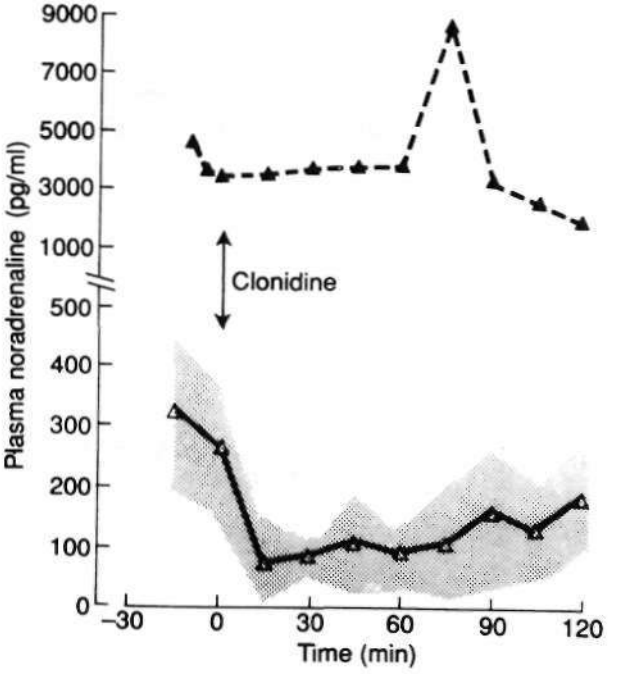


FIGURE 83.21 Plasma noradrenaline levels in a patient with a pheochromocytoma (interrupted line) and in a group of patients with essential hypertension (continuous line) before and after intravenous clonidine, administration of which is indicated by an arrow (2 mg/kg over 10 minutes). Plasma noradrenaline levels fell rapidly in the patients with essential hypertension after clonidine and remained low over the period of observation. The stippled area indicates the ± standard error of means. Plasma noradrenaline levels are considerably higher in the patient with pheochromocytoma and are not affected by clonidine. (Reprinted with permission from Mathias, C. J. & Bannister, R. 2002, "Investigation of autonomic disorders," in *Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System*, 4th ed, eds C. J. Mathias & R. Bannister, Oxford University Press, Oxford, pp. 169-195.)

response provides an indicator of β_1-adrenoceptor sensitivity, although the fall in blood pressure may increase heart rate through withdrawal of vagal tone, if intact. A rise in heart rate with atropine (usually up to 105 beats per minute with 1800 mg intravenously) indicates preservation of cardiac parasympathetic activity. In primary autonomic failure, there is usually an impaired or absent response. The pressor and noradrenaline responses to infused tyramine provide a measure of the store of noradrenaline in sympathetic nerve endings.

Certain pharmacological challenges, as with the α_2-adrenoceptor agonist clonidine, can provide information in different disorders. In some patients, basal plasma noradrenaline levels may be elevated due to stress and other factors; in these situations, the central sympatholytic actions of this agent result in a reduction in plasma noradrenaline levels. This suppression does not occur when autonomous secretion occurs, as in pheochromocytoma (Figure 83.21). Another central action of clonidine through the hypothalamus and anterior pituitary is stimulation of growth hormone release. The rise in serum growth hormone levels that occurs in normal subjects is also observed in patients with PAF who have distal autonomic lesions (Figure 83.22A). There is no response in patients with MSA, however, in whom the lesions are central (Kimber et al. 1997b); this is not due to an inability to release growth hormone, as there is a response to L-dopa (Kimber et al. 1999). Thus the growth hormone response to neuropharmacological challenge with clonidine separates the two disorders, MSA and PAF. The clonidine–growth hormone test may also aid in distinguishing parkinsonian forms of MSA from idiopathic Parkinson's disease (Figure 83.22B) (Kimber et al. 1997b).

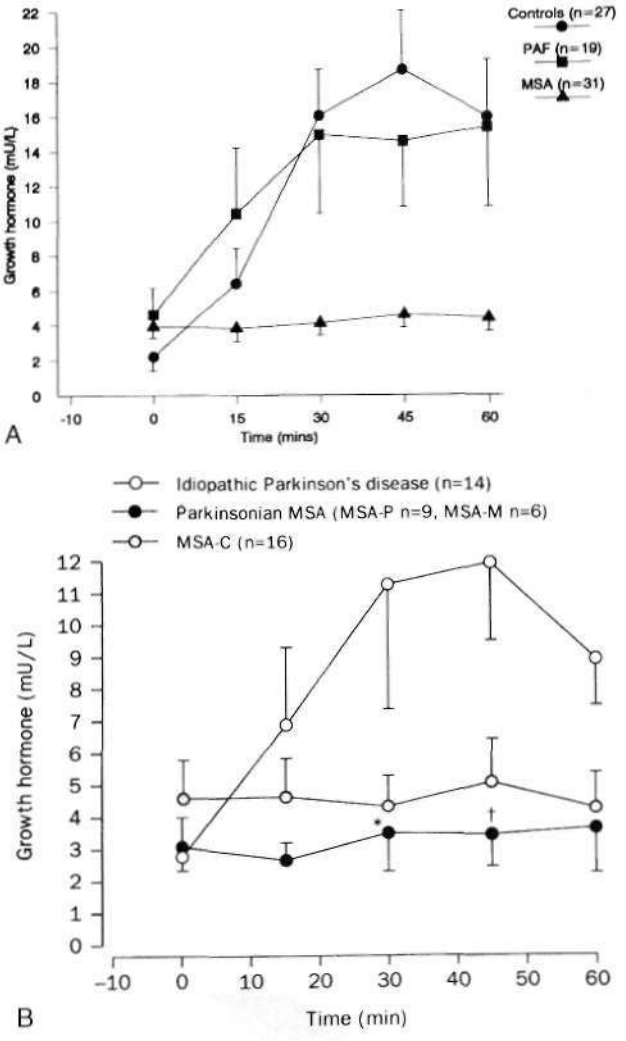


FIGURE 83.22 (A) Serum growth hormone (GH) concentrations before (0) and at 15-minute intervals for 60 minutes after clomdine (2 ug/kg per minute) in normal subjects (controls) and in patients with pure autonomic failure (I'AK) and multiple system atrophy (MSA). GH concentrations rise in control subjects and in patients with PAF with a peripheral lesion; there is no rise in patients with MSA with a central lesion, (B) Lack of serum GH response to clonidinc in the two forms of MSA (the cerebellar form [MSA-C1 and the parkinsonian form [MSA-P]) in contrast to patients with idiopathic Parkinson's disease with no autonomic deficit, in whom there is a significant rise in GH levels, (MSA-M = mixed form.) (Reprinted with permission from Kimber, J. R., Watson, L., &£ Mathias, C. J. I 997, "Distinction of idiopathic Parkinson's disease from multiple system atrophy by stimulation of growth hormone release with clonidine," *Lancet,* vol. 349, p. 1877.)

Many techniques using the advances of modern technology arc being applied to the study of cardiovascular autonomic function in humans. These include techniques for the noninvasive measurement of cardiac function and blood flow in various regions (Puvi-Rajasingham et al. 1997; Chandler and Mathias 2002). A variety of computer and spectral analytic techniques assess cardiovascular function (Parati et al. 2002) and measure total body and regional noradrenaline spillover in regions such as the heart, splanchnic and renal circulations, and the brain (Lambert et al. 1997). Radionuclide [^{121}Ijmetaiodoben/yl-guanidine is used to image sympathetic nerves in the heart (Mantysaari et al. 1996), and PET scanning (using 6-|'^{K}F]fluorodopamine) is used to visualize sympathetic innervation of cardiac tissue (Goldstein et al. 1997). These techniques have a role in the clinical research setting, and in due course some of them may be applied to the routine investigation of cardiovascular autonomic function.

In the majority of autonomic disorders affecting the circulation, physiological testing using head-up postural challenge, a scries of pressor tests, the Valsalva maneuver, deep breathing, and hyperventilation is often adequate for screening purposes. Depending on the disorder, additional tests may be needed, such as food and exercise challenge, carotid sinus massage, and appropriate biochemical and pharmacological studies.

Sweating

The thermoregulatory sweating response is tested by elevating body temperature by 10C, with either a heat cradle or hot water bottles and a space blanket. This tests the integrity of central pathways, from the hypothalamus to the sweat glands. Sweating is assessed using powders, such as quina/arin or Ponceau red, which turn a vivid red on exposure to moisture. In autonomic failure, the thermoregulatory sweating response is lost, and additional tests are needed to distinguish between central and peripheral lesions. In postganglionic lesions, the sudomotor and pilomotor response to intradermal acetylcholine is lost. Various measures can be used, including the quantitative sudomotor axon reflex test. Intradermal pilocarpine assesses the function of sweat glands directly. In DBH deficiency syndrome, sympathetic cholinergic function and sweating is preserved, providing a clue to selective impairment of sympathetic noradrenergic function. In gustatory sweating, spicy foods, cheese, or substances containing tyramine arc ingested to provoke sweating.

The sympathetic skin response (SSR) measures electrical potentials from electrodes on the foot and hand and may provide a measure of sympathetic cholinergic activity to sweat glands. The SSR can be induced by stimuli that arc physiological (inspiratory gasps, loud noise, or touch) or electrical (median nerve stimulation). The response is usually absent in axonal neuropathies but present in demyelinating disorders. Despite numerous reports on the SSR in various disorders, there have been limited observations on factors that influence it and few studies in adequate numbers of patients with clearly defined autonomic disorders. In peripheral disorders, such as PAF and pure cholinergic dysautonomia (Figure 83.23), the SSR is a reliable marker of sympathetic cholinergic function. However, this reliability depends on the use of the presence or absence of the response, rather than latency and amplitude, which are highly variable (Magnifico et al. 199b'),

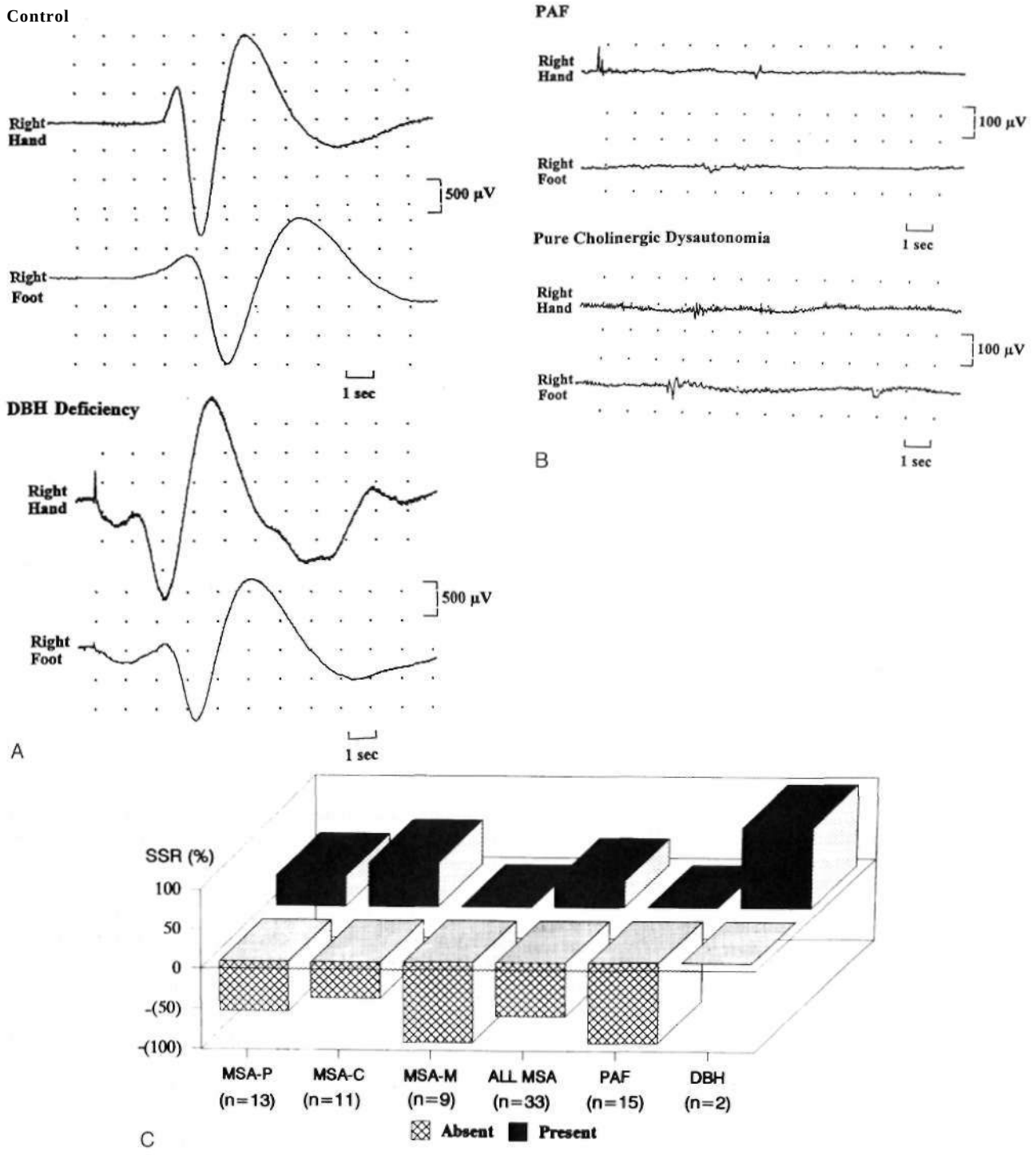


FIGURE 83.23 (A) The sympathetic skin response (in microvolts) from the right hand and right foot of a normal subject (control) and a patient with dopamine ^-hydroxylase (DBH) deficiency. (B) The sympathetic skin response could not be recorded in two patients, one with pure autonomic failure (PAF) and the other with pure cholinergic dysautonomia. (Reprinted with permission from Magnifico, F., Misra, V. P., Murray, N. M, F., & Mathias, C. J. 1 998, "The sympathetic skin response in peripheta autonomic failure—Evaluation in pure autonomic failure, pure cholinergic dysautonomy and dopaminc-heta-hydroxylase deficiency," *Clin Auton* fies, vol. 8, pp. 133-138.) (C) Presence or absence of the sympathetic skin response (SSR) in *ii* patients with multiple system atrophy (MSA), 15 patients with PAF, and two siblings with DBH deficiency. The SSR (as occurs in normal subjects) was present in the two patients with DBH deficiency who had adrenergic failure but preserved cholinergic function; it was absent in all patients with PAF with a peripheral sympathetic lesion. A proportion of patients (up to 30%) with the parkinsonian (MSA-P) and cerebellar (MSA-C) forms had preservation of the SSR despite postural hypotension and definite sympathetic adrenergic failure. (MSA-M = mixed form.) (Data from Magnifico, F., Misra, V. P., Murray, N. M. F., & Mathias, C. J. 1997, "The laboratory detection of autonomic dysfunction in multiple system atrophy—The role of the sympathetic skin response," *Neurology,* vol. 48, **suppl.,** p. A 190.)

The value of the SSR in central autonomic disorders requires further definition. In MSA with confirmed sympathetic adrenergic failure, up to one third of patients with the parkinsonian or cerebellar forms had a recordable SSR (see Figure 83.23C). This makes it unlikely that the SSR would be a valuable discriminatory test in separating MSA from idiopathic Parkinson's disease (without autonomic failure), especially in the early stages (Magnifico et al. 1997).

Gastrointestinal Tract

Video-cine-fluoroscopy is of value in assessing swallowing and the presence of oropharyngeal dysphagia (higure 83.24). This is especially useful in patients with MSA, who in the later stages develop difficulties in deglutition, which appear to enhance the tendency to aspiration pneumonia. A barium swallow, meal, and follow-through are helpful in patients suspected of having upper gastrointestinal disorders, although alternative investigation by endoscopy provides the opportunity for biopsy. Esophageal manometry is of value in disorders of motility and esophagogastric function. Several methods (radioisotope methods and scintigraphic scanning) are available to determine gastric motility noninvasively. When bacterial overgrowth is a suspected cause of diarrhea, a therapeutic trial with broad-spectrum antibiotics, such as neomycin or tetracycline, may be used along with investigations such as jejunal aspiration and the [^{M}C|glycocholate test. *Helicobacter pylori* infection occurs commonly in patients with MSA and PAL and may contribute to gastric dysfunction (Maule et al. 2002). Small bowel manometry and telemetric devices are of value in separating myopathic from neuropathic disorders of the gut. The measurement of transit time and proctological function tests ate used to investigate lower bowel disorders causing diarrhea, constipation, and fecal incontinence.

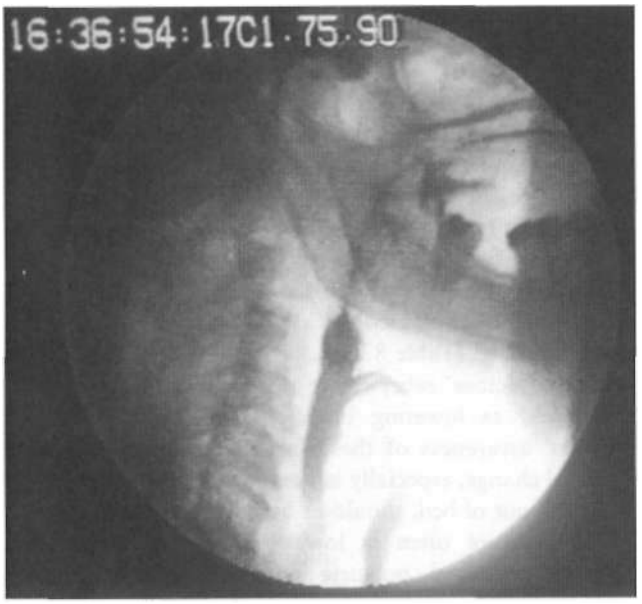


FIGURE 83.24 Still frame from video-cine-fluoroscopic examinatinn in .: p.iiK'iu with oropharyngeal •,lv,ph.u-:.i '.hows penetration of the larynx by contrast medium, indicating the potential to lead to tracheal aspiration. (Reprinted with permission from Mathias, C. J. 1996, "Gastrointestinal dysfunction in multiple system atrophy," *Sernin Neurol*, vol. 16, p. 251.)

Urinary Tract

Nocturnal polyuria can be assessed by separate day and night measurement of urine volume. Measurements of urine osmolarity and the concentrations of sodium and potassium may be helpful. When the urinary bladder is involved, an intravenous pyclogram and micturating cystometrogram may be needed. Urodynamic measurements are valuable in defining the function of the bladder musculature and sphincter mechanisms. They may differentiate idiopathic Parkinson's disease from MSA; in the former, detrusor hyper-reflexia may be present, whereas in MSA, there is usually a combination of both detrusor hyper-reflexia and stress incontinence due to a weak urethral sphincter. Measurement of postmicturition residual volume (e.g., by ultrasound) is of particular importance. It may be high when the bladder is involved, .is in MSA, and may result in urinary infection, which should be detected early and promptly treated. There arc some groups, such as patients with spinal cord lesions, to whom particular care must be provided because recurrent infections, along with calculi, may result in renal failure.

Urethral sphincter electromyography provides an analysis of motor units affected when there is neuronal degeneration of OnuPs nucleus in the sacral cord. This results in sphincter denervation with subsequent reinnervation. Electromyography indicates an increase in amplitude and duration of individual motor units, which are often polyphasic. This combination of denervation and reinnervation is often present in the various forms of MSA unlike idiopathic Parkinson's disease without autonomic involvement (Palace et al. 1997), Similar changes occur in the anal sphincter.

Respiratory System

Respiratory rate and arterial blood gases should be measured to determine the degree of hypoxia, especially during sleep in patients with apneic episodes. Indirect and direct laryngoscopy detect laryngeal abductor paresis.

Eye

Various pharmacological preparations administered locally help determine the degree of sympathetic or parasympathetic involvement of pupils. Lacrimal secretion can be tested by Scfiirmer's test, and damage from deficient

secretion can be assessed using rose bengal instillation followed by slit-lamp examination.

Miscellaneous

A range of additional investigations may be needed to ill [• iiiiiii- the i-niiM' (it die disorder or ;lssi >L ialri.1 i "Hip nations. Computed tomographic scans and magnetic resonance imaging of the brain help in assessing basal ganglia and cerebellar and brainstem involvement in the primary autonomic failure syndromes, especially in MSA (Schrag et al. 2000). PET scanning has provided valuable information in central disorders, such as MSA (Oilman et al. 1996; Rinne et al. 1995). Brainstem auditory evoked responses are often abnormal in MSA but normal in PAF. In suspected peripheral nerve involvement, electrophysiological studies together with sural nerve biopsy are indicated. In amyloidosis, a rectal or renal biopsy may be diagnostic; the latter is indicated if there is renal involvement. To exclude adrenal insufficiency, a short or long Synacthcn test should be performed.

In patients with localized lesions, specific investigations to determine the cause may be warranted. In Horner's syndrome, for example, this may include a computed tomographic or MRI scan of the brain to exclude a midbrain or medullary hemorrhage, bronchoscopy and radiography to exclude an apical bronchial neoplasm, and carotid artery angiography to assess lesions of the internal carotid artery.

PROGNOSIS

In primary autonomic failure, the prognosis depends on the diagnostic category, the degree of autonomic impairment, and the ability to prevent complications. In patients with acute and subacute dysautonomias, complete recovery may occur, although mild or substantial residual autonomic deficits often persist. In chronic autonomic failure syndromes, there are differences in prognosis. Subjects with PAH survive for many years, often with a virtually normal life expectancy, despite the disabilities resulting from autonomic failure. The disorder is usually not progressive, but dysfunction may increase with age, with coincidental illnesses (such as diarrhea), or with use of drugs with vasodilator properties. For patients with MSA, the prognosis is poorer, with a mean life expectancy of around 9 years (Wcnning et al. 1994), although there is considerable individual \ana', mil. 1 a. lias vach a-, rrspa .ilur;, umiplica tions, difficulties with swallowing, and increasing motor deficits contribute to mortality. With improved awareness of these complications and the ability to prevent life-threatening events, survival of patients with MSA is likely to increase.

For patients with secondary autonomic dysfunction, the prognosis depends largely on the associated disorder. With some (e.g., subarachnoid hemorrhage and brain tumors), the primary pathological process often dominates the outcome. In other disorders, such as tetanus, the complications arising from autonomic dysfunction may play a key role in determining morbidity and mortality. In conditions such as diabetes mcllitus (Gcrritscn et al. 2001) and familial amyloid polyneuropathy, autonomic impairment worsens the overall prognosis.

In the subgroups with rarer isolated disorders, there arc considerable differences in prognosis. Patients with specific acetylcholine receptor abnormalities may have severe complications, whereas those with DISH deficiency seem to manage despite severe postural hypotension.

In certain localized disorders, such as Horner's syndrome, the prognosis depends on the initiating cause; in others, such as Chagas' disease, the outcome is determined by complications, such as those arising from cardiac involvement,

MANAGEMENT

Management depends on the autonomic abnormalities and their functional deficits, the associated clinical condition, and the degree of disability. In this section major principles of management relating to autonomic deficits are discussed.

Cardiovascular System

Postural Hypotension

Postural hyporension may cause considerable disability, with the potential risk of serious injury, blood pressure maintenance is dependent, especially in the absence of sympathetic control, on the output of the heart; on tone in resistance and capacitance vessels, which is influenced by various pressor and depressor hormones present systemically or locally; and on intravascular fluid volume. Because no single drug can effectively mimic the actions of the sympathetic nervous system, a multipronged approach combining nonpharmacological and pharmacological measures is needed (Table 83.10).

Many factors other than postural change are now recognized as lowering blood pressure, and increasing patients' awareness of these factors is important. Rapid postural change, especially in the morning when the patient is getting out of bed, should be avoided because the supine blood pressure often is lowest at this time, probably because nocturnal polyuria reduces extracellular fluid volume. Prolonged bed rest and recumbency may contribute even in healthy individuals Perhonen et al. 2001) and can considerably worsen postural hypotension in patients with sympathetic failure. Head-up tilt at night is beneficial and appears to reduce salt and water loss by stimulating the renin-angiotensin-aldosterone system or by

Tabic 83.10: Summary outline of non pharmacological and . 11. i rii..-.. illogical iiiiMvaiv. in 11 ii m.uiagi incnl til poslural hypotension due to neurogenic failure*

Nonpharmacological measures
- To be avoided
  - Sudden hcrtd-up postural change (especially on waking)
  - Prolonged recumbency
  - Straining during micturition and bowel movement
  - High environmental temperature (including hot baths)
  - Severe exertion
  - Large meals (especially with refined carbohydrate)
  - Alcohol
  - Drugs with vasodepressor properties
- To be inttoduced
  - 1 lead-up tilt during sleep
  - Small frequent meals
  - 1 iigh salr intake
  - Judicious exercise (including swimming)
  - Body positions and maneuvers
- To be considered
  - Elastic stockings
  - Abdominal binders
  - Positive-gravity suits
  - Water ingestion

I'll anna co logical
- Startet drug: fludrocortisone
- Sympathomimetics: ephedrinc or midodrine
- Specific targeting: octreotide, desmopressin, or erythropoietin

[&]lt should be emphasized that non-neurogenic factors (such as fluid loss due to vomiting or diarrhea) may substantially worsen postural hypotension. (Adapted with permission from Mar bias, C. J. & ICimber, j. R. 1998, "Treatment of postural hypotension," / *Neurol Neurosurg Psychiatry,* vol. *65,* pp. 285-289.)
'Mathias, C. J, 2000, "A 21st century water cure," *lancet,* vol. 356, pp. 1046-1048.

activating other hormonal, neural, or local renal hemodynamic mechanisms, which reduce recumbency-induced diuresis. In some, head-up tilt may be impractical or the degree of tilt achieved inadequate. In these patients, nocturnal polyuria and nocturia can be reduced with the antidiuretic agent desmopressin (Mathias and Young 2003). Straining during micturition and bowel movement can lower blood pressure further by inducing the Valsalva maneuver. In toilets in small enclosed areas, this is dangerous because the person cannot fall to the floor and thereby recover blood pressure and consciousness. In hot weather, the elevation of body temperature because of impairment of thermoregulatory mechanisms, such as sweating, may increase vasodilatation and worsen postural hypotension. Ingestion of alcohol or large meals, especially those containing a high carbohydrate content, may cause postprandial hypotension and aggravate postural hypotension. Various physical maneuvers (Wieling ct al. 1993), such as leg crossing, squatting, sitting in the knee-chest position, and abdominal compression, arc of value in reducing postural hypotension (Figure 83.25),

A number of devices have been used to prevent venous pooling during standing. These include elastic stockings for the lower limbs, abdominal binders, and, in extreme cases, positive-gravity suits. Each has its limitations and may increase susceptibility to postural hypotension when not in use. In patients with amyloidosis and accompanying hypoalbuminemia, positive-gravity suits may be the last resort because it is virtually impossible to maintain intravascular volume in these patients without causing tissue edema.

Ingestion of 500 mL of water raises blood pressure substantially in patients with primary autonomic failure; this may be of value although the ensuing diuresis may be troublesome, especially in patients with MSA who have associated bladder disturbances (Cariga and Mathias 2001; Shannon et al. 2002),

Drugs often are needed to help sustain blood pressure (Table 83.11). The major mechanisms by which they act include constticting blood vessels, increasing cardiac output, preventing vasodilatation, and retaining salt and water. It should be recognized that enhanced responses usually occur to pressor and vasodepressor agents; the former may result in severe hypertension, especially when rhc patient is supine, and vasodepressor substances may cause marked hypotension. There arc exceptions; patients with infiltration of blood vessels due to amyloidosis may not exhibit supersensitivity, despite a peripheral autonomic neuropathy. With increasing awareness of the precise biochemical deficit in some patients, agents can be given that bypass deficient enzyme systems and result in appropriate neurotransmitter replacement (Figure 83.26). An example is in DBH deficiency, in which the amino acid L-rhreo-3,4-dihydroxyphenylserine is directly converted by do pa-decarboxylase into noradrenaline (Figure 83.27). Whether this occurs intra- or extraneuronally (or both) is unclear. Its potential value in the management of postural hypotension in primary chronic autonomic failure remains to be determined (Mathias et al. 2001b).

A valuable starter drug, especially in mild postural hypotension, is fludrocortisone in a dose of 0.1 or 0.2 mg at night. There is no evidence of a mineralocorricoid deficiency in primary autonomic failure, and low-dose fludrocortisone probably acts by reducing the inability to retain salt and water, especially when recumbent, and by increasing the sensitivity of blood vessels to pressor substances. In the doses used, it is less likely to induce side effects such as ankle edema and hypokalemia. If nocturnal polyuria is not reduced by head-up tilt, fludrocortisone can be effectively combined with desmopressin, a vasopressin-2 receptor agonist with potent antidiuretic but minimal direct pressor activity. Five to 40 mg intranasally or 100-400 mg orally at night reduces the diuresis but, when used without fludrocortisone, does not prevent nocturnal natriuresis. These drugs have been used mainly in patients with primary chronic autonomic failure (Mathias and Young 2003). Patients with PAF require smaller doses (usually 5-10 mg only) because they appear to be more sensitive to the drug than are patients with

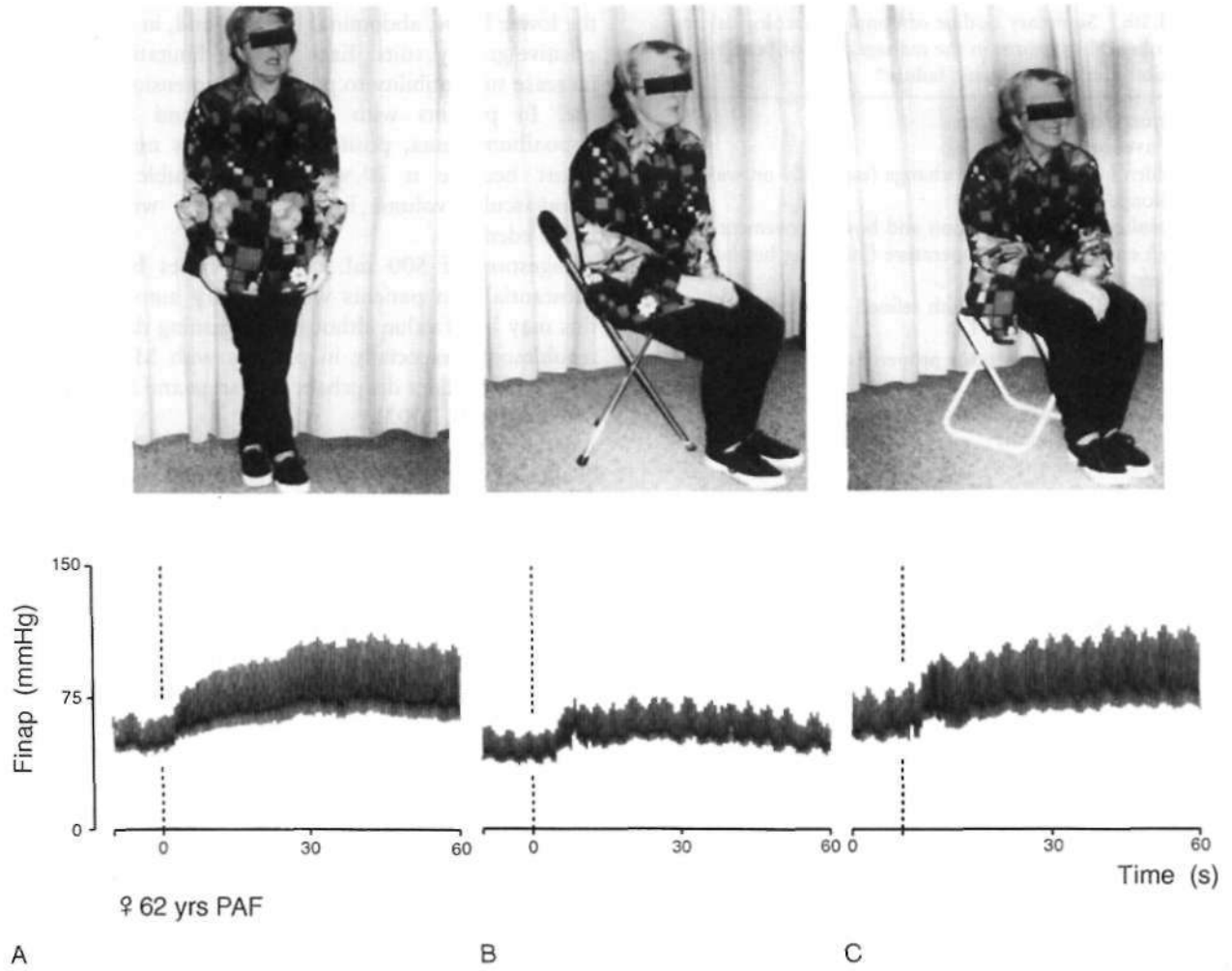


FIGURE 83.25 The effect of standing in a crossed-leg position with leg muscle contraction (A), sitting on a derby chair (B), and sitting in a fishing chair (C) on finger arterial blood pressure in a patient with postural hypotension. Postural symptoms wetc present while the patient was standing and disappeared while the patient had crossed legs. Sitting on a derby chair did not completely relieve the patient's symptoms. Note the greater increment in blood pressure while the patient was standing with crossed legs and leg muscle contractions or sitting on the fishing chair compared with sitting on a derby chair. (Reprinted with permission from Smit, A. A. J., Hardjowijono, M A,, 6c Wieling, W. *1997,* "Are portable folding chairs useful to combat orthostatic hypotension?" *Ann Neurol,* vol. 42, pp. 975-978.)

MSA. The plasma sodium concentration must be monitored to exclude hyponatremia and water intoxication. These can he reversed by stopping the drug and withholding water, hut a diuresis then ensues, which may enhance postural hypotension.

A number of drugs that mimic the activity oi noradrenaline, either directly or indirectly, have been used. Ephedrine acts both directly and indirectly and is of value in central and incomplete autonomic lesions, including MSA. In severe peripheral sympathetic lesions (as in PAF), it may have minimal or no effects. A dose of 15 mg three times daily initially, with an increase to 30 or 45 mg three times daily, can be used, although central side effects limit use of the higher doses. Drugs that act directly on or-adrenoceptors are of value, especially in patients with peripheral lesions. These drugs often act mainly on resistance vessels, with the potential risk of deleterious arterial constriction, especially in elderly patients and in those with peripheral vascular disease. A well-studied example is midodrine, which is converted to the active metabolite, desglymidodrinc (Low ct al. 1997). The ergot alkaloid dihydroergotamine acts predominantly on venous capacitance vessels, but its effects ate limited by its poor absorption; high oral doses (5-10 mg three times daily) may be needed.

Other therapeutic attempts to raise blood pressure have concentrated on pre- and postsynaptic a2⁻ad$^{rcn(>(;cP^{r<,r}}$ mechanisms. They have limited application in practice. Clonidine is mainly an (^-adrenoceptor agonist, which predominantly lowers blood pressure through its central effects by reducing sympathetic outflow. It also has peripheral actions on postsynaptic (^-adrenoceptors, which may raise blood pressure in the presence of pressor supersensitivity. These peripheral vasoconstrictor effects

Table 83.11: Outline of the major actions by which a variety of drugs may reduce postural hypotension

Reducing salt loss or plasma volume expansion:
  mineralocorticoids (fludrocortisone)
Reducing nocturnal polyuria: VVrecepror agonists (desmopressin)
Vasoconstriction, sympathetic
  Directly
    On resistance vessels (midodrinc, phenylephrine, noradrenaline, clonidine)
    On capacitance vessels (dihydroergoramine)
  Indirectly (ephedrine, tyraminc with monoamine oxidase inhibitors, yohimbine)
    Prodrug (t.-dihydroxyphcnylserine)
Vasoconstrictor, nonsympathomimetic: Vpreceptor agents (terli press in)
Preventing vasodilatation
  Prostaglandin synthetase inhibitors (indomethacin, flurbiprofen) .
  Dopamine receptor blockade (metoclopramide, dompetidone)
  ^-Adrenoceptor blockade (propranolol)
Preventing postprandial hypotension
  Adenosine receptor blockade (caffeine)
  Peptide release inhibitors (somatostatin analogue: octreotide)
Increasing cardiac output
  Beta blockers with intrinsic sympathomimetic activity (pindolol, xamoterol)
  Dopamine agonist (ibopnmine!
Increasing red cell mass: erythropoietin

probably account for its modest success in severe, distal sympathetic lesions. Yohimbine blocks presynaptic ^-adrenoceptors, which normally suppress release of noradrenaline and should theoretically be of benefit in incomplete sympathetic lesions, as observed in single-dose studies.

Supine hypertension is not uncommon in autonomic failure and may be worsened by treatment. It may occasionally result in cerebral hemorrhage, aortic dissection, myocardial ischemia, or cardiac failure. This may be a greater problem with certain drug combinations, such as tyramine (which releases noradrenaline) and monoamine oxidase inhibitors (such as tranylcypromine and moclobemide), which prolong its actions. Supine hypertension may increase symptoms of cerebral ischemia during subsequent postural change, probably through an unfavorable resetting of cerebral autoregulatory mechanisms. To prevent these problems, head-up tilt, omission of the evening dose of vasopressor agents, a prebedtimc snack to induce postprandial hypotension, and even nocturnal use of short-acting vasodilatates have been suggested.

One approach to overcoming the problems with blood pressure variability is to use a subcutaneous infusion pump, (as in the control of hyperglycemia with insulin in diabetes mellitus), and a short-acting but effective vasoconstrictor, such as noradrenaline. A pilot study with such a device had been successful, but there were a number of practical problems, including the accurate monitoring of blood pressure without an intra-arterial catheter. Some of these problems have been overcome (Oldenburg ct al, 2001), and this approach may be of benefit to the patient with severe hypotension that is refractory to the combination of ncmpharmacological and conventional drug therapy.

Other therapeutic approaches in postural hypotension include prevention of vasodilatation. Prostaglandin synthetase inhibitors, such as indomethacin and flurbiprofen, have been used with some success and may act by blocking vasodilatory prostaglandins, by causing salt and water

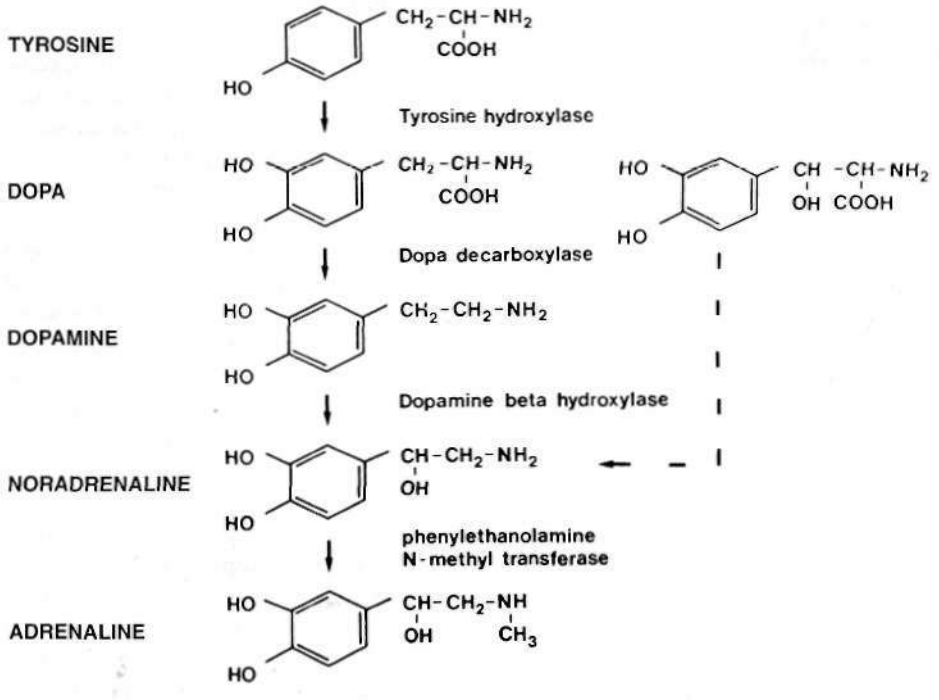


FIGURE 83,26 Biosynthetic pathway for noradrenaline synthesis and the structure of L-threo-3,4-dihydroxyphenylserine (DOPA) alongside. The enzyme dopa-decarboxylase, which is present both intra- and extraneuronally, converts it to noradrenaline, thus bypassing the hydroxylanon step, which depends on dopamine *ft* hydroxylase.

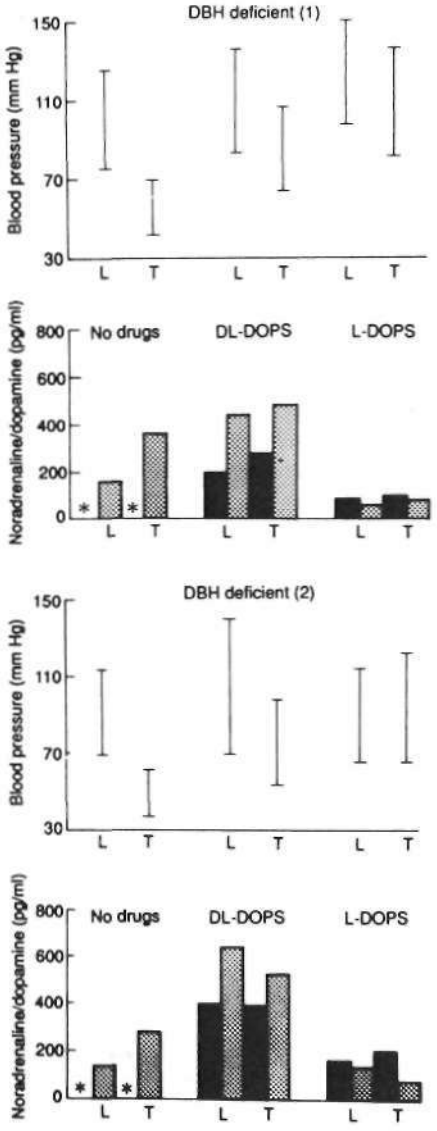


FIGURE 83.27 Blood pressure (systolic and diastolic) while the patient is lying flat (I.) and during head-up tilt (T) in two siMings with dopamine ^-hydroxylase (DBH) deficiency (1 and 2) before and during treatment with m,-dihydro\yphenvlserine (DL-DOPS) and i.-DOPS. Plasma noradrenaline *(histogram)* and dopamine *(stippled histogram)* levels ate indicated before and during head-up rilt. Plasma noradrenaline was undetectable (asterisk <5 pgftnL) in both while the patient is not taking drugs. (Reprinted with permission from Mathias, C. J,, Bannister, R., Cortelli, P., et al. 1990, "Clinical autonomic and therapeutic observations in two siblings willi [Kwt lira I hypotension and sympathetic failure due to an inability to synthesize noradrenaline from dopamine because of a deficiency of dopamine beta-hydroxylase," *Q] Med,* vol. 75, p. 617.)

retention through their renal effects, or both. They have potentially serious side effects, however, such as gastrointestinal ulceration and hemorrhage. The dopamine antagonists metoclopramide and domperidone are occasionally of value when an excess of dopamine is a contributing factor. Whether preventing the vasodilator effects of nitric oxide will be of value remains speculative (Kimber et al. 2001).

£-Adrenoceptor blockers, such as propranolol, may be successful when postural hypotension accompanies tachycardia; the combination of blocking of ^-adrenoceptor vasodilatation and /$J_r$adrenoceptor-induced tachycardia may account for the benefit. Certain ^-adrenoceptor blockers, such as pindolol, with a high degree of intrinsic sympathomimetic activity, may increase cardiac output and through this, or other less well-understood mechanisms, raise blood pressure. Complications such as cardiac failure may occur. Use of another agent with similar properties, xamorerol, has bad limited success, and it has been withdrawn because of deleterious effects. The dopamine agonist ibopaminc has been used in a few patients only with varying success.

Various therapeutic approaches have been used to reduce severe postprandial hypotension. Caffeine has been advocated and may act by blocking vasodilatory adenosine receptors. A dose of 250 mg, present in two cups of coffee, may be of benefit. The prodrug I.-d ill ydrnxy phenyl serine, presumably through adrenoceptor-induced vasoconstriction, reduces postprandial hypotension in primary autonomic failure (Freeman et al. 1996; Mathias et al. 2001). The somatostatin analogue octreotide, which inhibits release of a variety of gastrointestinal tract peptides, including those with vasodilatory properties, has been successfully used to prevent postprandial hypotension; it also may partly reduce postural and exercise-induced hypotension (Smith and Mathias 1995). The need for subcutaneous administration is a drawback. It does not appeat to enhance nocturnal (supine) hypertension (Alam et al. 1995). The development of an oral preparation will be a substantial advance in therapy.

Other strategies must be used in patients with specific disorders causing syncope. In vasovagal syncope, management consists of various nonpharmacological approaches that include salt and fluid repletion (Cooper and Haitisworth 2002; Wieling et al. 2002), lower limb exercises, sympathetic activation techniques, antipooling measures, and maneuvers to introduce, especially in the presyncopal phase (van Dijk et al. 2000); in some a cardiac demand pacemaker (Benditt 1999) and drugs to raise blood pressure may be needed. In carotid sinus hypersensitivity, a cardiac demand pacemaker may be of benefit in the cardioinhibitory form; in the mixed and vasodepressor forms, rhe use of vasopressor drugs and even carotid sinus denervation may be necessary. Bradycardia in patients with high spinal cord injuries who are receiving mechanical ventilation may require a combination of atropine, oxygen, and, if necessary, a temporary demand pacemaker (Mathias and l-'rankel 2002). Tachypacing with an implanted cardiac pacemaker is of no benefit in the management of postural hypotension (except in the rare situation when bradycardia also occurs), because raising the heart rate without

increasing venous return (which is impaired because of pooling due to sympathetic vasoconstrictor failure) docs not elevate cardiac output and therefore does not raise blood pressure.

Hypertension

Hypertension due to increased sympathetic nervous activity occurs in patients with tetanus, Guillain-Barre syndrome, porphyria, certain cerebral rumors, and subarachnoid hemorrhage. It usually responds to propranolol and other •••••. mpntluilytk and .imihypi r tensive as^nls. In patient-, \\:*V.* high spinal cord injuries, it is important to look for the precipitating cause of autonomic dysreflexia (Table 83.12) and tectify it. A range of drugs, based on knowledge of the pathophysiological mechanisms, has been used to prevent or reduce hypertension in these patients (Table 83.13).

V<,"r'i7/;i,'.L,' *I')i>in-il!ri:<*

In idiopathic hyperhidrosis, pharmacological approaches may be beneficial. In hypcrhidrosis over the palms and soles, local astringents containing glutaraldchyde and antiperspirants containing aluminum salts may reduce sweating. Anticholinergics, such as propantheline bromide, and topical applications of hyoscine hydrobromide, may help. Low-dose clonidine may be of benefit, especially in those in whom there is a central or emotional component; in some patients, behavioral psychotherapy may provide relief. Minimally invasive (thoracic endoscopic) sympathectomy often is successful in reducing or abolishing palmar hyperhidrosis, but there is a high incidence of compensatory hyperhidrosis (Adar 1997), which in some may be more distressing than the original symptoms. In gustatory sweating, avoidance of foods that induce attacks may help. Botulinum toxin has been used to treat axillary, palmar (Naumann et a). 1997), and gustatory (Schulze-Bonhage et al. 1996; Tugnoli et a!. 2002) hyperhidrosis.

Table 83.12: Some causes of autonomic dysreflexia in patients with high spinal cord injuries

Cutaneous
- Pressure sores
- Burns
- Infected ingrowing toenails

Skeletal muscle
- Spasms, especially in limbs with contractures

Abdominal viscera
- Ureter
  - Calculus
- Urinary bladder
  - **Distention** by Nocked catheter
  - Infection
  - **Discoordinatcd con tract ion**
  - Irritation by catheter, calculus, or bladder washout
- Rectum/anus
  - Fecal retention
  - Anal fissure
  - Enema ta
- Uterus
  - **Contraction during pregnancy**
  - Menstruation occasionally
- Gastrointestinal organs
  - Gastric ulceration
  - Appendicitis
  - Cholecystitis, cholelithiasis

Miscellaneous
- Fractures of bones
- Urethral abscess
- Vaginal dilation
- **Ejaculation**
- Intrathecal neostigmine or electrical stimulation to **induce ejaculation**

Table 83.13: Drugs used in autonomic dysreflexia with their major site of action

Afferent: Topical lignocaine
Spinal cord
- Clonidine
- Reserpine
- Spinal anesthetics

Sympathetic efferent
- Ganglia: hcxamethonium
- Nerve Terminals: guanethidinc
- <i - A d ren occ p to rs: phen ox y ben za m i ue

Target organ
- Blood vessels: glyceryl trinitrate
- Sweat glands: propantheline bromide

Note; Drugs such as clonidine may act at multiple sites. Some must be given at specific sites, such as lignocaine into the bladder, if this is the source of the stimulus causing autonomic dysreflexia.

Thermo regula turn

hi hypothermia, the standard management ot slowly warming patients, preferably with a space blanket and warm drinks, is recommended. In hyperpyrexia, cold drinks, tepid sponging, a fan to increase heat loss by convection, and, if possible, an air-conditioned environment are helpful; immersion in ice-cold water is occasionally necessary.

Gastrointestinal System

Xerostomia may be helped by artificial saliva. Achalasia of the esophagus may require surgery or dilatation. Patients with MSA who have oropharyngeal dysphagia need advice on the type and quantity of food to be ingested; if there is severe dysfunction and a risk of tracheal aspiration, a feeding gastrostomy may be necessary. Metoclopramide and domperidone increase gastric emptying and may be useful in gastroparesis. The prokinctic drug cisapride, which acts through intrinsic cholinergic plexuses, and the macrolide erythromycin, which stimulates motilin receptors, may be of

value. In paralytic ileus, nasogastric suction with intravenous feeding is necessary. Peptic ulceration, as occurs in the early stages after high spinal cord injury, can be prevented by the prophylactic use of histamine H^-antagonists (such as cimetidine and ranitidine) or proton-pump inhibitors (such as omeprazole). In those with diarrhea, broad-spectrum antibiotics (neomycin or tetracycline) may be the initial step before codeine phosphate or other opiate-based antidiarrheal agents are used. The somatostatin analogue, octreotide, may reduce diarrhea in some patients with amyloidosis and diabetic autonomic neuropathy. Aperients and laxatives, together with a high-fiber diet, are often needed in patients with constipation.

Urinary Tract

In outflow tract obstruction, procedures that include prostatectomy, transurethral resection, or sphincterotomy may be needed. Surgical procedures often worsen incontinence in MSA. Bladder dysfunction may be helped by drugs that influence detrusor muscle activity (such as the anticholinergic, oxyburynin) or sphincter malfunction (e.g., alpha blockers phenoxybenzamine and prazosin). Side effects may be enhanced in patients with generalized autonomic failure. Intermittent or indwelling catheterization may be necessary. The urine should be checked often to detect infection. Nocturnal polyuria in chronic primary autonomic failure is often helped by desmopressin; it is also of value in other disorders, such as multiple sclerosis, in which nocturia may occur. Women often have difficulties with urinary drainage, even by catheterization, and the use of urinary diversion procedures, such as an ileal conduit, is occasionally necessary.

Reproductive System

Erectile failure in men may be helped by suction devices. an implanted prosthesis, or a variety of pharmacological approaches, including local instillation (intracavernosal or urethral) or oral administration of drugs (e.g., sildenafil) (Hussain et al. 2001). In DBH deficiency, difficulty in ejaculation is improved by treatment with L-dihydroxyphenylserine. In patients with spinal cord injuries, elcctroejaculatory procedures followed by artificial insemination have been successful. Pregnant women with high spinal injuries may develop severe hypertension with cardiac dysrhythmias and eclampsia during uterine contractions and delivery. This is best managed by spinal anesthesia, which reduces spinal sympathetic discharge and permits a normal delivery.

Respiratory System

A tracheostomy may be necessary if inspiratory stridor is due to laryngeal abductor paresis and there is evidence of oxygen desaturation, especially at night (Harcourt et al. 1996), In those with periodic apneic episodes, timed or triggered bilevel positive airway pressure ventilation may be useful.

Eye

In alacrima, tear substitutes such as hypromellose eye drops arc of value.

Neurological Deficits

In the parkinsonian forms of MSA, a trial of i.-dopa is indicated because some patients show a response, especially in the early stages of the disease. It may, however, cause or enhance postural hypotension. The monoamine oxidasc-B inhibitor, selegiline, has been used in combination with L-dopa, although there is no evidence that it delays progression of MSA; it may worsen postural hypotension. Postural hypotension also may occur with selegiline treatment in patients with idiopathic Parkinson's disease who do not have autonomic failure; the mechanisms that lower blood pressure may include the central effects of its metabolite, methylamphetamine (Churchyard et al. 1997). There is no effective pharmacotherapy for cerebellar deficits in MSA. Supportive therapy using disability aids must be provided. The family and community must be involved in overall care. Various therapies have been reputed to influence diabetic autonomic neuropathy (Manzella et al. 2001). There is limited evidence that transplantation of the pancreas in diabetes mellirus or of the liver in familial amyloid neuropathy favorably influences the neuropathy in these otherwise relentlessly progressive disorders.

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Chapter 84
Disorders of Neuromuscular Transmission

Donald B. Sanders and James F. Howard, Jr.

MYASTHENIA GRAVIS

Myasthenia gravis (MG) is the most common primary disorder ol lU'iirniinisciihr Transmission. An acquired immunological abnormality is the usual cause, but some cases result from genetic abnormalities at the neuromuscular junction. Much has been learned about the pathophysiology and immunopathology of MG during the past 20 years. What was once a relatively obscure condition of interest primarily to neurologists is now the best characterized and understood autoimmune disease. A wide range of potentially effective treatments are available, many of which have implications for the treatment of other auto immune disorders. This chapter is based on the authors' experience with more than 1500 patients with MG seen with out colleagues over a period of 25 years.

Epidemiology

[• pi d c n iio logical studies have shown a trend for an increasing prevalence of and a falling death rate attributed to MG over the past 50 years. The primary factor for both appears to be an increased life span after diagnosis. The current prevalence in the United States is estimated to be 20 per 100,000 population—between 53,000 and 60,000 discs Phillip-, 2()i)i). I'uvaiisi' VIG is often undiagnosed the true incidence is probably higher. Women are affected more in the second and third decades and men in the sixth decade. As the population ages, the average age at onset has increased correspondingly. Men are now more often affected than women, and the majority of patients with MG in the United States are older than 50 years of age.

Clinical Presentation

Patients seek medical attention for specific muscle weakness or dysfunction. Although tbey may also have fatigue, it is not usually the major or presenting complaint. Ptosis or diplopia was the initial symptom in two thirds of our patients; almost all had both within 2 years of disease onset. Difficulty chewing, swallowing, or talking was the initial symptom in one sixth of patients and limb weakness in one tenth. The initial weakness was rarely limited to single muscle groups, such as neck or finger extensors, hip flexors, or ankle dorsiflexors.

Weakness typically fluctuates during the day, usually being least in the morning and wotse as the day progresses, especially after prolonged use of affected muscles. Ocular symptoms typically become worse while the patient is reading, watching television, or driving, especially in bright sunlight. Many patients find that dark glasses reduce diplopia and hide drooping eyelids. Jaw muscle weakness typically becomes worse during prolonged chewing, especially of tough meats or chewy candy.

Careful questioning often reveals evidence of earlier, unrecognized myasthenic manifestations, such as frequent purchases of new- eyeglasses to correct blurred vision, avoidance of foods that became difficult to chew or swallow, or cessation of activities that require prolonged use of specific muscles, such as singing. Friends may have noted a sleepy or sad facial appearance caused by ptosis or facial weakness.

The course of MG is variable but usually progressive. In our experience, weakness remains restricted to the ocular muscles in approximately 10% of patients, although others have reported lack ol spread *u:* more than 10",:. The rest have progressive weakness during the first 2 years that

ultimately involves oropharyngeal and limb muscles. Maximum weakness occurs during the first year in two thirds of patients. Before corticosteroids were used for treatment, approximately one third of patients had spontaneous improvement, one third had progressive disease, and one third died of the disease. Periods of spontaneous improvement occur early in the course but are rarely permanent. Symptoms typically fluctuate over a relatively short period and then become more severe (active stage). Left untreated, the active stage is followed by an inactive stage, in which fluctuations in strength still occur but are attributable to fatigue, intercurrent illness, or other identifiable factors. After 15-20 years, untreated weakness becomes fixed, and the most severely involved muscles are often atrophic (burnt-out stage). Factors that worsen myasthenic symptoms are emotional upset, systemic illness (especially viral respiratory infections), hypothyroidism or hyperthyroidism, pregnancy, the menstrual cycle, drugs affecting neuromuscular transmission (see Drugs That Adversely Affect Myasthenia Gravis and the Lambert-Eaton Myasthenic Syndrome, later in this chapter), and fever.

The diagnosis is often delayed for months or even years. The unusual distribution and fluctuating weakness of MG often suggest psychiatric illness. Conversely, ptosis, diplopia, and oropharyngeal symptoms suggest intracranial pathologic conditions and often lead to unnecessary cranial imaging studies or arteriography.

Physical Findings

The examination must be performed in a manner that will detect variable weakness in specific muscle groups. Strength should be assessed repetitively during maximum effort and again after brief periods of rest. Performance on such tests fluctuates in diseases other than MG, especially if testing causes pain. The strength fluctuations of MG arc best shown by tests of ocular and oropharyngeal muscle function because these muscles are less likely to be affected by other factors. However, the weakness in MG does not always vary over short time intervals, which makes the differential diagnosis difficult, especially if edrophonium (Tensilon) does not improve the weakness.

Ocular Muscles

Most patients with MG have weakness of ocular muscles (Table 84.1). Asymmetrical weakness of several muscles in both eyes is typical. The pattern of weakness is not characteristic of lesions of one or more nerves, and the pupillary responses are normal. Weakness occurs most often and is usually most severe in the medial rectus muscles. Ptosis is usually asymmetrical and varies during sustained activity. To compensate for ptosis, the frontalis muscle may be chronically contracted, producing a worried or surprised look. Unilateral frontalis contraction is a clue that the lid elevators are weak on that side. This also may be the only visible evidence of facial weakness. Patients with ocular muscle weakness usually have weakness of eye closure.

Oropharyngeal Muscles

Oropharyngeal muscle weakness causes changes in the voice, difficulty chewing and swallowing, inadequate maintenance of the upper airway, and altered facial appearance. The voice may be nasal, especially after prolonged talking, and liquids may escape through the nose when swallowing because of palatal muscle weakness. Weakness of the laryngeal muscles causes hoarseness. This can also be shown by asking the patient to make a high-pitched "eeeee" sound. Difficulty swallowing is detected from a history of choking or clearing of the throat or coughing after eating.

Myasthenic patients, particularly those with severe or long-standing disease, may have a characteristic facial appearance, as seen in Figure 84.1. At rest, the corners of the mouth droop downward, making the patient appear depressed. Attempts to smile often produce contraction of the medial portion of the upper lip and a horizontal contraction of the corners of the mouth without the natural upward curling, which gives the appearance of a snarl.

Jaw weakness can be shown by manually opening the jaw against resistance, which is not possible in normal people. The patient may support a weak jaw with the thumb under the chin, the middle finger curled under the nose or lower lip, and the index finger extended up the cheek, producing a studious or attentive appearance.

The strength of eye closure is usually diminished and may be the only residual weakness after treatment.

Table 84.1: Ocular findings in myasthenia gravis (MG)

Weakness usually involves one or more ocular muscles without overt pupillary abnormality.
Weakness is typically variable, fluctuating, and fatigahle.
Ptosis that shifts from one eye to the other is virtually pathognomonic of MG.
With limited ocular excursion, saccades are superfast, producing ocular "quiver."
Afrer downgaze, upgaze produces lid overshoot ("lid twitch").
Pseudo-internuclear ophthalmoplegia-limited adduction is present, with nystagmoid jerks in abducting ryi-.
In asymmetrical ptosis, covering the eye with the ptotic lid may relieve contraction of the opposite frontalis.
Passively lifting a ptotic lid may cause the opposite lid to fall,
Edrophonium may improve only one of several weak ocular muscles; others may actually become weaker.
Edrophonium may relieve asymmetric ptosis and produce retraction of the opposite lid from frontalis contraction.
The opposite lid may droop further as the more involved lid strengthens after edrophonium.
Cold applied to the eye may improve lid ptosis.

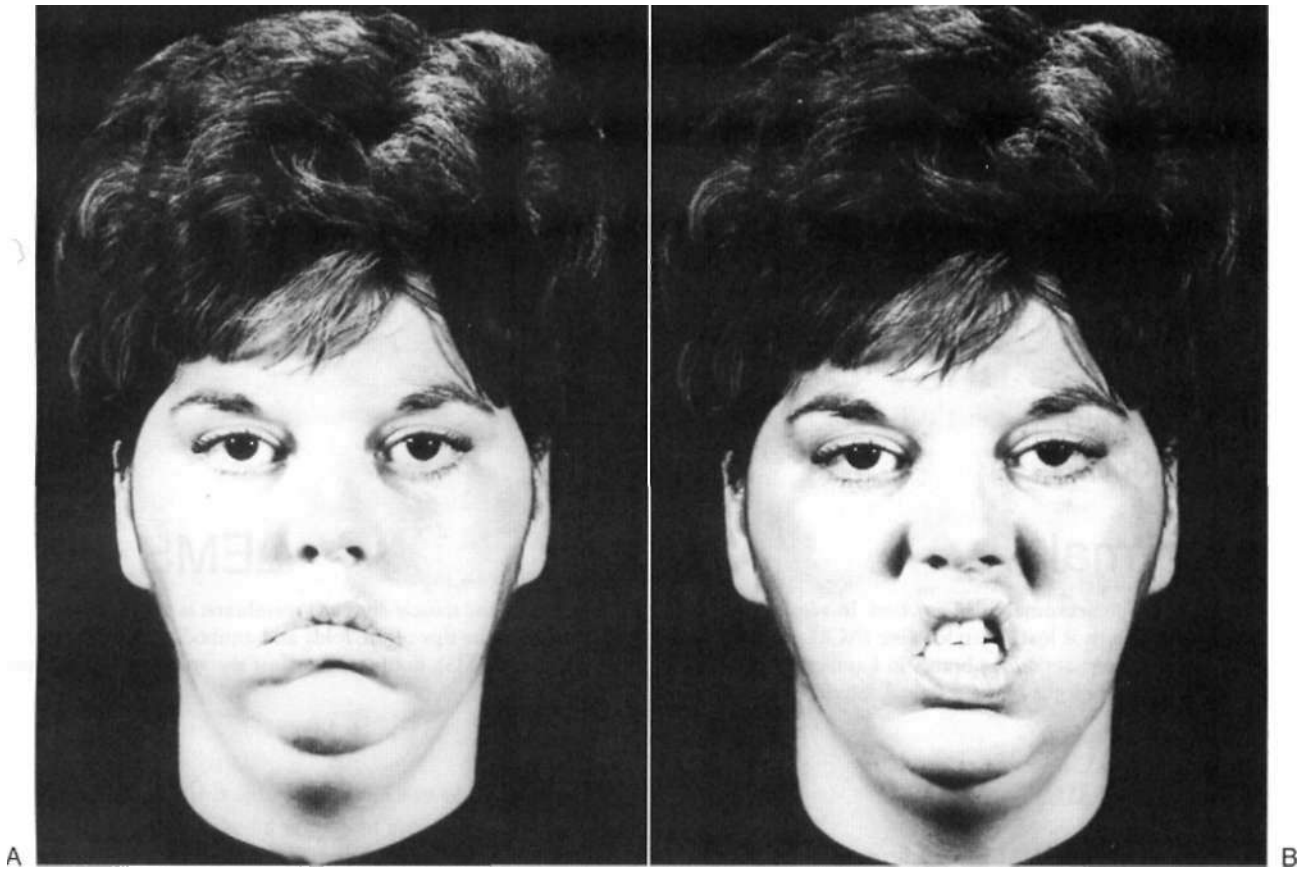

FIGURE 84.1 The characteristic facial appearance of a woman with moderately severe myasthenia gravis. (A) At rest: Note the bilateral lid ptosis and downward curve of the corners of the mouth, giving the patient a sad appearance. (B) Smiling: The "myasthenic snarl" that results from an upward movement of the medial portion of the upper lip and a horizontal contraction of the corners of the mouth rather than a norma! upward turn. This gives the patient an angry appearance and may be seen even when the patient is attempting to laugh.

Limb Muscles

Weakness may affect any trunk or limb muscle, but some are affected more often than others. Neck flexors arc usually weaker than neck extensors, and the deltoids, triceps, and extensors of the wrist and fingers and ankle dorsiflexors are often weaker than other limb muscles.

Inheritance of Myasthenia Gravis

MG is not transmitted by Mendelian inheritance, but family members of patients are approximately 1000 times more likely i> develop the disease nan -. 1 In- L-I'IKT.;I population. Increased jitter on single-fiber electromyography (SFEMG) has been demonstrated in 33—45% of asymptomatic first-degree family members, and levels of antibodies to the acetylcholine receptor (AChR) arc slightly elevated in up to 50%. These observations suggest that there is a genetically determined predisposition to develop MG.

Pathophysiology of Myasthenia Gravis

The normal neuromuscular junction releases acetylcholine (ACh) from the motor nerve terminal in discrete packages (quanta). The ACh quanta diffuse across the synaptic cleft and bind to receptors on the folded muscle endplate membrane (Figure 84.2). Stimulation of the motot nerve causes muscle contraction by the release of ACh quanta that depolarize the muscle endplate region and then the muscle membrane.

In acquired MG, the postsynaptic muscle membrane is distorted and simplified, having lost its normal folded shape (see Figure 84.2). The concentration of AChRs on the muscle endplate membrane is reduced, and antibodies and complement ate attached to the membrane. ACh is released normally, but its effect on the postsynaptic membtane is reduced. The postjunctional membrane is less sensitive to applied ACh, and the probability that any nerve impulse will cause a muscle action potential is reduced.

Several lines of evidence indicate that MG results from an autoimmune attack on the postsynaptic muscle membrane that impairs neuromuscular transmission (Tabic 84,2).

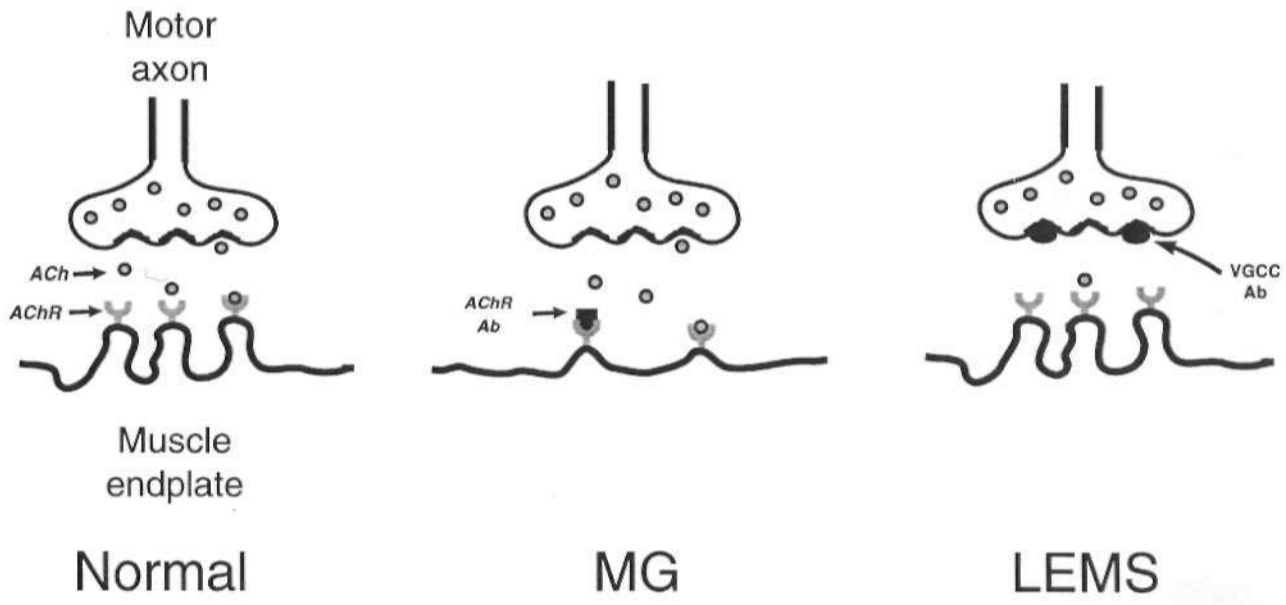

FIGURE 84.2 The neuromuscular junction. In acquired myasthenia gravis (MG), the muscle endplate membrane is simplified and the normal folded pattern is lost. Acetykholine (ACh) receptors (AChR) are lost from the tips of the folds and antibodies (AChR Ab) are attached to the postsynaptic membrane. In Lambert-Eaton myasthenic syndrome (LEMS), antibodies against the voltage-gated calcium channel (VGCC Ab) on the netve terminal interfere with release of ACh.

Autoantibodies in MG

Sttiational antibodies (StrAbs), which react with contractile elements of skeletal muscle, were the first autoantibodies discovered in patients with MG. These antibodies are not pathogenic. They are found in more than 90% of patients with MG and thymoma, and in one third of patients with thymoma who do not have MG. One third of patients with MG without thymoma also have these antibodies; they are seen more often in older patients and in those with more severe disease. The antibody titer does not correlate with disease severity. StrAb levels arc also elevated in patients with autoimmune liver disease and rarely in patients with Lambert-Eaton myasthenic syndrome (LEMS) and in patients with primary lung cancer.

Table 84.2: Evidence that myasthenia gravis (MG) is an immune-media ted disease of the acetylcholine receptor (AChR) complex

Patients with MG have an increased incidence of other presumed or known immune-mediated diseases, such as rheumatoid arthritis.
A transitory neonatal form of the disease occurs in myasthenia and other immune-mediated diseases.
The 1 11, A bnplorypi's ih.ir are common in patients with MG are also common in patients with other autoimmune diseases.
The weakness in MG improves after removal of lymph by thoracic duct drainage and worsens utter rein fusion of a high-molecular-wcight protein fraction from the lymph, probably immunoglobulin G (IgG).
Immunosuppressive treatment, including plasma exchange, produces improvement in most patients with MG.
An animal model of MG can be produced by immunization with purified AChR protein.
Antibodies against human AChR are found in the serum of most patients with MG.
IgG and complement components arc attached to the postsynaptic endplate membrane in myasthenic muscle.
Myasthenic serum or IgG produces abnormal neuromuscular transmission when injected into animals.

StrAb levels are rarely, if ever, elevated in patients with MG in the absence of AChR antibodies and arc therefore of questionable value in confirming the diagnosis of MG. The main clinical value of StrAbs is in predicting thymoma: 60% of patients with MG with onset before age 50 who have elevated StrAb levels have thymoma. Changes in the StrAb titer have been associated with tumor recurrence. However, these antibodies may disappear in patients with persistent thymoma, and they may reappear after thymectomy and immunotherapy without tumor recurrence. Thus they do not consistently indicate the persistence or recurrence of tumor.

We have found antibodies to the AChR in 80% of patients with generalized MG and in more than one half of patients with ocular myasthenia. The assay for these antibodies is a major diagnostic test for MG, and they are only rarely found in the absence of MG (see Antibodies against Acetylcholine Receptors, later in this chapter).

The role of serum antibodies against AChRs in the pathophysiology of MG is not fully understood. Although antibody concentrations are usually higher in patients with more severe disease, these values vary widely among patients, and as many as 25% of patients are seronegative.

Even seronegative patients show improvement aftet plasma exchange, and the neuromuscular abnormality can be transferred to animals by injecting setum from seronegative patients. The antibodies responsible for the neuromuscular abnormality may not always be those that ate measured, and the serum antibody concentration may not refleci the amotini ot antibody attached ro the muscle endplate.

Antititin antibodies have an association with MG similar to that for StrAbs: They are found only in patients with AChR antibodies with late-onset disease ot thymoma (Somnier and Engel 2002). No clinical role for these antibodies has been identified.

Antibodies to muscle-specific receptor rytosinc kinase have recently been desctibed in patients with generalized MG who are seronegative for AChR antibodies (see Seronegative Myasthenia Gravis, later in this chapter).

It is hypothesized that the predominant involvement of ocular muscles in MG is due to the presence of antibodies specific for the y-subunit of the AChR, which is found in adult extraocular muscle. However, the levatot palpebrae, which has a different AChR subumt composition, is as involved clinically as other ocular muscles, and y-subunits have been found even in normal limb muscle.

Autoantibodies to the AChR ate T cell dependent. T lymphocytes also play a pivotal role in the initiation and maintenance of the autoimmune response against the AChR complex, although the precise mechanism by which this occurs is not fully understood. T cells are activated through the T-cell receptor by majot histocompatibility complex (MHC) class II molecules bound with antigenic peptide. The role of HLA linkage has not been fully elucidated. In some instances, certain MHC molecules (e.g., HLA-DRW3, -B8, and -A1) predispose the individual to MG whereas other molecules may provide resistance to disease. CD4^ T cells that tegulate the production of AChR antibodies are found in increased numbers in patienrs with MG. The a-subunit of AChR contains the majority of T-cell recognition sites. These recognition sites are different from those of the main immunogenic region that are recognised by binding antibodies. Sensitization to $CD4^+$ T cells spreads across the AChR complex with disease duration. This ptobably accounts for the large and varied antibody tepertoire of the myasthenic patient. Universal epitopes on the AChR complex tecognize large numbers of CD4' T cells and are expressed in the majority of patients with MG. These drive the synthesis of AChR antibody production (Conti-Fine et al. 1997).

The Thymus in Myasthenia Gravis

The primary abnormaliry in MG appears to be a breakdown in immune tolerance toward self-antigens. The thymus gland plays a role in the induction of tolerance to self-antigens. It contains all the necessary elements for the pathogenesis of MG: myoid cells that express the AChR antigen, antigen-ptesenting cells, and immunocompetent T cells. Cultured thymic myoid cells express transcripts that encode fot AChR subunits. It is likely that the expression of these subunits serves as an anrigen for the auto sensitization of the patient against the AChR. Thymic abnormalities are associated with MG. Ten percent of patients with MG have a thymic tumor, and 70% have hyperplastic changes (germinal centers) that indicate an active immune response.

Almost 20% of our patients with MG whose symptoms began between the ages of 30 and 60 had thymoma; the incidence of thymoma was much lower when symptoms began after age 60. Most thymic tumors in patients with MG arc benign, well-differentiated, and encapsulated and can he reiivv. ed completely at surgery (see Thymectomy, later in this chapter).

Diagnostic Ptocedures

Edrophonium Chloride (Tensilon) Test

Weakness caused by abnormal neuromuscular transmission characteristically improves aftet intravenous administration of edrophonium chloride (Tensilon). This response forms the basis of the Tensilon test, in which strength is examined before and after injection of the drug. Except when examining ocular and pharyngeal muscle function, the clinician must rely on the patient to exert maximum effort before and after drug administration to assess its effect. For this reason, the test is most reliable when the patient has ptosis, discernible limitation of eye movements, or nasal speech.

Results of the Tensilon test are found to be positive in more than 90% of patients with MG. Howevet, improved sttcngth after edrophonium is not unique to MG. For example, it may also be seen in motor neuron disease, in which neuromuscular Transmission is abnormal because of rapidly progressive denervation. We have also seen improved eye movements after edrophonium in patients with lesions of the ocular motor nerves.

The ideal dose of edrophonium cannot be predetermined. A single fixed dose, such as 10 mg, may be too much in some patients and cause increased weakness. Thus an incremental dosing schedule is recommended. A dose of 2 mg is injected intravenously, and the response is monitored for 60 seconds. Subsequent injections are 3 and 5 mg. If improvement is seen within 60 seconds after any dose, no further injections arc given. Ten milligrams of edrophonium does not weaken normal muscle, and the occurrence of weakness afrer its injection indicates a neuropathy or neuromuscular ttansmission defect. The total dose of edrophonium in children is 0.15 mg/kg administered incrementally. Subcutaneous administration can be used in newborns and infants, but the response may be delayed for 2-5 minutes.

Some clinicians administer edrophonium in a blinded or double-blinded fashion to improve objectivity. This is not needed when the end point is well defined, such as relief of ptosis.

Some patients whose MG docs not respond to intravenous edrophonium may show a response to intramuscular neostigmine, which has a longer duration of action. Intramuscular neostigmine is particularly useful in infants and children whose response to intravenous edrophonium maybe too brief for adequate observation. In some patients, a therapeutic trial of oral pyridostigmine (Mcstinon) for several days may produce improvement that cannot be recognized after a single dose of edrophonium or neostigmine.

Techniques that show a more objective effect of cholincsterase (ChE) inhibitors on ocular muscles include electromyography (EMG) of the ocular muscles, tonometry, oculography, and Lancaster red-green tests of ocular motility. These tests increase sensitivity but are nonspecific and may yield false-positive results.

Antibodies d^iiitut Acetylcholine Receptors

Eighty percent of our patients with acquired generalized myasthenia and 55% with ocular myasthenia have serum antibodies that bind human AChRs (Figure 84.3). The serum concentration of AChR Abs varies widely among patients with similar weakness and cannot be used to predict the severity of disease in individual patients. Approximately 10% of patients who lack binding antibodies have antibodies that modulate the turnover of AChR in tissue culture. The concentration of binding antibodies may be low at symptom onset and rise later. Repeat studies are appropriate when initial values arc normal. In general, finding AChR-binding antibodies in a patient with compatible clinical features confirms the diagnosis of MG, but normal concentrations do not exclude the diagnosis. AChR-binding antibody concentrations may be elevated rarely in patients with systemic lupus erythematosus, inflammatory neuropathy, amyotrophic lateral sclerosis, rheumatoid arthritis who are taking D-penicillamine, and thymoma without MG and in normal relatives of patients with MG.

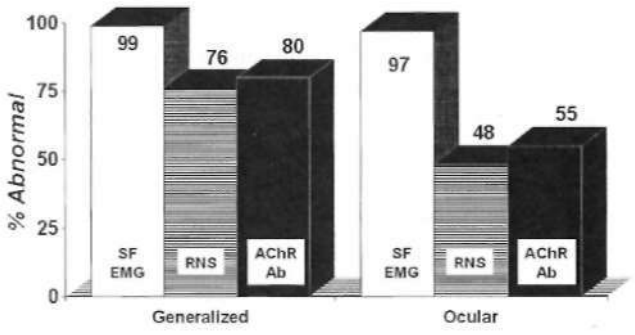

FIGURE 84.3 Comparison of abnormalities demonstrated by single-fiber electromyography (SFEMG), repetitive nerve stimulation of hand and shoulder muscles (RNS), and serum acetylcholine receptor antibody levels (AChR Ah) in 550 patients with acquired i'.nnT.ili/.rd or ocular myasthenia gravis (D. B. Sanders, J. M, Masscy, and J. F. Howard, unpublished observations).

Virtually all patients with MG and thymoma have elevated concentrations of AChR-binding antibodies, and many have high concentrations of AChR-modulating, AChR-blocking, and antistriatcd muscle antibodies as well. However, many patients with MG without thymoma also have high concentrations of these antibodies, and these serological findings cannot be used to predict the presence of thymoma.

E lectromyogrctph y

The following arc Practice Recommendations of the American Association of Electrodiagnostic Medicine regarding the use of EMG in MG (AAEM Quality Assurance Committee 2001):

Repetitive nerve stimulation (RNS) of a nerve supplying a symptomatic muscle should be performed. Abnormality in MG is considered to be a reproducible 10% decrement in amplitude when the first stimulus is compared to the fourth or fifth, which is found in at least one muscle. Anticholinesterase medications should be withheld 12 hours before testing, if this can be done safely.

If results of RNS are normal and there is a high suspicion of a neuromuscular junction (NMJ) disorder, SFEMG of at least one symptomatic muscle should be performed. If results of SFEMG of one muscle arc normal and clinical suspicion for a NMJ disorder is high, a second muscle should be studied.

Option: If the patient has very mild or solely ocular symptoms and it is believed that results of the RNS will be normal or if the discomfort associated with RNS prevents completion of RNS, SFEMG testing may be performed in place of RNS as the initial NMJ test. In laboratories with the capability to perform SFEMG, it may be performed as the initial test for disorders of neuromuscular transmission because it is more sensitive than RNS. Routine needle EMG and nerve conduction studies may be necessary to exclude disorders other than MG or Lambert-Fa ton myasthenic syndrome.

The decremented response to RNS is seen more often in proximal muscles, such as the facial muscles, biceps, deltoid, and trapezius, rather than in hand muscles. We have found a significant decrement to RNS in cither a hand or shoulder muscle in (i I % of patients with MG.

SFEMG {see Chapter 36B) is the most sensitive clinical test of neuromuscular transmission and shows increased jitter in some muscles in almost all patients with MG (Trontelj et al. 2002). Jitter is greatest in weak muscles but is often seen even in muscles with normal strength. Patients with mild or purely ocular muscle weakness may have increased jitter only in facial muscles. Studies to detenu in e whether jitter in limb muscles predicts the development of generalized myasthenia in patients with purely ocular weakness show that at least one half of patients with persistent ocular myasthenia have increased jitter in the limb (Weinberg et al. *1999;* Rostedt et al. 2000). Therefore increased jitter in a limb muscle does not predict the subsequent development of generalized myasthenia, and no threshold jitter value predicts the development of generalized weakness.

Increased jitter is a nonspecific sign of abnormal neuromuscular transmission and can occur in other motor unit diseases. Therefore when jitter is increased, EMG should be performed to exclude neuronopathy, neuropathy, and myopathy. The presence of normal jitter in a weak muscle excludes abnormal neuromuscular transmission as the cause of weakness.

Ocular Cooling

Improvement in lid ptosis after the eye is cooled with an ice pack has been proposed as a simple, fast, and relatively sensitive technique to differentiate myasthenic from nonmyasthenic eyelid ptosis i.Golnik el al. IVSJS*). '['bis test is used as an alternative to the Tensilon test in the clinical evaluation of ocular MG; however, its specificity has not been fully determined.

Comparison of Diagnostic Techniques

The Tensilon test is often diagnostic in patients with ptosis ot ophthalmoparesis, but it is less useful when othet muscles are weak. An elevated serum AChR-binding antibody level vittually ensures the diagnosis of MG, but a normal level does not exclude it. RNS confirms impaired neuromuscular transmission but is not specific to MG and is often normal in patients with mild or purely ocular disease. SFEMG demonstrates abnotmal neuromuscular transmission in almost all patients with MG, but abnormal test results can occur when other motot unit disorders cause defects in neuromuscular transmission. A normal SFEMG test result in a weak muscle excludes the diagnosis of MG.

Other Diagnostic Procedures

Patients in whom MG is diagnosed should have thyroid function tests and a chest-imaging study (computed tomography or magnetic resonance imaging) to assess possible thymoma. A skin test for tuberculosis should be done if the use of immunosuppression is contemplated.

Treatment

Controlled clinical trials for any medical or surgical treatment of MG are rare. Al! recommended regimens are empirical, and experts disagree on treatments of choice. Treatment decisions should be based on knowledge of the ptedicted coutsc of disease in each patient and the ptedictcd response to a specific treatment. Treatment goals must be individualized according to the severity of disease, the patient's age and gender, and degree of functional impairment. Successful treatment of MG tcquires close medical supervision and long-term follow-up. Return of weakness after a period of improvement should be considered an indication of further progression that requires reassessment of current treatment and evaluation for underlying systemic disease ot thymoma,

Cholinesterase inhibitors

ChE inhibitors retard the enzymatic hydrolysis of ACh at cholinergic synapses so that ACh accumulates at the neuromuscular junction and its effect is prolonged, (hi. inhibitors produce considerable improvement in some patients and little to none in others. They have a major role as a diagnostic test and as early, symptomatic treatment in most patients. They are used as adjunctive therapy in most patients undergoing more definitive tteatment. ChE inhibitors alone may provide adequate chronic treatment in some patients, but the response usually becomes less with chronic use,

Pyridostigmine bromide (Mestinon) and neostigmine bromide (Prostigmin) are the most commonly used ChE inhibitors. Pyridostigmine is generally preferred because it has a lower incidence of gastrointestinal side effects and longer duration of action. The initial oral dose in adults is 30-60 mg every 4-8 hours. The equivalent dose of neostigmine is 7.5-15,0 mg. In infants and children, the initial oral dose of pyridostigmine is 1.0 mg/kg and that of neostigmine is 0,3 mg/kg. Equivalent dosages of these drugs are listed in Table 84.3. Pyridostigmine is available as a syrup (60 mg/5 mL) for children or for nasogastric tube administration in patients with impaired swallowing. A timed-release tablet of pyridostigmine (Mestinon Timespan, 180 mg) is useful as a bedtime dose for patients who are too weak to swallow in the morning. Irs absorption is erratic, leading to possible overdosage and underdosage, and it should not be used during waking hours. Even at night, it is sometimes preferable for the patient to awaken at the appropriate dosing intervals and take the regular tablet. Neostigmine and pyridostigmine can be administered by nasal spray or nebulizer to patients who cannot tolerate or swallow oral medications.

No fixed dosage schedule suits all patients. The need fot ChE inhibitors varies from day to day and during the same day. Different muscles respond differently; with any dose, some muscles get stronger, others do not change, and still

Tabic 84.3: Equivalent doses of anticholinesterase drugs

	Route and dose (mg)			
Drug	*Oral*	*Intramuscular*	*Intravenous*	*Syrup*
Neostigmine bromide (Prostigmil) bromide)	15			
Neostigmine me thy (sulfate (Prostigmin methylsulfate)	1.3		0.5	
Pyridostigmine bromide (Mestinon bromide)	60	2.0	0.7	60 mg/5 ml.
Mestinon Timespan	90-180			
Ambenonium chloride (Mytelase chloride)	5			

Note: These values are approximations only. Appropriate doses should be determined for each patient based on the clinical response.

others become weaker. The drug schedule should be titrated to produce an optimal response in muscles causing the greatest disability. Patients with oropharyngeal weakness need doses timed to provide optimal strength duting meals. Ideally, the effect of each dose should last until time for the next, without significant underdosing or overdosing at any time. In practice, this is not possible. Attempts to eliminate all weakness by increasing the dose or shortening the interval causes overdose at the time of peak effect. Different muscles show different dose-response curves, so that some become stronger while others become weaker. We aim to keep the dose low enough to provide definite improvement in the most important muscle gtoups within 30-45 minutes, and we expect the effect to wear off before the next dose. This minimizes the possibility that the dose will be increased to the point of causing cholinergic weakness. The practice of giving edrophonium at the time when pyridostigmine has its maximal effect, to determine if the patient will respond to greater dosages of ChE inhibitors, is not without danger. Acute overdosage may cause cholinergic weakness of respiratory muscles and apnea.

Adverse effects of ChE inhibitors result from ACh accumulation at muscatinic teceptors on smooth muscle and autonomic glands and at nicotinic receptors of skeletal muscle. Central nervous system side effects are rarely seen with the doses used to treat MG. Gastrointestinal complaints are common: queasiness, nausea, vomiting, abdominal cramps, loose stools, and diarrhea. Increased bronchial and oral secretions are a serious problem in patients with swallowing or respiratory insufficiency. Symptoms of muscarinic overdosage may indicate that nicotinic overdose (weakness) is also occurring. Gastrointestinal side effects can be suppressed with lopetamide hydrochloride (Imodium), propantheline bromide (Pro-Banthine), glycopyrrolate (Robinul), and diphenoxylate hydrochloride with atropine (Lomotil). Some of these drugs produce weakness at high dosages.

Bromism, presenting as acute psychosis, is a rare complication in patients taking latge amounts of pyridostigmine bromide. The diagnosis of bromide intoxication can be confirmed by ditect measurement of the serum bromide level. Some patients are allergic to bromide and develop a rash even at modest doses.

Thymectomy

Although thymectomy is widely used as a treatment for autoimmune MG, it has never been demonstrated to be effective in a prospective, controlled study. Based on a review of existing studies, the Quality Standards Subcommittee of the American Academy of Neurology concluded dial ;\LIIC:H-, with ,VK who underwent thymectomy were twice as likely to have a medication-free remission, 1.6 times as likely to become asymptomatic, and 1.7 times as likely to show improvement (Gronscth and Barohn 2000). The following practice recommendation was made:

> For patients with non thymoma to us autoimmune MG, thymectomy is recommended as an option to increase the probability of remission ot improvement.

Wc recommend thymectomy for most patients with MG whose symptoms begin before age 60. The response is relatively unpredictable, and significant impairment may continue for months or years after surgery. The best responses to thymectomy are seen in young people, especially women, early in the course of their disease, but improvement can occur even aftet many years of symptoms. In our experience, patients with disease onset after age 60 rarely show substantial improvement after thymectomy, but others have reported improvement after thymectomy even in older patients. In our experience, the response in patients with thymomas is not as good as that in patients without thymomas; however, others have reported good responses after removal of the tumor and the thymus (Schrager et al. 2002). Although thymectomy is not generally recommended for patients with purely ocular myasthenia, these patients also may show a good response after thymectomy (Schrager et al. 2002), and we do recommend it in cettain circumstances, particularly in young patients with relatively recent onset of myasthenia. The major advantage of thymectomy is its potential to induce a sustained, drug-free remission. Another advantage is to rule out or remove a thymoma.

Out preferred surgical approach is ttansthotacic; the sternum is split and the ametior mediastinum is explored.

Transcervical and endoscopic approaches have less postoperative morbidity but do not allow sufficient exposure for total removal of the thymus and are not recommended when there is a thymoma. However, it has not been demonstrated that the extent of removal of the thymus determines outcome, and until there has been a prospective study comparing different thymectomy techniques, the value of different surgical approaches will not be clear. In our experience, the operative morbidity from transthoracic thymectomy is very low when patients are optimally prepared with plasma exchange or immunosuppression and skilled postoperative management is provided. Extubation is usually accomplished within hours after surgery, and patients may be discharged to home as early as the second or third postoperative day.

Repeat thymectomy provides significant improvement in some patients with chronic, refractory disease and should be considered when there is concern that all thymic tissue was not removed at prior surgery and when a good response to the original surgery is followed by later relapse,

Thymectomy may be followed by improvement, even in seronegative patients. We do not base the decision to perform thymectomy on the presence or level of AChR antibodies.

Corticosteroids

Marked improvement or complete relief of symptoms occurs in more than 75% of patients treated with prednisone, and some improvement occurs in most of the rest. Much of the improvement occurs in the first *6-H* weeks, but strength may increase to become total remission in the months that follow. The best responses occur in patients with recent onset of symptoms, but patients with chronic disease also may show improvement. The severity of disease does not predici the ultimate improvement. Patients with thymoma show an excellent response to prednisone before or after removal of the tumor.

We have found that the most predictable response to prednisone occurs when treatment begins with a daily dose of 1.5-2.0 mg/kg per day (Bedlack and Sanders 2002). This dose is given until sustained improvement occurs, which is usually within 2 weeks, and is then changed to an alternate-day schedule, beginning with 100-120 nig. This dose is gradually decreased over many months to the lowest dose necessary to maintain improvement, which is usually less than 20 mg every other day. The rate of decrease must be individualized: For patients who have a prompt, complete response to prednisone the alternate-day dose can be reduced by 20 mg each month until the dose is 60 mg. The dose can then be reduced by 10 mg each month until it is 20 mg and then by 5 mg every 3 months to a minimal dose of 10 mg every other day. If any weakness returns as the prednisone dose is reduced, further reductions are usually followed by even greater weakness. At this point, the prednisone dose should be increased and another immunosuppressant should be added or both. Most patients who have a good response to prednisone become \u\ik if tin- dni.L; is Mopped bin may maintain strength with very low dosages (5-10 mg every other day). For this reason, we do not reduce the dose further than this unless another immunosuppressant is also being given. Others recommend discontinuing prednisone if the patient is doing well after 2 years. In our experience, weakness ultimately returns if this is done.

Approximately one third of patients become wcaket temporarily after prednisone treatment is started, usually within the first 7-10 days and lasting for up to 6 days. This worsening usually can be managed with ChE inhibitors. In patients with oropharyngeal weakness or respiratory insufficiency, we use plasma exchange before prednisone is begun to prevent or reduce the severity of corticosteroid-induced exacerbations and to produce a more rapid response. Because high-dose prednisone may exacerbate weakness, patients with oropharyngeal or respiratory involvement should be hospitalized to start this treatment. Once improvement begins, subsequent corticosteroid-induccd exacerbations are unusual.

An alternative approach is to begin treatment with 20 mg per day of prednisone and increase the dose in 10-mg increments every 1 to 2 weeks until improvement begins. The dose is maintained constant until improvement is maximum, then decreased as above. This protocol may reduce the frequency or severity of corticosteroid-induced exacerbations, but exacerbations still may occur, and the Lici.qv.ihi' iv.pmiM In ;his iv;;:iih':i is k-,- piVikl:i/>'-.-. A similar dose schedule is often used in purely ocular myasthenia. Complete resolution of ocular symptoms is achieved in most patients with ocular myasthenia after treatment with prednisone; early immunotherapy also may reduce the proportion of patients who develop generalized MG.

The major disadvantages of chronic corticosteroid therapy are the side effects. Hypercorticism occurs in approximately one half the patients treated with the suggested regimen. The severity and frequency of adverse reactions increase when high daily doses are continued for more than 1 month. Fortunately, this is rarely necessary, especially if plasma exchange is begun at the same time as prednisone. Most side effects begin resolving as the dose of prednisone is tapered and become minimal at doses of less than 20 mg every other day. Side effects are minimized when patients use a low-fat, low-sodium diet and take supplemental calcium. Postmenopausal women should also take supplementary vitamin D. Patients with peptic ulcer disease or symptoms of gastritis need H_2 antagonists. Prednisone should not be given to people who have untreated tuberculosis,

Prednisone with azathioprine, cyclosporinc, mycophenolate, or other immunosuppressant drugs may produce more benefit than either drug alone (see next section, Immunosuppressant Drugs).

We have seen improvement in several patients with prednisolone treatment when equivalent doses of prednisone did not produce improvement or side effects.

Immunosuppressant Drugs

Several immunosuppressant drugs are effective in MG {Table 84.4). Azathioprinc is the drug used most often. It reverses symptoms in most patients, but the effect is delayed by 4-8 months. The initial dose is 50 mg daily, which is increased in increments of 50 mg per day every 7 days to a total dose of 150-200 mg per day. Improvement is maintained as long as the drug is given, but symptoms almost always recur 2-3 months after the drug is discontinued or the dose is reduced below therapeutic levels. Patients whose MG does not improve with corticosteroids may have a response to azathioprine, and the reverse is also true. Some have a better response to treatment with both drugs than to either alone. Because the response to azathioprine is delayed, both drugs may he started simultaneously with the intent of rapidly tapering the dose of prednisone when azathioprine becomes effective.

A prospective, randomized study showed that the addition of azathioprine to prednisolone significantly reduced the dose of prednisolone required to maintain remission and reduced the number of treatment failures (Palace et al. 1998).

A severe allergic reaction, with flu-like symptoms and possibly a tash, occurs within 2 weeks after azathioprine is started in 15-20% of patients; this reaction requires that the drug be stopped. It is not clear whether this teaction is product specific or related to the active ingredient in the compound. Othet patients may have mild, dose-dependent side effects that can be reversed by dose reductions but do not require stopping of treatment. Gasttointestinal irritation can be minimized by using divided doses after meals or by dose reduction. Leukopenia and even pancytopenia can occur any time during treatment but are not common. To guard against these, the blood count must be monitored every week during the first month, each month for a year, and every *l>-6* months thereafter. If the peripheral white blood cell (WBC) count falls to less than 3500 cells/mm\ the dose should be temporarily reduced and then gradually increased after the "WBC count rises above this level. WBC counts less than 1000 cells/mm require that the drug be temporarily discontinued. Serum transaminase concentrations may be slightly elevated, but clinical liver toxicity is rare. We discontinue treatment if transaminase concentrations exceed twice the upper limit of normal and restart the drug at lower doses when values become normal. Rare occurrences of azathioprine-induced pancreatitis arc reported, but the cost effectiveness of monitoring serum amylase concentrations has not been established, because azathioprine is potentially mutagenic, women of child-beating age should practice adequate contraception.

Table 84.4: Immunosuppressant drugs in myasthenia gravis

Azathioprine
- Onset action: 4—*8* months
- Common side effects: allergic reaction ("flu-like syndrome")
- Less common side effects: hepatic toxicity, leukopenia

Cyclosporine
- Onset action: 2-3 months
- Common side effects: renal toxicity, hypertension, multiple potential drag interactions

Cycli iphosphamidc
- Onset action: variable
- Common side effects: leukopenia, hair loss, cystitis

Mycophenolate mofetil
- Onser action: *2-A* weeks
- Common side effects: diarrhea, mild leukopenia

Cyclosporine (CYA) is a potent immunosuppressant that inhibits predominantly T-lymphocyte-dependent immune responses. Retrospective analyses have reported improvement in most patients taking CYA, with or without corticosteroids (Ciafaloni et al. 2000). We begin CYA at a daily dose of 5-6 mg/kg, given in two divided doses 12 hours apart. Trough serum levels of CYA should be measured after 1 month when tissues have become saturated. The dose is then adjusted to produce a trough serum CYA concentration of 75—150 ng/mL. Serum creatinine should be measured monthly and the dose adjusted to maintain a creatinine level of less than 150% of pre treatment values. Thereafter, serum creatinine should be measured at least every 2-3 months and more often after any new medications are begun. Blood pressure should also be monitored at least monthly until the maintenance CYA dose has been determined.

Renal toxicity and hypertension are the important adverse reactions of CYA. Many medications interact with CYA and must be avoided or used with caution. If the creatinine or blood pressure begins to rise, the clinician should determine whethet any contra indicated medications have recently been started.

Most patients with MG improve 1-2 months after Uvnuninl with I YA is -.'a I U.vl, arid r:u Milium iniprowr.H'in is achieved after 6 months or longer. As with azathioprine, prednisone *iv*,\\ be started at the same tunc, and thr iluse is decreased when CYA becomes effective. After the maximal response is achieved, the CYA dose is gradually reduced to the minimum that maintains improvement. The annual cost of a daily dose of 300 mg of CYA is about $6000, including blood tests,

Cyclophosphamide given intravenously in monthly pulsed doses has been used effectively in severe, generalized MG that is refractory to other therapy (de leo et al. 2002; Drachman et al. 2002). The initial dose was 500 mg/m , which was subsequently titrated according to changes in strength and to reduce side effects. Cyclophosphamide can also be given orally, at a dose of 150-200 mg per day to a total of 5-10 g, as required to relieve symptoms. Alopecia is

the major side effect. Cystitis, leukopenia, nausea, vomiting, anorexia, and discoloration of the nails and skin occur less often.

Mycophenolate mofetil (MM) (CellCept) selectively inhibits the proliferation of B- and T-lymphocyte clones responding to antigenic stimulation. It also suppresses the formation of antibodies active in complement-dependent lysis and antibody-dependent, cell-mediated cytotoxicity. A potential role for MM as a corticosteroid-sparmg agent and as adjunctive therapy in refractory MG has recently been reported in an open-label pilot study (Ciafaloni et al. 2001) and in a few case reports and retrospective scries. The usual dose is 2 g per day, in divided doses 12 hours apart, at a cost of $4500-4800 per year. Improvement has been reported as early as 2 weeks and is usually seen within 2 months in responding patients. The most common side effect is diarrhea, which can usually be managed by altering the dose schedule. The risk of leukopenia requires periodic blood counts, especially after therapy is begun. MM does not inhibit production of interleukin-1 and interleukin-2 as does CYA, and the two drugs have been used synergistically in other conditions. A controlled, randomized multicenter trial is underway to establish efficacy in MG and the optimal dosage. We currently consider using MM in patients with refractory MG and as a corticosteroid-spa ring agent when azathioprine has produced intolerable side effects or has not been effective.

The use of immunosuppressants in MG is usually a long-term commitment: few patients maintain improvement with these agents unless they are continued at effective doses. Life-threatening infections are an impottant risk in all immunosuppressed patients, but in our experience, this risk is limited in MG. The long-term risk of malignancy has not been established, but there are no reports of an increased incidence of malignancy in patients with MG who are receiving immunosuppressive therapy.

Plasma Exchange

Almost all patients with acquired MG show temporary improvement after plasma exchange. It is used as a short-term intervention for patients with sudden worsening of myasthenic symptoms for any reason; to rapidly improve strength before surgery, concomitantly with starting high dose corticosteroids; and as a chronic intermittent treatment for patients whose MG is refractory to all other treatments. The need for plasma exchange and the timing of use are determined by the clinical response in individual patients.

A typical protocol of plasma exchange is to remove 2-3 liters of plasma three times a week until improvement plateaus, usually after five to six exchanges. Improvement usually begins after the second or third exchange. Maximum improvement may be reached as early as the first exchange or as late as the fourteenth. Improvement lasts for weeks or months and then the effect is lost unless the exchange is followed by thymectomy or immunosuppressive therapy. Most patients who have a response to the first course have a response again to subsequent courses. Repeated exchanges do not produce a cumulative benefit and should not be used as chronic maintenance therapy unless other treatments have failed or are contraindicated.

Adverse reactions to plasma exchange include transitory cardiac arrhythmias, nausea, lightheadedness, chills, obscured vision, and pedal edema. The major complications are related to the route of access. Peripheral venipuncture should be used whenever possible to minimize the risk of thromboses, thrombophlebitis, and subacute bacterial endocarditis, as well as pneumothorax and brachial plexus injury when subclavian lines, arteriovenous shunts, or grafts are placed for vascular access. A flulike illness has been reported in patients with reduced immunoglobulin levels.

Intravenous Immunoglobulin

Many groups have reported a favorable response to high-dose (2 g/kg infused over 2-5 days) intravenous immunoglobulin (IVIG), although no adequate prospective, controlled trial has been done. The precise mechanism(s) of action in MG are not known. In general, there appears to be modulation of the inhibitory pathways or down-regulation of production of antibodies against AChR.

Improvement occurs in 50-100% of patients, usually beginning within 1 week and lasting for several weeks or months. Common adverse effects of IVIG are related to the rate of infusion and include headaches, chills, and fever. These reactions can be reduced by giving acetaminophen or aspirin with diphenhydramine (Benadryl) before each infusion.

Severe reactions, such as alopecia, aseptic meningitis, leukopenia, and retinal necrosis, are rare but have been reported in patients receiving IVIG for diseases other than MG. Renal failure may occur in patients with impaired renal function. Vascular-type headaches are often sufficiently severe to limit the use of IVIG, but we find that these headaches can be managed by administration of oral acetaminophen 1 g and ibuprofen 600 mg or intravenous dihydroergotamine before and immediately after the IVIG infusion. Recent reports of vascular occlusion have been reported in patients receiving IVIG. Cerebrovascular and myocardial infarction have occurred, but the mechanism for this is not known, and it is unclear if it is related to the infusion rate, the immunoglobulin concentration of by-products, or the osmolality of the preparation. Pre-existing arteriosclerosis appears to be a prerequisite for the occurrence of strokes or heart attacks. IVIG is contraindicated in patients with selective immunoglobulin (Ig)A deficiency because they may develop anaphylaxis to the IgA in IVIG preparations. IgA levels may be measured in all patients before IVIG therapy is started to detect this condition. Human immunodeficiency virus is not known to

be transmitted by IVIG, but the transmission of non-A, non-B hepatitis by IVIG has been reported. IVIG preparations are now prepared from donors shown to be without these viral infections, and the preparations are pasteurized. Although contamination of human blood products by donors having Creutzfeldt-Jakob disease has been reported, there is no reported case of transmission of this disease by blood products.

The indications for IVIG are similar to those for plasma exchange. IVIG is an effective alternative to plasma exchange, especially in patients with poor vascular access or when plasma exchange is not available. As with plasma exchange, IVIG should not be used as chronic therapy unless other treatments are contraindicated or have been ineffective.

Miscellaneous Treatments

Splenectomy, splenic radiation, and total body or total lymphoid irradiation have been used in a small number of patients who did not show improvement with all other forms of immunotherapy. Ammopyndines facilitate transmitter release at central and peripheral synapses. 4-Aminopyridine produces significant and sometimes dramatic improvement in acquired MG, congenital myasthenia, I.EMS, and botulism, especially when given with pyridostigmine. Confusion and seizures are the side effects that limit its use. 3,4-Diaminopyridinc (DAP) has similar peripheral effects with less central toxicity but is available only under a treatment-use investigational new drug application (see Treatment of Lambert-Eaton Myasthenic Syndrome, later in this chapter).

Ephedrine has been used in patients with congenital myasthenia and in patients with acquired myasthenia in whom ChE inhibitors alone are not effective, but it is not currently available in the United States. Terbutaiine (Brethine, Breathaire, Bricanyl), a /3-adrcnergic agonist, has also been used in this fashion. These agents are associated with a significant risk of arrhythmia, hypotension, and pulmonary edema and should be used with great caution.

Single case reports indicate that MG improves **after** treatment with rituximab (Zaja et al. 2000) and tacrolimus (Evoli et al. 2002). Further observations are necessary to determine the value of these immunosuppressants in MG.

Association of Myasthenia Gravis with Other Diseases

MG is often associated with other immune-mediated diseases, especially hyperthyroidism and rheumatoid arthritis. Seizures have been reported to occur more often in children wirh MG. One fifth of our myasthenic patients have another disease: 7% have diabetes mellitus before corticosteroid treatment, 6% have thyroid di sease, 3% have nonthymus neoplasm, and less than 2% have rheumatoid arthritis. Occurrences of MG related to human immunodeficiency virus and after allogeneic bone marrow transplantation suggest that the relationship may be more than coincidental.

Treatment of Associated Diseases

The effect of concomitant diseases and their treatment on myasthenic symptoms is an important consideration. Thyroid disease should be vigorously treated; both hypo- and hyperthyroidism adversely affect myasthenic weakness. Intercurrent infections require immediate attention because they exacerbate MG and can be life threatening in patients who are immunos up pressed.

Drugs rhar cause neuromuscular blockade must be used with caution. Many antibiotics fall into that category. Ophthalmic preparations of bera blockers and aminoglycoside antibiotics may cause worsening of ocular symptoms. D-PerucUlarnine should not be used because it can induce or exacerbate MG. If corticosteroids are needed to treat concomitant illness, tin- potential adverse and benefitul effects on MG must be anticipated and explained to the patient.

Patients treated with interferon-cr develop several autoantibodies and autoimmune diseases including MG. MG has been reported to develop in patients during interferon-«-2b treatment for malignancy and chronic active hepatitis C. In some individuals treated with inrerferon-a, the presentation of MG has been fulminant with myasthenic crisis. The mechanism is not well understood, but it is recognized that the expression of interferon-^ at motor endplates of transgenic mice results in generalized weakness and abnormal NMJ function that improve with cholinesterase inhibitors. Such studies suggest that the expression of interferon-}/ at motor endplates in these transgenic mice provokes an autoimmune humoral response, similar to that which occurs in human MG.

Patients with neuromuscular disease, such as MG or I.EMS, are at risk of systemic side effects, including dysphagia and respiratory compromise, from typical doses of botulinum toxin, which should be injected with great caution.

Annual immunization against influenza is recommended for all patients with MG, and immunization against pneumococcus is recommended in at-risk patients before prednisone or other immunosuppressive drugs are given. Inactivated polio vaccine rather than attenuated live oral polio vaccine should be used in people who are immunocompromised or in children who have household contacts with immunocompromised individuals. The Centers for Disease Control and Prevention reports that those taking less than 2 mg/kg per day of prednisone or evcry-other-day prednisone are not at risk.

Treatment Plan

We use the following protocols to treat patients with MG.

Ocular Myasthenia. Most patients are given CliE inhibitors. li the response is unsatisfactory, prednisone is added, cither in increments or high daily doses. Thymectomy may be considered in young patients with relatively recent onset of ocular weakness that persists despite treatment with ChE inhibitors in an effort to reduce the possibility that the disease will become generalized and ultimately require long-term medications. Patients with ocular myasthenia who develop weakness in muscles other than the ocular or periocular muscles are moved to the generalized myasthenia treatment protocol.

Generalized Myasthenia, Onset before Age 60. Thymectomy is offered to all patients. High-dose daily prednisone, plasma exchange, or both are used preoperatively in patients with oropharyngeal or respiratory muscle weakness to minimize the risks of surgery. If disabling weakness recurs or persists after thymectomy or if continual improvement is not seen 12 months after surgery, immunosuppression with high-dose daily prednisone, a/.athioprinc, cyclosporine, or MM is recommended (see Immunosuppressant Drugs, earlier in this chapter).

Generalized Myasthenia, Onset after Age 60. Life expectancy and concurrent illness are important considerations in developing a treatment plan. The initial treatment is usually ChE inhibitors. If the response is unsatisfactory, we add azathioprinc in patients who can tolerate a delay before a response is seen, ff treatment with azathioprine is unsatisfactory, high-dose daily prednisone is added or cyclosporine or MM is substituted for azathioprine. If a rapid response is needed, we use high-dose daily prednisone as the first drug, with or without plasma exchange or IVIG. Azathioptinc may be started at the same time, and the prednisone dose can be reduced or even discontinued after the maximum response has been obtained.

Thymoma. Thymectomy is indicated in all patients with thymoma. The patients are pretreated with high-dose daily prednisone, with or without plasma exchange, until maximal improvement is attained.

Postopetative radiation is used if tumor tesection is incomplete or if the tumor has spread beyond the thymic capsule. Medical treatment is then the same as for patients without thymoma.

Elderly patients with small tumors, who are not good candidates for surgery because of other health problems, may be treated medically while tumor size is monitored radiologically.

Juvenile Myasthenia Gravis. The onset of immune-mediated MG before age 20 is referred to as *juvenile myasthenia gravis* (Andrews and Sanders 2002). The pathophysiology is the same as that in adults.

In our experience, 20% of children with juvenile MG and almost 50% of those with onset before puberty are seronegative {see Seronegative Myasthenia Gravis, in the next section). The female-to-male ratio in children is 3:1 compared with almost 1:1 in adult-onset disease. Thymomas are rare in this age group, but the few that we have seen were malignant.

When myasthenic symptoms begin in childhood, it is important to determine whether the patient has acquired autoimmune MG or a genetic form that does not respond to immunotherapy (see Genetic Myasthenic Syndromes, later in this chapter). Because the absence of AChR antibodies does not distinguish these conditions, a therapeutic trial of plasma exchange or IVIG may be indicated. Those who definitely show improvement arc candidates for thymectomy or immunotherapy, but failure to respond does not exclude autoimmune MG.

Treatment decisions in childten with autoimmune MG arc more difficult because the rate of spontaneous remission is high. We recommend ChE inhibitors alone in prepubertal children who are not disabled by weakness. If these drugs do not prevent disability or progressive weakness, we proceed to thymectomy. Removal of the thymus in infants or children does not have a deleterious effect on subsequent immunological development.

Children with postpuberal onset of disease are treated the same as adults.

Seronegative Myasthenia Gravis. One fourth of patients with acquired, presumably immune-mediated MG do not have detectable scrum antibodies against AChRs (Sanders et al. 1997). Seronegative patients are more likely than seropositive patients to be male and to have milder disease, ocular MG, and fewer thymomas; they are less likely to have thymic hyperplasia and more likely to have thymic atrophy. In seronegative patients, the diagnosis is based on the clinical presentation, the response to ChE inhibitors, and electromyographic findings. Genetic myasthenia must be considered in all childhood-onset seronegative MG. The treatment of seronegative MG is the same as that for seropositive MG. The absence of AChR antibodies docs not necessarily mean that an unsatisfactory response to immunosuppression, plasma exchange, or thymectomy is expected.

Antibodies to muscle-specific receptor tyrosine kinase have recent l v been reported n; ,U least Id",, nt p,molts with ;>,rivtalized seronegative MG (Hoch et al. 2001; Scuderi et al. 2002). Many of these patients have scvete ocular and bulbar weakness, which is resistant to many forms of therapy. In such patients, we have seen sustained and significant improvement after plasma exchange and immunosuppression with cyclosporine MM and prednisone (Sanders et al. 2003). Detection of muscle-specific receptor tyrosine kinase antibodies will be an important tool in diagnosing MG in patients who do not have detectable antibodies to the AChR.

Special Situations

Myasthenic or Cholinergic Crisis, Myasthenic crisis is respiratory failure from myasthenic weakness. Patients in

myasthenic crisis who previously h.nl well compensated respiratory function usually have had a definable precipitating event, such as infection, surgery, or rapid tapering of immunosuppressive therapy (Bedlack and Sanders 2000). Cholinergic crisis is rcspitatory failure from an overdose of ChE inhibitors. It was more common before the introduction of immunosuppressive therapy, when very large dosages of ChE inhibitors were used. Respiratory failure of any cause is a medical emergency and requires prompt intubation and ventilatory support.

In theory, it should be easy to determine if a patient is weak because of too little ot too much ChE inhibitor, but in practice this is often difficult. Administration of edrophonium si ion kl distinguish overdose from underdose, hut its use in myasthenic crisis is dangerous unless the patient is already intubated and ventilated. Also, an apprehensive patient in myasthenic crisis usually cannot cooperate with the test. Further, edrophonium may make some muscles stronger and others weaker. Serial measurements of forced vital capacity and blood gases do not predict which patients with MG will need mechanical ventilation. The safest approach to crisis is to admit the patient to an intensive care unit, discontinue all ChE inhibitors, and support ventilation. ChE inhibitors should be resumed at low doses and the dose should be slowly increased as needed.

Respiratory assistance is needed when the patient cannot maintain an inspitatory force of more than —20 cm ETO, when tidal volume is less than 4-5 mL/kg body weight and maximum breathing capacity is less than three times the tidal volume, or when the forced vital capacity is less than 15 mL/kg body weight. A mask and breathing bag can be used in an emergency situation, but ttacheal intubation should quickly be done with a low-pressure, high-compliance cuffed endotracheal tube. A volume-controlled respirator set to provide tidal volumes of 400-500 mL and automatic sighing every 10-15 minutes is preferred. The pressure of the tube cuff should be checked often and the tube position verified daily by chest radiographs. Assisted respiration is used when the patient's own respiratory efforts can trigger the respirator. An oxygen-enriched atmosphere is used only when arterial blood oxygen values fall to less than 70 mm Hg. The inspired gas must be humidified to at least 80% at 37"C to prevent drying of the tracheobronchial tree. Tracheal secretions should be removed periodically using aseptic aspiration techniques. Low-pressure, high-compliance endotracheal tubes may be tolerated for long periods and usually obviate the need for tracheostomy. When respitatory strength improves, weaning from the respirator should he started for 2 or 3 minutes at a time and increased as tolerated. Extubation should be considered when the patient has an inspiratory pressure greater than —20 cm H_20 and an expiratory pressure greater than .35^10 cm H_20. The tidal volume should exceed 5 mL/kg, which usually corresponds to a vital capacity of at least 1000 mL. If the patient complains of fatigue or shortness of breath, extubation should be deferred even if these values and the results of blood gas measurements are normal.

Prevention and aggressive treatment of medical complications offer the best opportunity to improve the outcome of myasthenic crisis.

Anesthetic Management. The stress of surgery and some drugs used perioperatively may worsen myasthenic weakness. As a rule, local or spinal anesthesia is ptcferred over inhalation anesthesia. Neuromuscular blocking agents should be used sparingly, if at all. Adequate muscle relaxation usually can be produced by inhalation anesthetic-agents alone. The required dose of depolarizing blocking agents may be greater than that needed in nonmyasthenic patients, but low doses of nondepolarizing agents cause pronounced and long-lasting blockade that requires prolonged postoperative assisted respiration.

Pregnancy. Myasthenia in women may improve, worsen, or remain unchanged during pregnancy. Eirst trimester worsening is more common in first pregnancies, whereas third-trimester worsening and postpartum exacerbations are more common in subsequent pregnancies. Therapeutic abortion is rarely, if ever, needed because of MG, and the incidence of spontaneous abortion is not increased (Abel 2002). Oral ChE inhibitors are first-line treatment during pregnancy. The use of inttavenous ChE inhibitors is contraindicated because they may produce uterine conrtactions. Prednisone is the immunosuppressive agent of choice. Adverse outcomes in children born to myasthenic mothers taking high-dose prednisone throughout pregnancy have not been reported. We do not use cytotoxic drugs during pregnancy because of their theoretical potential mutagenic effects. Others feel these agents can be used safely during pregnancy. Plasmapheresis or IVIG has been used when immediate, albeit temporary, improvement is needed.

Labor and delivery are usually normal, and cesarean section is needed only for obstetrical indications. Regional anesthesia is preferred for delivery or cesarean section, Magnesium sulfate should not be used to manage preeclampsia because of its neuromuscular blocking effects. Barbiturates usually provide adequate treatment. In our experience, breast-feeding is not a problem, despite the theoretical risk of passing maternal AChR antibodies to the newborn.

The serum concentrations of AChR antibodies in the mother and her newborn arc similar. It is also likely that the fetus of an affected mother has an elevated concentration of AChR antibodies. Decreased fetal movement suggests the diagnosis of intrauterine myasthenia. Affected newborns may have arthrogryposis multiplex congenita because of decreased intrauterine movement, and decreased fetal movement is considered an indication fot plasmapheresis or IVIG. Birth of a child with arthrogryposis should prompt a search for MG in the mother.

Transitory Neonatal Myasthenia. A transitory form of MG affects 10-20% of newborns whose mothers have

immune-mediated MG (Andrews and Sanders 2002). The severity of symptoms in the newborn does not correlate with the severity of symptoms in the mother. The maternal antibody level correlates with the frequency and severity of transitory neonatal myasthenia, and it occurs only rarely in infants of seronegative mothers. If an affected mother delivers an infant with transitory neonatal myasthenia, her subsequent infants are likely to be similarly affected. Affected newborns are hypotonic and feed poorly during the first 3 days. In some newborns, symptoms may be delayed for 1-2 days. Symptoms usually last less than 2 weeks but may continue for as long as 12 weeks. Neonatal antibodies have a half-life of 2-3 weeks and are not detected after 5 months. This time course is consistent with the duration of clinical weakness. Passive transfer of maternal antibodies to the newborn does not fully explain the clinical syndrome of transitory neonatal myasthenia. The mechanism by which some newborns develop weakness and others, with equally high antibody concentrations do not, is uncertain.

All children of myasthenic mothers should be assessed for transitory neonatal myasthenia. The diagnosis is established by administration of edrophonium or RNS. Affected newborns require symptomatic treatment with ChE inhibitors if swallowing or breathing is impaired. Plasma exchange should be considered in newborns with respiratory weakness.

u-Petiidllaniitw-Induced Myasthenia Gravis. D-Penieillamine is used to treat rheumatoid arthritis, Wilson's disease, and cystinuria. Rarely patients treated with o-penicillamine for several months develop a myasthenic syndrome that disappears when the drug is stopped, n-Pen icil I a mine-induced myasthenia is usually mild and is often restricted to the ocular muscles. The diagnosis is often difficult because weakness may not be recognized when there is severe arthritis. The diagnosis is established by the response to ChE inhibitors, characteristic electromyographic abnormalities, and serum AChR antibodies. It is likely that n-penicillaminc stimulates or enhances an immunological reaction against the NMJ. The myasthenic response induced by D-pcnicillamine usually remits 1 year after the drug is stopped. ChE inhibitors usually relieve the symptoms. If myasthenic symptoms persist after D-penicillamine is stopped, the patient should be treated for acquired MG.

The Future. The future of treatment of MG lies in the elucidation of the molecular immunology of the anti-AChR response, with the goal of developing a rational treatment that cures the abnormality in the immune system. The simplistic understandings of T-cell and B-cell function and the myasthenic autoimmune response have not explained the pathophysiology. A more detailed understanding of the mechanisms of synaptogenesis and the molecular basis of autoimmunity is necessary to develop rational, directed therapies that target the specific autoimmune responses while minimally affecting the host.

Genetic Myasthenic Syndromes

Genetic forms of myasthenia arc not immune mediated. They are a heterogeneous group of disorders caused by several abnormalities of neuromuscular transmission (Engel 2002). Some have characteristic physiological or histological features. Symptoms are typically present at birth or early childhood but can be delayed until young adult life. Abnormal neuromuscular transmission is confirmed by the response to edrophonium chloride and characteristic electromyographic findings.

The onset of myasthenic symptoms at birth is always genetic, with the exception of the transitory neonatal form. All generic forms of myasthenia are known or presumed to be transmitted by autosomal recessive inheritance, except slow-channel syndrome, which is transmitted by autosomal dominant inheritance. Myasthenia that begins in infancy or childhood may be genetic or acquired.

Congenital Myasthenia

Congenital myasthenia is a clinical term that encompasses several generic neuromuscular defects. Overall, there is a 2:1 male predominance. Children with congenital myasthenia develop ophthalmoparesis and ptosis during infancy. Mild facial paresis may be present as well. Ophthalmoplegia is often incomplete at onset but progresses to complete paralysis during infancy or childhood. Some children develop generalized fatigue and weakness, but limb weakness is usually mild compared with ophthalmoplegia. Respiratory distress is unusual.

Congenital myasthenia should he suspected in any newborn or infant with ptosis or ophthalmoparesis. Subcutaneous injection of edrophonium usually produces a transitory improvement in ocular motility. A dccremental response to RNS is found in some limb muscles, but it may be necessary to test proximal or facial muscles if hand muscles show a normal response. SFEMG shows increased litter.

ChE inhibitors improve limb muscle weakness in many forms of congenital genetic myasthenia and may be effective even when edrophonium is not. Ocular muscle weakness is less responsive ro ChE inhibitors. The weakness in some children responds to DAP (Harper et al. 2000), which is only available as an investigational new drug in the United States (see Treatment of Lambert-Eaton Myasthenic Syndrome, later in this chapter).

Congenita! Myasthenic Syndrome with Episodic Apnea (Familial infantile Myasthenia)

This condition has characteristic clinical and electrophysiological features that differ from those of other congenital myasthenic syndromes. Generalized hypotonia is present at birth, and the neonatal course is complicated by repeated episodes of life-threatening apnea and feeding difficulty.

Assisted ventilation is often required. Arthrogryposis may be present. Ocular muscle function is usually normal. Within weeks after birth, the child becomes stronger and ultimately breathes unassisted. However, episodes of life-threatening apnea occur repeatedly throughout infancy and childhood and even into adult life. There is often a history of sudden infant death syndrome in siblings, and the correct diagnosis may not be suspected until a second affected child is born.

Administration of edrophonium usually improves both weakness and respiratory distress. A decremental response to RNS is usually present in weak muscles but may be demonstrated in strong muscles only after the muscle is exhausted by several minutes of RNS. Abnormal resynthesis and repackaging of ACh in the motor nerve has been shown in some patients.

ChE inhibitors improve strength in most affected children, but sudden episodes of respiratory distress occur with intercurrent illness. As the patients get older, weakness improves, attacks of respiratory distress occur less often, and the need for medication decreases. In children from : il families with this syndrome, we have seen sustained symptomatic improvement when DAP is given with pyridostigmine.

Slow-Channel Congenital Myasthenic Syndrome

This syndrome may be difficult to distinguish from acquired MG because the onset of symptoms may be delayed until adult life. The disease is transmitted by autosomal dominant inheritance, and a family history of similar illness often is obtained.

Slow-channel congenital myasthenic syndrome is rare. Onset of symptoms always occurs after infancy and may present as late as the third decade. Slowly progressive weakness selectively involves the arm, leg, neck, and facial muscles. Unlike other myasthenic syndromes, atrophy of symptomatic muscles is expected.

RNS shows a decremental response. Repetitive discharges are seen after nerve stimulation, similar to those seen in ChE inhibitor toxicity or congenital deficiency of endplatc acetylcholinesterase. The underlying defect is prolonged open time of the ACh channel.

ChE inhibitors, thymectomy, and immunosuppression are not effective treatment. Quinidine sulfate and fluoxetine may improve strength in this condition (Harper et al. 2002).

Lambert-Eaton Myasthenic Syndrome

LEMS is a presynaptic abnormality of ACh release that was first described in association with malignancy, usually small cell lung cancer (SCLC). The probable mechanism in most, ii in it all,]\n inn v is .in iiniinn';: incdiak'd pi occss directed against the voltage-gated calcium channels (VGCCs) on nerve terminals (see Figure 84.2). LEMS usually begins after age 40 but has been reported in children. Males and females are affected equally. Approximately one half of patients with LEMS have an underlying malignancy; 80% of these have SCLC. The cancer may be discovered years before or after the symptoms of LEMS begin,

Weakness of proximal muscles, especially in the legs, is the major symptom. The weak muscles may ache and are occasionally tender. Oropharyngeal and ocular muscles may be mildly affected but not to the degree seen in MG. The weakness demonstrated on examination is usually relatively mild compared to the severity of symptoms. Strength may improve initially after exercise and then weaken with sustained activity. Administration of edrophonium chloride does not improve strength to the degree seen in MG. Tendon reflexes are reduced or absent but arc often enhanced by repeated muscle contraction or repeated tapping of the tendon. Dry mouth is a common symptom of autonomic dysfunction; other features are impotence and postural hypotension.

LEMS may be first discovered when prolonged paralysis follows the use of neuromuscular blocking agents during surgery. Clinical worsening has been described after administration of aminoglycoside antibiotics, magnesium, calcium-channel blockers, and todinated intravenous contrast agents.

Although LEMS and MG are both immune-mediated disorders of neuromuscular transmission, their clinical features are quite distinct. The weakness in LEMS is not usually life threatening and more closely resembles cachexia, polymyositis, or a paraneoplastic neuromuscular disease.

Diagnostic Procedures

The diagnosis of I.F.MS is confirmed by EMG (see Chapter 36B). The characteristic findings are decreased size of compound muscle action potentials (CMAPs) with further size reduction in response to RNS at frequencies between 1 **and** 5 Hz, doubling of CMAP size in response to repetitive stimulation at 20-50 Hz, and a transitory increase in CMAP size after brief maximum voluntary contraction. Virtually all patients with LEMS have a decrementing response to 3-Hz stimulation in a hand or foot muscle, and almost all have low-amplitude CMAPs in some muscle (Tim et al. 2000). Facilitation of more than 100% is not seen in all muscles; several muscles may need to examined to demonstrate this important finding. Abnormalities of these measurements may be partially masked by low muscle temperature; thus hand and foot muscles should be warmed. In proximal muscles, the CMAP amplitude is normal, there is usually a decrementing pattern, and the amount of facilitation is less than in distal muscles.

When LEMS and MG are difficult to distinguish by cluneal features and electrophysiology, the presence of elevated concentrations of AChR or VGCC antibodies or

lung cancer clarifies the diagnosis. Sometimes, the diagnosis is defined only by the response to treatment or the course of disease.

Immunopatkology of Lambert-Eaton Myasthenic Syndrome

Patients with LEMS, like those with MG, have an increased incidence of other immune-mediated diseases. Those who do not have cancer often have serum organ-specific auto-antibodies, further confirming that LEMS is immune mediated. In LEMS, the motor nerve **terminal** active zone particles, which represent the VGCCs, are disorganized in appearance and reduced in number. Similar changes are seen in recipient mice who are injected with IgG from pa lie ins with 1.1'.MS. 1 he mechanism is probably cross-linking of the VGCCs by antibodies.

SCLC cells are of neuroectodermal origin and contain high concentrations of VGCCs. Calcium influx into these cells is inhibited by LEMS IgG, and antibodies to the VGCC are found in the sera of almost all patients with LEMS, and in 10% of those with SCLC who do not have LEMS. VGCC antibody titers do not correlate with disease severity among individuals, but the antibody levels may fall as the disease resolves in patients receiving immunosuppression. These observations suggest that SCLC cells induce VGCC antibodies that react with the VGCCs of peripheral nerves and cause LEMS. In patients with LEMS who do not have SCLC, the VGCC antibodies are produced as part of a more general immune-mediated disease.

Treatment of Lambert-F.aton Myasthenic Syndrome

Once the diagnosis of LEMS is established, an extensive search for underlying malignancy, especially SCLC, is mandatory. Chronic smokers should undergo bron-choscopy or a positron-emission tomography scan if chest imaging studies are normal. Initial ttcatment is focused on the underlying malignancy, and weakness may improve after effective cancer therapy. In some parients, no further ttcatment is needed for the neuromuscular defect. If tumor is not found, the search for occult malignancy should be repeated periodically, especially during the first 2 years after onset of symptoms. The frequency of reevaluation is determined by the patient's cancer risk factors.

Therapy is railored to the individual based on the severity of weakness, underlying disease, life expectancy, and response to previous treatment. The treatment plan in the following paragraphs is a general guide that should be modified to suit specific situations.

ChE inhibitors may relieve weakness in occasional patients with LEMS. Pyridostigmine 30-60 mg every 6 hours should be tried for several days. In some patients, the major benefit is relief of dry mouth.

Guanidine hydrochloride increases the release of ACh and produces temporary improvement in strength in many patients with LEMS. Guanidine is started at an oral dose of 5-10 mg/kg daily, divided into three doses 4-6 hours apart; the dose may be increased to a maximum of 30 mg/kg per day. Bone marrow depression may occur with doses as low as 500 mg per day. The dose should not be incteased more often than every 3 days because the maximum response may be delayed for 2-3 days. The therapeutic response is enhanced by giving pyridostigmine (30-60 mg every 4-6 hours). In addition to bone marrow depression, side effects seen at higher doses include renal tubular acidosis, chronic interstitial nephritis, cardiac arrhythmia, hepatic toxicity, pancreatic dysfunction, paresthesias, ataxia, confusion, and alterations of mood. Monthly blood counts are recom-mended for any patient receiving guanidine.

Oral DAP 5-25 nig three to four times a day improves strength and autonomic symptoms in most patients with LEMS (Sanders et al. 2000; Tim ct al. 2000). Like guanidine, DAP facilitates release of ACh from motor nerve terminals. The response to DAP is enhanced by the concomitant use of pyridostigmine 30-60 mg three or four times a day. Side effects usually are negligible. Transient perioral and digital paresthesias occur with doses greater than 10-15 mg. Doses of 100 mg per day may cause seizures. Cramps and diarrhea may occur when DAP is given with pyridostigmine and can be minimized by reducing the dose of pyridostigmine. DAP is a safe and effective treatment for LEMS but is not available for general clinical use in the United States. It can he obtained for individual patients upon submission of a treatment-use investigational new drug application by the administering physician. Information on the application process can be obtained from Jacobus Pharmaceutical Co., Princeton, N'J (fax: 609-799-1176).

Both plasma exchange and IVTG provide transitory improvement in some patients with LEMS (Tim ct al. 2000), but the results arc usually not as good as in patients w ah MG.

if these treatments are not effective, it must be determined whether weakness is sufficiently severe to warrant immu-notherapy with prednisone, azathioprine, or cyclosporine. hi patients with severe weakness, plasma exchange or 1VIG may be used first and prednisone and azathioprine added after improvement begins. Repeated courses of treatment may be needed to maintain improvement,

The long-term prognosis for patients with LEMS is variable. In patients with cancer, it is determined by the response to cancer therapy. In patients without cancer, treatment with immunosuppression produces improvement in many patients, but most require substantial and con-tinuing doses of immunosuppressive medications {Maddison ct al. 2001).

The weakness of LEMS may be worse when the ambient temperature is elevated or when **the** patient is febrile. Patient-, should avoid hot shower•> or baths, svstenuc illness of any sort may cause transient worsening of weakness in patients with LEMS.

Drugs That Adversely Affect Myasthenia Gravis and the Lambert-Eaton Myasthenic Syndrome

Drugs that compromise neuromuscular transmission make patients with MG or LEMS weaker. Categorically, four clinical situations are encountered in which these drugs produce a worsening of neuromuscular function. First, there are the direct and augmented deleterious effects of the drug on synaptic transmission in an otherwise apparently normal individual; second, there is a drug-induced disturbance of the immune system that results in the development of MG; third, there is the unmasking of subclinical MG or the worsening of muscle strength in patients with disorders of neuromuscular transmission {MG, LEMS, and botulism); and fourth, those with delayed recovery of strength, particularly respiratory function, after general anesthesia during which neuromuscular blocking agents ma\ or may not have been used.

Pre-existing circumstances such as altered drug clearance due to renal or hepatic disease, concomitant drug administration, electrolyte disturbances, or direct toxicity may predispose the patient to neuromuscular weakness in the first situation. An example would be the patient with chronic renal failure, undergoing a surgical procedure during which a neuromuscular blocking agent and an aminoglycoside antibiotic were given. The second situation is most commonly encountered in n-penicillamine-induced MG. There are a few reports of similar occurrences in patients receiving tiopronin, pyrirhioxine, hydantoin drugs, trimethadione, and possibly chloroquine. In the third situation, failure of the neuromuscular manifestations to resolve after the drug is discontinued implies that the disorder was subclinical and unmasked by the pharmacological agent. This has been seen in previously asymptomatic patients given D-penicillamine in whom MG did not resolve when the drug was discontinued.

Drugs that affect neuromuscular transmission may act presynaptically by reducing ACh release due to local anesthetic-like activity on the nerve terminal or impairing calcium flux into the nerve terminal or by a hemicholinium effect (impaired resynthesis of ACh in the nerve). Drugs may act postsynapticsHy, with curare-like blockade of ACh receptors or potentiation of depolarizing or nondepolarizing neuromuscular blocking agents. In some instances there may be varying degrees of pre- and postsynaptic blockade.

The effects of competitive neuromuscular blocking agents, such as d-tubocurarine and pancuronium, art- exaggerated and prolonged in patients with MG or l.b.MS. Depolarizing agents, such as succinylcholine, also must be used with caution. Some antibiotics, particularly aminoglycosides, antiarrhythmics (quinine, quinidine, and procainamide), and a-adrcnergic blocking drugs, block neuromuscular transmission and increase weakness. Iodinated contrast agents have been reported to produce transitory worsening in patients with MG and LEMS, possibly because of the calcium-chclating effects of these agents. Ophthalmic beta blocker and tobramycin preparations may unmask or exacerbate myasthenic weakness. Many other drugs have been reported to increase myasthenic weakness in isolated patients. Unfortunately, many of these reports are merely anecdotal, often involving isolated cases of patients with increased weakness while using a particular drug. There have been only a few comprehensive in vitro studies of the effects of various drugs on animal or human neuromuscular transmission. The potential adverse effects of these medications must be taken into consideration when the clinician decides which drugs to use. All patients with MG and i KV1S should be observed foi clinical worsening after any new medication is started.

Although ir ˙s desirable to avoid drugs thai are known to impair neuromuscular transmission, this is not always possible. We find it useful to place a list of potentially hazardous drugs on the front of the hospital chart of patients with MG and LEMS (Table 84.5).

Tnhk' S4„S; Drug alert for patients with myasthenia gravis (MG) or Lambert-Eaton myasthenic syndrome

1. Interferon-a, hotulimim toxin, and o-peuicillamine should never be used in myasthenic patients.
2. The following drugs produce worsening of myasthenic weakness in most patients who receive them. Use with caution and monitor patient for exacerbation of myasthenic symptoms,
   - Succinylcholine, (f-tubocutarine, or other neuromuscular-blocking agents
   - Quinine, quinidine, and procainamide
   - Aminoglycoside antibiotics, particularly gentamicin, kanamycin, neomycin, and streptomycin
   - Beta blockers (systemic and oculat preparations): propranolol, timolol maleatc eyedrops
   - Calcium-channel blockers
   - Magnesium salts (including laxatives and antacids with high M(;"' concentrations)
   - Iodinated contrast agents
3. Many other drugs are reported to exacerbate the weakness in some patients with MG. All patients with MG should be observed for increased \vcak:v-.s whenever .'. nnv medie.˙'i<>u is •a.iru-d. \n up in Jau- ivkri ;;LV document loi s.idi .id verse interactions is maintained on the web site of the Myasthenia Gravis Foundation of America (www.myasthenia.org/drugs/refercnce.htm).

BOTULISM

Botulism is caused by a toxin produced by the anaerobic bacterium, *Clostridium hotulinum,* that blocks the release of ACh from the motor nerve terminal (Cherington 2002). The result is a long-lasting, severe muscle paralysis. Of eight types of botulinum toxins, types A and B cause most occurrences of botulism in the United States. Type E is transmitted in seafood. Intoxication usually follows ingestion of contaminated foods that were inadequately sterilized. Neuromuscular symptoms usually begin 12-36 hours after ingestion of contaminated food. Not all

people who ingest the contaminated food become symptomatic. Nausea and vomiting are the first symptoms of food-borne botulism, and the neuromuscular symptoms begin 12-36 hours after exposure.

The most common form of botulism in the United States is wound botulism, which occurs predominantly in drug abusers after subcutaneous injection of heroin. *Clostridium* bacteria colonize the injection site and release toxin that produces local and patchy systemic weakness.

Clinical Features

The major symptoms of botulism arc blurred vision, dysphagia, and dysarthria. Pupillary responses to light are impaired, and tendon reflexes arc variably reduced. The weakness progresses for several days and then reaches a plateau. Fatal respiratory paralysis may occur rapidly. Most patients have evidence of autonomic dysfunction, such as dry mouth, constipation, or urinary retention. Results of the Tensilon test are positive in only approximately one third of patients and do not distinguish botulism from other causes of neuromuscular blockade. The diagnosis of wound botulism is confirmed by wound cultures and serum assay for Botulinum toxin.

Infant botulism results from the growth of C. *botulinum* in the infant gastrointestinal tract and the elaboration of small quantities of toxin over a prolonged period (Jones 2002). Symptoms of constipation, lethargy, poor suck, and weak cry usually begin at approximately 4 months of age. Examination reveals weakness of the limb and oropharyngeal muscles, poorly reactive pupils, and hypoactivc tendon reflexes. Most patients require ventilatory support. The diagnosis of infant botulism is confirmed by demonstration of botulinum toxin in the stool or by isolation of C. *botulinum* from stool culture.

Electromyographic Findings in Botulism

Electrophysiological abnormalities in botulism tend to evolve with time and may not be present early in the disease. The electromyographic findings in botulism include the following:

- Reduced CMAP amplitude in at least two muscles
- At least 20% facilitation of CMAP amplitude during tetanic stimulation
- Persistence of facilitation for at least 2 minutes after activation
- No postactivation exhaustion

Not all patients with botulism meet the first criterion. If none of these criteria is met, the diagnosis of botulism is unlikely. If all four are met, only hypermagnesemia is in the differential diagnosis.

SFFMG demonstrates markedly increased jitter and blocking, and results have been abnormal in all reported patients with food-borne or wound botulism. Jitter and blocking may decrease as the firing rate increases, but this is not a consistent finding.

Treatment

[reatment .;nnsists of bivaleni (type A and U) or trivalenl (A, B, and E) antitoxin. Antibiotic therapy is not effective because the symptoms are caused by the ingestion of toxin rather than organisms. Otherwise, treatment is supportive; respiratory assistance is given when necessary. ChF, inhibitors are not beneficial; use of guanidine or DAP may improve strength but not respiratory function. Recovery takes many months but usually is complete.

The use of botulinum A toxin for the treatment of focal dystonia has resulted in focal or regional weakness after injection of the toxin. Such adverse events have included diplopia, dysphagia, urinary incontinence, focal weakness, brachial plexoparhy, and the unmasking of neuromuscular weakness due to LEMS and amyotrophic lateral sclerosis. SFEMG has demonstrated abnormal neuromuscular transmission in muscles remote from the site of injection, which persists for many months.

OTHER CAUSES OE ABNORMAL NEUROMUSCULAR TRANSMISSION

The NMJ is uniquely sensitive to the effects of neurotoxins and other disorders of the motor unit (Howard 2002). Unlike the blood-brain barrier that protects the brain and spinal cord and the blood-nerve barrier that protects peripheral nerve, there are no barriers to protect the NMJ from these agents. Envenomation is the most common cause of NMJ neurotoxicity worldwide. All forms of NMJ neurotoxicity are characterized by progressive, typically symmetrical muscle weakness. Muscles of eye movement or the eyelids are most often involved as well as the muscles of neck flexion and the pectoral and pelvic girdles. In more severe situations, bulbar or respiratory muscles are also involved. Cognition and sensation are usually spared unless other parts of the nervous system arc also involved. Muscle stretch reflexes are often preserved or only minimally diminished, particularly during the early phases of illness, but may be lost if muscle weakness is severe,

Venom toxicity at the NMJ occurs by four mechanisms: (1) an initial augmentation of ACh release with subsequent depletion of neurotransmitter, (2) facilitation of ACh release without subsequent depletion of neurotransmitter, (3) depletion of ACh release, and (4) blockade of the postjunctional ACh receptor. Most biological toxins of animal origin either facilitate the release of

neurotransmitter From the presynaptic nerve terminal or block the ACh receptor.

Examples of arthropod venoms that affect the NMJ are those of the funnel web and black widow spiders (latrodectism). Each produces marked facilitation of neurotransmitter release by depolarization of the presynaptic nerve terminal and increasing Ca^{2+} influx into the nerve KTiii.:i.il. 'I ick ;vi!-.ilvv-. results from *a* neurotoxin [hat blocks receptor function postsynaptieally. Envenomation by snakebite occurs primarily from the *Elapidae* and *Hydrophiodae* species. Snake toxins may act cither presynaptically or postsynaptieally. Presynaptic ^-neurotoxins (/^bungarotoxin, norexm, and taipn\iuj inhibit the normal release of ACh. Often, there is an initial augmentation of ACh release, followed by presynaptic depletion of neurotransmitter. These tend to be more potent than postsynaptic toxins. Postsynaptic W-neurotoxins produce a curare-mimetic, nondepolarizing neuromuscular block that is variably reversible. Most venoms contain both types of neurotoxins although one type may predominate in n given venom. Marine neurotoxins affecting the NMJ arc rare and come primarily from poisonous fish (stonustoxin), a few mollusks (conotoxins), and perhaps dinoflagellates. Most marine intoxications occur as the result of ingestion. Unique to some marine toxins is the fact that there is an increase in the concentration of toxin through successive predatory transvection up the food chain {Howard 2002).

Neuromuscular transmission may be abnormal in diseases of the motor unit that do not primarily affect the NMJ. For example, patients with amyotrophic lateral sclerosis may have fluctuating weakness that responds to ChE inhibitors, an abnormal decrements1 response to RNS, and increased jitter and blocking on SFEMG. Features that can be attributed to abnormal neuromuscular transmission also are reported in syringomyelia, poliomyelitis, peripheral neuropathy, and inflammatory myopathy.

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Chapter 85
Disorders of Skeletal Muscle

Anthony A. Amato and Michael H. Brooke

Disorders of skeletal muscle encompass several illnesses that cause weakness, pain, and fatigue in any combination. They vary from the protean symptoms of aches, cramps, and pains thai often dcf\ any explanation to the muscular dystrophies, which are readily recognized on clinical grounds. 'I'll- disorder^ wilh primary iiivnlvemciu "I die anterior horn cells (e.g., amyotrophic lateral sclerosis and the spinal muscular atrophies), neuromuscular junction disorders (myasthenia gravis, Lambert-Eaton syndrome, **and** congenital myasthenia), and certain polyneuropathies (e.g., chronic inflammatory demyelinating polyneuropathy) can cause similar symptoms and may be difficult to differentiate on clinical grounds from primary disorders of muscle. Some definitions are worth reviewing. *Myopathy* refers ro an abnormality of the muscle and has no other connotation. *Muscular dystrophies* are genetic myopathies, usually caused by a disturbance of a structural protein. *Myositis* implies an inflammatory disorder, and the term is usually reserved for disorders in which muscle histological preparations show an inflammatory response. The *myotonias* are diseases in which die normal coiuraculu process is distorted by the occurrence of involuntary, persistent muscle activity accompanied by abnormal repetitive electrical discharges, which may occur after percussion or voluntary contraction. *Metabolic myopathics,* in this context, refer mainly to abnormalities of muscle biochemistry that impair energy production. In a general medical context, *metabolic myopathy* is often synonymous with *endocrine myopathy. Congenital myopathies* are a group of genetic disorders with structural disturbances of the muscle cell that usually present at birth or during childhood. Many of these are relatively nonprogressive. Some myopathies with similar structural **features** may have a later onset, even into adult life (e.g., myofibrillar myopathy, central nuclear myopathy, and nemaline myopathy) and have a progressive course.

Striated muscle is the tissue that converts chemical energy into mechanical energy. The component processes include (1) excitation and contraction occurring in the muscle membranes, (2) the contractile mechanism, (3) structural supporting elements that allow muscle to withstand mechanical stress, and (4) the energy system that supports the activity and integrity of the other three systems. Logically, myopathies should be categorized according to the part of the system involved. This was previously impossible because the molecular basis of muscle activity was unknown. Recent advances in knowledge allow an attempt to classification along these lines.

Abnormalities in the membrane ion channels involved in muscle excitation are referred to as *channelopathies* and cause several forms of myotonia and periodic paralysis. The complex of proteins, which include dystrophin, the sarcoglycan proteins, and laminin, constitutes a vital structural mechanism linking the contractile proteins with the extracellular supporting structures. Defects in these proteins are found in many forms of muscular dystrophy. Although knowledge is still incomplete, it seems reasonable to modify the classic description of the myopathies to incorporate this new information. In the sections that follow, diseases are described under the heading of their known molecular defect, where possible; the classic appellation appears parenthetically. Before the description of the individual disorders is provided, the techniques used in the clinical evaluation of patients are briefly reviewed.

MUSCLE BIOl'SY

The technique of muscle biopsy is nor difficult, I tidcr local anesthesia, a small incision is made over the muscle, and with careful dissection, a small strip of muscle is removed. Needle biopsies may be used in some situations.

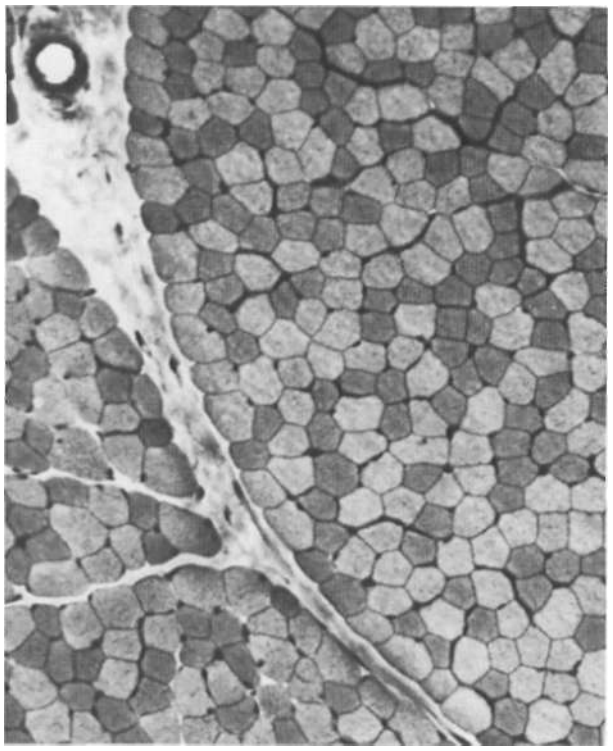


FIGURE 85.1 Normal muscle biopsy. The fibers are roughly equal in size, the nuclei are peripherally situated, and the fibers are tightly apposed to each other with no fibrous tissue separating them. (Verhoeff-Van Gieson stain.)

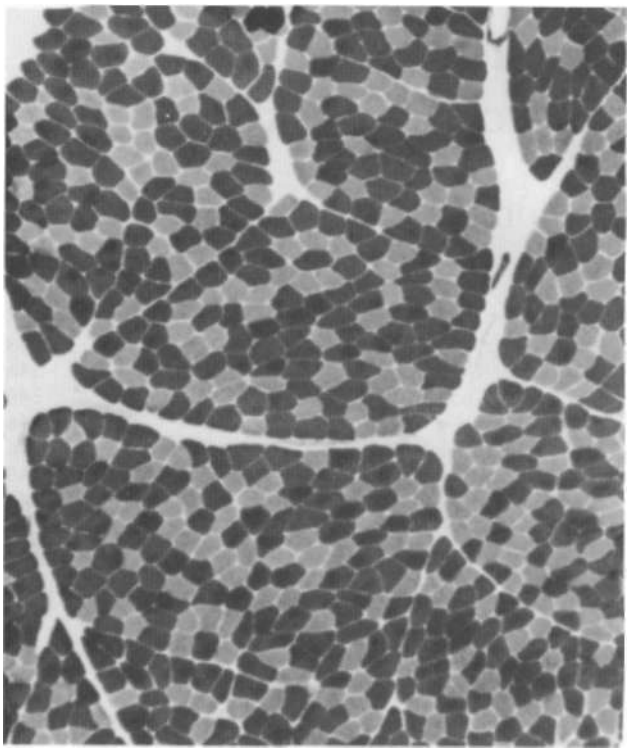


FIGURE 85.2 Normal muscle biopsy. Myosin adenosine triphosphatase stain at pH 9.4 demonstrates the relative proportions in the size of type 1 (light) and type 2 (dark) fibers. The muscle fibers belonging to one motor unit innervated by the same anterior horn cell are uniform in type, implying that there are fast and slow anterior horn cells. In addition, subsets of fiber rypes have been described, namely types 2A, 2B, and 2C The metabolism of type 2A fibers is more oxidative than that of type 2B fibers. The type 2C fiber is present in fetal muscle.

Histochemical studies of frozen sections are essential for proper interpretation. On transverse section, the fibers of normal muscle are roughly of equal size and have an average diameter of approximately 60 pm (Figure 85.1}. The muscle fibers of infants and young children are proportionately smaller. Each fiber consists of hundreds of myofibrils separated by an intermyofibrillar network containing aqueous sarcoplasm, mitochondria, and the sarcoplasmic reticulum with the associated transverse tubular system. A thin layer of connective tissue (the endomysium) surrounds each muscle fiber. The fibers are grouped into fascicles by strands of connective tissue, the perimysium, which separates the fascicles. Groups of fascicles are collected into muscle bellies surrounded by epimysium.

Situated at the periphery of the fibers are the sarcolemmal nuclei. The fibers are of different types. The simplest division is into type 1 and type 2 fibers, best demonstrated with the histochemical reaction tor myosin adenosine triphosphatase (ATPase) (Figure 85.2), The type 1 and type 2 fillers are roughly equivalent to slow and fast fibers or to oxidative and glycolytic fibers in human muscle. The inrermyofibrillar network pattern is best demonstrated with the histochemical reactions for oxidative enzymes, such as reduced nicotinamide adenine dinucleotide dehydrogenase. A regular network is seen extending across the whole fiber. In addition to routine stains with hematoxylin-cosin, modified Gomori-trichrome, myosin ATPasc, and nicotinamide adenine dinucleotide dehydrogenase, other special stains may be used to demonstrate fat (Sudan black or oil red O), complex carbohydrates (periodic acid-Schiff), amyloid (Congo red.i, or specific enzymes (e.g., phosphorylasc, lactate dehydrogenase, succinic dehydrogenase, and cytochrome oxidase). Immunoeytochcmical techniques are used to demonstrate the location and integrity of structural proteins, such as dystrophin, or to characterize the cell types in biopsies with inflammatory changes.

Changes of Denervation

When the muscle loses its nerve supply, the muscle fiber atrophies, often resulting in the fiber being squeezed into the spaces between normal fibers and assuming an angulated appearance (Figure 85.3). Scattered angulated fibers arc seen early in denervation. Sometimes, picturesque changes in the intermyofibrillar network occur, as in the *target fiber*, which characterize denervation and rein nervation. This is a three-zone fiber, on which the intermediate zone stains darker and the central "bull's-eye" stains much lighter than normal tissue (Figure 85.4). Often, a denervated fiber may

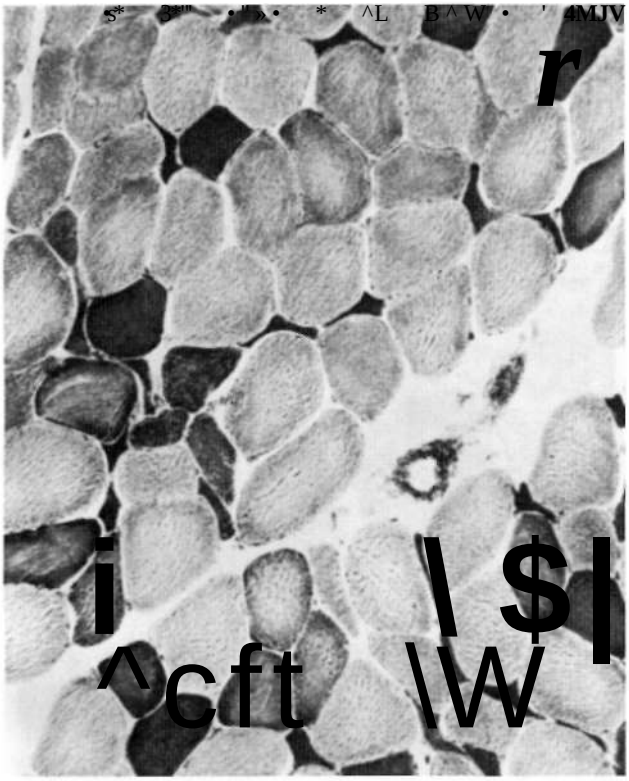


FIGURE 8S.3 Denervation. Notice the small, dark, angulated fibers demonstrated with this oxidative enzyme reaction, (Nicotinamide adenine dinucleotide dehydrogenase stain.)

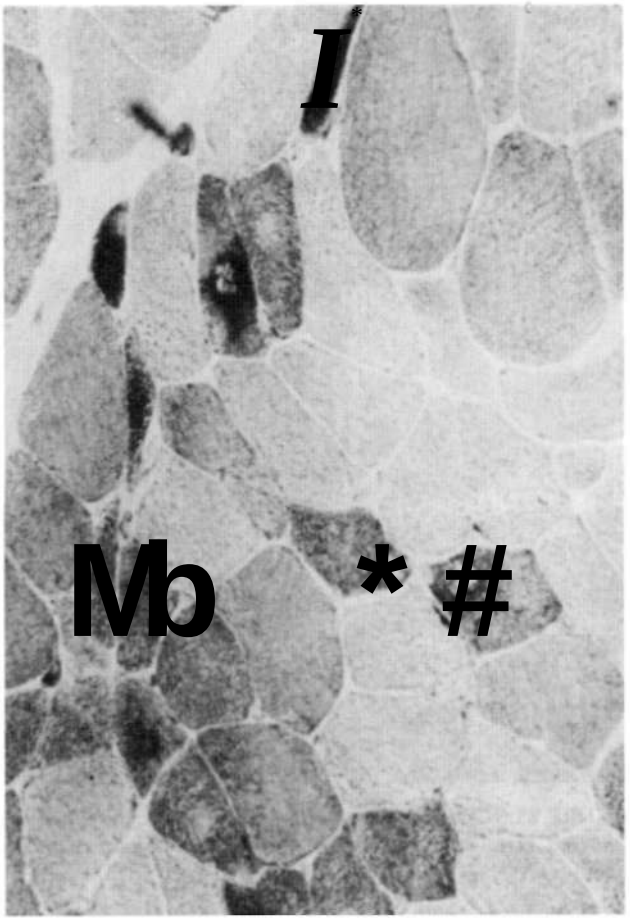
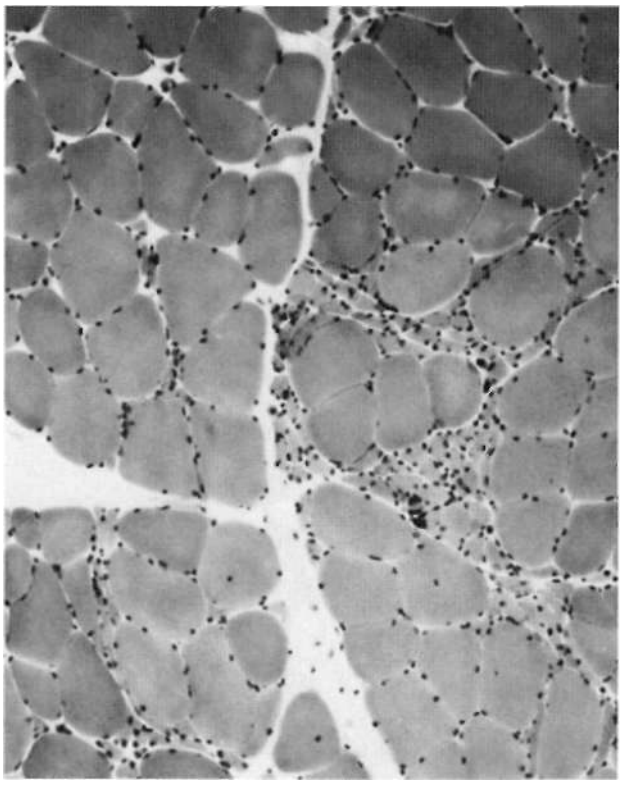


FIGURE. *HSA* Denervation. Target fibers. (Nicotinamide adenine d[nucleotide dehydrogenase stain.)

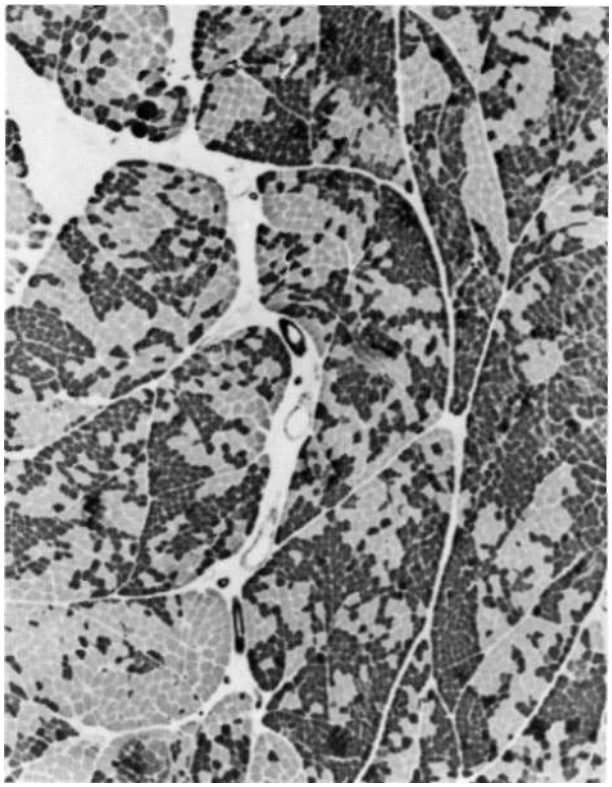
be reinnervatcd by a neighboring nerve twig, which results in two or more contiguous fibers being supplied from the same anterior horn cell. If that nerve twig then undergoes degeneration, instead of one small, angulated fiber being produced, a small group of atrophic fibers are produced. Small-group atrophy suggests denervation (figure 85.5). When the process continues, large-group or geographical atrophy occurs, in which entire fascicles may become atrophic. In addition to the change in size, the fiber types are redistributed. Normally, there is a random distribution of types 1 and 2 muscle fiber types, sometimes incorrectly called a *checkerboard* or *mosaic pattern.* The same process of denervation and reinnervation results in larger and larger groups of contiguous fibers being supplied by the same nerve. Because all fibers supplied by the same nerve arc of lhe same fiber lype. the normal mosaic pattern is replaced by groups of type 1 fibers next to groups of type 2 fibers. This **fiber** type grouping is pathognomonic of reinnervation (Figure 85.6). When long-standing denervation is present, the atrophic muscle fibers almost disappear, leaving small clumps of pyknotic nuclei in their place.

Myopathic Changes

The pathological changes associated with diseases of muscle have much greater variation than those associated with denervation. The type of change depends on the type of muscle disease. The normal peripherally placed nuclei may migrate toward the center of the fiber. In normal muscle, up to 2% of fibers have central nuclei. The presence of more numerous central nuclei usually indicates a myopathic, often dystrophic, process. In the myotonic dystrophies and limb-girdle muscular dystrophies (LGMDs), internal nuclei are numerous. Occasionally, internal nuclei are seen in some chronic denervating conditions (e.g., 1 LI veil lie spinal muscular atrophy). Necrosis of muscle fibers, in which the fiber appears liquefied and later presents as a focus of phagocytosis, is seen in many myopathies. These changes almost always represent an active degenerative process, such as myoglobinuria, toxic myopathies, inflammatory myopathies, metabolic myopathies, and dystrophies. Fiber-size variation with large fibers and small fibers intermingling in a random pattern often occurs in primary muscle diseases. It is sometimes the only indication of the pathological process. Fiber splitting often accompanies muscle fiber hypertrophy. Split fibers can be recognized in transverse section because of a thin fibrous septum, often associated with a nucleus that crosses part of the way but not all the way across the fiber, A detailed



HGURK K5.5 Denervation. .Small groups of atrophic fibers art-scattered throughout the biopsy. (Modified Gomori-trichrome stain,)



lHK .1 'Rl\ tf.S.d (linmic denervation and rcimuTvarioii. liisir.nl <. it the usual mosaic pattern of the uvo fiber types, the fibers arc clumped together, with groups of one type appearing next to groups of the other type. (Myosin adenosine triphosphatase stain, pH 9,4.)

study of serial transverse section may reveal more split fibers than a single section. Fiber splitting is particularly visible in dystrophic conditions, such .is LCi.VlD. 1: is rare in Duchenne's muscular dystrophy (DMD) and Becker's muscular dystrophy (BMD) and is usually not seen in acquired myopathics, such as polymyositis.

Many myopathies arc characterized by degeneration and regeneration of fibers. The regenerating fibets often become basophilic and the myonuclei enlarge as a result of **the** accumulation of RNA needed for protein synthesis. Fiber basophilia is a sign of an active regenerating myopathy. It is particularly characteristic of DMD, in which small basophilic groups of fibers may be prominent. Cellular responses include inflammatory reactions around blood vessels, which characterize the collagen vascular diseases and dermatomyositis. Endomysial inflammation with invasion of non-necrotic muscle fibers is seen in inclusion body myositis and polymyositis. Inflammatory cellular responses may be pronounced in dystrophics, particularly facioscapulohumeral muscular dystrophy and dysferlinopathies. Kven the so-called congenital inflammatory myopathics are actually forms of congenital muscular dystrophy (CMD).

In normal muscle, a very thin layer of connective tissue surrounds and separates the individual muscle fibers. In dyslrnplik ennd:; lulls, r hi, ki.-i I cu; ol [his layer (nr.i--.Llr fibrosis) may be pronounced. In DMD and some congenital dystrophies, muscle fibrosis gives the muscle a hard, gritty texture. In the inflammatory myopathies, a loose edematous separation of fibers may be seen, but fibrosis is not characteristic of the active disease phase, except when it is associated with systemic scletosis.

Changes in the inrramyofibrillar network pattern are common in myopathic disorders. Moth-eaten, whorled changes to the intermyofibrillar network arc seen in LGMD and facioscapulohumeral dystrophy (FSHD) (Figure 85.7). The intermyofihrillar network loses its orderly arrangement and becomes swirled, resembling the current in an eddying stream. Ringbmden (ringed fibers, snake coil fibers) are due to the peripheral reorientation of myofibrils in a circular direction. These changes, although not specific, occur more often in myopathies.

Other Changes

Selective fiber type changes are important. Type 2 fiber atrophy is one of the more common muscle abnormalities {Figure 85.8). This change, particularly if it is limited to type 2B fibers, is a nonspecific change that indicates muscle disuse. If muscle is examined some weeks after a limb is put into a cast, selective atrophy of type 2 fibers is noted. Many

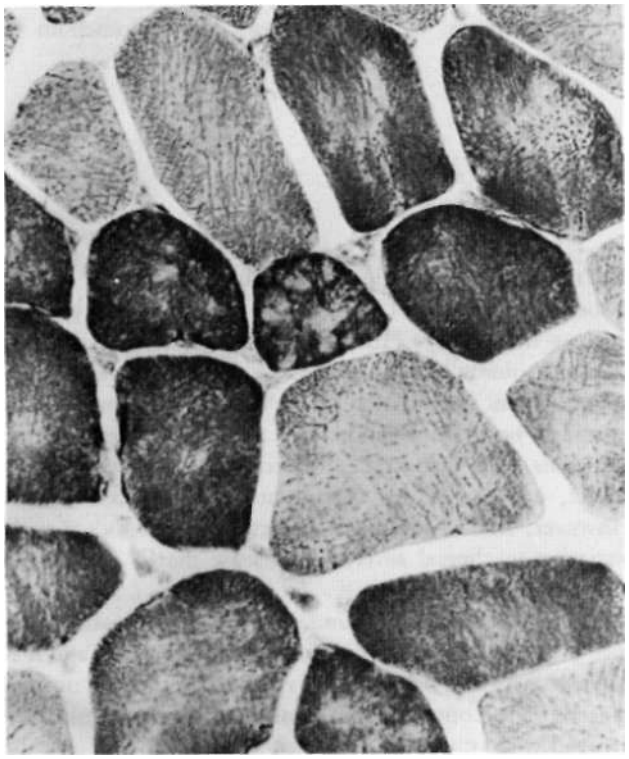


FIGURE 85.7 Myopathy. Moth-eaten, whorled fibers. The intramvofibnllnr network pattern is distorted, and some areas lack the proper stain, (Nicotinamide adenine dinucleotidc dehydrogenase stain.)

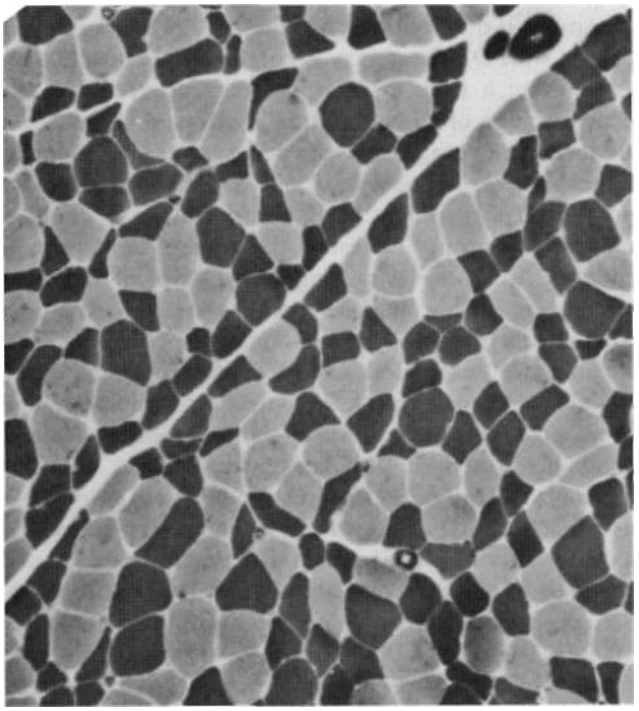


FIGURE 85.8 Type 2 fiber atrophy is a common change resulting from a number of different conditions affecting muscle contraction. (Myosin adenosine triphosphatase stain.)

chronic systemic illnesses tend to produce type 2 atrophy. It is associated with rheumatoid arthritis, nonspecific collagen vascular diseases, cancer (hence the name *cachectic atrophy),* mental retardation in children, and pyramidal tract disease. Type 2 fiber atrophy is regarded as a nonspecific result of anything less than robust good health.

Type 1 fiber atrophy has greater specificity. It is seen in some congenital nonprogressive myopathies, such as nemaline myopathy and congenital fiber type disproportion, and is characteristic of myotonic dystrophy. It can be seen in rheumatoid arthritis. Changes in the proportion of fibers in the biopsy are quite separate from changes in the fiber size. The name *fiher type predominance* has been given to a change in the relative numbers of a particular fiber type. Type 1 fiher predominance is a normal finding in the gastrocnemius and deltoid muscles. It is also the hallmark of congenital myopathies and many eatly-onset dystrophies. Type 2 fiber predominance is seen in the lateral head of the quadriceps muscle. Type 2 predominance is seen occasionally in juvenile spinal muscular atrophy and motor neuron disease, but type 1 predominance is more common in chronic denervating-reinnervating conditions.

Some histological changes ate pathognomonic. Perifascicular atrophy, in which the atrophic fibers are more numerous around the edge of the muscle fascicles, is the hallmark of dermatomyositis. Several metabolic myopathies are characterized by the presence of lipid vacuoles (carnitine deficiency} or abnormal pockets of glycogen (glycogen storage disorders). Several enzyme defects, such as phosphorylase deficiency, phosphofructokinase (1'EK) deficiency, lactate dehydrogenase (LDH) deficiency, and myoadenylatc deaminase deficiency, are detected with the appropriate histochemica! stains. The interpretation of a muscle biopsy should include a description of the morphological and histochemical changes and the association of these changes with a particular diagnosis. Characteristic histological changes are seen in infantile spinal muscular atrophy, dermatomyositis, inclusion body myositis, congenital nonprogressive myopathies, congenital fiber type disproportion, myotubular myopathy, lipid storage myopathies, acid maltase deficiency, and phosphorylase deficiency. Immunocytochemical staining of dystrophin and many other sarcolemmal and myofibcr proteins can distinguish several muscular dystrophies from each other. Although not disease specific, characteristic pathological changes differentiate chronic denervation from acute simple denervation.

IMMUNOCYTOCHEMICAL STUDIES

The availability of commercially produced antibodies has allowed missing proteins to be identified in muscle biopsy

specimens. If the DNA blood studies are unremarkable in a patient with DMD, as may occur with a point mutation rather than a large deletion, the diagnosis rests on the demonstration of no or abnormal dystrophin in the tissue. All the sarcoglycan proteins arc demonstrated using similar techniques. A deficiency of one or more sarcoglycan proteins is increasingly being recognized as a cause of muscular dystrophy. Because the sarcoglycans form a complex, when one is missing, all or some of the other sarcoglycan proteins may be absent as well. ar-Sarcoglycan is especially prone to be abnormal, which makes it a suitable and economical screening tool. The laminin «2 chain (merosin) is absent in some forms of CMD, and absence of nuclear membrane staining with anticmerin antibodies is seen in X-linked Emery-Dreifuss muscular dystrophy (EDMD). Dystroglycan staining can help recognize other LGMDs. Histochemical studies may be used to look for various proteins, such as desmin, ubiquitin, and amyloid. In addition, biopsy material may provide information aboiil intlaimtiarory cell types and iheu affinity for markers, such as CD8 and CD4, which identify cells involved in cytotoxic or humoral mechanisms of inflammation. Antibodies to the membrane attack complex may demonstrate the cells marked for destruction by the immune process, such as the vascular endothelium in dermatomyositis.

SI'ICIfK DISORDERS

Muscular Dystrophies

The muscular dystrophies are a group of hereditary muscle disorders (Table 85.1). They occur at all ages and with all degrees of severity. Historically, they were classified on clinical grounds and recognized by distinct clinical appearances. Recent information on molecular abnormalities has provided both clarification and additional questions for clinicians. The distinct clinical entities, such as BMD or DMD, are caused by distinct molecular abnormalities. However, similar molecular defects may produce a wide variation in clinical severity of disease that is not always easily explained.

For the most part, the underlying molecular abnormalities in the dystrophics involve structural proteins, and it is useful to review these proteins as they occur in normal muscle. The contractile ptoteins, actin and myosin, are arrayed with othet ptoteins, such as troponin, to form the

Table 85.1: Molecular defects of muscular dystrophies

Disease	*Chromosome*	*Protein*
DMD/BMD	Xp21	Dystrophin
fh\:n	Xq28	Emerin
Myotonic dystrophy	19ql3.2	Myotonin protein kinase
Myotonic dystrophy type 2/PROMM	3q	7.NF9
FSHD	4q35	³
Oculopharyngeal dystrophy	14q	Poiyalanine binding protein 2 (PABP2)
Bethlem myopathy I	21q22.3	Collagen type VI (or-1 or *a-2* subunits)
Billikm nv upatlr. *1*	2q37	Collagen type VI *{a-6* subunit}
LGMD IA	5q22-31	Myotilin
I.(AID Mi Willi L.irilio;i.L:liy.':in::>s. . . . . I Joniin.iiii [:)\II)	lqll-12	Nuclear lannn A/C
LGMD 1C	3p25	Caveolin-3
LGMD 2A	L5ql5	Calpain-3
LGMD 2B/Miyoshi's myopathy	2pl3	Dysferlin
IGMD2C	13ql3	y-Sarcoglycan
LGMD 2D	17q21	a-Sarcoglycan
LGMD 2E	4q12	^-Sarcoglycan
i(AID *n*	5q33	<S-Sarcoglycan
LGMD 2G	17qll-12	Telethon in
LGMD 211	9q31-q33	TK1M32
LGMD 21	19ql3.3	Fukunn-rclated protein, *FKRP1*
Congenital muscular dystrophy (CMD)		
Merosin-negative classic type	6q21-22	Merosin (a-2 subunit)
Merosin-positive integrin deficiency	12ql3	*a-1* Integrin
Merosin-positivc I-'IIRP deficiency	I9ql3.3	Fukutin-related protein, *FKRl'l*
Fukuyama type	9q31-33	LnkLIT n
Walker-War burg syndrome	•):\l ;i ;.;	?
Muscle-eye-bra in disease	Ip32-p34	POMGnTl
CMD with rij;id spine syndrome	lp35-36	Selenoprotein 1

DMD = Duchenne's muscular dystrophy; BMD = Becker's muscular dystrophy; EDMD = Emery-Dreifuss muscular dystrophy; PROMM = proximal myotonic myopathy; FSHD = facioscapulohumeral muscular dystrophy; LGMD = limb-girdle muscular dystrophy; POMGnTl =0-mannose-^-l,2-N-acetylglucosaminlyl transferase; ZNE9 = zinc finger 9.

familiar thick and thin filaments of the sarcomere. The reaction between actin and myosin results in realignment between the two molecules. In the sliding filament model, the thick and thin filaments form an array that slides back and forth.

The contractile proteins are connected to the "outside" of the cell by a complex of proteins that ultimately links to the basal lamina. The first step in this connection is the protein *dystrophin,* which is located on the cytoplasmic face of the muscle membrane. This large protein (427 kD) is coded by a gene on the short arm of the X chromosome. Dystrophin is related to spectrin and other structural proteins and consists of two ends separated by a long, flexible, rod-like region. The amino rerminus binds to the acmi molecule, and the carboxvl tern-.inns, which is rich in cysteine, links dystrophin to a a implex oi glycoproteins 1:1 the sarcolemma. Two of these, the dystroglycans, form a direct link between dystrophin and part of the laminin molecule, which is on the extracellular surface of the muscle membrane. or-Dystroglycan is a 156-kD prorein located outside the membrane and linked to the laminin «2 chain. It also connects with ^S-dystroglycan, which is a 43-kD transmembrane component of the complex and is linked with dystrophin. The other glycoproteins are the sarcoglycans; four have been identified and are labeled alphabetically a-sarcoglycan (50 kD), ^-sarcoglycan (43 kD), y-sarcoglycan (35 kD), and <5-sarcoglycan *{35* kD). They span the sarcolemma I membrane, but their relationship to the dystroglycans and their precise function is uncertain. The sarcoglycans are coded on different autosomal chromosomes; none is on the X chromosome. The a_2 chain of laminin (merosin) provides the anchor to the extracellular matrix because it is through the globular domain portion of the molecule that a-dystroglycan attaches to laminin. Merosin also binds to *afHD* integrin, a protein complex located on the sarcolemma membrane. Dystrophin, the sarcoglycans, rbe dystroglycans, and merosin appear ro function as a unit in stabilizing the muscle membrane. Together, these proteins arc referred as the dystrophin-glycoprotein complex. The complex may serve to propagate the force of contraction from the inside to the outside of the fiber to prevent membrane disruption.

Other sarcolemmal proteins not directly linked to the dystrophin-glycoprotein complex are also affected in some forms of muscular dystrophies (e.g., dysferlin and caveolin-3). Also, sarcomeric proteins (e.g., myotilin, titin, and telethon in), important in stabilizing the contractile apparatus, are mutated in certain dystrophies. Mutations of the muscle-specific calcium-dependent protease (calpain-3) gene are responsible for the majority of non-dystrophin/sarcogly can-re la ted LGMDs. In addition, secretary enzymes (e.g., O - ma nn os e- £-1,2 -N-acety Igluc os amin y 1 transferase, fukutin, and fukutin-related protein), which probably play a role in glucosylation of a-dystroglycan and other import proteins, arc responsible for some forms of CMD. Mutations in genes encoding for nuclear envelope proteins, emerin and lamin A/C, arc the causes of X-Iinked and autosomal dominant EDMD, respectively.

Dystrophin Deficiency (Duchenne's Muscular Dystrophy, Becker's Muscular Dystrophy, and Atypical Forms)

An absence or deficiency of dystrophin is implicated in two disorders lhai cause progressive destruction ol muscle. I he responsible gene is located on the short arm of the X chromosome at locus Xp21. It is an extremely large gene, comprising more than 2.5 million base pairs and 79 exons or coding regions. Approximately two thirds of cases are associated with a detectable deletion or duplication of segments within the gene. The others are presumably due to point mutations too small to be detected using standard techniques. There are "hot spots"' for these gene deletions, notably between exons 43 and 52 and particularly between exons 44 and 49 (Nobile et al. 1997). Whether the deletion is in frame or out of frame (see Chapter 44) determines whether dystrophin is absent from the muscle or present in a reduced, altered form. This has clinical significance because the former is usually associated with the severe (Duchenne's) form of muscular dystrophy (DMD), whereas the latter may cause the milder (Becker's) variant (BMD), in which the abnormal dystrophin preserves enough function to slow down the progress of the illness. The DNA code is read by triplet base pairs (bp). This *reading frame* must be maintained throughout the length of the gene to produce dystrophin. If a deletion removes a multiple of 3 bp, the reading frame may be intact upstream and downstream but may make limited sense, as if the sentence "You cannot cat the cat" were changed to "You not eat the cat," and some modified dystrophin may be formed. This is often the situation in the mild form (BMD) of dystrophin deficiency. In the severe form (DMD), the reading frame is destroyed, as if a deletion resulted in the sentence "Yoc ann ote att hec at." Exceptions to this rule exist, and frameshift deletions are associated with the milder form of the disease, particularly at the 5' end of the gene in exons 3 to 7 (Muntoni et al. 1994).

The prevalence rate of DMD in the general population is approximately 3 per 100,000, and the incidence among liveborn males is 1 per 3500. BMD is approximately one tenth as common. Although the inheritance is clearly X-linked recessive, almost one third of cases are sporadic, presumably due to spontaneous mutations occurring in either the child's or the mother's ovum.

It is easy to imagine that an absence of dystrophin would severely impair the integrity of the sarcolemmal membrane. Attention was previously focused on this membrane because of electron microscopic evidence thar it contains breaches associated with wedge-shaped areas of destruction in the subadjacent muscle cell. It is assumed that the absence of a supporting protein renders the membrane susceptible to mechanical damage. This presumably means that molecules, such as calcium, would have unlimited

access to the fiber interior and would initiate a chain of destructive processes, producing muscle fiber necrosis. The process would then involve continuing degeneration, with repeated attempts to regenerate on the part of the surviving satellite cells. Eventually, this process results in severe muscle fiber loss and replacement of muscle fibers with fibrous tissue.

Several animals have been found to have dystrophin deficiency; the better known include the *mdx* mouse and a dog model. The mouse model is unusual because the animals appear relatively normal, except for an early phase when inflammatory changes are noted in the muscle. In dogs, dystrophin deficiency is associated with progressive clinical weakness, and dystrophic muscle pathological changes, thus making this animal suitable for the evaluation of potential treatment.

Ducbenne's Muscular Dystrophy. Boys with DMD are usually normal at birth. The early clumsiness seen in all toddlers persists into the second year when walking begins. The children is noted to place one hand on the knee to assume an upright position when rising from the floor *(Gou/er's maneuver).* It is often at this stage that the calf muscles are found to be rather firm and rubbery (pseudo-hypertrophy) (l-'igure *#5.9).* Within 2 to 3 years, parents notice that the child does not run properly and is never able to jump clear off the floor with both feet. In the absence of therapy, tightness is noted in muscles that cross two joints in the legs. The iliotibial bands and the Achilles heel cords are usually the first to become tight. This is particularly noticeable in boys who habitually walk on their toes.

A period of apparent improvement may be seen between 2 and *(•>* years of age as the child gains motor skills. This represents the child's natural development, which has not yet been outpaced by the muscle weakness. By 5 or 6 years of age, stair climbing becomes labored, and the railing is used to pull upward. At the age of 6 or 7, sudden falls begin to occur, at first, when the child is hurrying or is knocked off balance by playmates. The fall is quite spectacular; the knees collapse abruptly and the child drops like a stone to the ground. At approximately 8 to 10 years of age, affected children cease to climb stairs or stand up from the floor. barlicr, affected boys began using a wheelchair and lost the ability to walk at approximately *9* years of age. Now, with prednisone therapy, bracing, reconstructive surgery, and physiotherapy, the average age of wheelchair confinement is 12.2 years. The true natural history of DMD is difficult to ascertain because many physicians and parents put considerable effort into keeping the children straight and the limbs supple.

Contractures of the hips, knees, and ankles become severe when the relatively untreated child spends much of the day in the wheelchair. The hips and knees become contracted to 90 degrees, and the feet turn downward and inward in an exaggerated position of equinovarus. It is very difficult to get normal shoes that fit and impossible for the child to sleep except in one position: usually with the knees propped up with pillows and slightly turned on one side. I [andling children at this stage becomes difficult, and back pain and limb pain almost always accompany this severe stage of muscular dystrophy. The development of severe scoliosis compromises respiratory function.

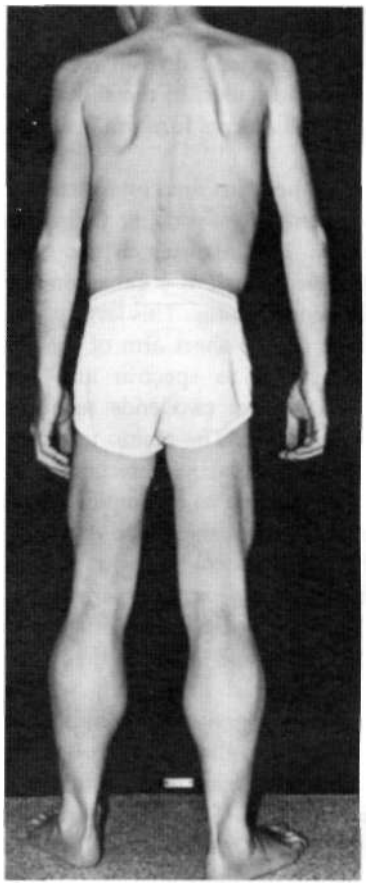


FIGURE 85.9 Duche Line's muscular dystrophy. Calf and thigh hypertrophy in an ambulatory 8-year-old patient.

The cardiac involvement is characterized by degeneration and fibrosis of the posterolateral wall of the left ventricle. Besides the abnormal electrocardiogram (ECG) that is seen at an early age in DMD, valve motion, wall thickness, and wall motion are also abnormal as revealed by echocardiograms. Death occurs due to cither respiratory failure or the catdiomyopathy that is relatively resistant to treatment.

I lie simplest tot to *a>* it inn the diagnosis is a blood DNA study that demonstrates a deletion in the dystrophin gene. In the 30% of patients in whom a deletion is not detected, a muscle biopsy is necessary to establish the absence of dystrophin. Three antibodies are available: Dys 1 for the rod region of the protein, Dys 2 for the carboxyl-terminal end, and Dys 3 for the amino-terminal end. Absence of the amino-terminal end, the end that binds with actin, is associated with more severe phenotypes. In DMD, the protein is absent and no staining is seen, whereas in BMD the stain is reduced, irregular, and fragmented. Approximately

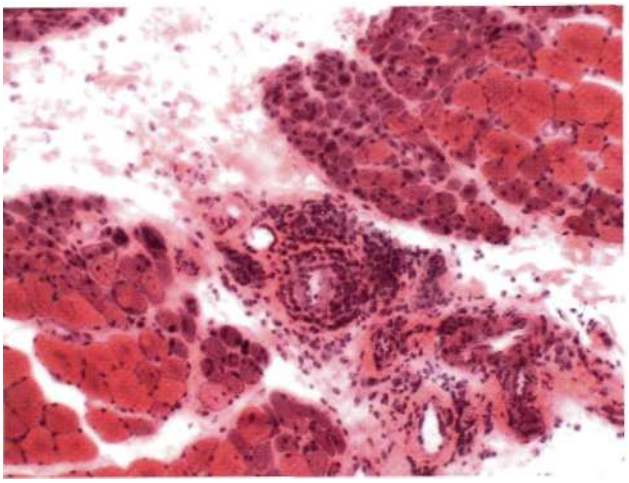


PLATE 85.1 Dermatomyositis. Muscle biopsy demonstrates perifascicular atrophy. Inflammatory cells when present are located around blood vessels (i.e., perivascular) and arc located primarily in the perimysial connective tissue as opposed to the endomysium as seen in polymyositis and inclusion body myositis.

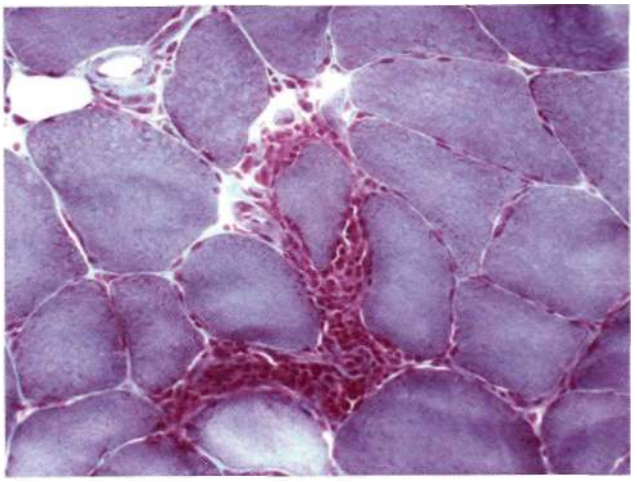


PLATE 8S.II Polymyositis. Mononuclear inflammatory cells composed of cytotoxic T-cells and macrophages surround and invade non-necrotic muscle in the endomysium.

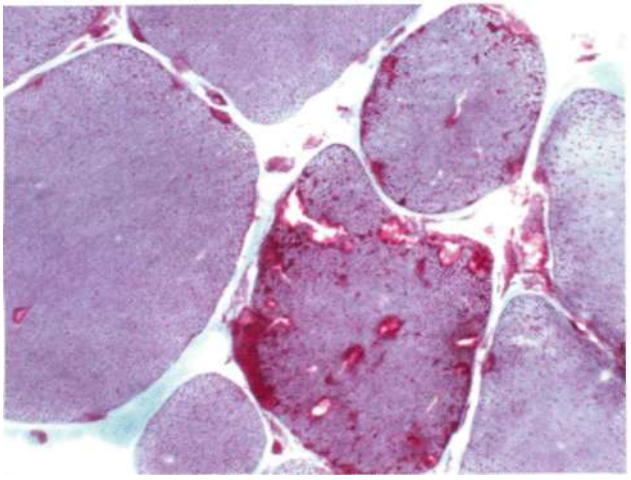


PLATE 85.ITI Inclusion body myositis. Scattered muscle fibers contain one or more rimmed vacuoles. (Hematoxylin-eosin stain)

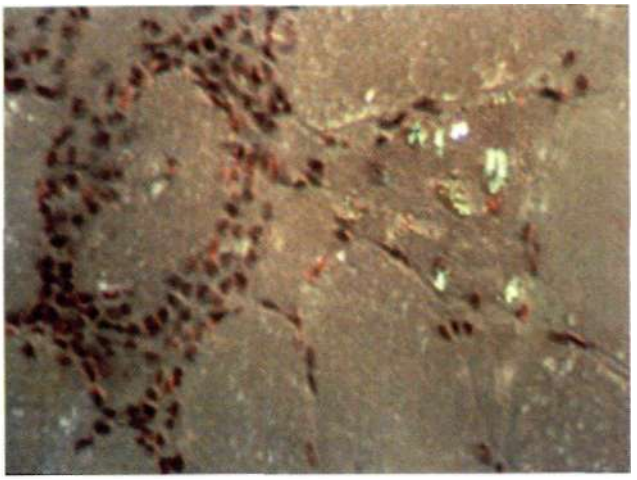


PLATE 85.IV Inclusion body myositis. Abnormal amyloid deposition can be seen in vacuolated muscle fibers. (Congo red stain)

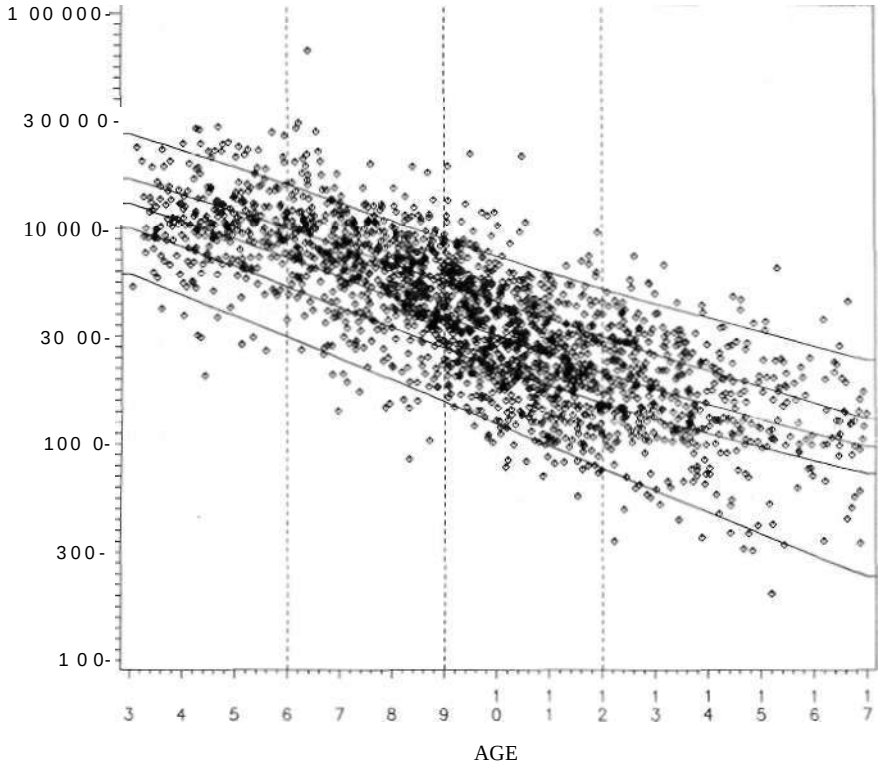


FIGURE 85.10 Duchenne's muscular dystrophy: change in scrum creatine kinase (CK) level with age. This is a scattergr.ini of scrum CK levels in individual patients. The lines represent the fifth, twenty-fifth, fiftieth, seventy-fifth, and ninety-fifth percentiles.

1 % of fibers demonstrate a rim of dystrophin. These are the revertant fibers, in which either the gene has undergone another mutation, putting the coding sequence back in frame, or alternative splicing of messenger RNA has occurred spontaneously, allowing for translation of some abnormal dystrophin. Where doubt exists, immu no blotting may show a decreased amount of dystrophin in the tissue.

The serum concentration of creatine kinase (CK) is markedly elevated to greater than 10,000 mU/mL. The elcctromyogram (EMG) shows myopathic changes (set-Chapter 36B), and the muscle biopsy shows muscle fiber necrosis, phagocytosis, variation in the size of fibers, fibrosis, groups of basophilic regenerating fibers, and opaque or hypercontracted fibers (hyaline fibers) (figures 85.10, 85.11, and 85.12).

Treatment

Physical Therapy. The primary aim of physical therapy is to keep the joints as loose as possible. Early on, the iliotibial bands and the heel cords are the tightest. Later, contractures of the elbow, wrist, and finger add to functional disability. Physical therapy is usually started at 3–4 years of age, when parents are taught to stretch the child's heel cords, hip flexors, and iliotibial bands on a daily basis. The goal of passive stretching of joints is not to increase the range of motion but, rather, to prevent further development of contractures. This should be carefully explained to parents because they may be discouraged to see no improvement in the tightness, even after many-months of therapy. The use of a night splint is important at an early age. The splint is a plastic shell molded around the

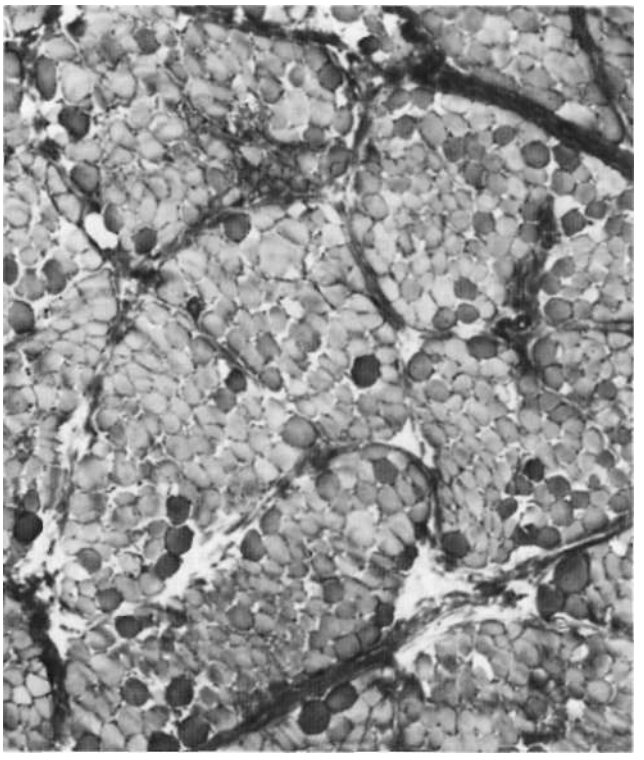


FIGURE 85.11 Duchenne's muscular dystrophy: muscle biopsy. The fibers are of variable size and separared by connective tissue. Large, heavily stained opaque fibers are noted. (Vcrhocff-Vnn Gieson stain.)

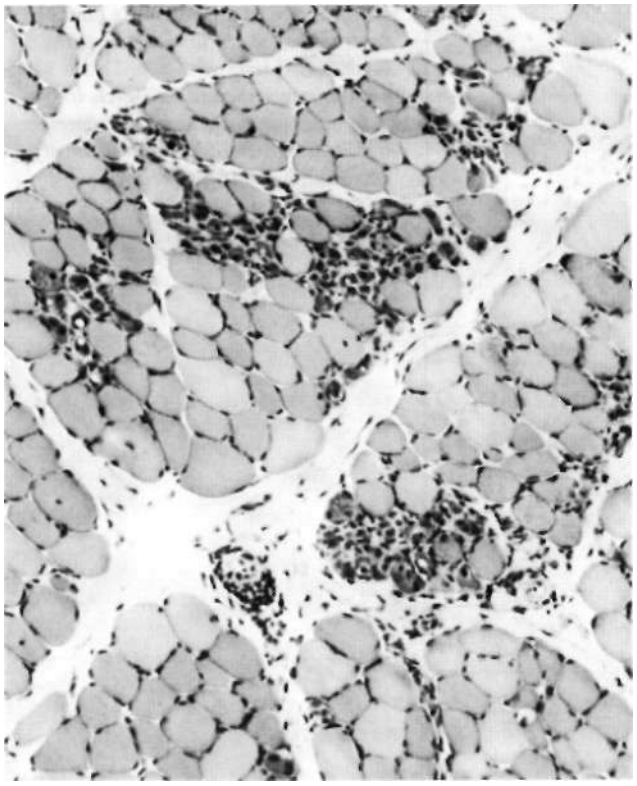


FIGURE 85.12 Duchenne's muscular dystrophy. Groups of small, basophilic (darkly staining) fillers are scattered in the biopsy. (Hematoxylin-eosin stain.)

lower part of the leg to maintain the foot at a right angle to the leg. Ankle contractures almost never occur in boys who use the splints regularly. Unfortunately, some boys, particularly those 6 years of age or older, cannot tolerate the splints. Parents often ask about an active exercise program. Such programs are largely unnecessary in a young child, who is running around to the best of his ability. By the time a child finds walking difficult or is in a wheelchair, muscle weakness is severe, and exercise does not effectively increase muscle strength.

Bracing. The appropriate use of bracing can delay progression to wheelchair use by 2 years. Weakness of the quadriceps is a major factor responsible for the inability to stand or walk. Such weakness causes the knee to collapse when even slightly flexed; the only stable position is in hyperextension. The boy is then reluctant to bend the knee in walking and may remain rooted to the ground, unable to move the feet. The addition of a long-leg brace (knee-foot orthosis) helps solve this problem. This device stabilizes the knee and prevents it from flexing. The child walks stiff-legged but does not have the same problem with falling. In general, the time for bracing is when the child has stopped climbing stairs, has difficulty arising from the floor, and falls daily. An indication for bracing seen on examination is a knee extensor muscle that is unable to straighten the knee against gravity. Parents often complain that the weight of the brace makes walking difficult. This is incorrccr. The brace basically functions as a pendulum, and slight elevation of the hip is sufficient to bring the leg forward. The disadvantage of a lightweight, plastic knee-foot orthosis is the difficulty in keeping the foot straight. In contrast, the high-top boot worn with a double-upright brace provides excellent stability, but is heavier. The choice between plastic and metal often comes down to personal preference of the patient or physician.

Surgery. Reconstructive surgery of the leg is often combined with bracing. The two are often performed during the same hospital admission. The purpose of leg surgery is to keep the leg extended and remove contractures of the iliotibial bands and hip flexors. Shortening of the iliotibial bands is associated with a stance in which the boy's legs are widely abducted. Because the long-leg brace is used like a pendulum, if the foot is widely abducted, the child cannot swing the leg forward. The only effect of lifting the hip in this case is that the leg tries to swing inward toward the midline. This is impossible because the abduction is due to the resistance of the iliotibial band contractures. A simple way to maintain function in the leg is to perform percutaneous tenotomies of the Achilles tendons, knee flexors, hip flexors, and iliotibial bands. This procedure often allows a child, who is becoming increasingly dependent on a wheelchair, to resume walking.

The modern techniques of spinal stabilization are used increasingly in boys with DMD and progressive scoliosis. Spinal surgery is now well accepted by patients and families because of the extreme discomfort and respiratory problems associated with severe scoliosis. This has had a positive impact on the management of late stages of disease. Surgery should be considered in patients with 35 degrees or more of scoliosis and significant discomfort. To reduce the risk of surgery, forced vital capacity should be greater than 35% of predicted. Noninvasive positive pressure ventilatory assistance is often used prophylactically in such patients.

Pharmacological Treatment. Prednisone is the only drug that improves muscle strength and function. Although the duration of its effect is uncertain, it seems to be at least 3 years. The synthetic steroid deflazacort has a similar therapeutic effect and approximately one half the side effects. It is available in Europe and Central and South America but not in the United States. The use of corticosteroids in DMD is increasing. The best time to initiate therapy is uncertain. Corticosteroids may be viewed as agents that can "buy time" for the patient until some better treatment comes along. In this light, we usually delay treatment until 5 years of age, just before the expected decline in strength, but at a stage when the muscles are relatively well preserved.

Gene Therapy. In theory, the treatment and cure of DMD would be a matter of replacing the defective gene early in life. The muscle wasting is caused by the lack of dystrophin, not by the presence of a toxic gene product. The possibility of replacing old muscle with new is enticing and has occupied scientists for the last decade. The first attempt

was to use normal myoblasts grown from muscle of a normal donor. These were then injected into the muscle with the hope that they would fuse with the dystrophic muscle and carry the normal gene with them. Although dystrophin was expressed in some of the muscle fibers, the percentage was so low that no clinical effect was detected. The reasons are many: The injected cells diffuse only a short distance, they are prone to rejection, and the surviving muscle proves resistant to fusion with these myoblasts. Attempts to uivimnvill ilic.se drawbacks an ongoing. Inn .11 iliis 11 me, myoblast transfer is only a future possibility.

A more promising approach is the effort to develop a vector inro which the dystrophin gene can be inserted and can then carry the gene into the muscle. Several problems must be overcome. The large size of the gene makes insert inn into the usual vectors difficult. An abbreviated version of the full gene may be satisfactory. Such truncated genes occur naturally and cause only mild BMD phenotypes. The gene will have to work in conjunction with a promoter that allows dystrophin production to be limited to the muscle. The viral vector must also have been proved to be safe. This necessitates removal of most or all of the viral genes. At present, the adenovirus is the best candidate from which a vector might be developed, but other viruses, such as retroviruses, are also being considered. Initial animal experiments have given some encouragement to this approach, and initial human studies have been performed.

Another possibility is upregulation of utrophin, a dystrophin-I ike protein found near the endplatc. Animal studies suggest both functional and pathological improvement if the amount of utrophin can be increased in the dystrophin-deficient animal. This finding is reinforced by the fact that utrophin is increased in patients with dystrophin deficiency. It is much easier to upregulate a mile ili.u .liiv.uh e\isls than II is lt> inlrodnet :i [mvii',11 ;:nu' to which the individual has had no prior exposure. It may also be possible to upregulate utrophin levels pharmacologically. Indeed, one of the effects of corticosteroids on cultured dystrophic cells is to increase utrophin levels.

Becker's Muscular Dystrophy. BMD shares all the characteristics of the severe form but has a milder course. The first signs of weakness usually appear in the first decade, although the onset of symptoms is sometimes delayed until the fourth decade or later. The muscular hypertrophy, contractures, and pattern of weakness are similar to that seen in DMD. Boys with BMD, however, continue to walk independently past 15 years of age and may not have to use a wheelchair until they are at least in their twenties, A common complaint in teenagers with **BMD** is leg cramps and other muscle pains, which arc often associated with exercise and arc more severe than those in ll.MH. Many p.iii.ns li.ne ;i cardiomyopathy thai car. be more disabling than the weakness. Cardiac transplantation has been very successful in some patients with this dilated cardiomyopathy form of the illness.

Serum CK concentrations are elevated but not as high as in DMD. The EMG demonstrates myopathic features. These abnormalities are nonspecific, and diagnosis requires demonstration of a mutation in the dystrophin gene or reduced quantity or size of dystrophin on muscle biopsy. Immunostaining of muscle tissue with Dys 1, Dys 2, and Dys 3 antibodies will usually demonstrate an abnormal staining pane 111, Definitive diagnosis often requires quantitation of the dystrophin in the muscle with immunobiot (Western blor) studies.

Because patients do not have much trouble in the first few years, aggressive physiotherapy, surgical reconstruction, and night splints are less often needed. Patients with BMD are less prone to development of kyphoscoliosis, perhaps because they are not confined to a wheelchair until after the spine has become fully mature. We have used corticosteroids only occasionally in patients with 15ML). The stabilizing effect of corticosteroids is less noticeable when the disease course is already fairly stable. In every other respect, including bracing and genetic counseling, BMD and DMD can be treated the same.

Other Pbcnotypes Associated with Dystrophinoparhy. With the development of genetic testing and dystrophin analysis, it is becoming clear that dystrophin deficiency is associated with several phenotypes. In one family, males with dystrophin deficiency were asymptomatic (Morrone et al. 1997). Dystrophin deficiency has been associated with very mild late-onset weakness, exercise intolerance, muscle cramps, and myoglobinuria (Figarella-Branger et al. 1997), Female carriers may have a phenotype similar to that of DMD due to symmetrical inactivation of the X chromosome (lyonization), may manifest symptoms and signs suggestive of LGMD (manifesting carriers), or may have a dilated cardiomyopathy.

It is impractical to perform genetic testing on ali patients with neuromuscular complaints. However, the combination of cramps, mild weakness, an elevated serum CK concentration, and large calf muscles warrants analysis of dystrophin and its associated proteins. Genotype-phenotypc correlations are inexact, but abnormalities in the amino-tcrmmal and the earboxyl-terminal domains of dystrophin arc associated with more severe phenotypes. Alterations in the rod domain are more variable and may be associated with a mild phenotype. In-frame deletions and insertions are associated with much more benign phenotypes than out-of-frame alterations.

Genetic Counseling. Because DMD is an X-linked recessive disorder, the carrier state of all women at risk should be ascertained. Up to 30% of cases may be sporadic, due to new mutations or deletions. The percentage of new cases that are sporadic appears to be increasing, perhaps because genetic counseling is widely available and women who are carriers decide nor to have children.

Most female carriers arc asymptomatic but approximately 8% manifest weakness and have a clinical phenotype similar to that of BMD. Manifesting carriers usually have an elevated serum CK level and myopathic changes on an EMG. Muscle biopsy usually demonstrates a mosaic pattern or patchy staining of dystrophin on the sarcolemma. However, these laboratory tests and muscle biopsy are not sensitive enough for the identification of carriers among asymptomatic females, and genetic studies ate required.

Genetic analysis of all potential carriers is advisable. When the disease is associated with a deletion of the dystrophin gene, carrier detection is available in many-genetics laboratories that have the ability to identify the presence of a mutant gene over the background contributed by the normal allele. This involves an analysis of the gene "dosage," comparing two normal alleles that have a double dose against a deleted allele and a normal allele that have a single dose (Voskova-Goldman et al. 1997). Thus current diagnosis of carrier status when a deletion has been identified in a proband is based on an analysis of a gene dosage. Unfortunately, situations exist in which a mutation is identified in a boy with "sporadic" DMD but not in the mother and yet the mother is still a carrier. This is due to germlinc mosaicism in which the mutation in the mother lies only in her oocytes. The recurrence rare of DMD has been estimated to be as high as 14% in such situations.

For women who are shown to be carriers of a dystrophin gene mutation it is possible to offer reproductive management techniques to avoid the birth of affected children. Prenatal diagnosis using amniotic cells or chorionic villus biopsies can identify an affected fetus with the mutated gene, and, more important, fetuses that are unaffected. In vitro fertilization followed by gamete in vitro cell sampling is also available, although it is expensive and not always successful. In families in whom the disease is associated with a point mutation too small to detect, carrier detection relies on demonstrating that the woman carries the same X chromosome as the affected individual. This necessitates linkage studies, which become reliable only if there are enough occurrences in the family and enough family members to provide reliable linkage. Research is decreasing the proportion of probands in whom no mutation can be detected (currently about 5%).

Other Limb-Girdle Dystrophies

One of the most important recent developments in muscle disease has been a better understanding of the LGMDs. Before the advent of modern neuromuscular diagnostic techniques, juvenile nr **.ii.iull ousel pseudi Htiynpathk** spinal muscular atrophy was included in this group of conditions. Despite separation of patients with these conditions, the LGMD group of disorders defied classification until the availability of molecular genetic testing. Weakness was generally proximal, but other features were disparate. In some patients inheritance was dominant and in others recessive. Some had more hip than shoulder weakness and others had the reverse. The onset of illness could be mild in late life; other patients had severe and early onset. It was generally recognized that the tetm LGMD encompassed several different disorders. The first discovery was that a defect in one of the sarcoglycans caused a severe form of dystrophy that occurred in a North African family. Since that time, many entities have been delineated that are characterized by defects in different structural and other proteins. These include, among others, the sarcoglycans, the *txi* chain of laminin (merosin), caveolin-3, and calpain-3. LGMDs transmitted by autosomal dominant inheritance are designated LGMD type 1 and those transmitted by autosomal recessive inheritance as LGMD type 2, Subclassification with an alphabetical letter characterizes distinct genetic forms of LGMD 1 and LGMD 2. In the following sections the known protein abnormalities and other forms of LGMD are discussed. As a group, their prevalence probably approaches 1 per 100,000 (van der Kooi ct al. 1996). The autosomal recessive LGMDs are more common than the autosomal dominant LGMDs.

Autosomal Dominant LGMDs (LGMD 1)

LGMD 1A (Myotilin Deficiency). LGMD 1A presents during the second and third decades with proximal arm weakness greater than leg weakness. Some patients have distal arm and leg weakness as well as facial and pharyngeal weakness. Serum CK concentrations can be normal or moderately elevated. Rimmed vacuoles within muscle fibers are seen on histological preparations.

LGMD 1A has been linked to mutations in the myotilin gene located on chromosome 5q22.3-31.3. Myotilin is a sarcomeric protein that is present at the Z-disc. The protein is probably important in myofibrillogenesis and stabilization of the Z-disc and sarcomere.

LGMD IB (Lamin A/C Deficiency). LGMD IB is allelic with the disorder previously reported as autosomal dominant EDMD. Limb-girdle weakness is the presenting feature in some patients, whereas humeral-peroncal weakness and early contractions are the initial features in others. Gardiomyopathy and severe conduction defects and arrhythmias may occur with or without skeletal muscle involvement. Sudden death due to fatal arrhythmias is common, and pacemakers are often needed. Scrum (K concentrations may be normal or elevated 25-fold. Muscle histological pteparations show dystrophic features and rare rimmed vacuoles.

The disorder is associated with mutations in the lamin .V(s;euc located on chromosome Iql 1-21. Lamins A and C are produced by alternative splicing of the lamin A/C messenger RNA (mRNA) transcript. Lamin A/C is an inter mediate-sized filament located on the nucleoplasmic surface of the inner nuclear membrane where it interacts with lamin-associated proteins, including emerin, the

protein associated with X-linkcd EDMD. Lamin A/C may also bind to heterochromatin. Normal immunostaining of the nuclear membrane with antiemerin antibodies helps distinguish this myopathy from X-linked FJDMD. Examination by electron microscopy shows alterations in myonuclei including the loss of peripheral heterochromatin, altered interchromatin texture, and fewer than normal numbers of nuclear pores.

LGMD 1C (Caveolin-3 Deficiency). LGMD 1C is a rare myopathy characterized by childhood onset of proximal weakness greater in the legs than in the arms and exertional myalgia. Progression is variable. The clinical phenotype associated with caveolin-3 mutations is heterogeneous, Some families have distal weakness, and others have the syndrome of *autosomal dominant rippling muscle disease* (Betz et al. 2001; Vogerd et al. 2001). Serum CK conccntniiions arc increased to 3-25 times greater than normal. Some patients have increased serum CK concentrations and no weakness.

LGMD 1C is caused by mutations in the gene encoding for caveolin-3 on chromosome 3p25. Caveolins are scaffolding proteins that interact with lipids and other proteins in caveolae, which are flask-shaped invaginations of the sarcolemmal membrane. Immunostaining of muscle tissue demonstrates a reduction of caveolin-3 along the sarcolemma. Electron microscopic examination reveals a decreased density of caveolae on the muscle membrane as well.

LGMD 2A (Calpain-3 Deficiency). A careful scries of studies conducted over a decade documented the existence of a form of autosomal recessive LGMD in an inbred population on Reunion Island in the Indian Ocean (Fardeau et al. 1996). The gene for LGMD 2A was localized to chromosome 15 and associated with a mutation in the gene for muscle-specific calcium-activated neutral protease (CANP-3 or calpain-3). Cases have been since described throughout the world, and LGMD 2A is estimated to account for as many as 20-26% of dystrophies in patients with normal dystrophin and sarcoglycan. The underlying pathophysiological process is uncertain. CANP-3 is not a structural protein but an enzyme that binds to titin. It may have a regulatory role in the modulation and control of transcription factors and thereby affect gene expression.

The onset is in childhood or early adult life. Most patients have a mild to moderately progressive disease course with loss of ambulation in adult life. In mote severe forms, weakness first occurs in the hips and then in the shoulders. The facial muscles and the neck flexors and extensors are strong. Scapular winging, different from that seen in FSHD, is characterized by a jutting backward-of the whole medial scapular border. The posterior thigh muscles arc affected more severely than the knee extensors, and the rectus abdominis muscles seem to be affected early. The serum concentration of CK is markedly elevated early and then decreases and may normalize later on. Treatment is not available, but it seems reasonable to apply the same principles used in treatment of dystrophin deficiency.

LGMD 2D (Dysferlin Deficiency). Mutations in the gene encoding for dysferlin on chromosome 2p13 lead to at least two phenotypes. One is a limb-girdle pattern of weakness (LGMD 2B), and the other is weakness and atrophy of the calf muscles (Miyoshi's myopathy}. Some patients have earlier involvement of the anterior tibial muscles. Dysferlinopathies account for only 1% of the LGMDs but 60% of the distal myopathies. From another perspective, 80% of patients with dysferlinopathy have a distal myopathy, 8% have LGMD, and 6% have only asymptomatic elevations of serum CK concentrations.

The dysferlinopathies typically present in adolescence or early adult life. Progression is usually slow but can be variable. Some lose the ability to walk in the second decade whereas others walk until late in life. Clinical variability in the pattern of weakness and disease progression exists within the same family.

Serum CK concentrations are elevated to 35-200 times normal. Muscle histological preparations show dystrophic features in severely affected muscles and nonspecific myopathic features in less affected muscles. The occasional finding of endomysial or perivascular inflammation may lead to an incorrect diagnosis of polymyositis. However, unlike polymyositis, the inflammatory cells do not invade non-nccrotic muscle fibers. A helpful immunohistological feature is the demonstration of a membrane attack complex on the sarcolemma of non-necrotic muscle fibers. This feature is also seen in other dystrophies with secondary inflammatory changes (e.g., FSHD) but not in primary inflammatory myopathies (i.e., polymyositis, dermatomyositis, or inclusion body myositis) {Spuler and Engel 1998). Diagnosis can be confirmed with immunostaining and immunoblot.

Dysferlin localizes to the sarcolemmal membrane but does not directly interact with dystrophin or the sarcoglycans. Its function is unknown, but it may be important for membrane fusion.

LGMD *2C, 2D, 2E, and 2F (Sarcoglycan Deficiencies).* Four sarxoglycans expressed in muscle arc associated with different forms of autosomal recessive LGMD 2. LGMD 2C, 2D, 2E, and 2F are caused by mutations in the genes for ^-sarcoglycan, a-sarcoglycan, ^-sarcoglycan, and *8*-sarcoglycan, respectively. The gene for a-sarcoglycan lies on chromosome 17, that for ^-sarcoglycan on chromosome 4, that for ^-sarcoglycan on chromosome 13, and that for 5-sarcoglycan on chromosome 5. The original cases of severe childhood autosomal recessive muscular dystrophy, although described as ff-sarcoglycan deficiency, were linked to chromosome 13, the locus of y-sarcoglycan rather than of-sarcoglycan. This illustrates one pitfall in the diagnostic testing for LGMD 2. The sarcoglycans are tightly knit, and when one is absent, the others may also be missing. This is particularly true of

or-sareoglycan, making it both useful and misleading as a screening tool. An absence of a-sarcoglycan is an indication to search for the abnormal gene associated with each sarcoglycanopathy.

Large population studies are not yet available, but surveys of muscle biopsies suggest that the sarcoglycanopathies account for more than 107o of patients with an LGMD syndrome and the presence of dystrophin (Duggan et al. 1997). Of these, a-sarcoglycanopathies account for *6%* of cases, ^-sarcoglycanopathies for 3%, *y-surco*-glycanopathies for 1%, and S-sarcoglycanopathics for less than 1%. However, in North Africa, sarcoglycan deficiencies are estimated to account for up to 50% of muscular dystrophies.

All sarcoglycanoparhies have the same features at onset: trunk and limb weakness, a serum CK concentration of 1000 lU/liter and higher, and calf hypertrophy. Facial strength is good, and cardiac findings are not prominent, A deficiency of y-sarcoglycan best mimics DMD in seventy of weakness and progressive loss of ambulation, *a*-Sarcoglycan and ^-sarcoglycan deficiencies are variable and may be severe or mild (Dincer et al. 1997). In some, the onset of weakness is delayed until adult life, and patients are able to function without severe disability, despite proximal weakness. Although the sarcoglycanopathies may resemble dystrophin deficiency, there is not enough information about corticosteroid treatment to make a specific recommendation for treatment.

LGMD *2G (Teletbonin Deficiency).* This rare form of muscular dystrophy may be associated with either proximal or distal weakness (Morcira et al. 1997), Mean age of onset is 12.5 years. Legs are affected more than arms, and the quadriceps and anterior tibial muscles show significant weakness. Serum CK concentrations are elevated to 3-17 times normal. Muscle histological preparations demonstrate dystrophic features, and rimmed vacuoles within muscle fibers are often seen.

LGMD 2G has been linked to mutations in the gene encoding for telethonin on chromosome 17ql 1-12. Telethonin is abundant at the sarcomere where it may interact with the large sarcomeric proteins titin and myosin. Abnormal telethonin may disrupt normal myofibrillogenesis.

IXiMD Hi. This disorder has been reported in several families of Manitoba Hutterite origin (Weiler et al. 1998). The age of onset is 8-27 years, and ambulation is not lost until the fourth decade. Serum CK concentrations range from 250 to more than 3000 lU/liter. The EMG shows a myopathic pattern. The genetic defect is believed to be a mutation in the gene that encodes for E3-ubiquitin ligase (also known as *TRIM32)* located on chromosome 9q31-' q33 (Frosk et al. 2002).

LGMD 21. This rare LGMD was initially described in a large consanguineous Tunisian family (Dris et al. 2000). Subsequently, the clinical, laboratory, and genetic features of 17 affected kinships have been reported (Brockington et al. 2002). Phcnotypic variation is considerable. The age of onset ranges from birth to the fourth decade. The clinical course can be similar to that of a CMD or mild BMD. Severe cardiomyopathy may develop. Scrum CK concentrations are elevated to 10-30 times normal in children but may be normal in adults.

The LGMD 21 gene was linked to chromosome 19ql3.3, where mutations in the gene that encodes for FKRP were identified (Brockington et al. 2002). Mutations in this gene were also found in some patients with CMD with normal mcrosin (CMD type 1C). FKRP is a glycosy I transferase, and its deficiency is associated with abnormal glycosylation of a-dystroglycan.

Congenital Muscular Dystrophies. The CMDs are a group of disorders that usually present at birth as severe hypotonia and weakness of the trunk and limbs. All are inherited as autosomal recessive traits and produce some degree of central nervous system (CNS) dysfunction. Contractures of the joints are prominent, particularly at the ankles, knees, and hips. Mental retardation may be present, and, in many infants, a magnetic resonance imaging (MR!) scan shows a striking increase in the T2-weigh ted signal in the cerebral white matter. Several forms of CMD have been characterized clinically and genetically. The besr characterized forms are classic or occidental CMD, Fukuyama type congenital muscular dystrophy (FGMD), Walker-Warburg syndrome, and muscle-eye-brain disease of Santa vuori. The classic form of CMD (CMD type!) is the most common type of CMD in the Western Hemisphere. It is genetically heterogeneous. Approximately one half of occurrences of CMD type 1 are associated with deficiency of merosin or »$_2$⁻kiminin. Other forms of CMD type 1 with normal or secondary deficiency of merosin have been linked to mutations in intcgrin and FKRP.

Laminin a_2 (Merosin} Deficiency. Laminin a_2 is one of a large family of glycosylated proteins located in the basement membrane. Laminin is composed of three dissimilar chains: «2, j9i, and y_t. The amino termini separate to form a crosslike structure and the other end of the molecule attaches to the dystroglycan complex. In the human, laminin *a*^ is coded by a gene on chromosome *6.* Laminin «i is found in muscle as well as skin and peripheral nerves.

The essential features of merosinopathy are severe weakness of the trunk and limbs and hypotonia at birth. The extraocular and facial muscles are usually spared. Contractures of the feet and hips are prominent. Intelligence is often normal, and the incidence of epilepsy is 12-20%. MRI of the brain often reveals increased signal in the white matter on T2-wcighted images. White matter abnormalities may also be seen on computed tomography (CT) scans of the brain. For the most part, affected children are severely disabled, and many arc dependent for life.

Milder forms have a delayed onset and produce milder weakness (Tan et al. 1997). Absence of the protein causes a severe myopathy, but symptoms arc less severe in patients

with partial deficiencies, similar to the situation for dystrophin deficiency. The diagnosis relies on showing alterations of muscle merosin. Antibodies to merosin are commercially available, but some antibodies fail to show the abnormality if part of the laminin a_2 chain is present. The use of at least two different antibodies is advantageous. Skin biopsy can be used for diagnosis because merosin is expressed in the skin. The final diagnosis relies on DNA testing of the gene because merosin may be reduced secondarily in other myopathies with membrane instability.

Merosin is absent in one half of patients with classic CMD. Serum CK concentrations are elevated as in all diseases with muscle membrane instability. The EMG shows myopathic changes and slowed nerve conduction velocities, the latter arising from abnormalities in laminin *ai* expression in the peripheral nerve.

Other Forms of Classic CMD Type 1. Some children with phenotypes identical to that of CMD type 1 have no abnormality in the laminin *ai* gene (Figure 85.13). Muscle symptoms are milder, and sufficient function may be regained with time to support independent walking. These myopathies progress more slowly than merosin-negativc CMD, and many patients survive to adult life.

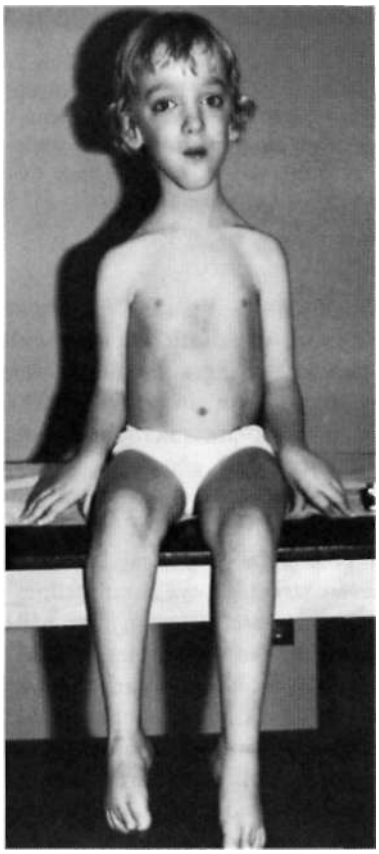


FIGURE 85.13 Congenital muscular dystrophy (classic type). This hoy also had weakness and contractures of the limbs. His illness was relatively static.

CMD type IB has been linked to mutations in the gene that encodes for the *a-7* subunit of a-7/*lD mtegrin. Integrin is a sarcolemmal protein that binds to merosin and is probably important for the structural integrity of the muscle membrane. CMD type IC with normal merosin is reported in patients with mutations in FKRP (Brockington et al. 2002). Mutations that involve this protein are described in LGMD 21. A range of severity of disease is associated with FKRP-associatcd myopathies as with the dystrophinopathies, sarcoglycanopathies, and mcrosinop-athies. FKRP is thought to play a role in glycosylation of other proteins, a-Dystroglycan, which binds merosin, is normally heavily glycosylated. FKRP mutations impair the normal glycosylation of tf-dystroglycan, which may result in instability of the muscle membrane.

Fukuyama Type Congenital Muscular Dystrophy. FCMD, like other CMDs, is inherited as an autosomal recessive disease. The myopathy is linked to mutations in the gene that encodes for fukutin i oca ted on chromosome 9q3T33. Secondary loss of laminin ot_2 and a-dystroglycan may be seen. Fukutin is an enzyme associated with the Golgi complex and is thought to participate in the glycosylation of other proteins. a-Dystroglyean is heavily glycosylated and a mutation in fukutin probably results in abnormal glycosyla-tion of ar-dystroglycan (and perhaps other important proteins), thereby altering the normal three-dimensional structure of the protein and the integrity of the glycoprotein-dystrophin complex. This complex is also expressed in the CNS and probably accounts for the CNS manifestations associated with FCMD.

Affected newborns usually have normal strength. Some are floppy, and joint contractures of the hip, knee, and ankles are present in 70% by 3 months of age. Mental retardation is often so severe that speech never develops. Convulsions, either major motor seizures or staring spells, are common (Figure 85.14). A curious finding noted on clinical examination is asymmetry of the skull. "Weakness is diffuse, sometimes involving the face and neck, and is often disabling, so that the child never walks. Affected children are completely dependent and never attain any degree of un-supervised activity. The muscle disease is moderately or slowly progressive, and survival into early adult life is common.

The serum CK concentration is usually markedly elevated. Muscle histological preparations show dystrophic changes, with variability in the si/.e of fibers and fibrosis. Internal nuclei are common, and there is diminished immunostaining with or-dystroglycan antibodies, which easily distinguishes this disorder from any of the congenital nonprogressive myopathies. As with other congenital dystrophies, muscle histological preparations may show features suggestive of neurogenic atrophy, with the fiber size changes being nonrandom and some fascicles contain-ing much smaller fibers than others. However, this nonrandom change differs from denervation atrophy, in

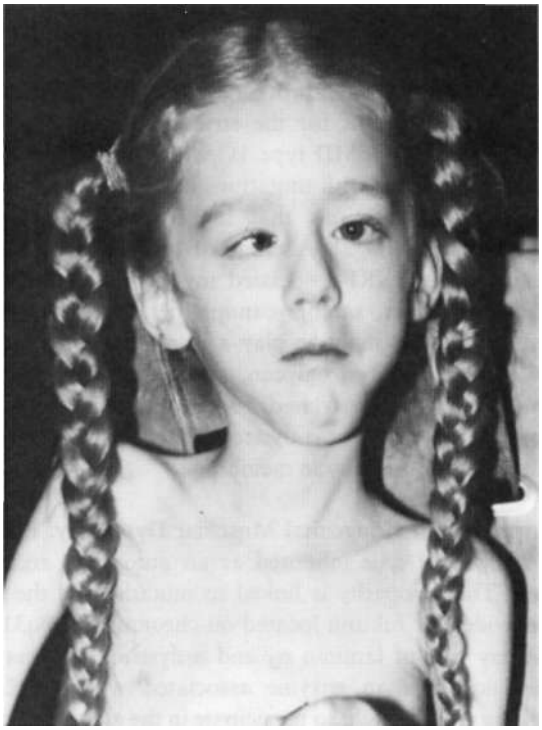
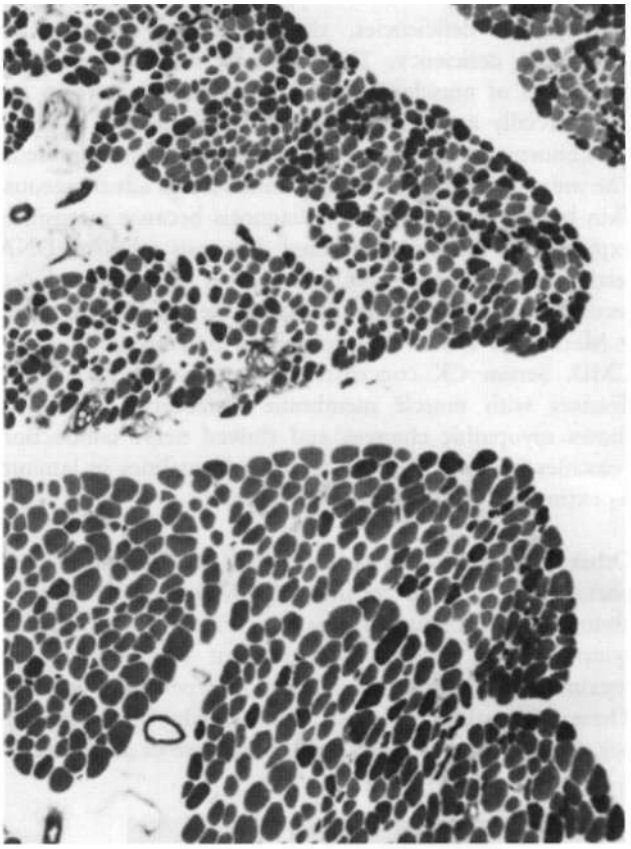


FIGURE 85.14 Fukuyama type congenital muscular dystrophy. This girl was severely retarded, had many seizures, and demonstrated marked contractures of the limbs. She was too weak to support her own weight. The disease was nonprogressive. Her two hrothers also had the same illness,



FIGURF. 85.15 A biopsy from a patient with Fukuyama type congenital muscular dystrophy. In addition to the variability in fiber size and the type 1 fiber predominance with fibrosis, notice the nonrandom distribution of atrophy. The fascicle in the lower part of the picture contains larger fibers than that in the upper part, (Myosin adenosine triphosphatase stain, pll 9.4.)

which there is a random variability in fiber size within individual fascicles {Figure 85,15).

'I l,i.- IMOM sinking brain change vrii mi MRI and til' scans is the presence of white matter abnormalities, particularly in the frontal area (Figure 85.16). This change seldom extends to the genu of the corpus callosum and the medial subependymal regions along the trigones and occipital horns are spared. With time, the abnormalities disappear in sequence from the occipital to the frontal region in a fashion resembling the progression of normal myelination. Occasionally, marked pallor of the myelin in the centrum semiovale is noted, together with mild gliosis or edema. At postmortem examination, several malformations of gyral formation are found, such as agyria, pachygyria, and microgyria. The cortex may have a cobblestone appearance. Lamination of the gray matter is absent. Other associated malformations are heterotopia in the brainstem and basal meninges, cerebellar micropolygyria, ventricular dilatation, enlarged cortical sulci, and aqueductal stenosis.

Walker-Warburg Syndrome and Muscle-Eye-Brain Disease. Walker-Warburg syndrome and muscle-cye-brain disease are characterized by the combination of muscular dystrophy, lisencephaly, cerebellar malformations, and severe retinal and eye malformations. Both disorders are more severe than FCMD. Walker-Warburg syndrome is a catastrophic disease, with death occurring within the first 2 years of life. The eye changes are more severe in Walker-Warburg syndrome than in muscle-eye-brain disease. Characteristic findings are microphthalmia, colobomas, congenital cataracts and glaucoma, corneal opacities, retinal dysplasia and nonattachment, hypoplastic vitreous, and optic atrophy. In muscle-cye-brain disease, high myopia and possibly a preretinal membrane or gliosis occurs, but severe structural eye abnormalities are not seen.

The CNS findings are different, and MRI is a useful technique to separate the two entities (van der Knaap et al. 1997). MRI scans in Walker-Warburg syndrome show various combinations of hydrocephalus, aqueductal stenosis, cerebellar and pontine hypoplasia with a small posterior vermis, Dandy-Walker malformations, and agyric or pachygyric cobblestone cortex. Tl-weighted images show a diffuse decreased white matter signal; T2-weightcd images show myelination defects. In muscle-eye-brain disease, the cortical changes are milder and the white matter changes more focal.

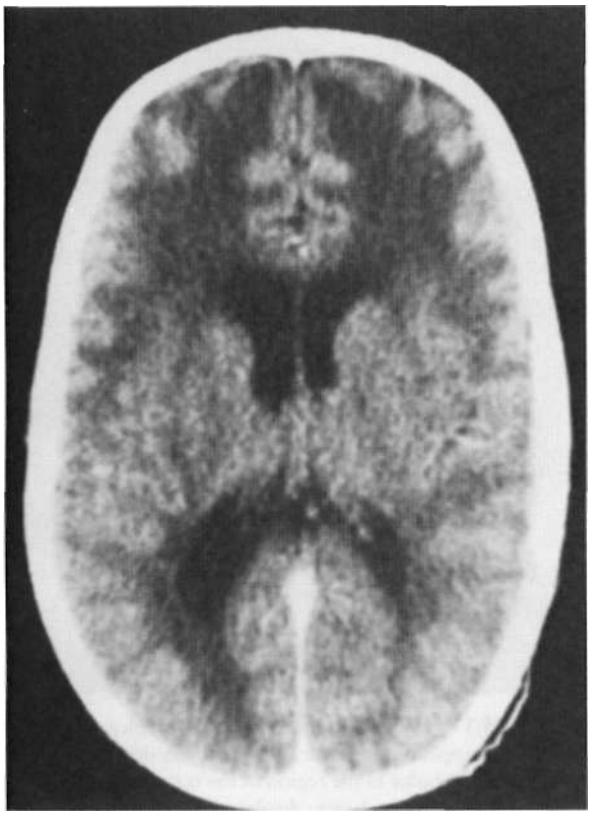


FIGURE 85.16 Computed tomographic scan of the head of a patient with Fukuyama type congenital muscular dystrophy demonstrating lucencies in the white matter, particularly toward the frontal poles.

It is not certain if Walker-Warburg syndrome and FCMD are genetically distinct. Both were linked to chromosome 9q31-q33 in one kinship. Muscle-eye-brain disease is caused by mutations in the gene that encodes for O-mannose jS-l,2-N-acctylglucosaminyl transferase located on chromosome lp3.

Other Congenital Muscular Dystrophies

Ullrich's Congenital Muscular Dystrophy. Ullrich's CMD (also known as atonic-sclerotic dystrophy) is associated with neonatal weakness, multiple contractures, and distal hyperlaxity. Marked protrusion of the calcanei in the feet is seen in affected children. The clinical course is static or slowly progressive. Serum CK concentrations are normal to slightly elevated. Mutations in subumts of collagen type VI have been reported, suggesting that this condition is allelic to Bethlem myopathy (Camacho Vanegas et al. 2001).

Congenital Muscular Dystrophy with Rigid Spine Syndrome. Infantile hypotonia and weakness are the initial symptoms. Motor milestones are delayed. Mobility cil the spine is reduced, and many children develop scoliosis and contractures at the knees and elbows,

Serum CK concentrations are normal or moderately elevated. Muscle histological preparations show type 1 predominance, increased internal nuclei, and nonspecific myopathic features. In some kinships, the myopathy is linked to mutations in the selenoprotein N1 gene located on chromosome lp3 (Moghadaszadeh et al. 2001). Other myopathic disorders, such as F.DMD, may be associated with the rigid spine syndrome.

Other Regional Forms of Muscular Dystrophies

X-Linked Emery-Dreifuss Dystrophy (Emerin Deficiency). The most common form of EDMD is inherited as an X-linked recessive disease. **The gene *(STA)* is** located at Xq2S and encodes for emerin. Emerin localizes to the inner nuclear membrane from which it projects into the nucleoplasm (Manilal et al. 1996). Emerin belongs to a family of lamin-associatcd structural proteins that are important in the organizing of the nuclear membrane and its attachment to hetcrochromatin.

EDMD is characterized by wasting and weakness of the upper arms, shoulders, and anterior compartment muscles of the legs. Contractures of the elbows, the posterior neck, the pataspinal muscles, and the Achilles tendon occur early in its course. Severe elbow contractures occur during childhood. F.DMD is slowly progressive. The weakness spreads to involve other muscles, especially the hip. Cardiac complications are common. Conduction block caused by atrial paralysis results in sudden, unexpected death. The atria become electrically inexcitable, and the heart responds only to ventricular pacing. Ventricular myocardial disease with ventricular failure also occurs. Sudden death may occur in female carriers because they develop the cardiac abnormalities at a later age. The severity of cardiopathy in men and women increases with age.

The clinical picture of EDMD is distinctive, and the diagnosis can be confirmed by DNA studies. The diagnosis may also be made from a skin biopsy if emerin is absent from nuclei in the skin. Results of muscle biopsy and electro-myography simply confirm that the disease is myopathic. The CK concentrations may be elevated. An ECG should he obtained annually for every patient with EDMD. An ECG is recommended for family members at risk because of the possibility of isolated cardiac involvement.

Analysis and treatment of the cardiac problems are the most pertinent aspects of therapy. Most patients with EDMD need a cardiac pacemaker at a relatively early age, and some need treatment for congestive cardiac failure due to ventricular failure. Because the atrial block is sudden, unpredictable, and fatal, early use of a pacemaker is recommended. The pacemaker does not retard the devel-opment of **the** cardiomyopathy and only protects against the complications of conduction block. Female carriers should be screened with an ECG beginning at 35 years of age.

Facioscapulohumeral Dystrophy. FSHD is inherited as an autosomal dominant trait. Its prevalence is 1-2 per 100,000 population. The responsible gene has been localized to chromosome 4q35 in many, but not all, families. The genetic abnormality is a deletion in a 3.3-kb repeating sequence. Digestion with the endonuclcase £coRI produces a fragment that is shorter than 34 kb in most families with FSHD compared with a length of more than 40 kb in normal individuals. In the past, the results were clouded by the existence of an identical sequence, unrelated to the disease, on chromosome 10. The problem has since been resolved, and DNA testing is reliable (Upadhyaya et al. 1997), although a few patients with the same phenotype show no abnormality in the chromosome 4q sequence. The severity of the illness bears a relationship to the size of the deletion: the largest deletions tend to be associated with severe illness. The phenomenon of *anticipation,* in which age at onset is younger and severity of illness is more severe with successive generations, occurs in FSHD. This suggests a dynamic mutation as in myotonic dystrophy. A puzzling feature of the abnormal chromosome 4q region is that it docs not seem to contain any actual genes. This suggests that the responsible gene is slightly removed from the deleted area but that it is influenced by the changes in its neighboring environment *(position effect variegation)* (Fisher and Upadhyaya 1997).

The severity of FSHD varies even within the same family. Some patients may have only mild facial weakness whereas others have total paralysis of the face and severe weakness of other muscles causing wheelchair confinement during childhood. The most common time of presentation is during adolescence. Facial weakness is expressed as difficulty in blowing up balloons or drinking through a straw. Affected children may sleep with the sclera of the eyes showing through partially opened lids. Facial expression is relatively preserved, but the smile is often flattened and transverse, as opposed to the usual upward curve. When the patient attempts to whistle, the lips move awkwardly and have a peculiar pucker (Figure 85.17). The mouth also may have a pouting quality, the so-called *boucbe de tapir.*

Weakness of the shoulder muscles affects scapular fixation. When the arms are outstretched in front, the scapulae jut backward (winging), with the inferomedial corner pointing backward. Deltoid muscle strength is well preserved even late in the disease course, and the distal part of the muscle is often pseudohypertrophic. The biceps and triceps muscles arc often weak. The forearm muscles are less involved (leading to a Popeye appearance), although a discrepancy between the stronger wrist flexors and weaker wrist extensors is often used to support the diagnosis. The muscles of the legs are involved in FSHD. Weakness of the hip flexor muscles and of the quadriceps is common, and the ankle dorsiflexors are often weak, whereas strength is preserved in the plantar flexors. The ankle dorsiflexors arc-often involved early and footdrop may be the presenting

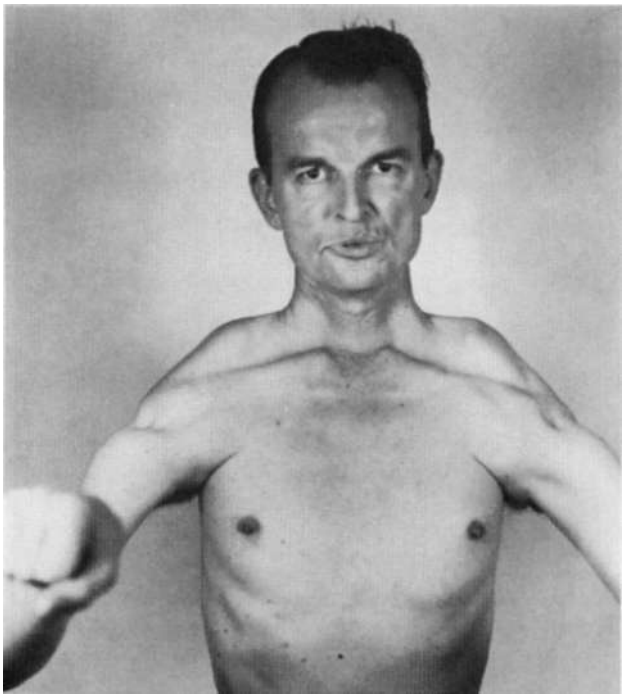


FIGURE 85.17 Facioscapulohumeral dystrophy. Notice the characteristic appearance of the shoulders, the downward-sloping clavicles, and the bulge in the region of the trapezius muscle, which is due to the scapula being displaced upward on attempted elevation of the arms. The patient also is attempting to purse his lips.

feature, blending FSHD with the scapuloperoneal syndromes. Asymmetry of weakness is common, often leading the inexperienced clinician to doubt the diagnosis of muscular dystrophy and to consider a peripheral nerve lesion, such as a lesion of the long thoracic nerve of Bell.

The most severe form of FSHD occurs in infancy. Such babies have severe weakness. The face has no move men I and remains passive and expressionless. Weakness of the limbs, although it conforms to the general pattern of FSHD, is so severe that the ability to walk is lost by 9 or 10 years of age. A striking feature is the extreme lumbosacral lordosis seen when the child walks or stands. This initially disappears on sitting, indicating that a compensatory mechanism :•, u.scJ to maintain balance. Deafness and Coats' disease, an oxidative vascular degeneration of the retina, arc associated abnormalities.

The diagnosis can be established reliably by DNA studies. The serum CK concentration is elevated, muscle histological preparations shows myopathic features, sometimes with scattered inflammatory foci (Figure 85.18). The EMG shows myopathic potentials (see Chapter 36R).

The treatment of FSHD is supportive. Scapular stabilization may be beneficial if the arms cannot be raised above the head (Twyman et al. 1996). This is especially true when deltoid function is preserved, and the patient is ambulatory. Because of the general severity of their weakness, wheelchair-confined patients do not find the problems in

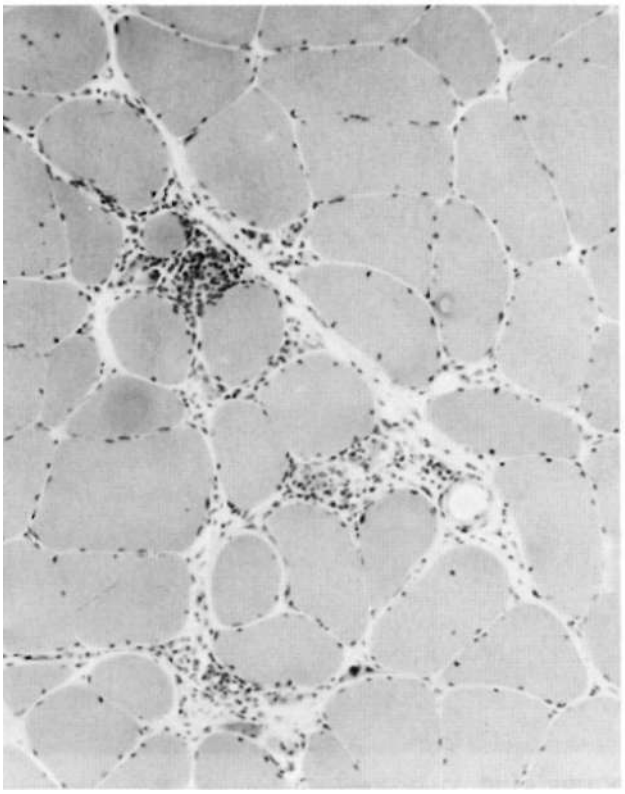


FIGURE 85.18 Facioscapulohumeral dystrophy. Cellular inflammatory responses are rioted in the biopsies from many patients with this illness. These are more often associated with necrotic fibers than with blood vessels. (Hemaroxylin-eosin stain,)

shoulder movements to be out of proportion to the rest of the muscular weakness. Such patients find a forearm orthosis or ball-bearing feeder device to be useful. An ankle-foot orthosis may be helpful for ambulatory patients with a footdrop. Surgical transposition of the posterior tibial tendon to the dorsum of the foot is useful in patients who have a marked intorsion of the foot when walking. The posterior tibial muscle remains relatively unaffected until very late in the illness. The posterior tibial tendon, in addition to its action of inversion, also dorsiflcxcs the foot. If the anterior tibial group is severely weak, overactivity of the posterior tibial muscle may be seen in an attempt to dorsiflex the foot and allow the toes to clear the ground. This causes marked inversion of the foot while walking and may lead to callus formation on the outer border of the foot. It also may make *in* ankle-foot orthosis impossible to use. Surgical transposition of the posterior tibial tendon to the dorsum of the foot can be an effective reconstructive procedure, which may prolong walking. Prednisone has been tried in some patients, but the results arc generally not beneficial, unless there is significant inflammation in the muscle biopsy.

Scapuloperoneal Syndromes. Weakness of the muscles of the shoulder and of the anterior compartment of the lower leg arc early symptoms of several diseases. Some forms of scapuloperoneal dystrophy are related to FSHD, but others have no linkage to the FSHD site on chromosome 4q35. Further studies are needed in a larger population of patients with this symptom complex. As in FSHD, in the scapuloperoneal syndrome a discrepancy between the weak ankle dorsiflexors and the strong plantar flexors is seen. However, facial weakness is only minor. Results of histopathological studies, electromyography, and other laboratory tests are identical to those seen in FSHD in some patients (Milanov and Ishpekova 1997). Scapulo-peroneal muscular dystrophy may be inherited as an autosomal dominant trait, although an X-linked recessive pattern also has been described. The importance of investigating this syndrome is that some congenital non-progressive diseases, such as ncmaline myopathy, may present with a scapuloperoneal distribution of weakness. It is therefore important to confirm the diagnosis with the appropriate tests in any patient with a scapuloperoneal syndrome. The only useful treatment is the application of ankle-foot orthoses, which may improve the patient's function by correcting the footdrop.

Oculopharyngeal Muscular Dystrophy. Oculopharyngeal muscular dystrophy (OPMD) is worldwide in distribution, hut prevalence rates are higher in Quebec, Uruguay, Germany, and the Spanish-American populations of Colorado, New Mexico, and Arizona. Isolated occurrences in families are described throughout the rest of the world. It is inherited as an autosomal dominant trait with almost complete penetrance. The genetic abnormality is mutations in the gene encoding for poly (A) binding protein 2 (PAR2) located on chromosome 14ql 1.2-13 (Brais et al. 1998). PAB2 is a nuclear protein involved in messenger RNA polyadenylation. The mechanisms by which mutations in this gene cause OPMD have not been established.

OPMD usually begins in the fifth or sixth decade, but onset can be in the foutth decade. Eye muscle weakness and ptosis are the initial features. The ptosis may initially be asymmetrical, but eventually both lids become severely ptotic, and all eye movements arc diminished (Figure 85.19), The severity of extraocular palsies is varied, but ptosis is a constant feature. Difficulty with swallowing occurs concomitant with or shortly after the development of ocular symptoms. At first, saliva pools in the pharynx, but swallowing eventually becomes impossible. Facial weakness is common, and proximal limb weakness is common in the late stages. Death may occur from starvation, but the terminal event is often pneumonia initiated by aspiration of secretions. Although symptoms may be severe, long-term survival is expected when nutritional status is maintained.

Initial laboratory tests should be used to exclude othet causes of ocular weakness such as myasthenia gravis (see Chapter 82). The definitive diagnosis relies on DNA testing of the genetic abnormality. Muscle biopsy reveals a random

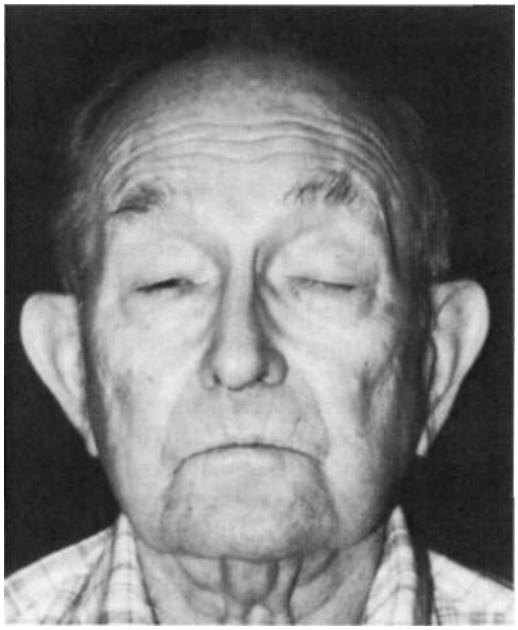


FIGURE 85.19 Oculopharyngeal dystrophy. The facial appearance of a patient who has ptosis and paralyzed eye movements.

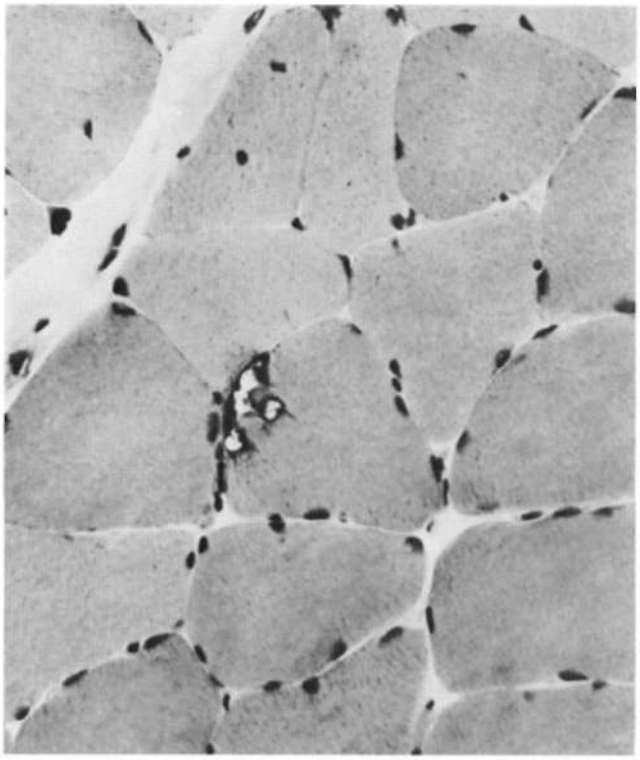


FIGURE 85.20 Oculopharyngeal dystrophy. Rimmed vacuoles are commonly seen in this illness. (Hematoxylin-eosin stain.)

variation in the size of the fibers, necrotic fibers, some fibrosis, and occasional internal nuclei. In addition, autophagic vacuoles (rimmed vacuoles) and intranuclear fibrillary inclusion bodies arc noted (Figure 85.20), which are features common to OCPD, inclusion body myositis, and several hereditary distal myopathies/dystrophies.

The presence of small (8-10 nm) intranuclear tubulofilamerits that appear as palisading filamentous inclusions is a hallmark of OCPD. The filaments are unbranched and may be stacked side by side or may occur in tangles. In addition, abnormal mitochondria and nemaline rods are seen in pharyngeal muscles.

Treatment is supportive. Dysphagia is first treated by a soft diet; the next step is pureed foods, and eventually a gastrostomy is needed. Surgical correction of ptosis is often successful.

Distal Muscular Dystrophies/Distal Myopathies

Several muscle dystrophies have a predominant distal pattern of weakness (Sapcrstein ct al. 2001), Such myopathies are often misdiagnosed as hereditary or acquired neuropalilies in evrr .is motor :u-.iron disease. Mild elevations in the serum CK concentration can be seen in rapidly progressive neuropathic disorders, but concentrations greater than .S00 IU/L should suggest a myopathic process. However, the serum CK concentration may be normal in some distal myopathics and cannot be used to exclude a myopathy. An EMG is useful in distinguishing a distal myopathy from a neutopathic disorder, and repetitive nerve stimulation can be used to exclude rare instances of distal weakness from myasthenia gravis. Other myopathic disorders with a distal pattern of weakness include myotonic dystrophy type *1*, inclusion body myositis, and certain forms of congenital myopathy {e.g., myofibrillar myopathy). The age at onset, inheritance pattern, histopathological features, and pattern of weakness are most useful in distinguishing the distal myopathies from each other.

Treatment of distal myopathy is largely symptomatic. A cock-up splint helps preserve hand function when wrist-drop is present, and an ankle-foot orthosis is used to correct footdrop.

Miyoshi's Myopathy. This disorder was first described in Japan but affects many ethnic groups. The disease has been linked to mutations in the gene encoding the sarcotemmal protein, dysferlin, located on chromosome 2pl2-14, The same gene is responsible for LGMD 2B. Both phenotypes may exist in the same family. Some members have a distal myopathy, usually affecting the gastrocnemius muscle but sometimes predominantly involving the anterior compartment of the leg, and others have a proximal myopathy. Muscle histological preparations show dystrophic changes without autophagic vacuoles.

Welandcr's Myopathy. Welander's myopathy was initially described in Scandinavia, where it is relatively common. It is inherited as an autosomal dominant trait. The initial symptoms begin between 40 and 60 years of age. Weakness begins in the hands and later causes footdrop.

The distal distribution suggests a neuropathy, but laboratory tests show little evidence of denervation, which favors i myopathy. Careful evaluation may show mild distal hypesthesia and temperature sensation loss associated with some loss of small myelinated fibers. Muscle histological preparations show myopathic features and the rimmed vacuoles that are charactetistic of other distal myopathies. The serum CK concentration is normal or slightly elevated.

Markesbery-Griggs-Udd Myopathy. Markesbery-Griggs-Udd myopathy is transmitted as an autosomal dominant trait. The disorder has been linked to mutations in the gene that encodes for titin on chromosome 2q31-33 (Hackman et al, 2002). Titin is a giant sarcomeric protein that serves as a ligand for calpain-3. Mutations in titin are also associated with a dilated cardiomyopathy.

The myopathy is characterized by footdrop due to weakness in the anterior tibial muscles. Onset is typically after 35 years of age. Eventually, wristdrop and fingerdrop develop because of extensor compartment weakness of the forearms. Proximal limb muscles are rarely involved. The serum CK concentration is normal or slightly elevated. Milsck- histology demonstrates myopathic features and rimmed vacuoles.

Nonaka's Myopathy, Autosomal Recessive Hereditary Inclusion Body Myopathy. This early adult-onset distal myopathy was first described in Japan. Similar patients were described as having an autosomal recessive hereditary inclusion body myopathy (IBM) (Sivakumar et al, 1996). The clinical phenotype is similar to that of Markeshery-Griggs-Udd myopathy. Weakness initially involves the anterior tibial muscles in the legs and extensor muscles of the forearm. It is inherited as an autosomal recessive trait, and the onset is before 30 years of age. Muscle histological preparations show rimmed vacuoles as in Markesbery-Griggs-Udd myopathy and Welander's myopathy. Electron microscopy reveals 15- to 18nm tubular filaments typical of inclusion body myositis. However, unlike *inclusion body myositis,* a significant inflammatory process is not seen. Kinships with Nonaka's myopathy and those with autosomal tecessive inclusion body myopathy were subsequently shown to be allelic.

Heteditary IBM may be heterogeneous. The form of quadriceps-sparing myopathy first described in Iranian Jews (Argov et al. 1997) and now recognized in many other genetic backgrounds is due to a mutation in the gene encoding for UDP-N-acctylglueosamine 2-epimerase/N-acetylmannosamine kinase on chromosome 9pl-ql (Eisenberg et al. 2001).

Laing's Distal Myopathy. A distinct autosomal dominant distal myopathy is characterized by weakness of the anterior tibial muscle groups and the neck flexors (I.aing et al. 1995). Onset is in childhood or early adult life. Scrum CK concentrations are normal or slightly elevated and the EMG shows a myopathic pattern. Unlike Markesbcry-Gnggs-Udd myopathy and Nonaka's myopa thy/hereditary IBM, muscle histological examination does not reveal rimmed vacuoles. The exact gene has not been identified, but linkage studies indicate that the gene is located on chromosome 14ql I.

Myotonic Dystrophies

Myotonic Dystrophy Type 1

Myotonic dystrophy type 1 (DM 1) is characterized by muscle wasting and weakness, myotonia, and multisystem abnormalities. It is inherited as an autosomal dominant trait. The incidence is 1 per 8000 live births The disorder is caused by mutations in ijir y.uu that ..nioiKs In: myotonic dystrophy protein kinase (DMPK) located on chromosome I9q13.3. The mutation occurs in an untranslated region of the gene. This region normally contains 5-30 repeating sequences of three nucleotides (CTG trinucleotide repeats). In DM 1, there are up to several thousand CTG repeats.

The size of the expansion correlates with severity of disease. Newborns with severe congenital myotonic dystrophy have very large expansions (>750 repeats). Mothers with more than 100 repeats are at greater risk of having a child with the severe infantile form than are mothers with a smaller expansion. Anticipation is explained by the tendency of the triplet repeat expansion to gtow with each mciosis in the female. The reverse is sometimes true of patients with paternally inherited disease, when the expansion may be reduced and the clinical state may return to normal or be very mild. Variation in the degree of gene expansion among different tissues of the body further complicates genotype-phenotype correlation.

The gene product is ubiquitously expressed in muscle and other tissues, such as the lens in the eye. Different studies have localized DMPK to the neuromuscular junction and myotendinous junction, the sarcolemma, and the perinuclear region. In experimental animals, DMPK affects the voltage-gated sodium channels in skeletal but not cardiac muscle, thereby decreasing the peak sodium current. Other experiments indicated a higher intracellular calcium concentration in cells with a flux abnormality in the l.-type calcium channel. However, the expansion is not in the coding region of the gene, and other experiments with knockout mice or with mice that overexpress the protein show no marked abnormality in muscle or in other systems. This has suggested that the mutation alters the expression of adjacent genes (Thornton et al. 1997). Studies have shown that the transcribed DMPK mRNA is directly toxic and causes abnotmal splicing of mRNA transcripts, including those of the muscle chloride ion channel (Mankodi et al. 2002), dysfunction of which is probably responsible for the myotonia.

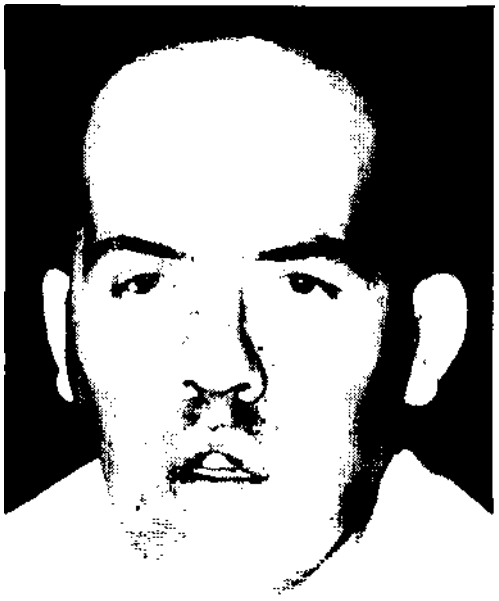


FIGURE 85.21 Myotonic dystrophy type 1, The facial appearance includes ptosis, hollowing of die masseter and temple?„ and facial weakness.

Once considered, DM 1 is readily diagnosed. However, the diagnosis is often missed because patients often present with what appears to be an unrelated problem. Patients may be referred for evaluation of mental retardation, present in the emergency room with fractures, or appear on the ward because they did not recuperate after cholecystectomy. The severity of DM 1 ranges from no symptoms, early cataracts, or mild weakness in some adults to profound mental retardation and severe weakness in children,

The more typical picture is hand weakness and often footdrop beginning in early adolescence. DM 1 is one of the forms of dystrophy that affects distal muscles more severely than proximal muscles. The sternocleidomastoid muscles are often atrophic and poorly defined. A rather long face with a mournful expression is accentuated by hollowing of the temples due to masscter and temporalis atrophy. In fully developed disease, the eyes are hooded due to ptosis, and the mouth is slack and often tented (Figure 85.21). Weakness is not limited to distal muscles; shoulder, hip, and leg weakness may be prominent

Repeated falls arc common in middle age. With time, weakness becomes sevete and myotonia may be lost. Absence of myotonia of the small muscles of the hand and pronounced myotonia of the deltoid or forearm muscles are common in advanced disease. The voice may be hollow and echoing, suggesting palatal weakness. Facial weakness makes consonants difficult to pronounce. Dysphagia is common but is usually a minor complaint. Recurrent dislocation of the jaw may occur, particularly when the mouth is widely opened, as in biting an apple.

Myotonia is demonstrated either by sharp percussion of the muscle with a reflex hammer or after firm voluntary contraction. Fither maneuver elicits a sustained, involuntary contraction of the muscle, which fades slowly over a matter of seconds. Percussion of the thenar eminence is a popular way of eliciting myotonia. It produces a sharp abduction of the thumb and a firm contraction of the thenar eminence, which gradually relaxes and allows the thumb to return to the resting position. Percussion myotonia is often easier to demonstrate by percussing the posterior muscles of the forearm. The normal response to forearm percussion is also a brisk contraction of the finger extensors or the wtist extensors, but the wrist or fingers then fall into the resting position without delay. In the patient with myotonia, the fingers extend sharply and subsequently drift downward toward the normal position. The wrist may remain extended for some seconds. Patients seldom complain spontaneously about myotonia except in cold climates. When questioned, they may admit to difficulty releasing a key after it has been firmly grasped or letting go of a hammer or vacuum cleaner, particularly in cold weather.

Cardiac disease is a well-known complication of DM 1. Advances in both molecular techniques and cardiological investigations have helped to provide a better understanding of the conduction disturbances and tachyarrhythmias that occur in more than one half of patients with advanced DM 1. They correlate in severity with both skeletal muscle disease and molecular defect in some studies. Clinical evidence of a generalized cardiomyopathy is unusual. Radionuclide .studies of cardiac function after relatively mild exercise may show outward ballooning of the ventricular wall and a deceased ventricular ejection fraction. The rate of progression varies widely between individuals. Sudden death can be caused by ventricular arrhythmias or by complete heart block and can occur at an early stage of disease. A familial tendency for cardiac complications exists. The histopathological examination shows fibrosis (primarily in the conducting system and sinoatrial node), myocyte hypertrophy, and fatty infiltration (Phillips and Harper 1997). Examination by electron microscopy shows prominent I-bands and myofibrillar degeneration. The role of other genes or the normal myotonic dystrophy allele in myotonic heart disease has not been determined. Myotonic dystrophy should be considered in patients who present with suspected arrhythmia or conduction block. Suggestions for management include an annual cardiac history and a 12-lead ECG with use of 24-hour Holtcr monitoring if necessary.

Excessive daytime somnolence is common (Damian et al. 2001). It may be mistaken for narcolepsy and is accompanied by a disturbed nighttime sleep pattern. The cause is an abnormal central ventilatory response, with an absence of the usual hyperpnea ptoduced by an increasing carbon dioxide concentration. This is associated with an abnormal sensitivity to barbiturates, morphine, and other drugs that depress the ventilatory drive. The risk of respiratory

complications Willi die use ui ;;ener.il ancsriclics is ahllnsl 10% (Marhieu et al. 1937). Anesthesiologists should be made aware of the possibility of complications with these drugs.

Several other organs are commonly involved in DM 1. Cataracts are almost universally seen by slit-lamp examination. Multihued specks (Christmas tree cataracts) are usually found in the anterior and posterior subcapsular zones. Disturbances of endocrine function involve the thyroid gland, pancreas, hypothalamus, and gonads. Testicular atrophy, with disappearance of the seminiferous tubules, leads to progressive infertility in males. Females may develop the tendency for habitual abortion and have menstrual irregularities. Although the incidence of clinical diabetes mellitus is probably not increased, abnormal results on glucose tolerance tests are common. The elevation of glucose concentrations late in the test is probably caused by an overproduction of insulin caused by an abnormal resistance of the insulin receptor. Involvement of smooth muscle accounts for cholecystitis and symptoms referable to gallbladder function, mild dysphagia, constipation, and urinary tract dysfunction.

DNA analysis is the definitive test for myotonic dystrophy. Genetic counseling should be offered to patients with clinical disease and all individuals at risk. Prenatal diagnosis is reliable and uses chorionic villus biopsies or cultured amniotic cells. A curious problem that makes genetic counseling less effective is that some people with advanced disease pay little attention to it. Denial of illness is distinctly different in patients with DM 1 compared with those with other muscle diseases. Many affected family members do not seem to know they have the illness despite being seen in the muscle clinic.

An EMG is useful and shows not only myopathic features but also myotonic discharges (see Chaptet 36B). The muscle histological preparations in fully developed disease are markedly abnormal (Figures 85.22 and 85.23). Fiber size is variable, and fibrosis is present. Internal nuclei and ringed fibers are abundant. These fibers are characterized by small bundles of myofibrils oriented at 90 degrees to the majority of fibers, rather like a thread wrapped around a stick. Other laboratory studies are less helpful. Scrum CK concentrations are often elevated. Some patients have low concentrations of immunoglobulin G. Abnormalities seen on brain MRI scans include cerebral atrophy, increased white matter signals on T2-weighted images, and thickening of the ctanial vault (Miaux et al. 1997). These seem to have little significance.

Supportive treatment includes the use of ankle-foot orthoses to treat footdrop. In theory, hand splints should increase hand function, but most patients prefer not to use

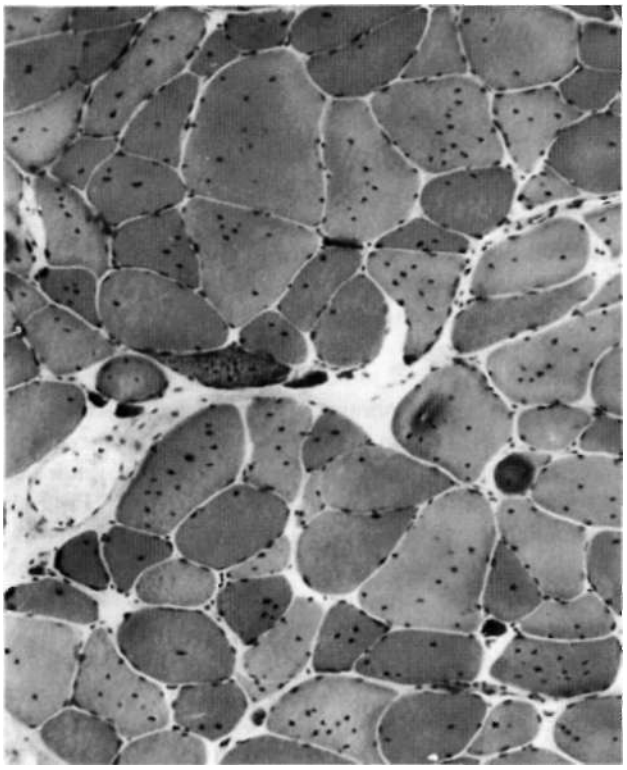


FIGURE 85.22 Myotonic dystrophy type 1. There are numerous internal nuclei, some scattered pyknotic nuclear clumps, and marked variability in the size of fibers. One ring fiber can he identified by its circular, dark-staining appearance. (Hematoxylin-eosin stain.)

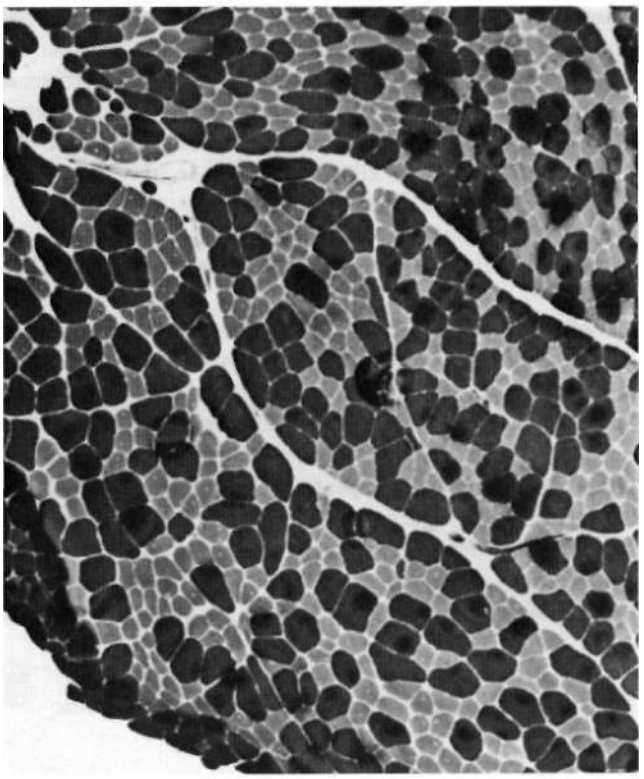


FIGURE 85.23 Myotonic dystrophy type 1. This myosin adenosine triphosphatase stain at pH 9.4 demonstrates that the majority of type I hhers are small. 1 vpe I fiber airopliy is noted in early disease and is obscured as the disease becomes more severe.

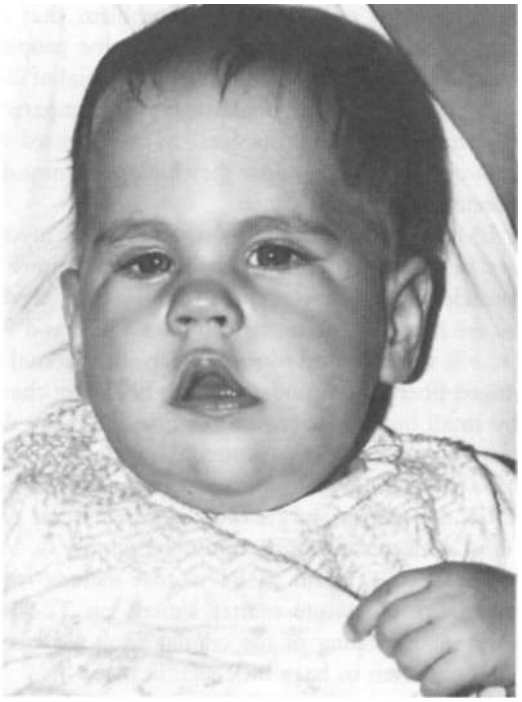


FIGURE 85.24 Infantile myotonic dystrophy. I'll is child is severely retarded and has a marked inverted-V mouth.

them. Breathing exercises and postural drainage can help ward off the respiratory infections often seen in advanced myotonia. Quinine, phenytoin, procainamide, mexiletine, acetazolamide, and even prednisone can be used to treat myotonia. However, most patients with DM 1 are bothered more by weakness than by myotonia and do not use the drugs. Modafinil at 200—400 mg per day improves hypersomnolence (Damian et al. 2001).

Congenita! Myotonic Dystrophy

Congenital myotonic dystrophy expresses itscl f in newborns of myotonic mothers. Extreme hypotonia, respiratory insufficiency, facial paralysis, failure to thrive, and feeding difficulty are the main features. Recurrent respiratory infections that develop into pneumonia are common. Other features are the appearance of the an inverted V or "shark mouth" (Figure 85.24), clubfeet, and severe mental retardation. Affected newborns have a large increase in the trinucleotide repeat region. This occurs with maternal transmission, particularly if the mother has a sizable expansion.

Myotonic Dystrophy Type 2 or Proximal Myotonic Myopathy

Whereas DM I has a predilection for the distal muscles, patients with proximal myotonic myopathy have greater stiffness, pain, and weakness in proximal than in distal muscles (Moxley 1996). Transmission is also by autosomal dominant inheritance. Cataracts are part of the phenotype but gonadal atrophy and cardiac conduction defects are much less common than in DM 1. Hyperinteusc areas on T2-weighted MRI scans in the cerebral white matter and progressive deafness have been reported.

The initial complaints—muscle stiffness and pain—usually begin in adult life. The stiffness is a sense of having a tight muscle that causes reluctance to move. It commonly affects the thighs and may be asymmetrical. Grip myotonia is noted, and the relaxation phase is jerky. The severity of myotonia may vary from day to day, and a "warm-up" phenomenon is noted in which the stiffness disappears after repeated contraction and telaxation. The pain is a sense of discomfort and varies from sharp to a deep visceral ache.

The prognosis is relatively good. Patients with proximal myotonic myopathy do not show the slow decline into helplessness and early cardiorespiratory death so often noted in patients with DM 1. An EMG shows myotonia, but this finding may require a careful search of several muscles. Muscle histological preparations shows features similar to those of DM 1. The serum CK concentration may be elevated.

The genetic defect has been localized to mutations in the gene that encodes for zinc finger 9 *{ZNF9)* on chromosome 3q21 (Liquori et al. 2001). The mutations are expanded CCTG repeats in intron 1. As with DM 1 the expanded repeat probably leads to the expression of a toxic pre-mRNA that impairs the splicing of other mRNA species, including those of ion channels,

Channelopathies (See Also Chapter 70)

The clinical disorders associated with abnormalities in ion channels range from myotonic syndromes to periodic paralyses (Kleopa and Barchi 2002). The classification of channelopathies has been revised based on molecular pathological changes. Ion channels control the passage of ions across cell membranes and shift ions between cell compartments. The ion channel proteins are cell membrane-associated and ate responsible for electrophysiological phenomena such as the muscle action potential. Electrical potentials across the cell membrane (voltage-gated) or ligands such as glutamate serve to open or close channels. The amino acid sequences in segments of ion channel proteins are conserved segments that arc remarkably similar across a wide range of species. It is logical to assume that the conserved segments are vital to normal function. Some mutations are presumably lethal; others produce intermittent symptoms (e.g., the periodic paralyses).

Ion Channels

The calcium channel in muscle is made up of five subunits: *a-1, a-1, f}, y,* and *S. a-* is the most important and forms

the ion pore across the membrane; The type of *a-1* subunit determines the sensitivity of the calcium channel. In muscle, the <*-] subunit is sensitive to dihydropyridines, such as nifedipine, and is called an I.-type channel because of its long open time. The subunit is formed from four similar transmembrane regions (domains D1-D4), each made up of six membrane spanning proteins (S1-S6) that are all linked in scries by "loops" that extend into the cytoplasm or extracellular space. S4 is rich in positively charged amino acids. It is highly charged and may confer voltage sensitivity to the channel. Calcium-channel abnormalities are associated with several neurological disorders, including hypokalemic periodic paralysis (Kleopa and Barchi 2002).

The calcium channel on the sarcoplasmic reticulum is the ryanodine receptor, which controls the flux of calcium from the sarcoplasmic reticulum into the cytoplasm. It plays an important role in the activation of the contractile mechanism, and malfunction causes malignant hyperthermia. Ryanodine receptors are made of four identical subunits, each of which is approximately 550 kD. The alkaloid ryanodine inhibits the receptor at high concentrations and potentially activates it at low concentrations. *RYR1* is the receptor type in muscle. The ryanodine receptor interacts with an L-type calcium channel. Mutations in the ryanodine receptor arc associated with central core myopathy and malignant hyperthermia.

The sodium channel has a composition similar to that of the calcium channel. The a-subunit, a 260-kD protein, confers the sodium channel activity with four domains, composed of six membrane-spanning proteins. The S4 segment is highly charged and may respond to voltage changes. Sodium channel gene mutations arc the most common cause of hypetkalemic periodic paralysis and paramyotonia congenita (Kleopa and Barchi 2002). Hypokalemic periodic paralysis in some families is linked to mutations in the sodium channel (Bulman ct al. 1999; Sternberg ct al. 2001).

Defects in the chloride channel arc associated with both autosomal dominant and recessive myotonia congenita. The structure of the chloride channel is different from those of the calcium and sodium channels. It is a homotetramer, in which each unit contains approximately 1000 amino acids.

The potassium channels are the most ubiquitous and diverse group of voltage-gated ion channels (Kleopa and Barchi 2002). They are composed of monotetramcrs or hete rote trainers with font *a* subunits. Mutations in voltage-gated K^{+1} channel genes are associated with hypokalemic periodic paralysis and Anderson's syndrome (Abbott et al 2001; Plaster etal 2001).

Calcium-Channel Abnormalities (Familial Hypokalemic Periodic Paralysis)

Familial hypokalemic periodic paralysis is inherited as an autosomal dominant trait. Most affected families have mutations on chromosome lq31-32 in the gene that encodes for the *a-1* subunit of the dihydropyridine-sensitive calcium channel. The voltage-sensitive S4 segment of domains 2 and 4 is presumed to be affected. Two common mutations account for most cases. In both, histidine is substituted for arginine: one at position 528 and the other at 1239. Each mutation is found in about one half of patients. The Arg^{2M} mutation is associated with incomplete penetrance of the disease in women, which accounts for the male preponderance in this disorder. The same mutation may also result in incomplete penetrance in males (Sillen et al. 1997).

In the attack, the paralyzed muscle is inexcitable either by stimulation or by the application of calcium on isolated muscle strips. The normal response to calcium can be restored by stripping the muscle of its sarcolemmal membrane, which allows the application of calcium to cause a local contraction of the underlying myofibrils. Studies on intact intercostal muscle fibers from patients with hypokalemic periodic paralysis indicate that the resting membrane potential of muscle fibers is depolarized by approximately 5-15 mV compared with the normal value of -85 mV. Further reductions of the external potassium concentration depolari/.e the fibers to 51) mV and render them inexcitable. Factors that lower the serum potassium concentration provoke attacks of weakness. During an attack, the serum potassium concentration may fall as low as 1.5 mEq/liter, but weakness is noted at higher concentrations. Unexplained findings are (1) the elevated intracellular sodium concentration in resting fibers, (2) the restoration of membrane stability by removal of sodium from the medium, and (3) the fact that the sodium channel is not blocked by tetrodotoxin, unlike in normal muscle.

The onset of familial hypokalemic periodic paralysis is usually in the second decade. Age of onset may be earlier, and the hypokalemia is more severe in the Argl239His mutation (Fouad et al. 1997). The attack begins with a sensation of heaviness or aching in the legs or back. This gradually increases and is associated with weakness of the proximal muscles. Distal weakness also develops. During severe attacks, the patient cannot get up from bed or even raise the head off the pillow. Respiration is not usually compromised, although respiratory function may be mildly decreased. At the height of weakness, the muscle is electrically and mechanically inexcitable, and reflexes are lost. The muscles feel swollen and may be firm to palpation. Attacks usually last for several hours, even up to a day, and strength returns as quickly as it left. A mild residual weakness is slow to clear. Sometimes permanent weakness ensues, associated with a vacuolar myopathy. Attacks vary in seventy and frequency and may occur as often as several times a week, but usually they are separated by weeks to months. Because a shift in the potassium concentration occurs during attacks, provoking factors include heavy exercise followed by a period of sleep or rest, a heavy carbohydrate load, or other causes of increased insulin

secretion. Most attacks occur in the morning hours on waking, probably because movement of ions, such as potassium, across the muscle membrane happens during sleep. Epinephrine, norepinephrine, and corticosteroids may provoke attacks. The greatest incidence of attacks is in the third and fourth decades, and a spontaneous reduction in the frequency of attacks is noted at later ages.

A fall in the concentration of serum potassium is usual, but not constant, during an attack. Weakness may commence at a potassium concentration at the low end of normal and may be profound by the time the serum potassium concentration reaches 2.0-2.5 mEq/liter. ECG changes include bradycardia, prolongation of the PR and QT intervals, and flattening of the T wave associated with prominent U waves. During profound paralysis, motor nerve stimulation may demonstrate reduced amplitudes or absent compound muscle action potentials. An EMG of paralyzed muscles shows an absence of electrical activity. The short exercise test can be helpful between attacks. Baseline ulnar compound muscle action potentials (CMAPs) are recorded, and then the patient is instructed to exercise the muscle for 5 minutes. CMAPs arc recorded at 1-minute intervals during the exercise period and for 25 minutes after exercise. About 50% of patients demonstrate an increment of the CMAP amplitude during exercise followed by a significant decrement after exercise. The test is not specific to the subtype of channelopathy because results arc positive in hypokalemic periodic paralysis, hyperkalemic periodic paralysis, paramyotonia congenita, and myotonia congenita.

The preferred method of diagnosis is genetic testing. Muscle histological preparations may be normal or show minor myopathic changes. A few vacuoles within fibers are ;i common feature, especially when permanent weakness is present. Tubular aggregates may be noted in hypokalemic periodic paralysis caused by sodium channel mutations (Sternberg et al. 2001).

The acute attack is treated with 5-10 g of oral potassium. The dose is repeated in 1 hour if the first dose is ineffective. Potassium administration can only be used in patients with normal renal function. Acetazolamide is used for prophylaxis. It produces a mild metabolic acidosis that may influence the potassium shifts that occur during an attack. Dichlorphenamide, another carbonic anhydrase inhibitor, may be effective as well. Adverse effects of acetazolamide therapy are tingling in the digits and a tendency for kidney stone formation. Hypersensitivity reactions may also occur. Triamterene and spironolactone arc used as adjunctive therapy as arc low-sodium or low-carbohydrate diets.

Secondary Hypokalemic Paralysis

An established association exists between periodic paralysis and thyrotoxicosis, especially in Asian populations. This predisposition is inherited as an autosomal dominant trait, but many cases are sporadic and men are affected more commonly than women. Kidney or adrenal failure may be associated with changes in serum potassium concentrations. A more common form of weakness caused by low potassium levels occurs in patients taking potassium-depleting diuretics. Other compounds, such as licorice, have been implicated in attacks of weakness associated with potassium loss. Renal tubular acidosis secondary to genetic defects in the kidney and secondary renal tubular acidosis secondary to inhalant abuse (e.g., toluene) are also causes of hypokalemia and paralysis.

Sodium-Channel Abnormalities (Potassium-Sensitive Periodic Paralysis, Hyperkalemic Periodic Paralysis, Paramyotonia Congenita, Myotonia Huctuans, and Hypokalemic Periodic Paralysis Type 2)

The combination of potassium-sensitive periodic paralysis and myotonia is associated with mutations in the or-subuuit of the sodium channel. The responsible gene is located on chromosome 17q. The association of decreased electrical activity, paralysis, and hyperactivity[7] (paramyotonia) was recognized even in early descriptions of these disorders. Molecular studies partially explain the relationship. Normal sodium channel activity depends on a complicated series of activation and deactivation processes that opens the pores to allow the passage of sodium while simultaneously protecting the cell against inadvertent excess sodium flux. The channel may exist in the closed, open, and inactivated state. The domain IV S3 segment is believed to have a dominant role in the recovery of inactivated channels, whereas the S4 segment is concerned with deactivation and inactivation of the open channel (fi et al. 1996). Mutations of the sodium channel may impair fast inactivation of the sodium channel or shift the voltage for channel opening to hyperpolarization. However, mutations within the domain II1-IV linker that cause myotonia, with or without weakness, do not impair slow inactivation.

Muscle is slightly depolarized during a paralytic attack. Intracellular potassium concentrations are elevated as are the contents of sodium, water, and chloride. The spontaneous muscle activity of intercostal muscle in vitro is increased even in normal physiological saline. Increasing the external concentration of potassium gradually depolarizes the cells and is associated with increased sodium conductance. Tetrodotoxin reverses the increased sodium conductance, implying that this sodium channel function is not affected. Cultured myotubes from patients with potassium-sensitive periodic paralysis were used to examine the sodium currents. Raising the potassium concentration in the media results in an increased open time or slowed inactivation of the sodium channel associated with sustained depolarization,

In paramyotonia, when intact intercostal muscle fibers were cooled, the resting membrane potential was reduced from approximately -80 to —40 mV, at which point the fibers were inexcitable. As the muscle cools, it passes

through a phase of hypercxcitability. Inexorability is prevented by tetrodotoxin, which blocks the sodium channels. The clinical features reflect the physiological findings.

The predominant symptom of hyperkalemic periodic paralysis is weakness provoked by potassium exposure. Myotonia may be present but is not a complaint. The features of paramyotonia congenita, an allelic disease, are different. Muscle stiffness is the predominant symptom and bouts of weakness arc mild and provoked by cold exposure. In some families, the distinction is clear, and in others the symptoms arc mixed.

Hyperkalemic Periodic Paralysis. Potassium-sensitive periodic paralysis is inherited as an autosomal dominant trait, with strong penetrance, that affects both genders. Onset may occur during infancy or early childhood. The infant's cry suddenly becomes altered or unusual, or the child may be found lying quietly in the crib. An unusual stare may develop, particularly on cold exposure. The first attack commonly occurs in the first few weeks of school because of enforced sitting. By adolescence, the attacks are fairly well characterized. Rest after exercise provokes an attack, and weakness develops quite rapidly, often within minutes. The weakness is milder than that in hypokalemic periodic paralysis, and the attacks are shorter in duration. The attack may be aborted by exercise early in the course, but many prefer inn [<> do so because an .muck is mild .ind followed by a period of relative freedom from symptoms. In addition to rest after exercise, other provocative factors include exposure to cold, anesthesia, and sleep. Patients often avoid fruit juices that contain high concentrations of potassium. Many patients differentiate two kinds of attacks, light and heavy. A light attack is characterized by a feeling of fatigue and mild weakness that usually disappears in less than 1 hour. A heavy attack may be associated with severe paralysis to the point where the patient is unable to arise from the chair or the bed. The frequency of attacks varies from two or three mild attacks a day to heavy attacks months apart. Residual weakness may be noted into middle age and beyond.

Paramyotonia Congenita. In addition to weakness, hyperkalemic periodic paralysis may be associated with a form of myotonia that involves the muscles of the face, eyes, tongue, and hands. Paramyotonia of the face may be noted by stiffness of the expression, narrowing of the palpebral fissures, or dimpling of the chin due to contraction of the mentalis muscle. Unlike the myotonia in myotonic dystrophy, paramyotonia is often accentuated by repeated exercise (myotonia paradoxical. Patients complain of aching or stiffness. A clinical test for paradoxical paramyotonia is repealed forced closure ol the eyes. After each repetition, difficulty with relaxation is accentuated until eventually the eyes cannot open. Exposure to cold not only w[r]orsens myotonia but produces muscle weakness in this condition. The same symptoms may be noted spontaneously when patients arc swallowing ice cream or going out into winter weather. A useful test is to soak a small towel in ice water and lay it over the patient's eyes for 2 minutes. Eyelid myotonia is demonstrated by asking the patient to look upward for a few seconds and then look down. The eyelids remain up, baring the sclera above the iris. When muscle is sufficiently chilled, the paramyotonia disappears, and the muscle is flaccid and paralyzed. The weakness may far outlast the cold exposure, and the muscle may not regain full use for hours after warming. Strong voluntary contraction may be associated with a long-lasting decrease in strength, which is not clearly caused by increased myotonia. Immersing the forearm in ice water may also cause weakness that was not seen on initial examination.

Diagnosis of the different types of potassium-sensitive conditions relics on demonstration of the genetic defects. The disorder is suspected when bouts of weakness are associated with a high concentration of serum potassium. In paramyotonia electromyographic examination of resting muscles at room temperature shows myotonic discharges that are present on percussion or with movement of the needle. More remarkable is the finding of spontaneous activity on cooling of the limb. Low-amplitude fibrillation potentials appear as the muscle is cooled and arc most intense when muscle temperature is around 30°C. This spontaneous activity completely disappears as cooling continues. In contrast to myotonia, during the delayed muscle relaxation of paramyotonia, electtical activity of the muscle is not prominent. EMG studies are also useful in demonstrating the worsening of the myotonic discharges with exposure to cold or to potassium. Because exercise may worsen symptoms, a brief exercise test as described in the section on hypokalemic periodic paralysis can be performed.

The EGG may show the changes of hyperkalemia, and the serum CK concentration may be elevated during or after an attack. Provocative testing may be dangerous and is best avoided.

Muscle histological preparations in patients with fixed paralysis may show tubular aggregates. Other myopathic features include internal nuclei, vacuoles, and fibrosis. In paramyotonia congenita, muscle histological preparations show variability in the size of fibers, internal nuclei, and occasional vacuoles.

Acute attacks usually do not require treatment because they are mild and brief. Patients learn to eat a candy bar or drink a sweet drink to ward off an attack. If weakness is more severe, intravenous administration of calcium gluconate has been recommended. Intravenous administration of sodium chloride sometimes may abort an attack. Maintenance therapy with dichlorphenamide or acetazolamide may be helpful. The combination of hydrochlorothiazide with potassium may be effective, although the reason is not clear. Mexiletine, a drug related to lidocaine and

tocainide, blocks the sodium channel. It may provide relief to patients with myotonia. It can be started at a dose of 200 mg three times per day. Most patients who derive benefit receive relatively low doses.

Myotonia Fluctuans. Myotonia fluctuans is a dominantly inherited disorder of the sodium channel. It is characterized by muscle stiffness exacerbated by exercise or potassium ingestion. The onset in adolescence is characterized by bouts of stiffness. The stiffness affects extraocular, bulbar, or limb muscles. It improves by loosening up the limb, as in myotonia congenita, but muscles become stiff after or during exercise. Unlike in paramyotonia congenita, weakness is not a part of the disorder. Abnormalities in exon 22 and in exon 14 of the sodium channel gene arc thought to be responsible. Mexiletine and acetazolamidc are effective therapeutic agents.

Secondary Hyperkalemic Periodic Paralysis. Hyperkalemia may cause weakness in disorders other than familial hyperkalemic periodic paralysis. The difference between secondary hyperkalemic periodic paralysis and genetic hyperkalemic periodic paralysis is that higher concentrations of potassium are required to cause weakness in secondary hyperkalemic periodic paralysis. Renal failure and potassium-retaining diuretics are causes of secondary hyperkalemic periodic paralysis.

Hypokalemic Periodic Paralysis Type 2, Hypokalemic periodic paralysis is caused by mutation in the muscle sodium channel gene (type 2) rather the calcium channel (type 1) in approximately 9% of patients (Kleopa and Barchi 2002). Clinical differences that help to distinguish patients with periodic paralysis type 2 from those with type 1 are that the former are more likely to suffer severe myalgias after paralytic attacks, to show tubular aggregates rather than vacuoles histologically, and to show disease worsening with acetazolamide therapy.

Andersen's Syndrome. The constellation of periodic paralysis, cardiac dysrhythmias, and dysmorphic features have been termed *Andersen's syndrome* (Sansone et al. 1997). The disorder is inherited in an autosomal dominant fashion and caused by mutations in the potassium channel gene *(KCNJ2)* located on chromosome 17q2.'5 (Plaster et al. 2001). The onset of paralysis may begin in early childhood or be delayed until the second decade. Attacks ate associated with both high and low serum potassium concentrations. Affected family members often have dysmorphic features that include wide-spaced eyes, low-set ears, a small chin, clinodactyly of the fifth finger, and syndactyly of the toes. Permanent muscle weakness is a featute in some patients.

The syndrome is important to recognize because of the high rate of cardiac involvement. This varies from prolongation of the QT interval through ventricular tachycardia to fatal cardiac arrest. The risk of cardiac complications is sufficiently high that provocative hypokalemic or hyperkalemic testing is not warranted. Some members of affected families have only fragments of the syndrome {e.g., clinodactyly or an abnormal QT interval), and a full pedigree evaluation is necessary.

Myotonia Congenita. Two forms of myotonia congenita are recognized; one is transmitted as an autosomal dominant and the other as an autosomal recessive trait. Both are associated with abnormalities in the gene for the chloride channel on chromosome 7q35. Introducing the gene tor the iinir.mt chloride channel ir.ro n cell system abolishes the chloride current and deranges the normal function of the chloride channel (Fahlke et al. 1997). Chlotidc conductance is also reduced in the patient's muscle, and the membrane resistance is greater than normal. The action potential in a normal muscle cell is associated with an outflow of potassium, which may accumulate in the transverse tubules simply because the physical structure of the tubule docs not favor easy diffusion. Ordinarily, this does not present a problem because the chloride conductance is so large that the relatively ftce passage of chloride ions negates the effect of any small change in potassium. If chloride conductance is impeded, the increase in potassium concentration in the transverse tubules may lead to enough depolarization to activate the sodium channels again and hence lead to repetitive electrical discharge of the membrane, producing electrical and clinical myotonia.

The dominant disease was originally described by Thomsen among members of his own family. It is usually milder than the recessive form described by Becker, in which weakness develops. The pattern of inheritance is sometimes difficult to determine in patients with sporadic disease because other family members with the abnormal mutation may be asymptomatic or have only mild involvement. This necessitates a thorough evaluation of the family with appropriate genetic testing.

On initial examination, especially if the patient has been sitting in the waiting room for some time, apparent weakness is observed because a severely myotonic muscle cannot be used with full voluntary power. With repetitive activity, the muscle loosens up, and the strength usually returns to normal. This is particularly true of the proximal limb muscles. Symptoms are described in a rather stereotyped way. After resting, the muscles are stiff and difficult to move. When the patient arises from a chair, muscles move en bloc, giving a stiff, wooden appearance, rather like the rusted Tin Man in *The Wizard of Oz.* As movement continues, the patients can walk freely and finally can run with ease. Myotonia is exacerbated by cold. All the muscles of the body are involved, and although it is most noticeable in the limbs, myotonia also can be found in the face and the tongue. In addition, particularly in the recessive form, muscular hypertrophy may be pronounced.

In myotonia congenita, the EMG shows well-marked myotonia with none of the associated dystrophic features of myotonic dystrophy. The muscle biopsy may demonstrate an absence of type 2B fibers; no explanation for the finding has been noted. Muscle biopsy also may reveal some increase in the size of fibers and internal nuclei and other mild, nonspecific changes.

Unlike patients with myotonic dystrophy, those with myotonia congenita may be quite disabled by myotonia. Treatment with mexiletine is worth trying and may provide dramatic relief in some patients. Older medicines include quinine, procainamide, and phenytoin,

Metabolic Myopathies

Any disturbance in the biochemical pathways that support adenosine triphosphatase (ATP) levels in muscle inevitably ••(.•suits m exercise intolerance. One common symptom is muscle fatigue, a sense that the muscle will no longer perform in a normal fashion. This is true fatigue and not simply a feeling of tiredness or weariness. It may be difficult for the patient to describe the fatigue in terms that the physician can understand because it is nothing like the sensations experienced by a healthy person after strenuous exercise. The fatigue has an unpleasant quality and is described in terms of a barrier through which the patient cannot break. Other symptoms include muscle pain and sometimes muscle cramps. The normal fatigue of strenuous exercise is painless. Muscle pain after strenuous exercise (e.g., the next day) is almost universal in the untrained individual, but pain during exercise suggests a disturbance of muscle function.

Normally functioning muscle has a series of safety mechanisms that prevent exercise to the point of muscle destruction. In the metabolic muscle diseases, maintenance of ATP levels is impaired, and the protective mechanism that functions in the normal person is absent. When a patient with a metabolic myopathy exercises, muscle pain develops followed by a muscle contracture in which the muscle is hard, swollen, and tender. This reflects destruction of the muscle and may be associated with the release of myoglobin into the blood and urine. This is sometimes noticed as a change in the color of the urine, which may resemble weak lea or to'.;, hinsnie, IIIIIM.1I' pain, contractures, and myoglobinuria are increasingly severe effects of the biochemical defect. Every effort should be made to prevent the development of myoglobinuria, which is associated with the potential complication of renal tubular necrosis. Although the final results are similar in many of the diseases, the metabolic myopathics can be grouped into three major categories: disorders of carbohydrate metabolism, disorders of lipid metabolism, and disorder-. nt mitochondrial function. Finally, some conditions, in theory, should disturb pathways for ATP maintenance but do not seem to cause any exercise intolerance. Tissues in which ATP is completely depleted are dead tissues. The muscle seldom reaches this critical state in the metabolic myopathies. Instead, most of the support pathways are overworked and unwelcome by-products are produced, which arc probably responsible for the symptoms.

Disorders of Carbohydrate Metabolism

Myophosphorylase Deficiency. Intramuscular carbohydrate stores play an important part in providing the energy source during the early stage of exercise, before the compensatory mechanisms of an increased supply of blood-borne metabolites and increased lipid metabolism catch up with the added demand. The first of the biochemical disorders to be recognized was a disorder of carbohydrate metabolism called *myophosphorylase deficiency* (McArdle's disease). In 1952, McArdle noted that a young man who presented with exercise intolerance experienced pain and tightness of his muscles on forced exercise. Ischemic forearm exercise caused a painful contracture of the muscle within minutes. Insertion of an electromyography needle showed no electrical activity, thereby differentiating this contracture from a muscle cramp, McArdle commented that the phenomenon resembled the reaction of a fish muscle poisoned by iodoacetate, *a* compound that blocks glycolysis. Subsequent studies showed the defect to be an absence of myophosphorylase activity, encoded by a gene on chromosome 1 lq13. Phosphorylase exists in two forms: phosphorylase a, the active tetramer, and phosphorylase b, an inactive dimer. Conversion of the inactive form to the active form is catalyzed by phosphorylase b kinase, which itself is activated by a protein kinase under the control of cyclic adenosine monophosphate (AMP). Any abnormality of this cascade of reactions results in an absence of phosphorylase activity. Both phosphorylase a and phosphorylase b kinase deficiencies are known to cause exercise intolerance, and both conditions appear to be inherited as autosomal recessive traits.

Symptoms are noted during the first 10 years of life but are recognized only in retrospect. As children, patients may complain of being tired and unable to keep up with their playmates. The typical symptoms appear in adolescence. Fatigue and pain begin within the first few minutes of exercise, particularly if it is strenuous. The sensation of hitting a barrier is noted, which causes activity to slow down. It exercise is continued, pain develops within the muscle, which at first is deep and aching but gives way to the rapid development of a painful tightening of the muscle. When the muscle is examined, it is hard and contracted, and any attempt to straighten it results in great pain. The muscle contracture may last for several hours and can be differentiated from a muscle cramp by two characteristics: the EMG is electrically silent, and the duration of the contracture is far longer than that of a physiological cramp, which disappears after a few minutes at most.

Another aspect of McArdie's disease is the development of the second-wind phenomenon. If, with the onset of fatigue, the patient slows down but does not stop, the abnormal sensation may disappear, and thereafter the muscle may function more normally. By gradually increasing the level of exercise again, the patient may be able to break through the barrier and may then be able to exercise at an adequate level for long periods of time. This second-wind phenomenon, which is similar to the phenomenon normally experienced by distance runners, may be marked in patients with phosphorylase deficiency. It probably is associated with a change in the blood supply in the muscle and with an intrinsic change in the muscle's metabolism. The second-wind phenomenon usually is associated with a rise in *fatty* acid use and may be blocked by nicotinic acid.

Unusual forms of phosphorylase deficiency have been described. One was seen in an infant girl who died of respiratory failure. Phosphorylase deficiency also has been noted in an occasional patient with proximal weakness, who has neither cramps nor fatigue. Oil examination, the patients have neither wasting nor detectable weakness but may be reluctant to exert full force during muscle strength testing because of the possibility of exacerbating muscle pain.

A simple diagnostic clinical test is the exercise forearm test (previously called *ischemic exercise test).* A butterfly needle is inserted in the antecubital vein, and baseline lactic acid and ammonia concentrations ate obtained. The patient then opens and closes the hand repeatedly and as fast as possible for 1 minute. Importantly, an ischemic arm is not required for the test. In fact, ischemic exercise is contra-indicated because it may lead to myoglobinuria. Scrum lactic acid and ammonia levels are obtained at 1, 2, 3, and 5 minutes aftet the exercise. The notmal response is a three to fourfold rise in lactic acid and ammonia. In deficiencies of phosphorylase, phosphorylase h kinase, phosphoIycerate mutase, phosphoglycerate kinase, lactate dehydrogenase, and enolase, ammonia concentrations rise but not lactic acid concentrations. The ammonia assay is imperative to ensure that the patient performed sufficient exercise. A rise in lactic acid without a rise in ammonia is seen in myoadenylate deaminase deficiency.

Light microscopic examination of the muscle biopsy specimen may show an increase in glycogen in subsarco-lemmal blebs. Muscle fiber necrosis also may be noted. Results with routine histological stains are entirely normal. However, staining for myophosphorylase is absent, and biochemical assay of enzyme activity on the muscle biopsy is significantly reduced.

Phosphofructokinase Deficiency. PFK is the enzyme that converts fructose 6-phosphate to fructose 1,6-diphosphate and is a step in the glycolytic chain downstream from that activated by phosphorylase. The reaction is rate limiting for glycolysis. PFK deficiency is inherited as an autosomal recessive trait, the gene is on chromosome 1, and hcterozygotes have dec teased hut not absent levels of enzyme activity.

PFK deficiency is an autosomal recessive disorder with clinical features almost identical to those of phosphorylase deficiency, although the second-wind phenomenon is uncommon. Most attacks are associated with nausea, vomiting, and muscle pain. Thete may also he mild hemo-lytic anemia and gallbladder pigment stones, with increased concentrations of bilirubin and increased reticulocyte counts due to deficiency of red blood cell PFK. PFK, like phosphorylase, is a tetramer of different su bun its, M and R. Muscle PFK is composed of identical M subunits, wheteas the enzyme in the red blood cell comprises both M and R types. In PFK deficiency, the M subunit is missing, resulting in absence of muscle PFK and impairment of the PFK in the red blood cell because the R subunit is still preserved.

Phosphoglycerate Kinase Deficiency. Phosphoglycerate kinase is involved in another step in the glycolytic pathway. Muscle deficiency produces a predictable picture very similar to that of phosphorylase deficiency. Venous lactate concentrations does not rise after exercise, as would be expected. The muscle histological preparation is normal, as is the glycogen concentration. Phosphoglycerate kinase is a single polypeptide, and many different point mutations of this enzyme have been described, most of which produce abnormalities in the red blood cell, with hemolytic anemia, mental retardation, and seizures. The gene is on chromo-some Xql3; hence the inheritance is an X-linked recessive trait.

Phosphoglycerate Mutase Deficiency. Phosphoglycetate mutase exists as a dimer wirh M and B subunits. The predominant form in normal muscle is MM, A small amount of residual activity may be present in muscle as a result of the existence of the BB form. Patients with an absence of the enzyme have attacks of muscle pain and myoglobinuria and, in one case, typical attacks of gouty arthritis. The high uric acid level may be associated with overactivity' of the adenylate kinase-adenylate deaminase reaction, which is seen in many metabolic disorders and produces uric acid as its end product. Exercise testing shows some elevation of lactate, but not to the concentra-tions usually seen in the other disorders of glycogen metabolism. Incremental bicycle ergometry in one patient was said to show a normal rise in lactate and a normal $V02_{m\cdot nx}$ and heart rate, which are difficult to explain. The responsible gene is located at chromosome 7pl2-13.

Lactate Dehydrogenase Deficiency. l.DH deficiency is as.socL.itI'd wall I'M'iviM.' iniiili.Taiuv, Lunelle, and myo dobinuria. Some differences exist in the laboratory studies between LDH deficiency and the other disotdcrs discussed here. In most muscle diseases, muscle LDH and serum CK concentrations fluctuate together. This disorder shows a marked discrepancy between the high concentrations of CK

and the low concentrations of LDH. Furthermore, because the action of LDH in exercise is to convert pyruvate to lactate, large amounts of pyruvate are produced even though no lactate is produced after ischemic forearm exercise. The gene is at chromosome 1 lp 15.4.

/i-F.nolasc Deficiency. A single patient has been reported with exercise intolerance, myalgias, and episodic elevated blood concentrations of serum CK caused by a muration in the gene that codes for /3-enolase.

Treatment of the Glycolytic Disorders. No effective treatment for glycolytic disorders is available. The patient should be counseled to avoid situations that might precipitate myoglobinuria. Attempts have been made to bypass the metabolic block by using glucose or fructose. Sublingual administration of isoproterenol has been tried without benefit. Administration of branched-chain amino acids and a protein-enriched diet has been suggested, but these regimens are no more effective than a well-balanced diet. One maneuver that can be adopted is to develop the patient's awareness of the second-wind phenomenon. Graded exercise on a treadmill can be used to train the patient to recognize how to slow down with the first onset of symptoms and then resume exercise in small increments. This training is best accomplished in an exercise physiology-laboratory.

Disorders of Lipid Metabolism

Carnitine Palmitoyl Transferase Deficiency. The synthesis of ATP from the oxidation of fatty acids is accomplished by as complex a system as that in glycolysis. Although fatty acids are not used at the beginning of exercise, they become increasingly important after 20-30 minutes of endurance exercise$_s$ and after 1 hour, they represent the major energy supply. Consequently, defects in lipid metabolism cause symptoms after sustained activity. Carnitine palmitoyl transferase (CPT) is the enzyme that links carnitine to long-chain fatty acids, which is necessary to transport the fatty acid across the mitochondrial membrane from outside to inside (CPT-I). It is also responsible for unhooking carnitine when the complex reaches the inside (CPT-II). CPT-II deficiency is one of the more common biochemical abnormalities in muscle. The disorder is inherited as an autosomal recessive rrair.

Typically, the patient with CPT deficiency is a young adult male who experiences his first bout of weakness and myoglobinuria after strenuous exercise, such as mountain climbing or playing several sets of tennis. In retrospect, patients[1] brief episodes of muscle pain were often experienced as children, but these were dismissed as growing pains or ordinary muscle cramps. Episodes of myoglobinuria are more likely when exercise is performed in the fasting state when there is greater dependence on fatty acids for energy. Several patients with this illness first experienced symptoms during military training when undertaking a forced march with a full backpack before breakfast. Attacks of myoglobinuria in CPT deficiency are often more severe than those occurring in disorders of glycolysis and have a greater tendency to cause renal damage. This may occur because the symptoms come on so rapidly in glycolytic disorders that cessation of exercise immediately returns the muscle to its resting condition. In disorders of lipid metabolism, the patient is often far away from home and must out of necessity use muscles that have already been damaged. In addition, muscles still depend on fatty acid metabolism even after work ends. Respiratory-paralysis may rarely accompany a severe attack.

Patients with CPT deficiency often notice that stamina depends on diet and carry a candy bar to be eaten during exercise. Others know that exercise in a fasting state is far more difficult for them. Despite these limitations, most patients with CPT deficiency are quite athletic. Usually, however, they are weight Sifters or sprinters rather than marathon runners. Both activities draw on carbohydrate energy supplies and use glycolytic fibers, not the oxidative fibers. Results of muscle examination are normal, and many patients are muscular, perhaps because their favorite exercise is weight lifting.

In general, routine laboratory studies are unrevealing. The serum CK concentration may be normal and muscle histological preparations arc normal unless the patient has had a recent attack of muscle damage. Biochemical analysis of the muscle biopsy reveals the deficiency of CPT. Analysis for CPT is not routine and must be requested. The respiratory exchange ratio (RER) is a useful screening test. The ratio of carbon dioxide produced to oxygen consumed indicates the type of fuel being used by the patient. In a normal individual at rest, the RER is apptoximately 0.8 because fatty acids are rhe predominant source of fuel at rest. In CPT deficiency, the RER is seldom much below 1.0, even with the patient at complete rest. It may be worthwhile to obtain incremental bicycle ergometry results because, in addition to the RER, the $Vo2_{max}$ and W_{m3X} also can be determined. Values for both are likely to he decreased. The maximum heart rate is normal, indicating full effort. Forearm exercise testing is not useful in CPT deficiency because the test stresses glycolytic pathways.

Patients with CPT deficiency should be cautioned to avoid any situation that provokes muscle pain and puts them at risk for myoglobinuria. The physiological effect of fasting should be explained, and the patient should be warned not to attempt exercise under such conditions. The use of glucose tablets or candy bars during exercise may raise exercise tolerance slightly. If myoglobinuria is noted, the patient should be admitted to the hospital, and renal function monitored. Forced alkaline diuresis may be helpful to prevent acute tubular necrosis. All exercise should be discontinued, and the patient should be restricted to bed rest until serum CK concentrations return to normal and renal function is normal.

Carnitine Deficiency Myopathy, Carnitine is an important compound in intermediary metabolism. It influences the balance between free coenzyme A (CoA) and acylated CoA in the mitochondria and is used to transfer long-chain fatty acids across the mitochondrial membrane under the action of the enzyme CPT, Carnitine supplied by the diet usually is supplemented by carnitine synthesized in the liver and kidney, which is transported to and then actively taken up by the muscle. Many metabolic processes produce acyl-CoA, which may then be employed in useful metabolic pathways, degraded by the liver, or excreted by the kidneys. The formation of acylcarnitinc is often a step in these processes, enabling the transport of fatty and organic acids across membranes, such as the mitochondrial membrane. However, an excess of acyl-CoA may cause a wide variety of damage, because it inhibits reactions as diverse as the oxidation of pyruvate, steps in the tricarboxylic acid cycle, and gluconcogencsis.

An adequate amount of carnitine is necessary for normal function. The adequacy of the carnitine supply can be judged from its absolute value and the percentage of free (nonaeylated) carnitine. If free carnitine is absent, carnitine deficiency exists, no matter how much total carnitine is present. Because 98% of the body carnitine is in muscle, it is not surprising that carnitine deficiency is associated with neuromuscular disease. In most patients with carnitine deficiency, the loss of free carnitine is due to a defect in some other enzyme system that results in an overproduction of organic acids or a defect in acyl-CoA disposal. Causes of secondary carnitine deficiency include multiple acyl-CoA dehydrogenase deficiencies, resulting in an overabundance of organic acids, which then bind the available carnitine; propionyl-CoA carboxylase deficiency; methylmalonyl-CoA mutase deficiency; and a number of mitochondrial disorders. Hemodialysis, cirrhosis, pregnancy, Reye's syndrome, valproate therapy, and renal Fanconi's syndrome also deplete cai nitinc stores. In must Ic carnitine deficiency, serum concentrations of carnitine are often normal, but both total and free carnitine concentrations are reduced in the muscle. In systemic catnitine deficiency, muscle carnitine, liver carnitine, and serum carnitine concentrations arc all decreased.

The most common clinical picture in patients with carnitine deficiency of the muscle is a slowly progressive weakness on which sudden exacerbations or a fluctuating course are superimposed. Fatigue and exercise-related pains have been described but usually do not constitute major complaints; myoglobinuria is almost never a problem. The weakness is usually proximal, and the symptoms begin during childhood or early teenage life. In addition to the limb and some trunk weakness, facial and bulbar weakness has been described.

Systemic carnitine deficiency may ptcscnt in infancy and childhood, when the muscular weakness occurs in association with an encephalopathy crises resembling Reye's Syndrome, fhe initial symptom ;r the e:icer»fMlop.i:hy usually is protracted vomiting, followed by changing levels of consciousness, culminating in coma. Hypoglycemia usually occurs and is associated with evidence of liver damage, an enlarged, tender liver, and increased serum concentrations of hepatic enzymes. Hypothrombinemia, hyperammonemia, and excess lipid in the liver arc common. Fasting may exacerbate the symptoms of carnitine deficiency, because the body becomes dependent on fatty acids.

The EMC appears myopathic but has no specific findings that suggest the diagnosis of carnitine deficiency. The disorder may be suspected with a muscle biopsy because of the accumulation of lipid droplets in muscle fibers (Figure 85.25), but the biochemical measurement of carnitine, both free and total, is necessary to establish the diagnosis. An abnormal value should initiate the search for the underlying defect.

Treatment of carnitine deficiency by replacing L-carnitine is not uniformly successful. Approximately 2-4 g per day have been given to adults in divided doses, with the equivalent of 100 mg/kg in infants and children. No serious adverse effects are seen, although patients find i-carnitine unpleasant to take because of accompanying nausea and a fishy odor of the sweat. Some patients show dramatic improvement, while others feel no change at all. The

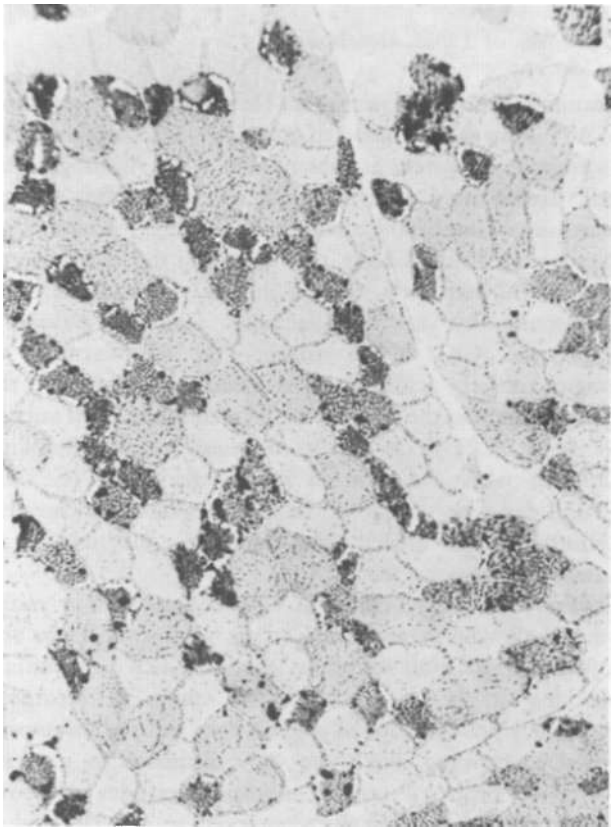


FIGURE 85,25 Carnitine deficiency. This lipid stain demonstrates deposition of fat in muscle fibers.

efficacy of other treatment is equally variable. One patient showed a response to riboflavin in high doses and others to ptcdmsone. Dietary manipulations, such as reducing the amount of long-chain fatty acids in the diet and supplying a medium-chain triglyceride diet, are successful in some patients.

Disorder of Abnormal Nucleotide Metabolism: Myoadenylate Deaminase Deficiency

Approximately 1-2% of the population has a deficiency of the enzyme myoadenylate deaminase (AMP deaminase [AMPDA]). The disorder is inherited as an autosomal recessive trait. The enzyme plays a role in supporting ATI[3] levels by acting in conjunction with adenylate kinase. Adenylate kinase converts two molecules of adenosine diphosphate to one each of ATP and AMP. Adenylate deaminase then converts AMP to inosine monophosphate with production of ammonia. This reaction is used when muscle is stressed.

Early studies suggested that AMPDA deficiency caused myalgia. However, most people with AMPDA deficiency are asymptomatic and show no signs of exercise intolerance. A deficiency of the enzyme has been described in almost every condition from congenital hypotonia to amyotrophic lateral sclerosis. The poor correlation between the enzyme defect and clinical symptoms makes it difficult to know how to interpret the entity.

Muscle histology is normal. The histochemical reaction for AMPDA is absent. On the forearm exercise test, patients with AMPDA deficiency produce normal amounts of lactate but little or no ammonia and hypoxanthine, both of which are by-products of the AMPDA reaction.

Mitochondrial Myopathies

A group of disorders known as the *mitochondrial myopathies* are caused by several different defects in respiratory chain function. The group includes Kearns-Sayre syndrome (KSS), other disorders of oxidative muscle metabolism with exercise intolerance, myoclonus epilepsy with ragged-red fibers (MERRF), and mitochondrial encephalopathy associated with lactic acidosis and stroke-like episodes (M FI .AS). Most of these patients present with CNS dysfunction and are discussed in Chapter 69,

The final products of fatty acid metabolism and glycolysis ate the two carbon fragments that enter the tricarboxylic acid cycle and are further oxidized in the mitochondrial respiratory chain. Major disturbances in mitochondrial function produce severe multisystem disease (brain, heart, kidney, and skeletal muscle). Less severe disturbances may primarily affect skeletal muscle and cause exercise intolerance. Under normal conditions, the rate of riilOi.lniridi:.'.l o\id.uion is coupk'd to the need for A I 1'. II ATP turnover is rapid, mitochondrial oxidation is turned on, with the resulting consumption of oxygen and other metabolites. When ATI' turnover is minimal, mitochondrial oxidation is relatively quiescent. The body's response to the increased demands of exercise {and increased iimochon • drial oxidation) is predictable. The higher oxygen consumption necessitates augmented delivery of oxygen to the muscle, evidenced by vasodilatation, tachycardia, and increased cardiac output and respiration. The heat generation that accompanies this oxidation results in sweating. These are the normal accompaniments of vigorous exercise. When mitochondrial function is impaired, maintaining \ IP levels al resi ma; require thai mitochondrial oxidation is fully turned on. In this situation, the patient at rest may experience all the symptoms that normally accompany vigorous exercise. In addition, because the oxidative mechanisms are insufficient to cope with the demand for ATP, anaerobic mechanisms are required, resulting in lactic acidosis.

Severe mitochondrial diseases can be detected at rest. High resting serum lactate concentrations are evidence of defective mitochondrial function after hyperthyroidism or intoxication with poisons (e.g., dinitrophenol) that uncouple mitochondria) oxidation are excluded. Incremental bicycle ergometry is the most useful test in patients whose disease is less severe. Increasing the workload even to low levels results in an excessive rise in pulse rate and oxygen consumption with a low W_{max}. This discrepancy between normal $Vo_{2m\cdot lx}$, normal heart rate, and a very low $W_{m;ix}$ is characteristic of the illness. If bicycle ergometry is nor available, incremental forearm exercise may demonstrate excessive lactate production for the levels of work needed. If the disorder is suspected from the clinical history and the results of exercise testing, a muscle biopsy should be carried out to confirm the diagnosis.

Histochemical analysis of affected muscle usually shows ragged-red fibers whereas unaffected muscle in the same patient may be normal. Abnormal mitochondria sometimes are seen on electron microscopic examination (Figure 85.26). Ragged-red fibers also arc seen in other diseases and in normal aging, although not in such quantities. The biopsy specimen may reveal scattered fibers that lack cytochrome oxidase. Even though the typical clinical picture associated with ragged-red fibers in the muscle makes the diagnosis apparent in many patients, some have few pathological changes and even normal biochemical values. Assay of mitochondrial enzyme activity and mutational analysis of the mitochondria] DNA can be performed to confirm the diagnosis.

r>uk. lieinn .'.I c\ .illi.il n in of tiie eymehninie eh.nn cm localize the defect. However, analysis of mitochondrial oxidation requires relatively large amounts of muscle. The introduction of noninvasive techniques to monitor muscle metabolism has had a major impact on the analysis of mitochondrial disorders, although it is perhaps less useful in the diagnosis of these conditions. Magnetic resonance spectroscopy of P compounds permits the analysis of

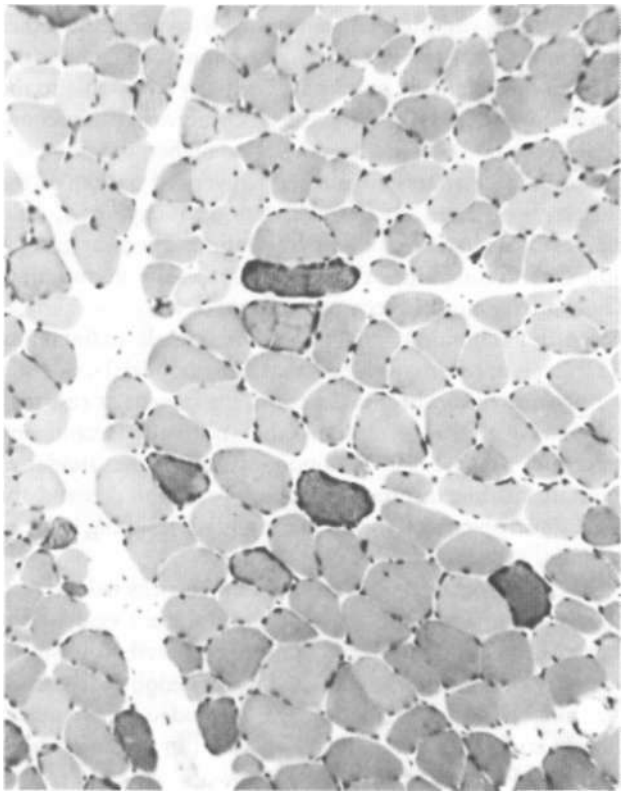


FIGURE 85.26 Kcarns-Sayrc syndrome. Typical appearance of the ragged-red fibers seen in the biopsy. (Modified Gomori trichrome stain.)

ATP, creatine phosphate, inorganic phosphate, and pH in muscle. In mitochondrial disorders, there is a rapid fall in concentrations of creatine phosphate and an abnormal accumulation of inorganic phosphates. Equally important, there is a delay in the recovery of phosphocreatine concentrations to normal after exercise. These techniques can be used to evaluate the effects of treatment in a way that invasive procedures, such .is muscle biopsy, cannot.

The treatment of most mitochondrial disorders is limited to the treatment of lactic acidosis when it occurs. A "cocktail" of compounds, including riboflavin, ubiquinone, vitamin C, menadione, coenzyme Q 10, and niacin has been popular, but its efficacy is unproven.

Myoclonic Epilepsy and Ragged-Red Fibers

The complete spectrum of MERRF includes myoclonus, generalized seizures (myoclonic and tonic-clonic), ataxia, dementia, sensorineural hearing loss, optic atrophy, and muscular weakness and atrophy. Weakness and atrophy are usually more prominent in proximal muscles. In addition, some patients have a generalized sensorimotor polyneuropathy along with high arched feet (pes cavus). The disorder can begin in childhood or adult life, Although the course and severity are often progressive, these can vary even within the same family. Cardiac-muscle is also affected, and patients can develop arrhythmias or heart failure. Patients with MERRF can develop life-threatening hypoventilation associated with surgery, sedation, or intercurrent infection.

Serum CK concentrations can be normal or mildly elevated. Serum lactate concentrations also are often elevated. An electroencephalogram may demonstrate generalized slowing of the background activity as well as bursts of spikes and slow waves. A MRI or CT scan of the brain reveals cerebral and cerebellar atrophy.

There is non-Mendclian maternal inheritance of MERRF. Approximately 80% of affected patients have a point mutation at nucleotide position 8344 of the mitochondrial genome, resulting in an A to G transition in the tRNA ^ gene. Other mutations in this gene (positions 8356 and 8366), in the $tRNA^{\wedge 11}$ gene (the gene most commonly mutated in MELAS; see later), and in the gene for tRNA ^{*r} also have been reported in patients with MERRF. MERRF may also be due to multiple mitochondrial DNA (mtDNA) deletions. The mitochondrial tRNA gene mutations impair the translation of mtDNA-encoded respiratory chain proteins. Decreased activity of complexes I and IV have been demonstrated. Mutations can be demonstrated by polymerase chain reaction of nit DNA in leukocytes or muscle specimens, but abnormal mtllXA is seen more often in muscle.

Mitochondrial Myopathy, Lactic Acidosis, and Strokes

MELAS is characterized by biochemical or morphological evidence of mitochondrial abnormalities, high lactate concentrations in the serum or cerebrospinal fluid (CSF), and strokelike episodes. The disorder usually manifests in childhood, but rare occurrences with onset as late as in the eighth decade have been reported. Most patients present with recurrent migraine-type headaches, hemiparesis, hemianopsia, or cortical blindness. These attacks may be provoked by exercise or intercurrent infection. Some patients develop progressive dementia after repeated attacks. Proximal muscle weakness is present in the majority of patients along with exercise intolerance. Many patients have short stature. Some patients also develop myoclonus, seizures, or ataxia.

Serum CK concentrations may be normal or elevated. Lactate concentrations are elevated in the serum and CSF in the majority of patients. Cortical atrophy and focal low signal abnormalities are evident on CT and MRI scans of the brain. Muscle biopsies are indistinguishable from those with othet mitochondrial myopathies as described earlier. Defects in complex I, III, IV, and V activities have been demonstrated in muscle specimens.

MELAS is inherited maternally in a non-Mcndelian pattern. The majority of cases are caused by an mtDNA mutation, .in A in *C,* substitution in the gene encoding tor $tRNA^{1""}$ at nucleotide position 3243. Mutations have also

been identified at other positions in the $tRNA^{Ltm}$ gene, as well as in the genes for $tRNA^{Val}$, $tRNA^{Cys}$, and ND.5 of complex 1 and in cytochrome *b* of complex III.

Mitochondrial Myopathies Associated with Recurrent Myoglobinuria

Mitochondrial myopathy may present as recurrent myoglobinuria beginning in infancy or early adult life. Laboratory and histopathological features are indistinguishable from those of other mitochondrial myopathies but serve to exclude more common causes of myoglobinuria, such as CPT deficiency, a glycogen storage disease, or a mild form of muscular dystrophy.

This is a genetically heterogeneous group of disorders. Multiple mtDNA deletions were demonstrated in two brothers with presumed autosomal recessive inheritance. In addition, point mutations in $tRNA^{pl,t}$ have been found in kinships with maternal inheritance of recurrent myoglobinuria, and micro deletions within the gene encoding for cytochrome oxidase III (COX III) have been reported in patients with sporadic disease. Other instances of exercise intolerance and recurrent myoglobinuria have been ascribed to mutations in the mtDNA genes encoding for subunit 4 of reduced nicotinamide adenosine dinucleotide (NADH) dehydrogenase (ND4) and cytochrome *b*.

Kear?is-Sayre Syndrome

KSS is characterized by the clinical triad of progressive external ophthalmoplegia (PEO), retinitis pigmentosa, and heart block with onset usually before age 20. Mild proximal weakness of the arms and legs may be apparent. KSS is also associated with other defects including short stature, sensorineural hearing loss, dementia, ataxia, depressed ventilatory drive, and multiple endocrinopathies.

The serum CK level is typically normal; however, lactate and pyruvate concentrations may be elevated. The CSF protein level is usually increased. The ECG reveals conduction defects. Muscle biopsy specimens demonstrate ragged-red fibers on Gomori-trichrome stain. The number of ragged-red fibers and COX-negative fibers correlate with the percentage of mitochondria with large deletions.

Single large mtDNA deletions of varying sizes (ranging from 1.3 to 8.8 kb) can be seen m most patients with KSS. mtDNA deletions may be present in leukocytes and other tissues, but the sensitivity is much lower than that seen in muscle. The large deletions usually involve several tRNA genes, thus impairing the adequate translation of rntDNA-encoded proteins.

Progressive External Ophthalmoplegia

Patients present with ptosis and ophthalmoparesis with or without limb weakness. Unlike in KSS, they typically do not have pigmentary retinopathy, cardiac conduction defects, or other systemic manifestations (e.g., endocrinopathies). Patients with PEO can develop hypoventilation in response to sedatives and anesthetic agents. Patients with mtDNA deletions often have dysphagia in addition to the extraocular weakness related to cricopharyngeal achalasia.

Serum CK, serum lactate, and CSF lactate concentrations can be normal or elevated. The CSF protein level may be increased. In contrast to classic KSS, the ECG does not demonstrate cardiac conduction defects. Muscle pathological changes are indistinguishable from those with KSS.

This is genetically a very heterogeneous disorder (Hirano and Di Mauro 2001). There are autosomal dominant and maternally inherited forms of PEO that are genetically distinguished from the sporadic subtype. Some patients with sporadic PEO have single large mtDNA deletions indistinguishable from those seen in KSS. This could represent a partial expression of KSS. Importantly, these deletions are felt to be sporadic in occurrence and not inheritable. Point mutations have been demonstrated within various mitochondrial tRNA (Leu, lie, Asn, and Trp) genes in several kinships with maternal inheritance of PEO. In addition, multiple mtDNA deletions have been described in a few kinships with autosomal dominant inheritance.

The molecular defects are suspected to lie in nuclear genes involved in regulating the mitochondrial genome. Autosomal dominant PEO appears to be genetically heterogeneous, because the disorder has been localized to mutations in the genes encoding for adenine nucleotide translocator 1 (ANTJ) on chromosome 4q34-q35, *Twinkle* on chromosome 10q23.3-q24.3, and *polymerase gamma* on chromosome 15q22-q26. ANT1 is responsible for transporting adenosine triphosphate across the inner mitochondrial membrane, whereas Twinkle and polymerase gamma are involved in mitochondrial DNA replication.

Mitochondrial DNA Depletion Syndrome

The severity of muscle weakness in this syndrome can vary. Fatal infantile myopathy is a severe early-onset form characterized by generalized hypotonia and weakness at birth. Weakness is progressive, leading to feeding difficulties, respiratory failure, and death usually within the first year of life. Some infants develop ptosis and ophthalmoplegia. A subclinical neuropathy is often is evident on examination. Deep tendon reflexes are diminished or absent.

There is also a benign form of infantile myopathy that early on can resemble the fatal form of myopathy. Generalized hypotonia and weakness and respiratory and feeding difficulties begin in infancy or early childhood. Although ventilatory assistance may be required, muscle strength often improves during the first year of life. Motor

milestones may be delayed but are usually attained, and occasionally children can appear normal by 2 or 3 years of age. Affected individuals can have a normal life expectancy, but some die in the first two decades of life.

Serum CK levels can be normal or elevated, as can the serum lactate level. The associated renal tubular defect results in glycosuria, proteinuria, and aminoaciduria. MRI of the brain may reveal cerebral atrophy and patchy areas of hypomyclination of subcortical white matter. Muscle biopsies demonstrate ragged-red fibers, foci of intense NADH and succinic dehydrogenase staining, and many COX-negative fibers. Biochemical assay of skeletal muscle tissue of affected patients shows that COX activity is greatly diminished or absent.

Inheritance of this disorder is autosomal recessive and is associated with a quantitative defect in mtDNA. Several different mutations of nuclear genes (e.g., thymidine kinase gene) important in regulation of the mitochondrial genome are felt to be responsible for mtDNA depiction (Saad et al. 2001). The severity of the depletion cot relates with the clinical severity of the disorder. As much as a *99%* reduction in mtDNA is present in the fatal infantile myopathy form of the disease, whereas the more benign myopathy has been demonstrated to have a smaller depletion (36-88%) of mtDNA.

Congenital Myopathies

Occasionally children exhibit a lack of tone at birth or shortly thereafter. In some children, this hypotonia is accompanied by obvious weakness of the limbs, and the baby lies immobile in the crib. Such children usually have one of the spinal muscular atrophies or a metabolic disorder (e.g., a mitochondrial myopathy), or, rarely, the cause may be a toxic substance (e.g., botulism). Other babies move the limbs, if not normally, at least through their full range of movement, and do so spontaneously. Determining muscle strength in a baby is difficult; however, when no obvious weakness is discernible, the babies are said to have congenital hypotonia. One of the most common causes of congenital hypotonia is damage to the CNS. As such children grow older, the hypotonia is often replaced by increased tone and an associated delay in intellectual development. This cerebral hypotonia is not due to any primary abnormality in the muscle but presumably accompanies .i disturbance ol roilc\ turn-. Selective atroph) of type 2 muscle fibers may be noted on biopsy, a change that is not indicative of a primary disease of the muscle but is secondary to the cerebral lesion.

Babies with benign congenital hypotonia do not show any neurological abnormality other than hypotonia. Tendon reflexes are preserved or slightly diminished. Results of muscle biopsy and electromyography are normal, and serum CK concentrations are appropriate to the child's age. As time progresses, the children gain tone, and normal motor development ensues. In teenage life, these children may not be star high school athletes, but, nevertheless, in general, their neuromuscular function is normal. The only treatment necessary in all these conditions is encouragement of the child to participate in play therapy, with the aim of increasing motor activity. A referral to an occupational therapist accomplishes this.

Central Core Disease

Centtal core disease was the first of the congenital nonprogressive myopathies to be described. The disease is inherited as an autosomal dominant trait, although sporadic cases occur. The faulty gene is on chromosome I9q13.1. The illness is associated with a mutation of the ryanodine receptor and is allelic to one form of hereditary malignant hyperthermia. Malignant hyperthermia and central core disease certainly coexist in some families; however, tin[1] association is not always clear.

The newborn with central core disease may be floppy and may have congenital hip dislocation. As the child grows older, motor milestones are delayed, and, at an age when children should be running easily, affected children are often ungainly and clumsy. The family soon recognizes that the weakness is not getting worse. Strength, although less than normal, usually is nor impaired enough to cause severe disability. As in other similar disorders, the child may be slender and short of stature. Examination reveals diffuse weakness of the limbs and mild facial and neck weakness. Deep tendon reflexes often are diminished but are sometimes normal. Skeletal abnormalities, such as pes cavus, a long face, and a high-arched palate, arc associated. For both central core disease and nemaline myopathy, a severe and disabling form may be seen with respiratory failure. The pathological changes in muscle do not appear to be any different, but the patient may be confined to a wheelchair, scarcely able to move the arms or legs, and have profound kyphoscoliosis. In this type of central core disease, surgical stabilization of the hack may be helpful, although the lack of respiratory reserve may prevent surgery.

The EMC shows nonspecific myopathic changes in central core disease. The scrum CK level is usually normal, although mild elevation may be seen. The muscle biopsy is diagnostic. On cross-section the muscle shows a combination of type 1 fiber predominance with central cores, an area in the muscle fiber where the central myofibrils are in disarray, and many of the oxidative histochemical reactions and the periodic acid-Schiff stain demonstrate an unstained central core (Figure 85.27).

No specific treatment for central core disease is available, although bracing may be needed to correct a deformity, such as a footdtop. Any family in whom central core disease has been found should be advised about the possibility of malignant hyperthermia because this is a potentially fatal complication,

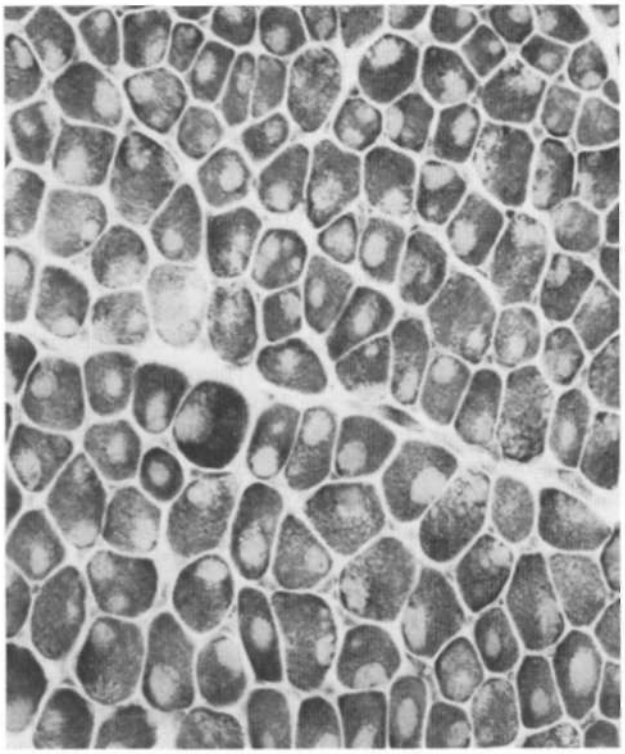


FIGURE 85.27 Central tore disease. The unstained area in most of the fibers is characteristic of this illness. (Nicotinamide adenine dinucleotide dchydrogenase-tetrazolium reductase stain.)

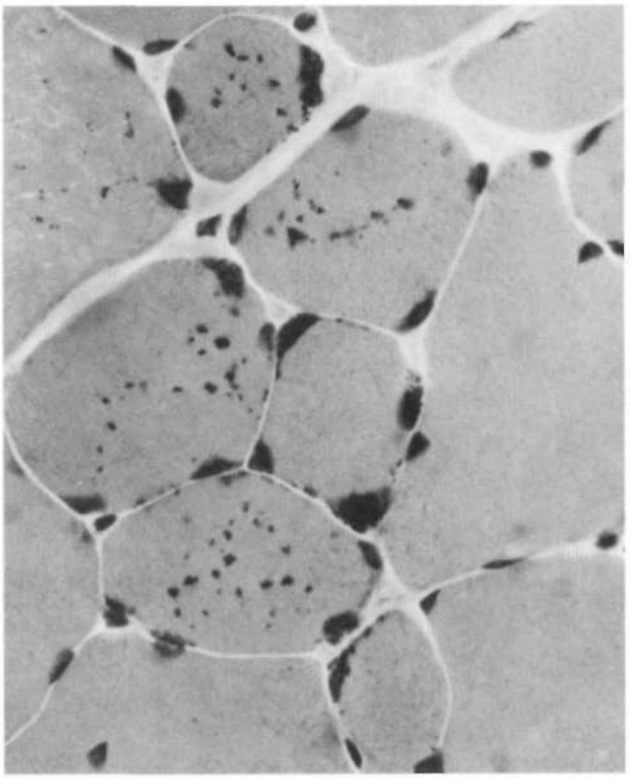


FIGURE 85.28 Nemaline myopathy. Although better demonstrated with the electron microscope, nemaline rods are also noted with histochemical reactions. The granular appearance of these fibers is due to the presence of many rods. (Modified Gomori trichrome stain.)

Nemaline Myopathy

The diagnosis of nemaline myopathy is based on the presence of small, todlike particles in the muscle fibers. They arc usually found with the modified trichrome stain (figure 85.28), hut they are most accurately characterized on electron microscopic examination. They originate in the Z-disc and exhibit structural continuity with the thin filaments. They have a regular structure, presenting as a tetragonal filamentous array when cut transversely and exhihiting periodic lines both perpendicular and parallel to the long axis. Major constituents of the rods include or-actin, desmin, and nebulin, proteins normally present in the Z line.

The disorder is genetically heterogeneic. Autosomal dominant nemaline myopathy has been linked to mutations in the gene for a-tropo myosin on chromosome Iq21-q23 (Laing et al. 1995) and for *fi*-tropomyosin on chromosome 9p13. Autosomal recessive nemaline myopathy has been associated with mutations in the genes that code for nebulin on chromosome 2q21.2-q22 and troponin T on chromosome 19q13 (Johnston er al. 2000). Both autosomal dominant and recessive occurrences have been described with mutations in cv-actin on chtomosome lq42.1.

The clinical picture of nemaline myopathy is heterogeneous (Ryan et al. 2001). The most common presentation is early hypotonia, followed by a diffuse weakness of the arms and legs, mild weakness of the face and othct bulbar muscles, and a dysmorphic appearance. The face is long and narrow, and the jaw may be either prognathous or abnormally short. The feet and palate are often high arched, and kyphoscoliosis is common as the children grow older. The disorder is considered nonprogressive, although some patients become weaker later in life. In some patients, respiratory failure out of proportion to the general weakness may ensue. Cardiomyopathy may be associated. A severe infantile variety is fatal. Such newborns have profound hypotonia and respiratory failure. Another form may have its onset in early adult life and present with a mild proximal weakness. No specific treatment fot nemaline myopathy is available. Bracing and surgery may be recommended when necessary.

In nemaline myopathy, the EMG demonstrates the nonspecific myopathic changes. Serum CK concentrations may be normal or elevated. The muscle biopsy specimen, in addition to demonstrating nemaline rods, often shows type 1 fiber predominance, selective atrophy of the type 1 fibers, and deficiency of type 2B fiber. Electron microscopic studies show the characteristic rods (Figure 85.29). These are seen most often in the cytoplasm, but intranuclear rods

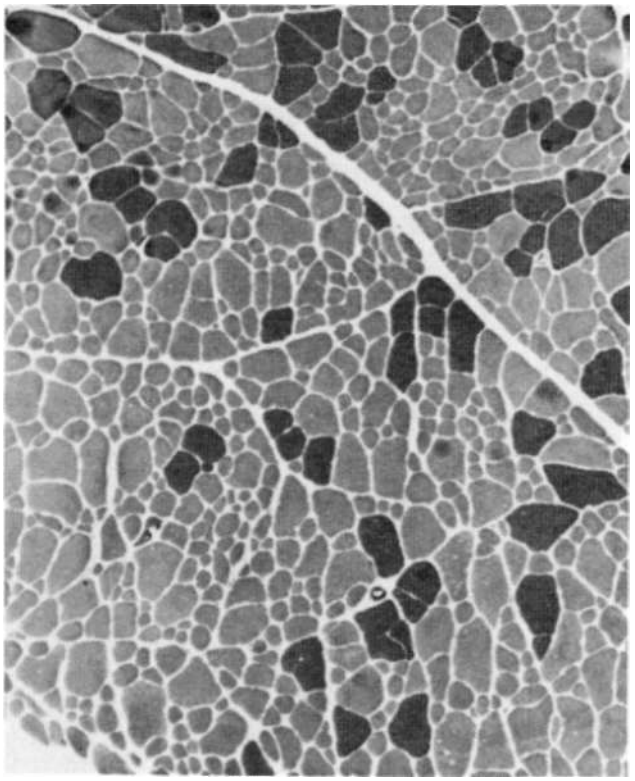


FIGURE 85.29 Nemaline myopathy. As in central tore disease, nemaline myopathy shows predominance and atrophy of type J fibers. Note that the very smallest fibers in this biopsy are all type 1. (Myosin adenosine triphosphatase stain, pH 9.4.)

also have been noted and are associated with the severe infantile form (Goebel and Warlo 1997),

Centronuclear or Myotubular Myopathy

The term *centronuclear* or *myotubular myopathy* (MTM) was used i" identify a group of diseases in whieh the pathological finding was the ptesence of fibers with central nuclei, which were thought to resemble the myotube stage in the development of muscle. The best known form is a severe infantile illness that is often fatal, the hallmarks of which are extraocular, facial, and limb weakness, often with respiratory failure. The gene locus has been identified to be the long ar:r. of the X chromosome ;;t Xi]_!iv i'lie sictie has been identified and is known as the *MTM1* gene. It encodes for myotuhularin, a protein with a tyrosine phosphatase domain (I.aporte et al. 1997). There appears to be another related gene on the X chromosome, *MTMR1,* and two other genes, *MTMR2* and *MTMR3,* on autosomes. Perhaps changes in the last two account for the occurrence of the autosomally inherited variety of illness, some of which are dominant and some recessive. The relationship between the gene product and the disease has not yet been elucidated. Mild and intermediate forms do exist. Large deletions of the gene have not been described, but missense and nonsense mutations and point deletions have been found in a number of families with X-linked disease,

The severe infantile variety of myotubular myopathy is inherited as an X-linked recessive disorder. It usually presents as severe hypotonia and respiratory distress. The disorder is usually fatal due to respiratory failure during the first few months. The weakness is severe and includes weakness of the facial and neck muscles as well as the extraocular muscles. Ptosis has not been as pronounced, but the eyes may appear puffy. The ribs are thin, and there are contractures at the hips and less often at the knees and ankles. Intermediate and milder forms of the illness are known. These vary among adults who have extraocular weakness, facial weakness, and mild difficulty with limb strength and adolescents who have more severe weakness and lose the ability to walk in early to middle adult life.

In the autosomal dominant form of myotubular myopathy, the illness is milder and occurs later in life. This form is less common than the severe X-linked form. Ptosis, extraocular weakness, and facial weakness are noted, and moderate limb weakness causes some disability, Equinovarus deformity of the feet has been noted. The autosomal recessive variety, which is also less common, seems to be intermediate in severity between the other varieties. Reports of electrical or clinical seizures were prominent in the early literature but have not been emphasized recently.

Laboratory studies show normal or slightly elevated serum CK levels. The EMG demonstrates marked muscle membrane instability in the torm ol fibrillation potentials, positive sharp waves, complex repetitive discharges, and occasionally even myotonic discharges. The only other congenital myopathy that usually has such prominent abnormal spontaneous and insertional activity on the EMG is myofibrillar myopathy.

The muscle biopsy has characteristic features. With routine hemaroxylin-eosin or tricbrome staining, variability in the size of fibers, most of which are small, is seen. In the center ot many of these fibers is a large, plump nucleus, resembling the myotube stage of muscle development. With the oxidative enzyme reaction, main ol the libers have a darkly staining central spot. Almost all the fibers have a palt siaining area, with tin ATPase reaction ihat runs through the middle of the fiber. Although this looks superficially like a core, most central cores are not visible with an ATPase stain. When viewed in longitudinal section, the fiber has a long central area containing nuclei interspaced with mitochondria-rich cytoplasm. Some features of the biopsy resemble those of other congenital disorders, with type 1 fiber predominance and often type 1 fiber atrophy. The biopsy findings in the X-linked recessive-illness appear similar. Although the muscle fibers superficially resemble myotubes, they arc in fact quite different, hence the preferred term *centronuclear myopathy.* The

differentiation into well-marked histochemical fiber types and the cytoarchitecture of the fiber more closely resemble those of the adult fiber. Two fetai cytoskeletal proteins (vimentin and desmin), which are found in fetal myotubes, have been demonstrated in fibers from patients with myotubular myopathy by immunocytochemical studies. The electroencephalogram has been reported on occasion to show a paroxysmal disturbance.

Treatment of the milder forms of myotubular myopathy includes respiratory support where indicated, treatment of any concurrent seizure disorder, and general supportive measures. Treatment of the severe infantile form must be considered in association with the very poor prognosis. The decision whether to provide life support for these children is a difficult one. Most die within the first 2 years.

Congenital Fiber-Type Disproportion

Affected children arc floppy at birth, with varying degrees of weakness. The weakness is diffuse, usually involving the face and neck. Sometimes in early childhood, there is an improvement in strength, although whether this represents a lessening of the disease or the child's natural growth is not certain. Conttactutes, particularly of the Achilles tendons, and congenital hip dislocation are commonly seen. Respiratory complications are common during the first 2 years of life, when the disease can be quite severe. As the children grow older, they remain weak and are short, with low weight. Accompanying the illness are various deformities of the feet, a high-arched palate, and kyphoscoliosis.

In congenital fiber-type disproportion, the EMG shows myopathic potentials but no evidence of muscle membrane instability (i.e., no fibrillation potentials or positive sharp waves). The serum CK level may be normal to slightly elevated. The muscle biopsy is diagnostic. The biopsy specimen in congenital fiber-type disproportion is characterized by a marked disproportion between the size of type 2 and type 1 fibers, with type 1 fiber atrophy and predominance. Originally, it was suggested that biopsy specimens in which the mean diameter of the type 1 fibers was 15% smaller than that of the type 2 fibers were indicative of the disorder. This assumption was a mistake, leading to the inclusion of patients with many different illnesses, such as CMD and FSHD. The diagnosis should only be made when the discrepancy between the type 1 and type 2 fibers is greater than 45% and when more than 75% of the fibers are type 1 (Figure 85.30). The reason for this discrepancy in fiber size is unknown.

The illness is inherited as an autosomal dominant trait in approximately 40% of reported cases. There is considerable debate in the literature on the specificity of this disorder, and many believe it to be a nonspecific biopsy finding. It is possible that this disorder represents nemaline myopathy without rods, a view that is strengthened by the fact that both rods and cores are inconsistently present in biopsy specimens from patients with both of these disorders. Only the appropriate DNA studies in the future will settle this question.

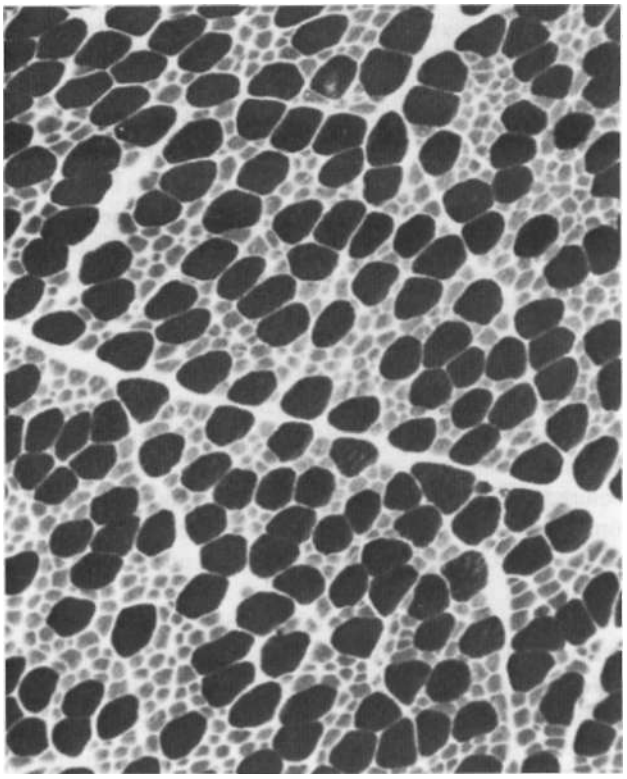


FIGURE 85.30 Congenital fiber-type disproportion. The diagnosis should not be made unless there is a clear discrepancy between hypertrophic type 2 fibers and atrophic type 1 fibers, as demonstrated in this picture. (Myosin adenosine triphosphatase stain, pH 9.4.)

Myofibrillar Myopathy

Myofibrillar myopathy (MFM) is characterized by the pathological finding of myofibrillar disruption on electron microscopic examination and excessive desmin accumulation in muscle fibers on immunostains (DeBleecker et al. 1996; Amato et al. 1998). Desmin is not the only protein that accumulates in this disorder; thus *myofibrillar myopathy* is the preferred term. This myopathy has been reported in the literature as desmin storage myopathy, desmin myopathy, familial desminopathy, spheroid body myopathy, cytoplasmic body myopathy, Mallory body myopathy, familial cardiomyopathy with subsarcolemmal vermiform deposits, myopathy with intrasarcoplasmic accumulation of dense granulofilamentous material, and hereditary IBM with early respiratory failure (Amato et al. 1998). In addition, some patients in whom other forms of distal myopathy were previously diagnosed

(e.g., Markesbery-Griggs-Udd distal myopathy) may actually have MFM.

A wide spectrum of clinical phenotypes exists {Amato et al. 1998). Most patients develop weakness between 25 and 45 years of age, but onset can occur in infancy or late .idnh life. Hither cardiac or skeletal muscles can be involved and dominate the clinical picture. Limb weakness can be predominantly distal and affect cither the arms or the legs. In other patients, proximal muscles are involved more than distal muscles. Facial and pharyngeal muscles can also be affected. Some patients have a facioscapulohumeral or scapuloperoneal distribution of weakness.

The cardiomyopathy may manifest as arrhythmias or conduction defects as well as congestive heart failure. Pacemaker insertion or cardiac transplantation may be required. Severe respiratory muscle weakness can also complicate MFM, In addition, there are rare reports of smooth muscle invohvmen! li'.uliiiy to intestinal pscudo obstruction.

The serum CK concentration is normal or only slightly increased. The ECG may demonstrate conduction defects or arrhythmia. An echocardiogram may reveal a dilated or hypertrophic cardiomyopathy. The EMG demonstrates markedly increased insertional and spontaneous activity with fibrillation potentials, positive sharp waves, and myotonic discharges. Motor units have myopathic morphological features and arc recruited early.

Muscle biopsies demonstrate variability in fiber size, increased central nuclei, and occasionally type 1 fiber predominance (Amato et al. 1998), Muscle fibers with rimmed vacuoles may also he evident. There are two major types of lesions seen on light and electron microscopic examination: hyaline structures and nonhyaline lesions. The hyaline structures are cytoplasmic granular inclusions that are typically eosinophilic on hematoxylin-eosiu stain and dark blue-green or occasionally red on modified-Gomori-trichrome stain. They appear as cytoplasmic bodies, spheroid bodies, or Mallory bodies on electron microscopic examination. The nonhyaline lesions appear as dark green areas of amorphous material on Gomori-trichromc stain. On electron microscopic examination, these nonhyaline lesions correspond to foci of myofibrillar destruction and consist of disrupted myofilaments, Z-disc-derived bodies, dappled dense structures of Z-disc origin, and streaming of the Z-disc.

Immunohistochemical examination reveals that both the hyaline and nonhyaline lesions contain desmin and numerous other proteins (Detileecker et al. 1996; Nakano et al. 1996). Immunohistochemical examination also reveals that the nonhyaline lesions react strongly for desmin, dystrophin, gelsohn, the N terminus of ^-amyloid precursor protein, and neural cell adhesion molecule (NCAM). However, the nonhyaline lesions arc depleted of actin, or-actinin, myosin, and less consistently of titin and nebulin. In contrast, the hyaline structures are composed of compacted and degraded remnants of thick and thin filaments and react to actin, a-actinin, and myosin in addition to dystrophin, gelsolin, and the N terminus of /^-amyloid precursor protein; they do not react to NCAM and react variably to desmin. Both types of lesions also react for *ciB*-crystallin, <*x-l* antichymotrypsin, and ubiquitin and can be congophilic. Interestingly, abnormal muscle fibers also abnormally express several cyclin-dependent kinases in the cytoplasm, including CDC2, CDK2, CDK4, and CDK7.

The pathogenesis of MFM is probably multifactorial, given the heterogeneous nature of the disorder. In most familial cases autosomal dominant inheritance is seen, although autosomal recessive or X-linkcd inheritance is possible in some families. Mutations in the desmin gene located on chromosome 2q.35 have been identified in several families with autosomal dominant myofibrillar myopathy as well as in a few occurrences of sporadic diseasi'. In addition, a homozygous or hemizygous mutation involving a 21-bp deletion in the first exon of the desmin gene was reported in a patient with presumed autosomal recessive inheritance of MFM. Mutations in the aB-crystallin gene on chromosome llq21-23 have been demonstrated in other patients. <*B-crystallin possesses molecular chaperone activity and is felt to interact with desmin in the assembly of the intermediate filament network. Some patients have no identifiable mutations in either the desmin or orB-cry stall in genes. The mechanism by which abnormal desmin or aB-crystallin leads to muscle cell destruction is not known.

Inflammatory Myopathies

Inflammatory eel hilar changes are sec: m tie muscle biopsies from patients with a wide range of myopathies and dystrophies. In many of these instances, the changes are presumed to be due to some other underlying disorder, hi the inflammatory myopathics, the basic disease is believed to be an abnormality of the immune system ot a direct infection of the muscle itself. Polymyositis and dermatomyositis are examples of abnormalities of the immune system, whereas the various forms of viral, bacterial, and parasitic infection of the muscle represent infections of the muscle. Pathological involvement of the muscle also may be seen in other autoimmune diseases, such as rheumatoid arthritis. Such involvement often is overshadowed by the primary condition.

Polymyositis and dermatomyositis, together with inclusion body myositis, represent the three most common inflammatory diseases seen by the clinician (Amato and Barohn 1997). Dermatomyositis and polymyositis both have an autoimmune basis, but the basic mechanism is very different. In dermatomyositis, the illness is the result of a humoral attack on the muscle capillaries, whereas in polymyositis the muscle fibers are under attack by cytotoxic T cells.

As in all autoimmune illnesses, the membrane-associated proteins, which are determined by the major

histocompatibility complex (MHC), play an important role. These molecules may act as antigens if they find theit way into an animal or human with a different characteristic type, In humans, the MHC system is equated with HLA typing. Class 1 antigens (HI.A-A, HLA-B, and HLA-C) are present on the membranes of virtually all ceils. Class 2 antigens (HLA-DR) are not so widespread and are limited predominantly to the lymphorcticular system, vascular endothelium, and some epithelia. For a cell to be the target of an attack from a cytotoxic T cell, the two cells must share the I II A class 1 molecule. The reactions in which CD4 cells participate require class 2 molecules to he shared. There is a predominance of B8 and DR3 antigens in patients with myositis. Although muscle normally expresses class 1 HLA molecules, class 2 expression may be induced under the influence of cytokines or other abnormal situations, T cells may be typed by means of a series of surface markers (CD markers) to determine whether they are cytotoxic, helper, inducer, and so forth. Because CD8 cells are involved in cytotoxic mechanisms, analysis of the type of cell involved in the cellular response is one way to determine whether the primary process is due re cellular or humoral factors.

Dermatomyos'ttis

Dermatomyositis is an illness in which weakness is associated with a characteristic skin rash. It is the common form of myositis occurting in childhood through middle adult life. The rash usually occurs with onset of muscle weakness, although it may develop during the course of the disease. It is characteristically a purplish discoloration of the skin over the cheeks and eyelids. It often has a butterfly distribution and blanches on pressure. Another area that may he affected is a V-shaped distribution on the chest below the neck. The rash may spread widely over the body and be associated with edema of the skin, which often becomes sealy and weeping. The skin over the elbows, knees, and knuckles is particularly prone to development of a reddened, indurated appearance (Gottron's sign and papules). Because the hallmark of the disease is the capillary abnormality, it may he helpful to use a hand lens to examine the skin around the nail beds. There small hemorrhages and looped, dilatated, and sometimes thrombosed capillaries often may be combined with avascular areas. The cuticle is discolored. In chronic, long-standing det ma tomyositis of childhood, the skin changes may be more disabling than the muscle weakness. In the terminal stage, the skin may be a shiny, fragile, shell-like covering that cracks at the slightest movement. Soft tissue calcification also is seen in some patients as die disease progresses; it usually occurs late in the illness and is not necessarily an indication of active disease,

The weakness is symmetrical and affects the proximal more than distal muscles of the arms and legs. Muscle pain is noted in one third of patients. The illness often follows a relapsing-remitting course, although occasionally it is clearly monophasic even to the point of recovering spontaneously without treatment.

Tissues other than muscle may also be involved, as mentioned later m the section on polymyositis, with lung, heart, and gastrointestinal findings being not uncommon.

Diagnosis, Serum CK concentrations are usually elevated in dermatomyositis but can be normal early or in patients whose disease has a very indolent course. Serum CK levels do not necessarily reflect activity of the disease. Thus one can see a clinical exacerbation unaccompanied by marked changes in serum CK concentrations in patients whose illness appears quiescent and who have a moderately elevated serum CK level. The CK concentrations may rise several weeks before a clinical relapse occurs.

The FMG demonstrates a combination of myopathic features together with indications of muscle hyperirritabiliry. Thus small polyphasic motor unit action potentials often are associated with increased insertional activity, fibrillation potentials, positive sharp waves, and complex repetitive discharges.

The characteristic histological feature of muscle biopsy specimens is perifascicular atrophy {a crust of small fibers surrounding a core of more normal-sized fibers deeper in the fascicle) (Figure 85.31). This feature is seen only in dennatomyositis and in overlap syndromes (see later).

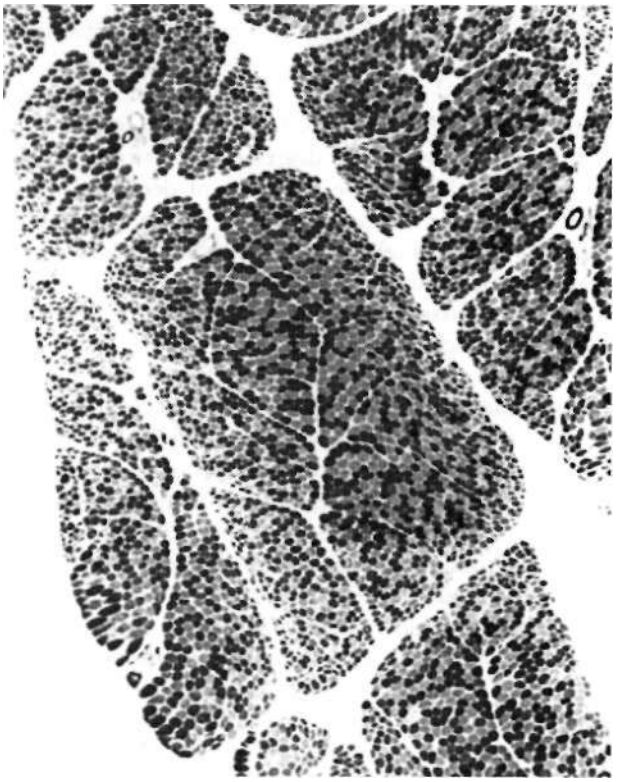


FIGURE 85,31 Dermatomyositis. Perifascicular atrophy. (Myosin adenosine triphosphatase stain, pH 9.4.)

In addition, many fibets arc undergoing changes of degeneration and necrosis that cause them to lose the staining characteristics with many of the enzyme reactions. Importantly, perifascicular atrophy is an uncommon finding (occurring in less than 10% of biopsies in the authots' experience), particularly in adults and in patients who underwent biopsy early in the course of their illness. Before perifascicular atrophy develops, the expression of the membrane attack complex and immunoglobulins is seen in capillaries and small blood vessels, and MHC class 1 exptession is seen on petifascicular muscle fibers. Inflammatory infiltrates can he scant if present at all. When present, the inflammatory cells are located around blood vessels (perivascular inflammation) and in the perimysial connective tissue father than in the endomysium (Plate 85.1). Further evidence for humoral rather than cytotoxic factors is found in the relative preponderance of B and CD4 (helper) cells rather than CDS (cytotoxic cells) in the inflammatory reaction associated with the blood vessels. With advancing disease, the capillaries arc destroyed and the muscle undergoes changes that resemble microinfarction. The fibers atound the edge of the fascicles ate particularly affected (perifascicular atrophy) because this area constitutes the watershed region in terms of blood supply. Unlike polymyositis and inclusion body myositis, endomysial inflammation with invasion of non-necrotic muscle fibers by macrophages is not seen in dermatomyositis. Electton microscopic examination reveals tubuloreticular inclusions in endothelial cells, another early histopathological abnormality that precedes perifascicular atrophy.

Unfortunately, many patients with dermatomyositis haveless definite changes. Scattered fiber necrosis and phagocytosis, associated with some degtcc of perivascular cuffing, should always lead to the suspicion of detmatomyositis. When the cellular responses are only associated with the muscle fibets themselves, the diagnosis is less certain because some fotms of muscular dysttophy and other illnesses are associated with inflammatory responses around the muscle fibers.

Blood tests also provide evidence of an altered immune state with the development of unusual antibodies. These fall into different categories, depending on the type of antigen. One set is ditected against the tRNA synthetases (anti-synthctases), and, of these, the Jo-1 antibody against histidyl tRNA synthetase seems to be particularly imporlant because ol us .issnei.un >n will', ntcrstuial lung disease. It is present in more than 20% of patients with dermatomyositis and is relatively specific to this disease group. A seties of antibodies specific to myositis have also been found. Of these, atiti-Mi-2 seems to be specific to dermatomyositis, but the low rate of its occurrence makes it only moderately useful as a diagnostic test. Test results for antinuclear antibody and rheumatoid factors may be positive, particularly when evidence of other collagen vascular diseases is noted.

Polymyositis

Polymyositis is an acute or subacute illness that occuts mainly in adults. Occurrences of polymyositis occurring in infants and children are most likely to represent muscular dystrophies with inflammation. Polymyositis is tare (with an incidence of less than 5-10 per 1,000,000 population) and is less common than dermatomyositis and inclusion body myositis. It is most common in the 40- to 60-year-old population and occurs slightly more often in women than in men, as do other autoimmune diseases. There is nothing very characteristic about the weakness. One would expect an inflammatory disorder of the muscle to cause severe pain, but this is not the case with polymyositis. Although there may be an aching, tender quality to the muscles in approximately one half of patients with polymyositis, the more severe the pain is, the less likely is the diagnosis of polymyositis. There are often systemic symptoms at onset, such as malaise, fever, and anorexia. Sometimes, the illness is preceded by a viral prodrome, but such events are common enough in the general population that the it association with the onset of polymyositis may be no more than coincidental.

The neuromuscular examination tevcals little that allows the clinician to make a specific diagnosis. The weakness is genetally diffusely proximal rather than the specific distribution seen in the muscular dystrophies. Usually when patients have severe proximal weakness {e.g., Medical Research Council grade 4 or less), a good examination will detect distal weakness as well in a patient with polymyositis. If a patient has severe proximal weakness in the absence of any distal weakness, an LGMD should be suspected. Fye muscles and bulbar muscles usually arc not involved, but dysphagia associated with altered pharyngeal and esophageal motility may be seen, particularly in the overlap syndromes, in which polymyositis is associated with other rhrum.uological diseases, such as scleroderma. Occasionally, the muscles may be sore to palpation and have a slightly nodular, grainy feel. Tendon reflexes generally are decreased or absent in established disease bin nay he increased early n the course ol the condition.

Muscle is not the only tissue involved in inflammatory myopathies. Vascular abnormalities, such as Raynaud's phenomenon, occur in the overlap syndromes. Catdiac involvement ranges from conduction defects ro congestive heart failure due to an inflammatoty cardiomyopathy. Interstitial pneumonitis and fibrosis may cause a nonproductive cough and respiratory distress. Chest radiographs show changes in the majority of patients with patchy consolidation, particularly subplcural, and peribronchovascular thickening. The changes arc reversible with treatment (Mino ct al. 1997). Gastric and esophageal emptying may also be delayed in the illness, indicating an abnormality in the smooth muscle of the upper gastrointestinal tract.

The natutal history of polymyositis and dermatomyositis is not well defined. Attempts have been made to

characterize these disorders, but there has been no clear agreement on what diagnostic criteria can be used. The situation is complicated by the fact that most clinicians believe that these myositides should be treated with corticosteroids or immunosuppression; therefore the course of the untreated illness will never be discovered. When the disease is relentlessly progressive, death usually occurs from inanition, intercurrent infection, or cardiac and respiratory failure, often complicated by the side effects of corticosteroid therapy. The course commonly relapses and remits, especially when the disease is treated with immunosuppressants or corticosteroids. It is difficult to determine the mortality rate of rhe illness; some studies have placed this at 15-30%, In a study of 69 patients the 5-year survival rate was 66%, which is not very reassuring (Maugars ct al. 1996). A substantial number of patients have profound disability even though the illness is "burned out." The morbidity and mortality associated with high-dose immunosuppressive therapy, particularly corticosteroids, have to be considered in the prognosis of the disease.

Diagnostic studies for polymyositis are similar to those for dermatomyositis and include scrum CK concentrations, serum antibodies, and an EMC with muscle biopsy as the mainstay. Serum CK concentrations may be markedly elevated during the course of the illness. Anti-Jo-1 antibodies are found in one fifth of patients.

Polymyositis is a cell-mediated disorder, the immune attack being directed against some unknown antigen(s) on the muscle fibers. The inflammatory cells are predominantly composed of T lymphocytes (more CDS than CD4) and macrophages. The cytotoxic T cells are seen to surround and invade non-necrotic muscle fibers (Plate 85.0). Pcrifascicular atrophy and deposition of immunoglobulin or complement on small blood vessels are not seen.

The major unsolved question is how the immune system becomes activated. Viral mechanisms have long been suspected of playing a part in polymyositis and dermatomyositis. Coxsackie B virus has been implicated in both animals and humans as a cause of an acute myositis, and indirect evidence of Coxsackie B infection is found in a number of patients with polymyositis or dermatomyositis. Coxsackie B is a member of the same class of virus as the encephalomyocarditis virus (KMCV), another virus causing myositis. These picornaviruses have a shell made up of several coat proteins. The sequence of amino acids in a region of one of these proteins is very similar to the sequence in an enzyme (histidyl tRNA synthetase, the antigen to the Jo-1 antibody) present in many patients with polymyositis and to sequences in the myosin light chain. The coat protein of EMCV demonstrates additional homology with the myosin heavy chain. The induction of polymyositis might be due to infection with one of the picornaviruses, such as Coxsackie B or EMCV, which might induce the formation of an antibody against these viruses. However, al! this remains speculative, and supporting evidence is lacking at present. Polymyositis is more common in patients infected with the human immunodeficiency virus, which may infect the muscle tissue, directly damaging the vascular endothelium and releasing cytokines. Cytokines may then induce abnormal MHC expression and render the muscle tissue susceptible to destruction.

Dermatomyositis and Polymyositis Associated with Other Collagen Vascular Diseases (Overlap Syndromes)

lupus erythematosus, mixed connective tissue disease, systemic sclerosis, rheumatoid arthritis, and Sjogren's syndrome all may have weakness as a facet of the disease complex. The overlap syndromes are those in which features of all these illnesses coexist with an inflammatory myopathy. 1 he cluneal, laboratory, and histological features are otherwise typical of dermatomyositis or polymyositis.

Polymyositis or Dermatomyositis Associated with Neoplasia. A relationship between malignancy and polymyositis and, more particularly, dermatomyositis, has long been suspected. At one time, it was believed that the incidence of neoplasia in patients with dermatomyositis was approximately 50%, but subsequent studies showed that the incidence was much less, probably in the neighborhood of 10-20% overall. In elderly patients, particularly those with dermatomyositis, the incidence of an associated neoplasm is higher, reaching 100% in some series. The type of neoplasm is usually a carcinoma. The breast, lung, ovary, and stomach have been commonly affected. The incidence of carcinoma may simply represent the normal incidence in the particular population of patients referred, but in some series, the incidence has exceeded by many times that seen in the control population. In practical terms, it is wise to carry out a rectal and vaginal examination and obtain a chest radiograph, mammogram, pelvic ultrasound or CT scan, hematological studies, and a test for occult blood in the stools in any patient with adult-onset polymyositis or dermatomyositis.

Treatment of Dermatomyositis and Polymyositis. There have been no good double-blind trials of corticosteroid treatment in the myositides. In the therapeutic trials that have been conducted, the critctia on which the diagnosis was made in the different studies were quite varied. Nevertheless, there is general agreement that polymyositis and dermatomyositis should be treated with corticosteroids or some other form of immunosuppression or a combination of these (Amato and Barohn 1997).

Daily administration of prednisone may be used in the early stages of the disease in doses of up to 1.5 mg/kg or with a usual maximum of 100 mg. After 2-4 weeks the prednisone regimen can usually be switched to alternate day therapy (e.g., 100 mg every other day). In extremely weak patients or those with systemic involvement, a slower taper by 10 mg per week to an alternate day regimen (i.e., taking 10 weeks to taper to a dose of 100 mg every other

day) is recommended. When significant improvement has occurred, the prednisone dose can then be decreased by 5 mg every 2-3 weeks. Once the patient's dose is reduced to 20 mg every other day, further reduction continues in steps of 2.5 mg. If symptoms recur, it may be necessary to return to a higher dose of prednisone. If rhere is no response after 8-12 weeks, the clinician should seriously consider some oilier form nl treatment. The development ol significant side effects may influence use of this regimen. Side effects may be minimized in some patients by careful attention to diet and consumption of a high-potassium diet, salt restriction, use of Hi-receptor blockers, and use of adjunctive calcium.

A recent development is the use of high-dose intravenous pooled human immunoglobulin (IVIG) (2 g/kg per day over 2-5 days). In a controlled, double-blind trial of IVIG, patients with dermatomyositis showed improvement in functional ability and strength. IVIG was administered every month, with a total dose of 2 g/kg spread over a period of 2 days. The improvement was noted by the second or third treatment in most patients. Whether the improvement will be sustained over years is uncertain, The treatment itself poses some hazard and is extremely expensive. Thrombotic events may be seen in some patients. Common complications include vasomotor symptoms, headache, rash, leukopenia, and fever. Almost one half of patients have some minor adverse event. In our experience, IVIG is not very effective in polymyositis.

Most neurologists use azathioprine as their second-line agent of choice. Unfortunately, it often takes 9 months or longer to see an effect from azathioprine. It is tolerated easily by most patients in otal doses of 1.5-2.0 mg/kg per day. Before treatment is begun, a baseline complete blood count, platelet count, and livet function studies are obtained. Therapy often is initiated with a low dose (e.g., 50 mg per day in an adult). The dose then is increased gradually with monitoring of the blood studies. With an effective dose (usually 2.0-3.0 mg/kg), the white blood cell count may be reduced to around 4000, and the total lymphocyte count to approximately 750 cells/mL. An abnormal decrease in platelets to less than 150,000/ml. or a total neutrophil count of less than 1000/mL is an indication for reducing the dosage or stopping the drug temporarily. Blood studies should be obtained twice a week at first. After a stable dose has been attained, blood studies can be obtained weekly and then monthly. Liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT|, and y-glutamy I transferase [GGT|) should be performed monthly at the beginning of treatment. It is important to monitor the GGT concentration because it is specific for the liver, whereas AST and ALT concentrations can be elevated due to the underlying muscle disease. An idiosyncratic response to azathioprine is seen in some patients. This consists of severe gastrointestinal distress, with nausea and vomiting associated with fever and some elevation of the liver function test values. The response disappears when the drug is withdrawn. If it is not certain that such an episode is due to azathioprine, a test dose of 25 mg can be given, which usually causes the symptoms to recur within 1 hour or so. There are advantages to combining prednisone and azathioprine therapy because a lower dose of both drugs may be used in the combination than when each is used alone.

We prefer methotrexate as the second-line agent of choice rathet than azathioprine because it appears to wotk much faster (e.g., within 2-3 months). Methotrexate is usually administered orally at a dose of 7.5 mg per week and gradually increased as necessary up to 20 mg per week. If higher doses (up to 35 mg per week) are required, we .uln. . . .stei methotrexate intramuscularly or intravenously. Patients should be given folate at the same time.

Methotrexate can cause interstitial pulmonary fibrosis. For this reason, it is important to obtain measurements of anti-Jo-1 antibodies and pulmonary function tests for patients with inflammatory myopathies because of the associated risk nl M:\TS1III.I1 lur.;; dise • -•• \\ U;i myositis. We would avoid methotrexate in patients with interstitial lung disease. Methotrexate is also associated with hepatotoxicity and bone marrow suppression. As with azathioprine it is important to monitor results of complete blood counts and liver function tests in patients receiving methotrexate. Cyclophosphamide and mycophcnolate are also used.

Inclusion Body Myositis

This is the most common myopathy in patients older than 50 years of age and only rarely does it occur in anyone younger than 50. Unlike dermatomyositis, polymyositis, and other autoimmune disorders, inclusion body myositis is much more common in men than in women. The disease weakens the distal muscles of the arms and legs. The deep finger flexors (particularly of the ulnar two fingers), including the flexor pollicis longus and wrist flexors, are affected quite early and are almost always more involved than the wrist and finger extensors (Amato et al. 1996). In the legs there is early involvement of the quadriceps and anterior tibial muscles. Profound atrophy can be seen in the flexor forearms and quadriceps. Muscle atrophy and weakness arc often asymmetrical and may lead to an erroneous diagnosis of motor neuron disease (Dabby et al. 2001). However, unlike amyotrophic lateral sclerosis, there is no significant atrophy of the hand intrinsic muscles, fasciculations are absent, and deep tendon reflexes are normal or red need. The progression is gradual but relentless, and disability may be severe. Facial weakness and dysphagia may be found in approximately one third of patients. Muscle vvutis are absent. Sometimes the sporadic form occurs in a familial setting (Sivakumar et al. 1997; Amato and Shebert 1998). Thete are extremely rare cases of familial inclusion body myositis that should not be confused with hereditary inclusion body myopathies.

The disease generally has a chronic progressive course and is relatively unresponsive to prednisone and other immunosuppressive (e.g., methotrexate) and immunomodulating (e.g., IVIG) therapies (Griggs et al. 1995). Indeed, this is one of the criteria by which the diagnosis may be suspected. It is tempting to embark on a therapeutic trial when the inflammatory reaction is marked, hut the side effects of cotticosteroids and other immunosuppressive/ immunomodulating therapies in the elderly population are not to be taken lightly, particularly in the absence of any objective improvement with these agents in several double-blind, placebo-controlled trials.

The diagnosis of IBM should he suspected on the basis of the clinical history and examination and can usually be confirmed by muscle biopsy. The serum CK concentration may be normal or only mildly elevated (<10 times upper limit of normal). The EMG demonstrates fibrillation potentials and positive sharp waves. There is a mixture of small and large polyphasic motor unit potentials. These large motor units may represent a neurogenic process or remodeling of the motor unit that can be seen in a chronic myopathy

The muscle biopsy demonstrates endomysial inflammation, increased variation in fiber si/e with fiber hypertrophy, and macrophage invasion of non-necrotic muscle fibers similar to those seen in polymyositis. In addition, characteristic "rimmed" vacuoles may be profuse. On light microscopic examination, the structures have a sharply-demarcated vacuole, around which is a rim of altered tissue that stains red with trichrome stain and bluish-purple with hematoxylin-eosin (Plate 85.III). There are also inclusion bodies and eosinophilic inclusions in the nuclei and sometimes also in the cytoplasm adjacent to nuclei. Amyloid deposits arc seen in the vacuolated muscle fibers with Congo red and other stains (Plate 85,1V). Klectron microscopic examination demonstrates the presence of cytoplasmic and nuclear tubulofilamentous structures. The filaments are paired and twisted together and often are stacked in parallel arrays. They are 15-21 nm in diameter, with an inner diameter of 3–6 nm. There may also be orher paired helical filaments that are 6-10 nm thick. The paired helical filaments may now be detected with light microscopy using a commercial antibody (Askanas el al. $l^{l}J$"(.).

Unfortunately, because of sampling error the biopsy is not definitively diagnostic 20-30% of the time. When the muscle shows only a cellular reaction, the diagnosis may be considered if the clinical picture is typical (Griggs ct al. 1995; Amato et al. 1996). The absence of rimmed vacuole inclusions can lead to the misdiagnosis of polymyositis if the clinician is not attuned to the distinct differences in the clinical pattern of muscle weakness seen in inclusion body myositis and polymyositis.

Besides the presence of amyloid in vacuolated muscle fibers, there are also curious similarities to the changes seen in the brain in Alzheimer's disease. Investigation of the muscle using antibodies or probes against several proteins (including ^-amyloid, amyloid precutsor protein, prion protein, ubiquitin, o^{r}-antichymotrypsin, neuronal microtubule-associated protein, and *r)* has shown all of these to be associated with the vacuoles. Ubiquitin and a hyperphosphorylatcd form of T decorate the larger filaments, whereas /^-amyloid is in the smaller paired helical filaments and associated with more amorphous structures. The possibility that inclusion body myositis is also a disease with an abnormality in protein processing has been considered. An interesting and unexplained finding is that there is a protein in the muscle that binds single-stranded DNA and localizes to the nucleus and the vacuoles.

An increased number of deletions of mitochondrial DNA have also been found in patients with inclusion body myositis compared with normal age-matched control subjects. This is probably reflected in the increased number of cytochrome oxidase-ncgative fibers and ragged-red fibers noted on the muscle biopsy. The findings do not cast any light on the etiology of the illness, which shares no clinical features with the mitochondrial disorders (Moslemi et al. 1997).

Despite the fact that the histological hallmark of the disease is the inclusion body, the most abundant change in the biopsy from inclusion body myositis is the invasion of muscle fibers by $CD8^{+}$ cytotoxic cells, suggesting a cell-mediated cytotoxicity with an immune basis. This is reinforced by the presence of the necessary MHC class I antigens on the invaded muscle fibers. On the other hand, a study of patients treated with prednisone showed that although the cellular reaction was lessened, the patient's condition worsened along with the vacuolar changes, suggesting that the cellular response might be secondary (Barohn et al. 1995). Direct transfer of the /i-amyloid protein precursor gene into cultured muscle cells reproduced some of the changes seen in inclusion body myositis.

Other Inflammatory Conditions

Muscle often shows subclinical involvement in chronic granulomatous diseases, such as sarcoidosis and tuberculosis. Bacterial infection (pyomyositis) is rare outside of tropical countries, although it has been recorded. The organism involved is often *Staphylococcus aureus,* and sometimes *Streptococcus,* Usually, the large muscle groups, such as those of the thigh, are the sites of infection. The muscle is hot, painful, and swollen, and any movement exacerbates pain. Parasitic infections of muscles include those due to trichinosis, cysticercosis, and toxoplasmosis. In trichinosis, general symptoms of malaise and fever are associated with muscle pains and stiffness. There may be periorbital edema, and the jaw muscles commonly are involved. Laboratory studies include muscle biopsy, which may show evidence of hypersensitivity, such as eosinophilia and hypergammaglobulinemia. Treatment with thiobendazole has been recommended. Myopathies associated with

the retroviruses, such as human immunodeficiency virus, are discussed elsewhere {see Chapter 59E).

Polymyalgia Rheumatica

Polymyalgia rheumatica is an illness characterized by severe muscle pain. The clinician should be cautious about the indiscriminate use of this diagnosis without full investigation because of two major implications: the high incidence of temporal arteritis and the effectiveness of corticosteroid therapy. The diagnosis should be limited to those with the typical picture, including an increased erythrocyte sedimentation rate, and not used as an explanation for various aches, cramps, and pains. Women arc affected more commonly than are men, and the disorder is rare in patients younger than 55 years. The patient develops muscle stiffness and pain and a feeling that the **muscles** have "set." The arms are involved more commonly than the legs. Manipulation of the limb exacerbates the pain. The symptoms are particularly prominent in the morning when the patient arises and lessen as the patient loosens up. These symptoms may be associated with chronic malaise, pyrexia, **night** sweats, and weight loss. On examination, there are no specific muscle abnormalities other than soreness. There may be tenderness over the temples, reflecting temporal arteritis. The incidence of biopsy-positive temporal arteritis is about 20-30%.

The erythrocyte sedimentation rate is elevated (often more than 70 mm per hour), and this should be considered an essential part of the diagnosis of polymyalgia rheumatica. There may be a mild hypochromic anemia. Otherwise, results of laboratory studies arc generally normal. There is no elevation of the serum CK concentration, the EMG may be normal, and the muscle biopsy specimen may show type 2 fiber atrophy, a nonspecific finding that is not helpful in the diagnosis.

Polymyalgia rheumatica may be self-limiting but may take years to resolve. For this reason, prednisone and the nonsteroidal ami-inflammatory drugs have been recommended as a treatment. The response to prednisone may be quite dramatic, with resolution of symptoms in hours to days. For the most part, the doses can be lower than those used in other inflammatory autoimmune diseases. It is possible to commence with 30-50 mg of prednisone daily in an adult and maintain this dose for 2 months before a gradual decrease. Maintenance with a low dose of corticosteroids is often necessary for 2 years, and even then, only 24% of the patients were able to stop treatment in one prospective study.

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Chapter 86
Neurological Problems of the Newborn

Alan Hi

Increased survival of premature newborns as a result of improved obstetrical care and especially of the treatment of neonatal respiratory disease has focused attention on the morbidity and mortality resulting from neurological complications. Rational management of neurological problems in newborns must be based on sound principles of basic science, human and experimental pathological conditions, and phyMoJot'K..il and Imiuiciiik.il mechanisms.

Advances in fetal assessment, especially the use of real-time ultrasound (US) scanning, have increased awareness of the prenatal origin of many neurological abnormalities detected in the newborn. In many instances, methods of fetal assessment allow a limited neurological examination of the fetus. Intrauterine intervention for prevention of brain injury may be considered the primary objective for optimal management of neurological disorders that manifest in the newborn. Optimal management demands expertise from many disciplines, including obstetrics, neonatology, genetics, neurology, and neurosurgery. A cooperative team effort often is the most effective approach to neurological problems in neonates, especially when difficult ethical decisions are involved.

In this chapter, the practical aspects of diagnosis and management of relatively common neurological problems of the newborn encountered by practicing neurologists are reviewed.

GENERAL PRINCIPLES Of INVESTIGATION AND MANAGEMENT

The importance of a detailed history and neurological examination for the assessment of the newborn with neurological problems cannot be overemphasized. Although the genetal framework of the neurological examination used in older children is applicable ro the newborn, observations must be interpreted on the basis of known maturational changes at different gesrational ages. The ev.imin.it ion •dion'J not he prolonged unnecessarilj, especially in premature infants, because even routine handling may contribute to hypoxemia, hypertension, and h\ pott usion.

Neurological examination is often limited by associated systemic illness and the use of complex life support systems, especially in premature infants. Therefore, considerable attention has been focused on determining the role of adjunctive noninvasive neurodiagnostic techniques for the assessment of neurological injury at varying gestational ages. At the present time, most neurodiagnostic

investigations performed in older children and adults also have clinical applications in newborns.

NEONATAL SEIZURES

Seizures in newborns are rarely idiopathic and may be considered to be the most common feature of significant neurological disease in the newborn. Prompt recognition is essential because seizures are often caused by serious underlying diseases that require treatment and because they may interfere with supportive care, such as ventilation and feeding. Experimental studies have shown a decrease in brain glucose concentration during prolonged seizures, an increase in brain lactate concentration, and excessive release of excitatory amino acids, which may interfere with DNA synthesis and subsequently with glial proliferation, differentiation, and myelination (Holmes et al. 1999). Although the implications of these experiments for the human newborn are not entirely clear, their relevance is suggested by in vivo studies with magnetic resonance spectroscopy, which have demonstrated an association between abnormally low phosphocreatine to inorganic phosphate ratios during seizures and long-term neurological sequelae.

Diagnosis

Table 86.1 summarizes the common types of neonatal seizures. These seizure types are not specific for cause, but some are seen more often with certain underlying conditions. Tonic seizures, which may represent decerebrate posturing, occur in up to 50% of prcmatute newborns with severe intraventricular hemorrhage (IVH). Focal clonic seizures in the term newborn are most commonly associated with focal cerebral infarction or traumatic injury, such as cerebral contusion (Mizrahi and Kellaway 1998).

Differentiation of Seizures from Nonconvulsive Movements

Simultaneous monitoring with an electroencephalogram (EEG) and video display in newborns with movements suggestive of "subtle seizures" have not shown consistent electrographic discharges concomitant with the movement. This suggests that the abnormal movements may be nonictal brainstem release phenomena rather than seizures. Similarly, tonic extensor posturing in newborns with severe IVH is not usually accompanied by epileptiform discharges and responds poorly to anticonvulsant therapy. Myoclonic seizures, which may evolve inro infantile spasms, often have a dismal outcome and must be distinguished from benign neonatal sleep myoclonus, which occurs in healthy newborns.

Jirteriness, an exaggerated startle response, is often confused with clonic seizures, especially because **both** jitteriness and clonic seizures occur in conditions such as hypoxic-ischemic or metabolic encephalopathies and in drug withdrawal. Jitteriness is distinguished clinically from seizures by the absence of associated ocular movements and the presence of stimulus sensitivity; the predominant movement is tremor that stops when the affected limb is passively flexed.

Determination of the Underlying Cause

Diagnosis of the underlying cause allows specific treatment and a more precise prediction of outcome. Table 86.2 summarizes the major causes of neonatal seizures, their usual times of onset, and prognosis. Seizures are often caused by several factors (e.g., the combination of intracranial hemorrhage, metabolic derangement, and hypoxic-ischemic injury). Benign genetic epilepsies rarely have their onset in the neonatal period; the only example is benign familial neonatal epilepsy, an autosomal dominant trait for which two separate chromosomal loci have been

Table 86.1; Types of neonatal seizures

Neonatal seizure types	*Clinical manifestations*	*Age distribution*
Subtle	Eye deviation, blinking, fixed stare Repetitive mouth and tongue movements Apnea Pedaling, tonic posturing of limbs	Premature and term
Tonic: focal or generalized	Tonic extension of limbs Tonic flexion of upper limbs, extension of legs	Primarily premature
["lonic: multifocal or focal	Multifocal, clonic, synchronous, or asynchronous limb movements Nonordered progression Localized clonic limb movements Consciousness often preserved	Primarily term
Myoclonic: focal, multifocal, or generalized	Single or several synchronous flexion jerks of upper more than lower limbs	Rare

Table 86,2: Vlajor causes of neonatal seizures: clinical features and outcome

(*dllic*	*age at onset*	*Ri-Lilir:- incidvmv* i'lniuiiiir	*Ri-Lilir:- incidvmv* Fidl-term	*Outcome ("/<> of norma! development)*
Hypoxic-ischemic encephal opathy	<3 days	+++	+++	50
Intracranial hemorrhage				
Intraventricular hemorrl age	<3 davs	++		<10
Primary subarachnoid h •mori huge	< 1 day			90
) lypoglycemia	<2 days	+		50
Hypocalcemia				
Early-onset	13 davs	I	+	50
Late-onset	>7 days		-	I !0
Intracranial infection				
Bacterial meningitis	>3 days	++		50
Intrauterine viral	>?> days	++	++	<10
Developmental defects	Variable	++	++	0
Drug withdrawal	<3 days	+	...	Unknown

Note: +++ = most common; ++ = less common; -I-= least common,
Source: Reprinted with permission from Volpe, J. J. 2000, *Neurology of the Newborn,* 4th ed,, WB Saunders, Philadelphia.

identified on chromosome 20, which encodes for a potassium channel, and on chromosome 8 (Lerche et al. 1999).

Electroencephalography

Electroencephalography, particularly continuous monitoring of an EEG (when available), is a valuable aid in the diagnosis of neonatal seizures, especially in newborns who are paralyzed to assist ventilation and in those with suspected subtle seizures. EEG correlates of neonatal seizures are focal or multifocal spikes or sharp waves and focal monorhythmic discharges. Sharp transients arc normal in premature newborns and should not be confused with seizure activity. Similarly, the trace alternant pattern of quiet sleep in normal term infants, in which normal low-amplitude reactivity is preserved between bursts, must be distinguished from the abnormal burst-suppression pattern, in which long periods of voltage suppression or absence of activity are recorded between bursts of high-voltage spikes and slow waves (Biagioni et al. 1998).

The interictal EEG may have prognostic value. Severe suppression of the background activity, whether or not interrupted by high-amplitude bursts, is associated with an abnormal outcome in more than 90% of patients. In contrast, normal background activity is associated with good outcome.

Management

Neonatal seizures require iirgem Itvaimcni. Once adequate ventilation and perfusion are established, the blood glucose concentration is measured. If the glucose concentration is low, 10% dextrose should be administered in a dose of 2 ml/kg. In the absence of hypoglycemia, immediate treatment with anticonvulsant medications should be started, as outlined in Table 86.3. Studies for other underlying causes should proceed concurrently, and specific treatment should be initiated whenever possible.

Phenobarbital alone controls seizures in most newborns when adequate dosages are administered (up to a maximum of 40 mg/kg loading dose). Phenytoin 20 mg/kg is given if seizures continue (Painter et al. 1999). Fosphcnytoin, which is converted to phenytoin, has not been evaluated extensively in newborns, but initial data suggest that the rate of conversion is identical to that shown for older infants. Thus fosphcnytoin appears to have significant advantages over phenytoin and would be considered preferable to use (Takeoka et al. 1998). Seizures usually respond to intravenous loading doses of phenobarbital and phenytoin. When these drugs fail, other anticonvulsants (diazepam, lorazepam, and primidone) may be effective, but they are not recommended as first-hue drugs.

Phenobarbital may suppress seizures caused by hypocalcemia, and a favorable response does not exclude that diagnosis. Approximately 50% of newborns with hypocalcemia also have hypomagnesemia, which requires specific treatment.

I'yridoxinc deficiency is ,; rare causi ol neonatal seizures and should be considered whenever no other cause is determined. Most infants have an unusual paroxysmal pattern on an EEG with generalized bursts of synchronous high-voltage activity of 1^4 Hz intermixed spikes and sharp waves. The diagnosis of pyridoxine deficiency cannot be excluded on the basis of lack of response to a single latge dose of intravenous pytidoxine with concurrent LEG

Table 86.3: Treatment of neonatal seizures

I. Ensure adequate ventilation and perfusion		
II. Kcgin therapy for specific metabolic disturbances (if present)		
	Acute therapy	Maintenance therapy
Hypoglycemia: glucose {10% solution)	2 m1Ag IV (0.2 g/kg)	Up to 8 mg/kg/min IV
Hypocalcemia: calcium gluconate (5% solution)	4 mL/kg IV (Note: monitor cardiac rhythm)	500 mg/kg/24 hr PO
Hypomagnesemia: magnesium sulfate (50% solution)	0.2 ml/kg IM	0.2 mi/kg/24 hr IM
Pyridoxine deficiency: pyridoxine	50-100 mg IV	100 mgPO daily for 2 wk
III. Begin anticonvulsant therapy		
	Acute therapy	Maintenance therapy (begin 12 hr after loading dose)
Phenoharbital	20 mg/kg IV if necessary, additional 5-25 mg/kg IV in 5 mg/kg aliquots (Note: monitor blood pressure and respiration)	4-6 mg/kg/24 hr 1V/IM/PO
Phenytoin"	2 doses of 10 mg/kg IV, diluted in normal saline (Note: monitor cardiac rate and rhythm)	5-10 mg/kg/24 hr IV
Lorazepam	0.05-0.10 mg/kg IV	

* bos phenytoin may be the preferred form of phenytoin.
IV=intravenous; IM= intramuscular; PO= orally.

recording; rather, large doses (50-100 mg daily) should be given orally for several days.

Duration of Treatment and Outcome

The optimal duration of maintenance therapy for neonatal seizures has not been established. The duration of maintenance treatment for neonatal seizures depends on the risk of recurrence, the underlying cause (see Table 86,3), the neurological examination, and the EEC Phenytoin is usually discontinued when intravenous therapy is stopped, because adequate serum levels are difficult to maintain with oral phenytoin in the newborn. If seizures have stopped and the neurological examination and EEG are normal, phenoharbital may be discontinued before discharge from the hospital. If phenoharbital is continued after discharge, discontinuation should be considered as early as 1 month later based on the neurological status and EEG. Phenoharbital may be discontinued in an infant whose examination is not normal if the EEG does not show epileptiform activity. Concern has been raised about the potential deleterious effects of phenoharbital on brain development, and it is recommended that infants be treated with phenoharbital for the briefest possible time.

HYPOXIC-ISCHEMIC BRAIN INJURY IN THE TERM NEWBORN

Hypoxic-ischemic encephalopathy results from reduced oxygen delivery to the brain and from the excessive ncci:-inilariiin ot nn-rahi iu-v -ndi .-. lactate, free radicals, and excitotoxic amino acids. It is a major cause of morbidity and mortality in both premature and term infants. Hypoxic-ischemic cerebral injury in the premature newborn is discussed subsequently, together with IVH (see Hemorrhagic and Hypoxic-Ischemic Brain Injury in the Ptemature Newborn, later in this chapter). In this section, only hypoxic-ischemic injury in the tctm newborn is discussed. The pathophysiological and biochemical mechanisms that provide a rational approach to the diagnosis and management of neonatal hypoxic-ischemic encephalopathy are reviewed in Chapter 61. Because most hypoxic-ischemic brain injury in term infants occuts antepartum and intrapartum, prevention depends principally on optimal obstettical management, Advances in fetal heart rate monitoring, assessment of fetal movements, and the use of biophysical ptofile and scalp blood gases are helping to reduce the incidence and severity of acute hypoxic-ischemic encephalopathy.

Diagnosis

Because asphyxia is mainly an intrauterine event, a history of matetnal risk factors and abnormalities of labot and delivery must be documented carefully. An accurate history also may provide more precise information about the type of insult, which in turn may suggest a specific pattern of brain injury. The clinical features of hypoxic-ischemic encephalopathy arc determined by the severity, duration, and timing of the insult. Acute total asphyxia may cause disproportionate injury to tbalami, basal ganglia, and brainstem nuclei, whereas prolonged partial asphyxia causes injur) principal!) to cerebral coriev ami >.ii1v<>nic;i! white matter (Roland et al. 1998).

Table 86.4: Neuropathologies] patterns of neonatal hypoxic-ischemic brain injury and clinical correlation

Pattern of injury	*Neuropathoiogical injury*	*Clinical features in neonatal period*
vliviivi-]K-LI><:LI1 IUVUKK	Cerebral and cerebellar cortex thalamus, brainstem nuclei	Premature and term: coma, seizures, hypotonia, oculomotor abnormalities, abnormal sucking, swallowing
M.iiir, njannonitus	Thalamus, basal ganglia	Term > premature: unknown
Parasagittal	Cerebral cortex, subcortical white matter in parasagittal regions	Term: proximal limb weakness, upper > lower
Periventricular leukomalacia	Periventricular white matter	Premature: unknown (probably lower limb weakness)
Foe a l/mu I ti focal	Unilateral or bilarcral cerebral cortex and subcortical white matter	Premature and term: variable hemiparesis/ quadriparesis, stereotyped, nonhabituating reflex responses

The initial features of severe asphyxia are depressed level of consciousness, periodic breathing (due lo bihu-r.il hemisphere dysfunction}, hypotonia, and seizures. An apparent increase in alertness may occur between 12 and 24 hours, but seizures worsen and apnea may be noted. Between 24 and 72 hours of age, the level of consciousness deteriorates and brainstem abnormalities may become prominent. This timing corresponds to the development of maximum intracranial pressure. Specific patterns of weakness related to the distribution of neuronal injury may become evident (Table 86.4). After 72 hours, infants who survive show continued (although diminishing) stupor, abnormal tone, and brainstem dysfunction with disturbances of sucking and swallowing. The temporal profile of clinical features of severe hypoxic-ischemic encephalopathy in the term newborn are summatized in Table 86.5.

The classification of hypoxic-ischemic encephalopathy into mild, moderate, and severe is useful for prediction of outcome. Mild encephalopathy is characterized by increased irritability, exaggerated Moro and tendon reflexes, and sympathetic overreactivity. Recovery is usually complete within 2 days, and there are no long-term sequelae. Moderate encephalopathy with lethargy, hypotonia, diminished reflexes, and seizures is associated with a 20—40% risk of abnormal outcome. Infants with severe encephalopathy with coma, flaccid muscle tone, brainstem and autonomic dysfunction, seizures, and possible increased intracranial pressure cither die or survive with severe neurological abnormalities.

Electroencephalography and Cortical Evoked Responses

Hypoxic-ischemic encephalopathy is the single most important cause of seizures in term and premature newborns. Seizures associated with modetate or severe encephalopathy begin during the first 24 hours after the original insult and ate nototiously difficult to control. The pattern of background activity on the bL\G may have prognostic implications. Thus infants with a normal EEC 1 week after the initial insult usually have a favorable outcome,

Table 86.5: Clinical features of severe hypoxic-ischemic encephalopathy

Clinical features	*Time after insult*			
	0-12 br	*J 2-24 h;r*	*24-72 br*	*72 br*
Seizures	++	4-4-4-	4-4-	±
Increased intracranial pressure (full-term)		±	+++	
Stupor/coma	+++	++	+++	1
\pnea	+ (periodic breathing)	+ +	4-4-4-	1
Abnormal pupil/oculomotor responses		±	4-4-	
! 1; poionia	++4-	++ +	4-4-4-	+-t
Limb weakness	4-4-	4-	+	
Proximal, upper > lower (term)	±	±	±	J_
Hemiparesis	±	±	±	t
Lower limbs (premature)	±	±	±	±
Electroencephalographs features	Amplitude (suppression) frequency	Periodic pattern, ± mu!Itifocal sharp activity	Prominent periodic pattern ± more voltage suppression, isoelectric pattern	

Note: - = absent; ± = possibly present; 4- = present; ++ = more common; ++-J-= most common.

The usefulness of the visual, auditory, and somatosensory evoked responses in the diagnosis and prognosis of hypoxic-ischemic encephalopathy is less well established (see Chapter 36A). Limited data suggest a role for visual evoked responses in the diagnosis of periventricular [eukoninlacia (1'Vl,) and for auditors evoked responses in the diagnosis of brainstem injury.

Metabolic Parameters

Hypoglycemia, hypocalcemia, hyponatremia (inappropriate antidiuretic hormone secretion), and lactic acidosis may contribute to the neurological syndrome of hypoxic-ischemic encephalopathy. Metabolic derangements that are not corrected may worsen the cerebral injury (Hanrahan et al. 1998).

Neuroimaging

Neuroimaging is useful for locating and quantifying cerebral injury. Magnetic resonance imaging (MRI) and computed tomography (CT) in the term newborn (Figures 86.1 and 86.2) and US in the premature newborn are especially valuable. Decreased attenuation on a CT scan performed between 3 and 5 days of age shows the maximum severity of acute hypoxic-ischemic cerebral injury in the term newborn (see Figure 86.1). More precise anatomical delineation of mild brain injury or selective involvement of thalamus and basal ganglia or cerebellum may be assessed more accurately by MRI after the hypoxic-ischemic episode (Rutherford et al. 1998; Aida et al. 1998; Mcrcuri et al. 1 999). More advanced MRI techniques may prove especially useful; e.g., diffusion-weighted MRI may permit earlier diagnosis of injury (Indcr et al. 1999) and volumetric MRI may permit quantitative assessment of cerebral tissue loss,

Several newer techniques that provide insight into functional disturbances of newborn hypoxic-ischemic cerebral injury may have important implications for management. Positron-emission tomography, single-photon emission computed tomography, and near-infrared spectroscopy show disturbances of cerebral perfusion. Magnetic resonance spectroscopy shows decreased brain levels of high-energy phosphates in asphyxiated infants.

Management

Optimal management begins in utero by measures to prevent hypoxic-ischemic injury. Fetuses at risk must be identified early, monitored serially (discussed earlier), and considered for cesarean delivery when signs of fetal distress persist. An asphyxiated newborn requires immediate treatment to prevent additional hypoxic-ischemic cerebral injury. This includes close attention to ventilation, perfusion, blood glucose concentrations, control of seizures, and

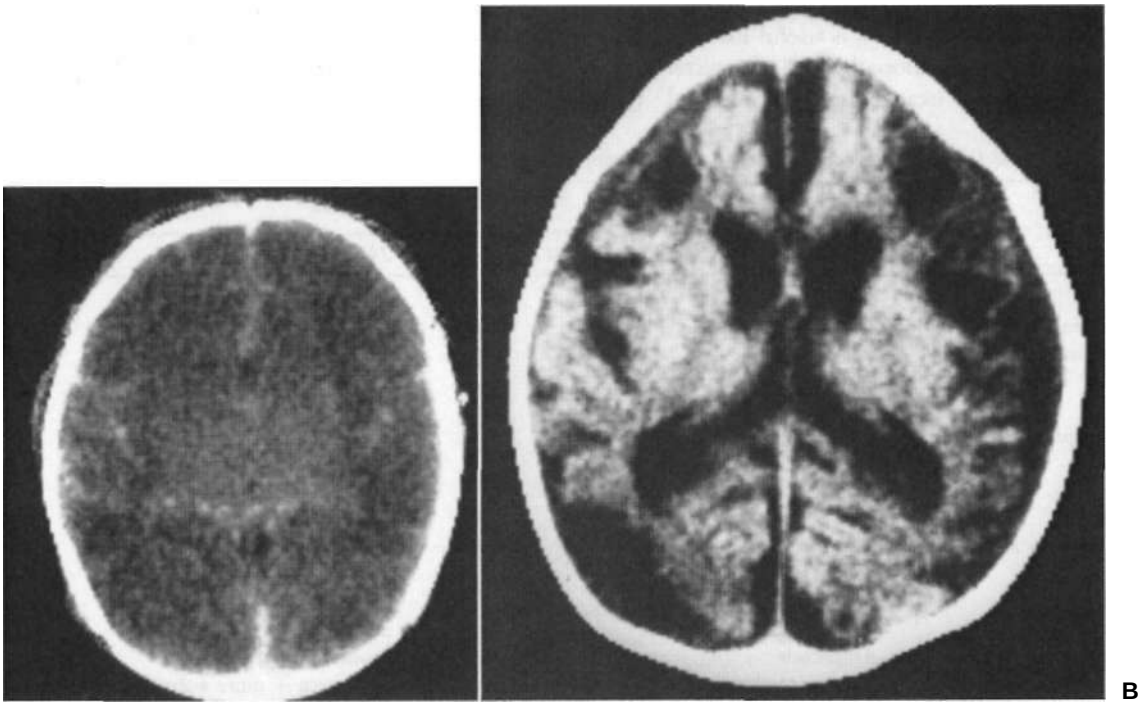

FIGURE 86.1 Computed tomographic scans of severely asphyxiated term newborn, (A) Sean at 3 days of age demonstrates diffuse low attenuation. (B) Scan at 5 months demonstrates wide sulci and enlarged ventricles consistent with severe generalized atrophy.

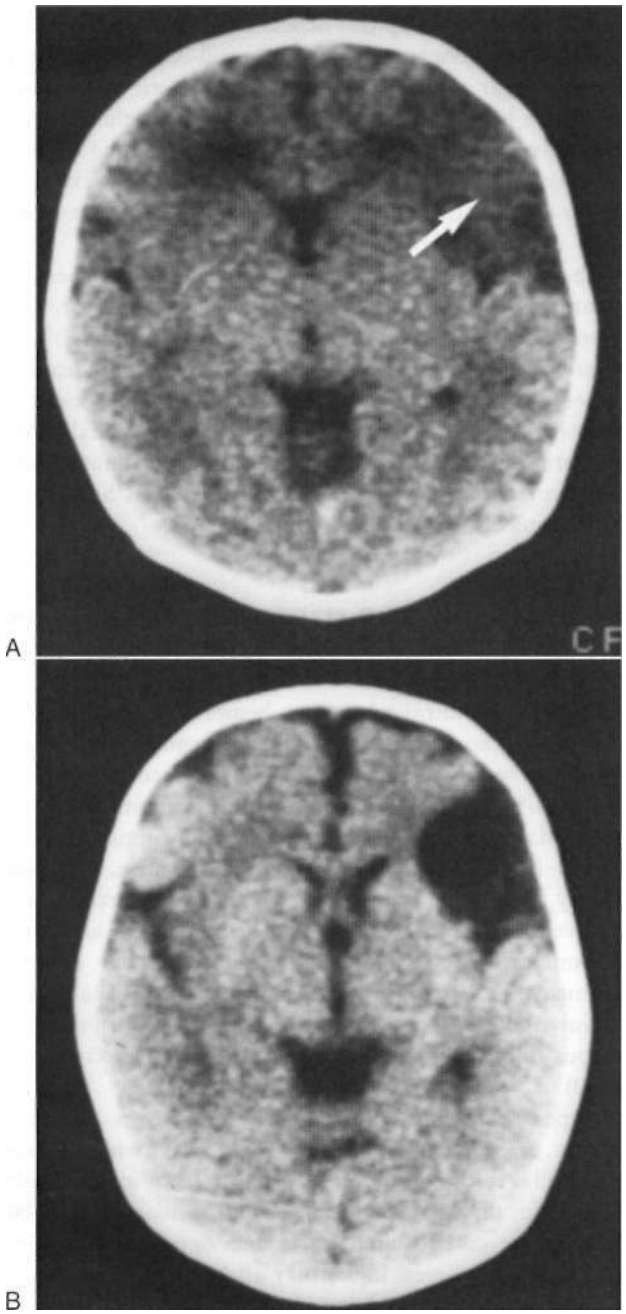

FIGURE 86.2 Computed tomographic scans demonstrate evolution of focal ischemic lesion in term infant who presented with focal seizures. (A) Scan at 3 days of age. Note low tissue attenuation in distribution of left middle cerebral artery *(arrow).* (B) Scan at 2 months of age. Note marked tissue loss in this region.

maintenance of perfusion and function of other affected organs, including the heart, liver, kidneys, and gastrointestinal tract.

Maintenance of Adequate Ventilation

Maintenance of adequate ventilation and avoidance of hypoxemia and hypercapnia are critical to outcome. Recognition of hypoxemia and hypercapnia has been facilitated by the availability of continuous transcutaneous oxygen and carbon dioxide monitoring. Significant hypoxemia occur in thi[1] premature newborn during routine care, such as suctioning or venipuncture; minimal handling is recommended. Persistent pos:n;ilal hypoxemia is caused by the respiratory distress syndrome in premature newborns and by persistent fetal circulation and pulmonary hypertension in term newborns. Overcorrection of hypoxemia should he avoided because hypcroxemia may cause chronic lung injury and retrolental fibroplasia as well as ponrosubicular necrosis, a specific pattern of selective neuronal necrosis involving principally the hippocampal and pontine neurons, I iypcrcapnia is deleterious because it worsens intracellular acidosis, impairs cerebrovascular autoregulation, or does both, with development of a pressure-passive cerebral circulation. The potential effects of hypocapnia on cerebral blood flow in the newborn have not been established. Experimental and human data do not support the use of hyperventilation in asphyxiated newborns, except perhaps in those with persistent fetal circulation.

Maintenance of Adequate Perfusion

The maintenance of adequate perfusion is critical to prevent further cerebral ischemia. Management of perfusion must be based on knowledge of normal systemic arterial blood pressure levels in the newborn at all gestational ages. Systemic hypotension must be avoided because cerebral blood flow is not autoregulated in asphyxiated newborns and reflects systemic blood pressure in a pressure-passive manner. Transitory myocardial ischemia, a common cause of hypotension in asphyxiated newborns, may respond to inotropic agents such as dopamine. Other important causes of systemic hypotension that may result in decreased cerebral perfusion are patent ductus arteriosus and recurrent apneic spells with bradycardia. Because of the pressure-passive relationship between the systemic and cerebral circulations, systemic hypertension must be avoided also, especially in the premature infant, in whom the presence of vulnerable germinal matrix capillaries predisposes to the development of 1VH.

Hyperviscosity due to polycythemia (venous hematocrit *>65%)* may further impair cerebral perfusion in asphyxiated newborns, especially in those who are small for gestational age. Jitteriness, apnea, poor feeding, and seizures are concomitant neurological features in approximately 40% of these newborns. Partial exchange transfusion with plasma is indicated in ail symptomatic newborns with polycythemia and perhaps also in those who are asymptomatic.

Prevention of Metabolic Derangements

Fluid overload is an important consideration in the maintenance of metabolic homeostasis. Inapptopriate

antidiuretic hormone secretion is common during the first 3 days after a severe hypoxic-ischemic episode and may lead to hypo-osmolality and hyponatremia, which in turn increase brain water content (cerebral edema) and seizures. The role of glucose supplementation in the management of **the asphyxiated** newborn is unclear. We recommend maintaining blood glucose concentrations in the normal r:iii.!!i'.

Control of Brain Swelling

The contribution of brain swelling to neurological outcome in terra newborns with hypoxic-ischemic encephalopathy is controversial. Experimental data from animals and human newborns suggest that brain swelling with increased intracranial pressure is a consequence of tissue necrosis rather than a cause of brain damage in scvete hypoxic-ischemic encephalopathy, and it is not associated with transtentorial or transmagnal herniation. Clinical evidence of increased intracranial pressure, a bulging anterior fontanelle, is most evident between 36 and 72 hours after the initial asphyxial episode. Mannitol reduces intracranial pressure in asphyxiated newborns, but its beneficial effect on outcome is not proven. Surveillance of intracranial pressure by palpation of the anterior fontanelle or by noninvasive monitoring with the Ladd monitor may have prognostic value. Elevated intracranial pressures 36-72 hours after the asphyxial episode correlate with extensive low attenuation of tissue on CT scans and a poor outcome.

Prognosis

Severe hypoxic-ischemic encephalopathy causes widespread injury. The resulting clinical features are microcephaly, mental retardation, seizures, and spastic quadnparesis (see Chapter 67). Less severe encephalopathies mainly injure the parasagittal regions, causing shoulder weakness. Involvement of tbalami and basal ganglia is often associated with choreoathetosis and dystonic cctebral palsy, which may be delayed in onset. Unilateral focal lesions result principally in hemiplegia.

Selected aspects of the neurological syndrome and neurodiagnostic studies are helpful in determining outcome in lupoxK ischemic encephalopathy (Table 86.6). Because most instances of hypoxic-ischemic encephalopathy begin before birth, assessment of fetal well-being in utero is useful. Apgar scores at I and 5 minutes are notoriously unreliable because of interobscrver variability, the effects of drugs given to the mother before delivery, and the stress of delivery, which may be reversible. In contrast, low extended Apgar scores after 10 minutes, may suggest that a major prior insult has occurred.

The severity and duration of hypoxic-ischemic encephalopathy is the single most useful prognostic factor. Our experience indicates that newborns who may have sustained intrapartum asphyxia but do not develop features of neonatal encephalopathy will not have major long-term neurological morbidity. The features of encephalopathy that are most predictive are its seventy and duration and the occurrence of seizures. Abnormalities on US, CT, and MRI scans also predict poor outcome.

Tabic 86.6: Prognostic factors in hypoxic ischemic encephalopathy in term infants

Neonatal encephalopathy: severity and duration (>J-7 days)
Presence of seizures
Presence of brain swelling
Electroencephalography: isoelectric, suppressed background, hurst-suppression
Radiological investigations: computed tomography, ultrasound, magnetic resonance imaging.

HEMORRHAGIC AND HYPOXIC-ISCHEMIC BRAIN INJURY IN THE PREMATURE NEWBORN

Periventricular-intraventricular hemorrhage (PIVH) is reported in approximately 20% of premature newborns with birth weight less than 1.500 g. PIVH occurs on the first day in 50% of affected premature newborns and before the fourth day in 90%. PIVH originates from rupture of small vessels in the subependymal germinal matrix. Approximately 80% of germinal matrix hemorrhages extend into the ventricular system. Severe hemorrhages are often accompanied by hemorrhagic lesions in the cerebral patenchyma. Parenchymal hemorrhages are usually unilateral and are considered to result from hemorrhagic venous infarction in the periventricular region (Volpe 2000).

Hypoxic-ischemic injury in the premature newborn affects predominantly the periventricular white matter bilaterally, resulting in PVL. This pattern of injury results in spastic diplegia, quadtiplcgia, or visual impairment because the corticospinal tracts and optic radiations are involved. More severe injury may affect the cerebral cortex, resulting in microcephaly and cognitive impaitment.

Diagnosis

The high incidence of PIVH in premature infants has led to the routine use of US scanning at 3-4 days in all newborns of less than 32 weeks' gestation. CT or MRI and US scans are informative, bur US is generally considered to be the technique of choice because it can be performed noninvasively in the intensive care nursery and there is no ionizing radiation involved. CT and MRI remain the techniques of choice for demonstration of epidural, subdural, and subarachnoid hemorrhage as well as most inttaccrcbral and posterior fossa hemorrhages.

PIVH can be predicted on the basis of clinical features in only 50% of patients in whom the hemorrhages have extended from the germinal matrix into the ventricular system. The spectrum of clinical features associated with PIVH ranges from an asymptomatic state, through stepwise neurological deterioration over several days, to rapid catastrophic deterioration characterized by coma, apnea, generalized tonic seizures, brainstem disturbances, and flaccid quadriparesis. Severe hemorrhage may be associated with the systemic abnormalities, which include metabolic acidosis, hypotension, bradycardia, and abnormal glucose and water homeostasis. Bloody or xanthochromic cerebrospinal fluid (CSF) from lumbar puncture also suggests PIVH.

CT scans have limited value in assessing acute hypoxic-ischemic cerebral injury in premature newborns because the immature brain has a high water content and low tissue attenuation is a normal feature. PVI. may be suggested on routine US scans in premature newborns by increased echogenicity in the periventricular regions during the first days of life and subsequent cyst formation in the same areas after the first several weeks (Figure 86,3). The ability to distinguish between hemotrhagic and ischemic injury (Figure 86.4} and to reliably identify mild or diffuse injury in the white matter with US is limited. MRI performed at term shows increased signal in cerebral white matter on T2-weighted images. Diffusion-weigh ted MRI may demonstrate diffuse white matter injury-even earlier than conventional MRI (Indcr et al. *1999).* After the neonatal period, PVL can be demonstrated by CT or MRI.

Pathogenesis and Management

Table 86.7 summarizes the current concepts of pathogenesis and management of PIVI I. Fluctuations of cerebral blood flow are a major factor in the pathogenesis of PIVH.

The primary management strategy for PIVH is prevention. Ideally, this is accomplished by preventing premature delivery. If premature delivery cannot be prevented, several strategies have been proposed, directed against the known intravascular, vascular, and extravascular mechanisms of hemorrhage. Muscle paralysis with pancuronium bromide in ventilated premature newborns has an established role in reducing the incidence and severity of PIVH by stabilizing fluctuations of cerebral blood flow. The role of other agents is less well established. Phenobarbital may dampen fluctuations of systemic blood pressure and cerebral blood flow and may have other cellular neuroprotective effects. However, one important study reported an increased incidence of PIVH in infants treated with phenobarbital. Indomethacin inhibits prostaglandin synthesis, thereby regulating cerebral blood flow. It prevents PIVH in animal models, but its efficacy in humans is inconclusive. Two other agents. •: itatnin I' and ethamsylnre, may hold promise for preventing PIVH, but the data are insufficient to recommend their routine use (see Table 86.7).

After PIVH has occurred, treatment is focused on preventing extension of hemorrhage, which occurs in 20-40% of patients, and preventing further hypoxic-ischemic cerebral injury. Severe 1VH may decrease circulating blood

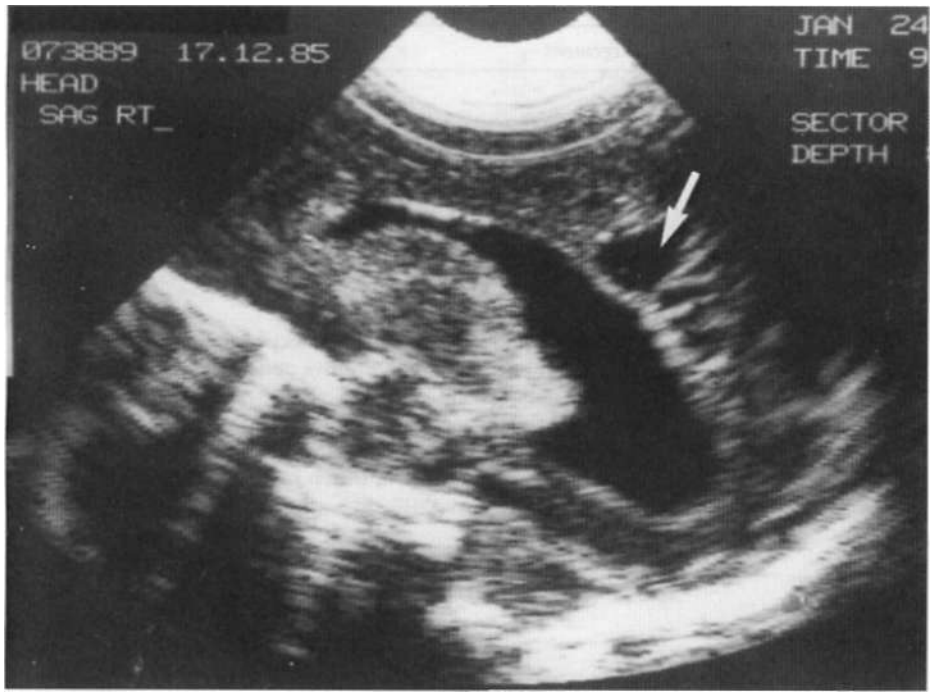

FIGURE 86..1 Cystic periventricular leukomalacia. Parasagittal ultrasound scan performed 5 weeks after intraventricular hemorrhage and hypoxic-ischemic insult. Note cystic lesion *(arrow).*

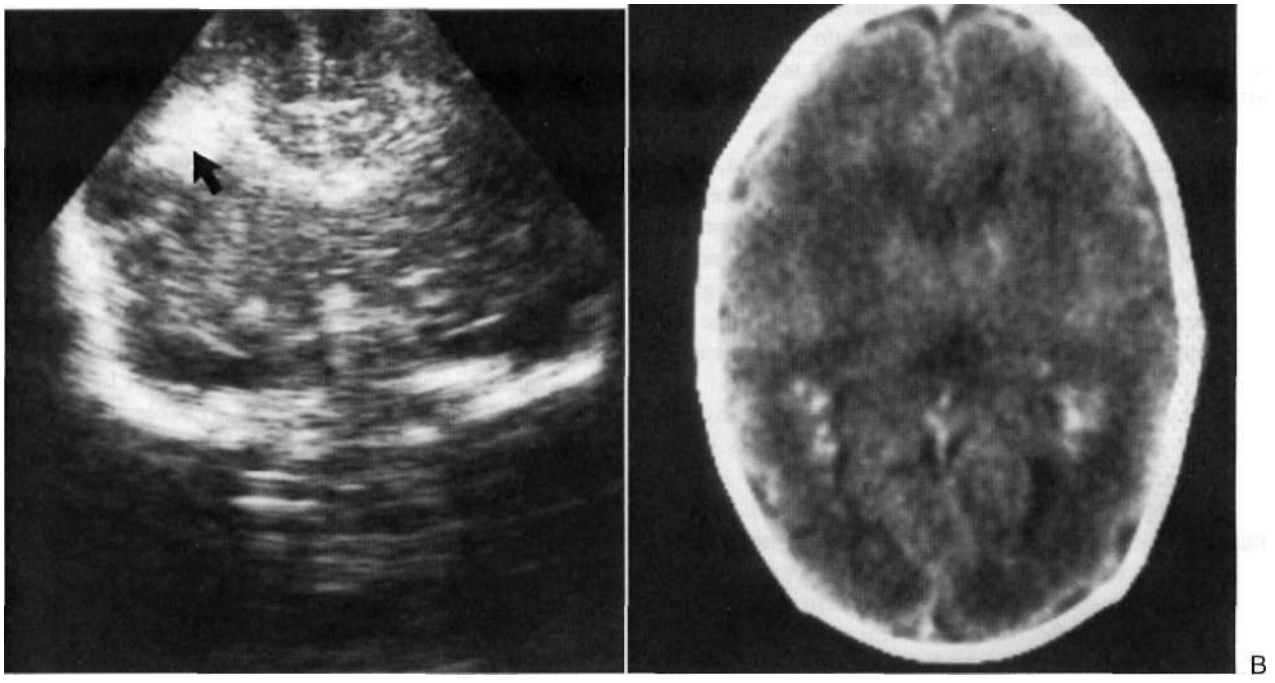

FIGURE 86.4 Hemorrhagic and nonhemorrhagic periventricular leukomalacia. (A) Ultrasound (US) scan demonstrates increased echoes in periventricular region *(arrow).* (B) In a computed tomographic scan performed at the same time, however, note the absence of hemorrhage in regions corresponding to increased echoes on the US scan. This illustrates that echogenicity on US examination does not distinguish between ischemic and hemorrhagic injury.

volume sufficiently to cause systemic hypotension that needs to be corrected by blood transfusion.

Serial US scans and measurements of head circumference are needed in every newborn with PIVH for early diagnosis of the development of posthemorrhagic hydrocephalus (Figure *86.5).* This complication is caused by arachnoiditis in the posterior fossa, by aqueductal obstruction, or by both. Significant ventriculomegaly may precede measurable

Table 86.7: Pathogenesis and management of periventricular-intraventricular hemorrhage

Pathogenesis	*Management*
Intravascular factors	
Fluctuating cerebral blood flow	Paralysis of ventilated preterm infants with pancuronium bromide
Increases in cerebral blood How	Avoidance of systemic hypertension associated with routine handling and rapid volume expansion, exchange transfusions, colloid infusions, seizures, pneumothorax
	Indomethacin
	Decreases in cerebral blood flow
	Increases in cerebral venous pressure and flow
	Avoidance of systemic hypotension
	Avoidance of prolonged labor and difficult vaginal delivery
	Avoidance of pneumothorax, positive pressure ventilation.
	Minimal handling
Platelet and coagulation disturbances	Avoidance of asphyxia
	Avoidance of maternal drug ingestion (such as aspirin)
	Prophylactic infusion of fresh, frozen plasma?
	Platelet infusion?
Vascular factors	
Venous vascular integrity	Ethamsylate, vitamin E?
Involuting vessels: subependymal germinal matrix	
Extra vascular factors	
Poor vascular support: subependymal germinal matrix	
Direct external effects on vessels	

FIGURE 86.5 Composite of four ultrasound scans in corona! section demonstrating ventriculomegaly after intraventricular hemorrhage at 3 days of age, with sp".....riff-.!-, ri^vunnn bv 2 months of age.

increases in head circumference. Factors that influence the management of posthemorrhagic hydrocephalus are the rate of progression, ventricular size, and intracranial pressure. In approximately 50% of premature newborns with posthemorrhagic hydrocephalus, vemrieulomegaly arrests or resolves spontaneously without intervention, usually within 4 weeks (see Figure *86.5).* In the other 50%, dilatation progresses beyond 4 weeks and requires intervention. However, rapid ventricular enlargement with clinical evidence of increased intracranial pressure requires intervention before 4 weeks of age. The definitive treatment is placement of a ventriculoperironeal shunt, but temporary measures are often needed. These measures include CSF drainage by serial lumbar punctures, external ventriculostomy, placement of a ventricular catheter with subcutaneous reservoir or subgalcal shunt, and administration of drugs that reduce CSF production, such as osmotic agents (isosorbide and glycerol) and carbonic anhydrase inhibitors and diuretics (acetazolamide and furosemidc). In infants with rapidly progressive hydrocephalus, placement of a ventriculoperitoneal shunt is often indicated, despite the morbidity associated with shunt placement in small, premature infants.

Prognosis

The prognosis after PIVH relates to the severity of hemorrhage and to the concomitant hypoxic-ischemic cerebral injury. Germinal matrix hemorrhage alone is rarely a cause of significant neurological morbidity. The prognosis after blood is found in the ventricles is relatively good unless ventricular dilatation occurs. Newborns with severe ventricular dilatation and intraparenchymal hemorrhage may die in the neonatal period, and most survivors develop posthemorrhagic hydrocephalus. Prognosis does not always correlate with the severity of PIVH and posthemorrhagic hydrocephalus; hypoxic-ischemic parenchymal injury, principally PVL, is the other important variable that cannot be overlooked. However, PVL may be more difficult to document radio logically (Ment ct al. 1999).

INTRAVENTRICULAR HEMORRHAGE IN THE TERM NEWBORN

Although IVH is considered to be primarily a lesion of the premature newborn, it has been reported to occur in approximately 3.5% of healthy term newborns. The pathogenesis of major IVH in term newborns is similar to that in premature infants in that hypoxia and trauma are relevant factors in approximately 50% of infants. However, traumatic delivery may be relatively more significant, presumably causing increased cerebral venous pressure and alrered cerebrovascular autoregulation. I-ml lu-: i in n\-. tin[1] s:;cs u1 origir. <i IVI I an more variable in the term newborn and include residual germinal matrix (2%), choroid plexus (1.1%), vascular malformations, tumor, or hemorrhagic venous infarction of the thalamus (Roland et al. 1998). IVH from the latter usually presents somewhat later, at several days or weeks of age.

The diagnosis and management of IVH and its complications in the term newborn are similar to those described for premature newborns. IVH may be suspected clinically and confirmed by ncuroimaging.

The prognosis for IVH in the term newborn may be worse than that for premature newborns, in whom less

severe lesions comprise the majority of cases. Long-term neurological sequelae are reported in more than 50% of infants and are related principally to associated parenchymal damage and to the underlying etiology, especially trauma and hypoxic-ischemic insult. Approximately 50% of term newborns with IVH develop posthemorrhagic hydrocephalus, which requires the placement of a ventriculoperitoneal shunt and an additional 20% develop ventricular dilation, which arrests or resolves spontaneously.

INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

Bacterial infections of the central nervous system (CNS) in the newborn include bacterial meningitis, epidural and subdural empyema, and brain abscess.

Neonatal Meningitis

Bacterial meningitis is more common in premature than in full-term infants and generally has a two-fold pattern of illness: "early-onset" disease within the first days of life caused by group B streptococcus, *Escherichia colt,* and *Listeria monocytogenes* acquired from an infected birth canal and "late-onset" disease after several days, which may be acquired from the mother or other contacts in the environment and may be caused by the organisms listed above, as well as by *Staphylococcus* or *Pseudomonas aeruginosa.* Maternal genital infection with group B streptococcus (which is usually asymptomatic) and maternal urinary tract infection during the weeks before delivery are considered to be particularly high-risk situations. Because as many as 20-30% of cases of neonatal sepsis are complicated by meningitis and because early diagnosis and treatment are critical to prevent morbidity and monthly, mniba: puncture must be performed .is soon .is a newborn appears sick; one cannot wait for the typical cliuiL.d Icaraics nt meningitis, such as a bulging tontanellc, neck retraction, seizures, irritability, pallor, and poor feeding. The characteristic CSF ptofile is pleocytosis, increased protein concentration, decreased glucose concentration, and identification of the otganism by Gram's stain and culture. Laboratory techniques that allow rapid detection of bacterial antigens also may be useful (e.g., Immunoelectrophoresis, latex agglutination, and radioimmunoassays). Valuable supporting data regarding the probable bacterial etiology may be derived from isolanon of an organism from body fluids other than CSF.

Management

In an attempt to prevent neonatal meningitis, the American College of Obstetrics and Gynecology and the American Academy of Pediatrics recommend intravenous administration of ampicillin during labor for mothers with rectal or genital cultures positive for group B streptococcus or other major risk factors for neonatal sepsis {Schrag et al. 2000). The initial empiric treatment of a neonate with bacterial meningitis of unknown cause is a combination of ampicillin, an aminoglycoside such as gentamicin, and possibly cefotaxime administered intravenously. The precise dosage varies according to the body weight and postnatal age of the affected infant. The optimal selection of antibiotics is determined when definitive bacteriological diagnosis is known and by the resistances of the infecting organism. Repeated sampling of CSF is required to ensure response to treatment. Parenteral antibiotic treatment is usually maintained for 21 days or at least 2 weeks after sterilization of CSF. A repeat CSF examination should be performed 48 hours after discontinuation of antibiotic therapy.

In addition to antimicrobial therapy, supportive measures such as maintenance of fluid and electrolyte balance and control of blood pressure and blood gases are essential. Because the syndrome of inappropriate antidiuretic hormone secretion is common, fluids should be restricted to 30-40 ml./kg per day during the first few days of illness. Seizures are a common complicarion and should be treated with pbenobarbital, phenytoin, or both (see Table 86.2). Serial measurements of head circumference and cranial US scans permit early diagnosis of the complications of ventriculitis, hydtocephalus, and subdural effusion.

Ventriculitis commonly causes hydrocephalus, either durine the acute phase ol the illness or subsequently {Figure 86.6). Meningitic hydrocephalus is treated by external ventricular drainage, often with a reservoir for intermittent draining of CSF, instillation of antibiotics in selected infants if active infection is present, or both. Most newborns require a permanent ventriculoperitoneal shunt after the infection has been eradicated.

Cerebral abscess is a rare complication of neonatal meningitis. It occurs most often with *Citrobacter* infection but may also occur after other virulent gram-negative infections or rarely, gram-positive organisms. Abscess should be suspected when newborns with increased intracranial pressure respond poorly to treatment. Diagnosis is confirmed by brain imaging. The duration of antibiotic therapy is prolonged, and surgical exploration and drainage are usually considered to be the treatments of choice. The mortality is approximately 15%, and survivors often have major neurological impairment.

Prognosis

The important variables that determine mortality are the type of infecting organism and the gestational age of the infant. Mortality is reportedly between 20-30% and is highest for gram-negative infections. Permanent

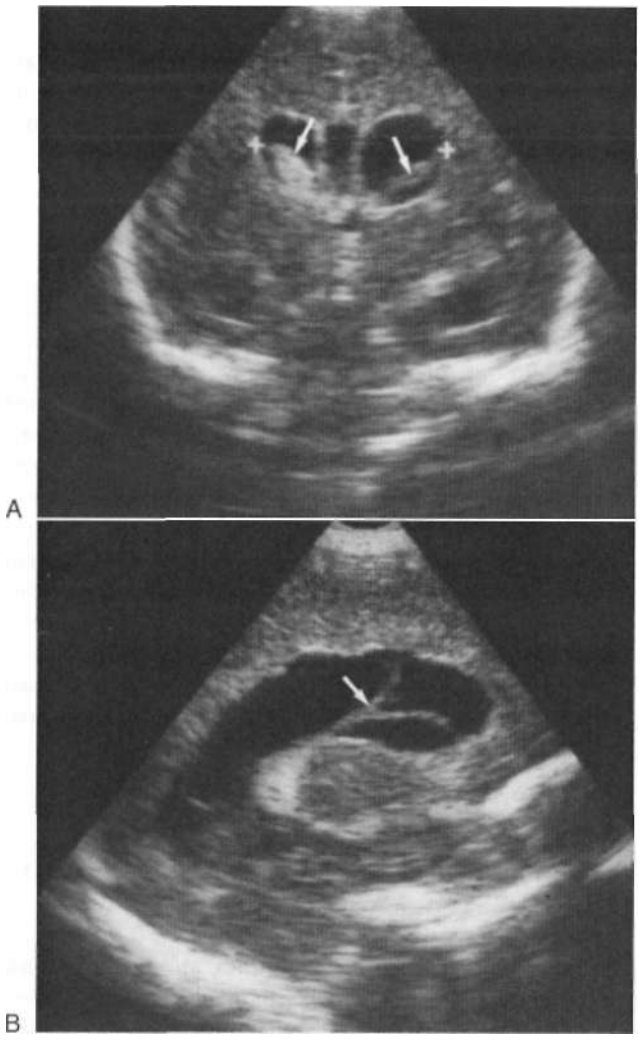

FIGURE 86.fi Ultrasound scans of newborn infant with bacterial meningitis and ventriculitis. Note intraventricular strands in both (A) coronal and (B) parasagittal images *[arrows).*

neurological sequelae occur in 30-50% of survivors and include hydrocephalus, cerebral palsy, epilepsy, intellectual deficits, and deafness.

Viral and Parasitic Infections

Viral, protozoan *{Toxoplasma gondii),* and fungal infections occur in the newborn. The acronym TORCH is used as a reminder of the major nonbacterial neonatal infections: toxoplasmosis, others (such as syphilis), rubella, cytomegalovirus (CMV), and /jcrpes simplex. All of the TORCH infections occur during pregnancy by transplacental inoculation, except for herpes simplex, which usually is contracted by passage of the fetus through an infected birth canal. Although most newborns with 1 OIU 1 I syndromes have clinical features of disease during the first month of life, symptoms can be delayed until later infancy and childhood.

Congenital Rubella

Although the incidence of congenital rubella infection has diminished markedly since widespread use of the rubella vaccination, it remains a significant problem in many parts of the world (Zerr et al. 2001; Reef et al. 2002) The congenital rubella syndrome occurs when the fetus is infected before 20 weeks' gestation. The clinical features in the newborn include low birth weight, jaundice, hepatosplenomegaly, petechial rash, congenital heart disease, cataracts, sensorineural deafness, microcephaly, bone lesions, and thrombocytopenia. Less severely affected infants appear normal at birth and later show features of neurological and ocular defects, deafness, and congenital heart disease. Infected infants arc highly infectious, may shed virus for several years, and must be considered a hazard to nonimmune women. Diagnosis is confirmed by culture of virus (throat swab and urine) and demonstration of rubella-specific immunoglobulin M (IgM) in neonatal plasma. Neuroimaging may reveal periventricular calcifications, subependymal cysts, or PVL. The only effective management is prevention by universal immunization. Antiviral treatment is unavailable. Infants who survive may develop progressive sensorineural hearing loss, behavioral •nunriou.i. prob-Mm, *y.um* ih failure, or Jialv;,'-, mellitus later in childhood.

Cytomegalovirus

CMV infection is the most common congenital viral infection and results cither from primary maternal infection or from reactivation of virus in the mother. Almost all newborns with congenital CMV infection are asymptomatic. The fewer than 10% who arc symptomatic have hepatosplenomegaly, jaundice, perechiac, microcephaly with periventricular calcifications, and chorioretinitis and are blind. In symptomatic infants, virus can be cultured from throat swabs or urine, and CMV-specific IgM is present in serum. Urine culture results are also positive in asymptomatic infants. Preliminary data suggest that specific therapy with a 3-month course of ganciclovir may provide clinical benefits for symptomatic newborns. However, further evaluation is required, because most of the brain injury occurs in urero. Supportive therapy involves control of seizures.

Most asymptomatic newborns with congenital CMV infection develop normally. However, a percentage develop impaired intellectual function, deafness, microcephaly, chorioretinitis, ataxia, and seizures. The mortality in symptomatic newborns is 20-30%, and most survivors have multiple, severe neurological sequelae (Boppana et al. 1997).

Herpes Simplex

Neonatal herpes simplex infection is acquired during passage through an infected birth canal in the vast majority of newborns. The incidence of this infection in the newborn is increasing, which reflects the high prevalence of herpes infection in adults in the United States, reported to be between 20 and 60%. It may present as localized oral, cutaneous, or ophthalmic disease; localized disease of the CNS, such as meningitis; or disseminated disease with hepatosplcnomegaly, severe disseminated intravascular coagulation, renal failure, and meningoencephalitis. Any infant with CSF suggestive of encephalitis should be considered to have herpes simplex infection until proven otherwise. Intranuclcat inclusions may be detected in vesicular fluid, CSF, or conjunctival scrapings. A throat swab, as well as urine and stool samples, should be cultured. Negative culture results do not exclude the diagnosis. Studies of the CSF usually are consistent with vir.ii meningoencephalitis, and diagnosis may be established quickly using polymerase chain reaction (sec Chapter 59B). Polymerase chain reaction assay is the best technique to identify the virus rapidly in the CSF. CT or MRI, especially diffusion-weighted MRI, is useful for delineating the extent and severity of brain injury. In term newborns a 14-day course of acyclovir (30 mg/kg per day given in evenly divided doses every 8 hours) should be started even before the results of cultures are known. Dosage should be reduced in premature infants and infants who have impaired renal function. Acyclovir may improve outcome but is not as effective as in postnatally acquired infection (Kesson2001).

Toxoplasmosis

Toxoplasmosis is a parasitic infection that is acquired transplacental^ and affects principally the CNS and the eye in the newborn. The result is extensive necrosis and calcification of the cerebral cortex and periventricular tissue. Cerebral injury in the periaqueductal region obstructs CSF flow and causes hydrocephalus. Cataracts and microphthalmia are the main eye abnormalities. Other organs that may be involved are the liver, bone marrow, lungs, muscles, and myocardium.

Antibody screening for neonatal infection may suggest congenital toxoplasmosis, but test results for *Toxoplasma*-specific Ig.Vl often are negative (Pinon et al. 2001). Examination of the CSF may show lymphocytosis, high protein content, and trophozoites. Diffuse intracerebral calcifications may be seen on skull radiography, CT, and US.

Spiramycin, pyrimethamine, and sulfadiazine with folinic acid are used to treat the infected mother and her infant during the first year (Foulon ct al, 2000). Specific doses and regimens are beyond the scope of this discussion. In severe meningoencephalitis, the use of corticosteroids may be considered. Approximately one third of infected infants are symptomatic, and their mortality is 25%. Most survivors have significant neurological sequelae. In contrast, asymptomatic newborns have a good prognosis.

Human Immunodeficiency Virus

The number of newborns who are seropositive for human immunodeficiency virus (HIV) is increasing. Transmission may occur in urero, during labor and delivery, or postnatally by breast-feeding. The vast majority of infected newborns are asymptomatic but later develop opportunistic systemic infections (e.g., CMV or *P>teumocystis)* and dementia with cerebral atrophy and acquired microencephaly caused by viral infection of the brain (Tardieu 1998). The management of HIV-infected women to prevent maternal-infant transmission is beyond the scope of this discussion. Studies have shown that the risk of transmission may be reduced by a program of prenatal, perinatal, and postnatal therapy with zidovudine and may be decreased further by elective cesarean section and avoidance of breast-feeding (Mofenson 1999; Gibb and Tess 1999).

MECHANICAL TRAUMA TO EXTRACRANIAL, CENTRAL, AND PERIPHERAL NERVOUS SYSTEM STRUCTURES

The occurrence of traumatic injuries at birth has been greatly reduced by improvements in obstetrical management. This section discusses the diagnosis and management of traumatic injury according to its anatomical location.

Intracranial Hemorrhage

Othet types of intracranial hemorrhage, such as primary subarachnoid, epidural, subdural, and intracerebcllar hemorrhage, are usually associated with traumatic delivery or a bleeding diathesis and occur less commonly than PIVH (Figure 86.7). Subdural hemorrhage occurs in both ptemature and term newborns and results from laceration of major veins and sinuses. It is often related to excessive molding of the head. CT is the investigational technique of choice for diagnosis of subdural hemorrhage. Convexity subdural hematoma, especially if associated with midline shift, may require decompression by craniotomy or subdural tap. Subarachnoid hemorrhage can also be of venous origin but is usually self-limited, originating from small vessels in the leptomeningeal plexus or bridging veins within the subarachnoid space. Infants may be asymptomatic with minor subarachnoid hemorrhage or present with seizures. Diagnosis may be suspected on the basis of uniformly blood-stained or xanthochromic CSF and

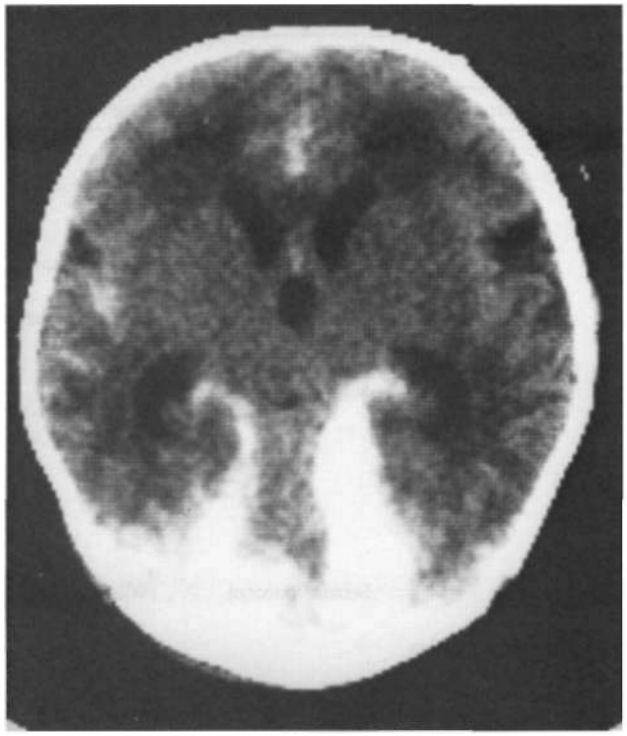

FIGURE 86.7 Computed tomographic scan of posterior fossa hemorrhage (intracercbcllar and subdural).

confirmed by CT scans. In the absence of severe trauma or major hypoxic-ischemic injury, normal outcome is seen in *90%* of patients. Table 86.8 summarizes the clinical features, management, and outcome of these types of intracranial hemorrhage.

Extracranial Hemorrhage

Extracranial hemorrhage is classified according to the tissue planes involved. Caput succedaneum is superficial bleeding between the skin and the epicranial aponeurosis, subgaleal hemorrhage is located between the aponeurosis and the periosteum of the skull, and cephalhematoma occurs in the deepest plane between the periosteum and cranial bones. The major clinical features and the usual outcome for extracranial hemorrhages are summarized in Table 86.9.

Skull Fractures

Skull fractures may be linear or depressed. Linear skull fractures usually are parietal in location. Rony continuity is lost without depression. Depressed skull fractures are called *ping-pong fractures* because the bone buckles inward without loss of continuity, like a depression in a ping-pong ball. Occipital diastasis is not an actual fracture but rather a traumatic separation of the squamous and lateral parts of the occipital bones that is usually associated with breech delivery.

Depressed skull fractures may be suspected clinically by palpation of the skull, but a CT scan is needed to visualize the relation of the depressed bone to the cerebral surface. CT scans are useful also to show a linear fracture beneath a cephalhematoma. Occipital diastasis may be associated with posterior fossa subdural hemorrhage, cerebellar contusion, and brainstem compression without hemorrhage or contusion. The importance of recognizing fractures and diastases is that they alert the physician to the possibility of a more serious intracranial disorder.

In the absence of intracranial lesions, treatment is required only when a depressed fracture impinges on the brain. Spontaneous elevation of the bone may occur with skull molding. Nonsurgical methods for elevation are digital pressure or use of a breast pump or an obstetrical vacuum extractor. Surgical intervention usually is reserved for complicated fractures with extradural or subdural blood clot or bone fragments. A leptomeningeal cyst may develop at the site of a skull fracture. This unusual complication may be identified by transillumination of the region or radiographical evidence of a widening bony defect ("a growing fracture").

Spinal Cord Injury

Spinal cord injury is uncommon. It is caused by excessive **torsion** or traction. Injuries associated with breech delivery (75%) involve principally the lower cervical and upper thoracic regions, whereas injuries after vertex delivery more commonly involve the upper cervical and midcervical cord. Injuries of the lower thoracic and lumbar spinal cord arc even less common and are usually related to vascular occlusion due to umbilical artery catheterization or air embolus from peripheral intravenous injection.

The neurological features reflect the segmental level of the lesion. Newborns with high cervical lesions are often stillborn or die quickly from respiratory failure in the absence of rapid ventilatory support. Lower cervical, upper thoracic lesions cause urinary retention, hypotonia, weakness, and arcflcxia of all limbs, evolving subsequently to spastic paraplegia or quadriplegia. Cord injuries are distinguished from neuromuscular disorders and brain injuries by the demonstration of a distinct sensory level of response to pinprick, **urinary retention,** and **a** patulous anus. Autonomic dysfunction may cause wide fluctuations of body temperature.

Spinal cord injury of fetuses in the breech position can be minimized by cesarean delivery of all fetuses with a hyperextended head. Unfortunately, cesarean section does not entirely eliminate the risk because some fetuses sustain injuries in utero, perhaps caused by vertebral artery (KVIUSLMM. (ord injury after vertex deliver;, ma; be a rare complication of forceps rotation. The diagnosis of spinal

Table 86.8: Other types of intracranial hemorrhage

Type nf hemorrhage	*Clinical features*	*Diagnostic technique*		*Management*	*Prognosis*
		Computed tomography	*Ultrasound*		
I piilur.il	Increased ICP ± unilateral fixed, dilated pupil Seizures (50%)			**Immediate surgical** evacuation	Poor
Subdural (convexity or infra tentorial)	Variable: asymptomatic or increased ICP			Close observation sIIII'.I IV ll deterioration or severe lesions	Hydrocephalus Focal abnormalities Major lesions: 100% morralin
	Brainstem disturbances Opisthotonus Seizures Coma				
Primary subarachnoid	Variable			Seizure control	90% normal
	Minimal signs Seizures Well in interictal period	Control of hydrocephalus	Hydrocephalus		
Intracerebellar	Premature > term		+	Close observation	Variable outcome
	Brainstem dysfunction Increased ICP		Surgery if deterioration		

Nole: + = useful; - = nor useful; ± = variable usefulness.
ICP — intracranial pressure.

cord injury is made on the basis of the clinical features. Ultrasonography, radiography, and MR] of the spine are sometimes indicated to exclude surgically correctable lesions such as spinal dysraphism or extramedullar}' compression. Because the cord injury is a tear or inrrnparenchyma] hemorrhage, surgical decompress inn and laminectomy generally are not helpful. Supportive management consists of adequate ventilation and prevention of urinary tract infection, decubitus ulcers, and contractures. High-dose corticosteroids have not been used in controlled trials in spinal cord injury in the newborn age group.

Traumatic Injury to the Peripheral Nervous System

b a rial Paralysis

facial paralysis occurs more commonly in utcro by compression of the facial nerve against the bony sacral

Table 86.9: Clinical features and outcome of extracranial hemorrhage

	Must common location	*Increases after birth*	*Crosses suture lines*	*Marked jcute blood loss*	*Usual outcome*
Caput succedaneum	Vertex	No	Yes	***So***	Resolves in first days of life
Subgaleal hemorrhage	Wide spread entire scalp	Yes	Yes	Yes	Resolves in 2-3 wks
Cephalhematoma	Unilateral parietal	Yes	No	\n	May calcify Resolves in weeks ro months

Note: Extracranial hemorrhage rarely requires intervention, except for subgaleal hemorrhage, in which the amount of acute blood loss may cause shock. Urgent blood transfusion and surveillance for hyperbilirubinemia are sometimes needed. Cephalhematoma is often associated with skull fracture, but does not require treatment.

promontory than by the pressure of forceps blades during delivery. The clinical features are a unilateral widened p.il|v'-•ml '⁚-MIIV i-111 Hinvni-d nasili.iln.i' told with the infant at rest and inability to close the eye completely or grimace when crying. Facial paralysis must be distinguished from *asymmetrical crying fades* resulting from congenital aplasia of the depressor angularis oris muscle.

Facial palsy is managed by the use of artificial tears and taping the affected eye closed at night to prevent corneal injury. Most cases resolve within weeks or months.

Brachial Plexus Injury

Brachial plexus injury occurs in 0.5-2,6 per 1000 live term births. The injury almost always occurs in large newborns who are difficult to deliver (Figure 86.8). The upper roots of the brachial plexus are involved most commonly (Erb's palsy). In other instances, lesions may involve the lower nerve roots down to the first thoracic root (Klumpke's palsy). Approximately 5% of instances are associated with diaphragmatic paralysis caused by injury of the third to fifth cervical roots. Such paralysis may result in tachypnea and hypoventilation, with consequent cyanosis and hypercapnia. Brachial plexus injury also may be associated with Horner's syndrome, a fractured clavicle or humerus, subluxation of the shoulder or cervical spine, cervical cord injury, and facial palsy.

The neurological features of brachial plexus injury may be deduced from an understanding of the function of the involved cervical roots. Thus involvement of the upper cervical roots results in loss of shoulder abduction and external rotation and of elbow flexion and supination, with variable impairment of wrist and finger extension (see Figure 86.8). Absence of the biceps reflex on the affected side and an impaired abduction phase of the Moro reflex are demonstrable. With involvement of the lower roots, paralysis extends to intrinsic hand muscles and includes an absent gtasp reflex. Horner's syndrome occurs in one third of such patients. Deficits of motot function and reflexes are usually more striking than are sensory deficits.

fn the majority of infants, diagnosis is based primarily on careful neurological examination and may be confirmed if necessary by showing electromyographica! evidence of denervation 2-3 weeks after the injury (Sundholm et al. 1998). Clinical suspicion of diaphragmatic paralysis should be confirmed by either fluoroscopy or US scanning. This complication necessitates careful surveillance of respiratory status and perhaps ventilatory support or surgical plication of the affected diaphragm. Other traumatic or bony lesions should be excluded by radiography of the cervical spine, clavicles, and humerus.

Management

The affected arm is usually painful and should be immobilized across the upper abdomen for 7-10 days. Passive range-of-motion exercises are then initiated to prevail contractures. Supportive wrisl splints are important. The value of electrical stimulation techniques is controversial. Prognosis relates largely to the severity of the injury and to the time of onset and rate of initial improvement. Evidence of improved arm function within 2 weeks is a favorable prognostic sign. As many as 88% of infants recover by 4 months and 92% by 12 months. Mirgical reconstruction ol the plexus e.g., nerve grafts and neuroma excision) should be considered in infants with no evidence of spontaneous recovery at 4 months (Strombeck etal. 2000).

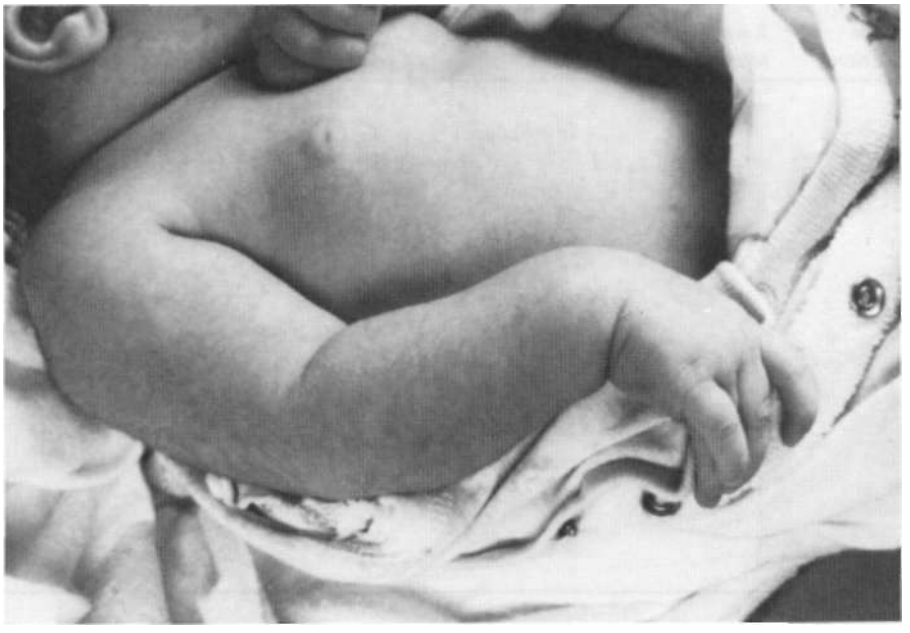

FIGURE S6.R Brachial plexus injury in newborn. Upper extremity held adducted, internally rotated, and pronated. Note "waiter's tip" position of affected wrist and fingers,

EFFECTS OF DRUGS AND TOXINS

Exposure of the fetus to medications and toxins may have profound adverse effects on the function of the newborn's central and peripheral nervous systems. These effects may lit' dn idrti :iro;ui'.> mio [/lost- that are teratogenic and those that cause passive addiction. It is often difficult to distinguish between the adverse effects of a specific agent and those associated with confounding influences, such as intrauterine undernutrition, infection, genetic factors, and toxicity of other medications or exogenous substances.

Table 86.10 lists the major adverse effects of the most commonly used ncuroactive agents taken during pregnancy. Prevention is the most important aspect ol management, and women of childbearing age must be advised of the risks to the fetus of noxious agents before conception because the risk of malformations is greatest during the early weeks of gestation.

Teratogenic Effects and Intrauterine Growth Retardation

Congenital malformations and intrauterine growth retardation often are associated. In general, maternal alcohol abuse causes growth retardation and intellectual deficits, whereas anticonvulsant drugs cause congenital heart disease and cleft lip and palate. Exposure to valproate during the first weeks of gestation is associated with a 5% risk of neural tube defects. This risk may be diminished to some degree by preconceptional and periconceptional maternal folate supplementation. Because neural tube defects originate very early during pregnancy (5-6 weeks' gestation), folate administered after confirmation of pregnancy is not helpful in this regard. Distinct syndtomes of growth retardation, developmental delay, dysmorphism, and distal limb abnormalities arc attributed to fetal exposure to phenvtoin (Figure 86.9), barbiturates, alcohol, trimethadione, and valproate (Report of Quality Standards Subcommittee 1998; Kaneko et al, 1999).

Microcephaly and mental retardation arc the most disturbing teratogenic effects attributed to fetal exposure to toxins. Microcephaly occurs in approximately 40% of infants who arc passively addicted to heroin.

Risk of Intracranial Hemorrhage

A hemorrhagic diathesis caused by reduced levels of vitamin K-dependent clotting factors (factors II, VII, IX, and X) may occur in newborns of mothers treated with phenytoin, barbiturates, and primidone; cither prothrombin or partial thromboplastin times are prolonged. Severe bleeding may take place in the skin and internal organs. All newborns exposed to anticonvulsant drugs during pregnancy should be treated with inttavenous vitamin K immediately after delivery, and those with abnormal clotting factors should be given fresh fro/en plasma. Exchange transfusion is indicated if the newborn has hemorrhagic disease.

Passive Addiction and Withdrawal Syndrome

Passive addiction occurs in 60-90% of newborns of mothers using neuroactive drugs (i.e., drugs that affect the CNS during pregnancy). The clinical features of

Table 86.10: Major adverse effects of neuroactive drugs administered during pregnancy

Neuroactive drugs	*Passive addiction*	*Known teratogenic*	*Neonatal seizures*	*Intrauterine growth retardation*	*Coagulation disorders (neonatal intracranial hemorrhage)*
Alcohol	+	+	+	+	
Hcroin/mcthadone	+		+ (methadone)	+	
Cocaine	+	+	?	+	
Benzodiazepines	+				
Tricyclic antidepressants	+		+		
Hydroxyzine (Atarax)	+				
Ethchlorvynol (Plaeidyl)	+				
Propoxyphene (Darvon)	+		+		
Pentazocine (Talwin)	+				
"T's and blues" (pentazocine, tripelennamine}	+		+		
Codeine	+				
Hydantoins		+			+
Barbiturates	+	+	+ (short-acting)		+
Primidone	+	+			+
Valproate		+		±	
Oxazolidine derivatives (trimethadione)		+		+	

Mote: + = present; =nut present: ± —possibly present,

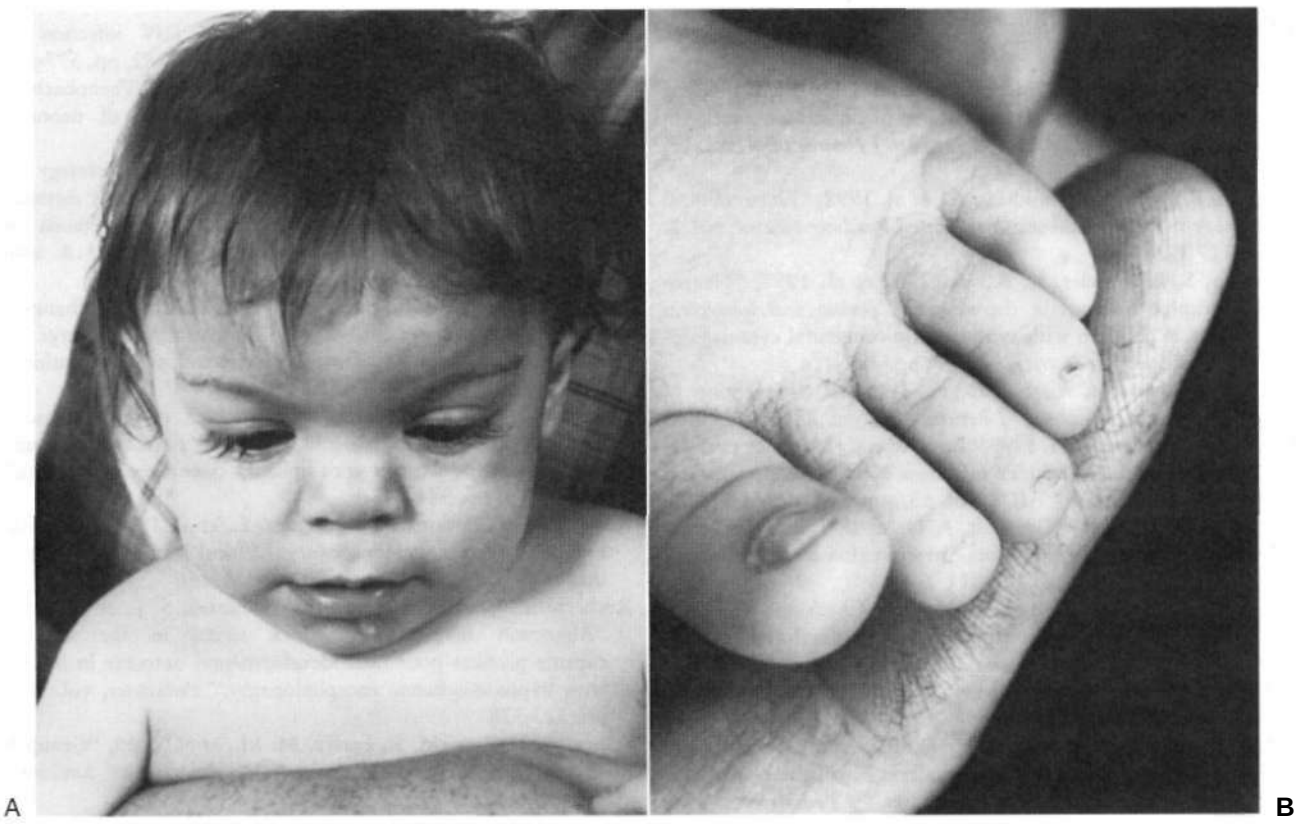

FIGURE 86.9 Infant with fetal hydantom syndrome. (A) Typical facial appearance with broad, deptessed nasal bridge, and widely spaced eyes. (B) Hypoplasia of nails and distal phalanges.

addiction and withdrawal are similar for most drugs, but the time of withdrawal differs according to the half-life of elimination for the specific drug. Withdrawal symptoms usually start on the first day with heroin, alcohol, short-acting barbiturates, diazepam, tricyclic antidepressants, hydroxyzine, propoxyphene, and pentazocine; at 2-3 days of age with methadone and cocaine; as laic as 7 days of age with longer-acting barbitutates; and at up to 21 days of age with chlordiazepoxide.

The initial features of withdrawal reflect CNS over-activity: jitteriness, irritability, disturbed sleep-wake patterns, shrill cry, and frantic sucking. These may be accompanied In gastrointestinal dislurbaiRvs, MICII as poor feeding, vomiting, and diarrhea, and less commonly by sneezing, tachypnea, and excessive sweating. Fever and seizures are uncommon manifestations of the neonatal withdrawal syndrome (see the exceptions listed in Table 86.10] and suggest the possibility of sepsis or other serious neonatal disorders.

The withdrawal syndrome associated with long-acting barbiturates and hydroxyzine may persist for several weeks. Newborns withdrawing from heroin often appear to recover initially, but latet experience a significant worsening of symptoms that may persist for as long as 6 months.

Effective management requires early diagnosis. Attention is focused on management of respiratory complications, infection, dehydration, and metabolic derangements. In addition, severe and persistent irritability, vomiting, and diarrhea may require treatment with tincture of opium, paregoric, phenobarbital, chlorpromazine, or diazepam.

Tincture of opium (0.4 mg/mL of morphine equivalent) may be given at a dose of 0.1 mL/kg and increased as needed every 3-4 hours by 0.05- to 0.10-mI. increments. The usual dose is 0.2-0.5 mL every 3-4 hours. Other options are oral paregoric (0.8-2.0 ml./kg per day, given in six to eight divided doses) and chlorpromazine (2-3 mg/kg per day given in four divided doses), which effectively control both the CNS and gastrointestinal symptoms. Paregoric contains camphor, which is a stimulant and may have adverse effects in premature infants. Chlorpromazine may cause extra-pyramidal disorders and a lowered seizure threshold. Treatment must be continued for several weeks and tapered gradually to avoid recurrence of symptoms.

Phenobarbital (loading dose of 20 mg/kg, followed by a maintenance dose of 5 mg/kg per day) or diazepam (0.5-1.0 mg intramuscularly every 8 hours! controls only the CNS abnormalities but ii"cs not relieve the gastro-intestinal symptoms. These drugs also cause sedation that may worsen feeding problems. Therefore tincture of opium should be used first and phenobarbital added if CNS abnormalities are not controlled by the narcotic agent alone, which is a distinctly unusual situation.

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Chapter 87
Neurological Problems of Pregnancy

D. Malcolm Shaner

Diseases of the nervous system develop and continue despite pregnancy. The good neurologist maintains a broad perspective, balancing the needs of the woman, her fetus, and her loved ones. Insofar as this audience creates an atmosphere for performance, the clinician may feel like a stage character prompted by cues from scattered, incomplete, and occasionally contradictory findings reported in the literature. Still, neurologists who enjoy drama find gratification in caring for the pregnant woman with neurological disease.

NEUROLOGICAL COMPLICATIONS OF CONTRACEPTION

The neurologist can help to plan *a* pregnancy in a woman with pre-existing neurological disease. The expected burden of the woman's neurological disease must be balanced against her perceived need for procreation. Asking her to consider the effect of a child on her life and how the child might be affected by her illness can be beneficial. For instance, a patient who is wheelchair-bound with spinal muscular atrophy or muscular dystrophy may have difficulty with breathing during the later stages of pregnancy, may need cesarean section to deliver the baby, and may have great difficulty lifting the baby as it grows. The neurologist may discuss prenatal genetic testing with women affected by inherited neurological disease. Many-women welcome the neurologist's uninvolved opinion.

Women who decide against pregnancy and use oral contraceptives should be informed that agents containing more than 80 ug of esrrogen are linked to increased incidence of stroke. Information on rhe use of agents containing less than 50 fig of estrogen in nondiabetic, nou hypertensive patients indicates that these agents pose no additional risk or at most a true relative tisk of ischemic stroke of no more than 2,5. Given the very low annual incidence of ischemic stroke in the normal population of women aged 15-44 of approximately 11.3 per 100,000, this small or nonexistent added risk can be considered safe. When women taking this dose smoke cigarettes, the risk of hemorrhagic stroke increases the odds ratio to 3.64 with a 95% confidence interval of 0.95-13.87. Stroke in pregnancy and the puerpenum is discussed later.

Some neurologists advise their female epileptic patients taking microsomal enzyme-inducing anticonvulsants to increase the dose of estrogen in their contraceptives to at least 50 pg. Although this adjustment increases contraceptive effectiveness, the efficacy of the regimen is untested. The result is that barrier, spermicidal, or other contraceptive measures often are recommended for use simultaneously or exclusively. Valproic acid does not induce microsomal enzymes significantly, but there are no studies confirming !,ick n! ilnm iiueracdor with estrogen contraception,

Anticonvulsants do not affect the efficacy or dose of medroxyprogesterone. Medroxyprogesterone may be the contraceptive of choice in women with seizure disorders (Kaunitz 2000). Unwanted pregnancies with levonorgestrel

use have occurred in women taking phenytoin and in women taking carbamazepinc. Some authors advise against the use of levonorgestrcl in patients taking liver enzyme-inducing drugs of any kind, including enzyme-inducing anticonvulsants.

Some neurologists recommend that hormonal contraceptives not be used in women with activated protein C resistance. Estrogen-containing oral contraceptive agents may worsen chronic inflammatory demyelinating polyneuropathy (CIDP), unmask systemic lupus erythematosus, worsen migraine, and produce chorea in patients with antiphospholipid antibody syndrome. The heightened risk of cerebral venous thrombosis (CVT) in women taking oral contraceptive agents increases with prothrombin or factor V gene mutations.

ETHICAL CONSIDERATIONS

Partially settled and unresolved ethical difficulties complicate care of the gravid woman with neurological disease. These problems arc rooted in the occasionally conflicting goals of therapy between mother and fetus. In nearly every instance, physicians juggle responsibilities toward a pregnant woman and the unborn child. In complex situations, multiple interested parties may demand a determining say including the husband, the father (if not the same as the husband), the family, the state, legal representatives, and political and religious groups.

When the neurologist diagnoses maternal death by neurological criteria, a decision must be made whether to conlinue medic;;l inicrvnirious for the sake of a viable or marginally viable fetus. There is no consensus as to the conditions under which such medical intervention must be offered. Physicians sometimes turn to the ethically appropriate surrogate(s) (sometimes one for the mother and one tor the fetus) to discuss the foreseeable possible futures and to ask the surrogate to make a decision with regard to offered medical therapies. A model for this procedure, which the Ethics, Law, and Humanities Committee of the American Academy of Neurology Committee, recommended for affirmation, can be obtained though the Council on Ethical Affairs of the California Medical Association (Council on Ethical Affairs 2002). In some states, the physician helps to select surrogates. In others, a statute-driven "hierarchy" exists. Some states prohibit an appropriate surrogate from permitting the termination of pregnancy for an incapacitated patient but not when the patient is dead. Advising pregnant women to execute advance directives for medical care seems an unlikely and incomplete solution.

HEADACHE

Headache during pregnancy is common. Usually a patient visits the neurologist to receive reassurance that no serious medical problem is apparent. Of the headaches that occur during pregnancy, benign tension headaches are seen most often (sec Chapter 75), There is no known association with hormones and, specifically, no association with the hormonal changes of pregnancy. Treatment for mild headaches often includes behavioral therapy, adequate rest, moist heat, massage, exercise, avoidance of triggering factors, and use of acetaminophen. For severe headaches, the use of a tricyclic antidepressant, such as amitriptyline or nortriptyline, may be helpful. No evidence of embryopathy has been reported with amitriptyline, and preschool children exposed m utero to tricyclic antidepressants have notmal global IQs, language, and behavioral development. When significant comorbid depression is treated, fluoxetine may also be helpful,

Approximately 80% of women with migraine clearly show improvement during pregnancy, but 15% continue to have headaches and in 5% headaches worsen. The prognosis for women with migraine without aura is better than that for women with migtaine with aura. For women anticipating pregnancy, the physician may consider the discontinuation or reduction in dose of all migraine medications because of possible fetal damage. Vigorous treatmen r with behavioral therapy, moist heat, and the judicious use of acetaminophen or opioid preparations can be considered. Migraine usually lessens during the second and third trimesters. The diagnosis of complicated migraine, or de novo migraine with aura, should be made during pregnancy only after a thorough consideration of other diagnoses.

Pregnancy complicates usual migraine therapy. Ergotamine and dihydroergotamine are associated with high rates of fetal malformation and are contra indicated. Eor newer drugs, such as sumatriptan, data are incomplete, and theit general use cannot be advised. Limited information compiled by the makers of sumatriptan and a small prospective study suggest a low teratogenic potential. This news has provoked some authors to suggest that prescription of sumatriptan may be acceptable in pregnant women who suffer physiologically and psychologically disabling migraine, whose headaches respond to sumatriptan, and in whom safer medications have failed (Von Wald 2002). Valproic acid causes fetal ma 1 format ions. During pregnancy, the use of valproic acid to treat headache eithet abortively or prophylactically should be avoided.

There are rare descriptions of fetal toxicity with propranolol, atenolol, and other beta blockers but not with metoprolol. Although often safe during pregnancy, these drugs usually are discontinued or usage is reduced to the lowest effective dose. When physician and patient are convinced that prophylactic therapy is required, the benefit of metoprolol, propranolol, or verapamil may outweigh risks. Incomplete data are available for lithium usage in humans. In animals, lithium is teratogenic. Use during pregnancy to treat headache should be avoided. Naproxen sodium is relatively safe throughout pregnancy but safest

when used during the first two trimesters. Metoclopramidc, acetaminophen, and meperidine do not increase fetal risk and may be of benefit.

In general, the breast-feeding woman with migraine should avoid ergotamine and lithium. Sumatriptan, antidepressants, and neuroleptics can be used cautiously.

LEG MUSCLE CRAMPS

Between 5 and 30% of pregnant women experience painful leg cramps, which do not adversely affect the fetus and are not dangerous but can be very bothersome to the patient. The condition resolves rapidly postpartum. Typically, cramps occur in the morning or evening during the last trimester of pregnancy. Changes in the ionic concentrations of potassium, magnesium, sodium, and calcium may be important in the pathogenesis. Magnesium lactate or magnesium citrate tablets (122 mg in the morning and 244 mg in the evening) relieve or considerably lessen symptoms in approximately 80% of patients. Placebo is similarly effective in 40%. Some physicians report successful therapy with oral calcium carbonate or gluconate 500 mg three or four times daily. Passive stretch and massage are helpful for the acute cramp,

RESTLESS I.ECS

Unpleasant paresthesias (desctibed as creeping, crawling, aching, or fidgetiness) localized deep within both legs affect 10-27% of pregnant women. Usually they begin 30 minutes after the patient lies down and are reported mainly in the last trimester. An irresistible desire to move the legs accompanies the discomfort,

Approximately 80% of patients complaining of restless legs experience periodic movements of sleep {see Chapter 74). These are stcteotyped flexion movements of the legs during non-rapid eye movement sleep, which may awaken the patient, leading to sleep loss and excessive daytime somnolence. Caffeine ingestion, uremia, alcohol use, iron deficiency, hypothyroidism, vitamin deficiency, rheumatoid arthritis, peripheral neuropathy, and medications are important, if only occasional, associated factors.

Folic acid 500 mg daily may be of benefit in treating restless legs during pregnancy. Anecdotal reports suggest a benefit from vitamin E, vitamin C, and magnesium supplements. Electric vibrators, stretching, walking, decreased activity, and massage also may be helpful. For severe restless legs during pregnancy, i.-dopa/carbidopa 25 mg/100 mg may be preferable to several other dopamine agonist medication-; sliowr. to *he* effective in nonpregnant patents. A single dose before bedtime, increasing to efficacy or the use of several doses through the night has been anecdotally reported to be helpful. Advantages of the use of the L-dopa/carbidopa combination include its demonstrated clinical effectiveness for both restless legs and periodic movements of sleep and its low teratogenic potential.

MYASTHENIA GRAVIS

Fertility is unaffected by myasthenia gravis, and oral contraceptive agents do not weaken the patient with myasthenia gravis. No single study offers certainty with regard to the cumulative risk that pregnancy causes in the patient with known myasthenia gravis. Pregnancy did not worsen the long-term outcome of patients with myasthenia gravis in one small prospective Italian study (Batocchi et al. 1999). Patient conditions may remain stable, improve, worsen, or both improve and worsen at different stages of pregnancy. Approximately two thirds of patients report some worsening at some time during pregnancy or the puerperium. The puerperium and first trimester are times of greatest risk. The course of myasthenia gravis for a future pregnancy cannot be predicted from the course of previous pregnancies.

The effect of thymectomy on myasthenia gravis usually is delayed. The potential mother can be advised that the procedure may be helpful for a pregnancy beginning approximately 1 year after surgery. Generally, the woman who may become pregnant is best served when the physician uses drugs other than azathioprine and cyclosporine, Azathioprine is teratogenic, and the safety of cyclosporinc during gestation is uncertain.

Myasthenia gravis docs not influence the contractile strength of the smooth muscle of the uterus, the incidence of postpartum hemorrhage, or the occurrence of toxemia. Usually, the course of labor and delivery is unaffected. Premature labor may be more common in women widi myasthenia gravis but varies considerably among studies.

The medical therapy of myasthenia gravis changes little with pregnancy. Anticholinesterase agents including edrophonium (Tensilon) and plasmapheresis arc relatively safe, Rapid drug metabolism during pregnancy may require increasing the rate or dose of anticholinesterase drugs. Corticosteroids may increase the risk of gestational diabetes and preeclampsia. Abortion does not lessen the manifestations of myasthenia gravis. Although human immunoglobulin has been used safely during pregnancy, the number of patients studied is small.

Regional anesthesia is preferred for cesarean section. When the patient is taking anticholmestetase agents, the metabolism of procaine is slowed and poorly predictable. In those patients, lidocaine is favored for local anesthesia, Neuromuscular blocking agents, such as curariform drugs, must be avoided, because they may have a greatly prolonged effect in patients with myasthenia gravis. The use of magnesium sulfate as a tocolytic agent or as a treatment for preeclampsia may precipitate a myasthenic crisis and is contraindicated.

When the pregnant woman with myasthenia gravis develops the rare complication of immunologically mediated thrombocytopenia, intravenous immunoglobulin may be helpful before delivery to increase the platelet count to greater than 50 x 10^9/litcr (Ellison 2000).

Perinatal mortality increases to 6-8% for infants of women with myasthenia gravis, which is approximately five times that of the normal population. Approximately 2% of these are stillborn. Transient neonatal myasthenia affects 10-20% of infants born to women with myasthenia gravis. Most infants who develop transient myasthenia gtavis do so within the first day, but weakness may begin up to 4 days after delivery and usually resolves within 3-6 weeks. Neonates must be observed carefully for at least 4 days. An imperfect correlation has been observed between maternal levels "I ai....cetylcholine receptor antibodies and the likelihood that the neonate will develop transient myasthenia gravis. Intrauterine exposure to these receptor antibodies rarely may result in arthrogryposis.

Breast-feeding poses no significant difficulty, although there is evidence that the antiacetylcholine receptor antibodies do pass to the baby in the breast milk. Cyclosporine and azathioprine are secreted in breast milk; they should be avoided because of theit tisk of immunosuppression and riimorigcnic potential. Corticosteroids also are secreted into breast milk but in small amounts. Large doses of anticholinesterase drugs taken by the mother may lead to gastrointestinal upset in the breast-fed newborn.

DISORDERS OF MUSCLE

Myotonic Dystrophy

Pregnancy is uncommon in women who have advanced myotonic dystrophy, probably because of progressive ovarian failure. Before the development of advanced disease, there is no significant reduction in fertility. For women who are able to conceive, pregnancy can be hazardous for both mother and fetus. Myotonic weakness often worsens during the second half of pregnancy. Congestive heart failure is reported. Ineffective uterine contractions, premature labor, and breech presentation often complicate labor. Tocolysis may result in aggravation of myotonia. Oxytocin can stimulate the myotonic uterus to produce increased contractions. Myotonic dystrophy complicates obstetric anesthesia, and regional anesthesia is preferred. Patients with myotonic dystrophy are unduly sensitive to respiratory suppression with pentobarbital. After delivery, hypotonic uterine dysfunction results in an increased risk of retained placenta and postpartum hemorrhage. One half of the children bom to women with myotonic dystrophy inherit the disordet. Anticipation due to an increased number of triplet repeats (see Chapter 44) is responsible for the syndrome of congenital myotonic dystrophy in the neonate (see Chapter 85). Many neonates are hypotonic, and high rates of morbidity are reported. Fetal myotonic dystrophy may affect fetal swallowing, causing polyhydramnios. Prenatal diagnostic testing with amniocentesis or chorionic villus biopsy is available.

Inflammatory Myopathy

Pregnancy worsens or activates polymyositis and derma tomyositis. Manifestations of collagen vascular disease commonly associated with myositis may complicate pregnancy. More than one half of fetuses die, but surviving infants thrive. Immunosuppressive treatment is advised for gravid women.

Neuropathy

Bell's Palsy

Facial nerve palsy is three to four times more common during pregnancy and the puerperium. A retrospective chart review found the prognosis for recovery of facial nerve function to be worse when facial palsy occurs during pregnancy (Gillman 2002). Some researchers found an increased incidence of toxemia in patients with gestational facial palsy. Herpes simplex virus type 1 is implicated as the cause of most facial palsies and varicella-zoster far less often. Pharmacological therapy of Bell's palsy during pregnancy remains controversial. Prednisone 1 mg/kg for 5 days, tapering rapidly over a total 10-day course when begun within 3 days of onset of facial weakness, may be effective in improving the prognosis in nongravid adults. Simultaneous administration of acyclovit 400 mg five times daily for 10 days is more effective than prednisone alone in a similar population. This combination of drugs has not been tested adequately during pregnancy, but individually the drugs pose low risk. Patching of the eye and lubricating eye drops may help prevent corneal irritation (see Chapter 76).

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Approximately one in five pregnant women reports nocturnal hand paresthesias, primarily during the last trimester, often associated with peripheral edema. Excessive weight gain and fluid retention increase the occurrence of these complaints. This irritation can be expected to disappear spontaneously within weeks after parturition. During pregnancy, conservative therapy is indicated. Splinting of the wrist in the neutral position at night is helpful. Additionally, some physicians inject corticosteroids into the carpal tunnel. When hand muscles supplied by the median nerve weaken, surgical decompression using fiberoptic techniques is indicated.

Meralgia Paresthetica

The expanding ahdominal wall and the increased lordosis of pregnancy stretch the lateral femoral cutaneous nerve to the thigh as it penetrates the tensor fascia lata or at the inguinal ligament. This unilateral or bilateral affliction of late pregnancy resolves within 3 months postpartum.

Acute Polyradiculoneuropathy (Guillain-Barre Syndrome)

Pregnancy does not affect the incidence or course of acute polyradiculoneuropathy. Usually, infants of a mother without complications are born healthy. Some authors recommend fluid loading before plasmapheresis to prevent hypotension. Others suggest avoidance of tocolytics in the presence of autonomic instability. Intravenous human immunoglobulin has been used safely during pregnancy, but the number of patients who received this therapy and were srudied remains small.

Chronic Inflammatory Demyelinating Polyneuropathy

CIDP is three times more likely ro relapse during the last trimester and puerperium than in the absence of pregnancy. Infants are unaffected. Corticosteroids, plasmapheresis, and intravenous immunoglobulin are used to treat exacerbations during pregnancy. Oral contraceptives can worsen CIDP.

Charcot-Marie-Tooth Disease Type 1

Small studies indicate that Charcot-Marie-Tooth disease type 1 worsens in approximately one half of affected women during pregnancy. The magnitude of the effect of pregnancy on this disease remains unclear. Risk is less when weakness begins in adulthood. After delivery, this deterioration improves in one third of patients and becomes persistently progressive in two thirds of patients. The course and outcome of pregnancy are unaffected. Epidural anesthesia for labor has been used safely.

Gestational Polyneuropathy

Distal symmetrical neuropathy affects malnourished women. Presumably, thiamine and possibly other nutrients are deficient in these patienrs. The acute presentation of symmetrical neuropathy and Wernicke's encephalopathy (see later) in the third and fourth months may be due to the thiamine deficiency associated with hyperemesis gravidarum.

Maternal Obstetric Palsy

Peripheral nerves are occasionally the objects of intrapartum compressive trauma by the fetal head, the application of forceps, and improperly positioned leg holders. Craniopelvic disproportion, dystocia, prolonged labor, and primigravida status contribute to these injuries.

Unilateral lumbosacral (L4, L5, and rarely SI) plexus injury is most common. The fetal brow strikes the nerves as they cross the posterior brim of the true pelvis. The associated sensory deficir usually involves more widespread sensory loss than that due to peroneal neuropathy. Peroneal nerve injuries often are caused when the nerve is compressed between a leg holder and the fibular bead. Less common obstetric palsies include those of the femoral and obturator nerves.

Most maternal obstetric palsies are neuroapraxic and resolve **willnn** (> WIVKS. 1:I iutii:v **pnr.i)i iki;.-..** women **with** recurrent craniopelvic disproportion, dystocia, or axonal degeneration with their initial neuropathy are candidates for cesarean delivery. Otherwise, a cautious trial of labor may be prudent.

WERNICKE'S ENCEPHALOPATHY

More than three fourths of women experience nausea and vomiting during pregnancy, most commonly between 6 and 16 weeks' gestation. When vomiting becomes severe enough to result in weight loss or metabolic derangement requiring intravenous therapy, the term *hyperemesis gravidarum* is applied. Commonly, hyperemesis is isolated and idiopathic. Molar pregnancy, hyperthyroidism, and hepatitis are differential diagnostic considerations. Studies on treatment with vitamin B_6 (pyridoxine) 10 mg three times per day for 5 days showed little benefit, but enthusiasts continue to recommend this treatment, sometimes with ginger (Niebyl 2002).

Apathy, drowsiness, memory loss, catatonia, ophthalmoplegia, nystagmus, ataxia, optic neuritis, and papilledema may result, typically between 14 and 20 weeks" gestation, and are described as features of Wernicke's encephalopathy (see Chapter 63). This condition is sometimes associated with gestational polyneuropathy and central pontine myclinolysis. Exacerbating factors include persistence of the hyperemesis over at least 3 weeks and the administration of intravenous glucose without other nutrients. Death or severe morbidity results when this condition is not treated. In a small study, only one half of women with this condition delivered normal children.

The amount and duration of parenteral thiamine supplementation that are required is unknown and must be titrated to the clinical state. Generally, parenreral therapy for at least 1 week is recommended or until a normal diet can be resumed. Despite therapy, some women continue to have ataxia and visual difficulties months to years afterward. Several authors suggest treating any patient with prolonged nausea and vomiting with oral thiamine 100 mg daily.

CHOREA GRAVIDARUM

Chorea of any cause beginning in pregnancy is chorea gravidarum. Historically, rheumatic heart disease (often fatal) was associated with most cases. Rheumatic heart disease has virtually disappeared. Today, the disease linked most strongly with this condition is the antiphospholipid antibody syndrome, with or without systemic lupus erythematosus. Additional etiologies include tardive dyskinesia due to neuroleptics, hyperthyroidism, Wilson's disease, vascular disease, other hypercoagulable states, and a variety of intoxications.

Chorea commonly presents during the second to fifth months of pregnancy and uncommonly may begin postpartum. Subtle, sometimes severe, cognitive change may accompany the chorea. Usually, this condition resolves spontaneously within weeks to months, often shortly after delivery. Choice of therapy tor this often benign condition depends on the severity of the disorder and other accompanying clinical manifestations. Expectant observation, cautious use of haloperidol, and use of corticosteroids have been successful. Oral contraceptives also have been associated with the appearance of chorea. The mechanism by which pregnancy and oral contraceptives cause chorea is unknown. Chorea may recur in subsequent pregnancies.

MULTIPLE SCLEROSIS

Uncomplicated multiple sclerosis has no apparent effect on fertility, pregnancy, labor, delivery, the rate of spontaneous abortions, congenital malformations, or stillbirths. The approximately 13% reduction in pregnancy rate among women with multiple sclerosis noted in one study may resell Iron: plusioi] di-,abilil\ and from iviimtii deciding not to have children. Oral contraceptive agents do not affect the incidence of multiple sclerosis (Hernan et al. 2000).

Despite several careful studies, the effect of pregnancy on the course of multiple sclerosis remains controversial. Small, prospective analyses challenge the long-held conclusion that multiple sclerosis worsens overall as a result of pregnancy. Some authors suggest that pregnancy has either a beneficial effect or no significant effect on disease course. Larger, retrospective studies describe a decrease in the exacerbation rate of multiple sclerosis during the last trimester and an increased rale during the 6 months after parturition. Glatiramer acetate, interferon-/3-1a, and interferon-^-lb have not been studied adequately during pregnancy. Until information is available regarding safety, these medications should be discontinued before an anticipated pregnancy. Mitoxantrone causes fetal damage in animals. Mitoxantrone should not be used during pregnancy and only with contraceptives in fertile women.

Management strategies for multiple sclerosis must be adapted to the individual pregnant patient. Anecdotal reports detail the success of plasmapheresis in a pregnant woman with rapidly progressive multiple sclerosis and in another woman with Devic's syndrome. Clinical improvement has been associated with the use of intravenous immunoglobulin in a few case studies. Short-term courses of corticosteroids during pregnancy seem safe, but baclofen and tizanidinc have not been well studied.

TUMORS

Primary Brain Neoplasms

Brain tumors of all types occur during pregnancy, but only at 38% of the rate expected in nonpregnant women of fertile age. Diminished fertility in women with these tumors may explain this reduction, because pregnancy probably does not protect against the development of neoplasms. Studies show increased numbers of abortions before the symptoms of tumor appear. Whether pregnancy worsens morbidity and mortality in women with brain tumors is not known, hut certain tumors grow more rapidly during pregnancy. Meningiomas have estrogen receptors, which may explain the enlargement usually seen during pregnancy. The rate at which spinal hemangiomas rupture inert .sis with the duration of gestation, Symptoms ol meningioma, vascular tumors, and acoustic neuromas may remit postpartum due to tumor shrinkage.

Gestational brain tumors tend to present at different stages dependent on tumor type: gliomas usually present problems during the first trimester, meningiomas during and after the second trimester, and vascular tumors in the third trimester.

Malignant tumors or tumors threatening compression of vital brain structures usually require surgery during pregnancy. Surgery for some benign tumors can wait several weeks postpartum to observe for spontaneous improvements. Babies of most women with brain tumors arc delivered by cesarean section. Vaginal delivery is reserved for patients whose tumor would not pose a threat of herniation with the shifts of intracranial pressure associated with labor. Pregnancy interruption is considered when increased intracranial pressure, vision loss, or uncontrolled seizures develop as a result of the tumor.

Administration of corticosteroids commonly lessens symptoms of brain tumors (see Chapter 58), but fetal hypoadrenalism may result from their use. Physicians usually defer potentially teratogenic chemotherapy until after delivery. Cranial radiation therapy during pregnancy may be helpful to the mother, but no dose of radiation can be considered completely safe for the fetus. The fetus usually is seriously affected when it receives doses greater than 0.1 Gy (10 rads), which may cause growth retardation, microcephaly, and eye malformations. The fetus may be affected by lower amounts of radiation, particularly early in gestation. Researchers

estimate that in utero exposure to 0.01-0.02 Gy of radiation increases the incidence of leukemia by 1 case per 6000 exposed children. Estimates of the fetal dose during radiation for brain tumors range from 0.03-0.06 Gy. One study suggests that alternative positioning of the patient may reduce fetal exposure to as little as 0.003 Gy when a dose of 30 Gy is delivered to the brain (Magnc 2001).

Pituitary Tumors

Women with untreated hyperprolactinemia often are anovulatory and infertile. Treatment with dopamine agonists restores ovulation in 90% of patients. During pregnancy, medical therapy focuses on preventing complications of tumor growth. Bromocriptine reduces prolactinoma size usually within 6 weeks to 6 months. Although this drug has not been demonstrated to have teratogenic potential, some authors recommend discontinuation of the medication unless it is clearly needed during pregnancy. Bromocriptine suppresses lactation. Puerperal maternal hypertension, seizures, stroke, and cerebral angiopathy have been reported anecdotally with its use. Data on other dopamine agonists during pregnancy are limited. The normal pituitaty gland and most pituitary tumors grow during pregnancy. The woman with a pituitary microadenoma (<I0 mm I may be reassured that fewer than 5% of these tumors grow enough to become symptomatic. The risk for a macroadenoma becoming symptomatic tanges from 16 to 36% but is considerably less for patients who receive radiation or surgical therapy before pregnancy. Commonly, physicians advise women with macroadenomas to have transsphenoidal surgery before attempting pregnancy or to receive bromocriptine therapy during pregnancy. Visual fields and acuity can be checked monthly. Monitoring of prolactin levels is not helpful. Magnetic resonance imaging (MRI) is indicated after delivery and should be performed if symptoms are increasing. For the woman in whom a symptomatic macroprolactinoma is diagnosed during pregnancy, therapeutic options include bromocriptine therapy, pregnancy termination, or surgery.

Usually, women with pituitary tumors deliver vaginally. Studies have not demonstrated tumor growth associated with breast-feeding. Pituitary apoplexy may present within days, weeks, or occasionally years after delivery. Uncommonly, a pituitary mass presenting in late pregnancy, or up to 1 year postpartum, may be lymphocytic hypophysitis.

Choriocarcinoma

Cerebral metastases are a common manifestation of this rare tumor of trophoblastic origin. The tumor metastasizes first to the lung and then from lung to brain. This often happens months after a molar pregnancy or abortion. Approximately 15% of tumors follow normal pregnancies, but most are discovered after pregnancies characterized by spontaneous abortion or by vaginal bleeding, premature labor, and an enlarged uterus due to a molar pregnancy. Women with such cerebral metastases present with seizures, hemorrhage, Infarction, or gradually progressive deficits. Tumor may invade the sacral plexus, cauda equina, or spinal canal. A ratio of serum to cerebrospinal fluid chorionic gonadotropin less than 60 suggests the presence of choriocarcinoma brain metastasis. Chemotherapy, radiation, and surgery have yielded successful results when the diagnosis is made early.

Idiopathic Intracranial Hypertension (Pseudotumor Cerebri) {see Chapter 65)

Idiopathic intracranial hypertension (IIH) usually worsens with pregnancy. Some authors advise a delay in pregnancy until all signs and symptoms of pre-existing 11H abate. Termination of pregnancy is of unknown value and is not indicated. Healthy babies usually result tegardless of whether IIH begins before or during pregnancy,

Commonly, IIH develops during the fourteenth gestational week and disappears after 1-3 months, but it sometimes persists until the early puerperium. Typically, these women are obese and gain weight rapidly with pregnancy. Brain imaging is normal or may show slitlike ventricles. Protein levels may be slightly low in otherwise normal spinal fluid.

Frequent checks of optic fundi, visual acuity, and visual fields are recommended to monitor the condition and the results of treatment. Initial cerebrospinal fluid pressures that exceed 350 mm H2O usually indicate more severe disease. Careful studies of the effectiveness of treatment arc unavailable. Most physicians advise moderation in diet to reduce weight gain. Two-week courses of corticosteroids, most commonly dexamethasone or prednisone, may be added for vision loss. Four to six serial lumbar punctures can be performed, sometimes weekly, before optic nerve sheath fenestration or lumbopentoneal shunt is considered.

The use of acetazolamide remains controversial; human studies are inadequate to determine its efficacy or teratogenic potential. Nevertheless, acetazolamide has been used to treat IIH during many pregnancies productive of healthy infants. Some physicians recommend restricting its use until after 20 weeks' gestation.

Headaches may be improved by acetaminophen with or without codeine. More aggressive therapy usually is reserved for vision loss. Adequate pain control during labor may decrease expected rises in intracranial pressure.

Usually, these patients can undergo vaginal delivery with epidural analgesia. Recurrence of IIH in a subsequent pregnancy is unusual.

EPILEPSY AND ITS TREATMENTS

Maternal Considerations

Women with epilepsy have approximately 15% fewer children than expected. Reasons offered for this decrease in fertility include social effects of epilepsy, menstrual irregularity, the effect of some antiepileptic medications on the ovaries, and an effect of seizures oil reproductive hormones.

The effect of pregnancy on seizure occurrence can be predicted from the control of epilepsy during the 9 months preceding gestation. The fewer seizures there are in the 9 mn:uhs (•:••:in- ₍-:>iKY-iruii. -In- Im'.iT ihe risk of wors ening during the pregnancy. Women who have at least one seizure in a month can be expected to have mote seizures during pregnancy. Women who have less than one seizure in 9 months usually do not experience an increase in seizure rate during pregnancy.

Most studies suggest that approximately one fourth of women experience an increase in seizure rate during gestation, which may result from lowered levels of circulating unhound antiepileptic drugs (AEDs). Pregnancy alters protein binding of many AEDs and increases the volume of distribution and metabolism of many drugs. However, even when blood levels of drugs are maintained adequate!;.. .ip^iiixiiirrrb I!)',',', ◁] women can expect worsened seizure control during pregnancy. During labor, approximately 1-2% of epileptic women have a convulsive seizure, and another 1-2% have a seizure within 24 hours of delivery. Other factors that may contribute to an increase in seizure rate include hormonal changes, sleep deprivation, mild chronic respiratory alkalosis, the use of folic acid supplements, and emotional factors. Seizure type did not play a role in some studies, but in othets, partial complex epilepsy worsened more often during gestation,

Convulsive seizures during pregnancy can result in blunt trauma to the mothct. Trauma is the leading nonobstetric cause of maternal death in women with epilepsy, but its incidence is ven low .

Controversy continues over whether seizures increase risks for developing eclampsia, preeclampsia, blood loss, placental abruption, and premature labor. For studies that claim increased risk, these risks are calculated to be approximately 1.5-3.0 times the risk of women without epilepsy. These reports have been based largely on retrospective and registry studies. The limited prospective data suggest that women with epilepsy have no or minimal additional risk for these complications.

Fetal Considerations

Nearly 90% of epileptic women deliver healthy, normal babies, but risks of miscarriage, stillbirth, prematurity, developmental delay, and major malformations are increased in epileptic mothers. Maternal seizures; AEDs; and socioeconomic, genetic, and psychological aspects of epilepsy affect outcome.

Although AEDs may cause significant problems for the fetus, the consensus among neurologists has been that maternal seizures probably are more dangerous. Convulsive seizures cause fetal hypoxia and acidosis and are associated with the potential for blunt trauma to the fetus and placenta (Holmes et al. 2001). Fetal heart rate slows during and for up to 20 minutes after a maternal convulsion, which suggests the presence of fetal asphyxia. The child of an epileptic mother experiencing convulsions during gestation is twice as likely to develop epilepsy as the child of a woman with epilepsy who does not have a convulsive seizure during gestation,

In previous studies, the rate of major birth defects in the general population has been estimated to be approximately 2.0—4.8%, depending on the population studied and methodology used. The risk of birth defects increases for infants of women with epilepsy to a rate of 3.5-6.0%, independent of the effect of medication. In general, use of a single AED increases the risk of congenital malformations to 4-8%. Researchers found a 5.5% incidence of malformations with two anticonvulsant drugs, 11 % with three anticonvulsant drugs, and 23% with four AEDs.

Data from a large study add to our knowledge of the influence of gestational seizures and the diagnosis of maternal epilepsy on fetal malformation (Holmes et al, 2001). In a prospective study, investigatots screened 128,049 singleton pregnancies in nondiabetic, English-speaking patients at delivery between 1986-1993. They physically examined 414 children of epileptic mothers and 508 control subjects and reported the incidence of major malformations (structural abnormalities of surgical, medical, or cosmetic importance not including microcephaly, growth retardation, or hypoplasia) to be 1.8% in their normal, control population. With one AED (phenytoin, carbamazepine, or phenobarbital), this rate rises to 3,4-5.2% and with two or more to 8.6%. Some women with a history of seizures did not take anticonvulsants during pregnancy and had a rate of major malformation statistically the same as the control population at 0%. Women who suffered seizures during the first trimester and were taking their .lnlkniivukiiil drugs **k.ul** .1 rale **◁ii nujoi malli** iriiiation of 7.4-7.8%, This carefully gathered information challenges the notion that the diagnosis of maternal epilepsy itself contributes to major malformation of the fetus and lays blame for teratogenesis squarely on the use of AF.Ds. Pregnant women may be reassured that current data do not indicate risk of malformation to their fetus Iron-, an uncomplicated seizure during the first trimester.

AEDs exert their most serious effects during the first 2.5 months of gestation. Changes in medication must be made before or during the first trimester to be maximally useful. The neural tube closes between 3 and 4 weeks. Cleft lip and palate occur with exposure before 5 and 10 weeks, respectively, where.is congenital heart disease due to anticonvulsant exposure occurs before 6 weeks' gestation.

Studies disagree on whether the anomalies caused by phenytoin and carbamazepine are dose dependent. Valproic acid increases the risk of neural tube defects and other malformations 3- to 20-fold, to approximately 1-2%, and *as* teratogenic effect ^ are dim[1] related. (.arkiala/cp-.iie also is associated with neural tube defects, with an incidence of 0.5-1.0%. A syndrome described initially as *fetal hydantoin syndrome*—including midfacial hypoplasia, long upper lip, low birth weight, cleft lip and palate, digital hypoplasia, and nail dysplasia—occurs with carbamazepine, primidone, and valproic acid and is more accurately called *fetal anticonvulsant syndrome.* Some minor anomalies usually disappear during the first years of life. Investigators speculate that midfacial hypoplasia associated with hypoplasia of the facial bones could be a marker for cognitive dysfunction. Trimethadione has such a high teratogenic potential that its use during pregnancy is contraindicated, and it should not be used in women who might become pregnant.

Adequate human studies of newer anticonvulsant drugs during pregnancy are lacking. The teratogenic potential of gabapentin, vigabatrin, tiagabine, zonisamidc, lamotriginc, topiramate, clobazam, levetiracetam, and oxcarbazepine is known incompletely. At this time, the physician may consider reevaluating the need for these anticonvulsants in a patient planning pregnancy or substituting an agent whose potential for risk is known,

Common Advice and Management Strategy

The need for AED therapy should be reevaluated before conception. Monotherapy at the lowest effective dose is preferred. Warning the patient about the effects of sleep deprivation and noncompliance with the drug regimen may be helpful when paired with a thorough description of the potential consequences of seizures and benefits of AEDs. AED levels can be monitored more often during gestation and the postpartum period and dosage adjusted as indicated. Women with a family history of neural tube defects probably should be weaned from valproic acid or carbamazepine, particularly if there is a suitable substitute,

Pregnant women with epilepsy who are already taking AEDs when seen by the neurologist should be managed on an individual basis. During pregnancy and particularly after the period of organogenesis has passed, changes in medications are likely to cause more harm than good.

Women who take folic acid supplements before and during pregnancy lower their risk of delivering a child with major malformations. The use of folic acid has become routine, but recommendations vary. The Department of Health in the United Kingdom and the Centers for Disease Control and Prevention in the United States have recommended, respectively, 5 and 4 mg of folic acid daily for women who have had a child with a neural tube defect and 0.4 mg for all other women planning pregnancy. Anticonvulsants inhibit the absorption of folic acid. Occasionally, folic acid lowers levels of anticonvulsants. Some authors suggest that 5 mg of folic acid be given daily to women treated with valproic acid or carbamazepine. Others recommend 2-4 mg daily for all women with epilepsy who are taking anticonvulsants, beginning as long as 3 months before conception until 12 weeks' gestation.

In one study, women taking AEDs and a multiple vitamin supplement containing folic acid had no teduction in the risk to their infants of developing cardiovascular defects, oral clefts, or urinary tract defects compared with women who took no supplements (Hernandez-Diaz 2000).

Eor patients taking AEDs during pregnancy, a second-trimester high-resolution ultrasound evaluation helps to exclude spina bifida aperta, cardiac anomalies, and limb defects. When results of the ultrasound scan are inconclusive, amniocentesis can be considered and tv-feroprorein and acetylcholinesterase levels obtained.

A deficiency of vitamin K-dependenr clotting factors occurs in some neonates born to women who take phenobarbital, primidone, carbamazepine, ethosuximide, or phenytoin. Although rarely reported, neonatal intracerebral hemorrhage may be attributable to this vitamin K deficiency. In an attempt to lower this risk, physicians prescribe oral vitamin Ki 10-20 mg daily beginning 2-4 weeks before expected delivery and until birth. Often, the neonate receives a single 1- to 2-mg intramuscular injection of vitamin K| immediately after delivery. The American Academy of Pediatrics has recommended that physicians inject every newborn with 1 mg of vitamin K_L intramuscularly. When hemorrhage occurs, fresh-frozen plasma corrects the hemorrhagic state acutely. When the expectant mother who is taking AEDs presents in labor without having received vitamin K, supplements, some authors recommend administration of 10 mg of intravenous vitamin K| to the mother during labor, 2 mg to the neonate immediately postpartum, and fresh-frozen plasma if needed on the basis of fetal cord coagulation studies. Despite this sage advice, a study by Kaaja (2002) could not support the hypothesis that maternal enzyme-inducing AEDs increase the risk for bleeding in offspring, yet the author endorses antenatal administration of vitamin K in selected women taking AEDs during pregnancy.

Occasionally, seizures occur for the first time during pregnancy. Pregnancy has little effect on the use of diagnostic examinations and treatment considerations. The most common causes of seizures during child bearing years include idiopathic epilepsy, trauma, congenital defects, neoplasms, meningitis, intracerebral hemorrhage,

and drug or alcohol toxicity. In addition, pregnancy predisposes women to certain epileptogenic conditions, such as eclampsia, water intoxication, thrombotic thrombocytopenic purpura, sinus or cortical venous thrombosis, and amniotic fluid embolus. Common iatrogenic causes of epilepsy include hyponatremia due to intravenous fluid infusion during the intrapartum period, and the use of epidural or parenteral anesthetics.

A single first-onset seizure resolving within minutes usually can be managed acutely without anticonvulsants. Once the physician determines the cause for the seizure and whether further seizures are likely, the need for anticonvulsant medication can be reviewed.

There arc no special considerations during pregnancy when potentially fatal generalized convulsive status epilepticus is treated. The choice of initial anticonvulsant regimen remains controversial. Physicians agree that use of a specific treatment regimen they arc familiar with and prompt application generally assure the best chance of success. Monotherapy with phenobarbital or lorazepam and combined therapies with phenytoin are effective.

Anticonvulsants are secreted in breast milk and ingested by the infant. Sedation and hypcrirritability are reported. Infants may show withdrawal reactions from phenobarbital after lactational exposure. The World Ilea lib Organization Working Group on Human Lactation and the American Academy of Pediatrics disagree on the safety of breast milk containing ethosuximide, which may cause hypercxcitability and poor suckling. Known health benefits of breast milk probably outweigh potential suhtle and theoretical effects of AEDs on the nervous system. Zonisamide, lamotrigine, and oxcarbazepine arc classified as unsafe to use during breast-feeding, whereas the safety of other newer AEDs remains uncertain.

CEREBROVASCULAR DISEASE

Arteriovenous Malformations

The risk of repeat hemorrhage from a *previously ruptured arteriovenous malformation* (AVM) generally outweighs the risk from surgical excision or an obliterative procedure. Usually, surgical excision can be performed shortly after the diagnosis and before pregnancy is considered. When proton beam irradiation is performed, some authorities advise the woman to wait 2 years before conception. The decision about whether an *unruptured AVM* should be observed, i'\i i-i-ii, c:i::vili/i-ii. or ir:-.idiaii-d rem.lins control **ersial. No** specific therapeutic course can be recommended for patients planning pregnancy.

The risk of hemorrhage from an AVM (whether unruptured or previously ruptured) rises from a low point during childhood and teenage years to a higher risk during childhearing years. Whether pregnancy poses an additional risk remains uncertain. The best retrospective review suggests that risk of hemorrhage during pregnancy resulting from an unruptured AVM may be as low as *3.5"/o.* This is probably no different from the risk to nonpregnant women with unruptured AVMs. Multiple pregnancies do not increase the rate of hemorrhage. In the past, physicians routinely advised women with an AVM, previously ruptured or not, to avoid pregnancy. This conclusion might have been expected from information available from early retrospective studies that 87% of AVMs rupture during pregnancy and that 25-30% of initial tuptures are fatal. Subsequent analysis has contradicted these dismal estimates. Still, we have no prospective studies. The clinician must exercise caution in interpreting this information.

Women whose AVM is repaired surgically can undergo vaginal delivery. Physicians usually perform cesarean section for incompletely repaired or partially treated previously ruptured AVMs. Epidural anesthesia is preferred.

Intracranial Hemorrhage

Women presenting with pregnancy-associated stroke are as likely to have an infarct as an intracerebral hemorrhage. Compared with the nonpregnant state, intracerehral hemorrhage occurs 2.5 times more often during pregnancy and almost 30 times more often during the 6 weeks postpartum. Up to 44% of these hemorrhages are associated with eclampsia and preeclampsia. In France, nearly one half of women with intracerehral hemorrhage associated with eclampsia die. Additional diagnostic considerations include bleeding diatheses, cocaine toxicity, bacterial endocarditis, sickle cell disease, and metastatic choriocarcinoma. In approximately one third of patients who have intracerebral hemorrhage, no specific cause is uncovered.

Subarachnoid hemorrhage is a common cause of nonobstetric maternal death. Hemorrhage from aneurysms and vascular malformations account for 25-35% of intracranial hemorrhages. Management strategies are generally the same as those applied outside of pregnancy. Definitive therapy for AVMs may usually he postponed until after delivery, whereas surgery or obliterative therapy for an aneurysm usually is urgent. The effects of some treatment agents for subarachnoid hemorrhage, such as nimodipine, on the human fetus have not been studied well. However, the potentially fatal consequences of the vasospasm associated with subarachnoid hemorrhage make their use reasonable during pregnancy.

Anticonvulsants, specifically phenytoin, are unnecessary and ineffective in nongravid patients who have had an intracranial hemorrhage hut have not had a seizure. Data during pregnancy are unavailable. Anticonvulsants probably are best reserved for women whose hemorrhage may herniate if intracranial pressure rises with a seizure or after the first convulsion.

Although many physicians recommend cesarean section for patients with gestational intracranial hemorrhage, mode of delivery did not affect outcome in the studies available. Vaginal delivety can be performed with epidural anesthesia.

Ischemic Stroke

Most women who have a stroke before gestation complete uneventful pregnancies with excellent outcomes. Women in whom emboligenic cardiac disease, systemic lupus erythematosus, antiphospholipid antibody syndrome, or other coagulopathies are diagnosed have the added risk tor stroke during pregnancy associated with those conditions. Stroke during one pregnancy by itself is not a risk factor for stroke in subsequent pregnancies.

MRI can be used selectively to scan the brain and the venous and arterial circulations and is useful during pregnancy. No study or clinical observation has detailed harmful effects on mother or child, but detailed longitudinal studies on children exposed in utero to MRI are lacking.

Two-dimensional echocardiography may be the test of greatest importance when a woman with gestational stroke is evaluated. Computed tomography and selective angiography are associated with a small risk to the fetus and must be performed with adequate shielding and hydration. Magnetic resonance angiography may help in the diagnosis of aneurysm, AVM, arteritis, venous thrombosis, or vasospasm, because it is important to avoid radiation wherever possible.

One woman in every 10,000-20,000 deliveries has a stroke. During pregnancy, the risk of cerebral infarction does not exceed the risk in age-matched fertile control subjects, but during the 6 weeks postpartum, the risk is approximately nine times that of the risk of nonpregnant women. Cesarean delivery and gestational hypertension place women at increased risk for stroke.

Eclampsia and preeclampsia are associated with approximately one fourth of pregnancy-related infarcts in the United States and approximately one half of such infarcts in France. In 25-35% of patients, the cause remains unclear. In the remainder, the stroke is symptomatic of a systemic illness, including premature atherosclerosis, hypertension, cardiac disease, hyperlipidemia, diabetes, arterial dissection, Takayasu's disease, vasculitis, antiphospholipid antibody syndrome, systemic lupus erythematosus, sickle cell disease, thrombotic thrombocytopenic purpura, cerebral venous thrombosis, coagulopathies, tobacco, cocaine, and other drug use. Etiologies of stroke unique to pregnancy include chotiocarcinoma, postpartum cerebral angiopathy, and postpartum cardiomyopathy. Stroke during labor or shortly after vaginal delivery may result from an amniotic fluid embolus.

Aspirin at a low dose (60-150 mg per day) has been used throughout pregnancy and is demonstrably safe in the second and third trimesters. No longitudinal studies have confirmed the efficacy of aspirin in the prevention of stroke during pregnancy. The safety and efficacy of clopidogrel and ticlopidine are unknown during pregnancy, and their use in this situation has not been advised.

Cardiac Disease

Prosthetic heart valves are associated with embolization; rates depend on whether the valves are aortic, mitral, bioprosthetic, or mechanical. Mechanical valves have the highest rate, Bioprosthetic valves are associated with better pregnancy outcomes, but some researchers postulate that gestation accelerates the natural rate of calcification and degeneration of these prostheses, ultimately leading to valve failure. We lack convincing studies that demonstrate an effect of pregnancy on these valves.

Attempts to resolve the most pressing issue of anticoagulation in women with mechanical hcatt valves have been unsatisfactory. Risk of thromboembolism of some mechanical valve prostheses during pregnancy has been reported to be 25-35%, much higher than the annual risk m the nonpregnant state of about 1.25-5.4%. In the nonpregnant state, target values for warfarin therapy and the use of aspirin 80-100 mg per day vary, depending on whether the valves are caged ball, tilting disk, or bileaflet. Aortic or mitral valvular location, the presence of atria! fibrillation, left atrial size, or thrombus, and previous thromboembolic episodes also influence some recommendations for anticoagulation (Stein 2001), Conflicting data and incomplete studies impede attempts to ttanslate these recommendations for the pregnant patient.

Warfarin is teratogenic, with maximal effect during the first 6-12 weeks of gestation, and is associated with a high rate of fetal loss, congenital malformations, and mental and physical disability. Physicians postulate that serious complications of warfarin use during the second and third trimesters are caused by microhemorrhages within the brain. Included among these are dorsal midline dysplasia such as corpus callosum dysgcncsis/Dandy-Walker malformation or ventral midline dysplasia with optic atrophy, mental retardation, developmental delay, seizures, and microcephaly. Approximately 30% of living progeny suffer fetal embryopathy. *Fetal warfarin syndrome* includes nasal hypoplasia/stippled epiphyses, limb hypoplasia, low birth weight, hearing loss, and ophthalmic anomalies. One study found that women taking more than 5 mg of wariflrin daily had an increased likelihood of fetal complications—an effect independent of the extent of anticoagulation as measured by the international normalized ratio. Insignificant quantities of warfarin are found in breast milk.

One systematic review and pooling of literature on fetal outcome for women with mechanical heart valves suggests that warfarin embryopathy occurs in 6.4% of live births when warfarin is taken throughout pregnancy (Chan 2000).

A logical therapeutic alternative to warfarin during pregnancy is heparin. Heparin does not cross the placenta and is not associated with teratogenic effects. The substitution of unfractionated heparin for warfarin at or before 6 weeks' gestation eliminates the risk of warfarin embryopathy, but increases the risk of thromboembolic complications over warfarin alone. Regardless of anticoagulant therapy, maternal mortality is approximately 3%, and fetal wastage is 16.3-44.4%. Additional, carefully controlled studies arc needed to clarify the validity of these data.

Some authors recommend that patients with mechanical heart valves who require warfarin be counseled against pregnancy. Others suggest substituting unfractionated or low-molecular-weight heparin (L.V1WH) for warfarin during 6-12 weeks' gestation. Warfarin may then be i . . . >iiikiV w i n disL(>i:lini:.-.[]()ii ol |I:L- h e p a r i n al the thirteenth week. At the middle of the third trimester or at about 36 weeks, warfarin should be discontinued. Heparin may be given optionally until just before early induced labor or cesarian section. Some European experts, based on a belief that the risks of warfarin are overstated, recommend use of warfarin throughout pregnancy (Vcrstracte et al. 2000). In the United States warfarin is categorized by the U.S. Food and Drug Administration as possessing fetal risk "which clearly outweighs any possible benefit to the patient (USFDA Category X)." Complete data on the use of LMWH fot this indication are unavailable.

like unfractionated heparin, LMWH does not cross the placenta and offers additional benefits, including reduced incidence of heparin-induccd thrombocytopenia, osteoporosis, and bleeding complications. No blood test is required to monitor its safety. Relative safety has been demonstrated in small studies that include women with antiphospholipid antibody syndrome and active lupus disease, but clear indications for the use of these preparations are still under investigation. Each vatiety of LMWH has its own therapeutic level and properties. Case reports document thromboembolic complications in women with mechanical valves who receive certain preparations of LMWH during pregnancy.

The incidence of cerebral embolism associated with chronic atrial fibrillation during pregnancy is 2-10%. When atrial fibrillation is associated with cardiac disease, physicians recommend anticoagulation throughout gestation, commonly with high-dose subcutaneous heparin.

Antiphospholipid Antibody Syndrome

Women with circulating antiphospholipid antibodies and without a history of pregnancy loss do not require treatment to prevent stroke during pregnancy. Successful pregnancies without treatment are common. Women with ven high antibody liters, habitual nrst-irimosu-r ahorrion, a single miscarriage in the later trimesters, or a symptomatic antiphospholipid antibody syndrome, particularly with previous stroke, usually receive treatment. Various studies have examined the use of monotherapy or polytherapy in widely ranging doses and combinations of aspirin, prednisone, subcutaneous unfractionated heparin (UFH), intravenous immunoglobulin, and, occasionally, placebo. Studies on LMWH are optimistic, but preliminary. Stroke in these women may occur at doses of heparin sufficient to produce a therapeutic partial thromboplastin time. Some authors advise women seriously ill with symptomatic antiphospholipid antibody syndrome not to become pregnant.

For women with previous thromboembolism, subcutaneous heparin {UFH or LMWH) is recommended, ideally just before conception and throughout pregnancy. Suggested regimens include 10,000 U of unfractionated heparin twice daily with monitoring of partial thromboplastin time, cnoxaparin 40 mg once daily, or dalteparin 5000 U once daily. The dose may be reduced during labor and then continued postpartum usually for 3-7 days.

Women with antiphospholipid antibodies and monosymptomatic habitual pregnancy loss should receive subcutaneous, high-dose UFH, together with low-dose aspirin until 34 weeks' gestation. A combination of low-dose aspirin and LMWH during pregnancy appears to be current practice in the United Kingdom (Shehata et al. 2001) for women with antiphospholipid antibodies and a history of fetal loss after 16 weeks' gestation, intrauterine growth retardation, early-onset preeclampsia, placental abruption, or stillbirth.

Postpartum Stroke

Debate continues over classification of syndromes described as postpartum cerebral angiopathy, delayed peripartum vasculopathy, or postpartum stroke. These patients present with puerperal focal neurologic signs and symptoms and often with headaches and have hypertension without edema or proteinuria. Brain MRI scanning depicts ischemia primarily in the parietooccipital region, and angiography commonly demonstrates vasospasm. The course often is benign, but permanent deficits are reported, When these occurrences include reversible headache, altered sensorium, seizures, or visual loss without hemorrhage, they can be considered to belong in the category of a reversible posterior leukoencephalopathy syndrome. Some researchers believe postpartum stroke is a form of eclampsia/prceclampsia and suggest relaxation of requirements for diagnosis of eclampsia/prceclampsia.

Witlin et al. (2000) provide a case series and describe "postpartum stroke" as an uncommon and unprevcntable complication of pregnancy. After excluding trauma, neoplasm, infection, or eclampsia, they describe women suffering ischemic or hemorrhagic stroke without specific warning. The hemorrhage may follow initial ischemia with injury to the blood vessel walls. In general, these events

were most common around the eighth day after delivery (range 3-35 days) and were associated with cesarean delivery. Seizures in one half of patients, an increase in the mean arterial pressure to 1.5 times above the baseline, and headache herald the onset. Two of 20 patients died of severe intracerebral hemorrhage. Included in this series were patients with cerebral venous thrombosis and a ruptured AVM. The authors postulated that the hypercoagulabte or thrombophilic state of pregnancy may emerge as a major risk factor, perhaps interacting with underlying coagulopathies.

Cerebral Venous Thrombosis

Aseptic thrombosis of the cerebral venous system, in its most obvious clinical state, presents with puerperal headache that worsens over several days, a change in behavior or personality, convulsive seizures, and neurological deficits. The patient may be emotionally regressed, anxious, or lethargic, with mild to obvious neurological signs, and, occasionally, papilledema. Initial symptoms generally begin 1 day to 4 weeks postpartum and peak in occurrence at "-14 Jus poMpanjm.

CVT has been associated with hypcrcoagulable states, infection, sickle cell disease, dehydration, and ulcerative colitis, in addition to gestation. Differential diagnoses include eclampsia, meningitis, and cerebral mass.

Brain MRI scanning with magnetic resonance venography is the initial imaging procedure of choice. Although it detects occlusion of major sinuses with high sensitivity, when smaller veins are involved, detection may be more difficult. The MRI may show multiple small infarcts involving the gray and white matter, sometimes with minor hemorrhage. Selective or digital subtraction angiography may be considered in some patients.

Geographic location influences the frequency of CVT. India reports a high rate of puerperal CVT, estimated at 400-500 per 100,000 births. This high rate is attributed primarily to dehydration and has a predilection for women delivering at home. Incidence in the United States is comparatively low, approximately 9 per 100,000 deliveries.

CVT associated with pregnancy is relatively more benign than that occurring without pregnancy. Researchers in Mexico describe a mortality of approximately 10% for gestational CVT and 33% for CVT not associated with pregnancy. In the United States, estimates of the mortality of CVT from all causes suggest that approximately 1 of 10 patients dies. However, death did not occur in a national survey of 4454 patients with penpartum CVT in the United States. Cesarean section and age oldet than 25 are risk factors for CVT.

Researchers find diminished activity of protein S and antiphospholipid antibodies in women with gestational and puerperal CVT. Occasionally, multiple defects in coagulation are encountered in the same woman. Current theory suggests that levels of proteins, such as C4b-binding protein, increase during pregnancy and the puerperium, creating a hypcrcoagulable state. Some women have conditions that predispose them to hypercoagulation during pregnancy, such as activated protein C resistance (factor V Leiden mutation), protein S deficiency, or antithrombin III antibodies. Homocystinuria (hyperhomocyst|ejinemia) may increase risk.

Heparin anticoagulation may be of benefit, particularly if the patient has concurrent thrombophlebitis in the pelvis and legs. Some observers recommend heparin therapy only when clinical indicators suggest that a poor prognosis is likely. Therapy with antifibrinolytic agents is controversial. Thrombolysis of an occluded dura] sinus with urokinase or with [issue plasminogen activator via selective venography has been used as initial therapy without significant deterioration. Physicians performing this procedure claim therapeutic success, even for some patients with cerebral hemorrhage. Heparin and antifibrinolytic therapies are relatively contraindicatcd when the patient has had an intracranial hemorrhage. Long-term anticonvulsant therapy usually is unnecessary.

ECLAMPTIC ENCEPHALOPATHY

Preeclampsia (toxemia gravidarum) and eclampsia remain the principal causes of maternal perinatal morbidity and death. Edema, proteinuria, and hypertension after 20 weeks' gestation characterize the syndrome of preeclampsia. Epileptic seizures and this preeclamptic triad comprise the syndrome of eclampsia. Defining the terms *preeclampsia* and *eclampsia* in this way simplifies a complex disorder. Important and common manifestations, such as hepatic hemorrhage, disseminated intravascular coagulation, ahruptio placentae, pulmonary edema, papilledema, oliguria, headache, hyper-reflexia, hallucinations, and blindness seem relatively neglected in this definition. Occasionally, eclamptic seizures may precede the clinical triad of preeclampsia. Reasoning that pedal edema is ubiquitous and nonspecific during pregnancy, a consensus group recommended that physicians exclude edema as a criterion for the diagnosis of preeclampsia and concluded that the dyad of hypertension and proteinuria is sufficient, more sensitive, and no less specific (Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000).

Preeclampsia develops in approximately 4-8% of the pregnancies in prospective studies. Eclampsia accounts for nearly OIK- half of intracranial hemorrhages and nearly one half of cerebral infarcts in pregnancy and puerperium in French hospitals. In the United States, the figures are lower {14 and 24%, respectively). Methodological problems plague these studies, and accurate estimates are difficult to obtain. Neurological symptoms are more likely when the onset of eclampsia is postpartum. Maternal morbidity and

mortality Increase when eclampsia occurs at 32 weeks' gestation.

A specific laboratory test for rhis disorder is lacking, and understanding of the pathogenesis remains incomplete. Conditions considered to place women at added risk for preeclampsia include multifetal gestations, previous preeclampsia, insulin-treated diabetes mellitus, hypercoagulable states, and chronic hypertension. Geneticists have associated preeclampsia with a molecular varianr of the angiotensinogen gene and suggest a possible genetic predisposition. Some authors postulate that damage to the fetal-pi a cental vascular unit {such as defective placentation) may release products toxic to die endothelium, causing diffuse vasospasm and organ injury. Researchers point to soluble fms-like tyrosine kinase 1, a substance produced in toxic amounts by the placenta and implicated in reducing levels of angiogenic trophic factors, vascular endothelial growth factor (VEGF) and placenta! growth factor (P1GF). Lack of these trophic factors may result in the clinical and pathological syndrome of preeclampsia. Short intervals between pregnancies reduce the risk of preeclampsia (Skjaervcn et al. 2002). No theory explains satisfactorily the tendency for preeclampsia or eclampsia to affect primarily young, primigravid women.

At autopsy of patients who died of eclampsia, pathologists find cerebral edema; hypertensive encephalopathy; subarachnoid, subcortical, and petechial hemorrhages; and infarction of multiple areas of the brain and brainstem. The occipital lobes, parietal lobes, and watershed areas are most vulnerable. Although any of these lesions may cause seizures, the patient may not have a seizure. This observation has led to criticism that the definition of eclampsia solely on the basis of a seizure is too restrictive.

Two theories compete to explain the genesis of the cerebral lesions. Elevated blood pressure may overcome protection that is usually provided by the precapillary-arteriolar sphincter. Loss of autoregulation then leads to rupture of fragile capillaries, resulting in ring hemorrhages and thrombosis. Alternatively, diffuse cerebral endothelial dysfunction may precipitate generalized cerebral vasospasm, producing the same pathologic changes.

One review observed that many women in whom preeclampsia or eclampsia was diagnosed had, in retrospect, clinical presentations most consistent with other diseases. These included cerebral arterial infarction, hypertensive encephalopathy, and CVT. Eagerness to diagnose (o\;i:ii.i, '•iiv,ih", ilur :n [In niu. i which tin condition naturally presents, may overestimate its incidence in epidemiological studies. The neurologist must consider alternative diagnoses carefully.

Biuiul pressure elevations consistent!; equal to 140/90 without proteinuria beyond 20 weeks after conception in a woman previously normotensivc is gestational hypertension. Gestational hypertension complicates 6% of pregnancies. Within this group arc women suffering from unrecognized chronic hypertension and transient hypertension of pregnancy. One quarter of them will develop preeclampsia/eclampsia. Transient, mild hypertension does not affect mother or fetus. When the physician discovers end-organ damage associated with gestational hypertension, the patient is managed according to the recommendations for preeclampsia. When proteinuria (>300 mg per 24 hours) accompanies gestational hypertension, physicians may diagnose preeclampsia; although this definition has not been substantiated by research, it is used commonly,

Severe preeclampsia is defined hy the magnitude of blood pressure elevation (usually a systolic pressure of 160 mm Hg or a diastolic pressure of 110 mm Hg on two occasions at least 6 hours apart while the patient is resting in bed), amount of proteinuria (>500 mg of protein per 24 hours or 3+ in random urine samples taken at least 4 hours apart), the presence of end-organ injury, or symptoms of possible end-organ injury (headache, right upper quadrant pain, visual disturbance, or altered sensorium) in a woman with preeclampsia. Approximately 4-14% of women with preeclampsia develop a syndrome called HELLP—an acronym for hemolysis, elevated *liver* enzyme levels, and low platelets. All three components must be present, Hemolysis is detected by an abnormal peripheral blood smear, a bilirubin level of 1.2 mg/dL, or a lactate dehydrogenase level of 600 EU/liter. Liver enzyme levels are considered elevated when aspartate aminotransferase is 2 times normal. A plateler count of less than 100 x 10 /p.L is low. HELLP syndrome is considered a form of severe preeclampsia with a high rate of maternal and fetal injury. Patients complain of malaise, nausea, right upper quadrant pain, and vomiting. Occasionally, HELLP syndrome presents without preeclampsia and is considered a separable clinical entity.

Women in whom preeclampsia is diagnosed and rheir fetuses should receive careful monitoring (ACOG 2002}. When preeclampsia is severe or hypertension is more than mild (systolic pressure of 160 mm Hg or diastolic pressure of 105-110 mm Hg), consensus groups recommend methyldopa and labetalol as appropriate first-line therapies. Hydralazine is used commonly.

Severe preeclampsia, eclampsia, or HELLP syndrome requires definitive therapy. Commonly, women are delivered within 24—48 hours of presentation, and all gestational products must be removed from the utetus by vaginal or cesarean delivery.

Parenteral magnesium sulfate is used extensively to treat symptoms of severe preeclampsia and eclampsia while the woman awaits delivery. In a large clinical trial, women presenting for delivery with hypertension were given either phenytoin or magnesium sulfate. Among the women receiving magnesium sulfate, fewer developed seizures. In a separate analysis of women with eclampsia, magnesium sulfate therapy reduced recurrent seizures better than regimens using cither diazepam or phenytoin. The mechanism of action remains unclear. The most coherent theory

suggests that magnesium sulfate affects the pathogenesis of cerebral disease, resulting in a secondary effect on the seizures rather than functioning as an anticonvulsant itself. Usually, the drug is continued for a day after delivery. AEDs commonly used to prevent and control eclamptic seizures include barbiturates, phenytoin, and benzodiazepines.

For some women, thrombocytopenic purpura and hemolytic-uremic syndrome may be seen with or complicate toxemia and HELLP syndrome. Death and severe neurological disease are common. Survival may be improved with the use of plasma transfusion and plasmapheresis.

Low-dose aspirin thctapy was effective in preventing eclampsia in small trials, but larger studies of women at high risk for preeclampsia showed no benefit for aspirin 60 mg taken daily. French researchers claimed beneficial effects for aspirin 100 mg daily when doses are given by about 17 weeks' gestation. Women whose bleeding time increased were more likely to benefit (Dumont 1999). The combination of aspirin with ketanserin, a selective seroronin-2 receptor blocker, may prevent preeclampsia in women with hypertension diagnosed before 20 weeks' gestation. However, consensus opinion has not endorsed the use of aspirin with or without ketanserin to prevent preeclampsia,

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